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[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

# Studies on the Barks of the Family *Salicaceae*. I. Tremuloidin, a New Glucoside from the Bark of *Populus tremuloides*[1]

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A new glucoside has been isolated from the bark of *Populus tremuloides*. This glucoside, which we have named tremuloidin, is a monobenzoate of salicin and an isomer of populin. Tremuloidin was completely methylated to tetramethyltremuloidin which, in turn, was debenzoylated to a tetramethylsalicin yielding 3,4,6-tri-*O*-methyl-D-glucopyranoside on acid hydrolysis. Thus, tremuloidin was identified as 2-benzoylsalicin. Tremuloidin was oxidized with dilute nitric acid to 2-benzoylhelicin. All products and intermediates were characterized by means of infrared absorption spectra.

In 1830 the glucoside salicin was discovered in the bark of *Salix helix* by Leroux,[2] and in the same year Braconnot[3] isolated salicin from the bark of the European quaking aspen, *Populus tremula*, along with a new substance which he named "populin." Although the structural formulas for these compounds remained unknown for a long time, Piria[4] demonstrated that salicin could be hydrolyzed with dilute acid or enzymatically to yield salicyl alcohol and glucose and that the phenolic hydroxyl in salicyl alcohol was involved in the glucosidic linkage because salicin could be oxidized to helicin, the glucoside of salicylaldehyde. Piria even showed the relationship between salicin and populin by demonstrating that populin yielded salicin and benzoic acid when saponified with barium hydroxide solution. Somewhat later Schiff[5] showed that the benzoyl group in populin must be attached to the glucose and not the salicyl alcohol moiety because populin could be oxidized to benzoylhelicin, a compound he prepared by benzoylating helicin. In addition, Schiff benzoylated salicin by several methods and obtained a synthetic populin which he compared with a sample of natural populin from Piria's laboratory. Identity was established by such properties as taste, solubility, and color with concentrated sulfuric acid, properties now known to be exhibited by similarly related and constituted substances. Dobbin and White[6] improved Schiff's benzoylation technique for preparing synthetic populin from salicin and noted that their synthetic compound had the same melting point (180°) as a purified natural material. The uncertainty of absolute identity was continued by Dobbin and White who wrote: "The purified natural product behaved in every other respect exactly as our synthetic sample did." In 1906, Irvine and Rose[7] completely methylated salicin and hydrolyzed the resulting pentamethylsalicin to 2,3,4,6-tetramethylglucose. This finding together with the fact that salicin is hydrolyzed by emulsin proves salicin to be *o*-hydroxymethylphenyl-*O*-β-D-glucopyranoside (I). Many years later Richtmyer and Yeakel[8] methylated synthetic populin with methyl iodide and silver oxide. The resulting tetramethylpopulin was debenzoylated to a tetramethylsalicin, which on hydrolysis with hydrochloric acid yielded 2,3,4-tri-*O*-methyl-D-glucose. Thus, the structure of synthetic populin was proved to be 6-benzoylsalicin (II), and the intermediate tetramethylpopulin and tetramethylsalicin had the structures III and IV, re-

(1) Presented before the Division of Cellulose Chemistry at the 135th meeting of the American Chemical Society, Boston, Mass., April 5–10, 1959.

(2) Leroux, *Ann. Chim. Phys.*, [2] **43**, 440 (1830).

(3) H. Braconnot, *Ann. Chim. Phys.*, [2] **44**, 296 (1830).

(4) R. Piria, *Ann.*, **56**, 35 (1845); **96**, 375 (1855).

(5) H. Schiff, *Ann.*, **154**, 1 (1870).

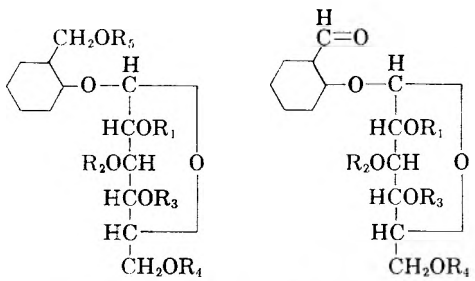
(6) L. Dobbin and A. D. White, *Pharm. J.*, [4] **19**, 233 (1904).

(7) J. C. Irvine and R. E. Rose, *J. Chem. Soc.*, **89**, 814 (1906).

(8) N. K. Richtmyer and E. H. Yeakel, *J. Am. Chem. Soc.*, **56**, 2495 (1934).

spectively. Richtmyer and Yeakel reported for synthetic populin $[\alpha]_D$ − 2.0° ($c$ = 5 in pyridine). It is interesting to note that as early as 1852 Biot and Pasteur[9] recorded for natural populin $[\alpha]_D$ − 20.75° ($c$ = 1 in absolute ethanol), while much later Bridel[10] reported $[\alpha]_D$ − 24.73° (in 60% acetone). However, none of the investigators of synthetic populin ever compared rotations of synthetic and natural populins.

During the past century the presence of salicin and populin has been reported in the barks of a number of species of *Populus*,[11] but unfortunately, the presence of these glucosides was usually demonstrated by some indirect physical, chemical, or biochemical procedure such as increase in glucose concentration upon hydrolysis, oxidation, and determination of salicylic acid, or calculation of enzymolytic indices. Some of these procedures would give valid results when applied to solutions of glucose and only the two pure glucosides, but results obtained on aqueous extracts of *Populus* barks might be very misleading when interpreted in the light of our present knowledge of possible components of *Populus* bark extracts.



I. $R_1 = R_2 = R_3 = R_4 = R_5 = H$
II. $R_1 = R_2 = R_3 = R_5 = H$; $R_4 = C_6H_5CO$
III. $R_1 = R_2 = R_3 = R_5 = CH_3$; $R_4 = C_6H_5CO$
IV. $R_1 = R_2 = R_3 = R_5 = CH_3$; $R_4 = H$
V. $R_1 = R_2 = R_3 = R_4 = H$; $R_5 = C_6H_5CO$
VI. $R_1 = C_6H_5CO$; $R_2 = R_3 = R_4 = R_5 = H$
VII. $R_1 = R_3 = R_4 = R_5 = H$; $R_2 = C_6H_5CO$
VIII. $R_1 = R_2 = R_4 = R_5 = H$; $R_3 = C_6H_5CO$
IX. $R_1 = H$; $R_2 = R_3 = R_4 = R_5 = CH_3$
XII. $R_1 = C_6H_5CO$; $R_2 = R_3 = R_4 = R_5 = CH_3CO$
XIII. $R_1 = C_6H_5CO$; $R_2 = R_3 = R_4 = R_5 = CH_3$
X. $R_1 = R_2 = R_3 = H$; $R_4 = C_6H_5CO$
XI. $R_1 = C_6H_5CO$; $R_2 = R_3 = R_4 = H$

In the course of our investigations on *Populus tremuloides*, American quaking aspen, some fresh bark obtained in late May was extracted with 95% ethanol, and the ethanol extract was concentrated to approximately 25% solids. The fresh concentrated extract was evaporated to dryness and extracted with water at 25°. The extract was purified by treating with basic lead acetate, filtering, and removing the lead with hydrogen sulfide. Upon partial concentration, the clear filtrate deposited colorless needles melting at 201–202°. The yield amounted to 0.37% based on the original oven-dried *P. tremuloides* bark. Further concentration of the filtrate yielded crystals of salicin melting at 193–194° and very different from the first crystals in water solubility and taste.

Recrystallization of the 201–202° melting material from water and then from methanol raised the melting point to 207–208°. The specific rotation in pyridine $[\alpha]_D^{25}$ + 17.1° ($c$ = 3.1) increased slightly on standing 72 hr. to $[\alpha]_D^{25}$ + 19.5°. The rotation in 80% acetone $[\alpha]_D^{25}$ − 12.3° ($c$ = 1.5) remained unchanged on standing. Hydrolysis with alkali at room temperature yielded benzoic acid and salicin, and analysis of the pure compound and of its acetate indicated it to be a monobenzoate of salicin. Thus, the new compound, which we have named "tremuloidin," is an isomer of synthetic populin.

In order to obviate the remote possibility that natural populin and synthetic populin are not identical and that the populin isolated by investigators more than one hundred years ago without recording the melting point might actually be identical with our tremuloidin, the work of the early investigators was repeated. Natural populin was isolated from the bark of *P. tremula* according to Braconnot[3] and from the leaves of *P. alba* according to Herberger.[12] The isolated populin was compared with synthetic populin[8] by means of optical activity, mixed melting point, and infrared absorption spectra, and the two were found to be identical. Therefore, "tremuloidin" was a new monobenzoate of salicin with benzoyl substitution at some position other than the 6-position on the glucose, which is the known benzoyl substitution of populin.[8]

Controlled periodate oxidation[13] of tremuloidin developed no acidity and consumed one mole of periodate, indicating a compound containing only two adjacent hydroxyl groups. Of the possible monobenzoates of salicin other than 6-glucose substitution (V–VIII) only VI and VIII with substitution at positions 2 and 4, respectively, would satisfy these criteria. The anomalous dextrorotation of the tetraacetate of tremuloidin, $[\alpha]_D^{24}$ + 33.9° ($c$ = 2.5 in chloroform); suggested the structure VI because the data of Pigman[14] indicated that acetates of several glucosides substituted in the 2-glucose position demonstrated this anomalous dextrorotation. For determining the exact location of benzoyl substitution in tremuloidin, the general procedure of Richtmyer and Yeakel[8] was employed.

Tremuloidin was methylated completely with methyl iodide and silver oxide to yield tetramethyltremuloidin as a sirup which failed to crystallize.

(9) J. B. Biot and L. Pasteur, *Compt. rend.*, **34**, 606 (1852).

(10) M. Bridel, *J. Pharm. Chim.*, [7] **20**, 14 (1919).

(11) For a complete bibliography see W. Thies and C. Wehmer, in G. Klein, Handbuch der Pflanzenanalyze, Bd. III, 2 Teil, 845, Vienna, 1932. See also A. Kuhn and G. Schäfer, *Pharm. Ztg.*, **82**, 949 (1937).

(12) J. E. Herberger, *Buchners Report Pharm.*, **51**, 266 (1835).

(13) J. R. Dyer in D. Glick, Methods of Biochemical Analysis, Vol. 3, pp. 123, Interscience, New York, 1946.

(14) W. W. Pigman, *J. Research Natl. Bur. Standards*, **33**, 129, 144 (1944).

but whose purity was demonstrated by paper chromatography and by the fact that paper chromatography of its acid hydrolyzate indicated only one sugar spot, that for a trimethylglucose. The oily tetramethyltremuloidin was debenzoylated by means of sodium methylate in methanol to yield the corresponding tetramethylsalicin as a crystalline compound. The tetramethylsalicin was hydrolyzed by boiling with hydrochloric acid in aqueous methanol to yield 3,4,6-tri-*O*-methyl-D-glucopyranoside which was identified by mixed melting point and by identity of infrared absorption spectra with authentic material.[15] Thus, the structure of the tetramethylsalicin must be ω,3,4,6-tetramethylsalicin (IX) and that of tremuloidin, 2-benzoylsalicin (VI).

The locating of the benzoyl group in populin by Richtmyer and Yeakel[8] establishes the structure of the benzohelicin obtained by Piria[4] and by Schiff[5] by dilute nitric acid oxidation of populin as 6-benzoylhelicin (X). Similar oxidation of tremuloidin gave 2-benzoylhelicin (XI).

Because populin had been reported in the bark of *P. tremuloides* by earlier investigators,[11,16] on the basis of indirect evidence which may have been misleading, it was desired to determine whether this were true or whether tremuloidin had been responsible for earlier reports. Accordingly, the original ethanol extractives left after water extraction at 25° were reextracted with boiling water, and the hot water extract was processed as before. Partial concentration yielded an additional 0.15% tremuloidin as relatively pure material melting at 200–202°. Further concentration yielded 0.26% of crystals melting between 178 and 186° which proved to be a mixture of tremuloidin and populin. Further concentration yielded salicin and other glucosidic material to be described in future papers. Tremuloidin, populin, and salicin were easily recognized separately or in a mixture of all three when paper chromatograms were developed in either 10:3:3 butanol-pyridine-water or 9:2:2 ethyl acetate–acetic acid–water and spots located by means of a modification of Trevelyan's[17] silver spray. In this modification, Trevelyan's procedure for removing unreduced silver oxide with 6*N* ammonium hydroxide is replaced with a concentrated sodium thiosulfate wash resulting in chromatograms with glycoside spots appearing as black spots against a white background instead of brown spots against a light brown background.

The mixture of populin and tremuloidin obtained above was submitted to column chromatography by adsorption on a dry packed column of powdered cellulose and elution with the ethyl acetate–acetic acid–water developer noted above. Collection of the

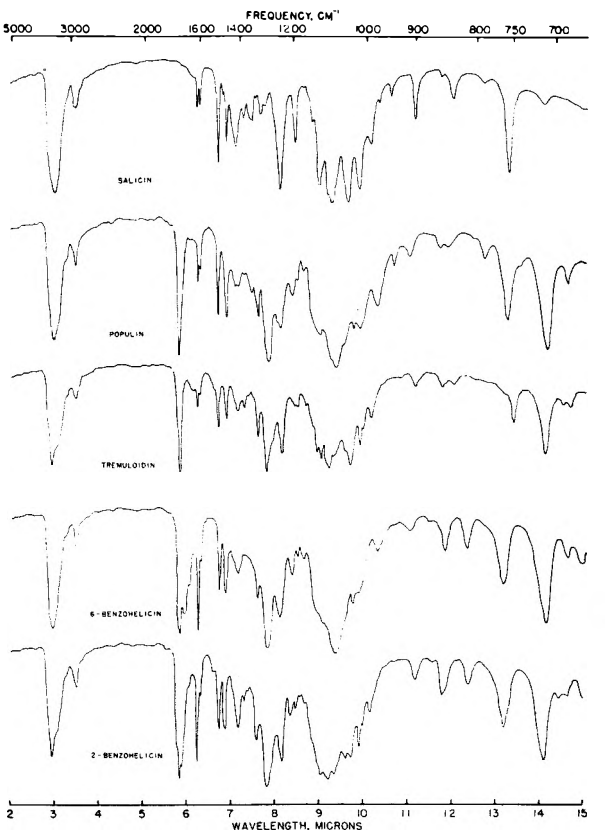



Fig. 1. Infrared absorption curves: salicin, populin, tremuloidin, 6-benzohelicin, 2-benzohelicin

eluate in fractions gave complete separation of populin and tremuloidin, and both glucosides were recrystallized and identified by mixed melting point and by identity of infrared absorption spectra (Fig. 1) and optical activity with authentic samples.

## EXPERIMENTAL[18]

*Isolation of tremuloidin* (VI). An amount of 15 kg. (ovendry basis) of fresh whole bark peeled from a 35-year-old quaking aspen (*Populus tremuloides*) in late May was broken into strips, placed in three 5-gal. jars, and covered with 95% ethanol. After standing at room temperature one week, the ethanolic extract was decanted, and the bark was covered with fresh ethanol. After another week, the solvent was changed again. The process was repeated once more, and the combined ethanolic extracts were filtered and concentrated under reduced pressure in a circulating evaporator to 8395 g. containing 2240 g. of solids. After a few days, a well mixed sample containing 291 g. of solids was evaporated to dryness below 25° in a rotating evaporator. The residue was stirred with 3 l. of water at 25° and allowed to stand overnight. The aqueous extract was decanted and filtered through a Celite pad. The slightly turbid yellow solution was treated with stirring with an excess of a slurry of basic lead acetate, and the resulting precipitate was filtered. The filtrate was saturated with hydrogen sulfide and filtered to yield a colorless clear solution. This was concentrated under reduced pressure to approximately 1500 ml. volume and cooled. The crystals which separated were fil-

(15) Kindly supplied by Dr. N. K. Richtmyer, National Institutes of Health, Bethesda, Md.

(16) R. L. Hossfeld and F. H. Kaufert, *Forest Products J.*, **7**, 437 (1957).

(17) W. E. Trevelyan, D. P. Proctor and J. S. Harrison, *Nature*, **166**, 444 (1950).

(18) All melting points are uncorrected. Analyses were performed by Huffman Microanalytical Laboratories, Wheatridge, Col.

tered and washed with water to yield 7.0 g. of crude tremuloidin melting at 201–202°. Stepwise concentration of the filtrate and washings yielded crude salicin as bitter crystals melting at 193–194°. The yield in three batches amounted to 12 g., but more precipitated in the filtrate after concentration to a sirup and standing.

The 201–202° crystals were recrystallized from water and then from methanol to give colorless needles melting at 207–208° and with specific rotation in pyridine $[\alpha]_D^{25}$ +17.1° ($c$ = 3.1) which increased slightly on standing 72 hr. to $[\alpha]_D^{25}$ +19.5°. The rotation in 80% acetone $[\alpha]_D^{25}$ −12.3° ($c$ = 1.5) remained unchanged on standing.

*Anal.* Calcd. for $C_{20}H_{22}O_8$: C, 61.53; H, 5.68. Found: C, 61.44; H, 5.66.

Acetylation of tremuloidin with acetic anhydride and pyridine and recrystallization from ethanol yielded crystals of tremuloidin tetraacetate (XII) melting at 114–115°, $[\alpha]_D^{24}$ +33.9° ($c$ = 2.5 in chloroform).

*Anal.* Calcd. for $C_{28}H_{30}O_{12}$: C, 60.21; H, 5.41. Found: C, 60.25; H, 5.36.

*Alkaline hydrolysis of tremuloidin.* One g. of tremuloidin was covered with 150 ml. of 1% sodium hydroxide solution and allowed to stand at 25° overnight. The clear yellow solution was exactly neutralized with dilute sulfuric acid and concentrated to half volume in a rotating evaporator. The shiny crystals which separated were filtered, washed with water, and recrystallized from ethanol to give colorless platelets which melted at 119–120° and did not lower a mixed melting point with authentic benzoic acid. The aqueous filtrate was concentrated further, and the crystalline precipitate was filtered and recrystallized from ethanol to give white crystals which melted at 190–191° and did not depress a mixed melting point with authentic salicin.

*Populin* (II) *from salicin* (I). Salicin was benzoylated with benzoyl chloride and potassium hydroxide solution according to Richtmyer and Yeakel[8] and the product was recrystallized first from water and then from ethanol to give colorless needles of synthetic populin melting at 178–179°, $[\alpha]_D^{24}$ −2.0° ($c$ = 5 in pyridine); $[\alpha]_D^{25}$ −29.7° ($c$ = 5 in 80% acetone).

*Populin* (II) *from Populus alba leaves.* A batch of fresh leaves from an authentic *P. alba* obtained in June was extracted with hot water according to Herberger,[12] and the hot water extract was purified by means of basic lead acetate. The purified solution was freed from lead by means of hydrogen sulfide and partially concentrated. Some ash-containing crystals which separated were filtered, and the clear filtrate was evaporated further to yield crystals. These were recrystallized from water in the presence of decolorizing carbon to give colorless needles of natural populin which melted at 179–180° and did not depress a mixed melting point with synthetic populin prepared above. Infrared absorption spectra of the two populins were superimposable. The specific rotation of natural populin in both pyridine and 80% acetone was identical with that of synthetic populin.

Natural populin was also isolated from the fresh bark of *P. tremula* in accordance with Braconnot[3] by essentially the same procedure.

*Periodate oxidation of tremuloidin.* The general procedure outlined by Dyer[13] was modified to some extent. Approximately 50 mg. of tremuloidin was dissolved in 40 ml. of 50% ethanol with warming and then treated with 25 or 50 ml. of 0.01$M$ sodium metaperiodate. The solution was diluted with water to 100 ml. and maintained at 4° in "actinic red" flasks. Aliquots of 5 ml. each were taken at appropriate times for analysis. To each 5-ml. aliquot was added 10 ml. of saturated aqueous sodium bicarbonate, 5 ml. of 0.01$M$ sodium arsenite and 1 ml. of 1% potassium iodide in saturated sodium bicarbonate solution. After 15 min., the remaining arsenite was titrated with iodine to a starch end point. Data for tremuloidin indicated 1 mole periodate consumed per mole of glucoside.

Acidity developed was determined by a modification of the method of Abdel-Akher and Smith[19] in which the aliquot is allowed to stand 60 min. after addition of 10% ethylene glycol to ensure complete destruction of excess periodate before addition of potassium iodide solution. Data indicated no developed acidity with tremuloidin.

Similar oxidations on salicin in water at 25° consumed two moles of oxidant and developed one mole of acid as expected. Oxidations on populin showed overoxidation at 25°, while at 4°, populin was insoluble in water or in the dilute ethanol solutions employed.

*Methylation of tremuloidin.* In a small flask fitted with a reflux condenser and silicone-sealed stirrer was placed a mixture of 1.0 g. of tremuloidin, 10 ml. of methyl iodide, and 15 ml. absolute methanol. With stirring and boiling under reflux, 6.0 g. of freshly prepared silver oxide was added over a period of 3 hr. in 1-g. lots. After the second addition, 5 ml. of acetone were added to completely dissolve all tremuloidin. The mixture was allowed to stand overnight at room temperature and filtered. The silver oxide was washed thoroughly with acetone, and the combined filtrate and washings were evaporated to dryness in a rotating evaporator. The colorless sirup was dissolved in 10 ml. of methyl iodide and a few drops of methanol and methylated as before. The process was repeated three times making a total of four methylations. After the third methylation, the product was completely soluble in methyl iodide without the addition of methanol. The final product tetramethyltremuloidin (XIII), was obtained as 1.05 g. of clear colorless viscous oil having a specific rotation $[\alpha]_D^{25}$ +6.56° ($c$ = 4.2 in chloroform). All attempts at crystallization failed. Complete methylation was demonstrated by the fact that, upon hydrolysis with hydrochloric acid, paper chromatograms of the hydrolyzate showed only one sugar spot, that for a trimethylglucose. Paper chromatograms were developed with 9:2:2 ethyl acetate–acetic acid–water, and spots were located by means of the *p*-anisidine spray.[20]

*Debenzoylation of tetramethyltremuloidin to ω,3,4,6-tetramethylsalicin* (IX). A solution of 1.05 g. of tetramethyltremuloidin in 20 ml. of anhydrous methanol was treated with a solution of 0.1 g. of metallic sodium in 10 ml. of anhydrous methanol, and the mixture was boiled under reflux for 10 min., diluted with 30 ml. of water, and partially evaporated in a rotating evaporator to remove all methanol. The turbid aqueous solution was extracted with ether, and the ether was washed with water, dried with sodium sulfate, and evaporated in a rotating evaporator to yield a colorless oil which solidified upon standing. The crystals were dissolved in a little anhydrous ether and filtered. The clear filtrate was diluted with petroleum ether (b.r. 30–60°) and placed in the freezer. The colorless needles which separated were filtered and recrystallized again in the same manner to yield 0.31 g. of IX melting at 85–86°, $[\alpha]_D^{25}$ −39.1° ($c$ = 1.2 in chloroform).

*Anal.* Calcd. for $C_{24}H_{26}O_7$: C, 59.63; H, 7.65; $CH_3O$, 36.3. Found: C, 59.64; H, 7.68; $CH_3O$, 36.1.

The aqueous layer remaining after the ether extraction was acidified with dilute hydrochloric acid and allowed to stand. The crystals which separated were filtered and recrystallized from water to give shiny platelets of benzoic acid which melted at 119–120° and did not depress the melting point of a mixture with authentic benzoic acid.

*Hydrolysis of ω,3,4,6-tetramethylsalicin.* A mixture of 0.35 g. of ω,3,4,6-tetramethylsalicin, 4 ml. of methanol, and 6 ml. of 2$N$ hydrochloric acid was heated on the steam bath under reflux for 2 hr. The mixture became turbid after 1 hr. and had deposited a reddish gum after 2 hr. Methanol was removed under reduced pressure, and the residual aqueous mixture was filtered with the aid of a little Celite. The clear

(19) M. A. Abdel-Akher and F. Smith, *J. Am. Chem. Soc.*, **73**, 996 (1951).

(20) L. Hough, J. K. N. Jones, and W. H. Wadman, *J. Chem. Soc.*, 1950, 1702.

filtrate was treated with excess IR-4B ion-exchange resin in the acetate form and filtered. The resin was washed thoroughly with water, and the combined filtrate and washings were evaporated to dryness under reduced pressure in the rotating evaporator to leave a slightly yellow syrup. Paper chromatography in the ethyl acetate–acetic acid–water developer and spraying with *p*-anisidine indicated only a trimethylglucose and some phenolic aglucone material with good separation. The entire yellow sirup was dissolved in 2.5 ml. of methanol and streaked on four eight-inch wide Whatman 3M papers, previously washed with methanol. The papers were developed in the ethyl acetate–acetic acid–water developer. One-fourth inch strips were cut from each paper for monitoring, and the located bands of trimethylglucose were cut from the papers. These bands were eluted with methanol in a Soxhlet apparatus, and the methanol eluate was evaporated in a rotating evaporator to yield a colorless sirup. After standing for two weeks, the partially crystalline sirup was covered with a few milliliters of diisopropyl ether and filtered. The crystals were recrystallized from 2 ml. of diisopropyl ether to give colorless crystals which melted at 97–98° and did not depress a mixed melting point with authentic 3,4,6-tri-*O*-methyl-D-glucopyranoside.[15] The infrared curves of the authentic 3,4,6-tri-*O*-methyl-D-glucopyranoside and the trimethylglucose obtained by hydrolysis of IX were identical.

*Paper chromatography of glucosides.* The silver spray procedure of Trevelyan and co-workers[17] indicated the glucosides under study as dark brown spots on a light brown background. As such, the procedure was unsatisfactory for the location of small amounts of glycosidic materials. In the Trevelyan procedure the chromatogram is sprayed with an acetone solution of silver nitrate, allowed to dry, sprayed with an alcoholic solution of sodium hydroxide, and allowed to stand at room temperature for 5 to 10 min. to develop the spots. The paper is then washed with 6*N* ammonium hydroxide to remove unreduced silver oxide, then washed with water and dried. The procedure was modified as follows. The paper, after standing at room temperature to develop the spots, is bathed a few times in a concentrated (350 g. per liter) solution of sodium thiosulfate, washed thoroughly with water and dried. In this modified procedure, glycoside spots appear as almost black spots against a white background, and much smaller amounts of glycosidic materials can be detected. It is important in this modified procedure that all excess sodium thiosulfate be removed from the paper by washing if it is desired to store the chromatograms. Otherwise, the spots will gradually fade over a period of several weeks. Very recently, Hathaway and Seakins[21] published a modification of the Trevelyan procedure in which a 4% sodium thiosulfate wash was employed.

The three glucosides, salicin, populin, and tremuloidin, were easily recognized separately or in admixture when paper chromatograms were developed in either 10:3:3 butanol-pyridine-water (BPW) or 9:2:2 ethyl acetate–acetic acid–water (EAW) and sprayed with the modified silver spray. $R_f$ values at 25° for BPW are: salicin, 0.52; populin, 0.69; and tremuloidin, 0.77. $R_f$ values for EAW are: salicin, 0.60; populin, 0.84; and tremuloidin, 0.85.

*Isolation of populin from P. tremuloides.* The residue remaining after water extraction at 25° noted above under the isolation of tremuloidin was covered with 1 l. of hot water, and the mixture boiled under reflux for 1 hr. The mixture was allowed to cool, and the turbid yellow aqueous layer was decanted from the residual heavy oil. The boiling water extraction was repeated on the heavy oil, and the combined turbid aqueous extracts were filtered through Celite and purified by means of basic lead acetate precipitation followed by hydrogen sulfide treatment. The resulting clear solution was concentrated to one-half volume and allowed to stand overnight. The crystals which separated were filtered, washed with water, and dried to yield 2.8 g. of almost pure tremuloidin melting at 200–202°. The filtrate and washings were concentrated again to a smaller volume and allowed to stand. The crystals which separated at this point weighed 0.8 g. and melted at 178–181°. Paper chromatography indicated about 75% tremuloidin and 25% populin. Another concentration and crystallization yielded 4.1 g. of crystals melting at 185–186° comprising about 50% each of tremuloidin and populin. Crystalline products obtained on further concentration contained substantial amounts of salicin and other glucosidic materials.

A 0.1-g. sample of the 50% mixture of populin and tremuloidin melting at 185–186° was dissolved in EAW developer and absorbed on a dry-packed column of powdered cellulose (Whatman Standard Grade) 2 cm. in diameter and 15 cm. in height. The column was eluted with EAW, and the eluate was collected in 5-ml. fractions. The fractions were monitored by means of paper chromatography as follows: 1, pure tremuloidin; 2, tremuloidin with trace of populin; 3, pure populin; 4, pure populin; 5, pure populin; 6, trace of populin; 7 ff., nothing. Fractions 3, 4, and 5 were combined and evaporated to dryness. The residue was covered with a little water and filtered to give crystals of populin which melted at 179–180° and did not depress a mixed melting point with synthetic populin.

It is interesting to note that Fraction 1 deposited crystals of tremuloidin melting at 209–210°, slightly higher than that of any sample purified by recrystallization alone.

*Infrared spectra.* Infrared absorption spectra were obtained with a Perkin-Elmer model 21 recording spectrophotometer using a sodium chloride prism and potassium bromide pellets prepared by hand grinding with sample before pressing

*Acknowledgment.* The authors wish to thank Dr. John W. Green for the controlled periodate oxidation data and Mr. Lowell Sell for the infrared spectra reported in this paper.

APPLETON, WIS.

(21) D. E. Hathaway and J. W. T. Seakins, *Biochem. J.*, **70**, 158 (1958).

[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

# Studies on Lignin and Related Products. XIV.[1] Spectral and Chromatographic Data on Lignin Model Compounds in the Phenylpropane Series

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*Received Dec. 31, 1958*

The $R_f$ value in two solvent systems and the infrared absorption spectra of twenty-five lignin model compounds are reported. These model compounds comprise phenylpropane derivatives with 4-hydroxy-, 4-hydroxy-3-methoxy-, and 3,5-dimethoxy-4-hydroxy-substitution. Many of these compounds were prepared by new procedures, and in other cases many intermediates were new or were prepared by new procedures.

During the past few years, in connection with our studies on the isolation and identification of individual compounds from lignin reaction mixtures, pulping spent liquors, and wood extracts, we had the occasion to prepare many phenylpropane derivatives with 4-hydroxy-, 4-hydroxy-3-methoxy-, and 3,5-dimethoxy-4-hydroxy- substitution. These compounds have proved invaluable for compound identification in these isolation studies. The use of paper chromatographic, electrophoretic, and countercurrent distribution techniques in recent years has enabled investigators in many laboratories to isolate from lignin and wood mixtures individual compounds in amounts much too small for identification by conventional procedures. Under such conditions $R_f$ values in several developing systems together with color reactions of spray reagents known for individual functional groups serve for preliminary identification, and infrared spectra serve admirably for positive identification of isolated compounds. The present paper reports infrared absorption spectra and $R_f$ data for the butanol saturated with 2% aqueous ammonia and 10:3:3 butanol-pyridine-water systems at 20° for a number of phenylpropane derivatives with the above noted substitution. Many of these compounds were prepared by known procedures and others required new procedures or intermediates prepared by new procedures. New compounds, new intermediates, and new procedures are noted in the experimental portion.

4-Hydroxy-3-methoxyphenylpropane was prepared by hydrogenation at room temperature over palladium on charcoal catalyst of either eugenol or isoeugenol. 3,5-Dimethoxy-4-hydroxyphenylpropane was prepared by similar hydrogenation of 4-allyl-2,6-dimethoxyphenol[2] and 4-hydroxyphenylpropane by hydrogenation of anethole followed by demethylation with hydrobromic acid.

Ferulic acid, *p*-coumaric acid, and sinapic acid were prepared by condensation with malonic acid in the presence of piperidine of vanillin, *p*-hydroxybenzaldehyde, and syringaldehyde,[3] respectively, in accordance with an earlier described procedure.[4] Hydrogenation of ferulic and *p*-coumaric acids yielded dihydroferulic and dihydro-*p*-coumaric acids, respectively. Similar hydrogenation of sinapic acid failed to yield the dihydro acid, but dihydrosinapic acid was prepared simply by reduction of sinapic acid with Raney nickel alloy in alkaline solution.

Coniferyl alcohol was prepared by the lithium aluminum hydride reduction of ethyl acetylferulate according to Allen and Byers,[5] and *p*-coumaryl alcohol was prepared by similar reduction of ethyl acetyl-*p*-coumarate in accordance with Freudenberg and Gehrke.[6] The procedure of Freudenberg and co-workers[7,8] was also employed for the preparation of sinapyl alcohol from ethyl acetylsinapate. Dihydroconiferyl alcohol was prepared by low-pressure hydrogenation of coniferyl alcohol and by lithium aluminum hydride reduction of ethyl acetyldihydroferulate at room temperature. Attempted hydrogenation of *p*-coumaryl alcohol and sinapyl alcohol failed to give the desired dihydroalcohols, but dihydro-*p*-coumaryl alcohol was readily prepared by lithium aluminum hydride reduction of methyl acetyldihydro-*p*-coumarate at room temperature, and dihydrosinapyl alcohol was prepared by sodium and ethanol reduction of methyl dihydrosinapate according to Brewer, Cooke, and Hibbert.[9]

Coniferaldehyde and *p*-coumaraldehyde were prepared by reduction with lithium tri-*t*-butoxyaluminohydride of acetylferuoyl chloride and acetyl-*p*-coumaroyl chloride, respectively, and hydrolysis of the acetylated aldehydes as described earlier.[10] Similar reaction with acetylsinapoyl chloride

(1) For paper XIII of this series, see I. A. Pearl, *J. Am. Chem. Soc.*, **78**, 5672 (1956).

(2) G. Hahn and H. Wassmuth, *Ber.*, **67**, 702 (1934).

(3) I. A. Pearl, *J. Org. Chem.*, **22**, 1229 (1957).

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(5) C. H. F. Allen and J. R. Byers, Jr., *J. Am. Chem. Soc.*, **71**, 2683 (1949).

(6) K. Freudenberg and G. Gehrke, *Chem. Ber.*, **84**, 443 (1951).

(7) K. Freudenberg and R. Dillenburg, *Chem. Ber.*, **84**, 70 (1951).

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(9) C. P. Brewer, L. M. Cooke, and H. Hibbert, *J. Am. Chem. Soc.*, **70**, 57 (1948).

(10) I. A. Pearl and S. F. Darling, *J. Org. Chem.*, **22**, 1266 (1957).

yielded sinapaldehyde. Sinapaldehyde was also prepared by reduction of acetylsinapoyl chloride with sodium trimethoxyborohydride and hydrolysis of the resulting acetylated aldehyde.

Propiovanillone was prepared by oxidation of 1-(4-hydroxy-3-methoxyphenyl)-1-propanol with alkaline silver oxide,[11] propiosyringone by Fries rearrangement of the propionate of pyrogallol 1,3-dimethyl ether[12] and 4-hydroxypropiophenone was obtained commercially. Propiovanillone and propiosyringone were converted to their α-bromo derivatives by direct bromination, and these bromo compounds were converted to α-hydroxypropiovanillone and α-hydroxypropiosyringone, respectively, by the procedures of Hibbert and co-workers.[13,14] Copper sulfate and pyridine oxidation of these α-hydroxypropiophenones according to Hibbert and co-workers[15,16] yielded vanilloyl methyl ketone and syringoyl methyl ketone, respectively.

$R_f$ values determined at 20° by the descending technique in butanol saturated with 2% aqueous ammonia and in 10:3:3 butanol-pyridine-water developers are given in Table I. Infrared absorption spectra are given in Figs. 1–9.

TABLE I

$R_f$ VALUES AT 20°[a]

| Compound | Butanol–2% Aqueous Ammonia | 10:3:3 Butanol-Pyridine-Water |
|---|---|---|
| 4-Hydroxy-3-methoxyphenylpropane | 0.79 | 0.90 |
| 4-Hydroxyphenylpropane | 0.93 | 0.89 |
| 3,5-Dimethoxy-4-hydroxyphenylpropane[b] | 0.86 | 0.84 |
| Ferulic acid[c] | 0.13 | 0.48 |
| *p*-Coumaric acid | 0.18 | 0.57 |
| Sinapic acid[c] | 0.06 | 0.36 |
| Dihydroferulic acid | 0.20 | 0.42 |
| Dihydro-*p*-coumaric acid | 0.25 | 0.50 |
| Dihydrosinapic acid[c] | 0.13 | 0.47 |
| Coniferyl alcohol | 0.81 | 0.79 |
| *p*-Coumaryl alcohol | 0.84 | 0.88 |
| Sinapyl alcohol | 0.70 | 0.75 |
| Dihydroconiferyl alcohol | 0.87 | 0.81 |
| Dihydro-*p*-coumaryl alcohol | 0.89 | 0.85 |
| Dihydrosinapyl alcohol | 0.85 | 0.78 |
| Coniferaldehyde[c] | 0.55 | 0.84 |
| *p*-Coumaraldehyde | 0.65 | 0.84 |
| Sinapaldehyde[c] | 0.47 | 0.80 |
| Propiovanillone | 0.76 | 0.84 |
| *p*-Hydroxypropiophenone | 0.61 | 0.88 |
| Propiosyringone | 0.60 | 0.81 |
| α-Hydroxypropiovanillone | 0.45 | 0.82 |
| α-Hydroxypropiosyringone[c] | 0.33 | 0.78 |
| Vanilloyl methyl ketone | 0.53 | 0.87 |
| Syringoyl methyl ketone[d] | 0.40 | 0.81 |

[a] $R_f$ values were located by means of bis-diazotized benzidine spray. [b] An immediate red spot appears, but disappears after a few moments. [c] Blue fluorescence under ultraviolet light before spraying. [d] Negative fluorescence under ultraviolet light before spraying.

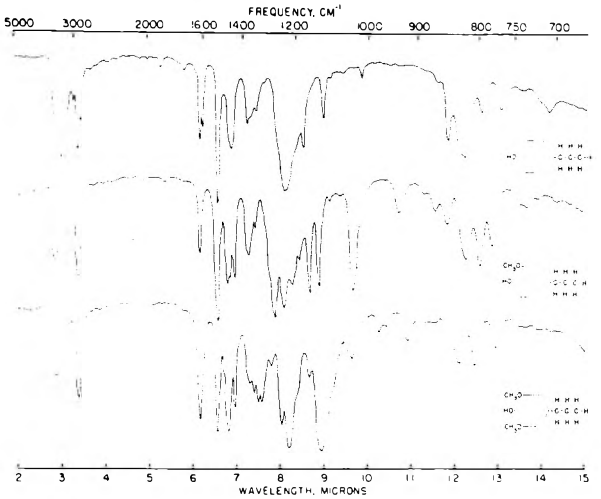


Fig. 1. Infrared absorption spectra for 4-hydroxyphenylpropane, 4-hydroxy-3-methoxyphenylpropane, and 3,5-dimethoxy-4-hydroxyphenylpropane

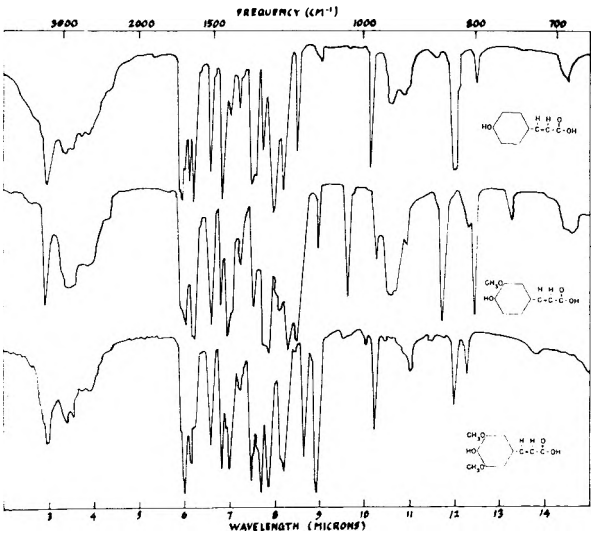


Fig. 2. Infrared absorption spectra for *p*-coumaric acid, ferulic acid, and sinapic acid

(11) I. A. Pearl, *J. Am. Chem. Soc.*, **78**, 4433 (1956).

(12) M. J. Hunter, A. B. Cramer, and H. Hibbert, *J. Am. Chem. Soc.*, **61**, 516 (1939).

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(16) M. Kulka, W. L. Hawkins, and H. Hibbert, *J. Am. Chem. Soc.*, **63**, 2371 (1941).

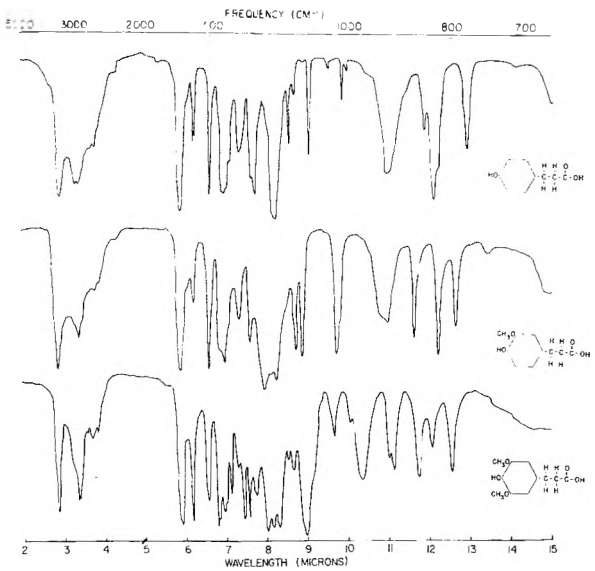


Fig. 3. Infrared absorption spectra for dihydro-*p*-coumaric acid, dihydroferulic acid, and dihydrosinapic acid

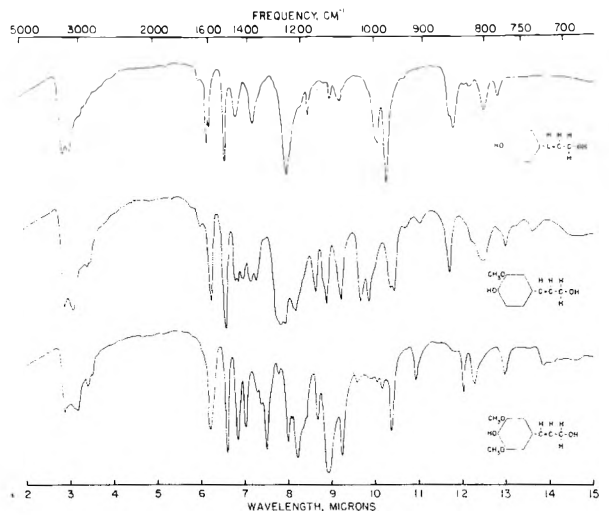


Fig. 4. Infrared absorption spectra for *p*-coumaryl alcohol, coniferyl alcohol, and sinapyl alcohol

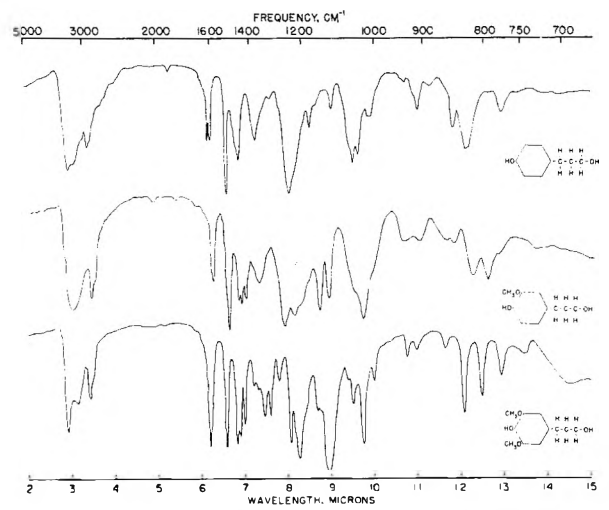


Fig. 5. Infrared absorption spectra for dihydro-*p*-coumaryl alcohol, dihydroconiferyl alcohol, and dihydrosinapyl alcohol

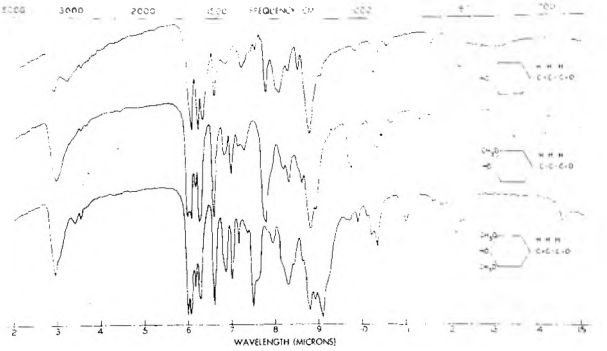


Fig. 6. Infrared absorption spectra for *p*-coumaraldehyde, coniferaldehyde, and sinapaldehyde

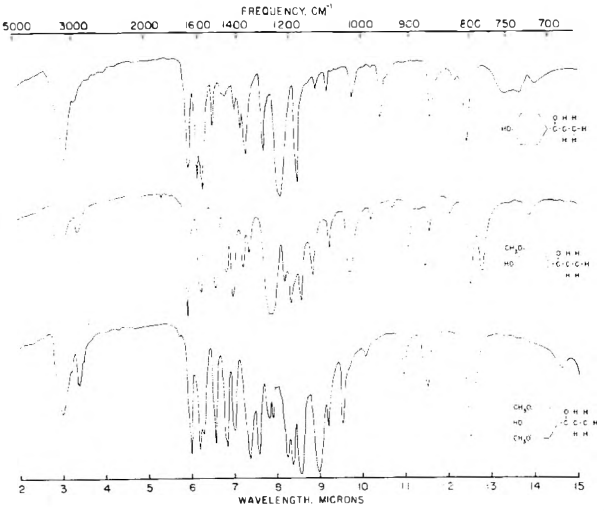


Fig. 7. Infrared absorption spectra for *p*-hydroxypropiophenone, propiovanillone, and propiosyringone

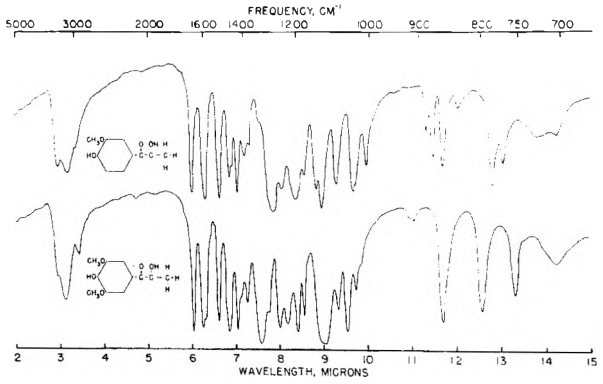


Fig. 8. Infrared absorption spectra for $\alpha$-hydroxypropiovanillone and $\alpha$-hydroxypropiosyringone

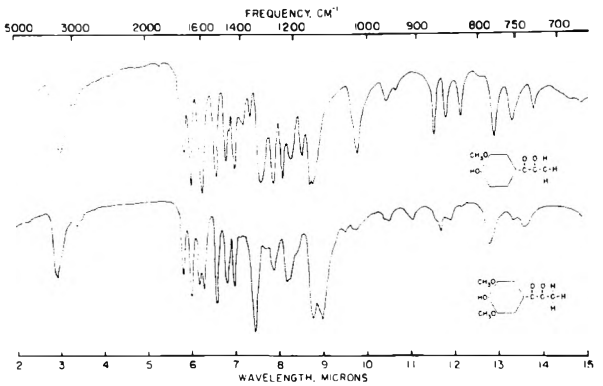


Fig. 9. Infrared absorption spectra for vanilloyl methyl ketone and syringoyl methyl ketone

## EXPERIMENTAL

All melting points are uncorrected, and ultraviolet spectral data are for solutions in 95% ethanol (concentration, 0.02 g. per liter).

*4-Hydroxy-3-methoxyphenylpropane.* A solution of 50 g. (0.3 mole) of eugenol (or isoeugenol) in 200 ml. of absolute ethanol was treated with 0.5 g. of 10% palladium on carbon catalyst and hydrogenated at 24° with an initial pressure of 48 p.s.i. After 15 min., 0.3 mole of hydrogen had been absorbed, and no further pressure drop was observed. The mixture was filtered, and the clear filtrate was concentrated to dryness to yield 50 g. of oil which was distilled under reduced pressure to yield 4-hydroxy-3-methoxyphenylpropane as a colorless oil boiling at 110° at 3.5 mm. and having an index of refraction $n_D^{24}$ 1.5196. The product was identical with that produced according to Brochet and Bauer[17] by hydrogenating eugenol at 60° over active nickel.

*3,5-Dimethoxy-4-hydroxyphenylpropane.* Similar hydrogenation of 2,6-dimethoxy-4-allylphenol[2] yielded 3,5-dimethoxy-4-hydroxyphenylpropane as a viscous light-colored oil boiling at 160° at 6.0 mm. and having an index of refraction $n_D^{25}$ 1.5259. Melting points of its acetate and benzoate agreed with recorded values.[9,18]

*4-Methoxyphenylpropane.* Hydrogenation of anethole under the same conditions yielded 4-methoxyphenylpropane as a colorless oil boiling at 67° at 2.0 mm. and having an index of refraction $n_D^{23}$ 1.5024. Klages[19] reported a boiling point of 215–216° at atmospheric pressure and an index of refraction $n_D^{20}$ 1.5045 for the compound prepared by reduction of anethole with sodium and ethanol.

*4-Hydroxyphenylpropane.* A solution of 60 g. of 4-methoxyphenylpropane in 600 ml. of acetic acid was heated to boiling under reflux and treated over a period of 1 hr. with 120 ml. of 48% hydrobromic acid. The solution was boiled an additional 4 hr., concentrated under reduced pressure to 200 ml. volume, and stirred into excess water. The aqueous mixture was neutralized with a slurry of sodium bicarbonate and extracted with ether, and the ether was dried and distilled to leave an oil. Redistillation under reduced pressure yielded 49 g. of pure 4-hydroxyphenylpropane boiling at 90° at 3.0 mm. and having an index of refraction $n_D^{23}$ 1.5231. The benzoate melted at 36–37°, agreeing with the benzoate prepared by Coulthard, Marshall, and Pyman[20] from 4-hydroxyphenylpropane obtained by Clemmenson reduction of 4-hydroxypropiophenone.

*Dihydroferulic acid.* A solution of 19.4 g. (0.10 mole) of ferulic acid in 125 ml. of tetrahydrofuran was treated with 0.1 g. of platinum oxide and hydrogenated at 27° with an initial pressure of 49 p.s.i. Hydrogen uptake was complete after 90 min. The mixture was filtered, and the clear filtrate was concentrated to dryness under reduced pressure. The white residue was recrystallized from water to give white crystals of dihydroferulic acid melting at 90–91° and not depressing a mixed melting point with authentic dihydroferulic acid prepared by alkaline hydrolysis of ethyl acetyldihydroferulate.[21]

*Dihydro-p-coumaric acid.* Similar reduction of *p*-coumaric acid and recrystallization of the product from benzene gave dihydro-*p*-coumaric acid melting at 125–126° and not depressing a mixed melting point with authentic material prepared by alkaline hydrolysis of ethyl acetyldihydro-*p*-coumarate.

*Dihydrosinapic acid.* A solution of 10 g. of sinapic acid in 400 ml. of 4% sodium hydroxide solution was treated with stirring with 10 g. of Raney nickel alloy in 1-g. amounts over a period of 15 min. After stirring an additional 15 min., the mixture was filtered, and the filtrate was stirred into a mixture of ice and excess hydrochloric acid. The clear solution was extracted with ether, and the ether was dried and distilled. The white residue was recrystallized from benzene to give crystals of pure dihydrosinapic acid melting at 102–103°.

*Anal.* Calcd. for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24. Found: C, 58.54; H, 6.34.

Dihydrosinapic acid was also prepared by alkaline hydrolysis of ethyl dihydrosinapate.

*Methyl dihydrosinapate.* Esterification of dihydrosinapic acid with absolute methanol and sulfuric acid yielded methyl dihydrosinapate as a viscous colorless oil boiling at 165–167° at 0.5 mm. and having an index of refraction $n_D^{25}$ 1.5302; $\lambda_{max}$ 264 m$\mu$, $\epsilon$ 866.

*Anal.* Calcd. for $C_{12}H_{16}O_5$: C, 59.99; H, 6.71. Found: C, 59.99; H, 6.71.

*Ethyl dihydrosinapate.* A solution of 19.7 g. of ethyl acetylsinapate[8] in 150 ml. of acetic acid was treated with 10 ml. of water and then with 20 g. of zinc dust. The mixture was heated to boiling under reflux with occasional shaking for 2 hr. and filtered hot. The precipitate was washed with hot acetic acid, and the combined filtrate and washings were stirred into 1 l. of mixed cracked ice and water. The white precipitate which separated was filtered, washed with water, and recrystallized to give 12 g. of ethyl dihydrosinapate as colorless crystals melting at 48–49°. Brewer, Cooke, and Hibbert[9] recorded only a boiling point of 178–179° at 1 mm.

*Anal.* Calcd. for $C_{13}H_{18}O_5$: C, 61.40; H, 7.14. Found: C, 61.25; H, 6.99.

Ethyl dihydrosinapate was also prepared by esterification of dihydrosinapic acid with absolute ethanol in the presence of sulfuric acid.

*Acetyldihydroferulic acid.* Acetylferulic acid[22] was hydrogenated in tetrahydrofuran with platinum oxide at 25°, and the product was recrystallized from Skellysolve "C" to give white crystals of acetyl dihydroferulic acid melting at 93–94°; $\lambda_{max}$ 273 m$\mu$, $\epsilon$ 2,785.

*Anal.* Calcd. for $C_{12}H_{14}O_5$; C, 60.50; H, 5.92. Found: C, 60.68; H, 6.04.

*Acetyldihydro-p-coumaric acid.* Similar hydrogenation of acetyl-*p*-coumaric acid[23] and recrystallization from petroleum ether (88–95°) yielded acetyldihydro-*p*-coumaric acid melting at 94–95°; $\lambda_{max}$ 265 m$\mu$, $\epsilon$ 500.

*Anal.* Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81. Found: C, 63.53; H, 5.86.

*Ethyl acetyldihydro-p-coumarate.* Hydrogenation of ethyl acetyl-*p*-coumarate[6] in tetrahydrofuran in the presence of palladium oxide at 28° and distillation of the resulting oil

(17) A. Brochet and M. Bauer, *Compt. rend.*, 159, 192 (1914).

(18) A. W. Hoffman, *Ber.*, 11, 331 (1878).

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(20) C. F. Coulthard, J. Marshall, and F. L. Pyman, *J. Chem. Soc.*, 1930, 280.

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(22) K. Kratzl and G. Billek, *Monatsh.*, [2] 84, 413 (1953).

(23) F. E. King, M. F. Grundon, and K. G. Neill, *J. Chem. Soc.*, 1952, 4580.

under reduced pressure gave an 85% yield of ethyl acetyldihydro-*p*-coumarate as a colorless oil boiling at 145–146° at 0.5 mm. and having an index of refraction $n_D^{25}$ 1.4950; $\lambda_{max}$ 266 mμ, ε 1,110; $\lambda_{max}$ 210 mμ, ε 9,650.

*Anal.* Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 66.10; H, 6.89.

*Methyl acetyldihydro-p-coumarate.* Similar hydrogenation of methyl acetyl-*p*-coumarate[6] in the presence of platinum oxide and distillation under reduced pressure gave 90% of methyl acetyldihydro-*p*-coumarate as a sweet smelling oil boiling at 149–150° at 0.5 mm. and having an index of refraction $n_D^{25}$ 1.5010; $\lambda_{max}$ mμ, ε 695.

*Anal.* Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.85; H, 6.36.

*Dihydroconiferyl alcohol.* Hydrogenation of coniferyl alcohol in tetrahydrofuran in the presence of palladium oxide at 28° gave a quantitative yield of dihydroconiferyl alcohol as a viscous colorless oil boiling at 155° and having a refractive index $n_D^{25}$ 1.5518, identical with an authentic sample prepared according to Granath and Schuerch[21] by lithium aluminum hydride reduction at low temperature of ethyl acetyldihydroferulate. Dihydroconiferyl alcohol was also prepared in almost quantitative yield by the reduction of ethyl acetyldihydroferulate at room temperature with lithium aluminum hydride according to the procedure described for the preparation of dihydro-*p*-coumaryl alcohol and by the reduction of acetyldihydroferuoyl chloride with sodium trimethoxyborohydride in tetrahydrofuran.

*Dihydro-p-coumaryl alcohol.* A mixture of 3.5 g. of powdered lithium aluminum hydride and 400 ml. of anhydrous ether was placed in a one-liter 3-neck flask fitted with a gas inlet tube, reflux condenser, silicone oil-sealed stirrer, and dropping funnel. Nitrogen was introduced, and stirring was begun. After 1 hr. of stirring at room temperature a solution of 7.6 g. of methyl acetyldihydro-*p*-coumarate in 500 ml. of anhydrous ether was added dropwise over a period of 2 hr. After addition was complete, the mixture was stirred an additional hour, treated dropwise with 100 ml. of water, and then with 150 ml. of 2*N* sulfuric acid. The ether layer was removed, and the slightly acid aqueous layer was extracted twice with ether. All ether solutions were combined, dried, and concentrated to dryness to yield 5.5 g. crude dihydro-*p*-coumaryl alcohol as a white crystalline solid. Two recrystallizations by solution in a little anhydrous ether, addition of petroleum ether (b.r. 30–60°) to incipient turbidity, and freezing yielded colorless crystals melting at 54–55°. This is the melting point recorded by Braun and Deutsch[24] for dihydro-*p*-coumaryl alcohol prepared by reaction of *p*-hydroxyphenylpropyl chloride with acetic acid and sodium acetate and hydrolysis of the reaction product with sodium hydroxide.

*Acetylsinapaldehyde.* Reduction of 14.2 g. of acetylsinapoyl chloride in diglyme (diethylene glycol dimethyl ether) with lithium tri-*t*-butoxyaluminohydride as described earlier[10] for acetylconiferyl aldehyde yielded 4.8 g. crude acetylsinapaldehyde melting at 132–134° which, upon recrystallization from methanol, gave colorless crystals melting at 134–135°; $\lambda_{max}$ 230 mμ, ε 16,430; $\lambda_{max}$ 310 mμ, ε 18,410.

*Anal.* Calcd. for $C_{13}H_{14}O_5$: C, 62.39; H, 5.64. Found: C, 62.44; H, 5.64.

Reduction of acetylsinapoyl chloride in tetrahydrofuran with sodium trimethoxyborohydride at −5° and then at room temperature gave a 30% yield of acetylsinapaldehyde melting at 134–135° and not depressing a mixed melting point with the authentic aldehyde prepared above.

*Sinapaldehyde.* Acetylsinapaldehyde was reduced with sodium methylate in methanol-chloroform solution as described for coniferaldehyde[10] to give an almost quantitative yield of sinapaldehyde which was recrystallized from benzene to give slightly yellow needles melting at 107–108°. This agrees with the melting point reported by Freudenberg and Hübner[25] who prepared the compound by Rosenmund reduction of acetylsinapoyl chloride and that reported by Pauly and Strassberger[26] who condensed methoxymethylsyringaldehyde with acetaldehyde and hydrolyzed the resulting methoxymethylsinapaldehyde. Sinapaldehyde gives a very strong violet-red color with phloroglucinol-hydrochloric acid reagent.

Sinapaldehyde was prepared directly by reduction of acetylsinapoyl chloride in tetrahydrofuran by lithium tri-*t*-butoxyaluminohydride. Acetylsinapoyl chloride was prepared from 10 g. of acetylsinapic acid with thionyl chloride and recrystallized from xylene. The chloride was dissolved in 150 ml. of tetrahydrofuran and treated at room temperature with a solution of 15 g. of lithium tri-*t*-butoxyaluminohydride in 100 ml. of tetrahydrofuran. The mixture was allowed to stand at 20° for 6 hr. and then poured into 1 l. of cold water. The mixture was filtered, and the filtrate was concentrated to a small volume in a rotating evaporator. The crystals which separated were recrystallized from benzene to give 3.4 g. of yellow sinapaldehyde melting at 106–107° and not depressing the melting point of a mixture with the authentic material prepared above.

*Acknowledgment.* Infrared spectral data were determined by Samuel P. Sadtler & Son, Inc., and by Lowell Sell of The Institute of Paper Chemistry; ultraviolet spectral data were determined by the Analytical Department of the Institute; and analyses were made by the Analytical Department of the Institute and by Huffman Microanalytical Laboratories of Wheatridge, Colo. The author gratefully acknowledges these contributions.

APPLETON, WIS.

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(26) H. Pauly and L. Strassberger, *Ber.*, **62**, 2277 (1929).

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

# Steroidal Sapogenins. LIII. Permanganate-Periodate Oxidation of Pseudosapogenins[2]

MONROE E. WALL AND SAMUEL SEROTA

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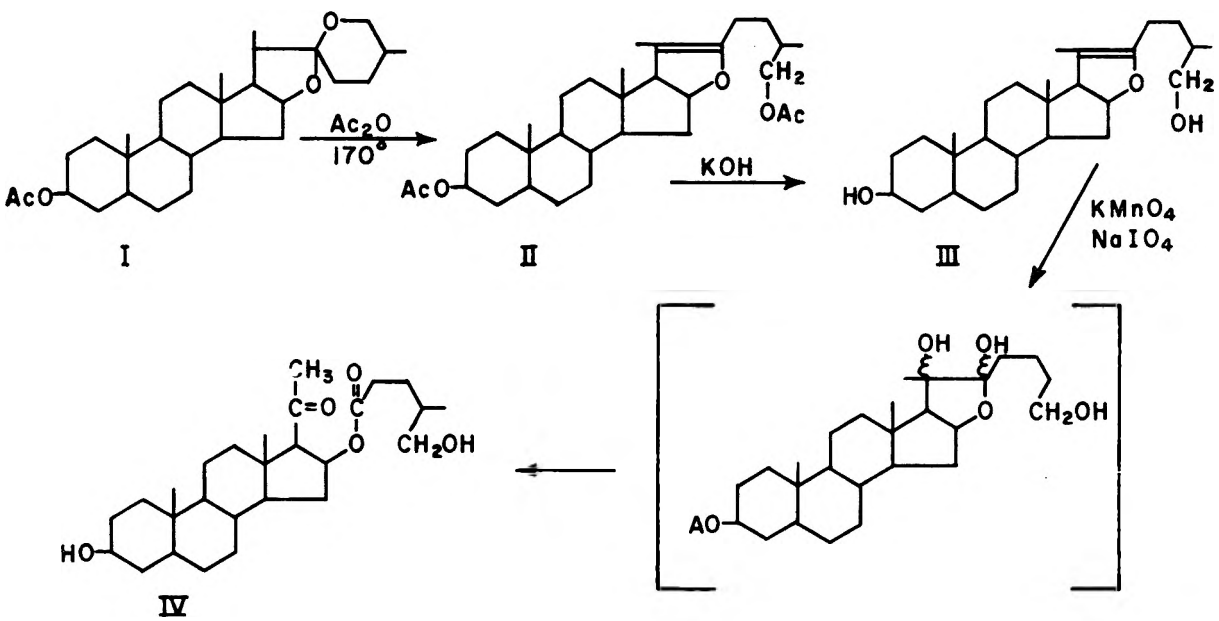
Pseudosapogenins and certain other steroid olefins with especially reactive double bonds can be smoothly oxidized with a permanganate-periodate reagent.

Modern steroid hormone technology is based in large part on 16-dehydro-20-oxo-pregnenes obtained by oxidative degradation of the steroidal sapogenin side chain. The classical three-step process was first developed by R. E. Marker and his associates[3] consisting of (1) conversion of sapogenins to pseudosapogenins, (2) oxidation of pseudosapogenins to give 16$\beta$-acyl esters of 20-oxo-pregnanes, and (3) alkaline cleavage of the 16$\beta$-ester followed by dehydration to give 16-dehydro-20-oxo-pregnanes. The over-all process has been studied in a number of laboratories[4a-h] leading to a degree of improvement in the classical procedure. However, in all of the cited references the oxidation agent has been chromic acid in acetic acid. As we have reported previously,[4c] the 16$\beta$-esters formed during oxidation of pseudosapogenins invariably undergo partial hydrolysis under the acidic reaction conditions giving 16-dehydro-20-oxo pregnenes which may then further react with excess oxidant. In order to avoid this undesirable hydrolysis we have studied the oxidation of pseudosapogenins under neutral or slightly alkaline conditions. A procedure developed by Lemieux and von Rudloff[5] involving permanganate-periodate oxidation of olefins soluble in slightly alkaline aqueous media seemed to offer promising possibilities. With some slight modifications the procedure was readily adapted to the oxidation of water insoluble pseudosapogenins by the route shown in Chart I.

The details of the procedure were developed




with speudosarsasapogenin, readily obtainable in pure, crystalline condition.[6] The conversion of

(1) Eastern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) Previous paper in this series, "Steroidal Sapogenins. LII. Structure and Properties of the Acetyl Hypobromite Adduct from a $\Delta^{16}$-Pregnen-20-one," S. G. Levine and M. E. Wall, *J. Am. Chem. Soc.*, in press.

(3) R. E. Marker *et al.*, *J. Am. Chem. Soc.*, **62**, 3350 (1940); *J. Am. Chem. Soc.*, **64**, 468 (1942); *J. Am. Chem. Soc.*, **69**, 2167 (1947).

(4) (a) D. H. Gould, H. Staeudle, and E. B. Hershberg, *J. Am. Chem. Soc.*, **74**, 3685 (1952); (b) W. G. Dauben and G. J. Fonken, *J. Am. Chem. Soc.*, **76**, 4618 (1954); (c) M. E. Wall, H. E. Kenney, and E. S. Rothman, *J. Am. Chem. Soc.*, **77**, 5665 (1955); (d) M. E. Wall and S. Serota, *J. Am. Chem. Soc.*, **79**, 6481 (1957); (e) A. F. B. Cameron, R. M. Evans, J. C. Hamlet, J. S. Hunt, P. G. Jones, and A. G. Long, *J. Chem. Soc.*, 2807 (1955).

(5) R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1710 (1955).

(6) M. E. Wall, S. Serota, and C. R. Eddy, *J. Am. Chem. Soc.*, **77**, 1230 (1955).

pseudosapogenins III to the corresponding 16β-ester, IV, was conveniently followed by noting the decrease or disappearance of the ultraviolet absorption band at 215 mμ found in pseudosapogenins,[3e] and by observing the concomitant appearance of strong infrared absorption bands at 1725 cm.$^{-1}$ and 1707 cm.$^{-1}$ due to 16β-ester and 20-ketone groups, respectively, found in IV. After some experimentation the correct conditions for conducting the oxidation of the water-insoluble pseudosapogenins were developed. It was found that the steroid, in the free hydroxyl form, must be dissolved in a water-miscible, inert solvent such as dioxane or tertiary butylalcohol. The steroid solution was then added to the aqueous solution of inorganic reagents and the mixture strongly agitated or shaken. The general reaction conditions of Lemieux and von Rudloff,[5] which utilize for 1 Mm. of olefin an oxidizing mixture of 3 Mm. of potassium carbonate, 8 Mm. of sodium metaperiodate, and 0.34 Mm. potassium permanganate at room temperature, were satisfactory under our experimental conditions and gave rapid oxidation of the $C_{20}$,$C_{22}$ double bond. Due possibly to their lower solubility in the aqueous dioxane or tertiary butyl alcohol solutions, pseudosapogenin diacetates were poorly oxidized under similar conditions. The yield was not improved by adding benzene as a co-solvent to the aqueous organic solutions. As shown in the experimental section the procedure was applicable to a variety of pseudosapogenins including those with unsaturation at $C_5$ or with a 12-ketone group.

Because of the noncrystalline nature of the pseudosapogenin oxidation products of structure IV it was difficult to ascertain yields. All oxidation products were checked by infrared spectroscopy and then subjected to alkaline hydrolysis[4c] to the corresponding 16-dehydro-20-keto-pregnenes, all of which were known crystalline compounds. We have not made a thorough comparison of yields of 16-dehydro-20-ketopregnenes by the chromium trioxide[4c] and the present procedure. However, with simple cases, i.e. no $\Delta^5$-unsaturation or absence of 12-keto groups, higher yields are obtained by the present method. Thus from pseudosmilagenin we obtained a 40% yield of 3β-acetoxy-16-pregnen-20-one and 70% by the permanganateperiodate procedure, using potassium hydroxide in *t*-butyl alcohol[4c] in both cases.

Because of the mild, smooth oxidation action of the permanganateperiodate reagent we tested its effect on several types of steroidal olefins available to us. Oxidation of 12-methylene tigogenin[7] proceeded smoothly to give hecogenin in excellent yield. Similar treatment of 3β-hydroxy-16-pregnen-20-one converted this steroid completely to acidic products which were not further characterized. An enol-acetate, 3β,20-diacetoxy-17-pregnene, and stigmasterol, a steroid with both a tri- and a di-substituted olefinic linkage, were recovered unchanged. From our brief experiences with a limited variety of steroid olefins we conclude that only highly reactive steroid double bonds are attacked by the permanganate-periodate reagent. This is not a general observation because as previously shown by Lemieux and von Rudloff the disubstituted olefinic bond in oleic acid is easily oxidized. Whether this is due to the greater solubility of sodium oleate in the aqueous medium or to steric factors which may be encountered with steroids cannot be decided by evidence on hand.

## EXPERIMENTAL

All pseudosapogenins were prepared in a manner described previously.[4d] The following oxidation procedure is typical. A solution of 1.2 g. of potassium permanganate (3.2 Mm.), 10.0 g. of anhydrous potassium carbonate (71.4 Mm.), and 41.0 g. of sodium metaperiodate (190.4 Mm.) in 1.0 l. of water was mixed with a solution of 10.0 g. (23.8 Mm.) of pseudosarsasapogenin in 500 ml. of purified dioxane and 500 ml. of benzene. The mixture was vigorously shaken for 1 hr. Probe tests on smaller quantities indicated the reaction was substantially complete in 5 min. The benzene layer was separated from the aqueous fraction, the latter extracted several times with benzene, and all the benzene extracted united and washed with distilled water. The benzene was concentrated to dryness *in vacuo* leaving a pale yellow glass which was undoubtedly 3β-hydroxy-16β-(γ-methyl-δ-hydroxy)-valeroxy-pregnan-20-one. The compound had negligible ultraviolet absorption at 215 mμ in contrast to the starting pseudosarsasapogenin. The infrared spectrum of I showed two strong carbonyl bands at 1720 and 1707 cm.$^{-1}$ and a strong band at 1250 cm.$^{-1}$ attributable to the C—O—C bond of the 16β-ester. Because of the well known difficulty in crystallizing compounds with structures similar to IV and because of the general instability of 16β-ester steroids no further attempts were made to characterize it. The viscous product was taken up in 200 ml. of *t*-butyl alcohol by warming on the steam bath. To the solution was added 5.0 g. of potassium hydroxide in 4 ml. of water. Nitrogen was passed through the *t*-butyl alcohol solution. The flask was stoppered and vigorously stirred with a magnetic stirrer for 3 hr. The initial temperature was 40° which fell to 30° at the expiration of 3 hr. To the hydrolyzed solution was added 400 ml. of water with vigorous stirring. The aqueous solution was seeded with authentic 3β-hydroxy-16-pregnen-20-one and another 400 ml. of water added with stirring. Crystalline plates began to form and the stirring was continued for 1 hr. The crystalline product was filtered, washed with water, and dried, yield 6.91 g., m.p. 170–180°, 85% purity based on ultraviolet absorption at 239 mμ, equivalent to 77% of theory. Crystallization from methanol gave 5.0 g. of plates, m.p. 185–187°[4c] with infrared spectrum identical to an authentic specimen.

In exactly the same manner described above pseudodiosgenin, pseudotigogenin, and pseudohecogenin were oxidized to their corresponding 16β-acyl esters and hydrolytically cleaved to give respectively 3β-hydroxy-5,16-pregnadiene-20-one, 3β-hydroxy-5α-pregn-16-en-20-one, and 3β-hydroxy-5α-pregn-16-en-12,20-dione, all characterized by melting point and identity with known samples.[4c] The yields were not so high as in the pseudosarsasapogenin oxidation ranging from 30–50% of theory by ultraviolet absorption analysis. It was found that *t*-butyl alcohol was as effective a solvent as dioxane for this purpose and since it was much easier to purify, the former solvent was adopted for all subsequent work. It was also found that the use of benzene during oxidation was unnecessary. However no reaction occurred if an aqueous solution of the inorganic oxidant was

shaken with a benzene solution of steroid in the *absence* of dioxane or *t*-butyl alcohol.

*Oxidation of 12-methylene-tigogenin to hecogenin.* 0.4 g. of 12-methylene tigogenin[7] in 100 ml. of *t*-butyl alcohol was oxidized with a solution of 1.7 g. of sodium metaperiodate, 0.42 g. of potassium carbonate, and 0.05 g. of potassium permanganate in 100 ml. of water, shaking the mixture in a 500-ml. bottle. Infrared analysis for carbonyl indicated maximum formation in 5 hr. The solution was extracted with benzene, yielding after the usual work-up 0.3 g. of hecogenin, m.p. 250–253°, infrared spectrum identical with that of an authentic specimen.

*Oxidation of 3β-acetoxy-16-pregnen-20-one.* A solution of 0.42 g. of 3β-acetoxy-16-pregnen-20-one in 100 ml. of *t*-butyl alcohol was shaken overnight with the aqueous oxidation solution used above. The aqueous mixture was further diluted with water and extracted with ether. The ether solution contained a negligible weight of steroid. The aqueous layer was acidified with hydrochloric acid and the resultant precipitate extracted with ether to yield 0.4 g. of amorphous glass. The infrared absorption spectrum showed, as might be expected, a strong carboxyl carbonyl band at 1700 cm.$^{-1}$.

Under the above reaction conditions stigmasterol and 3β,20-diacetoxy-17-pregnen-20-one were recovered unchanged.

(7) F. Sondheimer and R. Mechoulam, *J. Am. Chem. Soc.*, **79**, 5029 (1957).

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[CONTRIBUTION FROM THE DIVISION OF CHEMICAL RESEARCH OF G. D. SEARLE AND CO.]

# Steroidal Aldosterone Blockers. I

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The synthesis and specific biological activities of a variety of C-17 steroidal 5 and 6 membered spirolactones are presented. The 19-nor compound with a 5 membered lactone (Xa) is the most potent aldosterone blocker.

Since the first reports of the antialdosterone activity of several steroidal 17-spirolactones[1(a),(b)] we have prepared a number of new spirolactones in order to test the effect on blocking activity of changes in both the lactone and steroid portions of the molecule. It is our purpose in this article to record the experimental details of synthesizing the drugs reported in earlier communications[1(a),2] and to report on some of the new compounds in this series.

The first member of this series to show aldosterone blocking activity was 3-(3-keto-17β-hydroxy-4-androsten-17α-yl)propanoic acid lactone (VIa). This was prepared by the sequence shown on Chart 1. The Grignard reagent of 17α-ethynyl-5-androstene-3β,17β-diol (Ia)[3] was carbonated in good yield to give an acetylenic acid (IIa). The acetylenic bond was selectively reduced to an olefin by catalytic hydrogenation over palladium on calcium carbonate using dioxane and pyridine as solvents. The resulting product on treatment with mineral acid yielded an unsaturated lactone (IIIa) which could be readily reduced to a saturated lactone (Va) by hydrogen over palladium on charcoal. Oxidation of IIIa and Va by the Oppenauer method produced the corresponding 3-oxo-4-ene compounds IV and VIa.

Because of the interesting antialdosterone activity of VIa we decided to make the correponding 19-nor compound. To this end the spirolactone side chain was built onto a steroid nucleus containing an aromatic A ring by the same series of reactions used in the androstane series (Chart I). 17α-Ethynyl-3-methoxy-1,3,5(10)-estratrien-17β-ol[4] (Ic) was carbonated to give an acetylenic acid (IIc) which could be hydrogenated partially or completely to give an unsaturated (IIIc) or saturated (Vc) lactone. As shown on Chart 2, the A ring of this could be most effectively reduced to the dihydroaromatic system (VIIIa) by preparing the sodium salt (VIIa) of the saturated lactone (Vc) and reducing this with lithium in ammonia and *t*-butyl alcohol.[5] Hydrolysis of the enol ether (VIIIa) with dilute acetic acid afforded a compound (IXa) in which simultaneous lactonization of the liberated hydroxy acid had occurred. On the other hand, hydrolysis with mineral acid gave the compound (Xa) containing not only a lactone, but also a conjugated ketone. Xa was also prepared by treating IXa with strong acid. Lactonization of the hydroxy acids was best accomplished by treating them with strong acid in solution; stirring the precipitated hydroxy acid with aqueous acid was usually ineffective.

In the hope of reducing the triple bond and aromatic A ring simultaneously the acetylenic acid (IIc) was subjected directly to reduction by lithium in ethanol and ammonia. After hydrolysis of the uncharacterized intermediate enol ether with strong acid, there was obtained not only the satu-

(1) (a) J. A. Cella and C. M. Kagawa, *J. Am. Chem. Soc.*, **79**, 4808 (1957). (b) C. M. Kagawa, J. A. Cella, and C. G. Van Arman, *Science*, **126**, 1015 (1957).

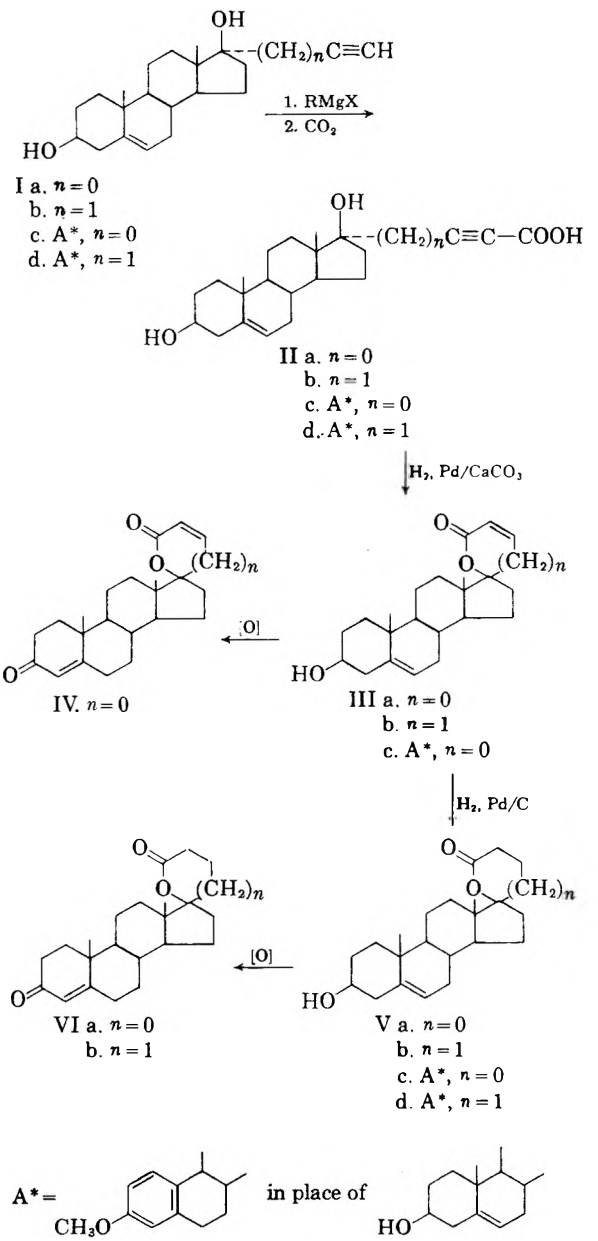
(2) J. A. Cella, U. S. Patent **2,705,712**, April 5, 1955.

(3) H. E. Stavely, *J. Am. Chem. Soc.*, **61**, 79 (1939).

(4) F. B. Colton, U. S. Patent **2,666,769**, June 19, 1954.

(5) This is a modification of the Birch reduction described by A. L. Wilds and N. A. Nelson, *J. Am. Chem. Soc.*, **75**, 5360 (1953) which was developed by Dr. H. Dryden of these laboratories.

Chart I

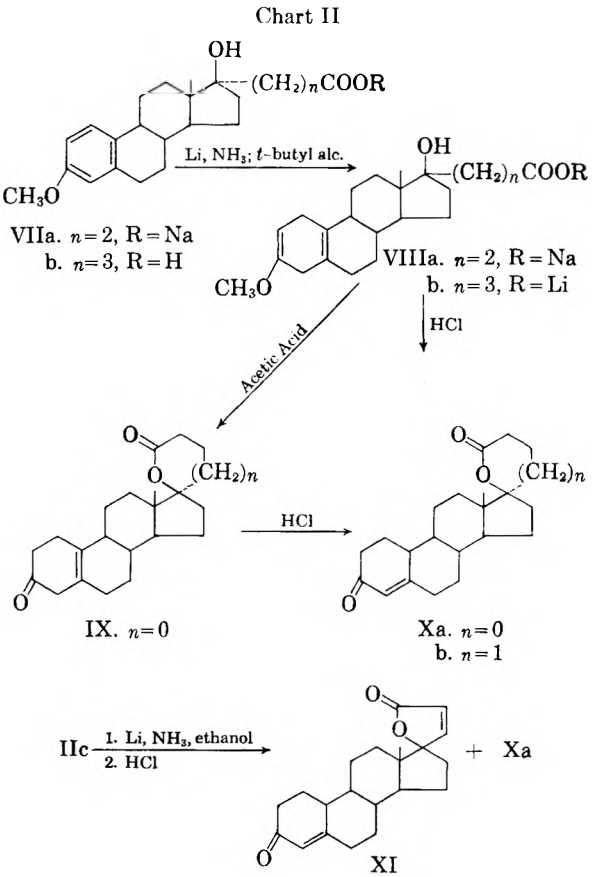



rated lactone (Xa) but also the unsaturated lactone (XI).

We now turned our synthetic efforts to making the six-membered lactones analogous to VIa and Xa. The same sequence of lactone building reactions was used on 17$\alpha$-propargyl-5-androstene-3$\beta$,17$\beta$ diol[6] (Ib), *e.g.*, carbonation of the Grignard reagent to give 4-(3$\beta$,17$\beta$-dihydroxy-5-androsten-17$\alpha$-yl)-2-butynoic acid (IIb). This compound (IIb) was hydrogenated stepwise to the saturated lactone (Vb), which was oxidized by the Oppenauer method to the corresponding 3-oxo-4-ene derivative (VIb).

The 19-nor six-membered lactone was prepared by a similar route. Estrone methyl ether was reacted with propargyl bromide in the presence of zinc to yield Id. This was carbonated as described earlier to yield IId which was then hydrogenated to the corresponding 4-[17$\beta$-hydroxy-1,3,5(10)-estratrien-17$\alpha$-yl]butanoic acid which was lactonized to Vd. The free acid (VIIb) was reduced to a dihydroaromatic intermediate (VIIIb) which was acidified without isolating, to give 4-(3-oxo-17$\beta$-hydroxy-19-nor-4-androsten-17$\alpha$-yl)butanoic acid which yielded the lactone (Xb) by treatment with *p*-toluenesulfonic acid in benzene. Xb was also prepared by an alternate route. The Grignard reagent of Ic was treated with ethylene oxide to give 1-[3-methoxy-17$\beta$-hydroxy-1,3,5(10)-estratrien-17$\alpha$-yl]-1-butynol-4, which was reduced catalytically to the corresponding 1-[3-methoxy-17$\beta$-hydroxy-1,3,5(10)-estratrien-17$\alpha$-yl]butanol-4. Chromic acid oxidation of this diol yielded the lactone (Vd). This method was not so satisfactory as the other because of the poor yield in the Grignard step.

Chart II



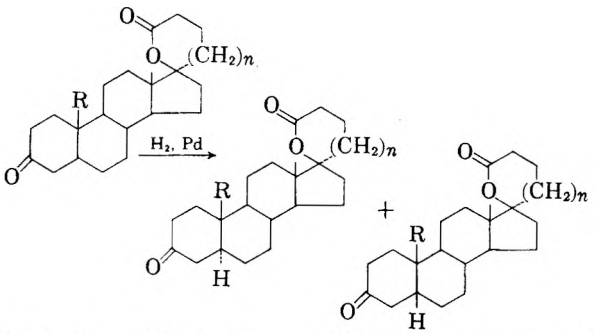

Some of the lactones containing a 3-oxo-4-ene system were hydrogenated in the presence of palladium (Chart III), to yield a mixture of epimers at C-5 which was separated by chromatography. The first of these was VIa, which gave about a 70–30 mixture of A/B *trans* (XIIa) to A/B *cis* (XIIIa). The stereochemistry of XIIa was established by hydrogenating Va in neutral alcohol to give a single compound (XIV),[7] which was oxidized in good

(6) C. W. Greenhalgh, H. B. Henbest, and E. R. H. Jones, *J. Chem. Soc.*, 1190 (1951).

(7) L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene*, 3rd ed., Reinhold, New York, p. 375.

yield to XIIa. The other isomer (XIIIa) was therefore assigned the A/B *cis* configuration.

Chart III



VI. a, R = $CH_3$, $n$ = 0
VI. b, R = $CH_3$, $n$ = 1
X. a, R = H, $n$ = 0

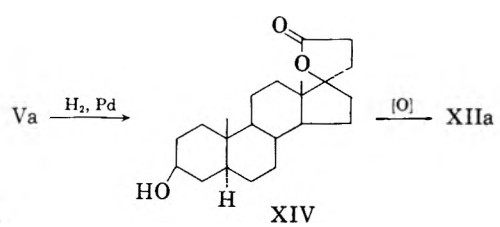
XII. a, R = $CH_3$, $n$ = 0
b, R = $CH_3$, $n$ = 1
c, R = H $n$ = 0

XIII. a, R = $CH_3$, $n$ = 0
b, R = $CH_2$, $n$ = 1
c, R = H $n$ = 0

Catalytic hydrogenation of Xa yielded two dihydro isomers (XIIc and XIIIc). The stereochemistry of XIIc was established as the A/B *trans* ring fusion by reducing Xa with lithium in ammonia and alcohol[8] and then oxidizing the uncharacterized product with chromic acid to give a single compound (XIIc). The configuration of XIIIc was therefore A/B *cis*.

Similar treatment of VIb with hydrogen over palladium gave two dihydro isomers (XIIb and XIIIb) in the six-membered series. The stereochemistry of these isomers was assigned by analogy to the two previous cases, *e.g.*, the *trans* isomer was eluted first from a chromatographic column and the *trans* isomer is lower melting.

*Biology.*[1(b),9] The anti-DCA blocking activities available are in Table I. Active compounds were screened further against aldosterone. Examination of the blocking activities listed in Table I will show that changing the 3-oxo-4-ene system to a 3-hydroxy-5-ene, 3-oxo-4,5-dihydro, or an aromatic A ring reduces blocking activity as does introducing a double bond at C-20 to C-21, or expansion of the lactone to a six-membered ring. On the other hand, going from the normal series to the 19-nor compound enhances activity. Hence the most active compound of this series is Xa.



XIV

TABLE I

| Compound | Relative Blocking Potency[a] | Compound | Relative Blocking Potency[a] |
|---|---|---|---|
| IV | <0.01 | XIIa | 0.3 |
| Va | 0.1 | XIIb | <0.1 |
| Vc | <0.01 | XIIc | 0.6 |
| VIa | 1.0 | XIIIa | <0.01 |
| VIb | 0.08 | XIIIb | <0.1 |
| IXa | 0.8 | XIIIc | <0.3 |
| Xa | 3.8 | XIV | 0.1 |
| Xb | 1.0 | | |

[a] VIa was arbitrarily assigned the value of 1.0. A dose of 0.22 mg. of VIa produces a 50% block of the effect of 12 μg. of desoxycorticosterone acetate on the urinary Na/K ratio in adrenalectomized rats.

## EXPERIMENTAL

*General.* The microanalyses and optical determinations recorded here were carried out by Dr. Robert T. Dillon and his associates of these laboratories.

A number of preparations were made by the same general procedures. These are listed and reference is made to them under specific preparations where they were used.

Temperatures are reported in degrees centigrade. Melting points were determined on a Fisher-Johns block and are reported uncorrected. Ultraviolet spectra were determined in methanol.

*Procedure A. Carbonation of acetylenic Grignard reagents.* One g. of the ethynylated steroid was dissolved in 5 ml. of tetrahydrofuran. This solution is added to a refluxing solution of 6 ml. of 3*M* methylmagnesium bromide in 15 ml. of tetrahydrofuran. The tetrahydrofuran was previously purified by distillation from excess Grignard reagent. The resulting gray suspension was stirred and refluxed for 24 hr. It gave a strong positive test for RMgX at this point. A slight positive pressure of carbon dioxide was then maintained over the rapidly stirred solution for 24 hr. The mixture was poured into excess ice-cold 0.2*M* sulfuric acid and most of the solvent removed by vacuum distillation. The crude granular product was filtered, washed free of mineral acid, and set to dry.

*Procedure B. Preparation of unsaturated lactones from acetylenic acids.* One g. of 17α-steroidylalkynoic acid (II) was dissolved in 10 ml. of dioxane containing 1 ml. of pyridine. This solution was stirred under hydrogen at atmospheric pressure in the presence of 0.3 g. of 5% palladium on calcium carbonate until one equivalent was absorbed. The stirring was then stopped, the catalyst filtered off, and the solvent removed by vacuum distillation. The viscous residue was dissolved in 10 ml. of cold ethanol and 1.4 ml. of concentrated hydrochloric acid added. After standing for 5 min. the solution was diluted with 175 ml. of cold water and the crude unsaturated lactone collected by filtration and set to dry.

*Procedure C. Oppenauer oxidation of 3β-hydroxy lactones.* One g. of the appropriate 3β-hydroxy-5-ene lactone (V) was dissolved in a boiling solution of 25 ml. of toluene and 8 ml. of cyclohexanone. Five ml. of toluene was removed by distillation to insure dryness. Then to this refluxing solution was added a solution of 0.5 g. of aluminum isopropylate in 5 ml. of toluene. The resulting solution was refluxed and stirred for an additional 20 min. whereupon it was cooled to 95° and 5 ml. of water added. The heterogeneous mixture was cooled to room temperature and made strongly acid with 6*N* sulfuric acid. The layers were separated, washed, and each back-extracted. The combined organic layers

(8) W. S. Johnson, E. R. Roger, J. Szmuszkovicz, H. I. Hadler, J. Ackerman, B. K. Bhattacharyya, B. M. Bloom, L. Stalmann, R. A. Clement, B. Bannister, and H. Wynberg, *J. Am. Chem. Soc.*, **78**, 6289 (1956).

(9) The biological testing was carried out by Dr. C. M. Kagawa and his associates of these laboratories. The experimental details of testing will be reported elsewhere.

were then steam distilled exhaustively. The cooled distillation residue was extracted with chloroform. This extract was dried and evaporated to dryness to give the crude 3-oxo-4-ene lactone (VI).

*Procedure D.*[5] *Reduction of aromatic compounds to dihydroaromatic compounds with lithium in ammonia and t-butyl alcohol.* A solution of 10 g. of the aromatic acid or salt (VII) in 150 ml. of *t*-butyl alcohol and 150 ml. of tetrahydrofuran was diluted to 650 ml. with anhydrous ammonia in a flask equipped with a sealed stirrer and a Dry Ice condenser. Then 5.5 g. of lithium wire was added during a 30-min. period, producing a heterogeneous mixture of a deep blue ammonia layer and an oily bronze colored lithium-ammonia alloy layer. Stirring was adjusted so as to produce thorough mixing of the two layers. After 3 hr., 25 ml. of ethanol was added to destroy any unreacted lithium. An additional 25 ml. of ethanol was added, the condenser removed, and the ammonia allowed to evaporate under a stream of nitrogen overnight. Then 200 ml. of water was added and the mixture vacuum distilled until about 250 ml. of reaction mixture remained. This mixture was then worked up in a suitable way which will be described for the individual compounds.

*17α-Propargyl-5-androstene-3β,17β-diol* (Ib). The following modification of the method of Jones *et al.*[6] was employed. Freshly distilled propargyl bromide (64.2 g.) was added during a 20-min. period to a stirred, refluxing suspension of 35.2 g. of 20-mesh zinc (acid washed and dried with solvents) and 36 g. of dehydroisoandrosterone acetate in 1 l. of tetrahydrofuran. When about half of the bromide had been added, a vigorous reaction set in which required ice bath cooling. After 5 min. the reaction subsided, whereupon the balance of the bromide was added at a rate to cause spontaneous refluxing. When the spontaneous effect ceased, the mixture was refluxed for 15 min. longer, then cooled and poured into 2 l. of water containing 100 ml. of 12*M* hydrochloric acid. Extraction with benzene and removal of solvent gave the crude acetate as a brown crystal paste which was then saponified by refluxing under nitrogen for 0.5 hr. with 25 g. of potassium hydroxide in 1 l. of methanol. After dilution with 8 l. of water, the precipitate was collected on a funnel, rinsed free of base and dried (40 g.). Since an infrared spectrum at this point showed the presence of unreacted ketone, the crude product was refluxed with 15 g. of Girard's T reagent and 15 ml. of acetic acid in 380 ml. of absolute alcohol for 0.5 hr. Work-up in the conventional manner yielded the crude propargyl derivative (Ib) which, after crystallization from methanol, weighed 20 g. and melted at 152–154°.

*3-Methoxy-17α-propargyl-1,3,5(10)-estratrien-17β-ol* (Id). The procedure for preparation of this compound from estrone-3-methyl ether was like that for 17α-propargyl-5-androstene-3β,17β-diol (Ib). The reaction was a little sluggish and, after the exothermic period, reflux was continued for 2 hr. The crude propargyl derivative was separated from unreacted starting material by means of Girard's T reagent and recrystallized from methanol. From 10 g. of estrone-3-methyl ether 2.9 g. of the starting material was recovered and 6.0 g. of the desired product, melting at 49–60°C., was obtained. Infrared spectrum (KBr), 2.82μ, 3.05μ, (O—H, ≡C—H).

*Anal.* Calcd. for $C_{22}H_{28}O_2$: C, 81.44; H, 8.70. Found: C, 81.18; H, 8.65.

*3β,17β-Dihydroxy-5-androsten-17α-ylpropynoic acid* (IIa). Procedure A was used on 25 g. of 17α-ethynyl-5-androstene-3β,17β-diol.[3] The crude product was dissolved in 250 ml. of tetrahydrofuran and 12.1 g. of triethylamine added. The triethylamine salt, 28.8 g., which precipitated was dissolved in 300 ml. of 50% aqueous dioxane and the boiling solution then acidified with concentrated hydrochloric acid. Upon chilling, 20 g. of IIa precipitated as a monohydrate, m.p. 234–235° dec. (loses $H_2O$ at 120–140°), $[\alpha]_D$ −132.5° (dioxane).

*Anal.* Calcd. for $C_{22}H_{30}O_4.H_2O$: C, 70.18; H, 8.57. Found: C, 70.19; H, 8.46.

*4-(3β,17β-Dihydroxy-5-androsten-17α-yl)-2-butynoic acid* (IIb). Procedure A was used on 4.58 g. of 17α-propargyl-5-androstene-3β,17β-diol (Ib). The crude product (4.9 g.) was triturated with 30 ml. of boiling chloroform to give 3.5 g. of the desired acid (IIb), m.p. 201–205°. A sample, m.p. 203–206°, for analysis was obtained by recrystallization from acetonitrile.

*Anal.* Calcd. for $C_{23}H_{32}O_4$: C, 74.16; H, 8.66. Found: C, 74.09; H, 8.83.

*3-Methoxy-17β-hydroxy-1,3,5(10)-estratrien-17α-ylpropynoic acid* (IIc). Procedure A was used on 132 g. of 17α-ethynyl-3-methoxy-1,3,5(10)-estratrien-17β-ol (Ic).[4] The 142 g. of dark yellow crude acid was suspended in 2 l. of boiling carbon tetrachloride for 5 min. The slurry was cooled to room temperature and filtered. The white solid was rinsed on the funnel with 100 ml. of carbon tetrachloride and dried to give 108 g. of anhydrous acid (IIc) melting at 198–200° with decomposition. About 15 g. of Ic can be recovered from the liquors. Crystallization of the acid IIc from 50% aqueous dioxane gave a monohydrate, m.p. 204–207° dec. (-$H_2O$, 120–140°), $[\alpha]_D$ −17.7° (diox.).

*Anal.* Calcd. for $C_{22}H_{26}O_4.H_2O$: C, 70.94; H, 7.58. Found: C, 70.74; H, 7.93.

*4-[3-Methoxy-17β-hydroxy-1,3,5(10)-estratrien-17α-yl]-2-butynoic acid* (IId). Procedure A was used on 6.5 g. of 17α-propargyl-3-methoxy-1,3,5(10)-estratrien-17β-ol (Id). The crude dry product was suspended in 35 ml. of boiling carbon tetrachloride for 5 min. and the slurry then cooled to room temperature. Filtration yielded 7.0 g. of acceptable product IId. Crystallization from 50% aqueous ethanol gave an analytical sample, m.p. 187.5–191.5° dec.

*Anal.* Calcd. for $C_{23}H_{28}O_4$: C, 74.97; H, 7.66. Found: C, 75.25; H, 7.95.

*3-(3β,17β-Dihydroxy-5-androsten-17α-yl)propenoic acid lactone* (IIIa). Procedure B was used on 0.2 g. of acetylenic acid hydrate IIa. Two crystallizations of the crude product from aqueous methanol yielded 0.07 g. of the desired product IIIa, m.p. 201–203°, $[\alpha]_D$ +2° ($CHCl_3$), $\epsilon^{220}$ 9550.

*Anal.* Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 76.95; H, 8.81.

*4-(3β,17β-Dihydroxy-5-androsten-17α-yl)-2-butenoic acid lactone* (IIIb). Procedure B was used on 3.0 g. of acetylenic acid IIb. The crude product (IIIb) was not characterized but rather used directly in the preparation of Vb.

*3-[3-Methoxy-17β-hydroxy-1,3,5(10)-estratrien-17α-yl]propenoic acid lactone* (IIIc). Procedure B was used on 5 g. of acetylenic acid hydrate IIc. The 4.0 g. of crude lactone was recrystallized from ethyl acetate to yield 2.55 g. of unsaturated lactone IIIC, m.p. 170–173°, $[\alpha]_D$ +94° (diox.).

*Anal.* Calcd. for $C_{22}H_{26}O_3$: C, 78.07; H, 7.74. Found: C, 78.17; H, 7.45.

*3-(3-Oxo-17β-hydroxy-4-androsten-17α-yl)propenoic acid lactone* (IV). Procedure C was used on 0.81 g. of IIIa. The crude product was chromatographed over silica gel and the product eluted with 10% ethyl acetate–90% benzene. Upon crystallization from ethyl acetate–cyclohexane there was obtained 0.30 g. of unsaturated lactone IV, m.p. 153.5–154.5°, $[\alpha]_D$ +203.5° ($CHCl_3$), $\epsilon^{237}$ 20,200, IR (KBr) 5.78μ (unsaturated lactone).

*Anal.* Calcd. for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.41; H, 8.44.

*3-(3β,17β-Dihydroxy-5-androsten-17α-yl)propanoic acid lactone* (Va). The unsaturated lactone (IIIa) (20 g.) was dissolved in 225 ml. of absolute ethanol and treated with hydrogen at atmospheric pressure and at room temperature in the presence of 4 g. of 5% palladium on carbon. When one equivalent of hydrogen was absorbed the reaction was stopped, the catalyst filtered off, and the filtrate evaporated to dryness. The residue was recrystallized from ethyl acetate. There was obtained 14 g. of Va, m.p. 190–191°, $[\alpha]_D$ −91.5° ($CHCl_3$).

*Anal.* Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.40; H, 9.90.

*4-(3β,17β-Dihydroxy-5-androsten-17α-yl)butanoic acid lac-*

*tone* (Vb). The crude lactone IIIb derived from 3.0 g. of IIb was dissolved in 50 ml. of absolute ethanol containing 0.1 ml. of concentrated hydrochloric acid and hydrogenated at atmospheric pressure over 0.5 g. of 5% palladium on carbon. After one equivalent of hydrogen was absorbed the reaction was stopped. The catalyst was filtered off and the filtrate diluted with water. Extraction of the aqueous phase with chloroform yielded upon evaporation of the extracts, 3 g. of the saturated lactone Vb as a viscous oil which resisted crystallization. The infrared spectrum showed a peak at 5.80$\mu$, characteristic of a six-membered saturated lactone. The crude product was used directly in the next step.

*3-[3-Methoxy-17β-hydroxy-1,3,5(10)-estratrien-17α-yl]-propanoic acid lactone* (Vc). A solution of 2.55 g. of IIIc in 150 ml. of ethyl acetate was treated with hydrogen at atmospheric pressure in the presence of 0.5 g. of 5% palladium on charcoal at 21°. When hydrogen uptake had ceased the catalyst was filtered off and the solvent evaporated. The residue was recrystallized from ethyl acetate–isopropyl ether to yield 1.8 g. of Vc, m.p. 150–152°, $[\alpha]_D$ +12.5° (diox.).

*Anal.* Calcd. for $C_{22}H_{28}O_3$: C, 77.61; H, 8.29. Found: C, 77.49; H, 8.13.

*4-[3-Methoxy-17β-hydroxy-1,3,5(10)-estratrien-17α-yl]-butanoic acid lactone* (Vd). To 6.5 g. of IId dissolved in 130 ml. of ethanol, 2.0 g. of triethylamine was added to form the salt. The solution was hydrogenated over 1.0 g. of 5% palladium on carbon at room temperature at about 24 p.s.i. of hydrogen pressure. Hydrogen uptake ceased in 40 min. The solution was filtered to remove the catalyst and evaporated to a small volume which was poured into an excess of dilute hydrochloric acid. The product was collected on a funnel and washed free of acid with water. After drying, the product was crystallized from ethyl acetate to yield 4.05 g. of 4-[3-methoxy-17β-hydroxy-1,3,5(10)-estratrien-17α-yl]-butanoic acid (VIIb), m.p. 164–168.5° dec.

*Anal.* Calcd. for $C_{23}H_{32}O_4$: C, 74.15; H, 8.66. Found: C, 74.31; H, 8.77.

To obtain the lactone (Vd), 3.1 g. of hydroxy acid was dissolved with 100 mg. of *p*-toluenesulfonic acid in 500 ml. of benzene and the solution distilled slowly to a residual volume of 100 ml. The residual solution was washed twice with water and dried over sodium sulfate. Removal of solvent *in vacuo* and two crystallizations of the residue from ethyl acetate yielded 1.5 g. of Vd, m.p. 161–166°, after vacuum drying at 100° for 2 hr.

*Anal.* Calcd. for $C_{23}H_{30}O_3$: C, 77.93; H, 8.53. Found: C, 77.57; H, 8.46.

*3-(3-Oxo-17β-hydroxy-4-androsten-17α-yl)propanoic acid lactone* (VIa). Procedure C was used on 10 g. of Va. The crude product was recrystallized from ethyl acetate to yield 4.8 g. of the 3-oxo-4-ene lactone (VIa), m.p. 148–150° (polymorph melts 163–165°), $[\alpha]_D$ +76.5° ($CHCl_3$), $\epsilon^{241}$ 17,000.

*Anal.* Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 77.31; H, 8.94.

*4-(3-Oxo-17β-hydroxy-4-androsten-17α-yl)butanoic acid lactone* (VIb). The crude product (Vb) was oxidized according to Procedure C. This crude product was chromatographed over silica and the product eluted with 15% ethyl acetate–85% benzene. The crude fractions weighing 1.2 g. were recrystallized twice from ethyl acetate–isopropyl ether to give 0.7 g. of VIb, m.p. 192–193°, $\epsilon^{240}$ 17,000. Infrared spectrum (KBr) 5.77$\mu$ (six-membered lactone).

*Anal.* Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.43; H, 9.09.

*3-(3-Oxo-17β-hydroxy-19-nor-4-androsten-17α-yl)propenoic acid lactone* (XI) *and 3-(3-oxo-17β-hydroxy-19-nor-4-androsten-17α-yl)propanoic acid lactone* (Xa) *by direct reduction of IIc.* A suspension of 7.8 g. of the hydrate of IIc in 500 ml. of *t*-butyl alcohol and 1 l. of ammonia was treated with 8.0 g. of lithium added portionwise over a period of 30 min. After a total of about 2 hr. all the lithium had reacted and the ammonia was allowed to evaporate overnight in a stream of nitrogen. The solution was quenched with 250 ml. of water and the *t*-butyl alcohol removed by distillation. Then the solution was made acid with acetic acid and the product extracted with ether. The tacky product obtained from the ether was dissolved in 50 ml. of methanol and treated with 2 ml. of concentrated hydrochloric acid for 1 hr. to complete isomerization of the 5(10) double bond and to insure closure of the lactone ring. This was quenched in water and the product extracted with ether. Upon removal of the ether the gummy residue was chromatographed over silica using mixtures of benzene and ethyl acetate as developing solvents. In the 10% ethyl acetate eluate there was obtained by crystallization from ethyl acetate–isopropyl ether, 0.14 g. of the unsaturated lactone (XI) m.p. 117–118°, $[\alpha]_D$ +55.2° (diox.), $\epsilon^{239.5}$ 18,700, infrared (KBr), 5.78$\mu$ (unsatd. five-membered lactone carbonyl).

*Anal.* Calcd. for $C_{21}H_{26}O_3$: C, 77.27; H, 8.03. Found: C, 77.48; H, 8.84.

Elution with 15% ethyl acetate yielded after crystallization from ethyl acetate 1.0 g. of the saturated lactone (Xa), m.p. 135.5–137° (another form melted 126.5–127°), $[\alpha]_D$ +22.7° ($CHCl_3$), $\epsilon^{240}$ 17,500. The analytical sample melted at 137–138°.

*Anal.* Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.49; H, 8.34.

*Sodium 3-[3-methoxy-17β-hydroxy-1,3,5(10)-estratrien-17α-yl]propanoate* (VIIa). A solution of 124 g. (0.35 mole) of acetylenic acid IIc and 40.4 g. of triethylamine in 1 l. of absolute ethanol was hydrogenated[10] over 12.4 g. of 5% palladium on carbon at about 500 p.s.i. at laboratory temperature. The reaction was complete in about 25 min.

To this solution of the triethylamine salt of 3-methoxy-17β-hydroxy-1,3,5(10)-estratrien-17α-ylpropanoic acid was added with good mixing a solution of 28 g. (0.7 mole) of sodium hydroxide in 200 ml. of methanol. A dense white precipitate of the sodium salt formed promptly. After 5 hr. the salt was collected on a funnel, rinsed with 100 ml. of alcohol and finally dried in a vacuum oven at 75° for 12 hr. to give 116 g. of the desired product (VIIa) which is completely soluble in warm water. The mother liquor was vacuum evaporated to a small volume and then poured into an excess of dilute hydrochloric acid. After several hours the granular precipitate was collected on a funnel, rinsed free of mineral acid and dried to furnish 20 g. of a mixture of the hydroxy acid and its lactone (Vc). Extraction with 200 ml. of boiling ethyl acetate left 10 g. of the insoluble 3-methoxy-17β-hydroxy-1,3,5(10)-estratrien-17α-ylpropanoic acid, melting at 150–152° with decomposition.

*Anal.* Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44. Found: C, 73.71; H, 8.44.

Heating this acid at 160° for a few minutes resulted in loss of water and quantitative conversion to the lactone (Va). Lactonization may also be achieved by treating a concentrated solution of the hydroxy acid in alcohol with a small amount of 3*N* hydrochloric acid, letting the solution stand for 5 min. and then recovering the product by dilution with water.

*3-(3-Oxo-17β-hydroxy-19-nor-4-androsten-17α-yl)-propanoic acid lactone* (Xa) *by reduction of sodium salt* (VIIa). Procedure D was used on 114 g. of the sodium salt VIIa. The reaction mixture was diluted to a volume of 3 l. with water and acidified by the addition of 600 ml. of acetic acid. After 2 hr. the finely divided white solid was collected on a filter, rinsed well with water, and pressed as dry as possible on the funnel. This crude enol ether (VIIIa) was hydrolyzed and rearranged by stirring it with 200 ml. of hydrochloric acid and 360 ml. of water in 2 l. of methanol for 2 hr. The resulting solution was treated with Darco, filtered, poured into 8 l. of water, and the mixture was allowed to stand overnight. The white crystals were collected, rinsed free of acid, and dried to give 79.1 g. of crude (Xa). Crystallization

(10) This hydrogenation was carried out by Mr. W. M. Selby.

from 237 ml. of ethyl acetate and 553 ml. of isopropyl ether yielded 52 g. of the lactone melting at 134–135°. Concentration of the mother liquor gave 14 g. of material which was chromatographed to furnish an additional 6 g. of pure product.

*3-[3-Oxo-17β-hydroxy-19-nor-5(10)-androsten-17α-yl]propanoic acid lactone* (IXa). Procedure D was followed on 3.7 g. of VIIa to the point where excess ammonia was evaporated. Addition of 250 ml. of water at this point produced a two-phase solution. The upper solvent layer was separated, carefully acidified with hydrochloric acid, and diluted with several volumes of water. The precipitate was collected on a funnel and washed free of acid with water. The product was dried and crystallized twice from ethyl acetate to yield 0.470 g. of lactone (IXa), m.p. 173–177°.

*Anal.* Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.65; H, 8.14.

*4-(3-Oxo-17β-hydroxy-19-nor-4-androsten-17α-yl)butanoic acid lactone* (Xb). Procedure D was used on 6.9 g. of 4-[3-methoxy-17β-hydroxy-1,3,5(10)-estratrien-17α-yl]butanoic acid (VIIb). The dilute aqueous solution containing the crude lithium salt was carefully acidified with dilute hydrochloric acid and the precipitate collected on a funnel and washed free of acid with water. Two crystallizations from ethyl acetate yielded 1.45 g. of 4-[3-oxo-17β-hydroxy-19-nor-5(10)-androsten-17α-yl]butanoic acid as the semihydrate, m.p. 108–111°, after vacuum drying at 80°.

*Anal.* Calcd. for $C_{22}H_{32}O_4 \cdot {}^1/_2H_2O$: C, 71.51; H, 9.00. Found: C, 71.09; H, 9.03.

The ethyl acetate mother liquors were evaporated to dryness and dissolved in 500 ml. of benzene. After adding 150 mg. of *p*-toluene sulfonic acid the solution was distilled to a residual volume of 100 ml. which was washed twice with water and then dried over sodium sulfate. After evaporation of the solvent the crude residue was chromatographed over silica gel. Elution with 15% ethyl acetate–85% benzene produced a fraction which was crystallized from ethyl acetate with isopropyl ether to yield 84 mg. of Xb, m.p. 143–145°, $\epsilon^{240}$ 17,700, infrared ($CHCl_3$) 5.75μ (six-membered lactone).

*Anal.* Calcd. for $C_{22}H_{30}O_3$: C, 77.15; H, 8.83. Found: C, 76.77; H, 8.82.

*3-(3-Oxo-17β-hydroxy-5α-androstan-17α-yl)propanoic acid lactone* (XIIa) *and 3-(3-oxo-17β-hydroxy-5β-androstan-17α-yl)propanoic acid lactone* (XIIIa). A solution of 1.0 g. of VIa in 25 ml. of ethyl acetate was treated with hydrogen at atmospheric pressure at 30° in the presence of 0.2 g. of 5% palladium on carbon. When the uptake of hydrogen ceased, the catalyst was filtered off and the filtrate evaporated to dryness. The residue was chromatographed over silica and the products were eluted with 10% ethyl acetate–90% benzene. The early fractions gave 0.50 g. of the *trans* isomer (XIIa), which on recrystallization from ethyl acetate yielded 0.45 g. of XIIa, m.p. 178–179°, $[\alpha]_D$ +5.2° ($CHCl_3$).

*Anal.* Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.41; H, 9.12.

The later eluates yielded on recrystallization from ethyl acetate 0.14 g. of the *cis* isomer (XIIIa), m.p. 183–185°, $[\alpha]_D$ +6.8° ($CHCl_3$).

*Anal.* Calcd. for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.62; H, 9.17.

*4-(3-Oxo-17β-hydroxy-5α-androstan-17α-yl)butanoic acid lactone* (XIIb) *and 4-(3-oxo-17β-hydroxy-5β-androstan-17α-yl)butanoic acid lactone* (XIIIb). Seven and one-half g. of the crude lactone (VIb), which assayed 80% by ultraviolet, was dissolved in 100 ml. of ethanol and hydrogenated at atmospheric pressure in the presence of 1.5 g. of 5% palladium on carbon until absorption ceased (8.0 hr.). The catalyst and the solvent were removed, leaving 7.3 g. of a viscous product which could not be crystallized. The mixture was chromatographed over silica and eluted with ethyl acetate–benzene solution. Early in the 10% ethyl acetate eluate there was obtained 720 mg. of solid product which was crystallized from ethyl acetate–isopropyl ether to furnish 260 mg. of the *trans* isomer (XIIb) as fine white needles, m.p. 191–193°, $[\alpha]_D$ +30° ($CHCl_3$). Infrared (KBr) 5.78μ.

*Anal.* Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.02; H, 9.24.

Late in the 10% ethyl acetate eluate, 1.7 g. of solid fractions were collected, which, after crystallization from ethyl acetate–isopropyl ether, weighed 800 mg. and melted at 196–197°, (*cis* isomer, XIIIb), $[\alpha]_D$ +28.6° ($CHCl_3$). Infrared (KBr) 5.78μ.

*Anal.* Calcd. for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 76.90; H, 9.43.

A mixture of the *cis* and *trans* isomers melted at 175°.

*3-(3-Oxo-17β-hydroxy-19-nor-5α-androstan-17α-yl)propanoic acid lactone* (XIIc) *and 3-(3-oxo-17β-hydroxy-19-nor-5β-androstan-17α-yl)propanoic acid lactone* (XIIIc). A solution of 6.0 g. of Xa in 100 ml. of ethyl acetate at 30° was treated with hydrogen at atmospheric pressure in the presence of 1.0 g. of 5% palladium on carbon. After hydrogen uptake ceased, the solution was filtered and the filtrate evaporated to dryness. The residue was chromatographed over silica and the products were eluted with 15% ethyl acetate–85% benzene. The early fractions were recrystallized from ethyl acetate to give 0.45 g. of XIIc, m.p. 198–201° (also obtained as a polymorph melting 168–170°), $[\alpha]_D$ +9.7° (diox.).

*Anal.* Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.41; H, 9.27.

The middle fractions of this eluate contained a mixture of XIIc and XIIIc. However, pure XIIIc could be obtained from the later 15% ethyl acetate eluates by crystallization from ethyl acetate. In this fashion 1.63 g. of XIIIc, m.p. 218–222°, $[\alpha]_D$ 0.0° (diox.), was obtained.

*Anal.* Calcd. for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.36; H, 9.50.

*3-(3β,17β-Dihydroxy-5α-androstan-17α-yl)propanoic acid lactone* (XIV). A solution of 0.60 g. of Va in 20 ml. of absolute ethanol was treated with hydrogen at atmospheric pressure and 24° in the presence of 0.1 g. of 5% palladium on charcoal. After 7 hr., hydrogen uptake ceased and the mixture was filtered and the filtrate evaporated to dryness. Recrystallization from ethyl acetate yielded 0.40 g. of product, m.p. 196–199°. An analytical sample of the product, XIV, prepared by recrystallization from ethyl acetate, melted 199–201° and showed an $[\alpha]_D$ of −20.0° ($CHCl_3$).

*Anal.* Calcd. for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 76.29; H, 9.91.

*3-(3-Oxo-17β-hydroxy-5α-androstan-17α-yl)propanoic acid lactone* (XIIa) *from* XIV. Procedure C was used on 10 g. of XIV. The crude product was recrystallized from ethyl acetate to give 7.1 g. of XIIa, m.p. 177–179°. This was shown to be identical with XIIa, obtained above by hydrogenation, by determination of mixture melting points, and comparison of infrared spectra.

*3-(3-Oxo-17β-hydroxy-19-nor-5α-androstan-17α-yl)propanoic acid lactone* (XIIc) *from* Xa. To a solution of 1.5 g. of Xa in 50 ml. of *t*-butyl alcohol, 50 ml. of tetrahydrofuran, and 150 ml. of ammonia was added 1.0 g. of lithium. After the blue color disappeared the solvents were removed by distillation. The residue was treated with water and made strongly acid with hydrochloric acid. The precipitate was collected, washed with water, and dried. Then it was suspended in 150 ml. of acetone and treated with 3.5 ml. of 6*N* chromic acid–sulfuric acid solution. The excess chromium was destroyed with isopropyl alcohol and the solution filtered and evaporated to dryness. The residue was crystallized from ethyl acetate (Darco) to give a total of 0.65 g. of material m.p. 195–197°. This was shown to be identical with XIIc, obtained by hydrogenation, by mixture melting point determination and comparison of infrared spectra.

CHICAGO 80, ILL.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OKLAHOMA STATE UNIVERSITY]

# Reaction of Cystine with Sodium Sulfide in Sodium Hydroxide Solution

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The reaction of cystine with sodium sulfide in 0.2*M* sodium hydroxide solution produces a product with an absorption maximum at 335 mμ; it is postulated that this absorption is due to ($^{-}SSCH_2CHNH_2COO^{-}$). In the presence of excess sulfide this species reacts further, and, overall, there are produced two cysteinate ions and disulfide or polysulfide ions. When the reaction mixture is made strongly acid, the absorption at 335 mμ disappears, sulfur precipitates, and cysteine is found; with 5–10 equivalents of sodium sulfide the reaction of cystine is more than 95% complete. The change of optical rotation with time in mixtures of cystine and sulfide has been measured, and the approximate speed of reaction determined.

Cystine is a substance of considerable importance in biochemistry, primarily because of its participation in the composition of many proteins, and of the unique role which it plays in establishing and maintaining protein structure. Owing to the interest which attaches to this substance, many of its physical and chemical properties have been intensively studied, but these studies have not extended, except in a cursory way, to the reaction with sodium sulfide.[1,2] This is rather surprising, because the solubilizing and softening action of sodium sulfide on wool and hair, a phenomenon of some practical importance, is largely due to reaction with the cystinyl residues in these protein materials.[3] Sodium sulfide also interacts in an interesting way with globular proteins, for instance with the enzyme papain.[4] The present investigation was undertaken to obtain fundamental information concerning this type of reaction.

Before entering upon a discussion of the experimental results, it is necessary to make reference to two problems which are pertinent to that discussion, namely, the acid-base properties of sulfide ion, and the nature and absorption of polysulfide ions.

The second ionization constant of hydrogen sulfide is so small that sulfide ion is almost completely hydrolyzed in aqueous solution; unfortunately, there is lack of agreement in the values reported for the ionization constant,[5,6] so that the relative concentrations of sulfide and hydrosulfide cannot be calculated accurately. In most of the experiments to be described, 0.2*M* sodium hydroxide was used as a medium. This would serve to reduce the hydrolysis, and maintain a nearly constant, although undetermined, ratio between the sulfide and hydrosulfide ions. Even in this alkaline medium, considerable hydrosulfide ion is present,[7] and it should be kept in mind that reactions and equations ascribed to the sulfide ion might involve hydrosulfide ion instead, or both ions.

With reference to the nature and properties of polysulfide ions, it should first be admitted that they are not well understood. However it is known that polysulfide ions form when sulfur is dissolved in sodium sulfide solution, and that they exist in mobile equilibrium with each other;[8] these facts are of importance in the work to be discussed. This usually involved comparatively small amounts of sulfur and an excess of sulfide, and disulfide was, accordingly, the predominant species, but higher polysulfide ions were probably present to an appreciable extent. This should be understood in the discussion to follow, even though disulfide will be the only species specifically named. Disulfide has a characteristic lemon-yellow color, and absorbs fairly strongly in the near ultraviolet. Attempts to determine its spectrum by dissolving known amounts of sulfur in excess sodium sulfide resulted in an absorption that changed gradually with time, probably because of the gradual establishment of the polysulfide equilibria previously alluded to, and of the occurrence of side reactions, such as interaction with oxygen. The solutions were protected from air as well as was conveniently possible, but oxidation could not be completely prevented. Qualitatively, the spectrum exhibits a broad band with a maximum about 270 mμ, and a gradually decreasing absorption toward higher wave lengths; for the purposes of comparisons to be made below, it should be noted that the molar absorption coefficient (calculated from the amount of sulfur) at 335 mμ is about 310, and the absorption at 310 mμ is four times greater.[9]

Figure 1 shows a series of curves that represent spectra obtained in the reaction of cystine and sodium sulfide. In all cases, development of the absorption was fairly rapid, although slow alterations

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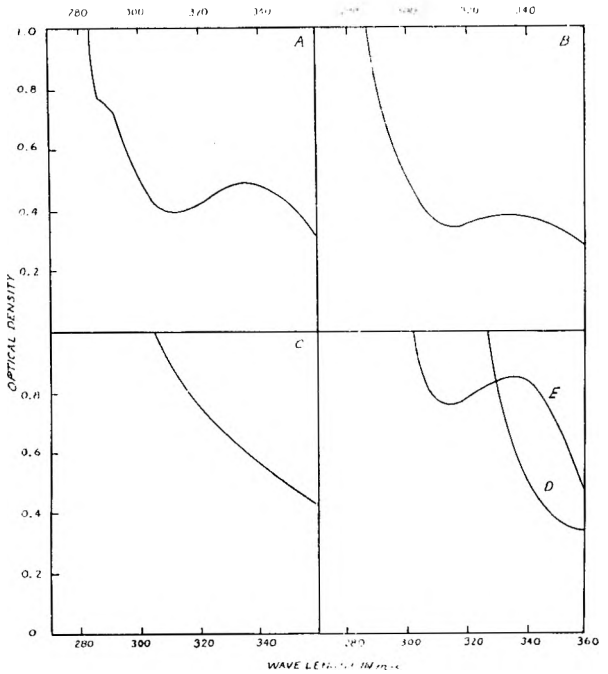
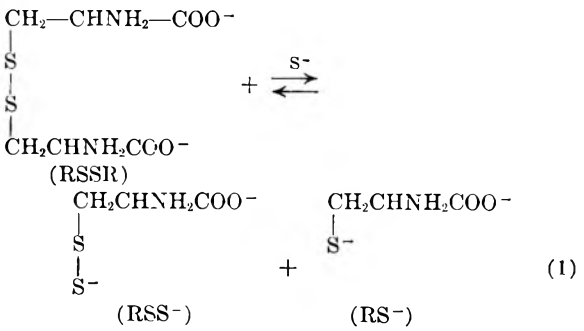



Fig. 1. A: 25 ml. 0.04*M* cystine + 1 ml. 0.052*M* $Na_2S$, 1 hr. after mixing, *vs.* 0.0385*M* cystine. B: 25 ml. 0.04*M* cystine + 4 ml. 0.52*M* $Na_2S$, 28 min. after mixing and diluted 25 times with 0.2*M* NaOH *vs.* 0.2*M* NaOH. C: 3 ml. 0.008*M* cystine + 2 ml. 0.516*M* $Na_2S$ + 7 ml. 0.2*M* NaOH, 25 min. after mixing, *vs.* 0.086*M* $Na_2S$. *D*: 0.05*M* disulfide solution prepared by dissolving 0.054 g. sulfur in 30 ml. of 1.5*M* $Na_2S$, diluted 25 times with 0.2*M* NaOH *vs.* 0.06*M* $Na_2S$. E: 0.002*M* disulfide solution + 0.36 g. of cysteine *vs.* 0.06*M* $Na_2S$ + 0.36 g. cysteine. (Cystine and $Na_2S$ solutions prepared in 0.2*M* NaOH).

of the spectrum would generally be observed over a long period of time; the curves represent the spectra developed when the first rapid reaction had reached essential completion. Curve A represents the spectrum developed from a large excess of cystine and sodium sulfide, and a clearly defined absorption maximum is seen at 335 mμ. This maximum cannot be due to disulfde, or to cysteinate ion,[10] and it is postulated that it is due to the species $RSS^-$, formed according to Equation (1).




The assumption is supported by the observation that the absorption maximum at 335 mμ was also formed when sulfur was dissolved in alkaline cysteinate solution.

(10) R. E. Benesch and R. Benesch, *J. Am. Chem. Soc.*, 77, 5877 (1955).

As the proportion of sulfide was increased, the absorption at 310 mμ increased, both in absolute value and especially with respect to that at 335 mμ. In the experiment represented by Curve B, sodium sulfide and cystine were mixed in 2:1 molar ratio, and the maximum at 335 mμ is still visible, but the relative absorption at 310 mμ is a little higher than in Curve A. The concentrations of reaction product in experiments A and B are not known exactly, but are not the same, and therefore the intensities of absorption should not be compared directly. In the experiment represented by Curve C, sodium sulfide was used in large excess, and it is seen that the absorption at 310 mμ is now much higher than that at 335 mμ. It is postulated that, in excess sulfide, disulfide ion is formed, according to Equation (2), and that its absorption

$$RSS^- + S^- \rightleftharpoons RS^- + S_2^- \qquad (2)$$

obliterates the minimum at 310 mμ, observed in the other two cases. Unfortunately, the absorption of disulfide is not very distinctive, and its quantitative features are somewhat uncertain, as has already been stated; furthermore, the other product of the reaction, cysteinate ion, absorbs fairly strongly in the region of the disulfide maximum. For these reasons, a quantitative interpretation of the curves has not been attempted. However, it can be deduced from the appearance of Curve B that only a little disulfide could have been formed in that experiment, even though sufficient sulfide had been added to react with $RSS^-$ completely according to Equation (2); it follows that the equilibrium constant of reaction (2) is small.

This conclusion is supported by Curves D and E. Curve D represents the spectrum of a disulfide solution prepared by dissolving 0.002*M* sulfur in excess sodium sulfide, and Curve E the spectrum developed when cysteine was added to this in a concentration comparable to that of sulfide, it is seen that the absorption typical of $RSS^-$ is developed, by reversal of reaction (2).

When solutions showing the absorption maximum at 335 mμ were treated with strong hydrochloric acid, the maximum disappeared quickly, and sulfur precipitated. In the very dilute solutions used for spectrophotometric measurements, the precipitate was, of course, very light.

More concentrated solutions were next investigated. In this series of experiments, the reaction between cystine and sulfide was allowed to come to substantial completion, the reaction mixture was made strongly acid, excess hydrogen sulfide was expelled, and the remaining solution was titrated with iodine, in the conditions prescribed by Lavine[11] for the determination of cysteine. The results are shown in Table I. At sulfide-cystine ratios smaller than 2:1, the amount of cysteine formed was greater than the amount of

(11) T. F. Lavine, *J. Biol. Chem.*, 109, 141 (1935).

sulfide; this shows that the reaction cannot be represented by an equation such as (3), according

$$RSSR + 2S^{=} \longrightarrow 2RS^{-} + S_2^{=} \quad (3)$$

to which the amount of cysteine and sulfide should be at most equivalent. The data can be explained, however, if it is further postulated that the species $RSS^{-}$ is unstable in acid solution, and decomposes according to Equation (4). Such a postulate is

$$RSS^{-} + H^{+} \longrightarrow [RSSH] \longrightarrow RSH + S\downarrow \quad (4)$$

reasonable, in view of the similar behavior of inorganic disulfides toward acidification. The decomposition, however, is probably not instantaneous. In many cases, it was observed that the deposition of sulfur, although largely complete upon the first addition of acid, continued for some time afterwards. This may be due to the temporary existence of RSSH. In the experiments described, where acidification was followed by expulsion of hydrogen sulfide and long standing, the separation of sulfur appeared to be complete before other determinations were undertaken, and it has been assumed that no RSSH remained.

TABLE I

CONVERSION OF CYSTINE TO CYSTEINE

| $10^{-4}$ Moles in 20-Ml. Samples | | |
|---|---|---|
| Cystine | $Na_2S$ | Cysteine |
| 5.0 | 2.5 | 3.8 |
| 5.0 | 5.0 | 7.0 |
| 5.0 | 7.5 | 8.8 |
| 5.0 | 10.0 | 9.0 |
| 5.0 | 15.0 | 9.4 |
| 5.0 | 50.0 | 9.6 |
| 3.8 | 3.8 | 5.4 |
| 7.6 | 3.8 | 6.2 |
| 26.6 | 3.8 | 7.2 |

The results of Table I indicate that the reactions do not go to completion. However, there is a gradual shift toward completion as the excess of either reagent is increased, in accordance with the Law of Mass Action. It cannot be deduced from the data to what extent reactions (1) and (2) contribute to the total reaction; indeed, the results might be explained in terms of reaction (1) and (4) alone. However, the occurrence of reaction (2) and formation of disulfide is clearly indicated by the spectrophotometric experiments, and by the strong yellow coloration observed in the more concentrated solutions containing excess disulfide.

Further confirmation of these conclusions was obtained by polarimetric measurements. In a typical experiment, an 0.02*M* solution of cystine in 0.2*M* sodium hydroxide, having a rotation of $-0.415°$ (1-dm. tube; $[\alpha]_D - 87°$) was treated with varying amounts of approximately 1*M* sodium sulfide; in one case, 5.00 ml. was added, giving a concentration of 0.0166*M* cystine and 0.188*M* sulfide. The levo-rotation decreased rapidly, and finally leveled off at a value of $-0.033°$; this value varied little in the interval between 2000 and 6000 seconds. The final value of the rotation is significant only as to order of magnitude, because it was found that the final rotation given by samples of similar initial composition was not closely reproducible. It is believed that exposure to oxygen was a major cause of the variation, and care was taken to minimize such exposure, but it did not prove practicable to eliminate it. Fully significant values of the final rotation were consequently not obtained.

The reaction mixture was allowed to stand about 90 minutes after attaining constant rotation, and then was made strongly acid. After removal of precipitated sulfur and hydrogen sulfide, the optical rotation of the solution, then approximately 1*M* in hydrochloric acid, was found to be $-0.016°$; this corresponds to less than 2% of the original amount of optically active cystine. An aliquot portion of this solution was made 1*M* in potassium iodide, then treated with iodine solution drop by drop until a small excess had been added, and finally decolorized with a drop or two of sodium thiosulfate. Measurement of the optical activity then gave a value of $-0.296°$, which corresponded to regeneration of 95% of the original cystine activity (the solution having been diluted 3.3 times, but the activity now being measured in 1*M* hydrochloric, in which $[\alpha]_D - 215°$). These results confirm that cysteine was a product of the reaction and that the reaction was better than 90% complete in those conditions.

Table II summarizes some data obtained with varying concentrations of sulfide. The values called "half-life" actually measure the times required for the initial rotation to decrease to half the value, and do not truly correspond to half-lives of reaction, because the final rotations were not zero. However, these values were small enough to make little difference. The values decrease as the concentration of sulfide increases, as might be expected, and serve to indicate the approximate speed of the reaction, which is fairly great. The final values of the rotation are of qualitative significance only, as has already been explained. Although not exactly reproducible, the values obtained in any one experiment were constant for long periods of time after the initial rapid decrease. The gradual decrease in the final levo-rotation with increasing sulfide concentration is consistent with the existence of an equilibrium which is gradually shifted toward completion of the reaction. The specific rotation of cysteine is so small[12] it can be neglected in the interpretation of the observed rotation in these experiments.

To evaluate from these results the possible utility of sodium sulfide for reducing disulfide bonds in proteins, one must keep in mind that the

(12) J. P. Greenstein, *Adv. Protein Chem.*, 9, 184 (1954).

TABLE II

POLARIMETRIC STUDY OF CYSTINE-SULFIDE MIXTURES

| Concn. Cystine *M* | Concn. Sulfide *M* | "Half-Life" Sec. | Final Rotation 1-dm. Tube |
|---|---|---|---|
| 0.0185 | 0.0689 | 760 | −0.068° |
| 0.0180 | 0.103 | 503 | −0.043° |
| 0.0167 | 0.155 | 250 | −0.030° |
| 0.0166 | 0.188 | | −0.017° |
| 0.0143 | 0.310 | | −0.012° |

free energy of disulfide bonds in proteins is not the same as that of the bond in cystine; accordingly the values of the equilibrium constants may be different. To the extent that protein disulfide bonds would show the same reactivity as those in cystine, it can be inferred that sodium sulfide in moderate excess would reduce disulfide bonds almost completely to give —$S^-$ and —$SS^-$ residues, and that, in a large excess of sulfide, reduction to two —$S^-$ residues would be expected. Acidification of the solution would convert both types of residue to —SH groups in any case; some time may be required for reaction. During and after acidification, excess reagent, now in the form of hydrogen sulfide, can be removed easily.

## EXPERIMENTAL

*Materials.* All reagents were of analytical reagent grade, except as otherwise specified. L-Cystine, "cfp" grade, and L-cysteine, purified grade, were obtained from the California Foundation for Biochemical Research, Los Angeles; the former compound was estimated to be 98% pure, but no correction for the 2% impurity was made in the calculation of yields. The water used in the preparation of all solutions was distilled, deionized by passage through Amberlite MB-1 resin, deaerated by boiling and cooling with a stream of nitrogen bubbling through it, and stored in a siphon out of contact with the air. Sodium sulfide solutions were prepared by dissolving crystals of $Na_2S.9H_2O$ which had been washed clean of yellowish spots of sulfur and polysulfide; the titer was determined iodimetrically.[13] Cystine solutions were also prepared in sodium hydroxide, 0.2 or 0.6*M*, freshly before use, since the disulfide bond suffers slow hydrolytic fission in strong alkali; in the period of time involved in the experiments described, this reaction would occur only to a very small extent.

Nitrogen was of commercial grade, except in one case as noted below; the commercial gas was purified by passing it through a solution of vanadous ion.[14]

*Reaction of cystine with sulfide and titration of cysteine.* For the first set of data reported in Table I, 0.123 g. of cystine was weighed in a 50-ml. round-bottom flask, and sufficient 0.2*M* sodium hydroxide added so the final volume, after addition of sulfide, would be 20.0 ml. The solution was stirred with a magnetic stirrer until the cystine had dissolved, sodium sulfide in 0.2*M* sodium hydroxide solution was added, the air above the solution was displaced with nitrogen, the flask was closed, and the solution stirred for the length of time required to give constant cysteine titer (1 hr. for the smallest concentration of sulfide to 15 min. for the largest). The temperature was maintained at 30°. Then approximately 5 ml. of ice-cold 6*N* HCl was added, and the hydrogen sulfide was expelled: in one set of measurements, this was accomplished by stirring and bubbling nitrogen through the solution for 1.5 hr., and in another set by boiling the solution under vacuum with gentle heating and vigorous stirring for 10–15 min., both procedures giving the same results. The solution freed from hydrogen sulfide was added to about 25 ml. of standard iodine solution, prepared from standard potassium iodate and sufficient potassium iodide and hydrochloric acid to give a final concentration of approximately 1*M* in iodide and hydrogen ions; after standing a few minutes, the excess iodine was titrated with standard sodium thiosulfate. Blank experiments were run, first on solutions containing a representative amount of sodium sulfide, by which it was established that the procedure employed expelled all but a small amount of hydrogen sulfide; and secondly, on mixtures of cysteine and sodium sulfide, in which about 97% of the cysteine originally taken could be recovered; the two corrections, *i.e.* for residual hydrogen sulfide and for loss of cysteine during manipulation nearly cancelled one another, so no correction was applied to the results obtained by titration on the cystine-sulfide samples. The accuracy of the determination is believed to be about ±3%.

The second set of data was determined in a similar way, except that in all the experiments the sodium sulfide concentration was kept constant at about 0.019*M* and the concentration of cystine varied; 0.6*M* sodium hydroxide was used to dissolve the sodium sulfide and cystine.

*Spectrophotometric measurements.* Spectra were scanned with a Beckman DK-1 Spectrophotometer; some optical density measurements at a fixed wave length were made with a Beckman DU Spectrophotometer. Sodium sulfide solutions were prepared shortly before measurement. Both cystine and sulfide solutions were made up in deaerated 0.2*M* sodium hydroxide and stored under nitrogen. They were mixed and transferred to the spectrophotometer cell, taking care to minimize exposure to air. The cell had a ground glass stopper and was filled completely with liquid; *i.e.*, no air space was left above the solution.

*Polarimetric measurements.* Measurements were made with a Rudolph Model 80 High Precision Polarimeter, modified for photoelectric recording by Mr. Donald Sproul (Department of Biochemistry, University of California, Berkeley). The accuracy and precision of the instrument were checked with samples of cystine. Solutions of cystine in 0.2*M* sodium hydroxide solution were prepared and the temperature was allowed to rise to 25.0°, sodium sulfide was then quickly added with a pipet, and the time of mixing was noted. A sample was transferred to a jacketed polarimeter tube, and measurements of the optical rotation were made at 25° as soon as possible after mixing and at appropriate intervals thereafter. The bulk of the solution was kept in a flask under nitrogen; when the sample in the polarimeter tube had attained constant rotation, a fresh sample from the bulk of the solution was also measured. The two measurements usually disagreed by some appreciable amount; in very unfavorable cases, the discrepancy was as large as 0.03°, an amount which is not great when compared to the initial rotation, but of the same order of magnitude as the final rotation itself.

*Polarimetric study of the reaction products.* The solution, which typically would contain 0.016*M* cystine, 0.17*M* sodium hydroxide, and 0.18*M* sodium sulfide, was allowed to stand about 90 min. A 10-ml. aliquot was transferred to a 50-ml. centrifuge tube and 3.00 ml. of concentrated hydrochloric acid gradually added; the tip of a thin capillary was then introduced below the surface of the reaction mixture and *high-purity* (>99.8%) nitrogen was bubbled through for 30 min. The mouth of the tube was covered with foil and allowed to stand 2 hr. It was then centrifuged in a Servall Superspeed Centrifuge at about 8000 r.p.m. To an aliquot of the clear centrifugate was added sufficient solid potas-

(13) N. H. Furman, *Scott's Standard Methods of Chemical Analysis*, Vol. II, Van Nostrand Co., New York 1939, p. 2182.

(14) L. Meites, *Polarographic Techniques*, Interscience Publishers, New York, 1955.

sium iodide to make the solution approximately 1.1*M*, and 0.1*M* iodine was added drop by drop until a permanent iodine color remained. After the solution had stood for 10 min., 0.1*M* sodium thiosulfate was added drop by drop until the iodine color was just discharged.

*Acknowledgment.* The polarimetric measurements described in this paper were conducted largely in the Department of Biochemistry of the University of California at Berkeley; the kind hospitality afforded by that institution is gratefully acknowledged. Professor Joseph B. Neilands offered valuable advice and helpful discussion; Mr. Donald Sproul assembled and maintained the photoelectric polarimeter which was used. That portion of the work was performed under Contract No. AF 18(603)-135, with the United States Air Force, Office of Scientific Research and Development, Aeromedical Division. The remainder of this work was supported by Grant G-4669, United States Public Health Service.

STILLWATER OKLA.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CARNEGIE INSTITUTE OF TECHNOLOGY]

# Synthesis of a Chloro Derivative of DL-Vasicine[1]

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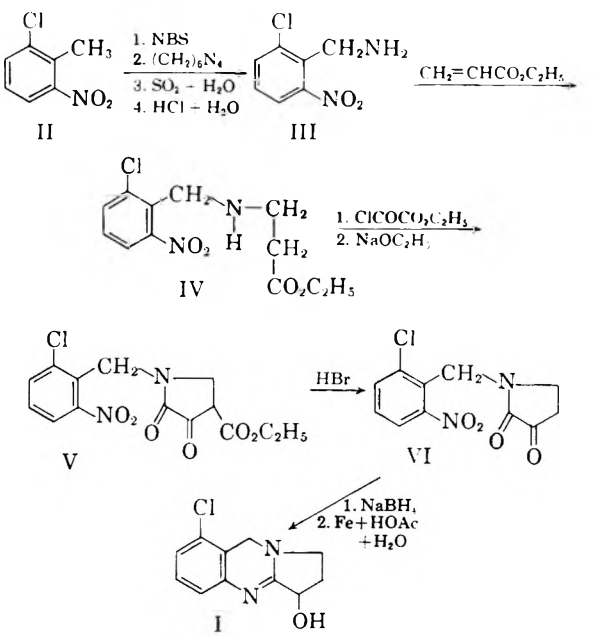
DL-7-Chlorovasicine (7-chloro-3-hydroxypeg-9-ene) has been prepared from 2-chloro-6-nitrotoluene. The compound displays a moderate activity against histamine-induced bronchospasm in guinea pigs, an activity which is potentiated by simultaneous administration of atropine. DL-Vasicine is less active, and DL-6-methoxyvasicine (6-methoxy-3-hydroxypeg-9-ene) showed no activity of this kind.

In a recent publication[2] from this laboratory there was described a new scheme of synthesis for the alkaloid vasicine which was successfully applied to the synthesis of an analog carrying a methoxyl group in the 6- position of the pegene ring system. The method has now been extended to the synthesis of a chloro derivative (I), which could be described as DL-7-chloro-3-hydroxypeg-9-ene according to the system of nomenclature introduced by Späth,[3] and which, for convenience, we have designated DL-7-chlorovasicine.

The general synthetic scheme was discussed in some detail in the previous paper.[2] In the present instance the starting point for the synthesis was the commercially available 2-chloro-6-nitrotoluene (II). The methyl group of II was brominated by use of *N*-bromosuccinimide (NBS),[4] and the crude bromide so obtained was converted into 2-chloro-6-nitrobenzylamine (III) in an over-all yield of 24.8% from II by first forming the hexaminium salt with hexamethylenetetramine and then hydrolyzing this product *via* an intermediate methylol sulfite.[2,5]

The 2-chloro-6-nitrobenzylamine (III) was treated with ethyl acrylate to produce a 93% yield of ethyl β-(2-chloro-6-nitrobenzylamino)-propionate, (IV), which was characterized in the form of the hydrochloride. Compound IV reacted with ethoxalyl chloride to from the *N*-ethoxalyl derivative, which, upon treatment with sodium ethoxide, underwent a cyclization of the Dieckmann type to yield 1-(2-chloro-6-nitrobenzyl)-4-carbethoxy-2,3-dioxopyrrolidine (V). The over-all yield of V from III was 44.6%.




Completion of the synthesis of DL-7-chlorovasicine (I) involved hydrolysis and decarboxylation of V to yield 1-(2-chloro-6-nitrobenzyl)-2,3-dioxopyrrolidine (VI) (74.5% yield), followed by two reduction steps. Reduction of crude VI with

(1) This investigation was supported by a research grant (RG-4371) from the Division of Research Grants, National Institutes of Health, Public Health Service.

(2) P. L. Southwick and J. Casanova, Jr., *J. Am. Chem. Soc.*, **80**, 1168 (1958).

(3) E. Späth, *Monatsh.*, **72**, 115 (1938).

(4) *Cf.* N. Kornblum and D. C. Iffland, *J. Am. Chem. Soc.*, **71**, 2137 (1949).

(5) *Cf.* B. Reichert and W. Dornis, *Arch. Pharm.*, **282**, 100 (1944); *Chem. Abstr.*, **45**, 1969 (1951).

sodium borohydride yielded 1-(2-chloro-6-nitrobenzyl)-3-hydroxy-2-oxopyrrolidine (VII), which was not purified, but was treated with iron and aqueous acetic acid to reduce the nitro group and permit spontaneous condensation of the resulting amino group with the lactam (pyrrolidone) carbonyl to yield I. The over-all yield of crude DL-7-chlorovasicine (I) from V was 50%, but purification losses reduced this figure to 16.8% of crystallized product. Thus the over-all yield of I from 2-chloro-6-nitrotoluene (II) was approximately 2%.

DL-7-Chlorovasicine has an infrared spectrum very similar to that of vasicine itself,[6] with prominent bands in the 5.5–6.5$\mu$ region at 6.10$\mu$, 6.25$\mu$, and 6.39$\mu$ (measured in chloroform solution). Comparison of this spectrum with that of vasicine[6] and 6-methoxyvasicine[2] shows that three bands (listed in decreasing order of intensity) at 6.09–6.10$\mu$, 6.22–6.25$\mu$, and 6.30–6.39$\mu$ are common to all three substances, and probably can be regarded as characteristic of simple vasicine derivatives.

In 1925 Chopra and Ghosh[7] reported that natural vasicine produced "a slight but a persistent broncho-dilation" which was rendered much more pronounced by simultaneous administration of atropine. These earlier results are supported in some degree by the finding that a sample of our synthetic DL-vasicine[2] had a slight activity against histamine-induced bronchospasm in guinea pigs, and that this activity was markedly potentiated by atropine. Toxic effects which resulted in the death of some animals were observed at dose levels as low as 5 mg./kg. when vasicine was administered intraperitoneally without atropine. DL-7-Chlorovasicine (I) proved to be more active (rated moderately active) and less toxic (no apparent side effects at 25 mg./kg.) than DL-vasicine itself when tested in guinea pigs in the same fashion. Again the activity was markedly potentiated by atropine. DL-Vasicine administered alone at intravenous dose levels up to 5 mg./kg. showed no bronchodilator activity in the pithed dog. DL-6-Methoxyvasicine appeared to be devoid of antihistaminic and bronchodilator activity.

## EXPERIMENTAL[8]

*2-Chloro-6-nitrobenzylamine* (III). A mixture prepared from 202 g. (1.18 mole) of 2-chloro-6-nitrotoluene, 230 g. (1.29 mole) of *N*-bromosuccinimide, 10 g. of benzoyl peroxide, and 1 l. of carbon tetrachloride was refluxed on a steam bath for 14 hr. with vigorous stirring. The mixture was cooled for 1 hr. in an ice bath, then filtered to remove the succinimide, which was extracted with 200 ml. of ether. The ether extract was added to the chloroform filtrate, and the resulting solution was passed through a 5 × 55 cm. column of alumina (1 lb., 80–200 mesh). The column was then washed with 1.5 l. of ether, and the total eluate was concentrated by evaporation under reduced pressure at a temperature maintained at 40° or below. A pale yellow oil was obtained, weight 310 g.

The oil was added cautiously to 165 g. (1.18 moles) of hexamethylenetetramine in 800 ml. of chloroform. The reaction began promptly with the evolution of heat. (Cooling may at times be needed to prevent overheating of the reaction mixture.) After the initial reaction had subsided somewhat the mixture was refluxed and stirred for 2 hr., then was cooled in an ice bath for several hours before the hexaminium salt was collected by filtration. The filter cake was washed with small portions of cold acetone. The separation of a second crop of the salt was induced by concentrating the filtrate to about one half the original volume and diluting the solution with acetone. The crude hexaminium salt was partially purified and freed of colored impurities by trituration with warm absolute ethanol, followed by cooling of the mixture in an ice bath and removal of the product by filtration. The product (284 g.; 61.6% yield) was a white powder m.p. 174–178°.

For conversion of the hexaminium salt to the benzylamine *via* the methylol sulfite, 197 g. (0.504 mole) of the hexaminium salt was added rapidly with stirring to 700 ml. of water at 5° which had been saturated with sulfur dioxide. After 1 hr. of stirring with cooling and continuous addition of sulfur dioxide, the product (the amine methylol sulfite) was collected by filtration and dried. The white powder, m.p. 164–168° with previous softening, weighed 90.0 g. (63.7% yield).

The methylol sulfite (120 g., 0.427 mole) was added to 250 ml. of 25% hydrochloric acid. The mixture was steam distilled for 3 hr. The volume was maintained at *ca.* 250 ml. throughout the distillation by regulating the rate of introduction of steam and the heating of the distillation vessel. The solution was next cooled and made strongly basic by addition of sodium hydroxide. The mixture was extracted with three 300-ml. portions of ether and the combined ether extract was dried over Drierite. The mixture was filtered and the filtrate was concentrated under reduced pressure to yield 2-chloro-6-nitrobenzylamine (50.5 g.; 63.1% yield) in the form of a low-melting yellow solid. The over-all yield from 2-chloro-6-nitrotoluene was 24.8%.

*The hydrochloride* was prepared in order to characterize 2-chloro-6-nitrobenzylamine (III). The free amine (*ca.* 2.5 g.) was dissolved in dry ether and the hydrochloride was precipitated by addition of dry hydrogen chloride. The compound was obtained as pale yellow diamond-shaped plates, m.p. 258–260°, following three crystallizations from absolute ethanol.

*Anal.* Calcd. for $C_7H_8O_2N_2Cl_2$: C, 37.69; H, 3.62; N, 12.56. Found: C, 38.03; H, 3.64; N, 12.55.

*Ethyl β-(2-chloro-6-nitrobenzylamino)-propionate hydrochloride* (IV). To a mixture prepared from 48.0 g. (0.256 mole) of 2-chloro-6-nitrobenzylamine (III) and 150 ml. of absolute ethanol, 25.6 g. (0.256 mole) of freshly distilled ethyl acrylate was added The mixture was allowed to stand for 24 hr., and the solvent was then removed by distillation under reduced pressure from a steam cone. The residual oil was dissolved in 300 ml. of dry ether and dry hydrogen chloride was added until precipitation was complete. The product was removed by filtration and dried in a vacuum desiccator. The yield was 77.0 g. (93%) of a white product, m.p. *ca.* 180°. Following two crystallizations from absolute ethanol and a final crystallization from acetone, white hexagonal prisms were obtained, m.p. 180–181.5°.

*Anal.* Calcd. for $C_{12}H_{16}O_4N_2Cl_2$: C, 44.59; H, 4.99; N, 8.67. Found: C, 44.30; H, 4.81; N, 8.83.

*1-(2-Chloro-6-nitrobenzyl)-4-carbethoxy-2,3-dioxopyrrolidine* (V). A solution prepared by dissol ing 100 g. (0.310 mole) of ethyl β-(2-chloro-6-nitrobenzylamino)propionate hydrochloride (IV) in a minimum volume of water was made basic by addition of an aqueous solution contairing 20 g. (0.5

(6) B. Witkop, *Experientia*, **10**, 420 (1954).

(7) R. M. Chopra and S. Ghosh, *Indian Med. Gaz.*, 60, 354 (1925).

(8) Melting points are corrected. The melting points of samples of 7-chlorovasicine were taken in evacuated capillaries. Microanalyses by Geller Microanalytical Laboratories, Bardonia, N. Y.

mole) of sodium hydroxide. The mixture was then extracted with three 300-ml. portions of ether, and the combined ether extract was dried over magnesium sulfate, filtered, and concentrated under reduced pressure at a temperature of about 40°. The residual oil was added dropwise to 46.5 g. (0.341 mole) of ethoxalyl chloride. The mixture was heated on a steam cone for 3.5 hr. in an apparatus protected from moisture.

The crude *N*-ethoxalyl derivative so obtained, a light orange viscous oil, was added dropwise over a 45-min. period to a vigorously stirred solution of 15.6 g. (0.68 mole) of sodium in 350 ml. of absolute ethanol which was held at a temperature of −5° in an apparatus protected from moisture. After a half hour of stirring without cooling the mixture was poured into 1 l. of boiling water. After the solution had cooled it was stirred and acidified by addition of *ca.* 1.2 moles of 6*N* hydrochloric acid. The mixture was kept overnight in a refrigerator, and the precipitated product was collected by filtration, then triturated with ether to remove colored impurities. The yield was 51.0 g. (48%) of a light tan product which was purified by crystallization from 95% ethanol to give 36 g. of light gray needles. (A second crop of 10 g. was recovered from the mother liquors.) A sample was purified by three crystallizations from absolute ethanol to give needles, m.p. 193–195.5° (dec., red melt) which retained a trace of gray color.

*Anal.* Calcd. for $C_{14}H_{13}O_6N_2Cl$: C, 49.35; H, 3.85; N, 8.22. Found: C, 49.26; H, 3.95; N, 8.19.

*1-(2-Chloro-6-nitrobenzyl)-2,3-dioxopyrrolidine* (VI). A mixture of 15.0 g. (0.044 mole) of 1-(2-chloro-6-nitrobenzyl)-4-carbethoxy-2,3-dioxopyrrolidine (V), 15 ml. of 48% hydrobromic acid, and 100 ml. of glacial acetic acid was refluxed for 55 min. The dark solution was poured onto 400 g. of ice. Approximately 6 g. of starting material was recovered by filtration after the ice had melted. The filtrate was extracted with three 150-ml. portions of chloroform, and the combined extracts were dried over anhydrous magnesium sulfate, then filtered, and concentrated by evaporation under reduced pressure. After removal of the chloroform, dry ether (*ca.* 25 ml.) was added to the residual oil and the mixture was kept overnight in a refrigerator. The product, a tan precipitate, was removed by filtration. The yield was 5.28 g. (74.5% yield, 44.7% conversion) of a material melting at 137–140° with previous softening.

Because pyrrolidinediones of this type often undergo condensation reactions during attempted purification, the compound was characterized as the *anil*. To a hot solution of 0.4 g. of the crude product in 5 ml. of absolute ethanol, 0.28 g. of aniline was added, and the solution was boiled for 5 min. The product, which crystallized when the solution was cooled, was washed with a 1:1 absolute ethanol–petroleum ether mixture, then recrystallized twice from ethanol and once from acetone. Yellow, hexagonal prisms were obtained, m.p. 207–209° (dec.).

*Anal.* Calcd. for $C_{17}H_{14}O_3N_3Cl$: C, 59.39; H, 4.11; N, 12.23. Found: C, 59.14; H, 4.03; N, 12.61.

*7-Chlorovasicine* (I). Crude 1-(2-chloro-6-nitrobenzyl)-2,3-dioxopyrrolidine (VI) (11.9 g.; 0.044 mole) was dissolved in 200 of warm absolute ethanol, and the solution was added to a mixture prepared by suspending 12.0 g. (0.318 mole) of 98% sodium borohydride in 100 ml. of absolute ethanol. The mixture was allowed to stand at room temperature for 12 hr. and then the solvent was removed by evaporation under reduced pressure. The gelatinous residue was treated with 100 ml. of 25% hydrochloric acid and the mixture was extracted with four 150-ml. portions of chloroform. The combined extract was dried over magnesium sulfate. It was filtered and the solvent was removed by evaporation under reduced pressure.

Because the reduction product, 1-(2-chloro-6-nitrobenzyl)-3-hydroxy-2-oxopyrrolidine (VII), as obtained in this way, was a viscous oil which did not respond to attempts at crystallization, it was not purified but was converted directly into 7-chlorovasicine. To the oil was added 200 ml. of a 50% aqueous acetic acid solution and 18 g. of iron filings. The mixture was stirred and heated on a steam cone for 3 hr. After the mixture had been cooled in an ice bath it was made strongly basic by addition of a 25% aqueous sodium hydroxide solution. The mixture, which was not filtered, was then extracted with three 500-ml. portions of chloroform. (Separation of layers was achieved by centrifugation.) The combined chloroform extract was dried over magnesium sulfate, filtered, and evaporated under reduced pressure. The residue was a pink solid weighing 6.6 g. (68% yield). The infrared spectrum of this material indicated the presence of a small amount of a pyrrolidone impurity. The product was purified by three crystallizations from absolute ethanol using charcoal to decolorize the solutions. The quantity of fully purified product obtained (white needles, m.p. 221–223°) was 1.58 g. (The mother liquors from the crystallizations yielded an additional 0.63 g. of pink needles, m.p. 217–219°, raising the yield of crystalline product to 2.21 g. (22.6%)).

*Anal.* Calcd. for $C_{11}H_{11}ON_2Cl$: C, 59.33; H, 4.98; N, 12.58. Found: C, 59.39; H, 4.97; N, 12.60.

In the 5.5–7.0μ region the infrared spectrum of the compound ($CHCl_3$ soln.) revealed bands at 6.10μ (20% transmittance), 6.25μ (32% transmittance), 6.39μ (56% transmittance), 6.66μ (61% transmittance), and 6.87μ (38% transmittance). The measurements were made with a Perkin-Elmer model 21 spectrophotometer.

*Acknowledgment.* The authors are indebted to the Smith Kline and French Laboratories and the Lilly Research Laboratories for the tests of physiological activity described above.

PITTSBURGH 13, PA.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

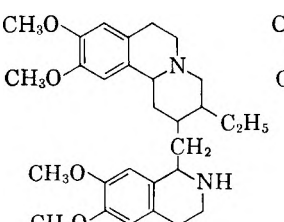
# Synthetic Approaches to Ipecac Alkaloids. III. Studies on the Synthesis and Partial Reduction of Pyridones[1,2]

JEROME A. BERSON AND JASJIT SINGH WALIA

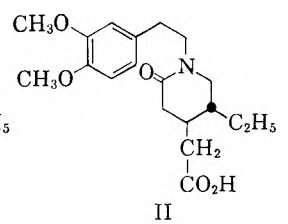
*Received December 29, 1958*

The double salt obtained from the reaction of iodine and pyridine with *N*-β-(3,4-dimethoxyphenylethyl)-4-carboxy-5-ethyl-2-methylpyridine is hydrolyzed by dilute alkali to pyridine and not to a pyridone. *N*-β(3,4-dimethoxyphenylethyl)-5-ethyl-2-pyridone and *N*-β(3,4-dimethoxyphenylethyl)-2-pyridone are, however, readily prepared by this method. The former pyridone is reduced by lithium aluminum hydride to a mixture of a (de-oxygenated) dihydropyridine and the γ,δ-unsaturated lactam, and by lithium, sodium or calcium in liquid ammonia to the γ,δ-unsaturated lactam and its phenolic, monodemethylated analog. Other transformation products of these substances are described.

The present paper reports an extension of a previously outlined[2] experimental approach to the synthesis of emetine(I) and other alkaloids of the ipecac group. The immediate objective of this work was the stereospecific synthesis of the *trans*-piperidoneacetic acid II, which has[3,4] the "natural" stereochemistry, and which, after having been prepared by non-stereospecific means,[3,5,6] had been

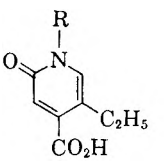


I

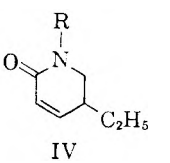


II

converted to emetine. We envisioned two means of control of the stereochemistry: (i) hydrogenation of the pyridonecarboxylic acid III to the next lower homologue of II— which would place the carboxyl group next to an epimerizable asymmetric center— followed by homologation, and (ii) attachment of a two-carbon chain to the dihydropyridone IV by Michael addition, a process that, being reversible, would be expected to afford the thermodynamically favored *trans*-stereochemistry. After this work was



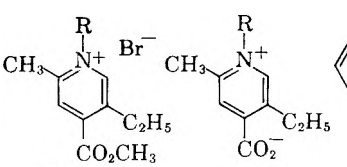
III R = β-(3,4-dimethoxyphenylethyl)



IV

under way, Battersby and Turner[7] reported a successful synthesis of IV by a method other than the one we were attempting; Michael addition of malonic ester to IV, hydrolysis, and decarboxylation gave II which was converted to emetine.[7] These developments prompt us to record our observations now.

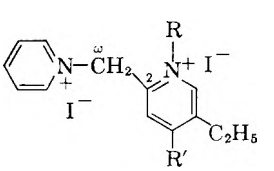
*Approach* (*i*) Homoveratryl bromide reacted with methyl 5-ethyl-2-methylpyridine-4-carboxylate[2b] to give the extremely hygroscopic quaternary bromide V. Reaction of V with moist silver oxide gave the hygroscopic, glassy betaine VI. Both V and VI reacted with iodine and pyridine[2a] to give the corresponding double salts VIIa and VIIb, which were also hygroscopic and were not obtained in the pure state.



V



VI



VIIa. R′ = $CO_2CH_3$
b. R′ = $CO_2H$
R = β-(3,4-dimethoxyphenylethyl)

That VIIa and VIIb were actually in hand, however, was evident from the characteristic[2a] transient blood-red color that both crude preparations gave with aqueous alkali. Although other double salts of this type are smoothly hydrolyzed by aqueous alkali to pyridones,[2a] VIIa and VIIb gave no pyridone under these conditions. The only identifiable product was pyridine, characterized as the picrate and as the hydroiodide. Apparently,

(1) (a) This work was supported in part by a grant from Abbott Laboratories, Inc. (b) From a dissertation to be submitted by J. S. Walia in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) For previous papers in this series see (a) J. A. Berson and T. Cohen, *J. Am. Chem. Soc.*, **78**, 416 (1956); (b) J. A. Berson and T. Cohen, *J. Org. Chem.*, **20**, 1461 (1955).

(3) E. E. van Tamelen, P. E. Aldrich, and J. B. Hester, *J. Am. Chem. Soc.*, **79**, 4817 (1957).

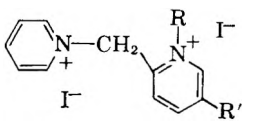
(4) A. R. Battersby and S. Cox, *Chem. & Ind. (London)*, 983 (1957). A. R. Battersby, R. Binks, D. Davidson, G. C. Davidson, and T. P. Edwards, *Chem. & Ind. (London)*, 982 (1957). A. R. Battersby, G. C. Davidson, and B. J. T. Harper, *Chem. & Ind. (London)*, 983 (1957).

(5) R. P. Evstigneeva, R. S. Livshits, M. S. Bainova, L. I. Zakharkin, and N. A. Preobrazhenskii, *J. Gen. Chem.*, **22**, 1467 (1952).

(6) M. Barash and J. M. Osbond, *Chem. & Ind. (London)*, 490 (1958).

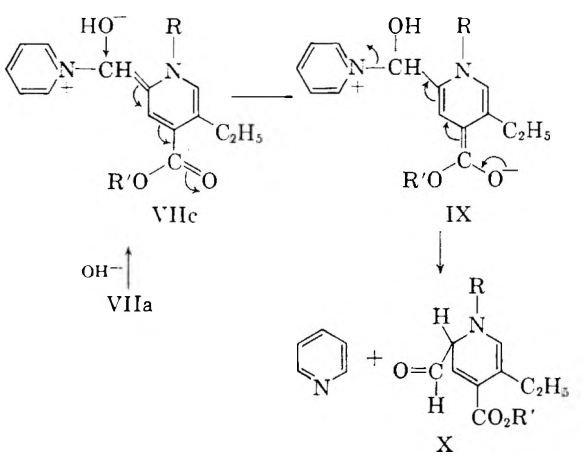
(7) A. R. Battersby and J. C. Turner, *Chem. & Ind. (London)*, 1324 (1958).

hydroxyl ion attacked VIIa and VIIb not at the desired position, C.2, which would have given pyridone, but at C.$\omega$, which resulted in displacement of pyridine. The previous pyridone syntheses[2a] had been carried out on double salts with the *N*-alkyl groups methyl or $\beta$-phenylethyl and without a substituent at C.4 of the pyridine nucleus. That the failures in the present cases were not caused by the use of a 3,4-dimethoxyphenylethyl group as the *N*-alkyl residue was established by the fact that the double salts (VIIIa and VIIIb) derived from *N*-$\beta$-(3,4-dimethoxyphenylethyl)-2-methylpyridinium bromide and *N*-$\beta$-(3,4-dimethoxyphenylethyl)-5-ethyl-2-methylpyridinium bromide, respectively, both gave pyridones in high yield.

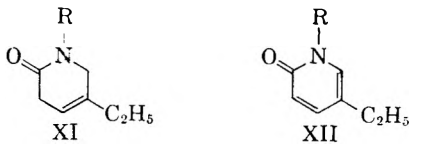


R = $\beta$-(3,4-dimethoxyphenylethyl)
VIIIa. R′ = H
b. R′ = $C_2H_5$

The difference in behavior of VIIa and VIIb compared to VIIIa and VIIIb is therefore presumably attributable to the ester or carboxyl function in the former salts. This is reasonable on the following grounds. In alkaline solution, the double salt is partially converted to the red anhydrobase. Attack of hydroxyl ion at C.2, leading to pyridone, most probably occurs on the double salt itself. An electron-withdrawing substituent like carbomethoxy at C.4 would increase the acidity of the methylene hydrogens, thus decreasing the amount of substrate in the double salt form, and also, would facilitate attack of hydroxyl ion at C.$\omega$ (see VIIa→VIIc→IX→X), leading to the undesirable side reaction that releases pyridine. The other product of such processes (X) would be expected to be unstable, and its transformation products may be the origin of the intractable tars observed.

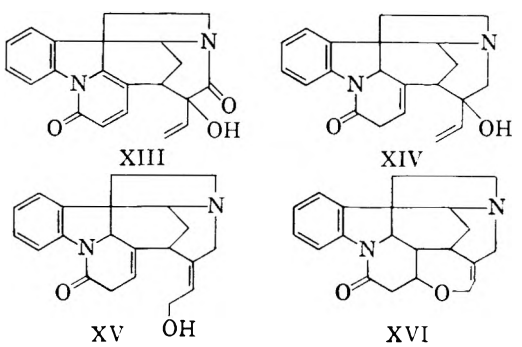


*Approach* (*ii*). Either the dihydropyridone IV or its $\beta,\gamma$-unsaturated isomer XI were the objectives of these experiments. Accordingly, we investigated the partial reduction of the readily available pyridone XII, obtained in 90% yield from the nicely crystalline double salt VIIIb.



R = $\beta$-(3,4-dimethoxyphenylethyl)

An attractive precedent for the reduction XII→XI existed in the reported[8] reduction of the pyridone XIII to the $\beta$-$\gamma$-unsaturated dihydropyridone XIV with lithium aluminum hydride. Further precedent was also available for the required

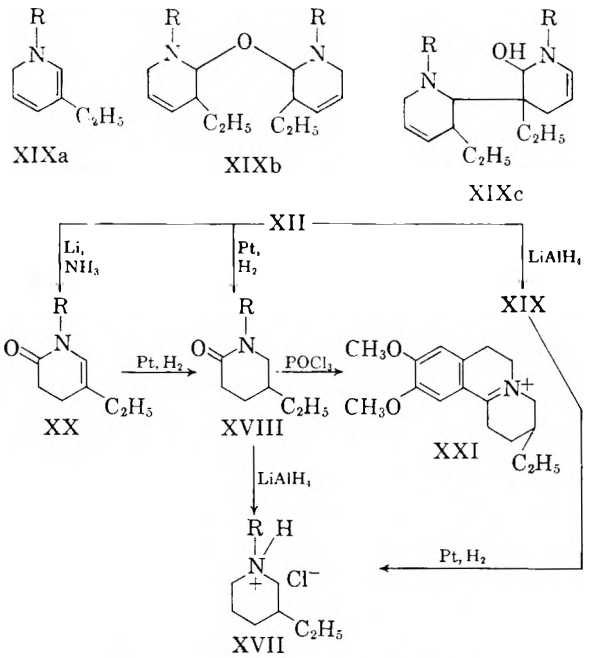


isomerization XI→IV in the cyclization of isostrychnine I (XV) to strychnine (XVI) under *alkaline* conditions.[8,9] However, lithium aluminum hydride reduction of XII gave undesirable results. In ether, the reaction was slow; starting material was recovered even after prolonged reaction periods. Even in refluxing tetrahydrofuran, complete reduction of XII required several hours. From this reaction, a new base was isolated in 27% yield as the crystalline, hygroscopic, chloroform-soluble hydrochloride XIX. The infrared spectra of the new base and of its hydrochloride showed no absorption in the lactam carbonyl region. The ultraviolet spectrum clearly demonstrated that the pyridone chromophore ($\lambda_{max}$ 312 m$\mu$) had been destroyed, since only the absorption ($\lambda_{max}$ 282 m$\mu$) associated with the 3,4-dimethoxyphenylethyl nucleus remained. The hydrochloride absorbed two moles of hydrogen over platinum to give a new hydrochloride (XVII), which was identical with the hydrochloride of a base obtained by catalytic hydrogenation (two moles) of the pyridone XII to the piperidone XVIII and lithium aluminum hydride reduction of the latter.

(8) R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. U. Daeniker, and K. Schenker, *J. Am. Chem. Soc.*, **76**, 4749 (1954). *Cf.*, R. B. Woodward, XIVth International Congress of Pure and Applied Chemistry, *Experientia Supplementum II*, Birkhauser Verlag, Basel, 1955, p. 213.

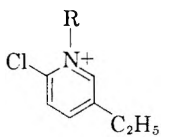
(9) V. Prelog, J. Battegay, and W. I. Taylor, *Helv. Chim. Acta*, **31**, 2244 (1948).

The elemental composition of the hydride reduction product XIX agreed best with the empirical formula $C_{17}H_{24}O_2NCl \cdot {}^1/_2\ H_2O$, although a formula with $C_3H_8O$ (from the isopropyl alcohol solvent) instead of ${}^1/_2\ H_2O$ was not completely excluded by the data. The former formula is consistent with structure XIXa for the free base,[10] and the dimeric formula, $C_{34}H_{50}O_5N_2Cl_2$, is consistent with that of the dihydrochlorides of the ether XIXb or the octahydrobipyridyl[10] XIXc. Regardless of which of these is correct, it is clear that the 1,6-addition observed in the change XIII→XIV did not occur, XIX being formed by formal 1,2-addition instead. The remainder of the reduction product was a mixture, a major component of which was probably the $\gamma,\delta$-unsaturated lactam XX.




With lithium, calcium, or sodium in liquid ammonia, XII was reduced to a mixture of the $\gamma,\delta$-unsaturated lactam XX and a crystalline phenolic unsaturated lactam. The empirical composition of the phenol corresponded to the next lower homologue of XX; this type of product is not unexpected, since monodemethylation of homoveratrylamine has been previously reported in a metal-ammonia reduction.[11] The phenol and the undemethylated product both consumed one mole of hydrogen over platinum. The ultraviolet ($\lambda_{max}$ 282 m$\mu$) and infrared ($\lambda_{max}$ 6.13 $\mu$) spectra of these substances demonstrated the destruction of the pyridone nucleus ($\lambda_{max}$ 282, 312 m$\mu$, 6.03 $\mu$) with retention of the homoveratryl nucleus and lactam function. The non-phenolic lactam XX gave upon catalytic hydrogenation the same piperidone (XVIII) that was obtained by catalytic hydrogenation of the pyridone XII.

Phosphorus oxychloride converted XVIII to the crystalline hexahydroquinolizinium salt XXI. It is of ancillary interest that the pyridone XII was converted by phosphorus oxychloride not to a quinolizinium salt but rather to the 2-chloropyridinium salt XXII. The latter was smoothly hydrolyzed to the pyridone XII by aqueous alkali. The failure of the Bischler-Napieralski cyclization has been noted previously with the analogue XII, R = $\beta$-phenylethyl.[2a] Apparently, even a




nucleus as reactive as $\beta$-(3,4-dimethoxyphenylethyl) can escape electrophilic attack under these conditions.

The assignment of the double bond of XX to the $\gamma,\delta$-position follows from the failure of the substance to react with sodiodiethylmalonate, potassium cyanide, or sodium bisulfite, reagents that would have been expected to add to the $\alpha,\beta$-unsaturated lactam IV. The remaining possible isomer, the $\beta,\gamma$-unsaturated lactam XI, would have been expected, under the basic conditions of the Michael addition, to isomerize to IV which would undergo condensation. Even treatment with lithium amide failed to produce any discernible change in the infrared spectrum of XX. Further, crude hydride and metal-ammonia reduction mixtures were subjected to vigorous Michael condensation conditions, using large excesses of malonic ester, and the products were scrutinized by chromatography and infrared analysis. In no case was there any evidence of adduct formation. Since IV has already been shown to give a Michael adduct with malonic ester in high yield,[7] it seems unlikely that our reduction mixtures contained appreciable amounts of IV. Metal-ammonia reduction, therefore, proceeded almost exclusively by formal 1,4-addition to give XX.

The results reported here demonstrate that partial reduction of pyridones can be achieved with lithium aluminum hydride or with metal-ammonia systems. The course of these reductions appears to be unpredictable at present.

(10) A referee has pointed out to us that A. G. Anderson and G. Berkelhammer, *J. Am. Chem. Soc.*, **80**, 992 (1958), have obtained a dihydropyridine from hydride reduction of a pyridone similar to XII. These authors also observed a dimeric product from acid treatment of 1-benzyl-3-acetyl-1,4-dihydropyridine.

(11) K. E. Hamlin and F. E. Fischer, *J. Am. Chem. Soc.*, **75**, 5119 (1953).

## EXPERIMENTAL[12]

*Preparation and hydrolysis of the double salts VIIa and VIIb.* A mixture of 4.80 g. of homoveratryl bromide and 3.58 g. of methyl 5-ethyl-2-methylpyridine-4-carboxylate[2b] (b.p. 95–96°/3 mm., picrate m.p. 115–116°, reported,[2b] picrate m.p. 114.2–115.5°) was heated on the steam bath for 2 days. The resulting viscous mass was dissolved in water and washed with ether to remove unreacted starting materials. Evaporation of the water left a thick glass, from which colorless crystalline material could be obtained by allowing an ethanol-ethyl acetate or pyridine solution to stand. The crystals (V) m.p. 253–256°, were extremely hygroscopic, and they liquified on exposure to moist air.

A mixture of 2.00 g. of the above salt and 1.41 g. of iodine in 25 ml. of pyridine was heated on the steam bath for 7 hr. After having been kept overnight at room temperature, the pyridine was removed *in vacuo*, and the residue was leached with several portions of warm water. The aqueous extract was washed with ether and evaporated leaving a thick glass which could not be induced to crystallize (VIIa).

The betaine VI was prepared by shaking a mixture of 1.00 g. of V in 10 ml. of water with freshly precipitated and washed moist silver oxide (from 2.38 g. of silver nitrate) until the supernatant liquor gave a negative test for bromide ion. The mixture was filtered through diatomaceous earth, the filtrate was treated with hydrogen sulfide (which gave no precipitate of silver sulfide), filtered again, and evaporated to dryness *in vacuo*. The resulting hygroscopic glass was readily soluble in water. The conjugate acid of VI, also a hygroscopic glass, was prepared by direct alkylation of 5-ethyl-2-methylpyridine-4-carboxylic acid with β-(3,4-dimethoxyphenylethyl)bromide.

A number of attempts to prepare crystalline double salts of the ester V, betaine VI and conjugate acid were carried out. Double salts were obtained in each case, as was indicated by the color reaction with alkali, but none could be induced to crystalline. The following experiment is typical.

A solution of 0.7764 g. of the conjugate acid of VI in 25 ml. of ice-cold pyridine was treated dropwise with a solution of 0.548 g. of iodine in pyridine during 20 min. The mixture was kept at room temperature for 1 hr., then heated briefly (3–4 min.) on the steam bath. At this point, the solution gave a negative test with starch-iodide paper. The pyridine was removed *in vacuo*, the residue was taken up in water, the aqueous solution was washed with ether (two 10-ml. portions) and the aqueous layer cooled and treated dropwise with cold 2*N* sodium hydroxide. Each drop of alkali produced a blood-red color which gradually faded. When further addition of alkali produced no more color, the solution was kept at room temperature for 2 hr. and then acidified with dilute hydrochloric acid. Evaporation of the solution left a salt residue which was leached with hot absolute ethanol. The ethanol solution was evaporated and the residue crystallized from isopropyl alcohol-hexane to give 0.247 g. of material of m.p. *ca.* 250–268° (dec.). A mixed m.p. with an authentic sample of pyridine hydroiodide (m.p. 255° dec.) was not depressed. The ultraviolet spectra of the two samples were identical. The *picrate* had m.p. 166–167° after recrystallization from ethanol. A mixed m.p. with an authentic sample of pyridine picrate, m.p. 165–166°, was undepressed. A mixed m.p. with β-(3,4-dimethoxyphenylethylamine) picrate, m.p. 165–166°, was depressed to 139–150°.

*Anal.* Calcd. for $C_{11}H_8N_4O_7$: C, 42.85; H, 2.60; N, 18.18. Found: C, 43.04; H, 2.60; N, 18.32.

The yield of pyridine hydroiodide was not decreased by repeated evaporation of the original pyridine reaction mixture with water or by exhaustive extraction of the aqueous solution with ether and chloroform before addition of alkali. This indicated that the pyridine isolated subsequent to the addition of alkali was a product of the hydrolysis of the double salt and not an artifact carried through from the original pyridine solvent. Similar results were obtained in experiments with VIIa. The crude reaction mixtures from several hydrolyses were free of absorption in the 6μ region.

*Preparation and hydrolysis of VIIIa and VIIIb.* A suspension of 1.69 g. of *N*-β-(3,4-dimethoxyphenylethyl)-2-methylpyridinium bromide (m.p. 179–181°, prepared in 85% yield from α-picoline and homoveratryl bromide) in 20 ml. of pyridine was treated dropwise with a solution of 1.29 g. of iodine in 20 ml. of pyridine while the reaction mixture was heated on the steam bath. After about 30 min., 2.40 g. of the double salt VIIIa had separated as pale pink crystals. This material was filtered off and hydrolyzed without further purification. A solution of the salt in 10 ml. of water was treated with dilute sodium hydroxide. A transient blood-red color was observed. When further addition of alkali produced no more color, the mixture was extracted with chloroform, the extract was dried, filtered, and evaporated. The residue was taken up in ether and washed with dilute hydrochloric acid to remove a little pyridine, dried, and evaporated. The residue, a black, viscous oil, was fractionally distilled in a Vigreux column to give 0.81 g. (69% based on VIIIa) of a pale yellow oil, b.p. 218–220°/3.5 mm., which crystallized upon standing at room temperature. After recrystallization from benzene-hexane, *N*-β-(*3,4-dimethoxyphenylethyl*)-*2-pyridone* was obtained as colorless needles m.p. 82–83°; the ultraviolet spectrum in ethanol showed $\lambda\lambda_{max}$ 286,303 mμ, log ε 3.84, 3.80, infrared maximum in chloroform at 6.02 μ.

*Anal.* Calcd. for $C_{15}H_{17}NO_3$: C, 69.50; H, 6.56; N, 5.41. Found: C, 69.36; H, 6.44; N, 5.32.

The *picrate*, m.p. 126–127°, was prepared in ether-ethanol and recrystallized from ethanol.

*Anal.* Calcd. for $C_{21}H_{20}O_{10}N_4$: C, 51.64; H, 4.10. Found: C, 51.50; H, 4.35.

Heating a mixture of homoveratryl bromide and 5-ethyl-2-methylpyridine gave the *quaternary bromide*, m.p. 153–156° (soft at 145°), after recrystallization from isopropyl alcohol.

*Anal.* Calcd. for $C_{16}H_{24}BrNO_2$: Br, 21.86. Found: Br, 21.80.

When 3.66 g. of the above bromide and 2.54 g. of iodine were heated in 15 ml. of pyridine for 3 hr., 4.3 g. of the double salt VIIIb were obtained. Recrystallization from aqueous ethanol gave faintly yellow plates, m.p. 210–210.5° with pre-darkening at 205°.

*Anal.* Calcd. for $C_{23}H_{28}O_2I_2N_2$: C, 44.64; H, 4.53; N, 4.53; I, 41.10. Found: C, 44.49; H, 4.41; N, 4.51; I, 41.26.

Hydrolysis of the double salt VIIIb was carried out as for VIIIa. Distillation gave 90% of *N*-β-(*3,4-dimethoxyphenylethyl*)-*5-ethyl-2-pyridone* (XII) as a viscous oil, b.p. 220–225°/3.5 mm., which crystallized slowly upon standing. Recrystallization from ether gave material of m.p. 57–58°; the ultraviolet spectrum in ethanol showed $\lambda\lambda_{max}$ 287, 313 mμ, log ε 3.77, 3.80; the infrared spectrum in chloroform showed $\lambda_{max}$ 6.02 μ.

*Anal.* Calcd. for $C_{17}H_{21}O_3N$: C, 71.08; H, 7.32; N, 4.88. Found: C, 70.97; H, 7.45; N, 4.85.

The *picrate*, prepared in ether-alcohol and recrystallized from ethyl acetate-hexane, had m.p. 99–100°.

*Anal.* Calcd. for $C_{23}H_{24}O_{10}N_4$: C, 53.52; H, 4.69; N, 10.66. Found: C, 53.57; H, 4.55; N, 10.63.

From a large scale preparation in which 106 g. of double salt gave 41 g. of XII, there was obtained as distillation fore-run 4.5 g. of a by-product, b.p. 95–97°/5 mm., which gave a picrate m.p. 161–162°.

*Reaction of* XII *with phosphorus oxychloride.* A solution of 2.75 g. of XII in 10 ml. of dry benzene was treated with a solution of 9 ml. of phosphorus oxychloride in 20 ml. of benzene and the mixture was boiled in a nitrogen atmosphere for 3 hr. The solvent and excess phosphorus oxy-

(12) Melting points are corrected. The microanalyses are by Dr. Adalbert Elek, Elek Microanalytical Laboratories, Los Angeles, 24, Calif., and by Truesdail Laboratories, Los Angeles, Calif.

chloride were removed *in vacuo* and the residue was taken up in water and treated with a saturated solution of potassium iodide. The resulting precipitate was recrystallized from aqueous alcohol to give XXII *iodide*, m.p. 194–195°; in ethanol, $\lambda_{max}$ 281 m$\mu$, log $\epsilon$ 3.87.

*Anal.* Calcd. for $C_{17}H_{21}O_2ClIN$: C, 47.05; H, 4.83. Found: C, 46.60; H, 4.77.

Heating this material with 10% aqueous sodium hydroxide regenerated XII.

*Conversion of* XII *to* XXI. Catalytic hydrogenation of XII was carried out over platinum oxide in methanol. Gas consumption ceased after 2.02 moles had been absorbed. The product, XVIII, was a colorless oil, whose infrared spectrum showed $\lambda_{max}$ 6.15 $\mu$.

Cyclization of 5.0 g. of XVIII was accomplished with phosphorus oxychloride in boiling benzene. Treatment with potassium iodide of an aqueous solution of the residue obtained by evaporation of the reaction mixture gave 6.0 g. of XXI *iodide*, m.p. 188–190°. Recrystallization from ethyl acetate-aqueous alcohol gave material of m.p. 195–196°. The ultraviolet spectrum in ethanol showed $\lambda\lambda_{max}$ 246, 302, 352 m$\mu$. log $\epsilon$ 4.23, 3.94, 3.99. A mixed m.p. with XXII iodide was depressed. Fifty milligrams of uncyclized XVIII were recovered from the reaction mixture by extraction with ether.

*Anal.* Calcd. for $C_{17}H_{24}O_2IN$: C, 50.88; H, 5.99; N, 3.49; I, 31.67. Found: C, 50.82; H, 6.11; N, 3.54; I, 31.63.

*Lithium aluminum hydride reduction of* XII *to* XIX. A solution of 12.0 g. of XII in 75 ml. of dry tetrahydrofuran (distilled from calcium hydride) was treated in portions with 2.00 g. of lithium aluminum hydride in tetrahydrofuran. The reaction mixture was boiled for 11 hr. and then evaporated, cooled, and treated with cold dilute hydrochloric acid. The mixture was repeatedly extracted with chloroform, the chloroform extract was dried with sodium sulfate and evaporated. The residue was treated with ether to give 3.50 g. of XIX, m.p. 163–165°, as a white precipitate. Recrystallization from isopropyl alcohol–ethyl acetate gave material of m.p. 169–170°. The infrared spectrum in chloroform showed no absorption on the 6.0–6.1 $\mu$ region. The ultraviolet spectrum in ethanol showed $\lambda_{max}$ 280 m$\mu$, log $\epsilon$ 3.51. The substance was readily soluble in water and its aqueous solution gave an immediate precipitate with silver nitrate. The crystals were hygroscopic.

*Anal.* Calcd. for $C_{17}H_{24}O_2NCl.{}^1/_2H_2O$: C, 64.13; H, 7.92; Cl, 11.10. Found: C, 64.20; H, 8.45; Cl, 10.76.

The free base was a colorless oil which also showed no absorption in the 6.0–6.1 $\mu$ region.

The non-crystalline portion of the chloroform extract (after separation of XIX) was chromatographed on alumina. A small amount of the free base of XIX was eluted from the column first with benzene, followed by a major fraction (1.64 g.) that appeared to be XX, since its infrared spectrum was identical with that of XX, it did not react with malonic ester in the presence of ethanolic sodium ethoxide, and it consumed 0.91 mole of hydrogen over palladium charcoal in absolute ethanol to give an oil whose infrared spectrum was identical with that of XVIII.

XVII. *A. By hydrogenation of* XIX. A solution of 0.206 g. of XIX in 20 ml. of absolute ethanol absorbed 16.0 ml. (2.13 moles) of hydrogen in 3.5 hr. over 10% palladium-on-charcoal, whereupon hydrogenation ceased. Evaporation of the solvent gave 0.200 g. of XVII, m.p. 186–187°. Recrystallization from isopropyl alcohol–ethyl acetate gave material of m.p. 187–187.5°, alone or mixed with a sample prepared by method B. A mixed m.p. with XIX was depressed. The salt was hygroscopic; it was dried to constant weight at 90° immediately before analysis.

*Anal.* Calcd. for $C_{17}H_{28}O_2ClN$: C, 65.05; H, 8.99; N, 4.48. Found: C, 65.00; H, 9.05; N, 4.50.

*B. By lithium aluminum hydride reduction of* XVIII. A solution of 0.50 g. of XVIII in 10 ml. of tetrahydrofuran was added during 7 min. to a stirred solution of 0.120 g. of lithium aluminum hydride in 10 ml. of tetrahydrofuran. Heat was evolved. The reaction mixture was boiled under reflux for 7 hr., evaporated, acidified with dilute hydrochloride acid, and extracted with chloroform. Evaporation of the chloroform left a residue which after recrystallization from isopropyl alcohol–ethyl acetate gave 0.50 g. of crystals, m.p. 187–188°, alone or mixed with a sample prepared by method A. The infrared spectra of chloroform solutions of the two samples were identical.

*Metal-ammonia reduction of* XII. A large number of experiments were carried out in which XII was reduced with varying atomic proportions of lithium, sodium, and calcium. A typical run was carried out as follows. A solution of 10 g. of XII in about 100 ml. of tetrahydrofuran was added slowly to a solution of 0.80 g. of lithium in about 20 ml. of liquid ammonia. The blue color was discharged in about 2 hr. The excess ammonia was evaporated and the residue was treated with dilute hydrochloric acid and extracted with chloroform. The chloroform extract was dried over sodium sulfate and evaporated, and the residue was distilled to give 6.0 g. of a viscous liquid, b.p. 210–215°/1.5 mm.

This material deposited crystals after standing several days. The mixture was triturated with ether to give 1.8 g. of a white crystalline product, m.p. 133–135°. The filtrate was evaporated to give 4.0 g. of a thick oil, $\lambda_{max}$ 280 m$\mu$, log $\epsilon$ 3.60, $\lambda_{max}$ 6.14 $\mu$. The oil consisted mainly of XX contaminated with about 25% of XII (as evidenced by weak absorption at 312 m$\mu$).

The crystalline material was recrystallized from ethyl acetate–ether to give material of m.p. 139.5–140°. It was phenolic, being insoluble in water or bicarbonate solution, but readily soluble in aqueous sodium hydroxide. Carbon dioxide precipitated it unchanged from alkaline solution. The substance showed a sharp O-H absorption in the infrared, and a sharp, strong lactam absorption at 6.15 m$\mu$. It gave a green-brown color with ferric chloride which was unstable to water. The ultraviolet spectrum had $\lambda_{max}$ 281.5 m$\mu$, log $\epsilon$ 3.53, and was completely blank at longer wave lengths. Catalytic hydrogenation over palladium-on-charcoal ceased after the absorption of 1.00 mole of gas.

*Anal.* Calcd. for $C_{16}H_{21}O_3N$: C, 69.82; H, 7.64; N, 5.10. Found: C, 69.81; H, 7.70; N, 5.21.

The yield of the crystalline phenolic product (isolated by alkali extraction) increased at the expense of the yield of XX when the amount of lithium was increased. A preparation of XX was re-distilled and submitted for analysis. This material contained 9% of XII as determined spectrophotometrically.

*Anal.* Calcd. for $C_{17}H_{23}O_3N$: C, 70.58; H, 7.95; N, 4.85. Found: C, 70.35; H, 7.73; N, 5.01.

This material had $\lambda_{max}$ 280 m$\mu$, log $\epsilon$ 3.61, $\lambda_{max}$ 6.14 $\mu$. Hydrogenation in ethanol over palladium-on-charcoal ceased after the consumption of 0.92 mole of gas. The product, identified by its infrared spectrum, was XVIII.

Attempts to add sodiomalonic ester, potassium cyanide, or sodium bisulfite to XX were fruitless. In each case, chromatography gave only starting material. None of the chromatographic fractions had infrared spectra (*e.g.*, both ester and lactam absorption) expected of an adduct.

*Acknowledgment.* We are indebted to Abbott Laboratories for financial support of part of this work.

LOS ANGELES 7, CALIF.

[CONTRIBUTION FROM THE ENTOMOLOGY RESEARCH DIVISION, AGRICULTURAL RESEARCH SERVICE, U. S. DEPARTMENT OF AGRICULTURE]

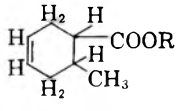
# *Cis-Trans* Isomers of 6-Methyl-3-cyclohexene-1-carboxylic Acid and Their *sec*-Butyl Esters

NATHAN GREEN AND MORTON BEROZA

*Received November 5, 1958*

Commercially produced *sec*-butyl 6-methyl-3-cyclohexene-1-carboxylate was less effective as a Mediterranean fruit fly lure than the laboratory-prepared compound. The difference in activity was traced to their *cis-trans* isomer content, the *trans* ester being much superior to the *cis* analog. In the laboratory the intermediate acid, which is prepared by a Diels-Alder condensation and is known to be the *trans* isomer, is converted to the ester *via* the acid chloride route. The *cis* acid was prepared and isolated in pure form for the first time by means of a partition chromatographic procedure, which also proved useful for determining the isomer content of acid mixtures. An isomer analysis of the *sec*-butyl ester depended on infrared spectroscopy. With the aid of the two analytical methods conditions affecting epimerization of the acid, acid chloride, and ester isomers were studied. Thus the acid was not epimerized by refluxing with 6*N* sulfuric acid or 1*N* alkali but epimerization did take place when the acid chloride was heated at 150° or when the ester was saponified. Epimerized solutions contained 50–62% of the *trans* isomer at equilibrium.

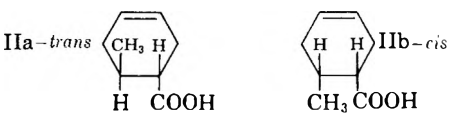
The recent successful eradication of the Mediterranean fruit fly [*Ceratitis capitata* (Wied.)] from Florida depended on traps baited with an attractant to delineate the infested areas. Angelica seed oil,[1] first used as the attractant, was replaced by a synthetic lure, the *sec*-butyl ester of 6-methyl-3-cyclohexene-1-carboxylic acid (Ia),[2] now known as siglure.



Ia. R = $-CH(CH_3)CH_2CH_3$
Ib. R = H

Commercially produced lots of the ester were consistently less attractive than those synthesized in the laboratory. The investigation of this problem shed much light on the chemistry of 6-methyl-3-cyclohexene-1-carboxylic acid (Ib) and its *sec*-butyl ester (Ia). *Cis-trans* isomerism was found to affect the attractiveness of the ester.

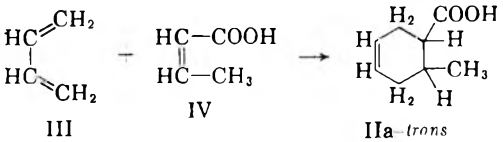
*Previous work.* Perkin[3] first prepared the free acid (Ib) from 4-hydroxy-*o*-toluic acid by a long, tedious procedure involving fractional esterification and hydrolysis. His final product was a liquid, and he made no attempt to separate the *cis* (IIb) and *trans* (IIa) isomers.



IIa-*trans* IIb-*cis*

Only the *cis* configuration of the double bond is possible in a six-membered ring; the *trans* configuration would give rise to too much strain.[4] This point was confirmed by the absence of a *trans* double-bond peak in the 10.3-$\mu$ region of the infrared spectra of the esters and acids of this study. A cyclohexene ring, which is not made rigid by ring fusion, can readily exist in two conformations which closely resemble the boat and chair (or "half-chair") forms.[5] X-ray data indicate that the half-chair form is the favored one and Barton, *et al.*[6] state that this conformation may exist in two interconvertible forms. In view of these investigations it is reasonable to assume that the compounds of this study exist mainly, if not entirely, as the half-chair conformation.

The Diels-Alder reaction provided a far simpler means of preparing the *trans* acid (IIa): Butadiene (III) is heated in a bomb with excess crotonic acid (IV) for 3 hours at 150–170°.[7]



III IV IIa-*trans*

According to the Alder rules,[8] the relative position of the substituents in the dienophile are retained in the adduct. Therefore, the product IIa of the foregoing reaction is *trans* because crotonic acid in *trans*. This fact was confirmed by hydrogenating the acid to the *trans*-2-methylcyclohexanecarboxylic acid, identified by its melting point and that of its amide.[7]

*Present Work.* Although the *trans* acid has been known for some time, we could find no report on the preparation or isolation of the *cis* isomer (IIb). We were able to isolate this acid by a partition-chromatographic method, which was also useful for the quantitative determination of the isomers.

(1) L. F. Steiner, D. H. Miyashita, and L. D. Christenson, *J. Econ. Entomol.*, **50**, 505 (1957).
(2) S. I. Gertler, L. F. Steiner, W. C. Mitchell, and W. F. Barthel, *J. Agr. Food Chem.*, **6**, 592 (1958).
(3) W. H. Perkin, Jr., *J. Chem. Soc.*, **99**, 741 (1911).
(4) F. Ebel, *Freudenberg's Stereochemie*, Franz Deuticke, Leipzig and Vienna, 1933, p. 650.
(5) M. S. Newman, "Steric Effects in Organic Chemistry," John Wiley & Sons, New York, 1956, p. 38.
(6) D. H. R. Barton, R. C. Cookson, W. Klyne, and C. W. Shopee, *Chem. & Ind. (London)*, 21, (1954), and references therein.
(7) O. Diels and K. Alder, *Ann.*, **470**, 88 (1929).
(8) M. C. Kloetzel, *Org. Reactions*, **4**, 10 (1948).

With slight modifications this method may be generally useful for the separation and determination of other *cis* and *trans* acids.

The pure *cis* acid is a liquid. Its identity was established by hydrogenation of the double bond to the known *cis*-2-methylcyclohexanecarboxylic acid. The melting point (151–153°) of the amide of this saturated acid agreed with that reported in the literature.

In laboratory preparations of the ester the *trans* acid (IIa) was treated with thionyl chloride to give the acid chloride, which was reacted with the alcohol to give the ester. Acid catalytic esterification of the *trans* acid gave low yields of product, probably due to dehydration of the alcohol. At first the acid chloride was prepared under reflux and was reacted with the alcohol without an acid acceptor. By the partition chromatographic method we were able to demonstrate that the *trans* acid was being changed partially to *cis* by this treatment. Thus, hydrolysis of the acid chloride, prepared from the *trans* acid under reflux, gave a product containing only 70% of the *trans* isomer. It was postulated that the acid may isomerize as a result of the hydrogen chloride being liberated in the formation of the acid chloride. Refluxing of the *trans* acid with 6*N* hydrochloric acid gave some substitution of hydrogen chloride onto the double bond of the ring, so that the results were not clear-cut. However, attempts to add dry hydrogen chloride to the *trans* acid directly or in a nonaqueous medium were unsuccessful, and it was noted that hydrogen chloride did not add appreciably to the double bond in the course of the thionyl chloride treatment. The fact that refluxing of the *trans* acid with 6*N* sulfuric acid caused no isomerization shows that heating with acidic reagents *per se* does not account for the conversion.

Additional experiments showed that epimerization of *trans*- and *cis*-rich acid chlorides could be effected thermally; isomerization took place after several hours of heating at 150° and 200° but not at 100°. When the acid chloride was prepared at room temperature, there was no epimerization.[9] In subsequent laboratory preparations of the ester the acid chloride was formed at room temperature and pyridine was included as an acid acceptor. Under these mild conditions little, if any, *cis-trans* isomerization took place.

We attempted to adapt the chromatographic procedure for determining the *cis* and *trans* contents of commercial lots of the ester, but saponification yielded isomerized acids. The free *trans* acid, oddly enough, did not isomerize even after prolonged heating with alkali. The method of Redemann and Lucas,[10] known to saponify refractory esters (*ca.* 125°), was ineffective in the saponification of the ester. Higher temperatures (obtained by refluxing with potassium hydroxide–diethylene glycol) were necessary to effect the conversion.

Other unsuccessful attempts to determine the isomer content of the ester included fractional distillation and gas chromatography.

The difficulty was finally overcome by employing infrared spectroscopy. In carbon disulfide solution the ester gives a *trans* peak at 14.26 $\mu$; the absorbance at 8.79 $\mu$, an isosbestic point, can be subtracted from that at 8.27 $\mu$ to give a measure of the *cis* content. Several acid mixtures of known *cis-trans* contents were esterified under mild conditions with *sec*-butyl alcohol and their spectra determined. By setting up calibration curves it was possible to get independent estimates of the two isomers, which generally were in good agreement.

These procedures enabled us to establish the relationship between *cis-trans* content and attractiveness to the Medfly. The all-*trans* product consistently outperformed products of lower *trans* content.[11] Commercial preparations were shown to contain only about 70% of the *trans* isomer, and thus their lesser activity was accounted for.

## EXPERIMENTAL

*trans-6-Methyl-3-cyclohexene-1-carboxylic acid* (IIa). The acid was prepared according to Diels and Alder.[7] It distilled at 132–142°/16 mm. and solidified in colorless crystals. After 3 crystallizations from aqueous methanol, it melted at 64–65° (lit. b.p. 144–145° *in vacuo*, m.p. 68°,[5] b.p. 240°[12]).

The previously unreported amide of IIa was prepared by allowing the acid to stand at room temperature overnight with a slight excess of thionyl chloride in benzene solution and then pouring the product into ice cold ammonia. It melted at 154.5–155.5° after crystallization from benzene-hexane.

*Anal.* Calcd. for $C_8H_{13}NO$: N, 10.06. Found: N, 9.69.

*The p-chlorophenacyl ester of* IIa was prepared in the usual manner.[13] It crystallized from ethanol as needles melting at 88–89°.

*Anal.* Calcd. for $C_{10}H_{17}ClO_3$: C, 65.64; H, 5.81. Found: C, 65.76; H, 6.00.

*The p-phenylphenacyl ester of* IIa was prepared in the usual manner,[13] m.p. 124–125° after recrystallization from ethanol.

*Anal.* Calcd. for $C_{22}H_{23}O_3$: C, 79.04; H, 6.59. Found: C, 78.75; H, 6.80.

*cis-6-Methyl-3-cyclohexene-1-carboxylic acid* (IIb). A commercial semiliquid acid (70% *trans*, 30% *cis*) was used for this preparation. The liquid portion was kept at −15° for several hours and filtered cold. The solid portion was mainly the *trans* isomer; it could be purified by several

(9) This experience parallels that reported by A. K. Macbeth, J. A. Mills, and D. H. Simmonds, *J. Chem. Soc.*, 1011 (1949), in their preparation of the anilide of *cis*-2-methylcyclohexane-1-carboxylic acid. They found that the acid was partially epimerized by refluxing with thionyl chloride but not by the cold reagent.

(10) C. E. Redemann and H. J. Lucas, *Ind. Eng. Chem., Anal. Ed.*, **9**, 521 (1937).

(11) L. F. Steiner, W. C. Mitchell, Nathan Green, and M. Beroza, *J. Econ. Entomol.*, **51**, 921 (1958).

(12) N. A. Chayanov and P. I. Grishin, *Colloid J. (U.S.S.R.)*, **3**, 461 (1937).

(13) R. L. Shriner and R. C. Fuson, *Systematic Identification of Organic Compounds*, 2nd ed., John Wiley and Sons, New York, 1940, p. 132.

crystallizations from petroleum ether. The liquid portion, which was found to contain 69% of the *cis* isomer, deposited no additional crystals even when solvents such as petroleum ether were added.

About 0.7 g. of the *cis*-rich fraction was chromatographed exactly as described later except that a 200-g. column was used. Yield of the *cis* isomer was about 0.5 g. Final purification was effected by distillation; b.p. 104–105°/0.6 mm.; $n_D^{25}$ = 1.4780. The compound would not crystallize even at Dry Ice temperatures.

*Anal.* Calcd. for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.92; H, 8.79.

*Hydrogenation.* Five g. (0.036 mole) of the crude *cis* acid absorbed 744 ml. (0.033 mole) of hydrogen to form *cis*-2-methylcyclohexanecarboxylic acid, also a liquid. Its amide, prepared as described in the next paragraph, deposited from aqueous methanol crystals melting at 151–152.5° (lit. 151–153°).[14] A mixed melting point using equal amounts of the *cis* and *trans* saturated amides was not depressed but fell between the two melting points.

*The amide of* IIb was prepared in the same manner as the amide of IIa; m.p. 122–124° after recrystallization from benzene-hexane.

*Anal.* Calcd. for $C_8H_{13}NO$: N, 10.06. Found: N, 9.66.

*The p-chlorophenacyl ester of* IIb was prepared in the usual manner,[13] m.p. 53.5–54° (ethanol).

*Anal.* Calcd. for $C_{16}H_{17}ClO_3$: C, 65.64; H, 5.81. Found: C, 65.34; H, 6.11.

*The p-phenylphenacyl ester of* IIb was prepared in the usual manner,[13] m.p. 90–91° (ethanol).

*Anal.* Calcd. for $C_{22}H_{23}O_3$: C, 79.04; H, 6.59. Found: C, 78.52; H, 6.50.

*Treatment of trans acid* (IIa) *with acidic reagents.* Fourteen g. of IIa was refluxed with 10 ml. of thionyl chloride for 2 hr.; water was cautiously added to the cooled mixture. Extraction of the acids with ether in the usual manner yielded a partially solid product which was shown by chromatography to contain 36% of the *cis* isomer.

Refluxing of the *trans* acid with 6*N* sulfuric acid failed to isomerize it. However, refluxing it with 6*N* hydrochloric acid for 4 hr. resulted in partial addition of hydrogen chloride to the double bond to give some 4- (or 5-)chloro-2-methylcyclohexanecarboxylic acid. The impure product distilled at 106–111°/0.4 mm. and melted at 50–65°.

*Treatment of trans acid* (IIa) *and ester with alkali.* Ten g. of the *trans* acid was refluxed with 100 ml. of an 8% solution of potassium hydroxide in diethylene glycol for 7 hr. After dilution with 10 volumes of water, the mixture was extracted several times with ether. The aqueous layer was acidified with 6*N* hydrochloric acid while the mixture was kept cool. Ether was added, and the organic layer was washed with water and saturated brine and then filtered through dry cotton. Evaporation of the ether and distillation of the residue (86°/0.7 mm.) gave a product which solidified immediately. The melting point, 62–64°, was undepressed in admixture with a sample of the untreated acid; practically no isomerization had occurred.

In another experiment 2.0 g. of the all-*trans* ester was saponified by refluxing for 2 hr. with 20 ml. of 1*N* potassium hydroxide in diethylene glycol. The mixture was worked up as outlined immediately above; the acid product distilled at 140°/4 mm. The isomer analysis (by partition chromatography) was 41% *cis* and 59% *trans*. A similar saponification of a 69% *cis*–31% *trans* ester gave an acid containing 55% *cis* and 45% *trans* isomers. In both cases epimerization had occurred upon saponification.

*Thermal isomerization of acid chlorides.* Although the isomers of 6-methyl-3-cyclohexene-1-carboxylic acid appear to be resistant to isomerization, their acid chlorides were readily epimerized by heating at 150–200°. Acid chlorides were prepared under mild conditions that avoid isomerization as described in the next section from acids of known *cis-trans* content, the excess thionyl chloride and benzene being evaporated as indicated. The undistilled acid chlorides were then heated with no solvent, as shown below, and the converted to their *sec*-butyl esters in order to analyze them for isomer content by the infrared method.

| Temperature, °C. | Duration of Heating, Hr. | Isomer Content, % Untreated Acid Chloride *cis* | Untreated Acid Chloride *trans* | Treated Acid Chloride *cis* | Treated Acid Chloride *trans* |
|---|---|---|---|---|---|
| 200 | 2.5 | 0 | 100 | 50 | 50 |
| 150 | 0.5 | 0 | 100 | 32 | 68 |
| | 1 | 0 | 100 | 36 | 64 |
| | 2 | 0 | 100 | 38 | 62 |
| | 0.5 | 66 | 34 | 47 | 53 |
| | 1 | 66 | 34 | 38 | 62 |
| | 2 | 66 | 34 | 38 | 62 |
| 100 | 1 | 0 | 100 | 0 | 100 |
| | 2 | 0 | 100 | 1 | 99 |

A sample of all-*trans* acid chloride that was refluxed for 2 hr. with 2 volumes of benzene was not isomerized.

*Preparation of esters to avoid isomerization.* The following procedure was sufficiently mild so that isomerization was avoided. To a solution of 420 mg. of *cis* acid (IIb) in 4 ml. of benzene was added 725 mg. (100% excess) of thionyl chloride, the temperature being kept below 28°. After the mixture had stood overnight at room temperature, the excess thionyl chloride and solvent were evaporated off below 50° at reduced pressure. To the cold product 500 mg. of pyridine mixed with an excess of *sec*-butyl alcohol was slowly added without allowing the temperature to rise above 30°. After the mixture had stood for 16 hr., it was taken up in ether, washed successively with water, dilute hydrochloric acid, sodium bicarbonate, and brine, and dried over sodium sulfate. After the solvent was removed, the product distilled at 112°/16 mm.; $n_D^{25}$ 1.4518.[15]

*Anal.* Calcd. for $C_{12}H_{20}O_2$: C, 73.43; H, 10.27. Found: C, 73.45; H, 9.85.

*Partition chromatography of cis and trans acids.* The immobile solvent was a solution of 1.5 g. of ethylenediamine and 50 mg. of bromthymol blue in 100 ml. of anhydrous methanol. The mobile solvent was prepared by equilibrating 1 l. of petroleum ether (b.p. 60–70°) with 25 ml. of 95% methanol. After the lower layer was rejected, the solvent was filtered through a cotton plug.

The column was prepared by mixing in a mortar 10 g. of silicic acid (Mallinckrodt's 100-mesh partition chromatographic grade dried overnight at 110°) with 11.5 ml. of immobile solvent to form a uniform free-flowing slurry; the latter was introduced into a glass column (400 mm. long, 21 mm. i.d.) fitted with a fritted disk at the bottom; the adsorbent was settled by tapping and applying gentle air pressure on the solvent in the usual manner. From 40 to 50 mg. of the acid sample was introduced in 1 ml. of the mobile solvent and washed into the adsorbent with three 1-ml. portions of solvent. The tube was then filled with solvent using a 250-ml. separatory funnel as a reservoir. The acids were visible on the column as yellow zones on a blue background. Twenty-five-ml. fractions were titrated with standardized 0.03*N* sodium ethoxide solution in ethanol. Titrations were conducted at the boiling point of the liquid after addition of 5 ml. of neutralized isopropanol containing a few drops of bromthymol blue solution in methanol. The *cis* acid is eluted between 150 and 290 ml. and the *trans* analog between 290 and 750 ml.

The foregoing procedure was set up for the quantitative determination of the acid isomers. For preparative purposes larger columns were employed.

(14) N. Zelinsky, *Ber.*, **41**, 2676 (1908).

(15) Constants of the corresponding *trans* ester have been reported by Gertler *et al.*[2] to be 113–114°/15 mm., $n_D^{25}$ = 1.4482.

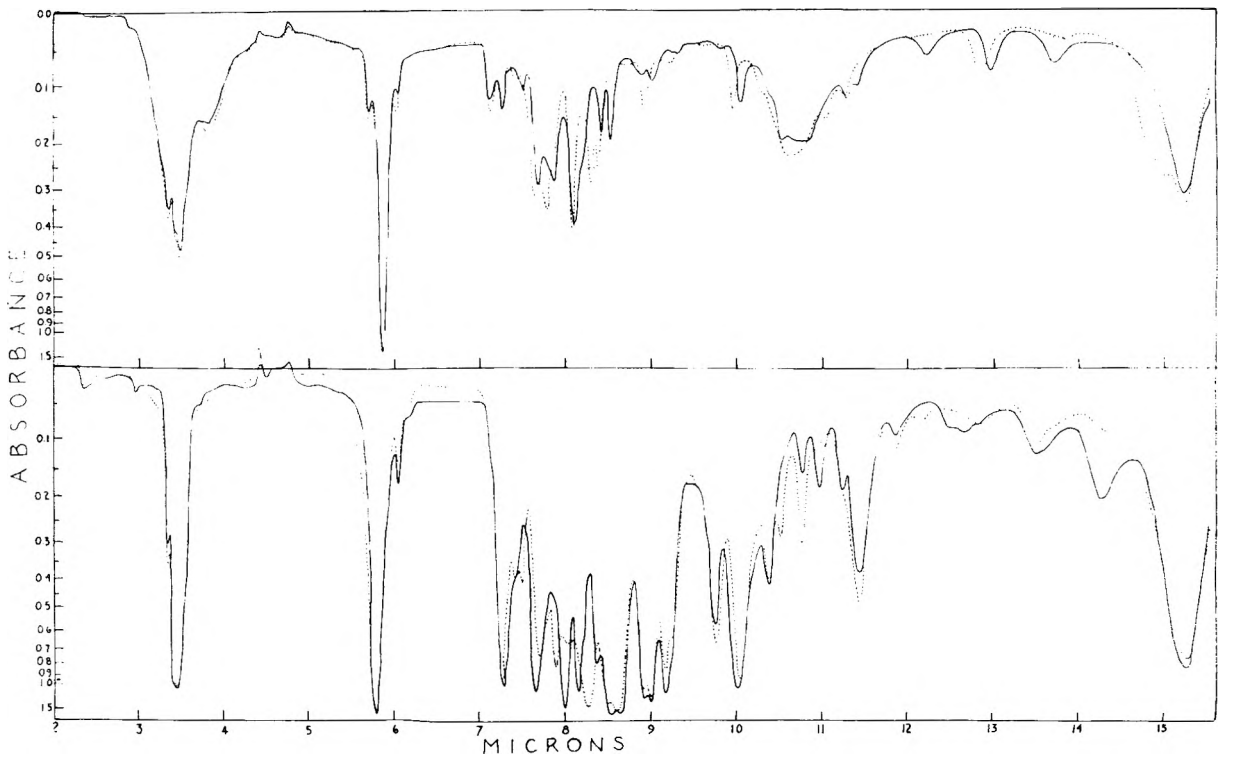



Fig. 1. Infrared spectra of 6-methyl-3-cyclohexene-1-carboxylic acid isomers (upper spectra) 10 mg./ml., and their sec-butyl esters (lower spectra) 50 mg./ml. in carbon disulfide. *Trans* isomers solid line, *cis* isomers broken line

*Determination of cis-trans content of the sec-butyl esters by infrared spectroscopy.* The infrared spectra of the acids and their *sec*-butyl esters are shown in Fig. 1. Two regions of the ester spectra exhibited absorbance differences that were adapted for analytical purposes. A *trans* peak appearing at 14.27 $\mu$ was measured by subtracting a background correction at 14.0 and 14.6 $\mu$. A measure of *cis* absorption was obtained by subtracting the absorbance at 8.79 $\mu$ (an isosbestic point) from that at 8.27 $\mu$. Several ester mixtures of known isomer content were prepared by careful esterification of known mixtures of the acid isomers and their spectra determined in the 2 regions. Although the absorbances did not follow Beer's law, this ideal was approached. Calibration curves made it possible to estimate isomer content, and in general the results obtained by the foregoing 2 procedures, which gave independent measures of *cis* and *trans* content, agreed within a few per cent.

*Acknowledgment.* The suggestion that *cis-trans* isomerism may affect the attractive properties of the ester was made by H. L. Haller, Agricultural Research Service, U. S. Department of Agriculture. We also acknowledge the assistance received from S. A. Hall, S. I. Gertler, W. F. Barthel, and B. H. Alexander of the Entomology Research Division during various phases of this problem. David Henley, student trainee, performed most of the chromatographic analyses reported here.

BELTSVILLE, MD.

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[CONTRIBUTION FROM THE LABORATORIES OF THE ORGANIC DIVISION OF THE CHEMISTRY DEPARTMENT AND PHARMACEUTICAL CHEMISTRY, COLLEGE OF PHARMACY, UNIVERSITY OF FLORIDA, GAINESVILLE, FLORIDA]

# Derivatives of Piperazine. XXXIV. Some Reactions of Trimethylene Chlorobromide with 1-Arylpiperazines

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The variety of pharmacological activities shown by piperazine derivatives led to the syntheses of 38 new compounds by the reactions of trimethylene chlorobromide with various 1-arylpiperazines and other amines. The 1-arylpiperazines required for these syntheses were prepared by the method of Pollard *et al.*[1,2]

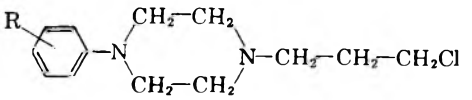
The compounds in Table I were prepared by the reaction of equimolar quantities of trimethylene

(1) C. B. Pollard and L. G. MacDowell, *J. Am. Chem. Soc.*, **56**, 2199 (1934).

(2) C. B. Pollard and T. H. Wicker, Jr., *J. Am. Chem. Soc.*, **76**, 1853 (1954).

TABLE I

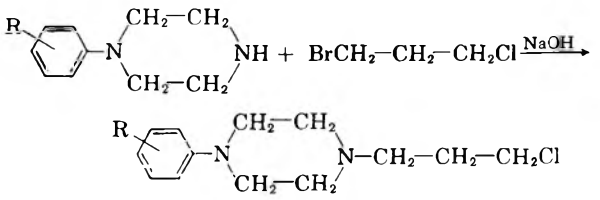
DATA CONCERNING COMPOUNDS HAVING THE GENERAL FORMULA



| R | Yield, % | B.P., Mm.[a] | $n_D^{25}$ | Empirical Formula | Analyses, % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | Nitrogen Calcd. | Nitrogen Found | Chlorine Calcd. | Chlorine Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| H | 53 | 132–138 0.5 | 1.5605 | $C_{13}H_{19}ClN_2$ | 65.39 | 65.55 | 8.02 | 8.19 | 11.73 | 11.92 | 14.85 | 14.70 |
| *o*-$CH_3$ | 43 | 143–151 1.2 | 1.5447 | $C_{14}H_{21}ClN_2$ | 66.52 | 66.60 | 8.37 | 8.19 | 11.08 | 10.85 | 14.03 | 14.42 |
| *m*-$CH_3$ | 46 | 152–159 0.8 | 1.5576 | $C_{14}H_{21}ClN_2$ | 66.52 | 66.84 | 8.37 | 8.03 | 11.08 | 11.10 | 14.03 | 14.25 |
| *p*-$CH_3$ | 40 | 148–150 0.5 | —[b] | $C_{14}H_{21}ClN_2$ | 66.52 | 66.59 | 8.37 | 8.37 | 11.08 | 10.81 | 14.03 | 13.91 |
| *o*-Cl | 66 | 151–154 0.8 | 1.5594 | $C_{13}H_{18}Cl_2N_2$ | 57.15 | 56.79 | 6.64 | 6.55 | 10.25 | 10.55 | 25.96 | 25.91 |
| *m*-Cl | 45 | 157–162 0.5 | 1.5715 | $C_{13}H_{18}Cl_2N_2$ | 57.15 | 56.92 | 6.64 | 6.49 | 10.25 | 10.45 | 25.96 | 26.36 |
| *p*-Cl | 47 | —[c] | — | $C_{13}H_{18}Cl_2N_2$ | 57.15 | 57.35 | 6.64 | 6.28 | 10.25 | 10.58 | 25.96 | 25.50 |

[a] All boiling points are uncorrected. [b] M.p. 35–36° (corr.). [c] M.p. 63–64° (corr.).

chlorobromide and the 1-arylpiperazine in the presence of sodium hydroxide.



The 1-(3-chloropropyl)-4-phenylpiperazine was previously prepared by Bach *et al.*[3] from the corresponding propanol and phosphorus pentachloride. These authors obtained a product with a boiling range of 146–150° at 0.1 mm.

Table II contains data concerning compounds prepared by either of two methods. The bis compounds were synthesized by the reaction of 1-arylpiperazines and trimethylene chlorobromide in the molar ratio 2:1, in the presence of sodium carbonate. The other compounds in this table were prepared by refluxing the 1-(3-chloropropyl)-4-arylpiperaiznes, shown in Table I, with the various 1-arylpiperazines, in the presence of sodium carbonate.

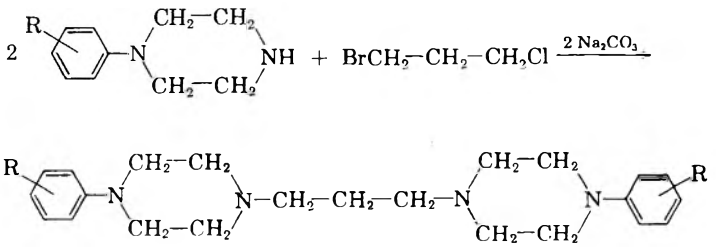
The compounds in Table III, with the exception of the carbazolyl derivative, were prepared by the reaction of the amine and 1-(3-chloropropyl)-4-phenylpiperazine in a molar ratio of 3:1. The carbazolyl compound was synthesized by first preparing the *N*-lithium salt of carbazole, by means of lithium amide in dimethylformamide,[4] and subsequent addition of 1-(3-chloropropyl)-4-phenylpiperazine.

All of the new compounds synthesized have been submitted for pharmacological testing.

## EXPERIMENTAL

*1-(3-Chloropropyl)-4-(3-tolyl)piperazine.* To a solution of 0.5 mole (88.1 g.) of 1-(3-tolyl)piperazine in 100 ml. of acetone was added 75 ml. of a 25% solution of sodium hydroxide. Trimethylene chlorobromide (0.55 mole, 86.6 g.) was added carefully to minimize its mixing with the aqueous layer. The mixture was stirred slowly for 8 hr. with a magnetic stirrer. The organic phase was then separated and the solvent removed under vacuum. Fractional distillation of the resulting oil yielded 57.8 g. (46%) of the product boiling at 152–159° (0.8 mm.).

*1,3-Bis[1-(4-phenyl)piperazinyl]propane.* A solution of 0.2 mole (32.4 g.) of 1-phenylpiperazine and 0.1 mole (15.7 g.) of trimethylene chlorobromide in 75 ml. of ethanol was stirred until the mixture became almost solid. It was then allowed to stand overnight and 200 ml. of a 30% sodium carbonate solution was added. The alcohol was removed by



distillation and the mixture refluxed for 16 hr. After cooling to room temperature, the resulting solid was filtered and air dried. Recrystallization from hexane yielded 10 g. (27%) of the product, m.p. 104.5–105°.

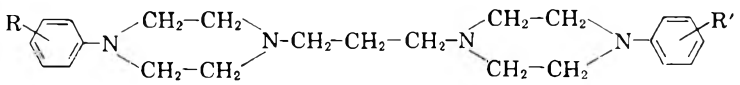
*1-[1-(4-Phenyl)piperazinyl]-3-{1-[4-(3-tolyl)]piperazinyl}-propane.* To 0.05 mole (12.6 g.) of 1-(3-chloropropyl)-4-(3-tolyl)piperazine was added 0.05 mole (8.1 g.) of 1-phenylpiperazine, 12 g. of sodium carbonate, and 40 ml. of water. The mixture was refluxed for 48 hr. and allowed to cool. The resulting solid was filtered and dried in vacuum. Recrystallization from hexane yielded 14.5 g. (77%) of the product, m.p. 70–72°.

(3) F. L. Bach, Jr., H. J. Brabander, and S. Kushner, *J. Am. Chem. Soc.*, **79**, 2221 (1957).

(4) R. F. Parcell, unpublished material.

TABLE II

DATA CONCERNING COMPOUNDS HAVING THE GENERAL FORMULA

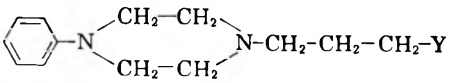


| R | R′ | Yield, % | M.P. (Corr.) | Empirical Formula | Analyses, % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | Nitrogen Calcd. | Nitrogen Found | Chlorine Calcd. | Chlorine Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| H | H | 27 | 104.5–105 | $C_{23}H_{32}N_4$ | 75.78 | 75.73 | 8.85 | 8.70 | 15.37 | 15.05 | — | — |
| H | *o*-$CH_3$ | 59 | 60.5–62 | $C_{24}H_{34}N_4$ | 76.15 | 75.75 | 9.05 | 8.87 | 14.80 | 14.84 | — | — |
| H | *m*-$CH_3$ | 77 | 70–72 | $C_{24}H_{34}N_4$ | 76.15 | 76.27 | 9.05 | 8.91 | 14.80 | 15.00 | — | — |
| H | *p*-$CH_3$ | 80 | 103–104 | $C_{24}H_{34}N_4$ | 76.15 | 76.02 | 9.05 | 9.05 | 14.80 | 14.95 | — | — |
| H | *o*-Cl | 63 | 69–71 | $C_{23}H_{31}ClN_4$ | 69.24 | 68.59 | 7.83 | 8.00 | 14.04 | 13.75 | 8.89 | 9.17 |
| H | *m*-Cl | 70 | 63–65.5 | $C_{23}H_{31}ClN_4$ | 69.24 | 69.15 | 7.83 | 7.73 | 14.04 | 13.73 | 8.89 | 8.79 |
| H | *p*-Cl | 66 | 119.5–120.5 | $C_{23}H_{31}ClN_4$ | 69.24 | 69.52 | 7.83 | 7.71 | 14.04 | 13.92 | 8.89 | 8.73 |
| *o*-$CH_3$ | *o*-$CH_3$ | 58 | —[a] | $C_{25}H_{36}N_4$ | 76.48 | 76.22 | 9.24 | 9.22 | 14.27 | 14.65 | — | — |
| *o*-$CH_3$ | *m*-$CH_3$ | 65 | —[b] | $C_{25}H_{36}N_4$ | 76.48 | 76.56 | 9.24 | 8.92 | 14.27 | 14.46 | — | — |
| *o*-$CH_3$ | *p*-$CH_3$ | 54 | 59–60.5 | $C_{25}H_{36}N_4$ | 76.48 | 76.52 | 9.24 | 9.25 | 14.27 | 14.15 | — | — |
| *o*-$CH_3$ | *o*-Cl | 52 | —[c] | $C_{24}H_{33}ClN_4$ | 69.79 | 69.93 | 8.05 | 7.90 | 13.57 | 13.74 | 8.59 | 8.43 |
| *o*-$CH_3$ | *m*-Cl | 53 | —[d] | $C_{24}H_{33}ClN_4$ | 69.79 | 69.86 | 8.05 | 8.06 | 13.57 | 13.85 | 8.59 | 8.42 |
| *o*-$CH_3$ | *p*-Cl | 74 | 85.5–86 | $C_{24}H_{33}ClN_4$ | 69.79 | 69.55 | 8.05 | 8.05 | 13.57 | 13.83 | 8.59 | 8.80 |
| *m*-$CH_3$ | *m*-$CH_3$ | 44 | 59–61 | $C_{25}H_{36}N_4$ | 76.48 | 76.24 | 9.24 | 9.21 | 14.27 | 14.34 | — | — |
| *m*-$CH_3$ | *p*-$CH_3$ | 62 | 61–63 | $C_{25}H_{36}N_4$ | 76.48 | 76.32 | 9.24 | 9.18 | 14.27 | 14.47 | — | — |
| *m*-$CH_3$ | *o*-Cl | 46 | —[e] | $C_{24}H_{33}ClN_4$ | 69.79 | 69.30 | 8.05 | 7.86 | 13.57 | 13.09 | 8.59 | 8.62 |
| *m*-$CH_3$ | *m*-Cl | 62 | 53–56 | $C_{24}H_{33}ClN_4$ | 69.79 | 69.74 | 8.05 | 7.68 | 13.57 | 13.64 | 8.59 | 8.44 |
| *m*-$CH_3$ | *p*-Cl | 85 | 88–90 | $C_{24}H_{33}ClN_4$ | 69.79 | 69.22 | 8.05 | 7.72 | 13.57 | 13.47 | 8.59 | 8.31 |
| *p*-$CH_3$ | *p*-$CH_3$ | 62 | 148–149 | $C_{25}H_{36}N_4$ | 76.48 | 76.69 | 9.24 | 9.20 | 14.27 | 14.17 | — | — |
| *p*-$CH_3$ | *o*-Cl | 72 | 76–77.5 | $C_{24}H_{33}ClN_4$ | 69.79 | 69.48 | 8.05 | 7.69 | 13.57 | 13.86 | 8.59 | 8.30 |
| *p*-$CH_3$ | *m*-Cl | 65 | 77–78 | $C_{24}H_{33}ClN_4$ | 69.79 | 69.79 | 8.05 | 8.04 | 13.57 | 13.55 | 8.59 | 8.87 |
| *p*-$CH_3$ | *p*-Cl | 70 | 157–158 | $C_{24}H_{33}ClN_4$ | 69.79 | 70.04 | 8.05 | 8.03 | 13.57 | 13.32 | 8.59 | 8.42 |
| *o*-Cl | *o*-Cl | 58 | 82–83 | $C_{23}H_{30}Cl_2N_4$ | 63.73 | 63.77 | 6.98 | 6.91 | 12.93 | 12.90 | 16.36 | 16.16 |
| *o*-Cl | *m*-Cl | 67 | —[f] | $C_{23}H_{30}Cl_2N_4$ | 63.73 | 63.26 | 6.98 | 6.91 | 12.93 | 13.01 | 16.36 | 16.64 |
| *o*-Cl | *p*-Cl | 74 | 75–76 | $C_{23}H_{30}Cl_2N_4$ | 63.73 | 63.62 | 6.98 | 6.52 | 12.93 | 12.93 | 16.36 | 16.72 |
| *m*-Cl | *m*-Cl | 34 | 69–70 | $C_{23}H_{30}Cl_2N_4$ | 63.73 | 63.66 | 6.98 | 7.13 | 12.93 | 12.81 | 16.36 | 16.09 |
| *m*-Cl | *p*-Cl | 63 | 84–86 | $C_{23}H_{30}Cl_2N_4$ | 63.73 | 63.15 | 6.98 | 7.07 | 12.93 | 12.95 | 16.36 | 16.75 |
| *p*-Cl | *p*-Cl | 85 | 172–173 | $C_{23}H_{30}Cl_2N_4$ | 63.73 | 63.78 | 6.98 | 6.70 | 12.93 | 12.84 | 16.36 | 16.28 |

[a] B.p. 236–240° at 0.3 mm. (uncorr.), $n_D^{25}$ 1.5707. [b] B.p. 246–250° at 0.6 mm. (uncorr.), $n_D^{25}$ 1.5779. [c] B.p. 248–252° at 0.7 mm. (uncorr.), $n_D^{25}$ 1.5805. [d] B.p. 258–263° at 0.75 mm. (uncorr.), $n_D^{25}$ 1.5879. [e] B.p. 260–262° at 0.7 mm. (uncorr.), $n_D^{25}$ 1.5875. [f] B.p. 286–292° at 1.1 mm. (uncorr.), $n_D^{25}$ 1.5977.

TABLE III

DATA CONCERNING COMPOUNDS HAVING THE GENERAL FORMULA



| Y | Yield, % | M.P. or B.P. (Mm.)[a] | $n_D^{25}$ | Empirical Formula | Analyses, % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | Nitrogen Calcd. | Nitrogen Found |
|---|---|---|---|---|---|---|---|---|---|---|
| $C_4H_{10}N$- (Diethylamino) | 44 | 164–169 (0.1) | 1.5330 | $C_{17}H_{29}N_3$ | 74.13 | 73.50 | 10.61 | 10.61 | 15.26 | 15.30 |
| $C_5H_{10}N$- (1-Piperidyl) | 20 | 148–150 (0.075) 46–47 | — | $C_{18}H_{29}N_3$ | 75.22 | 75.24 | 10.17 | 9.62 | 14.62 | 14.65 |
| $C_4H_8NO$- (4-Morpholinyl) | 52 | 170–172 (0.08) | 1.5513 | $C_{17}H_{27}N_3O$ | 70.55 | 69.92 | 9.41 | 9.52 | 14.52 | 14.42 |
| $C_{12}H_8N$- (9-Carbazolyl) | 32 | 130.5–131.5 | — | $C_{25}H_{27}N_3$ | 81.26 | 81.65 | 7.37 | 6.98 | 11.37 | 11.30 |

[a] All melting points are corrected, boiling points are not.

*1-[3-(Diethylamino)propyl]-4-phenylpiperazine.* To 0.1 mole (23.9 g.) of 1-(3-chloropropyl)-4-phenylpiperazine in 25 ml. of ethanol was added 0.3 mole (21.9 g.) of diethylamine. The mixture was refluxed for 8 hr., cooled, and the diethylamine hydrochloride filtered. After removal of the solvent and excess diethylamine under vacuum, the resulting oil was distilled. Fractional distillation yielded 12.2 g. (44%) of the product boiling at 164–169° (0.1 mm.).

*1-[3-(9-Carbazolyl)propyl]-4-phenylpiperazine.* A suspension of 0.1 mole (16.7 g.) of carbazole in 35 ml. of dimethylformamide was vigorously stirred while 0.105 mole (2.4 g.) of lithium amide was added. The addition caused the temperature to rise to 60°. When the temperature began to fall, heating was started. The mixture was maintained at 80–90° for 30 min., while partial vacuum was applied. When the mixture had cooled to 65°, 0.11 mole (26.3 g.) of 1-(3-

chloropropyl)-4-phenylpiperazine was added. Heating was resumed and the temperature was kept at 100–110° for 3 hr. After the mixture had cooled to 60°, it was poured, with stirring, into 600 ml. of ice and water. The solid was filtered, triturated with 100 ml. of water, and then dried under vacuum. Recrystallization from ethanol yielded 11.9 g. (32%) of the product, m.p. 130.5–131.5°.

The lithium amide was obtained from the Lithium Corp. of America and the trimethylene chlorobromide from the Dow Chemical Co. The amines were purchased from the Fisher Scientific Co. and were used without further purification.

GAINESVILLE, FLA.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, KANSAS STATE UNIVERSITY]

# The $pK_a$'s of Aromatic Sulfinic Acids[1]

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*Received July 25, 1958*

The $pK_a$'s of six aromatic sulfinic acids have been determined by means of potentiometric titration and found to be in the vicinity of 1.8 to 2.0.

During the course of research in the laboratory of the first author, the occasion arose to determine the neutral equivalent of *p*-nitrobenzenesulfinic acid.[3] The results from this determination not only yielded the desired neutral equivalent but also indicated that the acidic group being titrated was weaker than benzenesulfinic acid.[4–7] This observation suggested that the ionization constants of aromatic sulfinic acids be reinvestigated and accordingly such a program was undertaken.

Six aromatic sulfinic acids were selected for this study: benzene-, *p*-toluene-, *p*-chlorobenzene-, *p*-bromobenzene, *m*- and *p*-nitrobenzenesulfinic acids. Each of these was prepared from the corresponding sulfonyl chloride by reduction. The identity and purity of each compound was established by means of melting point and neutral equivalent determinations (Table I).

TABLE I

MELTING POINTS AND NEUTRAL EQUIVALENTS OF SULFINIC ACIDS

| Sulfinic Acid | M.P., °C. Obsd. | M.P., °C. Lit. | Neut. Equiv. Obsd. | Neut. Equiv. Theor. |
|---|---|---|---|---|
| Benzene | 81.5–83 | 84[7]<br>85[8,9] | 144.6 | 142.2 |
| *p*-Toluene | 84–85 | 84[10]<br>84–85[11]<br>86–87[8,9,12] | 160.1 | 156.2 |
| *p*-Chlorobenzene | 98.5–99.5 | 93–94[13]<br>98–99[10]<br>99[14]<br>100–102[15] | 179.7 | 176.7 |
| *p*-Bromobenzene | 113–114 | 114[10]<br>114–115[13]<br>115[16] | 229.8 | 221.1 |
| *m*-Nitrobenzene | 94.5–96 | 95–96[17]<br>98[18] | 190.4 | 187.2 |
| *p*-Nitrobenzene | s. 125<br>m. 152–154 | s. 136[19,20]<br>m. 159[19]<br>160[20]<br>120[21,22] | 195.5 | 187.2 |

(1) Supported in part by the Faculty Research Fund, Kansas State University and National Science Foundation Grant No. P-2670.

As a means of comparing the values obtained for benzenesulfinic acid with the values reported earlier in the literature two methods of sample preparation (A and B) were used. In method A the samples were dried *in vacuo* prior to use, while in method B the samples were used immediately after preparation. The $pK_a$'s and other data related to the potentiometric titrations are given in Table II.

With the exception of the value of 1.29 which Rumpf and Sadet report[7] for benzesulfinic acid there is reasonable agreement among the values reported in Table II and the earlier literature. Loven, for example, has reported that the dissociation

(2) Present address, Department of Chemistry, Southern Illinois University, Carbondale, Ill.

(3) Unpublished data taken by Harry A. Smith, deceased.

(4) J. M. Loven, *Z. Physik. chem.*, **19**, 456 (1896).
(5) R. R. Coats and D. T. Gibson, *J. Chem. Soc.*, 442 (1940).
(6) P. Rumpf and J. Sadet, *Bull. soc. chim. France*, 447 (1958).
(7) L. F. Fieser and M. Fieser, *Organic Chemistry*, 3rd ed., D. C. Heath and Co., New York, N. Y., 1956, p. 593.
(8) J. Thomas, *J. Chem. Soc.*, 342 (1909).
(9) S. Krishna and H. Singh, *J. Am. Chem. Soc.*, **50**, 795 (1928).
(10) E. Knoevenagle and J. Kenner, *Ber.*, **41**, 3315 (1908).
(11) S. Smiles and R. LeRossignol, *J. Chem. Soc.*, 745 (1908).
(12) P. K. Dutt, H. R. Whithead, and A. Wormall, *J. Chem. Soc.*, 2088 (1921).
(13) L. Gatterman, *Ber.*, **32**, 1136 (1899).
(14) M. E. Hanke, *J. Am. Chem. Soc.*, **45**, 1321 (1923).
(15) W. Davis and E. S. Wood, *J. Chem. Soc.*, 1122 (1928).
(16) R. F. Twist and S. Smiles, *J. Chem. Soc.*, 1252 (1925).
(17) B. Flurschein, *J. prakt. Chem.*, [2], **71**, 527 (1905).
(18) H. Limpricht, *Ann.*, **278**, 239 (1894).
(19) T. Zincke and S. Lenhardt, *Ann.*, **400**, 2 (1913).
(20) P. R. Carter and D. H. Hey, *J. Chem. Soc.*, 147 (1948).
(21) H. Limpricht, *Ber.*, **20**, 1238 (1887).
(22) M. S. Kharasch and L. Chalkley, *J. Am. Chem. Soc.*, **43**, 612 (1921).

TABLE II

$pK_a$'s FOR SULFINIC ACIDS (25°)

| Sulfinic Acid | Method of Sample Prep. | No. of Titrations | Mean $pK_a$ (Corr.) | Ave. Dev. |
|---|---|---|---|---|
| Benzene | A | 2 | 1.84 | 0.07 |
| | B | 2 | 2.16 | 0.05 |
| *p*-Toluene | A | 2 | 1.99 | 0.04 |
| *p*-Bromobenzene | A | 2 | 1.89 | 0.09 |
| *p*-Chlorobenzene | A | 2 | 1.81 | 0.01 |
| *m*-Nitrobenzene | A | 3 | 1.88 | 0.07 |
| *p*-Nitrobenzene | A | 5 | 1.86 | 0.08 |

constants for benzene- and *p*-toluenesulfinic acids are $3.5 \times 10^{-2}$ and $2.5 \times 10^{-2}$, respectively.[4] Coats and Gibson have recalulated Loven's data to obtain very similar values and have also reported that the dissociation constant for *o*-toluenesulfinic acid is near $3.4 \times 10^{-2}$.[5] Fieser and Fieser state that the $pK_a$ for benzenesulfinic acid is 1.80.[6]

It should be pointed out that two methods have been used for the determinations reported previously in the literature. Loven (and presumably Coats and Gibson) performed conductance experiments on freshly prepared samples of sulfinic acids. Rumpf and Sadet, in contrast, performed potentiometric titrations on dried samples of benzenesulfinic acid and its sodium salt. Since this latter method was also used by the authors of this paper it is quite surprising to find such great disagreement. The reasons for this are not apparent. However, from the brief description of the experimental procedure employed by Rumpf and Sadet it seems likely that there could have been appreciable differences between the two titration procedures.

A likely source of error in either type of measurement arises from the instability of sulfinic acids. Due to oxidation varying amounts of sulfonic acid might contaminate a solution of sulfinic acid. Loven used freshly prepared samples of sulfinic acid in order to minimize this source of error. Rumpf and Sadet, on the other hand, used dried samples. In this paper both types of samples were used in the case of benzenesulfinic acid and it was found that the $pK_a$ for the freshly prepared acid was slightly higher than for the dried acid. This difference could have been caused by oxidation of the sulfinic acid during drying and suggests that the true $pK_a$'s for sulfinic acids are probably higher than reported.

## EXPERIMENTAL

*Preparation of sulfinic acids.* Each sulfinic acid was prepared from the corresponding sulfonyl chloride by zinc or sodium sulfite reduction.[23-26]

*Sample preparation and titration.* Two methods of sample preparation (A and B) were used. In method A the sample of sulfinic acid was dried *in vacuo* over Drierite after recrystallization. Then a weighed, dry sample of acid was added to water, heated briefly on a steam cone to affect solution, cooled, and made up to volume. Aliquots of this solution were then titrated with standardized sodium hydroxide by use of a microburet and a Model H-2 Beckman *p*H meter.

Method B was patterned after that of Loven in that the acid was isolated and then recrystallized once from boiling water as rapidly as possible. An unweighed, wet sample of the acid was then placed in a titration vessel containing a known volume of water and titrated with standardized NaOH by use of a microburet and a Model G Beckman *p*H meter equipped with external electrodes.

In both methods the water which was used had previously been boiled and gassed with nitrogen during cooling. Also in both cases nitrogen was bubbled through each titration vessel during titration in order to exclude oxygen and affect stirring. The temperature of each titration vessel was maintained at 25° by use of a constant temperature bath. Each *p*H meter was standardized before use by checking against buffers of known *p*H. The author who used method A determined the end point of each titration by the parallelogram method. The authors who used method B determined each end point by plotting $\Delta pH/\Delta V$ versus V.

*Evaluation of $pK_a$.* The calculation of the $pK_a$ for each acid was achieved by the use of an IBM 650 computer. A program was devised[27] by which the data for each experimental point (up to the equivalence point) of a titration curve could be fed into the computer and from these data calculate a $pK_a$ for each experimental point and a mean $pK_a$ for each titration. The equations which the computer solved are derived below.

A solution of an acid (HA) when being titrated contains at at any point $i$ (up to the equivalence point) the species $H^+$, $A^-$, and HA whose concentrations at point $i$ can be expressed as follows: $[H^+]_i$ equals the concentration of the hydrogen ion due to ionization of the untitrated acid; the total concentration of $A^-$ equals that formed by titration, $[A^-]_i$, plus that formed by ionization of the untitrated acid, $[H^+]_i$; the total concentration of HA equals the untitrated acid, $[HA]_i$, minus that lost due to ionization, $[H^+]_i$. Thus at any point $i$ on a titration curve the ionization constant for HA (using concentration terms) can be given by Equation 1.

$$k_i = \frac{[H^+]_i \{[A^-]_i + [H^+]_i\}}{[HA]_i - [H^+]_i} \qquad (1)$$

Each of the quantities in Equation 1 can be expressed in terms of data taken during titration:

$$[H^+]_i = 10^{-x_i}$$

$$[A^-]_i = \frac{V_i N}{V_0 + V_i}$$

$$[HA]_i = \frac{(V_f - V_i)N}{V_0 + V_i}$$

where $x_i$ is the *p*H at point $i$, $N$ is the normality of the base used to titrate HA, $V_0$ is the volume of water used to dissolve the sample of sulfinic acid, $V_i$ is the volume of base added up to point $i$, and $V_f$ is the volume of base needed to reach the equivalence point.

(23) F. Ullman and G. Pasder Jadjian, *Ber.*, **34**, 1151 (1901).

(24) S. Smiles and C. Bere, *Org. Syntheses*, Coll. Vol. I, 7 (1946).

(25) F. C. Whitmore and F. H. Hamilton, *Org. Syntheses*, Coll. Vol. I, 492 (1946).

(26) M. Kulka, *J. Am. Chem. Soc.*, **72**, 1215 (1950).

(27) The authors are indebted to Mr. Thomas L. Hamilton of the IBM-650 Computer Center, Kansas State University for devising the program used to solve for $pK_a$.

Making these substitutions into Equation 1, one can obtain Equation 2 from which $k_i$ can be calculated at point $i$ on the titration curve (up to the equivalence point).

$$k_i = \frac{10^{-x_i}\left\{\frac{V_iN}{V_o + V_i} + 10^{-x_i}\right\}}{\frac{(V_f - V_i)N}{V_o + V_i} - 10^{-xi}} \qquad (2)$$

While Equation 2 corrects for the ionization of the untitrated acid and the volume change at each point on the titration curve, it does not correct for ionic strength. Accordingly, a correction term was then derived from the limiting equation of Debye and Huckel for the mean activity coefficients of strong electrolytes. The use of this limiting equation was considered valid since the ionic strengths involved were all in the vicinity of 0.01.

The correction which should be applied to any experimental $pK_i$ is equal to $-2 \log f_i$ where $f_i$ is the mean activity coefficient at point $i$. At 25° this correction is equal to $1.011 (u_i)^{\frac{1}{2}}$, where $u_i$ is the ionic strength at that point and is given by the equation

$$u_i = \frac{1}{2}\{[H^+]_i + [A^-]_i + [Na^+]_i\}$$

Using the symbols introduced above, $u_i$ can be expressed by Equation 3.

$$u_i = \left\{10^{-x_i} + \frac{V_iN}{V_o + V_i}\right\} \qquad (3)$$

Thus by use of Equations 2 and 3 it is possible to calculate a corrected $pK_a$ for each point on the titration curve (up to the equivalence point) and hence a mean corrected $pK_a$ for each titration.

Calculation by computer was deemed necessary since the denominator of Equation 1 may become very small because the solubilities of the sulfinic acids are limited and their extends of ionization are appreciable. With the aid of the computer, the $pK_a$'s were conveniently calculated from a sufficient number of points to permit statistical treatment.

It should further be pointed out that near the equivalence point the first term in the denominator of Equation 2 becomes very small. Experimental data on the steeply rising portion of the titration curve close to the end point were generally found to be less reliable than those on the more horizontal portion. Accordingly, experimental points in this region were not analyzed by the computer. The number of experimental points analyzed in each titration averaged 22, but ranged from a low of 12 to a high of 58 depending on the sample size and the experimentor.

MANHATTAN, KAN.

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[CONTRIBUTION FROM THE METCALF CHEMICAL LABORATORIES OF BROWN UNIVERSITY]

# Polyol Complexes and Structure of the Benzeneboronate Ion

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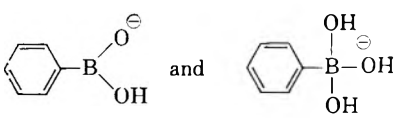
*Received September 11, 1958*

The complexing equilibria of aqueous benzeneboronate ion with several polyols have been studied and the measured constants compared with those of borate. The results indicate that the anion has the formula $C_6H_5B(OH)_3^-$ with tetrahedral coordination about boron; this is consistent with a steric effect, previously cited, on the acid-base equilibria of *ortho* substituted benzeneboronic acids. Examination of the data on complexing equilibria requires modification of an earlier assumption that only anionic complexes are formed.

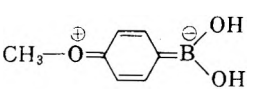
Following the recent elucidation of the structure of the borate ion in aqueous medium,[2] a study of the structure of aqueous benzeneboronate has been made, using quite different methods. Borate was previously thought to be either a trigonal Brönsted base form, $H_2BO_3^-$, or a tetrahedral Lewis acid-base adduct, $B(OH)_4^-$. The present case, likewise, offered a choice between




for the anion of benzeneboronic acid, $C_6H_5B(OH)_2$. The borate ion was studied by infrared and Raman spectroscopy, its behavior being found analogous to fluoborate, $BF_4^-$, because of the symmetry about boron. Such evidence was believed inapplicable to benzeneboronate because of the loss of symmetry and larger number of spectral bands.

Three different methods of attack were, however, available. The first two will be mentioned briefly, since the first proved inconclusive and the second has been previously cited. It was the third method for which complexing equilibria were experimentally studied.

Method A consisted of comparing *meta* and *para* substituted benzeneboronic acids[3] with benzoic acids[4] through their acid dissociation constants, using a plot of $pK_a$ for $X\text{-}C_6H_4B(OH)_2$ *vs.* Hammett's $\sigma$ values. It was thought that, if the tetrahedral form prdeominated, a curvature might be observed at negative values because of the presence of a resonance form,




(1) Taken from the Sc.B. thesis of John P. Lorand at Brown University (1958).

(2) J. O. Edwards, G. C. Morrison, V. Ross, and J. W. Schultz, *J. Am. Chem. Soc.*, **77**, 266 (1955).

(3) C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell Univ. Press, Ithaca, N. Y. (1953), Chapter XIII, pp. 738, 741, 750.

(4) J. Hine, *Physical Organic Chemistry*, McGraw-Hill, New York (1956), pp. 72.

possible for a triangular boron but not for the tetrahedral anion. Although a straight line is, in fact, obtained, suggesting the trigonal form, the reasoning involved is admittedly tenuous and the conclusions conflicts with those of the other methods.

Method B depends upon detection of a rather strong steric effect on the acidity of *ortho* substituted benzeneboronic acids. McDaniel and Brown[5] have shown that *ortho* substituents inhibit the acidity of benzeneboronic acids, by comparison with substituted pyridines. Interpretation of the result as a steric effect leads to postulation of the tetrahedral structure; the trigonal form does not adequately account for the observed inhibition of the acidic function by substituents. Comparison of *ortho* substituted benzeneboronic acids with the corresponding benzoic acids yields the same result. Table I[6] lists the ratio, "o/p", of $K_a$ for *ortho* substituted isomers in both series. Although the trigonal form would require that "o/p" be roughly the same for a given substituent in both series, the ratio is invariably smaller in the benzeneboronic acids. A steric effect is again implied, supporting the bulky tetrahedral structure for the benzeneboronate anion.

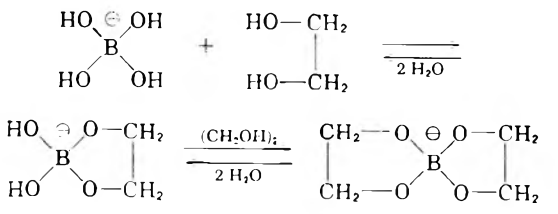
TABLE I

IONIZATION CONSTANTS OF SUBSTITUTED ACIDS

| Acid | Substituent | $K_a$ (*para*) | $K_a$ (*ortho*) | "*o/p*" |
|---|---|---|---|---|
| Benzoic[a] | $OCH_3$ | $3.38 \times 10^{-5}$ | $8.06 \times 10^{-5}$ | 2.38 |
| | $CH_3$ | 4.24 | 12.3 | 2.90 |
| | H | 6.27 | 6.27 | 8 |
| | Cl | 10.5 | 114. | 10.8 |
| | $NO_2$ | 37.0 | 671. | 18. |
| Benzeneboronic[b] | $OC_2H_5$ | $0.608 \times 10^{-10}$ | $0.91 \times 10^{-10}$ | 1.50 |
| | $CH_3$ | 1.0 | 0.261 | 0.26 |
| | H | 1.97 | 1.97 | 8 |
| | Cl | 6.30 | 14.0 | 2.22 |
| | $NO_2$ | 98. | 5.6 | 0.057 |

[a] In water at 25° [b] In 25% ethanol at 25°.

Method C involved measurements of equilibrium constants for formation of complexes between benzeneboronate ions and several organic polyhydroxy compounds, constants which had been measured for borate. Examples of such complexes

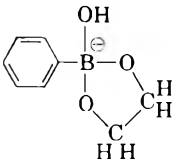


1:1 complex, I 2:1 complex, II

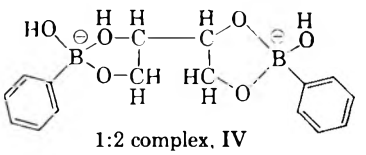
(5) D. H. McDaniel and H. C. Brown, *J. Am. Chem. Soc.*, **77**, 3756 (1955).

(6) Compiled from the data of Branch and Dippy; see ref. 3.

are shown by the equations and structures I and II for the borates and III and IV for the phenylboronates. Formation of such complexes is well



III



1:2 complex, IV

established, several having been isolated;[7,8] it is known that, at least in dilute solution, only anionic complexes are formed to a detectable extent;[9] and a simple method is available for measuring their formation constants.

Clearly, only the tetrahedral form of benzeneboronate ion has enough hydroxyl groups to form a complex. If, then, the tetrahedral form predominates, formation constants should be of the same order of magnitude as those of borate. If the constants were considerably smaller, it could be argued that the measured constants represent the product of the real constant for the tetrahedral form and a hydration constant for the trigonal form, which would then be seen as predominating.

For fourteen polyols (including 1,2- and 1,3-glycols and several sugars and derivatives), complex formation constants were calculated using the method of *p*H depression. The *p*H of a benzeneboronate–benzeneboronic acid buffer changes when a polyol is added, *i.e.*, the acid-base equilibrium shifts when some of the anion is removed by complex formation. This *p*H change, $\Delta p$H, is related, as shown in the appendix, to the formation constant, $K_c$, and equilibrium polyol concentration, $[P]_f$, by the Expression 1 which is more compact and

$$K_c = \frac{10^{-\Delta pH} - 1}{[P]_f} \qquad (1)$$

direct than that previously employed.[9] It is subject to the condition that the acid and base forms are in equal concentrations initially, and to the assumption that the concentration of acid form remains constant.

In addition to the measurement of formation constants in benzeneboronate systems, certain experiments in the borate series which gave data either anomalous or inconclusive were repeated; two polyols are introduced which had not been measured. Symbols, definitions, assumptions, and derivations are all presented in the Appendix.

## EXPERIMENTAL

*Reagents.* Polyols, with the following exceptions, were Eastman White Label grade and were used without further

(7) H. G. Kuivila, A. H. Keough, and E. J. Soboczenki, *J. Org. Chem.*, **19**, 780 (1954).

(8) J. M. Sugihara and C. M. Bowman, *J. Am. Chem. Soc.*, **80**, 2443 (1958).

(9) G. L. Roy, A. Laferriere, and J. O. Edwards, *J. Inorg. and Nucl. Chem.*, **4**, 106 (1957).

purification: Phenyl-1,2-ethanediol, Eastman practical, recrystallized from benzene and hexane; polyvinyl alcohol, Du Pont Elvanol grade 70-05, not further purified[9]; D-glucose, Matheson reagent; D-mannose, Pfanstiehl C.P.; 1,3-propanediol, Eastman practical, redistilled. Weighed amounts of each were dissolved in 0.5*M* $KNO_3$ (B&A reagent) solution to provide stock solutions, usually one molar. From these were prepared replicates for measurement.

Benzeneboronic acid was prepared in yields up to 50% by the method of Bean and Johnson,[10] and recrystallized from benzene. Since the anhydride, $C_6H_5B{=}O$, is more stable and its purity more readily established than the acid, all samples were dehydrated by heating overnight at 105°. The neutralization equivalent (by alkali titration to the phenolphthalein end point in the presence of a tenfold excess of mannitol) was within 0.5 of the theoretical value of 103.93 g./mol. The acid melted at 225° on a heated bar; melting point was not, however, utilized as a criterion of purity because of well known complications attributable to dehydration.[11] Finally, three infrared bands reported recently for a number of benzeneboronic acids[12] were found for a sample of anhydride in $CCl_4$, using the Perkin Elmer Infracord instrument.

Benzeneboronic anhydride was made up as a buffer solution about 0.1*M* benzeneboronate by half neutralizing with potassium hydroxide (B&A reagent) the solution of a weighed sample. Borax, $Na_2B_4O_7{\cdot}10H_2O$ (B&A reagent), yields a solution in which the acid and base forms already have equal concentrations. The stock buffer solution was about 0.2*M* in borate.

*Procedure.* Differences in *p*H between polyol-free (blank) and polyol-containing benzeneboronate buffer solutions (rather than absolute *p*H) were measured. The expanded scale of a Beckman Model GS *p*H meter with standard calomel and glass electrodes was used, affording sensitivity better than ±0.003 *p*H unit and reproducibility about ±0.005 *p*H unit. Solutions, always 50 ml. in volume, were placed in a jacketed flask in 25.00 ± 0.01° and stirred at a constant rate.

In general, for a given polyol, five buffer solutions were prepared for measurement from the stock solutions: one blank and four replicates varying in polyol over a fourfold concentration range. In certain cases replicates needed to be very dilute in polyol or to include more than four concentrations. Equilibrium in the complexing reaction was ostensibly reached immediately upon mixing polyol and buffer, as was previously found with borate systems.

*Results.* A fairly extensive series of complex formation constants was obtained from *p*H depression data; values of the constants, treated as explained in the Appendix, are listed in Table II, along with the corresponding values for borate equilibria. For purposes of the original problem, discussion of these constants is straightforward. A number of problems have arisen, however, in the interpretation of these data, and have been carried over from the borate studies which will be dealt with afterward.

All measured constants except that for 1,3-propanediol ranged, within experimental error, from slightly larger than the borate constant to twice as large. The correlation of pairs of values is illustrated by Fig. 1; this plot of log $K_c$ for benzeneboronate *vs.* log $K_1$ for borate is linear and shows a slope slightly greater than unity. The conclusion is inescapable that the benzeneboronate ion has the tetrahedral structure, the high degree of complex formation being unaccountable otherwise.

TABLE II

FORMATION CONSTANTS FOR POLYOL COMPLEXES

| Polyol | No. | Benzeneboronate K | Borate $K_1$ | Borate $K_{21}$ | Borate $K_1/K_2'$ |
|---|---|---|---|---|---|
| Ethylene glycol | 1 | 2.76 | 1.85 | 0.07 | 50 |
| Propylene glycol | 2 | 3.80 | 3.10 | 1.60 | 6.0 |
| 2,3-Butanediol[a] | 3 | (3.6)[b] | 3.45 | 4.85 | 2.5 |
| 3-Methoxy-1,2-propanediol | 4 | 8.45 | 7.50 | 5.55 | 10.1 |
| Phenyl-1,2-ethanediol | 5 | 9.90 | 7.45 | 7.16 | 7.8 |
| Catechol | 6 | 17500 | 7800 | 14200 | 4300 |
| Polyvinyl alcohol | 7 | (1.9)[b] | 1.8 | 4.3 | 0.75 |
| Pentaerythritol[c] | 8 | 650 | 240 | 1110 | 52 |
| 1,3-Propanediol | 9 | 0.88 | 1.15 | — | — |
| Glycerol | 10 | 19.7 | 16.0 | 41.2 | 6.2 |
| D-(+)-galactose | 11 | 276 | 127 | 298 | 54 |
| Fructose | 12 | 4370 | 650 | 98500 | 4.3 |
| L-(+)-arabinose | 13 | 391 | 130 | 675 | 25 |
| D-glucose[d] | 14 | 110 | 80 | 770 | 8.3 |
| D-mannose | 15 | 172 | 50 | 49 | 51 |
| Mannitol[e] | 16 | 2275[f] | 2100 | 88500 | 50 |

[a] Probably a mixture of *dl* and meso forms. [b] Estimate from the log-log plot (Fig. 1). [c] $K_{12}$ = 980,000 and $K_1/K_{12}'$ = 0.31. [d] $K_{12}$ = 39,500 and $K_1/K_{12}'$ = 0.30. [e] $K_{12}$ = 6,900,000 and $K_1/K_{12}'$ = 0.75. [f] Average of two values (2450 and 2100) from different plots.

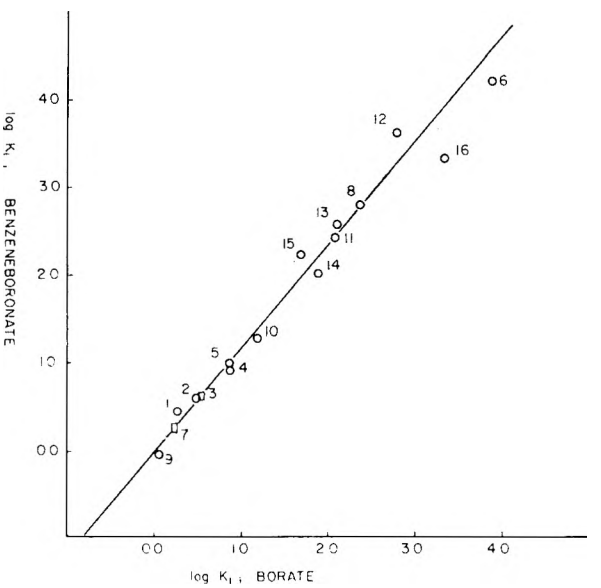


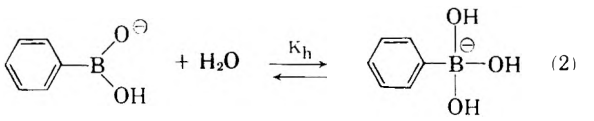

Fig. 1. Linear free energy plot of equilibrium constants forglycol-phenyl-boronates against glycol-borate. Numbers refer to glycols listed in Table II. Two points (3 and 7) shown as squares are not experimental points

The reasoning on which this conclusion is based is as follows: If the benzeneboronate ion were mainly trigonal, then the hydration equilibrium 2

(10) F. R. Bean and J. R. Johnson, *J. Am. Chem. Soc.*, 54, 4415 (1932).

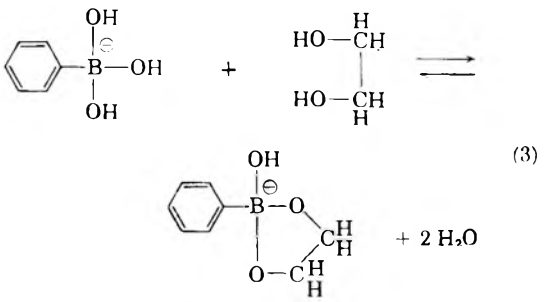
(11) L. M. Dennis and R. S. Shelton, *J. Am. Chem. Soc.*, 52, 3128 (1930).

(12) L. Santucci and H. Gilman, *J. Am. Chem. Soc.*, 80, 193 (1958).



(2)

would have a constant less than one. The over-all reaction of anion and glycol to form complex would have an equilibrium constant $K_c$ which would be the product of $K_h$ times $K_{C4}$, where $K_{C4}$ is the Reaction 3 of glycol with tetrahedral anion to form



(3)

complex. Now the values with borate ion are $K_{C4}$ values since the aqueous borate ion is tetrahedral.[2] Making the reasonable assumption that the replacement of hydroxyl by phenyl does not greatly influence the electronic picture about a four-coordinated boron, then one predicts that the $K_{C4}$ for phenylboronate should be the same size as for borate. Indeed the observed complexing constants are just slightly larger with phenylboronate than with borate, thus we feel that the anion is primarily tetrahedral. The alternative explanation (that $K_h$ is less than one and $K_{C4}$ for phenylboronate is much larger than $K_{C4}$ for borate) is unreasonable since no new types of bonds are formed or broken in the complexing reaction. In order to satisfy the quantitative aspects of these data, one must conclude that the phenylboronate ion is tetrahedral when uncomplexed as well as when complexed.

After submission of this paper, the recent article by Torssell[13] was called to our attention. From measurements on the fructose and benzeneboronate system, he draws a conclusion similar to the one presented here.

It might be argued that comparison of two such series of equilibria, in one of which a double complex is consistently observed, is not justified. To the extent, however, that extrapolation of all sets of values to zero polyol concentration eliminates the effect of the second equilibrium in the borate series, and introduces a standard concentration, the procedure is valid.

The first new problem in the interpretation of formation constants arose with the mannitol-benzeneboronate system as may be seen in Table III. In two series of measurements $K_c$ leveled off, and $\Delta p$H ceased to be a function of polyol concentration, with increasing $[P]$ although the $K_c - [P]_f$ plot is linear, with negative slope, at low concentrations. Such behavior has not been observed with other polyols, linear plots throughout being the rule. The usual significance of large variations in $K_c$ with concentration is given in the Appendix. The leveling off of $\Delta p$H is an indication of the formation of neutral complexes in competition with anionic complexes. Complexing of the acid form is a $p$H-increasing force, while that of the anion is a $p$H-decreasing one. This fact explains the observation that $\Delta p$H becomes virtually constant, within experimental error, if the concentrations of anionic and neutral complexes are conceived to increase at comparable rates. On this basis, one can derive the Equation 4 where $K_h$ is the formation constant for the neutral complex and $[H^+]_c$ is the value of hydrogen ion concentration when the $p$H has become constant. Using the values of $K_1 = 2275$ and $-\Delta p\text{H} = 2.80$, it is estimated the $K_h$ is about 3.6 for the mannitol-benzeneboronic acid complex.

$$K_h = \frac{K_a K_1}{[H^+]_c} \qquad (4)$$

TABLE III

EFFECT OF MANNITOL CONCENTRATION ON $p$H CHANGE

| $[\text{Mannitol}]_f$ | Series[a] | $-p\text{H}$ | $K_c$[b] |
|---|---|---|---|
| 0.183$M$ | A | 2.505 | 1750 |
| 0.338 | B | 2.630 | 1260 |
| 0.383 | A | 2.705 | 1330 |
| 0.499 | B | 2.730 | 1083 |
| 0.583 | A | 2.786 | 1050 |
| 0.597 | B | 2.760 | 955 |
| 0.697 | B | 2.795 | 881 |
| 0.783 | A | 2.830 | 865 |
| 0.797 | B | 2.795 | 771 |
| 0.897 | B | 2.825 | 747 |
| 0.977 | B | 2.805 | 655 |

[a] Series A; [benzeneboronate] = 0.0174$M$ and Series B; [benzeneboronate] = 0.00174$M$. [b] Calculated assuming only a "1:1 complex."

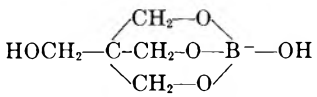
Another conclusion that seems quite certain is that the neutral complexes of benzeneboronic acid must be more strongly acidic than the free acid itself. Such a conclusion can be drawn directly from a thermodynamic cycle involving the possible species and the known constants. The reason for this is possibly linked up with the oxygen-boron-oxygen angle which is roughly 120° in the neutral species and about 109° in the anionic species. In this connection, it should be pointed out that the observation here that anionic complexes are favored is in no way contradictory to the discovery of neutral complexes elsewhere,[7,8] since gross differences in conditions prevail.

It is notable that polyvinyl alcohol gave a $p$H increase with benzeneboronate. Although precipitation from these systems occurred, the highest $p$H increase was observed in the solution containing the smallest amount of precipitate. Polyvinyl alcohol in borate buffers gave a small measurable $p$H

(13) K. Torssell, *Arkiv Kemi*, 10, 541 (1957).

decrease[9] (see Table II for constants). The most concentrated replicate in the pentaerythritol-benzeneboronate series gave a precipitate; whether this contained a neutral or anionic complex, or pentaerythritol itself, has not been ascertained. When more accurate measurement of the catechol-borate system was attempted in the range 0.2 to 0.8*M*, precipitation occurred in all replicates. Since precipitation was not observed in the previous borate work,[9] and since no potassium ion was then present it was concluded that the precipitate contained the potassium salt of the anionic "2:1 complex." Since, however, this precipitate appeared to contain two crystalline phases, the conclusion is tentative. It may be that the other precipitates noted contained potassium salts of complexes, and further work along these lines is needed.

The great difference between constants for 1,3-propanediol and pentaerythritol is intriguing, since both have apparently simple 1,3-diol systems. Statistical reasoning would suggest that $K_c$ for the former should be one sixth that for the latter: pentaerythritol can accommodate the first benzeneboronate (or borate) ion in six ways, 1,3-propanediol only one. Such things as statistical factors can not explain the orders of magnitude difference, however. Professor J. F. Bunnett has pointed out that pentaerythritol could form complexes of the type and this may well be the correct



reason for the high formation constants for this polyol as compared to 1,3-propanediol.

Mannitol, pentaerythritol, and glucose are the only polyols for which a value for the second formation constant $K_{12}$ has been estimated in the benzeneboronate system. This suggests an explanation for the notable deviation of mannitol on the log-log plot. If there are mannitol-borate complexes of the 1:2 type (in dilute mannitol solutions) the observed constant $K_1$ with borate will be slightly large. The result of any correction would be to lower the $K_1$ value and thereby to bring the point on the plot closer to the line.

Other borate values redetermined here included 3-methoxy-1,2-propanediol ($K_1$ lower than reported in ref. 9), and fructose, previous data for which contained too much scatter for either a precise extrapolation or slope determination.[14]

A second major problem was encountered in the relationship of $K_1$ and $K_{21}$. That $K_{21}$ is frequently far larger than $K_1$ is puzzling until it is realized that $K_{21}$ describes the formation of a "2:1 complex" not from the "1:1 complex," but from the borate (or benzeneboronate ion if one is referring to $K_{12}$). The Appendix gives a derivation of the relationship among $K_1$, $K_{21}$, and the constant for the former process, $K_2'$.

$$K_2' = K_{21}/K_1$$

By simple statistical reasoning, $K_1$ and $K_2'$ should be related by

$$K_1/K_2' = 4$$

if addition of the first glycol does not alter the binding capacity for the second glycol. It is this relationship which has significance, not that between $K_1$ and $K_{21}$. Values of $K_2'$ and $K_1/K_2'$ are presented in Table II. Departure from the ideal value for the ratio is widespread, approaching four only with simple 1,2-diols and fructose and glucose. There is little basis for speculation on this problem, but a few observations can be made; (1) Values may be accurate only within 50%. (2) Catechol gives an extremely large value and several sugars give values in the range 25–60. (3) Pentaerythritol, mannitol, and glucose with benzeneboronate are in the range 0.3 to 0.7 (reasoning for "1:2 complexes" of this type is analogous to that for 2:1 complexes of borate). (4) $K_{21}$ for 1,3-propanediol was not measurable because the medium effect predominated.

*Appendix.* Origin of formulas. Symbols used:

$K_c$ = measured equilibrium constant
$[P]_0$, $[P]_f$ = polyol concentration—initial and final, respectively
$[BH]$ = boric or benzeneboronic acid concentration
$[B^-]$ = borate or benzeneboronate concentration
$[BP^-]$ = "1:1 complex" concentration
$[BP_2^-]$ and $[B_2P^{--}]$ = "2:1 complex" and "1:2 complex" concentrations
$[BP_h^-] = [BP^-] + [BP_2^-] + \ldots$ = total complex concentration

Equilibria and constants: acid-base—

$$BH + H_2O = B^- + H_3O^+ \qquad K_a = \frac{[B^-][H^+]}{[BH]} \tag{5}$$

complex-formation—

$$B^- + P = BP^- + 2H_2O \qquad K_1 = \frac{[BP^-]}{[B^-]_f^2} \tag{6}$$

$$B^- + 2P = BP_2^- + 4H_2O \qquad K_{21} = \frac{[BP_2]}{[B^-][P]_f^2} \tag{7}$$

$$2B^- + P = B_2P^{--} + 4H_2O \qquad K_{12} = \frac{[B_2P^{--}]}{[B^-]^2[P]_f} \tag{8}$$

$$K_c = \frac{[BP_n^-]}{[B^-][P]_f} \text{ or } \frac{[B_nP^{-n}]}{[B^-][P]_f} \tag{9}$$

Conservation of mass:

$$[B^-]_0 = [B^-]_f + [BP_n^-] \tag{10}$$

$$[P]_0 = [P]_f + [BP_m^-] \tag{11}$$

$$[BH]_0 = [BH]_f \tag{12}$$

Equation 12 is based on two assumptions, both of which are reasonable. The first is that only the anion forms complexes appreciably; its validity is based on the fact that the change in *p*H with glycol

(14) G. L. Roy, Sc.M. thesis, Brown University (1956).

concentration cannot be explained if the acid form complexes (see text for the exceptional case of mannitol). The second assumption is that the change in concentration of acid form due to ionization (Equation 5) is negligible; such must be the case since the concentration of hydrogen ion never exceeded $10^{-6}M$.

From (5) $\log [H^+] = \log K_a + \log [BH] - \log [B^-]$

with polyol present,

$$-pH_f = -pK_a + \log [BH]_f - \log [B^-]_f$$

w/o polyol,

$$-pH_0 = -pK_a + \log [BH]_f - \log [B^-]_0$$

and by addition,

$$pH_f - pH_0 = \Delta pH = \log [B^-]_f - \log [B^-]_0$$

Then $\Delta pH = \log \frac{[B^-]_f}{[B^-]_0}$ or

$$10^{\Delta pH} = \frac{[B^-]_f}{[B^-]_0} = \frac{[B^-]_0 - [BP_n^-]}{[B^-]_0} \quad (13)$$

by equation (9), and, $10^{\Delta pH} = 1 - \frac{[BP_n^-]}{[B^-]_0}$

by equation (6), $[BP_n^-] = K_c[B^-]_f[P]_f$

and $10^{\Delta pH} = 1 - K_c[P]_f \frac{[B^-]_f}{[B^-]_0} = 1 - K_c[P]_f\, 10^{\Delta pH}$

division by $10^{\Delta pH}$ gives $K_c = \frac{10^{-\Delta pH} - 1}{[P]_f}$

Measurements yield $\Delta pH$; $[P]_f$ is found by correcting $[P]_0$ with the use of equations (10), (11), and (13).

*Treatment of constants.* $K_c = K_1$ if only "1:1 complex" is formed. $K_c$ is then usually found to decrease slightly with polyol concentration increase, owing to decline in the dielectric constant; a standard value is obtained by extrapolation to $[P]_f = 0$.

When 2:1 complex (from two polyol molecules) is present,

$$K_c = \frac{[BP^-] + [BP_2^-]}{[B^-]_f[P]_f} = K_1 + K_{21}[P]_f, \text{ from (7) and (9)}$$

$K_1$ and $K_{21}$ ore obtained by plotting $K_c$, extrapolating to $[P]_f = 0$, and measuring the slope.

For a complex formed from two anions and one polyol molecule, reasoning is similar, and $K_1$ and $K_{12}$ are obtained as above:

$$K_c = K_1 + 2K_{12}[B^-]_f$$

*Relationship of $K_2'$, $K_2$ and $K_1$.* The formation constant for "2:1 complex" from "1:1 complex" is

$$K_2' = \frac{[BP_2^-]}{[BP^-][P]_f}$$

since $[BP^-] = K_1[B^-][P]_f$, it follows from (6) and (7) that

$$K_2' \cdot K_1 = \frac{[BP_2^-]}{[B^-][P]^2_f} = K_{21}$$

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

# Thermal Decomposition of Mixed Carboxylic-Carbonic Anhydrides; Factors Affecting Ester Formation

D. S. TARBELL AND E. J. LONGOSZ[1]

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A number of new mixed benzoic (and mesitoic)-carbonic anhydrides ($C_6H_5COOCOOR$) have been prepared and characterized. They are stable at room temperature, but decompose around 150–170° with carbon dioxide evolution. It has been shown that the thermal decomposition of these anhydrides proceeds by two different paths: A, formation of an ester by loss of carbon dioxide and B, disproportionation to the symmetrical anhydride, alkyl carbonate, and carbon dioxide. Path A is favored when the point of attachment of the alkyl group is a secondary carbon or a primary carbon, with heavy substitution on the β-carbon. Both paths A and B occur about equally when the alkyl group is primary, as ethyl or butyl. Although tertiary amines lower the temperature of decomposition of the anhydrides, they do not alter the course of the decomposition. Rearrangement of the mixed anhydride from (−)-2-octanol proceeds with complete retention of configuration. *N*-Methylpiperidine is a much more effective catalyst than triethylamine in forming the mixed anhydride from a highly branched chlorocarbonate.

It was shown in an earlier paper[2] that mixed carboxylic-carbonic anhydrides, RCOOCOOR,' were, in general, reasonably stable compounds which could be obtained in pure form. It has been considered[2–4] that the mixed anhydrides decom-

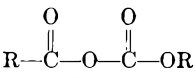
(1) National Science Foundation Fellow, 1958–59.

(2) D. S. Tarbell and N. A. Leister, *J. Org. Chem.*, **23**, 1149 (1958). This paper contains leading references to the literature describing the usefulness of the mixed anhydrides as acylating agents.

(3) J. Herzog, *Ber.*, **42**, 2557 (1909); A. Einhorn, *Ber.*, **42**, 2772 (1909); T. Wieland and H. Bernhard, *Ann.*, **572**, 190 (1951).

TABLE I

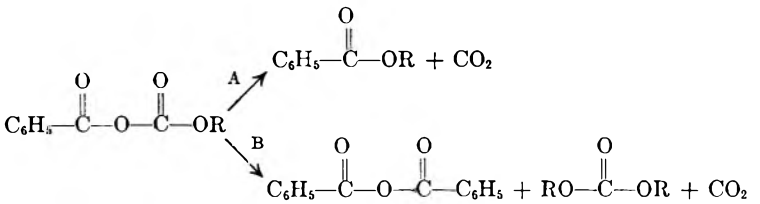
MIXED CARBOXYLIC-CARBONIC ANHYDRIDES



| R | R′ | $n_D$ | Formula | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Infrared Bands, Cm.$^{-1}$ |
|---|---|---|---|---|---|---|---|---|
| $C_6H_5$ | $CH_2CH_3$ | $n_D^{25}$ 1.4988 | $C_{10}H_{10}O_4$ | 61.85 | 62.23 | 5.19 | 5.32 | 1800, 1739 |
| $C_6H_5$ | $CH_2CH_2CH_2CH_3$ | $n_D^{25}$ 1.4902 | $C_{12}H_{14}O_4$ | 64.85 | 64.65 | 6.35 | 6.35 | 1802, 1745 |
| $C_6H_5$ | $CH_2$—$C(CH_3)_3$ | $n_D^{25}$ 1.4849 | $C_{13}H_{16}O_4$ | 66.08 | 66.44 | 6.83 | 7.05 | 1802, 1745 |
| $C_6H_5$ | $CH_2$—$C(CH_2CH_3)_3$ | $n_D^{25}$ 1.4913 | $C_{16}H_{22}O_4$ | 69.04 | 69.06 | 7.97 | 8.05 | 1802, 1745 |
| $C_6H_5$ | $CH_2$—$C_6H_5$ | | | [a] | | | | 1800, 1739 |
| $C_6H_5$ | $CH(CH_3)C_6H_{13}$ | $n_D^{25}$ 1.4801 | $C_{16}H_{22}O_4$ | 69.04 | 69.41 | 7.97 | 8.17 | 1795, 1739 |
| $C_6H_5$ | $CH(CH(CH_3)_2)_2$[b] | $n_D^{24}$ 1.4890 | $C_{15}H_{20}O_4$ | 68.16 | 68.45 | 7.63 | 7.73 | 1795, 1739 |
| 2,4,6-$(CH_3)_3$—$C_6H_2$ | $CH_2CH_3$ | $n_D^{26}$ 1.4919 | $C_{13}H_{16}O_4$ | 66.08 | 65.83 | 6.83 | 6.85 | 1802, 1754 |
| 2,4,6-$(CH_3)_3$—$C_6H_2$ | $CH(CH_3)C_6H_{13}$ | $n_D^{24}$ 1.4802 | $C_{19}H_{28}O_4$ | 71.22 | 71.08 | 8.81 | 8.85 | 1802, 1754 |

[a] Too unstable for valid elemental analysis. [b] Required *N*-methylpiperidine as the tertiary amine during synthesis. Triethylamine gives only 40% conversion of reactants to mixed anhydride.

pose by two routes, path A leading to ester, and path B giving the symmetrical disproportionation products. Thus, for the benzoic-carbonic anhydride:



The present paper gives evidence for this dual mode of decomposition of pure mixed anhydrides, studies the effect of structural changes in R on the proportion of paths A and B, and indicates the stereochemical course of the reaction when the R group is attached to oxygen through an asymmetric carbon.

The mixed anhydrides synthesized and studied are listed, along with analytical and infrared data, in Table I. They were prepared from benzoic (or mesitoic) acid and the appropriate alkyl chlorocarbonate in the presence of triethylamine or of *N*-methylpiperidine in ether solution. (The latter base proved superior in the case of the chlorocarbonate derived from the highly branched alcohol, 2,4-dimethyl-3-pentanol.) The chlorocarbonates were generated from phosgene and the appropriate alcohol.

With the exception of benzoic-benzylcarbonic mixed anhydride, the mixed anhydrides showed no essential changes in their infrared absorption spectra after standing at room temperature for several months. A temperature greater than 100° was required to effect a marked degree of decomposition. Even at the temperature of boiling toluene, 112°, no change in the infrared spectrum was observed for a sample of the mixed anhydride dissolved in toluene, after a heating period of 8 hr. The temperature range of 150–170° was selected for the rearrangements since it gave total decompositions within a convenient time interval of 2 to 4 hr. As seen from the reaction paths, both modes of decomposition of the mixed anhydride lead to the evolution of carbon dioxide. Assuming both these paths of decomposition to occur simultaneously, the measurement of the total quantity of carbon dioxide evolved should give a reliable indication of the predominant path taken by the reaction, since path A evolves one equivalent of carbon dioxide, and path B evolves one-half equivalent of carbon dioxide.

Hence, the mixed anhydrides were heated in a flask provided with a nitrogen sweep, and the carbon dioxide was trapped in an absorption tube filled with "Ascarite." Isolation of the three expected products from each of the rearrangements and in the yields required by the total quantity of carbon dioxide trapped, within experimental error, indeed proved the validity of the original assumptions. As seen from Table II, the course taken by the rearrangement depends on the type of alkyl group in the mixed anhydride. When the point of attachment of the alkyl component is a secondary carbon atom or a primary carbon atom with heavy substitution on the β-carbon atom, the decomposition is chiefly to the respective ester. When the point of attachment is a primary carbon atom, such as ethyl or butyl, the decomposition proceeds about equally along paths A and B. The mixed anhydride derived from mesitoic acid leads to

(4) D. S. Tarbell and J. A. Price, *J. Org. Chem.*, 22, 245 (1947); E. Schipper and J. Nichols, *J. Am. Chem. Soc.*, 80, 5714 (1958). A recent communication [T. B. Windholz, *J. Org. Chem.*, 23, 2044 (1958)] reports observation of paths A and B.

TABLE II

THERMAL REARRANGEMENT OF MIXED CARBOXYLIC-CARBONIC ANHYDRIDES (R—C(=O)—O—C(=O)—O—R')

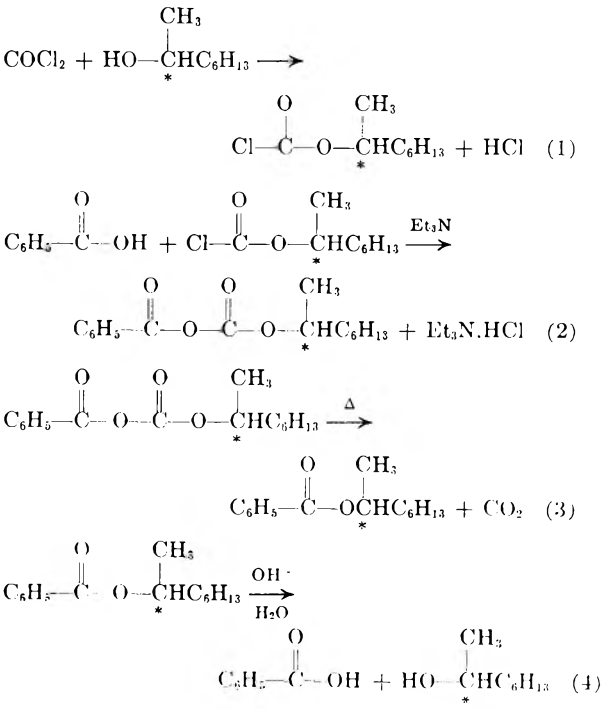
| R | R' | Temp. | Catalyst (Mole %) | $CO_2$ Evolved % of Theory | % Ester Predicted | % Ester Recovered |
|---|---|---|---|---|---|---|
| $C_6H_5$ | $CH_2CH_3$ | 150° | None | 69 | 38 | 41 |
| $C_6H_5$ | $CH_2CH_3$ | 155° | None | 70 | 40 | — |
| $C_6H_5$ | $CH_2CH_3$ | 130° | $C_6H_5N(CH_3)_2$(4) | 69 | 38 | 42 |
| $C_6H_5$ | $CH_2CH_3$ | 70° | $C_5H_{10}NCH_3$(4) | 68 | 36 | 35 |
| $C_6H_5$ | $CH_2CH_3$ | 125° | $C_5H_{10}NCH_3$(1) | 75[a] | 50 | — |
| $C_6H_5$ | $CH_2CH_2CH_2CH_3$ | 150° | None | 78 | 56 | 50 |
| $C_6H_5$ | $CH_2CH_2CH_2CH_3$ | 115° | $Et_3N$(3) | 75 | 50 | — |
| $C_6H_5$ | $CH_2C(CH_3)_3$ | 150° | None | 79 | 58 | 48 |
| $C_6H_5$ | $CH_2C(CH_2CH_3)_3$ | 150° | None | 89 | 78 | 85 |
| $C_6H_5$ | 1-$CH(CH_3)C_6H_{13}$ | 170° | None | 84 | 68 | 65 |
| $C_6H_5$ | $CH(CH_3)C_6H_{13}$ | 170° | None | 84 | 68 | — |
| $C_6H_5$ | $CH(CH_3)C_6H_{13}$ | 115° | $C_5H_{10}NCH_3$(4) | 84 | 68 | — |
| $C_6H_5$ | $CH(CH(CH_3)_2)_2$ | *Ca.* 170° | None | — | — | 71[b] |
| 2,4,6-$(CH_3)_3C_5H_2$ | $CH_2CH_3$ | 170° | None | 56 | 12 | 10 |
| 2,4,6-$(CH_3)_3C_5H_2$ | $CH(CH_3)C_6H_{13}$ | 170° | None | 90 | 80 | 77 |

[a] This rearrangement in 1.9 molar excess of ethyl carbonate. [b] Benzoate ester of 2,4-dimethyl-3-pentanol formed during attempted acylation of ethanol by mixed anhydride. This ester formed during distillation of reaction mixture, which contained unreacted mixed anhydride.

substantially the same result when the alkyl component is 2-octyl, but gives almost exclusively disproportionation when the alkyl component is ethyl. The presence of tertiary amines, such as triethylamine, *N*-methylpiperidine, or *N*,*N*-dimethylaniline during the rearrangement process evidently has a catalytic effect, since the elimination of carbon dioxide takes place at a much lower temperature. A significant fact is that the ratio of the two reaction paths is not altered. Neither does the presence of excess diethyl carbonate during the decomposition of benzoic-ethylcarbonic anhydride shift the reaction path markedly.

Ester formation (path A) occurs directly from the mixed anhydride, and not through prior disproportionation to symmetrical products (path B) followed by esterification of the anhydride by the organic carbonate.[4a] Equivalent amounts of diethyl carbonate and benzoic anhydride were heated under the conditions of the decomposition, but no carbon dioxide was eliminated. The same results were obtained with di-2-octyl carbonate and benzoic anhydride. The addition of tertiary amines had no effect in promoting this reaction; only starting materials were isolated in each case.

Some insight into the mechanism of the reaction was gained by the rearrangement of benzoic-2-octylcarbonic anhydride, where a center of asymmetry was introduced into the alkyl portion of the anhydride. It was found that the configuration at this center of asymmetry was completely retained in the resulting 2-octyl benzoate. This rules out the formation of an easily racemizable carbonium ion, resulting from an alkyl oxygen cleavage as a step in the rearrangement process. Also ruled out is a prior dissociation to a benzoate ion and a rearward attack by this ion on the center of asymmetry, to invert the configuration. The path leading to disproportionation products must also lead to retention of configuration, since the sample of optically active 2-octyl benzoate was contaminated with di-2-octyl carbonate, because of identity of boiling points of the two compounds. Hydrolysis of the mixture, however, yielded 2-octanol with a rotation identical to that of the starting alcohol. The following sequence of reactions was carried out with (−)-2-octanol:



(4a) *Cf.* T. B. Windholz, ref. 4.

It is unreasonable to suppose that the asymmetric center is disturbed in reactions (1) and (2) and it is well known that Reaction 4 proceeds with retention of configuration.[5] Hence two inversions of configuration in the sequence, one in Reaction 3 and another in one of the other three reactions, leading to apparent retention during the sequence, can be ruled out. Houssa and Phillips[6] obtained the same stereochemical result when they heated potassium benzoate and (−)-2-octyl chlorocarbonate. However, this procedure was attended by low yields of the optically active ester, the formation of large quantities of (−)-2-octanol, and a poor overall material balance; furthermore, threre was no evidence that the mixed anhydride was actually an intermediate.

Further evidence for the lack of formation of a carbonium ion during the decomposition of the mixed benzoic-carbonic anhydride is that no rearrangement of the neopentyl skeleton took, place. Under certain conditions, the neopentyl system undergoes a skeletal rearrangement, presumably through a carbonium ion.[7] In the light of this evidence, it is difficult to explain the ready decomposition of the benzyl mixed anhydride, which eliminated carbon dioxide even at room temperature. The major path followed in this decomposition could not be determined because of similarity of the boiling points of all three products. However, the three expected products are present in more than trace amounts, because of strong absorption at the expected frequencies in the infrared.

A procedure for making esters reported by Newman,[8] in which the sodium salt of an acid is heated with an alkyl chlorosulfite, is undoubtedly similar to the one discussed in this paper.

Work is currently in progress in these laboratories to elucidate the mechanism of these rearrangements and to establish their relationship to various 1,3-rearrangements, such as the decomposition of chlorocarbonates[9] and chlorosulfites,[10] and the rearrangement of thione carbonates.[11]

## EXPERIMENTAL[12]

*2,4-Dimethyl-3-pentanol,*[4] *2,2-diethyl-1-butanol,*[13] *and neopentyl alcohol*[14] were prepared following the references indicated, and had physical properties in agreement with those reported.

*Preparation of alkyl chlorocarbonates.* Except for ethyl chlorocarbonate, which was commercially available, all the chlorocarbonates used in this study were prepared by the action of phosgene on the respective alcohol. Following is the general method used: In a 250-ml., three necked flask set in a Dry Ice–acetone bath, was condensed approximately 100 g. (1 mole) of phosgene. The flask was transferred to an ice bath and fitted with a stirrer, a condenser, and a dropping funnel. Over a period of one hour, 0.7 mole of the alcohol was added. The ice bath was removed after the addition and the mixture allowed to stand at room temperature overnight. The excess phosgene was removed by means of an aspirator for *ca.* 2 hr., and the residue fractionally distilled. The chlorocarbonates synthesized in this manner are listed in Table III.

*Di-2-octyl carbonate* was made by the action of 2-octanol on 2-octyl chlorocarbonate. Our sample had b.p. 118–123° (0.7–1 mm.), $n_D^{25}$ 1.4280; the reported[15] b.p. is 168° (13 mm.).

*Preparation of carboxylic-carbonic anhydrides.* In a 250-ml. three-necked flask were placed benzoic acid, an equimolar quantity of pure triethylamine and dry ether (100 ml. for every 0.04 mole of reagent used). The flask was equipped with a stirrer, addition funnel, and reflux condenser. The mixture was cooled to 0 to 5° and an equimolar quantity of the alkyl chlorocarbonate was added at such a rate as to keep the temperature of the mixture between 0 and 5°. After the addition, the reaction was allowed to continue for an additional 0.5 hr. at the temperature of the ice bath, then slowly warmed to room temperature. The triethylamine hydrochloride was recovered by filtration in better than 95% yield in all cases. The filtrate was washed thoroughly with dilute hydrochloric acid, saturated sodium bicarbonate solution, and water, then dried over anhydrous magnesium sulfate. After thorough drying, the ether was removed under reduced pressure at room temperature, leaving behind a clear, mobile liquid. The mixed anhydrides thus prepared are listed in Table I. Little or no change in the infrared absorption spectra of the samples was noticed after standing at room temperature for several months.

*Thermal rearrangement of mixed carboxylic-carbonic anhydrides.* The mixed anhydride (about 0.05 mole) prepared and isolated as described above, was accurately weighed into a 50 ml. round bottomed flask, equipped with a gas inlet tube, thermometer, and a reflux condenser. The reflux condenser was attached to a U-trap filled with "Anhydrite," which in turn was attached to an absorption bulb filled with "Ascarite." Heating of the flask containing the mixed anhydride was accomplished by means of an oil bath. The carbon dioxide evolved was swept by a continuous stream of nitrogen. The absorption bulb was periodically weighed and the heating stopped when it reached constant weight. After dissolving the rearrangement product in ether and washing it with dilute hydrochloric acid, saturated sodium bicarbonate solution and water, it was dried over anhydrous magnesium sulfate. The products of the rearrangement were isolated by means of fractional distillation through a vacuum-jacketed Vigreux column (100 × 10 mm.). The experiments with ethyl, butyl, and neopentyl mixed anhydrides are not described in detail because their decomposition products represent known products. The yield of benzoate ester reported in Table II represents a corrected yield, that is, it includes benzoate ester obtained in a pure form and also that contaminated with organic carbonate in

(5) B. Holmberg, *Ber.*, **45**, 2997 (1912).

(6) A. Houssa and H. Phillips, *J. Chem. Soc.*, 2510 (1929).

(7) F. C. Whitmore and G. H. Fleming, *J. Chem. Soc.*, 1269 (1934). F. C. Whitmore, E. L. Wittle, and A. H. Popkin, *J. Am. Chem. Soc.*, **61**, 1586 (1939). I. Dostrovsky and E. D. Hughes, *J. Chem. Soc.*, 169 (1946).

(8) M. S. Newman and W. S. Fones, *J. Am. Chem. Soc.*, **69**, 1046 (1947).

(9) K. B. Wiberg and T. M. Shryne, *J. Am. Chem. Soc.*, **77**, 2774 (1955).

(10) C. E. Boozer and E. S. Lewis, *J. Am. Chem. Soc.*, **75**, 3182 (1953).

(11) H. R. Al-Kazimi, D. S. Tarbell, and D. Plant, *J. Am. Chem. Soc.*, **77**, 2479 (1955); D. H. Powers and D. S. Tarbell, *J. Am. Chem. Soc.*, **78**, 70 (1956).

(12) Melting points are uncorrected. Microanalyses are by Miss Annette Smith and Dr. Franz Pascher.

(13) S. Sarel and M. S. Newman, *J. Am. Chem. Soc.*, **78**, 5416 (1956).

(14) D. Y. Curtin and S. M. Gerber, *J. Am. Chem. Soc.*, **74**, 4052 (1952).

(15) H. Hunter, *J. Chem. Soc.*, 1389 (1924).

TABLE III

PROPERTIES OF ALKYL CHLOROCARBONATES

$$R{-}O{-}\overset{\overset{O}{\|}}{C}{-}Cl$$

| R | B.P. | $n_D$ | Literature, B.P. | Literature, $n_D^{20}$ |
|---|---|---|---|---|
| $n$-$C_4H_9$ | 45–46° (18 mm.) | 1.4095 (24°) | 138°[a] | 1.4128 |
| $CH_2C(CH_3)_3$ | 39° (15 mm.) | 1.4085 (23°) | 52° (27 mm.)[b] | 1.4091 |
| $CH_2{-}C_6H_5$ | 73–74° (3 mm.) | 1.5146 (25°) | 103° (19–20 mm.)[c] | — |
| $CH(CH(CH_3)_2)_2$ | 95–97° (69–70 mm.) | 1.4220 (20°) | 90–100° (60–70 mm.)[d] | 1.4225 |
| $CH(CH_3)C_6H_{13}$ | 92–93° (12 mm.) | 1.4252 (25°) | 92° (13 mm.)[e] | 1.4282 |
| $CH_2{-}C(C_2H_5)_3$[f] | 133° (85 mm.) | 1.4381 (24°) | — | — |

[a] A. N. Kost, Russian Doctoral Dissertation, *Chem. Abstr.*, **47**, 9907 (1953). [b] F. Strain *et al.*, *J. Am. Chem. Soc.*, **72**, 1254 (1950). [c] J. Thiele and F. Dent, *Ann.*, **302**, 257 (1898). [d] D. S. Tarbell and J. A. Price, *J. Org. Chem.*, **22**, 245 (1957). [e] H. Hunter, *J. Chem. Soc.*, 1389 (1924). [f] Calcd. for $C_9H_{17}O_2Cl$: C, 56.10; H, 8.90. Found: C, 56.63; H, 9.14. The carbamate, made by the action of concentrated aqueous ammonia on this chlorocarbonate had m.p. 93.5–94.5° after purification by sublimation. Calcd. for $C_9H_{19}NO_2$: C, 62.39; H, 11.05; N, 8.09. Found: C, 61.91; H, 10.98; N, 8.36.

intermediate fractions. These corrections were made by application of ultraviolet and hydrolysis experiments. The experiments with the optically active mixed anhydride, and cases in which new compounds were formed, are described in detail below.

*Rearrangement of optically active benzoic-2-octylcarbonic anhydride.* Optically active 2-octyl chlorocarbonate was made in the manner discussed above using 2-octanol having $\alpha_D^{26}$ −6.82 ± 0.03° (neat, l = 1) and b.p. 81–83° (14 mm.), $n_D^{20}$ 1.4250. Having generated the benzoic mixed anhydride (16.3 g., 0.059 mole) and decomposed it in the standard manner, an 84% yield of carbon dioxide was collected. Upon fractionation of the rearrangement product, there was obtained 11.1 g. of liquid, b.p. 117–119° (0.7–1 mm.), $n_D^{26}$ 1.4680 to 1.4799; reported[6] for 2-octyl benzoate, b.p. 171° (20 mm.), $n_D^{25}$ 1.4840. An authentic sample had b.p. 113–116° (0.5 mm.), $n_D^{20}$ 1.4885. An authentic sample of di-2-octyl carbonate had b.p. 118–123° (0.7–1 mm.), $n_D^{25}$ 1.4280. All fractions, besides showing a strong infrared absorption band at 5.80$\mu$, typical for aromatic esters, showed weaker absorption at 5.75$\mu$, apparently due to the presence of di-2-octyl carbonate. The residue from the distillation yielded benzoic anhydride, 1.8 g. (27%). Saponification of the above distillate in alcoholic potassium hydroxide gave an 80% yield of benzoic acid, indicating that only 80% of the liquid product obtained from the rearrangement was 2-octyl benzoate. From the infrared spectrum and boiling point, the remaining 20% is di-2-octyl carbonate. On this basis, the yield of 2-octyl benzoate from the rearrangement is 65%, reasonably close to the predicted 68%. The 2-octanol obtained from the saponification had $\alpha_D^{26}$ −6.87 ± 0.03° (neat, l = 1) and b.p. 77° (10 mm.), $n_D^{20}$ 1.4250.

*Rearrangement of benzoic-2,2-diethyl-1-butylcarbonic anhydride.* Fractionation of the rearrangement product resulting from this mixed anhydride (12.3 g., 0.044 mole) yielded two fractions, the first, 1.2 g., with b.p. 109–113° (1 mm.) was contaminated with a white solid (approx. 0.2 g.) which was benzoic acid. The second, b.p. 113–114° (1 mm.) $n_D^{26}$ 1.4942, amounted to 7.8 g. The residue from the distillation amounted to 0.5 g. and yielded 0.2 g. (4%) of benzoic anhydride. An infrared spectrum of the remaining material indicated the presence of organic carbonate and benzoic anhydride. A sample of the second fraction, redistilled before submitting for analysis, had b.p. 110° (0.7 mm.) $n_D^{25.5}$ 1.4945.

*Anal.* Calcd. for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.44; H, 9.75.

A similar sample of this material had a maximum in the ultraviolet at 228 m$\mu$ (log $\epsilon$, 4.03) in 95% ethanol. The ultraviolet absorption spectrum[16] of alkyl benzoates has a maximum at 228 m$\mu$ (log $\epsilon$, 4.02 to 4.09) in 95% ethanol. Saponification of this material yielded benzoic acid and an alcohol whose 1-naphthylurethan had m.p. 135–136°, undepressed by the 1-naphthylurethan of authentic 2,2-diethyl-1-butanol. The reported[17] m.p. for this derivative is 135–136°.

*Rearrangement of mesitoic-2-octylcarbonic anhydride.* Fractionation of the rearrangement product resulting from this mixed anhydride (12.9 g., 0.0403 m.) yielded 8.9 g. of liquid b.p. 137–148° (1 mm.), $n_D^{26}$ 1.4561–1.4871. The first two fractions, 1.3 g., b.p. 137–141°, contained an aromatic ester and an organic carbonate, as evidenced by peaks in the infrared at 5.80$\mu$, and 5.75$\mu$, respectively. The latter three fractions, 7.6 g., b.p. 141–148°, were redistilled, and a middle cut having b.p. 145–147° (1 mm.) $n_D^{25}$ 1.4835 submitted for analysis.

*Anal.* Calcd. for $C_{18}H_{28}O_2$: C, 78.21; H, 10.21. Found: C, 78.03; H, 10.26.

In addition, an authentic sample of 2-octyl mesitoate made from mesitoyl chloride and 2-octanol had the same properties and infrared spectrum as the above sample. The residue from the above distillation yielded 1.2 g. (19%) of mesitoic anhydride, m.p. 104°, undepressed by an authentic sample. The reported[18] m.p. for mesitoic anhydride is 106–107°.

*Attempted reaction of di-2-octyl carbonate and benzoic anhydride.* Di-2-octyl carbonate (4.1 g., 0.014 m.) and benzoic anhydride (3.2 g., 0.014 m.) were heated at 177° in the manner used for the decomposition of the mixed anhydrides. No carbon dioxide was trapped after 3 hr. of heating. The addition of *N,N*-dimethylaniline (0.10 g., 0.0008 m.) and continued heating likewise produced no carbon dioxide. Fractionation of the mixture yielded only starting materials. Repetition of the experiment with ethyl carbonate and benzoic anhydride yielded similar results.

ROCHESTER, N. Y.

(16) H. E. Ungnade and R. W. Lamb, *J. Am. Chem. Soc.*, **74**, 3789 (1952).

(17) R. V. Rice *et al.*, *J. Am. Chem. Soc.*, **59**, 2000 (1937).

(18) R. C. Fuson, J. Corse, and N. Rabjohn, *J. Am. Chem. Soc.*, **63**, 2852 (1941).

[COMMUNICATION NO. 1994 FROM THE KODAK RESEARCH LABORATORIES]

# The Structure of Certain Polyazaindenes. I. Absorption Spectra

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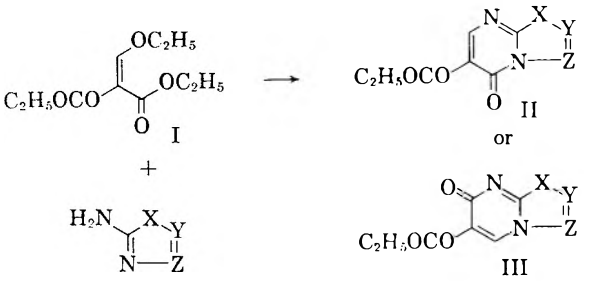
The structures of the polyazaindenes have been uncertain since their discovery many years ago, inasmuch as the syntheses are ambiguous, and no mild methods of degradation are available. The infrared and ultraviolet absorption spectra of a number of related heterocyclic ring systems are discussed. Structures are assigned based on the interpretation of the data.

The present paper is concerned with the interpretation of the ultraviolet absorption spectra of a large number of heterocyclic bases of related structures. The first part (A) deals with the condensation products of ethyl ethoxymethylenemalonate (I) with various heteroamines. The second part (B) covers the structure of the condensation products of ethyl acetoacetate with these same amines. Parts C and D are concerned with the thiadiazaindenes, the tetrazaindenes, and the pentazaindenes.

*A. Carbethoxyazanaphthalenes and carbethoxyazaindenes.* The substances (old and new) were prepared by condensing a number of heterocyclic amines having the amidino group, $-N=\overset{|}{C}-NH_2$, with ethyl ethoxymethylenemalonate (I) and ethyl acetoacetate. For instance, in a reaction involving I, X, Y, and Z may be nitrogen, sulfur, or carbon. The amines employed were 2-aminothiazoles, 2-amino-1,3,4-thiadiazoles, 5-amino-3-methyl-1,2,4-thiadiazole, 2-aminoimidazole, 3-amino-5-methyl-1,2-pyrazole, and 3-amino-1,2,4-triazoles. The reaction products of ethyl ethoxymethylenemalonate (I) with these amines and with certain alkyl derivatives are shown in Table I. The reaction failed with 5-aminotetrazole. As will become evident in the following discussion, the products have the oxo group in the position shown in II, rather than that in III.



The structures of 3-carbethoxy-4-oxo-4a-azanaphthalene (X)[1,2] and of 3-carbethoxy-4-oxo-1,4a-diazanaphthalene (XI),[3] which are isosteric with II, have been well established. These substances are taken as models with which to compare the spectra of derivatives of II. Inspection of Figs. 1 and 2 shows clearly that the shapes of the spectra of IV–IX are very similar to those of the two compounds (X and XI) of known structure.

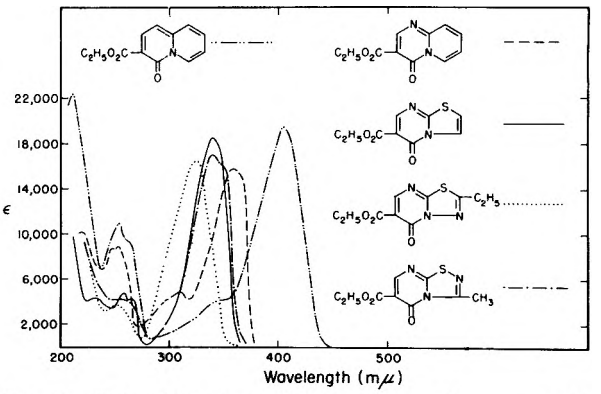



Fig. 1. Ultraviolet absorption spectra: IV, ———; V, . . . . . ; VI, ·—·—·—; XI, ———; X, · · —· · —

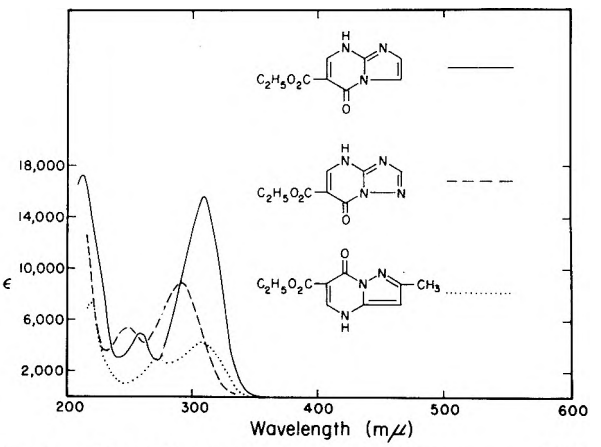



Fig. 2. Ultraviolet absorption spectra: VII, ———; VIII, . . . . . ; IX, ———

It is convenient, in discussing these spectra, to divide them into three regions: *a* (212–230 mμ) with high ε values, *b* (250–270 mμ) with medium ε

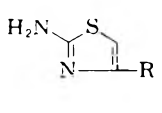
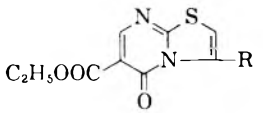
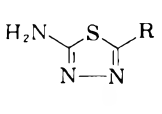
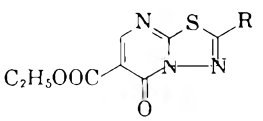
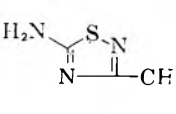
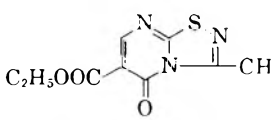
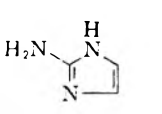
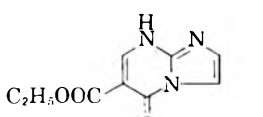
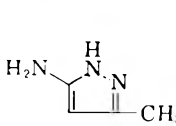
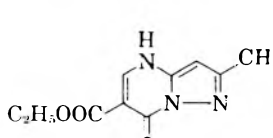
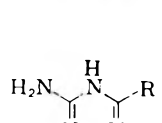
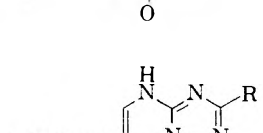
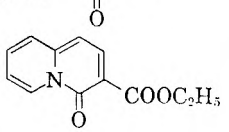
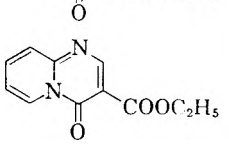
(1) F. Bohlmann, A. Englisch, J. Pollitt, H. Sander, and W. Weise, *Chem. Ber.*, **88**, 1831 (1955).

(2) V. Boekelheide and J. P. Lodge, Jr., *J. Am. Chem. Soc.*, **73**, 3681 (1951).

(3) R. Adams and I. J. Pachter, *J. Am. Chem. Soc.*, **74**, 5491 (1952).

TABLE I

ULTRAVIOLET ABSORPTION SPECTRA OF SOME HETEROCYCLIC OXOESTERS[a,b]

| Amine Used | Product | 5-Carbethoxy-4-oxo- Derivative of | No. | Absorption Bands λa | λb | λc | Δλc from X |
|---|---|---|---|---|---|---|---|
|  |  | 1-Thia-3a,7-diazaindene | IV | 236 (4.1) | 258 (4.6) | 340 (18.6) | 64 |
| | | 3-Methyl-1-thia-3a,7-diazaindene | IVa | | 265 (4.1) | | |
|  |  | 2-Ethyl-1-thia-3,3a,7-triazaindene | V | 215 (10.7) | 252 (3.8) | 324 (16.5) | 80 |
| | | 2-Methyl-1-thia-3,3a,7-triazaindene | Va | 218 (9.7) | 253 (4.0) | 322 (15.4) | 82 |
|  |  | 3-Methyl-1-thia-2,3a,7-triazaindene | VI | | 260 (5.7) | 339 (17.1) | 65 |
|  |  | 1,3a,7-Triazaindene | VII[c] | 211 (17.4) | 258 (5.0) | 308 (15.7) | 96 |
|  |  | 6-Carbethoxy-2-methyl-7-oxo-1,4,7a-triazaindene | VIII[c] | 218 (7.3)[d] | 272 (5.9) | 306 (4.1) | 98 |
|  |  | 1,3,3a,7-Tetrazaindene | IX[c] | | 248 (5.1) | 291 (9.0) | 113 |
| | | 2-Methyl-1,3,3a,7-tetrazaindene | IXa[c] | | | | |
| |  | 3-Carbethoxy-4-oxo-4a-azanaphthalene | X | 210 (22.4) | 253 (11.0) 262 (9.4) 248 (4.1) | 404 (19.5) | |
| |  | 3-Carbethoxy-4-oxo-1,4a-diazanaphthalene | XI | 220 (10.2) | 248 (8.8) 252 (9.0) 310 (5.0) | 358 (15.8) | 46 |

[a] In all tables, the wave length is given in mμ, and the extinction is $\epsilon \times 10^{-3}$. [b] The solvent was methanol. [c] A referee has suggested that these compounds should be named as 4,7-dihydro derivatives. We have chosen to omit this designation (1) in order to emphasize the relation to the derivatives in this table that have no other tautomers, since (2) the tautomeric hydroxy compounds are obviously completely unsaturated, (3) the rules covering specification of extra hydrogen specifically except cases of this sort, and (4) the name as given is unequivocal. [d] Incomplete solution.

values, and *c* (300–400 mμ) with high ε values. Table I shows that the *a* and *b* regions are relatively constant in position and intensity. Less fine structure is seen in the *b* region with increasing nitrogen content. The largest variation in these spectra occurs in the long wave-length band *c*. There is a hypsochromic shift of the *c* band as the ethylenic function in X is replaced successively by less efficient electrical conductors; thus, replacement of the carbon in the 1-position of X by a nitrogen atom, as in XI results in a hypsochromic shift of about 46 mμ and a corresponding decrease in intensity with respect to X. Similarly, substitution of a sulfur atom for the ethylenic function in the 7,8-position of X again results in a hyposchromic shift of about 64 mμ, as shown in IV. The pair V and VI are interesting in that position of a nitrogen atom relative to the sulfur atom has been changed. This affects the position of the long wave-length band, but does not alter the general shape of the absorption curve (Fig. 1). In VII, the ethylenic function in the 7,8-position of X has been replaced by a

nitrogen atom. Here again, the nitrogen atom has caused the long wave-length band to be shifted about 96 mμ toward shorter wave lengths in respect to X. The isomeric compound, VIII, shows about the same absorption as VII. Increasing the nitrogen content of the molecule, as in IX, resulted in a further bathochromic shift of the long wave-length band, as shown in Fig. 2.[4]

These arguments, by analogy and from the fact that in no case was the spectrum similar to that of the type B compounds (see B), can be accepted as good evidence for Formulations IV through IX.

*B. Azanaphthalenes and azaindenes.* The structure of the condensation product of ethyl acetoacetate and 2-aminopyridine has been the subject of numerous papers and has been shown to be 4-oxo-1,4a-diazanaphthalene (XII).[2] The structure of 4-oxo-4a-azanaphthalene (XIII) has also been established unequivocally.[2] The spectra of these two substances

XII XIII

will serve as reference spectra with which to compare the spectra of the condensation products of ethyl acetoacetate (or related esters) with the heterocyclic amines used in A.

The spectra of these compounds are shown in Figs. 3 and 4, and the values for the peaks of maximum absorption, together with their molecular extinction coefficients, are given in Table II.

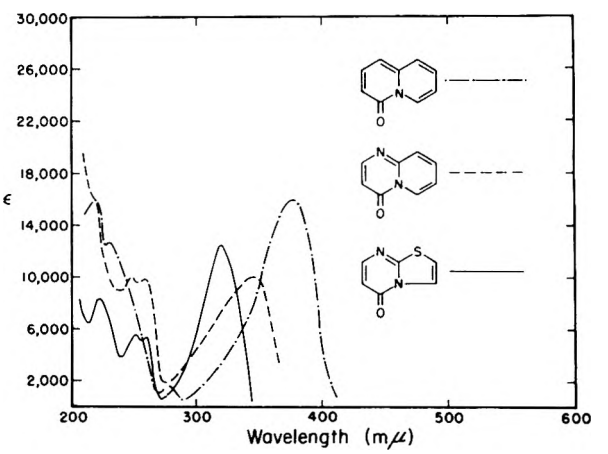



Fig. 3. Ultraviolet absorption spectra: XII, ———; XIII, ·—·—·; XIV, ———

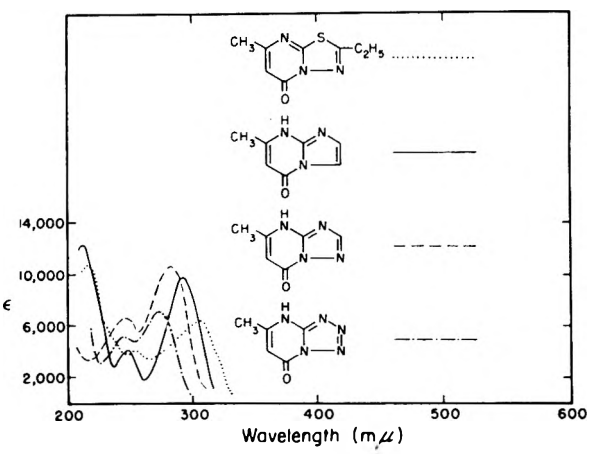
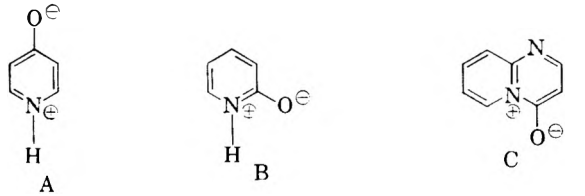



Fig. 4. Ultraviolet absorption spectra: XV, .....; XVI, ———; XVIII, ———; XIX, ·—·—·

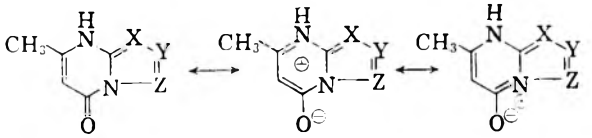
It is apparent, on comparison of Figs. 3 and 4 with Figs. 1 and 2, that there is a large hypsochromic shift of the entire spectrum between the two series, owing to the absence of the carbethoxy group. The general shape of the curves, however, remains unaltered. Furthermore, replacement of the 7,8-ethylenic group of XIII with sulfur or nitrogen has

(4) V. I. Bliznyukov and V. M. Reznikov, *J. Gen. Chem. U.S.S.R.* (*Eng. Transl.*), **25**, 1735 (1955). These authors have shown, on the basis of spectral evidence, that 2- and 4-pyridones are most accurately represented by the formulations, A and B. If this condition obtains in the bicyclic heterocyclic examples, then a more accurate formulation of the foregoing substances is illustrated by C.

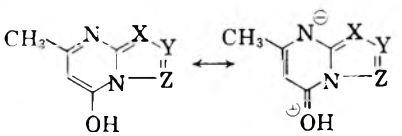


A B C

The anticipated spectrum of C should be reminiscent of naphthalene. The spectra of various substituted naphthalenes have been summarized by Morton and deGouveia [A. R. Morton and A. J. A. deGouveia, *J. Chem. Soc.*, p. 916 (1934)]. It is shown that their spectra fall into three regions, as follows: *a* about 220 mμ with high ε values; *b* 250–290 mμ with moderate ε values; *c* 295–325 mμ with low ε values. The *a* region has been identified as arising from the ethylenic chromophore and the *b* region from the styrene chromophore. It is seen immediately that there is a parallel between the spectra of naphthalene derivatives and the spectra of the compounds under discussion. This is good evidence that ionic structures would make important contributions to the resonance hybrid.



Formulation I

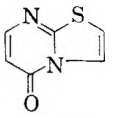
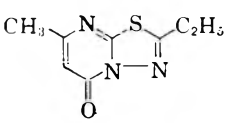
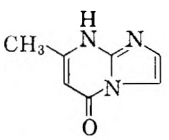
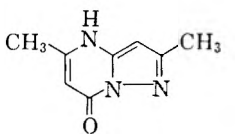
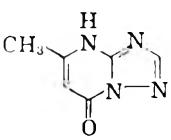
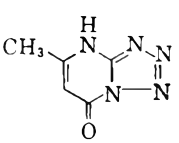


Formulation II

Formulation I is in better agreement with the infrared spectrum, which shows N—H absorption characteristic of an ammonium salt as a broad band at 3.6 to 4.0 μ and an amide carbonyl absorption at about 5.9 μ (not six-membered ring vibrations, which are unknown below 6.1 μ). The spectrum of 3,6-dimethyl-4-oxo-1,2,3a,7-tetrazaindene (Fig. 7) illustrates this point. (These absorptions do not enable us to distinguish between the 4- and 6-positions for the oxygen atom, but do show its carbonyl character. A different tautomer than that shown would also agree as well.)

TABLE II

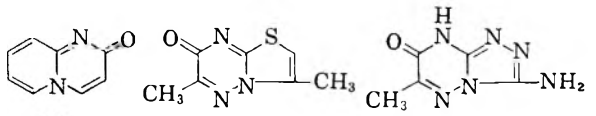
ULTRAVIOLET ABSORPTION SPECTRA OF SOME HETEROCYCLIC OXO BASES

| Substance | No. | Absorption Bands λa | λb | λc | Δλc from XIII |
|---|---|---|---|---|---|
| 4-Oxo-4a-azanaphthalene | XIII | 220 (16.0)<br>230 (12.6) | 277 (1.6) | 380 (16) | |
| 4-Oxo-1,4a-diazanaphthalene | XII | 220 (16.0) | 248 (10.0)<br>258 (9.6) | 348 (10.0) | 32 |
|  <br>4-Oxo-1-thia-3a,7-diazaindene | XIV | 220 (8.4) | 252 (5.6)<br>260 (5.4) | 320 (12.4) | 60 |
|  <br>4-Oxo-6-methyl *derivatives of*<br>2-Ethyl-1-thia-3,3a,7-triazaindene | XV | 215 (10.8) | 235 (5.4)<br>255 (4.1) | 305 (6.3) | 75 |
|  <br>1,3a,7-Triazaindene | XVI | 214 (12.4) | 248 (4.2) | 292 (9.9) | 88 |
|  <br>2-Methyl-3,3a,7-triazaindene | XVII | 218 (28.0) | 255 (6.4)[a] | 292 (6.8) | 88 |
|  <br>1,3,3a,7-Tetrazaindene | XVIII | | 256 (6.4) | 278 (10.8) | 102 |
| Its 5-methyl isomer | XVIIIa | | 244 (4.8) | 280 (9.0) | 100 |
|  <br>1,2,3,3a,7-Pentazaindene | XIX | | 244 (5.3) | 274 (6.3) | 106 |

[a] In order to make this peak more obvious, this spectrum was run in ammoniacal methanol; this treatment causes little change in the position of the peaks of the other isomers.

resulted in a shift of the long wave-length band to shorter wave lengths, a result which parallels the carbethoxy derivatives previously described. The main absorption bands again fall roughly into three regions, as described for the first series. The chief difference is in the position of the long wave-length band which is now at shorter wave lengths with respect to XII and XIII. The similarities and differences between the two series will be seen more clearly by comparisons made from Tables I and II. It is apparent from consideration of these data that the long wave-length band is shifted progressively toward shorter wave lengths as the carbon atoms of the indene ring system are successively replaced by hetero atoms.

It might be argued that the alternate method of ring closure to give a structure of type III rather than II is responsible for the shorter wave-length absorptions of XVI through XIX. For this reason, three compounds: 2-oxo-1,4a-diazanaphthalene (XX), 3,5-dimethyl-6-oxo-1-thia-3a,4,7-triazaindene (XXI), and 3-amino-5-methyl-6-oxo-1,2,3a,-4,7-pentazaindene (XXII)[5] were synthesized. These latter two substances may well be the 3,6-dimethyl-5-oxo-1-thia-3a,4,7-triazaindene and 3-amino-6-methyl-5-oxo-1,2,3a,4,7-pentazaindene isomers, respectively. In either case, the carbonyl group is connected to an exocyclic nitrogen atom, which is the relevant point for this discussion. Synthetic difficulties make the number of compounds for comparison in this series necessarily small.



XX XXI XXII

(5) E. C. Taylor, Jr., W. H. Gumprecht, and R. F. Vance, *J. Am. Chem. Soc.*, **76**, 619 (1954).

The structure of XX has been well established by Adams.[3] Its spectrum is shown in Fig. 5, together with the spectra of XXI and XXII. As is immediately apparent on comparison of Figs. 3 and 4 with Fig. 5, there is a considerable difference in

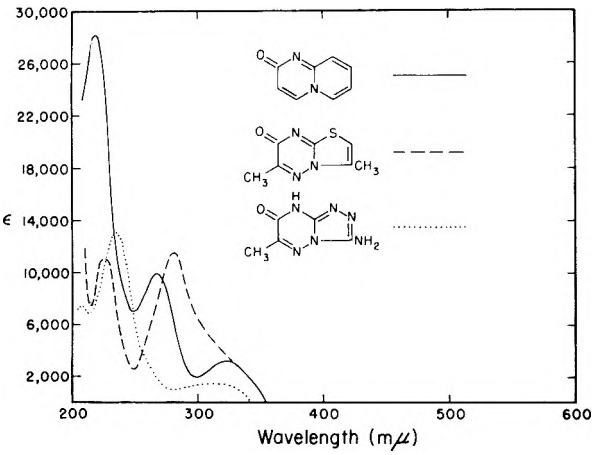



Fig. 5. Ultraviolet absorption spectra: XX, ———; XXI, – – – –; XXII, .....

the shapes of the absorption curves for the two series. The main difference is the relation of the long wave-length band in the *c* region to that of the absorption peak in the *b* region. In the II series (4-one), the ratio of the extinction coefficients of the *c* to that of the *b* band is always greater than 1, whereas, in the III (6-one) series, the *c* band is at best only one third the intensity of the *b* band. The relative intensities of these bands are shown in Table III. The values for XXI are included for comparison. Taking all the available evidence into account, the similarity of the absorption spectra of the condensation products described in this paper to those of the spectra of compounds with known II (4-one) configuration supports the thesis that the reaction of heterocyclic amines having the amidine structure $-N=\overset{|}{C}-NH_2$ with both ethyl ethoxymethylenemalonate and ethyl acetoacetate proceeds to give, as the principal products, compounds possessing the 4-one structure.

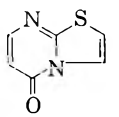
TABLE III

COMPARISON OF ULTRAVIOLET ABSORPTION DATA OF THE 4-*ONE* AND 6-*ONE* SERIES

| Compound | λa | λb | λc | Intensity Ratio, c/b |
|---|---|---|---|---|
| XVI | 214(12.4) | 248( 4.2) | 292(9.9) | 2.4 |
| XX | 218(28.2) | 268(10.0) | 324(3.2) | 0.31 |
| XXI | 226(11.1) | 280(11.6) | 322(3.4) | 0.29 |
| XXII | 218( 7.4) | 240(13.1) | 310(1.4) | 0.11 |

*C. Thiadiazaindenes.* A comparison of the ultraviolet absorption spectra of several derivatives of 4-oxo-1-thia-3a,7-diazaindene (XIV) may be of interest. The introduction of a methyl group into the 6-position of a thiadiazaindene nucleus, as in XIVa, produces a new band at 212 mμ and a splitting of the *c* band into a peak at 313 mμ and a shoulder at 323 mμ. An additional methyl group, as in 3,6-dimethyl-4-oxo-1-thia-3a,7-diazaindene (XIVb), again shows the 212 mμ band, and the *c* band has been split into two definite bands at 323 mμ and 338 mμ.

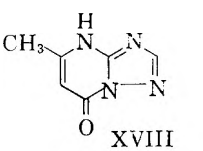
XIV. —
XIVa. 6-$CH_3$
XIVb. 3,6-di$CH_3$



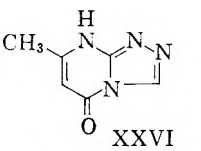
XXIII. 6-$CH_3$-3-$C_6H_5$
XXIV. 5-$CO_2C_2H_5$-3-$C_6H_5$
XXV. 5-$CO_2C_2H_5$-2-Cl

The 5-carbethoxy- (IV), the 5-carbethoxy-3-methyl- (IVa), and the 5-carbethoxy-3-phenyl- (XXIV) derivatives show a bathochromic shift of the long wave-length bands, as would be expected for the respective auxochromes. The *b* band in the spectrum of 5-carbethoxy-2-chloro-4-oxo-1-thia-3a,7-diazaindene (XXV) has almost disappeared, occurring only as a shoulder. The ultraviolet absorption data for this series are collected in Table IV.

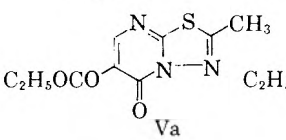
*D. 1,2,3a,7- and 1,3,3a,7-Tetrazaindenes.* 3-Amino-1,2,4-triazole reacts with ethyl acetoacetate and certain related substances to give a tetrazaindene, m.p. 278°, but an isomer, m.p. 254°, results when 2-hydrazino-4-hydroxy-6-methylpyrimidine is cyclized by warm formic acid.[6] The latter is isomerized to the former by treatment with hot formic acid. Both isomers show ultraviolet absorption spectra typical of a 4-one structure (Figs. 9 and 10); accordingly, the two structures (XVIII and XXVI) must be involved. It was shown in the related



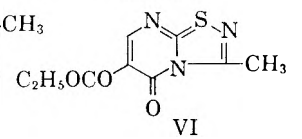
XVIII



XXVI



Va



VI

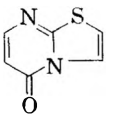
systems, Va and VI, that a shift of the nitrogen atom from the 3-position to the 2-position resulted in a bathochromic shift of about 17 mμ in the absorption of the long wave-length band (cf. Fig. 1, Table I). Since there is a 16-mμ difference in the long wave-length absorptions of the two isomers, structure XVIII has been assigned to the 278° isomer and XXVI to the 254° isomer.

It is curious that both XVIII and XXVI show one acidic hydrogen when titrated against potassium methoxide in a nonaqueous titration, yet form

(6) C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, J. F. Tinker, and J. A. VanAllan, *J. Org. Chem.*, 24, 787 (1959).

TABLE IV

ULTRAVIOLET SPECTRA OF 4-OXO-1-THIA-3a,7-DIAZAINDENES



| Compound | Substituent | Absorption Bands λa | λb | λc |
|---|---|---|---|---|
| XIV | None | 222 (8.4) | 252 (5.6) | 320 (12.5) |
| | | | 260 (5.3) | |
| XIVa | 6-$CH_3$ | 212 (9.7) | 252 (4.9) | 313 (10.3) |
| | | 225 (11.4) | 260 (4.8) | ~323 |
| XIVb | 3,6-di-$CH_3$ | 212 (9.6) | 258 (4.9) | 323 (10.8) |
| | | 231 (10.0) | 265 (4.8) | 338 (9.4) |
| XXIII | 6-$CH_3$-3-$C_6H_5$ | 228 (8.0) | 256 (7.0) | 350 (11.0) |
| | | | 280 (6.3) | |
| IV | 5-$CO_2C_2H_5$ | 336 (4.1) | 258 (4.6) | 340 (18.6) |
| | | | 261 (4.1) | |
| IVa | 5-$CO_2C_2H_5$-3-$CH_3$ | 243 (5.7) | 260 (4.2) | 348 (16.6) |
| XXIV | 5-$CO_2C_2H_5$-3-$C_6H_5$ | 222 (11.2) | 268 (10.3) | 352 (15.6) |
| XXV | 5-$CO_2C_2H_5$-2-Cl | 232 (6.9) | ~258 | 342 (17.4) |

well-defined salts with methyl *p*-toluenesulfonate. The absorption spectra of these salts (Fig. 6) parallel those of the parent compounds in respect to the relative positions of the long wave-length bands. These latter bands have increased intensity and a short wave-length band has appeared in the 210–220 mμ region. Attention is drawn to the marked similarity of the absorptions of the salts to XIV, again emphasizing the 4-one structures.

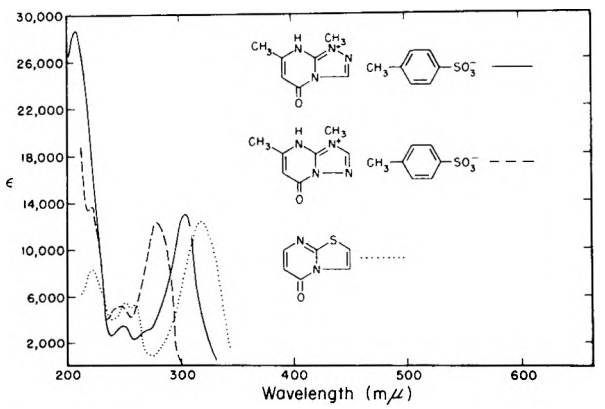
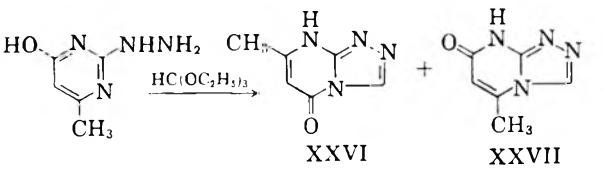
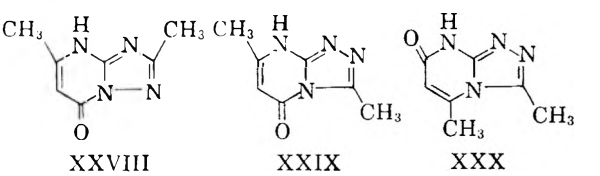



Fig. 6. Ultraviolet absorption spectra of two salts and XIV, .....

When 2-hydrazino-4-hydroxy-6-methylpyrimidine is treated with a nonacidic formylating agent (ethyl orthoformate, dimethylformamide), two isomeric tetrazaindenes are produced. One of these is identical with the isomer, XXVI, previously mentioned as having been obtained using warm formic acid. The second was also obtained from the same hydrazinopyrimidine and phenyl isothiocyanate; this reaction gave a mercapto derivative, in which the —SH group was replaced by hydrogen when catalytically reduced in the presence of Raney nickel.[6] The new isomer is 4-methyl-6-oxo-1,2,3a,7-tetrazaindene (XXVII).




The dimethylhydroxytetrazaindenes (XXVIII–XXX) corresponding to the monomethyl series have been prepared by analogous reactions. The




melting points of the three isomers are almost identical, and a mixture of the two 4-one isomers does not give a depressed melting point, whereas a mixture of 4-one and 6-one isomers does.[7]

Three of the four isomers theoretically possible from the reaction of 3-amino-1,2,4-triazole and ethyl acetoacetate have, thus, been prepared, along with the corresponding products from 3-amino-5-methyl-1,2,4-triazole. Numerous attempts to synthesize the fourth isomer in each series have met with failure. The ultraviolet spectra of these substances are collected in Table V. The ultraviolet spectrum of XXVII has a peak absorption at 248 mμ, which is consistent with the 6-one structure. The spectra of the dimethyl series, XXVIII, XXIX, and XXX, parallel exactly those of the monomethyl series, as shown in Table V. While the infrared spectra of XVIII and XXVI are about identical (see Figs. 9 and 10), there is considerable difference in their ultraviolet spectra. The infrared

(7) C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, J. F. Tinker, and J. A. VanAllan, *J. Org. Chem.*, 24, 793 (1959).

spectra of the 4-ones, XXIX and XXVIII, are quite similar but are not identical (see Figs. 7 and 8).

TABLE V

ULTRAVIOLET SPECTRA OF METHYL AND DIMETHYL OXOTETRAZAINDENES

| Compound | λa | λb | λc |
|---|---|---|---|
| XVIII | 210 | 256 (6.4) | 278 (10.8) |
| XXVI | 210 (17.7) | 246 (4.8) | 294 ( 6.8) |
| XXVII | 210 (22.7) | 248 (7.0) | |
| XXX | 210 (23.0) | 248 (6.6) | |
| XXIX | 209 (17.0) | 248 (4.6) | 298 ( 9.2) |
| XXVIII | 210 (23.5) | 238 (2.8) | 272 ( 9.5) |

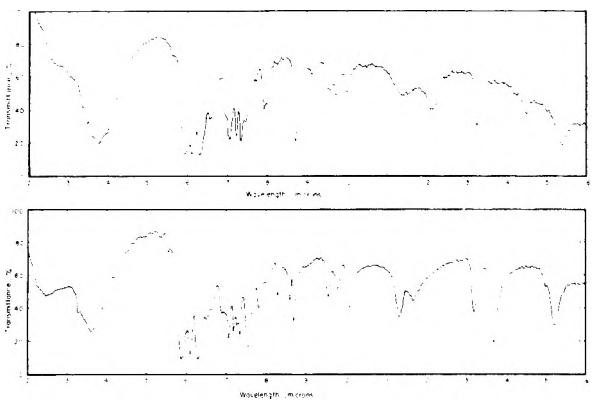


Fig. 7. Infrared spectrum of 3,6-dimethyl-4-oxo-1,2,3a,7-tetrazaindene (XXIX)

Fig. 8. Infrared spectrum of 2,6-dimethyl-4-oxo-1,3,3a,7-tetrazaindene (XXVIII)

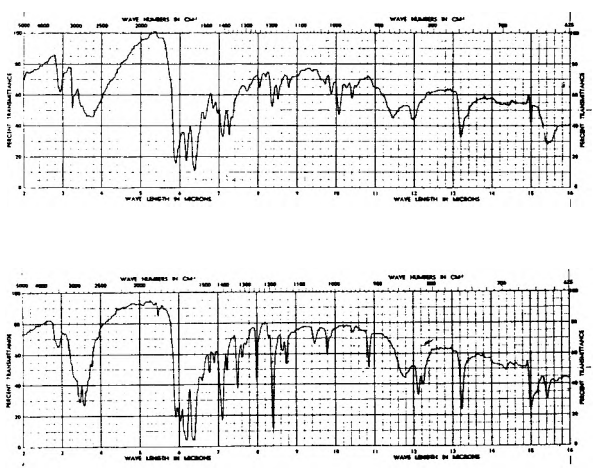


Fig. 9. Infrared spectrum of 6-methyl-4-oxo-1,2,3a,7-tetrazaindene (XXVI)

Fig. 10. Infrared spectrum of 6-methyl-4-oxo-1,3,3a,7-tetrazaindene (XVIII)

Attention is drawn to the remarkable similarity of spectra in the 6-one series. Thus, XXVII and XXX have very similar absorptions in the infrared (see Figs. 11 and 12), but they are greatly different from the isomeric 4-one series, particularly in the carbonyl region. The 4-one series has an amide band below 6 $\mu$, whereas the 6-one series

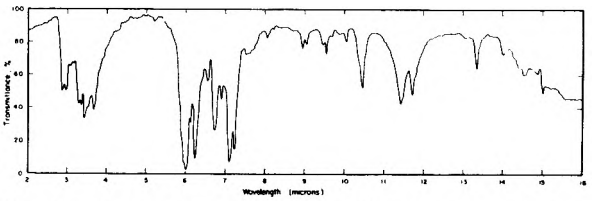


Fig. 11. Infrared spectrum of 3,4-dimethyl-6-oxo-1,2,3a,7-tetrazaindene (XXX)

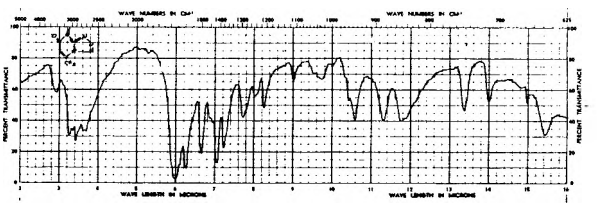
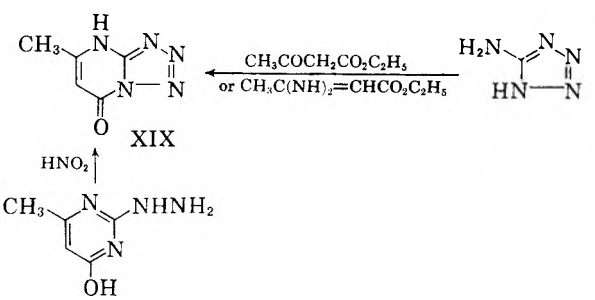


Fig. 12. Infrared spectrum of 4-methyl-6-oxo-1,2,3a,7-tetrazaindene (XXVII)

has a band at 6 $\mu$. The large amount of fine-structure vibrations between 3 and 4 $\mu$ seems to be characteristic of the 6-one series.

The condensation of 5-aminotetrazole with ethyl acetoacetate or with ethyl $\beta$-aminocrotonate gives a product (XIX) identical with that obtained by the action of nitrous acid on 2-hydrazino-4-hydroxy-6-methylpyrimidine.[7] Since the five-membered tetrazole ring is symmetrical, the only two

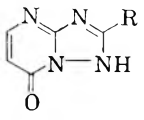



possible isomers are 6-methyl-4-oxo- (XIX) and 4-methyl-6-oxo-1,2,3,3a,7-pentazaindene. In all known instances,[4,8] ethyl $\beta$-aminocrotonate has been shown to give compounds of the 4-one configuration. For this reason, it seems highly probable that XIX represents the correct configuration of the reaction product of the tetrazole with ethyl $\beta$-aminocrotonate.

The effect of substituents on the ultraviolet absorption spectrum of 4-oxo-1,3,3a,7-tetrazaindene (XXXI) is shown in Table VI. The *a* band occurs at wave lengths of less than 200 m$\mu$ and can be seen only in the salts (Fig. 6). The *b* band is relatively constant in position and intensity in the whole series. Methyl substituents as in XVIII and XVIIIa do not affect the *c* band, in contrast to the 1-thia-3a,7-diazaindene series. As the 2-position is progressively substituted by more efficient electron donors, the long wave-length band is shifted

(8) H. Antaki and V. Petrow, *J. Chem. Soc.*, 551 (1951).

toward longer wave lengths (IX through XXXV, Table VI). It is clear then, that these substituents are attached to the end of a conjugated system, such as is indicated in XXXVI.



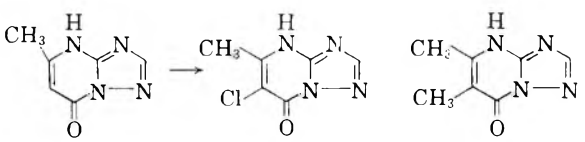
XXXVI

TABLE VI

ULTRAVIOLET ABSORPTION SPECTRA OF 4-OXO-1,3,3a,7-TETRAZAINDENES

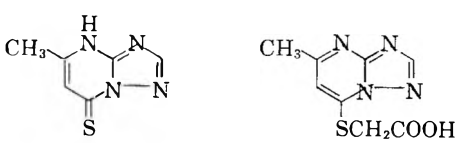
| Compound | Substituent | λb | λc |
|---|---|---|---|
| XXXI | | 248(10.8) | 282(12.9) |
| XVIII | 6-$CH_3$ | 256( 6.4) | 278(10.8) |
| XVIIIa | 5-$CH_3$ | 244( 4.8) | 280( 9.0) |
| XXXII | 6-Me-5-Cl | 262( 7.2) | 298(10.8) |
| IX | 5-$CO_2C_2H_5$ | 247( 5.3) | 290( 8.9) |
| IXa | 5-$CO_2C_2H_5$-2-$CH_3$ | 248( 5.4) | 291( 9.0) |
| XXXIII | 5-$CO_2C_2H_5$-2-$CH_2OH$ | 252( 5.8) | 298(10.0) |
| XXXIV | 5-$CO_2C_2H_5$-2-$SCH_3$ | 265( 6.6) | 308(16.2) |
| XXXV | 5-$CO_2C_2H_5$-2-$NH_2$ | 252( 3.0) | 310(14.0) |

Chlorination of XVIII gives the 5-chloro derivative (XXXII),[5] but the position taken by the entering methyl group when methylation is effected by dimethyl sulfate is unknown. It is probably on one of the nitrogen atoms, because of a negative Zeisel (not oxygen alkylation); carbon alkylation is excluded since the substance is not identical with the known isomer, XXXVII.[9] From the absorption spectra it is apparent that the -one structure of XVIII is still present (Table VII).



XVIII XXXII XXXVII

The sulfur analog[8] of XVIII has an ultraviolet spectrum comparable in respect to shape, showing that it, too, has the thiono structure (XXXVIII). When this substance is alkylated by sodium



XXXVIII XXXIX

chloroacetate, the alkylation product shows a hypsochromic shift of 40 mμ in the long wavelength band (Table VII). This indicates the disappearance of the thiono structure, i.e., S-alkylation has occurred to give XXXIX.

(9) E. Birr, *Z. wiss. Phot.*, 50, 107 (1955).

The 4-chloro- and 4-amino-derivatives (XL and XLI), as well as XXXIX, resemble the parent base (XLII), having quite similar spectra, with the expected modifications due to the substituents (Table VII).

TABLE VII

ULTRAVIOLET ABSORPTION SPECTRA OF MISCELLANEOUS 1,3,3a,7-TETRAZAINDENES

| Compound | Substituent | λ max b | λ max c |
|---|---|---|---|
| XVIII | 6-$CH_3$-4-oxo | 256( 6.4)[a] | 278(10.8) |
| XXXII | 6-$CH_3$-5-Cl-4-oxo | 262( 7.2) | 298(10.8) |
| XXXVII | 5,6-$(CH_3)_2$-4-oxo | 265( 4.7) | 298(12.5) |
| XXXVIII | 6-$CH_3$-4-thiono | 235( 9.0) | 336(20.8) |
| XXXIX | 6-$CH_3$-4-$SCH_2CO_2H$ | 210(15.0)[b] | 291(11.4) |
| XL | 6-$CH_3$-4-Cl | 222(23.8)[b] | 272( 5.0) |
| XLI | 6-$CH_3$-4-$NH_2$ | | 288(13.5) |
| XLII | 6-$CH_3$ | 234( 1.5) | 271( 4.0) |

[a] Run in ammoniacal methanol. Lacking a 5-substituent, XVIII shows a very faint *b* band in neutral or acidic methanol; see footnote *a*, Table II. [b] These are λa bands.

## EXPERIMENTAL

The various new substances were mostly prepared by one of the following general procedures. Their properties are collected in Table VIII.

A. Equimolecular quantities of the heterocyclic amine and ethyl acetoacetate or ethyl ethoxymethylenemalonate in 5 volumes of trichlorobenzene were refluxed and the ethanol was collected until the theoretical amount had been evolved. The reaction mixture was cooled and the solid collected. In some cases, it was necessary to add petroleum ether to the cooled reaction mixture to precipitate the product. The solid was washed with petroleum ether and recrystallized from the appropriate solvent.

B. A mixture of the amine and 10% excess of either of the esters in 3 to 5 volumes of acetic acid was refluxed 3–6 hr. and cooled. If a solid separated, it was collected and recrystallized. In some cases, it was necessary to concentrate the reaction mixture to obtain the product.

C. A solution of 0.1 mole of the carbethoxyindene in 150 ml. of 2*N* hydrochloric acid was refluxed for 5 hr., cooled, and the solid collected and recrystallized.

D. A mixture of the amine and a 10% molar excess of ethyl β-aminocrotonate was held at 180–190° for 8 hr. If the product was a low-melting solid, for example, XV, the reaction mixture was subjected to vacuum distillation. Otherwise, alcohol was added and the product was collected on a filter.

*3,5-Dimethyl-6-oxo-1-thia-3a,4,7-triazaindene* (XXXI). A mixture of 0.02 mole each of 3-amino-2-imino-4-methylthiazoline hydrochloride[10] and pyruvic acid in 50 ml. of 2*N* sulfuric acid was refluxed 4 hr. and evaporated *in vacuo* to 6 ml. The residue was carefully neutralized with 3*N* sodium hydroxide solution and the solid collected and recrystallized from water. Yield, 3 g. of the indene, m.p. 227°.

*Anal.* Calcd. for $C_7H_7N_3OS$: N, 23.2; S, 17.7. Found: N, 23.2; S, 17.3.

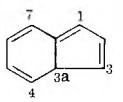
*Acknowledgment.* We are indebted to Dr. D. W. Stewart and Miss T. J. Davis, of these Laboratories, for the ultraviolet and infrared spectra.

ROCHESTER 4, N. Y.

(10) H. Beyer, W. Lassig, and E. Bulka, *Ber.*, 87, 1385 (1954).

TABLE VIII

PROPERTIES OF POLYAZAINDENES




| No. | Substituents and Positions | Method of Prep. | M.P., °C. | Empirical Formula | Analysis Calcd. % C | Calcd. % H | Calcd. % N | Found % C | Found % H | Found % N |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | 4-Oxo-1-thia-3a,7-diazaindenes | | | | | | |
| IV | 5-$COOC_2H_5$[a] | A | 186 | $C_9H_8N_2O_3S$ | 48.4 | 3.5 | | 48.3 | 3.5 | |
| IVa | 5-$COOC_2H_5$-3-$CH_3$[b] | A | 192 | $C_{10}H_{10}N_2O_3S$ | 50.5 | 4.1 | | 51.8 | 5.1 | |
| IVb | 5-COOH | C | 285 dec. | $C_7H_6N_2O_4S$ | 39.2 | 2.8 | | 39.0 | 2.6 | |
| XIV | None[c] | [d] | 116 | $C_6H_4N_2OS$ | 47.3 | 2.6 | | 47.3 | 2.9 | |
| XIVa | 6-$CH_3$[c] | B | 112 | $C_7H_6N_2OS$ | 50.6 | 3.6 | | 50.3 | 3.9 | |
| XIVb | 3,6-$(CH_3)_2$[e,f] | D | 133–135 | $C_8H_8NOS$ | | | | | | |
| XXIII | 6-$CH_3$-3-$C_6H_5$[g] | B | 238–240 | $C_{13}H_{10}N_2OS$ | 64.5 | 4.5 | | 63.4 | 4.3 | |
| XXIV | 5-$COOC_2H_5$-3-$C_6H_5$[a] | A | 174 | $C_{14}H_{12}N_2O_3S$ | 60.0 | 4.0 | | 60.1 | 4.1 | |
| XXV | 5-$COOC_2H_5$-2-Cl[b] | A | 149 | $C_9H_7ClN_2O_3S$ | 41.8 | 2.7 | | 42.0 | 2.7 | |
| | 5-$COOC_2H_5$-3-$C_6H_5C_6H_4$[b] | A | 169 | $C_{21}H_{16}N_2O_3S$ | 66.0 | 4.4 | | 66.8 | 4.3 | |
| | 5-$COOC_2H_5$-3-$NO_2$[h] | A | 225 | $C_9H_7N_3O_5S$ | 39.4 | 2.5 | | 39.4 | 2.9 | |
| | | | | 4-Oxo-1-thia-3,3a,7-triazaindenes | | | | | | |
| V | 5-$COOC_2H_5$-2-$C_2H_5$[g] | A | 96 | $C_{10}H_{11}N_3O_3S$ | 47.5 | 4.3 | | 47.6 | 4.6 | |
| Va | 5-$COOC_2H_5$-2-$CH_3$[a] | A | 140 | $C_9H_9N_3O_3S$ | 45.2 | 3.8 | | 45.2 | 3.6 | |
| XV | 2-$C_2H_5$-6-$CH_3$[c] | D | 40 | $C_8H_9N_3OS$ | 49.2 | 4.6 | | 49.0 | 4.7 | |
| | | | | 4-Oxo-1-thia-2,3a,7-triazaindene | | | | | | |
| VI | 5-$COOC_2H_5$-3-$CH_3$[c] | A | 110 | $C_9H_9N_3O_3S$ | 45.2 | 3.8 | 17.5 | 45.3 | 3.6 | 17.6 |
| | | | | 4-Oxo-1,3a,7-triazaindenes | | | | | | |
| VII | 5-$COOC_2H_5$[i] | B | 253 | $C_9H_9N_3O_3$ | 52.2 | 4.4 | 20.3 | 52.4 | 4.3 | 20.6 |
| XVI | 6-$CH_3$[i] | B | 239 | $C_7H_7N_3O$ | | | 28.2 | | | 27.8 |
| | | | | 7-Oxo-1,4,7a-triazaindenes | | | | | | |
| VIII | 2-$CH_3$-6-$COOC_2H_5$[j] | B | 294 | $C_{10}H_{11}N_3O_3$ | | | 19.0 | | | 18.7 |
| XVII | 2,5-$(CH_3)_2$[j] | B | 253 | $C_8H_9N_3O$ | 58.5 | 5.5 | 25.8 | 59.4 | 6.5 | 26.3 |
| | 2-$CH_3$-5-$C_6H_5$[j] | B | 286 | $C_{13}H_{11}N_3O$ | | | 18.6 | | | 19.3 |
| | 5-$CH_3$-2-$C_6H_5$[j] | B | >315 | $C_{13}H_{11}N_3O$ | 69.3 | 4.9 | 18.6 | 69.8 | 5.0 | 19.6 |
| | 5-$CH_3$[j] | B | 307 | $C_7H_7N_3O$ | 56.4 | 4.7 | 28.2 | 56.0 | 4.8 | 28.6 |
| | 2-$CH_3$-6-COOH | C | >285 dec. | $C_8H_7N_3O_3$ | 49.7 | 3.6 | | 49.4 | 4.0 | |

[a] Recrystallization from ethanol. [b] Butanol. [c] Ligroin. [d] Decarboxylation of IVb. [e] H. Antaki and V. Petrow, *J. Chem. Soc.*, 551 (1951). [f] Benzene-ligroin. [g] Toluene-ligroin. [h] Ethyl nitrate. [i] Water [j] Dimethylformamide.

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[COMMUNICATION NO. 1995 FROM THE KODAK RESEARCH LABORATORIES]

# The Structure of Certain Polyazaindenes. II. The Product from Ethyl Acetoacetate and 3-Amino-1,2,4-triazole

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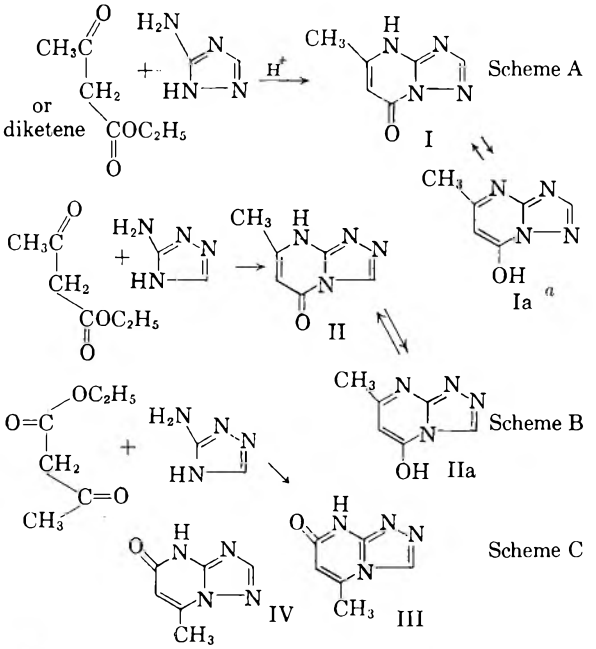
*Received December 19, 1958*

3-Amino-1,2,4-triazole and ethyl acetoacetate or diketene give only one of the four possible isomeric substances, which is 6-methyl-4-oxo-1,3,3a,7-tetrazaindene. Two of the other isomers are obtained from 2-hydrazino-4-methyl-6-hydroxypyrimidine and ethyl orthoformate. One of the latter is isomerized to the first substance by strong acid. A number of related compounds are described and their interrelationships are shown. The accumulated spectral and chemical evidence support the structure named; the latter is also in accord with theoretical considerations.

In a study of the reaction between aminotriazoles and 1,3-dicarbonyl compounds, Bülow[1,2] obtained a substance from 3-amino-1,2,4-triazole and ethyl acetoacetate to which he assigned the structure Ia, 4-hydroxy-6-methyl-1,3,3a,7-tetrazaindene.[2,3] Since the structure was not determined by the method of synthesis, it was assumed that the

(1) C. Bülow, *Ber.*, **42**, 2599, 3555, 4429 (1909).
(2) C. Bülow and K. Haas, *Ber.*, **42**, 4638 (especially, p. 4642)(1909).

*ketonic* carbonyl group had reacted with the amino group of the triazole, with subsequent cyclization, as shown in Scheme A. However, ring closure could equally well have occurred as shown in Scheme B, leading to isomer II. Furthermore, the *ester* group could have reacted with the amino group, with subsequent cyclization either way, Scheme C, leading to isomers III and IV. Thus, the synthesis is ambiguous. The empirical formula and bicyclic nature of the product are clearly established; the position of the substituents and the nature of the tautomerism are not.

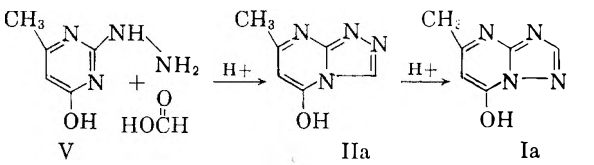



[a] The *a* designation represents the tautomeric form.

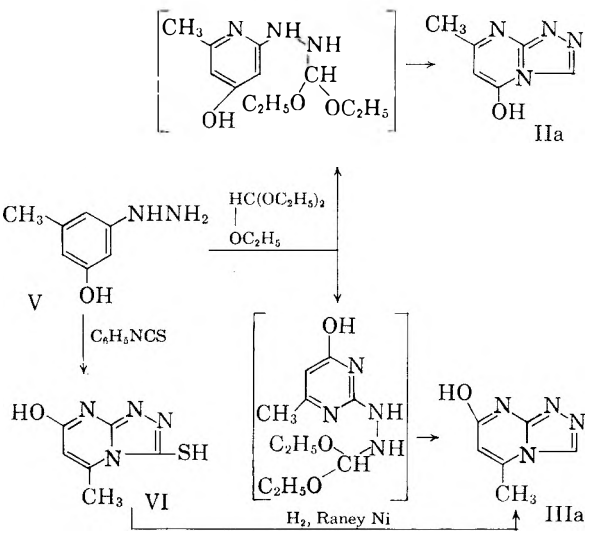
Birr and Walther[4] devised what appeared to them to be an unequivocal synthesis; by cyclizing 2-hydrazino-4-hydroxy-6-methylpyrimidine (V) with formic acid, the same substance was obtained as resulted from aminotriazole and ethyl acetoacetate. Hence, it was concluded that the nitrogen atoms had the 1,2,3a,7-arrangement, as shown in (IIa). Repetition of Birr and Walther's work in these Laboratories led to the discovery that the nature of the product depended on the acidity of the reacting solution. Under conditions milder than Birr and Walther's, an isomer was obtained, which, amazingly, in boiling formic acid, was isomerized to the long-known 1,3,3a,7-isomer! Thus, Birr and Walther's synthesis is not unambiguous. Homologs were obtained in a similar manner under slightly altered experimental conditions.

(3) The German authors used the name "6-methyl-1,3-triazo-7,*O'*-pyridazine-4-hydroxylic acid." Beilstein (main work, 4th ed., Vol. XXVI, p. 433) has renamed the oxo form I, "7-oxo-5-methyl-6,7-dihydro-1,3,4-triazaindolizine," dropping the "6,7-dihydro-" in the case of the tautomer shown in structure Ia. The authors of this paper have continued to use the "a" system, used in the preceding paper.

(4) E. Birr and W. Walther, *Ber.*, **86**, 1401 (1953).

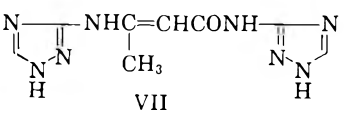



An independent synthesis of (II) (the 1,2,3a,7-isomer) was carried out here by the action of ethyl orthoformate on the same 2-hydrazinopyrimidine. This reaction can give two products (II and III), since ring closure can take place through either nitrogen atom of the pyrimidine, and *both* were obtained! The third isomer (IIIa)[5] was also formed from the hydrazine (V) and phenyl isothiocyanate, by way of the mercapto intermediate (VI). Thus,




*three* (I–III) *of the four isomers possible* are readily synthesized. Many attempts to obtain the fourth isomer (IV), and to accomplish an unequivocal synthesis of any *one*, were unsuccessful. For instance, 1-benzylthiourea and ethyl acetoacetate gave 1-benzylthiouracil, which was readily monomethylated by dimethyl sulfate and sodium hydroxide, but this product did not react with hydrazine. This suggested that *N*-methylation took place, rather than the desired attack at the sulfur atom.

Diketene and ethyl acetoacetate usually give the same products when employed in reactions of this type, and in this instance, both gave the same isomer, I. In addition, diketene gives a trimolecular product, which, it seems to us, is best represented as the amide, VII. Although the formation of this

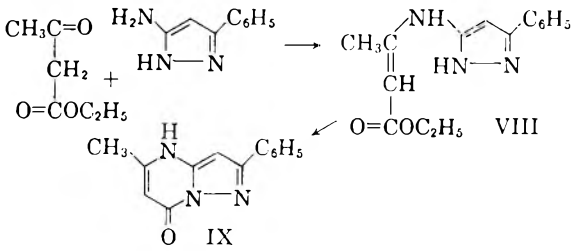



product indicates that the reaction proceeds stepwise, it cannot be used to show at which carbonyl

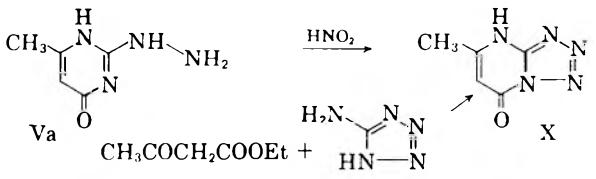
(5) Although these substances have the isomeric oxo structure (refer to 1st paper), for convenience in comparison the hydroxy form is often employed in this and succeeding papers.

group of ethyl acetoacetate the aminotriazole reacts first. This substance (VII) has been mentioned in the patent literature,[6,7] but given a different structure. The products are identical whatever procedure is followed.

Although it is generally known[8] that the ketonic carbonyl group of ethyl acetoacetate reacts preferentially with amines under acidic conditions, the only evidence applicable here is by analogy when a 3-aminopyrazole is substituted for the aminotriazole.[9] In this instance, the intermediate aminocrotonate (VIII) was actually isolated. It can cyclize in only one way, owing to the lack of the fourth nitrogen atom (*cf.* aminotriazole). The two reactions and the substances (I and IX) are entirely comparable. Corroborating evidence



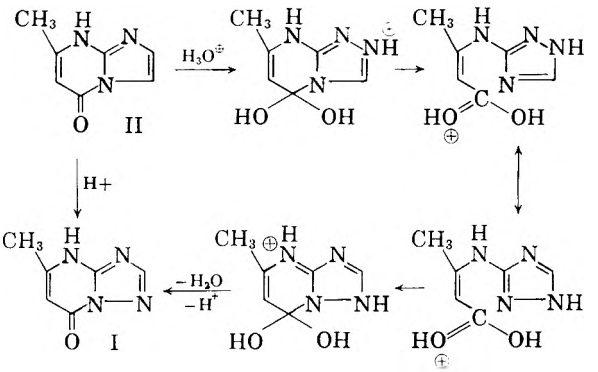
is also available from the corresponding compound in the pentazaindene series. Two independent reactions, (a) action of nitrous acid on the hydrazinopyrimidine (Va), and (b) interaction of ethyl acetoacetate and 5-aminotetrazole, gave products that were identical in all physical properties, including absorption spectra;[10] these are formulated as



Finally, a study was made of the residues from the preparation of the 1,3,3a,7-isomer (I) after removal of the latter. The residues, which amounted to 5% of the reaction mixture, were submitted to a countercurrent distribution in a Craig extractor.[11] Two products were definitely present; the major material (90+%) was the bisamide (VII); the remainder was 3-acetamido-1,2,4-triazole. A possible trace of the 1,2,3a,7-isomer (II) was suggested, but there was not the slightest evidence of anything that could be interpreted as the missing fourth isomer (IV). These products are consistent with the mechanisms that are suggested in this paper.

The rearrangement of the 1,2,3a,7-isomer (II) to the 1,3,3a,7-form (I) by strong acids is easily visualized as outlined in Chart I.

Chart I



Most of the physical and chemical properties of the tetrazaindene are best accounted for by the oxo structure (I);[5] among these may be mentioned absorption spectra, behavior at a dropping mercury electrode, and reactions outlined here. It behaves like similar heterocyclic nitrogen compounds, forming a 4-chloro derivative (XI) when treated with phosphoryl chloride. The chlorine atom is available for reactions of double decomposition. Thus, upon hydrolysis, the parent hydroxy compound (I) is regenerated. By suitable procedures, the 4-thiono (XII), 4-carboxymethylmercapto (XIII), 4-amino, 4-azido, and 4-triazolylamino derivatives (XIV) have been prepared. The chlorine atom can be replaced by hydrogen catalytically, giving 6-methyl-1,3,3a,7-tetrazaindene (XV); the latter has been prepared by two independent syntheses and a variety of conditions.[12]

Chlorination of I gives a 5-chloro derivative (XVI); the position of the chlorine atom was shown by an independent synthesis of the same substance from 3-aminotriazole and ethyl $\alpha$-chloroacetoacetate. Persulfate gives a 5-hydroxy compound (XVII). The reactions are summarized in Chart II.

It will be seen that the evidence in favor of structures I and Ia is cumulative; the most convincing is based on the absorption spectra (refer to Part I). Additional support, as well as an explanation of some of the reactions, is afforded by mechanistic considerations.

(6) N. Heimbach and W. Kelly, Jr., U. S. Patent **2,444,608** (1948); *Chem. Abstr.*, **42**, 7180 (1948).

(7) N. Heimbach and W. Kelly, Jr., U. S. Patent **2,475,136** (1949); *Chem. Abstr.*, **43**, 8294 (1949).

(8) C. R. Hauser and G. A. Reynolds, *J. Am. Chem. Soc.*, **70**, 2402 (1948).

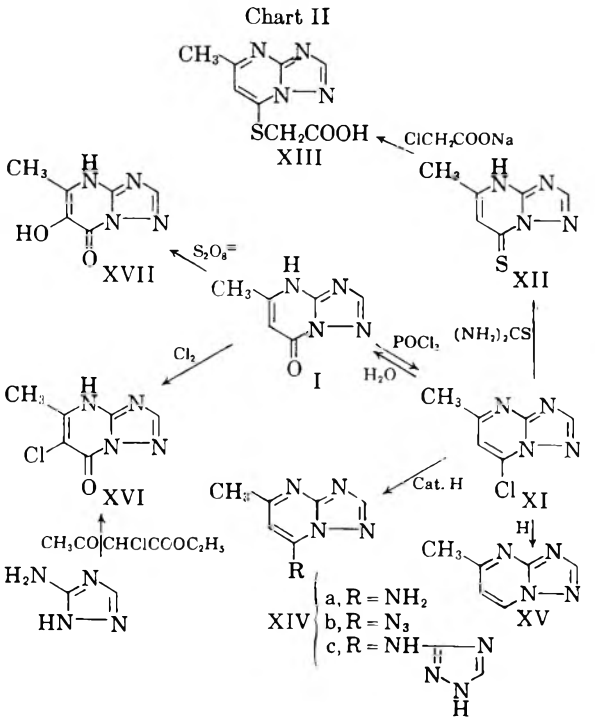
(9) S. Checchi, P. Papini, and M. Ridi, *Gazz. chim. ital.*, **85**, 1160 (1955); *Chem. Abstr.*, **50**, 10098 (1956).

(10) C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, J. F. Tinker, and J. A. VanAllan, *J. Org. Chem.*, **24**, 779 (1959).

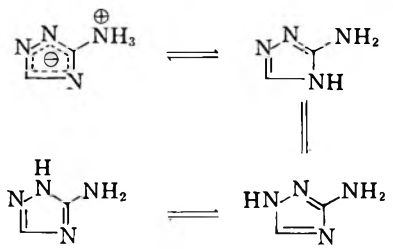
(11) L. C. Craig, W. Hausmann, E. H. Ahrens, Jr., and E. J. Harfenist, *Anal. Chem.*, **23**, 1236 (1951). We are indebted to Dr. M. Hill for this operation.

(12) C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, J. F. Tinker, and J. A. VanAllan, *J. Org. Chem.* **24**, 796 (1959).

Chart II



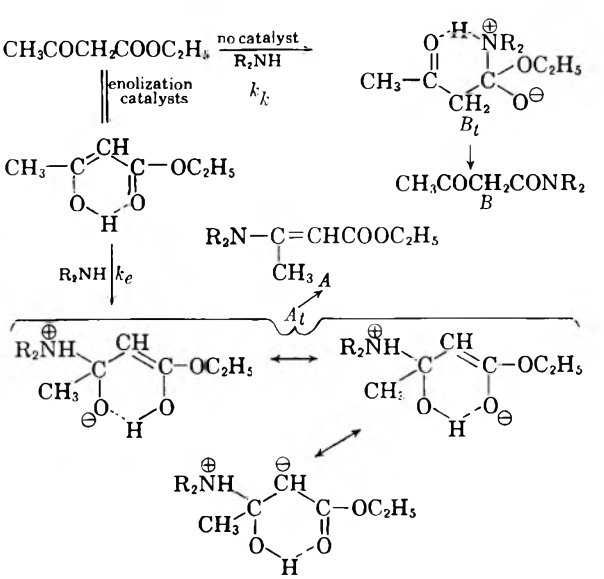

*Mechanistic discussion.* In ionizing solvents, the aminotriazole is best represented as:



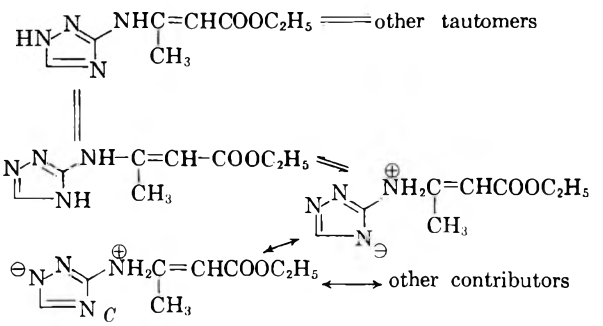
It is well known[8] that, under mild acedic catalysis, acetoacetic ester reacts with amines rapidly and exclusively at the ketonic carbonyl group, producing substituted aminocrotonates, *A*.[13]

$$R_2NH + CH_3COCH_2COOC_2H_5 \xrightarrow{\text{acid}} R_2N-C(CH_3)=CHCOOC_2H_5 \quad (A)$$

Clearly, catalysts promoting enolization favor the path to *A*. The rate of addition to the enol, $k_e$, is faster than that to the ketone, $k_k$, partly as a consequence of better stabilization of the charge in the transition state, $A_t$, compared to $B_t$. It is possible to mobilize all the equilibria between *A* and *B* so that the ratio of products obtained is

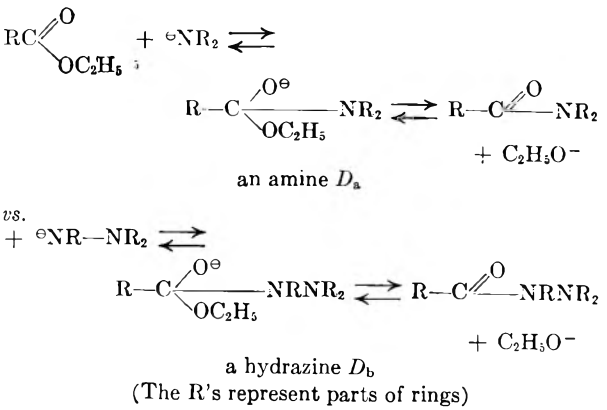



equal to the ratio of rates. Under these circumstances[8] the anil, *A*, is formed, showing experimentally that $k_e$ is much larger than $k_k$. Furthermore, the reaction forming *A* must occur with a basic nitrogen possessing an attached hydrogen. The NH of the triazole ring is not basic; the structure of the only possible intermediate is thus *C*. (If the two steps of the reaction were simultaneous, no true intermediate would be formed;




yet the influences would be the same, so that the argument as to the structure does not require the existence of the intermediate.) Birr's synthesis[4] from β-chlorocrotonic ester with aminotriazole should also, *via* a Michael addition, lead to *C*.

The subsequent step of the condensation is an addition to the ester carbonyl: Here, the reaction



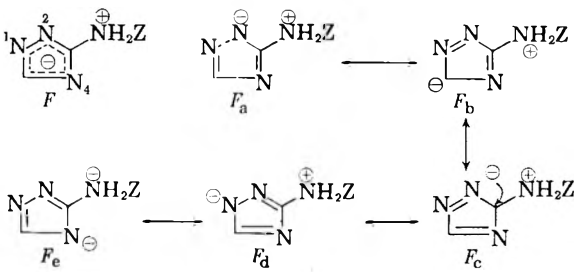

(13) The structure of vinylamines and of compounds like *A* has recently been discussed [B. Witkop, *J. Am. Chem. Soc.*, **78**, 2873 (1956)]. Aroyl (and acyl) acetic esters and aromatic amines form aroylacetanilides in the absence of an acidic catalyst; water must be excluded to get the best yields. Conversely, traces of acid and water favor reaction at the ketonic carbonyl group (*Org. Syntheses*, **Coll. Vol. III**, 108).

should be most rapid with that tautomer of *C* carrying a negative charge on the appropriate nitrogen atom. Of the two remaining paths, $D_a$ and $D_b$, the fastest will correspond to the reaction with the more nucleophilic site. Usually, the order of nucleophilicity follows the order of basicity, but hydrazine (a weaker base) is more nucleophilic than ammonia; trimethylhydrazine is a much weaker base than dimethylamine. (Comparing $E_a$ and $E_b$, we find that replacing $R_3C$— by $R_2N$—,

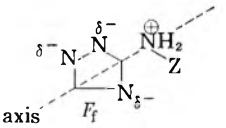
that is, substituting a more electronegative group, has decreased the electron contribution about $N^\alpha$ furnished by this bond. The $N^\alpha$ makes up for this decrease by becoming more electronegative, so that it is a stronger acid.[14,15]

Furthermore, groups in which the negative charge is diffuse are more highly nucleophilic; thiocyanate and azide, bases of medium strength, are among the most powerful nucleophilic agents. It follows that insight to the configuration of the transition state cannot be obtained from consideration of the separate parts.

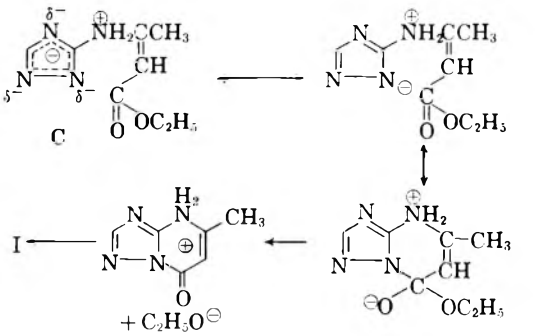
The whole is best represented as *F*, or, more explicitly, by the several contributors $F_a$ . . . $F_e$



(Z = β-crotonate residue). Of these, the forms with a negative charge on carbon $F_b$ and $F_c$ will contribute very little, and are ignored in the summary, $F_f$. The greater electronegativity of the hydrazine



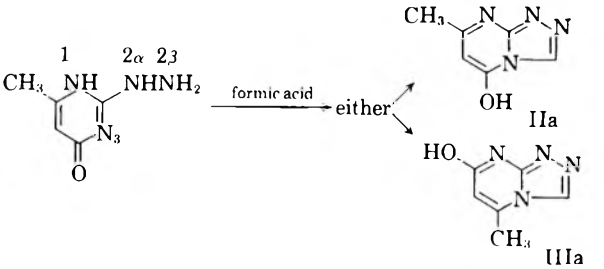
system may also increase its share of the charge at the expense of the nitrogen at position 4. The resulting effect, as shown in $F_f$, is a greater negative charge on the side of the axis toward position 2 than that toward position 4. This charge guides the carboxyl group toward the vicinity of position 2 (of the triazole ring) so that the reaction takes the path shown in Scheme G.



Scheme G

The acidity of the ring NH of aminotriazole and of the intermediate allows the ready tautomerization to the zwitterionic form, so that the further reaction, once the proper geometry has been achieved, can proceed through resonance contributors and loss of fragments. Consequently, we should expect this step to go rapidly: this has been confirmed experimentally.[16]

The cyclization of the 2-hydrazinopyrimidine by formic acid or its equivalent is equally well explained.



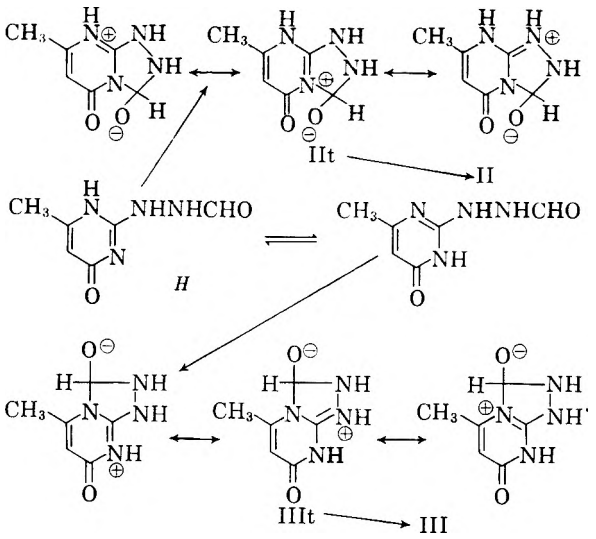
The first reaction of the hydrazine is formylation at 2β, since amines are easily converted to amides in warm formic acid. The reaction is reversible and proceeds most rapidly at the most basic 2β nitrogen. Thus, attention must be focused on the formyl derivative, *H*. (The formylhydrazine cannot be isolated, but the acetylhydrazine has been obtained.)

Since the nitrogen atoms of the pyrimidine ring in *H* are vinylogously related, any electrical character of either one of the atoms is conducted to the other. That is, a reaction can take place with equal facility at either nitrogen atom; the two possibilities of reaction correspond to $S_{N2}$ and $S_{N2'}$ types. The tautomerism between the two forms of *H* cannot control the course of the reaction (since it is, in all probability, a very fast interconversion). The stabilization of the charge is identical in both transition states; in both, the resonance of the pyrimidine nitrogens is lost. Ring closure to either

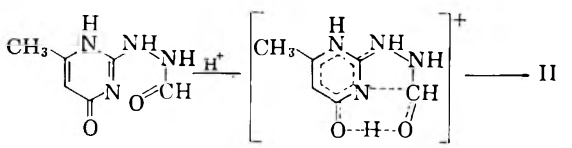
(14) The basic ionization constant of trimethylhydrazine [J. B. Class, J. G. Aston, and T. S. Oakwood, *J. Am. Chem. Soc.*, **75**, 2937 (1953)] is $6 \times 10^{-8}$, while that of dimethylamine is $5.2 \times 10^{-4}$.

(15) Quaternization of 1,2,4-triazole, a reaction that should proceed most rapidly at the most basic nitrogen, results in alkylation at position 4 [G. F. Duffin, J. D. Kendall, and H. R. J. Waddington, *Chem. & Ind. (London)*, 1458 (1954)] in agreement with the argument.

(16) That is, no matter how gentle the conditions, no intermediate can be isolated.



position might occur. Indeed, under neutral conditions, both isomers are formed. In an acidic solution, however, hydrogen-bonding between the two oxygen atoms in the transition state so favors the path leading to the 4-oxo isomer, II, that none of the other isomer can be found, despite its lower solubility.



## EXPERIMENTAL

*6-Methyl-4-oxo-1,3,3a,7-tetrazaindene* (I). 1. *Bülow's method:*[1] If very pure 3-amino-1,2,4-triazole is employed, the crude yield may be as high as 95%.

2. *The diketene reaction:* 3-Amino-1,2,4-triazole (32 g.; 0.38 m.) was dissolved in 700 ml. of hot, dry dioxane, the solution cooled to 50°, and diketene (34 g.; 0.387 m.) in 100 ml. of dry dioxane slowly added, with stirring. The solution was stirred 1 hr. and refluxed an additional hr., when a solid began to separate. The mixture was chilled and the solid collected. Evaporation of the filtrate to dryness and recrystallization from ethanol gave 5 g. of 3-amino-1,2,4-triazole. The solid obtained from the reaction was recrystallized from 400 ml. of 95% ethanol to give 15 g. of a solid which was a mixture of long rods and short crystals. No separation could be effected on repeated recrystallizations from ethanol but extraction of the mixture with cold water dissolved the short crystals. The long rods were recrystallized from ethanol to give 4 g. of 6-methyl-4-oxo-1,3,3a,7-tetrazaindene (I), m.p. 278°. The aqueous extract was evaporated to dryness and the residue recrystallized from alcohol to give 11 g. of *N,N'*-di-1,2,4-triazol-3-yl-β-aminocrotonamide (VII), m.p. 221–222°.

*Anal.* Calcd. for $C_8H_{10}N_8O$: C, 41.0; H, 4.3; N, 47.8. Found: C, 41.3; H, 4.6; N, 48.0.

Another run made as just described, using dry tetrahydrofuran as the solvent, gave the same azaindene, m.p. 278°, and an isomeric material which melted at 229–230°. It was not determined whether this was a single isomer or a mixture of isomers. When the experiment was repeated on a larger scale, only the compound melting at 278° and 3-acetamido-1,2,4-triazole were obtained.

*4-Chloro-6-methyl-1,3,3a,7-tetrazaindene* (XI). A mixture of 120 g. of 6-methyl-4-oxo-1,3,3a,7-tetrazaindene (I) and 600 ml. of phosphoryl chloride was refluxed for 2 hr., the excess chloride removed under vacuum, ice and chloroform were added to the residue, and the mixture was made basic with a saturated sodium carbonate solution. The chloroform layer was dried, and passed through a column packed with activated alumina to remove its orange color. Removal of the solvent from the effluent left 55 g. (37%) of the desired product, m.p. 151–152°. The yield was considerably higher without the alumina treatment, but the product was then highly colored. The yield was also higher if a very dilute solution was used and the alumina washed with much chloroform. It is quite soluble in chloroform and recrystallizes well from benzene.

*Anal.* Calcd. for $C_6H_5N_4Cl$: C, 42.7; H, 3.0; N, 33.2. Found: C, 42.8; H, 3.2; N, 33.7.

The substance is very easily hydrolyzed to I, even by the moisture in the air.

*6-Methyl-4-thiono-1,3,3a,7-tetrazaindene* (XII). A mixture of 5 g. (0.03 mole) of the chloro compound (XI) and 3.8 g. (0.03 mole) of thiourea in 50 ml. of ethanol was refluxed 3 hr. and then most of the alcohol was distilled off under vacuum. To the residue was added 75 ml. of 0.53*N* NaOH, the mixture was refluxed 0.5 hr., filtered hot, the filtrate was acidified with acetic acid and cooled, and the solid collected and recrystallized from aqueous dimethylformamide. Yield, 4 g. (72%) of product, m.p. 310° dec.

*Anal.* Calcd. for $C_6H_6N_4S$: C, 43.4; H, 3.6; N, 33.7. Found: C, 43.6; H, 3.8; N, 34.0

*4-Carboxymethylmercapto-6-methyl-1,3,3a,7-tetrazaindene* (XIII) A mixture of 3.2 g. of the thiono compound and 3 g. of sodium chloroacetate in 40 ml. of water was heated on the steam-bath, sodium carbonate was added until solution was nearly complete, and the heating was continued for 15 min. After filtering off a small amount of insoluble material (disulfide from the mercaptan), the filtrate was acidified with hydrochloric acid and cooled. Yield, 1.5 g. (44%) of product, m.p. 246–247° (recrystallized from water).

*Anal.* Calcd. for $C_8H_8N_4O_2S$: C, 42.8; H, 3.6; N, 25. Found: C, 42.4; H, 3.5; N, 24.4.

*4-(1,2,4-Triazolyl-3-amino)-6-methyl-1,3,3a,7-tetrazaindene* (XIVc). A mixture of 1.8 g. of sodium carbonate, 3.4 g. of 4-chloro-6-methyl-1,3,3a,7-tetrazaindene, 1.8 g. of 3-amino-1,2,4-triazole, and 25 ml. of nitrobenzene was refluxed for 2 hr. It was then cooled, the solid was collected, washed with water and ether, and recrystallized from dimethylformamide. Yield, 2 g. of white product, m.p. >315°.

*Anal* Calcd for $C_8H_8N_8$: N, 51 8 Found: N, 51.5

*4-Azido-6-methyl-1,3,3a,7-tetrazaindene* (XIVb). A mixture of 4 g. of the chloro compound, 3 g. of sodium azide in 10 ml. of water and 10 ml. of methanol was refluxed for 1.5 hr., then 20 ml. of water was added and the mixture chilled. The product that separated was removed and recrystallized from water; m.p., 120° dec. Yield, 3.4 g. (84%).

*Anal.* Calcd. for $C_6H_5N_7$: N, 56.1. Found: N, 56.4.

*4-Amino-6-methyl-1,3,3a,7-tetrazaindene* (XIVa).[17] A solution of 10 g. of the azide in 125 ml. of methanol was reduced at 25–30° and 50 p.s.i. of hydrogen in the presence of 1–2 g. of Raney nickel. The pressure rose as nitrogen was evolved.[18] The residue, after removal of the catalyst and solvent, was recrystallized from water, decolorizing with Norit. Yield, 7 g. (81%); m.p. 244°.

*Anal.* Calcd. for $C_6H_7N_5$: C, 48.3; H, 4.7. Found: C, 48.4; H, 4.7.

*5-Chloro-6-methyl-4-oxo-1,3,3a,7-tetrazaindene* (XVI). 1. *From 6-methyl-4-oxo-1,3,3a,7-tetrazaindene:* Into a stirred solution of 15 g. of 6-methyl-4-oxo-1,3,3a,7-tetrazaindene

(17) This amine has been mentioned in the literature several times. In our hands, none of the procedures were successful. N. Heimbach and W. Kelly, Jr., U. S. Patent 2,449,225 [*Chem. Abstr.*, **43**, 52 (1949)]. D. J. Fry, U. S. Patent 2,566,658 [*Chem. Abstr.*, **46**, 1379 (1952)].

(18) We are indebted to Mr. J. F. Stenberg for this reduction.

(I) in 750 ml. of water at 60° there was passed a current of chlorine for 45 min. After cooling to 35°, the solid (3.4 g.) was collected on a filter. It was recrystallized from dimethylformamide (with a Norit decolorization) on addition of one-third its volume of water. Yield, 2.7 g. (15%). It begins to char at about 300° but melts >350°.

*Anal.* Calcd. for $C_6H_5N_4OCl$: C, 39.0; H, 2.7; N, 30.4. Found: C, 39.3; H, 2.9; N, 30.4.

3. *From ethyl α-chloroacetoacetate and 3-amino-1,2,4-triazole:* To 28 ml. (0.15 mole) of ethyl acetoacetate there was added 24 ml. of sulfuryl chloride and the solution was heated on the steam-bath 2 hr. To this crude ethyl α-chloroacetoacetate there was added 100 ml. of acetic acid and 12.6 g. (0.15 mole) of 3-amino-1,2,4-triazole; the mixture was refluxed for 4 hr., cooled, and the solid collected and recrystallized from dimethylformamide. Yield, 25 g. The product was identical with that obtained by chlorination of I, as shown by the infrared absorption curve.

*5-Hydroxy-6-methyl-4-oxo-1,3,3a,7-tetrazaindene* (XVII). Ammonium persulfate (34 g.; 0.15 mole) in 70 ml. of water was added dropwise over a period of 1 hr. to a stirred, cold solution of 15 g. (0.1 mole) of 6-methyl-4-oxo-1,3,3a,7-tetrazaindene (I), dissolved in 220 ml. of 3*N* sodium hydroxide. The 6-methyl-4-oxo-1,3,3a,7-tetrazainden-5-yl sulfate was collected (15 g.) and recrystallized from water.

A mixture of 7 g. of the sulfate and 28 ml. of 5*N* hydrochloric acid was refluxed 0.5 hr., cooled, and the solid collected. The crude product was recrystallized from dimethylformamide to give 3.5 g. of XVII, m.p. above 330°, with progressive darkening above 300°.

*Anal.* Calcd. for $C_6H_6N_4O_2$: C, 43.4; H, 3.6. Found: C, 44.0; H, 4.0.

*4-Methyl-6-oxo-1,2,3a,7-tetrazaindene* (III); *synthesis via 3-mercapto-4-methyl-6-oxo-1,2,3a,7-tetrazaindene.* To a solution of 7 g. (0.05 mole) of 2-hydrazino-6-methyl-4-oxopyrimidine (V) in 2 l. of hot absolute alcohol there was added 7 g. of phenyl isothiocyanate, the mixture was refluxed for 15 min., was allowed to stand overnight, and the solid product was collected. After recrystallization from water, 5 g. of 3-mercapto-4-methyl-6-oxo-1,2,3a,7-tetrazaindene (VI), m.p. 280°, was obtained.

*Anal.* Calcd. for $C_6H_6N_4OS$: C, 40.0; H, 3.3; N, 30.1; S, 17.7. Found: C, 39.6; H, 3.7; N, 31.1; S, 18.5.

For desulfurization, 5 g. of VI in 250 ml. of water and 3 tablespoons of commercial Raney nickel was refluxed for 3 hr., with stirring. The mixture was filtered and the filtrate evaporated to 50 ml., cooled, and the solid collected and recrystallized from water to give 0.6 g. of product, m.p. 295–298°.

*Anal.* Calcd. for $C_6H_6N_4O$: C, 48.0; H, 4.0. Found: C, 47.7; H, 5.4. Although the analysis of this material was not considered to be satisfactory, it was shown to be identical with a pure sample, prepared as described below, both by mixed melting point and absorption curves.

*Synthesis and separation of mixture of 6-methyl-4-oxo- and 4-methyl-6-oxo-1,2,3a,7-tetrazaindenes.* A mixture of 2-hydrazino-6-methyl-4-oxopyrimidine (V) (5 g.) and ethyl orthoformate (200 ml.) was refluxed for 72 hr., cooled, and the orange solid collected.[19,20] The crude reaction product was recrystallized from water and the material that was obtained was recrystallized twice more from water and once from ethanol to give 1.7 g. (32%) of 4-methyl-6-oxo-1,2,3a,7-tetrazaindene (III), m.p. 296–298°.

*Anal.* Calcd. for $C_6H_6N_4O$: C, 48.0; H, 4.0; N, 37.3. Found: C, 47.9; H, 3.9; N, 37.3.

The filtrates from the recrystallizations were evaporated to a small volume, filtered hot, and the filtrate cooled in the refrigerator. The solid that was obtained was recrystallized three times from water to give 2.5 g. (48%) of 6-methyl-4-oxo-1,2,3a,7-tetrazaindene (II), m.p. 252–254°.

*Anal.* Calcd. for $C_6H_6N_4O$: C, 48.0; H, 4.0; N, 37.3. Found: C, 48.1; H, 4.0; N, 37.1.

In an alternate procedure, 100 ml. of dimethylformamide was used in place of the ortho ester, yielding 1 g. of III and 3 g. of II. A mixture of dimethylformamide and ethyl orthoformate gave about the same mixture.

*6-Methyl-4-oxo-1,2,3a,7-tetrazaindene.* A solution of 10 g. of 2-hydrazino-6-methyl-4-oxopyrimidine (V) in 15 ml. of 98% formic acid was kept at 50–60° for 1 hr. and evaporated to dryness below 60°. The solid was crystallized from water, yielding 7.7 g. (72%) of II, m.p. 251–253°, identical in all respects to that prepared as described in the preceding section. This material, when refluxed in formic acid, was transformed into 6-methyl-4-oxo-1,3,3a,7-tetrazaindene (I), identical in melting point, mixed melting point, and ultraviolet and infrared spectra with that prepared according to ref. (1).

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(19) It is believed that the orange color is due to a formazan formed by the reaction of 2 moles of hydrazine with 1 mole of ethyl orthoformate followed by oxidation, but a pure material has not been isolated.

(20) This reaction has also been studied by Mr. L. A. Williams, of the Kodak Limited Research Laboratories, Harrow, England.

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[COMMUNICATION NO. 1996 FROM THE KODAK RESEARCH LABORATORIES]

# The Structure of Certain Polyazaindenes. III. 1,2,3a,7- and 1,3,3a,7-Tetrazaindenes

C. F. H. ALLEN, H. R. BEILFUSS, D. M. BURNESS, G. A. REYNOLDS, J. F. TINKER, AND J. A. VANALLAN

*Received December 19, 1958*

This paper contains a description of the preparation and properties of 1,2,3a,7- and 1,3,3a,7-tetrazaindenes not specifically pertinent to topics discussed in the first two papers.

A considerable variety of tetrazaindenes is now known. Some examples having the nitrogen atom in the 1,2,3a, and 7- or the 1,3,3a, and 7-positions are described in this and the preceding papers of the series,[1] as well as in the earlier literature.[2–6]

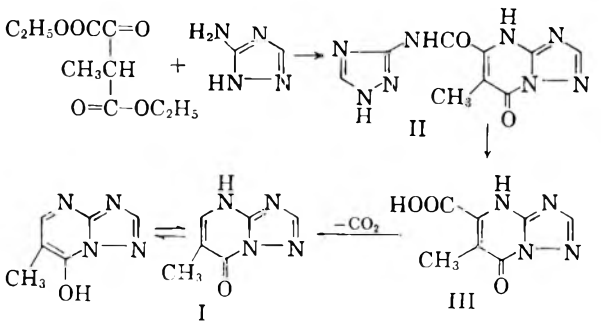
(1) C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, J. F. Tinker, and J. A. VanAllan, *J. Org. Chem.*, **24**, 779, 787 (1959).

(2) E. Birr and W. Walther, *Ber.*, **86**, 1401 (1953).

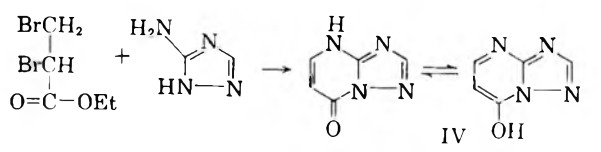
(3) E. Birr, *Z. wiss. Phot.*, **50**, 107 (1955).

Several preparative procedures have been employed. The most general is the interaction of ethyl acetoacetate and a 3-amino-1,2,4-triazole. Analogous reactions have been carried out using alkylated acetoacetic esters, diketene, ethyl ethoxalylpropionate, ethyl $\alpha,\beta$-dibromopropionate, and ethyl ethoxymethylenemalonate. A second procedure employs an ortho-ester and 2-hydrazino-4-hydroxy-6-methylpyrimidine. The ester may be replaced by formic acid or dimethylformamide. Substances obtained by the same procedures were assumed to have the same bond arrangement; in several instances, this was confirmed by a comparison of the absorption spectra.[1]

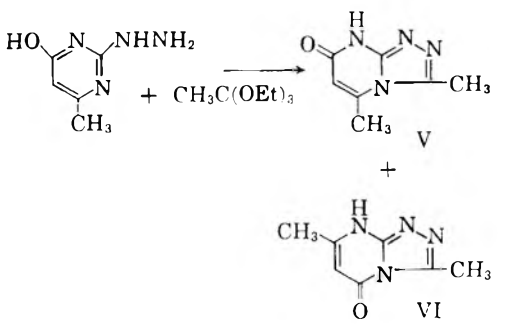
A few notes on the individual substances are in order. 5 - Methyl - 4 - oxo - 1,3,3a,7 - tetrazaindene (I) was obtained from 3-amino-1,2,4-triazole and ethyl ethoxalylpropionate. The first product that separated appeared to be a solvated 5-methyl-4-oxo-6-(3-triazolylcarbamyl)-1,3,3a,7-tetrazaindene (II), which, upon subsequent hydrolysis, gave 6-carboxy - 5 -methyl - 4 - oxo - 1,3,3a,7 - tetrazaindene (III). The latter underwent easy decarboxylation to the 5-methyl-4-oxo derivative (I).



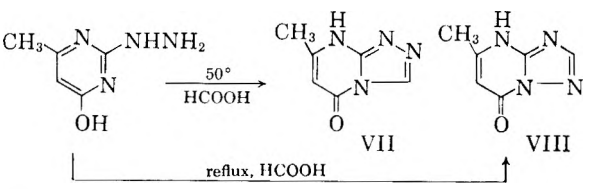
4-Oxo-1,3,3a,7-tetrazaindene (IV) resulted from the interaction of ethyl $\alpha,\beta$-dibromopropionate and 3-amino-1,2,4-triazole.



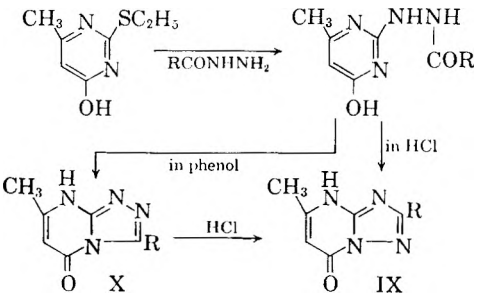
In a manner analogous to that discussed in the previous paper,[1] when 2-hydrazino-4-hydroxy-6-methylpyrimidine was treated with an ortho ester, a mixture of the two expected isomers (V and VI) in the 1,2,3a,7-series resulted; these were separated by fractional crystallization.



The cyclizations of hydrazinopyrimidines give different products under different conditions. For instance, 2-hydrazino-4-hydroxy-6-methylpyrimidine, on warming (50°) in formic acid, gives 4-oxo-6-methyl-1,2,3a,7-tetrazaindene (VII); in boiling formic acid, the hydrazine is converted to the 1,3,3a,7-isomer (VIII). In boiling phenyl acetate, the hydrazine is converted to the rearranged di-



methyl isomer, (IX, R = $CH_3$). When the free hydrazine in acetic acid or its acetyl derivative in formic acid is employed, only a trace of IX (R = $CH_3$) is produced, but hydrogen chloride in acetic acid brings about the rearrangement of X (R = $CH_3$) satisfactorily. 2-Ethylmercapto-6-methyl-4-hydroxypyrimidine can also be used as a starting material, provided it is given a prior treatment with acethydrazide. The analogous $\beta$-hydroxyethyl-tetrazaindenes (IX, X. R = $CH_2CH_2OH$) are obtainable by slight modifications of the same procedures. The 1,2,3a,7-form results from ring closure in phenol, whereas the rearranged 1,3,3a,7-isomer is obtained if hydrogen chloride in acetic acid is employed.

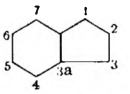


Birr has listed a series of 6-alkylated-4-oxo-1,3,3a,7-tetrazaindenes (erroneously named as "1,2-3a,7"). Some of these, and the 6-benzyl derivative were also prepared in these Laboratories. The 2-hydroxymethyl (IX. R = $CH_2OH$) compound was obtained by the standard synthesis from a substituted aminotriazole.

(4) C. Bülow, *Ber.*, **42**, 2208, 2599, 3555, 4429 (1909).
(5) C. Bülow and K. Haas, *Ber.*, **42**, 3648 (1909).
(6) N. Heimbach and W. Kelly, Jr., U. S. Patent 2,444,605 (1948).

TABLE I

PROPERTIES OF TETRAZAINDENES



| No. | Position of Subs. 1,3,3a,7-series 2 | 4 | 5 | 6 | M.P., °C. | Empirical Formula | Analyses, % Calcd. C | H | N | Found C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| IV | | OH | | | 204–205[a] | $C_7H_{10}N_4O_2$ | 46.4 | 5.5 | 30.9 | 45.9 | 5.2 | 30.6 |
| | | OH | $CH_3$ | $CH_3$ | 304–305[b] | $C_7H_8N_4O$ | 51.2 | 4.9 | 34.2 | 50.9 | 5.0 | 34.7 |
| XI | | OH | | $C_2H_5$ | 212–214 | $C_7H_8N_4O$ | 51.2 | 4.9 | 34.2 | 51.4 | 5.0 | 34.3 |
| | | OH | | $C_7H_{15}$ | 128–130 | $C_{12}H_{18}N_4O$ | 61.4 | 7.7 | 23.9 | 61.3 | 8.1 | 24.2 |
| | | OH | | $C_{11}H_{23}$ | 128–131[c] | $C_{16}H_{26}N_4O$ | 66.2 | 9.0 | 19.3 | 65.9 | 8.9 | 19.8 |
| | | OH | | $C_6H_5CH_2$ | 240 | $C_{12}H_{10}N_4O$ | 63.8 | 4.4 | 24.8 | 63.8 | 4.5 | 24.9 |
| | $CH_3$ | Cl | | $CH_3$ | 149–150[d] | $C_7H_7ClN_4$ | 46.0 | 3.8 | 30.7 | 46.1 | 4.6 | 31.0 |
| IX | $CH_2OH$ | OH | | $CH_3$ | 227–229 | $C_7H_8N_4O_2 \cdot {}^1/_2H_2O$ | 44.5 | 4.8 | 29.7 | 44.5 | 4.7 | 29.8 |
| IX | $CH_2OH$ | OH | | $CH_3$ | 275–277 | $C_7H_8N_4O_2$ | 46.6 | 4.5 | 31.1 | 45.8 | 4.8 | 31.1 |
| IX | $CH_2Cl$ | OH | | $CH_3$ | 211–260[d] | $C_7H_7ClN_4O$ | 42.4 | 3.5 | | 42.4 | 3.7 | |
| IX | $C_7H_{15}$ | OH | | $CH_3$ | 172 | $C_{13}H_{20}N_4O$ | 62.9 | 8.1 | 22.6 | 62.9 | 8.0 | 22.2 |
| IX | $C_{11}H_{23}$ | OH | | $CH_3$ | 163 | $C_{17}H_{28}N_4O$ | 67.1 | 9.2 | 18.4 | 66.9 | 9.4 | 18.6 |
| I | | OH | $CH_3$ | | >300 | $C_6H_6N_4O$ | | | 37.4 | | | 37.4 |
| III | | OH | $CH_3$ | COOH | >325 | $C_7H_6N_4O_3$ | 43.3 | 3.1 | 29.4 | 43.2 | 3.4 | 28.9 |
| IX | $C_2H_4OH$ | OH | | $CH_3$ | 262–263 | $C_8H_{10}N_4O_2$ | 49.5 | 5.2 | 28.8 | 49.7 | 4.9 | 28.4 |
| V | $CH_3$[e] | $CH_3$ | | OH | 309–310 | $C_7H_8N_4O$ | 51.2 | 4.9 | 34.2 | 50.9 | 5.0 | 34.5 |
| VI | $CH_3$[e] | OH | | $CH_3$ | 310–311 | $C_7H_8N_4O$ | 51.2 | 4.9 | 34.2 | 51.4 | 5.1 | 34.7 |
| X | $C_2H_4OH$[e] | OH | | $CH_3$ | 237–240 | $C_8H_{10}N_4O_2$ | 49.5 | 5.2 | 28.8 | 50.0 | 6.3 | 28.9 |

[a] The alcoholate. Birr[3] gives 287–288° for the unsolvated substances. [b] Birr[3] gives 291–292°. [c] Birr[3] gives 100–101°, doubtless a hydrate. [d] Cl: Calcd., 19.5. Found, 19.4. [e] In 3-position of the 1,2,3a,7- compound.

## EXPERIMENTAL

Most of the procedures employed for the preparation of the various substances have been described in the previous papers of this series. The properties of the new tetrazaindenes are collected in Table I.

The various tetrazaindenes that contain oxo groups resemble those described in the preceding paper.[1] The most conspicuous property is the tendency to retain solvent of crystallization. One solvent may partially or entirely replace another on recrystallization.

*5-Methyl-4-oxo-1,3,3a,7-tetrazaindene* (I). A mixture of 3-amino-1,2,4-triazole (8.4 g., 0.1 mole), ethyl ethoxalylpropionate (21 g., 0.1 mole), and 54 ml. of acetic acid was refluxed for 3 hr. After standing at room temperature overnight, the solid was collected and recrystallized from dimethylformamide to give 5–8 g. of 5-methyl-4-oxo-6-(3-triazolylcarbamyl)-1,3,3a,7-tetrazaindene (II) as the monohydrate,[7] m.p. 275°, and sometimes as the monoalcoholate,[7] m.p. 257°. Hydrolysis of 8 g. of this material by boiling for 5 hr. with 85 ml. of 4% hydrochloric acid gave 5 g. of 6-carboxy-5-methyl-4-oxo-1,3,3a,7-tetrazaindene (III). The latter compound was decarboxylated by heating for 10 min. in boiling Dowtherm to give 5-methyl-4-oxo-1,3,3a,7-tetrazaindene.

*4-Oxo-1,3,3a,7-tetrazaindene* (IV). A solution of 17 g. (0.2 mole) of 3-amino-1,2,4-triazole and 52 g. (0.2 mole) of ethyl $\alpha,\beta$-dibromopropionate in 100 ml. of pyridine was refluxed for 3 hr., cooled, and diluted with an equal volume of water. The cream-colored solid was collected and recrystallized from alcohol to give 7 g. of product as the alcoholate.

*2-Hydroxymethyl-6-methyl-4-oxo-1,3,3a,7-tetrazaindene* (IX, $R = CH_2OH$). The necessary 3-amino-5-hydroxymethyltriazole glycolate was prepared as follows: To 1.24 kg. of aminoguanidine bicarbonate in a 12-l. flask was added 2 kg. of 70% aqueous glycolic acid, octyl alcohol being added to control foaming. When foaming had ceased, 10 ml. of concentrated nitric acid was added so that it wet the sides of the flask above the liquid. The whole was refluxed for 24 hr. The liquid was poured into an enameled pan, cooled to 5° for 15 min., the solid was collected on a filter, sucked dry, and recrystallized from 2 l. of ethanol. This solution was cooled to 5° for 15 min. and filtered. Yield of triazole, m.p. 113–115°, 78–95 g. (45–55%).

*Anal.* Calcd. for $C_5H_{10}N_4O_4$: C, 31.5; H, 5.3; H, 29.5. Found: C, 32.0; H, 5.2; N, 31.4.

*Cyclization.* A mixture of 1 kg. of 3-amino-5-hydroxymethyltriazole glycolate, 4.5 l. of practical ethyl acetoacetate, and 80 ml. of glacial acetic acid was heated on the steam-cone for 24 hr., cooled to 25°, filtered, and washed with ethanol. The damp cake was dissolved in 3 l. of boiling water, decolorized and filtered, and 3 l. of concentrated hydrochloric acid was added to the hot solution. After cooling at 5° for 1 hr., the product was filtered and dried. A quantitative yield of the pure white anhydrous material resulted (crystallization from water yielded a hemihydrate).

*2-Chloromethyl-6-methyl-4-oxo-1,3,3a,7-tetrazaindene* (IX, $R = CH_2Cl$). A mixture of 900 g. of 2-hydroxymethyl-6-methyl-4-oxo-1,3,3a,7-tetrazaindene and 2 or 3 l. of recently distilled phosphoryl chloride was heated gently until dissolved, and then 20–40 min. longer and cooled. It was poured upon ice and filtered promptly (the filtrate will heat up in a few minutes if not drowned out). The solid was washed with cold water and recrystallized in portions from water (100 ml. per g.) using Darco, and allowing the hot solution to boil briskly for at least 10 min. Yield was 400 g.

*3,4-Dimethyl-6-oxo- and 3,6-dimethyl-4-oxo-1,2,3a,7-tetrazaindenes* (V *and* VI). 1. *From a pyrimidinehydrazine and an ortho ester.* A mixture of 5 g. of 2-hydrazino-4-hydroxy-6-methylpyrimidine[2] and 200 ml. of ethyl orthoacetate was refluxed for 24 hr., cooled, and the solid collected. The crude material was recrystallized from 3 l. of water to give 3,6-dimethyl-4-oxo-1,2,3a,7-tetrazaindene (VI), m.p. 310°. The filtrate was concentrated to half its volume to give more of the same material (3.5 g. combined yield). The filtrate was concentrated to about 25 ml. and cooled, and the solid that was obtained was recrystallized twice from water and once from ethanol to give 0.8 g. of 3,4-dimethyl-6-oxo-1,2,3a,7-

(7) Indicated by the analytical results; the solvent-free form is obtainable, but only by stringent drying.

tetrazaindene (V), m.p. 308–310°. The absorption spectra were given previously.[1]

2. *From 2-acethydrazido-4-hydroxy-6-methylpyrimidine.* A mixture of 10 g. of 2-hydrazino-4-hydroxy-6-methylpyrimidine[2] and 50 ml. of pyridine was treated with 5 ml. of acetyl chloride. The temperature rose to about 50°, and a solid separated. After 0.5 hr., the mixture was filtered. The white solid, m.p. 213–216°, was crystallized from 125 ml. of water. Yield was 1.7 g., m.p. 251–253° dec.

*Anal.* Calcd. for $C_7H_{10}N_4O_2$: C, 46.1; H, 5.5; N, 30.8. Found: C, 46.1; H, 5.8; N, 30.8.

It may be noted that the hydrazides melt with foaming, suggesting a loss of water on heating. Treatment of this material with formic acid at 70 ± 5° for 1 hr. leaves it unchanged. In boiling formic acid (4 hr.), substantially pure 3,6-dimethyl-4-oxo-1,2,3a,7-tetrazaindene (VI) is formed, contaminated with a detectable amount of the rearranged isomer, 2,6-dimethyl-4-oxo-1,3,3a,7-tetrazaindene (IX. R = $CH_3$).

*2,6-Dimethyl-4-oxo-1,3,3a,7-tetrazaindene* (IX. R = $CH_3$). A solution of 5 g. of 2-hydrazino-4-hydroxy-6-methylpyrimidine[2] in 50 ml. of phenyl acetate was refluxed for 4 hr., cooled, and filtered. The white solid was crystallized from water; it melted at 311–313°. The infrared absorption was identical with that of material prepared from ethyl acetoacetate and 3-amino-5-methyl-1,2,4-triazole.[8]

*4-Chloro-2,6-dimethyl-1,3,3a,7-tetrazaindene.* A mixture of 30 g. of 2,6-dimethyl-4-oxo-1,3,3a,7-tetrazaindene (prepared from 3-amino-5-methyl-1,2,4-triazole and ethyl acetoacetate[8]) and 100 ml. of freshly distilled phosphoryl chloride was refluxed for 1 hr., evaporated to dryness, the residue washed with chloroform, and then shaken with ice water and chloroform. The second chloroform solution was dried over sodium sulfate, passed through a 1½-in. by 36-in. column of alumina (Alcoa F-20, 200-mesh), and evaporated to dryness. The pure white chloride was obtained in a yield of 18 g. (54%).

*4-Hydroxy-2-β-hydroxypropionhydrazido-6-methylpyrimidine.* This was formed by refluxing equimolecular proportions of β-hydroxypropionhydrazide[9] and 2-ethylmercapto-4-hydroxy-6-methylpyrimidine in aqueous alcohol for 20 hr., cooling to 25°, and filtering. The crude solid (60–75% yield), m.p. 223–226°, with evolution of gas, was usually used directly, but could be recrystallized from water, after which it melted at 223–234°, with foaming.

*2-β-Hydroxyethyl-6-methyl-4-oxo-1,3,3a,7-tetrazaindene* (IX. R = $C_2H_4OH$). A mixture of 6.3 g. of the hydrazide, 500 ml. of glacial acetic acid, and 50 ml. of concentrated hydrochloric acid was refluxed for 20 hr., filtered hot from small impurities, and cooled. A white solid separated (12 g., m.p. 257–260°). Recrystallized from water, it yielded 6.5 g., m.p. 262–263°.

*3-β-Hydroxyethyl-6-methyl-4-oxo-1,2,3a,7-tetrazaindene* (X. R = $C_2H_4OH$). Eight g. of the hydrazide in about 100 g. of phenol was refluxed for 1 hr., cooled, and the phenol steam-distilled. A white solid crystallized from the water. Yield was 3.3 g., m.p. 237–240°.

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(8) J. Thiele and K. Heidenreich, *Ber.*, **26**, 2599 (1893).

(9) T. L. Gresham, J. E. Jansen, F. W. Shaver, R. A. Bankert, and F. T. Fredorek, *J. Am. Chem. Soc.*, **73**, 3168 (1951).

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[COMMUNICATION NO. 1997 FROM THE KODAK RESEARCH LABORATORIES, EASTMAN KODAK COMPANY]

# The Structure of Certain Polyazaindenes. IV. Compounds from β-Keto Acetals and β-Methoxyvinyl Ketones[1]

C. F. H. ALLEN, H. R. BEILFUSS, D. M. BURNESS, G. A. REYNOLDS, J. F. TINKER, AND J. A. VANALLAN

*Received December 19, 1958*

The reaction of 4,4-dimethoxy-2-butanone or 4-methoxy-3-buten-2-one with 3-amino-1,2,4-triazole leads to 6-methyl-1,3,3a,7-tetrazaindene. The mode of formation and relation to the product from ethyl acetoacetate are discussed. This reaction of β-keto acetals with amino-substituted azoles appears to be general for the synthesis of polyazaindenes.

The reaction between 3-amino-1,2,4 triazole (I) and ethyl acetoacetate is now known[2] to produce 6-methyl-4-oxo-1,3,3a,7-tetrazaindene (II); however, at the time the following work was undertaken there existed neither spectral evidence nor convincing chemical proof in that regard. Numerous attempts had been made to isolate an intermediate compound from this reaction, or related reactions, but to no avail.

In earlier work involving reactions of β-keto acetals with aromatic amines and hydrazines,[3] it was possible to isolate intermediate condensation products, which could be characterized so that the structure of the product of a subsequent cyclization was clearly evident. It seemed reasonable to expect a similar degree of success in the reaction of 3-amino-1,2,4-triazole with 4,4-dimethoxy-2-butanone (III).

β-Biketones are known to react with 3-amino-1,2-4-triazole to give dialkyltetrazaindenes,[4] while diethyl ethoxymethylenemalonate produces a product with an ethoxycarbonyl substituent.[5,6]

(1) This paper is Part III of another series from these Laboratories "Beta-Keto Acetals," Parts I and II of which appeared in *J. Org. Chem.*, **21**, 97, 102 (1956). A portion of the subject matter of this paper appears in U. S. Patent **2,837,521**, dated June 3, 1958.

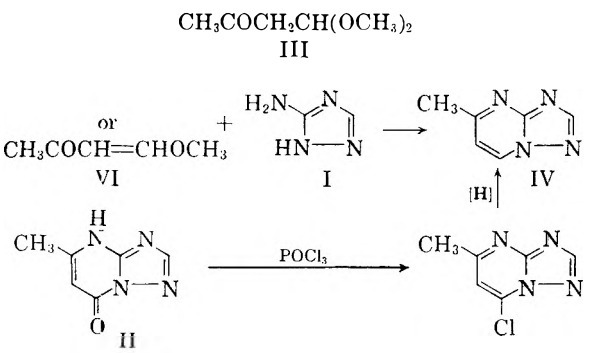
(2) C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, J. F. Tinker, and J. A. VanAllan, *J. Org. Chem.*, **24**, 787 (1959).

(3) D. M. Burness, *J. Org. Chem.*, **21**, 97 (1956).

(4) C. Bülow and K. Haas, *Ber.*, **42**, 4638 (1909); N. Heimbach, U. S. Patent **2,443,136** (1948); *Chem. Abstr.*, **42**, 6685 (1948).

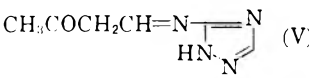
(5) N. Heimbach, U. S. Patent **2,450,397** (1948); *Chem. Abstr.*, **43**, 4165 (1949).

The reaction of 4,4-dimethoxy-2-butanone with I produced solely, and in good yield, a product which proved to be identical with the 6-methyl-1,3,3a,7-tetrazaindene (IV) obtained from II, as shown.




Thus, of the four possible products (methyl at 4 or 6, nitrogens at 1,2,3a,7 or 1,3,3a,7), only one was obtained. The relation demonstrated here between II and IV leads to the conclusion that each possesses the same C—N skeleton. This is not necessarily valid in the 1,2,3a,7-tetrazaindene series, since it has been shown[2] that acidic conditions (such as prevail during the phosphoryl chloride reaction) may cause rearrangement. That no rearrangement occurs in the present case was shown by the regeneration of II from the chloro compound by hydrolysis.

As with a β-keto ester, there are two possible sites for the initial reaction of the amino group (*i.e.*, the most basic center) of I with a β-keto acetal. By analogy to the corresponding reaction with aniline,[3] however, the acetal group of III would be expected to react first to give the intermediate,

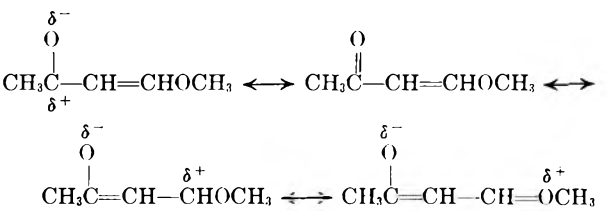


(V),[7]

which, when cyclized, would produce either 4-methyl-1,2,3a,7- or 4-methyl-1,3,3a,7-tetrazaindene. Obviously, this is at variance with the correct structure (II) of the oxo compound.

Efforts were made to isolate or determine in some fashion the nature of the intermediate, but to no avail. The reaction proceeded at the low temperature of boiling benzene, slowly but completely to the end-product. Determination of the composition of the initial distillate obtained at the start of the reaction showed a methanol–water ratio of 2.5 (theory for the complete reaction is 3.5), confirming the fact that the two steps occur simultaneously or in rapid succession.

Further evidence that the first step may well involve the intermediate, V, was obtained when the reaction was carried out with 4-methoxy-3-buten-2-one (VI). The latter reacts with aniline to yield, only under milder conditions, the same product ($C_6H_5N{=}CHCH_2COCH_3$) as is obtained with the β-keto acetal (III). The reaction of I with VI undoubtedly proceeds preferentially by a 1,4-addition mechanism[8] to produce the same intermediate (V) as before, and indeed the same methyltetrazaindene was isolated.



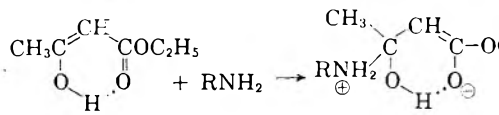

The reaction of 3-amino-1,2,4-triazole with VI was run under the mildest of conditions, at 25°, in *N*,*N*-dimethylformamide; again, it was impossible to isolate an intermediate compound. The methyltetrazaindene crystallized from the reaction mixture as a pure compound in 56% yield, practically identical with the yield of anil obtained with aniline.

In another experiment, this reaction was run at 25° in dimethyl sulfoxide as a solvent (which is essentially transparent in the region of 4.0–6.8 μ) and the reaction was followed by infrared examination of samples of the reaction mixture at various intervals. No definite conclusions could be drawn from the spectra, owing largely to overlapping absorptions.

It is possible that the course of the reaction of the aminotriazole with the β-keto acetal is identical with that of the methoxyvinyl ketone, after a preliminary step involving the loss of methanol, a reaction which proceeds readily under acid catalysis. The higher temperatures required for condensations with the acetal are similar to those necessary for this elimination reaction, which here

(6) C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, J. F. Tinker, and J. A. VanAllan, *J. Org. Chem.*, **24**, 779 (1959).

(7) This may appear at first to be contradictory to the reaction with acetoacetic ester which is known to condense with amines under mild acidic catalysis at the ketonic carbonyl group. The difference lies in the far greater electronegativity of the carbethoxy group which facilitates addition of the amine to the enolic form of the β-keto ester.

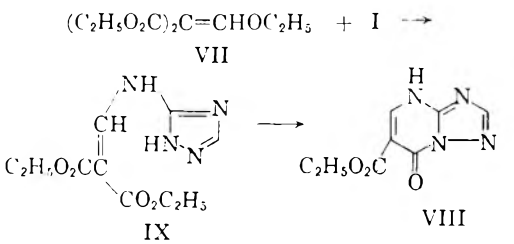



The acetal group, on the other hand, is not electronegative, so that the carbonyl of a β-keto acetal resembles more closely that of a simple ketone in reactivity; ketones ordinarily react with amines with considerable difficulty.

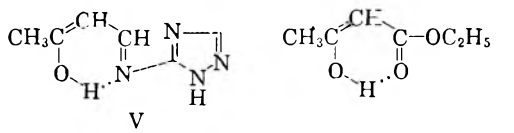
(8) The tendency for 1,4-addition to VI is actually somewhat greater than in the case of methyl vinyl ketone which also reacts in this manner [N. Murata, H. Arai, and Y. Tashima, *J. Chem. Soc. Japan*, **56**, 709 (1953); *Chem. Abstr.*, **49**, 7517 (1955)]. The additional resonance possibilities due to the methoxyl group make for a still more positive center at the number four carbon atom.

may well be catalyzed by the mildly acidic 3-amino-1,2,4-triazole.

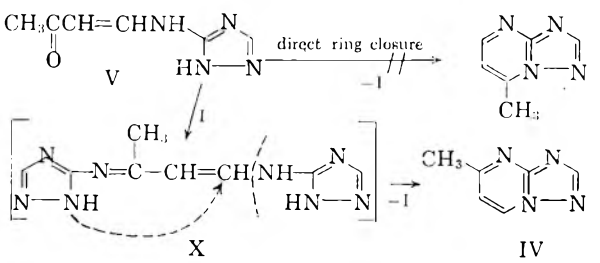
Another possibility which must be considered is that the 1,4-addition might involve the 2-position of the triazole ring rather than the amino group; this could lead directly to IV. This is most improbable in view of the results in the analogous case involving ethyl ethoxymethylenemalonate (VII). Addition to this enol ether necessarily involves the amino group of I, for the ultraviolet absorption spectrum of the product conforms to that of a 4-oxo-1,3,3a,7-tetrazaindene (VIII) rather than the alternate 6-oxo isomer.[6]



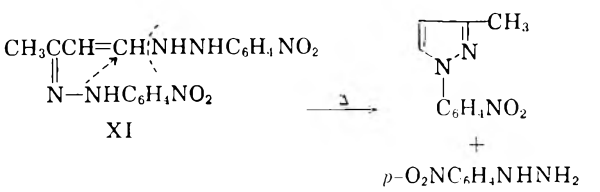

It is clear that some other intermediate must interpose between V and IV. Condensation of V with aminotriazole[9] leads to such an intermediate.




This bis compound, X, then spontaneously loses a mole of aminotriazole to form 6-methyl-1,3,3a,7-tetrazaindene (IV). The aminoanil (X) could not, however, be isolated.




Support for such a mechanism was gained from a study of the reaction of *p*-nitrophenylhydrazine with VI. An attempt to condense *a single mole* of the hydrazine with the methoxyvinyl ketone, under the same mild conditions employed with I, produced the bishydrazone, XI. This, when heated, cyclized to the known 3-methyl-1-*p*-nitrophenylpyrazole with loss of one mole of *p*-nitrophenylhydrazine. This is the same behavior as is postulated for X.




A similar process occurs in the related case where 5-aminotetrazole replaces I. Of the two isomers possible in this case, only one has been obtained in each of five syntheses; this is formulated by analogy as 6-methyl-1,2,3,3a,7-pentazaindene (XII). These methods involved (1) reaction of III with 5-aminotetrazole in xylene-DMF at 140°, (2) reaction of III with 5-aminotetrazole in glacial acetic acid, (3) reaction of VI with 5-aminotetrazole at 25°, (4) dehydroxylation of 6-methyl-4-oxo-1,2,3,-3a,7-pentazaindene, and (5) the action of nitrous acid on 2-hydrazino-4-methylpyrimidine.

Numerous other azoles were found to react with III, and III, in turn, could be replaced by other β-keto acetals; thus, the reaction is quite general for the synthesis of polyazaindenes containing only hydrocarbon substituents in the 6-membered ring. The actual structures of the products formed in most of these reactions are not known and the names assigned are based on analogy. The compounds prepared are listed in Tables I and II.

The reaction of 4,4-dimethoxy-3-methyl-2-butanone (XIII) with I in boiling xylene produced two isomers; one of these was found to be identical with the compound obtained by reduction of 5,6-dimethyl-4-oxo-1,3,3a,7-tetrazaindene (formed by interaction of ethyl α-methylacetoacetate with 3-amino-1,2,4-triazole) and is, therefore, 5,6-dimethyl-1,3,3a,7-tetrazaindene (XIV). The fact that the second isomer, although analytically pure, was low-melting and melted over a range (91–99°) might be due to inseparable isomers, although the infrared spectrum indicates the presence of very little, if any, of the higher-melting isomer.

It seems unlikely that the amino group of I would react first with the carbonyl; instead, this acetal loses methanol (much more readily than III) to form an unsaturated ketone,[10] the reactive species. Accordingly, the structure assigned to the second isomer is 4,5-dimethyl-1,3,3a,7-tetrazaindene (XV).

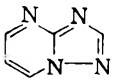
In two other instances, it was possible to isolate two separate, isomeric tetrazaindenes. These were from the reactions of 3,5-diamino-1,2,4-triazole with 2-methoxymethylenecyclohexanone (XVI), and with β,β-dimethoxypropiophenone (XVII). In these

(9) The carbonyl group of V should be more active than that of its precursors, III or VI; there is now a close resemblance between its enolic form and that of acetoacetic ester which, as stated earlier, has been found to condense with amines at the ketonic carbonyl.

(10) This behavior is parallel to that observed in the synthesis of XIII itself, in which a considerable quantity of unsaturated ketone is formed; very little is formed in the case of III. [E. Royals and K. Brannock, *J. Am. Chem. Soc.*, **75**, 2050 (1953) and unpublished observations of these Laboratories.]

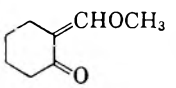
TABLE I

1,3,3a,7-TETRAZAINDENES

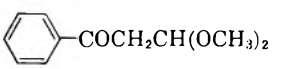


| Number | Substituents | Precursors Acetal | Azole | Reaction Solvent | Yield, % | M.P., °C. | Analyses Calcd. C | H | N | Found C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| XXI | Unsubstituted | [a] | I | Acetic acid[b] | 22 (crude) | 140–142[c] | 50.0 | 3.3 | 46.8 | 50.4 | 3.3 | 46.7 |
| IV | 6-$CH_3$ | III | I | Xylene | 63 | 182.5–183[c] | 53.7 | 4.5 | 41.8 | 53.7 | 4.5 | 42.0 |
| IV | 6-$CH_3$ | III | I | Benzene | 57 (crude)[d] | 173–180 | | | | | | |
| IV | 6-$CH_3$ | III | I | Acetic acid | 53 (crude) | 179–183[c] | | | | | | |
| IV | 6-$CH_3$ | III | I | None; heat only | 66 (crude) | 173–178[c] | | | | | | |
| IV | 6-$CH_3$ | VI | I | DMF[b] | 57 | 181.5–183 | | | | | | |
| XIV[b] | 5,6-Di-$CH_3$ | XIII | I | Xylene | 69[e] | 178–178.5[c] | 56.8 | 5.4 | 37.8 | 56.9 | 5.3 | 38.1 |
| XV[b] | 4,5-Di-$CH_3$ | | | | | 91–99[f] | 56.8 | 5.4 | 37.8 | 57.1 | 5.5 | 37.7 |
| XXII | 2-$SCH_3$-6-$CH_3$ | III | [g] | Xylene | 65 | 125–126[j] | 46.7 | 4.5 | 31.1 | 46.6 | 4.3 | 31.3 |
| XXIII | 2-$NH_2$-6-$CH_3$ | III | [h] | Xylene | 58 | 210–211.5[k] | 48.3 | 4.7 | 47.0 | 47.9 | 5.1 | 47.3 |
| XIX[i] | 2-$NH_2$-4-$C_6H_5$ | XVII | [h] | Xylene | 95[e] | 268.5–269[j] | 62.6 | 4.3 | 33.1 | 62.6 | 4.3 | 33.1 |
| XVIII[i] | 2-$NH_2$-6-$C_6H_5$ | XVII | [h] | Acetic acid | 85[e] | 236.5[l] | 62.6 | 4.3 | 33.1 | 62.4 | 4.3 | 33.6 |

[a] 1,1,3,3-Tetraethoxypropane, Eastman Chemical No. 7118. [b] See Experimental. [c] Recrystallized from benzene. [d] After a 4-day period at reflux. The yield based on unrecovered triazole was 79%. [e] Crude mixed isomers. [f] Unchanged after repeated recrystallization from methylcyclohexane or ligroin (65–75°). [g] 3-Amino-5-methylmercapto-1,2,4-triazole [F. Arndt and E. Milde, *Ber.*, **54**, 2089 (1921)]. [h] 3,5-Diamino-1,2,4-triazole; courtesy of American Cyanamid Co. [i] Both reactions produced small amounts of the other isomer and a by-product (XX). See Experimental. [j] Recrystallized from xylene. [k] Recrystallized from *N,N*-dimethylformamide. [l] Recrystallized from *n*-butanol.



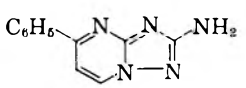
XVI



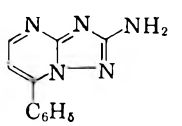
XVII

cases, steric effects might operate to change the course of reaction from that characteristic of III.

In the case of β,β-dimethoxypropiophenone, the two isomers obtained had vastly different ultraviolet spectra. The reaction run in xylene produced predominantly the higher-melting isomer of $\lambda_{max}$ 339. The lower-melting isomer, which was detected (*via* infrared) but not isolated from the xylene reaction, predominated when glacial acetic acid was used as solvent;[11] this had a $\lambda_{max}$ of 311. This difference could be attributed to a change in ring structure from a 1,3,3a,7- to a 1,2,3a,7-tetrazaindene,[12] but more likely is due to a difference in location of the phenyl substituent. Thus, the cross-conjugated type of structure such as exists in XVIII absorbs at a shorter wave length than the linear conjugated system of XIX.

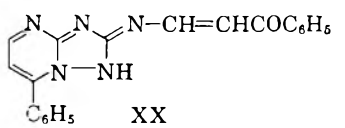


XVIII ($\lambda_{max}$ 311 mμ)



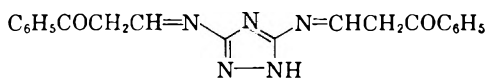
XIX ($\lambda_{max}$ 339 mμ)

The reaction in either solvent produced a by-product derived from two moles of the acetal (XVII) and one of 3,5-diamino-1,2,4-triazole. In view of the elemental composition and the ultraviolet spectra ($\lambda_{max}$ = 373; ε = 58,800), this by-product is tentatively considered to have the highly conjugated structure XX. Acid hydrolysis of XX produced the high-melting isomer, XIX.



XX

This series of transformations is most reasonable in terms of a 1,3,3a,7-tetraza structure (rather than a 1,2,3a,7- one) provided XX is formed only from the dianil, XXI. Both steric hindrance and statistical influence favor the rate leading to the 1,3,3a,7- isomer.



XXI

The formation of a product such as XX, in which it is evident that condensation with the second mole of β-keto acetal has occurred *via* the acetal group and not the carbonyl, lends additional support to the argument regarding the first step in the reaction of β-keto acetals with amino-substituted azoles.

## EXPERIMENTAL[13]

Conditions for the reactions of the various amino azoles with β-keto acetals and properties of the resulting products are shown in Tables I and II. Except as noted, the reac-

(11) The higher-melting isomer was also isolated from the reaction in acetic acid.

(12) The 1,3,3a,7-tetrazaindenes have a $\lambda_{max}$ in the longer-wave-length region of 16 to 26 mμ lower than the corresponding compounds of 1,2,3a,7-structure.[6]

(13) All melting points are corrected.

TABLE II

MISCELLANEOUS POLYAZAINDENES

| Number | Product | Precursors: Acetal | Precursors: Azole | Reaction Solvent | Yield, % | M.P., °C. | Analyses: Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| XII[a] | 6-Methyl-1,2,3,3a,7-pentazaindene | III | 5-Aminotetrazole | Xylene-DMF | 50 | 133.5–134[e] | 44.4 | 3.7 | 51.8 | 44.5 | 3.4 | 51.5 |
| XII[a] | 6-Methyl-1,2,3,3a,7-pentazaindene | III | 5-Aminotetrazole | Acetic acid | 91 (crude) | 130–132.5[f] | | | | | | |
| XII[a] | 6-Methyl-1,2,3,3a,7-pentazaindene | VI | 5-Aminotetrazole | DMF | 72 | 132.5–134 | | | | | | |
| XXIV | 5-Methyl-1,2,3a,4-tetrazaindene | III | 4-Amino-1,2,4-triazole | Xylene | 16 | 168–169[f] | 53.7 | 4.5 | 41.8 | 54.0 | 4.7 | 42.0 |
| XXV | 2-Methyl-1,4a,9-triazafluorene | III | 2-Aminobenzimiduzole | Xylene | 59 | 233.5–234[e] | 72.2 | 4.9 | 22.9 | 71.7 | 4.8 | 23.1 |
| XXVI | 2-Amino-5,6,7,8-tetrahydro-1,3,3a,9-tetrazabenz(f)indene | XVI[b] | 2,5-Diamino-1,2,4-triazole | Xylene | 52[c] | 317.5–318.5[g] | 57.1 | 5.8 | 37.1 | 57.3 | 5.9 | 36.9 |
| XXVII | (Isomeric structure) | | | | | 256–264[d] | 57.1 | 5.8 | 37.1 | 57.3 | 6.4 | 37.4 |

[a] See Experimental. [b] 2-Methoxymethylenecyclohexanone (XVI), see ref. 10. [c] Crude mixed isomers. [d] Undoubtedly unresolved mixture (from *n*-butanol); however, infrared analysis indicates absence of XXVI. [e] Recrystallized from ethanol. [f] Recrystallized from benzene. [g] Recrystallized from xylene.

tions were carried out in the refluxing solvent (no catalyst required) with a packed column and a water separator, until formation of the water–methanol phase was essentially complete. The product crystallized from the reaction mixture and was purified by recrystallization from the designated solvent with Pittsburgh Carbon Type RB. Reactions run in acetic acid were refluxed for 4 to 6 hr. Supplementary details are given in Tables I and II and in the following examples.

*1,3,3a,7-Tetrazaindene* (XXI). A solution of 8.4 g. of 3-amino-1,2,4-triazole (I) and 33 g. of 1,1,3,3-tetraethoxypropane was heated at reflux for 2 hr. in 50 ml. of glacial acetic acid containing 5 drops of concentrated hydrochloric acid. The solvent was removed under reduced pressure and the residue extracted with boiling benzene from which was obtained 2.9 g. (22% yield) of crude product, melting at 138–141°. Purification by passage of a benzene solution through a column of activated alumina, followed by elution with benzene-chloroform (3:1), produced the pure material of m.p. 140–142°.

*6-Methyl-1,3,3a,7-tetrazaindene* (IV). (a) *From 4,4-dimethoxy-2-butanone* (III) (see Table I).

(b) *From 4-methoxy-3-buten-2-one* (VI). A solution of 5 g. of VI and 4.2 g. of I in 25 ml. of *N,N*-dimethylformamide, held at 25° for 18 days, deposited 2.4 g. of peach-colored prisms, m.p. 181–182.5°. An additional 1.4 g. of slightly less pure material was obtained from the mother liquor after heating for 2 hr. and concentration to a small volume. Total yield, 3.8 g. (57%). Dimethyl sulfoxide can also be used advantageously in this reaction. Identity of the compound with that prepared from III was established by mixture melting points and the infrared spectra.

(c) *From 4-chloro-6-methyl-1,3,3a,7-tetrazaindene.* A mixture of 16.9 g. of the chloro compound,[2] 16.9 g. of magnesium oxide, 6 g. of 5% Pd-C, and 200 ml. of water was shaken under 37 p.s.i. of hydrogen in a Parr hydrogenation apparatus until the theoretical amount of hydrogen had been consumed (40 min.). Filtration and evaporation of the filtrate produced a solid which was dissolved in methanol and passed through a column of methanol-washed activated alumina. Evaporation of the effluent and recrystallization of the residue from benzene yielded 2.7 g. of pure IV, m.p. 180–182°. This was shown to be identical with the products in Parts *a* and *b* by mixture melting points and the infrared spectrum.

*Dimethyltetrazaindenes* (XIV and XV). The xylene reaction mixture, from 12 g. of 4,4-dimethoxy-3-methyl-2-butanone (XIII)[3] and 6.3 g. of I, deposited 5.3 g. of crystals, m.p. 119–148°, on cooling. These were recrystallized twice from benzene to give 1.2 g. of pure XIV, m.p. 178–178.5°, which was indistinguishable from the 5,6-dimethyl-1,3,3a,7-tetrazaindene (infrared spectrum and mixture melting point) prepared by the method which follows. Concentration of the xylene mother liquor produced 2.4 g. of the crude second isomer (XV), m.p. 90–105°. Repeated recrystallization from ligroin (65–75°) or methylcyclohexane failed to change the 91–99° melting point of the analytically pure material. Infrared analysis indicated the virtual absence of XIV.

*5,6-Dimethyl-1,3,3a,7-tetrazaindene* (XIV).[14] 4-Chloro-5,6-dimethyl-1,3,3a,7-tetrazaindene was prepared from the corresponding 4-hydroxy compound[4,15] by essentially the same procedure used for 4-chloro-6-methyl-1,3,3a,7-tetrazaindene.[2] Five grams of the chloro compound, 4.65 g. of magnesium oxide, 1.65 g. of 6% Pd-C, and 55 ml. of water were shaken for 1.5 hr. at 50 p.s.i. in a Parr hydrogenation apparatus (pressure drop, 7 lb.). The solution, after filtration, was taken to dryness and the residue recrystallized from benzene (Norit) to yield 2.3 g. (59%) of pure XIV, m.p. 177–178°.

(14) The authors are indebted to Mrs. M. K. Massad, of these Laboratories, for the preparation of this compound.

(15) E. Birr, *Z. wiss. Phot.*, **50**, 107 (1955).

*2-Amino-4-phenyl-1,3,3a,7-tetrazaindene* (XIX). The crude product (11.7 g.) from the reaction run in xylene was extracted with 400 ml. of hot chlorobenzene. The extract, on cooling, yielded 3.8 g. of a mixture of XVIII, XIX, and XX, which, when extracted with *n*-butanol, left 0.2 g. of the highly insoluble, pale yellow 2-(2-benzoylethylideneamino)-4-phenyl-1,3,3a,7-tetrazaindene (XX), m.p. 282–283°; $\lambda_{max}$ = 373 mμ, ε = 58,800 (solvent chloroform).

*Anal.* Calcd. for $C_{20}H_{15}N_5O$: C, 70.3; H, 4.4; N, 20.5. Found: C, 70.5; H, 4.4; N, 20.4.

A small amount (0.25 g.) of XIX was also isolated from the butanol extract, but the bulk of the material consisting essentially of a mixture of XVIII and XIX resisted separation. A second crop from the chlorobenzene extract consisted of 1.4 g. of nearly pure XIX which, after recrystallization from xylene, melted at 268.5–269° as slightly yellow platelets; $\lambda_{max}$ = 339 mμ, ε = 15,700 (solvent chloroform).

*2-Amino-6-phenyl-1,3,3a,7-tetrazaindene* (XVIII). The crude product (12.2 g.) from the reaction run in glacial acetic acid was fractionally crystallized from *n*-butanol to give 0.6 g. of XX, 1 g. of XIX, and 3.1 g. of XVIII. The latter had m.p. 236.5°; $\lambda_{max}$ = 311 mμ, ε = 10,500 (solvent chloroform).

*Acid cleavage of 2-(2-benzoylethylideneamino)-4-phenyl-1,3,3a,7-tetrazaindene* (XX). A small sample (0.1 g.) of XX in 50 ml. of 0.1*N* hydrochloric acid was heated under reflux for 48 hr. and the solution filtered. The filtrate was neutralized with dilute carbonate solution and cooled. Recrystallization of the resulting solid from xylene gave faintly yellow platelets, identical in melting point and ultraviolet spectra with XIX; the mixture melting point was not depressed.

*6-Methyl-1,2,3,3a,7-pentazaindene* (XII). (a.) *From 4,4-dimethoxy-2-butanone.* (1) The reaction in xylene required the addition of 0.15 volume of *N,N*-dimethylformamide to help solubilize the 5-aminotetrazole and allow the reaction to proceed. The bulk of the product separated on cooling the reaction mixture; the remainder was obtained by evaporation of the solvent and recrystallization from ethanol. (2) The reaction in acetic acid gave a good yield directly, which was enhanced by evaporation of the solvent and recrystallization from benzene.

(b.) *From 4-methoxy-3-buten-2-one.* In a manner similar to that described for the corresponding reaction in the tetraza series, a 72% yield of analytically pure material (m.p. 132.5–134°) was obtained after 3 days.

(c.) *From 2-hydrazino-4-methylpyrimidine.* A solution of 4.0 g. of the hydrazine[16] in 120 ml. of water was treated with 2.0 g. of sodium nitrite in 4 ml. of water, followed by 4 ml. of glacial acetic acid. After heating for 1.5 hr. at 90°, the solution was evaporated to dryness and extracted with benzene, from which 2.9 g. (68%) of slightly impure XII crystallized. Recrystallization produced material of m.p. 133–133.5°.

(d.) *From 6-methyl-4-oxo-1,2,3,3a,7-pentazaindene.* (1) *6-Methyl-4-oxo-1,2,3,3a,7-pentazaindene.* Ten grams of 2-hydrazino-4-hydroxy-6-methylpyrimidine[17] and 5 g. of sodium nitrite were dissolved in 500 ml. of hot water, and acidified with excess acetic acid. The mixture was allowed to cool slowly, and finally chilled. The solid, recrystallized from water, yielded pure white needles; 5.5 g. (51%); m.p. 258–260° dec.

*Anal.* Calcd. for $C_5H_5N_5O$: C, 39.7; H, 3.3; N, 46.4. Found: C, 39.8, 40.0; H, 3.6, 3.4; N, 46.9.

(2) *4-Chloro-6-methyl-1,2,3,3a,7-pentazaindene.* A mixture of the hydroxy compound (50 g.) and phosphoryl chloride (250 ml.) was heated under reflux for 1.2 hr. and evaporated to dryness at reduced pressure on the steam-bath. The partially crystallized residue was stirred briefly with ice water and extracted with several portions (900 ml. total) of chloroform. The chloroform solution was dried over anhydrous magnesium sulfate, evaporated to dryness, and the residue recrystallized from benzene, yielding 24.8 g. of pale yellow crystals; m.p. 106.5–107.5°. The aqueous slurry from the chloroform extraction was filtered, and the crystalline solid dried over calcium chloride in a vacuum desiccator to yield an additional 19 g. of crude product. Recrystallization from benzene resulted in a total yield of 39.3 g. (70%); m.p. 106.5–107.5°.

*Anal.* Calcd for $C_5H_4ClN_5$: C, 35.4; H, 2.4; N, 41.3. Found: C, 35.7; H, 2.5; N, 41.4.

(3) *6-Methyl-1,2,3,3a,7-pentazaindene.* By a procedure similar to that described for the tetraza analog, the chloro compound was reduced in very poor yield (apparently due largely to the sensitivity of the product to basic conditions) to XII, m.p. 132.5–133°.

The identity of the products of all five methods of synthesis was shown by mixture melting points and by comparisons of the infrared and ultraviolet spectra.

*Reaction of 4-methoxy-3-buten-2-one* (VI) *with p-nitrophenylhydrazine.* A solution of 2.2 g. of VI (10% excess) and 3.0 g. of *p*-nitrophenylhydrazine in 5 ml. of *N,N*-dimethylformamide was allowed to stand for 22 hr. and then filtered, yielding 1.45 g. of orange crystals of m.p. 155–180° (dec.). Recrystallization from 500 ml. of acetonitrile gave 0.7 g. of m.p. 151–187° (dec.), which was unchanged on further recrystallization.

*Anal* Calcd. for $C_{16}H_{16}N_6O_4$ (dihydrazone): C, 53.9; H, 4.5; N, 23.6. Found: C, 54.3; H, 4.6; N, 24.1.

Heating the DMF filtrate produced 0.4 g. of 3-methyl-1-*p*-nitrophenylpyrazole,[3] m.p. 165.5°. When 0.6 g. of the pure bis(*p*-nitrophenylhydrazone) was heated at 180–200° for 5 minutes and the resulting solid recrystallized from ethanol, two fractions were obtained: (1) 0.25 g. of pure 3-methyl-1-*p*-nitrophenylpyrazole, and (2) 0.22 g. of a mixture of the latter with *p*-nitrophenylhydrazine (shown by the infrared spectrum).

*Acknowledgment.* The authors are indebted to Dr. D. W. Stewart and Miss T. J. Davis for infrared and ultraviolet spectra, and to Mr. D. Heseltine for his interest and efforts to help elucidate the structures of some of the products.

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(16) T. Matsukawa, S. Ban, K. Shirakawa, and M. Yoneda, *J. Pharm. Soc. Japan*, **73**, 159 (1953); *Chem. Abstr.*, **47**, 11185 (1953).

(17) E. Birr and W. Walther, *Ber.*, **86**, 1402 (1953).

[CONTRIBUTION FROM THE BIOCHEMICAL RESEARCH DIVISION, U. S. ARMY CHEMICAL WARFARE LABORATORIES]

# Ultraviolet Absorption Spectra of Some Hydroxamic Acids and Hydroxamic Acid Derivatives

ROBERT E. PLAPINGER

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Ultraviolet absorption spectra of several hydroxamic acids and hydroxamic acid derivatives were determined and correlated. An attempt has been made to describe the structure of benzohydroxamic acid anion on the basis of the spectral data.

In connection with studies involving a series of *p*-substituted benzohydroxamic acids, it was deemed desirable to obtain ultraviolet absorption spectra of these materials in acid and alkaline solution. The compounds studied, their absorption maxima ($\lambda$) and their molar extinction coefficients ($\epsilon$) are given in Table I. The unexpected behavior of the anion with respect to its acid, prompted us to investigate the spectra of other hydroxamic acids. The data on the second group of acids are presented in Table II.

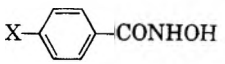
The similarity in the $\lambda_{max}$ of acids I and IX, the latter of which can exist only in the keto form, and the dissimilarity between I and XIV, the latter of which can exist only in the enol form, suggests that benzohydroxamic acid (I) exists predominantly at the keto state (Fig. 1). Mathis came to the


keto form enol form

Figure 1

TABLE I

WAVE LENGTHS OF MAXIMUM ABSORPTION AND MOLAR EXTINCTION COEFFICIENTS FOR SERIES




| | Compound | Acid[a] $\lambda_{max}$ ($M\mu$) | Acid[a] $\epsilon_{max}$ | Anion[b] $\lambda_{1max}$ ($M\mu$) | Anion[b] $\epsilon_{1max}$ | Anion[b] $\lambda_{2max}$ ($M\mu$) | Anion[b] $\epsilon_{2max}$ |
|---|---|---|---|---|---|---|---|
| I | X=H | 227 | 8,750 | 215 | 9,510 | 268 | 5,350 |
| II | $CH_3$ | 232 | 11,800 | 224 | 10,350 | 267 | 6,650 |
| III | $OCH_3$ | 253 | 18,250 | 236 | 10,600 | 264 | 9,460 |
| IV | $NH_2$[c] | 220 | 8,260 | | | 272 | 12,350 |
| V | Cl | 237 | 13,800 | 227 | 11,600 | 272 | 6,150 |
| VI | F | 230 | 8,530 | 219 | 8,390 | 265 | 5,600 |
| VII | CN | 236 | 16,500 | 232 | 16,400 | 291 | 6,160 |
| VIII | $NO_2$[d] | 268 | 11,180 | | | | |

[a] Determined in 0.1*N* HCl. [b] Determined in 0.005*N* NaOH. [c] Compound IV exists as  in acid solution. [d] Decomposes in base.

TABLE II

WAVE LENGTHS OF MAXIMUM ABSORPTION AND MOLAR EXTINCTION COEFFICIENTS OF SEVERAL HYDROXAMIC ACIDS AND DERIVATIVES

| | Compound | Acid[a] $\lambda_{max}$ ($M\mu$) | Acid[a] $\epsilon_{max}$ | Anion[b] $\lambda_{max}$ ($M\mu$) | Anion[b] $\epsilon_{max}$ |
|---|---|---|---|---|---|
| IX | $C_6H_5CONCH_3OH$ | 228 | 10,000 | 220 | 9,250 |
| X | $C_6H_5CONHOCH_3$[c] | 223 | 11,000 | 257 | 5,150 |
| XI | $CH_3CH{=}CH{-}CONHOH$ | 211 | 13,000 | 263 | 7,200 |
| XII | $CH_3{-}(CH{=}CH)_2{-}CONHOH$ | 262 | 29,500 | 255 | 20,000 |
| XIII | $CH_3{-}(CH{=}CH)_2{-}COOH$ | 256 | 25,200 | 254 | 25,100 |
| XIV | $C_6H_5(C{=}NOH)OC_2H_5$[d] | 238 | 8,520 | 265 | 8,020 |
| XV | *p*-$CH_3OC_6H_4CONCH_3OH$ | 248 | 11,600 | 235 | 10,600 |

[a] Determined in 0.1*N* HCl. [b] Determined in 0.005*N* NaOH. [c] Determined in ethyl alcohol and at *p*H 13 in water. [d] Determined at *p*H 6.7 and 13. The $pK_a$ of XIV is *ca.* 11.

same conclusions through infrared analysis of various hydroxamic acids and oximes.[1]

The absorption maxima of all the *p*-substituted benzohydroxamic acids shown in Table I (except *p*-aminobenzhydroxamic acid cation) are displaced toward longer wave lengths with respect to benzohydroxamic acid. The shifts shown by compounds II, III, IV, V, and VIII are qualitatively similar to those observed with *p*-substituted derivatives in the benzoic acid series.[2] The *p*-fluoro group appears to exert a slight bathochromic shift.

Benzohydroxamic acid anion and the anions of its *p*-substituted derivatives exhibit two absorption maxima, one, bathochromic, the other, hypsochromic to that of the corresponding hydroxamic acids. *p*-Aminobenzohydroxamic acid anion is an exception showing only a bathochromic shift.

In contrast to the *p*-substituted benzohydroxamic acid anions which give two absorption bands, the anions of *N*-methylbenzohydroxamic acid (IX), *O*-methylbenzohydroxamic acid (X) and ethylsynbenzhydroximic acid (XIV) exhibit only one absorption band. The anion of *N*-methylbenzohydroxamic acid is hypsochromic with respect to its conjugate acid; *O*-methylbenzohydroxamic acid anion, bathochromic to its conjugate acid. Tautomerism is prohibited in IX and its anion leading to absorption behavior analogous to benzoic acid–benzoate ion while such is not the case with X. Ethylsynbenzhydroximic acid anion is bathochromic with respect to its acid form.

Benzohydroxamic acid anion is capable of existing in several forms (Fig. 2). A, B, and C represent

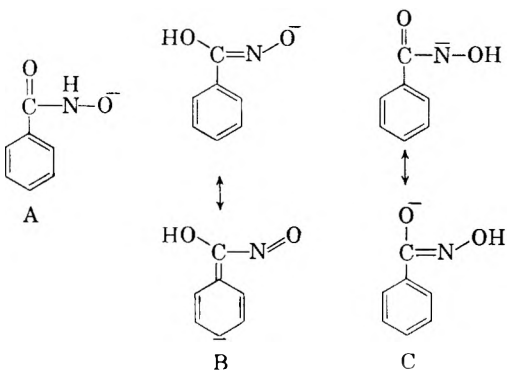



Figure 2

various possible structures. If we assume that internally hydrogen bonded structures of B and C do not contribute appreciably to the excited state of the anion, then replacing a hydrogen in the hydroxamate group by an alkyl group in B and C should give spectra which are representative of B and C. Similarly, replacing the hydrogen on the nitrogen atom of structure A with a methyl group should give a spectral curve representative of A. Thus *N*-methylbenzohydroxamic acid anion should give an absorption curve typical of A, ethylsynbenzhydroximic acid anion would represent B and *O*-methylbenzohydroxamic acid anion would be characteristic of C.

Since the anions of these three compounds (IX, X, and XIV) all exhibit only one absorption band, while benzohydroxamic acid anion and its *para*- substituted derivatives exhibit two bands, it seems plausible that benzohydroxamic acid anion contains contributions from at least two and possibly three forms, one of which is form A and the other is either form B or C or both. Thus, the bathochromic shift exhibited by benzohydroxamic acid anion is probably due to structures B or C or both, contributing to the excited state of the molecule. The hypsochromic shift is probably due to the contribution of structure A.[3]

It is interesting to note that the 268 mμ absorption band of benzohydroxamic acid anion is hardly affected by introduction into the *para*-position of a methyl, methoxyl, chloro, amino or fluoro group. It is likewise noteworthy that no reasonable resonance structures involving participation of the benzene ring, the *para*- substituent and the hydroxamate group can be readily represented for these substances. Introduction of the electron attracting cyano group in the para position readily displaces the 268 mμ band to 291 mμ as the possibilities for conjugation of this group with the benzene ring and the hydroximate group are now greatly enhanced (Fig. 3).

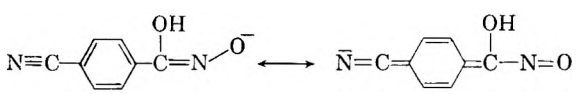


Figure 3

Two olefinic hydroxamic acids, *trans*-crotonohydroxamic acid (XI) and sorbohydroxamic acid (XII) were also studied. The anion of the former gave a bathochromic shift with respect to its acid form. It is possible that crotonohydroxamic acid anion has a band which is also hypsochromic, however if it does exist, this band would be expected in the vacuum ultraviolet region. Sorbohydroxamic acid anion was hypsochromic with respect to its conjugate acid. A broad shoulder appeared in the region of 277 mμ to 293 mμ which could well be the manifestation of a bathochromic band. The 255 mμ band of this anion is not due to the formation of sorbic acid anion which absorbs at 254 mμ. A colorimetric study of the hydrolysis of sorbohydroxamic acid indicated that this substance was stable in the *p*H range of 11 to 13.[4]

(1) M. F. Mathis, *Compt. rend.*, **232**, 505 (1951).

(2) L. Doub and J. M. Vandenbelt, *J. Am. Chem. Soc.*, **69**, 2714 (1947).

(3) Through an infrared study of the potassium salt of benzohydroxamic acid, Mathis (ref. 1) concludes that the anion has the structure of A only. His conclusion is based upon the absence of a band indicative of the OH bond and, an absorption of the molecule at 3.0μ, which he attributes to the NH bond.

(4) Determined by the disappearance of sorbohydroxamic acid analyzed as its ferric chloride complex; S. Hestrin, *J. Biol. Chem.*, **180**, 249 (1949).

## EXPERIMENTAL

*Compounds investigated.* Most of the hydroxamic acids used in this study were prepared by procedures already described in the literature.[5]

*N*-Methyl benzohydroxamic acid and its *p*-methoxy derivatives were prepared by the reaction of benzoyl and anisoyl chloride, respectively, with *N*-methylhydroxylamine. *N*-Methylbenzohydroxamic acid was a colorless liquid which boiled at 103–105° at 0.6 mm.

*Anal.* Calcd. for $C_8H_9NO_2$: C, 63.5; H, 5.95; N, 9.3. Found: C, 63.1; H, 6.1; N, 9.7.

*p*-Methoxy-*N*-methylbenzohydroxamic acid melted at 108°.

*Anal.* Calcd. for $C_9H_{11}NO_3$: C, 59.7; H, 6.1. Found: C, 60.2; H, 6.2.

*trans*-Crotonohydroxamic acid was synthesized from crotyl chloride and hydroxylamine and melted at 116°.

*Anal.* Calcd. for $C_4H_7NO_2$: C, 47.5; H, 6.9. Found: C, 47.4; H, 6.9.

*Spectra.* The ultraviolet absorption spectra were determined by means of a Beckman Quartz DU Photoelectric spectrophotometer or a Cary Spectrophotometer. Solutions of the hydroxamic acids (*ca.* $5.8 \times 10^{-5}$ molar) were made up in 0.1*N* hydrochloric acid and 0.005*N* sodium hydroxide except as noted in Tables I and II. To minimize decomposition of the hydroxamic acids, the solution was made alkaline just prior to use.

*Acknowledgment.* The author wishes to express gratitude to Mr. Omer O. Owens for preparing some of the compounds used in this investigation. The author also wishes to thank the Analytical Research Branch of these Laboratories for the use of their Cary recording spectrophotometer.

ARMY CHEMICAL CENTER, MD.

(5) Benzohydroxamic acid—W. B. Renfrew and C. R. Hauser, *J. Am. Chem. Soc.*, **59**, 2312 (1957); *p*-substituted benzohydroxamic acids—B. E. Hackley, Jr., R. E. Plapinger, M. Stolberg, and T. Wagner-Jauregg, *J. Am. Chem. Soc.*, **77**, 3651 (1955); ethylsynbenzhydroximic acid—E. Eiseler, *Ann.*, **175**, 328 (1875) and O. Gurke, *Ann.*, **205**, 285 (1905); sorbohydroxamic acid—G. M. Steinberg and J. Bolger, *J. Org. Chem.*, **21**, 660 (1956); and *O*-methylbenzohydroxamic acid—W. Lossen, *Ann.*, **281**, 186 (1894).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

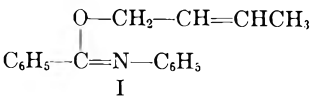
# Rearrangement of *N*-Phenylbenzimidoyl γ-Ethylallyl Ether

W. M. LAUER AND C. S. BENTON[1]

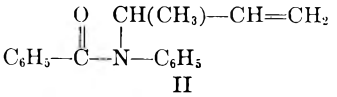
*Received September 22, 1958*

Thermal rearrangement of *N*-phenylbenzimidoyl γ-ethylallyl ether leads to the formation of *N*-ethylvinylcarbinyl benzanilide. Thus, migration of the γ-ethylallyl group from the oxygen to nitrogen occurs with inversion. At somewhat higher temperatures this initial pyrolysis product rearranges to *o*-benzamido-γ-ethylallylbenzene. This nitrogen to carbon migration also proceeds with inversion.

Relatively few *N*-phenylbenzimidoyl allyl ethers have been rearranged. Mumm and Möller[2] demonstrated that *N*-phenylbenzimidoyl γ-methylallyl ether (I) rearranges with inversion to produce *N*-α-methylallyl benzanilide (II). In order to obtain

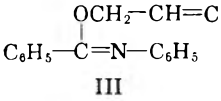


I

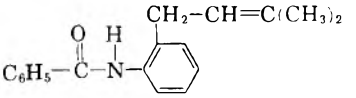


II

further information concerning the similarity of this transformation and the Claisen rearrangement, Lauer and Lockwood[3] studied the pyrolysis of *N*-phenylbenzimidoyl γ,γ-dimethylallyl ether, III. No normal rearrangement product had been obtained in the case of the γ,γ-dimethylallyl ether of ethyl *p*-hydroxybenzoate[4] and likewise, no shift of the γ,γ-dimethylallyl group from oxygen to nitrogen occurred in the case of *N*-phenylbenzimidoyl γ,γ-dimethylallyl ether. Instead, the migrating γ,γ-dimethylallyl group became attached to the aromatic nucleus without inversion, and the structural change was represented as follows:

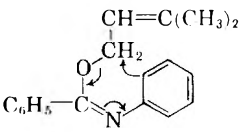


III



IV

This process can be viewed as a double inversion; the first step involving migration from oxygen to nitrogen and the second from nitrogen to carbon. A first step of this kind might be expected to be hindered by steric factors. No normal migration of the γ,γ-dimethylallyl group with inversion occurs in the Claisen rearrangement and therefore by analogy such a step might be considered to be unlikely. A single six-membered cyclic transition state of type A, which would not require oxygen to nitrogen migration with inversion, can be postulated.



A

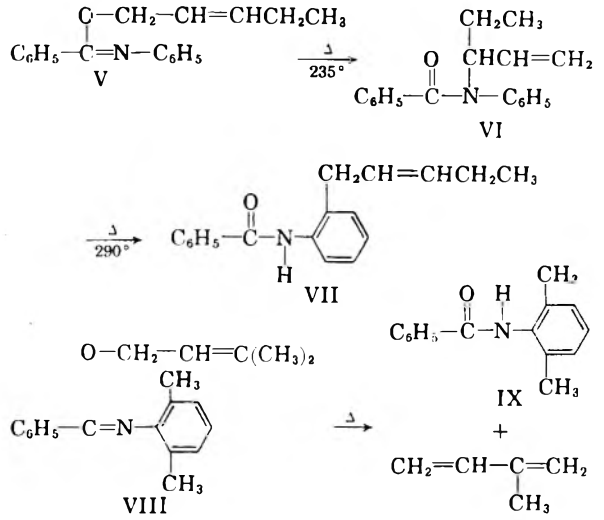
(1) From the Ph.D. Thesis of C. S. Benton submitted in August 1957.

(2) O. Mumm and F. Möller, *Ber.*, **70**, 2214 (1937).

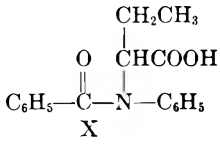
(3) W. M. Lauer and R. G. Lockwood, *J. Am. Chem. Soc.*, **76**, 3974 (1954).

(4) W. M. Lauer and O. Moe, *J. Am. Chem. Soc.*, **65**, 289 (1943).

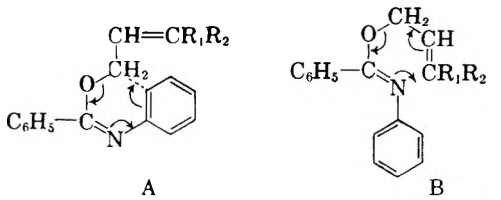
In the present study two *N*-phenylbenzimidoyl substituted allyl ethers were pyrolyzed. One, *N*-phenylbenzimidoyl γ - ethylallyl ether (V), in which oxygen to nitrogen migration is more probable than in III and *N*-2,6-dimethylphenylbenzimidoyl γ,γ-dimethylallyl ether (VIII), in which migration into the aromatic nucleus is hindered and in which, perhaps, oxygen to nitrogen migration may occur. The results of this study can be described by means of the following equations.



*N*-ethylvinylcarbinylbenzanilide (VI) was degraded to *N*-phenyl-*N*-benzoyl-α-aminobutyric acid (X), which was synthesized starting with ethyl α-bromo-*n*-butyrate. *o*-Benzamido-γ-ethylallyl-



benzene (VII) was degraded to *N*-benzoyl anthranilic acid and propionaldehyde, which was identified as its 2,4-dinitrophenylhydrazone. Benz-2,6-dimethylanilide (IX) was identified by means of its melting point and infrared spectrum. The above equations represent the main products which are produced on pyrolysis. Certainly, in the case of *N*-phenylbenzimidoyl γ-ethylallyl ether (V), oxygen to nitrogen migration with inversion, followed by a second migration from nitrogen to the aromatic nucleus with inversion can occur. However, the cases of *N*-2,6-dimethylphenylbenzimidoyl γ,γ-dimethylallyl ether (VIII) and *N*-phenylbenzimidoyl γγ-dimethylallyl ether do show that there is little or no tendency for the γ,γ-dimethylallyl group to undergo oxygen to nitrogen migration. Apparently, migration of this group with normal inversion is beset with difficulty—a feature also manifested in the Claisen rearrangement. Therefore the following facts emerge. (a) *N*-Phenylbenzimidoyl γ-methylallyl ether (I) and the next higher homolog, *N*-phenylbenzimidoyl γ-ethylallyl ether (V), undergo oxygen to nitrogen migration with inversion of the γ-substituted allyl group. (b) There is no indication of a comparable oxygen to nitrogen migration in the case of *N*-phenylbenzimidoyl γγ-dimethylallyl ether III, but instead oxygen to carbon migration occurs. (c) The product of oxygen to nitrogen migration (VI) in the case of the ether V is capable of undergoing nitrogen to carbon migration (with inversion). These findings become understandable if it is assumed that the two transition states A and B are in competition, and if assignment of determinative



power is made to the steric effect of the γ-substituents, $R_1$ and $R_2$, in the allyl group.

In the limiting sense, it can be argued that, where the intermediate resulting from transition state B cannot be isolated, its rate of decomposition must be as fast as its rate of formation, so that there is no necessity for postulating its existence at all. Thus, in the case in which $R_1 = R_2 = CH_3$, there appears to be no present justification for postulating a double migration with inversion at each step.

## EXPERIMENTAL

*N-Phenylbenzimidoyl γ-ethylallyl ether* (V). Ethylvinyl carbinol (b.p. 110–113° at 735 mm.; $n_D^{20}$ 1.4233) was obtained by the action of ethylmagnesium bromide on freshly distilled acrolein. The carbinol was next transformed to *γ-ethylallyl chloride* (b.p. 103–110°; $n_D^{20}$ 1.4372) by means of thionyl chloride. The chloride was then added slowly to glacial acetic acid containing fused potassium acetate and heated under reflux for 4 hr. After the reaction mixture was poured into ice water, extraction with ether yielded *γ-ethylallyl acetate* (b.p. 142–152°). Saponification of this ester (10% aq. NaOH and ethanol) gave *γ-ethylallyl alcohol* (b.p. 138–139°; $n_D^{20}$ 1.4347). *N-Phenylbenzimidoyl chloride* was obtained by heating benzanilide and thionyl chloride under reflux with stirring for 4 hr. The greenish reaction mixture was then distilled (b.p. 190–210° at 15–20 mm.). The clear yellow chloride (m.p. 39–39.5°) solidified on cooling and was obtained in 95% yield.

*N-Phenylbenzimidoyl γ-ethylallyl ether* (V) was prepared by the action of sodium γ-ethylallyloxide on *N*-phenylbenzimidoyl chloride. The γ-ethylallyl alcohol was treated in benzene solution with sodium sand in an atmosphere of purified nitrogen. After the disappearance (*ca.* 10 hr.) of the metallic sodium, an equimolar amount of *N*-phenylbenzimidoyl chloride was added to the benzene solution. Stirring and heating in an atmosphere of nitrogen was continued for several hours and the reaction mixture was then allowed to stand. The benzene was removed by distillation and the material remaining was subjected to distillation under diminished pressure using a motor-driven pump. A small amount of γ-ethylallyl alcohol (b.p. 135° at 740 mm.; $n_D^{20}$ 1.4358) was isolated from the forerun. Likewise, a small amount of benzanilide separated from the main fraction. It was removed by filtration and the yellow imido ether was redistilled (b.p. 150–155° at 0.005–0.01 mm.).

*Anal.* Calcd. for $C_{18}H_{19}NO$: C, 81.5; H, 7.22; N, 5.28. Found: C, 81.7; H, 7.25; N, 5.27.

Hydrolysis using methanolic potassium hydroxide gave benzoic acid, aniline and γ-ethylallyl alcohol (identified by means of b.p. and infrared spectrum).

*The rearrangement of N-phenylbenzimidoyl γ-ethylallyl ether* (V). Preliminary studies were conducted at 250° (7 hr.). The pyrolysis products were dissolved in benzene and then chromatographed on alumina. The two main products were (a) a compound (58% yield) with an infrared spectrum similar to that of *N*-allyl benzanilide which was shown to be *N*-ethylvinylcarbinyl benzanilide and (b) a compound (*ca.* 20%) with an infrared spectrum similar to that of *o*-benzamido-γ,γ-dimethylallylbenzene, which had been prepared earlier by Lauer and Lockwood. This second pyrolysis product was shown to be *o*-benzamido-γ-ethylallylbenzene. Subsequent studies showed that rearrangement at 235° yielded *N*-ethylvinylcarbinyl benzanilide which rearranged at 290° to give *o*-benzamido-γ-ethylallylbenzene (m.p. 110–110.5° Fisher-Johns melting block).

*At 235°.* The ether (V) was heated for 7 hr. under nitrogen in a tube immersed in a boiling diethylene glycol bath. The contents of the tube were then fractionally distilled. A sample of the middle fraction (120–125° at 0.03–0.05 mm.) was analyzed.

*Anal.* Calcd. for $C_{18}H_{19}NO$: C, 81.5; H, 7.22. Found: C, 81.5, 81.5; H, 7.39, 7.20.

A sample of this rearrangement product, dissolved in ethyl acetate was subjected to ozonolysis at 0°. Hydrogen peroxide (200 ml. 3%) containing sodium hydroxide was then added and the resulting mixture was stirred. The aqueous layer was neutralized (Congo Red) with concd. hydrochloric and extracted with ether. The ether solution (positive peroxide test) was then extracted several times with aqueous sodium hydroxide (5%). Acidification followed by extraction with benzene, drying ($MgSO_4$), evaporation to a small volume and the addition of petroleum ether (b.p. 30–60°) produced crystalline degradation product. After several recrystallizations from benzene and petroleum ether the colorless product (m.p. 129–131° Fisher-Johns melting block) was analyzed.

*Anal.* Calcd. for $C_{17}H_{17}NO_3$: C, 72.1; H, 6.05; N, 4.94. Found: C, 72.2, 72.4; H, 6.22, 6.22; N, 5.18, 5.19. Neutralization equivalent 281.

This degradation product, *N*-phenyl-*N*-benzoyl-α-aminobutyric acid was synthesized by treatment of ethyl α-bromobutyrate with aniline, condensing the resulting anilino compound with benzoyl chloride and saponifying the ester. The melting point (129–131° Fisher-Johns melting block) of the synthetic material was not changed by mixing with the degradation product. A comparison of the infrared spectra of the two samples showed no significant differences.

*At 290°.* Either the unrearranged ether (V), or the product of rearrangement at 235° (VI) when heated at 290° for 3 hr. in an atmosphere of nitrogen produced a solid. Purification by passage through a column of activated alumina, followed by elution with benzene containing a small amount of ethanol and by recrystallizing several times gave a product (m.p. 110–110.5°) which was analyzed.

*Anal.* Calcd. for $C_{18}H_{19}NO$: C, 81.5; H, 7.22. Found: C, 81.4; H, 7.35.

Ozonolysis of this rearrangement product was carried out in ethyl acetate. After removal of the ethyl acetate, the ozonide was gradually added to a mixture of boiling water containing a small amount of hydrochloric acid and zinc dust. The resultant mixture was then subjected to steam distillation. The steam distillate was treated with 2,4-dinitrophenylhydrazine in sulfuric acid. The 2,4-dinitrophenylhydrazone of propionaldehyde (m.p. 154–155° after recrystallization from alcohol) was obtained. A mixture of authentic propionaldehyde 2,4-dinitrophenylhydrazone with this material showed no change in melting point.

The residue from the steam distillation was extracted with ether. After removal of the ether, the ether soluble material was treated with aqueous potassium permanganate and heated. Dilute sulfuric acid was then added to the cool solution. A small amount of sodium bisulfite removed the manganese dioxide precipitate from the slightly acidic solution. Extraction with benzene was followed by an extraction of the benzene extracts with aqueous sodium hydroxide (5%). Acidification of the alkaline solution yielded a solid acid. Purification by recrystallization from benzene and petroleum ether gave a product (m.p. 186–187.5°) which was identical with an authentic specimen of *N*-benzoyl anthranilic acid.

*Preparation and pyrolysis of N-2,6-dimethylphenylbenzimidoyl γ,γ-dimethylallyl ether,* (VIII). γ,γ-Dimethylallyl bromide, prepared by the addition of hydrogen bromide to isoprene in glacial acetic acid, was converted to γ,γ-dimethylallyl acetate by means of acetic anhydride and fused potassium acetate. Saponification of the acetate gave γ,γ-dimethylallyl alcohol (b.p. 139–141°, lit.[5] 141°). The *N*-phenyl urethane melted at 63.5° (lit.[5] 63.5–64.5°).

2,6-Dimethylaniline was benzoylated and the benzoyl derivative (m.p. 163–164°) was converted to *N*-2,6-dimethylphenylbenzimidoyl chloride by means of thionyl chloride. The addition of *N*-2,6-dimethylphenylbenzimidoyl chloride in benzene to sodium γ,γ-dimethylallyloxide in an atmosphere of nitrogen yielded the desired ether, *N*-2,6-dimethylphenylbenzimidoyl γ,γ-dimethylallyl ether (b.p. 117–129°/0.005–0.03 mm.).

*Anal.* Calcd. for $C_{20}H_{23}NO$: C, 82.0; H, 7.93. Found: C, 81.9; H, 7.90.

Pyrolysis, either without solvent or dissolved in dimethylaniline yielded *N*-2,6-dimethylphenyl benzamide (m.p. 163–164°) as the only isolable solid product. A substance believed to be isoprene ($n_D^{20}$ 1.4098) was collected in a cold trap.

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[CONTRIBUTION FROM THE DEPARTMENT OF APPLIED CHEMISTRY, COLLEGE OF ENGINEERING, UNIVERSITY OF OSAKA PREFECTURE]

# Synthesis of Dibenzhydryl and Dibenzyl Penta- and Hexasulfides

JITSUO TSURUGI AND TAKESHIGE NAKABAYASHI

*Received November 12, 1958*

New methods are here reported for the preparation of dibenzhydryl and dibenzyl penta- and hexasulfides by condensation of the corresponding alkyl hydrodisulfide with sulfur di- or monochloride. The ultraviolet absorption spectra and molar refractions of these compounds were determined and compared with those of the corresponding mono-, di-, tri- and tetrasulfides. No anomaly was observed among them as the number of sulfur atoms increased from one to six.

Some organic polysulfides have been prepared by condensation of two moles of a mercaptan and one mole of sulfur mono- or dichloride. It has been proved by various methods, for instance, by determining ultraviolet absorption spectra,[1-3] dipole moments,[4] x-ray,[5] and electron diffraction[6] diagrams, that the tri- and tetrasulfides thus obtained have linear S—S linkages. Polysulfides which contain a definite number of sulfur atoms, more than four, and linear sulfur linkages, are rare. Thomas and Riding[7] prepared dibenzyl pentasulfide as an oily substance from benzyl chloride and sodium pentasulfide. Recently Fehér *et al.*[8] prepared diethyl pentasulfide by condensation of ethylmercaptan with trisulfur dichloride ($ClS_3Cl$). Organic polysulfides containing more than four sulfur atoms were often isolated from the reaction products of hydrocarbons[9,10] with sulfur, but these compounds were found to be a mixture of polysulfides, each of which contains a different number of sulfur atoms. Higher polysulfides have also been obtained by sulfur disproportionation reactions such[10] as

$$RS_nR \longrightarrow RS_mR + RS_{m-n}R \qquad (m > n)$$

or by exchange reaction[11] of polysulfides with sulfur such as

$$RS_nR - S_8 \longrightarrow RS_mR \qquad (m > n)$$

but the products are considered to be merely a mixture of polysulfides, each of which contains a different number of sulfur atoms, unless the products are separable from each other by vacuum distillation or by other methods.

Recently Böhme and Zinner[12] have prepared so called alkyl hydropolysulfides ($RS_nH$) in which the sulfur linkage has been shown to be linear. They oxidized the alkyl hydrotrisulfide with iodine and isolated the organic hexasulfides (dibenzyl and dimethyl and diethyl hexasulfides) containing linear sulfur linkages. The organic pentasulfides (dibenzyl and diethyl) were also obtained as an oily substance in their laboratory by distilling the corresponding alkyl hydrotrisulfide under high vacuum.

However, the higher polysulfides may be prepared by condensation of the alkyl hydropolysulfide with sulfur mono- or dichloride. Polysulfides containing an odd number of sulfur atoms, for instance, pentasulfide can be prepared by condensation of alkyl hydrodisulfide with sulfur dichloride more easily than by other methods. In this paper dibenzhydryl and dibenzyl penta- and hexasulfides were prepared by condensation of the corresponding alkyl hydrodisulfide with sulfur di- or monochloride, respectively, some of which were obtained in crystalline state (the pentasulfides) and some of which were new compounds (dibenzhydryl penta- and hexasulfides). Apparently this synthetic method is preferable to other methods, by which dibenzyl pentasulfide was obtained as an oily substance. The synthetic method is indicated in Equations 1 to 7, where R represents benzhydryl or benzyl groups.

$$(CH_3CO)_2O + H_2S \longrightarrow CH_3COSH + CH_3COOH \quad (1)^{13}$$

$$CH_3COSH + CH_3COCl \longrightarrow CH_3COSCOCH_3 + HCl \quad (2)^{14}$$

$$CH_3COSCOCH_3 + Cl_2 \longrightarrow CH_3COSCl + CH_3COCl \quad (3)^{15}$$

(1) H. P. Koch, *J. Chem. Soc.*, 394 (1949).
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(15) H. Böhme and M. Clement, *Ann.*, **576**, 65 (1952).

$$CH_3COSCl + RSH \longrightarrow RSSCOCH_3 + HCl \quad (4)^{12}$$

$$RSSCOCH_3 + C_2H_5OH \longrightarrow RSSH + CH_3COOC_2H_5 \quad (5)$$

$$2RSSH - ClSCl \longrightarrow RSSSSSR + 2HCl \quad (6)$$

$$2RSSH + ClSSCl \longrightarrow RSSSSSSR + 2HCl \quad (7)$$

Some of the physical constants and ultraviolet absorption spectra of these polysulfides were determined together with the corresponding mono-, di-, tri-, and tetrasulfides. Table I indicates melting points and color of these compounds.

TABLE I

MELTING POINTS AND COLOR OF DIBENZHYDRYL AND DIBENZYL SULFIDES AND POLYSULFIDES

| | Dibenzhydryl (Color) | Dibenzhydryl (M.P.) | Dibenzyl (Color) | Dibenzyl (M.P.) |
|---|---|---|---|---|
| Mono- | White | (66.5°)[16] | White | (48.5°)[2] |
| Di- | White | (152°)[16] | White | (71°)[2] |
| Tri- | White | (72.8°) | White | (49°)[2] |
| Tetra- | Faintly yellow | (82–83°)[17] | Faintly yellow | (54°)[2] |
| Penta- | Faintly yellow | (80–81.5°) | Faintly yellow | (57.5–58.5°) |
| Hexa- | Yellow oil | | Yellow oil | |

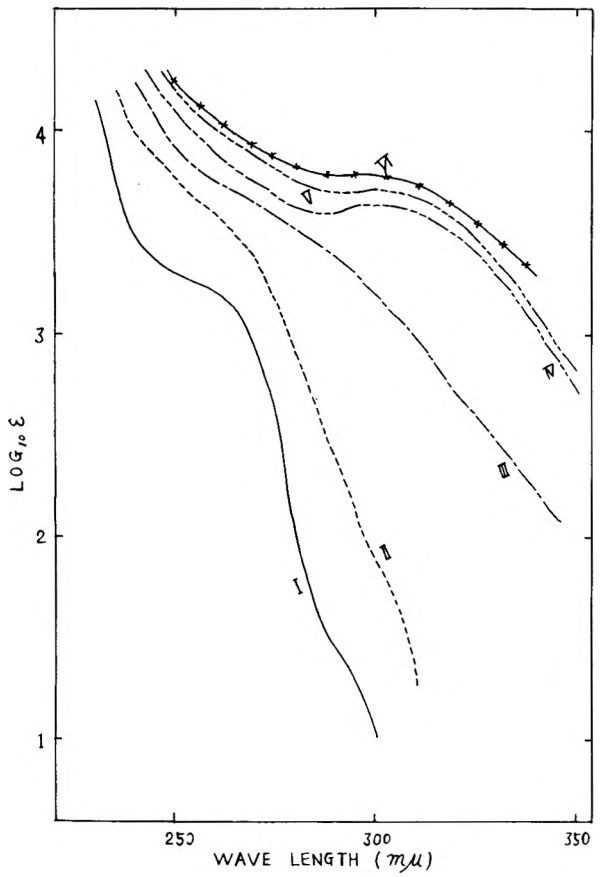



Fig. 1. Ultraviolet absorption spectra of dibenzhydryl polysulfides in alcoholic solution. I, mono-[17]; II, di-[17]; III, tri-; IV, tetra-[17]; V, penta-; VI, hexa-[18]

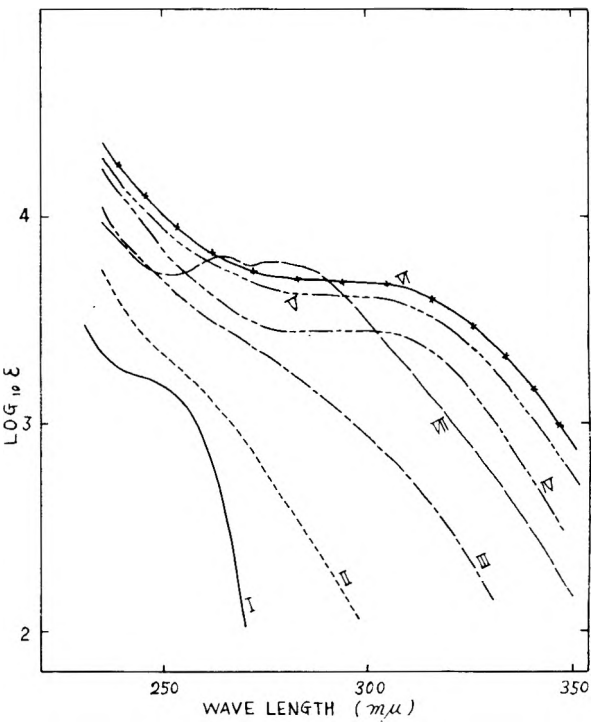



Fig. 2. Ultraviolet absorption spectra of dibenzyl polysulfides in alcoholic solution. I, mono-; II, di-; III, tri-; tetra-; V, penta-; VI, hexa-[18]; VII, sulfur molecule.[3] The spectra of dibenzyl mono- to tetra-sulfide have been already determined in *n*-hexane solution.[2] These coincide with those indicated in Fig. 1, completely in the range of the wave length determined.

The ultraviolet absorption spectra (Figs. 1 and 2) were measured in alcoholic solution between 230 and 360 mμ.

It is noteworthy that as the number of sulfur atoms in these compounds increases, the absorbance becomes more intense, and the displacement toward the longer wave lengths occurs as in the polyene series.[19] However, passing through from tetrasulfide to hexasulfide, the increase of intensity of the absorbance and the wave-length displacement become smaller for each additional sulfur atom. The shape of curves of tetra-, penta- and hexasulfides resembles each other. Especially that of the pentasulfide can coincide almost completely with that of the hexasulfide by shifting the former toward the longer wave lengths. This means that as the sulfur chain becomes longer, the excitation energy decreases, but the excited state is almost the same regardless of the chain length. Comparing the curves of the corresponding higher polysulfides in Figs. 1 and 2 with each other, one can conclude

(16) J. Tsurugi and T. Nakabayashi, *Nippon Kagaku Zasshi*, **77**, 578 (1956).

(17) J. Tsurugi and T. Nakabayashi, *Nippon Kagaku Zasshi*, **77**, 583 (1956).

(18) After long standing, the hexasulfide in the solution, especially in a polar solvent, decomposes slowly to a mixture of sulfur and lower polysulfides, but within the time period necessary for the determination no alteration in the shape of the spectra was observed.

(19) A. E. Gillam and E. S. Stern, *Electronic Absorption Spectroscopy*, E. Arnold Ltd., London, 1954, p. 67.

that even if the organic group attached to the sulfur chain differs, the absorption spectra do not differ very much. The yellow color of the higher polysulfides indicated in Table I can be accounted for by the fact that the spectra of higher polysulfides are in the same range of that of the sulfur molecule.

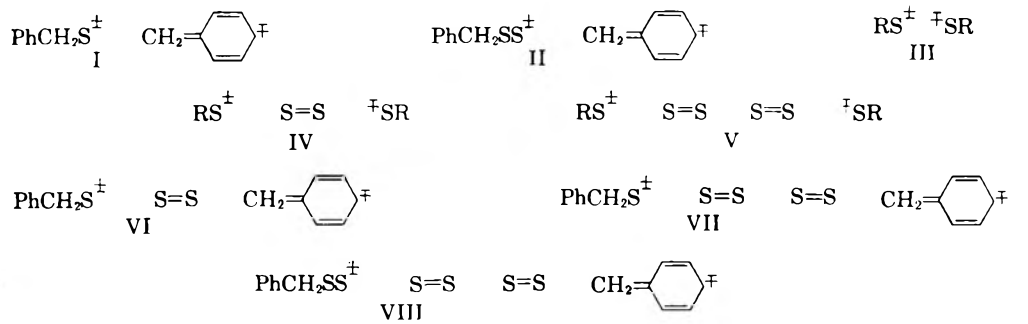
Koch suggested that canonical structures of the polar (*o*- or *p*-) quinoid type I make a significant contribution to the optically excited state of benzyl monosulfide,[20] and canonical structures II in addition to III to that of benzyl disulfide.[1] He also suggested that the enhanced absorption of dialkyl tetrasulfide over the disulfide may be correlated with the fact that further possible conjugated polar structures IV would be expected to stabilize the excited level of the tetrasulfide, and that the still greater absorption of a dialkyl hexasulfide may follow from the more highly conjugated polar structure V participating in the excited state. By analogy with Koch's consideration it is deduced that canonical structures VI and VII may participate in the excited state of dibenzyl tri- and pentasulfide, respectively. Additional canonical structures may be plausible in correspondence with the related formulations above, for instance, in hexasulfide the

TABLE II

MOLAR REFRACTIONS OF DIBENZHYDRYL AND DIBENZYL POLYSULFIDES AND ATOMIC REFRACTION OF SULFUR IN THESE COMPOUNDS

| Polysulfides, $RS_nR$ | Molar Refraction, $MR_D(RS_nR)$ | Refraction of Group $S_n$, $R_D(S_n)$ | Atomic Refraction of Sulfur $R_D(S_n)/n$[a] | Atomic Refraction of Sulfur $R_D(S_n) - R_D(S_{n-1})$ |
|---|---|---|---|---|
| $(Ph_2CH)_2S$ | 120.8 | 9.8 | 9.8 | 9.8 |
| $(Ph_2CH)_2S_2$ | 131.0 | 20.0 | 10.0 | 10.2 |
| $(Ph_2CH)_2S_3$ | 141.2 | 30.2 | 10.1 | 10.2 |
| $(Ph_2CH)_2S_4$ | 151.0 | 40.0 | 10.0 | 9.8 |
| $(Ph_2CH)_2S_5$ | 160.3 | 49.3 | 9.8 | 9.3 |
| $(Ph_2CH)_2S_6$ | 170.1 | 59.1 | 9.8 | 9.8 |
| | | | 9.9 ± 0.2 | 9.9 ± 0.5 |
| $(PhCH_2)_2S$ | 70.5 | 10.0 | 10.0 | 10.0 |
| $(PhCH_2)_2S_2$ | 81.3 | 20.8 | 10.4 | 10.8 |
| $(PhCH_2)_2S_3$ | 91.7 | 31.2 | 10.4 | 10.4 |
| $(PhCH_2)_2S_4$ | 100.2 | 39.7 | 9.9 | 8.5 |
| $(PhCH_2)_2S_5$ | 109.3 | 48.8 | 9.7 | 9.1 |
| $(PhCH_2)_2S_6$ | 118.2 | 57.7 | 9.6 | 8.9 |
| | | | 10.0 ± 0.4 | 9.6 ± 1.2 |

[a] The much better agreement was obtained by this method. In Table III cited below the values of atomic refraction of sulfur calculated by this method are indicated.




VIII structures and the similar ones may be plausible in correspondence with V structures.

Various canonical forms cited above were written with regard to dibenzyl polysulfides. However, if an $\alpha$-hydrogen atom of the benzyl group is replaced by a phenyl group, the same structures may be applicable to benzhydryl polysulfides. The results on the ultraviolet absorption spectra of these polysulfides indicated in Figs. 1 and 2 can be interpreted qualitatively by the above discussion.

It is more important that no anomaly was observed among the curves of a series of polysulfides as the number of sulfur atoms increases from one to six. If the higher polysulfides would have any coordinate sulfur atoms in branches, its spectrum would differ from that of the linear one. As stated above the tetra- and trisulfides have been proved to have linear sulfur chains. It is concluded that polysulfides thus prepared have suffered no rearrangement of sulfur atoms. Here also no evidence has come to light in support of the possible existence of structural isomers of the branched chain type.

(20) H. P. Koch, *J. Chem. Soc.*, 387 (1949).

The above conclusion is supported by the determination of molar refraction of the polysulfides. The results are indicated in Table II.

Table II indicates that even if the length of the sulfur chain increases or the organic group attached to sulfur chain differs, the atomic refraction of sulfur remains nearly constant. The same constant value of atomic refraction of sulfur has been observed by others in various polysulfides containing sulfur atoms less than four or five. These values are shown in Table III.

## EXPERIMENTAL

The preparation of dibenzhydryl mono-, di-, and tetrasulfides has been already reported in other papers.[16,17] Dibenzyl mono-, di-, tri-, and tetrasulfides were prepared by method in the literature.[2]

Dibenzhydryl trisulfide was prepared by the ordinary method from benzhydrylmercaptan[16] and sulfur dichloride.

*Anal.* Calcd. for $C_{26}H_{22}S_3$: C, 72.51; H, 5.15; S, 22.34. Found: C, 72.37; H, 5.44; S, 21.74.

In order to prepare acetyl sulfenyl chloride the most convenient method appeared in the literatures was found to be the course indicated in Equations 1 to 3.

TABLE III

ATOMIC REFRACTION OF SULFUR $R_D(S_n)/n$ IN VARIOUS POLYSULFIDES $RS_nR$

| R — n | Tolyl[21] | Ethyl[8] | Methyl[9] | n-Hexadecyl[22] |
|---|---|---|---|---|
| 1 | 9.2 | 7.85 | — | 8.4 |
| 2 | 9.5 | 8.0 | 7.9 | 9.0 |
| 3 | 10.4 | 8.3 | 8.3 | 8.7 |
| 4 | 10.2 | 8.4 | 11.1 | 9.2 |
| 5 | — | 8.5 | — | — |

*Acetyl benzhydryl disulfide* (Eq. 4). A solution of 9.2 g. of benzhydrylmercaptan in absolute ether was added dropwise under stirring in the stream of carbon dioxide to a solution of 6 g. of acetyl sulfenyl chloride in 30 ml. of absolute ether. During the reaction the temperature should be kept under 5° by cooling. After standing for 1 hr. the mixture was washed with water, aqueous sodium bicarbonate solution, and dried with anhydrous sodium sulfate. After evaporating the solvent, 8.6 g. of white crystals remained, recrystallized from petroleum ether, m.p. 43.5–45°.

*Anal.* Calcd. for $C_{15}H_{14}OS_2$: S, 23.37. Found: S, 23.57.

*Benzhydryl hydrodisulfide.* (Eq. 5.) Ten g. of acetyl benzhydryl disulfide and 100 ml. of absolute alcohol were placed in a four necked flask equipped with reflux condenser, the top of which was protected with a calcium chloride tube, dropping funnel, thermometer, and carbon dioxide inlet tube. In the stream of carbon dioxide 20 ml. of dry 5*N* alcoholic hydrogen chloride was added to the content of the flask, which was kept at 25°. The crystals of acetyl benzhydryl disulfide disappeared completely after 4 hr. By evaporating alcohol and ethyl acetate (which was formed during the reaction) at room temperature under reduced pressure, separating the solid by cooling, adding a small amount of petroleum ether–ether mixture, and again cooling, 8.3 g. of raw crystals were obtained, from petroleum ether, m.p. 32.5–34°. This compound in absolute alcohol was oxidized by alcoholic iodine solution and gave quantitatively dibenzhydrul tetrasulfide, m.p. 82–83°, mixed m.p. with authentic sample,[16] 82–83°. Under room temperature the slow evolution of hydrogen sulfide was observed from benzhydryl hydrodisulfide. This compound should be stored in a solid carbon dioxide bath in an inert atmosphere.

*Dibenzhydryl pentasulfide.* (Eq. 6.) Under cooling 0.45 g. of freshly distilled sulfur dichloride in absolute ether was added dropwise under stirring in the stream of carbon dioxide gas to 2 g. of benzhydryl hydrodisulfide in absolute ether. After the evolution of hydrogen chloride gas the solvent was evaporated at room temperature. The residue gave 2 g. of raw crystals from petroleum ether–ether mixture, recrystallized once more from the same solvent mixture, m.p. 80–81.5°.

*Anal.* Calcd. for $C_{26}H_{22}S_5$: C, 63.11; H, 4.48; S, 32.40. Found: C, 62.78; H, 4.75; S, 31.28.

*Dibenzhydryl hexasulfide.* (Eq. 7.) Freshly distilled sulfur monochloride (0.55 g.) was added to benzhydryl hydrodisulfide (2 g.) as above. After evaporating the solvent, the residue could not be crystallized by any method. Distillation under high vacuum resulted in its decomposition. After washing with petroleum ether, cooling separates the oily substance. A slight excess of benzhydryl hydrodisulfide was dissolved in petroleum ether and detected by iodine. The washing was repeated as long as the formation of tetrasulfide was observed. The oily residue, dried in vacuum, weighed 1.5 g.

*Anal.* Calcd. for $C_{26}H_{22}S_6$: C, 59.27; H, 4.21; S, 36.52. Found: C, 59.04; H, 4.42; S, 35.30.

*Acetyl benzyl disulfide.* (Eq. 4.) As in the preparation of acetyl benzhydryl disulfide, 8.15 g. of benzylmercaptan was added to 14.5 g. of acetyl sulfenyl chloride. The crude product was recrystallized from petroleum ether, m.p. 54–55° (lit.[11] 58–59°).

*Benzyl hydrodisulfide.* (Eq. 5.) As for the benzhydryl compound, 10 g. of acetyl benzyl disulfide was treated with 25 ml. of dry 5*N* alcoholic hydrogen chloride. After evaporating the solvent and ethyl acetate, the residue was distilled under vacuum, b.p. 65–70°/0.01 mm. (lit.[11] 67–70°/0.01 mm.) to yield, 5.6 g. This oil was oxidized by iodine, and gave dibenzyl tetrasulfide, m.p. 53.5–54°, mixed m.p. with an authentic sample, 53.5–54°.

*Dibenzyl pentasulfide.* (Eq. 6.) From 1.5 g. of benzyl hydrodisulfide and 0.5 g. of sulfur dichloride, 1.5 g. of crude product was obtained. After recrystallization from ether, it melted at 57.5–58.5° (lit.[7,12] oily substance).

*Anal.* Calcd. for $C_{14}H_{14}S_5$: C, 49.1; H, 4.12; S, 46.78. Found: C, 49.08; H, 3.93; S, 45.40.

*Dibenzyl hexasulfide.* (Eq. 7.) From 3 g. of benzyl hydrodisulfide and 1.1 g. of sulfur monochloride 2 g. of an oily substance was obtained. The preparing and refining procedures were the same as for the benzhydryl compound.

*Anal.* Calcd. for $C_{14}H_{14}S_6$: S, 51.53. Found: S, 50.70.

*Determination of the spectra.* The ultraviolet absorption spectra were determined with a Hitachi EPU-2 spectrophotometer, using alcohol as the solvent.

*Determination of the molar refractions.* The refractive indices $n_D^{20}$ of dilute carbon tetrachloride solutions of a polysulfide in various concentrations were determined by Abbe Refractometer, and densities $D_4^{20}$ of the same solutions were determined by Ostwald-Sprengel pycnometer. Molar refraction values were calculated by Lorenz-Lorentz equation from $n_D^{20}$ and $D_4^{20}$ of the dilute solutions, and the value of a polysulfide was obtained by extrapolating these values to infinite dilution.[23]

*Acknowledgment.* The authors wish to express their thanks to Prof. E. Campaigne of Indiana University for his kindness in revising the manuscript.

SAKAI CITY, OSAKA, JAPAN

(21) Y. Minoura, *Nippon Kagaku Zasshi*, **75**, 870 (1954).

(22) C. C. Woodrow, M. Carmack, and J. G. Miller, *J. Chem. Phys.*, 19, 951 (1951).

(23) F. Daniels, J. H. Mathews, and J. W. Williams, *Experimental Physical Chemistry* (1949), pp. 14, 232.

[CONTRIBUTION FROM THE R. B. WETHERILL LABORATORY OF CHEMISTRY, PURDUE UNIVERSITY]

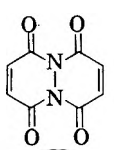
# Preparation of 1-(3′,1′H,6′-Pyridazinone)-3,6-pyridazinedione. Attempts to Prepare Bicyclic Dimaleic Hydrazide[1,2]

HENRY FEUER AND HARRY RUBINSTEIN[3]

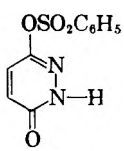
*Received November 18, 1958*

The reactions of maleic hydrazide (I) were found to be different from those of cyclic succinhydrazide (II). Under conditions such that II gave bicyclic disuccinhydrazide, I did not react. Compound I reacted with benzenesulfonyl chloride to give in addition to 3-(1′H,6′-pyridazinonyl)benzenesulfonate, 1-(3′,1′H,6′-pyridazinone)-3,6-pyridazinedione (III). Its structure was established by converting it to the known 1-(3′-chloro-6′-pyridazyl)-3-chloro-6-pyridazone (IV). The reaction of compound I and maleic anhydride with chlorine is discussed.

Cyclic succinhydrazide reacted readily with diethyl succinate, succinoyl chloride, or benzenesulfonyl chloride to give bicyclic disuccinhydrazide.[4] But attempts to synthesize bicyclic dimaleichydrazide (1,4,6,9-tetraketopyridazo[1,2-α]pyridazine) (V) by treating maleic hydrazide (I) with diethyl maleate or maleic anhydride in various solvents and under various conditions were fruitless.[5]

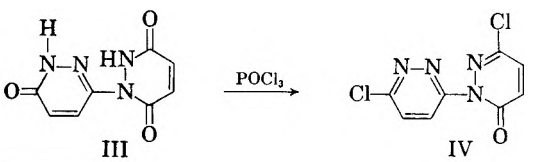


V



XIV

The reaction of compound I with benzenesulfonyl chloride gave 3-(1′H,6′-pyridazinonyl)benzenesulfonate as the major product.[6] The filtrate of the reaction mixture, on further heating, gave a new product which was not the expected compound V. On the basis of the empirical formula $C_8H_6N_4O_3$, calculated from the elemental analysis, and the infrared spectrum, which showed a carbonyl absorption maximum similar to that of compound I, the material was thought to be 1-(3′,1′H,6′-pyridazinone)-3,6-pyridazinedione (III). A search of the literature revealed that Druey and coworkers[7] had isolated in small amounts from the reaction of compound I with phosphorus oxychloride[8] a compound to which they assigned structure IV. The assignment of structure was made on the basis of elemental analysis, molecular weight, and infrared and ultraviolet spectra. It was therefore decided to synthesize compound IV and to prove the structure of compound III by relating it to compound IV.

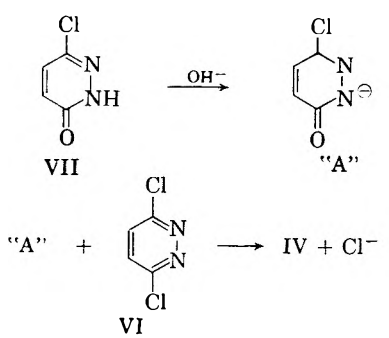


III IV

Toward the preparation of compound IV we have found that the crude reaction product of compound I and phosphorus oxychloride[8] gave on fractional crystallization from carbon tetrachloride, 3,6-dichloropyridazine (VI), 3-chloro-6-pyridazinone (VII), and a third material which had a distinct melting point. By infrared anlaysis, molecular weight determination, and elemental analysis, the latter was shown to be an equimolar mixture of compounds VI and VII. The actual structure of this "complex" is not known; however, compound VI could be readily removed from compound VII by sublimation, indicating that actual compound formation had not occurred.

When the published procedure[7] for the preparation of compound IV was followed, that is, recrystallizing the above crude reaction mixture from cyclohexane and then from isopropyl ether followed by sublimation, compound IV could not be obtained. It was, however, obtained[9] after the crude reaction mixture was sublimed in vacuum *without prior purification*, and the residue subsequently recrystallized.

It is believed that compound IV formed during heating (sublimation) from compounds VI and VII in the following way:



VII "A" (1)

"A" + VI → IV + $Cl^-$

(1) Paper V in the series, "The Chemistry of Cyclic Hydrazides."

(2) Abstracted in part from the Ph.D. thesis of Harry Rubinstein (February 1958).

(3) Purdue Research Foundation Fellow 1956-1957.

(4) H. Feuer, G. B. Bachman, and E. White, *J. Am. Chem. Soc.*, **73**, 4716 (1951).

(5) H. Rubinstein, Master's thesis, Purdue University, February 1956.

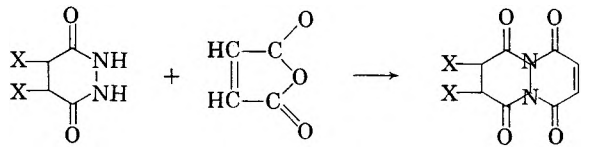
(6) H. Feuer and H. Rubinstein, *J. Am. Chem. Soc.*, **80**, 5873 (1958).

(7) J. Druey, K. Meier, and K. Eichenberger, *Helv. Chim. Acta*, **37**, 121 (1954).

The base (excess ammonium hydroxide), indicated in step (1) was introduced on neutralizing the crude reaction mixture[8] prior to sublimation.

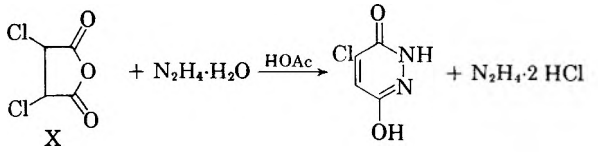
Efforts to convert compound IV into III by hydrolysis with aqueous base, resulted only in decomposition. Compound III was, however, readily converted into IV on refluxing with phosphorus oxychloride, and the structure of compound III was thereby established.

*Reaction of maleic anhydride and maleic hydrazide with bromine and chlorine.* In further efforts toward the synthesis of compound V, it was hoped that perhydro-4,5-dihalo-3,6-pyridazinedione (VIII) would react with maleic anhydride to give the bicyclic compound (IX) which then could be converted to V on treatment with zinc.



VIII IX

However, all efforts to prepare VIII by reacting I with either chlorine or bromine were fruitless. An alternate method for its preparation was then chosen by following the directions of Ligett, Closson, and Wolf,[10] who reported that the reaction of hydrazine hydrate and $\alpha,\alpha'$-dichlorosuccinic anhydride (X) gave compound VIII (X = Cl). Compound X was prepared from maleic anhydride and chlorine in carbon tetrachloride in the presence of ultraviolet light and treated with hydrazine hydrate in a mixture of benzene and ethanol.[10] This, however, gave only polymeric material. When acetic acid was used as a solvent, the reaction afforded monochloromaleic hydrazide[11] (XI), m.p. 263° dec., and hydrazine dihydrochloride instead of compound VIII. Since it was possible that dehydrohalogenation was caused by the basic hydrazine hydrate, it was substituted by hydrazine sulfate; but this also gave only compound XI.



X XI

The failure of compound I to add bromine or chlorine to its double bond, the failure encountered in the preparation of compound V from I, and the preferred dehydrohalogenation with the formation of compound XI rather than the expected compound VIII are believed to be due to resonance stabilization of compounds I and XI. This is supported by the work of Arndt *et al.*[12] who state that the double bond in compound I is not olefinic because of its failure to add diazomethane.[12] Furthermore, by comparing 2-methyl-6-methoxy-3-pyridazinone (XII) and 1,2-dimethyl-3,6-pyridazinedione (XIII) as to their reactivity to bromine, Eichenberger *et al.*[13] found that only compound XIII added bromine. This was explained by the fact that in order to become aromatic, compound XIII would have to form a structure which would violate the adjacent charge rule. On the other hand, compound XII can easily gain aromaticity without any such restriction.

It is also not surprising that compound I resists any chemical transformation which would lead to the loss of resonance stabilization. This would be the case in the conversion of compound I to V since the latter cannot have aromatic stabilization, due to the fact that it would involve two adjacent positive charges on the nitrogens.

## EXPERIMENTAL

*1-(1',1'H'6'-Pyridazinone)-3,6-pyridazinedione* (III). Five g. (0.044 mole) of maleic hydrazide and 25 g. of benzenesulfonyl chloride were heated in a beaker until a slight brown solution resulted. Then, 50 ml. of water was added with stirring and the mixture was left standing overnight on ice. The precipitated 3-(1'H'6'-pyridazonyl)benzenesulfonate was removed and the filtrate was then heated gently until a single layer had formed while more water was added to compensate for losses due to evaporation. Upon cooling, 1 g. (20%) of compound III deposited, m.p. >350° after two recrystallizations from water.

*Anal.* Calcd. for $C_8H_6O_3N_4$: C, 46.60; H, 2.93; N, 27.18. Found: C, 46.46; H, 2.75; N, 26.99.

*Reaction of maleic hydrazide and phosphorus oxychloride.* Maleic hydrazide (37.5 g., 0.29 mole) and 450 ml. of phosphorus oxychloride were refluxed for 5 hr. The solution was the concentrated *in vacuo* to a volume of 50 ml., poured into ice, and neutralized with concd. ammonium hydroxide until slightly basic. Filtration and drying gave 46 g. of crude reaction product, m.p. 150–190° dec. Boiling 5 g. of this material for 1 hr. with carbon tetrachloride and filtering gave the following products: (1) 0.8 g. of an insoluble material, m.p. 185–278° dec., which was not identified; (2) 1.3 g. of product which came out of the carbon tetrachloride solution on cooling to 25° in a Dewar containing warm water. This product consisted of a mixture which was separated manually to give needles, m.p. 140° and clusters, m.p. 116–117°; (3) 0.6 g. of crystals, m.p. 115–116° which deposited after placing the carbon tetrachloride filtrate from (2) on ice for several hours; (4) 1.7 g. of solid, m.p. 60–65° which was obtained on evaporating to dryness the filtrate from (3).

Mixture (2) was recrystallized from hot carbon tetrachloride by allowing it to cool to 25° overnight. This gave needles "A," m.p. 142–142.5°, the infrared spectrum of which was found to be identical with that of 3-chloro-6-

(8) R. H. Mizzoni and P. E. Spoerri, *J. Am. Chem. Soc.*, **73**, 1874 (1951).

(9) We are indebted to Dr. Druey for this advice and for an authentic sample of this compound.

(10) W. B. Ligett, R. D. Closson, and C. N. Wolf, U. S. Patent **2,640,005**, May 26, 1953.

(11) The patent[10] indicates an m.p. 260–263° for VIII (X = Cl), which agrees with our value of 263° for compound XI. Furthermore, the chlorine analysis indicated is 2% high for compound VIII.

(12) F. Arndt, L. Löwe, and L. Ergener, *Rev. Faculte Sci Univ. Istanbul*, **13**, 104 (1948).

(13) K. Eichenberger, H. Staehelin, and J. Druey, *Helv. Chim. Acta*, **37**, 837 (1954).

pyridazinone[14] (VII) and a mixture of authentic VII melted at 138–140°. The analytical data of "A" was as follows:

*Anal.* Calcd. for $C_4H_3ON_2Cl$: C, 36.80; H, 2.30; N, 21.4. Found: C, 36.90; H, 2.41; N, 21.26.

The above mother liquor gave after cooling on ice, clusters "B," m.p. 115–116°. Products "B" and (3) were identified as equimolar mixtures of 3,6-dichloropyridazine (VI) and compound VII. The infrared spectrum of a prepared equimolar mixture of compounds VI and VII was similar to "B" and (3) and a mixture of "B" and (3) melted at 115–116° after recrystallization from carbon tetrachloride.

*Anal.* Calcd. for (an equimolar mixture of VI and VII) $C_8H_5ON_4Cl_3/2$: N, 20.0; mol. wt. 139.7. Found: N, 19.95; mol. wt. 145 (Rast).

Subjecting mixtures "B" or (3) to heating *in vacuo* caused sublimation of compound VI and gave pure VII as the residue.

*Anal.* Calcd. for $C_4H_3ON_2Cl$ (VII): C, 36.8; H, 2.30; Cl, 27.21. Found: C, 36.95; H, 2.53; Cl, 27.22.

Product (4) on sublimation *in vacuo* gave pure VI, m.p. 69°, lit. value,[8] m.p. 68–69°, and no appreciable residue remained.

*1-(3'-Chloro-6'-pyridazyl)-3-chloro-6-pyridazone* (IV). A 7 g. sample of the crude reaction product resulting from the reaction of maleic hydrazide and phosphorus oxychloride was sublimed for 28 hr. at 70–80°. The residue was boiled with about 500 ml. of cyclohexane and after cooling, 1 g. of compound IV, m.p. 151–152° was obtained. This material gave no depression in a mixed melting point determination with authentic IV[9] and had a similar infrared spectrum.

*Conversion of compound III to compound IV.* In a 50-ml. flask fitted with an efficient condenser were placed 0.182 g. (0.88 mmole) of III and 15 ml. of phosphorus oxychloride. The mixture was refluxed 5.5 hr., filtered, and the filtrate concentrated *in vacuo* until 2 ml. of liquid remained. Addition of crushed ice, followed by sufficient concd. ammonium hydroxide to basify the solution, cooling on ice overnight, and filtering gave 0.12 g. (57% yield) of slightly tan product, m.p. 150–153°. Recrystallization from cyclohexane gave a m.p. 151–152°. A mixed melting point determination with authentic IV gave no depression.

(14) This material has previously been reported, but was obtained with a half mole of water of hydration,[7] m.p. 138–140°.

*α,α'-Dichlorosuccinic anhydride*[15] (X). A three necked 1000-ml. flask was equipped with a coarse sintered glass gas dispersion tube and a condenser. Into this flask were placed 50 g. of maleic anhydride and 500 ml. of carbon tetrachloride. The mixture was heated to reflux and irradiated with an ultraviolet light while chlorine was introduced for about 14 hr. Upon cooling, light gray crystals deposited and evaporation of the solvent *in vacuo* gave additional material. Several recrystallizations from benzene gave a m.p. 91–92° which was raised to m.p. 95–97° (lit. value[15] m.p. 95°) after recrystallization from carbon tetrachloride.

It was found necessary to purify the crude reaction product immediately, since it discolorized readily on standing. The purified product (X) was converted very rapidly to the acid on standing in air and had to be kept dry.

*Reaction of α,α,-dichlorosuccinic anhydride with hydrazine hydrate.* To a mixture of 10 g. (0.059 mole) of α,α'-dichlorosuccinic anhydride and 100 ml. of acetic acid was added in 3 min. 3 g. (0.06 mole) of hydrazine hydrate with stirring. Refluxing for 1 hr., cooling, and filtering gave 4.4 g. of crystals, m.p. 225–240° dec. Concentrating the filtrate to 10 ml. gave an additional 2.5 g. of material, m.p. 256–257° dec. and evaporation to dryness afforded 3 g. of a dark residue. These solids were partially soluble in boiling ethanol. The residue was identified as hydrazine dihydrochloride, by a mixed melting point determination with an authentic sample which gave no depression, and by comparison of the infrared spectra which were identical.

On cooling, the filtrate gave 4.0 g. (50%) 4-chloromaleic hydrazide, m.p. 263° dec., lit. value,[16] 254° dec., after recrystallization from ethanol.

*Anal.* Calcd. for $C_4H_3O_2N_2Cl$: C, 32.8; H, 2.04; N, 19.13; neut. equiv. 146.5. Found: C, 33.12; H, 2.28; N, 19.36; neut. equiv. 147.

*Acknowledgment.* The authors are grateful to the Purdue Research Foundation for financial support of this investigation.

LAFAYETTE, IND.

(15) A. Michael and G. Tissot, *J. prakt. Chem.*, **46**, 392 (1892).

(16) Yu. A. Baskakov and N. N. Melnikov, *J. Gen. Chem. U.S.S.R.*, **24**, 1205 (1954).

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[CONTRIBUTION FROM THE DIVISION OF CHEMICAL RESEARCH, G. D. SEARLE AND CO.]

# Syntheses in the 1,2,4-Benzotriazine Series

JAMES JIU AND GEORGE P. MUELLER

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A series of 3-substituted-1,2,4-benzotriazine-1-oxides together with a few of the 3-substituted-1,2,4-benzotriazines have been synthesized for pharmacological evaluation.

The variety of structural modifications possible in substituted 1,2,4-benzotriazines and their kinship to existing chemotherapeutic agents prompted us to explore further derivatives for biological activity. Earlier work in this field, though limited, is well documented[1] and more recently claims for the utility of 1,2,4-benzotriazines have been registered;[2,3] as yet no member of this series has found widespread use.

A group of 1,2,4-benzotriazine-1-oxides together with a few of the corresponding 1,2,4-benzotriazines has been prepared by the general synthetic scheme I–VI.

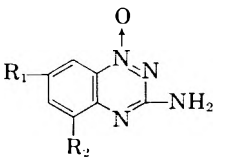
(1) J. G. Erickson, P. F. Wiley, and V. P. Wystrach, *The 1,2,3- and 1,2,4-Triazines, Tetrazines and Pentazines*, Interscience Publishers, Inc., New York, N. Y., 1956, p. 44.

(2) B. H. Shoemaker and C. M. Loane, U. S. Patent 2,160,293 (May 30, 1939).

(3) F. J. Wolf and K. Pfister III, U. S. Patents 2,489,351 to 2,489,359 (November 29, 1949), and *J. Am. Chem. Soc.*, 76, 3551, 4611 (1954).

TABLE I

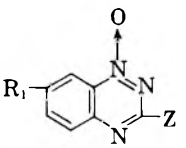
3-AMINO-1,2,4-BENZOTRIAZINE-1-OXIDES

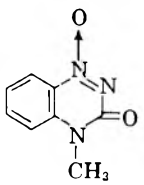


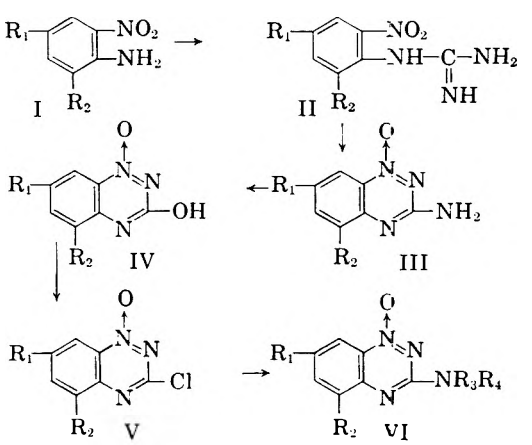
| $R_1$ | $R_2$ | M.P.[a] | Formula | Analyses, %[b] Calcd. C | H | N | Found C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| Me | Me | 251–253 | $C_9H_{10}N_4O$ | 56.83 | 5.30 | 29.46 | 56.92 | 5.29 | 29.18 |
| $C_6H_5$ | H | 303–305 | $C_{13}H_{10}N_4O$ | 65.53 | 4.23 | 23.52 | 65.46 | 4.23 | 23.25 |
| EtO | H | 276–278 | $C_9H_{10}N_4O_2$ | 52.42 | 4.89 | 27.17 | 52.61 | 4.97 | 26.77 |
| MeO | H | 278–281[c] | $C_8H_8N_4O_2$ | 50.00 | 4.19 | 29.16 | 49.99 | 4.19 | 29.05 |
| Cl | H | >300[d] | $C_7H_5ClN_4O$ | 42.76 | 2.56 | 28.50 | 43.01 | 2.41 | 28.60 |

TABLE II

3-OXYGENATED-1,2,4-BENZOTRIAZINE-1-OXIDES



| $R_1$ | $Z$ | M.P.,[a] | Formula | Analyses, %[b] Calcd. C | H | N | Found C | H | N |
|---|---|---|---|---|---|---|---|---|---|
| H | OH | 244–246[e] | $C_7H_5N_3O_2$ | 51.53 | 3.09 | 25.76 | 51.31 | 3.12 | 25.90 |
| MeO | OH | 244–246 | $C_8H_7N_3O_3$ | 49.74 | 3.66 | 21.75 | 49.32 | 3.49 | 21.64 |
| Cl | OH | 259–262[f] | $C_7H_4ClN_3O_2$ | 42.55 | 2.04 | 21.27 | 42.75 | 2.07 | 21.55 |
| H | OEt | 111–113 | $C_9H_9N_3O_2$ | 56.54 | 4.74 | 21.98 | 56.78 | 4.82 | 22.10 |
| H | OBu | 52.5–53.5 | $C_{11}H_{13}N_3O_2$ | 60.26 | 5.98 | 19.17 | 60.47 | 6.45 | 18.96 |
|  | | 237–241 | $C_8H_7N_3O_2$ | 54.23 | 3.99 | 23.72 | 54.59 | 4.15 | 23.89 |



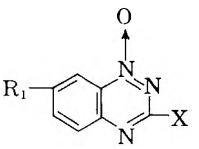
The substituted *o*-nitroanilines (I) were condensed with cyanamide or monosodium cyanamide under acid conditions, yielding *o*-nitrophenylguanidines (II), which were cyclized directly to the 3-amino-1,2,4-benzotriazine-1-oxides (III) (Table I), in alkali.[3–5] Diazotization converted the latter to 3-hydroxy-1,2,4-benzotriazine-1-oxides (IV) (Table II), and these on treatment with phosphorous oxyhalides[3,6] yielded 3-chloro- or 3-bromo-1,2,4-benzotriazine-1-oxides (V) (Table III). A mixture of the 3-hydroxy- and 3-chloro-1,2,4-benzotriazine-1-oxides was also obtained by diazotization, as recorded,[5] in the presence of a mixture of potassium ferrocyanide and potassium ferricyanide.

Condensation of the 3-chloro-1,2,4-benzotriazine-1-oxides with selected amines yielded the appropriately 3-substituted amino-1,2,4-benzotriazine-1-oxides (VI) (Table IV).

(4) F. Arndt, *Ber.*, **46**, 3522 (1913).
(5) F. Arndt and B. Rosenau, *Ber.*, **50**, 1248 (1917).
(6) R. F. Robbins and K. Schofield, *J. Chem. Soc.*, 3186 (1957).

TABLE III

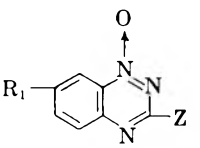
3-HALOGENATED-1,2,4-BENZOTRIAZINE-1-OXIDES



| | | | | Analyses, %[b] | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Calcd. | | | Found | | |
| $R_1$ | $X$ | M.P.[a] | Formula | C | H | N | C | H | N |
| H | Cl | 117–119[g] | $C_7H_4ClN_3O$ | 46.30 | 2.22 | 23.14 | 46.36 | 1.92 | 22.93 |
| Cl | Cl | 157–158.5[h] | $C_7H_3Cl_2N_3O$ | 38.92 | 1.40 | 19.45 | 39.02 | 1.67 | 18.93 |
| MeO | Cl | 188.5–190.5 | $C_8H_6ClN_3O_2$ | 45.41 | 2.86 | 19.86 | 45.48 | 2.77 | 19.78 |
| H | Br | 154–156 | $C_7H_4BrN_3O$ | 37.19 | 1.78 | 18.59 | 37.48 | 1.86 | 18.44 |

TABLE IV

3-SUBSTITUTED AMINO-1,2,4-BENZOTRIAZINE-1-OXIDES



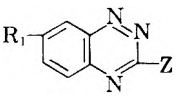
| | | | Analyses, %[b] | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Calcd. | | | Found | | |
| $R_1$ = H, $Z$ | M.P.[a] | Formula | C | H | N | C | H | N |
| Morpholino | 174–176 | $C_{11}H_{12}N_4O_2$ | 56.88 | 5.21 | 24.13 | 56.42 | 5.38 | 24.19 |
| Piperidino | 108–110 | $C_{12}H_{14}N_4O$ | 62.59 | 6.13 | 24.33 | 62.75 | 5.96 | 23.97 |
| Hexamethyleneimino | 121–122.5 | $C_{13}H_{16}N_4O$ | 63.91 | 6.60 | 22.94 | 64.40 | 6.77 | 23.38 |
| 3-Ketopiperazino | 254–257 | $C_{11}H_{11}N_5O_2$ | 53.87 | 4.52 | 28.56 | 53.62 | 4.53 | 28.23 |
| Isoquinolino | 125–126.5 | $C_{16}H_{14}N_4O$ | 69.05 | 5.07 | 20.13 | 68.80 | 5.29 | 19.93 |
| β-Phenylethylamino | 193–195 | $C_{15}H_{14}N_4O$ | 67.65 | 5.30 | 21.04 | 67.74 | 5.34 | 20.64 |
| β-Dimethylaminoethylamino | 128.5–131 | $C_{11}H_{15}N_6O$ | 56.63 | 6.48 | 30.03 | 56.94 | 6.48 | 30.05 |
| β-Diethylaminoethylamino | 77.5–80 | $C_{13}H_{19}N_5O$ | 59.75 | 7.33 | 26.80 | 59.93 | 7.22 | 26.59 |
| β-Morpholinoethylamino | 170.5–173 | $C_{13}H_{17}N_5O_2$ | 56.71 | 6.23 | 25.44 | 56.66 | 6.35 | 25.49 |
| γ-Di-*n*-butylaminopropylamino | 77–78.5 | $C_{18}H_{29}N_5O$ | 65.22 | 8.82 | 21.13 | 64.97 | 8.72 | 21.57 |
| γ-Morpholinopropylamino | 143–144.5 | $C_{14}H_{19}N_5O_2$ | 58.11 | 6.62 | 24.21 | 57.95 | 6.38 | 23.97 |
| Thiosemicarbazido | 253–255 (dec.) | $C_8H_8N_6OS$ | 40.67 | 3.41 | 35.57 | 40.50 | 3.24 | 35.32 |
| β-Hydroxyethylamino | 114–116 | $C_9H_{10}N_4O_2$ | 52.42 | 4.89 | 27.17 | 52.42 | 4.79 | 26.93 |
| β-Hydroxy-β-methylpropylamino | 159–160 | $C_{11}H_{14}N_4O_2$ | 56.40 | 6.02 | 23.92 | 56.48 | 6.00 | 24.26 |
| (α,α-Bishydroxymethylene)ethylamino | 127–128 | $C_{11}H_{14}N_4O_3$ | 52.79 | 5.64 | 22.39 | 53.04 | 5.66 | 22.67 |
| Methylglucamino | 135–137 | $C_{14}H_{20}N_4O_6$ | 49.40 | 5.92 | 16.46 | 49.27 | 5.99 | 15.93 |
| Furfurylamino | 172–178 | $C_{12}H_{10}N_4O_2$ | 59.50 | 4.16 | 23.13 | 59.55 | 4.38 | 22.96 |
| Hydrazino | 207.5–209 | $C_7H_7N_5O$ | 47.45 | 3.99 | 39.53 | 47.46 | 3.92 | 39.02 |
| α-Methylhydrazino | 134–135 | $C_8H_9N_5O$ | 50.25 | 4.74 | 36.63 | 50.69 | 5.11 | 37.21 |
| $R_1$ = Cl | | | | | | | | |
| Methylphenylamino[i] | 158.5–160 | $C_{14}H_{11}ClN_4O$ | 58.64 | 3.87 | 19.54 | 58.37 | 3.78 | 19.61 |
| β-Dimethylaminoethylamino | 157–161 | $C_{11}H_{14}ClN_5O$ | 49.35 | 5.27 | 26.16 | 49.67 | 5.50 | 26.37 |

Direct *O*-alkylation of 3-hydroxy-1,2,4-benzotriazine-1-oxide was not feasible as shown by attempts to methylate in the usual way with methyl iodide; the product proved to be 4-methyl-3-keto-3-4-dihydro-1,2,4-benzotriazine-1-oxide.[7] The 3-alkoxy derivatives were obtained in other ways; for example, the attempted displacement in 3-chloro-1,2,-4-benzotriazine-1-oxide with sodium cyanide and ethanol led to formation of 3-ethoxy-1,2,4-benzotriazine-1-oxide (VIII) R = $C_2H_5$; also with potassium fluoride, or potassium glutamate, and *n*-butanol the reaction yielded 3-*n*-butoxy-1,2,4-benzotriazine-1-oxide (VIII) R = $C_4H_9$. Similar displacement where

(7) L. Ergener, *Rev. fac. sci. univ. Istanbul*, **15***A*, No. 2, 91 (1950); *Chem. Abstr.*, **44**, 10718 (1950).

TABLE V

3-SUBSTITUTED AMINO-1,2,4-BENZOTRIAZINES

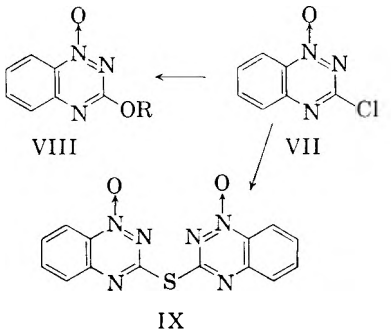


| $R_1$ = H | M.P.[a] | Formula | Analyses, %[b] Calcd. C | Calcd. H | Calcd. N | Found C | Found H | Found N |
|---|---|---|---|---|---|---|---|---|
| 3 Ketopiperazino | 237–239.5 | $C_{11}H_{11}N_5O$ | 57.63 | 4.84 | 30.55 | 57.95 | 4.93 | 30.73 |
| β-Dimethylaminoethylamino | 98–100 | $C_{11}H_{15}N_5$ | 60.80 | 6.96 | 32.24 | 60.82 | 6.83 | 32.00 |
| Hydrazino | 173–175 | $C_7H_7N_5$ | 52.16 | 4.38 | 43.46 | 52.14 | 4.51 | 44.06 |
| α-methylhydrazino | 85–89 | $C_8H_9N_5$ | | | 39.98 | | | 40.44 |

[a] Melting points taken on a Fischer-Johns block, uncorrected. [b] The authors express their appreciation to Dr. R. T. Dillon and his staff of the Analytical Department of the G. D. Searle and Co. for the analytical data presented here. [c] Lit. m.p. 258–259°, see ref. 3. [d] Lit. m.p. 302° (dec.), see ref. 3. [e] Lit. m.p. 219°, see ref. 4. [f] Lit. m.p. 230–231°, see ref. 3. [g] Lit. m.p. 117–118°, see ref. 6. [h] Lit. m.p. 153–154°, see ref. 3. [i] Obtained as a by-product in the preparation of 3,7-dichloro-1,2,4-benzotriazine-1-oxide using phosphorus oxychloride and dimethylaniline. This was probably formed from traces of monomethylaniline present in the reaction medium.

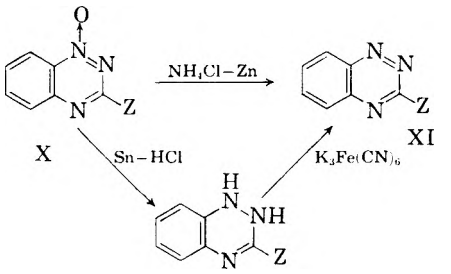
solvolysis preponderates was recently reported to occur in the purines.[8]

3 - Mercapto - 1,2,4 - benzotriazine - 1 - oxide has been prepared from *o*-nitrophenylthiourea[5] but our attempts to do so starting either with 3-hydroxy-1,2,4-benzotriazine-1-oxide and phosphorus pentasulfide, or with the 3-chloro-1,2,4-benzotriazine-1-oxide and sodium hydrosulfide were unsuccessful. Turning to the thiuronium-complex reaction[9–11] we found that treatment of the chloro compound with thiourea in absolute alcohol formed the sulfide (IX).



VIII VII IX

The 1,2,4-benzotriazines (XI) were prepared either by direct treatment of the 1-oxides (X) with zinc dust and ammonium chloride in water,[3] or by reduction



X XI

with tin and hydrochloric acid[4] to give first the 3 - substituted -1,2 - dihydro - 1,2,4 - benzotriazines (XII) which were readily oxidized by potassium ferricyanide to the 3-substituted-1,2,4-benzotriazines (XI) (Table V).

## EXPERIMENTAL

*Preparation of the 3-amino-1,2,4-benzotriazine-1-oxides. Method A. 3-Amino-1,2,4-benzotriazine-1-oxide.* A mixture of 5.00 g. of *o*-nitroaniline and 10.95 g. of monosodium cyanamide in a large beaker was heated gently on a hot plate until the nitroaniline melted. The cooled solid was then mixed well, and then 25 ml. of concentrated hydrochloric acid was added all at once. Immediately a very vigorous reaction ensued, which subsided in a few minutes. The reaction mixture was allowed to cool slowly to room temperature; then 25 ml. of water was added followed by 20 g. of sodium hydroxide. After the vigorous reaction subsided, the mixture was heated on a steam bath for 30 min. On cooling, crystals formed, which were collected and washed well with water. (This material may be used in this form for subsequent reactions.) Recrystallization from ethanol gave 3-amino-1,2,4-benzotriazine-1-oxide, yield 2.60 g., m.p. 285.5–288°.

*Method B. 3-Amino-1,2,4-benzotriazine-1-oxide.* A mixture of 10 g. of *o*-nitroaniline and 10 g. of cyanamide was fused by heating on a steam bath. To the cooled mixture was added 25 ml. of concentrated hydrochloric acid. The reaction mixture was swirled and heated gently on a steam bath until all solids were liquefied. After allowing to cool to room temperatures, 25 ml. of water and 20 g. of sodium hydroxide were added to the reaction mixture. The reaction mixture was heated on a steam bath for 30 min., and then diluted with water. The solid, 8.30 g., was collected by filtration

(8) As an example, L. Goldman, J. W. Marsico, and M. J. Weiss, at the 133rd American Chemical Society Meeting at San Francisco, April 13, 1958, obtained a 6-methoxy β-purine on treating the 6-chloro-β-purine with di*iso*-propylamine in refluxing methanol.

(9) R. K. Robins, L. B. Holum, and F. W. Furcht, *J. Org. Chem.*, **21**, 833 (1956).

(10) J. K. Landquist and J. A. Silk, *J. Chem. Soc.*, 2052 (1956).

(11) C. L. Arcus and P. A. Hallgarten, *J. Chem. Soc.*, 2987 (1956)

and washed well with water. Recrystallization from ethanol gave 3-amino-1,2,4-benzotriazine-1-oxide, m.p. 284–287°C.

*3-Hydroxy-1,2,4-benzotriazine-1-oxide.* A solution of 130 g. of 3-amino-1,2,4-benzotriazine-1-oxide in 1400 ml. of water and 510 ml. concentrated sulfuric acid was cooled to 0°. Over a period of 2.5 hr. a solution of 254 g. of sodium nitrite in 350 ml. of water was added dropwise. During the addition an ice-bath was used to maintain a 0° temperature. The reaction mixture was stirred at room temperatures for 39.5 hr., filtered, and the product washed well with water; yield 120.9 g. This product melting at 241–244°, was satisfactory for use in further reactions. Recrystallization from methanol gave 3-hydroxy-1,2,4-benzotriazine-1-oxide, m.p. 244–246°.

*3-Chloro-1,2,4-benzotriazine-1-oxide.* A solution of 170 g. of 3-hydroxy-1,2,4-benzotriazine-1-oxide in 1350 ml. of phosphorus oxychloride was heated at reflux for 2 hr. The reaction mixture was distilled to dryness *in vacuo*, and the residue was poured over cracked ice. The mixture was diluted with water and extracted with chloroform. The combined chloroform extracts were washed with water, dried over sodium sulfate, and evaporated to dryness. The oily residue was taken up in hexane and allowed to crystallize to give 3-chloro-1,2,4-benzotriazine-1-oxide, m.p. 115–117°; yield 106.1 g.

*Preparation of both 3-hydroxy- and 3-chloro-1,2,4-benzotriazine-1-oxide.* A stirred suspension consisting of 10 g. of 3-amino-1,2,4-benzotriazine-1-oxide, 6 g. of potassium ferrocyanide, 6 g. of potassium ferricyanide, 200 ml. concentrated hydrochloric acid, and 300 ml. of water was cooled to 4°. To the cooled mixture was added over a period of 2 min. a solution of 6 g. of sodium nitrite in 20 ml. of water. The mixture was stirred at 4° for an additional 30 min., then at 25° for 30 min. The precipitate was filtered. The filtrate on neutralization with sodium carbonate yielded 0.75 g. of starting material.

The precipitate was slurried with water and twice with ethyl ether. The combined ethyl ether extracts were washed with water and dried over sodium sulfate. Evaporation of the solvent *in vacuo* left a white residue which was taken up in hexane and allowed to crystallize, giving 1.64 g. of 3-chloro-1,2,4-benzotriazine-1-oxide, m.p. 114–116°. Recrystallization from aqueous methanol gave the pure compound, m.p. 117–119°.

The ether-extracted aqueous mixture was filtered, and the greenish precipitate dissolved in 50 ml. of 10% potassium hydroxide. The basic solution was filtered and the filtrate acidified with diluted hydrochloric acid. The 3-hydroxy-1,2,4-benzotriazine-1-oxide was collected by filtration and recrystallized from methanol, m.p. 244–247°; yield 1.55 g.

*3-Bromo-1,2,4-benzotriazine-1-oxide.* To 4.00 g. of 3-hydroxy-1,2,4-benzotriazine-1-oxide was added 35 ml. of phosphorus oxybromide. The mixture was heated to reflux for 10 min. and then allowed to cool to room temperatures for 15 min. The cooled solution was then poured over cracked ice and water. The heterogeneous mixture was extracted with chloroform. The combined chloroform extracts were washed with water, filtered through a sintered-glass funnel to remove any tarry material, then dried over sodium sulfate. The solvent was distilled *in vacuo* and the residue taken up in methanol and allowed to crystallize to give 2.82 g. of 3-bromo-1,2,4-benzotriazine-1-oxide, m.p. 154–156°.

*3-(β-Dimethylaminoethyl)amino-1,2,4-benzotriazine-1-oxide.* A solution of 1.50 g. of 3-chloro-1,2,4-benzotriazine-1-oxide and 5 ml. of β-dimethylaminoethylamine in 130 ml. of 1-butanol was allowed to stand at room temperatures for 16 hr., then heated to reflux for 1.5 hr. The solvent was distilled under reduced pressure and the resulting residue taken up in chloroform and washed with water. After drying with sodium sulfate and evaporating the solvent *in vacuo*, the residue was crystallized from hexane to give 3-(β-dimethylaminoethyl)amino-1,2,4-benzotriazine-1-oxide, m.p. 128.5–131°C.; yield 1.36 g.

*3-Thiosemicarbazido-1,2,4-benzotriazine-1-oxide.* A mixture of 1.00 g. of 3-chloro-1,2,4-benzotriazine-1-oxide and 1.00 g. thiosemicarbazone in 50 ml. of 1-butanol was heated to reflux for 2 hr. The reaction mixture was allowed to cool and the solid collected by filtration. The crystalline solid was recrystallized from aqueous dimethyl formamide to give 0.85 g. of 3-thiosemicarbazido-1,2,4-benzotriazine-1-oxide, m.p. 253–255° (dec.).

*3-(α,α-Bishydroxymethylene)ethylamino-1,2,4-benzotriazine-1-oxide.* A solution of 2 g. of 3-chloro-1,2,4-benzotriazine-1-oxide, 5 g. of 2-amino-2-methyl-1,3-propanediol in 125 ml. of 1-butanol was heated to reflux for 2 hr. The solvent was distilled *in vacuo*, and the residue taken up in chloroform and water. The water layer was further extracted with chloroform. The combined chloroform extracts were washed with water, dried over sodium sulfate, and evaporated to dryness. The oily residue was chromatographed on 75 g. of silica gel. Elution with ethyl acetate–benzene (7:13) gave 3-(α,α-bishydroxymethylene)ethylamino-1,2,4-benzotriazine-1-oxide, which was recrystallized from ethyl acetate, m.p. 127–128°; yield 0.37 g.

*4-Methyl-3-keto-3,4-dihydro-1,2,4-benzotriazine-1-oxide.* To 2 g. of 3-hydroxy-1,2,4-benzotriazine-1-oxide, 10 g. potassium carbonate and 150 ml. of methanol in a pressure bottle was added 50 ml. of methyl iodide. The pressure bottle was sealed and heated at 65–70° for 18 hr. The excess methanol was blown off with nitrogen and the residue taken up in chloroform and water. The water layer was further extracted with chloroform. The combined chloroform extracts were washed with water and dried over sodium sulfate and then evaporated to dryness *in vacuo*. The solid residue was recrystallized from methanol to give 1.22 g. of 4-methyl-3-keto-3,4-dihydro-1,2,4-benzotriazine-1-oxide, m.p. 235.5–240°.

*3-Ethoxy-1,2,4-benzotriazine-1-oxide.* A suspension of 2 g. of 3-chloro-1,2,4-benzotriazine-1-oxide and 2 g. of sodium cyanide in 50 ml. of ethanol was heated at reflux for 1 hr. The solvent was evaporated under nitrogen and the residue taken up in water and chloroform. The aqueous layer was further extracted with chloroform. The combined chloroform extracts were washed with water, dried over sodium sulfate, and evaporated *in vacuo*. The residue was taken up in hexane and allowed to crystallize, yielding 3-ethoxy-1,2,4-benzotriazine-1-oxide, m.p. 106.5–109°. Further recrystallization from methanol gave 1.20 g., m.p. 111–113°.

*Preparation of 3-n-butoxy-1,2,4-benzotriazine-1-oxide. Method A.* To a solution of 1.5 g. of 3-chloro-1,2,4-benzotriazine-1-oxide and 6 g. of glutamic acid in 150 ml. of 1-butanol was added about 5 g. of potassium carbonate. The heterogeneous mixture was stirred mechanically for 2 hr. and then evaporated to dryness *in vacuo*. The residue was taken up in chloroform and water, the water layer further extracted with chloroform, and the combined chloroform extracts were washed with water, dried over sodium sulfate, and evaporated to dryness *in vacuo*. Crystallization from aqueous isopropyl alcohol gave 3-*n*-butoxy-1,2,4-benzotriazine-1-oxide, m.p. 53–54°.

*Method B.* A suspension of 2 g. of 3-chloro-1,2,4-benzotriazine-1-oxide and 5 g. of potassium fluoride in 175 ml. of 1-butanol was distilled until 50 ml. of distillate was collected. A condenser was put on the reaction flask and the reaction mixture was heated at reflux for 21 hr. The solvent was distilled and the residue diluted with water and extracted with chloroform. The combined chloroform extracts were washed with water, dried over sodium sulfate, and then evaporated to dryness. Crystallization of the residue from pentane gave 3-*n*-butoxy-1,2,4-benzotriazine-1-oxide, m.p. 52–53°.

*Bis[3-(1-oxo-1,2,4-benzotriazyl)]sulfide* (IX). A mixture of 2.0 g. of 3-chloro-1,2,4-benzotriazine-1-oxide and 2.0 g. of thiourea in 125 ml. of absolute ethanol was heated to reflux for 4 hr. The solution was cooled and the solid collected and washed with a few ml. of ethanol. The solid was slurried in 100 ml. of hot ethanol, cooled, and filtered to give bis[3-(1-oxo-1,2,4-benzotriazyl)] sulfide, yield 1.20 g., m.p. 267–271.

*Anal.* Calcd. for $C_{14}H_8N_6OS_2$: C, 51.84; H, 2.49; N, 25.92; S, 9.89. Found: C, 51.80; H, 2.43; N, 26.35; S, 10.29.

*3-Chloro-1,2,4-benzotriazine.* A suspension consisting of 1.00 g. of 3-chloro-1,2,4-benzotriazine-1-oxide, 0.40 g. of zinc dust, and 0.30 g. of ammonium chloride in 25 ml. of water was stirred mechanically for 17 hr. at room temperature. The reaction mixture was diluted with an equal volume of acetic acid and then filtered. The filtrate was extracted with hexane and the combined hexane extracts were washed with water, dried over sodium sulfate, and evaporated to dryness *in vacuo*. Crystallization of the residue from pentane yielded 0.35 g. of 3-chloro-1,2,4-benzotriazine, m.p. 96–98°.

*3-Hydrazino-1,2,4-benzotriazine.* Treatment of 1.0 g. of 3-chloro-1,2,4-benzotriazine with 0.5 gm. of hydrazine hydrate with warming gave immediately a dark yellow solution which on standing crystallized. The solid was taken up in 35 ml. of ethanol and allowed to crystallize. The crystals were collected and recrystallized from benzene to give 3-hydrazino-1,2,4-benzotriazine, yield 0.55 g., m.p. 173–175°.

*3-(β-Dimethylaminoethyl)amino-1,2,4-benzotriazine.* A suspension of 1.0 g. of 3-(β-dimethylaminoethyl)amino-1,2,4-benzotriazine-1-oxide, 0.4 g. of zinc dust, and 0.3 g. of ammonium chloride in 25 ml. of water was stirred mechanically for 17 hr. at room temperature. The reaction mixture was diluted with water and extracted with chloroform and benzene. The combined chloroform and benzene extracts were washed with water, dried over sodium sulfate, and evaporated to dryness *in vacuo*. The residue was taken up in hexane and allowed to crystallize giving 0.57 g. of 3-(β-dimethylaminoethyl)amino-1,2,4-benzotriazine, m.p. 98–100°.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, ST. OLAF COLLEGE]

# Reactions of Diamines with Isocyanates and Isothiocyanates

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Diamines react with less than equivalent quantities of isocyanates and isothiocyanates to yield the mono- and disubstituted ethylenediamines and recovered diamine. The distribution of products is dependent on the reactivity of the reagent, on concentration, and on the solvent.

Recently it was shown[2] that acids react with diamines to give amides and recovered diamine in nearly the predicted yields based on random distribution. It was of interest to observe if the more facile reactions of diamines with isothiocyanates and isocyanates might yield similar distributions of products.

Amines react with isocyanates to give substituted ureas.[3] Similarly, reaction of diamines with equivalent amounts of isocyanates would be expected to give addition at each of the two amino groups. With less than two moles of isocyanates, the diamines should give mixtures in which the relative yields of the products would depend on the ratios of reactants.

$$H_2N(CH_2)_xNH_2 + b\ RNCO \longrightarrow \underset{(I)}{H_2N(CH_2)_xNH_2} + \underset{(II)}{RNHCONH(CH_2)_xNH_2} + \underset{(III)}{RNHCONH(CH_2)_xNHCONHR}$$

There is the possibility that II would react with a second molecule of isocyanate to give $(RNHCO)_2N(CH_2)_xNH_2$ (IV), but the decreased basicity of the substituted nitrogen in II relative to the primary amine should minimize this reaction.

In the above equation, when $b$ is greater than 0 but less than 2, the recovery of I would be $\left(\frac{2-b}{2}\right)^2$, the formation of III would be $\left(\frac{b}{2}\right)^2$, and the yield of II would be $\left(b - \frac{b^2}{2}\right)$. When the reactants are present in equimolar quantities and $b$ therefore is 1, the respective yields of I, II, and III would be 25%, 50%, and 25%.

The reaction of amines with isocyanates is known to occur very rapidly. It thus would be anticipated, as frequently was encountered, that the yield of III might be above the expected value due to a concentration effect at the instant of mixing the reactants. It is known[3] that isocyanates vary appreciably in their reactivities depending on the nature of the alkyl or aryl groups. It would be reasonable to expect that the isocyanates with the lesser reactivity would approach the statistical distribution more closely. The reactions of diamines with isothiocyanates[4] would parallel these considerations and substituted thioureas would result. The lower reactivity of the isothiocyanates would cause slower reactions and thus allow an approach to the statistical distribution.

Ideally, in each run the three products, I, II and III, would be isolated quantitatively. However, once the existence of all three products was established, it was expeditious to isolate only the disubstituted product III quantitatively and on occasion product II. The separation was accomplished due to the low solubility of the disubstituted compound in dilute acid solution in contrast to the appreciable solubility of the other products.

The data presented in Table I relate to the yields

(1) To whom requests for reprints should be addressed.

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TABLE I

DISUBSTITUTED PRODUCTS III[a] FROM ETHYLENEDIAMINE AND RNCS OR RNCO

| RNCS | Solvent | Value "b"[b] | Per Cent III[c] | M.P.,[d] °C. | Recryst. Solvent | Formula | N Analysis Calcd. | N Analysis Found |
|---|---|---|---|---|---|---|---|---|
| Ethyl | Isopropyl alcohol | 1.0 | 88 | 127–128 | Ethanol | $C_8H_{18}N_4S_2$ | 23.9 | 23.8 |
| Allyl | Isopropyl alcohol | 1.0 | 87 | 98–99 | Ethanol | $C_{10}H_{18}N_4S_2$ | 21.7 | 21.4 |
| *n*-Butyl | Isopropyl alcohol | 1.0 | 88 | 137–138 | Ethanol | $C_{12}H_{26}N_4S_2$ | 19.3 | 19.3 |
| *n*-Heptyl | Isopropyl alcohol | 1.0 | 83 | 134–135 | Ethanol | $C_{18}H_{38}N_4S_2$ | 15.0 | 15.1 |
| Phenyl | Isopropyl alcohol | 1.0 | 99 | 195–196 | Acetic acid | $C_{16}H_{18}N_4S_2$ | 17.0 | 17.2 |
| Phenyl | Water | 1.0 | 164 | | | | | |
| Phenyl | Benzene | 1.0 | 11 | | | | | |
| Phenyl | Ether | 1.0 | 17 | | | | | |
| Phenyl | Chloroform | 1.0 | 54 | | | | | |
| Phenyl | Xylene | 0.5 | 15 | | | | | |
| RNCO | | | | | | | | |
| *o*-Nitrophenyl | Isopropyl alcohol | 1.0 | 176 | 256–258 | Acetic acid | $C_{16}H_{16}N_6O_6$ | 21.6 | 21.1 |
| 2,5-Dichlorophenyl | Isopropyl alcohol | 1.0 | 154 | 295–299 | Dimethylformamide | $C_{16}H_{14}Cl_4N_4O_2$ | 12.8 | 13.1 |
| α-Naphthyl | Isopropyl alcohol | 1.0 | 166 | 282–284 | Dimethylformamide | $C_{24}H_{22}N_4O_2$ | 14.1 | 14.3 |
| *m*-Chlorophenyl | Isopropyl alcohol | 1.0 | 151 | 261–263 | Acetic acid | $C_{16}H_{16}Cl_2N_4O_2$ | 15.3 | 15.2 |
| *o*-Tolyl | Isopropyl alcohol | 1.0 | 125 | 250–252 | Acetic acid | $C_{18}H_{22}N_4O_2$ | 17.1 | 17.3 |
| Octadecyl | Chloroform | 0.9 | 104 | 185–186 | Acetic acid | $C_{40}H_{82}N_4O_2$ | 8.6 | 8.6 |
| Phenyl | Isopropyl alcohol | 1.0 | 128 | 247–248[e] | Acetic acid | $C_{16}H_{18}N_4O_2$ | 18.8 | 18.7 |
| Phenyl | Isopropyl alcohol | 0.4 | 230 | | | | | |
| Phenyl | Benzene | 1.0 | 107 | | | | | |
| Phenyl | Chloroform | 1.0 | 135 | | | | | |

[a] Disubstituted products $RNHCONHCH_2CH_2NHCONHR$ or $RNHCSNHCH_2CH_2NHCSNHR$. [b] Ratio of moles of RNCS or RNCO to moles of ethylenediamine. [c] Based on yield expected from random distribution. [d] All melting points are uncorrected. [e] Recorded melting points: 263,[5] 245,[6] 298[7].

of disubstituted products III obtained from ethylenediamine. The isocyanates, in practically every instance, gave relatively high yields of III, due probably to a concentration effect. In contrast to this, products from the isothiocyanates were formed in some instances in approximately the expected yields. There is an appreciable solvent effect, which we shall not now try to explain, as shown by some of the reactions involving phenyl isothiocyanate in which the yield of III is much lower than expected. It is evident that a solvent like benzene can be used to good advantage in the preparation of high yields of monosubstituted compounds (II), since the formation of III is very low. This solvent effect appears less significant with the isocyanates.

Similar results were encountered in the data of Table II, which represent the yields of III when the diamine was hexamethylenediamine. Concentration effect again apparently was responsible for the high yield of III from isocyanates. Throughout this research III was obtained in unusually high yield when "*b*" was appreciably below unity, especially with the isocyanates.

In a number of instances the monosubstituted products II were isolated and characterized, as shown in Table III. Except in the systems where the alkyl groups were relatively short aliphatic chains, these products were solids. These monosubstituted products from ethylenediamine decompose slightly above their melting points.

Titration of aliquot portions of the reaction mixtures showed active amine in quantity equal to the total equivalents of original amine minus the iso(thio)cyanates employed. A portion of this amine in each instance was accounted for by the product II. The balance ought to be unreacted diamine. In a number of instances this excess diamine, at least in part, was isolated and identified. However, the recovery of I and II were seldom attempted quantitatively.

## EXPERIMENTAL

The following example is a typical illustration of the procedure employed in this study.

*Addition of phenyl isothiocyanate to ethylenediamine.* A solution of 27 g. (0.20 mole) of phenyl isothiocyanate in 50 ml. of absolute ether was added dropwise to a vigorously stirred solution of 12 g. (0.20 mole) of anhydrous ethylenediamine in 300 ml. of isopropyl alcohol. Addition required 40 min., during which period the temperature rose slightly and a white precipitate separated. The mixture was stirred for 2 hr., was diluted with water to about 800 ml., and was allowed to stand overnight. Titration of a portion of the clear solution with aqueous hydrochloric acid (methyl orange) indicated a residual free amine content equivalent to 5.9 g., or 49% of the original diamine.

The solution was poured into a Pyrex baking dish, 18 ml. concd. hydrochloric acid was added, and evaporation to dryness was effected on a steam bath. The white residue was suspended in 250 ml. of water at about 50° and was stirred to dissolve all soluble material. The remaining solid was removed by filtration and was washed with warm water. The *N,N'*-bisphenylthiocarbamylethylenediamine weighed 13.7 g., equivalent to 21% of the original diamine. Recrystallization was effected from acetic acid, m.p. 195–196°.

*Anal.* Calcd. for $C_{16}H_{18}N_4S_2$: N, 17.0. Found: N, 17.2.

The aqueous filtrate was cooled and then made very basic

TABLE II[a]

DISUBSTITUTED PRODUCTS III FROM HEXAMETHYLENEDIAMINE AND RNCS OR RNCO

| RNCS | Solvent | Value "b" | Per Cent III | M.P., °C. | Recryst. Solvent | Formula | N Analysis Calcd. | N Analysis Found |
|---|---|---|---|---|---|---|---|---|
| Ethyl | Isopropyl alcohol | 1.0 | 102 | 102–103 | Ethanol | $C_{12}H_{26}N_4S_2$ | 19.3 | 19.2 |
| Allyl | Isopropyl alcohol | 1.0 | 107 | 103–104 | Ethanol | $C_{14}H_{26}N_4S_2$ | 17.8 | 17.8 |
| *n*-Heptyl | Isopropyl alcohol | 1.0 | 98 | 112–113 | Ethanol | $C_{22}H_{46}N_4S_2$ | 13.0 | 12.9 |
| Phenyl | Isopropyl alcohol | 1.0 | 95 | 145–147 | Ethanol | $C_{20}H_{26}N_4S_2$ | 14.5 | 14.5 |
| Phenyl | Chloroform | 1.0 | 98 | | | | | |
| Phenyl | Chloroform | 0.5 | 103 | | | | | |
| RNCO | | | | | | | | |
| *m*-Chlorophenyl | Isopropyl alcohol | 1.0 | 154 | 188–190 | Ethanol | $C_{20}H_{24}Cl_2N_4O_2$ | 13.2 | 13.4 |
| α-Naphthyl | Isopropyl alcohol | 1.0 | 155 | 248–251 | Acetic acid | $C_{28}H_{30}N_4O_2$ | 12.4 | 12.4 |
| *o*-Tolyl | Isopropyl alcohol | 1.0 | 126 | 229–231 | Acetic acid | $C_{22}H_{30}N_4O_2$ | 14.7 | 14.7 |
| Phenyl | Isopropyl alcohol | 1.0 | 148 | 219–221 | Ethanol | $C_{20}H_{26}N_4O_2$ | 15.8 | 15.7 |
| Phenyl | Chloroform | 1.0 | 186 | | | | | |
| Phenyl | Chloroform | 0.5 | 330 | | | | | |

[a] Same interpretations as in Table I.

TABLE III

MONOSUBSTITUTION PRODUCTS II[a] AND DERIVATIVES

| Material | M.P., °C. | Solvent | Formula | Neutral Equiv. Calcd. | Neutral Equiv. Found | Nitrogen Calcd. | Nitrogen Found |
|---|---|---|---|---|---|---|---|
| *N*-Phenylthiocarbamylethylenediamine | 135–136 | Chloroform | $C_9H_{13}N_3S$ | 195 | 196 | ... | ... |
| *N'*-$C_6H_5NCO$ derivative | 185–187 | Acetic acid | $C_{16}H_{18}N_4OS$ | ... | ... | 17.8 | 18.2 |
| *N'*-Benzoyl derivative | 150–152[b] | Acetone | | | | | |
| *N*-Phenylcarbamylethylenediamine | 115–116 | Chloroform | $C_9H_{13}N_3O$ | 179 | 182 | 23.3 | 22.8 |
| *N'*-Benzoyl derivative | 214–215[c] | Acetone | $C_{16}H_{17}N_3O_2$ | ... | ... | 14.8 | 14.8 |
| *N'*-$C_6H_5NCS$ derivative | 185–186 | | | | | | |
| *N*-Phenylthiocarbamylhexamethylenediamine | 89–92 | | $C_{13}H_{21}N_3S$ | 251 | 251 | ... | ... |
| *N'*-$C_6H_5$ NCO derivative | 132–133 | Ethanol | $C_{20}H_{26}N_4OS$ | ... | ... | 15.1 | 15.1 |
| *N*-Phenylcarbamylhexamethylenediamine | 114–117 | | $C_{13}H_{21}N_3O$ | ... | ... | 17.8 | 17.5 |
| *N'*-$C_6H_5NCS$ derivative | 132–134 | | | | | | |

[a] II represents $C_6H_5NHCONH(CH_2)_xNH_2$ or $C_6H_5NHCSNH(CH_2)_xNH_2$. [b] Reported[8] m.p. 150°. [c] Reported[8] m.p. 215°.

with concentrated sodium hydroxide solution. There separated an abundant yield (20.3 g., or 104% based on random distribution) of the monosubstituted product, phenylthiocarbamylethylenediamine. This was recrystallized from water, m.p. 136–137°. The neutral equivalent was determined by titration with aqueous hydrochloric acid (methyl orange).

*Anal.* Calcd. for $C_9H_{13}N_3S$: neut. equiv., 195. Found: neut. equiv., 196.

The filtrate from the above product was distilled to dryness to recover the diamine. The distillate was acidified with hydrochloric acid and was evaporated to dryness to leave 3.5 g. of the salt. Treatment with benzoyl chloride in aqueous alkali gave the known dibenzylethylenediamine.

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NORTHFIELD, MINN.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

# Thermal Stability of Triphenylsilane, Di- and Tri(aralkyl)silanes, Dibenzylmethane, and Tribenzylmethane

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The thermal stabilities were tested by heating in partially evacuated sealed Pyrex tubes for 24 hr. at approximately 300°. Tribenzylsilane was found to be very stable under these conditions. The other organosilanes tested disproportionated to some extent. Of the di(aralkyl)silanes, dibenzylsilane appeared to be the most stable. Tribenzylmethane was found to be less stable than tribenzylsilane; however, dibenzylmethane proved to be somewhat more stable than dibenzylsilane. The results of isoteniscope studies on dibenzylsilane, dibenzylmethane, tribenzylsilane, and tribenzylmethane nearly parallel those obtained from the sealed tube reactions. The preparations of (β-phenylethyl)silane, di(β-phenylethyl)silane, and di(γ-phenylpropyl)silane are described.

Recently, it was reported that diphenylsilane undergoes a disproportionation reaction when heated in the absence of any added catalyst[1] (Reaction 1). Ethyl-, diethyl- and triethylsilanes

$$(C_6H_5)_2SiH_2 \longrightarrow SiH_4 + C_6H_5SiH_3 + (C_6H_5)_2SiH_2 + (C_6H_5)_3SiH + (C_6H_5)_4Si \quad (1)$$

have also been observed to undergo disproportionation and decomposition when heated in sealed tubes at temperatures in excess of 400°.[2]

Many Lewis acid- catalyzed redistribution reactions of organosilicon compounds may be found scattered throughout the literature. Only within the last few years has interest turned toward disproportionation reactions of compounds containing silicon hydrogen bonds.[3]

This study was primarily concerned with the effects of heating some organosilicon hydrides in partially evacuated sealed Pyrex tubes for 24 hr. at temperatures around 300°. The results of these experiments are summarized in Tables I and II of the Experimental. It is realized that the results of these thermal stability tests may be valid only under the specific reaction conditions used; however, the results obtained are significant in themselves and may apply to other conditions.

With one exception, all of the organosilanes underwent redistribution reactions. Tribenzylsilane, the one exception, was outstanding because it did not disproportionate to any appreciable extent, if at all, under the conditions employed.

Also, it is interesting to note that silane was not formed in detectable amounts in any of the pyrolysis reactions of aralkyl substituted silanes. This is quite contrary to the case of diphenylsilane.[1] There was, however, slight evidence of the formation of silane when triphenylsilane was heated.

Furthermore, in the case of dibenzylsilane,[4] another difference was observed; there was no indication of the formation of tetrabenzylsilane. Further data on the relative thermal stability of dibenzylsilane was obtained in another experiment in which dibenzylsilane was refluxed at 310±5° for 3 hr. on a vacuum line system under a pressure of about 500 mm. of nitrogen. In this experiment, there was no evidence of redistribution or decomposition of the dibenzylsilane.

The infrared spectra of the products obtained from heating di- and tri(*gamma*-phenylpropyl)-silanes contained an additional absorption band at 9.0 microns, indicative of silicon-phenyl bonds. It is believed that these products possibly contain rearranged and/or cyclized compounds.

In view of the uncommon thermal stability of tribenzylsilane and the relative stability of dibenzylsilane, as compared with diphenylsilane,[1] it was of interest to empirically compare the thermal stability of their carbon analogs under similar conditions, even though the modes of decomposition of the two classes of compounds may be quite different. Tribenzylmethane[5] was found to decompose slightly; a small amount of charring was detected, the heated material had a carbonaceous odor, its melting point was depressed 6°, and its infrared spectrum was not quite identical to that of the pure hydrocarbon. Recrystallization of the heated material led to a recovery of 92.2% of pure tribenzylmethane.

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(4) Preparation described by H. Gilman and R. A. Tomasi, *J. Am. Chem. Soc.*, **81**, 137 (1959).

(5) Prepared according to the directions of G. A. Hill, M. H. Little, S. Wray, Jr., and R. J. Trimbey, *J. Am. Chem. Soc.*, **56**, 911 (1934), in an 80% yield. The reported yield was 70%.

The only indications of decomposition of dibenzylmethane after heating were a slight yellow coloration and a decrease in the refractive index by 0.0005. The infrared spectrum of the heated material was identical with that of pure dibenzylmethane. Distillation of the heated material yielded 96.9% of colorless dibenzylmethane boiling over a two-degree range.

Thus, it can be seen that tribenzylsilane is more thermally stable than tribenzylmethane and that dibenzylsilane is somewhat less stable than dibenzylmethane under the reaction conditions employed.

To obtain further data on the thermal stability of dibenzylsilane, dibenzylmethane, tribenzylsilane, and tribenzylmethane, these compounds were subjected to isoteniscopic studies. Dibenzylsilane gave no evidence of decomposition during the measurement, which was carried out over the temperature range between 83.7 and 304.5°. Similar results were obtained with dibenzylmethane over the temperature range of 69.0 to 303.5°. Furthermore, when the logarithms of the pressures were plotted against the reciprocals of the absolute temperatures for both dibenzylsilane and dibenzylmethane, nearly straight lines were obtained. In neither case did these plots exhibit a break, which indicates that the temperatures at which these compounds begin to decompose are above 300°.

Tribenzylsilane gave results similar to those obtained for dibenzylsilane and dibenzylmethane over the temperature range between 117.2 and 363.9°, with the exception that it turned slightly yellow during the measurement. A plot of $\log_{10}P$ *vs.* $1/T$ was also nearly a straight line which did not show a break, again indicating that the decomposition temperature of tribenzylsilane had not been reached during the determination. Tribenzylmethane also yellowed slightly during the isoteniscopic measurement which covered the temperature range of 121.8 to 364.1°. Furthermore, the plot of $\log_{10}P$ *vs.* $1/T$ was nearly a straight line which exhibited a break at 349°, indicating thermal decomposition began at that temperature.

Thus, the results of the isoteniscopic measurements on dibenzylsilane, dibenzylmethane, tribenzylsilane, and tribenzylmethane nearly parallel the results obtained from the other thermal stability tests on these compounds.

## EXPERIMENTAL[6]

*General procedures for pyrolysis reactions.* The reactions were carried out in Pyrex Schlenk tubes of approximately 50 ml. volume, which were dried in an oven,[7] flushed with oxygen-free, dry nitrogen, charged with the sample to be tested, evacuated, filled again with nitrogen, evacuated again to pressures varying from 1 to 10 mm., and sealed. The sealed tubes were heated slowly in an oil bath to the reported temperatures (temperature of the oil bath) for 24 hr.

The tubes were allowed to cool to room temperature and were then cooled in a Dry Ice–acetone bath before opening. The tubes were examined for the presence of silica which would be indicative of the combustion of silane formed during the reaction. Infrared spectra were run on all reaction mixtures; melting points or refractive indices were also determined. With the exceptions of tribenzylsilane and tribenzylmethane, which were recrystallized from petroleum ether (b.p. 60–70°), the products were distilled under reduced pressure. Identification of all pyrolysis products was made by comparisons of infrared spectra with those of authentic samples; in the case of liquids, refractive indices, and in the case of solids, melting points and mixed melting points were also used for identifications. The results of these experiments are summarized in Tables I and II.

TABLE I

PYROLYSIS[a] OF DI(ARALKYL)SILANES

| Compound | Types of Products, % | | | |
|---|---|---|---|---|
| | $RSiH_3$ | $R_2SiH_2$ | $R_3SiH$ | $R_4Si$ |
| $(C_6H_5CH_2)_2SiH_2$[b] | 1[c] | 20.2[d]<br>59.3[c,e] | 0.4[c,e] | 0 |
| $(C_6H_5CH_2CH_2)_2SiH_2$ | 3[c] | 13[d]<br>58.6[c] | 10.5[c,f] | —[f] |
| $(C_6H_5CH_2CH_2CH_2)_2SiH_2$ | —[g,h] | 84[c,h] | 2.8[c,h] | —[h,i] |

[a] Heated in partially evacuated sealed tubes for 24 hr. at 310–320°. See Experimental for details. [b] Heated to 400° for 1 hr., cooled to and maintained at 310–320° for 23 hr. [c] Product not quite pure. [d] Pure product. [e] The distillation residue contained an additional 6.8% of a mixture of $R_2SiH_2$ and $R_3SiH$, from which the $R_3SiH$ was isolated. [f] No products were isolated from the distillation residue. The infrared spectrum indicated the presence of some $R_3SiH$ with a high probability of the presence of $R_4Si$. [g] A low boiling fraction containing 2.8% of a mixture of $RSiH_3$ and $R_2SiH_2$. [h] The infrared spectra contained an additional absorption band at 9.0 microns. [i] The distillation residue contained 3.5% of a yellow oil which appeared to be mainly $R_4Si$; however, the infrared spectrum indicated the presence of a small amount of $R_3SiH$.

TABLE II

PYROLYSIS[a] OF TRIPHENYLSILANE AND TRI(ARALKYL)SILANES

| Compound | Types of Products, % | | | |
|---|---|---|---|---|
| | $RSiH_3$ | $R_2SiH_2$ | $R_3SiH$ | $R_4Si$ |
| $(C_6H_5)_3SiH$[b] | 0.5 | 4.5 | 69 | 16 |
| $(C_6H_5CH_2)_3SiH$ | 0 | 0 | 100[c] | 0 |
| $(C_6H_5CH_2CH_2)_3SiH$ | Traces | 5.8 | 72.5 | 8.5 |
| $(C_6H_5CH_2CH_2CH_2)_3SiH$ | Traces | 2.5[d] | 88.5 | 4.7 |

[a] Heated in partially evacuated sealed tubes for 24 hr. at 300–310°. See Experimental for details. [b] A small explosion occurred upon opening the tube, indicating the possible formation of $SiH_4$. No evidence in other reactions. [c] Melting point lowered by 0.5°. [d] Two fractions were obtained; $n_D^{20}$ 1.5460 and $n_D^{20}$ 1.5512 compared to $n_D^{20}$ 1.5444 for di(*gamma*-phenylpropyl)silane. The infrared spectra of these fractions contained additional absorption bands at 8.0 and 9.0 microns.

*Isoteniscopic studies (by A. Dobry).*[8] Dibenzylsilane, dibenzylmethane, tribenzylsilane, and tribenzylmethane

(6) Temperatures reported are uncorrected.

(7) In the cases of the tri(aralkyl)silanes and the hydrocarbons, before drying, the tubes were rinsed with dilute alkali and then with distilled water until the rinse water was neutral to litmus.

(8) The isoteniscopic measurements and calculations were made through the courtesy of Dr. Alan Dobry, Standard Oil Co. of Indiana, Whiting, Ind.

were tested on a conventional Smith-Menzies type isoteniscope. The temperatures were found with an iron-constantan thermocouple and a Rubicon Type 2745 portable precision potentiometer. Pressures were measured with an Ace Type C tilting McLeod gauge and a Wallace and Tiernan Type FA-135-173 manometer. The temperature ranges covered and the corresponding vapor pressures are listed in Table III.

TABLE III

TEMPERATURE RANGES AND CORRESPONDING VAPOR PRESSURES

| Compound | Temp., °C. | | Vapor Pressure, Mm. | |
|---|---|---|---|---|
| | Initial | Final | Initial | Final |
| Dibenzylsilane | 83.7 | 304.5 | 1.10 | 794.6 |
| Dibenzylmethane | 69.0 | 303.5 | 0.17 | 776.7 |
| Tribenzylsilane[a] | 117.2 | 363.9 | 0.55 | 777.1 |
| Tribenzylmethane[a] | 121.8 | 364.1 | 0.13 | 780.7 |

[a] Slight yellowing of the sample occurred during the measurement.

Plots of $\log_{10}P$ *vs.* $1/T$ were nearly straight lines in all cases. Only in the case of tribenzylmethane did the plot exhibit a break, which was at 349°.

The data obtained from the isoteniscopic studies were fitted to the regression equation $\log_{10}P$ (mm.) $= -A/T$-(°K.) $+ C$. The values of $A$ and $C$, as well as $Lv$, the latent heat of vaporization, were calculated and are tabulated in Table IV.

TABLE IV

CONSTANTS CALCULATED FROM ISOTENISCOPE DATA

| | Di-benzyl-silane[a] | Di-benzyl-methane[b] | Tri-benzyl-silane[c] | Tri-benzyl-methane[d] |
|---|---|---|---|---|
| $A$ | 2926 | 3211 | 4280 | 4128 |
| $C$ | 7.94 | 8.49 | 9.61 | 9.26 |
| $Lv$ (K cal./mole) | 13.4 | 14.7 | 19.6 | 18.9 |

[a] Points below 3.1 mm. were left out of this calculation. [b] Only the observation at 0.17 mm. was rejected. [c] Points below 2.1 mm. were rejected. [d] Points below 1.47 mm. and above 497.7 mm. were rejected.

*Refluxing of dibenzylsilane.* In a dry 25 ml., round-bottomed flask, equipped with a reflux condenser was placed 0.85 g. (0.004 mole) of dibenzylsilane, $n_D^{20}$ 1.5742. This was attached to a vacuum line system and cooled with a liquid nitrogen bath. The system was evacuated and filled with nitrogen to a pressure of *ca.* 500 mm. The dibenzylsilane was heated to 310 ± 5° for 3 hr. and cooled to room temperature. The heated material, 0.84 g. (98.0%), had a refractive index and infrared spectrum identical to those of the starting material.

*Di(β-phenylethyl)silane.*[9] A solution of 0.1 mole of β-phenylethylmagnesium bromide in 100 ml. of tetrahydrofuran was added rapidly to 13.6 g. (0.1 mole) of (β-phenylethyl)silane (see next experiment), and stirred overnight. The reaction mixture was hydrolyzed by the slow addition of 50 ml. of 5% hydrochloric acid. The work-up consisted of separating the aqueous layer from the organic layer, washing it twice with 75-ml. portions of ether, drying the combined organic layer and ether washings over sodium sulfate, filtering, removal of the solvents by distillation, and distilling the products under reduced pressure. Di(β-phenylethyl)silane, 15.4 g. (64.3%), was collected at 140–144° (0.9–0.95 mm.), $n_D^{20}$ 1.5562, $D_4^{20}$ 0.9728.

*Anal.* Calcd. for $C_{16}H_{20}Si$: Si, 11.68; $MR_D$, 79.56. Found: Si, 11.55, 11.58; $MR_D$, 79.47.

*(β-Phenylethyl)silane.* To 13.5 g. (0.356 mole) of lithium aluminum hydride suspended in 100 ml. of sodium-dried ether was added 102 g. (0.426 mole) of β-phenylethyltrichlorosilane in 150 ml. of ether at a rate which maintained refluxing of the ether. The reaction mixture was refluxed for 16 hr., and hydrolyzed by pouring cautiously onto a mixture of cracked ice and 50 ml. of concentrated sulfuric acid. The work-up was the same as described in the previous reaction. Two fractions of (β-phenylethyl)silane were collected: 16.2 g. (26.9%), b.p. 82–85° (45–48 mm.), $n_D^{20}$ 1.5122; and 20.4 g. (35.2%), b.p. 85–86° (48–49 mm.), $n_D^{20}$ 1.5119, $D_4^{20}$ 0.8815. The infrared spectra had absorption bands characteristic of silanes of the type $RSiH_3$.[10]

*Anal.* Calcd. for $C_8H_{12}Si$: Si, 20.61; $MR_D$, 46.12. Found: Si, 20.18, 20.23; $MR_D$, 46.48.

*Di(γ-phenylpropyl)silane.* γ-Phenylpropylmagnesium bromide, 0.97 mole in 1000 ml. of ether solution, was added to 75.4 g. (0.44 mole) of silicon tetrachloride in 100 ml. of ether at a rate which maintained refluxing. The reaction mixture was refluxed for 1 hr. and cooled to room temperature. The magnesium salts were removed by filtration under nitrogen pressure and washed with 300 ml. of ether. The combined filtrate and ether washings were added to 9.47 g. (0.25 mole) of lithium aluminum hydride suspended in 100 ml. of ether at a rate which maintained refluxing. The reaction mixture was refluxed for 2 hr., and worked up as described in the previous reaction. The products were distilled under a pressure of 25 mm. until the temperature of the distillate was 100°. The infrared spectrum of this low-boiling material indicated the presence of (γ-phenylpropyl)-silane. The distillation was continued at a lesser pressure to give 58.5 g. (49.2%) of di(γ-phenylpropyl)silane, b.p. 139–145° (0.2–0.3 mm.), $n_D^{20}$ 1.5445. A portion of this material was redistilled and was collected at 153–154° (0.55 mm.), $n_D^{20}$ 1.5444, $D_4^{20}$ 0.9530.

*Anal.* Calcd. for $C_{18}H_{28}Si$: Si, 10.46; $MR_D$, 88.82. Found: Si, 10.34, 10.24; $MR_D$, 88.98.

*Dibenzylmethane (1,3-diphenylpropane).* 1,3-Diphenyl-2-propanone, b.p. 142–146° (0.16 mm.), m.p. 36°, was reduced to the hydrocarbon by a Wolff-Kischner reaction using the modified, general procedure of Huang-Minlon[11] for other ketones. A mixture of 31.9 g. (0.15 mole) of the ketone, 20 g. (0.36 mole) of potassium hydroxide, 13.5 ml. of 95% hydrazine and 150 ml. of triethylene glycol was heated slowly to 140° over a period of 2 hr. The temperature was slowly raised to 190°, during which the aqueous distillate was removed by means of a take-off adapter on the reflux condenser. The reaction mixture was refluxed for 16 hr. and cooled to room temperature. The aqueous distillate and the reaction mixture were combined with 100 ml. of water and extracted four times with 50-ml. portions of ether. The combined ether extracts were washed twice with 100-ml. portions of water, dried over sodium sulfate, and filtered. The ether was removed by distillation and the product distilled under reduced pressure to give two fractions of dibenzylmethane: 4.81 g. (16.4%), b.p. 123–124° (1.7 mm.); and 22.92 g. (77.8%), b.p. 124° (1.7 mm.). The infrared spectra and physical constants of the two fractions were identical: $n_D^{20}$ 1.5595,[12] $D_4^{20}$ 0.9818.

(9) The tetrahydrofuran used was dried by refluxing over sodium for at least 24 hr. and distilling, immediately before use, from lithium aluminum hydride. The reaction was carried out under an atmosphere of dry oxygen-free nitrogen.

(10) Unpublished studies.

(11) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

(12) Wide variations of the value for the refractive index of 1,3-diphenylpropane have been reported in the literature. However, a refractive index of $n_D^{15}$ 1.5634 with a temperature dependence of 0.0008 per degree was reported by J. F. Sirks, *Rec. trav. chim.*, **62**, 193 (1943). His value, when corrected to 20° is $n_D^{20}$ 1.5594.

*Anal.* Calcd. for $C_{15}H_{16}$: $MR_D$, 64.80. Found: $MR_D$, 64.61.

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AMES, IOWA

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[CONTRIBUTION FROM THE MATERIALS LABORATORY, WRIGHT AIR DEVELOPMENT CENTER]

# Derivatives of Ferrocene. VI. Heteroannular Disubstitution of Ferrocene[1]

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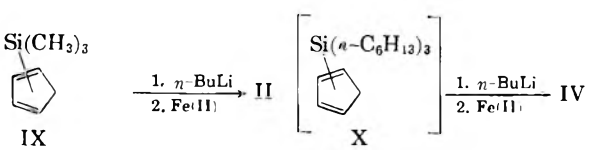
Confirmation of previous postulates regarding the steric course of two metalation reactions of ferrocene is presented. It is rigorously shown that treatment of ferrocene with *n*-butyllithium or with phenylsodium gives rise to 1,1′-dilithioferrocene or 1,1′-disodioferrocene, respectively. Dilithio- and disodioferrocene were converted to silyl derivatives which are identical to those obtained from reactions of correspondingly substituted cyclopentadienes and iron(II) chloride.

In a previous publication from this laboratory[2] some work concerning the metalation of ferrocene was described. Included in that report was the preparation of two silylferrocenes which were obtained from treatment of the reaction mixture of ferrocene and *n*-butyllithium with trimethylchlorosilane. Analytical values obtained from these products were consistent with a monosubstituted ferrocene, trimethylsilylferrocene (I), and a disubstituted ferrocene which was assigned the structure, 1,1′-bis(trimethylsilyl)ferrocene (II). The assignment had as its basis the absence of absorption near 9 and 10 $\mu$ in the infrared spectrum of the compound (9–10 Rule[3]).


| | $R_1$ | $R_2$ |
|---|---|---|
| I. | $(CH_3)_3Si$— | H— |
| II. | $(CH_3)_3Si$— | $(CH_3)_3Si$— |
| III. | $(n\text{-}C_6H_{13})_3Si$— | H— |
| IV. | $(n\text{-}C_6H_{13})_3Si$— | $(n\text{-}C_6H_{13})_3Si$— |
| V. | Li— | H— |
| VI. | Li— | Li— |
| VII. | Na— | H— |
| VIII. | Na— | Na— |

In the present study, treatment of the mixture of lithioferrocenes (V and VI) with tri-*n*-hexylbromosilane also yielded a mono- and disubstituted silylferrocene. The infrared spectra of both compounds, in this case, exhibited strong absorption at 9 and 10 $\mu$. This observation, therefore, caused us to consider the correctness of the previous structural assignment for II.[2] The fact that the spectrum of tri-*n*-hexylbromosilane also showed strong absorption at 9 and 10 $\mu$, could not, at first, be taken to mean that these bands were the ones present in the spectrum of IV since it was not possible to preclude the absence of 9–10 absorption due to the ferrocene nucleus of IV. Additional experimental work, however, conclusively showed both disubstituted silylferrocenes, II and IV, to possess heteroannular orientation; so that the absorption at 9 and 10 $\mu$ in the spectrum of IV was, in fact attributed to the substituents and not to a possible inconsistency with the 9–10 Rule.

The heteroannular locations of the silyl functions in II and IV were proven by synthesis of both compounds from the correspondingly substituted cyclopentadiene derivatives, IX and X.




IX X

Trimethylsilylcyclopentadiene (IX) was prepared according to the procedure reported by Frisch.[4] This material was treated with *n*-butyllithium followed by iron(II) chloride to yield 1,1′-bis(trimethylsilyl)ferrocene (II). The product gave rise to an infrared spectrum identical to that obtained from the disubstituted product previously prepared *via* lithiation of ferrocene.[2]

(1) Presented before the Division of Organic Chemistry, 134th Meeting, ACS, Chicago, September 1958.

(2) M. Rausch, M. Vogel, and H. Rosenberg, *J. Org. Chem.*, 22, 900 (1957).

(3) M. Rosenblum and R. B. Woodward, *J. Am. Chem. Soc.*, 80, 5443 (1958); *cf.* M. Rosenblum, doctoral dissertation, Harvard University 1953.

(4) K. C. Frisch, *J. Am. Chem. Soc.*, 75, 6050 (1953).

The tri-*n*-hexylsilylferrocenes, III and IV, were also prepared from the mixture of V and VI, but during the present investigation an improved method for the lithiation of ferrocene[5] was used. The extent of metalation was checked after 18 hr. by carbonation of an aliquot of the reaction mixture. The amount of ferrocenedicarboxylic acid thus obtained indicated a 56% conversion of ferrocene to VI. After treatment of the mixture with tri-*n*-hexylbromosilane and isolation of the products by means of chromatography on alumina, the relative amounts of III and IV obtained indicated that an incomplete reaction between VI and the bromosilane took place since an unaccountably large yield of III was isolated. Replacement of both lithio groups of VI by bulky tri-*n*-hexylsilyl radicals was probably attended with difficulty because of steric factors. The high yield of III was best explained by hydrolysis of the intermediate, 1-lithio-1′-tri-*n*-hexylsilylferrocene.

The same two products, III and IV, were also obtained from treatment of the reaction mixture of ferrocene and phenylsodium with tri-*n*-hexylbromosilane. Formation of III in this case may have also resulted from an incomplete reaction of disodioferrocene (VIII) with the bromosilane since it was reported[6] that a negligible quantity of monosodioferrocene (VII) is formed by the action of phenylsodium on ferrocene.

Unequivocal synthesis of IV was achieved by the preparation of tri-*n*-hexylsilylcyclopentadiene (X) (not isolated), and treatment of the latter with *n*-butyllithium followed by iron(II) chloride. Although IV was formed in small yield (4%), it was isolated in the pure state by means of chromatography on alumina. This authentic heteroannularly substituted compound possessed properties (infrared spectrum and refractive index) identical to those of the same two disubstituted products obtained *via* lithiation and sodiation of ferrocene.

The chemical evidence obtained in this work, which rigorously proves the structures II and IV and establishes the steric course of the two metalation reactions described, serves an additional purpose as well. The intermediates VI and VIII are directly relatable to 1,1′-diacetylferrocene through 1,1′-ferrocene dicarboxylic acid,[7] and the results of the present investigation, therefore, serve as further confirmation for the structures previously assigned to these compounds.[8]

## EXPERIMENTAL[9]

*1,1′-Bis(trimethylsilyl)ferrocene* (III). Trimethylsilylcyclopentadiene[4] (IX) (12.2 g.; 0.88 mole in 100 ml. of dry benzene) was added to a solution of *n*-butyllithium (125 ml. of a 0.70 molar solution in petroleum ether, b.p. 40–60°) during 30 min. The reaction mixture was heated under reflux during 1 hr. while it was kept under $N_2$. After the mixture had cooled to room temperature, anhydrous iron(II) chloride [prepared from 27 ml. of chlorobenzene and 9.7 g. of anhydrous iron(III) chloride[10]] was added as a slurry in 150 ml. of benzene. The petroleum ether was then removed by distillation, and 200 ml. of pure dry tetrahydrofuran (THF) was added in its place. After the reaction mixture was stirred overnight at room temperature, it was treated with ice water; and the THF removed by evaporation. The residue was filtered, and the filtrate phase-separated. Ether extracts of the aqueous phase, combined with the bulk organic phase obtained from the filtrate, were evaporated to a dark-colored oil which was fractionated *in vacuo*. The distillation yielded II (7.3 g.; 50% yield based on 0.88 mole of IX), $n_D^{25}$ 1.5437, which was collected at 96–104° (0.04–0.15 mm.). This orange-red-colored oil gave rise to an infrared spectrum which was superimposable upon the spectrum obtained from the disubstituted product prepared *via* the lithiation of ferrocene.[2]

*Tri-n-hexylsilylferrocenes.* A. III and IV *via* lithiation of ferrocene.[6] *n*-Butyllithium (1100 ml. of a 0.88*M* ethereal solution), cooled to −10°, was added to ferrocene (35.0 g.; 0.19 mole in 1100 ml. of THF) which was stirred in an atmosphere of dry $N_2$. The solution of ferrocene was initially cooled to −35°. Addition of the solution of *n*-butyllithium, although carried out as fast as possible (15 min.), was made so that the temperature of the reaction mixture did not rise above −10°. Stirring was continued while the mixture was allowed to warm to room temperature (2 hr.), and the reaction was then kept at room temperature for an additional 18 hr. At that time an aliquot was withdrawn and treated with carbon dioxide (Dry Ice) to form ferrocenedicarboxylic acid. The amount of diacid obtained (304 mg.) indicated a 56% conversion of ferrocene to VI. The lithiation was allowed to continue for another 4 hr. (24 hr. total time), after which time tri-*n*-hexylbromosilane[11] (73.6 g.; 0.23 mole) was rapidly added. A mild exothermic reaction was observed during the addition. The reaction mixture, adequately protected from light and kept in an atmosphere of $N_2$, was stirred during 4 days at room temperature. Enough water was then added (200 ml.) to dissolve the solid material (presumed to be LiBr) which was deposited, and the dark orange-red mixture was heated on a steam bath until the odor of THF was no longer detected.

The residue was extracted with $CHCl_3$, and the extracts evaporated to a dark, red-brown, mobile oil which was subsequently heated *in vacuo* (90–100°) to sublime the un-

(5) D. W. Mayo, P. D. Shaw, and M. Rausch, *Chem. & Ind. (London)*, 1388 (1957).

(6) A. N. Nesmeyanov, E. G. Perevalova, and Z. A. Beinoravichute, *Doklady Akad. Nauk S. S. S. R.*, 112, 439 (1957).

(7) Carbonation of VI by R. A. Benkeser, D. Goggin, and G. Schroll [*J. Am. Chem. Soc.*, **76**, 4025 (1954)], A. N. Nesmeyanov, E. G. Perevalova, R. V. Golovnya, and O. A. Nesmeyanova [*Doklady Akad. Nauk S. S. S. R.*, **97**, 459 (1954)] and D. W. Mayo, P. D. Shaw, and M. Rausch (Ref. 5), and carbonation of VIII by A. N. Nesmeyanov, E. G. Perevalova, R. V. Golovnya, and O. A. Nesmeyanova (above), produced a dicarboxylic acid (1,1,-ferrocenedicarboxylic acid) with properties identical to those of the diacid obtained by Rosenblum and Woodward (Ref. 3) through hypoiodite oxidation of diacetylferrocene-A (1,1,-diacetylferrocene).

(8) See. M. Rosenblum and R. B. Woodward, Ref. 3 and other work cited therein.

(9) All boiling points are uncorrected. Analyses by Schwartzkopf Microanalytical Laboratory, Woodside 77, N. Y. and Spang Microanalytical Laboratory, Ann Arbor, Mich.

(10) P. Kovacic and N. O. Brace, *J. Am. Chem. Soc.*, **76**, 5491 (1954).

(11) The authors wish to express their gratitude to Dr. C. Tamborski of this laboratory for the tri-*n*-hexylbromosilane used in this work.

reacted ferrocene (3.9 g.; 11% of the original amount). Distillation of the ferrocene-free residue gave III (34.7 g.; 32% yield) which was collected as an orange-red oil within the temperature range of 180–198° (0.17–0.25 mm.). This material was subsequently column-chromatographed on 1000 g. of Woelm, nonalkaline, Grade I alumina. The product, III, was eluted from the column with a benzene–ethanol mixture (35 parts of benzene and 1 part of ethanol) after the column was developed with benzene. The material was chromatographically homogeneous; $n_D^{25}$ 1.5202.

*Anal.* Calcd. for $C_{28}H_{48}FeSi$: C, 71.76; H, 10.32; Fe, 11.92. Found: C, 71.96; H, 10.30; Fe, 11.85.

The residue obtained from the distillation of the crude reaction product was column-chromatographed on 800 g. of alumina. Development and elution were carried out with benzene, and IV (29.8 g.; 35% yield) was obtained from the eluate. A portion of the product was rechromatographed for analysis; $n_D^{25}$ 1.5054.

*Anal.* Calcd. for $C_{46}H_{86}FeSi_2$: C, 73.55; H, 11.54; Fe, 7.43. Found: C, 73.23; H, 11.36; Fe, 7.24.

B. III and IV *via* sodiation of ferrocene.[6] Ferrocene (23.3 g.; 0.125 mole), dissolved in toluene, was treated with phenylsodium[12] (0.25 mole) at room temperature during 24 hr.; and at 75–80° for an additional 7 hr. Tri-*n*-hexylbromosilane (90.8 g.; 0.25 mole) was rapidly added (mild exothermic reaction), and the mixture stirred at room temperature overnight; then heated at 70–80° for 24 hr. The reaction mixture, cooled to 10°, was passed through a bed of "Filter-Aid," and the filtrate (500 ml.) was heated on a steam bath *in vacuo* (20 min.) to sublime the unreacted ferrocene (17.9 g.; 77% of the initial amount). The residue was then heated under distillation conditions, and material which was collected up to 100° (0.04 mm.) was not investigated. The undistilled portion (28.2 g. of a dark fluid) was chromatographed on 400 g. of alumina. The chromatogram was developed with cyclohexane and eluted with benzene. Two bright orange-colored bands were successively eluted. The slower-moving band yielded III (580 mg., 0.5% yield) which when rechromatographed was obtained analytically pure; $n_D^{25}$ 1.5202.

Elution of the faster-moving band gave IV (5.63 g., 8% yield); $n_D^{25}$ 1.5054.

C. IV *via* tri-*n*-hexylsilylcyclopentadiene (X). Freshly distilled cyclopentadiene (13.7 g.; 0.21 mole) was added to sodium shot (2.34 g.; 0.10 mole) over a 15-min. period. Evolvement of hydrogen ceased 45 min. after the addition was completed. The reaction mixture was cooled to 5°, and tri-*n*-hexylbromosilane (36.5 g.; 0.10 mole), dissolved in 20 ml. of THF was added with stirring during a 1-hr. period. The mixture was allowed to reach room temperature while the stirring was continued for an additional 2 hr. After the reaction mixture was subsequently heated under reflux during 24 hr., it was cooled to room temperature and passed through a bed of Filter-Aid to remove the white precipitate (NaBr) which was present. The filtrate was evaporated on a steam bath *in vacuo*, and the residue distilled.

Infrared analysis of a fraction collected at 140–160° (0.5–0.7 mm.), $n_D^{25}$ 1.4750–1.4743, indicated the presence of a substituted cyclopentadiene compound. A portion of this material (3.5 g.; 0.01 mole based on the presence of pure X) was dissolved in benzene and treated with *n*-butyllithium (9 ml. of a 0.18*M* ethereal solution), and then heated under reflux during 1 hr. Iron(II) chloride (3.5 g.; 0.02 mole) was added as a slurry in THF, and the reaction mixture heated under reflux for 3 hr.; then stirred at room temperature during an additional 24 hr. After the mixture was poured onto 200 ml. of water–crushed ice and phase-separated, ether extracts of the aqueous phase were combined with the bulk organic portion. The presence of the ferrocene nucleus in this solution was indicated by means of a paper chromatography test.[13] Evaporation of the solvent yielded a dark fluid which was heated to 250° (0.1 mm.) until no further distillate was obtained. The undistilled portion was chromatographed on 30 g. of alumina, and the compound, IV (56 mg., 4% yield), $n_D^{25}$ 1.5056, was obtained from the benzene eluate.

The infrared spectrum of the product was found to be identical to those of the disubstituted compounds (both IV) prepared *via* the 2 metalation procedures.

*Acknowledgment.* The authors wish to express their appreciation to Mr. F. F. Bentley and associates of this laboratory for the infrared spectra cited in this work.

WRIGHT-PATTERSON AIR FORCE BASE, OHIO

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DE PAUL UNIVERSITY]

# The Active 12-Methyloctadecanoic Acids

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The (+)- and (−)-12-methyloctadecanoic acids have been prepared from (+)- and (−)-2-octanols by the procedure pioneered by Prout, Cason, and Ingersoll.[2] The active acids have higher melting points than the DL-acid.

The preparation of the active 12-methyloctadecanoic acids represents an extension of earlier work[2,3] and the scheme is given in the chart.

The (+)- and (−)-2-octanols[4] (I) were converted to the antipodally pure (−)- and (+)-3-methylnonanoic acids (V) by a four-step procedure in which optical purity was assured by fractional crystallization of the (−)- and (+)-2-octylmalonic acids (IV). The active forms of IV (m.p. 106–108°) were obtained readily by crystallization from hexane; however, the DL-form (m.p. 80–82°) did

(1) This work was abstracted from the Master of Science theses submitted to the faculty at De Paul University by Donald E. Dickson (1952) and Robert J. Klimkowski (1958).

(2) F. S. Prout, J. Cason, and A. W. Ingersoll, *J. Am. Chem. Soc.*, **70**, 298 (1948).

(3) J. Cason and R. A. Coad, *J. Am. Chem. Soc.*, **72**, 4695 (1950).

(4) J. Kenyon, *Org. Syntheses*, Coll. Vol. I, 2nd ed., 418–21 (1941).

not crystallize except when equal amounts of the two purified antipodes were mixed.

The active 3-methylnonanoic acids[5] ($[\alpha]_D \mp 4.5°$) (V) which resulted from decarboxylation of the (−)- and (+)-2-octylmalonic acids (IV) were esterified and reduced catalytically over copper chromite. The yields of (−)- and (+)-3-methyl-1-nonanol (VII) were low, presumably because conditions for reduction were too severe and gave hydrocarbon (3-methylnonane). Action of hydrogen bromide gave the (+)- and (−)-1-bromo-3-methylnonanes (VIII). These bromides were lengthened to the ethyl (±)-12-methyl-9-oxo-octadecanoate (IX) and the keto esters were reduced[6] to give (±)-12-methyloctadecanoic acid (XI). The properties of these acids and their derivatives are summarized in Table I.

TABLE I

MELTING POINTS OF 12-METHYLOCTADECANOIC ACID AND DERIVATIVES

| | Acid °C. | Acid $\alpha_D^{27}$[a] | Amide, °C. | Tribromoanilide, °C. |
|---|---|---|---|---|
| DL- | 26–27 | | 84–86 | 93–94 |
| | 27.6–28.2[b] | | 86–88.2[b] | 94.2–95.2[b] |
| (+) | 37–38 | +0.09° | 74–75 | 89–91 |
| (−) | 36–37 | −0.10° | 72–75 | 90–92 |

[a] Rotation is homogeneous, 2 d. tube. [b] Ref. 7.

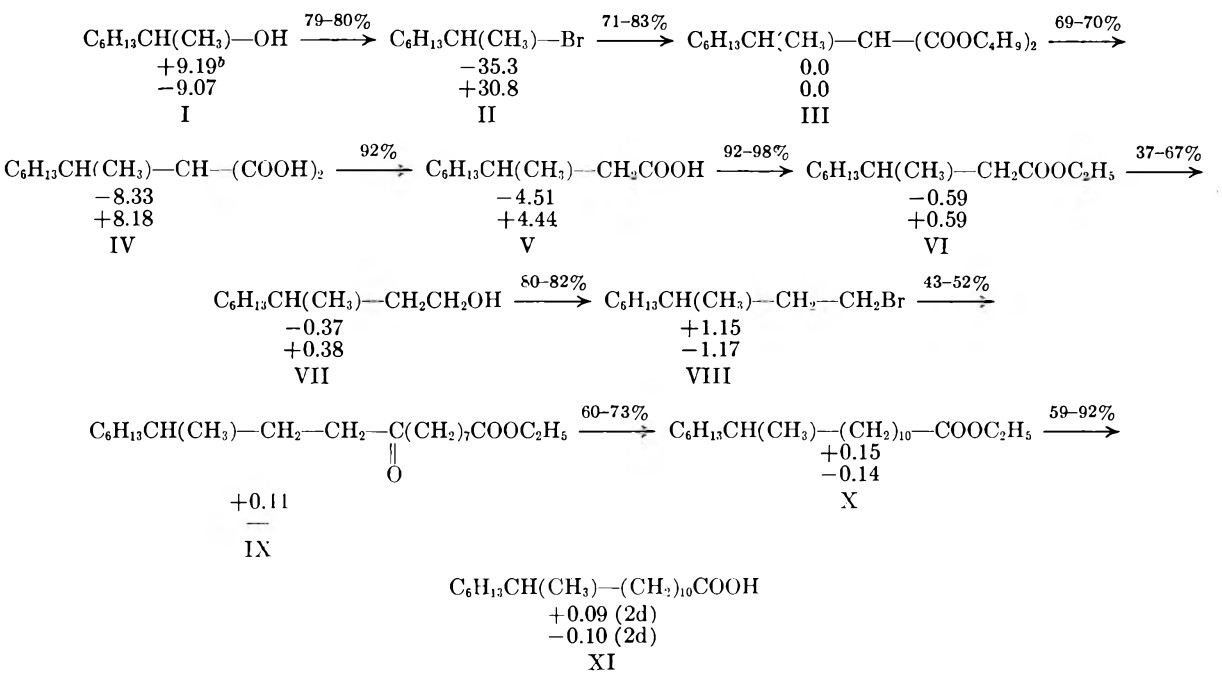
## EXPERIMENTAL

All melting points and boiling points were uncorrected. Most products were fractionated through a 60-cm., heated Vigreux column. Density is reported in absolute units (g./cc.). The expression "hexane" refers to Skellysolve B, a ligroin fraction, b.p. 60–70°, supplied by the Skelly Oil Company, Kansas City, Mo. All rotations were observed in a Rudolph Universal High Precision polarimeter through a two-decimeter tube unless otherwise noted. The elemental analyses were performed by Abbott Laboratories, North Chicago, Ill., by Micro-Tech Laboratories, Skokie, Ill. or by Drs. Strauss and Weiler, Oxford, England.

*2-Octanol* (I) was resolved by the method of Kenyon.[4] The alcohols used had specific activities of $[\alpha]_D^{26}$ +7.92° to +9.19° and $[\alpha]_D^{26}$ −5.91° to −9.07°. Pickard and Kenyon[8] reported maximum values $[\alpha]_D$ ±9.9°. Highly purified alcohol was not required because the very efficient crystallization of antipodal 2-octylmalonic acids (below) effected separation of pure antipodal 2-octylmalonic acid where the excess of one form was small.

The *2-bromo-octanes* (II) were prepared in 50–80% yields using the basic procedure of Hseuh and Marvel:[9] DL-form, b.p. 110–115° (90 mm.), $d^{23}$ 1.111; (−)-form, b.p. 105–108° (60 mm.), $d^{25}$ 1.105, $[\alpha]_D^{26}$ −35.3° (homogeneous); (+)-form, b.p. 95–97° (13 mm.), $d^{24}$ 1.10, $[\alpha]_D^{25}$

Scheme for Synthesis of 12-Methyloctadecanoic Acid[a]




[a] The yields refer to those obtained with the active antipodes. [b] These numbers are the specific rotation in degrees (except for XI, an "observed" rotation) for the two forms using the light of the sodium D-line. The first rotation listed throughout is the optical activity of the compound ultimately prepared from (+)-2-octanol; the rotation below the first is the activity of the compund derived from (−)-2-octanol.

(5) This acid was resolved previously by P. A. Levine and R. E. Marker who reported $[\alpha]_D$ +0.78°, *J. Biol. Chem.*, **91**, 98 (1931).

(6) Huang-Minlon, *J. Am. Chem. Soc.*, **68**, 2487 (1946).

(7) J. Cason, E. L. Pippen, P. B. Taylor, and W. R. Winans, *J. Org. Chem.*, **15**, 135 (1950).

(8) R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **99**, 49 (1911).

(9) C.-M. Hseuh and C. S. Marvel, *J. Am. Chem. Soc.*, **50**, 855 (1928).

+30.8° (homogeneous). The maximum optical activity is ±38.9°.[10]

*Butyl 2-octylmalonates* (III) were prepared by adaptation of the malonic ester procedure in 1-butanol of Reid and Ruhoff.[2,11] Thus 21 g. of DL-2-bromo-octane and 27 g. of ethyl malonate were condensed to furnish 33 g. (92%) of butyl DL-2-octylmalonate; b.p. 160–210° (3 mm.); $d^{20}$ 0.932; $n_D^{25}$ 1.4361

The (+)-form[12] was prepared from 27.4 g. of (−)-2-bromo-octane ($[\alpha]_D^{26}$ −35.3°). The yield of ester was 39.0 g. (83%); b.p. 131–134° (0.3 mm.); $n_D^{25}$ 1.4360; $d^{25}$ 0.925; $[\alpha]_D^{26}$ +0.0° (homogeneous).

The (−)-form[12] was prepared in 71% yield (140 g.) from 116 g. of (+)-2-bromo-octane ($[\alpha]_D^{26}$ +29.3°): b.p. 131–134° (0.3 mm.); $n_D^{25}$ 1.4360; $d^{25}$ 0.925; $[\alpha]_D^{26}$ −0.0° (homogeneous).

*Anal.* Calcd. for $C_{19}H_{36}O_4$: C, 69.46; H, 10.88; sapon. equiv., 164. Found: C, 68.97; H, 11.05; sapon. equiv., 169 (DL), 159 (+), 161 (−).

DL-*2-Octylmalonic acid* (IV). Butyl DL-2-octylmalonate (33 g.) was heated under reflux for an hour in a solution of 23 g. of potassium hydroxide, 150 ml. of 95% ethyl alcohol, and 6 ml. of water. After extraction the solvent was removed furnishing 17 g. (78%) of crude acid as an oil.

DL-2-Octylmalonic acid failed to crystallize directly. However, the DL-acid made from mixing the two forms had a melting point of 80–82° after two crystallizations from hexane.

(−)-*2-Octylmalonic acid* was prepared from 145 g. of butyl (+)-2-octylmalonate[12] and furnished 120 g. (126%) of crude acid. The acid was systematically crystallized from hexane to give 66 g. (69%) of pure (−)-2-octylmalonic acid; m.p. 106–108° (apparently polymorphic); $[\alpha]_D^{26}$ −8.3° (0.901 g. dissolved up to 10 ml. in 95% ethanol, $\alpha_D^{26}$ −0.75°, 1 d. tube).

*Anal.* Calcd. for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32; equiv. wt., 108.1. Found: C, 61.30; H, 9.27; equiv. wt., 107.2.

(+)-*2-Octylmalonic acid* was prepared in 130% (120 g.) crude yield by saponifying 140 g. of the butyl (−)-2-octylmalonate.[12] Systematic crystallization from hexane gave 64 g. (70%) of pure (+)-2-octylmalonic acid: m.p. 106–108° (probably polymorphic); $[\alpha]_D^{26}$ +8.2° (0.882 g. of acid dissolved up to 10 ml. in 95% ethanol, $\alpha_D^{26}$ +0.72°, 1 d. tube); equiv. wt., 108.6 (calcd. for $C_{11}H_{20}O_4$: 108.1).

DL-*3-Methylnonanoic acid* (V). Seventeen g. of DL-2-octylmalonic acid was heated at 165–170° for an hour. The product was distilled: b.p. 122–125° (3 mm.); 10 g. (76%); $n_D^{23}$ 1.4318; $d^{23}$ 0.888; equiv. wt., 174.1 (calcd. for $C_{10}H_{20}O_2$: 172.3).

The *p-bromoanilide*[13] was prepared in 83% yield and crystallized twice from methanol, m.p. 93–94°.

*Anal.* Calcd. for $C_{16}H_{23}BrNO$: N, 4.31. Found: N, 4.39.

The *amide*[2] was prepared in 93% yield. Three crystallizations from acetone gave a waxy solid, m.p. 85–86°.

*Anal.* Calcd. for $C_{10}H_{21}NO$: N, 8.18. Found: N, 8.48.

(−)-*3-Methylnonanoic acid* was prepared from 59.5 g. of (−)-2-octylmalonic acid ($[\alpha]_D^{26}$ −8.3°): b.p. 140–141° (11 mm.); 43.5 g. (92.2%); $n_D^{25}$ 1.4326; $d^{24}$ 0.899; $[\alpha]_D^{26}$ −4.51° (homogeneous, 1 dm.); equiv. wt., 169.6 (calcd. for $C_{10}H_{20}O_2$: 172.3).

The *p-bromoanilide* had m.p. 109–109.5° after two crystallizations. The *amide* had m.p. 86.5–88°.

(+)-*3-Methylnonanoic acid* was prepared from 72 g. of (+)-2-octylmalonic acid ($[\alpha]_D^{25}$ +8.3°) in 92% yield (52.5 g.): b.p. 131–133° (9 mm.); $n_D^{25}$ 1.4323; $d^{24}$ 0.898; $[\alpha]_D^{26}$ +4.44° (homogeneous, 1 dm.); equiv. wt., 174.5 (calcd. for $C_{10}H_{20}O_2$: 172.3).

The *p-bromoanilide* melted at 109–110°. The *amide* melted at 86–88°.

*Ethyl* DL-*3-methylnonanoate* (VI). DL-3-Methylnonanoic acid (96.9 g.) was esterified with ethanol in the usual way to give 100.9 g. (92.1%); b.p. 108–109° (16 mm.); $n_D^{25}$ 1.4240; $d^{25}$ 0.864.

*Anal.* Calcd. for $C_{12}H_{24}O_2$: C, 71.95; H, 12.08. Found: C, 71.70; H, 11.98.

*Ethyl* (−)-*3-methylnonanoate* was prepared from 41.5 g. of (−)-3-methylnonanoic acid ($[\alpha]_D^{26}$ −4.51°) in 91.9% yield: 44.2 g.; b.p. 108–109° (16 mm.); $n_D^{25}$ 1.4238; $\alpha_D^{33}$ −1.02° (homogeneous); $[\alpha]_D^{33}$ −0.59°.

*Ethyl* (+)-*3-methylnonanoate*, prepared from 32.5 g. of (+)-3-methylnonanoic acid ($[\alpha]_D^{30}$ +4.54°), was obtained in 98.1% yield: 36.9 g.; b.p. 101–102° (1 mm.); $n_D^{25}$ 1.4238; $\alpha_D^{33}$ +1.02° (homogeneous); $[\alpha]_D^{33}$ +0.59°.

DL-*3-Methyl-1-nonanol* (VII). A mixture of 100.9 g. of ethyl DL-3-methylnonanoate and 8 g. of copper chromite[14] in a bomb was charged with hydrogen at 1575 p.s.i. at 30°. The mixture was then heated and shaken at 285° for 3 hr. Upon fractionation two products were obtained: (1) 16.7 g., b.p. 48–84° (1 mm.), $n_D^{25}$ 1.4536; and (2) 42.0 g. (55.8%), b.p. 95–97° (1 mm.), $d^{25}$ 0.847, $n_D^{25}$ 1.4355. Fraction 1 was insoluble in concentrated sulfuric acid and presumably is DL-3-methylnonane. The literature[7] reports b.p. 103–109° (11 mm.).

*Anal.* Calcd. for $C_{10}H_{22}O$: C, 75.88; H, 14.01. Found: C, 75.29; H, 13.86.

(−)-*3-Methyl-1-nonanol* was prepared from 39.1 g. of ethyl (−)-3-methylnonanoate ($[\alpha]_D^{31}$ −0.59°). Fractionation gave two fractions: (1) 7.2 g., probably hydrocarbon; b.p. 62–73° (30 mm.); $n_D^{25}$ 1.4326; and (2) 21.1 g. (67.4%) of alcohol; b.p. 125–126° (30 mm.); $n_D^{25}$ 1.4353; $\alpha_D^{35}$ −0.63° (homogeneous); $[\alpha]_D^{35}$ −0.37°.

(+)-*3-Methyl-1-nonanol* was prepared from 36.2 g. of ethyl (+)-3-methylnonanoate ($[\alpha]_D^{33}$ +0.59°). Distillation gave 14.6 g. of forerun; b.p. 43–65° (1 mm.); $n_D^{25}$ 1.4330 and 13.0 g. (37.2%) of alcohol; b.p. 96–97° (1 mm.); $n_D^{25}$ 1.4356; $\alpha_D^{35}$ +0.64° (homogeneous), $[\alpha]_D^{35}$ +0.38°.

DL-*1-Bromo-3-methylnonane* (VIII). DL-3-Methyl-1-nonanol (43.0 g.) was treated at 100° with hydrogen bromide.[15] The reaction mixture, dissolved in benzene, was washed with cold concentrated sulfuric acid, water, and saturated sodium chloride solution. After drying over potassium carbonate the bromide was distilled: 45.0 g. (74.8%); b.p. 92–94° (1 mm.); $n_D^{25}$ 1.4553; $d^{25}$ 1.060.

*Anal.* Calcd. for $C_{10}H_{21}Br$: C, 54.30; H, 9.57; Br, 36.13. Found: C, 54.63; H, 9.60; Br, 35.87.

The literature gives b.p. 121–122° (25 mm.).[7]

(+)-*1-Bromo-3-methylnonane* was prepared in 81.8% yield from 19.8 g. of (−)-3-methyl-1-nonanol ($[\alpha]_D^{35}$ −0.37°). Distillation gave 22.5 g. of bromide; b.p. 92–94° (1 mm.); $n_D^{25}$ 1.4550; $\alpha_D^{27}$ +2.43° (homogeneous); $[\alpha]_D^{27}$ +1.15°.

(−)-*1-Bromo-3-methylnonane* was prepared in 80.3% yield from 13.0 g. of (+)-3-methyl-1-nonanol ($[\alpha]_D^{35}$ +0.38°). Distillation furnished 14.6 g. of bromide; b.p. 92–94° (1 mm.); $n_D^{25}$ 1.4552; $\alpha_D^{27}$ −2.48° (homogeneous); $[\alpha]_D^{27}$ −1.17°.

*Ethyl* DL-*9-oxo-12-methyloctadecanoate* (IX). Di-(DL-3-methylnonyl-)cadmium[16] was made using 2.70 g. of magnesium, 24.2 g. of DL-1-bromo-3-methylnonane and 12.1 g. of cadmium chloride. After the solvent had been changed to benzene, 20.7 g. of ω-carbethoxycaprylyl chloride [b.p.

(10) W. Gerrard, *J. Chem. Soc.*, 848 (1945).

(11) E. E. Reid and J. Ruhoff, *Org. Syntheses*, **Coll. Vol. II**, 474–5 (1943).

(12) The plus or negative sign here is arbitrary because the optical activity is zero. The sign corresponds to the sign observed by Prout, Cason, and Ingersoll (Ref. 2) for the active butyl 2-decylmalonates.

(13) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed., John Wiley and Sons, New York, N. Y. (1956), p. 200.

(14) W. A. Lazier and H. R. Arnold, *Org. Syntheses*, **Coll. Vol. II**, 142–5 (1943).

(15) E. E. Reid, J. Ruhoff, and R. Burnett, *Org. Syntheses*, **Coll. Vol. II**, 246–8 (1943).

(16) J. Cason and F. S. Prout, *Org. Syntheses*, **Coll. Vol. III**, 601–605 (1955).

148–152° (3 mm.)][17] was added. After the usual work-up the product was fractionated to give 17.8 g. (47.7%) of keto ester; b.p. 195–230° (1 mm.); $n_D^{25}$ 1.4482; $d^{25}$ 0.864. Two carbon-hydrogen analyses indicated that the keto ester was contaminated with ethyl azelate: C, 72.44, 72.54; H, 11.56, 11.65 (calcd. for $C_{21}H_{40}O_3$: C, 74.06; H, 11.87). Cason *et al.*[7] report a 43% yield, b.p. 216–220° (5 mm.).

*Ethyl (+)-9-oxo-12-methyloctadecanoate.* This ester was prepared using 18.6 g. of (+)-1-bromo-3-methylnonane ($[\alpha]_D^{27}$ +1.15°), 2.02 g. of magnesium, 9.3 g. of cadmium chloride, and 15.9 g. of ω-carbethoxycaprylyl chloride. Distillation gave 14.8 g. (51.9%); b.p. 198–225° (1 mm.); $n_D^{25}$ 1.4481; $\alpha_D^{28}$ +0.10° (homogeneous, 1 dm. tube); $[\alpha]_D^{28}$ +0.11°.

*Ethyl (−)-9-oxo-12-methyloctadecanoate.* The levorotatory ester was made from 14.4 g. of (−)-1-bromo-3-methylnonane ($[\alpha]_D^{27}$ −1.17°), 1.60 g. of magnesium, 7.16 g. of cadmium chloride, and 12.2 g. of ω-carbethoxycaprylyl chloride. The yield was 9.4 g. (43%); b.p. 191–212° (1 mm.); $n_D^{25}$ 1.4479.

*Ethyl* DL-*12-methyloctadecanoate* (X). Ethyl DL-9-oxo-12-methyloctadecanoate (17.0 g.), 9.5 g. of potassium hydroxide, 8.5 ml. of 85% hydrazine hydrate, and 85 ml. of diethylene glycol was heated under reflux for 1.5 hr.[6] The mixture was concentrated until the temperature of the solution was 195°, then reflux was continued 4 hr. The reaction mixture was worked up to furnish the acid. The crude acid was esterified with absolute ethanol and sulfuric acid. The ester was ultimately distilled to give 12.3 g. (75.4%) of ethyl DL-12-methyloctadecanoate; b.p. 205–212° (1 mm.); $n_D^{25}$ 1.4425; $d^{25}$ 0.824; sapon. equiv., 319 (calcd. for $C_{21}H_{42}O_2$: 327). Cason *et al.*[7] report b.p. 183–185° (2 mm.), $n_D^{25}$ 1.4463.

*Ethyl (+)-12-methyloctadecanoate* was prepared by the procedure used above with 14.8 g. of ethyl (+)-9-oxo-12-methyloctadecanoate ($[\alpha]_D^{28}$ −0.10°). After extraction and esterification 10.5 g. (73.1%) of (+)-ester was obtained; b.p. 191–204° (0.5 mm.); $n_D^{25}$ 1.4428; $\alpha_D^{28}$ +0.23° (homogeneous); $[\alpha]_D^{28}$ +0.15°; sapon. equiv., 322 (calcd. for $C_{21}H_{42}O_2$: 327).

*Ethyl (−)-12-methyloctadecanoate* was prepared by reduction of 9.4 g. (ethyl (−)-9-oxo-12-methyloctadecanoate. After the work-up 5.4 g. (60%) reduced (−)-ester was obtained; b.p. 190–198° (0.5 mm.); $n_D^{25}$ 1.4429; $\alpha_D^{30}$ −0.22° (homogeneous); $[\alpha]_D^{30}$ −0.14°; sapon. equiv., 325 (calcd. for $C_{21}H_{42}O_2$: 327).

DL-*12-Methyloctadecanoic acid* (XI). Ethyl DL-12-methyloctadecanoate (5.2 g.) was heated under reflux for 1 hr. with 3.6 g. of potassium hydroxide in 100 ml. of 95% ethanol. The mixture was diluted with water and extracted with ether. The aqueous phase was acidified with hydrochloric acid and the acid was extracted with benzene. Removal of the solvent and crystallization of the acid from acetone-water mixtures furnished 3.7 g. (78%), m.p. 26–27°, equiv. wt., 299.1 (calcd. for $C_{19}H_{38}O_2$: 298.5). The literature[7] reports m.p. 27.6–28.2°.

The *amide*[2] after 5 crystallizations from methanol-water melted at 84–86°. A mixture containing equal amounts of the (+)- and (−)-amides melted at 76–78°.

The *tribromoanilide*[18] after 5 crystallizations from methanol-water melted at 93–94°. A mixture of equal amounts of (+)- and (−)-forms melted at 91–92°.

*(+)-12-Methyloctadecanoic acid* was prepared in 92% yield using 5.8 g. of ethyl (+)-12-methyloctadecanoate. Two crystallizations from acetone-water gave 4.9 g. of the (+)-acid; m.p. 37–38°; $\alpha_D^{27}$ +0.09° (homogeneous, 2 dm., tube); equiv. wt., 298.9 (calcd. for $C_{19}H_{38}O_2$: 298.5).

The *amide*[2] after 5 crystallizations melted at 74–75°.

The *tribromoanilide*[18] after 5 crystallizations melted at 89–91°.

*(−)-12-Methyloctadecanoic acid* was prepared like the other two forms using 5.4 g. of ethyl (−)-12-methyloctadecanoate. Two crystallizations from acetone-water furnished 2.9 g. (59%) of (−)-acid, m.p. 36–37°, $\alpha_D^{27}$ −0.10° (homogeneous, 2 dm. tube); equiv. wt., 299.4 (calcd. for $C_{19}H_{38}O_2$: 298.5).

The *amide*[2] after 5 crystallizations melted at 72–74°.

The *tribromoanilide*[18] melted at 90–92° after 5 crystallizations.

CHICAGO 14, ILL.

(17) F. S. Prout and J. Cason, *J. Org. Chem.*, **14**, 132 (1949); *cf.* also H. McKennis, Jr., and V. du Vigneaud, *J. Am. Chem. Soc.*, **68**, 832 (1946).

(18) J. Cason, *J. Am. Chem. Soc.*, **64**, 1106 (1942).

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[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT DIVISION OF HUMBLE OIL AND REFINING CO.]

# Ozonolysis of Norbornylene

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Ozonolysis of norbornylene in methanol, a "reacting" solvent, gave a mixture of an aldehydic methoxyhydroperoxide and its condensation products, whereas "inert" solvents afforded a polymeric, active oxygen-containing substance tentatively characterized as a polymeric ozonide. The nature and modes of formation of these materials are discussed. Conversion of both products to *cis*-cyclopentane-1,3-dicarboxylic acid was effected in high yield.

In a course of study concerned with the preparation of carboxylic acids from olefins employing ozone as an oxidant, the conversion of norbornylene to cyclopentane-1,3-dicarboxylic acid was investigated. Since the literature does not reveal any reports of ozonolysis studies utilizing this olefin, it was of interest to characterize the intermediate, or active oxygen-containing, products formed prior to oxidative decomposition to the desired acid.

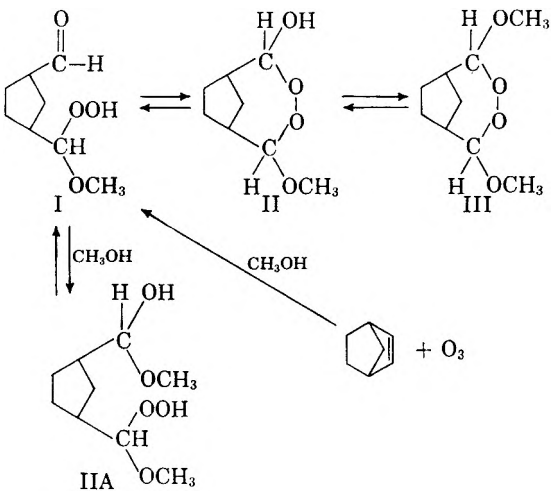
Criegee and co-workers have shown[1] that, in general, the ozonolysis of olefins in hydroxylic or "reacting" solvents gives rise to hydroperoxides

(1) (a) R. Criegee, *Ann.*, **583**, 1 (1953); (b) R. Criegee, G. Blust, and H. Zincke, *Chem. Ber.*, **87**, 766 (1954); (c) R. Criegee, A. Kerchow, and H. Zinke, *Chem. Ber.*, **88**, 1878 (1955); (d) R. Criegee and G. Lohaus, *Chem. Ber.*, **86**, 1 (1953); (e) R. Criegee and G. Lohaus, *Ann.*, **583**, 6 (1953); (f) R. Criegee and G. Wenner, *Ann.*, **564**, 9 (1949); (g) R. Criegee, *Record of Chemical Progress*, **18**, 111 (1957); (h) G. Lohaus, *Chem. Ber.*, **87**, 1708 (1954); (i) P. S. Bailey, *Chem. Ber.*, **88**, 795 (1956); (j) P. S. Bailey, *J. Am. Chem. Soc.*, **78**, 3811 (1956); (k) P. S. Bailey, *J. Org. Chem.*, **22**, 1548 (1957); (l) P. S. Bailey, *J. Org. Chem.*, **21**, 1335 (1956).

in addition to a carbonyl fragment, whereas aprotic ("inert") solvents allow the formation of ozonides or polymeric peroxides.

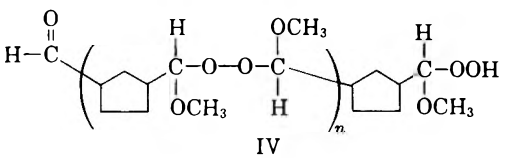
It should be noted that some olefins, *e.g.*, 1,2-diphenylindene[2] and 2,3-disubstituted indenones,[2,3] form ozonides in both solvent types. Furthermore, the extent of formation of monomeric ozonides or polymeric peroxidic products, particularly from cyclic olefins, is influenced by substitution in the olefin and the amount of strain in the intermediate.[1c,g] Cyclic olefins which can form a six- or seven-membered ring in addition to the five-membered trioxolane ring give ozonides, whereas polymerization products predominate from cyclic olefins of larger or smaller size.

*Discussion and results* A. *"Reacting" solvents.* Norbornylene was ozonized in methanol at −78°, and the product appeared to consist largely of an equilibrium mixture of the peroxidic compounds (I, II, and III). It is believed that the aldehydic



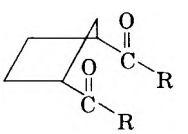

methoxyhydroperoxide (I) was formed as the initial product, following which intramolecular condensation occurred, in part, to give the labile peracetals (II and III). The possibility exists that some IIA was produced by the other mode of hemiacetal formation, *i.e.*, that involving the aldehyde group and methanol. Although the results did not enable a definite distinction of IIA from the other structures shown, this substance was probably not formed to an appreciable extent, since an aldehyde generally interacts preferentially with a hydroperoxide when the two functions are produced by ozonolysis in alcohols as solvents.[1k] Evidence for the mixture of peroxidic compounds (I–III) as the main product was afforded by qualitative tests, analyses, and conversion to the corresponding dicarboxylic acid and dicarboxaldehyde. Due to the physical nature (viscous oil) and instability of the product, it was not possible to effect a separation of this mixture into analytically pure components by techniques such as distillation, fractional crystallization, or chromatography.

Treatment of the intermediate with sodium iodide resulted in a rapid liberation of iodine followed by a slower reaction. Such behavior would be consistent with the expected lower peroxidic activity of the peracetal forms following the initial, rapid reaction of the hydroperoxide. Treatment with lead tetraacetate brought about oxygen evolution, which is characteristic of hydroperoxides. The material responded weakly to aldehyde tests and decomposed to intractable products when hydrolyzed in the presence of strong acids or bases. Infrared analysis showed strong hydroxyl and carbonyl bands at 3.0$\mu$ and 5.85$\mu$, respectively. Elemental and methoxyl group analyses were in accord with the existence of a mixture, with III probably preponderating because of its higher methoxyl content. Active oxygen analyses were low, a result often observed with peroxides. The molecular weight was slightly higher than that calculated for III, indicating the presence of some intermolecular condensation product, probably of the type shown by IV.




The results with norbornylene were similar in many respects to those obtained with cyclohexene in methanol,[1k] except that in the present work the preponderant product was not polymeric. Apparently the intramolecular reaction in the case of cyclohexene was not favored due both to steric limitations in the formation of an eight-membered ring and to the fact that the interacting ends of the molecule are far apart. Moreover, the *cis*-1,3-configuration in I should facilitate the intramolecular reaction.

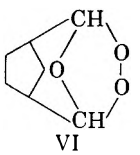
The active oxygen-containing intermediate was converted to *cis*-cyclopentane-1,3-dicarboxylic acid (Va) in excellent yield (95%) by means of hydrogen peroxide in formic acid. Conversion of the aldehydic methoxyhydroperoxide to suitable derivatives was not successful due to the instability of the material and to the low availability of the aldehyde function under the weakly alkaline conditions of the reactions. Reductive decomposition by means of zinc, or catalytic hydrogenolysis, gave cyclopentanedicarboxaldehyde (Vb).



(a) R = OH
(b) R = H

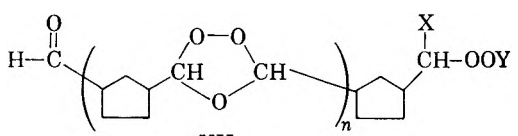
(2) P. S. Bailey, *Chem. Ber.*, **87**, 993 (1954).
(3) R. Criegee, P. de Bruyn, and G. Lohaus, *Ann.*, **583**, 19 (1953).

B. *"Inert" solvents.* Norbornylene was ozonized in several "inert" solvents and the products isolated in all instances appeared to possess identical properties. At the low temperatures of the reaction (−20° to −78°) the product remained in solution until the mixture was allowed to warm to room temperature, whereupon a highly swollen peroxidic solid precipitated. Purification of this material was difficult because of its insolubility and moderate instability. Similarly, the determination of certain physical properties such as molecular weight and infrared spectrum was not successful. Elemental analysis gave values near those calculated for VI ($C_7H_{10}O_3$):

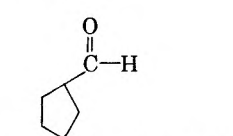


VI

The fact that the properties of the product were those characteristic of polymers precludes VI and suggests VII and VIII as structures for this material. Its ease of hydrolytic decomposition to aldehydic products as well as its oxidation in high yield (95%) to Va favor the polymeric ozonide (VII).

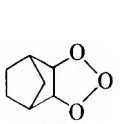


VII

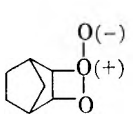


VIII

The soluble substance formed initially during low temperature ozonolysis presumably is unstable and polymerizes as the temperature is increased to near ambient conditions. This intermediate could be the simple ozonide (VI) or one of the forms of a molozonide (IX or X), although the existence of the latter two structural types has not been established. There is no evidence in support of any one structure,



IX



X

but reduction[4] of the low temperature-soluble product should afford *cis*-bicyclo[2.2.1]heptane-2,3-diol from the molozonide, whereas the dialdehyde (Vb) or the corresponding dicarbinol would be the expected product from VI.

(4) Suggestion by Prof. W. von E. Doering.

Experiments conducted thus far in this regard have been largely without avail due to the lack of suitable reducing agents which are effective at low temperature. Lithium aluminum hydride was partly reactive, but the product was a complicated mixture containing aldehydic function as well as the usual polymeric active oxygen-containing product. Stronger reducing agents are currently being studied, and the nature of the low temperature-soluble substance is being investigated.

## EXPERIMENTAL[5]

*Norbornylene.* This compound was prepared by the method of Joshel and Butz[6] from dicyclopentadiene and ethylene at elevated temperature and pressure. The material used had b.p. 95.0–95.8° (762 mm.), m.p. 44.8–45.2°.

*Ozonolysis of norbornylene in methanol.* In a typical run 4.0 g. (0.042 mole) of norbornylene in 50 ml. of methanol solution contained in a tubular reactor with a fritted gas inlet were treated at −75° to −20°[7] with an oxygen-ozone stream[8] containing 3 to 4 wt. % ozone. One molar equivalent of ozone was absorbed by the mixture. The methanol was subsequently removed under high vacuum by means of a rotating evaporator maintained at room temperature, and the nonvolatile product was a viscous syrup amounting to 8.4 g. (theory for the monomeric aldehydic methoxyhydroperoxide is 7.5 g.). Analyses of this product are presented in Table I.

TABLE I

OZONOLYSIS PRODUCT FROM METHANOL

| Analysis, % | Calculated[a] for III | IIA | I, II | Found[b] |
|---|---|---|---|---|
| C | 57.10 | 52.41 | 55.16 | 54.73 |
| H | 8.53 | 8.80 | 8.10 | 8.39 |
| Active oxygen | 8.50 | 7.77 | 9.20 | 7.16 |
| | | | — | 6.73 |
| Methoxyl | 32.80 | 30.09 | 17.82 | 33.16 |
| Molecular weight[c] | | | | |
| Immediately | 189 | 206 | 174 | 212 |
| After 21 days | | | | 225 |

Infrared analysis (film): Strong —OH absorption band at 3.0$\mu$; strong carbonyl band at 5.85$\mu$.

[a] $C_9H_{16}O_4$ (III); $C_9H_{18}O_5$ (IIA); $C_8H_{14}O_4$ (I, II). [b] Elemental and methoxyl group analyses by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. [c] Determined cryoscopically in benzene at several concentrations; M. W. obtained from extrapolated values.

The sirup reacted with sodium iodide and liberated oxygen with lead tetraacetate. With the former reagent the iodine liberated in the initial rapid reaction was removed by sodium thiosulfate solution, but the iodine color repeatedly returned, although more slowly, even after several successive treatments with thiosulfate. No reaction occurred in the

(5) Melting points are uncorrected. Infrared spectra were determined either with a Baird Model B or a Perkin-Elmer Model 21 infrared spectrophotometer fitted with a sodium chloride prism.

(6) L. M. Joshel and L. W. Butz, *J. Am. Chem. Soc.*, **63**, 3350 (1941).

(7) Reactions conducted at room temperature or slightly below resulted in appreciable attack by ozone on methanol, thus giving indistinct end points in the ozone-olefin reaction.

(8) Produced by a laboratory ozonator, Model T-23, manufactured by the Welsbach Corp., Philadelphia, Pa.

cold with water, mineral acids and bases, or hydrogen peroxide. Decomposition of the product occurred when these mixtures were heated. The sirup responded mildly to Tollen's and Fuchsin's tests.

*Oxidation of peroxidic product (methanol) to cis-cyclopentane-1,3-dicarboxylic acid.* The sirup remaining from the evaporated methanolic solution was dissolved in 35 ml. of 90% formic acid, and 20 g. (0.18 mole) of 30% hydrogen peroxide was added. The solution was warmed to approximately 52°, and a strongly exothermic reaction ensued causing refluxing for 15–20 min. Excess peroxide was destroyed by heating 1 hr. longer. The solution was evaporated to dryness on a rotating evaporator, leaving a fine white crystalline residue; m.p. 110–115°. Recrystallization from cold water and recovery from mother liquors afforded 6.5 g. (95% yield) of pure *cis*-cyclopentane-1,3-dicarboxylic acid; m.p. 120.5–121.0°; lit.,[9] 121°. Neut. equiv.: calcd., 79.1. Found, 79.4.

*Anal.* Calcd. for $C_7H_{10}O_4$: C, 52.98; H, 6.18. Found: C, 53.17; H, 6.38.

*Attempted preparation of derivatives of ozonolysis intermediate (methanol).* Attempts were made to prepare aldehyde derivatives from the active oxygen intermediate before and after isolation from methanol. Hydroxylamine hydrochloride with pyridine or sodium acetate solutions, semicarbazide hydrochloride under similar conditions and 2,4-dinitrophenylhydrazine in acidified ethanol gave intractable mixtures.

*Reductive decomposition of peroxidic product (methanol) to cyclopentane-1,3-dicarboxaldehyde.* The alcoholic solution was reduced by catalytic hydrogenolysis employing platinum oxide or by means of zinc dust and water. In the latter instance the methanolic solution (0.1 mole) was added dropwise to a stirred mixture of zinc dust (0.1 mole) and water (100 ml.), during which time the temperature rose to 54°. The mixture was heated to 85° for 2 hr., filtered, the filtrate saturated with salt, and extracted continuously with ether for 24 hr. The material boiling at 70–75°/1 mm. was collected; lit.[10] b.p. 74–75°/1.5 mm. The crude product was converted to the *bis*-2,4-dinitrophenylhydrazone using an acetic acid solution of 2,4-dinitrophenylhydrazine rather than mineral acid; m.p. 225–226°.

*Anal.* Calcd. for $C_{19}H_{18}N_8O_8$: C, 46.91; H, 3.70; N, 23.04. Found: C, 46.50; H, 3.71; N, 22.75.

*Ozonolysis in "inert" solvents.* Reactions in these media (ethyl acetate, carbon tetrachloride, chloroform, tetrahydrofuran, etc.) were performed in a stirred reactor provided with gas inlet tube (without fritted tip) in a manner similar to that described previously. The temperatures normally were maintained at −75° or as low as the solvent would allow. Ozone was rapidly absorbed until 0.90 to 0.95 molar equivalent had been added, following which absorption was incomplete. The solvents allowing reactions at −75° to about −40° gave essentially clear solutions at the end of the ozonolysis period. Normally, as the mixture warmed to near room temperature the solution became turbid, and after 2–3 hr. at room temperature, complete precipitation of a highly swollen "gel" occurred. The solvent was removed from the solid (*S*) by suction filtration and freeze drying, the last traces being removed very slowly. A small amount of gummy residue (*G*), *ca.* 5% or less of the product, remained on evaporation of the filtrate. This material exhibited similar chemical behavior to *S*. It swelled with partial dissolution in the original solvent. Substance *G* from analyses and properties was suspected as being a lower molecular weight polymer, similar otherwise to the main product. Both *S* and *G* were insensitive to shock but burned violently in an open flame. Substance *S* appeared to be stable in a vacuum desiccator for several days but decomposed to gummy aldehydic products on standing in contact with air at room temperature over the same period.

Due to the insolubility of *S* and *G* in solvents other than those which caused decomposition [the latter including pyridine, dimethylformamide, methanol (hot) and acetic acid (hot)], the preparation of an analytically pure species was difficult (analyses, Table II). Active oxygen analyses were lower than those calculated for VI, a result which has often been observed[11] with ozonides and other peroxidic compounds, due partly to their tendency to undergo the "acid rearrangement." No reaction occurred in the cold with water or hydrogen peroxide, whereas decomposition occurred when these mixtures were heated. Mineral acids and bases caused moderately rapid decomposition.

TABLE II

OZONOLYSIS PRODUCT FROM INERT SOLVENTS

[M.p. (*S*) 95–105° (dec.)]

| Analysis, % | Calculated[a] | Found[b] Precipitate (*S*) | Found[b] Gum (*G*) |
|---|---|---|---|
| C | 59.15 | 58.30 | 57.63 |
| H | 7.04 | 7.48 | 7.31 |
| O | 33.80 | 34.31 | — |
| Active oxygen | 11.3 | 5.22[c] | 4.38 |
| | | 5.70[d] | 4.34 |

[a] For $C_7H_{10}O_4$ (VI). [b] See footnote *b*, Table I. [c] Allowed to stand 1 hr. at room temperature with sodium iodide and glacial acetic acid followed by 1 hr. reflux; less blank. [d] Allowed to stand 2 hr. at room temperature; less blank.

Infrared analysis was attempted in KBr and mulls with decomposition occurring during each preparation. Infrared analyses were made on solutions removed from the reactor during ozonolyses in methyl chloroform, since precipitation of product in this solvent was very slow. These mixtures exhibited an increasingly intense carbonyl absorption at 5.85μ, but this was suspected as being due to the presence of decomposition products.[12]

*Oxidation of peroxidic product (inert solvents) to cis-cyclopentane-1,3-dicarboxylic acid.* This reaction was conducted in a manner similar to that with the product from methanol. The yield was 95% of high purity product.

*Attempted reduction of low temperature-soluble "ozonide."* Norbornylene was ozonized at −55° in carefully dried tetrahydrofuran. An excess of lithium aluminum hydride solution in tetrahydrofuran was slowly added to the completely ozonized mixture containing the dissolved product, and an exothermic reaction occurred accompanied by copious precipitation of white solid. The mixture was stirred at −50° for 2 hr., then allowed to warm to room temperature, and the hydride and the complex were destroyed with water and dilute sulfuric acid, respectively. In addition to the normal peroxidic product (*S*), an oil was obtained which contained hydroxyl and aldehyde function. Attempts to separate the components in this mixture were not successful.

Other reducing agents including ferrous sulfate, sodium sulfite and catalytic hydrogenolysis were unreactive at −40°.

(9) W. H. Perkin and H. A. Scarborough, *J. Chem. Soc.*, **119**, 1405 (1921).

(10) K. B. Wiberg and K. A. Saegebarth, *J. Am. Chem. Soc.*, **79**, 2824 (1957).

(11) R. Criegee, *Fortsch. Chem. Forsch.*, **1**, 508 (1950).

(12) E. Briner and E. Dallwigk, *Helv. Chim. Acta*, **39**, 1446 (1956).

*Acknowledgments.* The author wishes to thank the Humble Oil and Refining Co. for permission to publish this work. The helpful counsel and advice of Professor Philip S. Bailey is especially appreciated. Thanks are due Mr. Harold Kail for assistance in conducting the experimental work and Dr. B. H. Johnson and Miss Marjorie Walker for certain analyses.

BAYTOWN, TEX.

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[CONTRIBUTION FROM MELLON INSTITUTE]

# Ultraviolet Spectra of Benzo[c]phenanthrenes

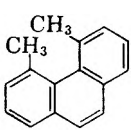
A. WILLIAM JOHNSON

*Received November 17, 1958*

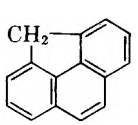
1,8,9-Naphthanthracene (VI) has been prepared by reduction of the ketone (VII). A second hydrocarbon, 2,3-trimethylenepyrene (VIII), was also isolated. Comparison of the ultraviolet spectra of VI with those of other benzo[*c*]phenanthrenes provided evidence for intramolecular overcrowding between the $C_1$ and $C_{12}$ hydrogens in benzo[*c*]phenanthrene.

Jones[1] has attempted to correlate the differences in fine structure observed in the ultraviolet spectra of many polynuclear aromatic hydrocarbons. The "Fine Structure (Fs) Effect," which was an outgrowth of these correlations, referred to an increase of fine structure produced by the fusion of alicyclic rings to an aromatic nucleus.[2] However, Jones and, more recently, Friedel[3] both pointed out a large number of exceptions to the general rule. The latter indicated that the Fs effect, as originally outlined by Jones, was not generally applicable to polynuclear hydrocarbons and in its place offered a tripartite correlation of the spectra of aromatic hydrocarbons containing fused alicyclic rings.

The ultraviolet spectrum of 4,5-dimethylphenanthrene (I) shows a marked decrease in fine structure (band splitting) when compared with the spectrum of 4,5-methylenephenanthrene (II)[2a]

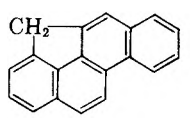



I

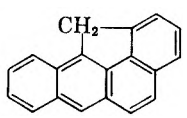



II

(Fig. 1). However, the parent hydrocarbon, phenanthrene, exhibits a spectrum very similar in detail to that of II. Analogous relationships are found in the chrysene[4] and 1,2-benzanthracene[5] series. 4,5-Methylenechrysene (III) and chrysene exhibit more fine structure in their spectra than does 4,5-dimethylchrysene. Similarly, both 1′,9-methylene-1,2-benzanthracene (IV) and 1,2-benzanthracene show more band splitting than 1′,9-dimethyl-




III




IV

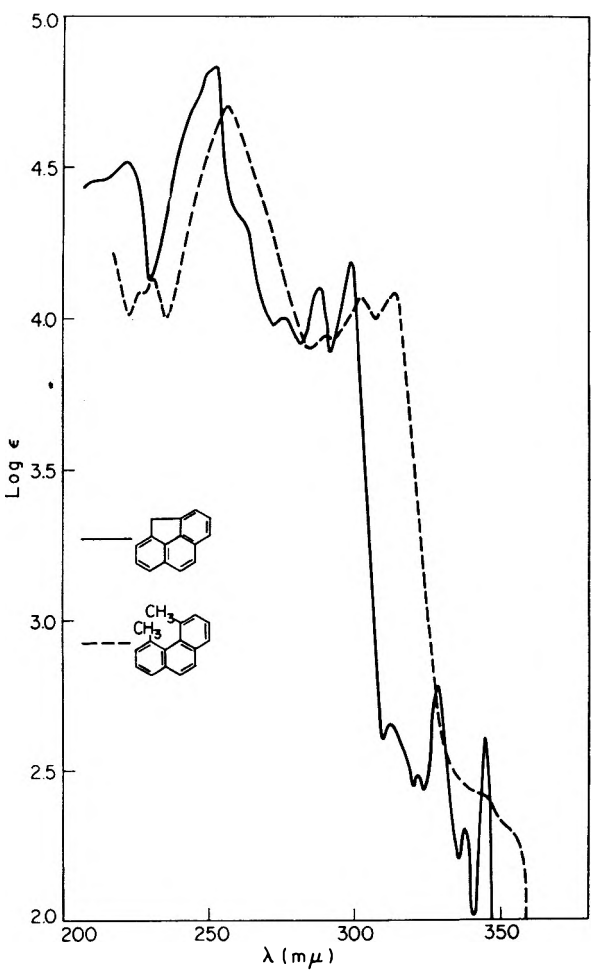



Fig. 1. 4,5-Dimethylphenanthrene (Ref. 2 (b), Spectrum No. 352) (I). 4,5-Methylenephenanthrene (Ref. 2 (b), Spectrum No. 363) (II)

(1) R. N. Jones, *J. Am. Chem. Soc.*, **67**, 2127 (1945).

(2) (a) R. N. Jones, *Chem. Revs.*, **32**, 1 (1945). (b) For a brief review of the Fs effect see R. A. Friedel and M. Orchin, *Ultraviolet Spectra of Aromatic Hydrocarbons*, John Wiley and Sons, Inc., New York, 1951, p. 23.

(3) R. A. Friedel, *Applied Spectroscopy*, **11**, 13 (1957).

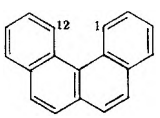
(4) R. N. Jones, *J. Am. Chem. Soc.*, **63**, 313 (1941).

(5) R. N. Jones, *J. Am. Chem. Soc.*, **62**, 148 (1940).

1,2-benzanthracene. These observations have been designated as Fs effects by Jones[2] and Ring-strain effects by Friedel.[3]

It is known that molecules of the 4,5-dimethylphenanthrene type possess streric interferences between the $C_4$ and $C_5$ substituents. This was demonstrated by the resolution of 4,5,8-trimethylphenanthryl-1-acetic acid into its optical enantiomorphs.[6] It seems likely that this "intramolecular overcrowding"[7] is responsible for the decrease in fine structure shown by their spectra.[3] In accord with this postulate, the spectrum of 4-methylphenanthrene, which should be intermediate in degree of intramolecular overcrowding between phenanthrene and the 4,5-dimethyl derivative, exhibits fine structure detail intermediate between the latter two compounds. An analogous relationship has been shown to exist in the chrysene series.[2b,3] In all cases, the spectrum of the unsubstituted hydrocarbon, which possesses no steric interferences between the 4 and 5 substituents, exhibits the same amount of fine structure as that of the methylene-bridged compounds.

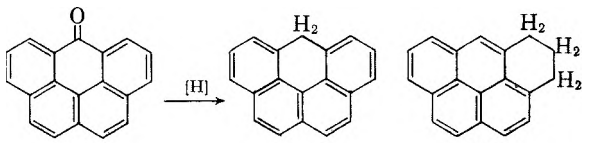
*Discussion.* It was of interest to ascertain if the above effect, regardless of its name or origin, existed in the benzo[*c*]phenanthrene (V) ring sys-




V

tem. It has been noted that the degree of fine structure present in the spectra of derivatives of V increased in the order 1,12-dimethyl<1-methyl< unsubstituted V.[8] Newman and co-workers have demonstrated that 1-methylbenzo[*c*]phenanthryl-4-acetic acid[9a] and 1,12-dimethylbenzo(c)phenanthryl-5-acetic acid[9b] are nonplanar by resolving them into their optical enantiomorphs. This nonplanarity was attributed to intramolecular overcrowding between the 1 and 12 substituents.

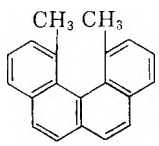
By analogy with the phenanthrene and related systems, it could be predicted that a methylene-bridged hydrocarbon, 1,8,9-naphthanthracene (1,12-methylenebenzo[*c*]phenanthrene) (VI), should afford the spectrum of a 1,12-disubstituted benzo[*c*]phenanthrene devoid of any steric interferences characteristically associated with the 1,12- positions. Its spectrum was expected to exhibit considerable fine structure.




VII VI VIII

Vollmann and co-workers[10] originally prepared VI *via* zinc dust distillation of 1,8,9-naphthanthrone-10 (VII) or of 3-carboxy-1,8,9-naphthanthrone-2. In our hands zinc–sodium hydroxide reduction of the ketone (VII) afforded the hydrocarbon (VI) in 20% yield, but Clemmensen reduction afforded a mixture of VI and a second hydrocarbon. The latter, through a comparison of ultraviolet spectra, has been tentatively identified as 2,3-trimethylenepyrene (VIII), previously prepared by Scholl and Meyer.[11] Recently, Clar and Stewart[12a] performed a reduction of VII and reported isolating only VIII, no mention being made of VI.[12b] The formation of VIII in these reductions finds analogy in the report that reduction of benzanthrone with phosphorus and hydriodic acid afforded only 1,10-trimethylenephenanthrene.[13]

As expected, the spectrum of VI was similar in over-all shape to that of 1,12-dimethylbenzo[*c*]-phenanthrene (IX) but the former possessed a much




IX

larger number of well defined absorption maxima (Fig. 2). A comparison with the spectrum of benzo[*c*]phenanthrene (V) indicated that VI exhibits even more fine structure than the former (Figs. 2 and 3). In fact, the spectrum of V resembles that of IX more closely than that of VI. This relationship is in contrast with the phenanthrene-like systems in which there is essentially no difference between the spectra of the unsubstituted and the bridged hydrocarbons. This suggested that even in benzo[*c*]phenanthrene (V) itself there exists significant intramolecular overcrowding between the $C_1$ and $C_{12}$ hydrogen atoms. This conclusion has been supported by the recently completed x-ray analysis of benzo[*c*]phenanthrene in which the molecule was found to be considerably distorted in order to prevent carbons 1 and 12 from approaching closer than 3.0 Å, the minimal approach distance of $sp^2$ hybridized carbon atoms

(6) M. S. Newman and A. B. Hussey, *J. Am. Chem. Soc.*, **69**, 3023 (1947).

(7) M. S. Newman, *J. Am. Chem. Soc.*, **62**, 2295 (1940).

(8) M. S. Newman and M. Wolf, *J. Am. Chem. Soc.*, **74**, 3225 (1952).

(9) (a) M. S. Newman and W. B. Wheatley, *J. Am. Chem. Soc*, **70**, 1913 (1948). (b) M. S. Newman and R. M. Wise, *J. Am. Chem. Soc.*, **78**, 450 (1956)

(10) H. Vollman *et al.*, *Ann.*, **531**, 1 (1937).

(11) R. Scholl and K. Meyer, *Ber.*, **69**, 156 (1936).

(12) (a) E. Clar and D. G. Stewart, *J. Am. Chem. Soc.*, **75**, 2667 (1953). (b) In spite of this report, Clar and Stewart (ref. 16) had described the spectrum of VI earlier. However, their method of preparation of VI was not revealed and remains a mystery.

(13) E. Clar and Fr. Furnari, *Ber.*, **65**, 1420 (1932).

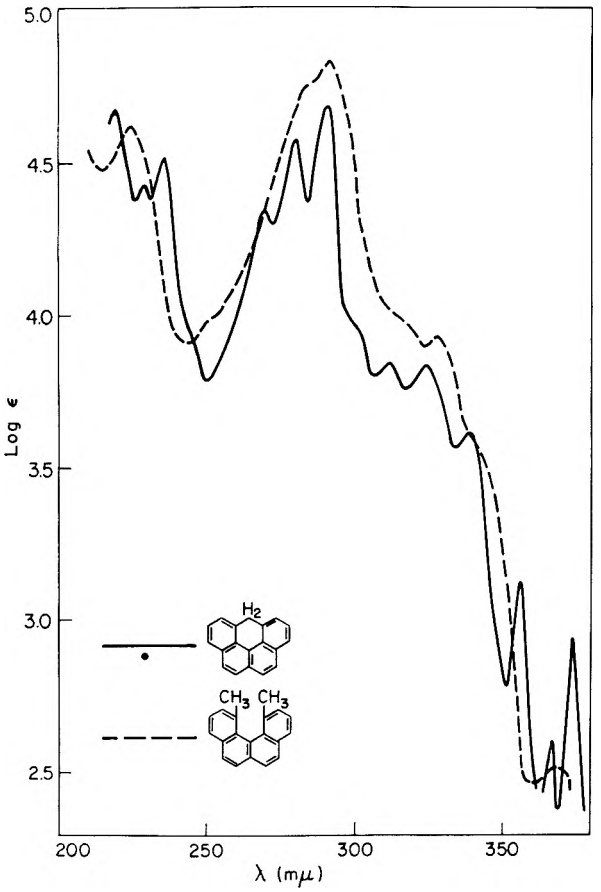



Fig. 2. 1,12-Dimethylbenzo[c]phenanthrene (IX). 1,8,9-Naphthanthracene (VI)

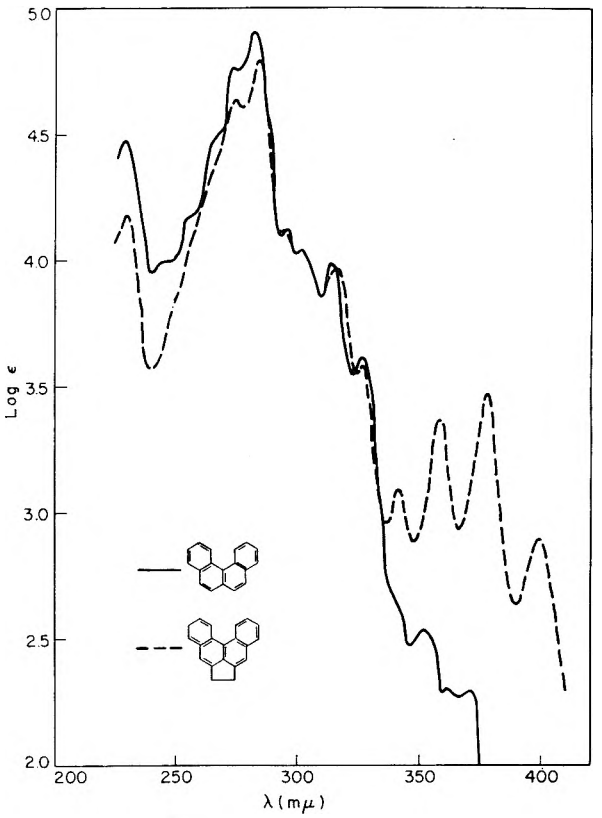
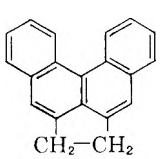



Fig. 3. Benzo[c]phenanthrene (V). 6,7-Dimethylenebenzo-[c]phenanthrene (X)

carrying hydrogen.[14] This is the first time in a series of this type that the unsubstituted hydrocarbon has been found to spectrally and, therefore, structurally resemble an overcrowded derivative more closely than a planar, bridged derivative. It is thus apparent that reliable evidence regarding steric interactions in polynuclear systems may be obtained by an examination of the UV spectra of a properly constituted series of derivatives.

Further evidence for steric interferences between the 1 and 12 hydrogens in benzo[c]phenanthrene was obtained by a comparison of its spectrum with that of the elusive and only recently synthesized hydrocarbon, 6,7 - dimethylenebenzo[c]phenanthrene (X)[15] (Fig. 3). The latter exhibited more




X

fine structure detail than V in the long wavelength region. This is probably due to the severe limitations imposed on the freedom of the aromatic nucleus by the restraining dimethylene bridge. The spectrum of 6,7-trimethylenebenzo[c]phenanthrene[16] also exhibited fine structure detail similar to that shown by X. Since introduction of a carbon bridge increased the fine structure, the original molecule must have been somewhat flexible due to intramolecular overcrowding.[17]

Friedel[3] observed that the greatest spectral effect of a fused alicyclic ring was the enhancement of the intensity of the longest wave-length bands. This effect has indeed been observed in the spectra of both VI and X.

## EXPERIMENTAL[18]

*Reduction of 1,8,9-naphthanthrone. A. Clemmensen reduction.* A solution of 2.5 g. (0.01 mole) of ketone (VII) in 15 ml. of toluene was heated under reflux for 26 hr. with 4.3 g. of zinc amalgam and 10 ml. of concentrated hydrochloric acid. The solution was cooled, the organic layer separated, and the aqueous portion extracted exhaustively with benzene. The combined organic layers were dried and the solvent removed

(14) G. M. J. Schmidt and F. H. Herbstein, *J. Chem. Soc.*, 3302 (1954).

(15) D. D. Phillips and D. N. Chatterjee, *J. Am. Chem. Soc.*, **80**, 4364 (1958).

(16) E. Clar and D. G. Stewart, *J. Am. Chem. Soc.*, **74**, 6235 (1952).

(17) L. L. Ingraham in "Steric Effects in Organic Chemistry," ed. by M. S. Newman, John Wiley and Sons, Inc., New York, 1956, p. 479.

(18) Ultraviolet spectra were recorded in 95% ethanol solution using Beckmann DK and Cary model 11 spectrophotometers. Analyses are by Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y. Melting points are uncorrected.

leaving 2.3 g. of a brown solid mass, m.p. 140°. A solution of 0.5 g. of the latter was taken up in 10 ml. of benzene and passed through a column containing 15 g. of neutral alumina (Merck) to afford 0.05 g. of crude hydrocarbon (benzene eluent) and 0.30 g. of unchanged ketone (VII) (chloroform eluent). The former was recrystallized from 95% ethanol as pale yellow needles, m.p. 118–120°, unchanged upon further recrystallization.

This hydrocarbon (50 mg.) was dissolved in 2 ml. of benzene-hexane (50:50) and passed through a column containing 5 g. of acidic alumina (Merck). The first fraction (10 mg.) was recrystallized from 95% ethanol to afford VIII as colorless fine needles, m.p. 108–109°, $\lambda_{EtOH}^{max}$ (log $\epsilon$) 235 m$\mu$ (4.7), 244 (4.9), 256 (4.1), 266 (4.5), 277 (4.7), 313 (4.1), 327 (4.5), 343 (4.6), 357 (3.5), 369 (2.8), and 377 (3.4). (Lit., m.p. 107–108°,[11] 112–113°[12]; the spectra were superimposable in all respects.[12])

The second fraction (20 mg.) was recrystallized from 95% ethanol to afford VI as pale yellow plates, m.p. 123–124°, $\lambda_{EtOH}^{max}$ (log $\epsilon$) 218 m$\mu$ (4.6), 228 (4.4), 235 (4.5), 269 (4.4), 279 (4.6), 290 (4.7), 311 (3.9), 325 (3.9), 340 (3.8), 356 (3.3), 367 (2.9), 374 (3.2). (Lit.,[10] m.p. 134°.)

*Anal.* Calcd. for $C_{19}H_{12}$: C, 94.97; H, 5.03. Found: C, 94.80; H, 5.09.

*B. Zinc-sodium hydroxide reduction.* A mixture of 1.0 g. of ketone (VII) and 8 g. of zinc dust in 60 ml. of 10% sodium hydroxide solution was covered with 10 ml. of 1-hexanol and heated under reflux for 6 hr. The solution was evaporated and acidified with 6*N* hydrochloric acid. The resulting black precipitate was filtered, dried, and pyrolyzed for 15 min. at 280° and 0.5 mm. pressure. The yellow sublimate (0.30 g.) was chromatographed on 10 g. of acidic alumina to afford 0.13 g. of hydrocarbon (VI) and 0.08 g. of unchanged ketone (VII). The former was recrystallized from 95% ethanol as pale yellow plates, m.p. 123–124°, undepressed on admixture with that prepared *via* method A.

*Acknowledgment.* The author acknowledges the technical assistance of W. B. White in recording some of the spectra. He wishes to thank Prof. Newman and Dr. Vollmann for their gifts of IX and VII, respectively. He also wishes to thank Drs. Phillips and Chatterjee for information concerning X prior to its publication.

PITTSBURGH 13, PA.

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[CONTRIBUTION FROM THE RESEARCH DEPARTMENT OF THE KOPPERS COMPANY, INC.]

# Carboxylation of Propargyl Halides

ROBERT W. ROSENTHAL AND LOUIS H. SCHWARTZMAN

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The reactions of propargyl halides with nickel carbonyl have been studied. Carboxylation of propargyl bromide at 70° and atmospheric pressure yielded ethyl 3-bromo-3-butenoate (I). Partial reduction of I with $LiAlH_4$ yielded 3-bromo-3-buten-1-ol which upon ozonolysis yielded formaldehyde. A mechanism is given which postulates the formation of an allenic ester, ethyl 2,3-butadienoate (II), intermediate. In the case of propargyl chloride both II and ethyl 3-chloro-3-butenoate (III) were isolated. Lower yields of product were obtained when the reaction was run under carbon monoxide pressure. This result is consistent with the hypothesis of Wender that the first step of the reaction is the formation of an acetylenic-carbonyl complex and carbon monoxide.

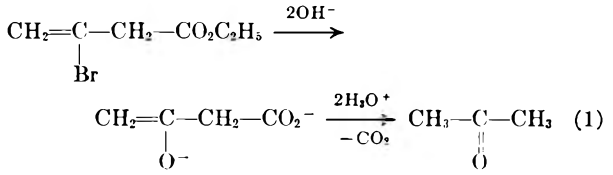
In the course of investigations being carried out in our laboratories, propargyl halides were carboxylated with nickel carbonyl. The recent disclosure by Jones, Whitham, Whiting[1] of similar work made it desirable for us to release our findings.

According to Raphael[2] propargylic bromides in ethanol react with nickel carbonyl and water to yield bromine-free allenic acids. In our laboratories when propargyl bromide in ethanol was caused to react with nickel carbonyl at 70° and atmospheric pressure, an evolution of heat took place and instead of a halogen-free allenic acids being formed, ethyl 3-bromo-3-butenoate, $CH_2{=}CBrCH_2CO_2C_2H_5$ (I), was obtained in 21% yield. The characterization of I presented some interesting problems. Due to the presence of the bromine atom, infrared analysis could not distinguish whether the ester contained a terminal methylene group or a double bond conjugated with the carbonyl group. Semimicro hydrogenation revealed that two moles of hydrogen was absorbed per mole of compound. Although the compound did not give a positive halide test when tested directly with alcoholic silver nitrate, it was found to contain approximately 39% bromine when the solution formed by either hydrogenating the sample or heating it one hour with caustic, was analyzed for halide ion. Saponification equivalents of several samples averaged 190. Vapor phase chromatographic analysis indicated the presence of a single compound of 90+% purity. All these data were consistent with the ethyl ester of a monobromobutenoic acid, which would have a molecular weight of 193 and would, under the conditions used, absorb two moles of hydrogen (hydrogenation of the double bond and hydrogenolysis of the bromine atom). The problem of which isomer was present, however, was as yet undecided. Therefore, the hydrogenated solution was saponified and yielded the potassium salt of an acid which was converted to *n*-butyro-*p*-toluide, and the *p*-bromo- and *p*-phenylphenacyl esters of *n*-butyric acid. Thus the carbon skeleton was that of *n*-butane. The location of the halogen atom was assigned to the third carbon atom by the fact that

(1) E. R. H. Jones, G. H. Whitham, and M. C. Whiting, *J. Chem. Soc.*, 4628 (1957).

(2) R. A. Raphael, *Acetylene Compounds in Organic Synthesis*, Academic Press, N. Y., 1955, p. 138.

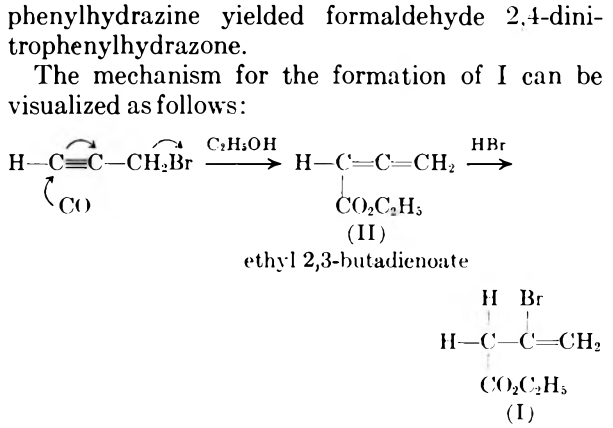
saponification of the ester followed by acidification with further refluxing yielded acetone. The reaction sequence is pictured as in equation (1).



(1)

Despite the fact that infrared analysis suggested a terminal methylene group, this was not confirmed by ozonolysis. The compound was ozonized but attempts to isolate formaldehyde either as the 2,4-dinitrophenylhydrazone or as the dimedone adduct failed. However, the presence of the terminal methylene group was established by the method of Lemieux and Rudloff[3] which consisted of oxidizing the compound with a periodate-permanganate mixture at *p*H 7 and then observing the color formed by the addition of chromotropic acid to the formaldehyde formed. Partial reduction of I with lithium aluminum hydride yielded 3-bromo-3-buten-1-ol which was characterized by infrared analysis, bromine analysis, hydrogen and hydroxyl numbers, and preparation of a derivative. Ozonolysis of this compound in the presence of 2,4-dinitrophenylhydrazine yielded formaldehyde 2,4-dinitrophenylhydrazone.

The mechanism for the formation of I can be visualized as follows:



ethyl 2,3-butadienoate

(II)



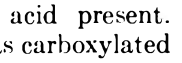
(I)

It was hoped that ethyl 2,3-butadienoate (II) could be isolated from the reaction mixture and caused to react with hydrobromic acid to form I and thus lend support to this mechanism. However, none was isolated from the propargyl bromide carboxylation mixture. Because of the well-known relationship of the rates of addition of hydrobromic acid and hydrochloric acid to double bonds, it was hoped that II (formed from the analogous carboxylation of propargyl chloride) could be isolated before it reacted with the hydrochloric acid present. Consequently, propargyl chloride was carboxylated at atmospheric pressure and small yields of both II and ethyl 3-chloro-3-butenoate (III) were isolated. II was identified by its infrared spectrum, hydrogen number, and saponification equivalent. The index of refraction of II was the same as reported by Eglenton *et al.*,[4] but the boiling point (44°/130 mm.) differed from ours (92–94°/140 mm.). However, hydrolysis of II with dilute sodium hydroxide yielded 2,3-butadienoic acid, m.p. 63–65°, the same melting point reported by them. III, which was not either ethyl β-chlorocrotonate or -isocrotonate reported by Hatch and Perry,[5] was characterized by the same sequence of reactions used to identify I. Some support for the mechanism was gotten from the fact that when hydrochloric acid was caused to react with II, the only products obtained were II and III.

The low yield obtained in the carboxylation of propargyl chloride was believed to be due to the fact that the boiling point (65°) of propargyl chloride was lower than the reaction temperature (70°). The carboxylation, therefore, was carried out in an autoclave and a 30% yield of a mixture of II and III was isolated. No heat was used, an exotherm was avoided, and 88% of the product was II.

This work is comparable to that of Jones, Whitham, and Whiting[2] in which they carboxylated 3-chloro-3-methyl-1-butyne in the presence of sodium acetate buffer to remove the hydrochloric acid formed and obtained a 34% yield of 4-methylpenta-2,3-dienoic acid along with 11% of its ethyl ester. In the case of propargyl chloride they reported a 6% yield of buta-2,3-dienoic acid, but made no mention of an ester fraction.

Several attempts were made to carboxylate propargyl chloride under an elevated carbon monoxide pressure (400–2000 p.s.i.g.) and it was found that considerably less carboxylation took place. These data indicate it is possible that carbon monoxide inhibits the carboxylation. This conclusion is analogous to that of Natta, Ercoli, Castellano, and Barbieri[6] who, in a study of the hydroformylation reaction, found that above carbon monoxide partial pressures of 10 atm. the percent olefin conversion decreased with increasing pressure. They postulated that the first step involved the reaction of the olefin with cobalt carbonyl to form an olefin-carbonyl complex and carbon monoxide. It is possible, therefore, that the first step of the carboxylation of acetylenic compounds with nickel carbonyl involves the reaction of the two compounds to form an acetylenic-carbonyl complex and carbon monoxide. This has been shown[7] to be the case in the reaction of acetylenes and cobalt carbonyl as shown in equation (2). Carboxylations of



(2)

(3) R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1710 (1955).

(4) G. Eglenton, E. R. H. Jones, G. H. Mansfield, and M. C. Whiting, *J. Chem. Soc.*, 3197 (1954).

(5) L. F. Hatch and R. H. Perry, *J. Am. Chem. Soc.*, **77**, 1137 (1955).

(6) G. Natta R. Ercoli, S. Castellano, and F. H. Barbieri, *J. Am. Chem. Soc.*, **76**, 4049 (1954).

(7) I. Wender, H. W. Sternberg, H. Greenfield, R. A. Friedel, J. Wotiz, and R. Markby, *J. Am. Chem. Soc.*, **76**, 1457 (1954).

propargyl chloride with cobalt carbonyl both in the absence of carbon monoxide and under elevated carbon monoxide pressure were attempted and yielded no carboxylation product.

## EXPERIMENTAL

*Carboxylation of propargyl bromide.* A mixture of freshly distilled propargyl bromide (119 g., 1.0 m.), absolute ethanol (100 ml.), and concentrated hydrochloric acid (59.5 g., 0.6 m.) was placed into a 4-necked flask having a stirrer, thermometer, dropping funnel, and condenser. Nitrogen was swept through the system while the stirred solution was heated to 70°. At this temperature a small portion of a solution of nickel carbonyl (39 g., 0.23 m.) in absolute ethanol (100 ml.) was added to the reaction mixture. After a short induction period an exothermic reaction took place and the solution was kept at 70° (heating mantle removed) by the rate of addition of carbonyl solution. At the end of the reaction (1.5 hr.) the temperature gradually dropped to 45°. Ether was added, the pot was heated, and everything distilling off below 82° was discarded. The contents were cooled, dissolved in ether, and washed with 5% sodium bicarbonate solution. The dried (magnesium sulfate) layer was distilled through a 6-in. Vigreux column and yielded 46 g. (24%) of ethyl 3-bromo-3-butenoate boiling at 82° (23 mm.). The crude product was redistilled through a helix-packed Todd column (900 × 12 mm.) and there was obtained 33.2 g. of product boiling at 85° (25 mm.); $n_D^{23}$ 1.4650. Infrared: 5.75 $\mu$ (vs), 6.12 $\mu$ (s), 8–9 $\mu$ (vs), 11.1 $\mu$ (vs).

*Anal.* Calcd. for $C_6H_9O_2Br$: Br, 41.4; Hydrogen No., 2.0; Sapon. Equiv., 193. Found: Br (hydrogenation), 39.8, Br (caustic), 39.1; Hydrogen No., 1.9; Sapon. Equiv., 191.

The experiment was repeated using acetic acid instead of hydrochloric acid and a 21% yield of the same product was obtained.

*Proof of structure of ethyl 3-bromo-3-butenoate.* (a) *Carbon skeleton.* (1) The carboxylation product (13 g., 0.07 m.) was hydrogenated over pre-reduced platinum oxide catalyst at atmospheric pressure and room temperature. The absorption was 1.9 moles of hydrogen per mole of compound. Solid potassium hydroxide (4 g., 0.07 m.) was added to the alcoholic ester solution and the mixture was refluxed 1 hr. The ethanol was removed under reduced pressure to give 5.8 g. of solid. This potassium salt was converted by standard methods into the *p*-bromophenacyl ester, the *p*-phenylphenacyl ester, and the *p*-toluidide. Table I summarizes the results. The acid, therefore, was *n*-butyric acid.

TABLE I

| Derivative | Literature Value, M.P., °C. Iso-butyric Acid | *n*-Butyric Acid | Observed M.P., °C. |
|---|---|---|---|
| *p*-Bromophenacyl ester | 77[a] | 63[a] | 62–63[e] |
| *p*-Phenylphenacyl ester | 89[b] | 82[b] | 79–80 |
| *p*-Toluidide | 106[c] | 73[d] | 68–70 |

[a] W. L. Judefind and E. E. Reid, *J. Am. Chem. Soc.*, **42**, 1055 (1920). [b] P. W. Clutterbuck, H. Raistrick, and F. Reuter, *Biochem. J.*, **29**, 880 (1935). [c] L. F. Fieser, J. L. Hartwell, and A. M. Seligman, *J. Am. Chem. Soc.*, **58**, 1226 (1936). [d] P. W. Robertson, *J. Chem. Soc.*, **115**, 1220 (1919). [e] Authentic sample melted at 61–62°; mixed m.p. with unknown sample, 61–62°.

(2) Carboxylation product (50 g., 0.26 m.) was dissolved in 125 ml. anhydrous ether and over a period of 3 hr. lithium aluminum hydride (9.5 g., 0.25 m.) was added with gentle refluxing. The reaction was stirred overnight and water was added to the mixture at such a rate that there was gentle refluxing. The solution was filtered, the filtrate was dried (magnesium sulfate), distilled under reduced pressure through a 6-in. Vigreux column, and there was isolated 11.6 g. of 3-bromo-3-buten-1-ol boiling at 80–85° (16 mm.); $n_D^{30}$ 1.4949.

*Anal.* Calcd. for $C_4H_7OBr$: Br, 53.0; Hydrogen No., 2.0; Hydroxyl No., 1.0. Found: Br, 53.0; Hydrogen No., 2.1; Hydroxyl No., 1.0.

3-Bromo-3-buten-1-ol was converted into its 3,5-dinitrobenzoate which after two recrystallizations (ethanol-water) melted at 57.5–58.0°.

*Anal.* Calcd. for $C_{11}H_9N_2O_6Br$: C, 38.3; H, 2.6; N, 8.1. Found: C, 39.0; H, 2.7; N, 8.3.

3-Bromo-3-buten-1-ol (1.1 g.) was dissolved in 25 ml. benzene and completely hydrogenated over pre-reduced platinum oxide catalyst at atmospheric pressure and room temperature and 2.0 moles of hydrogen was absorbed per mole of compound. The catalyst was removed by filtration and 1 g. of alpha-naphthyl isocyanate was added. The solution was warmed on the steam bath and the benzene removed by evaporation. *n*-Hexane was added and a high melting solid separated. The filtrate was concentrated and a solid melting at 60–65° separated. Recrystallization three times from *n*-hexane raised the m.p. to 68–69°. The melting point of a mixture of this compound and the alpha-naphthylurethane of *n*-butanol (m.p. 70°) was 68–69°.

(b) *Location of bromine atom.* Ethanol (40 ml.) was added to a mixture of propargyl bromide carboxylation product (10 g., 0.05 m.) and 150 ml. water containing 5 g. (0.13 m.) sodium hydroxide until the solution was homogeneous and the mixture was allowed to stand overnight at room temperature. Concentrated hydrochloric acid (15 ml.) was added and the solution was heated 1 hr. on the steam bath. The solution was cooled and a solution of 10 g. (0.05 m.) of 2,4-dinitrophenylhydrazine in 20 ml. concentrated sulfuric acid and 5 ml. water was added. There was obtained 5 g. (0.02 m.) of acetone 2,4-dinitrophenylhydrazone melting at 125–126°. No depression was observed on the melting point of a mixture of it and authentic acetone 2,4-dinitrophenylhydrazone.

(c) *Location of the double bond.* (1) *Permanganate-periodate oxidation.* A sample of the compound was oxidized according to the method of Lemieux and Rudloff.[3] Propargyl bromide carboxylation product (10 ml. of a solution made by dissolving 3 drops of compound in 300 ml. water) was adjusted to *p*H 7.0–7.6 with 0.1*N* potassium carbonate. Then 10 ml. of 0.02*M* potassium meta-periodate and 1 ml. of 0.005*N* $KMnO_4$ were added. The solution was made up to 25 ml. and a 5 ml. aliquot was removed and added to a mixture of 2 ml. of 1*M* sodium arsenite and 2 ml. of 2*N* sulfuric acid. The solution was allowed to stand 15 min. and then a 1 ml. aliquot was added to 10 ml. of chromotropic acid reagent (1 g. of acid dissolved in 100 ml. of $H_2O$ and the solution made to 500 ml. with 2:1 v/v sulfuric acid-water mixture) and heated on a boiling water bath for 30 min. An intense violet color appeared signifying the presence of a terminal methylene group.

(2) *Ozonolysis of 3-bromo-3-buten-1-ol.* 3-Bromo-3-buten-1-ol, (1 g.) was dissolved in 100 ml. of methanol and this solution was ozonized (Welsbach Corp. Model T-23 Laboratory Ozonator) at 0° for 100 min. Then 1.5 g. of 2,4-dinitrophenylhydrazine in 5 ml. of concentrated sulfuric acid was added. A small amount of amorphous solid precipitated. The addition of water to the filtrate yielded a yellow compound melting at 140–148°. Recrystallization from ethanol (charcoal) gave a solid melting at 166–168°. The melting point of a mixture of it and acetaldehyde 2,4-dinitrophenylhydrazone (m.p. 167–168°) showed melting point depression, m.p. 130+°; but with authentic formaldehyde 2,4-dinitrophenylhydrazone (m.p. 166–167°) no depression, m.p. 166–167°.

*Stoichiometric carboxylation of propargyl chloride with*

*nickel carbonyl.* Propargyl chloride (50 g., 0.66 m.), acetic acid (30 g., 0.66 m.), water (12 g., 0.66 m.), 95% ethanol (38 g., 0.83 m.), and hydroquinone (trace) were placed in Dry Ice and then placed in a stainless steel autoclave of 300 ml. capacity. Nickel carbonyl (26 g., 0.15 m.), was frozen in a test tube and the open tube carefully placed in the autoclave. The autoclave was sealed and rocked for 1 hr., during which time no heat evolution was observed. The contents were extracted with ether, the ether solution dried (magnesium sulfate), stripped, and the residue distilled under reduced pressure (nitrogen bleeder) through a 6-in. Vigreux column. There was obtained 21 g. of a mixture which was 88% ethyl 2,3-butadienoate (II) and 12% ethyl 3-chloro-3-butenoate (III). A portion of the product was distilled through a Todd column (900 × 12 mm.) at reduced pressure and compounds II and III were obtained.

II boiled at 92–94° (140 mm.); $n_D^{24}$ 1.4578. It exhibited infrared absorptions at 5.06 and 5.13 microns characteristic of the terminal allenic group, and at 5.82, 7.95, and 8.5 microns characteristic of an alpha,beta-unsaturated ester.

*Anal.* Calcd. for $C_6H_8O_2$: Cl, 0.0; Hydrogen No., 2.0; Sapon. Equiv., 112. Found: Cl, 0.3; Hydrogen No., 1.9; Sapon. Equiv., 121.

Saponification of II for 10 min. on a steam bath with 1*N* sodium hydroxide, followed by acidification to *p*H 4.5 with dilute sulfuric acid and extraction with ether yielded 2,3-butadienoic acid, m.p. 63–65° (4).

III boiled at 67° (75 mm.); $n_D^{24}$ 1.4389. It exhibited infrared absorptions at 5.76 and 8.40 microns characteristic of an ester group. Absorptions at 6.12 and 11.16 microns indicated the presence of a branched terminal vinyl group. No allenic group absorption could be detected in this sample.

*Anal.* Calcd. for $C_6H_9O_2Cl$: Cl, 23.6; Hydrogen No., 2.0; Sapon. Equiv., 74.0. Found: Cl, 23.5; Hydrogen No. 2.1; Sapon. Equiv., 75.6.

*Reaction of ethyl 2,3-butadienoate* (II) *with concentrated hydrochloric acid.* II (3.1 g., 0.03 m.) and 12*N* hydrochloric acid (3.5 ml., 0.03 m.) were mixed with 95% ethanol (10 ml.) at room temperature with stirring. After being allowed to sit overnight, the solution was warmed on a steam bath for 15 min. and allowed to sit 1 hr. while cooling. Water was added, the layers were separated, and the organic layer was washed again with water. The water layers were combined and found by titration to contain 0.016 m. hydrochloric acid, *i.e.*, about half had reacted. The organic layer (2.3 g.) was dissolved in ether, extracted with 5% sodium bicarbonate, dried over magnesium sulfate, filtered, and concentrated. An ester residue (0.7 g.) was obtained which infrared analysis indicated was a mixture of II and III.

*Proof of structure of ethyl 3-chloro-3-butenoate* (III). (a) *Carbon skeleton.* A sample of compound III was hydrogenated and saponified in a manner similar to that done to ethyl 3-bromo-3-butenoate (see above). The *p*-bromophenacyl ester made from the sodium salt of the acid melted at 63–64°. The melting point of a mixture of it and authentic *p*-bromophenacyl-*n*-butyrate showed no depression.

(b) *Location of the chlorine atom.* A portion of the ethyl 3-chloro-3-butenoate was saponified, acidified, and then treated with 2,4-dinitrophenylhydrazine as was done was to ethyl 3-bromo-3-butenoate (see above). There was obtained a 2,4-dinitrophenylhydrazone melting at 122–125°. The melting point of a mixture of it and authentic acetone 2,4-dinitrophenylhydrazone showed no depression.

*Catalytic carboxylation of propargyl chloride with nickel carbonyl.* A series of carboxylations was run and the following is a description of a typical experment. Propargyl chloride (50 g., 0.66 m.), acetic acid (30 g., 0.66 m.), water (12 g., 0.66 m.), 95% ethanol (48 g., 1.04 m.), and hydroquinone (trace) were placed in Dry Ice and then placed in a stainless steel autoclave of 300 ml. capacity. Nickel carbonyl (2.6 g., 0.02 m.), was frozen in a test tube and the open tube placed in the autoclave and the autoclave sealed. The system was charged with 2000 p.s.i.g. carbon monoxide and the system was heated and rocked at 90° for 2 hr. The cold absorption was 1400 p.s.i. The contents (26 g.) were extracted with ether, the ether solution dried (magnesium sulfate), and the ether removed under reduced pressure (nitrogen bleeder). The residue was distilled under reduced pressure through a 6-in. Vigreux column and yielded 13 g. (12%) of material boiling at 75–80° (30 mm.), $n_D^{23}$ 1.4330. The product by analysis was 73% ethyl 3-chloro-3-butenoate.

*Attempted carboxylation of propargyl chloride with cobalt carbonyl.* Cobalt carbonyl solution in benzene (0.1 g./ml.) was made from cobalt carbonate and $CO:H_2$ (1:1) according to the directions of Wender, Greenfield, and Orchin.[8] Propargyl chloride was treated with cobalt carbonyl in reactions analogous to those done with nickel carbonyl and in neither the stoichiometric nor the catalytic reaction was an insoluble carboxylation product obtained.

*Acknowledgment.* The authors are indebted to the General Aniline and Film Corp. for the generous supply of propargyl chloride and bromide. We acknowledge also the help of Dr. Charles Teitelbaum of the Battelle Memorial Institute for the vapor phase chromatographic analysis reported and the Analytical Group of the Koppers Co., with the aid of Mrs. Jean W. Biss, for the other analyses conducted.

VERONA, PA.

(8) I. Wender, H. Greenfield, and M. Orchin, *J. Am. Chem. Soc.*, **73**, 2656 (1957).

[CONTRIBUTION FROM THE CENTRAL RESEARCH LABORATORIES, AIR REDUCTION CO., INC.]

# Sodium Acetylide. II. Reactions of Sodium Acetylide in Organic Diluents. Preparation of Monoalkyl Acetylenes[1]

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Dimethyl sulfate reacted with sodium acetylide in organic diluents such as xylene to form 80–85% yields of propyne, along with 8–20% yields of 2-butyne. One of the unusual features of this reaction is that both of the methyl groups of the dimethyl sulfate are utilized in the alkylation. A mixture of xylene and dimethylformamide (35–45 volume %) was found to be an excellent medium for alkylation of sodium acetylide by alkyl bromides. *n*-Butyl bromide reacted with sodium acetylide to form 1-hexyne in 80% yield. Several other reaction media, such as *n*-butyl ether–dimethylformamide, were equally satisfactory.

Monoalkyl acetylenes (1-alkynes) usually are prepared by reaction of sodium acetylide with alkyl halides, sulfates, etc., in liquid ammonia. An excellent review has been prepared by Nieuwland.[3] Vaughn, Hennion, Vogt, and Nieuwland[4] have reported results of extensive investigations of the reaction of alkali acetylides with organic halides and sulfates in ammonia. Dimethyl sulfate and diethyl sulfate reacted to form the corresponding 1-alkynes in 50–100% conversions. Only one alkyl group reacted. Alkyl bromides, from *n*-propyl to *n*-amyl, formed 1-alkynes in 44–80% yields. The higher yields were obtained at elevated temperatures and at superatmospheric pressure, an operation described as hazardous by these authors[4]. Pressure reactions were necessary for alkyl halides of 10 carbon and greater chain length. Presumably the higher temperatures achieved in this way increased the solubility of the alkyl halides, thus allowing reasonably satisfactory reaction. Alkyl iodides were too reactive, forming large quantities of by-product olefins and amines. Alkyl chlorides were less reactive than bromides. Chlorides were inconvenient because their boiling points are usually very close to those of the product 1-alkyne, making separation and purification very difficult.

When these authors[4] attempted to dilute the ammonia with organic materials, such as diethyl ether, ethylene diamine, etc., yields of 1-alkynes were greatly reduced.

In a more recent paper, Pomerantz *et al.*,[5] reported larger scale (60 mole) preparations of various 1-alkynes. Their results confirm those reported earlier.[3,4]

Only one reference[6] was found which describes reaction of sodium acetylide with an alkyl sulfate in an organic diluent. Diethyl sulfate reacted with sodium acetylide in diphenyl ether at 190° to form 1-butyne in about 35% yield, based upon one ethyl group reacting.

The availability in our laboratories of pure finely divided sodium acetylide[1] was the starting point for the work reported here. Since the sodium acetylide was prepared in diluents such as xylene, it was decided to study these organic media for alkylation of sodium acetlide. The work was directed at simple fast reactions which could be carried out at atmospheric pressure.

*Reaction of sodium acetylide with alkyl sulfates.* When one mole of dimethyl sulfate was added to a slurry of two moles of sodium acetylide in xylene (prepared in xylene[1]) at 90° both methyl groups

TABLE I

REACTION OF SODIUM ACETYLIDE WITH DIMETHYL SULFATE IN XYLENE

| | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| Sodium acetylide, moles[a] | 0.688 | 0.643 | 0.706 | 1.17 |
| Dimethyl sulfate, moles | 0.344 | 0.321 | 0.353[b] | 0.58[b] |
| Xylene, grams | 165 | 150 | 173 | 274 |
| Mode of addition[c] | Normal | Normal | Reverse | Reverse |
| Temp., °C. | 90 | 120 | 90 | 120 |
| Time, min. | 90 | 90 | 65 | 58 |
| Conversion of Acetylide, Mole % | | | | |
| To propyne | 85.5 | 73.1 | 82.3 | 83.0 |
| To 2-butyne | 7.9 | 17.5 | 11.3 | 10.8 |
| Total conversion | 93.4 | 90.6 | 93.6 | 93.8 |

[a] 95% pure. Conversions are based on actual sodium acetylide content.

[b] 30% excess added subsequently to complete the reaction.

[c] "Normal" addition involved addition of dimethyl sulfate to sodium acetylide slurry. In "reverse" addition, sodium acetylide slurry was added to dimethyl sulfate.

(1) Part I. Preparation of Sodium Acetylide by Reaction of Acetylene with Sodium in Organic Media, *J. Org. Chem.*, **22**, 649–652 (1957).

(2) Present address: Atlas Powder Co., Wilmington, Del. This work was carried out at The Central Research Laboratories, Air Reduction Co., Inc., Murray Hill, N. J. The reactions described in this paper are covered by issued patents assigned to Air Reduction Co., Inc. (U.S. Patent **2,848,520** and U.S. Patent **2,846,491**).

(3) J. A. Nieuwland and R. B. Vogt, *The Chemistry of Acetylene*, Reinhold Publishing Company, N. Y., 1945, pp. 74–80.

(4) T. H. Vaughn, G. F. Hennion, R. R. Vogt, and J. A. Nieuwland, *J. Org. Chem.*, **2**, 1 (1937).

(5) P. Pomerantz, A. Fookson, T. W. Mears, S. Rothberg, and F. L. Howard, *J. Res. Nat'l Bur. Standards*, **52**, 51 (1954).

(6) O. Nicodemus, German Patent **562,010** (Feb. 20, 1931).

were observed to react. This is the first known case in which both alkyl groups of a dialkyl sulfate reacted completely with sodium acetylide. About 80–85% of the dimethyl sulfate formed propyne, and 8–10% went to 2-butyne (typical data are summarized in Table I). Total conversions were 90–95%. Addition of dimethyl sulfate at 120° resulted in less propyne, and about twice as much 2-butyne. "Reverse" addition, *i.e.*, addition of sodium acetylide slurry to dimethyl sulfate, was decidedly poorer at both temperatures. Excess dimethyl sulfate (25–30%) was required to form the same quantity of propyne, 2-butyne mixture as was obtained by "normal" addition. Again, conversion to 2-butyne was about 10%.

2-Butyne probably resulted from reaction of product propyne with unreacted sodium acetylide to form sodiopropyne (and acetylene), followed by reaction of sodiopropyne with dimethyl sulfate. Some acetylene was always found in the crude reaction products. Direct reaction of dimethyl sulfate with disodioacetylene (sodium carbide) contained in the acetylide was not possible, since disodioacetylene was never detected in the sodium acetylide.[1] Since the sodium acetylide contaned no free sodium, direct reaction of propyne to form sodiopropyne could not occur. However, in several cases sodium dispersion was added to the acetylide prior to "methylation," and increased 2-butyne formation was observed. Propyne reacted with sodium dispersion alone to form sodiopropyne under similar conditions. Thus, sodiopropyne once formed will react with dimethyl sulfate under these conditions to form 2-butyne. The necessity for a large excess of dimethyl sulfate in the "reverse" addition procedure implies that intermediate sodium methyl sulfate reacts more slowly than dimethyl sulfate, and that a small excess of sodium acetylide is necessary throughout the reaction for rapid conversion of the methyl group in sodium methyl sulfate into another mole of propyne. The following sequence of reactions is consistent with all the known facts:

$$NaC{\equiv}CH + (CH_3)_2SO_4 \longrightarrow CH_3C{\equiv}CH + NaCH_3SO_4$$

$$CH_3C{\equiv}CH + NaC{\equiv}CH \longrightarrow CH_3C{\equiv}CNa + C_2H_2$$

$$CH_3C{\equiv}CNa + (CH_3)_2SO_4 \longrightarrow CH_3C{\equiv}CCH_3 + NaCH_3SO_4$$

$$NaCH_3SO_4 + NaC{\equiv}CH \longrightarrow CH_3C{\equiv}CH + Na_2SO_4$$

When diethyl sulfate was treated with sodium acetylide as described above, 1-butyne was formed in 70% yield, based on both ethyl groups reacting. This represents an average of 1.4 ethyl groups reacting per mole of diethyl sulfate. Prolonged reaction times did not increase the yield of 1-butyne.

In one experiment the sodium acetylide was prepared by the conventional liquid ammonia procedure.[4] The ammonia was replaced by xylene, and methylation was conducted at 90° in the usual manner. Yield of propyne was only 50%. This was presumably due to the fact that the sodium acetylide from liquid ammonia could not be dispersed to any extent in the xylene. The solid remained coarse, hard, and flaky even after vigorous stirring. Hennion and Bell[7] have reported a similar experience.

*Reaction of sodium acetylide with alkyl halides.* Alkyl halides, such as *n*-butyl bromide, failed to alkylate our sodium acetylide in common organic diluents such as xylene, *n*-butyl ether, dioxane, and tetrahydrofuran. Consequently, a search for suitable organic diluents was undertaken. Highly polar solvents were studied first, since these alkylation reactions are ionic processes. A rapid "screening test" was devised. Sodium acetylide (dry or in xylene slurry) (0.3–0.5 gram) was placed in a few milliliters of the diluent. Two or three drops of *n*-butyl bromide were added to the slurry. After a few minutes, the characteristic odor of 1-hexyne was easily detected when suitable media were present. This simple test was used for screening dozens of diluents.

Although a number of diluents were "active" as judged by the screening test, only three diluents were found to be useful in preparative work. These were, in decreasing order of effectiveness, *N*,*N*-dimethylformamide, hexamethyl phosphoramide (tris-*N*,*N*-dimethyl phosphorus triamide), and *N*,*N*-dimethylacetamide. Since the best diluent (DMF) was also the most readily available and least expensive, it was studied most thoroughly. The reaction of *n*-butyl bromide with sodium acetylide to form 1-hexyne was chosen as the model. A few experiments showed that pure dimethyl formamide was not entirely satisfactory. Yields of 1-hexyne were only fair, and excessive decomposition of DMF occurred. Therefore, mixtures of DMF with other organic solvents were studied. From the data summarized in Table II (Runs 1–5), it is apparent that 35–45 volume % dimethyl formamide in xylene was quite satisfactory. This was a fortunate situation, since the sodium acetylide was usually prepared in xylene. Optimum "loading" of sodium acetylide was about 2 moles per liter of mixed diluent (Runs 8–10). Reaction time and temperature were not critical (Runs 6–7). Reaction for 4–10 hr. at 25–50° gave good yields of 1-hexyne. Best results were obtained when the butyl bromide was added to the acetylide-diluent mixture. "Reverse addition" (*i.e.*, addition of DMF to sodium acetylide and butyl bromide in xylene) resulted in lower yields. Mixtures of *n*-butyl ether and DMF were equally satisfactory.

*n*-Butyl chloride reacted with sodium acetylide in DMF-xylene to form 1-hexyne in only 32% yield. This parallels the yields obtained when alkyl chlorides were used in liquid ammonia.[4] *n*-Octadecyl bromide reacted with sodium acetylide in xylene-dimethyl formamide to form 1-eicosyne in 90% yield. This is superior to results obtained in liquid ammonia. No dialkyl acetylenes were found in any of the alkylation products.

(7) G. F. Hennion and E. P. Bell, *J. Am. Chem. Soc.*, **65**, 1847 (1943).

TABLE II

REACTION OF *N*-BUTYL BROMIDE WITH SODIUM ACETYLIDE IN XYLENE-DIMETHYL FORMAMIDE MIXTURES

| Run No. | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Sodium acetylide, moles | 0.25 | 0.25 | 0.25 | 0.2 | 0.25 | 0.25 | 0.25 | 1 | 1 | 1 |
| *n*-Butyl bromide, moles | 0.25 | 0.25 | 0.25 | 0.2 | 0.25 | 0.25 | 0.25 | 1 | 1 | 1 |
| Volume, % D.M.F.[a] | 25 | 35 | 44 | 75 | 92.3 | 91 | 35 | 37.5 | 37.5 | 37.5 |
| Total vol. diluent, cc. | 390 | 380 | 400 | 250 | 215 | 220 | 400 | 240 | 480 | 800 |
| Reaction time, hr. | 5 | 5 | 5 | 3 | 1 | 7 | 5 | 8 | 8 | 8 |
| Reaction Temp. | 25–30 | 25–30 | 25–30 | 30 | 15 | −10 | 45–50 | 25–35 | 25–30 | 25–30 |
| Product 1-Hexyne Conversion[b] | 20 | 60 | 64 | 44 | 31 | 32.5 | 68 | 60 | 81 | 67.5 |
| Yield[b] | 66 | 67 | 71 | 47 | 31 | 34.5 | 73 | 60 | 81 | 67.5 |

[a] Dimethylformamide. [b] Mole % on butyl bromide.

All of the xylene and most of the DMF were recovered by ordinary vacuum distillation. A small amount of the DMF was lost through decomposition. The odor of dimethylamine was noticed in many crude reaction mixtures.

Increased solubility of sodium acetylide is undoubtedly at least partly responsible for the excellent results obtained in mixed diluents. Even so, sodium acetylide solubility was probably less than 0.5%. Other factors, such as solvent polarity, and solubility of any intermediates, must also be involved. More work will be required in order to explain completely the unusual "solvent" effects noted here.

## EXPERIMENTAL

The procedures outlined here are typical of the many experiments conducted in the study of these alkylation reactions.

*Preparation of sodium acetylide.* The procedure described in Part I[1] of this series was used.

*Reaction of Sodium Acetylide with Alkyl Sulfates in Xylene.* A 1-liter three-necked flask was fitted with a thermometer, dropping funnel, and water jacketed reflux condenser. The exit end of the condenser was connected to two volumetrically calibrated dry ice traps. A tube of desiccant (Drierite) was placed at the end of the system to avoid condensation of atmospheric moisture in the traps.

The sodium acetylide slurry was placed in the flask, and heated rapidly to 90° (or 120°) while stirring at 600–800 r.p.m. The heat was turned off (heating mantle still in place), and dimethyl sulfate was added at a rate such that the reaction temperature was maintained at 90–95° (or 120–125°). After about 1.25 hr. the exothermic reaction ceased. The mixture was quickly heated to reflux (about 140°) until no additional material collected in traps. This usually required 5–10 min. of refluxing. The traps were then disconnected, and the total weight and volume of condensate were determined.

"Reverse" addition was identical, except that the sodium acetylide slurry was added to dimethyl sulfate heated to the desired temperature. Blank experiments showed that dimethyl sulfate was stable at these temperatures.

The composition of the crude product was determined by infrared spectrographic analysis. The instrument was calibrated with known mixtures of pure components. Composition of the crude product varied, but the product always contained a small amount of free acetylene and dimethyl ether in addition to propyne and 2-butyne. Fractionation through a low temperature column resulted in an acetylene-free propyne fraction which contained a trace of dimethyl ether, and a pure 2-butyne fraction. The dimethyl ether was removed by water scrubbing in some cases.

*Reaction of sodium acetylide with n-butyl bromide in xylene-DMF mixtures.* Sodium acetylide was suspended in the reaction medium (*cf.* Table II) in a 1-l. three necked flask equipped with a stirrer, dropping funnel, and water-cooled reflux condenser. The mixture was heated to reaction temperature, and *n*-butyl bromide was added over a period of 20 min. After the desired reaction time, the contents of the reactor were filtered (suction) into a chilled receiver. A Dry Ice trap was placed on the suction line to avoid loss of product 1-hexyne.

The filtrate was fractionated to isolate 1-hexyne (b.p. 69–71°) and unreacted *n*-butyl bromide (b.p. 100–102°). Total distilled 1-hexyne was confirmed in many cases by analysis.[8] Further distillation at reduced pressure was used to recover xylene and DMF. No 5-decyne was found in any of these fractions.

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MURRAY HILL, N. J.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

# Grignard Reagents with Cyclic α-Chloroketones

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Attractive intermediates for polynuclear syntheses are obtainable from the reaction of aryl Grignard reagents and cyclic α-chloroketones. The addition reaction leads predominately to the formation of the *cis*-chlorohydrin which rearranges in good yield to the α-aryl ketone. Factors affecting the yield of the latter have been investigated.

The reaction of Grignard reagents with cyclic α-haloketones may lead to a number of products[1] among which are the *cis*- and *trans*- halohydrin isomers resulting from addition to the carbonyl function. One of these isomers can be converted in good yield to the corresponding ketone simply by heating the halomagnesium addition product.[2] All of the evidence, including stereochemical[1c,3] and mechanistic considerations,[4] seems clearly to establish that this is the *cis* isomer. The *trans* isomer, when similarly treated, on the other hand, appears to rearrange by way of the epoxide and gives rise to a mixture of products.[3a,3b,4]

This reaction has considerable appeal as a synthetic procedure to obtain intermediates for polycyclic compounds and has been used in such syntheses with 2-chlorocyclohexanone[2b,3d,5] and with 4-methyl-2-chlorocyclohexanone.[3d] Because of dipolar repulsion the halogen atom in simple α-halocyclohexanones exists in an axial conformation.[5] Consequently, the least hindered side for the approach of the entering group to the carbon of the coordinated carbonyl group would be predicted to be the side opposite to the axial halogen atom.[7] The *cis*-halohydrin should therefore predominate in the addition of a Grignard reagent to simple α-halocyclohexanones or polycyclic haloketones such as 2-chloro-1-tetralone and 2-chloroindanone. This is the isomer which can be rearranged to give good yields of substituted cyclic ketone.

We report here a study of the reaction of 2-chlorocyclohexanone, 2-chloro-1-tetralone, 2-bromo-1-tetralone, 2-chloroindanone, and 2-chloro-1-keto-1,2,3,4,5,6,7,8-octahydroanthracene with aryl Grignard reagents. It is possible to isolate the corresponding ketones, in which chlorine has been replaced by the organic portion of the Grignard reagent, in yields of 50–70% by adding the Grignard reagent to a cooled solution of the chloroketone in ether-benzene followed by a period at reflux. If the reflux period is omitted, it is also possible to isolate the halohydrin addition products (except where rearrangement occurs even at low temperature or when the molecular weight of the chlorohydrin makes distillation difficult) in yields of 60–80%. These may subsequently be rearranged in 80–90% yield. The two-step procedure often results in a better over-all yield but the improvement in yield does not generally offset the extra work involved. These results are summarized in Table I.

TABLE I

REACTION OF PHENYLMAGNESIUM BROMIDE WITH α-CHLOROKETONES

| α-Chloroketone | Product Yield, % Ketone | Halohydrin | Ketone from halohydrin |
|---|---|---|---|
| 2-Chlorocyclohexanone | 68[a] | 83[b] | 86[b] |
| 2-Chloro-1-tetralone | 43[c] | 60 | 81 |
| 2-Chloro-1-indanone | 60 | 70 | 92 |
| 2-Chloro-1-keto-1,2,3,4,5,6,7,8-octahydroanthracene | 52 | — | — |

[a] With *p*-tolyl, *m*-anisyl, and α-naphthyl Grignard reagents the yields of ketone were 68%, 52%, and 50%, respectively. [b] With *m*-anisyl Grignard reagent the yields of halohydrin and its rearrangement product were 67% and 90%, respectively. [c] 2-Bromo-1-tetralone furnished 24% of ketone product.

The results of this study may be generalized in the following statements:

(1) For optimum yield, the addition of Grignard reagent in ether to a solution of the chloroketone (in benzene to prevent precipitation) is to be preferred, particularly where the chlorohydrin inter-

(1) (a) G. Vavon and B. Tchoubar, *Bull. soc. chim.*, **45**, 965 (1929). (b) E. P. Kohler and M. Tishler, *J. Am. Chem. Soc.*, **54**, 1594 (1932); **57**, 217 (1935). (c) M. Tiffeneau and B. Tchoubar, *Compt. rend.*, **198**, 941 (1934); **199**, 360 (1934). (d) B. Tchoubar and O. Sackur, *Compt. rend.*, **207**, 1105 (1938).

(2) (a) M. Tiffeneau, B. Tchoubar, and S. Letellier, *Compt. rend.*, **216**, 856 (1943). (b) M. S. Newman and M. D. Farbman, *J. Am. Chem. Soc.*, **66**, 1550 (1944).

(3) (a) P. D. Bartlett and R. H. Rosenwald, *J. Am. Chem. Soc.*, **56**, 1990 (1934). (b) P. D. Bartlett and R. V. White, *J. Am. Chem. Soc.*, **56**, 2785 (1934). (c) M. Tiffeneau, B. Tchoubar, and S. Letellier, *Compt. rend.*, **217**, 588 (1943). (d) M. S. Newman and W. T. Booth, *J. Org. Chem.*, **12**, 737 (1947).

(4) T. A. Geissman and R. I. Akawie, *J. Am. Chem. Soc.*, **73**, 1993 (1951).

(5) W. E. Bachmann, G. I. Fujimoto, and L. B. Wick, *J. Am. Chem. Soc.*, **72**, 1995 (1950).

(6) E. J. Corey, *J. Am. Chem. Soc.*, **75**, 2301 (1953); **77**, 5418 (1955).

(7) D. J. Cram and F. A. A. Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952).

mediate rearranges easily. This order of addition minimizes secondary reaction of the Grignard reagent with the ketone rearrangement product.

(2) When the addition is carried out at 0 to 5°, it is often possible to isolate the intermediate chlorohydrin in good yield; when the addition is followed by several hours at reflux, the ketone rearrangement product is obtained.

(3) Improved yield of ketone product may be realized in some cases by the isolation of the chlorohydrin followed by subsequent rearrangement by treatment with an equivalent of Grignard reagent and refluxing.

(4) The principal side reactions appear to be reaction of the chloroketone forming enolate and consuming Grignard reagent and formation of tertiary alcohols by the reaction of the ketone product with Grignard reagent.

(5) Chlorohydrin products formed in this reaction appear to be predominately the *cis* stereoisomers. These are not rearranged by refluxing in ether with powdered potassium hydroxide,[8] nor in benzene ether with sodium hydride, but are readily rearranged with one equivalent of Grignard reagent followed by refluxing.

(6) Ketone products in yields of 50% to 70% may reasonably be expected from the reaction of aryl Grignard reagents with cyclic α-chloroketones.

## EXPERIMENTAL[9,10]

*2-Chlorocyclohexanone.* 2-Chlorocyclohexanone was prepared by the chlorination of cyclohexanone as described earlier.[11]

*2-Chloro-1-phenylcyclohexanol* (Procedure A). To an ice-cold solution of 19.5 g. (0.15 mole) of 2-chlorocyclohexanone in 150 cc. of dry benzene was added 100 cc. of 2.3*M* phenylmagnesium bromide solution in ether (0.23 mole) over a 15-min. period. After the addition, the mixture was allowed to stir in the ice bath for 0.5 hr. and was then hydrolyzed by pouring into ice and hydrochloric acid. The residue, after removal of the solvent, was distilled at 0.2–0.3 mm. to give 3 g. forerun (mostly biphenyl), 26 g. (83%) of 2-chloro-1-phenylcyclohexanol, m.p. 32–36°, and 2 g. residue. After several recrystallizations from petroleum pentane, a sample for analysis melted at 37–38°.[3c]

*Anal.* Calcd. for $C_{12}H_{15}OCl$: C, 68.4; H, 7.2. Found: C, 68.6; H, 7.5.

*Rearrangement of 2-chloro-1-phenylcyclohexanol with phenylmagnesium bromide* (Procedure B). A solution of 7.0 g. (0.033 mole) of 2-chloro-1-phenylcyclohexanol in 60 cc. of dry benzene was cooled in an ice bath and 15.9 cc. of 2.1*M* phenylmagnesium bromide solution in ether (0.033 mole) was added rapidly. The mixture was refluxed for 6 hr. in an atmosphere of dry nitrogen then hydrolyzed by pouring into iced hydrochloric acid. After extracting with ether, washing, and removing the solvent, the residue crystallized to give 6.0 g. of crude product. One recrystallization from petroleum hexane furnished 5.0 g. (86%) of 2-phenylcyclohexanone m.p. 45–50° (pure m.p. 59–60°).[5] One g. of the ketone gave 1.96 g. of the *2,4-dinitrophenylhydrazone* derivative, m.p. 121–125°. After two recrystallizations from methanol pyridine, the derivative melted at 137–138°.[5] *With potassium hydroxide in ether*[3a]: A solution of 6 g. (0.029 mole) of 2-chloro-1-phenylcyclohexanol in 100 cc. of dry ether was refluxed with 3.2 g. (0.053 mole) of crushed potassium hydroxide for 4 hr. The product proved to be 5.5 g. (92%) unchanged chlorohydrin. A mixed melting point with the starting material showed no depression.

*2-(p-Tolyl)cyclohexanone* (Procedure C). To a solution of 164 g. (1.24 moles) of 2-chlorocyclohexanone in 600 cc. dry benzene was added 830 cc. (1.24 moles) of 1.5*M* *p*-tolylmagnesium bromide solution with good cooling in an ice bath. The mixture was allowed to come to room temperature, then refluxed for 2 hr. Hydrolysis was accomplished by pouring into dilute ammonium chloride solution. Distillation of the washed ether solution gave 169 g. of crude product distilling below 135° at 1.0 mm. Redistillation gave 160 g. (68%) of 2-(*p*-tolyl)cyclohexanone, b.p. 121–125° at 0.7 mm., m.p. 40–45°. A sample recrystallized from ether and from alcohol melted at 49–50°.

*Anal.* Calcd. for $C_{13}H_{16}O$: C, 83.0; H, 8.5. Found: C, 82.8; H, 8.6.

The *2,4-dinitrophenylhydrazone* derivative melted at 156–157°.

*Anal.* Calcd. for $C_{19}H_{20}O_4N_4$: N, 15.2. Found: N, 15.0.

*1-(m-Anisyl)-2-chlorocyclohexanol.* A Grignard solution prepared from 47 g. (0.25 mole) of *m*-anisyl bromide was added to 19.5 g. (0.15 mole) of 2-chlorocyclohexanone under the conditions of Procedure A. The product was 24 g. (67%) of 1-(*m*-anisyl)-2-chlorocyclohexanol, b.p. 147–148° at 0.3 mm.

*Anal.* Calcd. for $C_{13}H_{17}O_2Cl$: C, 64.9; H, 7.1. Found: C, 65.7; H, 7.1.

*Rearrangement of 1-(m-anisyl)-2-chlorocyclohexanol.* Under conditions as described in Procedure B, but with 22 hr. refluxing, 21.5 g. (0.09 mole) of 1-(*m*-anisyl)-2-chlorocyclohexanol was treated with 43 cc. of 2.1*M* phenylmagnesium bromide in ether solution (0.09 mole) to give 17 g. (90%) of 2-(*m*-anisyl)cyclohexanone, b.p. 124–127° at 0.2 mm.[5]

*Anal.* Calcd. for $C_{13}H_{16}O_2$: C, 76.4; H, 7.9. Found: C, 75.6; H, 7.9.

The *2,4-dinitrophenylhydrazone* derivative melted at 124–125°.[5]

*2-(1-Naphthyl)cyclohexanone.* A Grignard solution prepared from 31 g. (0.15 mole) of 1-bromonaphthalene was added to 20 g. (0.15 mole) of 2-chlorocyclohexanone under conditions of Procedure C to give 15.5 g. (48% based on the bromide) of 2-(1-naphthyl)cyclohexanone, m.p. 71–76°. A sample for analysis melted at 86–87°.

*Anal.* Calcd. for $C_{16}H_{16}O$: C, 85.7; H, 7.1. Found: C, 85.3; H, 7.3.

The *2,4-dinitrophenylhydrazone* derivative melted at 144–145°.

*2-Bromo-1-tetralone.* 2-Bromo-1-tetralone was prepared by the bromination of 1-tetralone as described by Wilds.[12]

*2-Chloro-1-tetralone.* 1-Tetralone was chlorinated in glacial acetic acid as previously described.[13] A 50% yield of 2-chloro-1-tetralone was obtained, m.p. 40–42°, b.p. 123–126° at 1.0 mm., $n_D^{25}$ 1.590.

*2-Phenyl-1-tetralone. A. From 2-bromo-1-tetralone.* The reaction of 15.0 g. (0.066 mole) of 2-bromo-1-tetralone with 45 cc. of 1.5*M* phenylmagnesium bromide solution in ether (0.068 mole) under conditions of Procedure C (with 1 hr. at reflux) gave 3.5 g. (24%) of crude 2-phenyl-1-tetralone. Several recrystallizations from alcohol gave a product melting at 76–77°.[14]

(8) P. D. Bartlett, *J. Am. Chem. Soc.*, **57**, 224 (1935).

(9) All m.p.'s corrected unless otherwise indicated.

(10) Microanalyses by J. Sorensen, V. Hobbs, and M. Hines, Microanalytical Laboratory, Department of Chemistry, Northwestern University.

(11) M. S. Newman, M. D. Farbman, and H. Hipsher, *Org. Syntheses*, **25**, 22 (1945).

(12) A. L. Wilds and J. A. Johnson, Jr., *J. Am. Chem. Soc.*, **68**, 86 (1946).

(13) German Patent **377,587**, *Chem. Centr.*, **95**, I, 956 (1924).

(14) M. S. Newman, *J. Am. Chem. Soc.*, **60**, 2947 (1938).

*Anal.* Calcd. for $C_{16}H_{14}O$: C, 86.5; H, 6.3. Found: C, 87.2; H, 6.0.

The *2,4-dinitrophenylhydrazone* derivative melted at 197–198°.[15]

*B. From 2-chloro-1-tetralone.* The reaction of 27 g. (0.15 mole) of 2-chloro-1-tetralone with 100 cc. of 1.5*M* phenylmagnesium bromide solution in ether (0.15 mole) under conditions of Procedure C gave 14 g. (43%) of 2-phenyl-1-tetralone with 10.0 g. chlorotetralone recovered. Recrystallization of the ketone from alcohol yielded 12.0 g. crystals, m.p. 71–74°.

*Reaction of 2-chloro-1-tetralone with excess Grignard reagent.* Under the conditions of Procedure C, 27 g. (0.15 mole) of 2-chloro-1-tetralone was treated with 200 cc. of 1.5*M* phenylmagnesium bromide solution in ether (0.30 mole) to give a product consisting of 10 g. of recovered 2-chloro-1-tetralone and 24 g. of residue which would not distill at 1 mm. No fraction corresponding to 2-phenyl-1-tetralone was obtained.

*2-Chloro-1-phenyl-1,2,3,4-tetrahydro-1-naphthol.* Eighteen g. (0.1 mole) of 2-chloro-1-tetralone was treated with 100 cc. of 1.5*M* phenylmagnesium bromide solution in ether (0.15 mole) according to Procedure A to give 15.5 g. (60%) of 2-chloro-1-phenyl-1,2,3,4-tetrahydro-1-naphthol (140–160° at 0.5 mm.) m.p. 90–95°, with 6.0 g. chlorotetralone recovered. A sample of the chlorohydrin recrystallized several times from ligroin melted at 98–99°.

*Anal.* Calcd. for $C_{16}H_{15}OCl$: C, 74.3; H, 5.8. Found: C, 74.2; H, 5.8.

This experiment was repeated and the reaction mixture was carbonated by adding powdered Dry Ice before hydrolysis. No benzoic acid was obtained. The product consisted of 42% 2-chloro-1-tetralone and 58% chlorohydrin.

*Rearrangement of 2-chloro-1-phenyl-1,2,3,4-tetrahydro-1-naphthol. A. With Phenylmagnesium bromide.* Under conditions of Procedure B, 10 g. (0.039 mole) of 2-chloro-1-phenyl-1,2,3,4-tetrahydro-1-naphthol was added to 26 cc. (0.039 mole) of 1.5*M* phenylmagnesium bromide solution to give 7.0 g. (81%) of 2-phenyl-1-tetralone, m.p. 71–74°.

*B. With sodium hydride.* Thirteen g. (0.05 mole) of the chlorohydrin, when refluxed for 3 hr. with 1.3 g. (0.055 mole) of sodium hydride in dry benzene ether, gave 12.0 g. of starting material unchanged, m.p. 85–90°.

*2-Chloroindanone.* The procedure used was that described for 2-chloro-1-tetralone. Fractionation of the product obtained from 132 g. (1.0 mole) of 1-indanone gave 92 g. (55%) of 2-chloroindanone [with 28 g. (21%) of 1-indanone recovered]; m.p. 34–38°, from petroleum heptane.[16]

*2-Chloro 1-phe l-1-indanol.* Under the conditions of Procedure A 25 g. (0 15 mole) of 2-chloroindanone was treated with 100 cc. of 2.1*M* phenylmagnesium bromide solution in ether (0.21 mole) to give 25 g. (69%) of 2-chloro-1-phenyl-1-indanol, m.p. 81–84°. A sample for analysis melted at 87–88°.

*Anal.* Calcd. for $C_{15}H_{13}OCl$: C, 73.6; H, 5.3. Found: C, 73.3; H, 5.2.

*2-Phenylindanone.* Ten g. (0.06 mole) of 2-chloroindanone was treated with 51 cc. (0.077 mole) of 1.5*M* phenylmagnesium bromide solution according to Procedure C to give 7.6 g. (60%) of 2-phenylindanone, m.p. 73–75°.[17] The *2,4-dinitrophenylhydrazone* derivative melted at 226–227°

*Anal.* Calcd. for $C_{21}H_{16}O_4N_4$: N, 14.4. Found: N, 14.1.

*1-Keto-1,2,3,4,5,6,7,8-octahydroanthracene.* This ketone was prepared as described by Krollpfeiffer and Schäfer.[18] A 75% yield of the ketone, m.p. 41–44°, was obtained.

*2-Chloro-1-keto-1,2,3,4,5,6,7,8-octahydroanthracene.* The procedure used was that described for the chlorination of 1-tetralone. Twenty-six g. of the ketone gave 20 g. (66%) of the chloroketone, m.p. 61–65°, after crystallization from alcohol. A sample for analysis melted at 66–67°.

*Anal.* Calcd. for $C_{14}H_{15}OCl$: C, 71.6; H, 6.4. Found: C, 71.1; H, 6.4.

*2-Phenyl-1-keto-1,2,3,4,5,6,7,8-octahydroanthracene.* Under the conditions of Procedure C, 16.5 g. (0.07 mole) of the chloroketone was treated with 33 cc. of 2.1*M* phenylmagnesium bromide solution in ether (0.07 mole) to give 10.0 g. (52%) of the phenyl ketone, m.p. 132–140°. A sample for analysis melted at 144–145°.

*Anal.* Calcd. for $C_{20}H_{20}O$: C, 87.0; H, 7.2. Found: C, 87.1; H, 7.3.

The *2,4-dinitrophenylhydrazone* derivative melted at 209–210°.

*Anal.* Calcd. for $C_{26}H_{24}O_4N_4$: N, 12.2. Found: N, 11.7.

EVANSTON, ILL.

(15) A. A. Plentl and M. T. Bogert, *J. Am. Chem. Soc.*, **63**, 989 (1941).

(16) C. Courtot, A. Fayet, and P. Parant, *Compt. rend.*, **186**, 372 (1928).

(17) P. A. Plattner, R. Sandrin, and J. Wyss, *Helv. Chim. Acta*, **29**, 1604 (1946).

(18) F. Krollpfeiffer and W. Schäfer, *Ber.*, **56**, 620 (1923).

[CONTRIBUTION FROM THE RESEARCH DIVISION, AMERICAN CYANAMID CO.]

# Triacylhalomethanes: 2-Halo-2-acyl-1,3-indandiones

K. C. MURDOCK[1]

*Received December 5, 1958*

Various 2-halo-2-acyl-1,3-indandiones were prepared for evaluation as blood anticoagulants. Stability and activity paralleled the degree of branching in the acyl group. A halogenation procedure was developed which was particularly useful for the synthesis of the more labile products. The structures of some anomalous bromination products are discussed.

Certain 3-alkyl-4-hydroxycoumarins and 2-acyl-1,3-indandiones have been found to be potent blood anticoagulants[2] and are in general use for the treatment of thrombo-embolism. Somewhat erratic dose-response relationships present the alternative hazards of embolism or hemorrhage and have required that such therapy be very carefully controlled. In a search for improved anticoagulants there have been prepared a number of 2-halo-2-acyl-1,3-indandiones (I), novel triacylhalomethanes.

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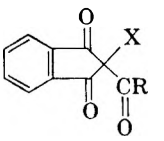
(2) W. H. Seegers, *Pharm. Rev.*, **3**, 278 (1951).

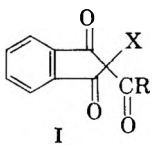
TABLE I

2-HALO-2-ACYL-1,3-INDANDIONES



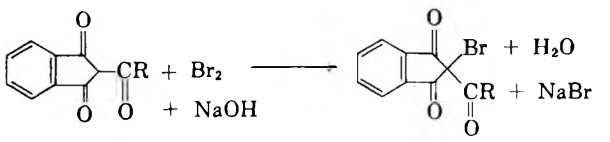
| R | X | Method | Yield, % | M.P., °C.[a] | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Halogen, % Calcd. | Halogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|
| $C_6H_5$ | Br | A[b] | 62 | 119 | 58.4 | 58.2 | 2.76 | 2.66 | 24.2 | 24.4 |
| 2-HOOC-$C_6H_4$ | Br | | 25 | 120–132[c] | 54.8 | 54.2[d] | 2.43 | 2.40[d] | 21.4 | 22.0 |
| $(C_6H_5)_2CH$ | Br | A[e] | 80 | 139–140 | 66.0 | 66.0 | 3.62 | 3.29 | 19.1 | 19.0 |
| $(C_6H_5)_2CH$ | Br | B[f] | 79 | 136–139 | | | | | | |
| $(C_6H_5)_2CH$ | Cl | B[e] | 20 | 157 | 73.7 | 73.1 | 4.03 | 4.01 | 9.46 | 9.75 |
| $(C_6H_5)_2COH$ | Br | A[e] | 2[g] | 160 | 63.5[h] | 63.0 | 3.48 | 3.46 | 18.4 | 18.9 |
| $C_6H_5CH_2$ | Br | B[e] | 42 | 86 | 59.5 | 59.5 | 3.23 | 3.19 | 23.3 | 23.0[d] |
| $CH_3CH_2$ | Br | B[e] | 7 | 74–75 | 51.3 | 51.4 | 3.23 | 3.45 | 28.4 | 28.1[d] |
| $(CH_3)_2CH$ | Br | B[e] | 78 | 60–61 | 53.0 | 52.9 | 3.76 | 3.79 | 27.1 | 27.2 |
| $(CH_3)_3C$ | Br | B[e] | 66 | 103 | 54.4 | 54.4 | 4.24 | 4.19 | 25.8 | 26.1 |

[a] All melting points are corrected. [b] Product recrystallized from carbon tetrachloride. [c] Lit. (ref. 3): no m.p. reported. [d] Average of two determinations. [e] Product recrystallized from a mixture of benzene and *n*-hexane. [f] Product was not recrystallized. [g] Obtained as a by-product. See text. [h] Calcd.: O, 14.7. Found: O, 15.5.



I

II. R = 2-$C_6H_4COOH$, X = Br
III. R = $CH(C_6H_5)_2$, X = Br
IV. R = $C(CH_3)_3$, X = Br




The only halogen compound of this type previously described in the literature was 2-bromo-2-(2-carboxybenzoyl)-1,3-indandione (II). This was an unstable substance for which no physical constants were reported.[3] In the present investigation early attempts to brominate 2-pivalyl-1,3-indandione resulted in the formation of 2,2-dibromo-1,3-indandione, a product of brominative cleavage. This result paralleled the findings of Hunter and Yackel who obtained the same product from the action of bromine on 2-benzoyl-1,3-indandione; they recommended this method of degradation as a proof of structure for 2-acyl-1,3-indandiones.[4]

Two bromination methods have been developed which have enabled the synthesis of the 2-bromo-2-acyl-1,3-indandiones listed in Table I. In the first method (A), the reaction was carried out in refluxing chloroform with two equivalents of bromine being preferred. The second method (B) was generally applicable and was the only method successfully used for the preparation of the more sensitive bromo compounds. This method involved a two-phase reaction at 0° of a chloroform solution of the triketone with bromine dissolved in an equivalent amount of aqueous sodium hydroxide. Stirring was adjusted so as to mix the two phases only slightly; thus, the sensitive brominated product, in the organic layer, was less subject to hydrolysis. 2-Chloro-2-diphenylacetyl-1,3-indandione was prepared with a commercial sodium hypochlorite solution.

The conditions of time and temperature and the use of an inert solvent for recrystallization were found to be important. Stability of the brominated products paralleled the degree of branching in the acyl side chain. The brominated 2-propionyl and 2-phenylacetyl compounds decomposed extensively on standing overnight. The 2-bromo-2-diphenylacetyl-1,3-indandione (III) and 2-bromo-2-pivalyl-1,3-indandione (IV) did not evidence decomposition for months. The 2-chloro analog of III was stable. This stability of the chloro analog as compared with the bromo compound parallels the reported relationship between the corresponding 2-halo-2-carbethoxy-1,3-indandiones.[5]

With those 2-acyl-1,3-indandiones having an $\alpha$-hydrogen atom in the acyl group, it was necessary to consider the possibility that halogenation replaced this hydrogen atom rather than that in the 2-position of the indandione nucleus. In the bromination of the somewhat analogous ethyl acetoacetate the $\alpha$-bromo derivative is the primary product, but it gradually rearranges to form the more stable $\gamma$-bromo isomer.[6] After one bromination of 2-diphenylacetyl-1,3-indandione the reaction mixture was allowed to stand at 100° for several hours

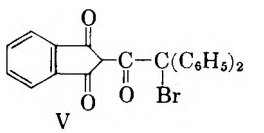
(3) W. Wislicenus and H. Schlichenmaier, *Ann.*, **460**, 278 (1928).

(4) W. H. Hunter and E. C. Yackel, *J. Am. Chem. Soc.*, **58**, 1395 (1936).

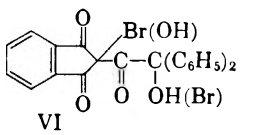
(5) L. Flatow, *Ber.*, **34**, 2145 (1901).

(6) A. Hantzsch, *Ber.*, **27**, 3168, 355 (1894).

during the removal of solvent. Though none of the usual monobromo derivative was isolated, there was obtained a small amount of an isomeric monobromide, along with what appears to be a *bis* compound from two molecules of starting material. In the infrared absorption spectrum of this isomeric monobromide twin maxima were seen[7] in the carbonyl region at 5.74 and 5.83$\mu$. These set it apart from the other monobromides (Table I) in which the location of the bromine atom was in question. The latter compounds, like 2-bromo-2-pivalyl-1,3-indandione (IV) in which the bromine atom is necessarily *alpha* to all three carbonyl groups, exhibited only a single strong maximum in that region (5.79$\mu$). They were accordingly designated as 2-bromo derivatives while the above, abnormal product was designated as V, 2-diphenylbromoacetyl-1,3-indandione.




V




VI

From the normal bromination of 2-diphenylacetyl-1,3-indandione there was isolated in addition to the 2-bromo derivative about 2% of another brominated substance. This compound exhibited an infrared absorption maximum at 2.98$\mu$ (Nujol mull), indicating the presence of a hydrogen-bonded hydroxyl group. From the location of the absorption peaks in the carbonyl region (5.63 and 5.77$\mu$), the alternative locations of the bromine and hydroxyl groups of this bromohydroxy-2-diphenylacetyl-1,3-indandione (VI) could not be firmly established.

An aminolysis of the bromine atom in 2-bromo-2-diphenylacetyl-1,3-indandione (III) was effected with piperidine, forming the corresponding 2-piperidino compound.

Most of the compounds of Table I were active as anticoagulants. In general their activities paralleled the degree of branching in the acyl side chain and were about the same as those[8] of the corresponding unhalogenated precursors. Toxicities were somewhat lower. The pharmacological evaluations were made by Mr. Vincent Downing and his associates at the Lederle Laboratories and are to be reported in detail elsewhere.[9]

## EXPERIMENTAL

*2-Acyl-1,3-indandiones.* 2-Benzoyl-, 2-propionyl-, 2-isobutyryl-, 2-pivalyl-,[10] 2-diphenylacetyl-,[11] and 2-phenylacetyl-1,3-indandione were prepared by the acylation of the appropriate methyl ketone with diethyl phthalate in the presence of sodium methoxide. The synthesis of 2-phenylacetyl-1,3-indandione[12] does not appear to have been described previously: m.p. 84°.

*Anal.* Calcd. for $C_{17}H_{12}O_3$: C, 77.3; H, 4.58. Found: C, 77.1; H, 4.63.

*2-(2-Carboxybenzoyl)-1,3-indandione.* Instead of following the reported synthetic sequence for the preparation of this compound,[3] which requires four steps after the preparation of 1,3-indandione, the magnesium salt of 1,3-indandione was acylated with phthalic anhydride. To a warm slurry of 0.16 mole of finely powdered magnesium methoxide in 80 ml. of dry benzene, protected from moisture, was added with stirring a solution at 50° of 23.4 g. (0.16 mole) of 1,3-indandione[13] in 320 ml. of benzene. (The magnesium methoxide, 19.4 g., had been dried *in vacuo* at 100° and appeared to be free of methanol, but from the apparently excessive yield obtained in its preparation it did not contain more than 63% of the desired compound.) A deep brown color developed with the addition. After 5 min. of stirring the mixture was chilled to 5° with an ice bath. There was then added with chilling and stirring a hot solution of 23.4 g. (0.16 mole) of phthalic anhydride in 240 ml. of benzene, at such a rate that the temperature of the reaction mixture did not rise above 10°. With the reaction flask initially chilled in the ice bath, stirring was continued for 42 hr. It was estimated that the ice bath used would require 3–4 hr. to come to room temperature.

The solid in the reaction mixture was collected by filtration and washed with benzene, giving 14.9 g. of a dark material (A) which did not melt by 360° (see below). The dark gray filtrate was extracted with 500 ml. of water. The intensely purple aqueous extract was neutralized just to the disappearance of the purple color by the gradual addition with swirling of 95 ml. of 1*N* hydrochloric acid. The mixture was allowed to stand 1 hr. as the precipitate agglomerated. The precipitate was collected (saving the dark brown filtrate—see below), washed with water, dried, and recrystallized from dioxane. The produt separated as yellow-orange granules, m.p. 208–211° (dec.). Wislicenus and Kötzle[14] reported the m.p. of 2-(3-oxo-1-indanylidene)-1,3-indandione ("bindone") as 206–208°.

*Anal.* Calcd. for $C_{18}H_{10}O_3$: C, 78.8; H, 3.68. Found: C, 78.6; H, 3.22.

After thorough extraction with water of the above-mentioned dark solid (A) present in the reaction mixture there remained after drying 4.0 g. of a green, infusible salt. This appeared to be inert to the action of dilute acid. Upon stirring with concentrated hydrochloric acid, however, the green color was discharged, leaving 3.4 g. of a yellow-orange solid, m.p. 205–207°. The melting point of this material was not depressed after admixture with bindone.

The above-mentioned filtrate remaining after removal of the bindone was acidified by the portionwise addition of *ca.* 150 ml. of 1*N* hydrochloric acid. A solid slowly separated during the next 1.5 hr. This solid was collected and washed with water; 2.2 g., m.p. 160–162°. Recrystallization from ethanol-water followed by drying *in vacuo* at 60° over phosphorus pentoxide gave a tan powder, m.p. (taken rapidly) 156–160°, with sudden gassing at about 180°; lit.,[3] m.p. 155–160°.

*Anal.* Calcd. for $C_{17}H_{10}O_5$: C, 69.4; H, 3.43. Found: C, 68.3, 68.0; H, 3.37, 3.45.

*2-Halo-2-acyl-1,3-indandiones.* The two halogenation methods used for the preparation of the 2-halo-2-substituted-1,3-indandiones of Table I involved the use of: (A) bromine in refluxing chloroform or (B) a two-phase mixture at 0°

(7) All infrared absorptions were determined in chloroform solution unless specified otherwise.

(8) J. T. Correll, L. L. Coleman, S. Long and R. F. Willy, *Proc. Soc. Exp. Biol. Med.*, **80**, 139 (1952).

(9) V. Downing, *et al.*, to be published.

(10) L. B. Kilgore, J. H. Ford, and W. B. Wolfe, *Ind. Eng. Chem.*, **34**, 494 (1942).

(11) D. G. Thomas, U. S. Patent **2,672,483** (1954).

(12) Prepared by Dr. R. L. Horton.

(13) W. Teeters and R. Shriner, *J. Am. Chem. Soc.*, **55**, 3026 (1933).

(14) W. Wislicenus and A. Kötzle, *Ann.*, **252**, 72 (1889).

of chloroform and a solution of bromine in an equivalent amount of aqueous sodium hydroxide.

The following examples are illustrative: *Method A. 2-Bromo-2-diphenylac tyl-1,3-indandione* (III). To a solution of 136.2 g. (0.4 mole) of 2-diphenylacetyl-1,3-indandione in 600 ml. of chloroform was added 41.9 ml. (127.8 g., 0.8 mole) of bromine. The mixture was heated under reflux for 6 hr. The hydrogen bromide evolved was trapped in a beaker of water. The solvent and excess bromine were distilled off until the rate of distillation diminished. To avoid overheating the sensitive product, the remaining volatile material was then distilled under aspirator pressure until the residue just began to crystallize. Immediately, 320 ml. of dry, boiling benzene was added. The resulting red solution was filtered through a plug of cotton, 800 ml. of warm *n*-hexane was added to the filtrate, and the resulting solution was allowed to cool to room temperature. On top of the main crop of large, white prisms which separated there were observed clumps of light tan, fine needles. The product was collected by filtration and thoroughly washed on the Büchner funnel with ethanol, thus removing the contaminating needles. (The isolation of this by-product, bromohydroxy-2-diphenylacetyl-1,3-indandione, VI, is described below.) After drying at 60° the product weighed 133.7 g. (80%), m.p. 139–140°.

*Anal.* Calcd. for $C_{23}H_{15}O_3Br$: C, 66.0; H, 3.62; Br, 19.1. Found: C, 66.0; H, 3.29; Br, 19.0.

After 2 months in a brown bottle at room temperature the melting point of a sample of this compound was not lower, nor were there observed any other signs of decomposition. But after 9 months the external surfaces had become yellow and the melting point had dropped to 129–136°.

*Method B. 2-Bromo-2-pivalyl-1,3-indandione* (IV). To an ice-cold solution of 4.5 g. (0.02 mole) of 2-pivalyl-1,3-indandione in 25 ml. of chloroform was added an ice-cold solution of 0.8 g. (0.02 mole) of sodium hydroxide and 3.2 g. (0.02 mole) of bromine in 25 ml. of water. The mixture was stirred for 5 hr. while chilling the reaction flask with an ice bath. The chloroform layer was separated, diluted with 25 ml. of cold chloroform, extracted rapidly with an ice-cold solution of 0.4 g. (0.01 mole) of sodium hydroxide in 25 ml. of water, washed with two ice-cold portions of water, and dried over anhydrous calcium chloride. The chloroform solution was filtered, then concentrated to dryness *in vacuo*. The pale yellow crystalline residue was dissolved in 11 ml. of warm, dry benzene and 25 ml. of *n*-hexane was added. Crystallization began rapidly and was allowed to continue, finally at 5°. The product was collected by filtration, washed with *n*-hexane, and dried at room temperature; 4.1 g. (66%), elongated prisms, m.p. 103°.

*Anal.* Calcd. for $C_{14}H_{13}O_3Br$: C, 54.4; H, 4.24; Br, 25.8. Found: C, 54.4; H, 4.19; Br, 26.1.

*Brominative cleavage of 2-pivalyl-1,3-indandione: 2,2-dibromo-1,3-indandione.* To a solution of 1.0 g. of 2-pivalyl-1,3-indandione in 2.5 ml. of chloroform was added portionwise about 1.5 ml. of bromine. The evolution of hydrogen bromide was accompanied by the separation of a crystalline material which, however, redissolved upon the addition of the last 0.5 ml. of bromine. The mixture was allowed to stand for 1 hr., whence the solvent and unreacted bromine were removed *in vacuo*. The residue, after four recrystallizations from ethanol, gave a small quantity of a white solid, m.p. 179–181°; lit.,[4] m.p. 178–179°.

*Anal.* Calcd. for $C_9H_4O_2Br_2$: C, 35.6; H, 1.33; Br, 52.5. Found: C, 35.0, 35.0; H, 1.53, 1.80; Br, 52.6, 52.4.

*Abnormal products from the action of bromine on 2-diphenylacetyl-1,3-indandione.* In an early attempt to prepare 2-bromo-2-diphenylacetyl-1,3-indandione by the procedure described in Method A, the molar ratio of bromine to 2-diphenylacetyl-1,3-indandione (96.1 g.) was only 1.2:1, rather than 2:1. After heating the reaction mixture under reflux for 3 hr., the chloroform and unreacted bromine were distilled off over the steam bath, allowing the distillation residue to stand over the steam bath for an additional 3 hr. Although this residue was thoroughly investigated by a series of fractional crystallizations, none of the desired product was isolated. In addition to 33% of recovered starting material there were finally isolated, on the basis of the solubilities mentioned below, the following two compounds:

1. *2-Diphenylbromoacetyl-1,3-indandione* (V). This compound separated from a mixture of benzene and *n*-hexane as white platelets, 3.6 g., m.p. 184° (orange melt). In contrast to the starting material it was relatively insoluble in carbon tetrachloride, though soluble in benzene and dioxane.

*Anal.* Calcd. for $C_{23}H_{15}O_3Br$: C, 66.0; H, 3.62; Br, 19.1. Found: C, 66.2, 66.2; H, 3.47, 3.44; Br, 19.0.

2. *"Bis(2-diphenylacetyl-1,3-indandione)."* This second compound was recrystallized with much loss from dimethylformamide (2 ml./g.). There was obtained 8.6 g. of deeply yellow prisms, m.p. 190–195°, with gassing. This material was almost insoluble in most solvents, although it was moderately soluble in hot 2-ethoxyethanol. It gave a negative Beilstein test for halogen. Though soluble in 2*N* methanolic potassium hydroxide, it was apparently insoluble in and did not color 20% aqueous sodium hydroxide.

*Anal.* Calcd. for $C_{46}H_{30}O_3$: C, 81.5; H, 4.46. Found: C, 80.9, 81.2; H, 4.14, 4.05.

*Bromohydroxy-2-diphenylacetyl-1,3-indandione* (VI). This compound was isolated, as indicated above in the example illustrating Method A, as a by-product from the synthesis of 2-bromo-2-diphenylacetyl-1,3-indandione. In three runs there was brominated a total of 680 g. (2.0 moles) of 2-diphenylacetyl-1,3-indandione. From the crude solids obtained by chilling and concentrating the mother liquor and alcoholic washes of the main product, there was obtained a total of 18.7 g. (2%) of the by-product. Its extraction from these crude solids was enabled by its ready solubility in unheated alcohol. The alcoholic extracts were concentrated to dryness *in vacuo* and the residue was recrystallized from mixtures of benzene and *n*-hexane. The product separated as fine, white needles, m.p. 160°.

*Anal.* Calcd. for $C_{23}H_{15}O_4Br$: C, 63.5; H, 3.48; Br, 18.4; O, 14.7. Found: C, 63.0; H, 3.46; Br, 18.9; O, 15.5.

From the above crude solids there was also obtained about 10% of unreacted starting material and 3.1 g. of "bis(2-diphenylacetyl-1,3-indandione)."

*2-Chloro-2-diphenylacetyl-1,3-indandione.* To a solution at 0° of 68.0 g. (0.2 mole) of 2-diphenylacetyl-1,3-indandione in 200 ml. of chloroform was added 94.0 ml. of a cold sodium hypochlorite solution (containing 15.1 g. of active chlorine per 100 ml. of solution. This hypochlorite was later found to contain free sodium hydroxide, which would be expected to convert some of the starting material to its sodium salt, thus lowering the yield in the chlorination). The mixture was kept cold with an ice bath and stirred for 7.5 hr. The yellow solid then present was removed by filtration and washed once with chloroform. The chloroform layer from the combined filtrate and wash was washed once with water and dried over anhydrous calcium chloride. The solvent was removed *in vacuo*, the yellowish residue dissolved in 180 ml. of hot benzene, 200 ml. of hot *n*-hexane added to the filtrate, and the solution allowed to cool, finally at 5°. The solid which separated was collected, washed with a mixture of benzene and *n*-hexane (3:1), and dried at 60°. There was thus obtained 16.7 g. of a pale, pink solid, m.p. 157°. After two more recrystallizations from mixtures of benzene (3 ml./g.) and *n*-hexane (6 ml./g.), using decolorizing charcoal, there was obtained 14.5 g. (20%) of a pinkish white solid, m.p. still 157°. After 1.5 months at room temperature a sample had become slightly yellow on the surface, where it was exposed to diffuse light, but the melting point had not dropped.

*Anal.* Calcd. for $C_{23}H_{15}O_2Cl$: C, 73.7; H, 4.03; Cl, 9.46. Found: C, 73.1; H, 4.01; Cl, 9.75.

The yellow solid which separated from the reaction mixture, 33.8 g., was suspended in hot water, and concentrated hydrochloric acid was added dropwise until the mixture was

acidic to benzopurpurin paper. The solid present was collected, washed with water, dried, and recrystallized from 80 ml. of 2-ethoxyethanol to give 18.5 g. (27% recovery) of yellow needles, m.p. 147–148°. A mixture melting point determination with starting material showed no depression (148–149°).

*2-Diphenylacetyl-2-piperidino-1,3-indandione.* To a solution at 20° of 29.7 g. (0.071 mole) of 2-bromo-2-diphenylacetyl-1,3-indandione (III) in 1200 ml. of dioxane was added gradually with swirling 21.0 ml. (18.1 g., 0.213 mole) of piperidine. The mixture warmed spontaneously to 43°. After standing overnight the piperidinium bromide which had separated was removed by filtration and washed with dioxane and acetone; 5.5 g. (47%), m.p. and mixture m.p. 240–241°. The bright orange mother liquor and the dioxane wash were combined, evaporated under reduced pressure, and the dark, viscous residue allowed to crystallize at 5° from 140 ml. of carbon tetrachloride. The solid which separated, after washing with carbon tetrachloride and water, amounted to 11.6 g., m.p. 181–187 . Recrystallization from methyl ethyl ketone gave 6.6 g. (22%) of bright yellow rods, m.p. 192–193°.

*Anal.* Calcd. for $C_{28}H_{25}O_3N$: C, 79.41; H, 5.95; N, 3.31. Found: C, 79.8; H, 6.12; N, 3.35.

*Acknowledgments.* The interest and helpful suggestions of Drs. P. F. Dreisbach, J. J. Denton, and R. P. Parker are acknowledged with appreciation. Thanks are given to Mr. O. E. Sundberg, Miss Irene Prokul, and Mr. David Green for the microanalyses and to Mrs. Cecelia Jorgensen for the infrared spectral analyses and their interpretation.

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# Decarboxylation of Thetin Salts

D. M. BURNESS

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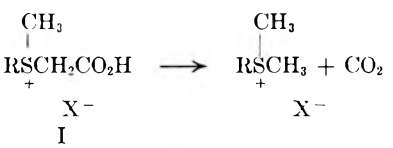
Dialkyl thetin salts, $R_1R_2\overset{+}{S}CH_2CO_2H\cdot X^-$, undergo facile decarboxylation to the corresponding trialkylsulfonium salts. The presence of an electron-donating (methyl) group on the alpha-carbon tends to suppress the reaction.

To the ever-increasing accounts of differences in reactivity,[1] conjugative ability[2,3] and the like between numerous sulfonium and ammonium compounds should be added another example of considerable interest. In the course of a study of various long-chain thetin salts (I), it was discovered that facile decarboxylation occurrred under relatively mild conditions to give the corresponding trialkyl sulfonium salts.



This reaction is virtually unknown in the corresponding betaine (ammonium) series, in which the compounds are ordinarily stable at temperatures below their melting points which often run in excess of 200°. A noteworthy exception[4] has been reported with the betaine derived from 2,5-dimethylpyrazine, in which case decarboxylation is facilitated by an intermediate capable of resonance stabilization.

The reaction was first encountered in alkaline hydrolysis of carbethoxymethyl(dodecyl)methylsulfonium *p*-toluenesulfonate. The identity of the product as dodecyldimethylsulfonium *p*-toluenesulfonate was shown by (1) analysis, (2) the infrared spectrum which indicated the absence of carboxyl ion and the presence of *p*-toluenesulfonate ion, and (3) comparison with an authentic specimen. Dodecylmethylthetin, the expected product, was prepared by the action of silver oxide on the thetin hydrochloride and proved to be quite stable in contrast to the report of Werntz,[5] who used alkali to liberate this thetin from its salt. The thetin can also be reconverted to a salt, as shown by the reaction of dodecylmethylthetin with *p*-toluenesulfonic acid. The decarboxylation of the thetin salts is quite general, as was later confirmed in the cases of the decyl, tetradecyl, hexadecyl, and decamethylenebis analogs.

The ease with which decarboxylation of dodecyldimethylthetin *p*-toluenesulfonate occurs was shown by experiments carried out in refluxing acetone. At this relatively low temperature (56°), decarboxylation occurred readily and was complete within 2 hours in the presence of such mildly basic catalysts as piperidine, Amberlite IR-4B, and dodecylmethylthetin, itself. In the absence of a catalyst, no reaction was apparent after 1 hour, but, after 6 hours, a 94% yield of decarboxylated product was obtained. Evidently the reaction is extremely slow at first, until a sufficient quantity

(1) W. E. Doering and K. Schreiber, *J. Am. Chem. Soc.*, **77**, 514 (1955).

(2) F. G. Bordwell and P. J. Boutan, *J. Am. Chem. Soc.*, **78**, 87 (1956).

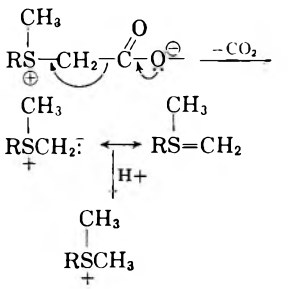
(3) N. F. Blau and C. G. Stuckwisch, *J. Org. Chem.*, **22**, 82 (1957).

(4) E. V. Hort and P. E. Spoerri, *J. Am. Chem. Soc.*, **77**, 5898 (1955).

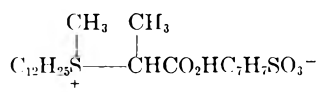
(5) J. H. Werntz, U. S. Patent **2,178,353**, October 31, 1939; *Chem. Abstr.*, **34**, 1419 (1940).

of the dodecyldimethylsulfonium *p*-toluenesulfonate[6] is formed to act as a catalyst. Acetic acid, however, did not completely inhibit the reaction, for, after 2 hours, decarboxylation was about one-third complete.

The ease with which thetin salts undergo decarboxylation may well be attributed to resonance forms arising from an expansion of the valence shell of the sulfur atom, a phenomenon which is essentially impossible with nitrogen; accordingly, the following course of reaction is proposed:



The effect of substitution at the alpha-carbon atom by the methyl group was investigated briefly with the expected result. Decarboxylation was rendered exceedingly more difficult; an acetone solution of dodecylmethyl-$\alpha$-propiothetin *p*-toluenesulfate (II) required prolonged refluxing (6 hours) in the presence of a piperidine catalyst to effect complete reaction. The reaction proceeded readily, however, at temperatures above the fusion



II

point of the pure substance (*ca.* 160°). It is apparent that the inductive effect of the sulfonium group is partially satisfied by the electron-donating $\alpha$-methyl group.

Previous evidence relating to the decarboxylation of thetin salts appears to be limited to that of Weibull,[7] who detected cyclohexyldimethylsulfonium and carbonate ions among numerous products of decomposition of cyclohexylmethylthetin hydrobromide under the influence of alcoholic potassium hydroxide.

## EXPERIMENTAL[8]

Although specific examples are given in the following paragraphs, most of the procedures are quite generally applicable to the other members of the homologous series with minor modifications. Properties and yields of the various compounds prepared are to be found in Tables I–IV.

(6) A 1% acetone solution of the sulfonium salt gave a reading of 7.65 at 40° on a Beckman *p*H meter.

(7) B. Weibull, *Arkiv Kemi*, **3**, 171 (1951); *Chem. Abstr.*, **46**, 3962 (1952).

(8) All melting points obtained by capillary method and corrected.

TABLE I

ETHYL *n*-ALKYLMERCAPTOACETATES ($RSCH_2CO_2C_2H_5$)

| R | B.P., °C./Mm. or M.P. | $n_D^{25}$ | Yield, % |
|---|---|---|---|
| $C_7H_{15}$ | 120–123/9 | — | 81 |
| $C_9H_{19}$ | 101–105/0.25–0.35 | 1.4585 | 65 |
| $C_{10}H_{21}$ | 117–119/0.7 | 1.4615 | 70+ |
| $C_{12}H_{25}$ | 137–139/0.35 | 1.4604 | 76 |
| $C_{14}H_{29}$ | 133–143/0.3 | 1.4629 | 83 |
| $C_{16}H_{33}$ | 166–168/0.35 | 1.4640 | 82 |
| $-(CH_2)_{10}-$ | 187–215/0.30–0.37 | 1.4902 | 81 |

TABLE II

*n*-ALKYL METHYL SULFIDES ($RSCH_3$ and $CH_3S(CH_2)_nSCH_3$)

| R | B.P., °C./Mm. or M.P. | $n_D^{25}$ | Yield, % |
|---|---|---|---|
| $C_{10}H_{21}$ | 118–119/11[a] | 1.4567 | 86 |
| $C_{12}H_{25}$ | 156–159/17[b] | 1.4582 | 87 |
| $C_{14}H_{29}$ | 134–140/0.35–0.5[c] | 1.4594 | 88 |
| $C_{16}H_{33}$ | 134–156/0.33–0.37[b] | 1.4615 | 81 |
| $-(CH_2)_7-$ | 181–183[d] | 1.5260 | 74 |
| $-(CH_2)_5-$ | 127/10[d] | 1.5065 | 49[e] |
| $-(CH_2)_{10}-$ | 117–131/0.4[f] | 1.4938 | 72 |

[a] J. von Braun, W. Teuffert, and K. Weissbach, *Ann.*, **472**, 139 (1929), report b.p. 125° (13 mm.) [b] R. Kuhn and O. Dann, *Ber.*, **73B**, 1092 (1940), report b.p. 163–165° (19 mm.) for dodecyl and m.p. 19.5–20.5° for hexadecyl compound. [c] *Anal.* Calcd. for $C_{15}H_{32}S$: C, 73.8; H, 13.1. Found: C, 74.0; H, 13.4. [d] M. Protiva, J. O. Jilek, and O. Exner, *Chem. Listy*, **47**, 580 (1953); [*Chem. Abstr.*, **49**, 155 (1955)] report b.p. 78–80° (10–12 mm.) for $C_2$ and b.p. 112–114° (8 mm.) for $C_5$ compound. [e] Low owing to accidental loss. [f] D. Jerchel, L. Dippelhoffer, and D. Renner, *Chem. Ber.*, **87**, 947 (1954), report b.p. 206° (19 mm.).

I. *Ethyl hexadecylmercaptoacetate.* To a solution of 6.9 g. (0.3 g. atom) of sodium in 150 ml. of methanol was added 36 g. (0.3 mole) of ethyl mercaptoacetate, followed by 91.5 g. (0.3 mole) of 1-bromohexadecane. The solution was heated at reflux for 2 hr., cooled, and 150 ml. of water added. The product was extracted with ether, dried, and distilled through a 10-inch heated column packed with Berl Saddles, using a variable reflux head. Yield, 84 g. (82%); b.p. 166–168° (0.35 mm.); $n_D^{25}$ 1.4640.

II. *Hexadecylmercaptoacetic acid.* A. *From the ester.* Hydrolysis of the ester in a 10% ethanol solution yielded 96% of the acid as colorless plates; m.p. 75–76° (from hexane).[9]

B. *By a Williamson synthesis.*[10] The acid was also prepared directly from 1-bromohexadecane and mercaptoacetic acid as in Section I, but using two equivalents of sodium. After the addition of water to the reaction mixture, it was heated until solution was complete, and was acidified with excess hydrochloric acid. Recrystallization of the crude product from methanol yielded 86% of the acid; m.p. 74.5–75.5°.

III. *$\alpha$-Dodecylmercaptopropionic acid.* To a cooled solution of 11.5 g. (0.5 mole) of sodium in 400 ml. of methanol was added 50.5 g. (0.25 mole) of *n*-dodecanethiol, followed by 38.2 g. (0.25 mole) of $\alpha$-bromopropionic acid. The solution was stirred and cooled in an ice bath during the addition and

(9) A. J. Hill and E. W. Fager, *J. Am. Chem. Soc.*, **65**, 2300 (1943), report 73.5–74° for m.p.

(10) By this procedure the decyl compound, m.p. 51–52°, and dodecyl compound, m.p. 61.5–62.5°, were prepared in 64 and 82% respective yields. L. Rapoport, A. Smith, and M. S. Newman, *J. Am. Chem. Soc.*, **69**, 693 (1947), report 52–53° and 61–62° for the melting points of decyl and dodecylmercaptoacetic acids.

TABLE III

SULFONIUM *p*-TOLUENESULFONATES

$$RSR'\cdot C_7H_7SO_3^-$$
(CH₃ on S⁺)

| R | R′ | Method Used | M.P., °C. | Yield, % | Analyses Calcd. C | Calcd. H | Calcd. S | Found C | Found H | Found S | Formula |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $C_7H_{15}$ | $CH_2CO_2C_2H_5$ | VA | [a] | 84 | | | | | | | |
| $C_9H_{19}$ | $CH_2CO_2C_2H_5$ | VA | 75–76.5[a] | 81 | | | | | | | |
| $C_{10}H_{21}$ | $CH_2CO_2C_2H_5$ | VA | 77–81[a] | 90 | | | | | | | |
| $C_{12}H_{25}$ | $CH_2CO_2C_2H_5$ | VA | 92–94[b] | 68 | 60.7 | 8.9 | 13.5 | 60.5 | 8.9 | 13.8 | $C_{24}H_{42}O_5S_2$ |
| $C_{14}H_{29}$ | $CH_2CO_2C_2H_5$ | VA | 82–86[a] | 74 | | | | | | | |
| $C_{16}H_{33}$ | $CH_2CO_2C_2H_5$ | VA | 87–90[a] | 78 | | | | | | | |
| —$(CH_2)_{10}$— | $CH_2CO_2C_2H_5$ | VA | 55–59[a] | 77 | | | | | | | |
| $C_7H_{15}$ | $CH_3$ | VB | 183.5–185 | 62 | 57.8 | 8.4 | 19.25 | 57.8 | 8.4 | 19.6 | $C_{16}H_{28}O_3S_2$ |
| $C_9H_{19}$ | $CH_3$ | VB | 179–181.5 | 68 | 60.0 | 8.9 | 17.8 | 60.0 | 8.9 | 17.9 | $C_{18}H_{32}O_3S_2$ |
| $C_{10}H_{21}$ | $CH_3$ | VA and B | 169.5 | 79 | 60.9 | 9.2 | 17.1 | 61.0 | 9.1 | 16.7 | $C_{19}H_{34}O_3S_2$ |
| $C_{12}H_{25}$ | $CH_3$ | VA and B | 164–170 | 74 | 62.8 | 9.5 | 15.9 | 62.8 | 9.3 | 15.6 | $C_{21}H_{38}O_3S_2$ |
| $C_{14}H_{29}$ | $CH_3$ | VA and B | 163.5–180.5 | 71 | 64.2 | 9.8 | 14.9 | 64.4 | 9.9 | 15.2 | $C_{23}H_{42}O_3S_2$ |
| $C_{16}H_{33}$ | $CH_3$ | VA and B | 163.5–182.5 | 78 | 65.4 | 10.0 | 14.0 | 65.1 | 10.3 | 14.3 | $C_{25}H_{46}O_3S_2$ |
| —$(CH_2)_5$— | $CH_3$ | VA | 129–130 | 50 | 51.5 | 6.7 | 23.9 | 51.6 | 6.7 | 24.2 | $C_{23}H_{36}O_6S_4$ |
| —$(CH_2)_{10}$— | $CH_3$ | VA and B | 182–183 | 92 | 55.4 | 7.6 | 21.1 | 55.4 | 7.7 | 20.9 | $C_{38}H_{46}O_6S_4$ |

[a] Not purified. [b] Crude product melted at 66–80°; purified by repeated recrystallization from acetone.

TABLE IV

THETINS AND THEIR SALTS

$$RSCHR'COO^- \text{ and } RSCHR'COOH\cdot X^-$$
(CH₃ on S⁺)

| R | R′ | X⁻ | Method Used | M.P., °C. | Yield, % | Analyses Calcd. C | Calcd. H | Calcd. S | Found C | Found H | Found S | Formula |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $C_{10}H_{21}$ | H | $C_7H_7SO_3^-$ | VA | 107–135 (dec.) | 50 | 57.4 | 8.2 | 15.3 | 57.6 | 8.5 | 15.1 | $C_{20}H_{34}O_5S_2$ |
| $C_{12}H_{25}$ | H | — | VIB | 102–108 (dec.) | 62 | 65.7 | 11.0 | 11.7 | 65.9 | 10.9 | 11.4 | $C_{15}H_{30}O_2S$ |
| $C_{12}H_{25}$ | H | $Cl^-$ | VIA | 68–100 | 41 | 57.9 | 10.0 | 10.3 | 57.6 | 10.3 | 10.5 | $C_{15}H_{31}ClO_2S$ |
| $C_{12}H_{25}$ | H | $C_7H_7SO_3^-$ | VA and VIC | 114–135 (dec.) | 73 | 59.2 | 8.6 | 14.4 | 59.1 | 8.4 | 14.2 | $C_{22}H_{38}O_5S_2$ |
| $C_{12}H_{25}$ | $CH_3$ | $C_7H_7SO_3^-$ | VA | 154–155 (dec.) | 55 | 60.0 | 8.7 | 13.9 | 60.3 | 8.9 | 13.7 | $C_{23}H_{40}O_5S_2$ |
| $C_{16}H_{33}$ | H | $C_7H_7SO_3^-$ | VA | 121.5–141 (dec.) | 65 | 62.2 | 9.2 | 12.75 | 62.5 | 9.5 | 12.7 | $C_{26}H_{46}O_5S_2$ |

allowed to warm up gradually to 25°. After 2 hr. at reflux, one half of the methanol was removed and 110 ml. of 10% hydrochloric acid added. The product which separated was isolated and recrystallized from hexane; yield 50.4 g. (74%); m.p. 51–52°.

*Anal.* Calcd. for $C_{15}H_{30}O_2S$: C, 65.75; H, 10.95. Found: C, 65.9; H, 11.2.

IV. *Dodecyl methyl sulfide.* This was prepared by essentially the same procedure as in I with added precautions. The low-boiling methyl mercaptan (b.p. 6°) was chilled in an ice-salt bath and added to an ice cold solution of sodium methoxide. After addition of the alkyl bromide, the solution was heated *carefully* to the reflux temperature. An exothermic reaction soon occurred, necessitating immediate cooling to avoid loss. Thereafter, the reaction and workup proceeded normally.

V. *Dodecyldimethylsulfonium p-toluenesulfonate.* A. *Direct synthesis.* A mixture of 216 g. of dodecyl methyl sulfide and 475 g. (a 7% excess) of freshly distilled methyl *p*-toluenesulfonate was heated on a steam-bath for 3 hr.; benzene was added as necessary to control frothing. When cool, the product was filtered, washed with benzene, and recrystallized from 1 l. of absolute ethanol, using Nuchar, and again from 800 ml. of fresh solvent, giving 530 g. of colorless plates; m.p. 164–170°. Concentration of the ethanolic filtrates produced a large second crop (172 g.) of slightly less pure material. Total yield, 702 g. (74%).

B. *From carbethoxymethyl(dodecyl)methylsulfonium p-toluenesulfonate.* A solution of 439 g. (0.93 mole) of the ester-salt (prepared as in A preceding paragraph from ethyl dodecylmercaptoacetate) in 650 ml. of 95% ethanol containing 61.2 g. of potassium hydroxide (85% pellets) was heated at reflux for 2.5 hr. and filtered hot. The filtrate was concentrated to 400 ml. and 4 l. of ether added. The crude, white crystalline product was isolated and extracted with 18 l. of boiling acetone, the undissolved potassium *p*-toluenesulfonate being filtered off. The filtrate was concentrated to one-half volume and cooled, to give 211 g. (57%) of large, colorless plates; m.p. 163–170°.

Further consecutive recrystallizations from acetonitrile, absolute ethanol, and acetone failed to change the melting point of this compound.

C. *From dodecylmethylthetin p-toluenesulfonate.* See Section VII.

VI. *Dodecylmethylthetin (DMT).* A. *DMT hydrochloride.* A mixture of 64.8 g. (0.3 mole) of dodecyl methyl sulfide and 28.5 g. (0.3 mole) of chloroacetic acid was heated, with stirring, at 60–65° for 1 hr. and allowed to stand overnight. Dry ether (800 ml.) was added, but the white, crystalline solid was too sticky to filter. The ether was removed, and 1 l. of benzene was distilled from the residue, using a 55° bath. This residue, after 3 hr. at 20 mm., was allowed to stand for several days until more than half the mass had crystallized. Dilution with 800 ml. of dry ether gave 40.4 g. (41%) of crude product, m.p. 65–98°, which, after recrystallization from 140 ml. of acetone, amounted to 21.5 g.; m.p. 68–100°. Further recrystallization failed to improve the melting point.

B. *DMT.* To a solution of 6.0 g. of DMT hydrochloride in 50 ml. of dry methanol was added 2.7 g. (20% excess) of silver oxide, and the mixture was shaken for 1.5 hr. After filtration through Super Filtrol and removal of the solvent (bath <40°), the white, crystalline residue was redissolved in 4 ml. of dry methanol and reprecipitated by addition of 50 ml. of dry ether; yield, 3.3 g. (62%); m.p. 101–109° (dec.); Beilstein test, negative. Recrystallization from methanol-ether, ether being added only up to the point of crystallization, produced m.p. 102–108° dec.).

C. *Dodecylmethylthetin p-toluenesulfonate.* Although for preparative purposes the method of Section VA would be used, the following is of interest.

An equimolar mixture of dodecylmethylthetin and *p*-toluenesulfonic acid was heated in acetone for 1.25 hr. Cooling produced silky needles of dodecylmethylthetin *p*-toluenesulfonate in 56% yield; m.p. 113–133° (dec.), not depressed by a sample prepared by the aforementioned method.

VII. *Decarboxylation of DMT p-toluenesulfonate.* An example has already been given (Section VB) where decarboxylation occurred during the course of the reaction. Other examples are outlined in succeeding sections.

A. *With Amberlite IR-4B.* A 4-g. sample of DMT *p*-toluenesulfonate was heated in 750 ml. of refluxing acetone for 2 hr. in the presence of 24 g. of acetone-washed Amberlite IR-4B. Filtration and cooling produced 2.5 g. (70%) of dodecyldimethylsulfonium *p*-toluenesulfonate; m.p. 163–170°.

B. *With piperidine.* Reaction as in A, with one small drop of piperidine in place of the Amberlite resin and concentration of the reaction mixture, produced 3.5 g. (97%) of the decarboxylated product, m.p. 163–169°.

C. *With DMT.* Reaction of equivalent amounts of DMT and DMT *p*-toluenesulfonate under conditions of Section A produced a 60% yield of the decarboxylated product; m.p. 163–169.5°.

D. *With acetic acid.* Reaction as in A, with one drop of acetic acid in place of the Amberlite resin and concentration to one-fifth volume, gave a 62% recovery of impure starting material. A second crop consisted of 27% of dodecyldimethylsulfonium *p*-toluenesulfonate, m.p. 163.5–169.5°.

E. *No catalyst.* When DMT *p*-toluenesulfonate was heated for 1 hr. in refluxing acetone without a catalyst, no reaction was apparent and the starting material was recovered unchanged. However, after 6 hr., a 94% yield of the decarboxylated product, m.p. 163.5–169°, was obtained.

VIII. *Decarboxylation of dodecylmethyl-α-propiothetin p-toluenesulfonate* (II). A. *No catalyst.* A solution of 4.0 g. of the thetin salt in 1400 ml. of boiling acetone was sampled at intervals of 1, 5, and 7 hr. The crystals separating from the concentrated (1/3 vol.) sample melted 2.5°, 5.5°, and 6.5° lower, respectively, than the original pure salt, and mixtures with the latter were undepressed. The recovered crystalline material (3.5 g.) was shown by infrared analysis to consist almost exclusively of thetin salt (strong band at 1710 $cm.^{-1}$).

B. *With piperidine.* A solution of 2 g. of the salt in 750 ml. of boiling acetone containing 6 drops of piperidine was sampled after 3 hr.; a 5.5° drop in melting point had occurred. After 6 hr., crystallization did not readily occur. The solvent was evaporated and the residue washed with ether to give 1.55 g. of colorless crystals, m.p. 75–88°. The infrared curve, showing the complete absence of thetin salt, strongly resembled that of dodecyldimethylsulfonium *p*-toluenesulfonate.

C. *By heat.* The dry salt was warmed in a test tube at 160° until the evolution of carbon dioxide had ceased. The resulting oil was shown by infrared analysis to contain a substantial amount (20–30%) of non-decarboxylated thetin salt. Under the same conditions decarboxylation of dodecylmethylthetin *p*-toluenesulfonate is essentially complete.

*Acknowledgment.* The author is indebted to D. W. Stewart and Thelma J. Davis, of these Laboratories, for infrared analyses.

ROCHESTER 4, N. Y.

# Notes

A department for short papers of immediate interest.

## The Three Symmetrical Hydrazophenols

M. Khalifa and (in part) W. H. Linnell

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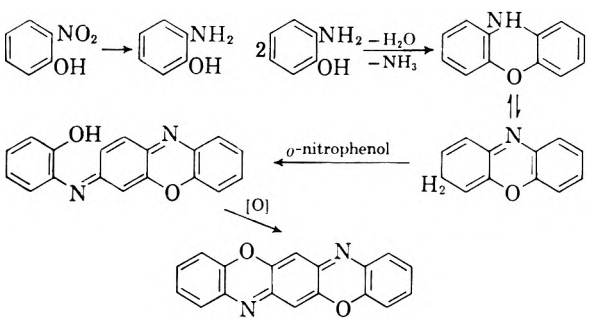
*p*-Hydrazophenol could not be prepared by the method reported for the ortho isomer.[1] However, acyl derivatives of the three hydrazophenols were obtained by reducing the corresponding azo or azoxy compounds according to Jacobson's method.[2] In the course of the reduction we have observed that substituents which increase the electron density of the azo- group favor reductive fission, while those which lower this density or at least do not increase it above that of azobenzene favor the reduction to the hydrazo stage only. The same applies to Jacobson's reported results.[2,3]

The intermediate azo- and azoxyphenols were prepared from the corresponding nitrophenols according to Willstatter's fusion method.[4] The formation of such compounds probably takes place through the reduction[5] of part of the nitrophenol to aminophenol and condensation of the latter with the nitro-body giving rise to the azoxy compound which may be reduced further to the azo compound. That such a mechanism is possible is supported by the fact that azoxy and azo compounds are prepared by fusing aromatic amines together with aromatic nitro compounds in the presence of powdered caustic alkalis.[6-8]

The formation of the by-product triphenodioxazine from *o*-nitrophenol probably takes place according to the following scheme:




Triphenodioxazine

The above scheme besides being in conformity with the one given for the formation of the azo and azoxy compounds gives a reasonable answer to the evolution of ammonia in the course of the fusion process. This suggested scheme finds support in the formation of phenoxazine[9] through the condensation of *o*-aminophenol and catechol and in the fact that triphenodioxazine itself had been prepared from 4,6-diaminoresorcinol and *o*-aminophenol[10]

### EXPERIMENTAL[11]

*2,2'-Dihydroxyazobenzene and 4,4'-dihydroxyazobenzene* were prepared according to a method described in the literature.[4]

*3,3'-Dihydroxyazoxybenzene* was obtained instead of the corresponding azo compound when the method[4] reported for the preparation of the latter was adopted.

*Acetylation and benzoylation.* The above compounds were acetylated by acetyl chloride in presence of glacial acetic acid and benzoylated according to Schotten-Baumann method of benzoylation. Yields were almost theoretical.

*Reduction.* The acyl derivatives were reduced in 80 to 90% yields by Jacobson's procedure[2] which was modified by stirring briskly the reaction mixture and concentrating the alcoholic filtrate[12] containing the hydrazo compound before its dilution with cold water.

*Acknowledgment.* Thanks are due to Messrs. J. R. Geigy of Basle, Switzerland, for the microanalyses of the new compounds and to Prof. Y. M. Abou-Zeid of the Faculty of Pharmacy, Cairo University for the facilities during this work.

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(1) Sen and Sadasivam, *J. Indian Chem. Soc.*, **9**, 405 (1932).
(2) Jacobson and Steinbrenk, *Ann.*, **303**, 384 (1898).
(3) Jacobson and Hönigsberger, *Ber.*, **36**, 4093 (1903).
(4) Willstatter and Benz, *Ber.*, **39**, 3495 (1906).
(5) The hydrogen for the reduction probable comes from the breaking down of part of the starting material.
(6) Martynoff, *Compt. rend.*, **223**, 747 (1946).
(7) Martynoff, *Compt. rend.*, **225**, 1332 (1947).
(8) Sidgwick, *Organic Chemistry of Nitrogen*, Oxford University Press, 1942, p. 436.
(9) Ref. 8, p. 75.
(10) Seidel, *Ber.*, **23**, 188 (1890).
(11) All melting points recorded here are uncorrected.
(12) The filtrate containing diacetyl-*o*-hydrazophenol instantaneously acquired a green coloration probably due to contamination with the very unstable *p*-diaminohydroquinone resulting from triphenodioxazine which is a by-product in the preparation of *o*-azophenol.

TABLE I

ACYL DERIVATIVES OF AZO- AND AZOXYPHENOLS

| Acryl Derivative | Solvent of Crystln.[a] | Color | M.P., °C. | Formula | Analysis: Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|---|
| 2,2′-Diacetoxyazobenzene | A | Orange | 154–155 | $C_{16}H_{14}N_2O_4$ | 64.42 | 64.23 | 4.69 | 4.58 | 9.39 | 9.45 |
| 3,3′-Diacetoxyazoxybenzene | B | Reddish brown | 102–103 | $C_{16}H_{14}N_2O_5$ | 61.14 | 61.16 | 4.45 | 4.58 | 8.92 | 8.82 |
| 4,4′-Diacetoxyazobenzene[b] | C | Golden yellow | 198–199 | $C_{16}H_{14}N_2O_4$ | | | | | | |
| 2,2′-Dibenzoyloxyazobenzene | A | Orange | 172–173 | $C_{26}H_{18}N_2O_4$ | 73.93 | 73.88 | 4.26 | 4.20 | 6.63 | 6.67 |
| 3,3′-Dibenzoyloxyazoxybenzene | B | Yellowish brown | 174–175 | $C_{26}H_{18}N_2O_5$ | 71.23 | 71.10 | 4.11 | 4.06 | 6.39 | 6.47 |
| 4,4′-Dibenzoyloxyazobenzene[b] | A | Reddish yellow | 210–211 249–251 | $C_{26}H_{18}N_2O_4$ | | | | | | |

[a] A, benzene; B, alcohol; C, glacial acetic acid. [b] Willstatter and Benz, *Ber.*, **40**, 1582 (1907).

TABLE II

ACYL DERIVATIVES OF THE THREE SYMMETRICAL HYDRAZOPHENOLS

| Acyl Hydrazophenol | Solvent of Crystln.[a] | M.P., °C. | Formula | Analysis: Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found | Nitrogen, % Calcd. | Nitrogen, % Found |
|---|---|---|---|---|---|---|---|---|---|
| Diacetyl-*o*-hydrazophenol[b] | A | 146–147 | $C_{16}H_{16}N_2O_4$ | 64.00 | 64.09 | 5.33 | 5.11 | 9.33 | 9.36 |
| Diacetyl-*m*-hydrazophenol | A | 136 | $C_{16}H_{16}N_2O_4$ | 64.00 | 64.05 | 5.33 | 5.27 | 9.33 | 9.38 |
| Diacetyl-*p*-hydrazophenol-[c] | B | 138–140 | $C_{16}H_{16}N_2O_4$ | 64.00 | 63.81 | 5.33 | 5.17 | 9.33 | 9.29 |
| Dibenzoyl-*o*-hydrazophenol | C | 169–170[d] | $C_{26}H_{20}N_2O_4$ | 73.58 | 73.52 | 4.71 | 4.64 | 6.60 | 6.50 |
| Dibenzoyl-*m*-hydrazophenol | A | 146–147 | $C_{26}H_{20}N_2O_4$ | 73.58 | 73.72 | 4.71 | 4.75 | 6.60 | 6.69 |
| Dibenzoyl-*p*-hydrazophenol | C | 188–190 | $C_{26}H_{20}N_2O_4$ | 73.58 | 74.11 | 4.71 | 4.65 | 6.60 | 6.56 |

[a] A, aq. alc.; B, benzene–pet. ether (80–100°); C, alcohol. [b] Purified by refluxing its alcoholic solution with charcoal in an atmosphere of nitrogen. [c] Hydrolysis with 5% sodium hydroxide did not yield the free hydrazophenol, but instead afforded the oxidation product viz. *p*-azophenol. [d] Ref. 1, m.p. 186°.

## Reduction of Organic Compounds by Lithium in Low Molecular Weight Amines. V. The Mechanism of Formation of Cyclohexanes. Utility of the Reducing Medium in Effecting Stereospecific Reductions

ROBERT A. BENKESER, JAMES J. HAZDRA, ROGERS F. LAMBERT, AND PATRICK W. RYAN

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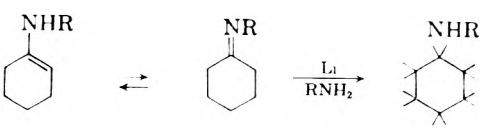
It was reported in a previous paper[1] in this series that reduction of aromatic nitro compounds with the lithium-amine reagent stops rather cleanly at the aromatic amine. On the other hand, aromatic amines (primary, secondary, or tertiary) are reduced by excess lithium in ethylamine to cyclohexane derivatives principally. This unusual behavior was shown to be due to the generation of alkyl amide ions during the reduction of the nitro group. These maintain the aromatic amino group as the anilide ion which resists further reduction. However, when one starts with an aromatic amine, the ring is reduced rapidly at first, since little or no amide ion is present, and hence reasonably good yields of reduction product can be realized in many instances.

In extending this work, we have found that all three isomeric toluidines are reduced to methylcyclohexylamines with excess lithium. In every case the most stable cyclohexane isomer was the predominant product (all substituent groups equatorial). Hence it appears that the lithium-amine reducing system should prove a valuable tool in the stereospecific synthesis of certain cyclohexanes.[2]

It was suggested previously[1] that complete saturation of the aromatic ring of certain 1° and 2° amines occurs because of the facile reduction of imine intermediates, arising from the isomerization of 1-aminocyclohexene isomers (enamines). Fur-




(1) R. A. Benkeser, R. F. Lambert, P. W. Ryan, and D. G. Stoffey, *J. Am. Chem. Soc.*, **81**, 228 (1959).

(2) We have observed also that certain of the xylidines undergo what appear to be similar stereospecific reductions. Details of these, and other stereospecific reductions will be published later.

thermore, any 3- or 4-olefin isomers formed in such reductions would undergo ready reduction as well.

This hypothesis has now been substantiated by a detailed study of the reduction of *N*-methylaniline and *N*,*N*-dimethylaniline. In the latter case, through the use of four equivalents of lithium as the reducing agent, a 40% yield of cyclohexanone was obtained following hydrolysis. Previous work[1] showed that cyclohexanone arises in this case only from hydrolytic cleavage of the enamine, 1-dimethylaminocyclohexene. Thus, a minimum yield of 38% of this olefin in the reduction mixture is indicated. Analysis of the basic fraction of the hydrolysate by gas chromatography indicated an olefin distribution of about 33% 3-dimethylaminocyclohexene and 62% 4-dimethylaminocyclohexene. When the reduction was repeated using an excess of lithium, a 35% yield of cyclohexanone was again obtained following hydrolysis. Analysis of the basic fraction of the hydrolysate indicated that virtually all of the 3- and 4-olefin isomers had been removed by reduction, with cyclohexyldimethylamine remaining as the principal product. When *N*-methylaniline was reduced with excess lithium only a trace of cyclohexanone could be detected in the hydrolysate of the reduction product. Thus it is clear that the enamine arising from *N*-methylaniline is reduced readily in this system, while the enamine from *N*,*N*-dimethylaniline is not. Reduction *via* an imine intermediate in the former case is clearly indicated.

These findings immediately raised the issue of whether the saturated products reported in earlier work[3] also were arising from a 1,2-reduction of 3- and 4-olefin isomers hitherto unreported. Accordingly a systematic study of the reduction of toluene, ethylbenzene, cumene, and *t*-butylbenzene was undertaken using both four equivalents of metal as well as an excess. The products were analyzed by gas chromatography (a technique not avilable when the initial work[3] on this reduction was done) and are listed in Table I.

TABLE I

REDUCTION OF AROMATIC HYDROCARBONS WITH LITHIUM IN METHYLAMINE[a,b]

| | 1-Alkylcyclohexene | 3 + 4-Alkylcyclohexene | Alkylcyclohexane | B.P. Range |
|---|---|---|---|---|
| Toluene | 59 (58)% | 37 (23)% | 4 (18)% | 100–110° |
| Ethylbenzene | 62 (60) | 38 (30) | 0 (10) | 130–136 |
| Isopropylbenzene | 46 (46) | 54 (44) | 0 (10) | 150–156 |
| *t*-Butylbenzene | 43 (40) | 57 (52) | 0 (9) | 169–172 |

[a] The olefin mixtures were analyzed by gas chromatography utilizing a 14-ft. column packed with either dibutylphthalate, di-*n*-octylphthalate or β,β′-oxydipropionitrile on firebrick. [b] The first percentage listed in each case was obtained using four equivalents of lithium. The percentage in parentheses resulted from six equivalents of lithium.

(3) R. A. Benkeser *et al.*, *J. Am. Chem. Soc.*, **77**, 3230 (1955) and **77**, 6042 (1955).

It becomes immediately apparent from Table I that appreciable quantities of 3- and 4-alkylcyclohexenes do form under the conditions employed.[4] It is also apparent that the cyclohexanes which are formed in the presence of excess lithium arise principally from a reduction of the 3- and 4-olefins rather than from reduction of the 1-isomer. As further confirmation of this point several alkylcyclohexenes were reduced under comparable conditions with two equivalents of lithium in methylamine (Table II). It is obvious that the rate of reduction of the 1-alkyl isomers is very slow relative to that of the 3- and 4-isomers. This is understandable in terms of an electronic influence, wherein the inductive effect of the alkyl group slows down the uptake of electrons by the double bond.[5]

TABLE II

REDUCTION OF 1-ALKYLCYCLOHEXENES WITH LITHIUM IN METHYLAMINE[a,b]

| Compound | Reaction Time, Hr. | Alkylcyclohexane, % |
|---|---|---|
| 1-Methylcyclohexene | 3 | 4 |
| 4-Methylcyclohexene | 3 | 59 |
| 1-Isopropylcyclohexene | 3 | 1 |
| 4-Isopropylcyclohexene | 3 | 21 |
| | 5 | 39 |

[a] Analysis was by gas chromatography. See (a) of Table II. [b] Two equivalents of lithium were employed in every case.

Another interesting piece of information which can be gleaned from Table I is that the percentage of 1-alkylcyclohexene gradually drops as the +I effect (and also steric bulk) of the substituent alkyl group increases. The significance of this observation is presently under investigation.

## EXPERIMENTAL

*Reduction of the toluidines with lithium in ethylamine.* To a mixture of 10 g. (1.4 g. atoms) of lithium in 300 ml. of ethylamine was added 21 g. (0.2 mole) of the toluidine. The mixture was stirred for 6 hr. The remaining lithium was then removed and the mixture hydrolyzed by the slow addition of 200 ml. of water. The ethylamine was evaporated with a steam cone and the product was dissolved in ether, dried, and distilled through a Todd column.

*o-Toluidine.* A 20% conversion (4.5 g.) into *trans*-2-methylcyclohexylamine was obtained (b.p. 151–153°, $n_D^{20}$

(4) It is possible that the percentages of 1-isomer reported in our earlier work (ref. 3) were high in some cases since the 1-isomer may have been contaminated with the 3- and 4-olefins. The conditions employed in these early reductions, however (excess lithium, prolonged reaction time), would tend to diminish the amounts of 3- and 4-olefins relative to the 1-isomer. There are indications that other techniques (to be reported later) can be employed as well to diminish the quantity of 3- and 4-isomer. We are at present reevaluating by gas chromatography some of the percentage yields we reported in our earlier work (ref. 3).

(5) A. J. Birch, *J. Chem. Soc.*, 430 (1944).

1.4547), and 10.5 g. (50%) of starting material was recovered. The product formed a benzamide derivative melting at 148–149.5° when crude, and at 150–150.5° after recrystallization from 95% ethanol (reported[6] m.p. for the benzamide, 151°). Its phenylthiourea derivative melted at 150–151° (reported[7] m.p. for phenylthiourea 145°).

*Anal.* Calcd. for $C_{14}H_{20}N_2S$ (phenylthiourea): C, 67.73; H, 8.13. Found: C, 67.76; H, 8.42.

*m-Toluidine.* A 41% conversion (9 g.) into *cis*-3-methylcyclohexylamine was obtained (b.p. 149–150°, $n_D^{20}$ 1.4512) and 7 g. (33%) of starting material was recovered. The product formed a benzamide derivative melting at 126–127° (reported[8] m.p. 124.5–125.8°) and a phenylthiourea melting at 139–140° (reported[7,9] m.p. 105–106°).

*Anal.* Calcd. for $C_{14}H_{20}N_2S$ (phenylthiourea derivative): C, 67.73; H, 8.13; N, 11.20. Found: C, 67.80; H, 8.40; N, 11.23.

*p-Toluidine.*[1] A 49% conversion (11 g.) into *trans*-4-methylcyclohexylamine was obtained ($n_D^{20}$ 1.4509),[1] and 3 g. (14%) of starting material was recovered.

*Alkylbenzenes* (Table I). The alkylbenzene reductions were carried out in the usual fashion with 500–600 ml. of methylamine, 0.34 mole of aromatic and either 4 or 6 equivalents of lithium. In the cases where 4 equivalents of metal were used, the reaction was allowed to proceed for approximately 3 hr. With six equivalents the reaction time was about 6 hr.

*Alkylcyclohexenes* (Table II). The alkylcyclohexenes were reduced in approximately 300 ml. of methylamine using 0.2 mole of olefin and two equivalents of lithium.

*N,N-Dimethylaniline.* (*a*) (*4-Equivalents of lithium*). The reduction of 41.2 g. (0.34 mole) of *N,N*-dimethylaniline by 10.2 g. (1.45 g. atoms) of lithium in 500 ml. of methylamine was carried out in the usual manner. After 2 hr. the solution was colorless, and the solvent was then allowed to evaporate. Five hundred ml. of water was added and then 10% hydrochloric acid until the aqueous layer was acidic. This aqueous layer was then extracted thoroughly with ether and the ether solution dried over anhydrous sodium sulfate (extract No. 1). The acidic solution remaining was made basic with solid sodium hydroxide, and the basic solution was then extracted with ether. This extract (extract No. 2) was also dried over anhydrous sodium sulfate. Subsequent distillation of extract No. 1 through a Todd column, gave 13.2 g. (40%) of cyclohexanone (b.p. 154–155°; $n_D^{21}$ 1.4490). Distillation of extract No. 2 gave 13.7 g. of material boiling at 162–164° ($n_D^{22}$ 1.4673). An infrared spectrum of this cut showed an olefin band at 6 microns. Subsequent analysis of this material by gas chromatography (carbowax "1500" on firebrick packing) showed it to contain approximately 5% *N,N*-dimethylcyclohexylamine, 33% 3-dimethylaminocyclohexene and 62% 4-dimethylaminocyclohexene.

(*b*) *Excess lithium.* The reduction was repeated with 41.2 g. of *N,N*-dimethylaniline (0.34 mole) and 16.8 g. (2.4 g. atoms) of lithium in 500 ml. of methylamine. The reaction time was 7 hr., after which the product was worked up as described above. Distillation of extract No. 1 gave 11.7 g. (35%) of cyclohexanone (b.p. 154–155°, $n_D^{21}$ 1.4492). Distillation of extract No. 2 gave 11.5 g. (27%) of cyclohexyldimethylamine (b.p. 159–161°, $n_D^{22}$ 1.4540). A gas phase chromatogram showed the latter to be only slightly contaminated with 3- and 4-dimethylaminocyclohexenes.

*N-Methylaniline* (*excess lithium*). The product from the reduction of 36.4 g. (0.34 mole) of *N*-methylaniline with 16.8 g. (2.4 g. atom) of lithium in 500 ml. of methylamine for 7 hr. was worked up as described above. Distillation of extract No. 1 gave 1 g. of residue whose infrared spectrum showed no carbonyl band. Distillation of extract No. 2 gave 6.1 g. (16%) of *N*-methylcyclohexylamine (b.p. 148–150°, $n_D^{24}$ 1.4562) and 22.7 g. (62%) of recovered *N*-methylaniline (b.p. 195–196°, $n_D^{24}$ 1.5685). A gas phase chromatogram and an infrared spectrum of the *N*-methylcyclohexylamine showed it to be slightly contaminated with cyclohexanone.

*Acknowledgment.* The authors are grateful to the Lithium Corp. of America and the National Science Foundation whose financial assistance made this work possible.

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(6) D. S. Noyce and F. W. Bachelor, *J. Am. Chem. Soc.*, **74**, 4577 (1952).

(7) A. Skita, *Ber.*, **56**, 1014 (1923).

(8) D. S. Noyce and R. J. Nagle, *J. Am. Chem. Soc.*, **75**, 127 (1953).

(9) It should be noted that Skita's assignment of configuration for *cis*- and *trans*-3-methylcyclohexylamine was reversed. See ref. 8.

## Substituted 12-Aminobenz[*a*]acridines

A. K. CHATTERJEE

*Received October 9, 1958*

The activity of a number of substituted 7-aminobenz[*c*]acridines against *E. histolytica in vitro* and in intestinal amaebiasis in rats has been reported by Elslager and co-workers[1,2] and by Short and co-workers.[3] The present communication deals with the preparation of a number of substituted 12-aminobenz[*a*]acridines for trials against *E. histolytica*.

The acridine derivatives were obtained by the interaction of 0.005 mole of 12-chlorobenz[*a*]acridine, prepared from *N*-(2-naphthyl)anthranilic acid according to Bachman and Picha,[4] with a slight excess of the appropriate amine in phenol at 120 for a period of 2 hr. in the presence of powdered sodium carbonate to neutralize the liberated hydrochloric acid. The reaction mixture was poured into an excess of an aqueous solution of potassium hydroxide and the sticky precipitate, on solidification, was filtered off and dried after washing with water. The dry solid was dissolved in ether and the ether extract was treated with hydrogen chloride gas to precipitate the hydrochloride, or with a solution of salicylic acid in ether to precipitate and salicylate. The salt was purified by crystal-

(1) E. F. Elslager, A. M. Moore, F. W. Short, M. J. Sullivan, and F. H. Tendick, *J. Am. Chem. Soc.*, **79**, 4699, (1957).

(2) E. F. Elslager, F. W. Short, M. J. Sullivan, and F. H. Tendick, *J. Am. Chem. Soc.*, **80**, 451, (1958).

(3) F. W. Short, E. F. Elslager, A. M. Moore, M. J. Sullivan, and F. H. Tendick, *J. Am. Chem. Soc.*, **80**, 223, (1958).

(4) G. B. Bachman & G. M. Picha, *J. Am. Chem. Soc.*, **63**, 1599 (1946).

TABLE I

SUBSTITUTED 12-AMINOBENZ[*a*]ACRIDINES

| No. | Base | Salt | Crystallizing Solvent | M.p.[a] of Salt | Carbon, % Calcd. | Carbon, % Found | Hydrogen, % Calcd. | Hydrogen, % Found |
|---|---|---|---|---|---|---|---|---|
| 1 | 12-*p*-Chloroanilinobenz[*a*]acridine | HCl | Methanol | 265 | 70.58 | 70.96 | 4.10 | 3.98 |
| 2 | 12-*p*-Iodoanilinobenz[*a*]acridine | $C_7H_6O_3$[b] | Benzene-ethanol | 212 | 61.64 | 61.99 | 3.60 | 3.22 |
| 3 | 12-Anilinobenz[*a*]acridine | $3\,C_7H_6O_3$ | Benzene | 220 | 71.93 | 71.72 | 4.63 | 4.86 |
| 4 | 12-*p*-Toluidinobenz[*a*]acridine | $2\,C_7H_6O_3$ | 50% Ethanol | 210 | 74.75 | 75.03 | 4.92 | 5.23 |
| 5 | 12-*m*-Chloroanilinobenz[*a*]acridine | $C_7H_6O_3$, $2H_2O$[c] | Chloroform | 190 | 68.12 | 68.00 | 4.72 | 4.48 |
| 6 | 12-*m*-Iodoanilinobenz[*a*]acridine | $C_7H_6O_3$ | Ethanol | 185 | 61.64 | 61.85 | 3.60 | 3.30 |
| 7 | 12-*m*-Toluidinobenz[*a*]acridine | $1.5\,C_7H_6O_3$ | Benzene | 195 | 76.53 | 76.90 | 4.99 | 4.97 |
| 8 | 12-*p*-Anisidinobenz[*a*]acridine | $1.5C_7H_6O_3$ | Ethanol | 207 | 74.33 | 74.45 | 4.85 | 4.80 |

[a] All melting points are uncorrected. [b] $C_7H_6O_3$ = salicylic acid. [c] $H_2O$, calcd., 6.81%; found, 6.72%.

lization from a suitable solvent. The data are recorded in Table I.

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## Derivatives of Sulfenic Acids. XXXIII. 2,4-Dinitrophenyl Selenium Trichloride[1]

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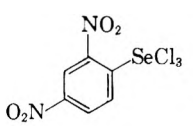
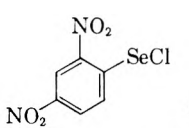
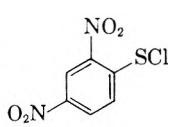
*Received October 27, 1958*

The recent papers of Jenny and co-workers[2] on various selenenyl derivatives prompt us to report a study, carried out some time ago, concerning 2,4-dinitrophenyl selenium trichloride (I).


I


II


III

Our purpose was to prepare 2,4-dinitrobenzeneselenenyl chloride (II) for comparison with the well known sulfur analog,[3] 2,4-dinitrobenzenesulfenyl chloride (III). While numerous selenenyl halides have been reported, including 2,4-dinitrobenzeneselenenyl bromide[4] and 2-nitrobenzeneselenenyl chloride,[5] II has not been described previously.

The synthesis of III is generally carried out by the catalytic chlorinolysis of bis(2,4-dinitrophenyl) disulfide.[6] This procedure, using chlorine gas, did not permit the convenient chlorinolysis of the very insoluble bis(2,4-dinitrophenyl) diselenide. In the course of the work, however, a superior method for cleaving bis(2,4-dinitrophenyl) disulfide was devised, involving the use of sulfuryl chloride and pyridine. This procedure was succesful in the chlorinolysis of the corresponding diselenide, but the product obtained was not the selenenyl chloride (II), but the trichloride (I). The use of sulfuryl chloride as reagent for chlorinolyses of disulfides and diselenides has been previously reported by Behaghel and Seibert.[4a]

Since selenocyanates are known to undergo brominolysis to selenenyl bromides,[7] the direct chlorinolysis of 2,4-dinitrophenyl selenocyanate was attempted. The reaction proceeded smoothly, the product again being the selenium trichloride (I). Further study established that the trichloride is in equilibrium with the monochloride (Equation 1);

$$\underset{\text{I}}{ArSeCl_3} \rightleftharpoons \underset{\text{II}}{ArSeCl} + Cl_2 \qquad (Ar = 2,4\text{-dinitrophenyl}) \quad (1)$$

and that pure I can be prepared by using excess sulfuryl chloride in the chlorinolysis of the selenocyanate or bis(2,4-dinitrophenyl) diselenide; and II results by heating I in an evacuated atmosphere. The reverse reaction was demonstrated by converting the monochloride (II) to trichloride, by reaction of the former with excess chlorine. Such reversible relations of the trichloride and monochloride derivatives have been noted previously, both in the selenium[8] and the sulfur series.[9]

2,4-Dinitrophenyl selenium trichloride (I) is an excellently crystalline solid, which may be stored for long periods without change. As expected, however, I decomposes on heating and does not exhibit a sharp melting point. The bright yellow crystals begin to turn orange at 70°; at 80–85°, chlorine is evolved and at 100°, the whole mass turns to an

(1) The research reported in this document was made possible, in part, through support extended by the Office of Scientific Research, Air-Research and Development Command, under Contract No. AF-49-638-330.

(2) W. Jenny, *Helv. Chim. Acta*, **41**, 317 (1958); G. Hölzle and W. Jenny, *Helv. Chim. Acta*, **41**, 331 (1958), and earlier papers.

(3) N. Kharasch, *J. Chem. Ed.*, **33**, 585 (1956). *Cf.* also R. B. Langford and D. D. Lawson, *J. Chem. Ed.*, **34**, 510 (1957) and reference cited therein.

(4) W. S. Cook and R. A. Donia, *J. Am. Chem. Soc.*, **73**, 2275 (1951). (4a) *Cf.* also O. Behaghel and H. Siebert, *Ber.*, **66**, 708 (1933).

(5) N. Kharasch, S. J. Potempa, and H. L. Wehrmeister, *Chem. Revs.*, **39**, 269 (1946). *Cf.* also ref. 3a.

(6) N. Kharasch, G. I. Gleason, and C. M. Buess, *J. Am. Chem. Soc.*, **72**, 1796 (1950).

(7) O. Behaghel and H. Seibert, *Ber.*, **65B**, 812 (1932).

(8) O. Behaghel and K. Hofmann, *Ber.*, **72**, 582 (1939).

(9) Houben-Weyl, "Methoden der Organischen Chemie," 4th ed., Vol. IX, p. 270, Georg Thieme Verlag, Stuttgart, Germany (1955).

orange melt. The proportion of II, in equilibrium with I was not estimated. In cyclohexane there is no appreciable apparent deviation from Beer's law at selected wave lengths, at room temperature, suggesting that the proportion of II in this solvent, at room temperature, is probably fairly low.

The equilibrium of Equation 1 and the reactivity of the monochloride are also shown by the fact that the products found when I is treated with various reagents are those expected for the monochloride (II). Thus, reactions of I with cyclohexene, ethanol, acetone, aniline, or dimethylaniline gave high yields of the products expected for the monochloride with these reagents. The product from cyclohexene is undoubtedly *trans*-2-chlorocyclohexyl 2′4′-dinitrophenyl selenide[10]; and with ethanol, I gave ethyl 2,4-dinitrobenzeneselenenate, which was identical with the product reported by Cook and Donia,[4] who prepared it by reaction of the sulfenyl bromide and the alcohol, in the required presence of silver salts to remove hydrogen bromide formed in the reaction. The product from acetone was acetonyl 2,4-dinitrophenyl selenide, while aniline and dimethylaniline, respectively, gave 2,4-dinitrobenzeneselenanilide and 4-dimethylaminophenyl 2′-4′-dinitrophenyl selenide. The reactions to obtain these products were conducted under conditions identical to those which readily yield the corresponding derivatives from the sulfenyl chloride (III).[3] The results therefore suggest that the readily prepared trichloride (I) may be used as the *in situ* precursor for reactions requiring the selenenyl chloride (II). However, if desired, II may be made from I and isolated as a crystalline, reactive substance, which can be kept for extended periods.

As Jenny has shown,[2] the ultraviolet and visible spectra of corresponding sulfur and selenium compounds are nearly superimposable, but with definite shifts in both position of maxima and absorbancy. This is also borne out by the several pairs of sulfur and selenium compounds whose ultraviolet spectra were compared in this study. In general, the selenium analogs showed a somewhat higher extinction and absorbed at slightly longer wave lengths than the corresponding sulfur analogs. Comparisons of the infrared spectra of these same pairs of compounds also showed them to be practically superimposable with only minor displacements of the bands (in both directions, toward longer and shorter wave lengths). Indeed, the spectral comparisons of analytical samples of the selenium compounds (with authentic sulfur analogs) served as good indications of whether the analytical results could be expected to conform to the calculated values. Samples showing deviations in the infrared patterns invariably failed to give satisfactory elementary analyses.

(10) For the proof of structure of trans-2-chlorocyclohexyl 2′4′-dinitrophenyl sulfide, *Cf.* A. J. Havlik and N. Kharasch, *J. Am. Chem. Soc.*, 78, 1207 (1956). The sulfide and the selenide showed identical x-ray powder diagrams, made with the kind assistance of Dr. J. Donohue.

## EXPERIMENTAL[11]

In view of the toxicities and vile odors of selenium compounds, a powerful hood and scrupulous avoidance of contact was assured throughout the work. To avoid accumulation, preparative runs involving possible volatilization were generally conducted on alternate days.

*Chlorinolysis of bis(2,4-dinitrophenyl) disulfide by sulfuryl chloride in presence of pyridine.* The disulfide (100 g.) was pulverized and dried in an oven (80–90°) for 12 hr. It was then suspended in 600 ml. carbon tetrachloride, in a 1-l. flask with a reflux condenser. Sulfuryl chloride (40 ml.) was added, followed by 5 ml. of dry pyridine. The mixture was refluxed (steam bath) for 1 hr., and 50 ml. more sulfuryl chloride was added, in 10 ml. portions, about every half hour. An additional 2 ml. of pyridine was also added during the course of the reaction, which was generally complete in 3 to 5 hr., as shown by the near disappearance of the insoluble disulfide. In some runs, tar may appear at the surface of the reactions mixture; but causes no difficulty.

The hot reaction mixture was treated with *ca.* 5 g. "Norit A" and filtered (hot) through "filter-aid." The filtrate was concentrated and the product collected; 91 g. (m.p. 97–98°). Six g. more were obtained from the mother liquor by further concentration. Total yield: 97 g.; 82.5%.

Runs of up to 500 g. disulfide were made, as above, with minor variations required in time of heating and proportion of pyridine for a particular batch. Yields of 80–90% of good product were obtained in these batches. Similarly as reported by Kharasch, Gleason, and Buess,[6] the mother liquor from one batch can be used advantageously in succeeding runs, to improve the over-all yield of product.[12]

*2,4-Dinitrophenyl selenium trichloride* (I). The above method was adapted to the chlorinolysis of 2,4-dinitrophenyl selenocyanate, as follows. To 200 ml. of redistilled sulfuryl chloride was added 27.2 g. (0.1 mole) of dry 2,4-dinitrophenyl selenocyanate, prepared in 70–75% yields from dinitrochlorobenzene and potassium selenocyanate[13] by the method of Fromm and Martin.[14] The mixture was refluxed for 10 min., filtered hot, and cooled slowly, giving a crop of bright yellow crystals. The liquid was decanted and the crystal crop was dried *in vacuo*, for 24 hr., over a mixture of calcium chloride and sodium hydroxide. Yield 30 g. (86%). The decomposition characteristics of this product were described in the introduction.

*Anal.* Calcd. for $C_6H_3N_2O_4SeCl_3$: C, 20.44; H, 0.85; Cl, 30.15; N, 7.96. Found: C, 20.63; H, 0.88; Cl, 30.39; N, 8.31. Cryoscopic mol. wt. (in benzene): 350 ± 8.5; Calcd. 352.

While the direct chlorination of bis(2,4-dinitrophenyl)-diselenide[15] failed to give I, in suitable yield, reaction of the diselenide with sulfuryl chloride and pyridine gave I.

*Conversion of 2,4-dinitrophenyl selenium trichloride* (I) *to 2,4-dinitrobenzeneselenenyl chloride* (II). The yellow trichloride (0.9665 g.) was placed in an Abderhalden pistol, evacuated to 1 ml. pressure, and heated at the reflux tem-

(11) Melting points were taken on a Fisher-Johns block.

(12) The same procedure, using sulfuryl chloride, was applied advantageously to the synthesis of 2-nitrobenzenesulfenyl chloride, 2-chloro-4-nitrobenzenesulfenyl chloride and benzenesulfenyl chloride. Only very small amounts of pyridine are required in these preparations. In the case of benzenesulfenyl chloride, we prefer not to use any pyridine or solvent, since this gives a product which appears to have better keeping qualities. The excess sulfuryl chloride serves as a good solvent medium for the reaction.

(13) G. R. Waitkins and R. Shutt, *Inorganic Synthesis*, Vol. II, p. 186; John Wiley and Sons Inc., New York, N. Y.

(14) E. Fromm and Martin, *Ann.*, 401, 177 (1917).

(15) D. F. Twiss, *J. Chem. Soc.*, 105, 1672 (1914).

perature of acetone. After 9 hr., a weight loss of 22.65% was observed (calcd. for full conversion of I to II, 21.50%). The resulting orange solid was collected and recrystallized from carbon tetrachloride. The m.p. was 88–89°.

*Anal.* Calcd. for $C_6H_3(NO_2)_2SeCl$: Cl, 12.58. Found: Cl, 13.42.

*2,4-Dinitrophenyl selenium trichloride* (I) *from 2,4-dinitrobenzeneselenenyl chloride.* The orange monochloride (0.3330 g.) was placed in an atmosphere of dry chlorine for 3 days at room temperature. A weight gain of 7.80% was noted, and a somewhat amorphous material resulted. Recrystallization from carbon tetrachloride gave an orange product, which lost chlorine typically at 80–85°, and turned to an orange melt at 100°.

*Anal.* Calcd. for $C_6H_3N_2O_4SeCl_3$: Cl, 30.15. Found: Cl, 30.54.

*Acetonyl 2,4-dinitrophenyl selenide.* 2,4-Dinitrophenyl selenium trichloride (3.52 g., 0.01 mole) was added to 10 ml. of acetone. The mixture was refluxed for 5 min., filtered, cooled, and the yellow product collected and recrystallized from absolute ethanol. The product melted at 116–118°.

*Anal.* Calcd. for $C_9H_8N_2O_5Se$: N, 9.54. Found: N, 9.94.

*Ethyl 2,4-dinitrobenzeneselenate.* Into 10 ml. of absolute ethanol 3.52 g. (0.01 mole) of I was added. Addition of 1 ml. of dry pyridine caused formation of an orange color. The volume of the solution was reduced to one third on the steam bath and the remaining solution cooled, causing deposits of orange needles, which were collected and washed with a few ml. of absolute alcohol. After recrystallizing from absolute alcohol, the product melted at 128–129°, which corresponds exactly to the literature value[4] for the ethyl ester.

*2,4-Dinitrobenzene selenenalide.* Into 15 ml. of dry ether was added 3.52 g. (0.01 mole) of 2,4-dinitrophenyl selenium trichloride. One g. of dry aniline was then added slowly, whereupon a deep red color was noted. The volume was reduced by one fifth and the residue taken up in 50 ml. of 95% ethanol. This was treated with decolorizing charcoal, the mixture was reduced to about two thirds of the original volume and the remaining solution was cooled. The red-orange crystals were collected, washed, and dried; m.p. 187–189°.

*Anal.* Calcd. for $C_{12}H_9N_3O_4Se$: N, 12.41. Found: N, 12.59.

*2-Chlorocyclohexyl, 2,4-dinitrophenyl selenide.* Into 10 ml. of dry cyclohexene, was added 3.52 g. of 2,4-dinitrophenyl selenium trichloride (0.01 mole). The reaction mixture became warm and turned a deeper yellow color. It was let stand for one hour and then, by using a stream of dry air, the solvent was removed. The residue was taken up in 10 ml. of 95% ethanol, filtered, and the filtrate cooled, yielding, 1.10 g. of yellow needles, m.p. 114–115°.

*Anal.* Calcd. for $C_{12}H_{12}N_2O_4ClSe$: N, 7.74. Found: N, 7.47.

The x-ray powder patterns of the selenide and corresponding sulfide were practically identical, indicating similar space distribution of the substituents and size of unit cells; *Cf.* ref. 9.

*4-Dimethylaminophenyl 2,4-dinitrophenyl selenide.* This was prepared from reaction of I (3.5 g.) and dimethylaniline (2 ml.) dissolved in dry benzene (10 ml.) at room temperature. The solution was concentrated and the crude deep red product recrystallized from hot methanol, giving bright red needles, m.p. 194–196°.

*Anal.* Calcd. for $C_{14}H_{13}N_2O_4Se$: N, 11.28. Found: N, 10.88.

*Spectra.* The ultraviolet and infrared absorption spectra of the several pairs of sulfur and selenium compounds encountered in this work are recorded in a catalog of spectra being prepared for publication from this laboratory. The ultraviolet spectra of I and II are defined by the following absorption coefficients, at the wave lengths stated.

2,4-Dinitrobenzenesulfenyl chloride, in ethylene chloride solution; 4180 Å (max.)/2.4 × $10^3$; 3660 Å (min.)/3.5 × $10^3$; 3190 Å (max.)/8.9 × $10^3$; 2930 Å (min.)/6.4 × $10^3$; 2640 Å (max.)/10 × $10^3$.

2,4-Dinitrophenyl selenium trichloride (in cyclohexane); 4180 Å (max.)/4.3 × $10^3$; 3660 Å (min.)/2.4 × $10^3$; 3235 Å (max.)/11.4 × $10^3$; 2921 Å (min.)/5.0 × $10^3$; 2640 Å (max.)/12.6 × $10^3$; 2480 Å (min.)/11.5 × $10^3$.

*Acknowledgment.* We are indebted to Mr. William R. Wilcox for assistance with experiments on the reactions of sulfuryl chloride with bis(2,4-dinitrophenyl) disulfide, to Dr. J. Donohue for help with the x-ray comparisons, to Dr. Adalbert Elek for microanalyses, and to the Office of Scientific Research, Air-Research and Development Command, for partial support of this study.

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## Amination of Tertiary Amines by Hydroxylamine-*O*-sulfonic Acid

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*Received November 3, 1958*

The reaction of chloramine with tertiary amines to form 1,1,1, trisubstituted hydrazinium chlorides has been clearly established.[1] It seemed desirable to us to investigate the possibility of a similar reaction with another compound of the type $NH_2X$ where X represents an electronegative group other than chlorine. We have, therefore, investigated the reactions of hydroxylamine-*O*-sulfonic acid ($NH_2OSO_3H$) with a variety of tertiary amines and have found that *N*-aminating reactions of the type

$$R_3N + NH_2OSO_3H \longrightarrow [R_3NNH_2^+]\,[HSO_4^-]$$

do indeed occur. The present communication reports the results of studies of a series of these reactions. Meuwsen and Gösl have very recently reported a similar reaction with trimethylamine and pyridine.[2]

Since our results show that the reaction of tertiary amines with hydroxylamine-*O*-sulfonic takes place in basic media and that it also occurs with the sodium salt, we may postulate the following equation for the reaction

$$R_3N + H_2NOSO_2O^- \longrightarrow R_3NNH_2^+ + SO_4^=$$

The question as to whether the sulfate or hydrogen sulfate crystallizes undoubtedly depends upon solubility factors as well as the basicity of the individual nitrogen base concerned. In the case of dimethylaniline the hydrogen sulfate is obtained. In all other cases studied where crystallization occurred the sulfate was obtained.

(1) G. Omietanski and H. Sisler, *J. Am. Chem. Soc.*, **78**, 1211 (1956).

(2) A. Meuwsen and R. Gösl, *Angew. Chem.*, 69, 754 (1957).

## EXPERIMENTAL

*Materials.* Hydroxylamine-*O*-sulfonic acid was prepared by the reaction of hydroxylammonium sulfate and chlorosulfonic acid according to the method of Sommer, Schulz, and Nassau.[3] After preparation it was stored in a vacuum desiccator. Commercially available tertiary amines were used, in most instances, without further purification.

*Procedure.* The reactions were carried out by mixing a methanol, ethanol, or water solution of hydroxylamine-*O*-sulfonic acid with a methanol, ethanol, or water solution of the corresponding amine. Where necessary to initiate the reaction, the reaction mixture was heated. After reaction the mixture was allowed to stand at room temperature until the product separated. Occasionally it was necessary to add a non-polar solvent such as chloroform to precipitate the product. The procedures used do not necessarily represent conditions for optimum yields.

All the aliphatic tertiary amines studied react vigorously with solid hydroxylamine-*O*-sulfonic acid or its solution in methanol. Aromatic amines react much more slowly and these reaction mixtures were usually heated, though reaction will occur at room temperature if the reaction mixture is allowed to stand for several days.

Ammonium sulfate and considerable amounts of unidentified tarry materials are obtained as by-products in the reactions with aromatic amines. This results from the fact that hydroxylamine-*O*-sulfonic acid is an oxidizing agent, though a less active one than chloramine.

It was found that the sodium salt of hydroxylamine-*O*-sulfonic acid may also be used as an aminating agent.

*Reaction with trimethylamine.* A solution of 20 g. of hydroxylamine-*O*-sulfonic acid in about 75 ml. of water at 0° was added over a one hour period to a refluxing aqueous solution of 5 molar equivalents of trimethylamine. The reaction mixture was evaporated to a sirup in vacuo and was cooled. The crystals which formed were removed by filtration and repeatedly recrystallized from aqueous ethanol. They were insoluble in ether but readily soluble in water. The product decomposes from 250° to 255°.

*Anal.*[4] Calcd. for $[(CH_3)_3NNH_2]_2SO_4$: C, 29.26%; H, 9.00%; N, 22.75%; S, 13.00%. Found: C, 27.20, 27.41%; H, 9.16, 9.38%; N, 21.29, 21.09%; S, 13.16, 13.27%.

A portion of the salt was converted by metathesis to the hexafluorophosphate. This salt decomposes above 300°.

*Anal.*[4] Calcd. for $[(CH_3)_3NNH_2]PF_6$: C, 16.36%; H, 5.04%; P, 14.07%. Found: C, 16.28, 16.38%; H, 4.98, 5.14%; P, 14.01, 14.13%.

*Reaction with triethylamine.* A solution of 20 g. hydroxylamine-*O*-sulfonic acid in 150 ml. of ice water was added dropwise to a solution of 300 ml. of triethylamine in 300 ml. of water.

The reaction mixture was vacuum evaporated to a sirup. The sirup was heated with excess sodium hydroxide solution to drive off the excess triethylamine. The residue was neutralized with sulfuric acid and evaporated to dryness. The product was separated from the sodium sulfate by ethanol extraction. The alcoholic solution was treated with a saturated alcoholic solution of picric acid. Triethylhydrazinium picrate separated as yellow needles, m.p. 215°,[5] (reported[1] m.p. 214–215°).

*Anal.*[4] Calcd. for $[(C_2H_5)_3NNH_2]C_6H_2O(NO_2)_3$: C, 41.73%; H, 5.54%; N, 20.28%. Found: C, 41.76%; H, 5.61%; N, 20.31%.

Triethylhydrazinium sulfate has been obtained only as a viscous hygroscopic sirup.

*Reaction with dimethylaminoethanol.* To a suspension of 5.6 g. of hydroxylamine-*O*-sulfonic acid in 75 ml. of absolute ethanol was added 22 g. of dimethylaminoethanol. The mixture became hot and soon became homogeneous. When the initial reaction subsided, the mixture was gently boiled for 5 min. and placed in a refrigerator.

Addition of ether caused the solution to become cloudy, and a viscous oil separated; this oil crystallized in platelets after 3 days. This colorless, hygroscopic product weighed 5 g. (66% yield).

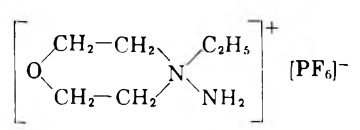
*Anal.*[4] Calcd. for $[HOCH_2CH_2N(CH_3)_2NH_2]_2SO_4$: C, 31.36%; H, 8.56%; N, 18.29%; S, 10.46%. Found: C, 31.00%; H, 8.50%; N, 19.25%; S, 10.69%.

The chloroplatinate salt was prepared by the method of Shriner and Fuson.[6] It melts with decomposition at 207–209°.

*Anal.*[4] Calcd. for $[HOCH_2CH_2N(CH_3)_2NH_2]_2[PtCl_6]$: C, 15.54%; H, 4.24%; N, 9.06%; Cl, 34.37%; Pt, 31.58%. Found: C, 16.04%; H, 4.34%; N, 8.90%; Cl, 33.20%; Pt, 31.90%.

*Reaction with N-ethyl morpholine.* Eastman Kodak Yellow Label *N*-ethylmorpholine was distilled through a Todd column packed with glass helices at a reflux ratio of 20:1, and the fraction distilling at 137.5° was collected. Forty grams of the purified *N*-ethylmorpholine and 50 ml. of water were heated to reflux and a solution of 8 g. of hydroxylamine-*O*-sulfonic acid in 50 ml. of ice water was added slowly and the mixture heated for 30 min. The mixture was allowed to cool and then concentrated by vacuum distillation of the solvent. The concentrated solution was treated with potassium hexafluorophosphate. The resulting solid was recrystallized twice from hot water. The product melted at 178–180° which agrees with the melting point obtained for the hexafluorophosphate obtained from the product of the *N*-ethylmorpholine-chloramine reaction.

*Anal.*[4] Calcd. for




C, 26.05%; H, 5.47%; N, 10.14%; F, 41.28%. Found: C, 25.46%; H, 5.44%; N, 10.25%; F, 41.01%.

*Reaction with dimethylaniline.* To a suspension of 5.6 g. of hydroxylamine-*O*-sulfonic acid in 75 ml. of absolute ethanol was added 30 g. dimethylaniline. There was no exothermic reaction. The mixture was heated to boiling for 10 min. during which time the mixture darkened. When the mixture stood overnight in a refrigerator, pink platelets separated. These platelets were filtered, washed with a small amount of absolute ethanol, and recrystallized from an ethanol-diethyl ether mixture. The product melted at 142–144°. Yield: 4.5 g. (38.5%). The analytical data below indicate that the hydrogen sulfate salt crystallizes in this instance.

*Anal.*[4] Calcd. for $[C_6H_5N(CH_3)_2NH_2]HSO_4$: C, 41.05%; H, 5.98%; N, 11.98%; S, 13.68%. Found: C, 41.01%; H, 5.80%; N, 12.72%; S, 13.72%.

The chloroplatinate salt was prepared. It melts at 156–157° (reported 156.7°,[1] 158–159°[7]).

*Anal* Calcd. for $[C_6H_5N(CH_3)_2NH_2]_2[PtCl_6]$: C, 28.16%; H, 3.84%; N, 8.21%; Pt, 28.61%. Found: C, 28.04%; H, 3.36%; N, 8.09%; Pt, 27.96%.

*Reaction with benzylidene-bis(N,N-dimethylaniline).* To a mixture of 6.6 g. benzylidene-bis(*N*,*N*-dimethylaniline, 50 ml. of methanol, and 50 ml. of a saturated solution of sodium hydroxide in methanol was added 5.6 g. of hydroxylamine-*O*-sulfonic acid dissolved in 25 g. methanol. There was a vigorous reaction. The reaction mixture was heated for 30 min. and filtered and washed with methanol. The combined fil-

(3) F. Sommer, O. Schulz, M. Nassau, *Z. anorg. allgem. Chem.*, **147**, 142 (1925).

(4) Microanalysis by the Clark Microanalytical Laboratory, Urbana, Ill.

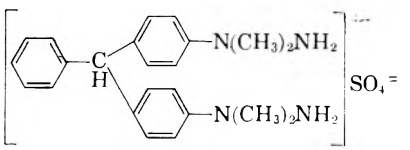
(5) All melting points are uncorrected.

(6) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th Edition, John Wiley and Sons, Inc., 1956, p. 230.

(7) B. K. Singh, *J. Chem. Soc.*, **105**, 1986 (1914).

trates were evaporated to dryness and the residue shaken with a 50/50 (by volume) mixture of water and ether. The aqueous layer was treated with Norit, and evaporated to dryness. The residue was taken up in isopropyl alcohol and reprecipitated with ethyl acetate. Weight of product: 2 g. (24% yield) m.p. (after recrystallization) 193–194°.

*Anal.*[4] Calcd. for




C, 60.24%; H, 6.59%; N, 12.22%; S, 6.99%. Found: C, 56.69%; H, 6.20%; N, 11.76%; S, 6.97%.

The chloroplatinate salt was prepared.

*Anal.*[4] Calcd. for $[C_{23}H_{30}N_4PtCl_6]$: C, 35.85%; H, 3.92%; N, 7.27%; Cl, 27.61%; Pt, 25.33%. Found: C, 36.27%; H, 4.17%; N, 7.01%; Cl, 24.19%; Pt, 25.24%.

*Reaction of sodium hydroxylamine-O-sulfonate with dimethylaniline.* To a methanolic solution of 5.6 g. hydroxylamine-*O*-sulfonic acid was added 6.2 g. sodium carbonate monohydrate. Carbon dioxide was immediately evolved. Dimethylaniline (6 g.) was added to the suspension of the sodium salt. The mixture was heated for 30 min. and filtered hot to remove inorganic salts. Addition of chloroform to the methanolic solution caused gradual precipitation of a dark colored product. Recrystallization of the dark material from ethanol–diethyl ether acidified with sulfuric acid produced 4.5 g. of pink platelets identical to those obtained by reaction of the free acid with the amine (38.5% yield).

*General characteristics of the hydrazinium sulfates.* The quaternized hydrazinium sulfates are colorless crystalline compounds, very soluble in water and generally insoluble in organic solvents. Those prepared from aminoalcohols are very hygroscopic and difficult to crystallize. The products from *N*-(2-hydroxyethyl) pyrrolidine and triethanolamine resisted all attempts at crystallization and were obtained only as viscous oils.

It was shown that hydroxylamine-*O*-sulfonic acid also reacts with *N*,*N*-diethyl cyclohexylamine, 3-dimethylamino propylamine, tri-*n*-heptylamine, *N*,*N*-dimethyl dodecylamine, but the hydrazinium salts were not isolated.

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## New Simple Preparation of Hexaphenylcyclotrisiloxane

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*Received November 10, 1958*

Hexaphenylcyclotrisiloxane (I) has usually been prepared by the method of Burkhard[1] which involves condensation of diphenylsilanediol in the presence of hydrochloric acid as a catalyst.

In separate papers the author has reported two methods[2] for the preparation of I directly from diphenyldichlorosilane. It is found now that I can be obtained easily from the reaction of diphenyldichlorosilane with ammonium thiocyanate dissolved in acetone.

Stoichiometry supports the following equation:

$$(C_6H_5)_2SiCl_2 + 2NH_4CNS + H_2O \longrightarrow {}^1/_3[(C_6H_5)_2SiO]_3 + 2NH_4Cl + 2HCNS$$

Although the details of reaction mechanism are not yet clear, the acidity of by-products including ammonium chloride would cause the formation of trimer in good yields.

### EXPERIMENTAL

*Reagents.* Ammonium thiocyanate was purified by recrystallization from methanol followed by drying in vacuum. Highest purity diphenyldichlorosilane was received from the Shin-etsu Chemical Industrial Company. Reagent grade acetone was used without further purification.

*Preparation of trimer.* In a 2 liter, 3-necked flask equipped with reflux condenser and dropping funnel in which 150 g. of diphenyldichlorosilane dissolved in 200 ml. of acetone had been placed, was placed 95 g. of powdered ammonium thiocyanate and 1000 ml. of acetone. When ammonium thiocyanate was dissolved by heating on a water bath, addition of silane solution portionwise immediately precipitated ammonium chloride as a fine white powder. After the addition was complete, the mixture was heated 10 min. further under reflux. After cooling, the product was filtered rapidly under suction and the precipitate was washed with a small amount of fresh acetone; 62 g. (99%) of ammonium chloride was obtained after drying. The filtrate then was transferred to a separate flask and was refluxed gently for about 1 hr. after the addition of 20 ml. of distilled water. The yellowish transparent product was transferred in a clean crystallizing dish and was concentrated to about 100 ml. on a water bath; a yellowish crystalline mass mixed with oily product having a pungent odor was obtained upon cooling. The crystalline mass was rinsed several times with a small amount of methanol and was recrystallized from ethanol-benzene (1:1); crude trimer was obtained as white shiny platelets melting at 187–188°. Further purification was effected by recrystallization from purified ethyl acetate; 108 g. (92%) of pure trimer was obtained as elongated hexagonal plates melting at 189.6°.

*Anal.* Calcd. for $C_{36}H_{30}Si_3O_3$: Si, 14.16; C, 72.68; H, 5.09; mol. wt., 594. Found: Si, 14.1; C, 72.5; H, 4.9; mol. wt., 588 (benzene), 579 (camphor).

The x-ray powder pattern data were in complete agreement with those given by Hyde and coworkers.[3]

*Acknowledgment.* The author gratefully acknowledges the helpful suggestions given by Dr. Fumio Hirata, the chief professor of this college.

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(1) C. A. Burkhard, *J. Am. Chem. Soc.*, **67**, 2173 (1945).

(2a) From oxygenation in acetone upon standing: *J. Org. Chem.*, **23**, 1213 (1958); *J. Chem. Soc. Japan (Ind. Chem. Sect.)*, **61**, 478 (1958).

(2b) From the reaction of diphenyldichlorosilane with formamide: *J. Chem. Soc. Japan (Ind. Chem. Sect.)*, **62**, 148 (1959).

(3) J. F. Hyde, L. K. Frevel, H. S. Nutting, P. S. Petrie, and M. A. Purcell, *J. Am. Chem. Soc.*, **69**, 488 (1947).

## Chemical Modification of Cellulose. Reaction of Cellulose Xanthate with β-Propiolactone[1]

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*Received November 12, 1958*

Although of primary commercial usefulness as a method for solubilizing cellulose for subsequent regeneration to form rayon, cellophane, and other cellulose products, cellulose xanthate, nevertheless possesses a high degree of chemical reactivity. In addition to the complex reactions that take place during ripening, viscose is reported to undergo a number of other chemical transformations. For example, when viscose or sodium cellulose xanthate (I), $C_{cell}$—OCSSNa, reacts with alkyl halides (or sulfates),[2] iodine, sodium chloroacetate,[3] aniline,[4] arenediazonium chloride,[5] or acrylonitrile[6] the products, respectively, are xanthic esters $C_{cell}$—OCSSR, a "disulfide" ($C_{cell}$—OCSS—)$_2$, an acetic derivative $C_{cell}$—OCSSCH$_2$COONa, a N-substituted thiourethan $C_{cell}$—OCSNHPh, an aryl cellulose xanthate $C_{cell}$—OCSSAr (with evolution of nitrogen), and a cyanoethyl ether $C_{cell}$—OCH$_2$CH$_2$CN.

The reaction of simple xanthates with β-propiolactone has been studied recently,[7] and the present study is an extension to include (I). Reaction with the beta lactone did occur as evidenced by the rise in temperature and a change in the color of solution from deep orange to yellow when an excess of β-propiolactone had been added. In conformance with earlier results[7] the following reaction is believed to have taken place.

$$C_{cell}\text{—OCSSNa} + \underset{\llcorner\text{O}\lrcorner}{\text{CH}_2\text{CH}_2\text{CO}} \longrightarrow C_{cell}\text{—OCSSCH}_2\text{CH}_2\text{COONa}$$

Upon acidification, β-carboxyethyl cellulose xanthate (II) precipitated. The product was quite insoluble in water, alcohol, ether, and acetone but could be dissolved in dimethylformamide by warming. Evaporation of the dimethylformamide from a glass plate left a transparent, colorless, tough film of the modified cellulose. Although insoluble, the film was softened appreciably by water with concomitant increase in elasticity and decrease in strength.

Having the free carboxyl group available for further reaction, the effect of internal esterification on the properties of the polymer was next investigated. Treatment of the dimethylformamide solution at 80–90° with a small amount of sulfuric acid and removal of water by azeotropic distillation effected internal esterification. After evaporating the solvent on a glass plate a brittle film was obtained. This brittleness is probably due to a certain amount of cross linking effected by the internal esterification.

Esterification of the β-carboxyethyl group with a simple alcohol was next accomplished. Reaction with butanol in the presence of sulfuric acid was effective in bringing about the desired esterification. The dimethylformamide solution upon evaporation left a film of greater flexibility, indicating some degree of internal plasticization.

Acetylation of the viscose–β-propiolactone reaction product by two different methods was investigated. Refluxing with acetic anhydride in the presence of a trace of sulfuric acid produced a material insoluble in dimethylformamide. Some cross linking through internal esterification may be a complicating side reaction in this case. Acetylation by the pyridine–acetic anhydride method produced a different material, still insoluble in dimethylformamide, however. During this treatment it is possible that a substantial amount of the xanthic ester is decomposed with concomitant loss of carbon disulfide is indicated by the sulfur analysis on the product.

Since the aging of alkali cellulose and ripening of the viscose solution produced therefrom play a significant role in the properties of the fiber or film obtained upon regeneration, efforts to obtain optimum conditions for achieving the most desirable products are not being reported at this time.

### EXPERIMENTAL

*Preparation of viscose solution.*[8] Ten grams of absorbent cotton was treated with 250 g. of 18% sodium hydroxide solution for 1.5 hr. at 25°. At the end of this time the excess NaOH was pressed out to a final weight of 32 g. The resulting alkali cellulose was shredded by hand and allowed to stand at room temperature for 72 hr.

After this aging period the alkali cellulose was reacted with 8 ml. of carbon disulfide in a closed vessel. The mixture was agitated for 4 hr. and excess $CS_2$ removed by evacuation, after which a mixture of 18 g. of 18% NaOH and 75 ml. water was added and stirring continued for 2 hr. Solution was essentially complete at this point. Filtration of the viscose was effective in producing a sparkling clear solution of 90–100 ml. volume.

*Reaction of* I *with β-propiolactone.* The above prepared viscose solution was diluted with 300 ml. of water and cooled to 20°. β-Propiolactone (15.0 g.) was added dropwise during 10 min. with cooling to maintain the temperature between 20–25°. At this point the color of the solution changed from deep orange to light yellow. Stirring at 25° was continued for 0.5 hr. longer and the mixture was poured into an excess of dilute hydrochloric acid. The light yellow solid which

(1) Presented at the 134th American Chemical Society Meeting, Chicago, Ill., September 7–12, 1958.

(2) L. Lilienfeld, U. S. Patent 1,680,224 (Aug. 7, 1928).

(3) T. Nakashima, *J. Soc. Chem. Ind., Japan*, **31**, Suppl. binding, 31 (1928).

(4) L. Lilienfeld, U. S. Patents 1,674,401 (June 19, 1928), 1,674,405 (June 19, 1928), 1,906,910 (May 2, 1933).

(5) J. H. Helberger, German Patent 562,180 (Oct. 1, 1931).

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(7) M. W. Farrar, *J. Org. Chem.*, **23**, 1065 (1958).

(8) E. Kline, *Cellulose and Cellulose Derivatives*, Part II, Interscience Publishers, Inc., New York, 1954, p. 960.

separated was filtered and washed with water and finally with acetone in a Waring blender. The resulting product was an almost white granular solid.

*Anal.* C, 39.65; H, 5.68; S, 11.16.

A portion was dissolved in dimethylformamide by heating to 50°. Evaporation of the solvent from a glass plate left the product as a clear, tough film.

*Internal esterification of* II. Two grams of the modified cellulose was dissolved in 25 ml. of dimethylformamide by warming. A small amount of concentrated $H_2SO_4$ was added from a stirring rod and the solution was heated under vacuum at 90–95° for 4 hr. with slow distillation of the solvent. The solution remained clear upon cooling. Upon evaporation of the solvent a clear, brittle film was obtained. *Anal.* C, 40.71; H, 5.58; S, 11.01.

*Esterification of* II *with butanol.* Two grams of the modified cellulose was dissolved in 25 ml. of dimethylformamide by warming. To this solution was added 10 ml. of butanol. Some gellation of the solution occurred at this point but it remained stirrable. Once again a trace of $H_2SO_4$ was added and the mixture was heated under vacuum at 80–85° for 3 hr. with slow distillation. Evaporation of the product left a clear film of better flexibility than the original modified cellulose.

*Anal.* C, 41.47; H, 5.82; S, 10.91.

*Acetylation of* II. (a) One gram of the modified cellulose was heated to reflux for 1 hr. with 10 ml. of acetic anhydride containing a trace of sulfuric acid. During this period appreciable swelling of the polymer took place. Upon cooling, water was added to decompose excess acetic anhydride after which the granular solid was separated by filtration and was washed thoroughly with water and finally ethanol. Upon drying there was obtained 1.27 g. of the acetylated product which was found to be completely insoluble in acetone, alcohol, and dimethylformamide.

*Anal.* C, 45.33; H, 5.52; S, 8.36.

(b) One gram of the modified cellulose was heated at 90–100° for 1 hr. with 10 ml. of pyridine, 10 ml. of acetic anhydride, and 10 ml. of dimethylformamide. After quenching with water, separation of the solid, and finally washing with water and alcohol, there was obtained 1.08 g. of material.

*Anal.* C, 44.20; H, 5.28; S, 6.55.

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## Synthesis of γ-Aminobutyryl-γ-aminobutyric Acid

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*Received November 17, 1958*

γ-Aminobutyric acid has been found in brain extracts by Awapara *et al.*,[2] Roberts and Frankel,[3] and Udenfriend.[4] Recently an analog, γ-guanidinobutyric acid, was isolated from brain by Irreverre *et al.*[5] Due to the demonstration of enzymatic interconversion between these two butyric acids[6,7] and their possible role as humoral agents,[8–10] we were prompted to synthesize the dipeptide of γ-aminobutyric acid for physiological testing and for comparison on paper chromatography.

The synthesized γ-aminobutyryl-γ-aminobutyric acid in a concentration of 5.3 μm/ml. is not effective in blocking the neutromuscular transmission of crustaceans while γ-aminobutyric acid was effective at the threshold concentration of $9.7 \times 10^{-3}$ μm/ml.[11] The dipeptide as well as the benzyl ester of γ-aminobutyric acid give negative reactions in the specific enzymatic method for the determination of γ-aminobutyric acid developed by Jakoby and Scott.[12]

### EXPERIMENTAL

*N-Carbobenzoxy-γ-aminobutyric acid.* This compound was prepared by a procedure similar to that used for the preparation of *N*-carbobenzoxyglycine,[13] using 0.05 mole of γ-aminobutyric acid and 0.05 mole of carbobenzoxy chloride. The yield was 7.8 g. (66%). Recrystallized from ethyl-acetate-petroleum ether the compound melted at 66–67°.

*Anal.* Calcd. for $C_{12}H_{15}O_4N$: C, 60.75; H, 6.37; N, 5.90. Found: C, 60.89; H, 6.23; N, 5.90.

*γ-Aminobutyric acid benzyl ester hydrochloride.* This derivative was prepared using the procedure employed by Erlanger and Hall[14] for the synthesis of D,L-phenylalanine benzyl ester hydrochloride. Using 0.033 mole of γ-aminobutyric acid and 70 ml. of benzyl alcohol there was obtained 5.2 g. of material (69%). Recrystallized three times from ethyl acetate it melted at 109–110°.

*Anal.* Calcd. for $C_{11}H_{16}O_2NCl$: C, 57.66; H, 7.02; N, 6.10. Found: C, 57.38; H, 7.05; N, 5.81.

*N-Carbobenzoxy-γ-aminobutyryl-γ-aminobutyric acid benzyl ester.* To a mixture of 2.6 g. of *N*-carbobenzoxy-γ-aminobutyric acid and 1.51 ml. of triethylamine in 20 ml. of methylene chloride pre-cooled to −5° was added 1.0 ml. of ethylchloroformate and stored at −5° for 5 min. A second flask containing a solution of 2.6 g. of γ-aminobutyric acid benzyl ester hydrochloride and 4.68 ml. of triethylamine in 20 ml. of methylene chloride pre-cooled to −5° was added to above mixture. An additional 10 ml. of methylene chloride was used for washing out the flask. The reaction mixture was kept at −5° for 20 min. and allowed to come to room temperature with continuous stirring (magnetic) for 4 hr. The solution was extracted with 50 ml. of dilute hydrochloric acid, then with a cold, saturated solution of $NaHCO_3$ and finally with water. The methylene chloride layer was

(1) Present address: Mead Johnson and Co., Evansville, Ind.

(2) J. Awapara, A. J. Landua, R. Fuerst, and B. Seale, *J. Biol. Chem.*, **187**, 35 (1950).

(3) E. Roberts and S. Frankel, *J. Biol. Chem.*, **187**, 55 (1950).

(4) S. Udenfriend, *J. Biol. Chem.*, **187**, 65 (1950).

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(11) J. Dudel and S. W. Kuffler, personal communication.

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(13) H. E. Carter, R. L. Frank, and H. W. Johnston, *Org. Syntheses*, Coll. Vol. III, 167 (1955).

(14) B. F. Erlanger and R. M. Hall, *J. Am. Chem. Soc.*, **76**, 5781 (1954).

dried over $Na_2SO_4$, filtered and concentrated *in vacuo* to the point of crystallization. The flask was warmed to redissolve the crystals, petroleum ether was added, and the flask placed in the ice box overnight. The precipitate of soft needles was filtered and washed with petroleum ether. The yield was 3.3 g. (73%) and it melted at 86–87°. After recrystallization from 75% ethyl alcohol and drying *in vacuo* the melting point was unchanged.

*Anal.* Calcd. for $C_{23}H_{28}O_5N_2$: C, 66.97; H, 6.84; N, 6.79. Found: C, 66.91; H, 7.06; N, 6.79.

*γ-Aminobutyryl-γ-aminobutyric acid.* To a solution of 2.1 g. (0.0051 mole) of *N*-carbobenzoxy-γ-aminobutyryl-γ-aminobutyric acid benzyl ester in 35 ml. of methyl alcohol were added 2 drops of glacial acetic acid and 0.7 g. of Palladium black catalyst (Fisher Scientific Co.). Hydrogen gas was bubbled through and after 2 hr., 20 ml. of $H_2O$ were added and the hydrogenation continued for an additional 3 hr. The catalyst was removed by filtration and washed with a small volume of water. The filtrate was concentrated *in vacuo* to a crystalline residue. The solid was recrystallized from absolute ethyl alcohol. The yield was 0.75 g. (79%). Dried *in vacuo* at 80–81° it melted at 178–179°. Another crop (0.2 g.) was recovered from the filtrate. Recrystallized from water–ethyl alcohol it melted at 177–178°. The total yield was practically quantitative.

*Anal.* Calcd. for $C_8H_{16}O_3N_2$: C, 51.04; H, 8.57; N, 14.88. Found: C, 50.89; H, 8.56; N, 14.76.

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## A Convenient Synthesis of Cyclohexyl Methyl Ketone and Cyclohexylmethylcarbinol

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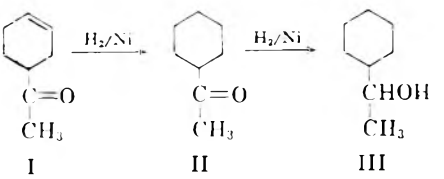
*Received November 24, 1958*

The preparation of a sizable quantity of vinylcyclohexane from cyclohexylmethylcarbinyl acetate[1] required that cyclohexylmethylcarbinol (III) be readily available. This alcohol has been previously prepared by several routes including the reaction of the cyclohexyl Grignard reagent with acetaldehyde,[2,3] the sodium and alcohol reduction of cyclohexen-1-yl methyl ketone[4] and the catalytic hydrogenation of acetophenone.[3,5] The latter method seemed to be the only reported route to III which might be particularly well suited to rather large scale laboratory operation. An investigation of the hydrogenation of acetophenone substantiated the observations of others[3,5] that the hydrogenation of acetophenone is very sensitive to poisons, and the reaction conditions must be controlled extremely carefully. A search for an alternate reliable method of preparing quantities of cyclohexylmethylcarbinol resulted in the development of a procedure based on the Diels-Alder adduct (I) of methyl vinyl ketone and butadiene-1,3.[6] The hydrogenation of I over W-4 Raney nickel was accomplished in two distinct steps, the first being the highly exothermic hydrogenation (25° at 200 p.s.i.g. $H_2$) of I to cyclohexyl methyl ketone (II) which is further reduced to III under somewhat more strenuous conditions (120° at 1500 p.s.i.g. $H_2$). The hydrogenation of I to III without isolation of II furnished III in 96% yield. II may




I II III

also be reduced to III with lithium aluminum hydride, the acetate being isolated to 90% yield.

### EXPERIMENTAL

*Cyclohexen-3-yl methyl ketone* (I). Equimolar amounts (5.3 moles) of butadiene-1,3 and methyl vinyl ketone[7] were heated at 140° in a sealed reactor during 9 hr. as described by Petrov.[6] The reaction temperature must be approached with caution as in several runs an uncontrollable exothermic reaction was observed. Distillation furnished a 90% yield of ketone; b.p. 78–80° (20 mm.), $n_D^{25}$ 1.4662 [reported b.p. 79.5–80° (20 mm.),[6] $n_D^{20}$ 1.4698[6]].

*Cyclohexyl methyl ketone* (II). A mixture of I (620 g.; 5 moles) and about 5 g. of W-4 Raney nickel catalyst[8] was treated with hydrogen at 150–200 p.s.i.g. The temperature of the reaction mixture was initially 25° and increased to 60° during 30 min. at which point no further hydrogen was consumed. Distillation furnished 569 g. (89% yield) of II, b.p. 73–74° (17 mm.), $n_D^{25}$ 1.4494 [reported b.p. 72° (18 mm.)[3], $n_D^{25.9}$ 1.44955[3]]. The semicarbazone, after recrystallization from methanol, melted at 177° which is in agreement with the literature value.[4]

*Cyclohexylmethylcarbinol* (III). A mixture of I (540 g.; 4.35 moles) and about 5 g. of W-4 Raney nickel catalyst in a rocking autoclave pressurized with hydrogen to 900 p.s.i.g. was hydrogenated to II as described above. The temperature of the reaction mixture rose from 20° to 63° in 10 min. and then slowly dropped. Hydrogen was then added until the pressure within the system was 1500 p.s.i.g., and the system heated by an external heater to 120°. By maintaining the hydrogen pressure at about 1500 p.s.i.g. by repressurizations, the hydrogenation of the carbonyl was completed in 1 hr. Distillation furnished 527 g. (96% yield) of alcohol b.p. 85–87° (17 mm.); $n_D^{25}$ 1.4659 [reported b.p. 189.4–189.8°

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(7) Purchased from Chas. Pfizer & Co., Brooklyn 6, N. Y.

(8) A. A. Pavlic and H. Adkins, *J. Am. Chem. Soc.*, **68**, 1471 (1946).

(761 mm.)[5], $n_D^{20}$ 1.4643[1], 1.4677[5]]. The α-naphthyl urethane melted at 123° after recrystallization from hexane.

*Anal.* Calcd. for $C_{19}H_{23}NO_2$: C, 76.74; H, 7.80; N, 4.71. Found: C, 76.88; H, 7.79; N (Dumas) 4.69.

*Cyclohexylmethylcarbinyl acetate.* The ketone II (252 g.; 2 moles) was reduced with lithium aluminum hydride (22.8 g.; 0.6 mole) in 900 ml. of ether in the conventional manner.[9] The crude undistilled alcohol III (255 g.) obtained was treated with 10 drops of concentrated sulfuric acid and acetic anhydride (250 g.) was added dropwise to the stirred mixture which was maintained at 80–90°. The mixture was then heated for an additional 2 hr. at 90°. Distillation furnished 305 g. (90% yield) of ester b.p. 92–93° (18 mm.), $n_D^{25}$ 1.4425 [reported b.p. 136° (93 mm.),[1] $n_D^{20}$ 1.4459[1]].

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## Reaction of Camphene and Dinitrogen Pentoxide

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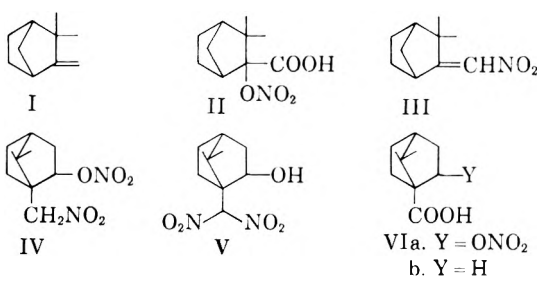
The addition of dinitrogen pentoxide to several simple olefins to produce 1,2-nitronitrates and α- and β-nitro-olefins has been reported.[1] In connection with this study and with the investigation of the dinitrogen tetroxide–camphene reaction,[2] the addition of dinitrogen pentoxide to camphene (I) was examined. An earlier study of this reaction[3] led to the isolation of a nitrato acid assigned structure II.[4]




Three compounds were isolated from the mixture of products produced in the camphene–dinitrogen pentoxide reaction. The first, m.p. 64–65°, was DL-ω-nitrocamphene[5] (III). The second product, a nitronitrate, m.p. 98–99°, was formulated as 10-nitro-2-nitratocamphane (IV) on the basis of its ready conversion to the known 10,10-dinitro-2-hydroxycamphane (V).[5] The significance of the rearrangement of IV to V has been discussed previously.[2] Formation of IV presumably occurred by addition of $NO_2^+$ to camphene to give the expected camphenyl-isobornyl cation which then produced the rearranged nitronitrate.

The third compound, a nitrato acid, m.p. 138–140°, undoubtedly was the acid reported previously.[3] In view of the structure IV assigned the nitronitrate, the acid may have structure VIa. Conversion of the nitrato acid to tricyclenic acid was the basis for its formulation as II,[3] but acids such as VI with Y = Br or OH appear to undergo the same conversion.[6] Since it has been shown that an α- or β-nitrato acid has a lower *p*K and higher carbonyl stretching frequency than the unsubstituted acid, these values were measured for VIa and for 1-apocamphane carboxylic acid (VIb). The *p*K of VIa (5.26) was lower than that of VIb (6.02), and the carbonyl frequency of VIa (1700 cm.$^{-1}$) was higher than that of VIb (1690 cm.$^{-1}$). While these values are about what should be expected for a β-nitrato acid such as VIa (the α-nitrato acids have much larger differences[7]) they are not definite evidence for the structure VIa since the corresponding values for an acid related to II were not available.

The camphene–dinitrogen pentoxide reaction also was carried out in the presence of tetraethylammonium nitrate, a process known to reduce the nitration by nitronium ion and to eliminate much of the oxidation in olefin–dinitrogen pentoxide reactions.[1] The products isolated were ω-nitrocamphene (12%) and 10-nitro-2-nitratocamphane (29%). The infrared spectrum of the crude mixture from the reaction conducted in the presence of excess nitrate ion indicated that the two products isolated were the major constituents of the reaction mixture. Apparently some hydrolysis or reaction of IV occurred on the chromatographic column for a considerable amount of the oily material eluted possessed hydroxyl and carbonyl absorption in the infrared that was not present in the original residue. However, the main point is that, in contrast with simple olefins, rearrangement did occur[8] even in the presence of added nitrate ion.

### EXPERIMENTAL[9]

*Addition of dinitrogen pentoxide to camphene.* A solution of 10 g. (0.073 mole) of camphene in 150 ml. of methylene chloride was cooled to −15°, and 0.080 mole of dinitrogen

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(3) N. Demjanov, *J. Russ. Phys. Chem. Soc.*, **33**, 284 (1901) [*Chem. Zentr.*, **72** (2), 346 (1901)].

(4) J. L. Simonsen, *The Terpenes*, 2nd ed., Vol. II, Cambridge University Press, Cambridge, England, 1949, p. 311.

(5) P. Lipp, *Ann.*, **399**, 241 (1913).

(6) Ref. 4, pp. 334, 335.

(7) K. S. McCallum and W. D. Emmons, *J. Org. Chem.*, **21**, 367 (1956).

(8) Addition of dinitrogen pentoxide to *cis*- or *trans*-stilbene, a reaction in which a relatively stable carbonium ion could be produced, has been found to be predominantly a *cis*- process. (Unpublished results from this laboratory.)

(9) All melting points are uncorrected. The infrared spectra of the compounds reported below were consistent with the structural assignments.

pentoxide[1] in 68 ml. of methylene chloride was added over 15 min. while the temperature of the reaction mixture was maintained between −15° and −10°. After addition of the dinitrogen pentoxide the solution was allowed to warm to 3° and stirred for 15 min. The reaction mixture was then quenched with aqueous sodium bicarbonate. The organic layer was washed with water, combined with the organic extracts of the neutralized aqueous washes, and dried over magnesium sulfate. Removal of the methylene chloride at reduced pressure left 15.5 g. of residue. A 3.1-g. portion of this residue was extracted with hot ligroin and the cooled extract was chromatographed on a silica acid–Celite (1:1) column packed in ligroin. Elution of the column with ligroin-ether (30:1) gave 0.43 g. (12%) of 10-nitro-2-nitratocamphane, m.p. 95–97°. Recrystallization of this material from ligroin gave white crystals, m.p. 98–99°.

*Anal.* Calcd. for $C_{10}H_{16}NO_5$: C, 49.18; H, 6.59; N, 11.47. Found: C, 49.38; H, 6.70; N, 11.14.

From the ligroin-ether (9:1) eluate was obtained 0.35 g. (10%) of the carboxylic acid (II or VIa), m.p. 138–140° reported 140–141°.[3]

The ligroin filtrate from the recrystallization of the nitronitrate was chromatographed on silicic acid–Celite and yielded ω-nitrocamphene, 0.12 g. (4.5%), m.p. 60–62°, m.p. 64–65° after recrystallization from aqueous ethanol, reported 64–65°.[5]

The addition of dinitrogen pentoxide to camphene in the manner described above except that an equivalent of tetraethylammonium nitrate was present[1] led to the isolation of 29% of 10-nitro-2-nitratocamphane and 12.4% of ω-nitrocamphene.

*Rearrangement of 10-nitro-2-nitratocamphane.* To 10 ml. of 50% ethanol containing 1.2 g. of potassium hydroxide was added 2.30 g. of 10-nitro-2-nitratocamphane. The mixture was warmed and swirled until solution occurred. On cooling in ice, a red salt separated and was removed by filtration. This red salt was suspended in a mixture of 25 ml. of water and 25 ml. of ether and acidified with aqueous hydrochloric acid. The ether layer was separated and the aqueous layer was extracted with ether. Evaporation of the ether left 1.97 g. of a solid, m.p. 155–156°. Two recrystallizations from ligroin gave 10,10-dinitro-2-hydroxycamphane (V) as white needles, m.p. 157–158°, reported 158.5°.[5]

*Anal.* Calcd. for $C_{10}H_{16}N_2O_5$: C, 49.18; H, 6.59; N, 11.47. Found: C, 49.56; H, 7.11; N, 11.14.

*pK determinations.* The pK's of the nitratoacid (II or VIa) and of VIb were estimated from the titration curves of the acids in 50% ethanol–water at 25°. Under these conditions benzoic acid was found to have a pK of 4.50.

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## 2-Nitro-6-methoxybenzaldehyde[1]

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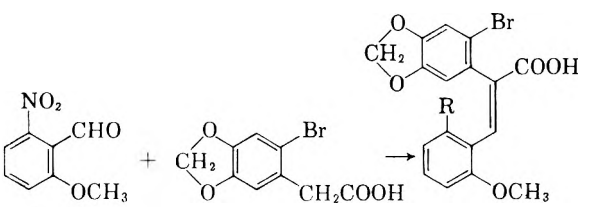
Incidental to another study, it was necessary to prepare *trans*-2-amino-6-methoxy-α-(3′,4′-methylenedioxy-6′-bromophenyl)cinnamic acid (IIIb) from 2-nitro-6-methoxybenzaldehyde (I). Synthesis of I from *m*-nitrophenol by means of a Reimer-Tiemann reaction followed by methylation had already been described by Ashley, Perkin, and Robinson.[2] However, conclusive evidence for the assigned orientation of the formyl group was unavailable since the original structural assignment was made on the basis of color reactions and a physical property.[2,3]

In order to remove any doubt concerning the reliability of the Reimer-Tiemann route to I, a sample for comparison purposes was obtained by the following unequivocal procedure. Conversion of 2,6-dinitrotoluene to 2-methyl-3-nitrophenol was accomplished as previously described.[4,5] Methylation of the phenol followed by chromyl chloride oxidation[6] of the methyl ether afforded an authentic specimen of the aldehyde (I) which was found to be identical with the compound described by Ashley.[2] Reaction of *m*-nitrophenol with chloroform in the presence of sodium hydroxide does indeed yield some 6-nitrosalicylaldehyde.

Condensing[7] I with 6-bromohomopiperonylic acid (II)[8–10] in the presence of triethylamine and acetic anhydride led to *trans*-2-nitro-6-methoxy-α-(3′,4′-methylenedioxy-6′-bromophenyl)cinnamic acid (IIIa). Reduction of IIIa with ferrous sulfate gave the required amino acid (IIIb).




(1) The author is pleased to acknowledge the financial assistance provided by the Coe Research Fund of the University of Maine.

(2) J. N. Ashley, W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.*, 382 (1930).

(3) The corresponding phenol, 6-nitrosalicylaldehyde, which was obtained in 3% yield, was shown to be steam volatile and therefore the product of *p*-formylation was excluded as a possible structure. After completion of the present investigation, it was found that additional experimental evidence favoring the 6-nitrosalicylaldehyde structure has been presented by H. Shirai and N. Oda, *Bull. Nagoya City Univ. Pharm. School* No. 4, 30 (1956); *Chem. Abstr.*, 51, 9522 (1957).

(4) O. L. Brady and A. Taylor, *J. Chem. Soc.*, 117, 876 (1920).

(5) K. G. Blaikie and W. H. Perkin, Jr., *J. Chem. Soc.*, 125, 296 (1924).

(6) W. H. Hartford and M. Darrin have recently reviewed the Étard reaction: *Chem. Revs.*, 58, 1 (1958).

(7) *Cf.*, M. Bailer, A. Schleppnik, and A. Meller, *Monatsh. Chem.*, 89, 211 (1958).

(8) D. Davidson and M. T. Bogert, *J. Am. Chem. Soc.*, 57, 905 (1935).

(9) W. F. Barthel and B. H. Alexander, *J. Org. Chem.*, 23, 1012 (1958).

(10) R. G. Naik and T. S. Wheeler, *J. Chem. Soc.*, 1780 (1938).

EXPERIMENTAL[11]

*2-Nitro-6-methoxytoluene.* A solution of 2-methyl-3-nitrophenol[4,5] (73 g.) in 400 ml. of water containing 19 g. of sodium hydroxide was cooled and treated with 60 g. of dimethylsulfate. The mixture was then stirred and heated on the steam bath for 2 hr. before subjecting the crude reaction mixture to a steam distillation. The cream colored product was collected with *ca.* 6 l. of water; yield 42 g. (53%), m.p. 55–57.5°. Simonsen and Nayak[12] report a melting point of 52–53°.

*2-Nitro-6-methoxybenzaldehyde* (I). A solution of 2-nitro-6-methoxytoluene (40 g.) in 250 ml. of carbon disulfide was added over a 30 min. period to a stirred solution of chromyl chloride (70 g.) in the same solvent (150 ml.). After 72 hr. at room temperature, the dark colored crystalline intermediate was collected and washed with carbon disulfide. After adding the solid to water, the aqueous mixture was extracted with chloroform and the combined chloroform extracts washed with saturated sodium bicarbonate solution and water. Removal of solvent afforded 15 g. (35%) of crude red colored crystalline product. Four recrystallizations from carbon tetrachloride gave an analytical sample as colorless needles, m.p. 110–111°, $\lambda^{CHCl_3}$ 5.85 $\mu$.

*Anal.* Calcd. for $C_8H_7NO_4$: C, 53.04; H, 3.90; N, 7.73. Found: C, 53.44; H, 4.23; N, 7.87.

The product was found to be identical (mixture melting point and infrared comparison) with a specimen prepared by Ashley's[2] procedure.

*Trans-2-nitro-6-methoxy-α-(3',4'-methylenedioxy-6'-bromophenyl)cinnamic acid* (IIIa). A mixture of 2-nitro-6-methoxybenzaldehyde (2.0 g.), 3.06 g. of 6-bromohomopiperonylic acid (II),[8–10] acetic anhydride (10 ml.), and triethylamine (1 ml.) was heated at reflux for 15 min. before cautiously treating the hot reaction mixture with 10 ml. of water. After cooling, the mixture was neutralized with saturated sodium bicarbonate solution and extracted with chloroform. Acidification of the aqueous solution with dilute hydrochloric acid yielded 0.87 g. (17%) of crude pale yellow product, m.p. 200–230°. Three recrystallizations from acetic acid–water afforded a pure sample as pale yellow crystals, m.p. 264–265° (dec.), $\lambda^{KBr}$ 5.95 $\mu$.

*Anal.* Calcd. for $C_{17}H_{12}BrNO_7$: C, 48.36; H, 2.87; N, 3.32. Found: C, 48.48; H, 3.03; N, 3.53.

*Trans-2-amino-6-methoxy-α-(3',4'-methylenedioxy-6'-bromophenyl)cinnamic acid* (IIIb). A suspension of IIIa (0.55 g.) in a solution composed of ferrous sulfate (3.3 g.), hydrochloric acid (0.2 ml.), and water (5 ml.) was heated to 90–95° before adding 3 ml. of 28% ammonium hydroxide. Heating on the steam bath and intermittent stirring were continued for 45 min. The hot reaction mixture was then filtered through Norit-A and after washing the filter cake with water the combined filtrate was acidified to *p*H 4.5 with hydrochloric acid. The gray colored crystalline product weighed 0.41 g. (81%) and melted at 160–164°. Three recrystallizations from methanol-water gave a pure sample of the amino acid as yellow needles, m.p. 205–206°, $\lambda^{KBr}$ 5.95 $\mu$.

*Anal.* Calcd. for $C_{17}H_{14}BrNO_5$: C, 52.07; H, 3.60; N, 3.57. Found: C, 52.04; H, 3.58; N, 3.62.

The amino acid was found to be virtually insoluble in dilute hydrochloric acid.[13]

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(11) All melting points were taken in open Kimble glass capillaries and are uncorrected. Elemental analyses were deformed by The Microanalytical Laboratory of Dr. A. Bernhardt, Mülheim, Germany. The infrared spectra were peterminated by Mr. Evan Thomas of this department.

(12) J. L. Simonsen and M. Nayak, *J. Chem. Soc.*, **107**, 828 (1915).

(13) Low solubility in dilute mineral acid has been encountered with other amino cinnamic acids. See for example: L. S. Hornig, *J. Am. Chem. Soc.*, **74**, 4572 (1952).

## Preparation of α,β-Unsaturated Sulfones

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In earlier papers[1,2] from these laboratories it was reported that β-amino and α,β-unsaturated sulfones are formed when aryl- or alkyl-sulfonylacetic acids are condensed with aromatic aldehydes in the presence of ammonia in glacial acetic acid. The yields of the α,β-unsaturated sulfones in such condensations were found to be generally very low. Being engaged in studies on α,β-unsaturated sulfones we were interested in getting increased yields of these compounds. It has been found that the use of benzylamine in place of ammonia and refluxing the reaction mixture for a longer period reduce the β-amino sulfone in the product to a negligible amount and greatly increase the yield of the α,β-unsaturated sulfone. Even with catalytic amounts of benzylamine excellent yields of the unsaturated sulfones were obtained. Using this procedure many new unsaturated sulfones have been prepared (see Table I). In the same Table are shown the increased yields of the previously reported α,β-unsaturated sulfones.

EXPERIMENTAL

*General procedure for the preparation of α,β-unsaturated sulfones.* A mixture of the sulfonylacetic acid (0.1 mole), the aldehyde (0.1 mole), glacial acetic acid (25 ml.) and benzylamine (0.1–0.2 g.) was refluxed on a hot plate for 50 min. The product was cooled, mixed with 100 ml. of dry ether and set aside for 1 hr. In most cases the α,β-unsaturated sulfone, being sparingly soluble in ether, partly crystallized out. It was removed by filtration and dry hydrogen chloride was passed into the ether solution. The precipitated β-amino sulfone hydrochloride, if any, was filtered off. Evaporation of the ether from the filtrate gave a mixture of the unreacted aldehyde, acetic acid, and unsaturated sulfone. Treatment of this mixture with a few ml. of methanol or isopropyl alcohol precipitated the unsaturated sulfone in many cases. In other cases the unchanged aldehyde had to be removed with sodium bisulfite before the unsaturated sulfone could be separated. The relevant data on the compounds prepared are given in Table I.

*Acknowledgment.* The authors wish to thank the Government of India for the award of a Research Scholarship to one of them (M.S.).

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(1) M. Balasubramanian and V. Baliah, *J. Chem. Soc.*, 1844 (1954).

(2) M. Balasubramanian, V. Baliah, and T. Rangarajan, *J. Chem. Soc.*, 3296 (1955).

TABLE I

$\alpha,\beta$-UNSATURATED SULFONES, $RSO_2CH{=}CHR'$

| R | R' | M.P., °C. | Yield,[a] % | Analysis | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Calcd. for | Carbon | | Hydrogen | |
| | | | | | Calcd. | Found | Calcd. | Found |
| $CH_3$ | $m$-$O_2NC_6H_4$ | 130–132 | 49 (16) | | | | | |
| $CH_3$ | $p$-$ClC_6H_4$ | 125–126 | 32 | $C_9H_9ClO_2S$[c] | 49.87 | 50.16 | 4.20 | 4.46 |
| $CH_3$ | 2,4-$Cl_2C_6H_3$ | 72–73 | 62 | $C_9H_8Cl_2O_2S$[c] | 43.04 | 42.91 | 3.21 | 3.42 |
| $C_6H_5$ | $C_6H_5$ | 74–74.5 | 39 (21) | | | | | |
| $C_6H_5$ | $o$-$O_2NC_6H_4$ | 131–132 | 44 (10) | | | | | |
| $C_6H_5$ | $m$-$O_2NC_6H_4$ | 142–143 | 64 (14) | | | | | |
| $C_6H_5$ | $p$-$O_2NC_6H_4$ | 169–170 | 52 | $C_{14}H_{11}NO_4S$[b] | 58.11 | 58.41 | 3.83 | 4.15 |
| $C_6H_5$ | $o$-$ClC_6H_4$ | 105–106 | 35 | $C_{14}H_{11}ClO_2S$[c] | 60.32 | 59.89 | 3.98 | 3.72 |
| $C_6H_5$ | $p$-$ClC_6H_4$ | 129–130 | 63 (28) | | | | | |
| $C_6H_5$ | 2,4-$Cl_2C_6H_3$ | 132–133 | 48 | $C_{14}H_{10}Cl_2O_2S$[b] | 53.68 | 54.20 | 3.22 | 3.47 |
| $C_6H_5$ | 3,4-$Cl_2C_6H_3$ | 156–156.5 | 44 | $C_{14}H_{10}Cl_2O_2S$[b] | 53.68 | 53.38 | 3.22 | 3.67 |
| $C_6H_5$ | $p$-$CH_3OC_6H_4$ | 117–118 | 19 | $C_{15}H_{14}O_3S$[b] | 65.64 | 65.70 | 5.14 | 5.23 |
| $C_6H_5$ | $p$-$HOC_6H_4$ | 109–110 | 10 | $C_{14}H_{12}O_3S$[d] | 64.59 | 64.43 | 4.65 | 4.93 |
| $C_6H_5$ | $p$-$CH_3C_6H_4$ | 135.5–136.5 | 28 (17) | | | | | |
| $C_6H_5$ | 3-Pyridyl | 85–86 | 13 | $C_{13}H_{11}NO_2S,2H_2O$[e] | 55.49 | 55.46 | 5.38 | 5.55 |
| $C_6H_5$ | 4-Pyridyl | 190–191 | 5 | $C_{13}H_{11}NO_2S,H_2O$[c] | 59.28 | 59.64 | 4.98 | 4.90 |
| $C_6H_5$ | 2-Thienyl | 86–87 | 40 | $C_{12}H_{10}O_2S_2$[c] | 57.58 | 56.90 | 4.04 | 4.51 |
| $p$-$C_7H_7$ | $C_6H_5$ | 120–121 | 40 (25) | | | | | |
| $p$-$C_7H_7$ | $o$-$O_2NC_6H_4$ | 159–160 | 71 (5) | | | | | |
| $p$-$C_7H_7$ | $m$-$O_2NC_6H_4$ | 146–147 | 75 (20) | | | | | |
| $p$-$C_7H_7$ | $p$-$ClC_6H_4$ | 151–152 | 68 (31) | | | | | |
| $p$-$C_7H_7$ | 2,4-$Cl_2C_6H_3$ | 129–129.5 | 64 | $C_{15}H_{12}Cl_2O_2S$[b] | 55.05 | 55.42 | 3.70 | 3.70 |
| $p$-$C_7H_7$ | 3,4-$Cl_2C_6H_3$ | 163–163.5 | 67 | $C_{15}H_{12}Cl_2O_2S$[b] | 55.05 | 55.58 | 3.70 | 3.69 |
| $p$-$C_7H_7$ | $p$-$CH_3OC_6H_4$ | 100–101 | 54 (12) | | | | | |
| $p$-$C_7H_7$ | $p$-$CH_3C_6H_4$ | 154–155 | 35 (22) | | | | | |
| $p$-$C_7H_7$ | 2-Thienyl | 133–134 | 31 (20) | | | | | |
| $p$-$C_7H_7$ | 3-Pyridyl | 84–85 | 20 | $C_{14}H_{13}NO_2S,2H_2O$[f] | 56.94 | 56.64 | 5.80 | 6.04 |
| $p$-$C_7H_7$ | 4-Pyridyl | 215–216 | 29 | $C_{14}H_{13}NO_2S,H_2O$[b] | 60.61 | 60.44 | 5.45 | 5.85 |
| $p$-$C_7H_7$ | 1-Naphthyl | 111–112 | 14 | $C_{19}H_{16}O_2S$[b] | 74.01 | 74.09 | 5.23 | 5.30 |
| $p$-$C_7H_7$ | $p$-$(CH_3)_2NC_6H_4$ | 204–205 | 23[h] | $C_{17}H_{19}NO_2S$[g] | 67.74 | 67.56 | 6.35 | 6.74 |

[a] The percentage yields in parentheses are those reported in the previous papers.[1,2] Recrystallized from [b] ethanol, [c] methanol, [d] isopropyl alcohol, [e] cyclohexane, [f] $n$-hexane and [g] acetone-water. [h] The reactants were refluxed for 90 min.

## 1,1-Dinitrocyclohexane in Nitrocyclohexane Still Residues

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Nitrocyclohexane was prepared by the reaction of cyclohexane with nitric acid.

During the course of an investigation which involved the identification of impurities in the nitrocyclohexane still residues, a white crystalline compound melting at 174°. was isolated. Its infrared spectrum indicated no functional groups other than the nitro group, and the carbon, hydrogen, and nitrogen contents of this compound agreed with those of a dinitrocyclohexane.

*Anal.* Calcd. for $C_6H_{10}N_2O_4$: C, 41.4; H, 5.75; N, 16.1. Found: C, 41.5; H, 5.90; N, 15.9.

1,1-Dinitrocyclohexane and 1,2-dinitrocyclohexane are known, having melting points of 36° and 46°, respectively. It seemed likely, therefore, that this new nitro compound was either 1,4-dinitrocyclohexane or 1,3-dinitrocyclohexane. No reference to either of these isomers was found in the literature, but the corresponding diketones were both listed in Beilstein.[1] 1,4-Cyclohexanedione has a melting point of 78° while 1,3-cyclohexanedione melts with decomposition at 104–106°.

The cyclohexanedione was prepared from the unknown dinitrocyclohexane by the Nef reaction. Two recrystallizations yielded a small amount of an off-white compound having a melting point of 74–76°. The infrared spectrum of this compound confirmed that this derivative was a ketone.

The conclusion drawn from the above data is that the compound isolated from the nitrocyclohexane still heels is 1,4-dinitrocyclohexane (having a melting point of 174°).

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(1) Beilstein, *Handbuch der organischen Chemie*, 4th ed., Vol. 7, pp. 554 and 556.

## Aldehyde Cotrimers

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*Received December 12, 1958*

Whereas the trimerization of individual aliphatic aldehydes is a familiar reaction, the formation of mixed trimers has received no systematic study. It has now been found that cotrimerization is a general reaction also, and that the suggestion[1] that aldehyde cotrimers must always contain at least one halogenated aldehyde unit is invalid. Binary mixture of individually polymerizable aldehydes are largely converted by acid catalysts to a mixture of two symmetrically substituted and two unsymmetrically substituted 1,3,5-trioxanes; under favorable circumstances the several trimers can be separated by fractional distillation.

The products obtained are shown in Table I. Since purity and not yield was stressed in fractionation, the yields shown are minimal and of little significance. Attempts to isolate cotrimers of formaldehyde with acetaldehyde and with propionaldehyde failed, but this is attributed to difficulties in separation rather than to failure of the reaction. As might have been expected, acetaldehyde formed no cotrimer with acetone or benzaldehyde.

The formation of the cotrimer containing three different aldehyde units is of particular interest since Hibbert, Gillespie, and Montonna[2] were unable to obtain such compounds from halogenated aldehydes.

A few trials of 2,4-dimethyl-6-ethyltrioxane as a hypnotic by hypodermic injection in rats showed it to be quite toxic, lacking the safety margin of paraldehyde. This extends the observation of Knoefel[3] that other symmetrical trialkyltrioxanes are inferior to paraldehyde. We are indebted to Dr. A. A. Hellbaum and Mr. Dwight L. Smith of the University of Oklahoma School of Medicine for the pharmacological tests.

### EXPERIMENTAL

Reagent grade or redistilled technical grade aldehydes were mixed, chilled in an ice bath, and treated with a small stream of hydrogen chloride for several seconds. The solution was stirred briefly, kept in a closed container in the ice bath for several hours, and then poured into aqueous potassium carbonate. The nonaqueous layer was dried over potassium carbonate and fractionally distilled, usually in either an Oldershaw or a Todd column. It consisted almost entirely of monomers and trimers; very little viscous or solid product was obtained.

TABLE I

ALDEHYDE COTRIMERS

| RCHO + R'CHO Used, Moles | Substd. Trioxane Obtained[a] | Yield, G. | B.P., °C./mm. | *d* at *t*, G./Ml. | $n_D$ at *t* | *t*, °C. |
|---|---|---|---|---|---|---|
| 2 MeCHO + 4 EtCHO | 2,4-$Me_2$-6-Et | 60 | 139.5/745 | 0.976 | 1.4098 | 20 |
| | 2,4-$Et_2$-6-Me | 16 | 155.5/745 | 0.961 | 1.4131 | 20 |
| 2.6 MeCHO + 3.0 PrCHO | 2,4-$Me_2$-6-Pr | 8 | 96/80 | 0.953 | 1.4141 | 20 |
| | 2,4-$Pr_2$-6-Me | 42 | 121/69 | 0.932 | 1.4208 | 20 |
| 3.3 MeCHO + 1.4 *iso*-PrCHO | 2,4-$Me_2$-6-*iso*-Pr | 46 | 97/140 | 0.939 | 1.4060 | 31 |
| | 2,4-(*iso*-Pr)$_2$-6-Me | 14 | 113/131 | 0.923 | 1.4150 | 29 |
| 1.8 MeCHO + 1.3 *n*-$C_6H_{13}$CHO | 2,4-$Me_2$-6-*n*-$C_6H_{13}$ | 21 | 102–103/11 | 0.917 | 1.4214 | 30 |
| | 2,4-(*n*-$C_6H_{13}$)$_2$-6-Me[b] | 12 | 164/11 | 0.895 | 1.4337 | 27 |
| 1.7 EtCHO + 2.5 PrCHO | 2,4-$Et_2$-6-Pr | 14 | 138–139/165 | 0.917 | 1.4156 | 26.5 |
| | 2,4-$Pr_2$-6-Et | 19 | 128/55 | 0.918 | 1.4192 | 28 |
| 2.7 MeCHO + 0.8 $EtOCH_2CH_2CHO$ | 2,4-$Me_2$-6-$EtOC_2H_4$[b] | 13 | 96/17 | 0.996 | 1.4202 | 25.5 |
| | 2,4-($EtOC_2H_4$)$_2$-6-Me[b] | 11 | 141–142/14 | 1.000 | 1.4294 | 24 |
| 1 MeCHO + 1 PrCHO + 1 *n*-$C_6H_{13}$CHO | 2-*n*-$C_6H_{13}$-4-Me-6-Pr[c] | 8 | 122/10 | 0.913 | 1.4289 | 22 |
| 3.6 MeCHO + 1.2 $CH_2$:CHCHO | 2,4-$Me_2$-6-vinyl[d] | 5 | 138–140/745 | 1.000 | 1.4199 | 26.5 |
| 1.8 MeCHO + 1.1 MeCH:CHCHO | 2,4-$Me_2$-6-(1-propenyl)[e] | 9 | 94/40 | 0.983 | 1.4301 | 29 |

[a] Purity was established for each by showing agreement of calculated and observed values for carbon and hydrogen content (except as noted), molecular refraction, and molecular weight. [b] No carbon-hydrogen analysis. [c] Other products were not sought. [d] Bromine number according to J. B. Bradstreet and R. B. Lewis, *Ind. Eng. Chem., Anal. Ed.*, **12**, 387 (1940): Calcd., 111; Found, 73. This and the results of analysis for hydrogen (Calcd., 8.39%; Found, 8.98%) suggest that the compound was very pure. [e] Bromine number: Calcd., 101; Found, 99.

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## Constituents of *Casimiroa Edulis Llave et Lex.* V.[1] Identity of Casimirolid and Obacunone

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*Received December 15, 1958*

The isolation of the lactone casimirolid (m.p. 229–231°, $[\alpha]_D$ −49°) from the seeds of *Casimiroa edulis Llave et Lex* was described in 1911 by Power and Callan[3] and recently by our group.[4] The lactone obacunone (m.p. 229–230°, $[\alpha]_D$ −51°) was first isolated by Kaku and Ri[5] from the bark of *Phellodendron amurense;* it was later obtained from citrus oil by Emerson,[6] who suspected it to be identical with casimirolid. We have now carried out a direct comparison between casimirolid and obacunone. The complete identity of the characteristic infrared spectra, as well as the fact that no melting point depression was observed on admixture, conclusively proves the two substances to be identical.

Casimirolid had been assigned the formula $C_{24}H_{28}O_6$ by Power and Callan[3] and $C_{28}H_{32}O_8$ by ourselves,[4] whereas obacunone undoubtedly possesses the formula $C_{26}H_{30}O_7$.[6,7] A series of new analyses of casimirolid has now shown the previously proposed formulas to be incorrect and favors the $C_{26}H_{30}O_7$ formulation also for this substance.

Although the name casimirolid has priority,[3] the structural investigations by Emerson[6] and especially by Dean and Geissman[7] have been carried out with obacunone, yielding degradation products the names of which have been derived from this substance. We propose therefore that the name obacunone be retained and casimirolid be abandoned.

### EXPERIMENTAL

*Comparison of casimirolid with obacunone.* A sample of casimirolid[4] was crystallized repeatedly from ethanol and was then dried for 24 hr. at 120° (0.1 mm.). It showed m.p. 230–231°, $[\alpha]_D$ −49.6° ($CHCl_3$).

*Anal.* Calcd. for $C_{26}H_{30}O_7$: C, 68.70; H, 6.65; O, 24.64; Calcd. for $C_{28}H_{32}O_8$: C, 67.73; H, 6.50; O, 25.78. Found: C, 68.90, 68.79; H, 6.76, 6.83; O, 24.57, 24.33.

The infrared spectrum (potassium bromide pellet, determined on a Baird double-beam spectrophotometer) showed more than 20 well defined bands, the main ones being at 2.87, 3.31, 5.78, 5.88, 6.68, 6.85, 7.20, 7.45, 7.63, 7.83, 8.17, 8.62, 8.95, 9.35, 9.40, 9.75, 10.16, 10.24, 10.92, 11.46, 12.17, and 12.48μ.

An authentic sample of obacunone showed m.p. 229–231°, $[\alpha]_D$ −49.8° ($CHCl_3$). There was no depression in m.p. on admixture with a sample of casimirolid. The infrared spectrum was completely identical with that of casimirolid.

*Acknowledgment.* We are indebted to Dr. O. H. Emerson and to Drs. F. M. Dean and T. A. Geissman for their courtesy in providing us with samples of obacunone.

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## Beckmann Rearrangement of 4-Trimethylsilylacetophenone Oxime

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*Received December 17, 1958*

Few reports of aminoaryltrialkylsilanes occur in the literature[2] as these compounds readily undergo fission of the aromatic carbon-silicon bond, particularly in acidic media. Those amines which have been reported were prepared by hydrogenation of the corresponding nitro compounds over a Raney nickel catalyst.[3–5]

Since 4-trimethylsilylacetophenone oxime (I) has recently become available[6] an attempt has been made to prepare 4-trimethylsilylacetanilide (II), by a Beckmann rearrangement, and then to hydrolyze this compound to 4-trimethylsilylaniline. Treatment of an ethereal solution of I with thionyl chloride or phosphorus pentachloride gave good yields of II. With sulfuric acid the yields of II were lower. The anticipated cleavage of the aromatic carbon-silicon bond of I did not occur under the conditions employed.[7] Analysis for nitrogen and silicon, and the infrared spectrum, confirmed the structure of II.

On heating the anilide under reflux with 40 or 70% aqueous-alcoholic potassium hydroxide for 30 minutes, then neutralizing, unreacted II was quantitatively recovered. The anilide is thus extremely difficult to cleave under basic conditions.

Heating II under reflux for 15 minutes with 10% aqueous-alcoholic sulfuric acid liberated a dark-brown oil (III). On distilling this oil and examining

(1) For reprints: 783 Cereza Drive, Palo Alto, Calif.

(2) F. S. Kipping and N. W. Cusa, *J. Chem. Soc.*, 1088 (1935); F. S. Kipping and J. C. Blackburn, *J. Chem. Soc.*, 1085 (1935).

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its infrared absorption spectrum no evidence was found for the presence of the trimethylsilyl group, and the spectrum resembled in every way that of aniline. This was confirmed by forming derivatives of III with phenyl isocyanate and 2,4-dinitrochlorobenzene. It thus appears that the Beckmann rearrangement of 4-trimethylsilylacetophenone oxime occurs in good yield; however, conditions for the preparation of 4-trimethylsilylaniline from this Beckmann product have not been found.

## EXPERIMENTAL

*Beckmann rearrangements of* I. A solution of I (20.7 g., 0.1 mole) in anhydrous diethyl ether (500 ml.) was treated with thionyl chloride (12 g., 0.1 mole). After the initially exothermic reaction had moderated, the mixture was heated at reflux for 0.5 hr. Water (500 ml.) was then added to decompose unreacted thionyl chloride. Excess powdered sodium bicarbonate was then cautiously added to the stirred mixture, the ether layer separated, washed three times with water, then dried over anhydrous sodium sulfate. On distilling off the ether a yellow crystalline solid remained, yield 18 g. (87%). After two treatments with charcoal, and a further recrystallization from alcohol, colorless flat crystalline plates were obtained of m.p. 171°,[8] in good agreement with the literature[5] value of 169–170°.

*Anal.* Calcd. for $C_{11}H_{17}NOSi$: N, 6.76; Si, 13.55. Found: N, 6.64; Si, 13.29.

Employing the same experimental conditions with phosphorus pentachloride (21 g., 0.1 mole) the yield of II was 18 g. With concentrated sulfuric acid (10 g., 0.1 mole) the yield of II was 15 g. (72.5%).

*Infrared absorption spectrum of* II. The spectrum was determined using a Perkin-Elmer Model 112 spectrophotometer with sodium bromide optics. Prominent bands included those assigned to NH stretching at 3257; aliphatic CH stretch at 2927; amide C:O at 1666; aromatic C:C at 1506 and 1592; NH bend at 1537; parasubstitution at 823; and three strong bands due to the trimethylsilyl group at 1248, 838, and 759 cm.$^{-1}$ [9,10]

*Attempted alkaline hydrolysis of* II. One-gram samples of II were dissolved in 20–30 ml. of 40% potassium hydroxide in dilute (1:1) alcohol. On heating at reflux for 30 min., cooling, and making slightly acid, II was quantitatively recovered, m.p. 170–171°. Similar results were obtained using 70% potassium hydroxide in dilute alcohol.

*Acid hydrolysis of* II. On heating II (10 g.) under reflux with excess dilute (1:10) sulfuric acid for 15 min. the solution turned dark brown. Heating was continued for a further 15 min. to ensure complete reaction. Excess 10% sodium hydroxide solution was then added to liberate the free base. The crude amine (approx. 7 g.) was extracted with ether, the extracts washed with water, dried, and the ether removed. Fractional distillation yielded 3.5 g. of a colorless oil, b.p. 100–120°/12–15 mm. The oil was redistilled and the fraction of b.p. 112–115°/12–15 mm. collected. Yield, 2.0 g.

*Identification of hydrolysis product.* The infrared absorption spectrum of the colorless oil obtained by acidic hydrolysis of II was identical with that of an authentic specimen of freshly distilled aniline.

Phenyl isocyanate reacted with the oil to give 1,3-diphenylurea, m.p. 238°; and 2,4-dinitrochlorobenzene reacted to give 2,4-dinitrodiphenylamine, m.p. 156°. Both these data are identical with those for the corresponding aniline derivatives.

*Acknowledgment.* The author thanks Mr. Joseph Wirth for preparing 4-trimethylsilylacetophenone from which the oxime was made; Dr. Allen E. Sencar for the spectral measurements; and Dr. Murray Taylor for the analytical data.

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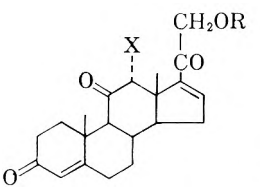
# 16-Hydroxylated Steroids. IX.[1] Synthesis of 12α-Bromo-16α-hydroxycortisone 21-Acetate and 16,21-Diacetate

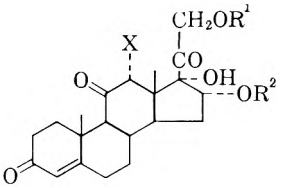
SEYMOUR BERNSTEIN AND RUDDY LITTELL

*Received December 18, 1958*

Recently described work from this Laboratory on 16α-hydroxycorticoids[2] has now been extended to include those containing a 12α-halogen group.[3] The present note describes the synthesis of 12α-bromo-16α-hydroxycortisone (12α-bromo-16α,17α-21-trihydroxy-4-pregnene-3,11,20-trione) in the form of its 21-acetate IIa and 16,21-diacetate IIb.



Ia. R = Ac; X = Br
Ib. R = Ac; X = H
Ic. R = X = H



IIa. $R^1$ = Ac; $R^2$ = H; X = Br
IIb. $R^1$ = $R^2$ = Ac; X = Br
IIc. $R^1$ = $R^2$ = Ac; X = H

Hydroxylation of 21-acetoxy-12α-bromo-4,16-pregnadiene-3,11,20-trione (Ia)[4] with potassium permanganate in aqueous acetone[5a,b] gave a mixture of products[6] from which the desired 21-acetoxy-12α-

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(6) The reaction mixture was shown by paper-strip chromatographic analysis to contain at least five products. No attempt was made to isolate and identify the by-products.

bromo-16α,17α-dihydroxy-4-pregnene-3,11,20-trione (IIa) was obtained by direct crystallization. Acetylation gave the solvated 16α,21-diacetate IIb in an 8% over-all yield from Ia. The same final product IIb was obtained in 10% yield when the hydroxylation was carried out with osmic acid in benzene.[7,8] These yields are to be compared with a 28% yield obtained by hydroxylation of the parent nonhalogenated compound 21-acetoxy-4,16-pregnadiene-3,11,20-trione (Ib) with permanganate,[5b] and with a 50% yield by hydroxylation of Ic with osmic acid.[7]

The lower yields observed in the preparation of the 12α-bromo-16α,17α-diols may, in part, be ascribed to steric hindrance. Examination of a molecular model of Ia shows the axial 12α-bromine atom to be in close proximity to the rear side of the C16,17-double bond. Consequently, the bromine atom may inhibit the formation of a large osmate or permanganate complex on the rear side of the D-ring.

The assigned structure of IIb was confirmed by the reductive removal of the bromine atom with zinc in acetic acid[9] to afford in good yield the known 16α,21-diacetoxy-17α-hydroxy-4-pregnene-3,11,-20-trione (IIc).[5b,7]

## EXPERIMENTAL[10]

*21-Acetoxy-12α-bromo-16α,17α-dihydroxy-4-pregnene-3,11,20-trione* (IIa). To a solution of 926 mg. of 21-acetoxy-12α-bromo-4,16-pregnadiene-3,11,20-trione (Ia) in 40 ml. of acetone at 0° was added 320 mg. of potassium permanganate dissolved in 25 ml. of 85% aqueous acetone. The mixture was stirred at 0° for 7 min. when a solution of cold saturated sodium bisulfite was added. The resulting inorganic precipitate was separated by filtration. The filtrate was concentrated and 440 mg. of white solid, m.p. 200–205°, was collected. Paper strip chromatographic analysis revealed the presence in appreciable amount of five Blue Tetrazolium reducing products.

Crystallization of this mixture from acetone–petroleum ether gave 88 mg. of crude product. m.p. 250° (dec.). Two further crystallizations from acetone gave 20 mg. of pure IIa, m.p. 263° (dec.), $[\alpha]_D^{25}$ +39° (*c*, 0.28, pyridine); $\nu_{max}$ 3400, 1738, 1714, 1664. 1662, and 1236 cm.$^{-1}$

*Anal.* Calcd. for $C_{23}H_{29}O_7Br$ (497.38): C, 55.54; H, 5.88; Br, 16.07. Found: C, 55.85; H, 5.95; Br, 16.21.

In another run with 1.4 g. of Ia in 60 ml. of acetone, 480 mg. of potassium permanganate in 50 ml. of 85% acetone, and 0.35 ml. of acetic acid there was obtained 180 mg. (12% yield) of IIa, m.p .261° (dec.);$\lambda_{max}^{methanol}$ 237 mμ (ε 16,400).

*16α,21-Diacetoxy-12α-bromo-17α-hydroxy-4-pregnene-3,11,20-trione* (IIb). (a) To a solution of 155 mg. of 21-acetoxy-12α-bromo-16α,17α-dihydroxy-4-pregnene-3,11,20-trione (IIa) in 6 ml. of pyridine was added 0.6 ml. of acetic anhydride. After standing at room temperature for 20 hr. the mixture was poured into ice water and filtered to afford 135 mg. of a white powder, m.p. 219–221° (dec.). Crystallization from acetone–petroleum ether gave 105 mg. of IIb, m.p. 228–229°. Further crystallization did not change the melting point; $\nu_{max}$ 3430, 1740, 1718, 1760, 1622, and 1238 cm.$^{-1}$

*Anal.* Calcd. for $C_{25}H_{31}O_8Br$ (539.42): C, 55.66; H, 5.79; Br, 14.82. Found: C, 56.46; H, 5.97; Br, 14.55.

(b) A solution of 575 mg. of osmic acid in 10 ml. of benzene was added to a solution of 926 mg. of the diene Ia in 25 ml. of benzene containing 0.4 ml. of pyridine. The mixture was stirred at room temperature for 7 hr. when a solution of 3.8 g. of sodium sulfite and 3.8 g. of potassium bicarbonate in 40 ml. of water and 25 ml. of methanol was added. After being stirred at room temperature overnight the mixture was filtered, and the residue was washed thoroughly with ethyl acetate. The combined filtrates were washed, dried, and filtered. Evaporation gave an intractable oil which on acetylation resisted crystallization.

The crude diacetate was subjected to partition chromatography on 150 g. of Celite[11] with a ternary system consisting of 10 parts petroleum ether (b.p. 90–100°), 3 parts dichloromethane, and one part ethylene glycol. The second hold-back volume (240 ml.) upon concentration gave 83 mg. of crystals, m.p. 225–227° (dec.). Three crystallizations from acetone–petroleum ether gave 50 mg. of pure IIb, m.p. 228–229° (dec.), $\lambda_{max}^{ethanol}$ 237 mμ (ε 13,700); $[\alpha]_D^{25}$ −26° (c, 0.99, chloroform). Infrared spectral analysis showed this product to be identical with that obtained from the potassium permanganate hydroxylation.

*16α,21-Diacetoxy-17α-hydroxy-4-pregnene-3,11,20-trione* (IIc). A mixture of 60 mg. of zinc dust and 54 mg. of the 12α-bromo-diacetate IIb in 5 ml. of glacial acetic acid was stirred at 15–20° for 20 min. It was then filtered and the separated solid was washed with several portions of ethanol. The combined filtrates were evaporated (bath temperature <40°), and the residue was extracted with ethyl acetate. The extract was washed with saturated sodium bicarbonate and saturated saline solution. The dried extract was filtered and evaporated. A single crystallization of the crude product from acetone–petroleum ether gave 36 mg. of IIc, m.p. 233–234°. The product exhibited a negative Beilstein test for halogen, and its infrared spectrum was identical with that of an authentic sample.[5b,7]

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(7) W. S. Allen and S. Bernstein, *J. Am. Chem. Soc.*, **78**, 1909 (1956).

(8) Here also the reaction mixture was complex and no attempt was made to isolate and identify the by-products.

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(10) Melting points are uncorrected. The petroleum ether used had a b.p. 60–70°, unless otherwise specified. The infrared absorption spectra were determined in a potassium bromide disk.

(11) The adsorbent was specially treated Celite "545" which was slurried in 6*N* hydrochloric acid and allowed to stand overnight. It was then filtered and was washed with water, followed by alcohol and/or acetone. Finally, it was dried at 100°. Celite is the trade-mark of Johns-Manville Co. for diatomaceous silica products.

## 4-(3-Pyridyl)-4-ketobutyric Acid

HARVEY N. WINGFIELD, JR.

*Received December 19, 1958*

A synthesis of 4-3-pyridyl-4-ketobutyric acid which would give increased yields was desired, as this compound is an intermediate in the synthesis of

DL-desmethycotinine and nornicotine.[1] Previous syntheses have been by the condensation of ethyl nicotinate and diethyl succinate[1] in the presence of sodamide[2] or by the condensation of ethyl bromoacetate with ethyl nicotinoyl acetate.[3]

The present method involving the condensation of diethyl sodiomalonate with bromomethyl ketone, reduces the possibility of concurrently formed condensation products to a minimum, and gives a good yield. The intermediate bromomethyl pyridyl ketone should also be a useful intermediate for synthesis of keto alcohols, esters, substituted malonic esters, keto aldehydes, thiazoles, and similar compounds.

## EXPERIMENTAL

*Bromomethyl pyridyl ketone.* A solution of 6 g. of 3-pyridyl methyl ketone in 20 ml. of acetic acid containing 32% hydrobromic acid was cooled and a solution of 16 g. of pyridine hydrobromide perbromide[4] in 200 ml. of glacial acetic acid was added. Warming slightly and shaking intermittently brought about decolorization and the precipitation of the bromoketone hydrobromide.

The contents of the flask were cooled and 400 ml. of ether were added. After standing at 4° overnight, the precipitate was filtered off, washed well with ether, vacuum dried, and placed in an icebox in a closed container. Under these conditions the hydrobromide was stable and was used in the next step without further purification. A small sample was dissolved in hot acetic acid and precipitated with ether several times to procure a pure sample for analysis.

*Anal.* Calcd. for $C_7H_7NOBr_2$: Br, 56.94. Found: Br, 56.98, 57.00. The yield of crude material was nearly quantitative.

*4-(3-Pyridyl)-4-ketobutyric acid.* To a solution of 0.2 mole of diethyl sodiomalonate in an excess of malonic ester as a solvent was gradually added 0.1 mole bromomethyl-3-pyridyl ketone, stirring continuously. If, after part of the ketone has been added, the reaction remains sluggish, about 20 ml. of ethanol may be added. Care was taken to prevent a rise in temperature.

After about 12 hr. stirring, while in an ice bath, the temperature was permitted to rise to about 25° and stirring continued for another 12 hr. The salt formed was removed by filtration and the filtrate made acid with hydrochloric acid and refluxed to hydrolyze the ester. After 16 hr. the solution was cooled, extracted with ether once, and evaporated to near dryness in a rotating film evaporator. The solution was brought to a *p*H of 5.7 and allowed to crystallize at 4°. The yield averaged about 60% of crude material based on the bromoketone used.

*Anal.* Calcd. for $C_9H_9NO_3$: C, 60.33; H, 5.08. Found: C, 60.32, 60.55; H, 5.13, 5.20.

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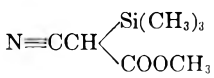
## The Structure of the Trimethylsilyl Derivative of Methyl Cyanoacetate

PETER L. DEBENNEVILLE, MARVIN J. HURWITZ, AND LAWRENCE J. EXNER

*Received December 22, 1958*

A recent note[1] corrects the structure which two of us had assigned to the trimethylsilyl derivative of ethyl acetoacetate. Since we presented the original paper,[2] we have had occasion ourselves to reexamine by spectral methods one other product which we had disclosed there. We had withheld publication pending a more complete clarification; however, none of us at present is working in this field, and it seems appropriate now to present what data we have.

Our original assignment was based primarily on the reaction of trimethylchlorosilane with methyl cyanoacetate.[3] The reported reactions of alkylating agents with cyanoacetic esters have, as far as we know, been observed to give only C-alkylation,[4] and our assignment of C-silylation to give structure I seemed to be a proper deduction. How-



I

ever, examination of the infrared spectrum of the carefully distilled compound showed strong absorption bands at 1623 cm.$^{-1}$ and at 2222 cm.$^{-1}$ The band at 2222 cm.$^{-1}$ is very likely displaced and strengthened absorption attributable to C≡N in a conjugated position.[5] The band at 1623 cm.$^{-1}$ is attributed to the absorption due to a carbon-carbon double bond in conjugation with the nitrile group. A relatively small absorption at 1761 cm.$^{-1}$, which progressively disappeared in successive fractions, is attributed to methyl cyanoacetate contaminant; otherwise no major carbonyl peak was apparent. Two strong bands at 850 cm.$^{-1}$ and 1250 cm.$^{-1}$ correspond to $Si(CH_3)_3$ absorption. There was no absorption in the reported range for normal Si—O stretching vibrations, but there were strong bands at 965 cm.$^{-1}$ and 1105 cm.$^{-1}$, either of which could be so assigned, in view of the evidently unusual structure.[6] A weak band at 3100 cm.$^{-1}$ is a

(1) R. West, *J. Org. Chem.*, **23**, 1552 (1958).

(2) M. J. Hurwitz, P. L. de Benneville, and R. A. Yoncoskie, Abstracts of Papers, 131st National Meeting, American Chemical Society, Miami, Fla., 1957, p. 52–160.

(3) M. J. Hurwitz and P. L. de Benneville, U.S. Patent **2,775,605**.

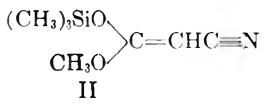
(4) A. C. Cope, H. L. Holmes, and H. O. House, *Org. Reactions*, IX, 109 (1957).

(5) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, 2nd ed., Methuen & Co., Lt., London, Eng., 1957, p. 264.

(6) Bellamy (footnote 5, p. 340) suggests 1090–1020 cm.$^{-1}$ for normal Si—O absorption. West (footnote 1) reports "near 1000 cm.$^{-1}$" for Si—O in a more closely related structure.

probable CH stretching vibration arising from the structural unit =CH—.

This evidence allows a probable assignment of the structure II to the compound. None of these



II

data corresponds to the original structural assignment. We therefore wish to withdraw the assignments that we had previously made.[2,3]

## EXPERIMENTAL

*Reaction of trimethylchlorosilane with methyl cyanoacetate.* To a solution of methyl cyanoacetate (49.5 g., 0.5 mole) and triethylamine (202 g., 2.0 moles) in benzene (264 g.) at −5° was added dropwise a solution of trimethylchlorosilane (54.5 g., 0.5 mole) in benzene (264 g.) over a period of 1.5 hr. During the addition, the temperature was held at 5° with an ice bath. The reaction mixture was filtered, and the filtrate was stripped and carefully distilled through a well dried 6-inch Vigreux column. After removal of unreacted cyanoacetic ester, the product (42.5 g., 50%) distilled as a colorless liquid, very sensitive to moisture, at 75–76°/0.65 mm., $n_D^{25}$ 1.4465.

*Anal.* Calcd. for $C_7H_{13}O_2NSi$: C, 49.1; H, 7.6; N, 8.2. Found: C, 49.1; H, 7.6; N, 8.2.

Infrared spectra were carried out on films, using a Perkin-Elmer Model 21 spectrophotometer.

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# Cleavage of Tetrahydrofuran by Triphenylmethylmagnesium Bromide

FREDERICK R. JENSEN AND RONALD L. BEDARD

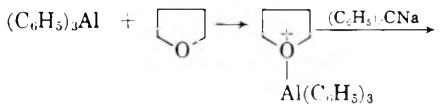
*Received December 23, 1958*

Most ethers, except strained cyclic ethers and allyl ethers, are not cleaved by Grignard reagents at temperatures below 175°.[1] For example, ethylene oxide reacts with Grignard reagents at room temperature,[2] trimethylene oxide is cleaved by Grignard reagents in refluxing benzene,[3] but anisole is cleaved by Grignard reagents at 200°. Cleavage of tetrahydrofuran, which is not highly strained, has not been generally found to occur, and tetrahydrofuran has been widely used as a solvent for the preparation and reaction of Grignard reagents.

In an attempt to prepare *t*-butylmagnesium bromide in tetrahydrofuran, Assarson[4] obtained a white precipitate which he assumed to be a product of the cleavage of tetrahydrofuran by the Grignard reagent, and was unable to find any gas evolved upon hydrolysis of the reaction mixture. However, in a reinvestigation of this reaction, Normant[5] was able to prepare *t*-butylmagnesium bromide in normal fashion in tetrahydrofuran, and obtained the normal addition product from further reaction with acetaldehyde. He proposed that the white precipitate was analogous to the precipitates obtained with dioxane.

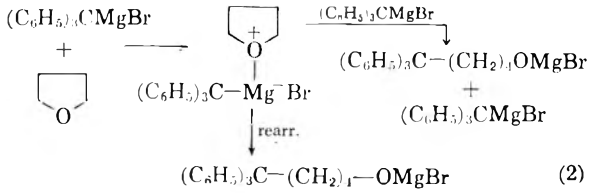
In a study of organometallic complexes, Wittig and co-workers[6] found that in the presence of triphenylaluminum and triphenylboron, triphenylmethylsodium reacts with tetrahydrofuran at room temperature to produce 5,5,5-triphenylpentanol-1 in good yield. Triphenylmethylsodium alone, however, was ineffective as a cleaving agent. These workers also found that 9-fluorenyllithium and 9-phenyl-9-fluorenyllithium also cleave tetrahydrofuran in good yield in the presence of triphenylaluminum.

It seems reasonable that triphenylaluminum forms an etherate complex with tetrahydrofuran, and the complex then undergoes attack by triphenylmethylsodium to lead eventually to the product obtained. The decreased complexing ability of sodium accounts for the fact that no cleavage was observed in the absence of triphenylaluminum.



$$(C_6H_5)_3C-(CH_2)_4-ONa + (C_6H_5)_3Al \quad (1)$$

We have found that triphenylmethylmagnesium bromide also cleaves tetrahydrofuran to produce 5,5,5-triphenylpentanol-1 in excellent yield. In this case, the Grignard reagent complexes strongly with the ether, and the complex can then undergo either further attack by another molecule of Grignard reagent, or intramolecular rearrangement to form the product:



$$(C_6H_5)_3C-(CH_2)_4-OMgBr \quad (2)$$

Triphenylmethylmagnesium bromide is ionized in solution to a sufficient extent to impart the dark red color of the triphenylmethylcarbanion[6] to the solution. Since most Grignard reagents are not highly ionized in solution and do not cleave tetrahydrofuran, it is not unlikely that the cleavage occurs by way of the carbanion.

(1) M. S. Kharasch and O. Reinmuth, *Grignard Reactions of Nonmetallic Substances*, Prentice-Hall, Inc., New York, 1954, pp. 961–1022.

(2) For example, see R. C. Huston and A. H. Agett, *J. Org. Chem.*, **6**, 123 (1941).

(3) S. Searles, *J. Am. Chem. Soc.*, **73**, 124 (1951).

(4) L. O. Assarson, *Acta Chem. Scand.*, **10**, 1510 (1956).

(5) H. Normant, *Bull. soc. chim. France*, 11-12, 1444 (1957).

(6) G. Wittig and A. Ruckert, *Ann.*, **566**, 111 (1950); G. Wittig and O. Bub, *Ann.*, **566**, 127 (1950).

There exists considerable evidence indicating that the addition of magnesium halides increases the rate of cleavage of ethers by Grignard reagents.[1-3] In the present case, because of the size of the group attached to magnesium, the Schlenck equilibrium should lie almost completely toward the monoalkylmagnesium compound and the concentration of magnesium bromide in solution should be very low. This does not preclude the possibility that magnesium bromide, even though present in very low concentration, is the effective complexing agent instead of triphenylmethylmagnesium bromide.

Triphenylmethylmagnesium bromide was prepared in normal fashion in tetrahydrofuran. The resulting dark red color disappears when reaction is complete. After 24 hr. at room temperature, the red color still persisted but upon analysis the products were 29.6% triphenylmethane, and 62.9% 5,5,5-triphenylpentanol-1. After 5 hr. reflux the red color had disappeared and the products were 13.0% triphenylmethane and 73.5% 5,5,5-triphenylpentanol-1.

In order to ascertain whether the results were due to possible cleavage of the tetrahydrofuran during formation of the Grignard reagent, the Grignard reagent was also prepared in 2:1 benzene-ethyl ether solution, and tetrahydrofuran was then added to the solution. After 10 hr. reflux the red color had disappeared, and upon hydrolysis, a 94.6% yield of 5,5,5-triphenylpentanol-1 was obtained.

## EXPERIMENTAL

Triphenylmethyl bromide was prepared using the method of Bachmann[7] by reacting triphenyl carbinol with acetyl bromide. The product was subjected to further purification by recrystallizing from 3:1 methylene chloride–benzene under a nitrogen atmosphere, m.p. 155.1–155.5° (lit.,[8] m.p. 153–155°). The tetrahydrofuran was purified by redistilling from potassium hydroxide pellets until the pellets remained white after distillation, then distilling from calcium hydride, and finally distilling from 0.1*M* solution of triphenylmethylmagnesium bromide under an atmosphere of nitrogen.

*Reactions in tetrahydrofuran as solvent.* The triphenylmethylmagnesium bromide was prepared by adding a solution of 22.7 g. (0.0703 mole) triphenylmethyl bromide in 200 ml. tetrahydrofuran to 2.30 g. (0.096 mole) magnesium shavings, which were covered with tetrahydrofuran, under a nitrogen atmosphere at 25°. The reaction began immediately and the solution turned deep red. After the reaction was complete the contents of the flask were diluted with tetrahydrofuran to a total volume of 270 ml.

After allowing the solution to stand at room temperature, a 42.5-ml. aliquot was hydrolyzed with dilute hydrochloric acid, ether was added to extract the organic material, the ether extraction was dried with calcium chloride, the drying agent removed by filtration, and the ether was removed. The material thus obtained was dissolved in pentane-benzene (5%) and this solution was placed on an alumina column. Elution with pentane gave 0.828 g. triphenylmethane (29.6%), m.p. 92.4–94.5° after recrystallization from hexane (lit.,[9] m.p. 94.5–95.5°). Elution with carbon tetrachloride gave 0.33 g. unidentified material. Elution with ether gave 2.28 g. 5,5,5-triphenylpentanol-1 (62.9%), m.p. 119–119.7° after recrystallization from cyclohexane and sublimation (lit.,[6] m.p. 118–119°).

*Anal.* Calcd. for $C_{23}H_{24}O$: C, 87.34; H, 7.59. Found: C, 87.23; H, 7.77.

*p*-Nitrobenzoate, m.p. 107.2–108.5°.

*Anal.* Calcd. for $C_{30}H_{27}O_4N$: C, 77.42; H, 5.81; N, 3.01. Found: C, 77.33; H, 5.87; N, 3.00.

A 50-ml. aliquot of the Grignard solution was refluxed 5 hr. and the solution was worked up as before. The products found were: 0.431 g. triphenylmethane (13.0%); 0.11 g. unidentified material; 3.14 g. 5,5,5-triphenylpentanol-1 (73.5%).

*The reaction of triphenylmethylmagnesium bromide with tetrahydrofuran in benzene-ether solution.* The Grignard reagent was prepared by mixing 16.42 g. (0.0508 mole) triphenylmethyl bromide, 1.23 g. (0.0513 mole) magnesium shaving, 60 ml. dry benzene and 30 ml. anhydrous ether and then refluxing the mixture for 30 min.[9] A 25-ml. portion of tetrahydrofuran was added and the mixture was refluxed for 10 hr. The products were isolated as before. The yields of crude materials were 15.2 g. 5,5,5-triphenylpentanol-1 (94.6%) and a small amount of triphenylmethane.

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(7) W. E. Bachmann, in *Org. Syntheses*, **Coll. Vol. III**, 841 (1955).

(8) C. G. Swain, C. B. Scott, and K. H. Lohman, *J. Am. Chem. Soc.*, **75**, 137 (1953).

(9) M. Gomberg and W. E. Bachmann, *J. Am. Chem. Soc.*, **52**, 2455 (1930).

## Clemmensen Reduction of Acetophenone

MARVIN POUTSMA AND ENNO WOLTHUIS[1]

*Received December 24, 1958*

The Clemmensen reduction of a carbonyl to a methylene group has been applied to a large variety of aldehydes and ketones. An excellent review has been published by Martin.[2] When applied to the more complex compounds, *e.g.* bifunctional, this reduction often leads to rearrangements, and this aspect of it has been studied fairly extensively in recent years. However, little work has been done to clarify the mechanism by which relatively simple compounds like acetophenone are reduced. It seemed likely that gas chromatography as an analytical tool might be useful in identifying the intermediates involved in such a reduction.

Literature references on the mechanism are confusing. While one[3] states that the alcohol cannot be an intermediate because alcohols are not reduced by the Clemmensen medium, another[4] assumes the alcohol to be formed but consumed as rapidly as formed. In a study on the Clemmensen reduction of acetophenone, Steinkopf and Wol-

(1) Calvin College, Grand Rapids, Mich.; Sr. author.

(2) E. L. Martin, *Org. Reactions*, I, 155–209 (1942).

(3) F. Royals, *Advanced Organic Chemistry*, Prentice-Hall, Englewood Cliffs, N. J., 1954, p. 110.

(4) C. Weygand, *Organic Preparations*, Heath and Co., Boston, 1954, p. 51.

fram[5] isolated ethylbenzene, styrene and its polymers, and the pinacolone of acetophenone. They suggested the likelihood of alcohol formation followed by dehydration and reduction, and postulated that (1-chloroethyl) benzene might take part in the reaction. Therefore, a study was undertaken to clarify the mechanism of the Clemmensen reduction of acetophenone with the help of gas chromatography to detect the intermediates and products of the reaction.

*Experimental observations.* Anticipating the possible intermediates to be ethylbenzene, styrene and $\alpha$-methylbenzyl alcohol, synthetic mixtures of these with acetophenone were prepared for analysis by gas chromatography to establish the efficiency of this method of analysis. It was found that a 10-foot column of 30% Harflex 370 plasticizer[6] on Burrell carrier, operated at 175°, with He at 40 ml. per min, successfully separated all of the components of such a mixture, and that as little as 1% of the alcohol could be detected with a filament current of 105 ma. in the conductivity cell detector.[7]

The reduction of acetophenone was faster than expected, only 15–20% of it remaining after 20 min refluxing. The ratio of ethylbenzene to styrene found was about 7:1, changing only slightly as the reaction progressed. After one hour, only traces of the ketone remained, but thereafter the styrene slowly changed to ethylbenzene, especially in the presence of a large excess of acid. At no time could the alcohol be detected in the reaction mixture, even at lower acid concentrations and lower temperatures.

$\alpha$-Methylbenzyl alcohol cannot long exist in the reducing medium. After 5 minutes it was completely changed to styrene and a little ethylbenzene, after which the styrene was gradually converted to ethylbenzene. Using 21% HCl, the amount of ethylbenzene in the total hydrocarbons was 70, 80, 83, and 88% after 15, 25, 35, and 60 min. respectively. As the acid concentration was reduced the ethylbenzene content dropped, after 15 min. reaction time, to 67 and 52% for 15 and 12.5% HCl respectively, 21% HCl alone quickly changed the alcohol to the corresponding chloride, which gradually dehydrated to styrene. Reduction of the alcohol by HCl with zinc instead of its amalgam gave only styrene and its polymer.

Styrene was reduced slowly by the usual Clemmensen medium. After 15, 30, 45, 60, 90, and 120 minutes the yields of ethylbenzene were 25, 45, 58, 63, 70, and 79% respectively. Omitting the zinc amalgam, styrene was partly changed to (1-chloroethyl) benzene, which was proved to be identical with that obtained from the alcohol with HCl.

(1-Chloroethyl)benzene was readily reduced by the C. procedure to ethylbenzene, with the formation of only traces of styrene.

Inasmuch as the experiments indicated that the chloride is an important intermediate, a few experiments were tried in which 20% sulfuric acid was substituted for HCl. Acetophenone was reduced in this way to ethylbenzene and styrene but more slowly, and the styrene/ethylbenzene ratio was greater than before. Again, no alcohol could be detected at any time. Although the alcohol was reduced by the amalgam in HCl to ethylbenzene, styrene was the chief product when sulfuric acid was employed, and was formed very rapidly. Even after 6 hours in 20% sulfuric acid at reflux temperature, only traces of ethylbenzene were detected. Likewise, styrene was not appreciably reduced to ethylbenzene in the sulfuric acid medium.

It should be mentioned in passing that whenever styrene was formed in the presence of HCl small deposits of polystryene were also detected among the products.

*Interpretation and conclusions.* Contrary to much of the literature, $\alpha$-methylbenzyl alcohol is reduced by the Clemmensen method to ethylbenzene, the rate of this reaction decreasing with lower concentrations of HCl. These facts, together with the fact that the alcohol is very rapidly changed to the corresponding chloride and styrene, make it reasonable to suppose that the alcohol can be an intermediate, even though it could not be detected by gas chromatographic methods. Furthermore, since the chloride is reduced more rapidly than styrene to ethylbenzene, and the change from styrene to the chloride is a reversible one under the conditions of the Clemmensen reduction, it seems likely that acetophenone is reduced to ethylbenzene primarily by way of the alcohol and the chloride, and secondarily *via* the alcohol-styrene-chloride route. This theory is supported by the fact that in sulfuric acid the alcohol, as well as acetophenone, gave much more styrene and much less ethylbenzene in a given time, and styrene was hardly at all reduced to ethylbenzene. In the presence of HCl the chloride–styrene equilibrium is established as fast as the chloride is formed, and the ethylbenzene is derived mainly from the reduction of the chloride.

## EXPERIMENTAL

*Preparation of amalgam.* Fifty grams of zinc, Baker's 20-mesh granules, were etched a few minutes with dilute HCl, rinsed well with water, and then stirred with 100 ml. aq. 5% mercuric chloride containing 3 ml. concd. HCl. After 15 min., the liquid was decanted and the amalgam thoroughly washed with water.

*Reduction procedure.* Two hundred milliliters of 21% HCl were heated to reflux temperature in a 500-ml. 3-neck flask,

(5) W. Steinkopf and A. Wolfram, *Ann.*, **430**, 113–161 (1922).

(6) Obtained from Harchem Div., Wallace and Tiernan, Belleville, N. J.

(7) The authors are indebted to R. S. Gohlke of the Dow Chemical Co. for assistance in assembling the apparatus.

fitted with a thermometer, a reflux condenser, and an agitator for vigorous agitation. The amalgam was then added, followed by 30 g. of the compound to be reduced, added through the condenser. Vigorous agitation was maintained at reflux temperature. Samples were taken at timed intervals by stopping the agitator, allowing the layers to separate, drawing off some of the top layer, and washing it well with water to remove all acid. Each sample was then analyzed by gas chromatography as described here.

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## Pyrolysis of 2-Butyl Acetate

WERNER O. HAAG AND HERMAN PINES

*Received January 3, 1959*

In conjunction with the study of the stereoselective dehydration of butanols over alumina catalysts[1,2] the pyrolytic decomposition of 2-butyl acetate was reinvestigated. It was reported in the literature[3,4] that the pyrolysis of acetates gives exclusively the least substituted olefins following the Hoffmann rule. Contrary to the above reported findings and in accordance with recently published results on the pyrolytic decomposition of 2-heptyl acetate,[5] it was found that the pyrolysis of 2-butyl acetate yields a mixture composed of 1- and 2-butenes. The concentration of 1-butene in the reaction product varied from 55 to 69%, depending upon the experimental conditions used. The remainder of the product was composed of *cis*-2- and *trans*-2-butene in an approximate ratio of *cis*/*trans* = 0.5. The percentage of 1-butene produced approximates that expected from statistical elimination of the neighboring hydrogen atoms.

The experimental results are summarized in Table I. The flow rate of 2-butyl acetate in the experiments carried out at 450° and 510° was varied and in the case of 450° experiments the composition of the butenes produced was plotted against the percentage of 2-butyl acetate which underwent pyrolysis. By extrapolating the plot to zero conversion, the composition of the primary products of the pyrolysis could be established. They were composed of 71% 1-butene, 9% *cis*-2- and 20% *trans*-2-butene (Fig. 1). The ratios of *cis*- to *trans*-2-butene approximate the thermodynamic equilibrium mixture.[6] Butenes *per se* do not undergo isomerization under the experimental conditions used for the pyrolysis of the acetate. The reason therefore for the change of the composition of the butenes with change in the extending of 2-butyl acetate decomposition is not immediately apparent

TABLE I

PYROLYSIS OF 2-BUTYL ACETATE

| Temp., °C. | Flow Rate, Ml./hr. | Nitrogen Added | Packing Kind | Conversion, % | Butenes 1- | *cis*-2- | *trans*-2 | *cis*/*trans* |
|---|---|---|---|---|---|---|---|---|
| 410 | 5 | – | Glass | 12 | 61.5 | 25.9 | 12.6 | 0.49 |
| 450 | 5 | – | Glass | 100 | 57.8 | 27.4 | 14.8 | 0.54 |
| 450 | 10 | – | Glass | 54 | 62.0 | 24.2 | 13.8 | 0.57 |
| 450 | 50 | – | Glass | 9 | 69.1 | 20.7 | 10.2 | 0.49 |
| 450 | 5 | + | Glass | 47 | 55.4 | 28.4 | 16.2 | 0.57 |
| 490 | 14 | + | Quartz | 82 | 55.4 | 28.6 | 16.0 | 0.56 |
| 510 | 5 | – | Glass | 81 | 58.3 | 27.0 | 14.7 | 0.54 |
| 510 | 20 | – | Glass | 69 | 58.2 | 27.1 | 14.7 | 0.54 |
| 510 | 40 | – | Glass | 65 | 61.6 | 25.2 | 13.2 | 0.52 |
| 525 | 12 | + | Quartz | 71 | 57.5 | 26.7 | 15.8 | 0.58 |

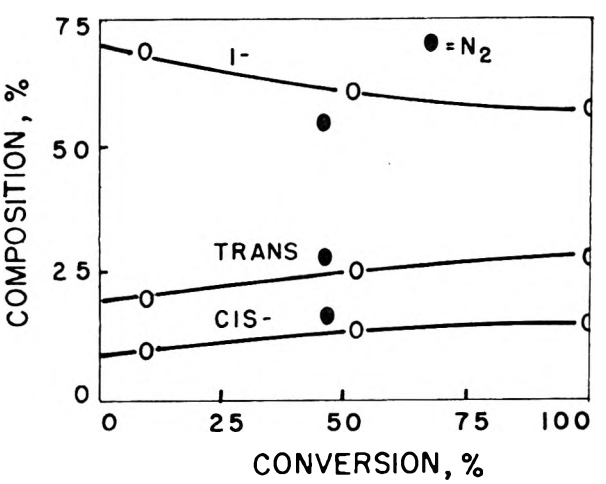


Fig. 1. Pyrolysis of 2-butyl acetate at 450°. Primary products: 71%. 1-butene, 20% *trans*-2-, 9%, *cis*-2-

*n*-Butyl acetate on pyrolysis formed only 1-butene.

(1) H. Pines and W. O. Haag, *J. Org. Chem.*, **23**, 328 (1958).

(2) H. Pines and W. O. Haag, Paper presented before the Division of Colloid Chemistry, American Chemical Society, April 13–18, 1958, San Francisco, Calif.

(3) W. J. Bailey and C. King, *J. Am. Chem. Soc.*, **77**, 75 (1955).

(4) W. J. Bailey, J. J. Hewitt, and C. King, *J. Am. Chem. Soc.*, **77**, 357 (1955).

(5) E. E. Royals, *J. Org. Chem.*, **23**, 1822 (1958).

(6) J. E Kilpatrick, E. J. Prosen, K. S. Pitzer and F. D. Rossini, *J. Research Natl. Bur. Stand.*, **36**, 554 (1946).

The apparatus used for the pyrolysis of the acetates consisted of a Pyrex reaction tube having a reaction zone of 1.5 cm. outside diameter and packed with 15 ml. of about 1/8 inch quartz chips or 1/8 inch glass beads. The tube was heated by a thermostatically controlled vertical furnace. The acetates were introduced by means of a motor driven syringe.

The butenes were analyzed by vapor phase chromatography using a column described previously.[1]

*Acknowledgment.* The authors wish to thank Mr. E. M. Lewicki for assisting in the experimental work.

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## Preparation of Pyrrole

JOHN M. PATTERSON AND PETER DRENCHKO

*Received January 5, 1959*

The requirement for relatively large quantities of pyrrole in this laboratory prompted an investigation for a rapid inexpensive synthesis of this material. Of the methods reported in the literature, the dehydrogenation of pyrrolidine using a flow system offered the greatest promise.

Catalysts which have been used in the dehydrogenation of cyclic amines include platinum or palladium on asbestos,[1] oxides of magnesium, calcium or zinc or mixtures of these,[2] and nickel–nickel chromite.[3] Although the catalysts most frequently employed in the dehydrogenation of pyrrolidine or substituted pyrrolidines have been platinum or palladium on asbestos, the effectiveness of rhodium on alumina in reducing nitrogen heterocyclic systems,[4] suggested that it might be a superior dehydrogenation catalyst for cyclic amines. Accordingly, this was the catalyst investigated in these experiments.

The optimum conditions for the dehydrogenation of pyrrolidine using rhodium on alumina were 650° with an HLSV[5] of 8–10. Shorter contract times resulted in lower yields of pyrrole while longer contact times produced more decomposition. It is interesting to note that the dehydrogenation using platinum or palladium on asbestos is reported to occur at 300°.[1]

Two other potential catalysts were investigated: Berl saddles were ineffective; activated alumina pellets were about half as effective as rhodium on alumina at optimum conditions.

In addition to pyrrole and unreacted pyrrolidine in the dehydrogenated product, there was obtained some of the 2-(2-pyrrolidyl)pyrrole reported by Fuhlhage and Vander Werf.[6] It appears that 1-pyrroline is an intermediate in dehydrogenation reactions in which rhodium on alumina is the catalyst.

The slightly better yield of pyrrole obtained in the distillation procedure is probably due to the dissociation of the 2-(2-pyrrolidyl)pyrrole present in the crude dehydrogenation mixture.

Bell[7] reports that diethylamine can be converted into pyrrole when introduced into a hot tube. Using the optimum conditions of the pyrrolidine experiments and a rhodium on alumina catalyst, pyrrole was produced in less than 1% yield.

### EXPERIMENTAL[8]

*Materials.* The pyrrolidine used in these experiments was the practical grade supplied by the Matheson, Coleman and Bell Co. The rhodium catalyst, 0.5% rhodium on 1/8" activated alumina pellets, was obtained from Baker and Co., Inc. and the Puralox catalyst, 1/8" activated alumina pellets, from the Harshaw Scientific Co.

*Apparatus.* The apparatus consisted of a vertically arranged vycor reactor tube (2.5 × 30 cm.) in a continuous flow system. The reactor contained 30 ml. of the catalyst and an upper layer (30 ml.) of Berl saddles. A vycor preheater tube containing 30-ml. Berl saddles was used to volatilize the sample which was introduced into the preheater from a buret and flushed through the system by a stream of dry nitrogen.

*Preparation of pyrrole.* Eighty-five grams of pyrrolidine was introduced into the flow type apparatus at an HLSV of 8–10 and nitrogen flow rate of 440 ml./min. The temperature of the reactor, containing 30 ml. of 0.5% rhodium on alumina was maintained at 650° and the preheater temperature was maintained at 300°. The weight of the condensed pyrolysis product was 70 g. The crude product was added to 200 ml. of water, saturated with Dry Ice and then separated from the carbonic acid solution. After a second treatment, the combined aqueous portions were extracted with three 100-ml. portions of ether, the ether extract combined with the carbonic acid insoluble layer and dried over sodium sulfate. Distillation of the residue after removal of the drying agent and the ether yielded 35.6 g. (45%) of pyrrole, b.p. 127–129°, $n_D^{20}$ 1.5040. Analysis by gas chromatography indicated the pyrrole to be 99.5% pure. In addition to the pyrrole, a tarry residue (5.1 g.) was obtained.

The crude product could also be purified by distillation in a Podbielniak High-Temperature Fractional Distillation Apparatus to give pyrrole in 50% yield. Columns of lesser efficiency were ineffective.

(1) N. D. Zelinsky and Y. K. Yur'ev, *Ber.*, **62**, 2589 (1929).

(2) I. G. Farben Ind., Brit. Patent **515,865**, Dec. 15, 1939.

(3) H. Adkins and L. G. Lundsted, *J. Am. Chem. Soc.*, **71**, 2964 (1949).

(4) Brochure, *The Role of Platinum Group Metal as Catalysts*, Baker and Co., Newark, N. J.

(5) Hourly liquid space velocity = volume of reactant/volume of catalyst/hour.

(6) D. W. Fuhlhage and C. A. Vander Werf, *J. Am. Chem. Soc.*, **80**, 6249 (1958).

(7) C. A. Bell, *Ber.*, **10**, 1868 (1877).

(8) Melting points were taken on a Fisher-Johns melting point apparatus and are corrected. Boiling points are uncorrected. Microanalyses were by Weiler and Strauss, Oxford, England.

*Investigation of the carbonic acid soluble portion.* The carbonic acid extract of the pyrolysis product was made strongly alkaline with sodium hydroxide, extracted with three 100-ml. portions of ether and the ether extract dried over potassium carbonate. Distillation of the ether extract, after removal of the ether, gave 16.3 g. of a water–pyrrolidine mixture, b.p. 78–98°, 4.8 g. of a semi-solid liquid, b.p. 122–169° (1 mm.) and 9.7 g. of tarry residue.

*2-(2-Pyrrolidyl)pyrrole* (I). The semi-solid liquid, b.p. 122–169° (1 mm.) on several recrystallizations from Skellysolve B gave 3.6 g. of a white crystalline solid, melting at 85.5–86.5°. The solid was basic and gave a positive Ehrlich test for pyrrole.

*Anal.* Calcd. for $C_8H_{12}N_2$: Neut. equiv., 136. Found: Neut. equiv., 134, 138.

Literature[6] b.p. 94° (0.5 mm.); m.p. 86.3–87.8°.

*Picrate of* I. Treatment of a solution of I in 95% ethanol with a saturated ethanolic picric acid solution produced a picrate which melted at 170–171° after several recrystallizations from 95% ethanol. Literature[6] m.p. 164–165.5° (uncorrected).

*Anal.* Calcd. for $C_{14}H_{15}N_5O_7$: C, 46.0; H, 4.2; N, 19.2 Found: C, 46.7; H, 4.2; N, 18.8.

*Acknowledgment.* One of us (J.M.P.) thanks the University of Kentucky Research Fund Committee for a grant-in-aid for the purchase of some of the equipment used in this research.

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## Rearrangement of 9α-Hydroxy-4-androstene-3,17-dione

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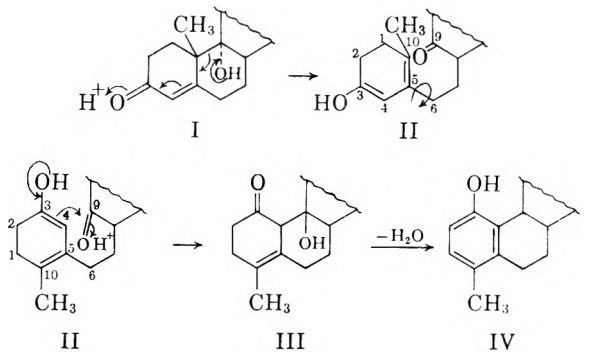
*Received January 5, 1959*

4-Androstene-3,17-dione was shown to be hydroxylated in the 9α-position with a species of Nocardia (A20-10) isolated from soil.[1] We have observed that treatment of the hydroxylated product (I) with pyridine hydrochloride at 218° resulted in a rearrangement to 1-hydroxy-4-methylestra-1,3,5(10)-trien-17-one (IV).[2]

A possible mechanism for this transformation is outlined in the partial formulas (I–IV). The initial step involves a reverse aldol type of reaction, which parallels that previously postulated for the microbiological conversion of 4-androstene-3,17-dione to 9,10-seco-3-hydroxy-1,3.5(10)-androstatriene-9,17-dione,[3] except in the present case the reaction is facilitated by acid. Rotation about the $C_5$—$C_6$ bond of II places $C_4$ in a favorable position to undergo an aldol condensation with the carbonyl group at $C_9$. Dehydration of the aldol product (III)




followed by migration of the resulting double bond into ring A and enolization complete the transformation.

### EXPERIMENTAL

A mixture of 1.00 g. of 9α-hydroxy-4-androstene-3,17-dione, m.p. 222–223.5°, and 10 g. of pyridine hydrochloride was maintained at 218° for 50 min. in an atmosphere of nitrogen. The reaction then was cooled, diluted with water, and chilled in an ice bath. The precipitate, which was collected by filtration, washed well with water, and dried, could not be induced to crystallize from ether–petroleum ether (60–68°). The residue remaining after the organic solvents had been removed was chromatographed on 70 g. of silica gel. The column was eluted with varying proportions of benzene–ethyl acetate. Elution with 5% ethyl acetate in benzene gave 404 mg. of a mixture of oil and solid. Two hundred sixty-seven mg. of this mixture was washed free of oil with ether. The solid, which remained, was recrystallized from ether–petroleum ether (60–68°) to afford 57 mg. of colorless massive rods, m.p. 239–248°. Repeated crystallization from ether–petroleum ether (60–68°) raised the m.p. to 251–254°, undepressed by an authentic sample of 1-hydroxy-4-methylestra-1,3,5(10)-trien-17-one (IV).[2,4]

Its infrared spectrum determined in KBr was identical with that of the authentic sample of IV. $\lambda_{max}^{MeOH}$ 281–286 mμ (ε 2250), $\lambda_{min}^{MeOH}$ 249.5 mμ (ε 182); $\lambda_{max}^{KBr}$ 3.07, 5.82, 6.28, 12.28μ.

Other fractions obtained from the column proved to be intractable tars and resins.

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(1) R. M. Dodson and R. D. Muir, *J. Am. Chem. Soc.*, 80, 6148 (1958).

(2) (a) A. S. Dreiding, W. J. Plummer, and A. J. Tomasewski, *J. Am. Chem. Soc.*, 75, 3159 (1953). (b) A. S. Dreiding and A. Voltman, *J. Am. Chem. Soc.*, 76, 537 (1954).

(3) R. M. Dodson and R. D. Muir, *J. Am. Chem. Soc.*, 80, 5004 (1958).

(4) We are indebted to Drs. Willard M. Hoehn and Richard A. Mikulec of our laboratory for providing us with a sample of 1-hydroxy-4-methyl-estra-1,3,5(10)-trien-17-one prepared according to ref. 2.

## Method for Preparing 2-Aryl-3-aroylpropionitriles

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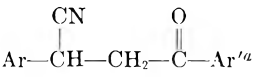
An attempt was made to prepare 2-phenyl-3-benzoylpropionitrile by treating benzaldehyde with acetophenone and sodium cyanide.[1] The major

(1) R. B. Davis, *J. Org. Chem.*, 24, 880 (1959).

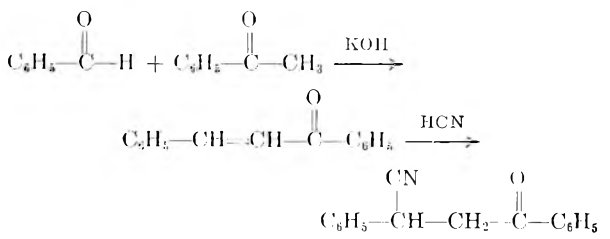
TABLE I



| Ar | Ar′ | Yield, % | M.P., °C.[b] Crude | Recrystd. | Carbon, % Calcd. | Found | Hydrogen, % Calcd. | Found |
|---|---|---|---|---|---|---|---|---|
| $C_6H_5$ | $C_6H_5$ | 77–82 | 124–126 | 126–127 | | | | |
| $p$-$CH_3OC_6H_4$ | $C_6H_5$ | 72 | 115–117 | 116–118 | 76.96 | 76.94 | 5.70 | 5.68[c] |
| $C_6H_5$ | $p$-$CH_3C_6H_4$ | 51 | 67–69 | 72–73 | 81.90 | 82.24 | 6.06 | 5.96[d] |
| $o$-$ClC_6H_4$ | $C_6H_5$ | 76 | 106–108 | 107–109 | 71.25 | 71.54 | 4.48 | 4.63 |
| $p$-$ClC_6H_4$ | $C_6H_5$ | 89 | 116–118 | 117–119 | 71.25 | 71.35 | 4.48 | 4.49 |
| $p$-$CH_3OC_6H_4$ | $p$-$CH_3C_6H_4$ | 67 | 95–99 | 103–105 | 77.39 | 77.49 | 6.13 | 6.22 |
| $o$-$ClC_6H_4$ | $p$-$CH_3OC_6H_4$ | 85 | 118–120 | 118–120 | 68.11 | 68.25 | 4.71 | 4.72 |

[a] Ar is from the aldehyde, Ar—C(=O)—H. Ar′ is from the aryl methyl ketone, Ar′—C(=O)—$CH_3$. [b] Melting points are uncorrected. [c] Nitrogen, Calcd. 5.28, found 5.18. [d] Nitrogen, Calcd. 5.62, found 5.74.

product of the reaction, however, was not the expected propionitrile. The preferred method for preparing 2-phenyl-3-benzoylpropionitrile has been by the addition of hydrogen cyanide to benzalacetophenone,[2] which in turn may be prepared by the base catalyzed condensation of benzaldehyde with acetophenone.[3] As was previously reported,[4] we have likewise found that hydrogen cyanide does not add to benzalacetophenone in the absence of a metal cyanide. Likewise the use of sodium or potassium cyanide alone, yields a mixture of products. The best method for adding hydrogen cyanide to benzalacetophenone employs an alkali cyanide and a weak acid such as acetic acid.[2,4] In search of a more convenient procedure for preparing 2-phenyl-3-benzoylpropionitrile, it occurred to us that there is no need to isolate the intermediate benzalacetophenone since it forms in excellent yield[3] in a basic medium. The addition of an excess of hydrogen cyanide to the original reaction mixture seemed, theoretically at least to constitute ideal conditions for the second step in the process.




When benzaldehyde and acetophenone were reacted in the manner proposed, 2-phenyl-3-benzoylpropionitrile was obtained in 77 to 82% yields. Furthermore it was found that the procedure is general to the extent that other aromatic aldehydes and other aryl methyl ketones can be used. Employing this method a number of new 2-aryl-3-aroylpropionitriles were prepared. Table I will serve to illustrate the versatility of the procedure.

(2) G. F. H. Allen and R. K. Kimball, *Org. Syntheses*, **10**, 80 (1930).

(3) E. P. Kohler and H. M. Chadwell, *Org. Syntheses*, **Coll. Vol. I**, 78 (1941).

(4) A. C. O. Hann and A. Lapworth, *J. Chem. Soc.*, **85**, 1355 (1904).

### EXPERIMENTAL

*Preparation of 2-phenyl-3-benzoylpropionitrile.* Twenty-six grams of potassium hydroxide (assay 85%) was dissolved in 400 ml. of absolute acetone-free methanol by heating. The solution was cooled to room temperature on a water bath; 66 g. of acetophenone and then 53 g. of benzaldehyde were added with stirring. Gentle stirring was continued while the water bath was heated at 25–30° for 3 hr. The reaction mixture was then allowed to stand at room temperature overnight.

Hydrogen cyanide (caution[5]) was prepared[6] by adding a solution of 100 g. of sodium cyanide in 200 ml. water to a solution of 200 g. concentrated sulfuric acid in 120 ml. water over 25 min. The hydrogen cyanide evolved was collected in 200 ml. absolute acetone-free methanol cooled on an ice bath. The hydrogen cyanide solution was added to the original reaction mixture described above. While gentle stirring was maintained, the water bath was heated slowly to 50–55°, holding this temperature for 1 hr. Then 150 ml. water was added dropwise with stirring over 20 min. The reaction mixture was allowed to cool, was filtered, and the solid was washed with a solution of two parts methanol and one part water. Upon drying, 91–96 g. (77–82% yield) of 2-phenyl-3-benzoylpropionitrile was obtained, m.p. 124–126°, recrystallized from ethyl alcohol, m.p. 126–127° (lit.[2] 127°).

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(5) The preparation of hydrogen cyanide and all subsequent operations must be performed in a well ventilated hood.

(6) A. I. Vogel, "*Practical Organic Chemistry*," Longmans, Green and Co., London, 1954, p. 179.

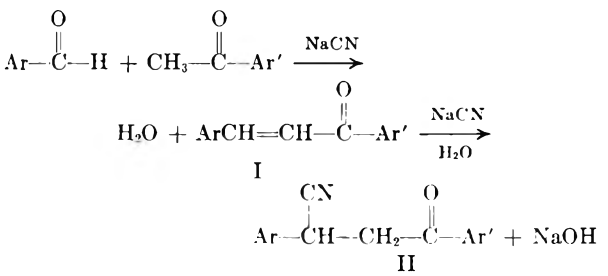
## Condensation of Aromatic Aldehydes with Methyl Aryl Ketones and Sodium Cyanide

R. B. Davis

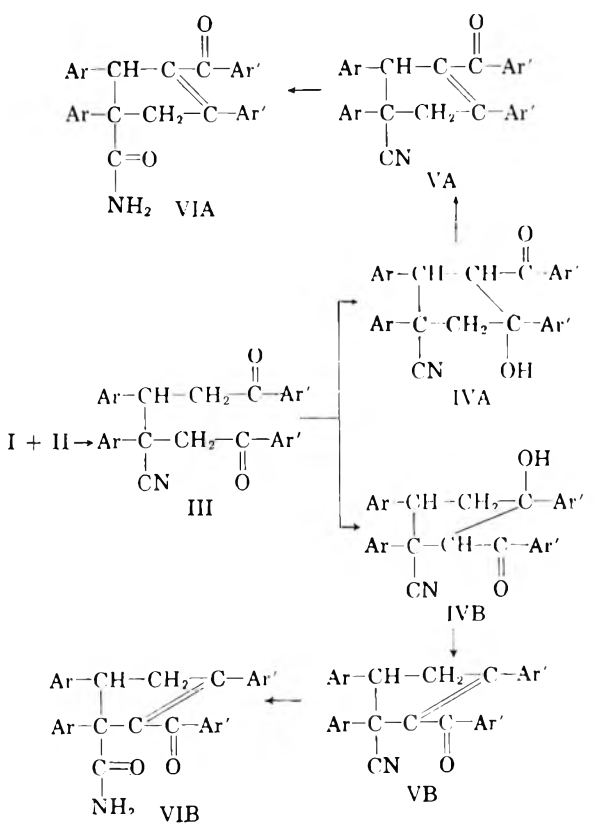
*Received January 5, 1959*

Previous work has shown that aromatic aldehydes condense with arylacetonitriles and sodium

cyanide to produce 2,3-diarylsuccinonitriles.[1,2] It was proposed that similar reactions might be employed as a useful method for preparing 2-aryl-3-aroylpropionitriles(II) by using methyl aryl ketones in place of the arylacetonitriles.



When benzaldehyde was reacted with acetophenone and sodium cyanide we obtained a solid product, $C_{31}H_{23}ON$. Infrared analysis indicated the presence of a nitrile group and a carbonyl group. The nitrile was converted to the corresponding amide by dissolving in concentrated sulfuric acid and then pouring the solution into water. Attempts to hydrolyze the nitrile and the amide to the corresponding acid were not successful. An examination of the literature indicated that other workers[3-5] had prepared the same compound, $C_{31}H_{23}ON$, the latter[4,5] having prepared it from benzalacetophenone and potassium cyanide. The following sequence of reactions in which all of the aryl groups are phenyl, has been adopted in large part from the reports of the previous workers[4,5] in an effort to rationalize the structure of the product.



These same authors were unsuccessful in their attempts to hydrolyze the compound, $C_{31}H_{23}ON$, and also in their attempts to prove the structure. While we have likewise been unsuccessful in our attempts to prove definitely the structure of the product, nevertheless our evidence is consistent with either VA or VB.

Upon reacting 2-thiophenaldehyde with acetophenone and sodium cyanide, a solid product, $C_{27}H_{19}S_2ON$, was obtained. Infrared analysis indicated the presence of a nitrile group and a carbonyl group. The evidence is consistent with either VA or VB in which the two Ar-groups are 2-thiophenyl and the two Ar′-groups are phenyl.

When benzaldehyde was reacted with methyl-*p*-tolyl ketone and sodium cyanide, the product obtained was $C_{33}H_{29}O_2N$. Infrared analysis indicated the presence of carbonyl and nitrile groups, and the absence of hydroxyl and amide groups. The evidence is consistent with structure III in which the Ar-groups are phenyl and the Ar′-groups are *p*-tolyl.

The reaction of *p*-methoxybenzaldehyde with acetophenone and sodium cyanide produced $C_{33}H_{29}O_4N$. The compound gave infrared absorption peaks characteristic of the carbonyl group and either nitrogen to hydrogen or oxygen to hydrogen bonds. No evidence was obtained for the presence of a nitrile group. These facts are consistent with either VIA or VIB in which the Ar-groups are *p*-methoxyphenyl and the Ar′-groups are phenyl.

Upon treating *p*-methoxylbenzaldehyde with methyl-*p*-tolyl ketone and sodium cyanide, $C_{35}H_{33}O_4N$ was obtained. Again infrared analysis indicated the presence of carbonyl and either nitrogen to hydrogen or oxygen to hydrogen bonds, but no evidence for a nitrile group. The facts are consistent with either VIA or VIB in which the Ar-groups are *p*-methoxyphenyl and the Ar′-groups are *p*-tolyl.

In conclusion it may be stated that aromatic aldehydes react with aryl methyl ketones and sodium cyanide to produce complex compounds involving two molecules of the aldehyde, two molecules of the ketone and one molecule of hydrogen cyanide with the loss of two or three molecules of water.

## EXPERIMENTAL[6,7]

*Reaction of benzaldehyde, acetophenone and sodium cyanide.* A mixture of 49 g. of sodium cyanide and 350 ml. of acetone-free methanol was heated with stirring to 55–60°, and 60 g. of acetophenone was added. A solution of 53

(1) R. B. Davis, *J. Am. Chem. Soc.*, **80**, 1752 (1958).
(2) R. B. Davis, U. S. Patent **2,851,477** (1958).
(3) H. Rupe and F. Schneider, *Ber.*, **28**, 960 (1895).
(4) A. C. O. Hann and A. Lapworth, *Trans. J. Chem. Soc.*, **85**, 1355 (1904).
(5) A. Michael and N. Weiner, *J. Am. Chem. Soc.*, **59**, 744 (1937).
(6) Analyses by Micro-Tech Laboratories, Skokie, Ill.
(7) All melting points are uncorrected.

g. of benzaldehyde, 20 g. of acetophenone and 50 ml. of acetone-free methanol was then added dropwise with stirring over 15 min. The reaction mixture was heated at 55–60° with stirring for an additional 1.5 hr., during which colorless solid precipitated. The mixture was cooled, filtered, and the precipitate was washed with methanol, water, again with methanol, and then ether. Upon drying, 49 g. of colorless solid was obtained, m.p. 244–248°, recrystallized from a large volume of acetone and also from benzene, m.p. 253–255°, (lit.[3] m.p. 249°). Infrared analysis showed significant absorption bands at 4.50 $\mu$ and 6.12 $\mu$.

*Anal.* Calcd. for $C_{31}H_{23}ON$: C, 87.50; H, 5.45. Found: C, 87.67; H, 5.51.

Molecular weight. Calcd.[8] for $C_{31}H_{23}ON$: 425. Found: 427.

*Hydrolysis of $C_{31}H_{23}ON$ to the corresponding amide.* Ten grams of $C_{31}H_{23}ON$ was added portionwise with stirring to 200 g. of concentrated sulfuric acid at room temperature. Stirring was continued until all the solid dissolved. After standing at room temperature for 4 hr., the solution was poured with stirring into 2 l. water, solid precipitating. The mixture was filtered and the solid washed with water. Upon drying, 8.7 g. of colorless solid was obtained, m.p. 169–173° (dec.), recrystallized from acetone, m.p. 194–196 (dec.).

*Anal.* Calcd. for $C_{31}H_{25}O_2N$: C, 83.94; H, 5.68. Found: C, 83.88; H, 5.82.

*Reaction of 2-thiophenaldehyde, acetophenone and sodium cyanide.* A mixture of 3 g. of sodium cyanide and 30 ml. of acetone-free methanol was heated to 55–60° with stirring, 10 g. of acetophenone was added, and then 4 g. of 2-thiophenaldehyde over 5 min. with stirring. The reaction mixture was heated at 55–60° for an additional hour, cooled, filtered, and the solid washed with methanol, water, a second time with methanol, and dried. The colorless solid, 2.3 g., melted at 198–204°, recrystallized from acetone, m.p. 205–207°. Infrared analysis showed significant absorption peaks at 4.50 $\mu$ and 6.13 $\mu$.

*Anal.* Calcd. for $C_{27}H_{19}S_2ON$: C, 74.13; H, 4.38. Found: C, 74.16; H, 4.46.

*Reaction of benzaldehyde, methyl-p-tolyl ketone and sodium cyanide.* In a similar manner, 53 g. of benzaldehyde was added over 20 min. at 55–60° to a mixture of 30 g. sodium cyanide, 400 ml. acetone-free methanol, 25 ml. water, and 90 g. of methyl-*p*-tolyl ketone. After stirring at 55–60° for 2 hr., the mixture was cooled, filtered, and solid washed with methanol, water, methanol, ether, and then dried. The colorless solid, 52.5 g., melted at 253–257°, recrystallized from dioxane, m.p. 263–266°. Infrared analysis showed significant absorption bands at 4.48 $\mu$ and 5.91 $\mu$.

*Anal.* Calcd. for $C_{33}H_{29}O_2N$: C, 84.04; H, 6.20. Found: C, 84.16; H, 6.24.

*Reaction of p-methoxybenzaldehyde, acetophenone and sodium cyanide.* In like manner, the addition of 20 g. of *p*-methoxybenzaldehyde over 10 min. at 60–65° to 20 g. sodium cyanide, 200 ml. acetone-free methanol and 35 g. acetophenone produced 10.5 g. of colorless solid, m.p. 252–255°, recrystallized from acetic acid, m.p. 258–260°. Infrared analysis showed significant absorption bands at 2.95 $\mu$, 3.06 $\mu$, and 5.98 $\mu$.

*Anal.* Calcd. for $C_{33}H_{29}O_4N$: C, 78.70; H, 5.80; N, 2.78. Found: C, 78.52; H, 5.94; N, 2.81.

*Reaction of p-methoxybenzaldehyde, methyl-p-tolyl ketone and sodium cyanide.* Similarly, the addition of 20 g. of *p*-methoxybenzaldehyde over 10 min. at 60–65° to a mixture of 20 g. sodium cyanide, 200 ml. acetone-free methanol and 40 g. methyl-*p*-tolyl ketone yielded 8.5 g. of solid, m.p. 231–233°, recrystallized from dioxane, m.p. 233–235°. Infrared analysis showed significant absorption bands at 2.95 $\mu$, 3.05 $\mu$, and 5.99 $\mu$.

(8) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, Fourth Edition, John Wiley and Sons, New York (1956), p. 55.

*Anal.* Calcd for $C_{35}H_{33}O_4N$: C, 79.07; H, 6.26; N, 2.63. Found: C, 78.82; H, 6.62; N, 2.67.

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## Quaternary Hydroxamic Acids Derived from Pyridine[1]

D. G. Coe[2]

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Within the past few years several publications have appeared[3–12] in which hydroxamic acids and oximes have been described and tested as protecting cholinesterase (or alternatively reactivating it) from the inhibiting effects of such substances as tetraethyl pyrophosphate, di-isopropyl phosphorofluoridate and isopropyl methylphosphonofluoridate. It has been shown that while the hydroxamic acids exhibit little toxicity of their own to enzyme preparations, the oximes which are more potent prophylactically and therapeutically manifest inhibiting properties of their own.[13] Some of the most effective compounds described to date are nicotin- and picolinhydroxamic acids and their methiodides, and in particular pyridine-2-aldoxime methiodide.[14–25] It seemed of interest to determine

(1) This research was carried out under Project D52-20-20-20 of the Defence Research Board of Canada, whose permission to publish this work is gratefully acknowledged. Published in lieu of Suffield Experimental Station, Ralston, Alberta, Technical Note No. 34.

(2) Present address: Jackson Laboratory, Box 525 Wilmington, Del.

(3) A. F. Childs, D. R. Davies, A. L. Green, and J. P. Rutland, *Brit. J. Pharmacol.*, **10**, 462 (1955).

(4) A. Funke, G. Benoit, and J. Jacob, *Compt. rend.*, **240**, 2575 (1955).

(5) B. E. Hackley, R. Plapinger, M. Stolberg, and T. Wagner-Jauregg, *J. Am. Chem. Soc.*, **77**, 3651 (1955).

(6) S. Ginsberg and I. B. Wilson, *Arch. Biochem. Biophys.*, **54**, 569 (1955).

(7) B. B. Roy and A. S. Kuperman, *Proc. Soc. Exptl. Biol. Med.*, **89**, 255 (1955).

(8) I. B. Wilson and E. K. Meislich, *J. Am. Chem. Soc.*, **75**, 4628 (1953).

(9) I. B. Wilson, S. Ginsberg, and E. K. Meislich, *J. Am. Chem. Soc.*, **77**, 4286 (1955).

(10) I. B. Wilson and S. Ginsberg, *J. Am. Chem. Soc.*, **79**, 481 (1957).

(11) F. Hobbiger, *Brit. J. Pharmacol.*, **10**, 356 (1955).

(12) G. Benoit and A. Funke, *Bull. soc. chim. France*, 757 (1958).

(13) R. Holmes and E. L. Robins, *Brit. J. Pharmacol.*, **10**, 490 (1955).

(14) T. Wagner-Jauregg, *Arzneimittel-Forsch.*, 6, 194 (1956).

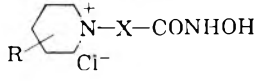
(15) I. B. Wilson and S. Ginsberg, *Biochim. et Biophys. Acta*, **18**, 168 (1955).

(16) I. B. Wilson and Sondheimer, *Arch. Biochem. Biophys.*, **69**, 468 (1957).

(17) H. Kewitz and I. B. Wilson, *Arch. Biochem. Biophys.*, **60**, 261 (1956).

TABLE I

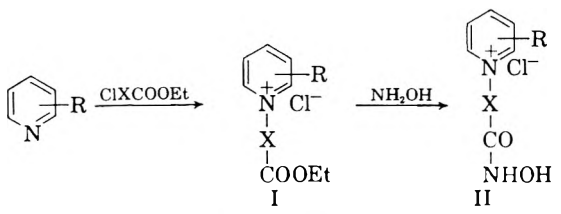
QUATERNARY HYDROXAMIC ACIDS DERIVED FROM PYRIDINE




| Compound[a] | R | X | Yield, %[b] | M.P., °C. | Analyses Found C | Found H | Calcd. C | Calcd. H | Formula |
|---|---|---|---|---|---|---|---|---|---|
| *N*-Carbhydroxamidomethyl pyridinium chloride | H | $CH_2$ | 58 | 186 | 44.26 | 4.68 | 44.57 | 4.81 | $C_7H_9ClN_2O_2$ |
| *N*-Carbhydroxamidomethyl-2-picolinium chloride | 2-$CH_3$ | $CH_2$ | 66 | 170 | 47.43 | 5.55 | 47.41 | 5.47 | $C_8H_{11}ClN_2O_2$ |
| *N*-Carbhydroxamidomethyl-3-picolinium chloride | 3-$CH_3$ | $CH_2$ | 64 | 190 | 47.63 | 5.51 | 47.41 | 5.47 | $C_8H_{11}ClN_2O_2$ |
| *N*-Carbhydroxamidomethyl-4-picolinium chloride | 4-$CH_3$ | $CH_2$ | 70 | 188 | 47.21 | 5.40 | 47.41 | 5.47 | $C_8H_{11}ClN_2O_2$ |
| *N*-Carbhydroxamidomethyl-2,3-lutidinium chloride | 2,3-$(CH_3)_2$ | $CH_2$ | 84 | 205 | 49.66 | 6.38 | 49.88 | 6.05 | $C_9H_{13}ClN_2O_2$ |
| *N*-Carbhydroxamidomethyl-2,4-lutidinium chloride | 2,4-$(CH_3)_2$ | $CH_2$ | 76 | 188 | 50.14 | 5.92 | 49.88 | 6.05 | $C_9H_{13}ClN_2O_2$ |
| *N*-Carbhydroxamidomethyl-3,5-lutidinium chloride | 3,5-$(CH_3)_2$ | $CH_2$ | 81 | 191 | 49.71 | 5.82 | 49.88 | 6.05 | $C_9H_{13}ClN_2O_2$ |
| *N*-Carbhydroxamidomethyl-3-ethyl-4-picolinium chloride | 3-$C_2H_5$,4-$CH_3$ | $CH_2$ | 63 | 147 | 52.15 | 6.32 | 52.08 | 6.56 | $C_{10}H_{15}ClN_2O_2$ |
| *N*-Carbhydroxamidomethyl-4-(3′-hydroxypropyl)pyridinium chloride | 4-($HOCH_2CH_2CH_2$) | $CH_2$ | 79 | 153 | 48.35 | 6.02 | 48.68 | 6.13 | $C_{10}H_{15}ClN_2O_3$ |
| *N*-(2′-Carbhydroxamidoethyl)pyridinium chloride | H | $CH_2$·$CH_2$ | 25 | 151 | 47.55 | 5.62 | 47.41 | 5.47 | $C_8H_{11}ClN_2O_2$ |
| *N*-(1′-Carbhydroxamidoethyl)pyridinium chloride | H | $CH(CH_3)$ | 84 | 158 | 47.73 | 6.09 | 47.41 | 5.47 | $C_8H_{11}ClN_2O_2$ |
| *N*-(1′-Carbhydroxamidoethyl)-4-picolinium chloride | 4-$CH_3$ | $CH(CH_3)$ | 91 | 206 | 49.75 | 6.24 | 49.88 | 6.05 | $C_9H_{13}ClN_2O_2$ |
| *N*-(1′-Carbhydroxamidoethyl)-3,5-lutidinium chloride | 3,5-$(CH_3)_2$ | $CH(CH_3)$ | 51 | 218 | 52.20 | 6.25 | 52.08 | 6.56 | $C_{10}H_{15}ClN_2O_2$ |

[a] These names have been used as conforming to standard rules of nomenclature. [b] Yield based on the amount of base ester–chloride.

whether or not the activity displayed by these pyridine compounds was retained when the hydroxamic acid residue was attached through the nitrogen atom, and a series of compounds have been prepared from pyridine and its homologs, utilizing the following sequence of reactions:




I II

R = H, alkyl or substituted alkyl
X = $-CH_2-$, $-CH_2CH_2-$, or $-CH(CH_3)-$

Treatment of the appropriate base with the ethyl ester of $\alpha$- or $\beta$-chloroaliphatic acids gave rise to substituted carbethoxyalkyl pyridinium chlorides (I). The ease of this reaction depends entirely on the nature of the reactants and in some cases proceeds very slowly. The reaction was carried out at a relatively low temperature in view of the fact that alkyl $\beta$-chloropropionates can be dehydrohalogenated by certain tertiary bases[26,27]; however, since this work was completed a paper has appeared describing the formation of a base ester–chloride from ethyl-$\beta$-chloropropionate and pyridine by refluxing in ethanol.[28] The base ester–chlorides are extremely hygroscopic solids which are difficult to purify. They were reacted with hydroxylamine in methyl alcohol to give the corresponding hydroxamic acid (II) in good yield as colorless crystalline solids. The hydroxamic acids prepared in this fashion are listed in Table I.

These compounds were found to be very effective in preventing and reversing some of the physiological effects of cholinesterase inhibition, presumably by protecting, or reactivating the cholinesterase. The precise results of the biological testing of these compounds will be published elsewhere.[29]

## EXPERIMENTAL[30]

*Base ester-chlorides* (I). The appropriate base[31] was mixed with an equivalent amount of the ethyl chloroacylate and an equal volume of ether added. If after standing at room temperature for 2 days little product had separated, then the mixture was heated under reflux for several days, ether being added if any was lost. The total time depended on the nature of the reactants.[32] No attempt was made to obtain the maximum possible yield and the reaction was terminated as soon as sufficient product had separated. The product was rapidly filtered through a sintered funnel, washed with ether, and dried in a vacuum desiccator. The base ester–chlorides obtained in this fashion were sufficiently pure for the subsequent reaction and as they are very hygroscopic, recrystallization is a tedious and wasteful procedure. These compounds form adducts with mercuric chloride from an aqueous solution. Most of them were obtained as oils which could not be crystallized; however, the adducts of *N*-carbethoxymethyl pyridinium chloride, m.p. 124–125° (Kruger[33], gives 124–125°); *N*-carbethoxymethyl-3-picolinium chloride, m.p. 149–151°; *N*-carbethoxymethyl-4-picolinium chloride, m.p. 104°; and *N*-carbethoxymethyl-2,3-lutidinium chloride, m.p. 95–98° were obtained and recrystallized from water.

*Hydroxamic acids.* A solution of hydroxylamine was prepared by mixing hot methanolic solutions of hydroxylamine hydrochloride (0.15 mole) and sodium methoxide (0.15 mole). The mixture was filtered under suction into a flask containing the base ester–chloride (0.1 mole) in methanol (40 ml.). The flask was stoppered and kept at 0° for 4 days. The solution was decanted from small amounts of solid that had separated and then concentrated under vacuum until crystallization of the hydroxamic acid commenced; ether was then added to precipitate the product which was finally recrystallized from ethanol. Data for these compounds are given in Table I.

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(18) H. Kewitz, I. B. Wilson, and D. Nachmansohn, *Arch. Biochem. Biophys.*, **60**, 261 (1956).
(18) H. Kewitz, I. B. Wilson, and D. Nachmansohn, *Arch. Biochem. Biophys.*, **64**, 456 (1956).
(19) I. B. Wilson, *Biochim. et Biophys. Acta*, **27**, 196 (1958).
(20) D. R. Davies and A. L. Green, *Biochem J.*, **63**, 529 (1956).
(21) F. Hobbiger, *Brit. J. Pharmacol.*, **12**, 438 (1957).
(22) B. M. Askew, *Brit. J. Pharmacol.*, **12**, 336 (1957).
(23) H. Kewitz, *Arch. Biochem. Biophys.*, **66**, 263 (1957).
(24) H. Kewitz and D. Nachmansohn, *Arch. Biochem. Biophys.*, **66**, 271 (1957).
(25) H. Kewitz, *Klin. Wochschr.*, **35**, 550 (1957).
(26) C. S. Marvel, J. Dec, H. G. Cooke, and J. C. Cowan, *J. Am. Chem. Soc.*, **62**, 3495 (1940).
(27) C. Moureu, M. Murat, and L. Tampier, *Ann. chim. (Paris)*, [9] **15**, 221 (1921).
(28) S. A. Heininger, *J. Org. Chem.*, **22**, 704 (1957).
(29) W. C. Stewart and D. G. Coe, unpublished work.
(30) Melting points are uncorrected.
(31) The gift of several of the pyridine bases used in this work by the Ansul Chemical Co. is gratefully acknowledged.
(32) Ethyl chloroacetate reacts fairly rapidly at room temperature with pyridine, 2-, 3-, and 4-picoline, also 4-(3′-hydroxypropyl)-pyridine. All of the lutidines and any of the reactions involving ethyl $\alpha$- or $\beta$-chloropropionate require heating; 2:6-lutidine gave no signs of reaction with ethyl chloroacetate even after standing for several months.
(33) M. Kruger, *J. prakt. Chem.*, **43** (2), 274 (1891).

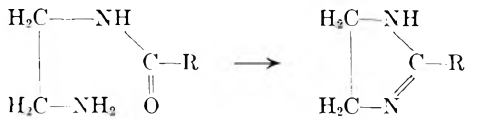
## Pyrolysis of *N*-Phenylthiocarbamylethylenediamine and Related Materials

LON HELGEN, OLIVER STOUTLAND, AND COURTLAND L. AGRE[1]

*Received January 9, 1959*

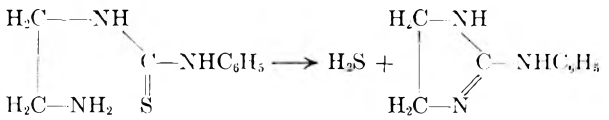
Imidazolines are formed readily from monoacyl- or diacylethylenediamines[2] by heating the materials

(1) To whom inquiries for reprints should be addressed.
(2) K. Hofmann, *The Chemistry of Heterocyclic Compounds. Part I. Imidazole and Its Derivatives*, Interscience Publishers, New York, 1953, p. 214.



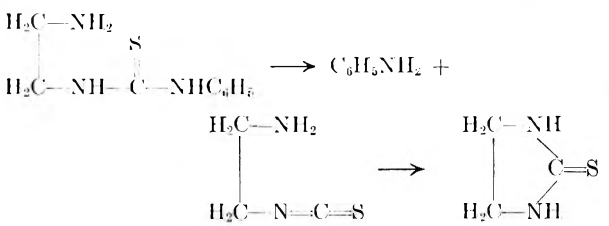
with selected reagents. In somewhat similar manner, Forssel[3] prepared 2-substituted 2-imidazolines from thioamides and ethylenediamine.

It seemed reasonable, therefore, to expect *N*-phenylthiocarbamylethylenediamine to eliminate hydrogen sulfide on heating to give 2-anilinoimidazoline. These substituted ethylenediamines are readily available by the process recently described.[4] It had been observed that these materials evolved hydrogen sulfide above the melting points. The expected reaction follows.



It was verified that this reaction did occur to an appreciable extent (about 20%). The hydrogen sulfide was precipitated as copper sulfide. The 2-anilinoimidazoline was isolated in quantity reasonably equivalent to the hydrogen sulfide. The 2-anilinoimidazoline and its picrate proved to be identical with the same products synthesized from the methyl thioether of ethylenethiourea and aniline.

The major reaction, however, was different. A liquid evolved during the pyrolysis proved to be aniline. The bulk of the residue was ethylenethiourea, about equivalent in quantity to the aniline. It thus appears that initially there might be an elimination of aniline to give an intermediate isothiocyanate which intramolecularly reacts to



give ethylenethiourea. This decomposition of ureas above the melting points is not unexpected for it has been shown repeatedly[5] that substituted ureas and thioureas are thermally unstable.

Similar results were obtained when the phenyl group was replaced by *n*-butyl and *n*-heptyl groups, respectively. The major reaction was the elimination of the amine and the formation of ethylenethiourea. The minor reaction was the elimination of hydrogen sulfide accompanied by imidazoline formation. The 2-alkylimidazolines were synthesized[6] and they and their picrates proved identical with those obtained from pyrolysis.

Attempts were made to prepare the benzoyl derivatives of each of the three mentioned imidazolines. All three materials proved to be *N,N'*-dibenzoylethylenediamine. This reaction is in line with the known[7] reactions of 2-alkylimidazolines.

*N*-Phenylcarbamylethylenediamine decomposed similarly to give a series of parallel products. Aniline was obtained in abundance and a small amount of ethyleneurea was recovered. However, the bulk of the residue was a white solid melting above 300°. This has not been identified but probably is a low polymer formed by the reaction of the hypothetical intermediate, $H_2NCH_2CH_2NCO$, to give a linear polymer as well as the cyclic urea.

It was interesting to observe the pyrolysis of *N,N'*-bis-phenylthiocarbamylethylenediamine, for a number of possible reactions might be encountered. Amongst the products obtained were hydrogen sulfide, aniline, *N,N'*-diphenylthiourea, and ethylenethiourea. It appeared, therefore, that in part the pyrolysis might have eliminated phenyl isothiocyanate and thus formed *N*-phenylcarbamylethylenediamine. This latter material would decompose according to the earlier comments in this research. Lastly, the aniline and the phenyl isothiocyanate would unite to give the diphenylthiourea.

## EXPERIMENTAL[8]

*N-Phenylthiocarbamylethylenediamine.* This material was prepared[4] using benzene as the solvent. The yield was 165% of the quantity anticipated on the basis of random distribution.

*Pyrolysis of N-phenylthiocarbamylethylenediamine.* A 500 cc. Claisen flask was partially filled with 168 g. (0.87 mole) of the amine. The flask was placed in an oil bath maintained at 155° and a slow flow of nitrogen was introduced. A heavy evolution of hydrogen sulfide resulted and the gas was trapped reasonably effectively by copper sulfate solution. After 90 min. the reaction appeared complete and the flask was gradually evacuated until at the end of 1 hr. the vacuum was 10 mm.

The distillate thus obtained weighed 60 g. (0.65 mole), boiled at 182–184°, and was identified as aniline by converting a portion to phenylthiourea.

The residue in the pyrolysis flask weighed 101 g. It was washed several times with ethanol and yielded 61 g. (0.60 mole) of a granular solid, m.p. 203–204°, which was identified as ethylenethiourea.

The balance of the residue was mainly 2-anilinoimidazoline. The alcoholic filtrate from above was evaporated to a low volume and was cooled to give an abundant precipitate. This was filtered and washed with cold alcohol. The solid was dissolved in dilute hydrochloric acid, treated with charcoal, and was recovered by making the solution strongly basic. The 2-anilinoimidazoline thus obtained was a white solid, recrystallized from water, m.p. 137–138°. Additional yield was obtained by working up the filtrate from this isolation. Even though the recovery was not quantitative, the yield was 9 g.

(3) Ref. 2, p. 216.

(4) O. Stoutland, L. Helgen, and C. Agre, *J. Org. Chem.*, **24**, 818 (1959).

(5) J. Saunders and R. Slocombe, *Chem. Revs.*, **43**, 211 (1948).

(6) *Chem. Abstr.*, **24**, P732 (1930); British Patent **310,534**.

(7) Ref. 2, p. 221.

(8) All melting points are uncorrected.

*Anal.* Calcd. for $C_9H_{11}N_3$: N, 26.0; equiv. wt., 161. Found: N, 26.2; equiv. wt., 163.

Treatment of the 2-anilinoimidazoline in alcohol with picric acid gave a picrate, recrystallized from alcohol, m.p. 201–202°. A mixed melting point with the authentic synthetic material was unchanged.

*Anal.* Calcd. for $C_{15}H_{15}N_6O_7$: N, 21.6. Found: N, 21.6.

The copper sulfide was recovered and weighed 14 g., equivalent to 4.6 g. hydrogen sulfide.

*2-Anilinoimidazoline.* This material was made by a modification of the process of Aspinall and Bianco.[9] A mixture of 12 g. of aniline, 16 g. of the methyl thioether of ethylenethiourea,[10] and 28 ml. of ethanol was refluxed for 2 days. The volatile material was removed by heating on a steam bath followed by evacuation for a few minutes. There remained a yellow, viscous oil which dissolved in dilute acid. Addition of base to the cold, filtered solution liberated an oil which solidified. The product, 1.8 g., is 2-anilinoimidazoline, m.p. 138–139° when recrystallized from water. The reported[6] value is 122°. Treatment of an alcohol solution with picric acid gave the picrate, recrystallized from alcohol, m.p. 201–203°.

Treatment of 2-anilinoimidazoline with benzoyl chloride in aqueous alkali gave *N,N'*-dibenzoylethylenediamine, m.p. 250° from alcohol.

*Acknowledgment.* The authors thank the Research Corporation for the generous grant under which this research was conducted.

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(9) S. Aspinall and E. Bianco, *J. Am. Chem. Soc.*, **73**, 602 (1951).

(10) A. McKay, M. Buchanan, and G. Grant, *J. Am. Chem. Soc.*, **71**, 766 (1949).

## Formation of a Cyclic Ester from the Reaction of Di-*n*-butyltin Dichloride with Ethylene Glycol

J. BORNSTEIN,[1] B. R. LA LIBERTE, T. M. ANDREWS, AND J. C. MONTERMOSO

*Received January 2, 1959*

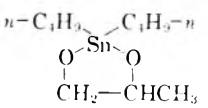
Recently, Ramsden and Banks[2] reported that the product formed from the reaction of di-*n*-butyltin dichloride with ethylene glycol in the presence of sodium hydroxide has the linear structure I.

$$HOCH_2CH_2OSn(C_4H_9\text{-}n)_2OCH_2CH_2OSn(C_4H_9\text{-}n)_2OCH_2CH_2OH$$

I

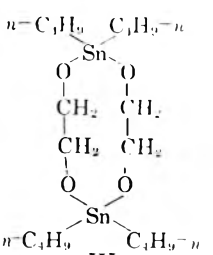
We have repeated this reaction and the resulting product has been found by means of its elemental analysis, melting point, and infrared spectrum to be identical to the compound obtained in this laboratory from the treatment of di-*n*-butyltin oxide with ethylene glycol. Our results of the investigation of the structure of this product do not support structure I, however. The following evidence shows that the product is a cyclic tin ester which should be formulated as III.

When equimolar amounts of ethylene glycol and di-*n*-butyltin oxide were heated under reflux in benzene, an equimolar amount of water was evolved and a crystalline product separated from the resulting solution. This solid was found consistently to have the molecular formula $C_{20}H_{44}O_4Sn_2$ from numerous elemental analyses[3] and from the determination of its molecular weight by three different methods. The infrared spectrum of the compound in the O—H stretching region was particularly interesting. The spectrum in chloroform solution displayed a broad, medium intense band at 3250 cm.$^{-1}$ which could be indicative of the presence of bonded O—H.[4] However, in carbon disulfide solution this band was completely absent. The identical behavior was observed with di-*n*-butyltin methyldioxolane (II).[5] In contrast, this

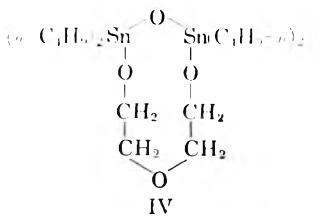


II

band was not observed with di-*n*-butyltin dichloride in chloroform. These observations indicate that the band is not due to the presence of a hydroxyl group but, rather, may be due to hydrogen bonding involving the hydrogen of the chloroform and the oxygen of the glycol derivative. Tests for the presence of active hydrogen with methylmagnesium iodide and with lithium aluminum hydride were negative and, hence, provided additional proof of the absence of the hydroxyl function. These facts demonstrate that the product is a cyclic tin ester whose structure must be either III or IV. Structure IV is precluded, however, since the compound is very rapidly hydrolyzed in boiling aqueous ethanol



III



IV

(1) Department of Chemistry, Boston College, Chestnut Hill, Mass.

(2) H. E. Ramsden and C. K. Banks, U. S. Patent 2,789,994 (Apr. 23, 1957).

(3) Ramsden and Banks (ref. 2) reported 36.95% Sn for their compound. Our Sn values were always significantly higher. *Cfr.* experimental section of this paper.

(4) Dr. Ramsden has kindly pointed out (private communication to J. B.) that although a hydroxyl group attached to tin is not always detectable by infrared, a hydroxyl bonded to carbon as in structure I should be observable.

(5) First prepared and characterized by Ramsden and Banks (ref. 2). Investigation of the structure of II in this laboratory supports their findings.

to di-*n*-butyltin oxide and ethylene glycol, which was characterized as its dibenzoate ester. No diethylene glycol was found in the products of hydrolysis.

### EXPERIMENTAL[6]

*The reaction of di-n-butyltin oxide with ethylene glycol.* A mixture of di-*n*-butyltin oxide (25.0 g., 0.10 mole, dried at 110° for 2 hr.), freshly distilled ethylene glycol (6.0 g., 0.097 mole), and 250 ml. of dry benzene was heated under reflux for 1.5 hr. in an apparatus fitted with a Dean-Stark water separator. At the end of this time a clear solution was obtained and 0.1 mole of water was collected. The crystals which deposited from the solution on standing at room temperature overnight were removed by filtration and washed with petroleum ether. Recrystallization from benzene gave III as matted, white needles, 24.0 g. (85%), m.p. 223–229° with decomposition.

*Anal.* Calcd. for $C_{20}H_{44}O_4Sn_2$: C, 40.99; H, 7.57; Sn, 40.52; mol. wt., 586. Found: C, 41.2; H, 7.5; Sn, 40.79, 40.81, 40.87; mol. wt., 606 (Rast, camphor), 611 (ebullioscopic, benzene), 638 (isothermal distillation, chloroform).

Refluxing of di-*n*-butyltin oxide with a three-fold excess of ethylene glycol in the absence of benzene afforded the same product. The material was identical with that prepared from di-*n*-butyltin dichloride and the glycol by the method of Ramsden and Banks,[2] m.p. 223–226°, mixed m.p not depressed.

*Hydrolysis of* III was readily effected by adding as light excess of water to a stirred, boiling solution of the compound in ethanol. Di-*n*-butyltin oxide precipitated immediately. After stirring and refluxing for an additional 10 min., the mixture was cooled to room temperature and filtered to remove the oxide. The filtrate was concentrated by heating gently under reduced pressure in order to remove the ethanol. The residue was dissolved in a small quantity of water, made alkaline with aqueous 10% sodium hydroxide, and shaken with benzoyl chloride. Crystallization of the product from petroleum ether gave the dibenzoate of ethylene glycol as felted needles m.p. 72.5–73.0°, which was found to be identical to an authentic sample[7] by means of m.p., mixed m.p., and comparison of the infrared spectrum.

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(6) Melting points are corrected. Infrared measurements were made using a Baird double beam recording spectrophotometer equipped with a sodium chloride prism. Analyses were performed by Dr. Carol K. Fitz, Needham Heights, Mass., and Dr. S. M. Nagy, Microanalytical Laboratory, Massachusetts Institute of Technology, Cambridge, Mass.

(7) E. H. Huntress and S. P. Mulliken, *Identification of Pure Organic Compounds, Order I*, John Wiley and Sons, Inc., New York, 1941, p. 469.

## Use of Tetracyanoethylene as a Color-Forming Reagent in Paper Chromatography of Aromatic Compounds[1]

D. S. TARBELL AND THERESE HUANG

*Received January 19, 1959*

In earlier publications,[2a] we have reported on a system for paper chromatography of polycyclic aromatic compounds, which has proved useful in separation and identification of benzyprene derivatives and other polycyclic compounds.[2b-4] In this scheme, the position of spots on the paper was determined by observation of the fluorescence of the spots under ultraviolet light. A spray reagent which would indicate the position of spots of aromatic compounds which were not fluorescent would be of obvious advantage in this procedure.[5]

The observation[6] that tetracyanoethylene[7] forms colored complexes with many aromatic compounds, including simple ones, suggested an examination of this reagent in paper chromatography of aromatic compounds. It is the purpose of the present note to indicate that it does have promise in this connection.

### EXPERIMENTAL

The pyrene derivatives were prepared by published procedures,[8] with some modifications, or were commercial samples purified by chromatography on alumina with petroleum ether as the eluant. The hydrocarbons were used as benzene solutions having concentration of 1 mg. per ml. About 10 $\gamma$ of the material was applied as a spot on the paper.

The dry developed paper chromatogram, prepared by the published procedure,[2] was laid on paper towels in the hood. The freshly prepared tetracyanoethylene (TCNE) solution in distilled acetone[9] (*ca.* 0.01*M*) was sprayed gently and evenly over the surface. The acetone was dried rapidly by playing a stream of air over the surface, or by waving the sheet in the air if it was not too wet. As the solvent evaporated, the temporary dark gray complex of TCNE-acetone-paper disappeared and a permanent yellow color was left on the paper. If a spot was not visible, even when the paper was scrutinized against the light, the spraying was repeated. Often three or four applications were necessary.

In the Table are given the $R_f$ values in hexane saturated with dimethylformamide, the color with TCNE, and for comparison, the color of the spots developed by spraying with picric acid in ethanol and with trinitrofluorenone[10] in acetone solution. As can be seen, the TCNE colors cover a much wider range than those produced with picric acid or

(1) Aided by Grant C-2654 from the National Institutes of Health.

(2) (a) D. S. Tarbell, E. G. Brooker, A. Vanterpool, W. Conway, C. J. Claus, and T. J. Hall, *J. Am. Chem. Soc.*, **77**, 767 (1955); (b) W. Conway and D. S. Tarbell, *J. Am. Chem. Soc.*, **78**, 2228 (1956).

(3) D. S. Tarbell, E. G. Brooker, P. Seifert, A. Vanderpool, C. J. Claus, and W. Conway, *Cancer Research*, **16**, 1 (1956).

(4) B. L. Van Duuren, *J. Nat. Cancer Inst.*, **21**, 1 (1958).

(5) Tetrachlorophthalic anhydride forms complexes with a variety of aromatic compounds: P. Pfeiffer, *Ber.*, **55**, 413 (1922); Ng. Ph. Buu-Hoï and P. Jacquignon, *Compt. rend.*, **234**, 1056 (1952).

(6) R. E. Merrifield and W. D. Phillips, *J. Am. Chem. Soc.*, **80**, 2778 (1958).

(7) T. L. Cairns *et al.*, *J. Am. Chem. Soc.*, **79**, 2340 (1957); **80**, 2775 (1958).

(8) H. Vollman *et al.*, *Ann.*, **531**, 1 (1937); M. de Clercq and R. H. Martin, *Bull. soc. chim. Belg.*, **64**, 367 (1955).

(9) Chloroform proved to be an unsatisfactory solvent because TCNE is only slightly soluble (less than 2 mg./100 ml.), and also it does not evaporate fast enough; rapid evaporation is necessary to prevent the dissolving of the complex and consequent spreading of the spot.

(10) M. Orchin and W. O. Woolfolk, *J. Am. Chem. Soc.*, 68, 1727 (1946).

TABLE

| Compound | Fluorescence | $R_f$ | TCNE | Color with | |
|---|---|---|---|---|---|
| | | | | Picric acid | Trinitro-fluorenone |
| Pyrene | Blue | 0.63 | Brown-violet | Orange | Orange |
| 3-Methylpyrene | Yellow-blue | 0.69 | Brown-violet | Red | Brown-red |
| 3,5-Dimethylpyrene | Yellow | 0.74 | Red-brown | Orange | Brown |
| 3,8-Dimethylpyrene | Green-yellow | 0.78 | Red-brown | Orange | Brown |
| 3-Nitropyrene | Orange | 0.38 | Gold | Yellow | Orange |
| 3-Bromopyrene | Blue | 0.68 | Green | Red-orange | Red-orange |
| 3,8-Dibromopyrene | Blue | 0.69 | Green | Orange | Orange |
| 3-Acetylpyrene | Bright yellow | 0.37 | Green | Yellow | Orange |
| 3-Hydroxymethylpyrene | Green | 0.05 | Brown | Red-orange | Brown |
| 3-Carboxypyrene | Yellow | 0.01 | Light green | Yellow | — |
| 3-Formylpyrene | Gold | 0.37 | Yellow | Orange | Orange |
| 3-Methyl-5-formylpyrene | Orange | 0.46 | Light green | Orange | Brown-orange |
| Anthracene | Violet | 0.70 | — | Orange | Brown-red |
| 9,10-Dibromoanthracene | Yellow | 0.77 | Green | Orange | Orange |
| 1,2-Benzanthracene[a] | Yellow | 0.60 | Blue | Orange | Red-orange |
| 1:2,5:6-Dibenzanthracene[a] | Violet | 0.47 | Green | Light orange | Orange |
| Chrysene[a] | Dark blue | 0.63 | Light violet | Light orange | Orange |
| Fluoranthene | Blue | 0.79 | Violet | Yellow | Yellow |
| 20-Methylcholanthrene[a] | Yellow | 0.82 | Gray-green | Brown | Gray-green |
| 10-Ethylbenzpyrene[a] | Yellow | 0.66 | Brown | Brown | Gray |
| 10-Acetylbenzpyrene[a] | Gold | 0.18 | Gray-brown | Light orange | Tan |
| 5-Acetylbenzpyrene[a] | Blue | 0.09 | Light brown | Orange | Brown-gray |
| Phenanthrene | Violet | 0.63 | Violet | Yellow | Yellow |
| 9-Bromophenanthrene | — | 0.78 | Violet | Yellow | Yellow |
| Naphthalene | Blue | 0.89 | Red-violet | Yellow | Yellow |
| 1-Nitronaphthalene | — | 0.50 | Orange | Yellow | Yellow |
| 2-Methylnaphthalene | Blue | 0.92 | Blue-gray | Yellow | Yellow |
| Di-m-xylylene[b] | — | 0.66 | Red | — | — |
| Di-(2-methyl-m-xylylene)[b] | — | 0.66 | Gold | — | — |
| Acepleiadiene[b] | Black-red | 0.69 | Gold | Dark gray | Brown |
| Acepleiadylene[b] | Orange-red | 0.59 | Brown | Red-brown | Red-brown |
| Tetrahydroacepleiadane[b] | Blue | 0.06 | Purple | Yellow | Yellow |
| Perinaphthanone[a] | Light blue-violet | 0.51 | Salmon | Yellow | Yellow |
| Benzpyrene[a] | Blue | 0.60 | Violet-pink | Brown | Gray-brown |
| Fluorene[a] | Light violet | 0.65 | Light brown | Yellow | Yellow |
| 1-Phenyl-1-(α-naphthyl)-propene-1[a] | Blue | 0.74 | Purple | Yellow | Yellow |

[a] Gift of Dr. S. C. Pakrashi of this Laboratory. [b] Gift of Dr. Leslie Humber of this Laboratory.

trinitrofluorenone. It is possible to detect the position of nonfluorescent compounds, such as the xylylenes and the substituted naphthalenes, by the TCNE spots. The method is sensitive to 1 gamma of pyrene, and 10 gamma of naphthalene; the equilibrium constants for the complex formation in methylene chloride solution for these two compounds[6] are 29.5 and 11.7.

A slight drawback to the method is the impermanence of the color, which fades in some cases in the course of 3 min. but generally is visible for over 1 hr. The rate of fading appears to depend on the stability and amount of the complex present.

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## 1-Phenyl-2,2-dimethylbutane

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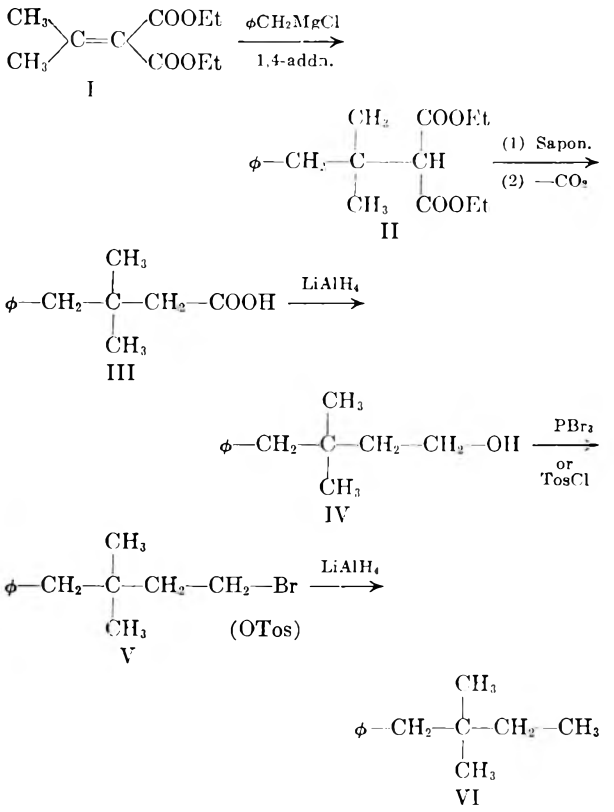
When Francis[1] published his review on the properties of the alkylbenzenes in 1948, fifteen of the seventeen possible monoalkylbenzenes of the formula $C_{12}H_{18}$ had been described. One of the two remaining unknown isomers, 1-phenyl-3,3-dimethylbutane, has since been prepared.[2] The other, 1-phenyl-2,2-dimethylbutane (VI), was reportedly obtained by Tafel and Jurgens[3] from the electrolytic reduction of "methylbenzylacetoacetic ester." Later Tafel and Andre[4] decided that their hydrocarbon was probably 1-phenyl-3-methylpentane rather than VI. Francis[1] stated that VI "must be considered unknown." This paper reports the synthesis of VI by the following reaction sequence.

Prout *et al.*[5] have reported carrying out the first two steps above, leading to the acid (III). The latter was smoothly reduced to the alcohol (IV) by means

(1) A. W. Francis, *Chem. Revs.*, **42**, 107 (1948).
(2) E. Berliner and F. Berliner, *J. Am. Chem. Soc.*, **72**, 222 (1950).
(3) J. Tafel and W. Jurgens, *Ber.*, **42**, 2556 (1909).
(4) J. Tafel and F. Andre, *Ber.*, **45**, 437 (1912).
(5) F. S. Prout, E. P.-Y. Huang, R. J. Hartman, and C. J. Korpics, *J. Am. Chem. Soc.*, **76**, 1911 (1954).




of lithium aluminum hydride.[6] The reduction resulted in the disappearance of the characteristic infrared absorption bands of the acid at 3.7$\mu$, 5.8$\mu$ and 10.5–11.5$\mu$ and the appearance of hydroxyl absorption bands at 3.4$\mu$ and 9.3–9.9$\mu$. This alcohol proved to be singularly nonreactive. It reacted only slowly with freshly cut sodium. Although it formed a small amount of the tosylate[7] on one occasion, in numerous other attempts this derivative did not form. The 3,5-dinitrobenzoate ester resulted only when the alcohol and acid chloride were heated together. An attempt to prepare the corresponding chloride using thionyl chloride and pyridine as described by Whitmore and Bernstein[8] for a similar alcohol resulted in recovery of the unchanged alcohol. When the alcohol was heated overnight at 75° with phosphorus tribromide following the procedure of Pines *et al.*,[9] only traces of the expected bromide were formed. However, when the temperature of the latter reaction mixture was maintained above 125° for several hours, the expected bromide (V) was obtained in reasonable yields. The infrared spectrum of the bromide no longer possessed the sharp hydroxyl absorption at 3.4$\mu$ nor the broad band at 9.3–9.9$\mu$. Inasmuch as the reaction conditions were rather severe, the possibility existed that some bromide other than V might have formed. That the expected bromide was formed was demonstrated by converting a sample of the bromide to the Grignard reagent, oxidizing the latter to the bromomagnesium alkoxide, hydrolyzing the latter, and recovering the alcohol.[8] This latter sample of alcohol formed a 3,5-dinitrobenzoate identical with the one prepared from the alcohol (IV). When bromide (V) was refluxed with lithium aluminum hydride in tetrahydrofuran solvent, hydrocarbon (VI) was formed. The infrared absorption spectrum of the hydrocarbon obtained by reduction of the tosyl ester was identical with that of the hydrocarbon obtained by reduction of the bromide. Samples of VI obtained *via* both the bromide and tosyl ester yielded the same acetamino derivative.

The physical properties of 1-phenyl-2,2-dimethylbutane (b.p. 212.4° (737 mm.), $n_D^{20}$ 1.4935, $d_4^{20}$ 0.8704) observed here compare favorably with the physical constants listed by Francis[1] for the other $C_{12}H_{18}$ alkylbenzenes with similar branching. The above refractive index and density are higher than the $n_D^{19}$ 1.4882 and $d_4^{19}$ 0.860 reported by Tafel and Jurgens[3] for presumably the same hydrocarbon and recalculated by Francis as $n_D^{20}$ 1.4878 and $d_4^{20}$ 0.8592.

## EXPERIMENTAL[10]

*Ethyl isopropylidene malonate* (I) was prepared in about 50% yield from acetone and malonic ester by the procedure of Cope and Hancock,[11] b.p. 110–111° (9 mm.), $n_D^{20}$ 1.4490 to 1.4503.

*Ethyl 4-phenyl-3,3-dimethyl-2-carbethoxybutanoate* (II). To the Grignard reagent prepared from 26.75 g. (1.1 moles) of magnesium and 139.1 g. (1.1 moles) of benzyl chloride in 400 ml. of anhydrous ether was added over a period of 4 hr., a solution of 200 g. (1.0 mole) of ester I in 200 ml. of anhydrous ether. After standing overnight the reaction mixture was hydrolyzed by pouring onto chipped ice, acidified (Congo paper) with dilute sulfuric acid and stirred vigorously and the oil layer cleared. The oil was separated, the water extracted with ether, and the combined extracts were washed, dried, and the ether was distilled. Fractionation through a 1-ft. Fenske-type column packed with $^3/_{32}$ in. glass helices yielded the following: *Fractions 1–3*, 14.8, b.p. up to 103° (1 to 2 mm.); *Fractions 4–6*, 24 g., b.p. 104–107° (1 mm.), which solidified as it distilled (probably bibenzyl); *Fractions 7–8*, 18.4 g., 119 to 148° (1 mm.), $n_D^{20}$ 1.4952–1.4935, ester II contaminated with a little bibenzyl; *Fractions 9–12*, 106.5 g., b.p. 148–153° (1 mm.), $n_D^{20}$ 1.4908–1.4912, $n_D^{25}$ 1.4887–1.4892; *Fractions 13–14*, 17.7 g., b.p. 148° falling to 131° (1 mm.), $n_D^{25}$ 1.4880–1.4862. Fractions 7 through 14 weighed a total of 142.6 g., or a 49% yield of crude product. Fractions 9–12 are essentially pure ester II, which is reported[5] to have b.p. 185–186° (8 mm.), $n_D^{25}$ 1.4890.

*4-Phenyl-3,3-dimethylbutanoic acid* (III). Saponification was achieved by refluxing ester II (206 g., 0.704 mole) for 3.5 hr. with 120 g. potassium hydroxide in 400 ml. ethylene glycol. The cold reaction mixture was poured into 1 l. of

(6) R. F. Nystrom and W. G. Brown, *J. Am. Chem. Soc.*, **69**, 2548 (1947).

(7) M. F. Clarke and L. N. Owen, *J. Chem. Soc.*, 2108 (1950).

(8) F. C. Whitmore and H. Bernstein, *J. Am. Chem. Soc.*, **60**, 2626 (1938).

(9) H. Pines, W. D. Huntsman, and V. N. Ipatieff, *J. Am. Chem. Soc.*, **75**, 2311 (1953).

(10) All melting points and boiling points are uncorrected unless otherwise indicated. Analyses by Micro-Tech Laboratories, Skokie, Ill.

(11) A. C. Cope and E. M. Hancock, *J. Am. Chem. Soc.*, **60**, 2644 (1938).

water, filtered (Celite) and neutral oils were removed by extraction with ether. After acidification, acidic materials were extracted into ether and the ether was stripped at the water pump. Decarboxylation of the malonic acid was brought about by heating under an air-cooled condenser to an internal temperature of 230°. A short-path distillation of the above oil, by placing a distilling head directly on a distilling flask, yielded the following at 2 mm.: *Fractions 1–2*, 12.3 g., b.p. up to 152°; *Fractions 3–4*, 78.2 g., b.p. 152–153°, $n_D^{20}$ 1.5142–1.5143; *Fractions 5–6*, 11.5 g., b.p. 154–163°, $n_D^{20}$ 1.5142–1.5140. Fractions 3 through 6 weighed 89.7 g., a yield of 66%. Other preparations gave yields of 49 and 72%. In a final preparation, the yield was low and the residue unusually large. This residue, about 75 g., possibly an ester of ethylene glycol, was saponified by refluxing with excess aqueous potassium hydroxide and worked up as described above. Distillation gave an additional 58 g. of acid, an amount sufficient to raise the yield to 89%.

Acid (III) has a reported[5] b.p. 181–182° (18 mm.), $n_D^{25}$ 1.5140.

*4-Phenyl-3,3-dimethyl-1-butanol* (IV). In a 1-l. three necked flask equipped with a stirrer, condenser, dropping funnel, and necessary drying tubes there were placed 16.35 g. lithium aluminum hydride[6] (about a 20% excess) and 300 ml. anhydrous ether. To this was added 91.7 g. (0.478 mole) of acid (III) in 100 ml. absolute ether during 2 hr. The reaction mixture was refluxed for an additional 1.5 hr. and permitted to stand overnight. Decomposition of the complex was accomplished by the slow dropwise addition of (a) 10 ml. ethyl acetate and then (b) water (care!). When the hydrolysis was complete, the mixture was acidified. The ether layer was separated, washed with sodium carbonate solution, and dried over anhydrous potassium carbonate. The solvent was stripped at the water pump and the last traces of water were azeotroped off with benzene. Distillation through a 2 × 20 cm. column packed with 3/16 in. glass helices gave the following fractions at approximately 1-mm. pressure: *Fraction 1*, 0.4 g., b.p. up to 103°; *Fraction 2*, 9.7 g., b.p. 103–108.5°, $n_D^{25}$ 1.5150; *Fractions 3–6*, 55.4 g., b.p. 107–108°, $n_D^{20}$ 1.5168, $n_D^{25}$ 1.5150; *Fraction 7*, 2.7 g., b.p. 106–96°, $n_D^{25}$ 1.5140. *Fraction 4*, selected as the analytical sample, had $d_4^{20}$ 0.9713. $d_4^{25}$ 0.9680. Fractions 2 through 7 weighed 67.8 g., a yield of 79.7%. The alcohol possesses the odor of roses. It reacts slowly with sodium.

*Anal.* Calcd. for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.70; H, 10.24.

The *3,5-dinitrobenzoate*, prepared by heating the acid chloride and alcohol together directly and recrystallized from ethanol (charcoal), melted at 75.5–76.5 corr. The mixture m.p. with 3,5-dinitrobenzoyl chloride was 55°.

*Anal.* Calcd. for $C_{19}H_{26}N_2O_6$: N, 7.52. Found: N, 7.59.

*4-Bromo-1-phenyl-2,2-dimethylbutane* (V). The above described alcohol (48.8 g., 0.274 mole) was placed in a 500-ml. three necked flask equipped with stirrer, thermometer, condenser and dropping funnel and supported in a Glas-Col mantle. The alcohol was heated to about 65° and redistilled phosphorus tribromide (74.3 g., 0.274 mole) was added rapidly dropwise. The temperature rose to and was maintained at 95° for 4 hr. by the application of external heat. The mixture was then heated at 120° for two additional hours, during which time it became orange colored. Excess phosphorus tribromide was hydrolyzed by pouring onto ice, and the product separated. The aqueous layer was extracted with benzene. Acidic materials were washed from the combined product and benzene phases with water, sodium carbonate solution, and salt water. After brief drying over anhydrous sodium sulfate, the benzene was stripped at the water aspirator and the product fractionated through the previously described column at about 1-mm. pressure. After a small forerun, there was collected a total of 57.1 g. (86.5% yield) of bromide, b.p. 103–106° (1–2 mm.), $n_D^{25}$ 1.5275–1.5302. Purification of a part of the bromide was achieved by repeated shaking with fresh portions of cold concentrated sulfuric until the acid no longer became colored. After washing and drying, the purified bromide distilled constantly at 95–96° (*ca.* 1 mm.), $n_D^{25}$ 1.5327, $d_4^{20}$ 1.2110, $d_4^{25}$ 1.2065.

*Anal.* Calcd. for $C_{12}H_{17}Br$: C, 59.76; H, 7.10; Br, 33.14. Found: C, 59.84; H, 7.21; Br, 33.06.

*Conversion of V to IV.* The Grignard reagent was made in the usual fashion in an 8-in. test tube from 2 g. of the bromide and 0.5 g. magnesium turnings. The test tube was cooled in an ice-salt bath and air (dried by a calcium chloride–sodium hydroxide–soda lime tube), was sucked through the ether solution and the latter permitted to stand overnight. After working up the reaction mixture in the usual way, the ether was evaporated to leave a thick oil. The latter formed a 3,5-dinitrobenzoate which melted at 75.5–76.5° after two recrystallizations (ethanol). The mixture m.p. with the previously prepared 3,5-dinitrobenzoate was 75.5–76.7°.

*1-Phenyl-2,2-dimethylbutane* (VI). (a) *From the bromide.* A suspension of 5 g. (0.13 mole) of lithium aluminum hydride in 50 ml. of dry purified tetrahydrofuran was prepared in a 500-ml. three necked flask equipped with a stirrer, condenser, thermometer, dropping funnel, and drying tubes. To this a solution of 50 g. (0.207 mole) of bromide (V) in 50-ml. tetrahydrofuran was added dropwise and the whole heated at 75° for 7 hr. Next morning the excess lithium aluminum hydride was destroyed by the dropwise addition of 15 ml. of ethyl acetate, followed by the dropwise addition of water. Finally excess water was added and the solution acidified (hydrochloric acid). The organic layer was separated and the water layer extracted with benzene. The combined organic layers were washed successively with water, 5% sodium carbonate solution and water, and then dried briefly with calcium chloride. The solvents were stripped at the water pump and the product was fractionated at 10 mm. A total of 22.2 g. (0.137 mole) of VI, b.p. 84–87°, $n_D^{25}$ 1.4915 to 1.4935 was collected.

(b) *Via the tosylate.* To a solution of 29.7 g. (0.167 mole) of alcohol (IV) in 50-ml. dry pyridine was added, over a period of 1 hr. and with frequent cooling, a solution of 31.8 g. (0.167 mole) of tosyl chloride in dry pyridine. After standing overnight the reaction mixture was poured onto a mixture of ice and excess dilute sulfuric acid. The emulsion was extracted successively with benzene and the benzene layer dried over anhydrous sodium sulfate. The benzene was stripped at the water aspirator, and the residual oil evacuated at 1–2 mm. pressure at room temperature. This oil, possessing the odor of the initial alcohol, was added to a suspension of 6.7 g. of lithium aluminum hydride in 125 ml. anhydrous ether[12] and refluxed for 4 hr. The next morning excess lithium aluminum hydride was destroyed by the addition of ethyl acetate, and water and excess acid were added. The organic phase was separated and the water extracted with ether. After the ethereal solution was washed (sodium carbonate solution) and dried, the ether was removed and the residual oil fractionated through the 2 × 20 cm. column. The following fractions were collected at 10 mm.: *Fraction 1*, 0.6 g., b.p. 81–83°, $n_D^{25}$ 1.4884; *Fraction 2*, 7.6 g., 83–84°, $n_D^{25}$ 1.4912; *Fraction 3*, 0.4 g., 83° and less, $n_D^{25}$ 1.4917. The *residue*, based on odor and refractive index, appeared to be largely unchanged alcohol (IV).

The purification of VI was carried out in the manner described by Berliner[2] for a similar hydrocarbon. A total of 53 g. of hydrocarbon was washed successively with four 25-ml. portions of ice-cold concentrated sulfuric acid, with water, and with sodium carbonate solution and was dried over anhydrous calcium chloride. A small amount of added benzene was distilled to remove any traces of water. The hydrocarbon was then distilled from 1 g. sodium metal through the 2 × 20 cm. Fenske-type column, giving the following at

(12) H. Rapoport and R. M. Bonner, *J. Am. Chem. Soc.*, **73**, 2872 (1951).

10 mm.: *Fraction 1*, 7.2 g., b.p. 85–86°, $n_D^{20}$ 1.4933, $n_D^{25}$ 1.4912; *Fractions 2–4*, 23.3 g., b.p. 85.3–86°, $n_D^{20}$ 1.4935, $n_D^{25}$ 1.4912; *Fraction 5*, 8.6 g., $n_D^{20}$ 1.4938, $n_D^{25}$ 1.4916; *Fraction 6*, 6.1 g., $n_D^{20}$ 1.4940, $n_D^{25}$ 1.4920. *Fraction 3*, taken as the pure hydrocarbon, had micro b.p. 213.5° (745 mm.) corr. and $d_4^{20}$ 0.8694, $d_4^{25}$ 0.8658.

*Anal.* Calcd. for $C_{12}H_{18}$: C, 88.82; H, 11.18. Found: C, 89.01; H, 11.38.

The diacetamino derivative (from ethanol) had a m.p. 231.5–232.5° corr.

*Anal.* Calcd. for $C_{16}H_{24}N_2O_2$: C, 69.53; H, 8.75; N, 10.14. Found: C, 69.44 H, 8.83; N, 10.42.

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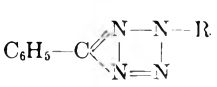
# Communications TO THE EDITOR

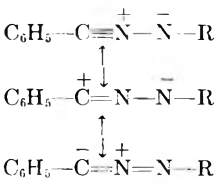
## The Formation of Nitrile Imines in the Thermal Breakdown of 2,5-Disubstituted Tetrazoles

*Sir:*

We wish to report evidence that nitrile imines (II) are intermediates in the thermal decomposition of 2,5-disubstituted tetrazoles (I). As one might expect from the structural and electronic relationship to azides and nitrile oxides, these compounds are quite reactive and attempts to isolate them have thus far been unsuccessful. However, these intermediates can be intercepted by various reagents. These reactions are of theoretical interest because they demonstrate the existence of II and they also appear to have synthetic possibilities.



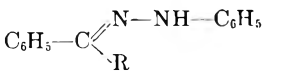
Ia. R = $CH_3$
Ib. R = $C_6H_5$



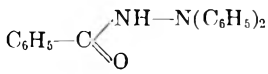
IIa. R = $CH_3$
IIb. R = $C_6H_5$

The first-order thermolysis of the 2,5-disubstituted tetrazoles (I) occurs at a convenient rate at temperatures of 150° for Ib and 200° for Ia. These compounds are less reactive than pentazoles and 5-substituted 2-acyl tetrazoles[1] but Ib undergoes ring opening faster than 1,5-disubstituted tetrazoles which are reported[2] to give carbodiimides at 220°.

When Ib is decomposed in aniline a 75% yield of IIIa is obtained. The thermal breakdown of Ib in thiophenol gives IIIb in 88% yield. Both of these reactions apparently involve a 1,3-addition to the intermediate nitrile imine IIb. The analogous reaction with phenol is followed by an O→N migration of the phenyl group to give 79% yield of benz-*N*,*N*-diphenylhydrazide IV.

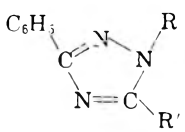


IIIa. R = $-NHC_6H_5$
IIIb. R = $-SC_6H_5$

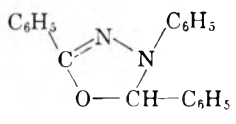


IV

Cyclic structures are formed when I is decomposed in nitriles, aldehydes or olefins with strained carbon-carbon double bonds. For example, the decomposition of Ib in benzonitrile gives 63% of 1,3,5-triphenyl-1,2,4-triazole (Va) (identified by comparison with an authentic specimen). The reaction of Ia with benzonitrile yields 1-methyl-3,5-diphenyltriazole (Vb); with *p*-chlorobenzonitrile the product is Vc. The product resulting from the decomposition of Ib in benzaldehyde (yield 75%) has analytical and spectral data indicating that it is VI. Both V and VI can be considered to arise by the 1,3-addition of a multiple bond to the nitrile imine intermediate.

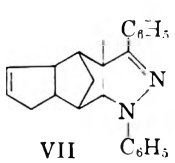


Va. R = R′ = $C_6H_5$
Vb. R = $CH_3$, R′ = $C_6H_5$
Vc. R = $CH_3$, R′ = *p*-$ClC_6H_4$

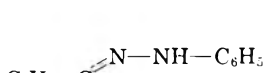


VI

The reaction of nitrile imines with olefins containing strained double bonds is apparently analogous to the reaction of azides and diazoalkanes with substances of this type.[3] The thermolysis of Ib in dicyclopentadiene gives a 68% yield of a crystalline compound which appears to be the tetracyclic product VII. This structural assignment is based on the chemical composition and the infrared spectrum. This same compound VII is obtained in 83% yield when a benzene solution of benzphenylhydrazide chloride (VIII) and dicyclopentadiene is treated with triethylamine. This alternate route to the nitrile imine intermediate by a 1,3-dehydrochlorination is probably analogous to the syntheses of nitrile oxides from hydroxamic acid chlorides.



VII



VIII

(1) Phenylpentazole gives a quantitative yield of phenyl azide and nitrogen at 0° in methanol with a half-life of 13 min. 5-Substituted tetrazoles react rapidly with carboxylic acid chlorides or imino chlorides in pyridine at 50–90° to give 1,3,4-oxadiazoles and 1,2,4-triazoles, respectively. It is noteworthy that these compounds represent substances which are highly aromatic in the sense that there is substantial resonance stabilization, but nonetheless are very reactive. See R. Huisgen and I. Ugi, *Chem. Ber.*, **90**, 2914 (1957); I. Ugi and R. Huisgen, *Chem. Ber.*, **91**, 531 (1958); I. Ugi, H. Perlinger, and L. Behringer, *Chem. Ber.*, **91**, 2324 (1958); R. Huisgen, J. Sauer, and H. J. Sturm, *Angew. Chem.*, **70**, 272 (1958); R. Huisgen, J. Sauer, and M. Seidel, *Chem. and Ind. (London,)* 1114 (1958).

(2) P. A. S. Smith and E. Leon, *J. Am. Chem. Soc.*, **80**, 4647 (1958); J. Vaughan and P. A. S. Smith, *J. Org. Chem.*, **23**, 1909 (1958).

(3) K. Alder and G. Stein, *Ann.*, **485**, 211 (1931); **501**, 1 (1933); K. Ziegler, H. Sauer, L. Bruns, H. Froitzheim-Kohlhorn, and I. Schneider, *Ann.* **589**, 122 (1954).

The addition reactions involving the nitrile imines and their formation by thermolysis of I and dehydrochlorination of VIII are novel in that they represent examples of 1,3-addition and elimination reactions. Apparently, the only nitrile imine described previously is "isodiazomethane,"[4] prepared by de- and reprotonation of diazomethane.

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(4) E. Müller and W. Kreutzmann, *Ann.*, **512**, 264 (1934); E. Müller and D. Ludsteck, *Ber.*, **87**, 1887 (1954); **88**, 921 (1955); E. Müller and W. Rundel, **90**, 2673 (1957).

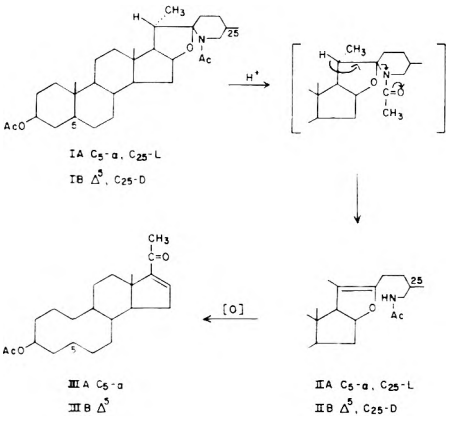
## Improvement in the Preparation of 3β-Acetoxy-5α-pregn-16-en-20-one and 3β-Acetoxypregna-5,16-dien-20-one from the Steroidal Alkaloids, Tomatidine and Solasodine

*Sir:*

The degradation of the steroidal alkaloids, tomatidine and solasodine into 3β-hydroxy-5α-pregn-16-en-20-one[1] (yield: *ca.* 60%) and 3β-acetoxypregna-5,16-dien-20-one[2,3] (yield: *ca.* 10%) has been previously reported. A recent article,[4] using a modification of the original method, reports a marked improvement in the yield of pregnadienolone from solasodine. We wish to report our findings on the conversion of the steroidal alkaloids which lead to a further substantial increase in the production of allopregnenolone and pregnadienolone from tomatidine and solasodine, respectively.

*O,N*-Diacetyltomatidine[5] (IA) and *O,N*-diacetylsolasodine[6] (IB) in an acidic medium undergo a remarkably facile prototropic rearrangement to yield the unsaturated *O,N*-diacetyl derivatives IIA and IIB. Thus, O,N-diacetyltomatidine (IA) can be converted in an almost quantitative manner (95–98%) to IIA, m.p. 128–132°,[7] $[\alpha]_D^{20}$ +1.5°, $\lambda_{max}^{chlf}$ 2.89, 2.97μ (N—H); 5.78μ (3-acetoxy); 5.99, 6.59μ (NH-acetyl) (*Anal.* Calcd. for $C_{31}H_{49}O_4N$: C, 74.51; H, 9.88. Found: C, 74.66; H, 10.02), by the treatment of IA with a solution of mineral acid in acetic acid at room temperature or more conveniently by the direct introduction of IA into boiling acetic acid followed by brief refluxing (15 min.). The partially hydrolyzed alcohol of IIA has been previously obtained by the alkaline hydrolysis of the so-called unsaturated triacetyltomatidine.[8]

Upon carefully controlled oxidation of IIA with chromic acid in acetic acid and subsequent cleavage of the side chain moiety with acetic acid[9] 3β-acetoxy-5α-pregn-16-en-20-one (IIIA) is obtained in excellent yields (*ca.* 80% based on IA), m.p. 165–167°, $[\alpha]_D^{20}$ + 42° ($CHCl_3$), $\lambda_{max}$ 239 mμ, log ε 3.98, (*Anal.* Calcd for $C_{23}H_{34}O_3$: C, 77.05; H, 9.56. Found: C, 77.32; H, 9.58). It agreed in all properties with an authentic sample of allopregnenolone.




In a similar manner the treatment with acetic acid of *O,N*-diacetylsolasodine (IB) yielded IIB (95–98%), m.p. 135–138°, $[\alpha]_D^{20}$ −23°, $\lambda_{max}^{chlf}$ 2.90, 2.98μ (N—H); 5.78μ (3-acetoxy); 5.98, 6.60μ (NH-acetyl). (*Anal.* Calcd. for $C_{31}H_{47}O_4N$: C, 74.81; H, 9.52. Found: C, 75.09; H, 9.36) which has also been previously obtained from the alumina chromatography of the unsaturated triacetylsolasodine[3] (pseudosolasodine A). Oxidation and removal of the consequent 16β-ester side chain of IIB resulted in a good yield (75–80% based on IB) of 3β-acetoxypregna-5,16-dien-20-one (IIIB) m.p. 173–175.5°, $[\alpha]_D^{20}$ −35°, $\lambda_{max}$ 239 mμ, log ε 4.0, (*Anal.* Calcd. for $C_{23}H_{32}O_3$: C, 77.49; H, 9.05. Found: C, 77.45; H, 9.11), identical in all respects with an authentic specimen. In a continuous operation from solasodine without isolation and purification of intermediates, an over-all yield of 65% of IIIB was obtained.

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This method of production of pregnadienolone appears to be superior to the hitherto published methods[3,4] where some by-product[10] formation is involved. The successful degradation of these steroidal alkaloids in high yields, particularly solasodine to pregnadienolone, a biologically important hormone intermediate, may be of considerable industrial importance.

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(10) The stucture and the various chemical manifestations of this substance will be published in the full report.
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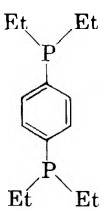
## *P,P,P′,P′*-Tetraethyl-*p*-phenylenediphosphine

*Sir:*

A recent preliminary report by Clifford and Olsen[1] prompts us to record at this time our preparation of *P,P,P′,P′*-tetraethyl-*p*-phenylenediphosphine (I). This substance is the phosphorus analog of the tetraalkyl-*p*-phenylenediamines, which are the precursors of the highly colored Wurster radical ions. Our studies on the behavior toward oxidizing agents of the diphosphine I and of the




I

corresponding N-P system, will be published elsewhere.

The diphosphine I was obtained in *ca.* 20% yield from the reaction of diethylchlorophosphine[2] with *p*-phenylenedilithium[3] in petroleum ether at temperatures below 30°, in a nitrogen atmosphere. I was isolated by extraction into hydrochloric acid followed by the usual alkaline treatment and fractional distillation. The diphosphine I had b.p. 172–174° (9 mm.), $n_D^{25}$ 1.5666, bands at 6.85, 7.00, 7.22, 8.1 and 8.90 $\mu$. Calcd. for $C_{14}H_{24}P_2$: C, 66.2; H, 9.5; P, 24.4. Found: C, 66.2; H, 9.4; P, 23.9.

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## A New Synthesis of Serotonin

*Sir:*

The nitroethylation of indoles and substituted indoles, yielding 3-(2-nitroethyl)indoles has been previously described.[1-3] Catalytic hydrogenation of the 3-(2-nitroethyl)indoles provides a general synthetic route to tryptamine and substituted tryptamines. We wish to record the successful application of this procedure to the synthesis of serotonin.

Dropwise addition of a 1*M* excess of nitroethylene[4,5] to molten 5-benzyloxyindole at steam-bath temperature (total time 1.83 hr.) gave 3-(2-nitroethyl)-5-benzyloxyindole (I, hygroscopic white crystals from methylene chloride-light petroleum (b.p. 60–68°), m.p. 93.5–95°, calcd. for $C_{17}H_{16}N_2O_2$ (296.31): C, 68.90; H, 5.44; N, 9.45; found: C, 68.62; H, 5.58; N, 9.13) in 45% yield. Use of excess nitroethylene is desirable since unreacted 5-benzyloxyindole (36% by wt.) and I (64%) form a eutectic mixture, m.p. 81–81.5°. Similar reactions of 5-benzyloxyindole with equimolar portions of $\beta$-nitrostyrene (6 hr., 72% yield) and $\beta$-methyl-$\beta$-nitrostyrene (22 hr., 37% yield), both at steam bath temperature, gave 3-(1-phenyl-2-nitroethyl)-5-benzyloxyindole (II, white platelets from ethanol, m.p. 117–118°, calcd. for $C_{23}H_{20}N_2O_3$ (372.41): C, 74.17; H, 5.41; N, 7.52; found: C, 74.36; H, 5.40; N, 7.36) and 3-(1-phenyl-2-nitropropyl)-5-benzyloxyindole (III, white rod-like crystals from ethanol, m.p. 152–152.5°, calcd. for $C_{24}H_{22}N_2O_3$ (386.43): C, 74.59; H, 5.74; N, 7.25; found: C, 74.80; H, 5.61; N, 7.26).

Hydrogenation at 2 atm. over platinic oxide catalyst of the adducts I–III gave in high yields the corresponding tryptamines, isolated as the picrates: Ia (84% yield from I), very hygroscopic reddish orange crystals from ethanol, m.p. 231.5–

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SPECTRAL DATA ON NEW COMPOUNDS

| | Ultraviolet: Wave lengths of maxima and inflections (*) in 95% ethanol are given in mμ with intensities in (log ε) | | | | | Infrared Frequencies in Cm.$^{-1}$ | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Medium | NH | $NO_2$ (Aliphatic) |
| I | 275 | 296* | | 307* | | $CHCl_3$ | 3520 | 1558, 1387 |
| | (3.83) | (3.70) | | (3.54) | | Nujol | 3380 | 1553, 1385 |
| II | 275 | 295* | | 308* | | $CHCl_3$ | 3440 | 1552, 1380 |
| | (3.85) | (3.74) | | (3.60) | | Nujol | 3400 | 1550, 1380 |
| III | 275 | 295* | | 309* | | $CHCl_3$ | 3450 | 1550, 1387 or 1360 |
| | (3.81) | (3.73) | | (3.57) | | Nujol | 3390 | 1547, 1385 or 1355 |
| Ia | 275* | 297 | | 309 | 357 | Nujol | 3400 | |
| | (3.92) | (3.85) | | (3.85) | (4.20) | | | |
| IIa | 277* | 297 | 302* | 309 | 357 | Nujol | 3360 | |
| | (3.91) | (3.87) | (3.87) | (3.87) | (4.20) | | | |
| IIIa | 277* | 298 | 304* | 309 | 357 | Nujol | 3400 | |
| | (3.90) | (3.88) | (3.87) | (3.89) | (4.20) | | | |

232° dec., calcd. for $C_{23}H_{21}N_5O_8$ (495.44): C, 55.75; H, 4.27; N, 14.14; found: C, 55.69; H, 4.58; N, 14.07; IIa (94% yield from II), red crystals from ethanol, m.p. 176–176.5°, calcd. for $C_{29}H_{25}N_5O_8$ (571.53): C, 60.94; H, 4.41; N, 12.25; found: C, 60.96; H, 4.74; N, 12.08; IIIa (62% yield from III), bright red crystals from ethanol, m.p. 213–215°, calcd. for $C_{30}H_{27}N_5O_8$ (585.56): C, 61.53; H, 4.65; N, 11.96; found: C, 61.83; H, 4.91; N, 12.09. The tryptamine from I was also characterized as the hydrochloride, which had m.p. 245–247° dec., in agreement with that reported, 248–250°.[6]

Hydrogenation of I at 2 atm. over 10% palladium on charcoal catalyst, resulting in concomitant reduction of the nitro group and debenzylation, gave serotonin in 69% yield as the hygroscopic creatinine sulfate monohydrate salt, m.p. 212–214°, mixed m.p. with an authentic sample (of m.p. 214–216°), 212–216°. The infrared spectra of the two samples in Nujol were identical and in agreement with the spectrum described in the literature[6]—$\lambda_{max}$ in water: 220 mμ (log ε 4.40), 274 (3.72), 293 inflection (3.63). Reported $\lambda_{max}$ in water: 275 mμ and 293 inflection.[7] Calcd. for $C_{14}H_{23}N_5O_7S$ (405.43): C, 41.47; H, 5.72; N, 17.28; S, 7.91; found: C, 41.43; H, 5.73; N, 17.54; S, 8.14. This new synthesis of serotonin in two steps from 5-benzyloxyindole is simpler than previously described methods. The over-all yield (31%) from 5-benzyloxyindole appears to be higher than that reported for all other methods except those of Speeter and Anthony[8] (probably greater than 60%) and Young (34%).[9]

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## Formylation of Aromatic Amines with Dimethylformamide[1]

*Sir:*

A variety of methods are available for the preparation of formamides.[2] However, only several procedures exist for the direct formylation of amines with more readily available formamides.

In 1886, Just described the formylation of phenylhydrazine with formamide at 130°.[3] Several years later Hirst and Cohen obtained formanilides from a number of aromatic amines using formamide in glacial acetic acid.[4] A more recent procedure employs the amine hydrochloride and formamide.[5]

We now wish to report the facile formylation of aromatic amines with dimethylformamide in the presence of sodium methoxide. Conversion to the formanilide is accomplished by heating a mixture of sodium methoxide (0.3 mole), the aniline (0.15 mole) and dimethylformamide (150 ml.) at reflux for 30 min. The reaction is accompanied by the evolution of dimethylformamine. Generally, the formanilide, obtained by diluting the reaction mixture with water, does not require further purification. Typical examples include 2-iodoformanilide, colorless needles, m.p. 113–113.5°, 68% yield (*Anal.* Calcd. for $C_7H_6INO$: C, 34.04; H, 2.45; N, 5.67.

(1) Support of this investigation by a Frederick Gardner Cottrell grant from the Research Corporation is gratefully acknowledged.

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Found: C,33.71; H, 2.27; N, 5.84), 4-bromoformanilide (70.5% yield, m.p. 117–119°; lit.[6] m.p. 119°), 2-chloroformanilide (88.4% yield, m.p. 77.5–78°, lit.[7] m.p. 77°), 3-chloro-4-methylformanilide, colorless needles, m.p. 97–97.5°, 68.5% yield (*Anal.* Calcd. for $C_8H_8ClNO$: C, 56.79; H, 4.77; N, 8.28. Found: C, 56.60; H, 4.66; N, 8.11), and 4-formamidobenzoic acid (45.6% yield, m.p. 270° dec., lit.[8] m.p. 268° dec.).

The composition of a water labile intermediate and the scope of this formylation reaction are presently under investigation.

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