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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Nuclear Alkylation of Salts of Naphthols and Anthranol[1]

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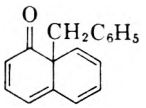
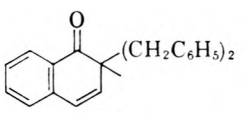
The alkylation with benzyl chloride of the lithium salt of α-naphthol suspended in toluene has been found to give in addition to the phenolic products 2,2-dibenzyl-1(2)-naphthalenone (II) and a tribenzyl ketone, presumably 2,2,4-tribenzyl-1(2)-naphthalenone (III), but none of the angular benzylation product I was found. Similarly, benzylation of the sodium salt of β-naphthol suspended in dioxane according to the procedure of Zagorevsky[5] has led to the dibenzylated ketone IV, in addition to the products previously reported. Procedures are described for the dibenzylation and dimethylation of the lithium salt of anthrone in the 10-position to give the dialkylated anthrones. Again, no evidence of any product formed by alkylation in an angular position is found.

In a continuation of a study of the formation of dienones by the direct alkylation of phenol salts[3] the alkylation of certain naphthol salts was undertaken. The pronounced tendency for *ortho* alkylation[3] made the alkylation of α-naphthols of particular interest because of the possibility of the formation of polyenones such as I, alkylated in an angular position.

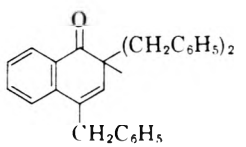


I

The sodium salt of α-naphthol had been reported by Claisen, Kremers, Roth, and Tietze[4] to give 2-benzyl-1-naphthol in good yield, but the neutral products, if any, had apparently not been examined. When the lithium salt of α-naphthol suspended in toluene was treated with benzyl chloride in excess under reflux, there was obtained in addition to some 50% phenolic products approximately 30% carbonyl-containing neutral products. Chromatography of the carbonyl-containing material led to the isolation of a dibenzyl ketone shown to be 2,2-dibenzyl-1(2)-naphthalenone (II) and a tribenzylketone, presumably 2,2,4 - tribenzyl - 1(2)-naphthalenone (III). None of product I formed by angular benzylation could be detected. A preliminary attempt to improve the preparation of the di- and tribenzylated products II and III by carrying out the benzylation of 2-benzyl-1-naphthol prepared by the method previously reported[4] led to an inseparable mixture of neutral products estimated by the infrared spectrum to contain only about 15% carbonyl compounds.



II



III

A rather extensive study of the alkylation of salts of β-naphthol has been reported by Zagorevsky.[5,6,7] For example, benzyl β-naphthyl ether and 1-benzyl-2-naphthol were obtained in yields of 23 and 26% respectively when sodium β-naphthoxide was alkylated in dioxane.[5] In view of the tendency toward polyalkylation shown by lithium

(1) Supported in part by the Office of Ordnance Research, U. S. Army. Taken from the Ph.D. Thesis submitted by Richard Clarence Tuites to the University of Illinois, 1959.

(2) Allied Chemical and Dye Fellow, 1957–58.

(3) See D. Y. Curtin and R. R. Fraser, *J. Am. Chem. Soc.*, **80**, 6016 (1958); **81**, 662 (1959), and references therein cited.

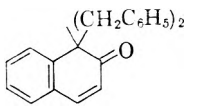
(4) L. Claisen, F. Kremers, F. Roth, and E. Tietze, *Ann.*, **444**, 213 (1925).

(5) V. A. Zagorevsky, *J. Gen. Chem.* (U.S.S.R.), **27**, 3055 (1957).

(6) V. A. Zagorevsky, *J. Gen. Chem.* (U.S.S.R.), **28**, 488 (1958).

(7) See also E. Wenkert and R. D. Youssefyeh, *J. Am. Chem. Soc.*, in press. We are indebted to Dr. Wenkert for a copy of this paper prior to publication.

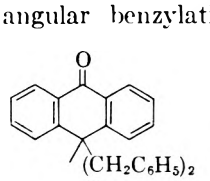
α-naphthoxide in our experiments. Zagorevsky's alkylation of sodium β-naphthoxide was repeated. Infrared examination of the acidic products led to an estimated yield of 1-benzyl-2-naphthol of 22% and examination of the neutral fraction indicated that 22% of benzyl β-naphthyl ether was present. These results are in excellent agreement with those reported by Zagorevsky.[5] However, in addition, the infrared examination of the neutral fraction revealed the presence of a carbonyl-containing compound which was isolated by chromatography on alumina and shown to be the dibenzyl ketone (IV). A comparison of the infrared spectrum of the original neutral fraction with that of IV indicated



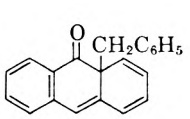
IV

that 13% of IV was formed and it was isolated in 9% yield. As IV undoubtedly arose from further alkylation of some of the 1-benzyl-2-naphthol first formed, the ratio of carbon- to oxygen-alkylation products is appreciably larger than was indicated by the work of Zagorevsky. As the amount of dialkylation product previously overlooked is probably greatest in those experiments in which there was considerable carbon-alkylation, the conclusions of Zagorevsky are not affected qualitatively by the presence of such dialkylated products. Alkylation of the lithium salt suspended in toluene of 1-benzyl-2-naphthol with α-deuterobenzyl chloride was used to prepare the deuterated counterpart of the ketone IV which was needed for an NMR study.[8]

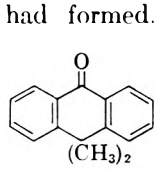
The reactions of the lithium salt of anthrone with benzyl chloride and methyl iodide were also examined. The reaction of the lithium salt suspended in toluene with benzyl chloride resulted in a 65% yield of 10,10-dibenzylanthrone (V) and the single narrow carbonyl absorption maximum in the infrared indicated that no significant amount of the angular benzylation product (VI) had formed.



V



VI



VII

Although the alkylation of anthrone with methyl iodide in the presence of aqueous potassium hydroxide had been reported to yield 10,10-dimethylanthrone (VII) in unspecified yield,[9] more recent attempts to prepare VII by this method have not been successful.[10] The major product of the reaction is 10-methyl-9-methoxyanthracene with yields of 0 to 3% of the dimethyl ketone VII being reported. More recently, Richardson[11] found that heating the lithium salt of anthrone suspended in methyl iodide at 130° for twenty four hours followed by removal of the excess methyl iodide, re-formation of the salt, and repetition of the heating to attempt to insure dialkylation led to only a 6.5% yield of isolated VII, and infrared examination of the crude reaction mixture indicated that not more than 23% of the desired ketone could have been present. A reexamination of this reaction has led to convenient synthesis of the dimethyl anthrone VII. A suspension of the lithium salt of anthrone together with an equimolar amount of lithium methoxide in methyl iodide containing a few drops of *t*-butyl alcohol gave, after heating at 150° for twenty-four hours and evaporation of the solvent, a 64% yield of dimethylanthrone VII. Again there was no evidence of the alkylation product analogous to VI.

It is concluded, then, that alkylation of polynuclear phenol salts in non-polar medium gives *para*- substitution in preference to alkylation in an angular position and also that the choice of a non-polar medium may be a valuable aid to directing alkylation to a *para*- carbon atom when the *ortho*- positions are blocked. Recently Kornblum and Lurie have advanced evidence that heterogeneity plays an important part in determining the position of alkylation of phenol salts.[12] As all the results described in the present paper were carried out in heterogeneous medium, they provide no information on this point.

EXPERIMENTAL[13]

Alkylation of lithium α-naphthoxide with benzyl chloride. 2,2-Dibenzyl-1(2)-naphthalenone (II). The lithium salt of α-naphthol was prepared by refluxing a solution of 6.0 g. (0.042 mol., 5% excess) of freshly sublimed α-naphthol in 80 ml. of toluene with a suspension of lithium methoxide in absolute methanol obtained from 0.28 g. (0.04 g. atom) of lithium metal and absolute methanol (24 ml.). The methanol was distilled until the refractive index of the distillate ($n_D^{25.2}$ 1.4930) was that of pure toluene. Benzyl chloride

(8) J. C. Martin, R. C. Tuites, D. H. Dybvig, and D. Y. Curtin, Manuscript in preparation.

(9) F. Hallgarten, *Ber.*, **21**, 2508 (1888); **22**, 1069 (1889).

(10) (a) K. H. Meyer and H. Schlossen, *Ann.*, **420**, 130 (1920). (b) H. Heymann and L. Trowbridge, *J. Am. Chem. Soc.*, **72**, 84 (1950). (c) N. J. Leonard and P. Mader, Unpublished Results. See P. Mader, Ph.D. Thesis, University of Illinois, 1950.

(11) W. Richardson, Ph.D. Thesis, University of Illinois, 1958.

(12) N. Kornblum and A. P. Lurie, *J. Am. Chem. Soc.*, **81**, 2705 (1959).

(13) Microanalyses were determined by Mr. J. Nemeth, Miss C. Higham, Mrs. M. Stingl and Mrs. F. Ju. Infrared spectra were measured by Mr. P. McMahon, Mr. J. Brader, Mr. B. Cloonan, Mr. S. Portnow, and Miss M. DeMott using 0.1-mm. cells with a Model 21 Perkin-Elmer spectrophotometer. Ultraviolet spectra were measured by Mr. M. Chao and Mr. J. Chiu in 1-cm. cells with a Cary model 14 M spectrophotometer. Photographs of the original spectra are in the thesis of R. C. T.[1] available on microfilm from University Microfilms, Ann Arbor, Michigan. The NMR spectra of the products described here are to be reported elsewhere.[8] All melting points are corrected.

(15 g., 0.12 mol.) was added and the reaction was refluxed for 2.5 hr. and filtered, yielding 3.5 g. of residue.

The neutral fraction remaining in the dried toluene layer (50 ml.) after separation of acidic products by extraction with Claisen's alkali[14] showed infrared absorption at 1675 and 1660 cm.$^{-1}$. Comparison of the spectrum with that of the naphthalenone II measured in chloroform (absorption at 1670 cm.$^{-1}$) suggested that the yield of ketonic products was roughly 30% and with that of benzyl α-naphthyl ether (absorption at 1098–1100 cm.$^{-1}$) indicated that about 4% of this ether was present. From the acidified alkaline extracts 3.7 g. of material was recovered. Removal of the toluene from the solution containing the neutral products gave 15 g. which was chromatographed on 100 g. of alumina not specially activated and eluted with hexane and hexane–benzene mixtures. After the first fractions containing benzyl chloride and a portion of the benzyl α-naphthyl ether there was obtained 5.6 g. of yellow liquid consisting mainly of carbonyl-containing products. Crystallization occurred on standing to give 1.13 g. of a light pink solid, m.p. 60–64°. Attempted recrystallization from methanol-water, acetic acid-water and *n*-hexane was unsuccessful, apparently because of instability of the product. (It discolored and its m.p. range broadened on standing.) Chromatography of the remaining carbonyl-containing fractions together with material from a previous run (total 4.5 g.) on 90 g. of activated alumina gave 50 fractions (100-ml. amounts of eluting solvent) from fraction 29, of which was obtained II as a pale yellow solid, m.p. 60–65°. The infrared spectrum of a 10% chloroform solution contained bands at 1670 and 1645 cm.$^{-1}$ (relative intensities 9/3). The ultraviolet spectrum of a 95% ethanol solution showed λ_{max} 237 mμ, ϵ 29,000. The assigned structure is strongly supported by the NMR spectrum which showed in addition to the characteristic absorption attributable to the benzylic[8] and aromatic hydrogens a quartette at −66, −57, −51 and −42 c.p.s. (40 Mc., 20% carbon tetrachloride solution). This is the absorption to be expected of two non-equivalent olefinic hydrogens *cis* to one another (J 9 c.p.s.).[15]

Anal. Calcd. for $C_{24}H_{20}O$: C, 88.9; H, 6.2. Found: C, 88.8; H, 6.6.

After several months, fractions 37–40 (0.67 g.) crystallized to give a yellowish solid which when recrystallized from *n*-hexane had m.p. 97–98° and is presumed to be *2,2,4-tribenzyl-1(2)-naphthalenone* (III). The infrared spectrum showed a maximum at 1665 cm.$^{-1}$ with a shoulder at 1650 cm.$^{-1}$ (10% chloroform solution). The ultraviolet spectrum of a solution in 95% ethanol showed λ_{max} 242 mμ, ϵ 16,000.

Anal. Calcd. for $C_{31}H_{26}O$: C, 89.8; H, 6.3. Found: C, 89.9; H, 6.2.

Reduction of 2,2-dibenzyl-1(2)-naphthalenone (II). When 102.4 mg. of ketone II in 15 ml. of ethyl acetate was reduced over 5.3 mg. of Adams' platinum catalyst at room temperature and atmospheric pressure with hydrogen gas for 19 hr. 8.4 ml. had been absorbed (the theoretical amount for the reaction of 1 mol. is 8.0 ml.). The reaction mixture was filtered and distillation of the solvent yielded 100 mg. of colorless gummy product which did not crystallize, and reddened on exposure to air. The ultraviolet spectrum of the reduced product in 95% ethanol showed λ_{max} 243–247 mμ, ϵ 9,250 and λ_{max} 290 mμ, ϵ 1,540 in good agreement with those previously reported for 2,2-dimethyl-1(2)-naphthalenone.[16] The NMR spectra of the reduced product showed no absorption in the region −66 to −42 c.p.s.

Alkylation of sodium β-naphthoxide with benzyl bromide. 1,1-Dibenzyl-2(1)-naphthalenone (IV). The reaction conditions employed were those of Zagorevsky.[6] To the sodium salt, prepared from the reaction for 16 hr. of 2.88 g. (0.02 mol.) of β-naphthol in 35 ml. of refluxing dioxane containing 0.46 g. (0.02 g. atom) of sodium metal was added 3.76 g. (0.022 mol.) of freshly distilled benzyl bromide in 5 ml. of dioxane over a period of 2.5 hr. and the reaction was heated for an additional 2 hr. at 104–106°. Separation of the acidic fraction with Claisen's alkali[14] left 3.1 g. of neutral residue the infrared spectrum of which (in chloroform) showed strong absorption at 1645 and a shoulder at 1630 cm.$^{-1}$. Comparisons with the spectra of 1,1-dibenzyl-2(1)-naphthalenone (IV) (using the absorption intensity at 1645 cm.$^{-1}$ and of benzyl β-naphthyl ether (absorption at 1175 cm.$^{-1}$) indicated that the yields of these products were 13 and 22% respectively. Removal of the diethyl ether from the acidic fraction gave 1.98 g. of residue. Comparison of the infrared spectrum with that of 1-benzyl-2-naphthol (absorption at 987 cm.$^{-1}$) indicated that the yield was 22%.

Chromatography on 60 g. of activated alumina of the neutral fraction described above gave 0.78 g. of yellow liquid which crystallized on standing. Rechromatography and recrystallization from *n*-hexane gave white crystalline IV (0.56, 8.7%), m.p. 96–97°. The infrared spectrum in chloroform showed a strong maximum at 1645 cm.$^{-1}$ and a shoulder at 1630 cm.$^{-1}$ The ultraviolet spectrum in 95% ethanol showed λ_{max} 314 mμ, ϵ 7,620 and λ_{max} 243 mμ, ϵ 10,500.

Anal. Calcd. for $C_{24}H_{20}O$: C, 88.9; H, 6.2. Found: C, 88.9; H, 6.4.

Alkylation of lithium 1-benzyl-2-naphthoxide with α-deuterobenzyl chloride. 1-Benzyl-1-benzyl-α-d-2(1)naphthalenone. The lithium salt of 1-benzyl-2-naphthol was prepared from 4.0 g. (0.017 mol., 5% excess) of the naphthol in 105 ml. of toluene and lithium methoxide made by the reaction of 0.11 g. (0.016 g. atom) of lithium metal with 15 ml. of methanol and distillation of the methanol. α-Deuterobenzyl chloride[17] (2.1 g., 0.016 mol.) was added and the reaction was heated under reflux for 20 hr. and filtered. After separation of the acidic fraction with Claisen's alkali,[14] removal of the solvent from the neutral fraction yielded 2.0 g. of residue. Comparison of the infrared spectrum at 1645 cm.$^{-1}$ with that of the undeuterated ketone IV indicated that the yield of carbonyl-containing product was about 24%. Chromatographic separation through 40 g. of neutralized alumina yielded about 1.2 g. of product which after recrystallization from *n*-hexane gave 1-benzyl-1-benzyl-α-*d*-2(1)-naphthalenone, m.p. 95–97°.

Anal. Calcd. for $C_{24}H_{19}DO$: C, 88.6; H, 6.1; D, 5.0. Found: C, 88.7; H, 6.4; D, 5.5.

A similar reaction carried out with undeuterated benzyl chloride yielded 2.7 g. of neutral residue indicated by the infrared spectrum to contain about a 40% yield of the dibenzylnaphthalenone IV.

Alkylation of the lithium salt of anthrone with benzyl chloride. 10,10-Dibenzylanthrone (V). The lithium salt of anthrone was prepared by allowing 3.9 g. (0.02 mol.) of anthrone in 80 ml. of toluene to react with a suspension of lithium methoxide in methanol, prepared from 0.56 g. (0.080 g. atom) lithium metal and 14 ml. of absolute methanol, at reflux. After the removal of the methanol, 7.6 g. (0.060 mol.) of benzyl chloride with 0.2 ml. of *t*-butyl alcohol was added and the reaction was allowed to run at reflux for 15 hr. and filtered, giving 2.4 g. residue.

After separation of acidic products with Claisen's alkali, the infrared spectrum of the neutral fraction showed a large single carbonyl peak at 1665 cm.$^{-1}$. Comparison with that of the purified V, described below, indicates that the yield of V was not more than 67%. The solution was concentrated under 20 mm. pressure to give 2.0 g. of crude V. Further concentration gave 3.5 g. of gummy residue, not identified. An attempt to sublime the product at 100°/0.8 mm for 3 days was unsuccessful. Rechromatography on alumina gave 1.8 g. (23%), m.p. 226–227.5°. This was recrystallized twice

(14) Prepared by dissolving 350 g. of potassium hydroxide in 250 g. of demineralized water and dilution with absolute methanol to make the volume 1 l.

(15) See M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(16) P. Ramart and M. J. Hoch, *Bull. soc. chim. France* [5] **5**, 860 (1938).

(17) We are indebted to Dr. J. C. Martin and Mr. D. Tuleen for this compound.

from pyridine-water and once from benzene-low boiling petroleum ether yielding white V, m.p. 226–227°. The ultraviolet spectrum in 95% ethanol had an ϵ of 18,000 at 270 mμ.

Anal. Calcd. for $C_{28}H_{22}O$: C, 89.8; H, 5.9. Found: C, 89.8; H, 6.2.

Alkylation of the lithium salt of anthrone with methyl iodide. 10,10-Dimethylanthrone (VII). The lithium salt of anthrone was prepared in the manner described for the benzyl chloride reaction using 7.3 g. (0.040 mol.) of anthrone and 0.56 g. (0.080 g. atom) of lithium metal, giving 2 equivalents of lithium methoxide. The toluene and methanol were removed from the salt by gently heating the flask with a steady stream of nitrogen gas passing over the mixture for 3.5 hr. The dry mixture of the lithium salt of anthrone and lithium methoxide was heated in a sealed tube previously flushed with nitrogen, together with 25 ml. (a 10-fold excess) of methyl iodide and 0.2 ml. of *t*-butyl alcohol at 150° for 24 hr., and cooled.

After most of the methyl iodide was distilled, the residue was digested with diethyl ether and acidic products extracted with Claisen's alkali.[14] Removal of the ether from the neutral fraction yielded 6.2 g. (70%) of the dimethylanthrone VII, m.p. 95–105°. Chromatography on alumina gave 5.7 g., 96.5–98° (64%). The ultraviolet spectrum of the analytical sample had an ϵ of 20,000 at 270 mμ.

Anal. Calcd. for $C_{16}H_{14}O$: C, 86.4; H, 6.4. Found: C, 86.4; H, 6.6.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Alkylations of Acetylacetone and Certain Other β-Diketones at the Terminal Methyl Group through Dicarbanions[1]

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The generality of the alkylation of the dicarbanion of acetylacetone was investigated. Good yields of terminal alkylation products were obtained when the dicarbanion was treated with primary alkyl halides, but only a fair yield was obtained with isopropyl bromide. Tertiary butyl chloride failed to alkylate the dicarbanion. Benzhydryl chloride and β-phenylethyl chloride gave tetraphenylethylene and styrene respectively when treated with the dicarbanion. Both mono- and symmetrical dialkylation products were obtained with *n*-octyl bromide. Benzylation of dipotassio-*o*-hydroxyacetophenone gave exclusively 2,2-dibenzyl-2′-hydroxyacetophenone. Alkylations of the dicarbanions of other β-diketones were also realized. Mechanisms and synthetic applications are indicated.

It was shown recently in this laboratory[3] that acetylacetone can be benzylated at the terminal methyl group rather than at the methylene carbon where alkylation has generally been observed. This was accomplished by converting the β-diketone to its dicarbanion[4] by means of two molecular equivalents of potassium amide in liquid ammonia, and then adding one molecular equivalent of benzyl chloride. The reaction may be represented by Equation 1, in which R is benzyl:

$$CH_3COCH_2COCH_3 \xrightarrow[\text{liq. } NH_3]{2\ KNH_2} \underset{\text{I}}{CH_3CO\bar{C}HCO\bar{C}H_2} \xrightarrow[2.\ NH_4Cl]{1.\ RX} \underset{\text{II}}{CH_3COCH_2COCH_2R} \quad (1)$$

In the present investigation a study was made of the generality of this mode of alkylation. First it was shown that, at least for the alkylation with benzyl chloride, the intermediate dicarbanion I may be prepared by means of sodium amide as well as potassium amide.[5] However, dicarbanion I is evidently not produced satisfactorily with two equivalents of lithium amide in liquid ammonia, since the subsequent addition of benzyl chloride failed to yield the alkylation product, the acetylacetone (61%) being recovered.

In Table I are summarized the yields and other data obtained in the alkylations of dicarbanion I with five primary halides and one secondary halide. It can be seen from this table that the primary halides produced good yields (60–77%), but that isopropyl bromide gave only a fair yield (27%). The alkylation failed with *t*-butyl chloride under similar conditions, and the acetylacetone (64%) was recovered.

Since the *n*-butyl, *n*-heptyl, and *n*-octyl halides employed are usually typical of the homologous series of primary alkyl halides, the reaction represented by Equation 1 may be considered quite general when R is primary.

The lower yield with the secondary halide and the failure with the tertiary halide are not surprising since similar observations have been reported in the alkylations of the more common monocarbanions, for example, that of malonic ester.[6]

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(1) Supported in part by the National Science Foundation.

(2) James B. Duke Fellow, 1958–1959.

(3) C. R. Hauser and T. M. Harris, *J. Am. Chem. Soc.*, 80, 6360 (1958).

(4) For the present purpose the dipotassio salt of the β-diketone is considered to consist of the 1,3-dicarbanion I, although other resonance forms may contribute more to the structure of the molecule.

(5) Whereas dipotassioacetylacetone is formed as a precipitate in liquid ammonia, disodioacetylacetone remains essentially in solution (black).

(6) See A. C. Cope, H. L. Holmes, and H. O. House, *Org. Reactions*, 9, 124 (1957).

TABLE I

ALKYLATIONS OF DIPOTASSIOACETYLACETONE

Alkyl Halide	Product	Yield, %	Ketone B.P.	Ketone Mm.	Ketone Lit. B.P.	Ketone Lit. Mm.	Copper Chelate M.P.	Copper Chelate M.P., Lit.	Infrared Peaks 6.0–6.7 μ[a]
Benzyl chloride	6-Phenyl-2,4-hexanedione	60[b,c]	162–165	16	164–166	16[f]	158.5–160	157–159[f]	6.32, 6.56
Allyl bromide	1-Octene-5,7-dione	65	80–86	15	87–89	16[g]	163–163.5		6.10, 6.40, 6.60
n-Butyl bromide	2,4-Nonanedione	68	101–102	19	101–103	19[h]	139–140	138[i]	6.35, 6.59
n-Heptyl bromide	2,4-Dodecanedione	77	140–143	14	150	15[i]	116–116.5	115.5[i]	6.40, 6.60
n-Octyl bromide	2,4-Tridecanedione	67[d] (49)[e]	155–160	16	150–152	16[j]	117–118	114[m]	6.35, 6.55
i-Propyl bromide	6-Methyl-2,4-heptanedione	27	77–80	21	78–79	20[k]	154–155	154[n]	6.38, 6.60

[a] Infrared spectra were produced with a Perkin-Elmer Infracord by the potassium bromide method. [b] Reported previously, see ref. (3). [c] A 69% yield was obtained from the disodiosalt. [d] Obtained under special conditions. [e] Obtained from the general procedure; also 27% of a dialkylation product was isolated. [f] G. T. Morgan and C. R. Porter, *J. Chem. Soc.*, **125**, 1269 (1924). [g] See ref. (8). [h] F. W. Swamer and C. R. Hauser, *J. Am. Chem. Soc.*, **72**, 1352 (1950). [i] G. T. Morgan and E. Holmes, *J. Chem. Soc.*, **127**, 2891 (1925). [j] See ref. (18). [k] J. T. Adams and C. R. Hauser, *J. Am. Chem. Soc.*, **67**, 284 (1945). [l] G. T. Morgan and E. Holmes, *J. Chem. Soc.*, **125**, 762 (1924). [m] See ref. (19). [n] G. T. Morgan and H. D. K. Drew, *J. Chem. Soc.*, **125**, 743 (1924).

That the alkylation actually occurred at the methyl group was shown by the agreement of the boiling points of the β-diketones and the melting points of their copper chelates with the recorded values (see Table I). Moreover, the infrared spectra of all the copper chelates showed strong adsorption bands at 6.32–6.40 μ and 6.55–6.60 μ (Table I) which is indicative of such β-diketones unsubstituted at the methylene group.[7] The structure of the alkylation product from allyl bromide was further established by independent synthesis from the acylation of allylacetone with ethyl acetate (Equation 2):[8,9]

$$CH_2{=}CHCH_2CH_2COCH_3 \xrightarrow[\text{ether}]{NaNH_2} CH_2{=}CHCH_2CH_2COCH_2Na \xrightarrow{CH_3COOC_2H_5} \text{II} \quad (2)$$
(R = allyl)

It should be pointed out that the 67% yield of mono-alkylation product of type II (R = *n*—C_8H_{17}) from *n*-octyl bromide was obtained when the halide was added very slowly (in 75 min.) to the reaction mixture. When the halide was added rapidly (in 3 min.) employing 300 ml. of liquid ammonia and 20 ml. of ether as in the general procedure (see Experimental), only 49% of the mono-octylation product was isolated. However, 27% of a dialkylation product was also obtained.[10] The structure of the dialkylation product is considered in the next section. The reason dialkylation was observed only with *n*-octyl bromide is not clear.

Liquid ammonia, with or without small amounts of ether, appears to be a much better medium for the alkylation of dipotassioacetylacetone than does anhydrous ether alone. While the dicarbanion was benzylated in 60% in liquid ammonia, only 9% of the benzylation product was obtained when the reaction was performed in refluxing ether. Similarly, *n*-octyl bromide gave only 23% monoalkylation and 5% dialkylation in ether.

In contrast to the typical primary alkyl halides, β-phenylethyl chloride, which has a relatively reactive β-hydrogen, failed to alkylate dicarbanion I. Instead, the halide underwent β-elimination to form styrene (89%), most of the acetylacetone being recovered. Since β-phenylethyl chloride is known to undergo β-elimination with ethoxide or amide, but substitution with diphenylmethide carbanion,[11] the dianion of acetylacetone appears to function more like an oxide base than like a carbanion towards this halide. This may be indicated by employing an oxide resonance form of the dianion (Equation 3):

$$CH_3\overset{O^-}{C}{=}CH\overset{O^-}{C}{=}CH_2 + C_6H_5CH_2CH_2Cl \longrightarrow CH_3\overset{O^-}{C}{=}CH\overset{O}{\overset{\|}{C}}CH_3 + C_6H_5CH{=}CH_2 \quad (3)$$

(7) R. P. Dryden and A. Winston reported [*J. Phys. Chem.*, **62**, 635 (1958)] that the copper chelates of acetylacetone and similar β-diketones unsubstituted at the methylene group show infrared bands at 6.10–6.45 μ and 6.52–6.60 μ whereas the chelates of their 3-substituted derivatives exhibit only the former bands.

(8) G. Leser, *Bull. soc. chim. France*, [3], **27**, 64 (1902).

(9) See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 122–123 (1954).

(10) When the reaction was carried out in a mixture of 150 ml. each of liquid ammonia and anhydrous ether the yields of mono- and dialkylation products were 31 and 42% respectively.

(11) C. R. Hauser and P. J. Hamrick, Jr., *J. Am. Chem. Soc.*, **79**, 3142 (1957).

Benzhydryl chloride, which has a more reactive α-hydrogen than benzyl chloride, failed to alkylate dicarbanion I. The halide, instead, underwent self-alkylation accompanied by β-elimination to give tetraphenylethylene (98%). Since benzhydryl chloride is known to undergo such a self-condensation with the amide ion[12] but the substitution type reaction with the diphenylmethide carbanion,[11] the dianion of acetylacetone again seems to function more like a strong base than as a nucleophilic carbanion. This may be represented by Equation 4:

$$CH_3\overset{O^-}{\overset{|}{C}}=CH\overset{O^-}{\overset{|}{C}}=CH_2 + (C_6H_5)_2CHCl \xrightarrow[\text{exchange}]{\text{proton}} CH_3COC\bar{H}COCH_3 + (C_6H_5)_2\bar{C}Cl$$

$$(C_6H_5)_2CCl^- \xrightarrow{(C_6H_5)_2CHCl} (C_6H_5)_2CHC(C_6H_5)_2(Cl) \xrightarrow[\text{of HCl}]{\beta\text{-elimination}} (C_6H_5)_2C=C(C_6H_5)_2 \quad (4)$$

Although all of the above results were obtained with acetylacetone, similar results might be expected with other β-diketones having a terminal methyl group. In fact the benzylations of the terminal methyl groups of benzoylacetone,[3] acetylcyclohexanone,[13] and acetylcyclopentanone[13] have been reported. The alkylation of the dicarbanions of β-diketones of type II is discussed below.

Alkylations of β-diketones of type II. In contrast to acetylacetone and benzoylacetone,[3] β-diketones of type II can form two different dicarbanions (III and IV) depending on whether a methyl or 5-methylene hydrogen undergoes the secondary ionization. It has recently been shown in this

$$\underset{\text{III}}{RCH_2CO\bar{C}HCO\bar{C}H_2} \qquad \underset{\text{IV}}{R\bar{C}HCO\bar{C}HCOCH_3}$$

laboratory[13] that 6-phenyl-2,4-hexanedione (II. R = $CH_2C_6H_5$) can be benzylated through a dicarbanion of type III to 1,7-diphenyl-3,5-heptanedione (Va) in 65% yield. No products corresponding to alkylation of a dicarbanion of type IV were observed.

In the present study other β-diketones of type II were alkylated. As with 6-phenyl-2,4-hexanedione only products corresponding to alkylations of a dicarbanion of type III were obtained.

The first ketone studied was 2,4-tridecanedione (II. R = n-C_8H_{17}) which was derived from the alkylation of the dicarbanion of acetylacetone with n-octyl bromide. This β-diketone was converted to its dicarbanion by means of two molecular equivalents of potassium amide in liquid ammonia and then alkylated with one molecular equivalent of n-octyl bromide (Equation 5): That the product (71%) ac-

$$\underset{\text{II}}{RCH_2COCH_2COCH_3} \xrightarrow[\text{liq. } NH_3]{2\ KNH_2} \text{III} \xrightarrow[2.\ NH_4Cl]{1.\ R'X} RCH_2COCH_2COCH_2R' \quad (5)$$

Va. R = R′ = $CH_2C_6H_5$
b. R = R′ = n-C_8H_{17}
c. R = $CH_2C_6H_5$, R′ = n-C_4H_9

tually had structure Vb was shown by alkaline cleavage to give capric acid and methyl nonyl ketone (isolated as the semicarbazone) in yields of 84 and 89% respectively (Equation 6):

$$\text{Vb} \xrightarrow[2.\ HCl]{1.\ KOH} CH_3(CH_2)_8COOH + CH_3CO(CH_2)_8CH_3 \quad (6)$$

Moreover, the infrared spectra of its copper chelate (blue-gray) showed strong infrared adsorption bands at 6.40 and 6.60 μ which is indicative of such a β-diketone.[7]

The β-diketone and chelate were identical with the dialkylation product obtained when the dicarbanion of acetylacetone was rapidly alkylated with n-octyl bromide (see above).

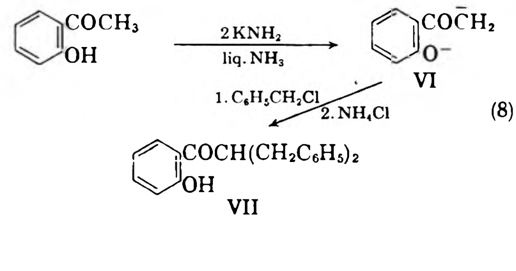
Secondly, 6-phenyl-2,4-hexanedione (II. R = $CH_2C_6H_5$), obtained as described above, was converted to its dicarbanion and alkylated with n-butyl bromide to give β-diketone Vc (67%). That the ketone actually had structure Vc was shown through an independent synthesis, by the condensation of methyl hydrocinnamate with methyl amyl ketone (Equation 7).[9] Also its copper chelate

$$CH_3(CH_2)_4COCH_3 \xrightarrow[\text{ether}]{NaNH_2} CH_3(CH_2)_4COCH_2Na \xrightarrow{C_6H_5CH_2CH_2COOCH_3} \text{Vc} \quad (7)$$

(blue) showed strong infrared adsorption at 6.40 and 6.60 μ which is characteristic of such a β-diketone.[7] The β-diketone Vc was also synthesized (52%) by the alkylation of the dicarbanion of 2,4-nonanedione (II, R = n-C_4H_9) with benzyl chloride.

The stepwise dialkylation of acetylacetone through intermediate dicarbanions of type I and III thus affords a convenient means for the synthesis of high molecular weight β-diketones.

Alkylation of o-hydroxyacetophenone. Although o-hydroxyacetophenone is not a typical β-diketone, it seemed of interest to determine whether it could be alkylated at the methyl group through the intermediate dianion VI. When o-hydroxyacetophenone was added to two molecular equivalents of potassium amide in liquid ammonia and the resulting suspension treated with one molecular equivalent of benzyl chloride (Equation 8) no mono-benzylation product was isolated:



VII (8)

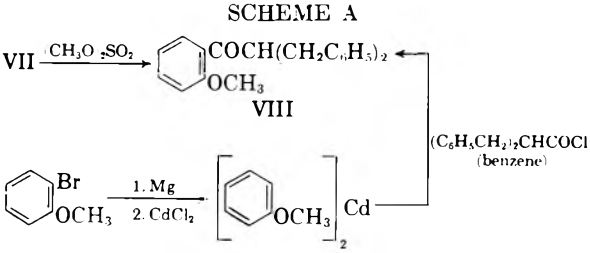
(12) C. R. Hauser, W. R. Brasen, P. S. Skell, S. W. Kantor, and A. E. Brodhag, *J. Am. Chem. Soc.*, **78**, 1653 (1956).

(13) T. M. Harris and C. R. Hauser, *J. Am. Chem. Soc.*, **81**, 1160 (1959).

Instead, the dibenzylation product VII was obtained (69–74% based on benzyl chloride) and unreacted *o*-hydroxyacetophenone was recovered (53%). Presumably the dianion of the mono-alkylation product was an intermediate. Rather surprisingly, when the reaction was performed using two molecular equivalents of benzyl chloride, a poorer yield (23%) of the dialkylation product was isolated. Again no mono-benzylation products were observed.

The dialkylation product gave a purple color with 1% methanolic ferric chloride, formed an oxime, and was thus assigned the structure VII. The structure of the dialkylation product was established as VII by converting it to its methyl ether VIII (79%) with dimethyl sulfate. This ether was independently synthesized (Scheme A) from di-(*o*-methoxyphenyl)-cadmium and dibenzylacetyl chloride.[14] That the ethers were the same was shown by comparison of the boiling points, refractive indices, and infrared spectra.

SCHEME A



EXPERIMENTAL[15]

General procedure for the alkylation of dipotassioacetylacetone. To a stirred solution of 0.2 mol. of potassium amide in 300 ml. of liquid ammonia[3] was added through a powder funnel 10 g. (0.1 mol.) of acetylacetone as the freshly precipitated ammonium salt.[16] After stirring 0.5 hr. the resulting white suspension was considered to contain 0.1 mol. of dipotassioacetylacetone.

To the stirred suspension of dipotassioacetylacetone was added in 3 min. 0.1 mol. of alkyl halide in 10–20 ml. of anhydrous ether. The resulting mixture was stirred 1 hr. and neutralized by the rapid addition of 12 g. of solid ammonium chloride. The ammonia was replaced by ether and the ethereal suspension extracted with water to remove the inorganic salts. The aqueous solution was acidified with 3*N* hydrochloric acid and extracted three times with ether. The combined ethereal solutions were dried over Drierite, filtered, and the solvent removed under reduced pressure. The residual liquid was vacuum distilled to give the 1-alkyl-2,4-pentanedione.

The copper chelates, formed by adding a hot, filtered aqueous solution of copper acetate to a methanolic solution of β-diketone, were crystallized from methanol or a mixture of benzene and ligroin (b.p. 60–90°).

The results are summarized in Table I.

Benzylation of disodioacetylacetone. To a stirred suspension of 0.1 mol. of sodium amide in 300 ml. of liquid ammonia[17] was added 5 g. (0.05 mol.) of acetylacetone as the freshly precipitated ammonium salt.[16] After stirring 0.5 hr. the resulting black solution was assumed to contain 0.05 mol. of disodioacetylacetone.

To this black solution was added in 3 min. 6.3 g. (0.05 mol.) of benzyl chloride in 10 ml. of anhydrous ether. After stirring 1 hr. the solution was neutralized with 6.0 g. of solid ammonium chloride and worked up as described above. The residual liquid after the removal of the ether was converted directly to the copper chelate of 6-phenyl-2,4-hexanedione (II. R = $CH_2C_6H_5$), 7.6 g. (69%), m.p. 159–160 (lit.[3] 158.5–160°).

Octylation of dipotassioacetylacetone. To a stirred suspension of 0.1 mol. of dipotassioacetylacetone in 300 ml. of liquid ammonia was added in 75 min. 19.3 g. (0.1 mol.) of *n*-octyl bromide in 20 ml. of anhydrous ether. The resulting suspension was stirred 1 hr. and neutralized with solid ammonium chloride (12 g.). The ammonia was replaced by ether and the ethereal suspension processed in the usual manner. Distillation afforded 14.1 g. (67%) of 2,4-tridecanedione (II. R = n-C_8H_{17}), b.p. 155–160° at 16 mm. lit.,[18] 150–152° at 16 mm.). The β-diketone gave an orange enol test with 1% methanolic ferric chloride and formed a blue copper chelate which was crystallized from methanol, m.p. 117–118° (lit.,[15] 114° and[18] 110°).

When the alkylation was carried out as described in the general procedure (halide added in 3 min.) the yield of 2,4-tridecanedione was 49% and a dialkylation product was obtained. This was processed in the following manner: The pot residue after the distillation of the mono-alkylation product was cooled and crystallized from methanol to give 10,12-henicosanedione Vb (27%), m.p. 39–39.5°. This β-diketone gave an orange color with 1% methanolic ferric chloride.

Anal. Calcd. for $C_{21}H_{40}O_2$: C, 77.72; H, 12.42; mol. wt., 325. Found: C, 77.73; H, 12.21; mol. wt., 335.

A sample of the β-diketone was converted to a blue-gray copper chelate which was crystallized from benzene-ligroin (b.p. 60–90°), m.p. 109.5–110°.

Anal. Calcd. for $C_{42}H_{78}O_4Cu$: C, 70.99; H, 11.06; Cu, 8.96. Found: C, 71.47 and 71.38; H, 11.05 and 11.14; Cu, 8.84 and 8.76.

Independent synthesis of 1-octene-5,7-dione (II. R = $-CH_2CH{=}CH_2$). To a stirred suspension of 0.2 mol. of sodium amide in 300 ml. of anhydrous ether was added 9.8 g. (0.10 mol.) of allylacetone in 20 ml. of ether, followed after 5 min. by 17.6 g. (0.20 mol.) of ethyl acetate in 40 ml. of ether according to the general sodium amide method A.[17] After refluxing 3 hr. the suspension was cooled and poured onto 200 g. of crushed ice containing 25 ml. of concentrated hydrochloric acid. The ether layer was separated and combined with three ether washings of the aqueous solution. After drying over Drierite, the ethereal solution was filtered and the ether removed under reduced pressure. The residue was dissolved in hot methanol and a hot, filtered, aqueous solution of copper acetate was added. The crude copper chelate (11.8 g., 69%, m.p. 163–164.5°) was decomposed with hydrochloric acid and the aqueous suspension extracted with petroleum ether (b.p. 30–60°). The

(14) Although di-(*m*-methoxyphenyl)-cadmium reacts with rearrangement, it has been shown that the ortho derivative reacts normally. See W. G. Dauben and J. W. Collette, *J. Am. Chem. Soc.*, **81**, 967 (1959).

(15) Melting points and boiling points are uncorrected. Melting points were taken on a Fisher-Johns melting point apparatus. Microanalyses were by Spang Microanalytical Laboratory, Ann Arbor, Mich.

(16) The direct addition of acetylacetone to the liquid ammonia solution of alkali amide was so vigorous that the reaction was difficult to control. The ammonium salt was prepared by freezing the acetylacetone in a Dry Ice–acetone bath and then adding liquid ammonia. The excess liquid ammonia was evaporated at room temperature and the residual salt added to the amide solution.

(17) See ref. (9), p. 122.

(18) C. Weygand and H. Baumgartel, *Ber.*, **62B**, 574 (1929).

(19) G. T. Morgan and E. Holmes, *J. Chem. Soc.*, **125**, 760 (1924).

organic solution was dried over Drierite, filtered, and the solvent removed under reduced pressure. Distillation of the residue afforded 6.25 g. (45%) of 1-octene-5,7-dione, b.p. 83–84° at 16 mm. (lit.[8] 87–89° at 16 mm.). The infrared spectrum of this β-diketone was identical with the spectrum of the β-diketone prepared by the alkylation of dipotassioacetylacetone with allyl bromide.

A sample of the β-diketone was reconverted to the copper chelate (blue) which was crystallized from methanol, m.p. 162–162.5° and not depressed on admixture with the copper chelate from the alkylation reaction. Repeated recrystallization from methanol raised the melting point to 163–163.5°.

Anal. Calcd. for $C_{16}H_{22}O_4Cu$: C, 56.21; H, 6.49; Cu, 18.38. Found: C, 56.21; H, 6.42; Cu, 18.42.

Reaction of dipotassioacetylacetone with β-phenylethyl chloride. The reaction was carried out as described in the general procedure using 0.1 mol. of dipotassioacetylacetone and 14.1 g. (0.1 mol.) of β-phenylethylchloride. A few crystals of hydroquinone were added to the dried ether solution before the removal of the solvent. The residue was dissolved in methanol and a hot, filtered solution of 12 g. of copper acetate in 200 ml. of 50% aqueous methanol was added. The mixture was cooled and the copper chelate filtered. The filter cake was washed successively with water and petroleum ether (b.p. 30–60°) until the washings were essentially clear, yielding 9.2 g. (70%) of the copper chelate of acetylacetone.

The filtrate was separated and the organic solution was combined with two petroleum ether washings of the aqueous solution. The dried organic solution was cooled in ice and a 10% solution of bromine in carbon tetrachloride was slowly added until the bromine color persisted for 5 min. The excess bromine was decomposed by the addition of a 10% sodium bisulfite solution. The organic layer was separated, washed with a 10% sodium bisulfite solution followed by water, dried over Drierite, filtered, and the solvent removed under reduced pressure. The residual solid was crystallized from aqueous ethanol to give 23.3 g. (89%) of styrene dibromide, m.p. 68–70° (lit.[20] 72–73°). After recrystallization from ethanol the m.p. and mixed m.p. with authentic styrene dibromide were 72.5–73°.

Reaction of dipotassioacetylacetone with benzhydryl chloride. To a stirred suspension of 0.1 mol. of dipotassioacetylacetone in 300 ml. of liquid ammonia was added in 5 min. 20.3 g. (0.1 mol.) of benzhydryl chloride in 10 ml. of anhydrous ether. An orange color appeared immediately. After stirring 1 hr. the suspension was neutralized by the addition of 12 g. of solid ammonium chloride and the ammonia was replaced by ether. Water was added to the ethereal suspension and the mixture was filtered to give 8.55 g. of tetraphenylethylene, m.p. 221.5–223.5° and 223.5–224.5° when mixed with an authentic sample (lit.[21] 223–224°).

The filtrate was separated and the ethereal solution combined with several ether washings of the aqueous solution. After drying over Drierite, the solvent was filtered and distilled under reduced pressure. The residual mixture was filtered and the filter cake washed with petroleum ether (b.p. 30–60°) until the washings were clear, yielding 7.65 g. of tetraphenylethylene, m.p. and mixed m.p. 223.5–224.5°. Total tetraphenylethylene 16.2 g. (98%).

The filtrate was concentrated, dissolved in hot methanol and converted to the copper chelate of acetylacetone (7.0 g., 54%).

Independent synthesis of 10,12-henicosanedione (Vb). To a stirred solution of 0.1 mol. of potassium amide in 300 ml. of liquid ammonia was added 10.6 g. (0.05 mol.) of 2,4-tridecanedione in an equal volume of anhydrous ether. The resulting gray suspension was stirred 0.5 hr. and 9.65 g. (0.05 mol.) of *n*-octyl bromide in an equal volume of anhydrous ether was rapidly added. After stirring 1 hr. the suspension was neutralized by the addition of excess ammonium chloride and the ammonia was replaced by ether. The ethereal suspension was extracted with water, combined with two ether washings of the aqueous solution, dried over Drierite, filtered, and the ether removed under reduced pressure. The residual solid was crystallized from methanol to give 11.55 g. (71%) of 10,12-henicosanedione, m.p. 38–39° and not depressed on admixture with the dialkylation product from dipotassioacetylacetone and *n*-octyl bromide.

Alkaline cleavage of 10,12-henicosanedione (Vb). A solution of 3.24 g. (10 mmol.) of β-diketone Vb and 2 g. of potassium hydroxide in 60 ml. of 80% ethanol was refluxed 10 hr. The ethanol was evaporated and ether and water were added to the residue. The ether layer was separated, dried over magnesium sulfate, filtered, and the ether was removed under reduced pressure. The residue was treated with semicarbazide hydrochloride and sodium acetate to give 1.9 g. (89%) of the semicarbazone of methyl nonyl ketone, m.p. 121.5–122.5° (lit.[22] 122–123°).

The aqueous layer from the cleavage mixture was saturated with carbon dioxide and extracted with ether to remove any unreacted β-diketone. The aqueous solution was then acidified with cold, dilute hydrochloric acid and extracted twice with ether. The ether solution was dried over magnesium sulfate, filtered, and the solvent removed yielding 1.45 g. (84%) capric acid, m.p. 24–27° (lit.[23] 31.5°). A portion of the acid was converted to its *p*-bromophenacyl ester, m.p. 66–67° (lit.[23] 67°).

1-Phenyl-3,5-decanedione (Vc). (A) *From the dicarbanion of 6-phenyl-2,4-hexanedione* (II. R = $-CH_2C_6H_5$). To a stirred solution of 0.1 mol. of potassium amide in 300 ml. of liquid ammonia was added 9.51 g. (0.05 mol.) of 6-phenyl-2,4-hexanedione in 7 ml. of anhydrous ether. The resulting dark red solution was stirred 0.5 hr. and 6.85 g. (0.05 mol.) of *n*-butyl bromide in 5 ml. of anhydrous ether was added over 1.5 min. The color faded and the resulting yellow suspension was stirred 0.5 hr. After neutralization by the addition of 6 g. of solid ammonium chloride the ammonia was replaced by ether and the mixture worked up in the usual manner. Distillation afforded 8.25 g. (67%) of 1-phenyl-3,5-decanedione (Vc), b.p. 148–152° at 2 mm. Repeated distillation gave b.p. 146° at 1 mm. The β-diketone gave an orange enol test with 1% methanolic ferric chloride.

Anal. Calcd. for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00. Found: C, 77.87; H, 8.89

A portion of the β-diketone was converted to its copper chelate which was crystallized from methanol, m.p. 124–124.5°.

Anal. Calcd. for $C_{32}H_{42}O_4Cu$: C, 69.35; H, 7.64; Cu, 11.35. Found: C, 69.48; H, 7.68; Cu, 11.47.

(B) *From the dicarbanion of 2,4-nonanedione* (II. R = n-C_4H_9). To a stirred solution of 0.2 mol. of potassium amide in 300 ml. of liquid ammonia was added 15.6 g. (0.1 mol.) of 2,4-nonanedione in 5 ml. of anhydrous ether. The resulting green suspension was stirred 0.5 hr. and 12.6 g. (0.1 mol.) of benzyl chloride in 5 ml. of anhydrous ether was added in 3 min. The resulting suspension was stirred 1 hr. and neutralized by the addition of 12 g. of solid ammonium chloride. The ammonia was replaced by ether and the mixture worked up in the usual manner. Distillation afforded 12.8 g. (52%) of β-diketone Vc, b.p. 147–152° at 1 mm. The infrared spectrum of this β-diketone was identical with the spectrum of the β-diketone prepared by method A.

A portion of the β-diketone was converted to its copper chelate, m.p. 125–126° and not depressed on admixture with the chelate from A.

Independent synthesis of β-diketone Vc. To a stirred suspension of 0.2 mol. of sodium amide in 300 ml. of anhydrous

(20) C. R. Hauser, J. C. Shivers, and P. S. Skell, *J. Am. Chem. Soc.*, **67**, 409 (1945).

(21) J. Schmidlin, *Ber.*, **39**, 4203 (1907).

(22) Heilbron, *Dictionary of Organic Compounds*, Oxford University Press, New York, N. Y., 1953, Vol. III, p. 464.

(23) Heilbron, *Dictionary of Organic Compounds*, Oxford University Press, New York, N. Y., 1953, Vol. I, p. 421.

ether was added 22.8 g. (0.2 mol.) of methyl amyl ketone in 25 ml. of ether, followed after 5 min. by 16.4 g. (0.1 mol.) of methyl hydrocinnamate in 25 ml. of ether according to the general sodium amide method B.[17] After refluxing 1.5 hr. the suspension was cooled and poured into 200 g. of crushed ice containing 18 ml. of concentrated hydrochloric acid. The ether layer was separated and combined with an ether washing of the aqueous solution. The combined ether solutions were washed successively with 100 ml. of a saturated sodium bicarbonate solution and 100 ml. of water. After drying over Drierite, the ether was filtered and solvent removed under reduced pressure. The residual liquid was distilled to give 14.65 g. (60% based on ester) of β-diketone Vc, b.p. 150–155° at 1.5 mm. The infrared spectrum of this β-diketone was identical with the spectra of the β-diketones prepared by methods A and B.

A portion of the β-diketone was converted to its copper chelate, m.p. 125–126°, not depressed on admixture with the chelates from methods A and B.

Alkylation of o-hydroxyacetophenone. To a stirred solution of 0.2 mol. of potassium amide in 300 ml. of liquid ammonia was added 13.6 g. (0.1 mol.) of *o*-hydroxyacetophenone in 20 ml. of anhydrous ether. A vigorous reaction occurred and a yellow precipitate formed. The suspension was stirred 10 min. and 12.6 g. (0.1 mol.) of benzyl chloride in 20 ml. of anhydrous ether was added in 3 min. The resulting yellow solution was stirred 1 hr. and neutralized by the addition of 12 g. of solid ammonium chloride. The ammonia was replaced by ether and the ethereal suspension was extracted with water. After being combined with three ether washings of the acidified aqueous solution, the ether solution was dried over Drierite, filtered, and the ether removed under reduced pressure. The residue was crystallized from methanol to give 2,2-dibenzyl-2′-hydroxyacetophenone (VII) (69–74% on benzyl chloride), m.p. 71–72°. Recrystallization from methanol raised the m.p. to 73–73.5°. The solid gave a purple color with 1% methanolic ferric chloride.

Anal. Calcd. for $C_{22}H_{20}O_2$: C, 83.51; H, 6.37; mol. wt., 316. Found: C, 83.28 and 83.25; H, 6.45 and 6.31; mol. wt., 327.

The filtrate was evaporated and the residue dissolved in ether. The ethereal solution was extracted with 10% sodium hydroxide which was subsequently acidified with 3*N* hydrochloric acid. The acidic solution was extracted with ether and the ether was evaporated. The residual liquid was converted to the phenylhydrazone of *o*-hydroxyacetophenone (52.5%), m.p. 109.5–110°, not depressed on admixture with an authentic sample.

An oxime was prepared by refluxing a solution of VII (1.00 g., 3.17 mmol.), hydroxylamine hydrochloride (1.0 g.) and potassium hydroxide (4.0 g.) in 20 ml. of 95% ethanol for 2 hr. The solution was then poured into 150 ml. of water and the suspension filtered. The filtrate was acidified with hydrochloric acid and allowed to stand overnight when a white precipitate settled out. Filtration yielded 0.8 g., m.p. 88–92° of a material which appeared to be a mixture. After several fractional crystallizations from hexane the material melted at 121–121.5°.

Anal. Calcd. for $C_{22}H_{21}NO_2$: C, 79.73; H, 6.39; N, 4.23. Found: C, 79.64; H, 6.50; N, 4.15.

Methylation of VII. To a hot solution of 3.16 g. (10 mmol.) of VII in 20 ml. of ethanol was added alternately in five portions, 4 g. of sodium hydroxide in 10 ml. of water and 10 ml. of dimethyl sulfate. Vigorous refluxing occurred after each addition of dimethyl sulfate. After the final portion of dimethyl sulfate had been added a solution of 1 g. of sodium hydroxide in 2 ml. of water was added and the mixture refluxed 2.5 hr. After cooling, the alkaline solution was extracted three times with ether. The ether was dried over Drierite, filtered, and the solvent removed under reduced pressure. Distillation of the residue afforded 2.6 g. (79%) of 2,2-dibenzyl-2′-methyoxyacetophenone VIII, b.p. 193–196° at 0.4 mm., n_D^{26} 1.5896. After two redistillations, b.p. 193–195° at 0.2 mm., n_D^{25} 1.5900.

Anal. Calcd. for $C_{23}H_{22}O_2$: C, 83.60; H, 6.71. Found: C, 83.54; H, 6.83.

Independent synthesis of VIII. Di-(*o*-methoxyphenyl)-cadmium was prepared by a procedure similar to that described by Cason and Prout for diisoamylcadmium.[24]

To 1.37 g. (0.0564 g.-atom) of magnesium shavings in 20 ml. of anhydrous ether was slowly added a solution of 10.5 g. (0.0563 mol.) of *o*-bromoanisole in 100 ml. of anhydrous ether and the resulting mixture was refluxed for 2.25 hr. The mixture was then cooled in ice and 5.50 g. (0.030 mol.) of anhydrous, powdered cadmium chloride was added. The ice bath was removed and the mixture was refluxed for 0.75 hr., when it gave a negative Gilman's test for Grignard reagent. The ether was rapidly distilled and thiophene-free benzene added. To the resulting suspension was added 11.6 g. (0.045 mol.) of dibenzylacetyl chloride (b.p. 148–152° at 0.5 mm.), prepared from dibenzylacetic acid and thionyl chloride (refluxed 8 hr.), in 50 ml. of benzene. The mixture was refluxed 2.5 hr., cooled, and decomposed by the cautious addition of 80 g. of ice followed by 40 ml. of 3*N* hydrochloric acid. The benzene layer was separated and combined with two ether washings of the aqueous solution. The combined organic solutions were washed successively with 50 ml. of water, 50 ml. of a saturated sodium bicarbonate solution, and 50 ml. of water. After drying over Drierite the ether was filtered and solvent removed under reduced pressure. Distillation afforded 5.10 g. (35%) of ether VIII, b.p. 187–190° at 0.25 mm., n_D^{25} 1.5887. Redistillation gave b.p. 196–198° at 0.4 mm., n_D^{25} 1.5891. The infrared spectrum of this compound was identical with the spectrum of the methylation product of VII.

DURHAM, N. C.

(24) See J. Cason and F. S. Prout, *Org. Syntheses*, Coll. Vol. III, 601 (1955).

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

Syntheses Utilizing γ-Cyano-γ-phenylpimelonitrile

C. F. KOELSCH

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Procedures for obtaining many derivatives from γ-cyano-γ-phenylpimelonitrile have been developed. An overall idea of the reactions studied is best obtained by examination of charts I to VII in the experimental part of this paper.

When Bruson and Riener reported[1] that benzyl cyanide and acrylonitrile reacted to form γ-cyano-γ-phenylpimelonitrile in good yield, it was at once apparent that the product afforded easy syntheses of interesting compounds distantly related to morphine. An investigation of the synthetic possibilities was begun, but it was interrupted in 1944 by the war. Since attempts to convert nitrogenous substances in the series to amines by sodium and alcohol were failures, the work was not published. However, in view of recent interest in some of the compounds involved,[2,3] it appears advisable to report the old synthetic work. It is planned to resume the study now, and to take advantage of the reducing properties of the metal hydrides.

In the interest of brevity, only positive results are presented. This is done in Charts I to VII. Cross references between important compounds depicted in the charts and descriptions in the text are made by parenthesized numbers. It has been found conducive to clarity to preserve numerical rather than chemical sequence in the text, so that in reading, one should follow the order indicated by arrows in the charts.

Many of the analytical results were obtained by the author. It is a pleasure to acknowledge help by Roger Amidon, Mrs. R. A. Barnes, J. S. Buckley, Mrs. O. Hamarston, W. C. Kuryla, and S. A. Sundet for others.

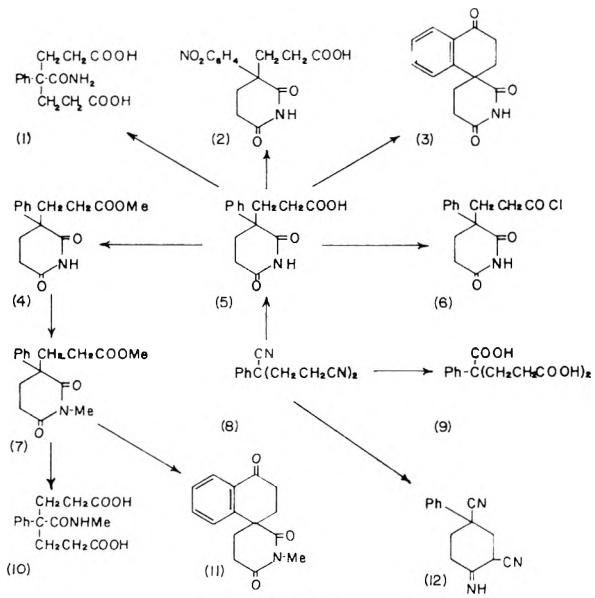

Chart I

EXPERIMENTAL

(1) A mixture of 1 g. of (5) and 10 ml. of 5% sodium hydroxide was boiled for 5 min., then cooled and acidified. The resulting *γ-carbamyl-γ-phenylpimelic acid* formed prisms from water, m.p. 178–179° with foaming; reported[3] 177–178°, dec. 179°.

Anal. Calcd. for $C_{14}H_{17}NO_5$: C, 60.2; H, 6.1; neut. equiv., 138. Found: C, 60.4; H, 6.23; neut. equiv., 139.

(2) A paste made from 75 ml. of sulfuric acid and 25 g. of (5) at 10° was kept at 10–15° while a mixture of 25 ml. of nitric acid (1.42) in 25 ml. of sulfuric acid was stirred in during 45 min. After 15 min. more, the mixture was poured on ice, and the solid product was removed and washed well with water (28.7 g. = 98%). Crystallization from 110 ml. of 10% acetic acid gave 25.4 g. of *3-p-nitrophenyl-2,6-piperidinedione-3-propionic acid,* colorless prisms, m.p. 176–178°.

Anal. Calcd. for $C_{14}H_{14}N_2O_6$: C, 54.9; H, 4.61. Found: C, 55.0; H, 4.69.

Hydrogenation of 10 g. of this nitro compound in 70 ml. of alcohol using platinum oxide took place rapidly. The product crystallized when it was kept for a week with ethyl acetate, and then became nearly insoluble in ethyl acetate, even hot. Recrystallization from water with very slow cooling gave 6.7 g. of *3-p-aminophenyl-2,6-piperidinedione-3-propionic acid,* yellowish prisms, m.p. 186–188°.

Anal. Calcd. for $C_{14}H_{16}N_2O_4$: C, 60.8; H, 5.84. Found: C, 60.6; H, 5.99.

A solution of 0.5 g. of the amino acid in 5 ml. of water containing 0.5 ml. of sulfuric acid was treated at 0° with 0.2 g. of sodium nitrite. After a few minutes a solution of 1 g. of potassium iodide was added, and the mixture was boiled. The resulting oil (0.7 g.) crystallized when it was rubbed with ether; recrystallization from dilute acetic acid gave yellow plates, m.p. 182–184°, *3-p-iodophenyl-2,6-piperidinedione-3-propionic acid.*

Anal. Calcd. for $C_{14}H_{14}INO_4$: C, 43.4; H, 3.62. Found: C, 43.4; H, 3.80.

(3) A mixture of 200 g. of (5) and 500 ml. of sulfuric acid was heated on a boiling water bath for 1.25 hr., then cooled and poured on ice slowly and with stirring so that the product separated directly as a crystalline powder. This was pressed on a filter and washed with 2 × 500 ml. of cold water. (The combined mother liquors deposited 9 to 13 g. of crude product on keeping for several days.) The main part of the material was suspended in cold water and stirred while dilute sodium carbonate was added to slightly basic reaction. This gave a nearly pure product in 77–82% yield. Recrystallization from acetone gave spiro-*1,2,3,4-tetrahydro-4-naph-*

(1) H. A. Bruson and T. W. Reiner, *J. Am. Chem. Soc.*, 65, 23 (1943).

(2) A. D. Campbell, *J. Chem. Soc.*, 1377 (1954).

(3) J. M. D. Blair and D. H. Hey, *J. Chem. Soc.*, 2921 (1957).

thalenone-[1:3']-2',6'-piperidinedione, needles, m.p. 201–202° (β-form); when the melt was kept at 202° it solidified during 5 min. and then melted at 204–205°. The higher melting α-form separated directly from 25% acetic acid as plates. (Only one form has been reported,[2] m.p. 198°.)

Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 69.1; H, 5.39. Found: (β) C, 69.1; H, 5.67; (α) C, 69.2; H, 5.52.

A solution of 1.2 g. of (3) in 5 ml. of alcohol and 5 ml. of acetic acid was treated with 0.5 g. of phenylhydrazine, warmed for 5 min., then diluted with water and cooled. Recrystallization from 50 ml. of dilute alcohol gave 1.3 g. of the phenylhydrazone, nearly colorless needles, m.p. 180–182°.

Anal. Calcd. for $C_{20}H_{19}N_3O_2$: C, 72.0; H, 5.74. Found: C, 71.9; H, 6.03.

When 1.5 g. of the above phenylhydrazone was boiled for a few minutes with 20 ml. of 2% sodium hydroxide, a pale yellow solution was formed. The product was precipitated with acetic acid and crystallized from 100 ml. of acetic acid by diluting the hot solution with water, giving 1.3 g. of the *phenylhydrazone of 4-carbamyl-1,2,3,4-tetrahydro-1-naphthalenone-4-propionic acid*, bronze prisms, m.p. 230° with effervescence, soluble immediately in cold dilute sodium carbonate.

Anal. Calcd. for $C_{20}H_{21}N_3O_3$: C, 68.4; H, 6.02. Found: C, 68.7; H, 6.12.

(4) A solution of 100 g. of (5) and 25 ml. of sulfuric acid in 250 ml. of methanol was boiled for 3 hr., then cooled and treated with water and ether. Acidic material was removed by washing with dilute sodium carbonate, but the neutral product formed a colorless glass (99 g.) that did not crystallize when it was kept under ether-ligroin during 4 winter months. Pure *methyl 3-phenyl-2,6-piperidinedione-3-propionate* was obtained as a colorless glass by distillation, b.p. 251° at 9 mm. After about a year, the compound crystallized, then formed prisms from ether-ligroin, m.p. 75–76°.

Anal. Calcd. for $C_{15}H_{17}NO_4$: C, 65.5; H, 6.22. Found: C, 65.5; H, 6.43.

(5) When a mixture of 175 g. of (8) with 400 ml. of water and 500 ml. of concd. hydrochloric acid was boiled and stirred, the organic material became crystalline after 1.5 hr. After 2.5 hr., the mixture was cooled, and the product was removed and washed with water; yield 91–98%, m.p. 169–171°. Recrystallization from 15 volumes of water gave *3-phenyl-2,6-piperidinedione-3-propionic acid* in the form of plates, m.p. 170–171°; (reported 165°,[2] 167–169°[3]).

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.4; H, 5.79. Found: C, 64.3; H, 5.91.

(6) When 2 ml. of thionyl chloride was added to 1 g. of (5), rapid evolution of gas took place. The mixture was kept at 35° for 15 min., then excess thionyl chloride was removed at 50° under reduced pressure. The residue crystallized when it was rubbed with a little ether; recrystallization from benzene-ligroin gave *3-phenyl-2,6-piperidinedione-3-propionyl chloride* in nearly quantitative yield; m.p. 101–103°.

Anal. Calcd. for $C_{14}H_{14}ClNO_3$: C, 60.1; H, 5.01. Found: C, 60.1; H, 5.10.

(7) A solution of 0.6 g. of sodium in 15 ml. of methanol was treated with 6.1 g. of (4) and then with 5 ml. of methyl iodide; after the spontaneous reaction was over, the mixture was boiled for 15 min., until it became neutral. Methanol was removed under reduced pressure, and the residue was taken up in ether and washed with dilute sodium hydroxide. Distillation gave *methyl 1-methyl-3-phenyl-2,6-piperidinedione-3-propionate*, a colorless viscous oil, 5.2 g., b.p. 232–235° at 9 mm.

Anal. Calcd. for $C_{16}H_{19}NO_4$: C, 66.4; H, 6.62. Found: C, 66.0; H, 6.61.

(8) γ-Cyano-γ-phenylpimelonitrile was prepared by the method of Bruson and Riener[1] and used without recrystallization; m.p. 70–72°; yield 85–95% in 2-mol. batches. About 12 kg. of the compound was used in the present research.

(9) Four hundred ml. each of water and concd. sulfuric acid were mixed in a 3-liter two necked flask fitted with a condenser and a stopper. The mixture was heated to boiling, the source of heat was removed, and 200 g. of γ-cyano-γ-phenylpimelonitrile was introduced in 50-g. portions, the mixture being swirled by hand after each addition. About 5 min. was allowed between each portion, so that the exothermic first stage of the hydrolysis might be completed. The mixture was boiled for 5 hr., then poured into 500 ml. of water, stirred until the original oily precipitate was completely crystalline, and kept overnight. The product was pressed out on a suction filter, using nitrated filter paper, and washed with a cold mixture of 40 ml. of water and 60 ml. of concd. hydrochloric acid. The still moist filter cake was dissolved in 300 ml. of warm water, 400 ml. of concd. hydrochloric acid was added, and the solution was stirred and cooled slowly, finally to 0°, so that the product separated crystalline directly. It was washed on a filter with 100 ml. of 1:1 hydrochloric acid and dried at 80°, giving 220–230 g. (88–92%) of pure γ-hydroxy-γ-phenylpimelic acid, m.p. 155–157° (reported[4] 153–154°).

(10) A mixture of 1.5 g. of (7) and 5 ml. of 10% sodium hydroxide gave a clear solution when it was boiled for 10 min.; boiling was continued to 20 min., and the solution was then acidified. The oily precipitate crystallized when it was rubbed with ether. Recrystallization from water gave 1.7 g. of *γ-N-methylcarbamyl-γ-phenylpimelic acid*, prisms, m.p. 182–183° with gas evolution.

Anal. Calcd. for $C_{15}H_{19}NO_5$: C, 61.4; H, 6.53. Found: C, 61.6; H, 6.81.

(11) A solution of 1 g. of (7) in 3 ml. of sulfuric acid was heated at 95° for 40 min., then cooled and poured on ice. The product was taken up in ethyl acetate and washed with dilute sodium carbonate. It crystallized slowly when it was rubbed with ethyl acetate–ligroin, and was then recrystallized from 50% alcohol, giving 0.6 g. of spiro-*1,2,3,4-tetrahydro-4-naphthalenone-[1:3']-1'-methyl-2',6'-piperidinedione*, coarse white needles, m.p. 142–143°; another preparation (14).

Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 70.0; H, 5.88. Found: C, 70.1; H, 6.19.

(12) To a solution of 2.3 g. of sodium in 25 ml. of absolute alcohol was added 22.3 g. of γ-cyano-γ-phenylpimelonitrile. The thick paste became yellow-brown and fluid when it was heated on a water bath, and after about 10 min. crystals started to form. Heating was continued for 30 min., until the mixture had nearly completely solidified. A solution of 6 g. of acetic acid in 50 ml. of water was then added, and the crystalline material was removed and washed with water, alcohol, and ether. Crystallization from 50% alcohol containing a few drops of ammonia gave 12 g. of *2,4-dicyano-4-phenylcyclohexanonimine*, large nearly colorless plates and needles, m.p. 149–150°.

Anal. Calcd. for $C_{14}H_{13}N_3$: C, 75.3; H, 5.87; N, 18.8. Found: C, 75.4; H, 5.85; N, 18.7.

(13) A mixture of 12 g. of (17), 60 ml. of acetic acid, 6 g. of butyl nitrite, and 1 ml. of hydrochloric acid was warmed to 50°, whereupon a slightly exothermic reaction took place and the solid dissolved. After it had been kept overnight, the mixture deposited 7.1 g. of spiro-*3-oximino-1,2,3,4-tetrahydro-4-naphthalenone-[1:3']-2',6'-piperidinedione*, small tan prisms, that darkened above 200° and melted at 238° with gas evolution and blackening.

Anal. Calcd. for $C_{14}H_{12}N_2O_4$: C, 61.7; H, 4.44. Found: C, 62.0; H, 4.55.

(14) A solution of 1 g. of sodium in 25 ml. of absolute alcohol was treated with 10 g. of (17) and then with 5.5 g. of methyl sulfate. A vigorous reaction took place and the sodio derivative dissolved. Addition of water gave an oil which crystallized when it was seeded; washing with ether and crystallization from dilute alcohol gave 5.3 g. of spiro-

(4) M. Rubin and H. Wishinsky, *J. Am. Chem. Soc.*, 68, 828 (1946).

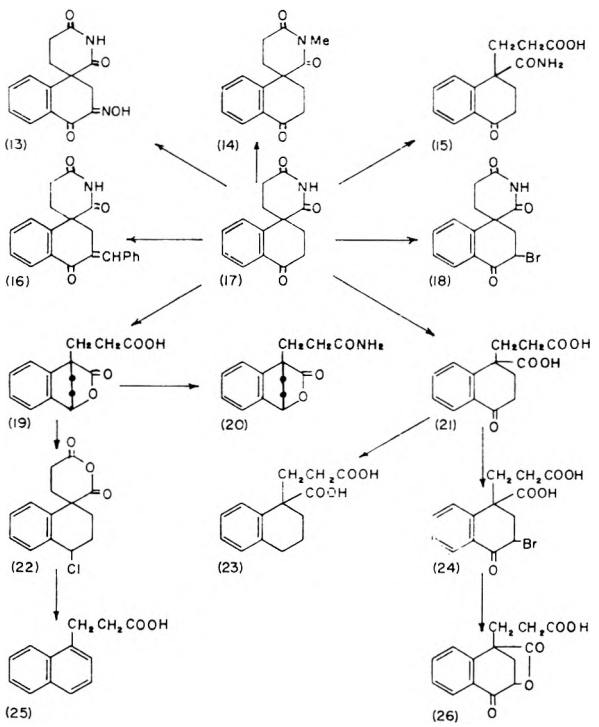

Chart II

1,2,3,4-tetrahydro-4-naphthalenone-[1:3']-1'-methyl-2',6'-piperidinedione, m.p. 142–143°, identical with (11).

(15) A suspension of 0.3 g. of (17) in 6 ml. of cold water dissolved immediately when 1 ml. of 40% sodium hydroxide was added. If the solution was acidified at once, unchanged (17) precipitated, but if it was boiled for 2 min., then cooled and acidified, no immediate precipitate was formed. When the acidified solution was kept, 0.25 g. of coarse needles slowly separated. Recrystallization from water gave *4-oxo-1,2,3,4-tetrahydro-1-naphthalenecarboxamide-1-propionic acid*, m.p. 197–198° with gas evolution.

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.4; H, 5.79. Found: C, 64.6; H, 5.80.

(16) A solution of 1 g. of (17) in 10 ml. of 2% sodium hydroxide was treated with 0.6 g. of benzaldehyde, boiled for 5 min., then cooled and acidified. The precipitate was removed, dried, and boiled for 2 min. with 5 ml. of acetic anhydride. Addition of water and crystallization from dilute acetic acid gave 0.55 g. of spiro-*3-benzal-1,2,3,4-tetrahydro-4-naphthalenone-[1:3']-2,6-piperidinedione*, faintly yellow plates, m.p. 228–230°.

Anal. Calcd. for $C_{21}H_{17}NO_3$: C, 76.1; H, 5.17. Found: C, 76.3; H, 5.19.

(17) See (3), Chart I.

(18) A solution of 12.1 g. of (17) in 60 ml. of acetic acid was treated with 8 g. of bromine and then warmed to 60°. The solution was then cooled, giving 14.1 g. of crystalline product. Recrystallization from dilute acetic acid gave spiro-*3-bromo-1,2,3,4-tetrahydro-4-naphthalenone-[1:3']-2',6'-piperidinedione*, colorless prisms, m.p. 208–210° with gas evolution.

Anal. Calcd. for $C_{14}H_{12}BrNO_3$: C, 52.2; H, 3.73. Found: C, 52.2; H, 3.81.

(19) A solution of 1 g. of (26) in 20 ml. of 1% sodium hydroxide was treated successively with two 6-g. portions of 3% sodium amalgam. After 1 hr, the solution was acidified. When it was heated, the solution deposited an oil. Extraction with ether removed a gum (0.7 g.) which furnished 0.2 g. of material m.p. 164–168°.

Large scale preparations were made as follows. A solution of 24 g. of (17) in 100 ml. of 10% sodium hydroxide was boiled for 15 min. while ammonia and 25 ml. of water were allowed to distil. The solution was cooled, treated with 3 g. of Raney nickel and shaken under hydrogen at 40 p.s.i. for 24 hr., or until one equivalent of hydrogen had been absorbed. The mixture was filtered, treated with 10 ml. of sulfuric acid, and heated to boiling. Addition of 45 ml. of acetic acid gave a clear solution, which deposited 7.8 g. of crystals when it was cooled and seeded. The mother liquor was boiled under reflux for 30 min., then cooled and seeded, giving an additional 5.6 g. of crystalline product. Recrystallization from 20% acetic acid (charcoal) gave 11.4 g. of pure *4-hydroxy-1,2,3,4-tetrahydro-1-naphthoic acid lactone-1-propionic acid*, colorless prisms, m.p. 167–168°. For another preparation, see (47).

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.3; H, 5.73; neut. equiv., 246. Found: C, 68.3; H, 5.96; neut. equiv., 240.

A solution of 6.6 g. of (19) and 5 ml. of sulfuric acid in 30 ml. of methanol was boiled for 1 hr., then cooled and treated with ether and water. The ether solution was washed with dilute sodium carbonate and evaporated at 100° and 20 mm., leaving 6.8 g. of a colorless oil that could not be crystallized. *Methyl 4-hydroxy-1,2,3,4-tetrahydro-1-naphthoic acid lactone-1-propionate* was obtained by distillation, b.p. 220–223° at 17 mm., as a colorless viscous oil.

Anal. Calcd. for $C_{15}H_{16}O_4$: C, 69.2; H, 6.20. Found: C, 69.3; H, 6.90.

(20) A mixture of 0.5 g. of (19) and 3 ml. of thionyl chloride was kept at room temperature for 15 min., then warmed to 45° under reduced pressure. The residue was taken up in dry ether and shaken for 1 min. with iced ammonium hydroxide, giving an oil which rapidly crystallized. Recrystallization from water containing a few drops of acetic acid gave 0.4 g. of *4-hydroxy-1,2,3,4-tetrahydro-1-naphthoic acid lactone-1-propionamide*, colorless prisms, m.p. 168–169°. The amide was not soluble in 10% sodium carbonate, and a mixture with (19) had m.p. 140–150°.

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.6; H, 6.16. Found: C, 68.8; H, 6.04.

(21) A solution of 12 g. of (17) and 6 g. of sodium hydroxide in 30 ml. of water was boiled for 4 hr., then cooled and acidified. The resulting red oil solidified when it was rubbed with a little ether. Washing with ether and then recrystallization from water gave 6.5 g. of pink crystals, m.p. 165–170°. This was treated with charcoal in ethyl acetate, then recrystallized from water, giving 5.5 g. of *4-oxo-1,2,3,4-tetrahydro-1-naphthoic acid-1-propionic acid*, m.p. 170–171°. A better preparation is described in (46). The form m.p. 135–136°, then 167°[2] was not encountered in the present work.

Anal. Calcd. for $C_{14}H_{14}O_5$: C, 64.1; H, 5.38; neut. equiv., 131. Found: C, 64.0; H, 5.33; neut. equiv., 132.

(22) A mixture of 22.5 g. of (19) with 45 ml. of thionyl chloride was boiled for 2 hr., and then excess reagent was removed at 100° under reduced pressure. The brown solid residue was recrystallized from benzene containing a few drops of acetyl chloride, giving 6.3 g. of spiro-*4-chloro-1,2,3,4-tetrahydronaphthalene-[1:3']-2',6'-pyrandione*, colorless needles, m.p. 163–165° with gas evolution.

Anal. Calcd. for $C_{14}H_{15}ClO_3$: C, 63.5; H, 4.95. Found: C, 63.5; H, 5.00.

When 0.5 g. of this chloro anhydride was boiled for 15 min. with 6 ml. of 5% sodium carbonate, it gave a clear solution. Acidification in the cold gave no precipitate, but boiling 5 min. caused separation of an oil that slowly solidified. Recrystallization from 10% acetic acid gave 0.2 g. of lactone-acid (19).

(23) Five grams of (21) and 5 g. of amalgamated zinc were boiled for 4 hr. with excess hydrochloric acid. The organic product was distilled at 20 mm. and the resulting anhydride was boiled with dilute sodium carbonate until it dissolved. Crystallization from dilute acetic acid gave *1,2,3,4-tetrahydro-1-naphthoic acid-1-propionic acid*, colorless prisms, m.p. 148–149°; yield 60%. The compound was reported[2] as "semisolid."

Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.7; H, 6.50. Found: C, 68.0; H, 6.57.

(24) When a solution of 8.7 g. of (21) in 10 ml. of acetic acid was treated with 5.4 g. of bromine and warmed gently, the bromine rapidly disappeared. Keeping the solution for 30 min. gave a nearly solid mass of gray crystals, which were removed and washed with acetic acid and water; 9.6 g. = 85%. Recrystallization from acetic acid led to decomposition, but crystallization from ethyl acetate–ligroin (charcoal) gave 6.9 g. of *3-bromo-4-oxo-1,2,3,4-tetrahydro-1-naphthoic acid-1-propionic acid*, faintly yellow plates, m.p. 183–185° with blackening and gas evolution.

Anal. Calcd. for $C_{14}H_{13}BrO_5$: C, 49.3; H, 3.82; Br, 23.4. Found: C, 49.1; H, 4.03; Br, 23.4.

(25) One-half gram of (22) was heated at 190° until hydrogen chloride evolution stopped, and the brown residue was distilled at 20 mm. The partly crystalline distillate was boiled out with 5% sodium carbonate, neutral material being discarded. The acidic product, 0.1 g., was identified as 1-naphthalenepropionic acid by comparison with an authentic sample kindly furnished by Dr. R. T. Arnold.

(26) Several small-scale preparations were carried out using purified (24), but for larger ones the following procedure was more convenient. A solution of 26 g. of (21) in 30 ml. of acetic acid was treated with 16 g. of bromine and kept for 2 hr. Then 50 ml. of 50% acetic acid was added, and the crystalline bromo compound was removed, washed with 25 ml. of 50% acetic acid, and finally with water. The moist product was boiled for 1 hr. with 300 ml. of water containing 30 ml. of acetic acid. When the resulting solution was kept overnight, it deposited 13.8 g. of orange crystals of nearly pure lactone. Recrystallization from dilute acetic acid (charcoal) gave *3-hydroxy-4-oxo-1,2,3,4-tetrahydro-1-naphthoic acid lactone-1-propionic acid*, coarse needles, m.p. 185–187°.

Anal. Calcd. for $C_{14}H_{12}O_5$: C, 64.6; H, 4.65. Found: C, 64.7; H, 4.90.

The *oxime*, obtained by boiling a solution of 0.5 of (26) and 0.5 g. of hydroxylamine sulfate in a slight excess of aqueous sodium carbonate, formed tan plates from dilute alcohol, m.p. 205° with blackening and gas evolution.

Anal. Calcd. for $C_{14}H_{13}NO_5$: C, 61.1; H, 4.73. Found: C, 61.4; H, 5.08.

The *methyl ester*, from (26) in methanol with ethereal diazomethane or from (26) in aqueous sodium carbonate with methyl sulfate, or from (26) by boiling 15 min. with 5% methanolic hydrogen chloride, crystallized after it had been distilled, b.p. 240° at 15 mm.; it formed coarse needles from methanol, m.p. 115–116°.

Anal. Calcd. for $C_{15}H_{14}O_5$: C, 65.7; H, 5.15. Found: C, 65.6; H, 5.46.

(27) A mixture of 3.1 g. of (30) with 3.5 ml. of 85% hydrazine hydrate, 3.5 ml. of water, and 2 ml. of alcohol became homogeneous when it was heated on a water bath for 10 min. After 10 min. more, the mixture was evaporated at 100° under reduced pressure; 10 ml. of alcohol was added and the evaporation was repeated. The resulting glassy froth was dissolved in absolute alcohol, treated with ether to turbidity and kept for several days, when it deposited 3.1 g. of colorless crystals that melted at 88–90° to a bubble-filled froth. This was a solvated form of *3-carbamyl-3-phenylpimelanilide hydrazide*.

Anal. Calcd. for $C_{20}H_{24}N_4O_3 + C_2H_6O$: C_2H_6O, 11.1. Found, loss in weight at 75°/25 mm., 9.95.

The solvent-free residue formed a white powder, m.p. 104–107°.

Anal. Calcd. for $C_{20}H_{24}N_4O_3$: C, 65.2; H, 6.53. Found: C, 65.3; H, 6.80.

Many fruitless experiments to carry out a Curtius degradation led only to liberation of hydrazoic acid from the intermediate amide-anilide-azide. But when the amide-anilide-hydrazide was treated with piperonal in alcohol, it was converted quantitatively into an *amide-anilide-piperonalhydrazide*, colorless prisms from ether or alcohol, m.p. 128–130°.

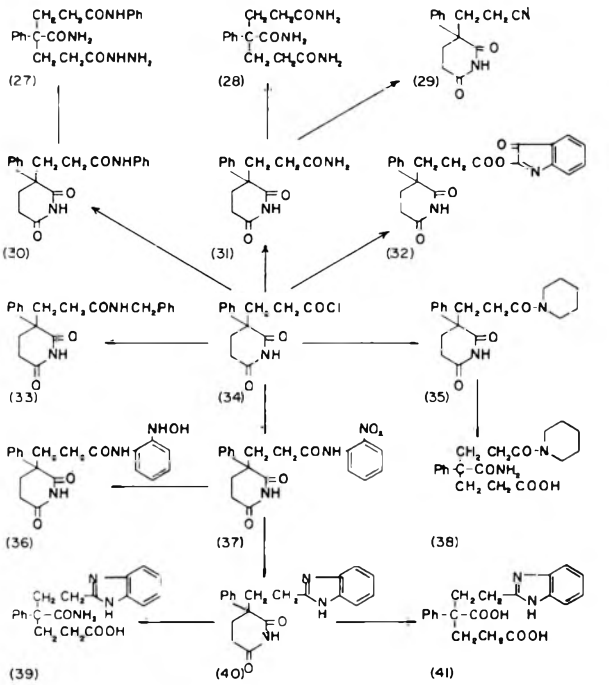

Chart III

Anal. Calcd. for $C_{28}H_{28}N_4O_5$: C, 67.2; H, 5.6. Found: C, 68.3; H, 5.90.

(28) A suspension of 0.5 g. of (31) in 4 ml. of ammonium hydroxide became clear when it was kept for 20 hr. Evaporation at 100° under reduced pressure left a viscous oil which crystallized when it was kept moist with nitromethane for several days. Recrystallization from a small volume of water followed by washing with a little alcohol and then ether gave *3-carbamyl-3-phenylpimelamide*, colorless prisms m.p. 215–218° with gas evolution.

Anal. Calcd. for $C_{14}H_{19}N_3O_3$: C, 60.6; H, 6.91. Found: C, 60.3; H, 6.95.

(29) When a mixture of 3.8 g. of (31) with 8 ml. of thionyl chloride was boiled for 45 min., a clear solution resulted. The mixture was evaporated at 100° under reduced pressure and treated with water and ether, giving 2.8 g. of crude crystalline product. Recrystallization from dilute alcohol and then water gave 1.4 g. of pure *3-phenyl-2,6-piperidinedione-3-propionitrile*, colorless plates, m.p. 131–132°.[5]

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.4; H, 5.83. Found: C, 69.4; H, 6.00.

(30) A solution of 6.9 g. of (34) in benzene was treated with 7 g. of aniline. The product was removed by filtration and washed with dilute hydrochloric acid, dilute sodium carbonate, and ether giving 8.3 g. of fine white crystals. Recrystallization from alcohol gave pure *3-phenyl-2,6-piperidinedione-3-propionanilide*, shining plates, m.p. 205–206°.

Anal. Calcd. for $C_{20}H_{20}N_2O_3$: C, 71.4; H, 5.99. Found: C, 71.2; H, 5.89.

(31) A solution of 6.5 g. of (34) in 25 ml. of toluene was shaken with 25 ml. of iced ammonium hydroxide for a few minutes; the product was then removed by filtration and washed with water and ether; yield 5.9 g. of nearly pure material. Crystallization from water gave *3-phenyl-2,6-piperidinedione-3-propionamide*, m.p. 201–203°.

(5) This confirms Blair and Hey's opinion[3] that their compound $C_{14}H_{14}N_2O_2$, m.p. 201°, does not have this nitrile structure.

Anal. Calcd. for $C_{14}H_{16}N_2O_3$: C, 64.6; H, 6.20. Found: C, 64.4; H, 6.18.

(32) To a suspension of 1.4 g. of isatin in 5 ml. of chloroform and 1 ml. of pyridine was added a solution of 2.6 g. of (34) in 5 ml. of chloroform. After 30 min., the resulting deep red solution was shaken with dilute hydrochloric acid; the aqueous layer and a small amount of flocculent material were separated by centrifugation. On keeping, the chloroform deposited 1.7 g. of crystalline product. Crystallization from 35 ml. of acetic acid gave 0.9 g. of the *O-isatin ester of 3-phenyl-2,6-piperidinedione-3-propionic acid,* fine yellow needles that sintered and darkened above 220°, m.p. *ca.* 235°. Formulation as an *O-* rather than *N-* derivative was indicated by action of several different bases, which yielded only γ-carbamyl-γ-phenylpimelic acid and isatin, and not a quinolone.

Anal. Calcd. for $C_{22}H_{18}N_2O_5$: C, 67.6; H, 4.65. Found: C, 67.4; H, 4.88.

(33) A solution of 2.6 g. of (34) in 5 ml. of benzene was added to 2.5 g. of benzylamine in benzene. After 3 min., water was added resulting in the formation of 3 liquid layers. The middle layer was taken up in ethyl acetate, washed with dilute bicarbonate and with dilute hydrochloric acid, and evaporated at 100° under reduced pressure. The resulting glass crystallized when it was kept for several days under ether containing a little ethyl acetate. Recrystallization from dilute alcohol gave 2.5 g. of the *benzylamide of 3-phenyl-2,5-piperidinedione-3-propionic acid,* poorly formed prisms, m.p. 143–144°. In later preparations when seed were available, the middle liquid layer crystallized directly and better yields (2.9–3.0 g.) were obtained.

Anal. Calcd. for $C_{21}H_{22}N_2O_3$: C, 72.0; H, 6.33. Found: C, 72.1; H, 6.77.

When 0.5 g. of (33) was boiled with 5 ml. of 4% sodium hydroxide for 1 min., then cooled and acidified, *γ-carbamyl-γ-phenylpimelic acid monobenzylamide* precipitated, plates from 10% acetic acid, m.p. 164–165°.

Anal. Calcd. for $C_{21}H_{24}N_2O_4$: C, 68.4; H, 6.57. Found: C, 68.4; H, 6.73.

(34) See (6), Chart I.

(35) A solution of 2 g. of (34) in 20 ml. of benzene was treated with 2 g. of piperidine and kept for 1 hr. The product was washed with dilute hydrochloric acid and with sodium carbonate and crystallized from dilute alcohol, giving 2 g. of the *piperidide of 3-phenyl-2,6-piperidinedione-3-propionic acid,* small prisms, m.p. 164–166°.

Anal. Calcd. for $C_{19}H_{24}N_2O_3$: C, 69.5; H, 7.37. Found: C, 69.4; H, 7.58.

(36) A suspension of 3.8 g. of (37) and 0.1 g. of platinum oxide in 25 ml. of alcohol shaken with hydrogen at 35 p.s.i. took up 1.5 lb. (calcd. 2.1 lb.) of the gas during 4 hr., and the reaction had stopped. The reaction mixture contained a thick suspension of nearly colorless needles. The product was removed and crystallized from alcohol, giving a nearly quantitative yield of *3-phenyl-2,6-piperidinedione-3-propion-o-hydroxylaminoanilide,* faintly yellow needles, m.p. 165° with gas evolution and darkening. The compound gave a black resin when it was treated with warm dilute aqueous hydrochloric acid, or with cold methanolic hydrogen chloride.

Anal. Calcd. for $C_{20}H_{21}N_3O_4$: C, 65.4; H, 5.76. Found: C, 66.0; H, 5.77.

(37) A solution of 56 g. of (34) in 50 ml. of benzene was treated dropwise with 28 g. of *o*-nitroaniline and 20 ml. of pyridine in 50 ml. of benzene. After it had been shaken for 1 hr., the mixture was treated with excess dilute hydrochloric acid and cooled. The yellow crystalline product was removed and washed with water and ether, yield 69.5 g. Recrystallization from acetic acid gave pure *3-phenyl-2,6-piperidinedione-3-propion-o-nitroanilide,* yellow needles, m.p. 155°.

Anal. Calcd. for $C_{20}H_{19}N_3O_5$: C, 63.0; H, 5.0. Found: C, 63.1; H, 5.29.

(38) The piperidide (35) dissolved immediately when it was added to 4 ml. of 5% sodium hydroxide. The solution was boiled for 30 sec., then cooled and acidified. The product was washed with water, and then triturated with 5% sodium bicarbonate, 0.2 g. of (35) remaining undissolved. Acidification of the bicarbonate extract gave the *acid piperidide of γ-carbamyl-γ-phenylpimelic acid,* solvated needles from 20% alcohol that fell to a white powder when dried at 150°; m.p. 200–203°.

Anal. Calcd. for $C_{19}H_{26}N_2O_4$: C, 65.8; H, 7.57. Found: C, 65.9; H, 7.72.

(39) When 0.5 g. of (40) was warmed with 3 ml. of 5% sodium hydroxide for 1 min. it gave a bright yellow solution. This was cooled and acidified with hydrochloric acid, and the yellow resin resulting was caused to crystallize by rubbing with ethyl acetate. Recrystallization from alcohol by adding ether gave pure *ε-(2-benzimidazolyl)-γ-carbamyl-γ-phenyl caproic acid hydrochloride,* colorless needles, m.p. 165–167° to a bubble-filled liquid.

Anal. Calcd. for $C_{20}H_{21}N_3O_3$ + HCl: C, 62.2; H, 5.72. Found: C, 62.0; H, 5.68.

(40) A solution of 69 g. of (37) in 750 ml. of hot 35% acetic acid was treated with 50 g. of iron filings. A smooth reaction took place which was completed by warming and stirring for 2 hr. The mixture was cooled and filtered, and the filtrate was neutralized with ammonium hydroxide, and the brown crystalline precipitate was removed and dried (61.3 g.). This was crystallized from 200 ml. of alcohol using a Soxhlet extractor, giving 53 g. of *3-(β-2-benzimidazolyl-ethyl)-3-phenyl-2,6-piperidinedione,* faintly tan plates, m.p. 260–262°.

Anal. Calcd. for $C_{20}H_{19}N_3O_2$: C, 72.0; H, 5.74. Found: C, 71.7; H, 6.04.

The *picrate* formed yellow needles from alcohol, m.p. 184–185°.

Anal. Calcd. for $C_{26}H_{22}N_6O_9$: C, 55.5; H, 3.94. Found: C, 55.8; H, 4.19.

(41) A mixture of 2 g. of (40) with 3 ml. of water and 10 g. of 85% potassium hydroxide was heated at 185–190° for 10 min., ammonia being evolved during the first 5 min. The mixture was cooled to about 100° and treated with enough water to allow the inorganic material to be separated by decantation. The potassium salt was dissolved in a little water and acidified strongly with hydrochloric acid. The *hydrochloride* precipitated and was purified by crystallization from alcohol-ether; tan needles, m.p. 173–175° with gas evolution; yield 1.0 g.

Anal. Calcd. for $C_{20}H_{20}N_2O_4$ + HCl: C, 61.6; H, 5.40. Found: C, 61.0; H, 6.01.

ε-(2-Benzimidazolyl)-γ-carboxy-γ-phenylcaproic acid was obtained by treating an aqueous solution of the hydrochloride with sodium acetate. Crystallization from formamide gave colorless crystals that fell to a powder at 100°, sintered at 160°, then resolidified and melted again at 192–194° with gas evolution.

Anal. Calcd. for $C_{20}H_{20}N_2O_4 + H_2O$: C, 64.9; H, 5.99. Found: C, 65.0; H, 6.21.

(42) A solution of 3 g. of (46) and 1 ml. of sulfuric acid in 10 ml. of methanol was boiled for 1 hr. and then concentrated to 0.5 volume under reduced pressure. Addition of water gave a gum which was taken up in ether and separated with dilute sodium carbonate into a neutral part (0.8 g.) and an acid (2.0 g.). The latter was crystallized from ether-ligroin giving *methyl 4-oxo-1,2,3,4-tetrahydro-1-naphthoic acid-1-propionate,* fine needles, m.p. 92–93°.

Anal. Calcd. for $C_{15}H_{16}O_5$: C, 65.2; H, 5.84. Found: C, 65.3; G, 6.15.

The neutral part was (43), b.p. 244–246° at 19 mm., described below.

(43) By solution in the calculated amount of *N*-sodium hydroxide and precipitation with silver nitrate, 3.0 g. of (46) was converted into the silver salt (Found: Ag, 44.3; $C_{14}H_{12}O_5Ag_2$ requires Ag, 45.3). Five grams of this salt and 5 g. of methyl iodide were heated together in 25 ml. of

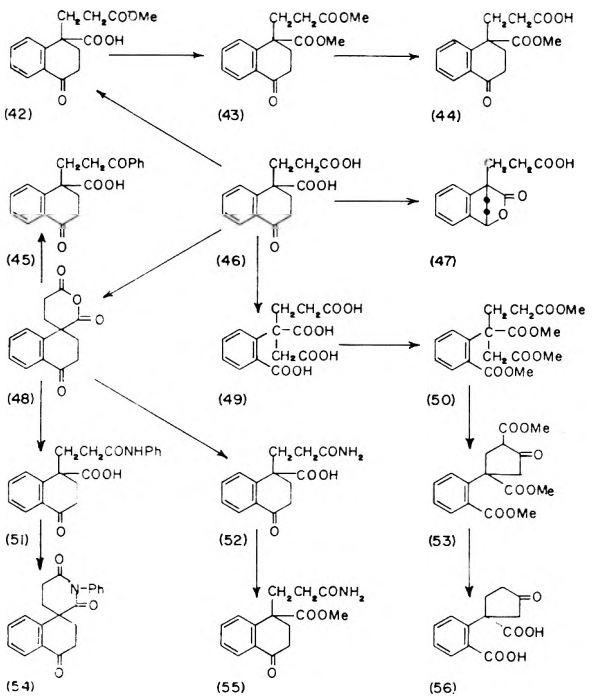

Chart IV

benzene for 30 min. The neutral product, 2.8 g., was *dimethyl 4-oxo-1,2,3,4-tetrahydro-1-naphthoate-1-propionate*, b.p. 242–244° at 18 mm. with no forerun or residue.

Anal. Calcd. for $C_{16}H_{18}O_5$: C, 66.2; H, 6.25. Found: C, 66.3; H, 6.44.

(44) When 0.7 g. of (43) was boiled with 0.2 g. of sodium hydroxide in 2.5 ml. of water and 0.5 ml. of alcohol, a clear solution was formed in 2 min. Acidification gave an oil that was obtained crystalline with some difficulty. Recrystallization from nitromethane gave *methyl 4-oxo-1,2,3,4-tetrahydro-1-naphthoate-1-propionic acid*, minute rosettes, m.p. 166–167° to a red liquid.

Anal. Calcd. for $C_{15}H_{16}O_5$: C, 65.2; H, 5.84. Found. C, 64.7; H, 5.37.

(45) A suspension of 4.1 g. of (48) and 8 g. of aluminum chloride in 30 ml. of benzene was boiled for 1 hr., then decomposed with iced hydrochloric acid. The acidic product was extracted with sodium carbonate, crystallized by keeping with ether-ligroin, and dried (4.2 g.). Washing with ether and recrystallization from 70% acetic acid gave 2.3 g. of *1-(β-benzoylethyl)-4-oxo-1,2,3,4-tetrahydro-1-naphthoic acid*, coarse needles, m.p. 150–151°.

Anal. Calcd. for $C_{20}H_{18}O_4$: C, 74.5; H, 5.63; neut. equiv., 322. Found: C, 74.38; H, 5.67; neut. equiv., 322.

(46) A mixture of 232 g. of (9) with 925 ml. of concd. sulfuric acid was stirred and heated on a boiling water bath for 45 min., then poured into 2500 ml. of water (not ice) and cooled. The crystalline product was recrystallized from 300 ml. of water, giving 191 g. of pure 4-oxo-1,2,3,4-tetrahydro-1-naphthoic acid-1-propionic acid, identical with (21).

(47) A solution of 10.5 g. of (46) in 35 ml. of 10% sodium hydroxide was treated with 3 g. of Raney nickel and shaken with hydrogen at 40 p.s.i. for 16 hr. Acidification gave an oil which soon crystallized, 9.3 g. Recrystallization from 35 ml. of 30% acetic acid gave 6.6 g. of 4-hydroxy-1,2,3,4-tetrahydro-1-naphthoic acid-lactone-1-propionic acid, m.p. 167–168°, identical with (19).

(48) A mixture of 5 g. of (46) with 10 ml. of acetyl chloride was boiled for 15 min. and then evaporated at 100° under reduced pressure. Crystallization of the residue from toluene (charcoal) gave 3.7 g. of spiro-*1,2,3,4-tetrahydro-4-naphthalenone-[1:3']-2',6'-dioxopyran*, m.p. 151–152°.

In another preparation, the same anhydride was obtained in 80% yield from the dibasic acid obtained as described before (21). The anhydride was also obtained using propionyl chloride.

Anal. Calcd. for $C_{14}H_{12}O_4$: C, 68.8; H, 4.95. Found: C, 68.7; H, 5.22.

When 2 ml. of piperidine was added to 0.5 g. of (48) an exothermic reaction took place. The product was isolated by adding ethyl acetate and dilute hydrochloric acid, and it was caused to crystallize by rubbing with ether. Crystallization from dilute alcohol gave fine white needles which changed to well formed prisms on keeping under the mother liquor; *4-oxo-1,2,3,4-tetrahydro-1-naphthoic acid-1-propionpiperidide* had m.p. 151°.

Anal. Calcd. for $C_{19}H_{23}NO_4$: C, 69.3; H, 7.04. Found: C, 69.2; H, 7.24.

(49) A solution of 10 g. of (46) in 50 ml. of hot water was kept boiling while 25 ml. of nitric acid was added dropwise during 30 min.; nitrous fumes were evolved. The solution was evaporated at 100° under reduced pressure; 25 ml. of water was added and the evaporation was repeated. When the resulting yellow glass was treated with a little ether, it slowly crystallized. Recrystallization from water (charcoal) gave nearly colorless prisms of *β-carboxy-β-(o-carboxyphenyl)-adipic acid*, that melted indefinitely above 120°, with loss of water and formation of an *anhydride*. ($C_{14}H_{14}O_8$ requires: H_2O, 5.8; found: H_2O, 5.9.) The dried (100°, 5 hr.) substance formed nearly colorless prisms from nitromethane, m.p. 178–179°; yield 8–8.5 g. In subsequent experiments it was found easier to remove the yellow color from the crude acid by boiling its solution in 1:1 hydrochloric acid with a little amalgamated zinc.

Anal. Calcd. for $C_{14}H_{12}O_7$: C, 57.5; H, 4.55. Found: C, 57.5; H, 3.99.

The *silver salt* formed an amorphous white powder, insoluble in water and stable to light.

Anal. Calcd. for $C_{14}H_{10}O_8Ag_4$: Ag, 58.5. Found: Ag, 59.0.

(50) A solution of 34 g. of (49) and 10 ml. of sulfuric acid in 125 ml. of methanol was boiled under a Soxhlet extractor containing calcium carbide for 20 hr. Addition of water gave a gum which was taken up in ether and separated with dilute sodium carbonate into 17.3 g. of crude neutral ester and 18.6 g. of crude acid-ester. The latter, with 50 ml. of methanol and 5 ml. of sulfuric acid, boiled for 20 hr., gave 8.5 g. of neutral ester and 7.6 g. of acid-ester. The latter treated again with 25 ml. of methanol and 3 ml. of sulfuric acid gave 2.2 g. of neutral ester and 3.5 g. of acid ester. The combined neutral ester fractions were distilled, giving 26.2 g. of *methyl β-carbomethoxy-β-(o-carbomethoxyphenyl)-adipate*, b.p. 270–275° at 20 mm.

Anal. Calcd. for $C_{18}H_{22}O_8$: C, 59.0; H, 6.05. Found: C, 59.0; H, 5.55.

The distilled ester had a saponification equivalent of 80.0 (calcd. 77.5) and gave back the tetrabasic acid when it was boiled for 5 min. with excess 30% sodium hydroxide.

(51) A mixture of 1.2 g. of (48) with 5 ml. of aniline was warmed at 100° for 5 min., then treated with ether and dilute hydrochloric acid. Removal of the ether left a glass which crystallized on rubbing with ether-ligroin. Recrystallization from dilute alcohol gave 1.6 g. of *4-oxo-1,2,3,4-tetrahydro-1-naphthoic acid-1-propionanilide*, fine needles, m.p. 199–200° with gas evolution.

Anal. Calcd. for $C_{20}H_{19}NO_4$: C, 71.2; H, 5.68. Found: C, 71.4; H, 5.96.

(52) A mixture of 5 g. of (48) and 40 ml. of 15% ammonia was warmed gently until solution took place, then evaporated to dryness at 100° under reduced pressure. Addition of water and dilute hydrochloric acid gave an oil which crystallized when it was kept with ethyl acetate–ligroin. Crystallization from water (charcoal) gave 3.7 g. of *4-oxo-1,2,3,4-tetrahydro-1-naphthoic acid-1-propionamide*, m.p. 170–172° with gas evolution.

Anal. Calcd. for $C_{14}H_{15}NO_4$: C, 64.4; H, 5.79. Found: C, 64.2; H, 5.96.

(53) A solution of 25 g. of (50) in 40 ml. of toluene was added to sodium methoxide prepared from 2 g. of powdered sodium and 3 ml. of methanol in 25 ml. of toluene. The mixture was heated for 1 hr. in a bath at 100°, then cooled and acidified with acetic acid. Extraction with 5% sodium carbonate removed 13.8 g. of a dark brown gum, which gave back 7 g. of (49) when it was boiled with 20% sodium hydroxide. The neutral material crystallized when it was kept with a little ether. Recrystallization from methanol (charcoal) gave 6.5 to 7.5 g. of *3,5-biscarbomethoxy-3-(o-carbomethoxyphenyl)cyclopentanone*,[6] square pink plates, m.p. 110–112°.

Anal. Calcd. for $C_{17}H_{18}O_7$: C, 61.1; H, 5.43. Found: C, 61.2; H, 5.71.

(54) When 1 g. of (51) was heated in a bath at 245° for 10 min. and the glassy residue was kept for several days under ether, crystals were obtained. Recrystallization from dilute alcohol gave 0.4 g. of spiro-*1,2,3,4-tetrahydro-4-naphthalenone-[1:3']-1'-phenyl-2',6'-piperidinedione*, flat needles, m.p. 125°.

Anal. Calcd. for $C_{20}H_{17}NO_3$: C, 75.2; H, 5.37. Found: C, 75.7; H, 5.67.

(55) The *silver salt* of (52) formed a nearly insoluble resin, that was powdered, washed with water, and dried at room temperature.

Anal. Calcd. for $C_{14}H_{14}NO_4Ag$: Ag, 29.4. Found: Ag, 30.1.

A suspension of 3 g. of this silver salt in 15 ml. of benzene was treated with 3 ml. of methyl iodide and boiled for 1 hr. Filtration and removal of benzene gave a gum which became crystalline when it was kept under ether for one week. Recrystallization from ethyl acetate–ligroin gave 0.4 g. of *methyl 4-oxo-1,2,3,4-tetrahydro-1-naphthoate-1-propionamide*, m.p. 139–140°. An additional 0.4 g. of the same substance was obtained by extracting the silver iodide with methanol and rubbing the gummy extracted material with dilute sodium carbonate and ether.

Anal. Calcd. for $C_{15}H_{17}NO_4$: C, 65.4; H, 6.22. Found: C, 65.4; H, 6.21.

(56) When 0.5 g. of (53) was boiled for 30 min. with 5 ml. of 10% sodium hydroxide, it yielded a partial hydrolysis product, probably *6-carbomethoxy-3-carboxy-3-(o-carboxyphenyl)cyclopentanone* on the basis of its analysis and its giving a strong purple ferric chloride test. The compound was isolated by acidification and ether extraction; it crystallized slowly when rubbed with ether-ligroin at −75°, and was then recrystallized from water, yielding rosettes, m.p. 163–164° with gas evolution.

Anal. Calcd. for $C_{15}H_{14}O_7$: C, 58.8; H, 4.61. Found: C, 58.7; H, 5.07.

In order to get complete hydrolysis, it was necessary to combine acidic and basic hydrolysis as follows. A mixture of 0.5 g. of (53) with 5 ml. of 20% hydrochloric acid was boiled for 1 hr. and then evaporated at 100° under reduced pressure. The solid residue was then boiled for 1 hr. with 5 ml. of 10% sodium hydroxide. Crystallization from water (charcoal) gave 0.3 g. of *3-carboxy-3-(o-carboxyphenyl)cyclopentanone*, colorless needles, m.p. 161–162°.

Anal. Calcd. for $C_{13}H_{12}O_5$: C, 62.9; H, 4.87. Found: C, 63.0; H, 5.55.

The *dimethyl ester* was obtained when 2.4 g. of (56) was boiled for 30 min. with 10 ml. of methanol containing 0.5 ml. of sulfuric acid. The product was taken up in ether, washed with dilute sodium carbonate, and distilled; b.p. 210–220° at 12 mm.; yield, 2.2 g.

Anal. Calcd. for $C_{15}H_{16}O_5$: C, 65.2; H, 5.84. Found: C, 65.2; H, 6.02.

When 0.7 g. of (56) was dissolved in 5 ml. of 10% sodium hydroxide, treated with 0.7 g. of benzaldehyde and boiled, nearly all of the aldehyde dissolved during 10 min. The remainder was removed with steam, and the solution was acidified. The resulting yellow gum (0.9 g.) crystallized slowly when it was kept with ether-ligroin. Recrystallization from dilute acetic acid gave a *monobenzal derivative*, yellow prisms, m.p. 200–201° with gas evolution.

Anal. Calcd. for $C_{20}H_{16}O_5$: C, 71.42; H, 4.80. Found: C, 71.47; H, 5.05.

(57) See (9), Chart I.

(58) A mixture of 200 g. of (57), 750 ml. of methanol, and 50 ml. of sulfuric acid was boiled for 45 min., then cooled and stirred into 2 l. of ice water. The product was removed, ground to a paste, and washed with water, giving 207 g. of diester, m.p. 89–93°, suitable for further use. Pure *methyl γ-carboxy-γ-phenylpimelate*, obtained by extraction with *N*/10 sodium hydroxide, precipitation, and crystallization from ether-ligroin, had m.p. 95–97°.

Anal. Calcd. for $C_{16}H_{20}O_6$: C, 62.3; H, 6.54; neut. equiv., 308. Found: C, 62.4; H, 6.79; neut. equiv., 311.

The corresponding *diethyl ester*, obtained similarly in 95% crude yield from 275 g. of (9), 600 ml. of absolute ethanol, and 60 ml. of sulfuric acid formed a sirup.

Anal. Calcd. for $C_{18}H_{24}O_6$: C, 64.3; H, 7.19; neut. equiv., 336. Found: C, 64.0; H, 7.34, neut. equiv., 351.

(59) The *silver salt* of methyl γ-carboxy-γ-phenylpimelate was obtained by titrating a suspension of 207 g. of (58) in 500 ml. of hot water with 10% sodium hydroxide (phenolphthalein), precipitation with 10% silver nitrate, and drying for 2 days at 50° under reduced pressure over sulfuric acid; yield 294 g. (105%).

Anal. Calcd. for $C_{16}H_{19}O_6Ag$: Ag, 25.3. Found: Ag, 26.0.

The silver salt was suspended in 1500 ml. of dry benzene (the salt dissolved almost completely, and the solution rapidly set to a gel) and stirred while 150 g. of methyl iodide was added as rapidly as the exothermic reaction would permit. The mixture was stirred and heated for an additional 15 min. and then filtered, the silver iodide being washed with 100 ml. of benzene. The product was washed with dilute sodium carbonate and then distilled, giving 175 g. of pure *methyl-γ-carbomethoxy-γ-phenylpimelate*, b.p. 237–242° at 22 mm.; prisms from ligroin, m.p. 52–54°.

Anal. Calcd. for $C_{17}H_{22}O_6$: C, 63.3; H, 6.88. Found: C, 63.3; H, 7.13.

Methyl γ-carbethoxy-γ-phenylpimelate, obtained similarly using ethyl iodide, had b.p. 240–242° at 20 mm. and could not be obtained crystalline.

Anal. Calcd. for $C_{18}H_{24}O_6$: C, 64.3; H, 7.19. Found: C, 64.4; H, 7.30.

When the silver salt of ethyl γ-carboxy-γ-phenylpimelate (Found: Ag, 30.0; $C_{18}H_{22}O_6Ag$ requires Ag: 24.4) (350 g.) was treated with 175 g. of ethyl iodide in benzene, there was obtained 238 g. of *ethyl γ-carbethoxy-γ-phenylpimelate*, b.p. 227–229° at 9 mm.

Anal. Calcd. for $C_{20}H_{28}O_6$: C, 65.9; H, 7.74. Found: C, 65.27; H, 7.68.

An apparently better preparation of this ethyl ester has been reported by Rubin and Wishinski.[4]

Partial hydrolysis of (59) was effected when 0.5 g. of it was boiled for 5 min. with 2 ml. of 10% sodium hydroxide and 1 ml. of alcohol. The resulting solution was evaporated and then treated with water and dilute hydrochloric acid, giving *γ-carbomethoxy-γ-phenylpimelic acid*, coarse needles from water, m.p. 147–148°.

Anal. Calcd. for $C_{15}H_{18}O_6$: C, 61.2; H, 6.17. Found: C, 61.3; H, 6.53.

Similar partial hydrolysis of either methyl or ethyl γ-carbethoxy-γ-phenylpimelate gave *γ-carbethoxy-γ-phenylpimelic acid*, prisms from 5% acetic acid, m.p. 126–127°.

Anal. Calcd. for $C_{16}H_{20}O_6$: C, 62.3; H, 6.54; neut. equiv., 154. Found: C, 62.3; H, 6.51; neut. equiv., 153.

The *silver salt* of γ-carbethoxy-γ-phenylpimelic acid gave no useful product when it was treated with bromine in carbon tetrachloride.

Anal. Calcd. for $C_{16}H_{18}O_6Ag_2$: Ag, 41.4. Found: Ag, 41.4.

(60) A boiling solution of 2.5 g. of (63) in 8 ml. of water was treated dropwise with 3.5 ml. of nitric acid, and boiling

(6) Formulated as a cyclopentanone rather than a tetralone, because the latter would yield (63) on hydrolysis and decarboxylation.

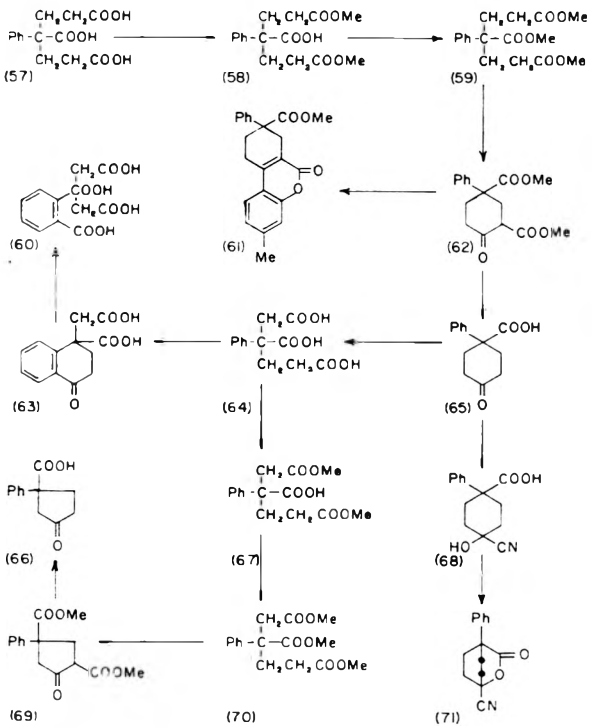

Chart V

was continued for 15 min. Filtration of the cooled mixture removed a red tar, and evaporation of the filtrate at 100° under reduced pressure left 1.2 g. of yellow crystals. The product was boiled for 15 min. with charcoal in 6 ml. of 20% hydrochloric acid, then recovered by evaporation and recrystallized from ethyl acetate–ligroin and then from water. *β-o-Carboxyphenyltricarballylic acid* formed transparent prisms that became opaque on drying at 100° and then analyzed as an anhydride, m.p. 237–239° with gas evolution.

Anal. Calcd. for $C_{13}H_{10}O_7$: C, 56.1; H, 3.62. Found: C, 56.2; H, 3.30.

(61) A mixture of 10 g. of (62) (methyl ester) and 5 g. of *m*-cresol was added to 15 ml. of sulfuric acid containing 3 ml. of water, external cooling being used to keep the mixture at 30–35°. The mixture was kept at room temperature for 2 hr., then poured on ice. The resinous precipitate became crystalline (11.0 g.) when it was boiled with water; recrystallization from 75% acetic acid gave 9.8 g. of *8-carbomethoxy-3-methyl-8-phenyl-7,8,9,10-tetrahydro-6-dibenzo[b,d]pyrone*, prisms, m.p. 181–182°.

Anal. Calcd. for $C_{22}H_{20}O_4$: C, 75.8; H, 5.79. Found: C, 75.8; H, 5.85.

(62) A mixture of 400 ml. of toluene and 10 g. of sodium was boiled and stirred vigorously while 18 ml. of methanol was added dropwise. When the sodium had all reacted, 100 g. of methyl γ-carbomethoxy-γ-phenylpimelate was added. The mixture was boiled and stirred for 1 hr., then cooled and stirred while 500 ml. of 5% acetic acid was added. The organic layer was separated, washed with sodium bicarbonate solution, and evaporated under reduced pressure at 100°. The residue (89 g., 98%) was nearly pure *2,4-biscarbomethoxy-4-phenylcyclohexanone*, m.p. 88–90°. The compound separated from methanol in the form of prisms, m.p. 91–92°; it gave a purple ferric chloride test.

Anal. Calcd. for $C_{16}H_{18}O_5$: C, 66.2; H, 6.25. Found: C, 66.6; H, 6.45.

2,4-Biscarbethoxy-4-phenylcyclohexanone, obtained similarly from ethyl γ-carbethoxy-γ-phenylpimelate in 94% yield, crystallized only after it had been distilled, forming prisms from alcohol, b.p. 216–218° at 10 mm., m.p. 53–55°; it gave a deep purple color with alcoholic ferric chloride. The compound has been reported[4] as an oil, b.p. 165–175° at 0.5 mm.

Anal. Calcd. for $C_{18}H_{22}O_5$: C, 67.9; H, 6.97. Found: C, 68.2; H, 7.38.

The ethyl ester formed a sodio derivative easily soluble in benzene, but difficultly soluble in water. Its *copper derivative* formed yellow-green needles from toluene-ligroin, m.p. 192–193°.

Anal. Calcd. for $C_{36}H_{42}O_{10}Cu$: C, 61.9; H, 6.03; Cu, 9.12. Found: C, 61.6; H, 6.06; Cu, 8.85.

(63) A solution of 5.6 g. of (64) in 25 ml. of sulfuric acid was heated for 20 min. on a boiling water bath, then cooled and poured into water. The product was extracted with ether and crystallized from water, giving 2.5 g. of tan needles m.p. 140–147°. Recrystallization from water gave *4-oxo-1,2,3,4-tetrahydro-1-naphthoic acid-1-acetic acid*,[7] colorless needles, m.p. 148–149°.

Anal. Calcd. for $C_{13}H_{12}O_5$: C, 62.9; H, 4.87. Found: C, 63.0; H, 4.90.

(64) To a mixture of 100 ml. of water and 20 ml. of nitric acid (d. 1.42) boiling under a good condenser, there was added 24.5 g. of (65) in 3- to 4-g. portions. A vigorous reaction with a short induction period took place after each addition. The mixture was finally boiled for 10 min., then cooled and seeded (seed were obtained by evaporating a similar reaction mixture to dryness under reduced pressure, and rubbing the product with ether-ligroin), giving a semi-solid crystalline paste. The product was washed with 2 × 5 ml. of water and dried at 60°, giving 22.3 g. of nearly pure *β-carboxy-β-phenyladipic acid*. Recrystallization from ethyl acetate–ligroin gave small prisms, that sintered at 160° and melted at 168–169° with gas evolution.

Anal. Calcd. for $C_{13}H_{14}O_6$: C, 58.6; H, 5.30. Found: C, 58.8; H, 5.23.

(65) A mixture of 100 g. of (62) (methyl ester), 1000 ml. of water and 45 g. of sodium hydroxide was boiled for 30 min., then distilled to half volume during 90 min. Acidification gave an oil which soon solidified, and recrystallization from benzene gave a partly solvated material m.p. 113–119° (73–75 g., 97%). Pure *4-carboxy-4-phenylcyclohexanone*, m.p. 120–121° (reported[4] m.p. 118.5–119.5°), was obtained by drying at 100° under reduced pressure followed by crystallization from ether-ligroin and drying at 75° for 2 hr.

Anal. Calcd. for $C_{13}H_{14}O_3$: C, 71.6; H, 6.47; neut. equiv., 218. Found: C, 71.8; H, 6.61; neut. equiv., 220.

The *silver salt* of (65), colorless needles from hot water, was quite sensitive to light (Found: Ag, 33.1; $C_{13}H_{13}O_3Ag$ requires Ag, 33.2). When 15 g. of this silver salt suspended in 30 ml. of dry toluene was treated with 10 g. of ethyl iodide and boiled for 15 min., there was obtained 11 g. of *4-carbethoxy-4-phenylcyclohexanone*, b.p. 200–205° at 16 mm. (reported[4] b.p. 144–146° at 0.5 mm.).

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.1; H, 7.37. Found: C, 72.9; H, 7.35.

2,6-Bisbenzylidene-4-carboxy-4-phenylcyclohexanone was obtained when 0.5 g. of (65), 0.5 g. of benzaldehyde, and 10 ml. of 1% sodium hydroxide were shaken together for 10 min. at 60–65°, then boiled for 0.5 min. and finally cooled and acidified. It formed yellow prisms from acetic acid, m.p. 273–276°.

Anal. Calcd. for $C_{27}H_{22}O_3$: C, 82.2; H, 5.62. Found: C, 82.3; H, 5.40.

(66) A suspension of 13 g. of (69) in 30 ml. of boiling water was treated dropwise during 30 min. with 30 ml. of 20% sodium hydroxide. Boiling was continued 30 min. more, and the solution was then cooled and acidified. The precipitated colorless oil became crystalline when it was rubbed with ether, yield 6.6 g. Crystallization from ethyl acetate–ligroin and then from water gave 4 g. of *3-oxo-1-*

(7) Formulated as a tetralone rather than a hydrindone on general principles and on the belief that oxidation of the latter would yield a thermally unstable malonic acid.

phenylcyclopentanecarboxylic acid, small prisms, m.p. 159–160°.

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.6; H, 5.92. Found: C, 70.6; H, 6.01.

The *oxime*, prepared in aqueous sodium carbonate, formed a fine white powder, m.p. 202° with blackening.

Anal. Calcd. for $C_{12}H_{13}NO_3$: C, 65.8; H, 5.98. Found: C, 65.8; H, 6.09.

(67) A solution of 24 g. of (64) and 10 ml. of sulfuric acid in 100 ml. of methanol was boiled for 1 hr., then cooled and treated with water and ether. The product was separated into a neutral part (3.9 g.) and an acidic part (18.8 g.) by washing the ether solution with dilute sodium carbonate. The neutral part was the trimethyl ester (70), prepared in quantity as described below. The acidic part was *methyl β-carboxy-β-phenyladipate;* it crystallized after it had been dried at 100° under reduced pressure and then allowed to stand without solvent for several days at room temperature. All solvents tried depressed its m.p. considerably, and it had to be recrystallized by allowing a methanol-water solution to stand at room temperature in a desiccator containing water. It formed colorless prisms, m.p. 93–95°.

Anal. Calcd. for $C_{15}H_{18}O_6$: C, 61.2; H, 6.17. Found: C, 61.2; H, 6.13.

(68) Ten grams of (65) was added in portions to a solution of 5 g. of potassium cyanide in 25 ml. of water with cooling to 25°. Then 0.5 g. of acetic acid was added and the solution was kept for 3 hr. Addition of hydrochloric acid gave an oil which soon solidified. The cyanohydrin mixture was ground and washed with water and dried (11.2 g.). Crystallization from nitromethane gave 5.2 g. of solvated *α*-(OH *cis* to COOH)-*4-cyano-4-hydroxy-1-phenylcyclohexanecarboxylic acid*, needles that became opaque when dried at 120°; m.p. 170–173°; the compound crystallized nicely from water, forming coarse needles, m.p. 170–173°.

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.5; H, 6.16. Found: C, 68.6; H, 6.42.

The nitromethane mother liquor was evaporated at 100° and reduced pressure; the residue, crystallized from nitromethane-benzene, gave 4.2 g. m.p. 145–155° (solvated). Recrystallization from 30 ml. of 20% acetic acid gave 2.2 g. of poorly formed solvated prisms that melted at 82–86°, then resolidified and melted again at 161–164°. A portion crystallized again from 10% acetic acid and dried for 2 hr. at 65° under reduced pressure gave pure *β*-(OH *trans* to COOH)-*4-cyano-4-hydroxy-1-phenylcyclohexanecarboxylic acid*, colorless prisms, m.p. 165–168°.

Anal. Calcd. for $C_{14}H_{15}NO_3$: C, 68.5; H, 6.16. Found: C, 68.4; H, 6.57.

When 1 g. of the *α*-cyanohydrin was boiled with 2 ml. of water and 3 ml. of hydrochloric acid, an oil was slowly formed and this later solidified in the boiling mixture. After 2.5 hr., the mixture was cooled and filtered giving 0.9 g. of *4-carboxy-4-hydroxy-1-phenylcyclohexanecarboxylic acid lactone*, coarse needles from ethyl acetate–ligroin, m.p. 199–200°.

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.3; H, 5.73. Found: C, 68.3; H, 6.04.

When 1 g. of the *α*-cyanohydrin was boiled for 3 hr. with 5 ml. of methanol containing 0.5 ml. of sulfuric acid, it gave 1 g. of *4-carbomethoxy-4-hydroxy-1-phenylcyclohexanecarboxylic acid lactone*, b.p. 230–235° at 17 mm., needles from dilute methanol or prisms from benzene-ligroin, m.p. 103–105°.

Anal. Calcd. for $C_{15}H_{16}O_4$: C, 69.2; H, 6.20. Found: C, 69.2; H, 6.54.

When 1 g. of the *β*-cyanohydrin was boiled with 2 ml. of water and 3 ml. of hydrochloric acid, separation of solid after 30 min. caused such severe bumping that 2 ml. of acetic acid, 1 ml. of water, and 1 ml. of hydrochloric acid had to be added. After 2.5 hr., the mixture was cooled, and the product (0.9 g.) was recrystallized from acetic acid. *1-Hydroxy-4-phenyl-1,4-cyclohexanedicarboxylic acid* formed small prisms m.p. 248° with gas evolution. It was nearly insoluble in ethyl acetate.

Anal. Calcd. for $C_{14}H_{16}O_5$: C, 63.6; H, 6.10. Found: C, 63.6; H, 6.23.

(69) When 15.4 g. of (70) was added under hydrogen to a suspension of sodium methoxide from 1.2 g. of powdered sodium and 2 ml. of methanol in 25 ml. of toluene, only slight temperature rise took place, but the base dissolved during 2 min. Six ml. of solvent (containing 3.5 ml. of methanol) was removed by distillation, and the remaining clear solution was cooled and treated with 40 ml. of 10% acetic acid. The toluene solution was washed with sodium bicarbonate and evaporated, leaving 14 g. of a honey-like oil that could not be crystallized. For analysis, a portion was distilled at 15 mm., b.p. 205–215° with some decomposition giving *2,4-biscarbomethoxy-4-phenylcyclopentanone* as a colorless oil that gave a purple color with alcoholic ferric chloride.

Anal. Calcd. for $C_{15}H_{16}O_5$: C, 65.2; H, 5.84. Found: C, 65.2; H, 6.06.

The *copper salt* precipitated as a green oil when the keto ester was treated with copper acetate in methanol. Crystallization from methanol gave yellow-green needles that sintered and darkened at 225°, m.p. 235° dec.

Anal. Calcd. for $C_{30}H_{30}O_{10}Cu + CH_3OH$: C, 57.6; H, 5.27; Cu, 9.85. Found: C, 57.9; H, 5.14; Cu, 9.95.

(70) A suspension of 22.8 g. of (67) in 50 ml. of water was neutralized with 10% sodium hydroxide and then treated with 15 g. of silver nitrate in 60 ml. of water. The resulting silver salt was washed and dried, giving 30 g. of a tan powder. A suspension of 29 g. of this silver salt in 50 ml. of benzene was treated with 15 g. of methyl iodide and boiled for 1.5 hr. Filtration, and distillation of the filtrate gave 17.5 g. of *methyl β-carbomethoxy-β-phenyladipate*, b.p. 218–219° at 15 mm. The distillate soon solidified; from dilute methanol the ester formed prisms, m.p. 56–58°.

Anal. Calcd. for $C_{16}H_{20}O_6$: C, 62.3; H, 6.54. Found: C, 62.5; H, 6.77.

(71) When 1 g. of the *β*-cyanohydrin (68) was dissolved in 3 ml. of acetic acid containing 0.1 g. of sulfuric acid and boiled for 2 min., it was recovered unchanged. But when the *α*-cyanohydrin was treated in this way it was converted into *4-cyano-4-hydroxy-1-phenylcyclohexanecarboxylic acid lactone*, 2-cm.-long needles from dilute acetic acid, m.p. 191°; the cyanolactone distilled at 15 mm. without decomposition.

Anal. Calcd. for $C_{14}H_{13}NO_2$: C, 74.0; H, 5.77. Found: C, 74.3; H, 5.79.

(72) See (65), Chart V.

(73) A solution of 2.2 g. of (72) in 25 ml. of 2% sodium hydroxide took up the calculated amount of hydrogen when it was shaken at 35 p.s.i. with 2 g. of Raney nickel for 16 hr. Acidification gave 2.0 g. of crystalline material; fractional crystallization from nitromethane gave 0.75 g. of the *α*-form (OH and COOH *cis*) of *4-hydroxy-1-phenylcyclohexanecarboxylic acid*, plates m.p. 194–196° with gas evolution.

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.9; H, 7.32; neut. equiv., 220. Found: C, 70.8; H, 7.08; neut. equiv., 222.

The *silver salt* formed fine needles from hot water, in which it was very difficultly soluble.

Anal. Calcd. for $C_{13}H_{15}O_3Ag$: Ag, 32.9. Found: Ag, 32.9.

Evaporation of the nitromethane mother liquors left a crystalline residue. Extraction with hot water and recrystallization from water gave 0.6 g. of the *β*-form (OH and COOH *trans*) of *4-hydroxy-1-phenylcyclohexanecarboxylic acid*, m.p. 154–158°.

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.9; H, 7.32. Found: C, 71.1; H, 7.45.

(74) When 0.5 g. of *β*-(73) in 3 ml. of acetic acid containing 2 drops of sulfuric acid was boiled for 1 min. and the solution was then diluted with water and cooled, the *β*-acid was recovered unchanged. But when *α*-(73) was treated in the same way, it gave 0.3 g. of *4-hydroxy-1-phenylcyclo-*

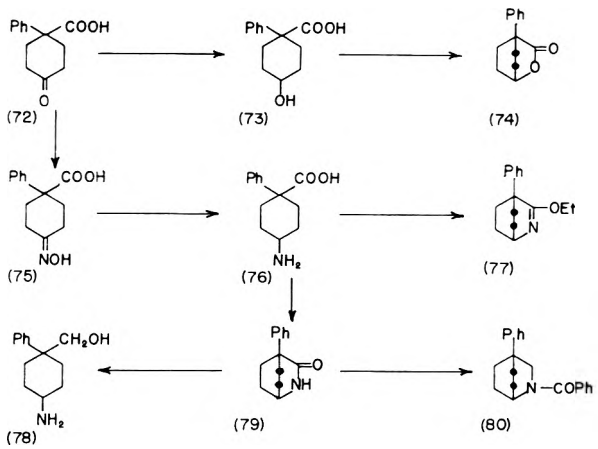

Chart VI

hexanecarboxylic acid lactone, plates from dilute acetic acid, m.p. 140–141°, not soluble in hot dilute sodium carbonate.

Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.2; H, 6.98. Found: C, 77.1; H, 7.15.

From the mother liquors of the lactonization of the α-(73), there was recovered about 50 mg. of the β-acid. Whether this was present in the α-(73) used or was formed by inversion was not determined.

(75) A solution of 20 g. of (72) in 100 ml. of 10% sodium carbonate was treated with 10 g. of hydroxylamine sulfate, boiled for 10 min. and then acidified. Crystallization of the precipitate from dilute alcohol gave 17.5 g. of coarse transparent needles that sintered at 120°, then melted at 157–159°. After drying at 100°, then 115°, then 138° under reduced pressure, *4-oximino-1-phenylcyclohexanecarboxylic acid* formed a powder, m.p. 160–161° (reported[4] 155.5–156.5°).

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.9; H, 6.48. Found: C, 67.3; H, 6.58.

The *silver salt* formed fine white difficultly soluble crystals that darkened when heated under the mother liquor.

Anal. Calcd. for $C_{13}H_{14}NO_3Ag$: Ag, 31.8. Found: Ag, 32.4.

(76) A solution of 2.3 g. of (75) in 40 ml. of 5% sodium hydroxide and 100 ml. of ammonium hydroxide was shaken with hydrogen at 35 p.s.i. and 2 g. of Raney nickel for 16–20 hr. The solution was boiled to remove ammonia, and then neutralized with acetic acid. The resulting precipitate (1.15 g.) was insoluble in boiling ethylene glycol, but easily soluble in dilute sodium hydroxide or dilute hydrochloric acid. It was obtained in the form of fine white plates by precipitation from an acid solution with sodium acetate; m.p. above 275° dec. Behavior of the substance towards phosphorus pentachloride (below) indicated that the substance was a mixture of *cis-* and *trans-4-amino-1-phenylcyclohexanecarboxylic acids.*

Anal. Calcd. for $C_{13}H_{17}NO_2$: C, 71.2; H, 7.82. Found: C, 69.8; H, 7.68.

The amino acid was recovered unchanged after 0.9 g. of it was boiled for 2 hr. with 10 ml. of alcohol containing 1 ml. of sulfuric acid, or after it was treated with excess sodium butoxide in dry butyl alcohol.

(77) Compound (76) (1.1 g.) was treated with phosphorus pentachloride as in preparation (79) but the residue was boiled with 5 ml. of absolute alcohol instead of water for 10 min. Dilute sodium hydroxide was then added to *p*H 8, and the mixture was distilled with steam. Ether extraction removed 0.25 g. of *2-ethoxy-1-phenyl-3-aza-Δ²-bicyclo-[2,2,2]-octane*, colorless crystals that were too soluble to be recrystallized; b.p. 170° at 15 mm., m.p. 72–75°.

Anal. Calcd. for $C_{15}H_{19}NO$: C, 78.6; H, 8.35. Found: C, 78.9; H, 8.54.

(78) A solution of 0.8 g. of (79) in 15 ml. of hot dry butyl alcohol was treated with 1 g. of sodium. After the metal had dissolved, dilute hydrochloric acid was added and the butyl alcohol was removed with steam. Filtration removed 0.3 g. of unchanged (79), and addition of potassium hydroxide precipitated 0.45 g. of basic material, m.p. 120–130°. 4-Hydroxymethyl-4-phenylcyclohexylamine had b.p. 190° at 13 mm., but was analyzed only as its *hydrochloride*, crystals from alcohol-ether, m.p. 257–258°.

Anal. Calcd. for $C_{13}H_{19}NO$ + HCl: C, 64.7; H, 8.3. Found: C, 64.7; H, 8.55.

(79) A mixture of 3.0 g. of (76) with 3 ml. of phosphorus oxychloride and 3 g. of phosphorus pentachloride was heated on a water bath for 30 min., then evaporated under reduced pressure. The residue was treated with water and dilute sodium carbonate, giving a crystalline precipitate. Extraction of this with dilute hydrochloric acid removed 0.7 g. of (76) and left 0.85 g. of neutral material. Sublimation of the latter at 15 mm. and crystallization from alcohol furnished *4-amino-1-phenylcyclohexanecarboxylic acid lactam* as large rhombs, m.p. 263–264°.

Anal. Calcd. for $C_{13}H_{15}NO$: C, 77.6; H, 7.51. Found: C, 77.6; H, 7.69.

The recovered amino acid was probably pure *trans* (76), since, although it was otherwise indistinguishable from starting material, retreatment with phosphorus pentachloride gave it back unchanged. It was analyzed as its *hydrochloride*, coarse needles from water, not melted at 285°.

Anal. Calcd. for $C_{13}H_{17}NO_2$ + HCl: C, 61.1; H, 7.5. Found: C, 60.83; H, 7.35.

(80) The hydrochloride remaining in the alcohol-ether mother liquors from (78) contained a small amount of a different substance which could not be separated as such. Treatment with aqueous sodium carbonate and benzoyl chloride followed by fractional crystallization from ether-ligroin and then dilute alcohol gave 40 mg. of colorless plates, m.p. 138–139°, probably *3-benzoyl-1-phenyl-3-aza-bicyclo-[2,2,2]-octane.*

Anal. Calcd. for $C_{20}H_{21}NO$: C, 82.4; H, 7.26. Found: C, 82.2; H, 7.28.

(81) See (65), Chart V.

(82) A solution of 21.8 g. of (81) in 75 ml. of sulfuric acid and 10 ml. of chloroform was treated during 1 hr. with 7 g. of sodium azide added in portions and with stirring and cooling. Gas was evolved even at 10°, but the mixture had to be warmed at 40° at intervals to break the froth, in which stirring was ineffective. After an additional hour, the mixture was poured on ice; the product was pulverized, washed with water, dried, and then washed with hot ethyl acetate; yield, 21.5 g. of nearly pure material. A sample of *5-phenylhexahydro-2-azepinone-5-carboxylic acid*, crystallized from water in dendrites that melted with vigorous effervescence when introduced into a bath at 170°.

Anal. Calcd. for $C_{13}H_{15}NO_3$ + H_2O: C, 62.1; H, 6.82. Found: C, 61.6; H, 6.92.

The anhydrous form of the acid, obtained by long drying at 100° under reduced pressure, was apparently amorphous, it sintered at 160° and flowed at 175°.

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.9; H, 6.48. Found: C, 66.5; H, 6.85.

(83) *Methyl 5-phenylhexahydro-2-azepinone-5-carboxylate*, obtained by treatment of a suspension of (82) in methanol-ether with ethereal diazomethane, formed small prisms from methanol or benzene, m.p. 150–151°.

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 68.0; H, 6.93. Found: C, 67.8; H, 6.89.

(84) A mixture of 19.5 g. of (82), 20 ml. of water, and 30 ml. of hydrochloric acid was boiled for 1 hr. and then evaporated under reduced pressure at 100°. The residue was treated with 50 ml. of water and evaporated again, then dissolved in 60 ml. of water and treated with a solution of 20 g. of hydrated sodium acetate in 20 ml. of water. Cooling and scratching gave 17.3 g. of α-(*2-aminoethyl*)-α-

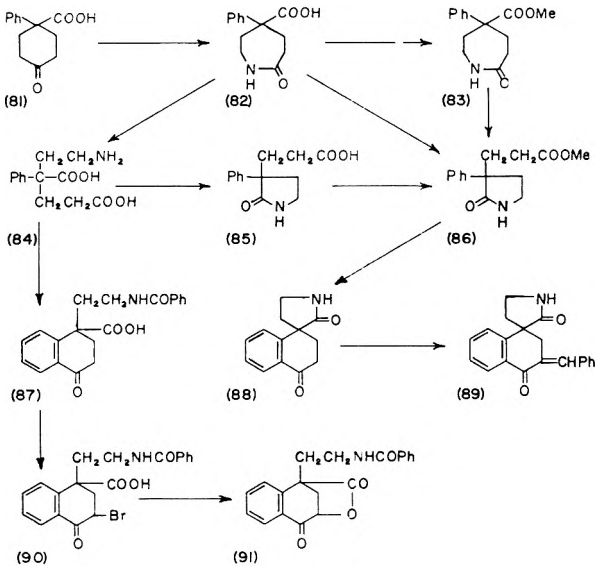

Chart VII

phenylglutaric acid, colorless crystals, m.p. 208–209° with gas evolution.

Anal. Calcd. for $C_{13}H_{17}NO_4$: C, 62.1; H, 6.82. Found: C, 62.1; H, 6.96.

(85) When (84) was heated at 220° for 5 min. it left a glass that crystallized when rubbed with ether; purification of the product by crystallization alone was successful but inefficient. A pure product was easily obtained through esterification.

Fourteen and one-half grams of (84) was added in portions to a flask heated in a bath at 225°. The melt was cooled and dissolved in 45 ml. of methanol containing 3.5 g. of hydrogen chloride. The solution was boiled 45 min., then distilled to half volume and cooled, giving 12.2 g. of (86), m.p. 118–119°. This was boiled for 5 min. with 200 ml. of 5% sodium carbonate, then acidified and cooled. The precipitate was recrystallized from water, giving 8.9 g. of pure *3-phenyl-2-pyrrolidone-3-propionic acid,* m.p. 150–151°.

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 67.0; H, 6.48. Found: C, 67.0; H, 6.66.

(86) A solution of 1.5 g. of (83) in 10 ml. of 25% methanolic hydrogen chloride was boiled for 1 hr. and then evaporated. The residue was treated with water and 0.5 g. of (83) was removed by filtration. Addition of dilute sodium hydroxide gave an oily precipitate (amino diester?) which was soluble in dilute hydrochloric acid when tested at once, but which became insoluble when it was allowed to stand or when warmed. Recrystallization from 5% methanol and then benzene-ligroin gave *methyl 3-phenyl-2-pyrrolidone-3-propionate,* prisms, m.p. 118–119°.

Anal. Calcd. for $C_{14}H_{17}NO_3$: C, 68.0; H, 6.93. Found: C, 67.8; H, 6.90.

The same compound was obtained similarly from (82) and from (85).

(87) A solution of 20 g. of (84) in 80 ml. of sulfuric acid was heated in a water bath for 30 min., then cooled, poured on ice and nearly neutralized with 40% sodium hydroxide. The mixture was cooled to 10°, treated with 10 ml. of benzoyl chloride and 100 ml. of 40% sodium hydroxide and shaken for 10 min. Acidification gave a gum which crystallized when it was rubbed with ether. Recrystallization from ethyl acetate gave 26 g. of a solvated product that melted at 113–114° with gas evolution, resolidified when held at 120° and remelted at 154–155°. Crystallization from dilute alcohol gave solvent-free *1-(β-benzoylaminoethyl)-4-oxo-1,2,3,4 tetrahydro-1-naphthoic acid,* m.p. 154–155°; yield 22 g.

Anal. Calcd. for $C_{20}H_{19}NO_4$: C, 71.2; H, 5.68. Found: C, 71.0; H, 5.94.

The *oxime,* prepared in aqueous sodium carbonate solution, formed small plates from alcohol, m.p. 200–203° with gas evolution.

Anal. Calcd. for $C_{20}H_{20}N_2O_4$: C, 68.2; H, 5.69. Found: C, 68.5; H, 6.20.

(88) A solution of 10 g. of (86) in 40 ml. of sulfuric acid was heated in a water bath for 45 min., then poured on ice. The crystalline precipitate (8.1 g.) was recrystallized from water; spiro-*1,2,3,4-tetrahydro-4-naphthalenone-[1:3′]-2′-pyrrolidone* formed colorless flat needles, m.p. 196–197°. The compound was recovered unchanged after it had been boiled for 1 hr. with excess 48% hydrobromic acid.

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 72.5; H, 6.09. Found: C, 72.7; H, 6.32.

The *oxime* formed colorless prisms from alcohol that darkened at 235°, m.p. 245–250° dec. It was soluble in 10% sodium hydroxide, whereas (88) was not.

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 67.8; H, 6.13. Found: C, 67.7; H, 6.00.

(89) A solution of 0.5 g. of (88) and 0.4 ml. of benzaldehyde in 3 ml. of alcohol was made basic with a few drops of 20% sodium hydroxide and boiled for 0.5 min. Addition of water gave an oil which was taken up in ether and washed with sodium bisulfite and with sodium carbonate. Removal of the ether left a glass which crystallized on keeping for several days with ether-ligroin. Recrystallization from alcohol gave 0.2 g. of spiro-*3-benzal-1,2,3,4-tetrahydro-4-naphthalenone-[1:3′]-2′-pyrrolidone,* yellow prisms m.p. 190–191°.

Anal. Calcd. for $C_{20}H_{17}NO_2$: C, 79.2; H, 5.65. Found: C, 78.8; H, 5.83.

(90) A solution of 16.5 g. of (87) in 40 ml. of acetic acid at 60° was treated with 8 g. of bromine and then exposed to strong light, causing rapid reaction. The mixture was then treated with 25 ml. of water at 70° and seeded, giving a nearly quantitative yield of crystalline *1-(β-benzoylaminoethyl)-3-bromo-4-oxo-1,2,3,4-tetrahydro-1-naphthoic acid,* m.p. 177–179° with foaming.

Anal. Calcd. for $C_{20}H_{18}BrNO_4$: C, 57.7; H, 4.33; Br, 19.2. Found: C, 57.6; H, 4.53; Br, 19.5.

(91) A mixture of 20 g. of (90), 200 ml. of water and 20 g. of sodium acetate was boiled for 2 hr. The crystalline product was removed and dried (14.5 g.) and then recrystallized from dilute alcohol giving *1-(β-benzoylaminoethyl)-3-hydroxy-4-oxo-1,2,3,4-tetrahydro-1-naphthoic acid lactone,* colorless plates, m.p. 180°. The compound was insoluble in warm dilute sodium carbonate, slowly soluble with blackening in boiling 10% sodium hydroxide.

Anal. Calcd. for $C_{20}H_{17}NO_4$: C, 71.6; H, 5.11. Found: C, 71.9; H, 5.36.

The *oxime,* prepared in alcohol, formed faintly green needles from dilute alcohol, m.p. 210–212° dec.

Anal. Calcd. for $C_{20}H_{18}N_2O_4$: C, 68.6; H, 5.18. Found: C, 68.9; H, 5.44.

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

Reactions of Perchloryl Fluoride and Salts of Mononitro Compounds[1a]

HAROLD SHECHTER AND ELBERT B. ROBERSON, JR.[1b]

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A preparative method has been developed by which sodium salts of secondary nitroalkanes and nitrocycloalkanes are converted by perchloryl fluoride to the corresponding fluoronitro compounds in moderate conversions (36–42%); competitive processes yield ketones (32–55%) and the *vicinal* dinitro compounds (1–7%) derived from oxidative dimerization of the parent mononitronate ions. Reactions of salts of primary nitro compounds with perchloryl fluoride under various conditions give aldehydes as principal products along with *vicinal* oxidative dimers; the method is inadequate for preparing 1-fluoro-1-nitroalkanes and 1,1-difluoro-1-nitroalkanes efficiently.

An investigation has been made of the reactions of perchloryl fluoride and sodium salts of mononitro compounds as a method for preparing fluoronitro derivatives.[2] It has been found that sodium salts of secondary nitro compounds react with perchloryl fluoride in methanol at 0° to 10° to give the desired fluoronitro compounds (Equation 1) in moderate conversions (36–42%); competitive processes result in the formation of ketones (32–55%, Equation 2) and of *vicinal* dinitro compounds (1–7%, Equation 3) derived by oxidative-coupling of the parent mononitronate ions. Thus reaction of sodium 2-propanenitronate and excess perchloryl fluoride in methanol gave 2-fluoro-2-nitropropane (36% conversion), acetone (54%), and 2,3-dimethyl-2,3-dinitrobutane (6%). Similarly, sodium 2-butanenitronate yielded 2-fluoro-2-nitrobutane (38%), 2-butanone (about 45%), and 3,4-dimethyl-3,4-dinitrohexane[3] (7%); sodium cyclohexanenitronate gave 1-fluoro-1-nitrocyclohexane (42%), cyclohexanone (53%), and 1,1′-dinitrobicyclohexyl (1.5%).[4]

$$R_2C{=}NO_2^- + ClO_3F \longrightarrow R_2CFNO_2 + ClO_3^- \quad (1)$$

$$R_2C{=}NO_2^- + ClO_3F \xrightarrow[(2)\ H_2O]{(1)\ CH_3OH} R_2C{=}O + [HNO_2] + HClO_3 + F^- \quad (2)$$

$$2R_2C{=}NO_2^- + ClO_3F \longrightarrow R_2C(NO_2){-}C(NO_2)R_2 + F^- + ClO_3^- \quad (3)$$

A study was made of reaction of sodium 2-propanenitronate with perchloryl fluoride[5] in methanol at different temperatures and with various ratios of base to nitro compound in an attempt to improve the selectivity in conversion to 2-fluoro-2-nitropropane. In general, formation of products was insensitive to the experimental conditions (−38–10°, mole ratio of base to 2-nitropropane from 1:1 to 2:1) in that 2-fluoro-2-nitropropane, acetone, and 2-3-dimethyl-2,3-dinitrobutane were obtained in 32–36%, 33–54%, and 5–7% conversions, respectively; the principal reaction of perchloryl fluoride and the nitronate anion is oxidation to acetone. Similar results were obtained in reaction of excess perchloryl fluoride at 0–10° with anhydrous sodium 2-propanenitronate suspended in ethyl ether.

Reactions of perchloryl fluoride and sodium salts of primary nitro compounds in methanol (0–10°) or dimethyl formamide (15–20°) gave aldehydes as principal products. Thus sodium 1-propanenitronate with excess perchloryl fluoride in methanol yielded propionaldehyde (64%), 3,4-dinitrohexanes (about 0.5%), 1-nitropropane (38% recovery) and a mixture of 1-fluoro-1-nitropropane and 1,1-difluoro-1-nitropropane in poor yields (3–5%). The results obtained in reactions of sodium ethane-

(1) (a) Abstracted from a portion of the Ph.D. Dissertation of E. B. Roberson, Jr., The Ohio State University, 1959. Financial support of this research was provided by the Office of Naval Research. (b) Present address: E. I. du Pont de Nemours and Co., Inc., Seaford, Del.

(2) (a) C. E. Inman, R. E. Oesterling, and E. A. Tyczkowski, *J. Am. Chem. Soc.*, **80**, 6533 (1958) have found that base-catalyzed reactions of perchloryl fluoride with active methylene compounds such as diethyl malonate, ethyl acetoacetate, 2,4-pentanedione, diethyl ethylmalonate, and diethyl phenylmalonate yield fluorinated derivatives. In general, the reaction replaces all hydrogens of an active methylene group. Similarly reaction of cholestan-3-one pyrrolidyl enamine with perchloryl fluoride and hydrolysis of the product affords 2α-fluorocholestan-3-one, R. B. Gabbard and E. V. Jensen, *J. Org. Chem.*, **23**, 1406 (1958). (b) J. P. Freeman and C. O. Parker, Abstracts of 135th Meeting of the American Chemical Society, April 5–10, 1959, p. 104-O, report that (1) salts of oximinomalonic esters are oxidized and fluorinated by perchloryl fluoride to produce fluoronitromalonic esters, (2) the sodium salt of α-benzil monoxime is converted by perchloryl fluoride to benzonitrile, benzil monoxime benzoate, and α-fluoro-α-nitro-α-phenylacetophenone, and (3) benzophenone and acetophenone oximes react with perchloryl fluoride to yield the parent ketones and nitrate ions; an unidentified nitro compound was also produced in the reaction of acetophenone oxime.

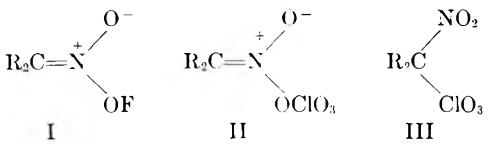
(3) This product may exist in *meso* and *dl*-modifications; the stereochemistry of the product has not been determined.

(4) Fluoronitro compounds derived from secondary mononitronates are quite stable to nucleophilic reagents as compared to the corresponding chloro, bromo, or iodo derivatives. Treatment of the fluoronitro compounds with aqueous 25% sodium hydroxide, methanolic sodium methoxide, or saturated sodium bisulfite gave no reaction. The fluorinated derivatives were thus conveniently separated from starting material and oxidation products by extraction with 10–25% aqueous base and saturated sodium bisulfite.

(5) 2-Nitropropane and perchloryl fluoride do not react in methanol unless a base is present.

nitronate with perchloryl fluoride under various conditions were similar to those for sodium 1-propanenitronate. Reaction of primary mononitronates with perchloryl fluoride is an unsatisfactory preparative method for monofluoronitro or difluoronitro compounds because of the poor yields and the difficulties in effecting their separation by physical or chemical methods.

The mechanisms of conversion of a nitronate salt to fluoronitro compound, aldehyde or ketone, and *vicinal* coupling product are as yet unknown. It is presumed that the fluoronitro compounds are derived by nucleophilic attack of the nitronate ion on perchloryl fluoride with displacement of chlorate ion.[6] Aldehydes or ketones and the *vicinal* dinitro compounds may be formed from intermediates such as I–III by thermal decomposition, hydrolysis, or by displacement by the nitronate anion, respectively.[7]



I II III

EXPERIMENTAL

Reaction of perchloryl fluoride and sodium 2-propanenitronate. 2-Nitropropane (66.8 g., 0.75 mol.) was added dropwise to a stirred solution of sodium methoxide (40.5 g., 0.75 mol.) in anhydrous methanol (500 ml.) at 0–5° in a glass flask equipped with a thermometer, gas inlet tube, Teflon paddle stirrer, and a Dry Ice condenser equipped with a calcium chloride drying tube. The mixture was stirred for 2 hr. at these temperatures and then 2 additional hr. at 15–20°.[8] Perchloryl fluoride was added to the vigorously stirred reaction mixture at 0° at a rate of 1 mol. in 45 min. *via* a flowmeter containing Fluorolube and connected by Tygon tubing. (Care was taken that the gas inlet tube did not project below the surface of the reaction mixture to prevent possible suckback into the perchloryl fluoride cylinder; gaseous perchloryl fluoride dissolves very readily in the solvents under these conditions.)[9] The reactions are very exothermic and, occasionally, it was necessary to interrupt the addition to prevent the temperature of the mixture from exceeding 10° even in an efficient ice-salt slurry. Perchloryl fluoride is sufficiently soluble in methanol at 0–10° so that reflux in the Dry Ice condenser did not occur until approximately 0.75 mol. of perchloryl fluoride had been added. In addition to judging the extent of reaction by the volume of perchloryl fluoride added, a sharp temperature drop occurred when the excess perchloryl fluoride began to reflux. Additional perchloryl fluoride was then added so that completion of reaction was assured and the mixture then stirred for 1 hr. at 0°. The ice bath and Dry Ice condenser were then removed, and the mixture was stirred until its temperature reached 20°. During addition of perchloryl fluoride the mixture turns blue; the color is presumed to be due to 2-nitro-2-nitrosopropane resulting from reaction of nitrous acid with 2-propanenitronic acid. The mixture was acidic upon completion of the experiment.

The reaction mixture was poured into five times its volume of ice water, and the resultant solution extracted thoroughly with ether. The combined ether extracts were washed with water until the volume of ether extract remained constant. This procedure removed the methanol from the ether solution and simplified isolation of the 2-fluoro-2-nitropropane. The ether solution was extracted with saturated brine, filtered through sodium sulfate and magnesium sulfate, respectively, and then rectified slowly in a glass-helix column (25 cm.). The fractionation was ineffective in separating the 2-fluoro-2-nitropropane from 2-nitropropane. An ether solution of the crude product was stirred with sodium hydroxide (20 g., 0.5 mol.) in water (150 ml., 13%) for two days, washed with water and saturated brine, and then dried over magnesium sulfate. Fractionation of the ether and distillation (twice) of the product yielded 2-fluoro-2-nitropropane (25.6 g., 32% conversion), colorless liquid, b.p. 111–111.2° (uncorr.), n_D^{20} 1.3739, D_4^{20} 1.083; infrared absorption for a nitro group (6.37μ, asymmetrical stretching; 7.37μ, symmetrical stretching).

Anal. Calcd. for $C_3H_6NO_2F$: C, 33.65; H, 5.61; N, 13.08. Found: C, 33.99; H, 5.61; N, 12.87.

Recrystallization of the distillation residue (7.1 g., 10.8% crude conversion) from ethanol-water gave 2,3-dimethyl-2,3-dinitrobutane (4.9 g., 7.4% conversion), white crystals, m.p. 205°, lit.[10] m.p. 209°, no depression by an authentic sample.

The yield of acetone was determined from a separate experiment in which perchloryl fluoride was added to 2-nitropropane (4.45 g., 0.05 mol.) and sodium methoxide (2.70 g., 0.05 mol.) in methanol (50 ml.) at 0°. The mixture was diluted to 100 ml.; addition of a 5.0-ml. aliquot to an acid solution of 2,4-dinitrophenylhydrazine (0.6 g., 0.003 mol.) gave acetone 2,4-dinitrophenylhydrazone (0.1406 g.), m.p. 125°, lit.[11] m.p. 126°. The correction in weight due to solubility of the derivative as derived from experiments with acetone as a blank was 0.052 g. The total weight of acetone 2,4-dinitrophenylhydrazone (0.1926 g.; theory 0.595 g.) corresponds to a 22% conversion.

(6) Sodium chlorate is isolated in 50–70% yields upon filtering the methanolic reaction mixtures at −20°.

(7) (a) An alternative mechanism for formation of carbonyl and of *vicinal* dinitro compounds involves oxidation of a nitronate ion to the corresponding radical; the radical may lose nitric oxide to yield the aldehyde or ketone or undergo dimerization; see H. Shechter and R. B. Kaplan, *J. Am. Chem. Soc.*, **75**, 3980 (1953). (b) Reaction of 2-fluoro-2-nitropropane and sodium 2-propanenitronate to give acetone or 2,3-dimethyl-2,3-dinitrobutane does not take place under the conditions of the fluorination experiments.

(8) The mixtures obtained from each nitro compound were heterogeneous, but addition of sufficient methanol to effect complete solution of the sodium salts did not increase the yield of fluoronitro compounds. In addition to increasing the amount of the relatively expensive perchloryl fluoride required, excess methanol increased the difficulty of extracting the products from the reaction mixture. Ethanol is a satisfactory solvent for this reaction, but it is more difficult to separate from the products. Water, water–ethylene glycol, and ethylene glycol were unsatisfactory solvents in that they led to poor efficiencies in fluorination.

(9) Perchloryl fluoride is a stable compound quite safe to handle. It is however a powerful oxidizing agent and all mixtures with oxidizable substances should be considered potentially dangerous. No difficulties were encountered in handling perchloryl fluoride under the conditions of the present experiments. The details of handling and safety of perchloryl fluoride have been fully described; Booklet DC-1819, "Perchloryl Fluoride," Commercial Development Dept., Pennsalt Chemicals Corp., 3 Penn Center, Philadelphia 2, Penn.

(10) L. W. Seigle and H. B. Hass, *J. Org. Chem.*, **5**, 100 (1940).

(11) R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," 3rd ed., John Wiley & Sons, Inc., New York, N. Y., 1948, p. 262.

In a subsequent experiment with excess perchloryl fluoride, 2-nitropropane (0.75 mol.) and sodium methoxide (1.5 mol.) at 0 to 10°, 2-fluoro-2-nitropropane, acetone, and 2,3-dimethyl-2,3-dinitrobutane were obtained in 36%, 54%, and 6% conversions, respectively. Reaction of 2-nitropropane (1.0 mol.), sodium methoxide (1.5 mol.) and excess perchloryl fluoride at −35 to −38° in methanol (1500 ml.) gave similarly 2-fluoro-2-nitropropane, acetone, and 2,3-dimethyl-2,3-dinitrobutane in 32%, 51%, and 5.4% conversions, respectively.

Reaction of perchloryl fluoride and sodium 2-butanenitronate. Reaction of 2-nitrobutane (51.6 g., 0.5 mol.), sodium methoxide (40.5 g., 0.75 mol.), and excess perchloryl fluoride in methanol (900 ml.) was effected at 0–5°. The initial ether extract was concentrated, stirred overnight with saturated aqueous sodium bisulfite, separated, and stirred for 6 hr. with 20% sodium hydroxide. The bisulfite and sodium hydroxide extractions were repeated to remove impurities indicated by infrared examination. Fractionation of the ether and distillation of the residue gave colorless 2-fluoro-2-nitrobutane (23.4 g., 38% conversion), b.p. 74° (115 mm.), n_D^{20} 1.3888; infrared absorption for a nitro group (6.36 and 7.33μ).

Anal. Calcd. for $C_4H_8NO_2F$: C, 39.67; H, 6.66; N, 11.57; F, 15.69. Found: C, 39.43; H, 6.64; N, 11.50; F, 15.58.

The distillation residue upon recrystallization from methanol gave 3,4-dimethyl-3,4-dinitrohexane[3] (3.54 g., 7% conversion), m.p. 77–78°, lit.[12] m.p. 79–80°; no depression by an authentic sample. An additional experiment with perchloryl fluoride and sodium 2-butanenitronate allowed isolation of 2-butanone as its 2,4-dinitrophenylhydrazone, m.p. 116°, lit.[11] 117°, in about 45% conversion.

Reaction of perchloryl fluoride and sodium cyclohexanenitronate. Reaction of nitrocyclohexane (129.2 g., 1.0 mol.), sodium methoxide (108 g., 1.0 mol.), and excess perchloryl fluoride was conducted at 0 to 10°. Isolation of the products (preferred procedure) after the initial ether solution was exhaustively extracted with saturated aqueous sodium bisulfite (twice, overnight) and 20% sodium hydroxide gave colorless 1-fluoro-1-nitrocyclohexane (62.1 g., 42% conversion), b.p. 94° (34 mm.), n_D^{20} 1.4416, D_4^{20} 1.153; infrared absorption for a nitro group (6.39 and 7.37μ).

Anal. Calcd. for $C_6H_{10}NO_2F$: C, 48.97; H, 6.85; N, 9.52. Found: C, 48.88; H, 6.94; N, 9.71.

The distillation residue (3.4 g., 2.6% crude conversion) yielded 1,1′-dinitrobicyclohexyl (1.84 g., 1.4%) upon recrystallization from ethanol, m.p. 215–219°, lit.[13] m.p. 217°, no depression by an authentic sample. The conversion to cyclohexanone was determined by separate experiment; the corrected crude conversion to cyclohexanone 2,4-dinitrophenylhydrazone, m.p. 159–161°, lit.[11] m.p. 161°, was 53%.

(12) I. Bevad and A. Pirinsky, *Ber.*, **39**, 1231 (1906).

Reaction of perchloryl fluoride and sodium 1-propanenitronate. Reaction of 1-nitropropane (133.6 g., 1.5 mol.), sodium methoxide (162 g., 3.0 mol.), and excess perchloryl fluoride in methanol (1.5 l.) was effected at 0–10°. The red, slightly acid mixture was allowed to warm to room temperature, poured into water, and extracted with ether. The ether extract was washed with water, dried with brine, sodium sulfate, and magnesium sulfate, respectively, and rectified to give, after removal of ether: (1) impure propionaldehyde dimethyl acetal (23 g.), b.p. 84.5–89.2°, (2) a mixture of fluorinated 1-nitropropanes and 1-nitropropane (6.6 g.), b.p. 77–78.5° (190 mm.), n_D^{20} 1.3926–1.3991, (3) crude 1-nitropropane (45.6 g., 34% recovery), b.p. 69–72° (100 mm.), n_D^{20} 1.3992–1.4028, lit.[14] n_D^{20} 1.4013, similar infrared absorption, and (4) residue (3.4 g.).[15]

Fraction 1 in ether was stirred overnight with aqueous 10% sodium hydroxide, separated, dried, and rectified to yield propionaldehyde dimethyl acetal (20.0 g., 13% conversion), b.p. 87°, n_D^{20} 1.3798, d_4^{20} 0.8505, lit.[16] b.p. 89°, n_D^{21} 1.3799.[16]

Anal. Calcd. for $C_5H_{12}O_2$: C, 57.66; H, 11.61. Found: C, 57.68; H, 11.77.

Its identity was confirmed by hydrolysis to propionaldehyde 2,4-dinitrophenylhydrazone, m.p. 153–154°, lit.[17] m.p. 154°. Fraction 2 (6.6 g.) in ether was extracted with excess 5% sodium hydroxide for 2 hr. Distillation of the ether solution gave only trace amounts of fluorinated nitropropanes.[18] Acidification of the alkaline extract at 0° with hydrochloric acid gave additional 1-nitropropane (about 3.0 g.), n_D^{20} 1.4014–1.4018; the apparent instability of 1-fluoro-1-nitropropane in alkaline aqueous media was indicated by the fact that the acidified aqueous extract gave very strong tests for fluoride ion.

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(13) S. S. Nametkin, *J. Russ. Phys. Chem. Soc.*, **42**, 586 (1910); *Chem. Zentr.*, **81**, II, 1376 (1910).

(14) A. I. Vogel, *J. Chem. Soc.*, 1833 (1948).

(15) In an experiment which simulated the one described propionaldehyde was formed in at least 40% conversion and 64% yield.

(16) A. Kirrmann, *Ann. chim.* (*Paris*), [10], **11**, 262 (1929).

(17) Ref. 11, p. 229.

(18) A reaction was conducted in which perchloryl fluoride (1.2 mol.) was added to a slurry of sodium 1-propanenitronate (1.5 mol.) in dimethylformamide (250 ml.) at 15°. After 2 hr., sodium methoxide (1.5 mol.) and perchloryl fluoride (excess) were added to the mixture; consecutive addition of the reagents was repeated again. The acidic reaction product was extracted with pentane; concentration and analysis of the pentane extract for fluorine indicated that the maximum conversion of 1-nitropropane to fluorine-containing products was 4%.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF PURDUE UNIVERSITY]

Nitration Studies. XI. Preparation of α-Nitroketones and Aldehydes. Nitration of Enol Acetates and Ethers[1]

G. BRYANT BACHMAN AND TAKEO HOKAMA[2]

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α-Nitroketones and aldehydes have been prepared in 12–36% yields by the nitration of enol acetates and ethers with nitryl chloride. Other nitrating agents gave lower yields.

The nitration of ketones with nitric acid in both the liquid and vapor phases has been reported to give extensive oxidation and degradation with only very small amounts of α-nitroketones being isolated.[3] Nitration of ketones with alkyl nitrates in alkaline media has been reported as a good preparative method for α,α′-dinitroketones.[4] Although mononitroketones may be obtained in good yields from ketones containing only one α-methylene group,[5] mixtures of mono- and dinitroketones are obtained with ketones containing two α-methylene groups by this method.[6] The preparation of α-nitroaldehydes by nitration of aliphatic aldehydes seems not to have been reported.

The limitations of direct nitration methods may be ascribed in part to the low concentration of enol form normally present, since α-substitution reactions of carbonyl compounds have generally been postulated to proceed through such enol intermediates.[7] For this reason, it seemed probable that mononitration of ketones and aldehydes might be achieved more successfully if a derivative of the enol form were prepared and nitrated under mild conditions. In continuation of our studies on the preparation of α-nitrocarbonyl compounds,[8] we have investigated the action of various nitrating agents on a series of enol esters and ethers. The results of these experiments are shown in Table I.

The over-all synthesis as applied to an enol acetate may be represented by the following equations:

$$RCOCH_2R' + CH_3C(OCOCH_3)=CH_2 \longrightarrow RC(OCOCH_3)=CHR' + CH_3COCH_3 \quad (1)$$

$$RC(OCOCH_3)=CHR' + NO_2X \xrightarrow{(+)(-)} RCX(OCOCH_3)-CHNO_2R' \quad (2)$$

$$RCX(OCOCH_3)-CHNO_2R' + HOH \longrightarrow RCOCHNO_2R' + CH_3CO_2H + HX \quad (3)$$

Enol ethers react similarly but form an alcohol instead of acetic acid as by-product on hydrolysis. The reactions were run in ether, chloroform, or methylene chloride solvents at temperatures of −40° to 0°. The following nitrating agents were studied: nitryl chloride, acetyl nitrate, dinitrogen tetroxide, mixtures of dinitrogen tetroxide and halogens, butyl nitrate in acidic and alkaline media, and nitric acid. Successful mono-nitration of enol acetates and ethers was observed with nitryl chloride in 12–36% yields. Smaller yields (13–20%) of α-nitroketones were obtained through nitration with acetyl nitrate. The principal side reaction with this reagent seemed to be oxidation to 1,2-diketones and lower molecular weight acids. Dinitrogen tetroxide alone in ether solution gave a very low yield of ketone from the enol acetate of methyl ethyl ketone. The other nitrating agents gave little or none of the desired products.

Since α-nitroaldehydes of structure $RCHNO_2CHO$ are readily capable of self-addition to form polymers, they cannot be isolated. For this reason, we have instead prepared the adducts only from the reactions of vinyl acetate and butyl vinyl ether with nitryl chloride and used them to prepare derivatives of the corresponding α-nitroacetaldehyde. With compounds of the structure R_2CNO_2CHO, such polymerizations do not occur and hence we have been able to prepare 2-nitro-2-methylpropanal as a constant-boiling fraction which gave an analytically pure 2,4-dinitrophenylhydrazone.

EXPERIMENTAL

The following experiments illustrate the procedures employed.

(1) Abstracted from a thesis submitted to the faculty of the Graduate School of Purdue University in partial fulfillment of the requirements for the Ph.D. degree, August 1958.

(2) American Cyanamid Fellow, 1957–58.

(3) (a) R. Behrend and N. Tryller, *Ann.*, **283**, 244 (1894); (b) G. Ponzio and M. Fileti, *J. prakt. chem.*, **51**, 504 (1895); **55**, 192 (1897); (c) H. B. Hass and D. E. Hudgin, *J. Am. Chem. Soc.*, **76**, 2692 (1954); (d) C. D. Hurd and M. E. Nilson, *J. Org. Chem.*, **20**, 927 (1955).

(4) H. Feuer, J. W. Shepherd, and C. Savides, *J. Am. Chem. Soc.*, **78**, 4364 (1956).

(5) F. Strauss and W. Ekhard, *Ann.*, **444**, 146 (1925).

(6) R. Boschan, R. T. Merrow, and R. W. Van Dolah, *Chem. Revs.*, **55**, 485 (1955).

(7) J. Hine, *Physical Organic Chemistry*, McGraw-Hill Book Co., Inc., New York, 1956, p. 224.

(8) G. B. Bachman and T. Hokama, *J. Am. Chem. Soc.*, **81**, 4882 (1959).

TABLE I

NITRATION OF ENOL ESTERS AND ETHERS

Enol Ester or Ether	Nitrating Agent	Solvent	Time, Hr.	Temp., °C.	Product	Yield, %
(1) CH_2=$CHOCOCH_3$	NO_2Cl	$(C_2H_5)_2O$	4	0	$ClCH_2CHClOCOCH_3$	10.8
					$O_2NCH_2CHClOCOCH_3$	36.0
(2) CH_2=$CHOC_4H_9$	NO_2Cl	$CHCl_3$	4	−20	$ClCH_2CHClOC_4H_9$	20.0
					$O_2NCH_2CHClOC_4H_9$[a]	Trace
(3) $(CH_3)_2C$=$CHOCOCH_3$	NO_2Cl	CH_2Cl_2	4	−40	$(CH_3)_2CClCHO$	21.0
					$(CH_3)_2CNO_2CHO$	12.0
(4) CH_3CH=$C(CH_3)OCOCH_3$	NO_2Cl	$(C_2H_5)_2O$	4	0	$CH_3COCHNO_2CH_3$[b]	36.0
(5) CH_3CH=$C(CH_3)OCOCH_3$	$CH_3CO_2NO_2$	CH_3CO_2H	4	25	$CH_3COCHNO_2CH_3$[b]	13.0
					$CH_3COCOCH_3$	17.0
(6) CH_3CH=$C(CH_3)OCOCH_3$	N_2O_4	$(C_2H_5)_2O$	2	0	$CH_3COCHNO_2CH_3$[b]	5.0
					$CH_3COCOCH_3$	40.0
(7) CH_3CH=$C(CH_3)OCOCH_3$	$N_2O_4 + Cl_2$	CCl_4	2	0	$CH_3COCHClCH_3$	58.0
(8) CH_3CH=$C(CH_3)OCOCH_3$	$N_2O_4 + Br_2$	CCl_4	2	0	$CH_3COCHBrCH_3$	50.0
(9) CH_2=$C(C_6H_5)OCOCH_3$	NO_2Cl	$(C_2H_5)_2O$	3	0	$C_6H_5COCH_2NO_2$[b]	36.0
					$C_6H_5COCH_2Cl$	14.0
(10) CH_2=$C(C_6H_5)OCOCH_3$	N_2O_4	$(C_2H_5)_2O$	4	0	$C_6H_5COCH_2NO_2$[b]	20.0
(11) CH_3CH=$C(C_6H_5)OCOCH_3$	NO_2Cl	$(C_2H_5)_2O$	2	0	$C_6H_5COCHNO_2CH_3$[b]	28.0
(12) CH_3CH=$C(C_6H_5)OCOCH_3$	$CH_3CO_2NO_2$	CH_3CO_2H	4	25	$C_6H_5COCHNO_2CH_3$[b]	21.0

[a] B.p. 76° (2 mm.); not analyzed but reacted with anthranilic acid to obtain the anil, m.p. 200°.[10] [b] *Cf.* reference 8.

α-Chloro-β-nitroethyl acetate. Reaction of vinyl acetate with nitryl chloride. Nitryl chloride,[9] 84 g. (1.0 mol.), was distilled in a current of nitrogen gas in 1 hr. into a stirred solution of vinyl acetate, 86 g. (1.0 mol.), in ether, 240 ml., at 0°, contained in a 500-ml., 3-necked flask equipped with a stirrer, gas inlet tube, and a reflux condenser fitted with a drying tube. After 2 hr. at 0°, the reaction mixture was allowed to warm to room temperature (2 hr.). The mixture was then concentrated under water aspiration, and distilled under nitrogen atmosphere at reduced pressure. α,β-Dichloroethyl acetate, b.p. 32° (10 mm.), n_D^{26} 1.4420, 17 g. (10.8% theory), and α-chloro-β-nitroethyl acetate, b.p. 66° (2 mm.), n_D^{26} 1.4446, 61 g. (36% theory), were obtained.

Anal. Calcd. for $C_4H_6NO_4Cl$: C, 78.67; H, 3.60; N, 8.36; Cl, 21.16. Found: C, 78.82; H, 3.67; N, 8.36; Cl, 21.01.

Hydrolysis of α-chloro-β-nitroethyl acetate in the presence of anthranilic acid gave the anil of nitroacetaldehyde, m.p. 200°. A mixture melting point with an authentic sample of the anil prepared from methazonic acid[10] showed no depression.

3-Nitro-2-butanone. Reaction of 2-buten-2-yl acetate with nitryl chloride. Nitryl chloride, 25 g. (0.3 mol.), was distilled in 1 hr. into a solution of 2-buten-2-yl acetate, 34 g. (0.3 mol.), in ether, 200 ml., at 0°, and the reaction mixture was stirred for 3 hr. Methanol, 30 ml., was added and the mixture was stirred for another 0.5 hr. The ether solution was washed twice with water, dried, and distilled. 3-Chlorobutanone, b.p. 40° (40–50 mm.), n_D^{26} 1.4168, 11 g. (30% theory), semicarbazone, m.p. 138°, lit.[11] m.p. 138–139°; and 3-nitro-2-butanone,[8] b.p. 56° (2 mm.), n_D^{26} 1.4360, 12.5 g. (36% theory), were obtained.

The aniline derivative, m.p. 102°, and the 2,4-dinitrophenylhydrazine derivative of 3-nitro-2-butanone, m.p. 124°, were prepared. Mixture melting points with authentic samples of these derivatives showed no depression. Lit.,[8,12] anil, m.p. 101–102°, 2,4-dinitrophenylhydrazone, m.p. 125°.

A similar experiment using dinitrogen tetroxide yielded only 5% of the nitroketone. Most of the product consisted of biacetyl (40% theory).

2-Nitro-2-methylpropanal. Reaction of 2-methyl-1-propen-1-yl acetate with nitryl chloride. 2-Methyl-1-propen-1-yl acetate, 61 g. (0.5 mol.), was added in 2 hr. to a solution of nitryl chloride, 37 g. (0.45 mol.), in dichloromethane, 200 ml., at −40°, and the mixture was stirred for another 2 hr. Methanol, 32 g., was added and the mixture was stirred for 1 hr., and then allowed to stand overnight at room temperature. Distillation gave: (a) 2-chloro-2-methylpropanal, b.p. 88–90°, 11 g. (21% theory); (b) 2-nitro-2-methylpropanal, b.p. 49° (3 mm.), n_D^{26} 1.4398, 5 g. (12% theory), the infrared spectrum showed absorption at 5.76 μ (carbonyl group) and at 6.34 and 7.25 μ (nitro group).

The oxime of 2-chloro-2-methylpropanal melted at 104°. Lit.,[13] m.p. 104–105°.

The 2,4-dinitrophenylhydrazone of 2-nitro-2-methylpropanal, m.p. 150°, was prepared and analyzed.

Anal. Calcd. for $C_{10}H_{11}N_5O_6$: C, 40.41; H, 3.73; N, 23.56. Found: C, 40.52 H, 4.00; N, 23.56.

α-Nitropropiophenone. Reaction of 1-phenyl-1-propen-1-yl acetate with acetyl nitrate. Acetic anhydride, 12.0 g. (0.12 mol.), was added in 0.25 hr. to a cooled solution of 100% nitric acid, 6.3 g. (0.1 mol.). 1-Phenyl-1-propen-1-yl acetate, 12 g. (0.068 mol.), was added in 0.5 hr. to the cooled solution of acetyl nitrate, and the mixture was stirred at room temperature for 4 hr. The reaction mixture was hydrolyzed with 10% urea solution, 200 ml., and the aqueous solution was extracted 3 times with ether. The ether layers were combined, dried, and distilled. α-Nitropropiophenone, b.p. 120–124° (1 mm.), n_D^{26} 1.5434, 2.5 g. (21% theory), was obtained.

The 2,4-dinitrophenylhydrazine derivative, m.p. 177–178°, was prepared. A mixture melting point with an authentic sample of the derivative showed no depression. Lit.,[8] m.p. 178°.

(9) Prepared by the procedure of H. Shechter, F. Conrad, A. L. Daulton, and R. B. Kaplan, *J. Am. Chem. Soc.*, **74**, 3052 (1952).

(10) German Patent **347,375** (to Badische Anilin-and-Soda Fabrik), Jan. 17, 1922.

(11) F. H. Curd and A. Robertson, *J. Chem. Soc.*, 717 (1933).

(12) C. D. Hurd and M. E. Nilson, *J. Org. Chem.*, **20**, 926 (1955).

(13) H. D. K. Drew and F. S. H. Head, *J. Chem. Soc.*, 49 (1934).

Attempted nitration of 2-buten-2-yl acetate with dinitrogen tetroxide–chlorine mixture. 2-Buten-2-yl acetate, 23 g. (0.2 mol.), was added in 1 hr. to a cooled solution of dinitrogen tetroxide, 9.2 g. (0.1 mol.), and chlorine, 7.1 g. (0.1 mol.), in carbon tetrachloride, 100 ml., and the reaction mixture was allowed to warm to room temperature (1 hr.). The carbon tetrachloride solution was washed with water, dried, and distilled. Only 3-chlorobutanone, b.p. 36° (40 mm.), n_D^{25} 1.4168, 12 g. (58% theory), and no 3-nitrobutanone was isolated.

LAFAYETTE, IND.

[CONTRIBUTION NO. 533 FROM THE CENTRAL RESEARCH DEPARTMENT, EXPERIMENTAL STATION, E. I. DU PONT DE NEMOURS AND COMPANY]

Fluoroalkanethiolcarboxylic Acids

WILLIAM A. SHEPPARD AND E. L. MUETTERTIES

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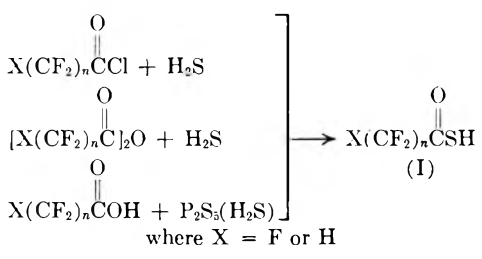
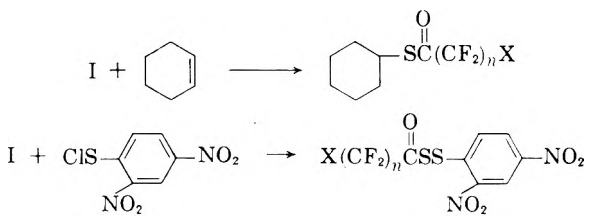
Fluoroalkanethiolcarboxylic acids (I) have been prepared by the reaction of the corresponding acid anhydride or halide with hydrogen sulfide or by reaction of the acid with phosphorus pentasulfide. The properties and reactions of these thioacids are described.

Esters of fluoroalkanethiolcarboxylic acids have been prepared by the reaction of fluoroacyl chlorides with mercaptans,[1] and by the oxidation of the bis(alkyl- and arylthio)-tetrafluorocyclobutenes.[2] However, parent fluoroalkanethiolcarboxylic acids (I) are an unknown class of compounds[3] and attempts to prepare these acids by hydrolysis of the corresponding thioesters yielded only the acids and thiols.[1] We have found that the fluoroalkanethiolcarboxylic acids (I) are readily prepared by heating the corresponding fluoroacyl chlorides or anhydrides with hydrogen sulfide at 200° in an autoclave. They can also be obtained by heating fluoroalkanecarboxylic acids with phosphorus pentasulfide under the same conditions.



These conditions are more drastic than needed for the preparation of the hydrocarbon analogs.[4] It was noted in preliminary exploratory experiments that no reaction occurred between the fluoroacyl halide and hydrogen sulfide below a temperature of 100° and that heptafluorobutyric acid was unaffected by being heated at 120° with phosphorus pentasulfide. Heptafluorobutyryl chloride reacted with a solution of hydrogen sulfide in pyridine but no free thiol acid could be isolated. The strongly acidic character of this fluoroalkanethiolcarboxylic acid (see below) may cause formation of very stable salts with pyridine.

The fluoroalkanethiolcarboxylic acids are pale yellow liquids with the characteristic overpowering thioacid odor. They appear to react in a manner analogous to the alkane–thiocarboxylic acids[4] as shown by the following equations:



The ionization constants of fluoroalkanethiolcarboxylic acids are in the region of 0.6; only approximate values of these constants could be determined by conductivity measurement[5] because of apparent instability of the aqueous solutions. These thiol acids are much stronger acids than the hydrocarbon analogs[6] and are of strength comparable to the fluoroalkanecarboxylic acids. The large increase in the acidity of fluoroalkanecarboxylic acids compared to the hydrocarbon analogs has

(1) M. Hauptschein, C. S. Stokes, and E. A. Nodiff, *J. Am. Chem. Soc.*, **74**, 4005 (1952).

(2) K. E. Rapp, J. T. Barr, R. L. Pruett, C. T. Bahner, J. D. Gibson, and R. H. Lafferty, Jr., *J. Am. Chem. Soc.*, **74**, 749 (1952).

(3) For a recent review of fluoroalkanecarboxylic acids and derivatives, see A. M. Lovelace, O. A. Rausch, and W. Postelnek, "Aliphatic Fluorine Compounds," Reinhold Publishing Corporation, New York, 1958, Chapters VII and XIII.

(4) E. H. Rodd, "Chemistry of Carbon Compounds," Elsevier, New York, 1951, Volume IA, pp. 593–595. Thiolacetic acid is prepared by passing hydrogen sulfide into a mixture of acetic anhydride and acetyl chloride at room temperature, by the reaction of excess hydrogen sulfide on acetyl chloride and pyridine, or by the distillation of the carboxylic acid from phosphorus pentasulfide.

(5) A. L. Henne and C. J. Fox, *J. Am. Chem. Soc.*, **73**, 2323 (1951) reported the ionization constants of trifluoroacetic acid and heptafluorobutyric acid as 0.59 and 0.68, respectively, at 25° in water.

(6) The ionization constant of thiolacetic acid is 4.7×10^{-4} compared to the value of 1.7×10^{-5} for acetic acid.

TABLE I

PREPARATION OF FLUOROALKANETHIOLCARBOXYLIC ACIDS

Acid Compound[a]	Sulfur Reagent	Temp.	Time (hr.)	Product	Yield, %
$(CF_3C)_2O$ 73 g., 0.52 mol.	H_2S, 1.0 mol.	200	5	CF_3CSH[b]	28
$(CF_3C)_2O$ 216 g., 1.53 mol.	H_2S, 3.0 mol.	200	5	CF_3CSH	24, 45
$(CF_3CF_2CF_2C)_2O$ 350 g., 1.17 mol.	H_2S, 3.0 mol.	200	4	C_3F_7CSH	21
$CF_3CF_2CF_2CCl$ 46.2 g., 0.20 mol.	H_2S, 2.0 mol.	200	6	C_3F_7CSH $C_3F_7CO_2H$	68 11
$CF_3CF_2CF_2CCl$ 23.2 g., 0.10 mole	H_2S, 1.0 mol.	90	0.1	C_3F_7CCl	[c]
$CF_3CF_2CF_2COH$ 21.7 g., 0.10 mol.	H_2S, 1.0 mol. P_2S_5, 0.06 mol.	200	6	C_3F_7CSH	39[d]
$CF_3CF_2CF_2COH$ 21.7 g., 0.10 mol.	H_2S, 1.0 mol. (HCl, 2 g.)	200	10	C_3F_7CSH $C_3F_7CO_2H$	0 83
$CF_3CF_2CF_2COH$ 21.7 g., 0.10 mol.	P_2S_5, 0.20 mol.	200	6	C_3F_7CSH	43
$[H(CF_2)_4C]_2O$[e] 83 g., 0.176 mol.	H_2S, 3.0 mol.	200	4	$H(CF_2)_4CSH$	31
$H(CF_2)_4CCl$[e] 26.4 g., 0.10 mol.	H_2S, 1.0 mol.	200	10	$H(CF_2)_4CSH$ $H(CF_2)_4CO_2H$	69 13
$H(CF_2)_4CCl$ 100 g., 0.38 mol.	H_2S, 2.0 mol.	200	5	$H(CF_2)_4CSH$ $H(CF_2)_4CO_2H$	39 19

[a] Unless indicated otherwise, the acid compounds were purchased or prepared by standard procedures (see Ref. 3). [b] No attempt was made to recover the carboxylic acid or other by-products in the majority of the runs. [c] No thiol acid could be detected. [d] Some of product may have been lost during course of run because of a leak in the autoclave. [e] Prepared by standard methods from the corresponding acid which was in turn prepared by permanganate oxidation of the alcohol; see U. S. Patent 2,559,629.

been attributed to the strong electron-withdrawing inductive effect of the fluorine atoms.[7]

EXPERIMENTAL[8]

Preparation of the fluoroalkanethiolcarboxylic acids, I. The reactions for preparation of these acids were all run in Hastelloy-lined autoclaves under autogenous pressure. The charges, conditions, and yields are summarized in Table I. The following procedures describe the method and the characterization of the products.

Trifluorothiolacetic acid. Trifluoroacetic anhydride (73 g., 0.52 mol.) was charged into a dry, nitrogen-flushed, Hastelloy-C-lined, 500-ml. autoclave. The autoclave was cooled to −80° in a solid carbon dioxide bath, evacuated, and charged with 34 g. (1.0 mol.) of hydrogen sulfide. The reaction mixture was heated to 200° for a period of 3 hr. After cooling to room temperature, the gaseous products were vented and the liquid residue of 72 g. was distilled to give 19 g. of trifluorothiolacetic acid, b.p. 35.5°, as a clear, colorless liquid.

Anal. Calcd. for C_2HF_3OS: C, 18.5; H, 0.77; S, 24.6. Found: C, 17.9; H, 1.08; S, 25.1.

Heptafluorothiolbutyric acid. Heptafluorobutyric acid (21.7 g., 0.10 mol.) and 45 g. (0.20 mol.) of phosphorus pentasulfide were charged into a 1-l. Hastelloy B-lined autoclave. The autoclave was cooled to −80°, evacuated, and then heated at 200° for 6 hr. under autogenous pressure. The product, absorbed in the solid phosphorus sulfides and oxides, was distilled at reduced pressure into a trap cooled in a solid carbon dioxide bath. The crude liquid product (11.2 g., contains a small amount of free sulfur) was distilled through a semimicro glass spiral distillation column to give 9.9 g. of heptafluorothiolbutyric acid, b.p. 80–82°, n_D^{27} 1.3259 (1.3 g. of liquid b.p. 82–160° was not characterized).

(7) See Ref. 3, p. 202.

(8) All melting points are uncorrected.

TABLE II

NUCLEAR MAGNETIC RESONANCE SPECTRA[a]

Compounds	Frequency Displacement in cps. at 40 Mc. and (Relative Intensities)[b]	
	Proton	Fluorine
$CF_3CF_2CF_2\overset{O}{\overset{\|}{C}}OH$	−374	+200(3) +1710(2) +1995(2)
$CF_3CF_2CF_2\overset{O}{\overset{\|}{C}}SH$	−6.4	+175(3) +1548(2) +1950(2)
$H(CF_2)_4\overset{O}{\overset{\|}{C}}OH$	−256(4) −90.0(1) −37.3(2) +18.0(1)	+1670(2) +1880(2) +2070(2) +2430(2)
$H(CF_2)_4\overset{O}{\overset{\|}{C}}SH$	−9.6(4) −89.0(1) −36.5(2) +16.0(1)	+1505(2) +1830(2) +2030(2) +2410(2)

[a] Spectra were obtained by means of a high-resolution, nuclear magnetic resonance spectrometer and associated electromagnet, both manufactured by Varian Associates, Palo Alto, California, operating at approximately 9988 gauss for fluorine and 9395 gauss for hydrogen. [b] Spectra were calibrated in terms of displacement in cycles per second (cps) from the proton resonance of water and the fluorine resonance of trifluoroacetic acid. Negative frequency displacements indicate resonances occurring at lower field relative to the reference.

Anal. Calcd. for C_4HF_7OS: C, 20.9; H, 0.44; F, 57.8; S, 13.9; mol. wt. 230. Found: C, 21.2; H, 0.75; F, 58.9; S, 13.6; mol. wt. 234, 235 (b.p. in benzene); neut. eq. 241, 236.

5-H-Octafluorothiolvaleric acid. 5-H-Octafluorovaleroyl chloride (100 g., 0.378 mole) was charged into a 1-l., "Hastelloy B"-lined autoclave with 68 g. (2.0 moles) of hydrogen sulfide as described above. The reaction mixture was heated at 200° for 5 hr., cooled, and the volatile products vented. There was obtained 120 g. of liquid which on distillation through an 18-inch spinning band column yielded 38.2 g. 5-H-octafluorothiolvaleric acid, b.p. 124–126°, n_D^{24} 1.3470, and 19.3 g. of 5-H-octafluorovaleric acid, b.p. 94° at 40 mm. (a fraction of 5.1 g., b.p. 99° at 40 mm. to 82° at 1.9 mm. was not characterized).

Anal. Calcd. for $C_5H_2F_8OS$: C, 22.9; H, 0.77; F, 58.0; S, 12.2; mol. wt. 262. Found: C, 23.4; H, 1.08; F, 57.9; S, 12.2; mol. wt. 248, 248 (f.p. in benzene).

Reaction of 5-H-octafluorothiolvaleric acid with cyclohexene. 5-H-Octafluorothiolvaleric acid (5.2 g., 0.020 mole) was added to 5 ml. of cyclohexene. After a short induction period, a vigorous exothermic reaction resulted. The resulting solution was distilled through a 12-inch micro spinning band column. The excess cyclohexene was discarded and 5.3 g. (77%) of cyclohexyl 5-H-octafluorothiolvalerate was collected as a colorless liquid, b.p. 72–72.5° (1.2 mm.), n_D^{23} 1.4085.

Anal. Calcd. for $C_{11}H_{12}F_8OS$: C, 38.4; H, 3.52; F, 44.2. Found: C, 39.2, 39.0; H, 4.15; F, 44.2.

Reaction of 5-H-octafluorothiolvaleric acid with 2,4-dinitrobenzenesulfenyl chloride. A solution of 2.62 g. (0.010 mol.) of 5-H-octafluorothiolvaleric acid was added to 2.34 g. (0.010 mol.) of 2,4-dinitrobenzenesulfenyl chloride partially dissolved in 35 ml. of ether. The reaction occurred immediately as indicated by the rapid solution of the undissolved sulfenyl chloride. The ether was evaporated to leave a residue of 4.33 g. of pale yellow oil that crystallized on chilling. The 2,4-dinitrophenyl-5-H-octafluorovaleroyl disulfide was recrystallized from a solution of approximately 1% benzene in pentane, m.p. 44.0–44.8°, pale yellow crystals.

Anal. Calcd. for $C_{11}H_4F_8N_2O_5S_2$: C, 28.7; H, 0.88; F, 33.0; S, 13.9. Found: C, 29.1; H, 1.44; F, 33.1; S, 14.0.

Infrared and NMR (Nuclear Magnetic Resonance) Spectra. The infrared and NMR (fluorine and proton) spectra were obtained on the thiol acids and derivatives and found to be in agreement with the assigned structures in every case. The infrared absorption maximum for the thiol group of the thiol acids was observed at 2580 cm.$^{-1}$ and the carbonyl absorption at 1733–1738 cm.$^{-1}$. These absorption maxima occur in the usual regions (for thiolacetic acid, thiol is at 2550 cm.$^{-1}$ and carbonyl at 1712 cm.$^{-1}$) with the expected shift to lower wave numbers resulting from the inductive effect of the fluorine atoms.

The NMR spectra for two of the thiol acids are compared with those for the corresponding carboxylic acids in Table II.

WILMINGTON 98, DELAWARE

[CONTRIBUTION FROM MELLON INSTITUTE]

The Chemistry of Ylids. IV. Triphenylarsoniumfluorenylide[1]

A. WILLIAM JOHNSON

Received September 9, 1959

Triphenylarsoniumfluorenylide (IIIe), the first example of an isolable arsenic-containing ylid, has been prepared. Its chemical and physical properties have been examined.

Although the reaction of ylids of type I (X = $(C_6H_5)_3P$) with carbonyl compounds

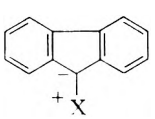
$$\overset{+}{X} - \overset{-}{R} \longleftrightarrow X = R$$
Ia Ib

X = heteroatom group
R = hydrocarbon group

was discovered in 1919 by Staudinger and Meyer,[2] it is only recently that its full scope and potential have been realized. Wittig and co-workers[3] demonstrated the synthetic usefulness of triphenylphosphoniummethylide (I, X = $(C_6H_5)_3P$, R = CH_2) and its derivatives as olefin-forming reagents. Since that time numerous examples of the preparation and reactions of these ylids have been reported.[4]

Few isolable, crystalline ylids have been characterized. In the phosphorus series triphenylphosphoniumbenzylide (I, X = $(C_6H_5)_3P$, R = C_6H_5CH),[5] triphenylphosphoniumbenzhydrylide (I, X = $(C_6H_5)_3P$, R = $C(C_6H_5)_2$),[6] triphenylphosphoniumcyclopentadienylide (IIa),[7] triphenylphosphoniumfluorenylide (IIIa),[1a] and tributylphosphoniumfluorenylide (IIIb)[8] are known. In the sulfur series, only dimethylsulfoniumfluorenylide

IIa. X = $(C_6H_5)_3P$
IIb. X = $(CH_3)_3N$
IIc. X = 1-pyridinium



IIIa. X = $(C_6H_5)_3P$
IIIb. X = $(C_4H_9)_3P$
IIIc. X = $(CH_3)_2S$
IIId. X = 1-pyridinium
IIIe. X = $(C_6H_5)_3As$
IIIf. X = $(CH_3)_3As$

(IIIc)[1c,9a] and its 2,7-dinitro derivative[9b] have been described. Three nitrogen ylids, trimethylammoniumcyclopentadienylide (IIb),[10] 1-pyridiniumcyclopentadienylide (IIc)[11] and 1-pyridiniumfluorenylide (IIId)[12] have been prepared and isolated. However, none of this latter group is comparable in stability to the phosphorus and sulfur ylids.

The unique stability of phosphorus- and sulfur-containing ylids is attributed to *d*-orbital resonance. This phenomenon depends on the ability of these hetero atoms to expand their octet to a decet by accepting an electron pair from a carbon 2*p*-orbital into a vacant sulfur or phosphorus 3*d*-orbital, thereby allowing the contribution of structure Ib as well as Ia to the resonance hybrid. If such is in fact the case, one may select other hetero atoms which should behave similarly and expect to produce stable, isolable ylids from a properly constructed molecule. Accordingly, we have undertaken to examine the ability of arsenic-containing compounds to form stable ylids and to compare their behavior to the phosphorus analog.

There is but little evidence in the literature concerning the ability of arsenic to expand its octet. By examining the deuteroxide-catalyzed exchange of deuterium in tetramethylphosphonium and trimethylsulfonium salts, Doering and Hoffmann[13] concluded that the heats of activation were lowered from the expected values (calculated on the basis of coulombic interactions only) by 15.4 and 17.2 kcal., respectively. This lowering was ascribed to *d*-orbital resonance in each case. In a less precise but analogous manner they indicated that in proceeding down the group V elements, the contribution of *d*-orbital resonance should remain nearly constant, the rate of exchange decreasing in proportion to and due solely to the increased bond distance. Chatt and co-workers[14] claimed that ar-

(1) For previous papers in this series see (a) III, A. W. Johnson, *J. Org. Chem.*, **24**, 282 (1959); (b) II, A. W. Johnson and R. B. LaCount, *Chem. and Ind.*, 52 (1959); (c) I, A. W. Johnson and R. B. LaCount, *Chem. and Ind.*, 1440 (1958).

(2) H. Staudinger and J. Meyer, *Helv.*, **2**, 619 (1919).

(3) G. Wittig and U. Schollkopf, *Ber.*, **87**, 1318 (1954) and succeeding papers.

(4) For a recent review of this reaction see J. Levisalles, *Bull. Soc. Chim.*, 1020 (1958).

(5) G. Wittig and G. Geissler, *Ann.*, **580**, 44 (1953).

(6) C. S. Marvel and C. Coffmann, *J. Am. Chem. Soc.*, **51**, 3496 (1929).

(7) F. Ramirez and S. Levy, *J. Am. Chem. Soc.*, **79**, 67 (1957).

(8) A. W. Johnson and R. B. LaCount, *Tetrahedron*, in press.

(9) (a) C. K. Ingold and J. H. Jessop, *J. Chem. Soc.*, 713 (1930); (b) E. D. Hughes and K. I. Kuriyan, *J. Chem. Soc.*, 1609 (1935).

(10) H. J. Dauben, Jr., Abstracts, American Chemical Society 126th meeting, pp. 18-O, September 1954.

(11) D. Lloyd and J. S. Sneezum, *Tetrahedron*, **3**, 334 (1958).

(12) F. Krohnke, *Ber.*, **83**, 253 (1950).

(13) W. von E. Doering and A. K. Hoffmann, *J. Am. Chem. Soc.*, **77**, 521 (1955).

(14) J. Chatt and R. G. Wilkins, *J. Chem. Soc.*, 4300 (1952).

sines participate in double bonding (*via* 4*d*-orbitals) to nearly the same extent as phosphines when used as ligands for complexes of certain metal ions. They presumed that the π-bond was formed by the donation of electrons from a filled *d*-orbital of the metal to the vacant 4*d*-orbital of arsenic.

As mentioned previously, most phosphorus ylids examined to date have been nonisolable, relatively unstable compounds necessitating their preparation *in situ*. It is difficult, however, to obtain reliable quantitative data from the reaction of these ylids with other compounds. It is obviously desirable to utilize stable, readily isolable ylids in these studies. Furthermore, it permits examination of their physical properties.

In this regard, Ramirez and Levy[7] prepared and examined the chemistry of triphenylphosphoniumcyclopentadienylide (IIa), an extremely stable, high melting solid. However, they were unable to effect a Wittig reaction between IIa and benzaldehyde, the electronic configuration of the former preferring to maintain its *status quo* as a pseudoaromatic system. In an effort to circumvent this difficulty we recently examined the chemistry of triphenylphosphoniumfluorenylide (IIIa).[1a] This crystalline ylid did undergo the Wittig reaction with selected carbonyl compounds, the sequence of which shed some light on the mechanism of this reaction.

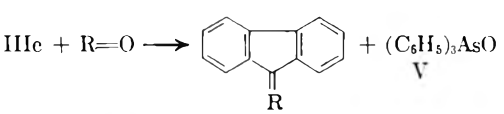
We chose to employ the fluorene nucleus as the hydrocarbon portion (I, R = fluorenylidene) in all our studies for several reasons. The expected products from a Wittig reaction were, for the most part, well characterized, crystalline compounds. In addition, the convenient electronic properties of this nucleus conferred on an ylid enough stability to permit isolation and modified the reactivity so as to permit some selectivity in the rate and facility of reaction. Further instances of these effects are evidenced by the behavior of IIIb[8] and IIIc.[1c] As a result of these successes we are continuing this approach and now wish to report on the chemistry of triphenylarsoniumfluorenylide (IIIe).

Only two arsenic-containing ylids have been reported to date, neither of which underwent a normal Wittig reaction. In 1953 Wittig and Laib[15] prepared solutions of trimethylarsoniumfluorenylide (IIIf) but found that 9-fluorenyldiphenylcarbinol, the result of simple carbanion addition, was the sole product from reaction with benzophenone. In addition, they found the ylid hydrolyzed to fluorene and trimethylarsine oxide on contact with water.

In a preliminary report Wittig and Henry[16] indicated that reaction between triphenylarsoniummethylide (I, X = $(C_6H_5)_3As$, R = CH_2) and benzophenone afforded a mixture of diphenylethylene, the normal product, and, in predominant amounts, diphenylacetaldehyde. It is possible to rationalize the unexpected aldehyde formation *via* an intermediate 1,1-diphenylethylene oxide presumably formed in an analogous manner to those from sulfur ylid reactions.[1c]

Treatment of triphenylarsine with 9-bromofluorene[17] afforded an 83% yield of triphenylfluorenylarsonium bromide. Upon dissolution of the salt in ethanol, followed by the addition of an equivalent amount of aqueous sodium hydroxide solution, triphenylarsoniumfluorenylide (IIIe) precipitated as bright yellow plates in 88% yield. We were unable to obtain satisfactory analytical data for this ylid. However, its mode of formation together with its physical and chemical properties left little doubt as to its constitution. The ylid, m.p. 188–190°, dissolved in dilute mineral acid forming a colorless solution from which it could be reprecipitated unchanged upon the addition of alkali. Its ultraviolet spectrum in chloroform solution was very similar to that of the phosphorus analog (IIIa).[1a] The ylid was hydrolyzed only by heating under reflux with ethanolic sodium hydroxide solution over long periods of time. Chromatography of the reaction mixture afforded fluorene and triphenylarsine oxide in 69% and 43% yields, respectively. A sample of the latter compound was prepared unambiguously by permanganate oxidation of triphenylarsine.

In order to test the reactivity of the ylid (IIIe) in the Wittig reaction and to permit a comparison with the phosphorus analog (IIIa),[1a] the former was treated with a series of carbonyl compounds to produce the fluorenylidene derivatives (IV) and triphenylarsine oxide (V). These



IVa. R = CHC_6H_5
IVb. R = *p*-$NO_2C_6H_4CH$
IVc. R = *p*-ClC_6H_4CH
IVd. R = *p*-$CH_3OC_6H_4CH$
IVe. R = *p*-$(CH_3)_2NC_6H_4CH$
IVf. R = $C(C_6H_5)_2$
IVg. R = $C(CH_3)_2$
IVh. R = $CHCH_3$

results are summarized in Table I.

It is apparent that the ylid (IIIe) distinguishes between aldehydes and ketones as effectively as did the phosphorus analog (IIIa).[1a] However, in contrast to the latter with which the reactivity sequence with *para*-substituted benzaldehydes clearly was $p\text{-}NO_2 > Cl > H > OCH_3 > N(CH_3)_2$, the arsenic ylid (IIIe) reacted with all benzaldehydes in nearly equal yields. For example, the phosphorus analog (IIIa) failed to react with *p*-dimethylaminobenzaldehyde whereas IIIe reacted in 97%

(15) G. Wittig and H. Laib, *Ann.*, 580, 57 (1953).

(16) G. Wittig and M. C. Henry, Abstracts, American Chemical Society 135th meeting, pp. 67–O, April 1959.

(17) G. Wittig and G. Felletschin, *Ann.*, 555, 133 (1944).

TABLE I

CONDENSATION OF IIIe WITH CARBONYLS

Reactant	Yield of Product, %	Expected Product	Yield of Oxide (V), %
Benzaldehyde	74	IVa	37
p-Nitrobenzaldehyde	92	IVb	26
p-Chlorobenzaldehyde	98	IVc	98
p-Anisaldehyde	89	IVd	65
p-Dimethylaminobenzaldehyde	97	IVe	51
Benzophenone	0	IVf	0
Acetone	0	IVg	0
Acetaldehyde	91	IVh	78

yield to produce *p*-dimethylaminobenzalfluorene (IVe). Furthermore, we isolated only the expected "Wittig reaction" products, finding no evidence of any ketonic products as would be expected if Wittig and Henry's observations[16] with arsenic-containing ylids were applied to this ylid (IIIe).

We conclude that arsenic and phosphorus differ slightly in their contribution to the stabilization and reactivity of ylids and therefore differ in their extent of *d*-orbital resonance. From mechanistic considerations it is clear that tetracovalent phosphorus undergoes octet expansion (*d*-orbital resonance) to a greater degree than does similarly substituted arsenic.

EXPERIMENTAL[18]

Triphenylfluorenylarsonium bromide. A solution of 6.25 g. (0.02 mol.) of triphenylarsine and 5.0 g. (0.02 mol.) of 9-bromofluorene[17] in 100 ml. of nitromethane was warmed on a steam bath for 1 hr. The nitromethane was removed *in vacuo* and 100 ml. of acetone was added, resulting in the formation of a colorless precipitate (9.3 g., 83% yield). Recrystallization from benzene-ethanol afforded *triphenylfluorenylarsonium bromide* as colorless microcrystals, m.p. 178–179.5°.

Anal. Calcd. for $C_{31}H_{24}AsBr$: C, 67.5; H, 4.4; As, 13.6; Br, 14.5. Found: C, 66.5; H, 4.6; As, 13.9; Br, 14.9.

The salt gave a positive test for ionic halogen and afforded a yellow precipitate (ylid) when treated with ammonia solutions. The salt was not affected by refluxing in aqueous solution.

Triphenylarsoniumfluorenylide (IIIe). To a stirred solution of 7.2 g. (0.013 mol.) of the above bromide in 500 ml. of absolute ethanol was added portionwise at room temperature 5 ml. of 2.5*N* sodium hydroxide solution. A copious yellow precipitate appeared which was removed by filtration and dried to constant weight (4.7 g., 78% yield). Recrystallization from benzene-hexane afforded *triphenylarsoniumfluorenylide* (IIIe) as fine yellow plates, m.p. 188–190° dec.

Anal. Calcd. for $C_{31}H_{23}As$: C, 79.1; H, 5.0; As, 15.9. Found: C, 80.4; H, 5.3; As, 13.6.

Ultraviolet spectrum: $\lambda_{max}^{CHCl_3}$ 250 mμ (log ε 4.74), 258 mμ (log ε 4.86), 294 mμ (log ε 3.74) and 390 mμ (log ε 3.15).

Hydrolysis of the ylid (IIIe). A heterogeneous solution of 0.55 g. (1.17 mmol.) of ylid in 25 ml. of ethanol containing 5 ml. of 2.5*N* sodium hydroxide solution was heated under reflux for 18 hr. The now homogeneous solution was quenched with water and extracted with ether. The ethereal solution was dried and the solvent removed leaving 0.43 g. of pale yellow solid. This was chromatographed on 15 g. of alumina. Elution with benzene afforded 0.13 g. of colorless solid which crystallized from 95% ethanol as colorless plates, m.p. 115–116°, undepressed on admixture with an authentic sample of fluorene. Elution with methanol afforded 0.15 g. pale yellow solid which crystallized from water as colorless needles, m.p. 189–191°, undepressed on admixture with an authentic sample of triphenylarsine oxide.

Triphenylarsine oxide (V). A solution of 1.0 g. (3.3 mmol.) of triphenylarsine and 1.0 g. (6.6 mmol.) of potassium permanganate in 60 ml. of 50% acetone-water solution was warmed on a steam bath for 5 hr. The solution was cooled, filtered through celite and the filtrate evaporated. Filtration of the resulting aqueous slurry afforded 0.6 g. (57%) of *triphenylarsine oxide* which was recrystallized from water as colorless needles, m.p. 193.5–195.5°, (lit.[19] m.p. 192°).

Anal. Calcd. for $C_{18}H_{15}AsO$: C, 67.1; H, 4.7; As, 23.3. Found: C, 66.5; H, 5.1; As, 22.8.

Reaction of IIIe with carbonyl compounds. A standard procedure was used in all reactions. To a solution of 0.47 g. (1.0 mmol.) of ylid (IIIe) in 20 cc. of chloroform was added 1.0 mmol. of carbonyl compound. After heating under reflux for 3 hr. the solvent was evaporated on a steam bath. The residue was taken up in benzene and chromatographed on 10 g. of alumina. The individual fractions were purified further by recrystallization.

A. Benzaldehyde (0.11 g.) and IIIe were treated as described. Elution with 50% benzene-hexane solution afforded 0.19 g. (74%) of benzalfluorene (IVa) which was recrystallized from 80% ethanol-water as pale yellow needles, m.p. 73–75°, undepressed on admixture with an authentic sample (lit.[20] m.p. 76°). Elution with methanol afforded 0.10 g. (37%) of triphenylarsine oxide (V) which crystallized from water as colorless microcrystals, m.p. 192–194°, undepressed on admixture with an authentic sample.

B. *p*-Nitrobenzaldehyde (0.15 g.) was treated with IIIe as described. Elution with benzene afforded 0.28 g. (92%) of *p*-nitrobenzalfluorene (IVb) which crystallized from ethanol as fine yellow needles, m.p. 167–168°, undepressed admixture with an authentic sample (lit.[21] m.p. 167°). Elution with methanol afforded 0.07 g. (26%) of triphenylarsine oxide (V). It crystallized from water as colorless needles, m.p. 191–193°, undepressed on admixture with an authentic sample.

C. *p*-Chlorobenzaldehyde (0.14 g.) and IIIe were treated as described. Elution with benzene afforded 0.28 g. (98%) of *p*-chlorobenzalfluorene (IVc) which crystallized from ethanol as pale yellow microcrystals, m.p. 147–148° (lit.[22] m.p. 149°).

Anal. Calcd. for $C_{20}H_{13}Cl$: C, 83.2; H, 4.5; Cl, 12.3. Found: C, 82.9; H, 4.7; Cl, 11.8.

Elution with methanol afforded 0.32 g. (98%) of triphenylarsine oxide (V) which crystallized from water as colorless needles, m.p. 190–192°, undepressed on admixture with an authentic sample.

D. *p*-Anisaldehyde (0.14 g.) and IIIe were treated as described. Elution with benzene afforded 0.16 g. (89%) of *p*-anisalfluorene (IVd) which crystallized from ethanol as pale yellow plates, m.p. 130.5–132.5°, undepressed on admixture with an authentic sample (lit.[23] m.p. 128–129°). Elution with methanol afforded 0.13 g. (65%) of triphenyl-

(18) Melting points are uncorrected. Analyses by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y. Ultraviolet spectra were recorded by a Cary model 14 spectrophotometer. All chromatograms were run on Merck alumina, No. 71707.

(19) M. P. Pascal, *Bull. Soc. Chim.*, [4], **33**, 171 (1923).

(20) J. Thiele, *Ber.*, **33**, 851 (1900).

(21) E. D. Bergmann *et al.*, *Bull. Soc. Chim.*, **19**, 705 (1952).

(22) A. Sieglitz, *Ber.*, **52**, 1513 (1919).

(23) J. Thiele and F. Henle, *Ann.*, **347**, 290 (1906).

arsine oxide (V) which crystallized from water as colorless needles m.p. 186–188°, undepressed on admixture with an authentic sample.

E. *p*-Dimethylaminobenzaldehyde (0.15 g.) and IIIe were treated as described. Elution with 50% benzene-chloroform afforded 0.29 g. (97%) of *p*-dimethylaminobenzalfluorene (IVe) which crystallized from ethanol as yellow microcrystals, m.p. 135–135.5° (lit.[21] m.p. 135–136°).

Anal. Calcd. for $C_{22}H_{19}N$: C, 88.8; H, 6.5; N, 4.7. Found: C, 88.6; H, 6.7; N, 4.6.

Elution with methanol afforded 0.16 g. (51%) of triphenylarsine oxide (V) which crystallized from water as colorless needles, m.p. 190–192°, undepressed on admixture with an authentic sample.

F. Acetaldehyde (0.30 g.) and IIIe were dissolved in 20 ml. of chloroform and the solution was heated in a sealed tube for 3 hr. The usual workup followed. Elution with benzene afforded 0.26 g. (91%) of 9-ethylidenefluorene (IVh) which crystallized from ethanol-water as colorless needles, m.p. 102–104°, undepressed an admixture with an authentic sample (lit.[24] m.p. 104°). Elution with methanol afforded 0.37 g. (78%) of triphenylarsine oxide (V) which crystallized from water as colorless needles, m.p. 191–194°, undepressed an admixture with an authentic sample.

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(24) F. Mayer, *Ber.*, 46, 2579 (1913).

[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, INDIAN INSTITUTE OF SCIENCE]

Synthesis of Cyclohexylideneacetaldehyde and 2-, 3- and 4-Methylcyclohexylideneacetaldehyde

M. C. CHACO AND B. H. IYER

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Cyclohexanone and 2-, 3- and 4-methylcyclohexanones have been condensed with acetylene to give the respective 1-ethinylcyclohexanols. The 1-ethinylcyclohexanols were hydrogenated to the respective 1-vinyl- and 1-ethylcyclohexanols. The 1-vinylcyclohexanols have been treated with phosphorus tribromide to give the corresponding rearranged β-cyclohexylidenethyl bromides which have been converted to the pyridinium salts. The latter were treated with *p*-nitrosodimethylaniline and alkali (Krohnke's method) to give the corresponding nitrones which were hydrolyzed to the corresponding aldehydes. The 1-ethinyl-, 1-vinyl- and 1-ethylcyclohexanols prepared were subjected to pharmacological tests.

In attempts to extend the application of Krohnke's method of synthesis of aldehydes[1] to the preparation of α,β-unsaturated aldehydes in the aliphatic and alicyclic series, the reaction conditions were first studied using cinnamyl bromide and geranyl bromide.[2] The optimum conditions thus obtained have been used for the preparation of cyclohexylideneacetaldehyde and 2-, 3- and 4-methylcyclohexylideneacetaldehydes.[3]

Cyclohexylideneacetaldehyde has been prepared by other workers by chromic acid oxidation of β-cyclohexylideneethanol (Dimroth[4]) and from 1-allylcyclohexanol by ozonization (Aldersley *et al.*,[5] Braude and Wheeler[6]). Braude and Wheeler[6] describe its preparation from cyclohexanone by the ethoxyacetylene method. These workers prepared 2-methylcyclohexylideneacetaldehyde by similar methods.[6 cf. 7-9]

The cyclohexanones (cyclohexanone, 2-methylcyclohexanone, 3-methylcyclohexanone, and 4-methylcyclohexanone) were first condensed with acetylene in the presence of sodium acetylide in liquid ammonia to give the corresponding 1-ethinylcyclohexanols. The three methyl 1-ethinylcyclohexanols can exist in *cis* and *trans* forms. Two forms (solid and liquid) of both 2- and 4-methyl-1-ethinylcyclohexanols have been reported.[10–13] In the present study these carbinols also have been separated into solid and liquid forms. Rupe and co-worker[14] prepared solid (m.p. 47.5°) and liquid forms of optically active 3-methyl-1-ethinylcyclohexanol. Following their procedure the

(1) F. Krohnke and E. Borner, *Ber.*, 69, 2006 (1936); F. Krohnke, *Angew. Chem.*, 65, 612 (1953).

(2) M. C. Chaco and B. H. Iyer, *J. Indian Inst. Sci.*, 36, No. 3, 160 (1954). (Part of the work is in press).

(3) The work is outlined in preliminary communications, *Chem. & Ind. (London)*, 155 (1956); *Curr. Sci. (India)*, 22, 240 (1953).

(4) K. Dimroth, *Ber.*, 71, 1333 (1938).

(5) J. B. Aldersley and G. N. Burkhardt, *J. Chem. Soc.*, 545 (1938); J. B. Aldersley, G. N. Burkhardt, A. E. Gillam, and N. C. Hindley, *J. Chem. Soc.*, 10 (1940).

(6) E. A. Braude and D. H. Wheeler, *J. Chem. Soc.*, 320 (1955).

(7) H. Rupe and E. Kambli, *Helv. Chim. Acta*, 9, 672 (1926); H. Rupe, W. Messner, and E. Kambli, *Helv. Chim. Acta*, 11, 449 (1928).

(8) F. G. Fisher and K. Lowenberg, *Ann.*, 475, 203 (1929); C. D. Hurd and R. E. Christ, *J. Am. Chem. Soc.*, 59, 118 (1937).

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(10) W. Shiuh and M. Hu, *J. Chinese Chem. Soc.*, 10, 1 (1943); [*Chem. Abstr.*, 39, 1394 (1945)].

(11) N. A. Milas, N. S. MacDonald, and D. M. Black, *J. Am. Chem. Soc.*, 70, 1829 (1948); Ian Heilbron, E. R. H. Jones, D. G. Lewis, and B. C. L. Weedon, *J. Chem. Soc.*, 2023 (1949); G. Stork, S. S. Wagle, and P. C. Mukharji, *J. Am. Chem. Soc.*, 75, 3197 (1953).

(12) J. D. Billimoria, *Nature*, 170, 248 (1952); *J. Chem. Soc.*, 2626 (1953).

(13) J. D. Billimoria and N. F. Maclagan, *J. Chem. Soc.*, 3257 (1954).

(14) H. Rupe and E. Kambli, *Ann.*, 459, 195 (1927).

optically inactive 3-methyl-1-ethinylcyclohexanol prepared here was separated into solid (m.p. 23–25°) and liquid forms. These probably correspond to two stereoisomers.

The ethinylcarbinols were hydrogenated to vinyl- and ethylcarbinols. For partial hydrogenation palladium–calcium carbonate catalyst was used initially, and later Lindlar's catalyst,[15] the latter proving to be excellent in such cases. For complete hydrogenation palladium-calcium carbonate was used.

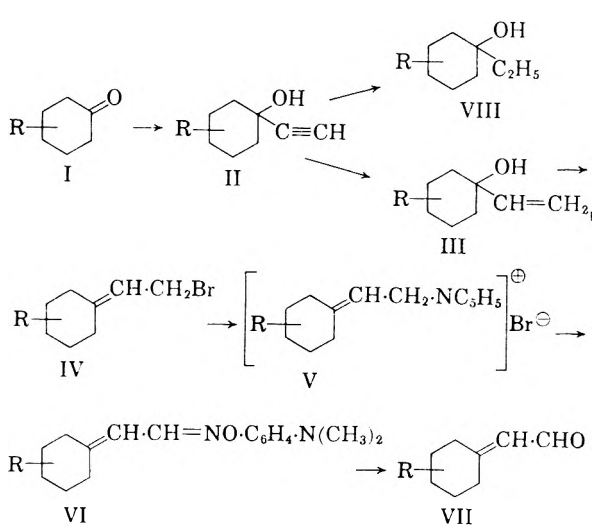
The vinylcarbinols were treated with phosphorus tribromide to give the corresponding rearranged cyclohexylideneethyl bromides. The unsaturated bromides are unstable at high temperatures and should be distilled using as low a temperature as possible. They may be used for the next step without distillation.

The bromides were converted to the pyridinium salts by mixing with absolute pyridine. Of the four pyridinium bromides, 3- and 4-methylcyclohexylideneethylpyridinium bromides were obtained in crystalline form; the others remained pasty.

The pyridinium bromides were treated with *p*-nitrosodimethylaniline and alkali to give the respective nitrones. Of the four nitrones only 2-methylcyclohexylidenemethyl-*N*-(*p*-dimethylaminophenyl)-nitrone was obtained in solid form; the others separated as a dark smeary mass which was not purified further. To obtain the aldehyde, benzene was used as the main solvent, as described in the Experimental section, and the benzene layer containing the nitrone was washed finally with dilute hydrochloric acid to hydrolyze the nitrone. When, in one case, methanol was used as solvent in the place of benzene, the yield of aldehyde was low. The aldehydes were characterized by both semicarbazone and 2,4-dinitrophenylhydrazone derivatives and their ultraviolet absorption spectra.

The yields of the aldehydes from the pyridinium bromides were generally 45–50%. The low yields may be due to the formation of appreciable amounts of cyclohexenylethyl bromides during the reaction of 1-vinylcyclohexanols with phosphorus bromide, which involves an allylic rearrangement. The tendency for the formation of a cyclic double bond in the cyclohexane ring is known.[16] Shifting of the double bond to the ring can take place at a later stage also. If cyclohexenylethylbromide is formed, it will also form the pyridinium salt which will then be present along with cyclohexylideneethylpyridinium bromide. However, bromides which are not activated by proximate activating groups are not known to react with *p*-nitrosodimethylaniline and alkali under the experimental conditions used to produce the respective nitrones. Therefore, although the over-all yield may be affected, it is unlikely that β,γ-unsaturated aldehydes arising from cyclohexenylethyl bromides are present along with α,β-unsaturated aldehydes. The ultraviolet absorption data afford evidence for the absence of any appreciable amount of the unconjugated isomer.

Pharmacology of 1-ethinyl-, 1-vinyl- and 1-ethylcyclohexanols and their monomethyl homologs. The announcement of the hypnotic activity of highly unsaturated carbinols by Papa and coworkers[17] stimulated interest in a systematic study of the group of the above-mentioned cyclohexanols to evaluate their hypnotic and anesthetic effects. It was thought further that the studies might throw some light on structure-activity relationship such as the effects of *cis-trans* isomerism, degree of unsaturation and variation of the position of the methyl group in the cyclohexane ring. Pharmacological experiments by M. Sirsi and P. Suryanarayanamurty[18] have shown that the activity of the vinyl- and ethylcarbinols is negligible compared with that of their parent ethinylcarbinols. This is in conformity with the observations of Papa *et al.*[19,20] It is interesting to note that (sol.)[21] -2-methyl-1-ethinyl-cyclohexanol showed the least toxicity of the ethinylcarbinols.



Ia to VIIa. R = H
Ib to VIIb. R = CH_3 in 2- position
Ic to VIIc. R = CH_3 in 3- position
Id to VIId. R = CH_3 in 4- position

(15) H. Lindlar, *Helv. Chim. Acta*, **35**, 446 (1952).

(16) G. A. R. Kon, *J. Chem. Soc.*, 248 (1931); G. A. R. Kon and R. S. Thakur, *J. Chem. Soc.*, 2217 (1930); H. C. Brown, *J. Org. Chem.*, **22**, 439 (1957).

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(18) M. Sirsi and P. Suryanarayanamurty, *J. Indian Inst. Sci.*, **37**, No. 4, 276 (1955).

(19) D. Papa, F. J. Villani, and H. F. Ginsberg, *J. Am. Chem. Soc.*, **76**, 4446 (1954).

(20) Cf. S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Chem. Soc.*, **77**, 4874 (1955).

(21) For convenience the solid isomers of the ethinyl carbinols and all the compounds obtained from them are prefixed (sol.) and the liquid forms and the compounds from them correspondingly (liq.).

EXPERIMENTAL

Absorption spectra were taken in 95% ethanol. Melting points are uncorrected.

1-Ethinylcyclohexanols (IIa, IIb, IIc, *and* IId). Cyclohexanone and 2-, 3- and 4-methylcyclohexanones were condensed with acetylene in liquid ammonia in the presence of sodium acetylide adopting the procedure described by earlier workers.[11] Cyclohexanone (1 mol.) in absolute ether (150 cc.) was added during 30 min. to a suspension of sodium acetylide, prepared from sodium (1.1 mol.) using ferric nitrate (0.5 g.) as catalyst in liquid ammonia (1 l.), while the mixture was stirred under a continuous stream of acetylene. Stirring and introduction of acetylene were continued for an additional period of 4 hr. A further 500 cc. of liquid ammonia was added to make up the loss due to evaporation. The reaction mixture was kept overnight at which time the ammonia was allowed to evaporate. The reaction product was worked up with water and ether; the ether layer was washed successively with 2*N* sulfuric acid, sodium bisulfite solution, and sodium bicarbonate solution, dried over anhydrous potassium carbonate, and distilled through a column. By similar experiments 2-, 3- and 4-methyl-1-ethinylcyclohexanols (IIb, IIc, and IId) were prepared. The yields and boiling points of the respective carbinols are given in Table I.

TABLE I

-ETHINYL- AND 2-, 3- AND 4-METHYL-1-ETHINYLCYCLOHEXANOLS

Carbinol	B.P., °C.	Pressure, mm.	Yield, %
1-Ethinylcyclohexanol (IIa)	86–88	26	75.2
2-Methyl-1-ethinylcyclohexanol (IIb)	98–102	44	92
3-Methyl-1-ethinylcyclohexanol[13,19] (IIc)	79–82	10	76
4-Methyl-1-ethinylcyclohexanol[13,19] (IId)	76–80	10	76.5

forms) were redistilled. The physical constants and the analytical data obtained for the ethinylcarbinols and the 3,5-dinitrobenzoates of the carbinols are given in Table II. All the 3,5-dinitrobenzoates crystallized in white flakes from petroleum ether.

1-Vinylcyclohexanols.[19] (IIIa, IIIb, IIIc, and IIId). 1-Ethinylcyclohexanol (30 g.) was shaken with hydrogen in the presence of palladium–calcium carbonate catalyst (2 g.) in ethanol (160 cc.) until the calculated volume of hydrogen (6.8 l.) was absorbed. The catalyst was filtered off, solvent removed, and the residue distilled to give 1-vinylcyclohexanol (26 g.). In a similar way (sol.) and (liq.) forms of 2- and 3-methyl-1-vinylcyclohexanols were prepared from the respective (sol.) and (liq.) 2- and 3-methyl-1-ethinylcyclohexanols.

For the preparation of (sol.) and (liq.) 4-methyl-1-vinylcyclohexanols, palladium-lead–calcium carbonate catalyst[15] was used. (Liq.)-4-Methyl-1-ethinylcyclohexanol (20 g.) in petroleum ether was hydrogenated over palladium-lead–calcium carbonate (2 g.) in the presence of quinoline (1 cc.). Absorption stopped almost completely when 4.1 l. (4.01:1 mol.) of hydrogen was taken up. The catalyst was filtered off, the filtrate washed with dilute hydrochloric acid, sodium bicarbonate solution, and water, dried over anhydrous sodium sulfate, and distilled to get (liq.) 4-methyl-1-vinylcyclohexanol (17 g.). The physical constants and analytical data obtained for the vinylcarbinols and the 3,5-dinitrobenzoates (all crystallized in white flakes from petroleum ether) of the respective carbinols are given in Table III.

1-Ethylcyclohexanols (VIIIa, VIIIb, VIIIc, *and* VIIId). 1-Ethinylcyclohexanol (4 g.) was shaken with hydrogen in the presence of palladium–calcium carbonate catalyst (0.25 g.) in ethanol until it ceased to absorb hydrogen. The catalyst was filtered off, solvent removed and the residue distilled to give 1-ethylcyclohexanol (3.25 g.) Similarly the (sol.) and (liq.) forms of 2-, 3- and 4-methyl-1-ethylcyclohexanols were prepared from the respective (sol.) and (liq.) methyl 1-ethinylcyclohexanols. The properties and the analytical data of the carbinols and the 3,5-dinitrobenzoates (white flakes from petroleum ether) of the respective carbinols are given in Table IV.

TABLE II

ETHINYLCARBINOLS AND THEIR 3,5-DINITROBENZOATES

Carbinol No.[a]	Data for Carbinol, $C_9H_{14}O$							Data for $C_{16}H_{16}N_2O_6$ 3,5-Dinitro- benzoate[b]		
	M.P., °C.	B.P., °C.	Pressure, mm.	Carbon, %		Hydrogen, %		M.P., °C.	Nitrogen, %	
				Calcd.	Found	Calcd.	Found		Calcd.	Found
1. (Sol.) IIb	60[c]	—	—	—	—	—	—	101[d]	8.43	8.52
2. (Liq.) IIb		84–85	7.5	78.25	78.11	10.14	10.1		8.43	8.52
3. (Sol.) IIc	23–25	82	10	78.25	78.23	10.14	10.11	113–115	8.43	8.12
4. (Liq.) IIc		82	10	78.25	78.36	10.14	10.13	—	8.43	—
5. (Sol.) IId	43[e]	84	10	78.25	78.21	10.14	10.15	147–148	8.43	8.48
6. (Liq.) IId		83–84	10	78.25	78.17	10.14	10.21	—	8.43	—

[a] (1) (Sol.)-2-Methyl-1-ethinylcyclohexanol. (2) (liq.)-2-Methyl-1-ethinylcyclohexanol. (3) (sol.) 3-Methyl-1-ethinylcyclohexanol. (4) (liq.)-3-Methyl-1-ethinylcyclohexanol. (5) (sol.)-4-Methyl-1-ethinylcyclohexanol. (6) (liq.)-4-Methyl-1-ethinylcyclohexanol. [b] The 3,5-dinitrobenzoates of (sol.) and (liq.) 2-methyl-1-ethinylcyclohexanols were prepared separately; but on repeated recrystallizations both melted at the same temperature with no depression in mixed melting point, showing their identity. Similar results were obtained in the case of the 3- and 4-methyl-1-ethinylcyclohexanols. [c] *Cf.* References 10, 11, and 12. [d] Cook and Lawrence[22] prepared the 3,5-dinitrobenzoate from 2-methyl-1-ethinylcyclohexanol without separating into solid and liquid forms, reported m.p. 76.5–79°. [e] Billimoria reports m.p. 36°.[13]

2-, 3- and 4-Methyl-1-ethinylcyclohexanols were chilled by an ice-salt mixture and filtered through a funnel kept well cooled by ice water. The residues were crystallized from petroleum ether (b.p. 30–60°). The filtrates (liquid

Cyclohexylideneethylbromides (IVa, IVb, IVc, *and* IVd). To 1-vinylcyclohexanol (16 g.) containing anhydrous pyridine (1 g.) in anhydrous petroleum ether, b.p. 40–60°, (30 cc.) was added phosphorus tribromide (20 g.) very slowly and carefully under efficient cooling and stirring. After being kept for 16 hr. at room temperature, the reaction mixture was decomposed with ice cold water and extracted with

(22) J. W. Cook and C. A. Lawrence, *J. Chem. Soc.*, 58 (1938).

TABLE III

VINYLCARBINOLS, AND THEIR 3,5-DINITROBENZOATES

Carbinol No.[a]	Data for Carbinol: B.P., °C.	Pressure, mm.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Data for 3,5-dinitrobenzoates, $C_{16}H_{18}N_2O_6$: M.P., °C.	Nitrogen, % Calcd.	Nitrogen, % Found
1. IIIa[b]	77–80	25							
2. (Sol.) IIIb[d]	49	0.5–1					104–105[c]	8.38	8.60
3. (Liq.) IIIb[d]	72–74	11.5	77.14	76.66	11.43	11.4		8.38	
4. (Sol.) IIIc[d]	51	1	77.14	77.2	11.43	11.34	91–92	8.38	8.48
5. (Liq.) IIIc[d]	61	3	77.14	77.06	11.43	11.45		8.38	
6. (Sol.) III[d]	54	1.5	77.14	77.18	11.43	11.37	111	8.38	8.42
7. (Liq.) IIId[d]	49	0.5–1	77.14	77.1	11.43	11.36		8.38	

[a] (1) 1-Vinylcyclohexanol,[4] (2) (sol.)-2-methyl-1-vinylcyclohexanol, (3) (liq.)-2-Methyl-1-vinylcyclohexanol,[12] (4) (sol.)-3-Methyl-1-vinylcyclohexanol, (5) (liq.)-3-Methyl-1-vinylcyclohexanol, (6) (sol.)-4-Methyl-1-vinylcyclohexanol, (7) (liq.)-4-Methyl-1-vinylcyclohexanol. [b] Formula: $C_8H_{14}O$. [c] Cook and Lawrence[22] prepared the 3,5-dinitrobenzoate of 2-methyl-1-vinylcyclohexanol without separating into (sol.) and (liq.) forms, reported m.p. 120–120.5°. [d] Formula: $C_9H_{16}O$.

TABLE IV

ETHYLCARBINOLS, AND THEIR 3,5-DINITROBENZOATES

No.[a] Carbinol	Data for Carbinol: M.P., °C.	B.P., °C.	Pressure, mm.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Data for 3,5-Dinitrobenzoates, $C_{16}H_{20}N_2O_6$: M.P., °C.	Nitrogen, % Calcd.	Nitrogen, % Found
1. VIIIa		81.5	2							
2. (Sol.) VIIIb[b]		94	23	76.05	76.7	12.68	12.51	138[c]	8.34	8.19
3. (Liq.) VIIIb[b]		91–92	24.5	76.05	76.00	12.68	12.60	—	8.34	
4. (Sol.) VIIIc[b]		66	3.5	76.05	76.09	12.68	12.60	91–92	8.34	8.33
5. (Liq.) VIIIc[b]		83–85	15	76.05	76.1	12.68	12.43		8.34	
6. (Sol.) VIIId[b]	30	64	3	76.05	76.02	12.68	12.60	114.5	8.34	8.21
7. (Liq.) VIIId[b]		53	1.5–2	76.05	75.67	12.68	12.66		8.34	

[a] (1) 1-Ethylcyclohexanol, (2) (sol.) 2-Methyl-1-ethylcyclohexanol, (3) (liq.)-2-Methyl-1-ethylcyclohexanol, (4) (sol.)-3-Methyl-1-ethylcyclohexanol, (5) (liq.)-3-Methyl-1-ethylcyclohexanol, (6) (sol.)-4-methyl-1-ethylcyclohexanol, (7) (liq.)-4-Methyl-1-cyelohexanol. [b] Formula: $C_9H_{18}O$. [c] Cook and Lawrence[22] prepared the 3,5-dinitrobenzoate of 2-methyl-1-ethylcyclohexanol without separating into (sol.)- and (liq.)- forms, reported m.p. 105.5–107.5°.

more petroleum ether. The petroleum ether extract was washed free of acid with saturated salt solution and finally with very dilute sodium bicarbonate solution, and water, dried over anhydrous sodium sulfate, and the solvent removed under vacuum and distilled to give β-cyclohexylideneethylbromide (15 g.). By a similar procedure 2-, 3-, and 4-methylcyclohexylideneethyl bromides (IVb, IVc, and IVd) were prepared from the respective (liq.)-1-vinylcyclohexanols. The boiling points and yields of the unsaturated bromides are given in Table V. The bromides were used for the next step immediately after distillation.

Cyclohexylideneethylpyridinium bromides (Va, Vb, Vc, *and Vd*). β-Cyclohexylideneethyl bromide (IVa) (7.9 g.) was mixed with anhydrous pyridine (38 cc.) and kept well stoppered. After 24 hr. the excess pyridine was removed under vacuum and the residue was repeatedly washed with anhydrous petroleum ether. The semisolid residue was dried under high vacuum at 50°, yield 8.78 g.

TABLE V

CYCLOHEXYLIDENEETHYL BROMIDES

Unsaturated Bromide	B.P., °C.	Yield, %
β-Cyclohexylidenethyl bromide[a] (IVa)	78–83°/11 mm.	66
2-Methyl-β-cyclohexylideneethyl bromide (IVb)	70–75°/2.5 mm.	72
3-Methyl-β-cyclohexylideneethyl bromide (IVc)	70–75°/4 mm.	77.6
4-Methyl-β-cyclohexylideneethyl (IVd)	66–72°/ 3.5 mm.	68.6

[a] See footnote 4.

2-, 3- and 4-Methyl-β-cyclohexylideneethylpyridinium bromides (Vb, Vc, and Vd) were prepared in a similar way. Of these, the latter two pyridinium bromides were obtained in crystalline form; the melting points were determined in sealed tubes. The pyridinium bromides are deliquescent. The melting points, yields, and analytical values for bromine of the pyridinium bromides are given in Table VI.

2-Methylcyclohexylidenemethyl-N-(p-dimethylaminophenyl)-nitrone (VIb). 2-Methyl-β-cyclohexylideneethylpyridinium bromide (Vb) (8.9 g.) in methanol (15 cc.) cooled to 0° was mixed with a cooled solution of *p*-nitrosodimethylaniline (6.2 g.) in methanol (80 cc.). To this 1*N* sodium hydroxide (37 cc.) at 0° was added. The reaction mixture was shaken and kept in the refrigerator. After 16 hr. ice cold distilled water (150 cc.) was added; the mixture was shaken and chilled 24 hr. longer. Dark brown needles separated along with some dark resinous material. The solid material was filtered off, dissolved in a little methanol, and diluted with water. A yellow solid precipitated and was removed by filtration (2.8 g.). It was crystallized repeatedly from ethyl acetate and petroleum ether–ethyl acetate to give yellow needles melting at 67–68°.

Anal. Calcd. for $C_{17}H_{24}N_2O$: N, 10.29. Found: N, 10.28. When similar experiments were carried out with the other pyridinium bromides (Va, Vc, and Vd), the nitrones separated as dark smeary liquids which did not solidify even after prolonged refrigeration. Therefore they were not isolated.

TABLE VI

PYRIDINIUM BROMIDES

Pyridinium Salt	M.P., °C.	Yield, %	Formula	Bromine, % Calcd.	Bromine, % Found
β-Cyclohexylideneethylpyridinium bromide (Va)		77.8	$C_{13}H_{18}NBr$	29.82	29.45
2-Methyl-β-cyclohexylideneethylpyridinium bromide (Vb)		76.5	$C_{14}H_{20}NBr$	28.31	29.87
3-Methyl-β-cyclohexylideneethylpyridinium bromide (Vc)	80–85	92.4	$C_{14}H_{20}NBr$	28.31	28.96
4-Methyl-β-cyclohexylideneethylpyridinium bromide (Vd)	60–62	86.5	$C_{14}H_{20}NBr$	28.31	29.45

TABLE VII

CYCLOHEXYLIDENEACETALDEHYDES

Aldehyde	Yield, %, from the Corresp. Pyridinium Bromide	B.P., °C.	Pressure, mm.	n_D	Temp., °C.	λ_{max},[a] mμ	ε	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	References
VIIa	47.3	88	11.5	1.5032[b]	32	241	16810	$C_8H_{12}O$	77.38	77.09	9.74	9.38	4,5,9,6
VIIb	48.8	78–80	3	1.4935[c]	25.5	241	16270	$C_9H_{14}O$	78.25	78.27	10.14	10.39	5,6
VIIc	46–8	75–77	4	1.4900[c]	25	241	18800	$C_9H_{14}O$	78.25	78.71	10.14	10.81	
VIId	50.2	68–70	1	1.4985[c]	25	240	18640	$C_9H_{14}O$	78.25	78.4	10.14	10.23	

[a] Ethanol. [b] 32°C. [c] 25°C.

TABLE VIII

CYCLOHEXYLIDENEACETALDEHYDE SEMICARBAZONES

Semicarbazone of	M.P. °C.	ε at λ_{max},[a] 273 mμ	Nitrogen, % Calcd.	Nitrogen, % Found
VIIa[4,5,9,6]	210	32200	23.2[b]	23.18
VIIb[5]	204	32500	21.54[c]	21.1
VIIc	192–193	32070	21.54[c]	21.86
VIId	198–200	31670	21.54[c]	21.06

[a] In ethanol. [b] Formula: $C_9H_{15}N_3O$. [c] $C_{10}H_{17}N_3O$.

tilled water, the aqueous layer separated and extracted with more benzene. The combined benzene extracts were washed with 2N hydrochloric acid until the aqueous layer was almost colorless, then with sodium bicarbonate solution and water, and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure the residue was distilled through a short column to give cyclohexylideneacetaldehyde (VIIa) (1.9 g.). A reddish brown residue was left.

Adopting similar procedures, 2-, 3- and 4-methylcyclohexylideneacetaldehydes (VIIb, VIIc, and VIId) were prepared. Middle cuts were analyzed. The yields, analytical

TABLE IX

CYCLOHEXYLIDENEACETALDEHYDE 2,4-DINITROPHENYLHYDRAZONES

2,4-Dinitrophenyl hydrazone of	M.P., °C.	λ_{max} mμ	ε	Nitrogen, % Calcd.	Nitrogen, % Found
VIIa[a,6]	201–202	256	16600	18.41[b]	18.65
(Red plates from ethanol)		290	9843		
		386	27450		
VIIb[a,6]	167–169	256	16530	17.61[c]	17.57
(Orange yellow plates from ethanol-chloroform mixture)		290	10600		
		386	28490		
VIIc[a]	158–159	256	16290	17.61[c]	17.04
(Orange red needles from ethanol)		290	10140		
		386	28030		
VIId[a]	177–178	256	17590	17.61[c]	17.8
(Orange plates from chloroform-benzene mixture)		290	10480		
		386	28180		

[a] Tables VII, VIII, and IX. (VIIa) Cyclohexylideneacetaldehyde, (VIIb) 2-Methylcyclohexylideneacetaldehyde, (VIIc) 3-Methylcyclohexylideneacetaldehyde, (VIId) 4-Methylcyclohexylideneacetaldehyde. [b] Formula: $C_{14}H_{16}N_4O_4$. [c] Formula: $C_{15}H_{18}N_4O_4$.

Cyclohexylideneacetaldehydes (VIIa, VIIb, VIIc, *and* VIId). Cyclohexylideneethylpyridinium bromide (Va) (8.7 g.) in methanol (15 cc.), cooled to 0° was mixed with a solution of *p*-nitrosodimethylaniline (10 g.) in methanol (20 cc.) and benzene (120 cc.) cooled below 10°. 1N sodium hydroxide (35 cc.), cooled below 0° was added with thorough shaking and cooling in ice-salt mixture, and the reaction mixture was refrigerated for 40 hr. with occasional thorough shaking. The reaction mixture was then diluted with dis-

values, and the physical constants of the aldehydes are given in Table VII, the semicarbazones in Table VIII, and the 2,4-dinitrophenylhydrazones in Table IX.

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BANGALORE 12, INDIA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Aromatic Cyclodehydration. XLV.[1] Benz[b]acridizinium Derivatives[2]

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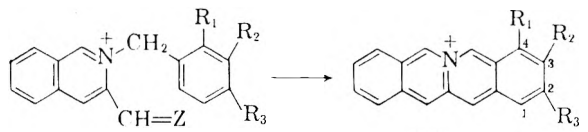
The method of aromatic cyclodehydration has been extended to the synthesis of alkoxybenz[b]acridizinium salts and to the synthesis of the dibenz[b,h] and dibenz[b,j]acridizinium systems.

Recently[1] the first synthesis of an interesting symmetrical cation, the benz[b]acridizinium ion (III) was described.



I. Z = NOH
II. Z = O

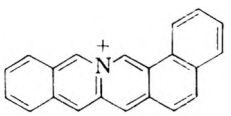
III
IV. $R_2 = OCH_3$
V. $R_1 = R_2 = OCH_3$
VI. $R_2 = R_3 = OCH_3$
VII. $R_2 = R_3 = OCH_2O$
(All group not otherwise indicated = H)

Our earliest attempts to synthesize this aromatic cation (III) were frustrated by the tendency of the ion to undergo dimerization under the conditions needed for the cyclization of 2-benzyl-3-formylisoquinolinium salts (II). While ultimately it was found[1] that 2-benzyl-3-aldoximinoisoquinolinium salts (I) cyclize fast enough to permit isolation of some of the desired benzacridizinium salt (III), it was observed that even 2-benzyl-3-formylisoquinolinium salts (II) may be cyclized if the benzyl group contains substituents which sufficiently enhance the rate of cyclization.

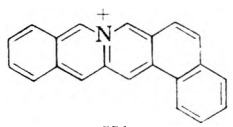
The present communication describes results obtained with alkoxybenzyl analogs[4] of II as well as with α- and β-naphthylmethyl bromides. Two of the quaternization reactions, one involving 3-methoxybenzyl bromide, and the other 3,4-dimethoxybenzyl bromide, yielded easily purified crystalline salts (II. $R_2 = OCH_3$ and $R_2 = R_3 = OCH_3$). This represents the first time that an aldehyde intermediate of this type has been obtained.

The 2-(3-methoxybenzyl)-3-formylisoquinolinium bromide salt (II. $R_2 = OCH_3$) was cyclized by allowing it to stand at room temperature for 2 hr. in concentrated hydrobromic acid, while the other quaternary intermediates were cyclized by heating in hydrochloric acid for 5–15 min. None of the cyclizations appeared to be accompanied by dimerization under these conditions. The alkoxybenz[b]acridizinium bromides are red-orange crystalline solids without well defined melting points, and are only sparingly soluble in water. Solution of these compounds are highly fluorescent.

By the use of 1-bromomethyl- and 2-bromomethylnaphthalene the previously unknown dibenz[b,h]- and dibenz[b,j]acridizinium ions [VIII and IX) were prepared in 43% and 66% over-all yields. These orange salts, possibly because of the



VIII



IX

operation of steric factors, show a remarkable resistance to thermal dimerization. No dimer formation was observed although refluxing periods as long as 6 hr. were used.

EXPERIMENTAL[5]

Spectroscopy. All visible and ultraviolet spectra were determined in 95% ethanol solution, using the Warren Spectracord recording spectrophotometer and 1-cm. matched silica cells.

2-(3-Methoxybenzyl)-3-formylisoquinolinium bromide (II. $R_2 = OCH_3$). A solution of 0.78 g. of isoquinoline-3-carboxaldehyde[6] and 1.0 g. of *m*-methoxybenzyl bromide[7] in 1.0 ml. of dimethylformamide was allowed to stand at room temperature for 48 hr. The reaction mixture, containing a pale yellow solid, was triturated with ethyl acetate until crystallization was complete. The product, suitable for cyclization, was collected and dried *in vacuo*, yield 1.40 g. (78%), m.p. 140–145° dec. The analytical sample crystallized from acetonitrile as colorless microscopic plates, m.p. 165–166° dec.

Anal. Calcd. for $C_{18}H_{16}BrNO_2$: C, 60.33; H, 4.50; N, 3.91. Found: C, 60.44; H, 4.62; N, 3.59.

3-Methoxybenz[b]acridizinium bromide (IV). The cyclization of 750 mg. of the crude bromide (II. $R_2 = OCH_3$) in 6 ml. of 48% hydrobromic acid was carried out at room temperature for 2 hr. The reaction mixture was diluted with 20 ml. of water and cooled in ice. The product, consisting of

(1) For the preceding communication of this series, see *J. Am. Chem. Soc.*, in press.

(2) This investigation was supported by research grants (NSF-G2364 and G6215) from the National Science Foundation.

(3) Taken from part of a thesis submitted by T. W. G. Solomons in partial fulfillment of the requirements for the Ph.D. Degree, Duke University, Du Pont Teaching Fellow, 1958–59.

(4) C. K. Bradsher and J. H. Jones, *J. Am. Chem. Soc.*, **79**, 6033 (1957).

(5) All melting points were taken in sealed capillary tubes and are not corrected. In most cases the capillary was inserted into a preheated block to minimize preliminary decomposition. Except where noted otherwise analyses were done by Dr. I. A. Schoeller, Kronach, West Germany.

(6) C. E. Teague and A. Roe, *J. Am. Chem. Soc.*, **73**, 689 (1951).

(7) E. Späth, *Monatsh.*, **34**, 1965 (1913).

orange-red clusters of blunt needles, was separated and dried, yield 540 mg. (76%). When this material, in a sealed capillary, was inserted into a block preheated to 200° it decomposed slowly from 235° with no defined melting point. Recrystallization from methanol–ethyl acetate did not change the melting behavior. λ_{max} (log ϵ): 264 (4.53), 285 (4.60), 338 (4.23), 400 (3.95), 423 (4.37) λ_{min}: 228 (4.15), 269 (4.48), 325 (4.19), 384 (3.50), 407 mμ (3.87).

Anal. Calcd. for $C_{18}H_{14}BrNO \cdot {}^1/_2H_2O$: C, 61.90; H, 4.33; N, 4.02. Found: C, 62.03; H, 4.40; N, 4.12.

The *picrate* was prepared from methanol as a red-orange powder, m.p. 271–272° dec.

Anal. Calcd. for $C_{24}H_{16}N_4O_8$: C, 59.02; H, 3.30; N, 11.5. Found:[8] C, 58.61; H, 3.61; N, 11.7.

3,4-Dimethoxybenz[b]acridizinium picrate (V). Isoquinoline-3-carboxaldehyde (0.78 g.) was quaternized by 2,3-dimethoxybenzyl bromide[9] (1.16 g.) by refluxing in absolute methanol (10 ml.) for 4 hr. Concentrated hydrochloric acid (10 ml.) was added and the solution refluxed 6 min. longer The acid and alcohol were removed *in vacuo* to leave a deep red oil which was taken up in alcohol and the picrate prepared, yield 0.90 g. (29%) of a red amorphous solid, m.p. 165–170°.

The analytical sample crystallized from acetonitrile as violet needles, m.p. 192–193°. λ_{max} (log ϵ): 280 (4.68), 355 (4.48), 413 (4.12), 436 (4.31); λ_{min}: 230 (4.45), 315 (4.34), 400 (4.07), 420 mμ (4.11).

Anal. Calcd. for $C_{25}H_{18}N_4O_9$: C, 57.91; H, 3.50; N, 10.81. Found: C, 57.85; H, 3.47; N, 10.97.

2-(3,4-Dimethoxybenzyl)-3-formylisoquinolinium bromide (II. $R_2 = R_3 = OCH_3$). A solution of 1.41 g. of isoquinoline-3-carboxaldehyde and 2.26 g. of 3,4-dimethoxybenzyl bromide[10] in 1.0 ml. of dimethylformamide was allowed to stand at room temperature for 22 hr., then worked up in essentially the same way as for II. $R_2 = OCH_3$, yield 3.47 g. (quant.) m.p. 156–158°.

Anal. Calcd. for $C_{19}H_{18}BrNO_3 \cdot {}^3/_4H_2O$: C, 56.79; H, 4.86; N, 3.49. Found:[8] C, 56.79; H, 4.96; N, 3.35.

2,3-Dimethoxybenz[b]acridizinium chloride (VI). The cyclization of 1.5 g. of the crude bromide (II. $R_2 = R_3 = OCH_3$) was carried out by heating in 10 ml. of concentrated hydrochloric acid on a steam bath for 5 min. The reaction mixture was worked up in the same way as for IV, yield 1.0 g. (74%) of a solid which when heated in a sealed tube decomposed from 220° without a defined melting point.

To ensure anion consistency, a small sample of this material was dissolved in methanol and passed over a column of Amberlite IRA-410 ion exchange resin loaded with chloride ion. Evaporation of the methanol and crystallization from acetonitrile gave red needles with the same melting point behavior. λ_{max} (log ϵ): 257 (4.49), 304 (4.67), 400 (3.97), 423 (4.28), 456 (3.75), 485 (3.42). λ_{min}: 232 (4.15), 271 (4.32), 380 (3.59), 408 (3.94), 446 (3.72), 475 mμ (3.34).

Anal. Calcd. for $C_{19}H_{16}ClNO_2 \cdot {}^3/_2H_2O$: C, 64.68; H, 5.42; N, 3.97. Found:[8] C, 64.68; H, 5.06; N, 4.35.

The *picrate* formed red-orange plates from methanol, m.p. 302–303° dec.

Anal. Calcd. for $C_{25}H_{18}N_4O_9$: C, 57.9; H, 3.50; N, 10.8. Found[8]: C, 58.2; H, 3.71; N, 11.3.

The *perchlorate* was obtained as an orange-red powder from dilute methanol, m.p. 282–284° dec.

Anal. Calcd. for $C_{19}H_{16}ClNO_6 \cdot H_2O$: C, 55.96; H, 4.45. Found:[8] C, 55.99; H, 4.67.

2,3-Methylenedioxybenz[b]acridizinium chloride (VII). The quaternization of 1.57 g. of isoquinoline-3-carboxaldehyde by 2.16 g. of 3,4-methylenedioxybenzyl bromide[11] in 80% benzene-methanol solution (5 ml.) was effected by refluxing for 2.5 hr. The solvent was decanted from the crude salt that settled out and this material (presumed to be II, R_2, $R_3 = OCH_2O$) was cyclized in 25 ml. of concentrated hydrochloric acid by heating on a steam bath for 15 min. The reaction mixture was worked up in the same way as for VI to give 1.30 g. (39%) of an orange solid which decomposed gradually from 275° without a defined melting point. Passing a solution of this material over an ion exchange resin loaded with chloride ion gave on crystallization orange rectangular plates with the same melting point behavior. λ_{max} (log ϵ): 256 (4.52), 304 (4.62), 400 (3.84), 421 (4.13), 448 (3.71), 478 (3.42). λ_{min}: 270 (4.22), 378 (3.46), 407 (3.83), 440 (3.67), 465 mμ (3.31).

Anal. Calcd. for $C_{18}H_{12}ClNO_2 \cdot {}^4/_3H_2O$: C, 64.77; H, 4.43; N, 4.20. Found:[8] C, 64.66; H, 4.48; N, 4.23.

The *picrate* was prepared from methanol and crystallized from dimethylformamide as red-orange needles, m.p. 289–289.5° dec.

Anal. Calcd. for $C_{24}H_{14}N_4O_9$: C, 57.37; H, 2.81; N, 11.15. Found:[8] C, 57.38; H, 2.62; N, 11.28.

Dibenz[b,h]acridizinium bromide (VIII). Isoquinoline-3-carboxaldehyde (1.57 g.) was quaternized by 1-bromomethylnaphthalene (2.21 g.) by refluxing in absolute methanol for 4 hr. Most of the methanol was evaporated and the yellow oil that remained was cyclized in 48% hydrobromic acid by refluxing for 6 hr. The reaction mixture was worked up by diluting with water (25 ml.) and cooling to give 1.60 g. (43%) of an orange solid, m.p. 266.5–268° dec.

The analytical sample crystallized from methanol–ethyl acetate as orange prisms, m.p. 278–280° dec. λ_{max} (log ϵ): 243 (4.56), 294 (4.68), 305 (4.85), 346 (4.27), 404 (4.11), 426 (4.30), 464 (3.59). λ_{min}: 223 (4.40), 269 (4.36), 297 (4.67), 337 (4.22), 376 (3.67), 408 (4.11), 457 mμ (3.54).

Anal. Calcd. for $C_{21}H_{14}BrN \cdot {}^2/_3H_2O$: C, 67.76; H, 4.06; N, 3.75. Found:[8] C, 67.50; H, 3.92; N, 3.83.

The *picrate* was prepared from ethanol as an orange powder, m.p. 289–289.2° dec.

Anal. Calcd. for $C_{27}H_{16}N_4O_7$: C, 63.78; H, 3.17; N, 11.02. Found:[8] C, 64.00; H, 3.53; N, 11.15.

Dibenz[b,j]acridizinium bromide (IX). Quaternization of isoquinoline-3-carboxaldehyde (1.57 g.) by 2-bromomethylnaphthalene (2.42 g.) in dimethylformamide (2 ml.) was carried out at room temperature for 45 hr. The bright yellow gum which formed was washed with ethyl acetate then taken up in 15 ml. of 48% hydrobromic acid. The resulting solution was refluxed for 3 hr., cooled, and diluted with water to given an orange solid. Recrystallization from ethanol gave 2.60 g. (66%) of broad orange spears m.p. 228–231°.

The melting point of the analytical sample was not changed. λ_{max} (log ϵ): 256 (4.70), 287 (4.65), 345 (4.48), 360 (4.53), 410 (4.23), 433 (4.40), 462 (3.67). λ_{min}: 228 (4.46), 267 (4.45), 326 (4.31), 352 (4.45), 378 (3.76), 420 (4.18), 456 mμ (3.81).

Anal. Calcd. for $C_{21}H_{14}BrN \cdot 2H_2O$: C, 63.64; H, 4.58; N, 3.53. Found:[8] C, 63.44; H, 4.44; N, 3.25.

The *picrate* was prepared from ethanol and crystallized from dimethylformamide as long orange needles, m.p. 309–309.1° dec.

Anal. Calcd. for $C_{27}H_{16}N_4O_7$: C, 63.78; H, 3.17; N, 11.07. Found:[8] C, 63.75; H, 3.54; N, 11.25.

The *perchlorate* was prepared from dilute methanol as an orange powder, m.p. 258–260° dec.

Anal. Calcd. for $C_{21}H_{14}ClNO_4 \cdot {}^2/_3H_2O$: C, 64.38; H, 3.94; N, 3.58. Found:[8] C, 64.17; H, 3.95; N, 3.18.

DURHAM, N. C.

(8) Analysis by Drs. Weiller & Strauss, Oxford, England.

(9) R. D. Haworth and W. H. Perkin, Jr., *J. Chem. Soc.*, 1434 (1925).

(10) R. D. Haworth, W. H. Perkin, Jr., and J. Rankin, *J. Chem. Soc.*, **127**, 1455 (1925).

(11) G. M. Robinson and R. Robinson, *J. Chem. Soc.*, **105**, 1456 (1914).

[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

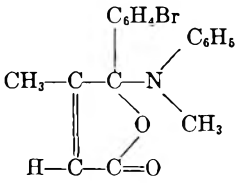
Acid-Catalyzed Rearrangements of the γ-(Methylanilino)lactone of *cis*-β-(*p*-Bromobenzoyl)-β-methylacrylic Acid, and of *trans*-β-(*p*-Bromobenzoyl)acrylic Methylanilide, to Oxindoles[1]

ROBERT E. LUTZ AND CARROLL T. CLARK[2,3]

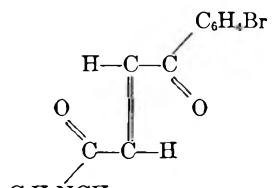
Received September 8, 1959

The structures of the acid-catalyzed rearrangement products of aroylacrylic "methylanilides" I and II to phenacyloxindoles III were shown by synthesis through condensations of *N*-methylisatin with appropriate aryl ketones followed by dehydrations and reductions. The properties and structures of the intermediate phenacylidineoxindoles are considered. A multistage rearrangement mechanism is proposed for formation of I, and a direct cyclization process for II.

In the study of acyclic and cyclic "amides" of β-(*p*-bromobenzoyl)-β-methylacrylic acid it had been observed that the action of hydrochloric acid–acetic acid mixture or methanolic hydrogen chloride on the cyclic "methylanilide" (the γ-methylanilinolactone, I), instead of hydrolyzing it, converted it into a new compound for which analysis appeared to support the empirical formula $C_{16}H_{16}BrNO$[4] but which also supports reasonably well that of an isomerization product $C_{18}H_{16}BrNO_2$.

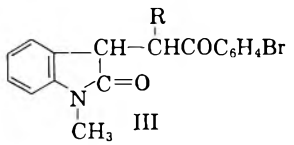


I



II

Similarly the *trans*-methylanilide of β-(*p*-bromobenzoyl)acrylic acid (II) was converted under acid conditions into an isomer, $C_{17}H_{18}NO_2$.[5] On the assumption that analogous isomerizations had actually occurred in both cases we have undertaken a study of these compounds and have established their structures as the *p*-bromophenacyloxindoles, III.

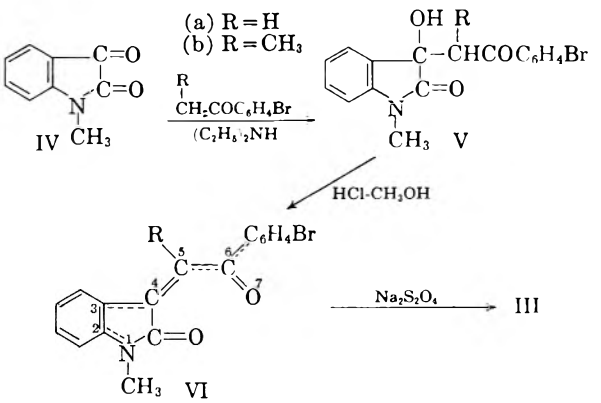


III

(a) R = H
(b) R = CH_3

Numerous attempts to hydrolyze or to reduce these compounds were without effect. Permanganate oxidation of one of them[5] to *p*-bromobenzoic acid had shown that the bromophenyl nucleus had not been involved. Ultraviolet and infrared absorption spectra were not immediately suggestive. Of the several types of structures that were empirically possible, only one, that of the oxindole III, fitted the facts and was consistent with the absorption characteristics of the compounds. The structures were then demonstrated by the following direct and unequivocal syntheses.

N-Methylisatin IV was condensed with *p*-bromoaceto- and propiophenones under mildly alkaline conditions, a procedure used successfully in other related cases.[6] The two resulting aldols V were then dehydrated by treatment with ethanolic hydrogen chloride to the unsaturated ketones VI. Reduction by sodium hydrosulfite converted these into the saturated phenacyl oxindoles III which showed no mixture melting point depressions with the rearrangement products of the two methylanilides, II and I, respectively.



IV V VI

One of the two intermediate unsaturated ketones, VIa, is red in color, and is assigned the *cis*-s-*cis* configuration and conformation (*cis* relative to the carbonyl groups) because examination of plane

(1) This work was carried out under a research contract with the Office of Ordnance Research, U. S. Army.

(2) Present location, University of Georgia, Athens, Ga.

(3) (a) C. T. Clark, dissertation, University of Virginia, 1958. (b) Reported (with R. E. Lutz) at the ACS Meeting, September 1959, Atlantic City, N. J., abstr. p. 14p. Since the abstract was submitted we have decided against formula VII in favor of VI. (c) Paper (with R. E. Lutz), *J. Org. Chem.*, in press.

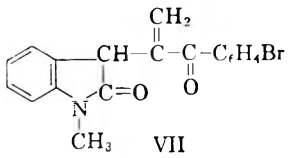
(4) R. E. Lutz and F. B. Hill, *J. Org. Chem.*, **6**, 175 (1941).

(5) R. E. Lutz and G. W. Scott, *J. Org. Chem.*, **13**, 284 (1948).

(6) (a) R. N. Dupois and H. G. Lindwell, *J. Am. Chem. Soc.*, **56**, 471, 2716 (1934). (b) H. G. Lindwell and J. S. Maclennan, *J. Am. Chem. Soc.*, **54**, 4739 (1932).

scalar drawings[3a,7] shows only this form to be almost devoid of atom overlaps. The ultraviolet absorption maxima at 267.5 and 340 mμ, ε 21,000 and 13,400, are attributable to the principal chromophore numbered 1–7 in VI, to which the bromophenyl contributes.[8] The great facility of the reduction of this compound to IIIa is understandable in terms of the quinone-like unsaturated 1,4-dicarbonyl conjugation involved.

The other unsaturated ketone is more weakly colored, yellow. If it is the direct dehydration product of Vb, it presumably would exist in the least hindered form, VIb, of the four possible *cis*-, *trans*, and conformational forms, all of which involve extensive group overlaps according to plane scalar drawings.[3a,7] However, under the dehydrating conditions rearrangement to the α-methylene ketone form VII in which through-conjugation is broken, is possible but seemingly unlikely[cf. 3b] in view of two analogies.[3,9]



VII

The facility of sodium hydrosulfite reduction is in accord with the formulation VIb.

The ultraviolet absorption maximum at 261 mμ, ε 38,000 and the shoulder on the curve centering at 300 mμ, ε 8,000, seem to be more consistent with formulation VIb than with VII, as will be seen from the following considerations. The colorless saturated compounds IIIa and IIIb gave simple and almost identical ultraviolet absorption curves (λ_{max} 256, 255 mμ, ε 27,800, 26,900) which must represent the summation of absorptions of two fully independent chromophores, bromobenzoyl (ε *ca.* 15,300, assumed from that of β-(*p*-bromobenzoyl)-β-methylacrylic acid[8b]) and acylanilido (*ca.* ε 12,500, estimated by difference[cf. 10]), and this result provides a reasonable basis for expecting no significant absorption in the 300-mμ range and no color for a compound of the type VII where the two chromophores, in this case the acylanilido and vinyl bromophenyl ketone systems, are conjugatively independent. Actually the extremely high ε at 261 mμ with the very considerable shoulder on the absorption curve at 300 mμ, and the yellow color, are contrary to such expectations and are better explained in terms of the assigned structure VIb, assuming that there is sufficient steric interference with coplanarity of the β-methyleneoxindole and the bromobenzoyl chromophores to cause these systems to absorb largely independently of each other, but assuming also that there is insufficient interference entirely to suppress through-conjugation (numbered 1–7 in VIb).

The infrared absorption spectra of the compounds III and VI did not seem to furnish useful evidence regarding the possibility of an α-methylene group (VII); the absence of a methylene band at *ca.* 11 μ, like that observed for styrene and for penicillic acid,[11] does not exclude the possibility of this group because no such band appears in the spectra of two cases related to VIb which are known to have a carbonyl group conjugated with the methylene, namely methylene-1,2-dibenzoylethane[9a] and α-methylene-β-(*p*-bromobenzoyl)propionic acid.[3c] Differences in the carbonyl group absorptivities seemed significant, however. Each of the saturated ketones IIIa and IIIb showed a keto band at 5.95 μ and a lactam carbonyl band at 5.85 μ, which excluded hydroxyindole structures and served as reference points. The unsaturated ketone VIa with its very effective through-conjugation, showed appreciable lengthening of the wave length of the keto band to 5.97 μ and lowering of that of the lactam carbonyl to 5.78 μ, whereas the wave lengths of these two groups in VIb were practically the same as in IIIa and IIIb, and indicated that the through-conjugation, if it exists, has only a small degree of effectiveness.

The nuclear magnetic resonance spectrum at 60 megacycles subsequently obtained[12c] confirms the conclusion that the through-conjugated structure VIb is correct, by showing signals for two tertiary methyl groups at 2.48 and 3.12 p.p.m. from the internal reference, tetramethylsilane, the former representing the methyl group attached to the doubly bonded carbon.

(7) (a) Plane scalar drawings analogous to those used in refs. c and d (below) were based on Pauling's bond distances and atomic radii. [(b) L. Pauling, *The Nature of the Chemical Bond*, Cornell University, Press, Ithaca, N. Y., 1944]. (c) L. P. Kuhn, R. E. Lutz, and C. R. Bauer, *J. Am. Chem. Soc.*, **72**, 5058 (1950). (d) R. E. Lutz, D. F. Hinkley, and R. H. Jordan, *J. Am. Chem. Soc.*, **73**, 4647 (1951).

(8) (a) *Cf.* H. H. Szmant and A. J. Basso, *J. Am. Chem. Soc.*, **74**, 4397 (1952). Absorptions of related chalcone systems: *p*-$RC_6H_4CH{=}CHCOC_6H_4Br$-*p*: R = OCH_3, λ_{max} 265, 348.5 mμ [(b) L. F. Ferguson and R. P. Barnes, *J. Am. Chem. Soc.*, **70**, 3907 (1948)]; R = $N(CH_3)_2$, λ_{max} 260, 420 mμ [(c) R. E. Lutz, T. A. Martin, J. F. Codington, T. M. Amacker, R. K. Allison, N. H. Leake, R. J. Rowlett, Jr., J. D. Smith, and J. W. Wilson, *J. Org. Chem.*, **14**, 988 (1949)].

(9) *Cf.* the relative instabilities of the methylene isomers of *cis* methyl-1,2-dibenzoylethylene and α-methyl-β-bromobenzoylacrylic acid [(a) P. S. Bailey, G. Nowlin, S. H. Pomerantz, J. V. Waggoner, and E. E. Kawas, *J. Am. Chem. Soc.*, **73**, 5560 (1951); (b) R. E. Lutz, P. S. Bailey, C.-K. Dien, and J. W. Rinker, *J. Am. Chem. Soc.*, **75**, 5042 (1953)].

(10) *N*-Acetyl-*N*-methyl-*o*-toluidine shows λ_{max} *ca.* 260–267 mμ [P. Grammaticakis, *Bull. soc. chim.*, 134 (1949)].

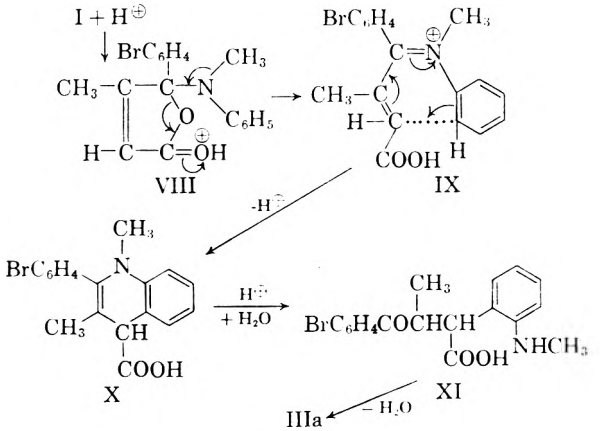
(11) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, John Wiley & Sons, New York, 1958, p. 87, 197.

(12) (a) Ultraviolet absorptions were determined at *ca.* $5 \times 10^{-5} M$ in 95% ethanol, using a Beckman DU spectrophotometer. Some of these determinations were by Joseph P. Feifer. (b) Infrared determinations were by Joseph P. Feifer on potassium bromide pellets, using a Perkin-Elmer Infracord spectrophotometer. (c) NMR data furnished and interpreted by LeRoy Johnson, Varian Associates.

Mechanistic Considerations. The mechanism of rearrangement of the methylanilinolactone (I) must involve several steps, because C—O and C—N bonds are broken and new C—N and C—C bonds are established. Passage through the acyclic *cis* or the *trans* methylanilide is precluded because the former rearranges under the reaction conditions to the latter which is stable[4]; and migration of the methylanilide nitrogen moiety from the α-carbon of I to the lactone carbonyl carbon also is precluded because had that happened the product isolated would have been the *trans* methylanilide.

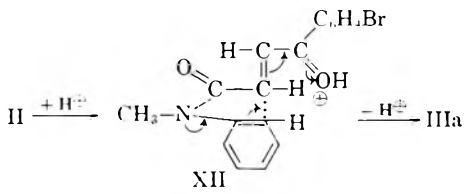
In this connection it is noteworthy that numerous unsuccessful attempts were made to displace aniline or methylaniline from the cyclic compounds of type I by other amines, aniline, methylaniline, and the stronger base dimethylamine, directly, or by nucleophilic attack at the lactam carbonyl. It should be noted also that unlike the methylanilinolactone I, the analogous parent γ-anilinolactone itself, instead of rearranging, undergoes hydrolysis with elimination of aniline. This difference is attributed[3c] to steric interference by the methyl group with hydrolysis, which affords more time and opportunity for the slow and competing rearrangement.

The mechanism VIII–XI is suggested in rationalization of the rearrangement of the methylanilinolactone I. In the first step protonation of the lactone carbonyl or bridge oxygen (VIII) leads through ring opening to an anil-onium ion IX, with cyclization to X, followed by ring contraction through hydrolytic enamine cleavage to XI, and ring reclosure through lactam formation to the oxindole IIIa.



The first step VIII → IX should go with ease, involving as it does disruption of a quaternary ketal type C—O bond, and the second, IX → X, is related to the Skraup ring closure or Claisen rearrangement. There is analogy for the reverse of the ring contraction X → IIIa wherein a compound of type III without the *N*-methyl group undergoes ring expansion to the type X under acid conditions.[6] However, in actual experiment under the conditions which rearranged 2-phenacyloxindole to 1,4-dihydrocinchophen,[6] the oxindoles III were recovered unchanged. It is postulated that ring contraction rather than retention of the 6-membered ring of X, and failure of ring expansion to occur (IIIa → X), is due to the great steric differences in group overlaps entailed in the presence of the *N*-methyl group which in the 6-ring would greatly lessen resonance stabilization, but which in the 5-ring would have relatively little effect. Plane scalar molecular drawings[7] of the two systems X and IIIa, with and without the *N*-methyl group, support this view.

For the mechanism of rearrangement of the simpler *trans* methylanilide II, which appears to be the species undergoing oxindole cyclization in this series (in marked contrast to the analogous β-methyl *trans* methylanilide which is not rearranged under the conditions[4]), it would appear that cyclization is direct, promoted by protonation of the α,β-unsaturated ketone system, as pictured in formulation XII. This reaction bears resemblance to the similar cyclizations of α-hydroxydiphenylacetic acid alkylanilides to *N*-alkyl-3,3-diphenyloxindoles.[13]



EXPERIMENTAL[12]

3-(p-Bromophenacyl)-3-hydroxy-1-methyloxindole (Va). (For analogous preparations, see ref. 6b). A mixture of 350 ml. of absolute ethanol, 17.9 g. (0.118 mol.) of *N*-methylisatin,[14] 23.6 g. (0.118 mol.) of *p*-bromoacetophenone and 35 drops of diethylamine was heated to 50° and allowed to stand at room temperature overnight; yields of yellowish crystals 29.1 g. (70%), melting with decomposition at 167–171° before and after repeated recrystallizations from absolute ethanol. λ_{max}, μ, 2.90s, 3.39w, 5.88s, 6.14s, 6.24s, 6.33m, 6.64w, 6.77s, 6.99m.

Anal. Calcd. for $C_{17}H_{14}BrNO_3$: C, 56.68; H, 3.92. Found: C, 56.64; H, 4.02.

3-(p-Bromophenacylidine)-1-methyloxindole (VIa). (*Cf.* ref. 6b). A mixture of 25 ml. of absolute ethanol, 50 ml. of conc. hydrochloric acid, and 8 g. of Va was allowed to stand overnight at room temperature. The resulting precipitate (7.43 g.; 98%) was recrystallized from absolute ethanol; red, m.p. 194.8–196°. λ_{max} 267.5, 340 mμ, ϵ 21,800; 13,300; μ, 5.78s, 5.97s, 6.12m, 6.22s, (shoulders, 6.27s, 6.35w) 6.70w, 6.78m, 7.10m.

Anal. Calcd. for $C_{17}H_{12}BrNO_2$: C, 59.66; H, 3.53. Found: C, 59.57; H, 3.80.

Reduction to 3-(p-bromophenacyl)-1-methyloxindole (IIIa). (*Cf.* ref. 6b). Treatment of 4 g. of VIa in 50 ml. of 95% ethanol with 4 g. of sodium hydrosulfite dissolved in 20 ml. of water (heated on the steam bath for 2 hr.) gave 3.4 g. (85%) of IIIa. After recrystallization from ethanol, it melted at 156.5–157.5°. It was identified by mixture melting point with IIIa, the product[5] of the action of acetic–conc. hydrochloric acid mixture on II. λ_{max}, 256 mμ, ϵ 27,800; μ, 3.38w, 5.85s, 5.91s, 6.15m, 6.26s (shoulder), 6.32m, 6.66s, 6.77s, 7.03m.

(13) R. F. Reeves and H. G. Lindwall, *J. Am. Chem. Soc.*, 64, 1086 (1942).

(14) W. Borsche and W. Jacobs, *Ber.*, 47, 354 (1914).

3-(α-Methyl-p-bromophenacyl)-3-hydroxy-1-methyloxindole (Vb). A solution of 11.8 g. of *N*-methylisatin, 15.6 g. of *p*-bromopropiophenone,[3a,15] and 44 drops of diethylamine in 260 ml. of absolute ethanol, after standing at room temperature for several days, was partially evaporated and some water was added dropwise to precipitate 25.7 g. (97%) of Vb. After recrystallization from absolute ethanol it melted at 158–161°. λ_{max}, μ, 2.87s, 3.19w, 3.37w, 5.84s, 5.92s, 6.16s, 6.28m, 6.36m (shoulder), 6.66m, 6.78s, 6.86m, 7.00m.

Anal. Calcd. for $C_{18}H_{16}BrNO_2$: C, 57.77; H, 4.31. Found: C, 57.69; H, 4.44.

3-(α-Methyl-p-bromophenacylidene)-1-methyloxindole (VIb). (*cf.* ref. 6b). A mixture of 7.25 g. of Vb in 21.5 ml. of absolute ethanol and 43 ml. of conc. hydrochloric acid, upon standing overnight at room temperature, gave 3.7 g. (54%) of VIb. After recrystallization from benzene it melted at 226–227°. λ_{max} 261 mμ, ϵ 38,000; shoulder, 300 mμ, ϵ 8,000; μ, 5.84s, 5.93s, 6.05m, 6.18s, 6.28s, 6.70m, 6.78s, 7.02m.

Anal. Calcd. for $C_{18}H_{14}BrNO_2$: C, 60.69; H, 3.96. Found: C, 60.44; H, 4.04.

3-(α-Methyl-p-bromophenacyl)-1-methyloxindole (IIIb). Reduction (as for VIa) of 0.22 g. of VIb in 70% ethanol by 0.22 g. of sodium hydrosulfite gave 0.2 g. of IIIb. After recrystallization from ethanol it melted at 137–139° and was identified by mixture melting point with the product[4] of the action of acetic–conc. hydrochloric acid mixture on I. λ_{max}, 255 mμ, ϵ 26,900; μ, 3.25w, 3.40w, 5.84s, 5.95s, 6.18s, 6.28s, 6.48w (shoulder), 6.68s, 6.79s, 6.89m, 7.05w.

Anal. Calcd. for $C_{18}H_{16}BrNO_2$: C, 60.4; H, 4.5. Found: C, 60.1; H, 4.8.

Miscellaneous reactions. Only resinous product was obtained when the *trans*-methylanilide of (I) was subjected to the action of a 56:7 (by volume) mixture of acetic and conc. hydrochloric acids (refluxing for from 2 to 3 hr.); no VIb was isolated.

Numerous attempts to displace aniline or methylaniline or to force further reaction of the γ-anilino and methylanilinolactones (I) were unsuccessful; *e.g.*, heating the mixture at 150° for 2 hr., with or without added aniline or methylaniline hydrochloride (although in one case some VI was obtained), and heating a benzene solution saturated with dimethylamine and its hydrochloride.

Acknowledgment. We are indebted to Joseph P. Feifer for the determination of the infrared and two of the ultraviolet absorption spectra.

CHARLOTTESVILLE, VA.

(15) A. Collet, *Compt. rend.*, 125, 717 (1897); 126, 1577 (1898).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DE PAUL UNIVERSITY]

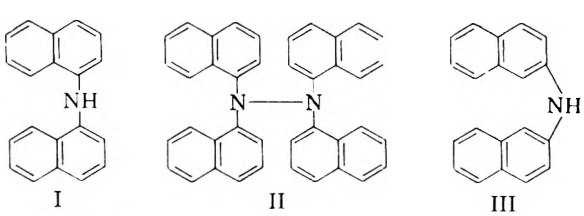
Formation of Tertiary Naphthylamines and Tetranaphthylhydrazines by *N*-Metallation[1]

EUGENE LIEBER[2] AND S. SOMASEKHARA

Received April 16, 1959

The discovery that the potassium metallation of 1,1′-dinaphthylamine (I) leads to significant yields of tetra(1-naphthyl)-hydrazine (II) has led to an extended study of the metallation of I and related secondary amines during which the syntheses of a number of tertiary amines have been achieved. Variation in the ratio of potassium to I and temperature did not increase the yields of II above 5%, the higher temperatures decreasing the yield. Diphenyl- and 2,2′-dinaphthylamines, respectively, failed to yield any evidence for hydrazine formation, under the conditions studied, while other related secondary amines gave only chromatogram fluorescent tests indicative of hydrazine formation. A free radical mechanism to account for I is proposed and discussed. The process is the reverse of the free radical dissociation of tetraarylhydrazines in solution.

In a preliminary communication Lieber[3] reported that a significant yield of tetra(1-naphthyl)-hydrazine (II) was obtained during an attempt to prepare the potassium salt of 1,1′-dinaphthylamine (I) by heating I under reflux with potassium in xylene.



I II III

(1) This investigation was sponsored by the Basic Research Group, Corps of Engineers, U. S. Army, Fort Belvoir, Va. The authors gratefully acknowledge this assistance.

(2) Present address: Roosevelt University, Chicago 5, Ill., to whom all correspondence should be addressed.

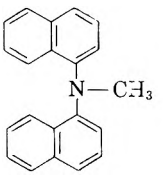
(3) E. Lieber and S. Somasekhara, *Chem. and Ind.*, 1262 (1958).

In the same reaction, methylation experiments offered evidence that the potassium salt of I was not the intermediate involved in the formation of II. Further experiments with I using potassium in boiling xylene, with the exclusion of atmospheric oxygen, verified the formation of II, the yields being about the same (5%). Reagents such as potassium butoxide, potassium methoxide, and potassium amide, used under a variety of conditions, failed to produce any detectable amount of the potassium salt of I. In order to examine further the novel conversion of I to II, an extended study of the potassium metallation of I and related secondary amines was undertaken during the course of which the syntheses of a number of tertiary amines was achieved.

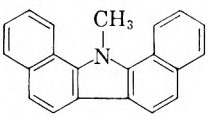
The metallation of I was carried out at various temperatures ranging from 110° to 200°. The experimental data revealed that the potassium salt of I was formed in good yields at lower temperatures.

At higher temperatures the reaction was accompanied by extensive decomposition forming unworkable tars. The effect of increasing the molar ratio of potassium to I, in refluxing xylene, had no effect on the yield of II, in all cases approximately 5% of product being obtained. When the above reaction was repeated with 2,2′-dinaphthylamine (III), no evidence could be found for the formation of the corresponding hydrazine, although an exhaustive search was made for it by techniques which could reveal trace amounts. An explanation for this curious contradiction of anticipation is discussed below. The behaviors of other secondary amines, *N*-methyl-, *N*-ethyl-, and *N*-phenyl-1-naphthylamine and *N*-phenyl-2-naphthylamine and diphenylamine, with metallic potassium under experimental conditions that led to II, were studied. In no case could the corresponding tetrasubstituted hydrazine be isolated. However, with the exception of diphenylamine it was demonstrated, by chromatographic fluorescent techniques in comparison with authentic specimens of the hydrazines,[4] that the tetrasubstituted hydrazines were indeed formed, albeit in quantities too small for isolation. Diphenylamine, unlike the other secondary amines studied, yielded its potassium salt under a variety of experimental conditions, and in no case, could evidence be obtained for the formation of tetraphenylhydrazine under the experimental conditions studied.

Heydrich[5] and Herz[6] have shown that some difficulty accessible tertiary amines can be synthesized by treating the alkali metal salts of secondary amines with aromatic halides. Heydrich[5] allowed molten diphenylamine to react with metallic sodium to obtain the sodium salt of diphenylamine. Herz,[6] on the other hand, used aniline as a solvent for obtaining the potassium salt of diphenylamine. In the present study solvents such as toluene, xylene, and decalin were employed. With the exception of diphenylamine, the experimental data indicates that the potassium salts of the secondary amines studied were thermally unstable above 110°. In all cases evidence for metallation was sought by the usual procedure of methylation (or ethylation). In the case of diphenylamine, benzylation was employed since the resulting tertiaryamine had been reported previously.[7] The melting point of *N*-methyl-*N*-phenyl-2-naphthylamine (88–90°) was found to be at variance with that previously reported[8] (52–53°). The methylation of *N*-methyl- and *N*-ethyl-1-naphthylamine, respectively, led to liquid tertiary amines which were therefore characterized as picrates. In an attempt to prepare *N*-methyl-1,1′-dinaphthylamine by the zinc chloride dehydration of *N*-methyl-1-naphthylamine with 1-naphthol, a high melting (188–190°) product was obtained which did not correspond to the *N*-methyl-1,1′-dinaphthylamine (IV) (melting point, 143–144°), prepared by methylation of the potassium salt of I. Analysis suggests that this product is *N*-methyl-1,3-dibenzo (a,i) carbazole, V:

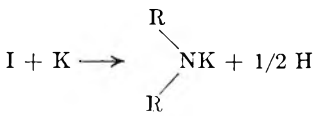


IV

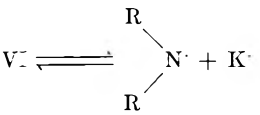


V

In order to account for the formation or nonformation of a tetrasubstituted hydrazine it is suggested that the potassium salts of the secondary amines under scrutiny, being more or less thermally unstable, are capable of homolytic dissociation to produce free radicals:



VI
(R = 1-Naphthyl)

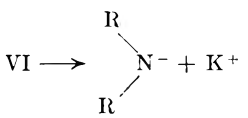


VII
(R = 1-Naphthyl)

It is also possible that potassium could generate the free radical in the following manner:

$$I + K \longrightarrow VII + KH$$

The tetranaphthylhydrazine (II) is then produced by recombination of VII. However, the electronic deficiency of VII and related substances could be satisfied by bonding to carbon, leading to more complicated products and thus account for the unworkable tars formed in many cases. A theory based on the acidic properties of the secondary amines studied, which would in turn involve the relative stabilities of the potassium salts, is not too satisfactory since the differences in the acidic properties are probably very small or nonexistent. On the other hand, heterolytic cleavage of the potassium salts, *e.g.*,



could be the concurrent and major process and would account for the alkylations carried out.

The dissociation of tetraarylhydrazines in solution into diarylnitrogen free radicals is a well

(4) E. Lieber and S. Somasekhara, *J. Org. Chem.*, **24**, 1775 (1959).
(5) C. Heydrich, *Ber.*, **18**, 2156 (1885).
(6) R. Herz, *Ber.*, **23**, 2541 (1890).
(7) R. D. Desai, *J. Ind. Inst. Sci. (India)*, **7**, 235 (1924); *Chem. Abstr.*, **19**, 2645 (1925).
(8) German Patent **96402**, *Chem. Centr.*, 69, II, 240 (1898).

known phenomenon.[9,10] Schlenk and Marcus[11] have shown that tetraphenylhydrazine in dry ether reacts slowly with potassium to yield the potassium salt of diphenylamine:

$$R_2NNR_2 + 2\ K \longrightarrow 2\ R_2NK\ (R = C_6H_5)$$

This is the only reaction reported in the literature which bears some relationship to the potassium metal induced formation of I. It is obvious that the observation of Schlenk and Marcus[11] and the present study bear an inverse relationship to one another even though this investigation has been unable to detect any reversal of the Schlenk and Marcus[11] process. This latter can only proceed by a free radical mechanism. The present observations with 1,1'-dinaphthylamine, and related secondary amines, however, suggest that the process should be reversible. Studies to this end are being continued.

EXPERIMENTAL[12,13]

N-Methyl-1,1'-dinaphthylamine (IV). (a) *By metallation in toluene.* To 2.7 g. (0.01 mol.) of 1,1'-dinaphthylamine dissolved in dry toluene (20 ml.) was added 0.5 g. (0.0125 mol.) of potassium cut into small pieces. The reaction mixture was stirred and refluxed for 2 hr. in a nitrogen atmosphere while the reaction mixture turned reddish brown. After cooling and treatment with methyl iodide (8.5 g., 0.06 mol.) the reaction mixture was allowed to stand overnight, then filtered hot, and concentrated *in vacuo*. The brown oily residue was dissolved in benzene and chromatographed over alumina. From the benzene elutes a yellow solid melting at 140–143° was obtained; yield, 1.5 g. (52%). Recrystallization from benzene-ethanol gave pale yellow needles, m.p., 143–144°.

Anal. Calcd. for $C_{21}H_{17}N$: C, 89.04; H, 6 00; N 4.95; Found: C, 88.74; H, 5.98; N, 4.78.

(b) *By metallation in liquid ammonia.* Potassium (0.34 g., 0.0087 mol.) was dissolved in dry liquid ammonia (40 ml.). On addition of 1,1-dinaphthylamine (2 g., 0.0074 mol.) a vigorous evolution of hyrdogen occurred and an orange-red solid separated almost immediately. The ammonia was allowed to evaporate and the solid residue was treated in the cold with methyl iodide (11.4 g., 0.08 mol.). When the initial vigor of reaction subsided, the mixture was gently refluxed for 3 hr. The reaction mixture was filtered hot and the precipitate washed with hot benzene (25 ml.). The filtrate and the washings were combined, concentrated to a small volume (15 ml.) and chromatographed on a 20-in. column of alumina with benzene as eluent. The benzene elute (60 ml.) was concentrated to small volume (5 ml.) and diluted with ethanol to obtain a yellow powder, m.p., 140°, yield, 1.2 g. (55%). Recrystallization was effected as above yielding pale yellow needles, melting at 143–144°. By mixed melting point, this was shown to be identical with IV obtained in (a).

(c) *By metallation in xylene. Formation of tetra(1-naphthyl)-hydrazine* (II). To 2.7 g. (0.01 mol.) of 1,1'-dinaphthylamine dissolved in 25 ml. of dry xylene was added 0.4 g. (0.01 mol.) of potassium. The reaction mixture was stirred and refluxed in an atmosphere of deoxygenated dry nitrogen for 4 hr. producing a tarry solid material. After filtration, the filtrate was concentrated *in vacuo*, diluted with benzene, decolorized with charcoal and chromatographed on alumina. The benzene elutes were concentrated and diluted with petroleum ether to obtain 120 mg. of a yellow solid melting around 130°. This was purified by repeated dissolution in acetone and precipitation with ethanol to obtain a yellow crystalline powder, m.p. 235°. Mixture melting point with an authentic specimen[3] of II showed no depression. The yield of II was 5%.

Repetition of the above experiment in the presence of air did not effect the nature of the reaction product, a 5% yield of II being obtained. Attempts to react the tarry material, *in situ*, with methyl iodide, failed to yield a methylation product. Rather II was repeatedly obtained in about 5% yields. Using 4, 6, and 10 mol. of potassium to 1 mol. of 1,1'-dinaphthylamine was without effect in increasing the yield of II above 5%. Increasing the reaction temperature to 193° (refluxing in decalin) decreased the yield of II to 2–3%.

(d) *By reaction of N-methyl-1-naphthylamine with 1-naphthol in the presence of zinc chloride. Formation of N-methyl-1,3-dibenzo (a, i) carbazole* (V). A mixture of *N*-methyl-1-naphthylamine (5 g., 0.032 mol.), 1-naphthol (5 g., 0.035 mol., ammonium chloride (5 g.), and freshly fused zinc chloride (5 g.) was gently heated to melting and held at that state for 15 min. On cooling, the dark brown cake was triturated with water and then extracted with benzene, filtered, washed with 10% potassium hydroxide (twice), water, 2*N* hydrochloric acid (twice), and finally with water. The benzene layer was separated, concentrated, and subjected to chromatographic separation. The first fraction yielded a very pale yellow solid (1.1 g., 12%) melting about 180°. Recrystallization from benzene-alcohol gave colorless needles melting at 188–190°. It was identified as V by analysis.

Anal. Calcd. for $C_{21}H_{15}N$: C, 89.69; H, 5.34; N, 4.98; Found: C, 89.76; H, 4.79; N, 4.64.

The subsequent chromatographic fractions yielded only contaminated material from which no definite substance could be obtained. Attempts to cyclize *N*-methyl-1,1'-dinaphthylamine to the carbazole by the same technique led only to recovery of the starting material in diminished yield.

N-Methyl-2,2'-dinaphthylamine. Metallation and methylation of 2,2'-dinaphthylamine was carried out as described in (a). The yield of *N-methyl-2,2'-dinaphthylamine was 50%*, crystallized from benzene-alcohol as pale brown fragile needles, m.p., 115–117° (lit.[14] 139–140°, and 123–124°[15]).

Anal. Calcd. for $C_{21}H_{17}N$: N, 4.95; Found: N, 4.68.

Metallation and methylation in liquid ammonia as described in (b) increased the yield of product to 68% identified as *N-methyl-2,2'-dinaphthylamine* by mixed melting point. When the metallations and attempted methylations were carried out in refluxing xylene only unworkable tars were obtained. Repeated and exhaustive chromatographic separation failed to yield any trace of tetra(2-naphthyl)-hydrazine.

N-Methyl-N-phenyl-1-naphthylamine. From 4.4 g. (0.02 mol.) of *N*-phenyl-1-naphthylamine by procedure (a) was obtained 3.5 g. (75%) of a pale brown powder, which on repeated crystallizations from ethanol gave a constant m.p. of 52–53°.

Anal. Calcd. for $C_{17}H_{15}N$: N, 6.01; Found: N, 6.27.

N-Methyl-N-phenyl-1-naphthylammonium chloride was obtained, in quantitative yield, by passing dry hydrogen chloride into a benzene solution of the base; m.p., 118–121°.

Anal. Calcd. for $C_{17}H_{16}NCl$: N, 5.20; Found: N, 5.58.

(9) J. E. Leffler, *The Reactive Intermediates of Organic Chemistry*, Interscience Publishers, Inc., New York, 1956, 66.

(10) C. Walling, *Free Radicals In Solution*, John Wiley and Sons, Inc., New York, 1957, 524.

(11) W. Schlenk and E. Marcus, *Ber.*, **47**, 1673 (1914).

(12) Melting points are uncorrected.

(13) Microanalyses by Drs. C. Weiler and F. B. Strauss, Oxford, England.

(14) C. Ris, *Ber.*, **20**, 2619 (1887).

(15) O. Kym, *Ber.*, **23**, 2460 (1890).

Repetition of the potassium metallation experiments with *N*-phenyl-1-naphthylamine at higher temperatures (refluxing xylene and decalin) led only to unworkable tars.

N-Methyl-N-phenyl-2-naphthylamine was obtained by procedure (a) in 33% yield, m.p. 88–90° (lit.[8] 52–52°).

Anal. Calcd. for $C_{17}H_{15}N$: N, 6.01; Found: N, 6.35.

Higher temperature experiments gave only unworkable tars.

N,N-Dimethyl-1-naphthylammonium picrate. A mixture of *N*-methyl-1-naphthylamine (3.1 g., 0.02 mol.), potassium (1.6 g., 0.04 mol.) and xylene (10 ml.) was refluxed and stirred for 4 hr. in a continuous stream of purified dry nitrogen to give a suspension of a greenish yellow solid. The reaction mixture was cooled and treated overnight with methyl iodide (11.4 g., 0.08 mol.) at room temperature the mixture was warmed, filtered, and the precipitate washed with hot benzene (10 ml.). The filtrate and washings were combined and concentrated. The concentrate was treated with an excess of a saturated solution of picric acid in ethanol. A yellow crystalline solid was obtained melting at 144–145° (lit.[16] m.p. 145°); yield, 4.2 g. (53%).

Anal. Calcd. for $C_{18}H_{16}N_4O_7$: N, 14.00. Found: N, 14.04.

After chromatography of the combined filtrates and washings, and development of the bands, fluorescent examinations show bands identical with those produced by an authentic specimen[3] of *sym*-dimethyl-di(1-naphthyl)hydrazine.

N-Methyl-N-ethyl-1-naphthylammonium picrate. By the same procedure as described above, 3.4 g. (0.02 mol.) of *N*-ethyl-1-naphthylamine gave 4.15 g. (50%) of a picrate melting at 146°.

Anal. Calcd. for $C_{19}H_{18}N_4O_7$: N, 13.53. Found: N, 13.50.

Chromatographic banding and fluorescent examination gave bands suggestive of a tetrasubstituted hydrazine.

Repetition of the same procedure on the ethylation of *N*-methyl-1-naphthylamine gave a 46% yield of a picrate, m.p., 146°, shown by mixed melting point to be identical with *N-methyl-N-ethyl-1-naphthylammonium picrate.*

N-Benzyl-diphenylamine. A mixture of diphenylamine (3.4 g., 0.02 mol.), potassium (0.8 g., 0.02 mol.) and xylene (20 ml.) was refluxed and stirred in a continuous stream of purified dry nitrogen for 4 hr. when a suspension of a pale yellow solid was obtained. The reaction mixture was cooled and allowed to react with benzyl chloride (2.6 g., 0.02 mol.) at room temperature overnight, warmed, and filtered. The filtrate was concentrated to a small volume (6 ml.). On dilution with petroleum ether, 2 g. (44%) of a crystalline solid melting at 84–86° was obtained. Recrystallization from ethanol gave needles, m.p., 88° (lit.[7] 88–88.5°).

Anal. Calcd. for $C_{19}H_{17}N$: N, 5.41; Found: N, 5.63.

Repeated experiments and exhaustive chromatographic separations in attempts to find evidence for the formation of *tetraphenylhydrazine* were negative.

CHICAGO 14, ILL.

(16) H. H. Hodgson and J. H. Crook, *J. Chem. Soc.*, 1500 (1936).

[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, UNION CARBIDE CHEMICALS CO., SOUTH CHARLESTON, W. VA.]

(Aminoalkyl)pyrenes

E. MARCUS AND J. T. FITZPATRICK

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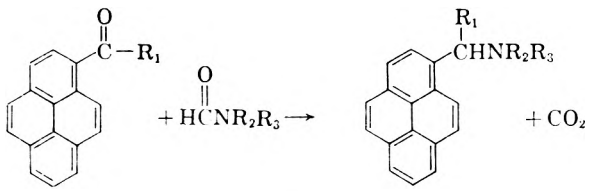
The synthesis of a variety of 1-pyrenemethylamines is described. Most of the compounds were prepared by the Leuckart reaction from the corresponding carbonyl derivative of pyrene and a formamide in the presence of formic acid. Some others were made by catalytic reduction of the imines obtained from 1-pyrenecarboxaldehyde and a primary amine. 1-Pyrenemethylamine was obtained best by reduction of the oxime.

During our study of derivatives of polycyclic hydrocarbons we became interested in the synthesis of 1-pyrenemethylamines. A convenient method for the preparation of such compounds appeared to be the Leuckart reaction.[1]



In the reaction of pyrenecarboxaldehyde with dialkylformamides good yields were obtained when the nitrogen of the dialkylamine part was attached to two methyl or ethyl groups, or when it was part of a heterocyclic system; with higher alkyl groups lower yields were realized. With monoalkylformamides or unsubstituted formamide and pyrenecarboxaldehyde the desired products could also be obtained, but only in low yields; the reaction proceeded further to give large amounts of bis- and tris(pyrenemethyl)amines. The monosubstituted pyrenemethylamines could be made more easily by catalytic hydrogenation of the imines derived from the aldehyde and the corresponding amines. The unsubstituted pyrenemethylamine was prepared best by catalytic reduction of the oxime.

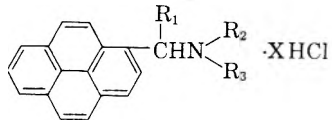
With acetylpyrene and dialkylformamides (we investigated the reaction with dimethylformamide in the presence of formic acid as well as magnesium chloride) the desired reaction did not occur at all. Acetylpyrene reacted fairly well with a monosubstituted formamide and very well with formamide itself; formation of bis- and tris(α-methyl-1-pyrenemethyl)amines was of no importance.

In benzoylpyrene the steric hindrance around the carbonyl group is apparently significant enough, that the reaction even with unsubstituted formamide proceeds only very slowly.

(1) E. Marcus and J. T. Fitzpatrick, *J. Org. Chem.*, **24**, 1031 (1959).

TABLE I

SUBSTITUENTS, MELTING POINTS, AND YIELDS OF PYRENEMETHYLAMINES



Compound No.	R_1	Substituents NR_2R_3	X	M.P.[a,b]	Yield,[b] %	Method
1	H	NH_2	1	244–250[c]	55[c,e]	C[d]
2	H	$NHCH_3$	1	245–253[c]	75[c,e]	B[d]
3	H	$N(CH_3)_2$	1	270–277	72	A
4	H	$N(C_2H_5)_2$	1	238–243[f]	78	A
5	H	$NH(n\text{-}C_4H_9)$	0	88–94[e]	58[c,e]	B
6	H	$NH(n\text{-}C_4H_9)$	1	225–235	54[e]	B
7	H	$N(n\text{-}C_4H_9)_2$	1	149–153[g]	35[g]	A
8	H	$N(n\text{-}C_6H_{13})_2$	1	134–136[g]	42[g]	A
9	H	$N(CH_2)_4$	1	250–260	87	A
10	H	$N(CH_2)_5$	1	256–259	91	A
11	H	$N(CH_2CH_2)_2O$	0	90–93[c]	93[c]	A
12	H	$N(CH_2CH_2)_2O$	1	256–263	95	A
13	H	$N(CH_2CH_2)_2NCH_3$	2	250–260[h]	86	A
14	H	$N[CH_2(1\text{-pyrenyl})]_2$	1	240–255[i]	50[i]	A
15	H	NHC_6H_5	0	143–145[c]	44[c,e]	B
16	H	$NH(\alpha\text{-pyridyl})$	0	165–167[c]	49[c,e]	B
17	CH_3	NH_2	1	230–250	79	A
18	CH_3	$NHCH_3$	1	237–242[j]	48	A
19	CH_3	$NH(n\text{-}C_6H_{13})$	1	220–225[j]	31	A
20	C_6H_5	NH_2	1	240–250[k]	25[l]	A

A. Leuckart reaction. B. Reduction of imines. C. Reduction of oximes. [a] Most of the higher melting compounds melted with decomposition. [b] Crude product unless otherwise indicated. [c] State of purity described in the Experimental section. [d] Compound was also obtained in very low yield by Method A. [e] Overall yield from the aldehyde. [f] After recrystallization from methanol. [g] After recrystallization from acetone. [h] After recrystallization from concentrated hydrochloric acid. [i] From formamide and pyrenecarboxaldehyde; after the mixture of amines had been extracted exhaustively with ether, the insoluble portion was converted to the hydrochloride by refluxing it with a mixture of butanol and concentrated hydrochloric acid. [j] After recrystallization from water. [k] Purified by dissolving the material in a large amount of hot water, filtering, and adding hydrochloric acid to the filtrate. [l] The remainder was largely unchanged starting material.

The difference in yields of the various products can best be rationalized on the assumption that the reaction is sensitive to changes in the steric requirements of both the formamide and the aldehyde or ketone.

The presence of formic acid was found to be essential to the success of the reaction. From pure dimethylformamide and pyrenecarboxaldehyde no product at all could be isolated, while in the presence of formic acid a 72% yield was obtained.[1] However, some crude dialkylformamides made according to Weilmuenster and Jordan[2] appeared to contain enough residual formic acid to catalyze the reaction, e.g., the addition of formic acid did not raise the already satisfactory yield with crude diethylformamide. On the other hand, crude *N*-formylmorpholine gave only a 19% yield, while additional formic acid improved the yield to 95%.

The effect which some of these (aminoalkyl)pyrenes have on the metabolism of yeast has been described recently.[3]

(2) E. A. Weilmuenster and C. N. Jordan, *J. Am. Chem. Soc.*, **67**, 415 (1937).

(3) J. Fellig and J. W. Brough, *Bacteriol. Proc.*, 130 (1959).

EXPERIMENTAL

All melting points are uncorrected. The neutralization equivalents of the amine hydrochlorides were determined by titration with sodium hydroxide using phenolphthalein as indicator; the values are estimated to be accurate within two or three percent.

The melting points, yields, formulas, and analytical data of the pyrenealkylamines are summarized in Table I and II.

METHOD A. Formamide, methylformamide, and dimethylformamide were obtained from Eastman Kodak Co. The other formamides were made by the method of Weilmuenster and Jordan[2] and used as residue products.

The mixture of about 5 to 7.5 mol. of formamide, 1 mol. of formic acid and 1 mol. of the carbonyl compound was refluxed gently for 4 hr. At the end of the reaction the excess of formamide was removed by distillation. When dialkylformamides were used, the residue was then dissolved in ether and filtered, and dry hydrogen chloride was introduced to precipitate the product. When monoalkylformamides or formamide itself were used, the residue was hydrolyzed with a mixture of butanol and concentrated hydrochloric acid for about 24 hr. The resulting amine hydrochlorides, after distillation of the solvent if necessary, were neutralized, dissolved in ether, and filtered. Introduction of hydrogen chloride precipitated the product.

As an example of the synthesis of the amines by the Leuckart reaction the preparation of *N*-(1-pyrenylmethyl)-morpholine is described.

N-(1-Pyrenylmethyl)morpholine. A mixture of 65.5 g. (0.75 mol.) of morpholine and 38.5 g. (0.75 mol.) of 90% formic

TABLE II

FORMULAS AND ANALYTICAL DATA[a] OF PYRENEMETHYLAMINES

Compound No.	Formula	Carbon, %		Hydrogen, %		Nitrogen, %		Chlorine, %		Neutral Equiv.	
		Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
1	$C_{17}H_{14}NCl$	76.25	76.02	5.27	5.09	5.23	5.30	—	—	268	272
2	$C_{18}H_{16}NCl$	76.73	77.24	5.72	5.85	4.99	5.05	12.58	12.32	282	283
3	$C_{19}H_{18}NCl$	77.14	77.00	6.13	6.43	4.74	4.70	—	—	296	299
4	$C_{21}H_{22}NCl$	77.88	77.36	6.85	7.18	4.33	4.05	—	—	324	327
5	$C_{21}H_{21}N$	87.76	87.33	7.37	7.41	4.87	5.23	—	—	—	—
6	$C_{21}H_{22}NCl$	77.88	77.65	6.85	6.53	4.33	4.34	10.95	10.85	324	328
7	$C_{25}H_{30}NCl$	79.02	78.40	7.96	7.97	3.69	3.73	—	—	380	383
8	$C_{29}H_{38}NCl$	79.87	79.99	8.78	9.11	3.21	3.53	—	—	436	436
9	$C_{21}H_{20}NCl$	78.41	77.84	6.22	6.36	4.35	4.55	11.02	11.05	322	324
10	$C_{22}H_{22}NCl$	78.66	78.19	6.61	6.86	4.17	4.37	10.56	11.02	331	332
11	$C_{21}H_{19}NO$	83.69	83.81	6.35	6.30	4.65	4.55	—	—	—	—
12	$C_{21}H_{20}NOCl$	74.65	74.74	5.97	6.17	4.15	4.24	—	—	338	347
13	$C_{22}H_{24}N_2Cl_2$	68.21	67.96	6.25	6.25	7.23	7.24	18.26	17.94	194	198
14	$C_{51}H_{34}NCl$	87.97	87.38	4.92	4.88	2.01	1.95	5.09	4.61	696	707
15	$C_{23}H_{17}N$	89.86	89.56	5.58	5.23	4.56	4.85	—	—	—	—
16	$C_{22}H_{16}N_2$	85.69	85.12	5.23	5.53	9.08	9.31	—	—	—	—
17	$C_{18}H_{16}NCl$	76.76	76.33	5.68	5.44	4.98	4.67	12.58	12.49	282	280
18	$C_{19}H_{18}NCl$	77.14	77.32	6.13	6.14	4.74	4.63	—	—	296	292
19	$C_{24}H_{28}NCl$	78.82	78.71	7.65	7.72	3.84	3.99	9.69	9.74	366	373
20	$C_{23}H_{18}NCl$	80.36	80.37	5.24	5.32	4.08	4.16	—	—	344	346

[a] The state of purity of the compounds is described in the footnotes to Table I referring to the M.P. column.

acid was heated slowly up to 200° to remove water and any unchanged amine and acid by distillation. To 82 g. of the residue were added 23.0 g. (0.1 mol.) of 1-pyrenecarboxaldehyde and 5 ml. of 90% formic acid. After refluxing for 4 hr. between 182 and 185° the excess of *N*-formylmorpholine was removed by vacuum distillation. The residual oil was dissolved in ether and filtered. Introduction of dry hydrogen chloride precipitated 32.3 g. (95%) of nearly white *N*-(1-pyrenylmethyl)morpholine hydrochloride, m.p. 256–263° with decomposition.

The hydrochloride (2.0 g.) was treated with a mixture of 100 ml. of ether, 20 ml. of concentrated ammonium hydroxide solution, and 20 ml. of water. The organic layer was separated, washed with water, dried over magnesium sulfate, and filtered. After removal of the ether by distillation, 1.75 g. of a viscous, yellow oil remained which was recrystallized from petroleum ether, b.p. 65–70°, to give an analytical sample of light yellow *N*-(1-pyrenylmethyl)morpholine, m.p. 90–93°.

METHOD B. N-Methyl-1-pyrenemethylamine hydrochloride. A rapid stream of methylamine was bubbled into 450 ml. of refluxing ethanol. Then 23.0 g. of 1-pyrenecarboxaldehyde was added with stirring during a 10 min. period. The solution was refluxed with stirring for another hour; during this time the introduction of methylamine was continued. After removal of solvent the residue was recrystallized from petroleum ether, b.p. 93–111°, to give 17.2 g. of a yellow solid, m.p. 102–104° with softening at 90°. Work-up of the mother-liquor gave an additional 3.0 g., m.p. 99–102° with softening at 90°, combined yield 89%. Two recrystallizations (one with the aid of charcoal) of material from the first crop afforded an analytical sample of *N*-methyl-1-pyrenemethylenimine, m.p. 104–105.5° with softening at 102°.

Anal. Calcd. for $C_{18}H_{13}N$: C, 88.86; H, 5.39; N, 5.76. Found: C, 88.75; H, 5.12; N, 5.81.

A mixture of 14.0 g. of *N*-methyl-1-pyrenemethylenimine, 200 ml. of ethanol, and 0.5 g. of Adams' catalyst was hydrogenated for 1 hr. at room temperature at 3.4 atm. pressure. After filtration and removal of solvent the residual oil was recrystallized from methanol to give 12.5 g. (88%) of a tan solid, m.p. 48–50° with softening at 40°. Introduction of dry hydrogen chloride into an ethereal solution of 8.0 g. of the amine gave 8.9 g. of a white solid whose neutral equivalent was 283 (calcd. 282).

N-Butyl-1-pyrenemethylamine hydrochloride. A mixture of 28.7 g. (0.125 mol.) of 1-pyrenecarboxaldehyde, 91.3 g. (1.25 mol.) of *n*-butylamine, and 500 ml. of ethanol was refluxed for 1 hr. After removal of solvent and excess butylamine the residue was recrystallized from petroleum ether, b.p. 65–67°, with the aid of charcoal to give a first crop of 24.5 g., m.p. 64–65.5°, and a second crop of 4.3 g., m.p. 63–65°, combined yield 81%. Another recrystallization from petroleum ether gave an analytical sample of yellow *N*-butyl-1-pyrenemethylenimine, m.p. 65–67°.

Anal. Calcd. for $C_{21}H_{19}N$: C, 88.38; H, 6.71; N, 4.91. Found: C, 88.08; H, 6.41; N, 5.28.

N-Butyl-1-pyrenemethylenimine was hydrogenated for 1 hr. at 3.4 atm. pressure in ethanol. The product was isolated by recrystallization from ethanol in 72% yield and converted to the amine hydrochloride in the usual way.

N-Phenyl-1-pyrenemethylamine. A mixture of 23.0 g. of 1-pyrenecarboxaldehyde, 9.3 g. (0.1 mol.) of aniline, and 100 ml. of ethanol was refluxed for 1 hr. and 40 min. to give 28.69 g. (94%) of a yellow solid, m.p. 126–128°. Another recrystallization from ethanol gave an analytical sample of *N*-phenyl-1-pyrenemethylenimine of the same melting point.

Anal. Calcd. for $C_{23}H_{15}N$: C, 90.46; H, 4.95; N, 4.59. Found: C, 90.99; H, 4.35; N, 4.59.

The imine was hydrogenated in acetic acid for 2 hr. at 3.4 atm. pressure. After neutralization and recrystallization from butanol a 47% yield of a golden-yellow solid, m.p. 141–143.5°, was obtained. Another recrystallization from ethanol gave an analytical sample, m.p. 141–143.5°.

N-(2-Pyridyl)-1-pyrenemethylamine. A mixture of 23.0 g. (0.1 mol.) of 1-pyrenecarboxaldehyde and 9.4 g. (0.1 mol.) of 2-aminopyridine was heated for 40 min. between 167 and 186°. A constant nitrogen stream removed the water formed during the reaction. Recrystallization from benzene gave 19.4 g. (63%) of a yellow solid, m.p. 152–157°. Another recrystallization from benzene afforded an analytical sample of *N*-(2-pyridyl)-1-pyrenemethylenimine, m.p. 158–160°.

Anal. Calcd. for $C_{22}H_{14}N_2$: C, 86.25; H, 4.61; N, 9.15. Found: C, 86.40; H, 4.57; N, 9.17.

The desired material could not be obtained by refluxing a solution of pyrenecarboxaldehyde and aminopyridine in ethanol.

The imine was hydrogenated for 4 hr. at 2.5 atm. pressure in ethanol. Recrystallization from butanol gave a 78% yield of fine ivory-colored needles, m.p. 165–167°. Another recrystallization from ethanol afforded an analytical sample of *N*-(2-pyridyl)-1-pyrenemethylamine of the same melting point.

METHOD C. 1-Pyrenemethylamine hydrochloride. 1-Pyrenecarboxaldehyde oxime was prepared by the pyridine method[4] from 1-pyrenecarboxaldehyde and hydroxylamine hydrochloride in the presence of pyridine using ethanol as a solvent. After recrystallization from butanol a 78% yield of yellow needles was obtained. Another recrystallization from butanol afforded an analytical sample, m.p. 191.5–192.5°.

(4) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Sytematic Identification of Organic Compounds," Wiley, New York, 1956, p. 254.

Anal. Calcd. for $C_{17}H_{11}NO$: C, 83.24; H, 4.52; N, 5.71. Found: C, 82.89, H, 4.32; N, 6.05.

The oxime was reduced catalytically according to a method described by Hartung[5] for the preparation of benzylamine from benzaldoxime. A mixture of 2.0 g. (0.0081 mol.) of 1-pyrenecarboxaldehyde oxime, 150 ml. of ethanol containing 0.0405 mol. of hydrogen chloride, and 2.0 g. of 5% palladium on charcoal was hydrogenated at 3.4 atm. pressure at room temperature for 2 hr. The mixture was brought to boiling and filtered. The filter cake was extracted with more boiling ethanol. After removal of solvent from the combined extracts, the residual solid was dissolved in much boiling water and filtered. Addition of hydrochloric acid to the filtrate and cooling afforded 1.56 g. (72%) of a nearly white solid.

SOUTH CHARLESTON, W. VA.

(5) W. H. Hartung, U. S. Patent 1,989,093, Jan. 29, 1935.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

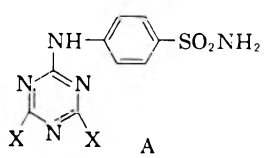
Preparation of Some Sulfonylhydrazide Derivatives of *s*-Triazine[1]

G. F. D'ALELIO AND ROBERT H. BECKER

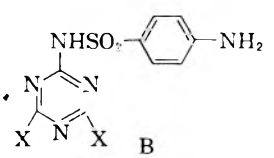
Received August 14, 1959

Arylsulfonylhydrazides react with cyanuric chloride at 0–10° to replace one chlorine atom; these products react smoothly with secondary amines to produce 2,4-diamino-6-arylsulfonylhydrazido-*s*-triazines. A series of new compounds were prepared by the reaction sequence which is described in this paper.

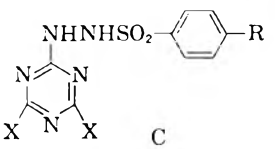
The preparation of a series of N^4-sulfanilamide derivatives of *s*-triazine (A) was described in a previous paper from this laboratory.[2] It was originally planned to prepare a corresponding series of N^1-sulfanilamide derivatives (B); however all attempts in this direction failed.[3] It was then decided to substitute the sulfonylhydrazido moiety ($R–SO_2–NHNH–$) for the sulfonamido group ($RSO_2NH–$) and prepare a series of arylsulfonylhydrazide derivatives (C) to be submitted for pharmacological screening.[4]



A



B



C

(1) Abstracted from a portion of the Ph.D. thesis of Robert H. Becker, University of Notre Dame, 1959.

(2) G. F. D'Alelio and H. J. White, Jr., *J. Org. Chem.*, **24**, 643 (1959).

(3) H. J. White, Jr., Ph.D. Thesis, University of Notre Dame, October, 1957.

(4) Pharmacological testing is being carried out by Merck Sharp and Dohme Research Laboratories, Rahway, New Jersey.

This work shows that cyanuric chloride (III) reacts with one mole of an arylsulfonylhydrazide (II), in the presence of sodium bicarbonate, at 0–10° to form a 2,4-dichloro-6-arylsulfonylhydrazido-*s*-triazine (IV). These compounds are isolated in good yield from aqueous dioxane solution. Because of the reactivity of the remaining chlorine atoms on the triazine nucleus, it is very difficult to effect a good purification of these dichloro-*s*-triazines. However, it was found that the products as obtained from the reaction mixture and washed with water and toluene would work very well in the subsequent reactions, thus eliminating a lengthy purification which involved high loss of material.

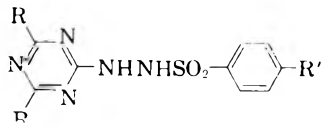
Although none of the dichloro intermediates were purified enough to obtain good analyses, they separated from the reaction mixture as dihydrates. When a sample was dried in a vacuum oven at 50° to 100° for varying periods of time, the calculated amount of weight was lost and subsequent reactions utilizing anhydrous material gave yields comparable to those utilizing the dihydrated intermediates.

The arylsulfonylhydrazides (II) used for the preparation of the dichloro-*s*-triazines were prepared from the corresponding arylsulfonyl chlorides (I) using the procedure of Curtius and Stoll[5] with slight variations.

(5) T. Curtius and W. Stoll, *J. prakt. Chem.*, 112, 117 (1926).

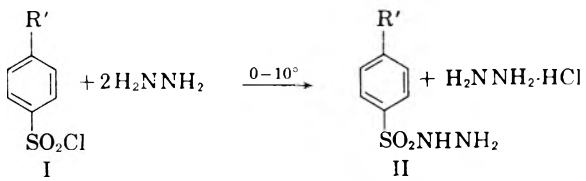
TABLE I

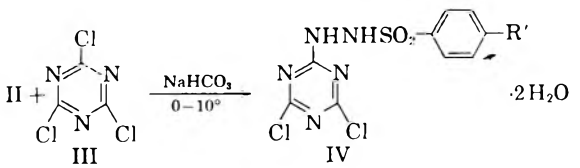
ARYLSULFONYLHYDRAZIDO-*s*-TRIAZINE



Compound	R	R′	Recryst. Solvent	M.P., °C.[a]	Yield, %
1	Cl·H_2O	H	—	161.0–163.0	64.2[b]
2	Cl·H_2O	CH_3	—	105.0–110.0	59.1[b]
3	Cl·H_2O	NHCCH$_3$ (O)	—	300.0	74.8[b]
4	$N(CH_3)_2$	H	C_2H_5OH	204.5–205.5	68.3
5	$N(CH_3)_2$	CH_3	C_2H_5OH–H_2O	163.0–165.0	48.6
6	$N(CH_3)_2$	NHCCH$_3$ (O)	C_2H_5OH–H_2O	213.0–215.0	51.3
7	$N(CH_3)_2$	NH_2	C_2H_5OH	212.5–213.5	71.5
8	$N(C_2H_5)_2$	H	C_2H_5OH–H_2O	140.0–141.0	30.3
9	$N(C_2H_5)_2$	CH_3	C_2H_5OH–H_2O	133.0–134.0	24.6
10	$N(C_2H_5)_2$	NHCCH$_3$ (O)	C_2H_5OH–H_2O	187.0–188.0	33.3
11	$N(C_2H_5)_2$	NH_2	C_2H_5OH–H_2O	157.0–159.0	24.4
12	Morpholino	H	Methyl cellosolve–H_2O	235.0–236.0	75.6
13	Morpholino	CH_3	C_2H_5OH	219.0–220.0	46.0
14	Morpholino	NHCCH$_3$ (O)	Methyl cellosolve–H_2O	252.0–253.0	66.9
15	Morpholino	NH_2	Methyl cellosolve–H_2O	239.0–240.0	56.8
16	Piperidino	H	C_2H_5OH	226.0–227.0	28.7
17	Piperidino	CH_3	C_2H_5OH–H_2O	173.0–174.0	23.2
18	Piperidino	NHCCH$_3$ (O)	C_2H_5OH–H_2O	222.0–223.0	27.4
19	Piperidino	NH_2	C_2H_5OH–H_2O	223.0–224.0	25.4
20	Pyrrolidino	H	Methyl cellosolve–H_2O	208.0–209.0	23.1
21	Pyrrolidino	CH_3	C_2H_5–H_2O	180.0–182.0	29.7
22	Pyrrolidino	NHCCH$_3$ (O)	C_2H_5OH–H_2O	214.0–215.0	33.6
23	Pyrrolidino	NH_2	C_2H_5OH–H_2O	226.0–227.0	24.7

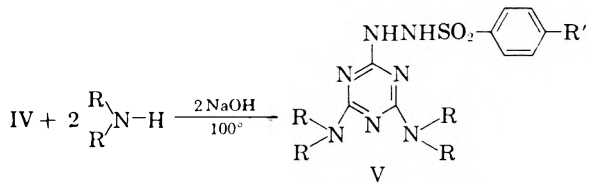
[a] All melting points were taken on a calibrated Fisher-Johns melting point apparatus. [b] Average yield.





The 2,4-dichloro-6-arylsulfonylhydrazido-*s*-triazines (IV) react with secondary amines to form 2,4-diamino-6-arylsulfonylhydrazido-*s*-triazines (V) in fair yields. The majority of these reactions ran smoothly in water at reflux temperature using aqueous sodium hydroxide as the hydrochloric acid acceptor.

When diethylamine was reacted with the dichloro-*s*-triazines in water, little or no final product was obtained. However, when toluene was used as reaction solvent and excess diethylamine as the hydrochloric acid acceptor, the desired products were formed in fair yields.



One of the sulfonylhydrazides utilized in this work was acetylsulfanilylhydrazide (II, R′ = NHCCH$_3$ (O)) which yielded a series of compounds (VI) which could be hydrolyzed to the corresponding free amino compounds (VII). This hydrolysis

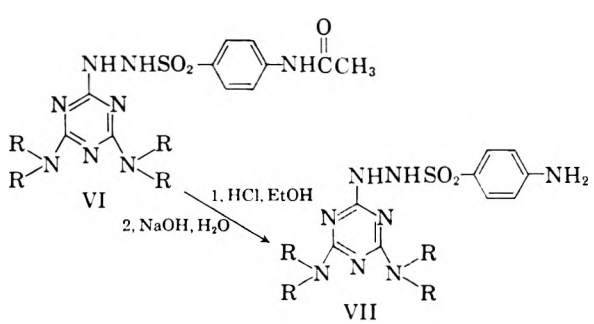
TABLE II

ANALYTICAL DATA[a]

Compound	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
1	$C_9H_7N_5O_2SCl_2 \cdot 2H_2O$[b]	—	—	—	—	—	—
2	$C_{10}H_9N_5O_2SCl_2 \cdot 2H_2O$[c]	—	—	—	—	—	—
3	$C_{11}H_{10}N_6O_3SCl_2 \cdot 2H_2O$[d]	—	—	—	—	—	—
4	$C_{13}H_{19}N_7O_2S$	46.28	46.43	5.68	6.07	29.06	29.27
5	$C_{14}H_{21}N_7O_2S$	47.84	47.77	6.02	6.31	27.90	27.82
6	$C_{15}H_{22}N_8O_3S$	45.66	45.96	5.62	5.67	28.40	28.23
7	$C_{13}H_{20}N_5O_3S$	44.30	44.51	5.72	5.85	31.80	31.87
8	$C_{17}H_{27}N_7O_2S$	51.89	51.96	6.92	6.98	24.92	24.71
9	$C_{18}H_{29}N_7O_2S$	53.05	53.10	7.17	7.30	24.06	24.28
10	$C_{19}H_{30}N_8O_3S$	50.64	50.75	6.71	6.71	24.86	24.96
11	$C_{17}H_{28}N_8O_2S$	49.98	50.25	6.91	6.91	27.43	27.07
12	$C_{17}H_{23}N_7O_4S$	48.44	48.96	5.51	5.92	23.26	22.85
13	$C_{18}H_{25}N_7O_4S$	49.64	50.05	5.79	6.28	22.51	22.57
14	$C_{19}H_{26}N_8O_3S$	47.69	47.78	5.47	5.62	23.41	23.79
15	$C_{17}H_{21}N_8O_4S$[e]	46.78	47.01[f]	5.54	5.86[f]	25.67	24.44[g]
16	$C_{19}H_{27}N_7O_2S$	54.65	55.37	6.52	6.58	23.48	23.56
17	$C_{20}H_{29}N_7O_2S$	55.66	56.00	6.77	6.91	22.72	22.80
18	$C_{21}H_{30}N_8O_3S$	53.14	53.18	6.37	6.53	23.61	23.52
19	$C_{19}H_{28}N_8O_2S$	52.76	52.84	6.52	6.69	25.91	26.45
20	$C_{17}H_{23}N_7O_2S$	52.42	52.41	5.95	6.02	25.18	24.79
21	$C_{19}H_{25}N_7O_2S$	53.58	53.04	6.25	6.28	24.30	23.88
22	$C_{19}H_{26}N_8O_2S$	51.11	50.41	5.86	6.21	25.09	25.06
23	$C_{17}H_{24}N_8O_2S$	50.48	50.26	5.98	6.09	27.70	27.75

[a] Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. [b] % H_2O: Calcd. 10.12%; found 9.50%. [c] % H_2O: Calcd. 9.73%; found 10.38%. [d] % H_2O: Calcd. 8.73%; found 8.78%. [e] Analysis shows that compound contains 5 ± 1% of methylcellosolve trapped in the crystal structure. [f] Average of three analyses. [g] Average of six analyses.

was carried out by refluxing the acetyl compounds with excess hydrochloric acid in 95% ethanol, neutralizing the resulting solution with 2*N* sodium hydroxide and precipitating the free amino compounds with water.



The arylsulfonylhydrazide derivatives of *s*-triazine prepared in this work are described in Table I and the analytical data are given in Table II.

EXPERIMENTAL

Preparation of arylsulfonylhydrazides. A solution of 1 mol. (100 g.) of hydrazine (64% aqueous) in an equal volume (100 ml.) of water or ethanol was prepared in a 1-l. three-necked flask equipped with agitation and thermometer and cooled to 0–10° in an ice bath. A 0.5-mol. sample of the arylsulfonyl chloride was added in small portions over a period of 1.5 hr., and the reaction mixture was agitated for an additional 1.5 hr. at ice bath temperature. More water or ethanol was added as needed during the addition, to allow complete mixing and to prevent caking of the solids. The crude product was collected by filtration, washed with water and toluene, and dried in a vacuum desiccator. The yields averaged 70–90%. Further purification could be accomplished by dissolving the crude product in boiling water (3–4 l.), filtering, and cooling the solution immediately. However, this lowered the yields and was unnecessary for the purpose of this work.

Preparation of 2,4-dichloro-6-arylsulfonylhydrazido-s-triazines. Cyanuric chloride (9.2 g., 0.05 mol.) and sodium bicarbonate (4.1 g., 0.05 mol.) were slurried in 100 ml. of a dioxane:water mixture in a 250-ml. three-necked flask equipped with agitation and thermometer and cooled to 0–10° in an ice bath. The arylsulfonyl hydrazide (0.05 mol.) was added in small portions over a period of 0.5 hr. and the reaction mixture was agitated for an additional 1 hr. at ice bath temperature and poured into 400 ml. of ice water. The product in some cases separated as a gummy semisolid which solidified on standing. This was collected by filtration, washed with water and toluene, and dried in a vacuum desiccator.

Preparation of 2,4-diamino-6-arylsulfonylhydrazido-s-triazines. A slurry of the 2,4-dichloro-6-arylsulfonylhydrazido-*s*-triazine (0.01 mol.) in 100 ml. of water was prepared in a 300-ml. three-neck flask equipped with agitation, reflux condenser, and dropping funnel. A solution of the desired amine (0.02 mol.) in 25 ml. of water was added over a period of 15 min. and the reaction mixture was heated to reflux. A few drops of phenolphthalein were added and 10 ml. of 2*N* sodium hydroxide (0.02 mol.) was added over a period of 15 to 30 min. at such a rate that the solution was always neutral or just slightly basic. The reaction mixture was refluxed for 2 to 3 hr., cooled, and filtered. The crude product was washed with water, recrystallized from the appropriate solvent, after clarification with activated charcoal, (Norit A or Darco G) and dried in a vacuum oven at 100° for 12 to 24 hr.

Preparation of 2,4-bis(diethylamino)-6-arylsulfonylhydrazido-s-triazines. A slurry of 2,4-diehloro-6-arylsulfonylhydrazido-*s*-triazine (0.01 mol.) in 75 ml. of toluene was prepared in a 300-ml. three-neck flask equipped with agitation, reflux condenser, and dropping funnel, and heated to reflux. A solution of diethylamine (3.1 g., 0.04 mol.) in 50

ml. of toluene was added over a period of 2 hr. and the reaction mixture was refluxed for an additional 5 hr. The hot toluene solution was decanted to a beaker, evaporated to one-fourth volume by a stream of air, and filtered. This solid was combined with any residue in the reaction flask, recrystallized from the appropriate solvent, after clarification with activated charcoal (Norit A or Darco G), and dried in a vacuum oven at 100° for 12 to 24 hr.

Preparation of 2,4-diamino-6-sulfanilylhydrazido-s-triazines from 2,4-diamino-6-acetylsulfanilylhydrazido-s-triazines. The 2,4-diamino-6-acetylsulfanilylhydrazido-s-triazine (0.01 mol.) was dissolved in 30 ml. of ethanol, to which 5 ml. of concentrated hydrochloric acid (0.05 mol.) had been added, in a 100-ml. flask equipped with a reflux condenser. The solution was refluxed on a steam bath for 1 to 2 hr., cooled, and made basic to phenolphthalein with 2*N* sodium hydroxide. The crude product was precipitated by flooding the solution with 300 ml. of water and was collected by filtration, washed with water, and recrystallized from the appropriate solvent, after clarification with activated charcoal (Norit A or Darco G), and dried in a vacuum oven at 100° for 12 to 24 hr.

Acknowledgment. The authors wish to express their sincere gratitude to the University of Notre Dame, U. S. Rubber Co., Monsanto Chemical Co., and the National Science Foundation for their generous grants of fellowships which made this work possible.

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

Preparation of 2,4-Dinitrophenylhydrazine Derivatives of Highly Oxygenated Carbonyl Compounds

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The reaction of α-hydroxycarbonyl compounds with 2,4-dinitrophenylhydrazine in boiling aqueous ethanol (90%) or in 2*N* hydrochloric acid (supersaturated with the reagent) at 0° has been shown to proceed to hydrazone formation without oxidation of the hydroxyl group. Chromatographic purification of reaction products demonstrated that other experimental conditions can lead to osazone formation accompanied by reduction of the terminal hydroxymethyl group to methyl. The reaction of triose reductone with 2,4-dinitrophenylhydrazine has been shown to proceed with oxidation. The 1,2-bis(2,4-dinitrophenylhydrazone) of mesoxaldehyde has been synthesized by a definitive method and converted to the tris derivative. The absorption spectrum of mesoxaldehyde 1,2-bis(2,4-dinitrophenylhydrazone) was markedly affected by the solvent medium. An explanation for this behavior is proposed.

In connection with the ignition decomposition of cellulose nitrate,[2] we became interested in 2,4-dinitrophenylhydrazine derivatives of short carbon chain (two and three carbon atoms) sugars and nonfragmented oxidation products thereof. These derivatives, and in some cases the parent carbonyl compounds as well, were little or not known. In addition, when literature was available on these 2,4-dinitrophenylhydrazine derivatives, it was often contradictory. The reactivity of α-hydroxycarbonyl compounds toward 2,4-dinitrophenylhydrazine is a case in point since some workers[3,4] have reported the sole formation of 2,4-dinitrophenylosazones whereas other workers[5–7] have been able to prepare the 2,4-dinitrophenylhydrazones. In the work herein reported, the reaction of glycolaldehyde, acetol (CH_3—CO—CH_2OH), dihydroxyacetone, and DL-glycerose (glyceraldehyde) with 2,4-dinitrophenylhydrazine in boiling ethanol, a method of preparing 2,4-dinitrophenylhydrazine derivatives introduced by Brady and Elsmie[8] and used by Reich and Samuels[7] to prepare the 2,4-dinitrophenylhydrazones of α-hydroxycarbonyl compounds, was shown to proceed without oxidation and, in the case of dihydroxyacetone and DL-glycerose, without hydroxymethyl group reduction[9] as well. These facts were established by isolative column chromatography[10] of the reaction products. By means of the same chromatographic method, it was shown that the use of a supersaturated solution of 2,4-dinitrophenylhydrazine in 2*N* hydrochloric acid at 0°, a reagent solution used by Collatz and Neuberg[5] to prepare glycolaldehyde 2,4-dinitrophenylhydrazone, to form a derivative of DL-glycerose resulted in no oxidation or reduction.[9]

Since dihydroxyacetone and glycerose are known to be converted to methylglyoxal in the presence of

(1) Fellow of The Monsanto Chemical Co. (1956–57).

(2) M. L. Wolfrom and G. P. Arsenault, *J. Am. Chem. Soc.*, in press.

(3) W. H. Linnell and I. Roushdi, *Quart. J. Pharm. Pharmacol.*, **12**, 252 (1939).

(4) T. Banks, C. Vaughn, and L. M. Marshall, *Anal. Chem.*, **27**, 1348 (1955).

(5) H. Collatz and Irene S. Neuberg, *Biochem. Z.*, **255**, 27 (1932).

(6) D. B. Sprinson and E. Chargaff, *J. Biol. Chem.*, **164**, 417 (1946).

(7) H. Reich and Barbara K. Samuels, *J. Org. Chem.*, **21**, 68 (1956).

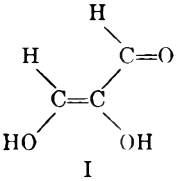
(8) O. L. Brady and Gladys V. Elsmie, *Analyst*, **51**, 77 (1926).

(9) C. L. Bernier and W. L. Evans, *J. Am. Chem. Soc.*, **60**, 1381 (1938).

(10) M. L. Wolfrom and G. P. Arsenault, *Anal. Chem.*, in press.

an acid catalyst,[9] reports of the preparation, starting from either of these trioses and using an acid catalyst, of hydroxypyruvaldehyde bis(2,4-dinitrophenylhydrazone) should be viewed with suspicion unless some evidence is presented to establish the absence of methylglyoxal bis(2,4-dinitrophenylhydrazone) in the product. No such evidence was shown by Reich and Samuels[7] and we have established the presence of methylglyoxal bis(2,4-dinitrophenylhydrazone) in the product obtained following their procedure. However, their product afforded hydroxypyruvaldehyde bis(2,4-dinitrophenylhydrazone) after chromatographic purification.

The reaction of mesoxaldehyde with an excess of 2,4-dinitrophenylhydrazine in hot 2*N* hydrochloric acid afforded a product which after chromatographic purification was shown to be the tris derivative. Triose reductone (I)



I

also afforded mesoxaldehyde tris(2,4-dinitrophenylhydrazone) when reacted at room temperature with an excess of reagent in 30% perchloric acid according to the procedure of Neuberg and coworkers.[11] In addition, several attempts were made to prepare a mono and a bis(2,4-dinitrophenylhydrazone) of triose reductone. The products thus obtained always contained a considerable amount of polymeric material and the only well defined constituents of these products were derivatives of mesoxaldehyde. The ease with which triose reductone was oxidized to mesoxaldehyde by 2,4-dinitrophenyhydrazine was not unexpected since reductones are strong reducing agents.[12] In addition, triose reductone had previously been shown to afford a mesoxaldehyde derivative when reacted with phenylhydrazine at room temperature.[13]

The periodate oxidation of D-*arabino*-hexose (D-glucose) 2,4-dinitrophenylosazone, carried out in *N*,*N*-dimethylformamide–water, afforded mesoxaldehyde 1,2-bis(2,4-dinitrophenylhydrazone). This derivative was identical with that obtained by reacting equimolar amounts of mesoxaldehyde and 2,4-dinitrophenylhydrazine in ethanol at room temperature. No method was found by which mesoxaldehyde 1,3-bis(2,4-dinitrophenylhydrazone) could be obtained by the action of 2,4-dinitrophenylhydrazine with mesoxaldehyde. The conversion of mesoxaldehyde 1,2-bis(2,4-dinitrophenylhydrazone) into the tris derivative was accomplished in dimethyl sulfoxide–water.

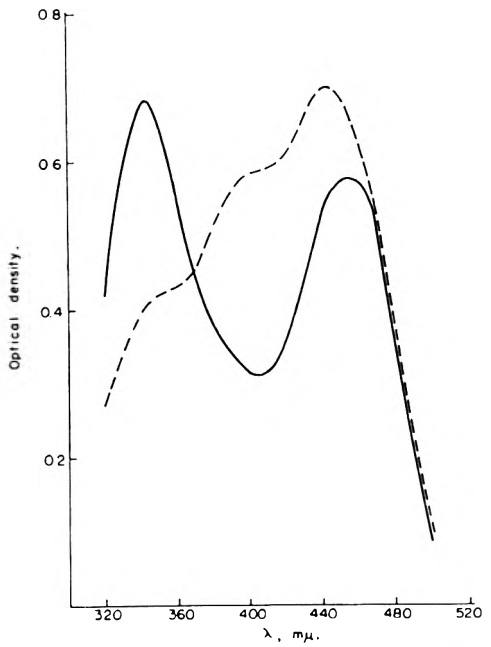
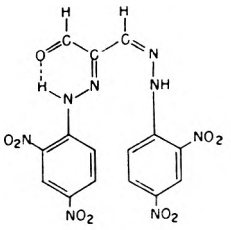
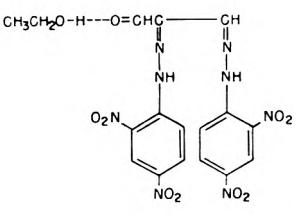


Fig. 1. Absorption spectrum of mesoxaldehyde 1,2-bis(2,4-dinitrophenylhydrazone); ———, in ethyl acetate; – – –, in ethanol (96%); *c* 0.0007

The absorption spectra of mesoxaldehyde 1,2-bis(2,4-dinitrophenylhydrazone) in ethanol (96%) and in ethyl acetate are shown in Fig 1. The difference between these two spectra is very marked and no solvent effect of this kind has heretofore been reported in the case of derivatives of 2,4-dinitrophenylhydrazine. It is suggested that this difference may be due to hydrogen bonding, since the hydrogen bonded species II may predominate in ethyl acetate, whereas the hydrogen bonded species III may predominate in ethanol (96%).



II



III

The bis- and tris(2,4-dinitrophenylhydrazones) which we prepared could not be obtained in a chromatographically pure form by recrystallization. The extreme insolubility of these compounds makes chromatographic treatment quite difficult. However, it was possible to purify these compounds by silicic acid chromatography using a method which bears some resemblance to the method of

(11) C. Neuberg, A. Grauer, and B. V. Pisha, *Anal. Chim. Acta*, **7**, 238 (1952).

(12) H. v. Euler and H. Hasselquist, *Reduktone. Ihre chemischen Eigenschaften und biochemischen Wirkungen*, 1st Ed., F. Enke, Stuttgart, Germany, 1950, p. 1.

(13) H. v. Euler, H. Hasselquist, and L. Lööv, *Arkiv Kemi, Mineral. Geol.*, 26A, No. 17 (1948).

frontal analysis of Tiselius, Claesson and collaborators.[14]

EXPERIMENTAL[15]

Hydroxypyruvaldehyde bis(2,4-dinitrophenylhydrazone). The method of preparation described by Reich and Samuels[7] was followed. Dihydroxyacetone (0.6 g.) was added to a solution of 4 g. of 2,4-dinitrophenylhydrazine in 1 l. of 2*N* hydrochloric acid. After being stirred to insure the complete solution of dihydroxyacetone, the preparation was allowed to stand for 3 days at 25°. The precipitate was filtered, and washed with 2*N* hydrochloric acid and water; yield 2.9 g. (97%). This product was extracted with chloroform and recrystallized from nitrobenzene to constant melting point; m.p. 280–284° (dec.), intermediate between those of hydroxypyruvaldehyde bis(2,4-dinitrophenylhydrazone) (see below) and methylglyoxal bis(2,4-dinitrophenylhydrazone) [m.p. 304.5–305.5° (dec.)]. Exploratory chromatograms, developed with benzene, of the crude reaction product and of the recrystallized material on silicic acid–Celite (5:1; 8% water)[10] revealed in each case the presence therein of two constituents, the less adsorbed of which had chromatographic properties identical with those of methylglyoxal bis(2,4-dinitrophenylhydrazone). Thus, hydroxypyruvaldehyde bis(2,4-dinitrophenylhydrazone) could not be obtained directly in a pure state by the procedure of Reich and Samuels.[7]

Methylglyoxal, a substance found in aged dihydroxyacetone,[16] was not present in the sample of dihydroxyacetone used in the above preparation. This fact was shown by refluxing a mixture of 0.99 g. of the dihydroxyacetone and 1.98 g. of 2,4-dinitrophenylhydrazine in 20 ml. of absolute ethanol for 3 hr. A clear orange solution resulted, indicating the absence of methylglyoxal bis(2,4-dinitrophenylhydrazone) in the reaction product since this substance is highly insoluble in ethanol.

The crude reaction product (500 mg.) obtained following the procedure of Reich and Samuels[7] was dissolved in 250 ml. of warm nitrobenzene. The solution was diluted with 1 l. of benzene and immediately adsorbed on a column (5.4 cm., diam., × 10 cm.) of silicic acid-Celite (5:1). Prior to use this adsorbent was dried overnight at 200°[17, 18] and will be referred to as (5:1; 0% water). The chromatogram was developed with 3.5 l. of benzene. The material obtained by elution with acetone of the orange-red zone located 2–45 mm. from the top of the column was rechromatographed and recrystallized from nitrobenzene to constant melting point; yield 35 mg., red needles, m.p. 267–268° (dec.) (lit.,[7] m.p. 278°); maxima in ethyl acetate at 400 and 437 mμ. This material was chromatographically pure and contained no methylglyoxal bis(2,4-dinitrophenylhydrazone).

Anal. Calcd. for $C_{15}H_{12}N_8O_9$: C, 40.18; H, 2.70; N, 25.00. Found: C, 40.19; H, 2.78; N, 24.94.

A second crop of chromatographically pure hydroxypyruvaldehyde bis(2,4-dinitrophenylhydrazone) was obtained from the nitrobenzene mother liquors; yield 60 mg., m.p. 268–272° (dec.).

The nitrobenzene-benzene effluent (400 ml.) from the above chromatogram was adsorbed on a column (5.4 cm., diam., × 20 cm.) of silicic acid–Celite (5:1; 0% water) and developed with 2 l. of benzene. The material in the orange zone located 20–100 mm. from the column top was extracted with boiling ethanol and identified as methylglyoxal bis-(2,4-dinitrophenylhydrazone) by infrared spectrum.

Mesoxaldehyde tris(2,4-dinitrophenylhydrazone). (a) Triose reductone, prepared as described by Bauer and Teed,[19] was oxidized to mesoxaldehyde with selenium dioxide following the procedure of Holker.[20] To a solution of 196 mg. of mesoxaldehyde in 10 ml. of water was added a solution of 2 g. of 2,4-dinitrophenylhydrazine in 250 ml. of 2*N* hydrochloric acid. The reaction mixture was heated at 90° for 3 hr. The material that separated was collected, and washed with 2*N* hydrochloric acid and water; yield 1.22 g. (86%), m.p. 286–288° (dec.). An exploratory chromatogram, developed with benzene, on silicic acid–Celite (5:1; 8% water) revealed the presence of three constituents in this material. The major constituent, least adsorbed, could not be obtained in a chromatographically pure form by recrystallization of the crude material from nitrobenzene.

An amount (500 mg.) of the 2,4-dinitrophenylhydrazine derivative of mesoxaldehyde was dissolved in 500 ml. of warm nitrobenzene. The solution was diluted with 2 l. of benzene and immediately adsorbed on a column (5.4 cm., diam., × 6 cm.) of silicic acid-Celite (5:1; 0% water). The chromatogram was developed with 870 ml. of nitrobenzene-benzene (1:4 by vol.) and 100 ml. of benzene. The red material obtained, on solvent removal under reduced pressure, from the column effluent was extracted with two 40-ml. portions of boiling chloroform and recrystallized from nitrobenzene to constant melting point; yield 93 mg., m.p. 306–308° (dec.); maxima in ethyl acetate at 402 and 465 mμ. This product, microscopic red needles, was chromatographically pure and no carbonyl absorption band was found in its infrared spectrum.

Anal. Calcd. for $C_{21}H_{14}N_{12}O_{12}$: C, 40.26; H, 2.25; N, 26.84. Found: C, 40.41; H, 2.39; N, 26.82.

A second crop of chromatographically pure mesoxaldehyde tris(2,4-dinitrophenylhydrazone) was obtained from the nitrobenzene mother liquors; yield 35 mg.

(b) An amount of 50 mg. of triose reductone,[19] dissolved in 5 ml. of water, was added to 1.2 g. of 2,4-dinitrophenylhydrazine in 50 ml. of 30% perchloric acid.[11] The mixture was allowed to stand at room temperature, in the dark, under nitrogen, for 48 hr. The precipitate was filtered and washed with water; yield 360 mg. (106%). The brick red product (200 mg.) was dissolved in 200 ml. of warm nitrobenzene. The solution was diluted with 800 ml. of benzene and immediately adsorbed on a column (3.5 cm., diam., × 6 cm.) of silicic acid-Celite (5:1; 0% water). The chromatogram was developed with 75 ml. of benzene. A red solid slowly precipitated out of the column effluent which stood at 4° for 5 days. The precipitate was filtered, and washed with nitrobenzene-benzene (1:4) and ether; yield 61 mg., red micro needles, m.p. 300–302° (dec.) undepressed on admixture with authentic mesoxaldehyde tris(2,4-dinitrophenylhydrazone). The identity of this precipitate with a specimen of mesoxaldehyde tris(2,4-dinitrophenylhydrazone) was further demonstrated by comparison of their chromatographic properties and infrared spectra.

Several attempts were made to prepare a mono and a bis(2,4-dinitrophenylhydrazone) of triose reductone. In all cases, even when the preparations were carried out in the absence of an acid catalyst, the products obtained contained a considerable amount of polymeric material and the only well defined constituents of these products were derivatives of mesoxaldehyde.

(14) E. Lederer and M. Lederer, *Chromatography. A Review of Principles and Applications*, 1st Ed., Elsevier Publishing Co., New York, N. Y., 1953, p. 3.

(15) All melting points were taken on a Kofler micro hot stage and are corrected. The ultraviolet absorption spectra, in the range 320–600 mμ, were taken in a Beckman spectrophotometer, Model DU. The infrared spectra were obtained with a Perkin-Elmer spectrophotometer Model 21 using the potassium bromide pellet technique.

(16) P. A. Levene and A. Walti, *J. Biol. Chem.*, **78**, 23 (1928).

(17) K. N. Trueblood and E. W. Malmberg, *Anal. Chem.*, 21, 1055 (1949).

(18) K. N. Trueblood and E. W. Malmberg, *J Am. Chem. Soc.*, 72, 4112 (1950).

(19) H. F. Bauer and Carol Teed, *Can. J. Chem.*, **33**, 1824 (1955).

(20) J. R. Holker, *J. Chem. Soc.*, 579 (1955).

D-*Arabino-Hexose* (D-*glucose*) *2,4-dinitrophenylosazone*. The procedure of Neuberg and Strauss[21] was followed. α-D-Glucose monohydrate (5 g.), dissolved in 50 ml. of water, was added to a hot solution of 14.9 g. of 2,4-dinitrophenylhydrazine in 900 ml. of 2*N* hydrochloric acid to which 9 ml. of ethanol (96%) had been added. The mixture was heated on a steam bath for 20 hr. The hot suspension was filtered, and the residue was washed with 2*N* hydrochloric acid and water; yield 13.0 g. (96%). The product was reddish brown and partially crystalline. It melted below 245° over a very wide range in temperature and contained much tar. Thus, the claim made by Neuberg and Strauss[21] for the preparation of crystalline D-glucose 2,4-dinitrophenylosazone is misleading. However, the product obtained by their method of preparation was readily purified since 2,4-dinitrophenylhydrazine tars were found to be very soluble in nitrobenzene. Thus, the crude product (8 g.) was extracted repeatedly with portions of nitrobenzene. On repeated extraction, the color of the nitrobenzene extracts changed from black to orange. The extraction residue was recrystallized once from nitrobenzene; yield 2.3 g., reddish orange microscopic needles, m.p. 263–267° (dec.) [lit.,[22] m.p. 256–257° (dec.)] unchanged by further recrystallization from nitrobenzene.

Anal. Calcd. for $C_{18}H_{18}N_8O_{12}$: C, 40.15; H, 3.37; N, 20.81. Found: C, 40.22; H, 3.51; N, 20.56.

Mesoxaldehyde 1,2-bis(2,4-dinitrophenylhydrazone). (a) An amount of 5 g. of D-*arabino*-hexose (D-glucose) 2,4-dinitrophenylosazone was dissolved in 500 ml. of *N*,*N*-dimethylformamide. While the solution was stirred and cooled in ice, 10.65 g. of paraperiodic acid (H_5IO_6), dissolved in 125 ml. of water, was added slowly. Stirring was continued for 30 min. The precipitate was filtered, and washed with a little *N*,*N*-dimethylformamide, water and acetone; yield 1.90 g. (46%), m.p. 250–253° (dec.). An exploratory chromatogram, developed with benzene, on silicic acid–Celite (5:1; 8% water)[10] revealed the presence of two constituents in this material. The major constituent, less adsorbed, could not be obtained in a chromatographically pure form by recrystallization from nitrobenzene (150°) since it was somewhat sensitive to heat.

The crude preparation (1 g.) was dissolved in 500 ml. of warm nitrobenzene. The solution was diluted with 2 l. of benzene and immediately adsorbed on a column (5.4 cm., diam., 5.5 × cm.) of silicic acid–Celite (5:1; 0% water). The chromatogram was developed with 160 ml. of nitrobenzene-benzene (1:4) and 200 ml. of benzene. A reddish orange crystalline (fine needles) precipitate formed in the column effluent when it stood at 4° for 24 hr.; yield 567 mg., m.p. 262–269° (dec.), infrared band at 6.0μ. This mesoxaldehyde 1,2-bis(2,4-dinitrophenylhydrazone) was chromatographically pure and its absorption spectrum is shown in Fig. 1.

Anal. Calcd. for $C_{15}H_{10}N_8O_9$: C, 40.36; H, 2.26; N, 25.11. Found: C, 40.51; H, 2.28; N, 25.11.

(b) A solution of 100 mg. of mesoxaldehyde[20] in 2 ml. of water was added to a suspension of 230 mg. of 2,4-dinitrophenylhydrazine in 48 ml. of absolute ethanol. The suspension was shaken at room temperature for 28 hr., filtered, and washed with ethanol (96%) and acetone; yield 66 mg. (25%). The product (60 mg.) was purified using the chromatographic method described in section (a) above; yield 35 mg., fine reddish orange needles, m.p. 263–269° (dec.) undepressed on admixture with authentic mesoxaldehyde 1,2-bis(2,4-dinitrophenylhydrazone). The chromatographic properties, the infrared absorption spectra, and the ultraviolet and visible absorption spectra of this material and of authentic mesoxaldehyde 1,2-bis(2,4-dinitrophenylhydrazone) were identical.

Conversion of mesoxaldehyde 1,2-bis(2,4-dinitrophenylhydrazone) into mesoxaldehyde tris(2,4-dinitrophenylhydrazone). To an amount of 100 mg. of mesoxaldehyde 1,2-bis(2,4-dinitrophenylhydrazone), dissolved in 100 ml. of warm dimethyl sulfoxide, was added 53 mg. of 2,4-dinitrophenylhydrazine and one drop of concentrated hydrochloric acid. The mixture was allowed to stand at room temperature for 3 days, during which time a total of 20 ml. of water was added to it in small aliquots at regular intervals. The preparation was centrifuged, and the residue was washed with dimethyl sulfoxide–water (4:1), water and acetone; yield 139 mg. (99%), red microscopic needles, m.p. 295–297° (dec.). After one recrystallization from nitrobenzene, a product of m.p. (and mixed melting point with authentic material) 306–308° (dec.) was obtained. The identity of this product with mesoxaldehyde tris(2,4-dinitrophenylhydrazone) was further shown by comparative chromatograms and infrared spectra.

Attempted preparation of mesoxaldehyde 1,3-bis(2,4-dinitrophenylhydrazone). Some eight separate and unsuccessful attempts were made to prepare mesoxaldehyde 1,3-bis(2,4-dinitrophenylhydrazone) by reacting mesoxaldehyde[20] with 2,4-dinitrophenylhydrazine in different solvent media. In five cases, precipitates were obtained and these precipitates were shown to contain no mesoxaldehyde derivative other than mesoxaldehyde 1,2-bis(2,4-dinitrophenylhydrazone) or mesoxaldehyde tris (2,4-dinitrophenylhydrazone) or both.

Reaction of 2,4-dinitrophenylhydrazine with α-hydroxycarbonyl compounds. (a) To an amount of 20 mmol. (1.8 g.) of DL-glycerose dimer dissolved in 10 ml. of hot water was added a suspension of 60 mmol. (11.9 g.) of 2,4-dinitrophenylhydrazine in 100 ml. of absolute ethanol. After refluxing for 16 hr., the suspension was filtered while still hot. The filtration residue, the evaporation residue obtained on solvent removal under reduced pressure from the filtrate, and a synthetic mixture of derivatives of 2,4-dinitrophenylhydrazine were chromatographed simultaneously, on separate columns, on silicic acid–Celite (5:1; 8% water) using successively benzene, ether-benzene (1:19) and ether-benzene (1:4) as developer, according to the method of Wolfrom and Arsenault.[10] The synthetic mixture contained DL-glycerose 2,4-dinitrophenylhydrazone, hydroxypyruvaldehyde bis(2,4-dinitrophenylhydrazone), 2,4-dinitrophenylhydrazine, methylglyoxal bis(2,4-dinitrophenylhydrazone) and 2,4-dinitroaniline. By means of this method of chromatographic comparison, it was shown that the filtration residue contained only 2,4-dinitrophenylhydrazine, and that the evaporation residue contained 2,4-dinitrophenylhydrazine and DL-glycerose 2,4-dinitrophenylhydrazone.

A method identical to that just described was used to show that the reaction of glycolaldehyde, acetal, and dihydroxyacetone with 2,4-dinitrophenylhydrazine, in refluxing ethanol, takes place without any oxidation of the hydroxyl group and, in the case of dihydroxyacetone, without rearrangement[9] as well. In these three cases, a carbonyl compound-reagent molar ratio of 1.0:0.9 was used and the preparations were refluxed for 3 hr.

(b) A solution of 4.0 g. (44 mmol.) of DL-glycerose dimer in 25 ml. of water at 0° was added to a supersaturated solution of 8.0 g. (40 mmol.) of 2,4-dinitrophenylhydrazine in 480 ml. of 2*N* hydrochloric acid at 0°. After the preparation stood at 0° for 6 hr., the precipitate was filtered, and washed with 2*N* hydrochloric acid and water; yield 10.0 g. (92%). The crude preparation was shown by the method of comparative chromatography described in section (a) above to contain only DL-glycerose 2,4-dinitrophenylhydrazone.

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(22) E. Glaser and N. Zuckermann, *Z. physiol. Chem.*, 167, 37 (1927).

[CONTRIBUTION FROM THE CHARLES F. KETTERING FOUNDATION]

Preparation of the Hydrazone and Azine of Pyridoxal-5-Phosphate

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In connection with some biochemical experiments, pure hydrazine derivatives of pyridoxal-5-phosphate were desired. Pyridoxal-5-phosphate hydrazone was prepared from pyridoxal-5-phosphate in the presence of a ten-fold excess of hydrazine and obtained in pure crystalline form by controlled acidification. It was also prepared from the corresponding azine in the presence of excess hydrazine. Pyridoxal-5-phosphate azine was also prepared from pyridoxal-5-phosphate and hydrazine. Both compounds were purified by recrystallization and examined for homogeneity by colorimetric analysis of their hydrazine content and by paper chromatography. The ultraviolet absorption spectra were examined in 0.1*N* hydrochloric acid and 0.1*M* potassium phosphate *p*H 7. Observations indicative of the instability of the azine in these solvents are presented.

The involvement of pyridoxal-5-phosphate as the coenzyme in many enzymatic reactions of amino acids is well established. These have recently been reviewed by Meister.[1] The compound is also found as the prosthetic group of crystalline muscle phosphorylase.[2] In connection with some biochemical experiments, hydrazine derivatives of pyridoxal-5-phosphate were desired.

This paper desdribes the preparation and some properties of pyridoxal-5-phosphate hydrazone and of the corresponding azine. The hydrazone was prepared by addition of the aldehyde to a ten-fold excess of hydrazine hydrate. The azine was prepared by adding hydrazine hydrate to a solution of pyridoxal phosphate. Both compounds can be purified by recrystallization induced by controlled acidification of the potassium salts.

EXPERIMENTAL

Pyridoxal-5-phosphate hydrazone (2-methyl-3-hydroxy-4-formyl-5-pyridylmethylphosphoric acid hydrazone). Pyridoxal phosphate[3] (0.330 g.) was dissolved in 20 ml. of distilled water at 55–60°. The resulting solution was added dropwise with stirring to a 10-fold excess of hydrazine hydrate (0.714 g. of an 85% solution) in 15 ml. of water at 55–60°. The mixture was maintained at the 55–60° temperature for 10 min. and then filtered. Filter and beaker were washed with a total of 5 ml. of water which was added to the main filtrate. Hydrochloric acid (0.1*N*) was added dropwise, reducing the *p*H to 5.7, at which point feathery crystals began to appear. As preliminary work had demonstrated that a somewhat discolored and impure product is obtained at low *p*H values, acidification was stopped at *p*H 5.7 and the solution allowed to stand for 2 hr.

The fine near-white needles with a barely perceptible yellow tinge were collected by suction filtration, washed twice with distilled water, three times with 95% ethanol, and six times with ether. The product was dried over phosphorus pentoxide at atmospheric pressure and stored in air. The yield was 0.161 g. (47.6%). Examination of the melting characteristics revealed preliminary darkening at 227° followed by decomposition at 236–237°. Analysis of the products agreed with theoretical values calculated for the monohydrate.

Anal. Calcd. for $C_8H_{12}O_5N_3P \cdot H_2O$: C, 34.45; H, 5.06; N, 15.00; P, 11.10. Found: C, 34.51; H, 5.25; N, 15.02; P, 11.10. The expected water of hydration was lost upon heating to constant weight at 120°.

A second batch of crystals was obtained from the filtrate, which had a *p*H value of 6.1 after removal of the first crystals, by the dropwise addition of 0.1*N* hydrochloric acid to *p*H 5.6. After standing overnight the crystals were collected and washed as described above. The yield was 0.066 g. (19.5%). These crystals appeared to be identical with those obtained in the first crystallization and had the same melting characteristics. The combined yield was thus increased to 67.3%.

Recrystallization of similarly prepared material has been effected by suspending the material in water and dissolving with the dropwise addition of 0.1*N* potassium hydroxide, filtering, and lowering the *p*H to 5.7 by the dropwise addition of 0.1*N* hydrochloric acid. The recovered material (60%) gave the same carbon-hydrogen analysis as the original preparation and exhibited the same melting characteristics.

Careful control of *p*H is recommended. When uncontrolled acidification is used, a discolored and impure product is obtained. When, for example, in an otherwise identical procedure, the *p*H during the crystallization was allowed to drop to 3.0, dark pink-brown needles were obtained which darkened at 217° and decomposed at 230–231°. This material can be recrystallized as described above to produce the pure product. The final yield, however, is reduced to 36%.

Pyridoxal-5-phosphate azine (2-methyl-3-hydroxy-4-formyl-5-pyridylmethylphosphoric acid azine). Hydrazine hydrate (0.136 g. of an 85% solution) was added with stirring to a solution of pyridoxal phosphate (0.50 g.) in 17 ml. of 0.87 *N* potassium hydroxide. The solution was stirred for 10 min. in a water bath at 45°, cooled to room temperature, and the *p*H was lowered to approximately 3 by the dropwise addition of 1*N* hydrochloric acid. The yellow precipitate was collected by suction filtration, washed twice with distilled water, twice with 95% ethanol, and three times with ether. Air was then drawn through the filter for 30 min.

Although the precipitate initially is quite sticky and filtration and washings are slow, it becomes flaky when the ether is removed and is readily separable from the filter paper as a bright yellow powder. The yield was 0.478 g. (87.8%).

The product was further purified by dissolving it in 0.1 *N* potassium hydroxide. The resulting solution was filtered and the *p*H lowered to 3 by the dropwise addition of 0.1 *N* hydrochloric acid. The resulting precipitate was filtered and washed as described above. The yield was 0.436 g. corresponding to an overall yield of 80% and a 91.3% recovery in the purification. The product was dried over phosphorus pentoxide at atmospheric pressure and stored in air. In the melting point apparatus this material darkened about 195°

(1) Alton Meister, "Biochemistry of the Amino Acids," Academic Press, Inc., New York, N. Y., 1957, pp. 202–213.

(2) Carl F. Cori and Barbara Illingworth, *Proc. Natl. Acad. Sci.* **43**, 547 (1957).

(3) The commercial material obtained from the Nutritional Biochemical Corp., Cleveland, Ohio, was used as received.

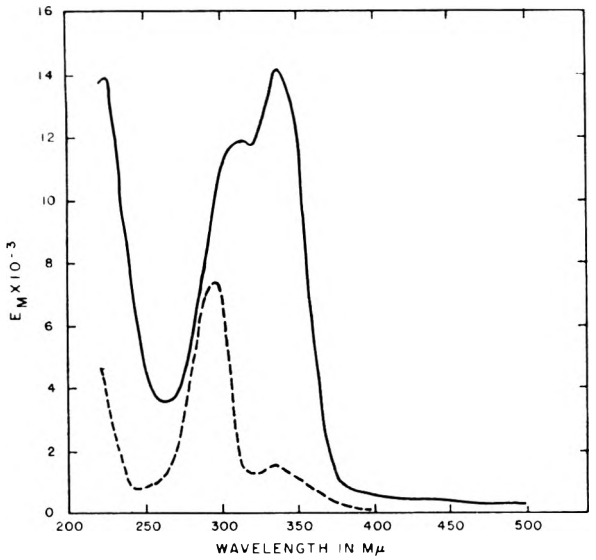

Fig. 1. Absorption spectra in 0.1*N* hydrochloric acid. Spectra determined on 2.6 × $10^{-5}M$ solutions. Solid line, pyridoxal phosphate hydrazone; dashed line, pyridoxal phosphate. E_M denotes molecular extinction coefficient (molar absorbance, ϵ, or molar absorbancy index, α_m)

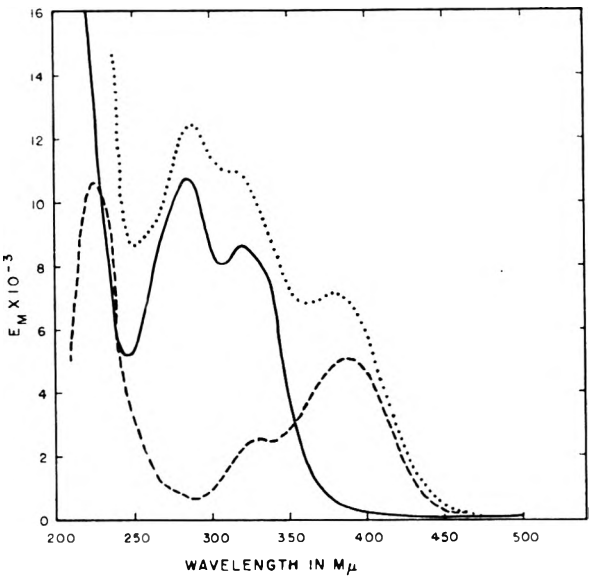

Fig. 2. Absorption spectra of 0.1*N* potassium phosphate *p*H 7.0. Dotted line, pyridoxal phosphate azine—ninety minutes after dissolving in buffer; solid line, pyridoxal phosphate hydrazone; dashed line, pyridoxal phosphate. E_M denotes molecular extinction coefficient

and became progressively darker to 280°. Analysis of the material agreed with the theoretical values calculated for the trihydrate.

Anal. Calcd. for $C_{16}H_{20}N_4P_2O_{10}\cdot 3H_2O$: C, 35.22; H, 4.79; N, 10.28; P, 11.44. Found: C, 35.11; H, 5.03; N, 10.26; P, 11.44. The expected water of hydration was lost upon heating to constant weight at 120°.

Conversion of pyridoxal-5-phosphate azine into pyridoxal-5-phosphate hydrazone. Pyridoxal phosphate azine (0.237 g.) was suspended in 5 ml. of water and mixed with a solution containing 0.248 g. of 85% hydrazine hydrate in 5 ml. of water. The mixture was stirred to dissolve the azine and heated on a water bath at 85° for 30 min. with frequent stirring. The hot solution was then filtered and the beaker and filter were washed with a total of 5 ml. of water. Hydrochloric acid (0.1 *N*) was added dropwise with stirring to reduce the *p*H to 5.9 and the solution was allowed to stand for 1 hr. The crystals were collected by suction filtration, washed twice with water, three times with ethanol, six times with ether, and dried in air. The yield was 0.159 g. (65.3%). The product was further purified by recrystallization as described previously, dried over phosphorus pentoxide, and stored in air. The crystals darkened at 224° and decomposed at 235–236°. Analysis agreed with theoretical values calculated for the monohydrate.

Anal. Calcd. for $C_8H_{12}O_8N_2P\cdot H_2O$: C, 34.45; H, 5.06; N, 15.00; P, 11.10. Found: C, 34.45; H, 4.95; N, 14.90; P, 11.26.

RESULTS AND DISCUSSION

Colorimetric determination of hydrazine content. In the presence of hydrochloric acid, *p*-dimethylaminobenzaldehyde reacts with hydrazine forming a quinoid structure possessing a yellow-orange color.[4] The color was observed to develop rapidly when 1 ml. of the reagent prepared as described by Pesez and Petit[4] is added to 5 ml. of solution containing the hydrazine. To insure completeness of the reaction, the mixture was allowed to stand 20 min. before examination. A standard curve was prepared from optical density values at 455 mμ obtained with known concentrations of hydrazine sulfate using a Beckman Model B spectrophotometer with 1 cm. cuvettes. The curve is linear with increasing hydrazine concentrations up to 0.44 μg. hydrazine per ml. of final reaction mixture. These values are within the range described by Audrieth and Ogg.[5] Various dilutions of standard solutions of the two pyridoxal phosphate derivatives were subjected to the same procedure. The hydrazine content of each determined from observed optical density values agreed well with calculated values of the hydrazine content. The results are presented in Table I.

TABLE I

Determination of Hydrazine Content[a]

Azine		Hydrazone	
Calcd.	Found	Calcd.	Found
0.274	0.260	0.330	0.340
0.220	0.210	0.275	0.270
0.164	0.164	0.221	0.218
0.107	0.105	0.166	0.166
0.054	0.058	0.110	0.119

[a] Expressed as μg. hydrazine per ml.

Ultraviolet absorption spectra. The ultraviolet absorption spectra of pyridoxal-5-phosphate and the corresponding hydrazone and azine were examined in 0.1 *N* hydrochloric acid and 0.1 *M* potassium phosphate at *p*H 7. The spectra of the preparation of pyridoxal phosphate, which was used as the

(4) M. Pesez and A. Petit, *Bull. Soc. Chim. France*, 1947, 122–123 (2 g. *p*-dimethylaminobenzaldehyde, 10 ml. conc. hydrochloric acid, 100 ml. 95% ethanol).

(5) L. F. Audrieth and Betty A. Ogg, "The Chemistry of Hydrazine," John Wiley and Sons, Inc., N. Y., 1951, p. 164.

starting material, are in good agreement both qualitatively and quantitatively with those obtained by Peterson and Sober[6] in these solvents.

Spectra obtained in 0.1 *N* hydrochloric acid are presented in Fig. 1. With the hydrazone, maxima are observed at 314 mμ (ϵ = 11,920) and 337 mμ (ϵ = 14,160). The 337 mμ maximum should be useful for spectrophotometric determinations, as the absorption of pyridoxal phosphate and pyridoxamine phosphate is minimal in this region.[6] The spectrum obtained with the azine in 0.1 *N* hydrochloric acid was essentially coincident with that resulting from the addition of the spectra of pyridoxal-5-phosphate and the hydrazone. Thus hydrolysis of the azine is essentially complete at low concentrations in acidic medium.

Spectra obtained in 0.1 *M* potassium phosphate at *p*H 7 are presented in Fig. 2. Upon formation of the hydrazone the maximum at 388 mμ which is specific for the –CHO group of pyridoxal phosphate[6] disappears as expected and maxima are observed at 284 mμ (ϵ = 10,800) and 320 mμ (ϵ = 8,630). Extinction values at the maxima were reproducible during the time required to examine the spectrum and exhibited no significant change after standing 14 hours in the buffer. The spectrum is indicative of the homogeneity of the hydrazone.

In addition to maxima observed at 288 and 316 mμ, the azine has a maximum at 379 mμ in the buffer. Similar azine structures show a maximum in this general region, e.g. 2,2′-dihydroxybenzalazine has a maximum at 355 mμ.[7] Immediately following solution of the azine in phosphate buffer *p*H 7 an initial decrease in absorption at both the 288 and 379 mμ maxima was observed. Reproducible values were obtained after approximately one hour and decreased less than 2% in 12 hours. The azine spectrum in Fig. 2 was obtained after 90 minutes. The spectrum of a mixture of equimolecular quantities of pyridoxal phosphate and its hydrazone in 0.1 *M* potassium phosphate buffer *p*H 7 was essentially coincident with that of the azine. This was interpreted as evidence for the existence of an equilibrium among azine, hydrazone, and pyridoxal phosphate in the solutions of the azine itself. Further support for this conjecture was obtained when additions of the separate spectra of the hydrazone and pyridoxal phosphate produced a curve which was not coincident with that of the azine. In the latter case the maximum at 379 mμ was about 25% lower than that for the azine itself. Available information does not permit a more complete explanation of this observation.

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(6) E. A. Peterson and H. A. Sober, *J. Amer. Chem. Soc.* **76**, 169 (1954).

(7) E. R. Blout and R. M. Gofstein, *J. Amer. Chem. Soc.* **67**, 13 (1945).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF FAIRFIELD UNIVERSITY, THE DEPARTMENT OF CHEMISTRY AND CHILDREN'S HOSPITAL, UNIVERSITY OF BUFFALO, AND ROSWELL PARK MEMORIAL INSTITUTE]

A 2-Trifluoromethyl Analog of Thiamin[1]

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Two synthetic routes for thiamin, adapted from classical methods, were found satisfactory for the preparation of 3-[(4-amino-2-trifluoromethyl-5-pyrimidinyl)methyl]-5-(2-hydroxyethyl)-4-methylthiazolium chloride hydrochloride [(VII) "trifluorothiamin"]. Solvolysis of intermediates occurred under certain conditions. "Trifluorothiamin" is biologically active as a thiamin antagonist in microorganisms and in mice where paralysis and opisthotonus occur. Growth of a transplanted carcinoma and a leukemia was suppressed in mice on a thiamin-deficient diet.

Although many analogs of thiamin have been prepared,[3a-d] the synthesis of a trifluoromethyl analog seemed pertinent because the presence of such a group could have a significant electronic effect on the molecule, but should not have a significant steric effect. In a preceding paper,[4] the syntheses of 4-amino-2-trifluoromethyl-5-hydroxymethylpyrimidine (I) and 4-amino-5-aminomethyl-2-trifluoromethylpyrimidine (IV) from trifluoroacetamidine were described. Their biological activity[5] contributed to our further interest in 2-trifluoromethylpyrimidines.

This paper is concerned with the use of compounds I and IV as starting materials for the preparation of 3-[(4-amino-2-trifluoromethyl-5-pyrimidinyl)methyl]-5-(2-hydroxyethyl)-4-methylthiazo-

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(2) To whom inquiries regarding this article should be sent.

(3) (a) F. Bergel and A. R. Todd, *J. Chem. Soc.*, 1504 (1937). (b) W. Huber, *J. Am. Chem. Soc.*, 65, 2222 (1943). (c) A. N. Wilson and S. A. Harris, *J. Am. Chem. Soc.*, 71, 2231 (1949). (d) T. Okuda and C. C. Price, *J. Org. Chem.*, 24, 14 (1959).

(4) J. A. Barone, E. Peters, and H. Tieckelmann, *J. Org. Chem.*, 24, 198 (1959).

(5) Unpublished results.

lium chloride hydrochloride (VII, "trifluorothiamin"). Information is presented on two alternate synthetic routes, and the two independent preparations constitute a proof of structure for the compound.

Okuda and Price[3d] found that Dornow and Petsch[6] had actually prepared 2-ethylthio-4-amino-5-isopropoxymethylpyrimidine hydrobromide, a solvolysis product, rather than the 2-ethylthiothiamin reported. In this research, alcoholysis of 4-amino-5-chloromethyl-2-trifluoromethylpyrimidine (II), prepared from I using thionyl chloride, was encountered during an attempt at recrystallization from ethanol-benzene and a preparative experiment for 4-amino-5-ethoxymethyl-2-trifluoromethylpyrimidine (III) is included. When the synthesis of VII, "trifluorothiamin," from compound II was attempted in nonhydrolytic solvents like acetone, 2-butanone, and dioxan, either the yields were not as satisfactory as described in method A (56%) or indications were that the reaction did not occur until the solvent was evaporated. Method A involved fusing compound II with 5-(2-hydroxyethyl)-4-methylthiazole to give "trifluorothiamin" (VII) as suggested by the work of Williams and Cline[7] in the synthesis of thiamin. In our preparation, it was possible to isolate the free base of VII, 3-[(4-amino-2-trifluoromethyl-5-pyrimidinyl)methyl] 5-(2-hydroxylethyl)-4-methylthiazolium chloride.

The synthesis of VII, "trifluorothiamin," from compound IV was accomplished *via* the reaction of potassium dithioformate with compound IV below 15° in dilute aqueous ethanol to give 4-amino-2-trifluoromethyl-5-thioformylaminomethylpyrimidine (V) in 86% yield. When the reaction mixture in aqueous ethanol solution was heated, 4-amino-2-trifluoromethyl-5-formylaminomethylpyrimidine (VI) was the product. The reaction of compound V with γ-bromo-γ-acetopropyl acetate (method B) according to the general procedure of Todd and Bergel,[8] gave VII, "trifluorothiamin," in 34% yield. When the method of Huber[3b] for the 2-amino analog was used, considerable decomposition was noted, and difficulty was encountered in the isolation of VII, "trifluorothiamin," because of the presence of the hydrochloride of IV, which was identified by comparison with an authentic sample.[4]

Although the procedure involving method A seems like the better one for the preparation of VII, "trifluorothiamin," from the data presented here, an examination of the previous paper[4] will show that compound IV, the precursor for method B, is easier to prepare than compound I, the precursor for method A.

(6) A. Dornow and G. Petsch, *Ann.*, **588**, 45 (1954).

(7) R. R. Williams and J. K. Cline, *J. Am. Chem. Soc.*, **58**, 1504 (1936).

(8) A. R. Todd and F. Bergel, *J. Chem. Soc.*, 364 (1937).

It was previously noted that certain 4-amino-5-hydroxymethyl-2-substituted analogs of the thiamin pyrimidine inhibited the growth of *Bacillus subtilis* and that the inhibition was completely reversed by the normal pyrimidine.[9] "Trifluorothiamin" (VII) was tested for possible activity as an antagonist of thiamin or its pyrimidine moiety (2-methyl-4-amino-5-hydroxymethylpyrimidine) or its thiazole moiety, 5-(2-hydroxyethyl)-4-methylthiazole, in bacteria by placing filter paper disks impregnated with 0.01 cc. of $10^{-2}M$ or $10^{-3}M$ solutions upon the surface of solid agar layers of medium seeded with the test organism. Simultaneous tests on *Bacillus subtilis* were carried out with the appropriate minimal synthetic culture medium (incubated at 30°) and with the medium supplemented by the pyrimidine or thiazole moiety of thiamin as well as by thiamin itself. "Trifluorothiamin" (VII) was found to be a more potent thiamin antagonist than either pyrithiamin (neo) or oxythiamin. The thiazole moiety reversed pyrithiamin inhibition and the pyrimidine moiety reversed oxythiamin inhibition. In contrast, inhibition by VII, "trifluorothiamin," was enhanced by the pyrimidine and thiazole moieties and reversed only by thiamin.

When administered in doses of 100 mg./kg. daily to mice on a thiamin-deficient diet, "trifluorothiamin" (VII) induced weight loss, extremity paresis and paralysis, opisthotonic convulsions, and inhibition of transplanted Leukemia L-1210 and Krebs 2 carcinoma. These effects have not been seen when the same doses have been given to mice with Leukemia L-1210 on a regular diet.

Detailed results of metabolic, pharmacologic, and tumor inhibition studies with these compounds will be published elsewhere.

EXPERIMENTAL[10]

4-Amino-2-trifluoromethyl-5-hydroxymethylpyrimidine (I). This compound was prepared[11] according to the method previously described.[4]

4-Amino-5-chloromethyl-2-trifluoromethylpyrimidine (II). Four g. (0.021 mol.) of I and 40 ml. of thionyl chloride in 160 ml. of dry chloroform were refluxed for 7 hr. The liquid was evaporated and the resulting solid was recrystallized from acetone-benzene to give 3.85 g. (88%) of crude II, m.p. 185–189°. The analytical sample, m.p. 191–192°, was obtained by recrystallizing from acetone–benzene.

Anal. Calcd. for $C_6H_5ClF_3N_3$: C, 34.05; H, 2.38. Found: C, 34.26; H, 2.35.

4-Amino-5-ethoxymethyl-2-trifluoromethylpyrimidine (III). One g. (0.0052 mol.) of I and 60 ml. of thionyl chloride in 40 ml. of chloroform were refluxed for 10 hr. After removal of the liquid phase, the solid was refluxed with 25 ml. of absolute ethanol for 2 hr. Most of the ethanol was evaporated and the residue was crystallized from ethanol-water

(9) R. Guthrie, M. E. Loebeck, and M. J. Hillman, *Proc. Soc. Exp. Biol. and Med.*, **94**, 792 (1957).

(10) Microanalyses by Galbraith Laboratories, Knoxville, Tenn. Melting points are uncorrected.

(11) The technical assistance of Mr. Antony Champ in the preparation of 5-carbethoxy-4-chloro-2-trifluoromethylpyrimidine, a precursor, is gratefully acknowledged.

to give 0.71 g. (62%) of crude III, m.p. 123–125°. The analytical sample, m.p. 126–127°, was obtained by recrystallizing from ethanol-water.

Anal. Calcd. for $C_8H_{10}F_3N_3O$: C, 43.44; H, 4.56. Found: C, 43.32; H, 4.65.

4-Amino-5-aminomethyl-2-trifluoromethylpyrimidine (IV). This starting material was also prepared according to the method previously described.[4]

Potassium dithioformate. The compound was prepared from potassium sulfide and chloroform in ethanol according to the method of Levi.[12]

4-Amino-2-trifluoromethyl-5-thioformylaminomethylpyrimidine (V). A solution of 2.93 g. (0.025 mol.) of potassium dithioformate in 15 ml. of water was added with stirring to 4.42 g. (0.023 mol.) of IV in 27 ml. of ethanol and 20 ml. of water keeping the temperature below 15°. After stirring in the cold for an additional 1 hr., 62 ml. of water was added and the mixture was placed in the refrigerator for 2 hr. The product was filtered to give 4.65 g. (86%) of crude V, m.p. 178–180°. The analytical sample, m.p. 184–185°, was obtained by recrystallizing from ethanol-benzene.

Anal. Calcd. for $C_7H_7F_3N_4S$: C, 35.59; H, 2.99. Found: C, 35.31; H, 3.08.

4-Amino-2-trifluoromethyl-5-formylaminomethylpyrimidine (VI). A solution of 5.18 g. (0.044 mol.) of potassium dithioformate in 15 ml. of water was added, with stirring, to 7.68 g. (0.040 mol.) of crude IV in 50 ml. of ethanol and 25 ml. of water at room temperature. After the addition, the stirring was continued for 2 hr. and then 50 ml. of solvent was evaporated at atmospheric pressure. After cooling the crystals were filtered. The product was dissolved in hot 50% acetic acid, decolorized with charcoal, neutralized with concentrated ammonium hydroxide while hot, cooled, and filtered. This treatment was repeated to give 6.4 g. (73%) of VI, m.p. 204–205°. The analytical sample, m.p. 204.5–205.5°, was obtained by recrystallizing from water. A small-scale experiment indicated that the solvolysis of the thioformyl to the formyl group, to a great extent, had taken place prior to recrystallization from 50% acetic acid.

Anal. Calcd. for $C_7H_7F_3N_4O$: C, 38.17; H, 3.20. Found: C, 38.12; H, 3.27.

γ-Bromo-γ-acetopropyl acetate.[13] 5-Hydroxy-2-pentanone[14] was acetylated with acetic anhydride and then brominated according to the method of Huber.[3b] It was noted that the product could be kept for at least 1 week without decomposition (coloration) if left in ether solution (over calcium chloride) in the refrigerator.

3-[(4-Amino-2-trifluoromethyl-5-pyrimidinyl)methyl]-5-(2-hydroxyethyl)-4-methylthiazolium chloride hydrochloride (VII). *Method A.* One g. (0.0047 mol.) of II and 1.0 g. (0.0070 mol.) of 5-(2-hydroxyethyl)-4-methylthiazole[15] were heated to a temperature of 145–150° inside the reaction flask by using an oil bath. The temperature was maintained for 10–15 min. The melt was allowed to cool and was dissolved in hot ethanol. The addition of ethanol–hydrogen chloride followed by concentration and cooling gave a white precipitate which was heated with ethanol–hydrogen chloride, cooled, filtered, and washed with ethanol–hydrogen chloride. After drying in a vacuum desiccator, there remained 1.07 g. (56%) of VII, m.p. 187–189° (dec.), as its monohydrate. The analytical sample, m.p. 192.5–194.5° (dec.) was obtained by recrystallizing twice from ethanol-hydrogen chloride.

Anal. Calcd. for $C_{12}H_{15}Cl_2F_3N_4OS \cdot H_2O$: C, 35.21; H, 4.19; S, 7.82. Found: C, 35.60; H, 4.13; S, 7.56.

When the fusion product prior to treatment with ethanol–hydrogen chloride was dissolved in hot 1-butanol, cooled, and precipitated with ether, the free base, 3-[(4-amino-2-trifluoromethyl-5-pyrimidinyl)methyl]-5-(2-hydroxyethyl)-4-methylthiazolium chloride, m.p. 196–197.5° (dec.) was obtained. However, formation of the hydrochloride led to a better recovery of product from the reaction mixture. 5-(2-Hydroxyethyl)-4-methylthiazole, II and III were very soluble in ethanol–hydrogen chloride whereas VII was not; hence the use of ethanol–hydrogen chloride in isolating the desired product.

Anal. Calcd. for $C_{12}H_{14}ClF_3N_4OS$: C, 40.61; H, 3.98. Found: C, 40.79; H, 4.12.

An attempt to use crude II which had only been washed with ether and dried, but not recrystallized, yielded, from acetone solution, a product which was purified by dissolving in 1-butanol and by precipitating with ether. This solid, m.p. 96–97°, evidently was 5-(2-hydroxyethyl)-4-methylthiazole hydrochloride[16] because it gave no melting point depression when mixed with a sample prepared by adding ether to a solution of 5-(2-hydroxyethyl)-4-methylthiazole in ethanol–hydrogen chloride. It also gave a picrate, m.p. 164–165° (lit.[17] 162–163°).

Method B. A 2.4-g. sample (0.010 mol.) of V was heated with 3.6 g. (0.015 mol.) of γ-bromo-γ-acetopropyl acetate with vigorous stirring. First a solution formed and then, at a temperature of 85–90°, an increase in viscosity was noted. The temperature was maintained with stirring for 15 min. The product was triturated with ether until a finely divided solid was obtained. This was dissolved in ethanol and precipitated with ethanol–hydrogen chloride. The mixture was cooled and filtered to give two crops, 1.88 g., of a solid which was recrystallized by dissolving in ethanol and adding ethanol–hydrogen chloride. The product, which was filtered after cooling, yielded 1.17 g. of crude VII, m.p. 186–188.5°, and gave a negative test for bromide ion (chlorine water and chloroform). An additional 0.23 g. was obtained by concentration of the mother liquor and recrystallization of the material which precipitated for a total yield of 34%. A sample which was recrystallized twice from ethanol–hydrogen chloride was identical with the analytical sample from Method A as evidenced by the melting points and mixed melting point. Both samples of VII gave the same picrate, m.p. 186–188°, from dilute aqueous ethanol.

Crude VII was also obtained by the method of Huber[3b] for the 2-amino analog of thiamin, but yields were lower due to decomposition and often extensive contamination with the hydrochloride of IV, most of which was separated by fractional crystallization. This was identified by comparison with an authentic sample.[4] Each specimen had the same melting point, there was no depression on mixing, and each gave the same picrate, m.p. 211–213°, from water solution.

FAIRFIELD, CONN.
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(12) T. G. Levi, *Atti reale accad. naz. Lincei*, [5] **32**, 56 (1923).

(13) H. Andersag and K. Westphal, *Ber.*, **70B**, 2035 (1937).

(14) The authors are indebted to Dr. T. E. Longergan, E. I. du Pont de Nemours and Co., for this compound.

(15) The authors are grateful to Dr. Max Tishler and Dr. Anthony H. Land, Merck Sharp and Dohme Research Laboratories, for a sample of this compound.

(16) R. R. Williams *et al.*, *J. Am. Chem. Soc.*, **57**, 536 (1935).

(17) E. R. Buchman, R. R. Williams, and J. C. Keresztesy, *J. Am. Chem Soc.*, **57**, 1849 (1935).

[CONTRIBUTION FROM THE MCPHERSON CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

The Syntheses of 3′-Fluoro- and 4-Fluoro-10-methyl-1,2-benzanthracenes[1]

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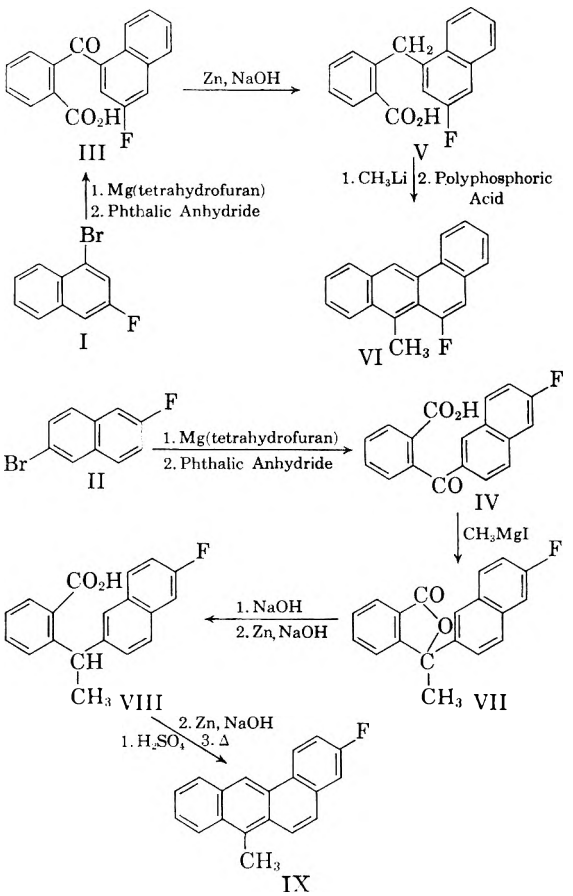
The syntheses of 3′-fluoro- and 4-fluoro-10-methyl-1,2-benzanthracenes are described.

A previous paper[2] presented reasons for synthesizing all the monofluoro-10-methyl-1,2-benzanthracenes in an attempt to locate the position or positions in the nucleus of 10-methyl-1,2-benzanthracene directly responsible for the carcinogenic activity. This sequel describes the syntheses of 4-fluoro- and 3′-fluoro-10-methyl-1,2-benzanthracenes, the routes to which involved, as before,[2] initial preparation of suitable bromofluoronaphthalenes.

1-Amino-2-nitro-4-bromonaphthalene[3] was the precursor of 1-bromo-3-fluoronaphthalene(I). Reduction of the nitro group[4] and deamination gave 1-bromo-3-naphthylamine. Best yields (60–65%) for replacement of the amino group by fluorine were obtained by decomposition of the diazonium hexafluorophosphate.[5] The normal Schiemann reaction using fluoboric acid afforded yields of 50–55%. The purity of the insoluble intermediate diazonium salt was of prime importance since the best yields on decomposition were obtained when thorough washing and drying of this salt were effected.

6-Bromo-2-fluoronaphthalene(II) was prepared similarly from 6-bromo-2-naphthylamine, the hexafluorophosphoric acid modification[5] once again giving slightly higher yields than the normal Schiemann. A 95% conversion of 6-bromo-2-naphthol to 6-bromo-2-naphthylamine by heating at 190° with ammonium sulphite under pressure for twenty-four hours has been reported.[6] In our hands, these conditions proved capricious and good yields (*ca.* 80%) could only be obtained consistently by lowering the temperature to 150°.

Condensation of the Grignard reagents of I and II with phthalic anhydride afforded the keto-acids, III and IV, respectively. Clemmensen reduction of III produced the acid IV which with excess methyllithium was converted to the methyl ketone. The



latter, without characterization, was cyclodehydrated[7] with polyphosphoric acid to give 4-fluoro-10-methyl-1,2-benzanthracene VI.

On treatment with methylmagnesium iodide, IV was converted to the lactone VII, which, by cleavage with alkali followed by zinc dust reduction, afforded the acid VIII. Cyclization was effected with concentrated sulfuric acid and the anthrone obtained was reduced and dehydrated to yield 3′-fluoro-10-methyl-1,2-benzanthracene (IX). The structure of IX was verified by comparison of its ultraviolet absorption spectrum with that of 10-methyl-1,2-benzanthracene, since the precursor

(1) This work was supported by a grant from the National Institutes of Health.

(2) M. S. Newman, D. MacDowell, and S. Swaminathan, *J. Org. Chem.*, **24**, 509 (1959).

(3) H. H. Hodgson and S. Birtwell, *J. Chem. Soc.*, 321 (1943).

(4) M. P. Cava and J. F. Stucker, *J. Am. Chem. Soc.*, **79**, 1706 (1957).

(5) We are greatly indebted to Dr. K. Rutherford, Chemistry Department, Essex College, Windsor, Canada, for information about this new method soon to be published.

(6) L. C. Anderson and D. Johnston, *J. Am. Chem. Soc.*, 65, 241 (1943).

(7) Cyclodehydrations of this sort have previously been carried out by Bradsher and his co-workers, *e.g.*, C. K. Bradsher and F. A. Vingiello, *J. Am. Chem. Soc.*, **71**, 1434 (1949), C. K. B. and S. T. Webster, *J. Am. Chem. Soc.*, **79**, 393 (1957) who used hydrobromic acid in acetic acid. To our knowledge, the first use of polyphosphoric acid for such cyclodehydrations was by M. S. Newman, D. MacDowell, and S. Swaminathan, *J. Org. Chem.*, **24**, 509 (1959).

acid VIII could conceivably give rise to an isomeric tetracene derivative.

EXPERIMENTAL[8]

6-Bromo-2-naphthylamine. 6-bromo-2-naphthol[9] (30 g.), ammonium hydroxide (60 ml., 28%) saturated with sulfur dioxide, and ammonium hydroxide (60 ml., 28%) were heated together at 150° for 27 hr. in a steel bomb. The bomb was washed out with boiling ethyl acetate and its contents extracted with the same solvent. Distillation of the residue from concentration of the organic extract afforded a distillate, b.p. 155–160° at 1 mm., which yielded 24.0 g. (80%) of colorless 6-bromo-2-naphthylamine, m.p. 126–127° (lit.[6] 128°) on crystallization from alcohol.

6-Bromo-2-fluoronaphthalene (II). The above bromoamine (49 g.) was heated for 15 min. with excess concentrated hydrochloric acid. To the cooled solution (0°) was added, dropwise, a solution of sodium nitrite (15.5 g.) in water (30 ml.). When diazotisation was complete, hexafluorophosphoric acid[10] (50 ml., *ca.* 65%, polyethylene measuring cylinder) was added rapidly in portions. Immediately a heavy yellow-brown precipitate separated and mixing was best effected by manual shaking. The diazonium hexafluorophosphate was filtered, washed thoroughly with water, methanol, and ether. After drying over phosphorus pentoxide the salt (68 g.) melted with decomposition at 107–110°. This salt was added in portions through a Gooch rubber tube from a flask fitted to a three-necked flask held at 120–130°. After decomposition was complete the decomposition residue was extracted with ether-benzene and worked up in the usual way. Distillation of the product followed by crystallization from aqueous methanol gave 27 g. (55% from bromoamine) of colorless 6-bromo-2-fluoronaphthalene, m.p. 66.0–67.0°. A second run gave a 58% yield.

Anal. Calcd. for $C_{10}H_6BrF$: C, 53.3; H, 2.7. Found:[a] C, 53.2; H, 2.9.

The normal Schiemann reaction using fluoboric acid afforded yields of 49 and 53%.

1-Bromo-3-fluoronaphthalene (I). I was prepared similarly from 1-bromo-3-naphthylamine by the hexafluorophosphoric acid modification; the yields were 58 and 64%, by the normal Schiemann, 50 and 55%. Decomposition of the diazonium hexafluorophosphate, m.p. 120–125° (dec.), at 140° gave 1-bromo-3-fluoronaphthalene (I), b.p. 84–88° at 1 mm. Since this compound was a liquid, it was characterized as the *trinitrobenzene complex*, m.p. 92.0–93.0° (from aqueous methanol).

Anal. Calcd. for $C_{16}H_9BrFN_3O_6$: C, 43.8; H, 2.1. Found:[a] C, 43.7; H, 2.1.

ortho-(6-Fluoro-2-naphthoyl)benzoic acid (IV). The Grignard reagent formed from 6-bromo-2-fluoronaphthalene (II) was treated with phthalic anhydride as in a similar case.[2] The ketoacid IV proved difficult to purify. Crystallization from benzene–ethyl acetate gave a 65% yield of crude acid, m.p. 185–195°. Further crystallizations afforded IV, m.p. 193–197°, in 50% yield. This material was used directly in the next step without further purification.

3-Methyl-3-(6-fluoro-2-naphthyl)phthalide (VII). Treatment of 8.0 g. of IV in 200 ml. of benzene-tetrahydrofuran (1:1) with two equivalents of methylmagnesium iodide as described[11] afforded 4.5 g. (56%) of VII as colorless plates, m.p. 129–130°. The analytical sample melted at 130.0–131.0°.

Anal. Calcd. for $C_{19}H_{13}FO_2$: C, 78.1; H, 4.5. Found:[a] C, 77.8; H, 4.7.

2-[1-(6-Fluoro-2-naphthyl)ethyl]benzoic acid (VIII). The lactone VII was reduced in 85% yield as described for a similar lactone[12] to VIII, m.p. 185.0–187.0°. The analytical sample was crystallized from a mixture of benzene and Skellysolve B (petroleum ether, b.p. 60–70°).

Anal. Calcd. for $C_{19}H_{15}FO_2$: C, 77.6; H, 5.1. Found:[a] C, 77.3; H, 5.2.

3′-Fluoro-10-methyl-1,2-benzanthracene (IX). The acid VIII (6 g.) was dissolved in concentrated sulfuric acid (75 ml.). After standing 2 hr. the solution was poured on ice. The organic product was treated at reflux for 7 hr. with zinc dust (24 g.), water (350 ml.), and 55% aqueous sodium hydroxide (90 ml.). From the neutral portion of this reaction mixture was isolated 1.75 g. (33%) of crude IX, m.p. 148–150°. Purification by means of formation of the 1,3,5-trinitrobenzene derivative, recrystallization of this, and chromatography over alumina gave 1.5 g. (28%) of pure IX, m.p. 146.0–147.0°.

Anal. Calcd. for $C_{19}H_{13}F$: C, 87.7; 5.0; F, 7.3. Found:[a] C, 87.4; H, 5.3. F, 7.8.

The 1,3,5-trinitrobenzene complex, m.p. 185.5–186.5°, formed red-orange prisms when crystallized from benzene.

Anal. Calcd. for $C_{25}H_{16}N_3O_6F$: N, 8.9. Found: N, 8.8.

ortho-(3-Fluoro-1-naphthoyl)benzoic acid (III). 1-Bromo-3-fluoronaphthalene (I) (20 g.) in tetrahydrofuran (150 ml.) was added to magnesium (2.3 g.) under dry nitrogen. In the best run the halide was added over 45 min. at the rate of about 2 drops per sec. After 30 min. the Grignard solution was transferred under nitrogen to a dropping funnel then added, dropwise, to a flask containing phthalic anhydride (13.5 g.) dissolved in tetrahydrofuran (150 ml.). After 2 hr. reflux the tetrahydrofuran was replaced by benzene. Work up of the reaction mixture as described for IV yielded by 12.6 g. (48%) of III, m.p. 183–188°. Recrystallization from aqueous methanol yielded 10.4 g. (40%) of pure III, m.p. 187–189°.

Anal. Calcd. for $C_{18}H_{11}FO_3$: C, 73.5; H, 3.7. Found:[a] C, 73.3; H, 4.0.

Distillation of the neutral fraction obtained in the Grignard reaction yielded small amounts of 3,3′-difluoro-1,1′-dinaphthyl, m.p. 58–59°, on crystallization from aqueous methanol.

Anal. Calcd. for $C_{20}H_{12}F_2$: C, 83.3; H, 4.2. Found:[a] C, 83.0; H, 3.8.

ortho-(3-Fluoro-1-naphthylmethyl)benzoic acid (V). III was reduced to yield crude V which, on crystallization from aqueous methanol yields pure V, m.p. 165–166°, in 75% yield.

Anal. Calcd. for $C_{18}H_{13}FO_2$: C, 77.2; H, 4.6. Found:[a] C, 77.1; H, 4.8.

4-Fluoro-10-methyl-1,2-benzanthracene (VI). A solution of 13.5 g. of V in 200 ml. of ether was added to a methyllithium solution prepared from 30 g. of methyl iodide and 2.8 g. of lithium in 100 ml. of ether. After the resulting purple solution had been stirred at room temperature for 30 min., the organic product, isolated in the usual way, was stirred into 150 g. of polyphosphoric acid. The resulting mixture was stirred at 100° for 15 min., overnight at room temperature, and was then poured on ice. The solid was taken up in benzene, and filtered through alumina. Chromatography over alumina in Skellysolve B afforded 5.4 g. (44%) of crude VI, m.p. 105–109°, in two crops. A further crystallization gave 37% yield of pure fluorohydrocarbon, VI, m.p. 109–110°.

Anal. Calcd. for $C_{19}H_{13}F$: C, 87.7; H, 5.0; F, 7.3. Found:[a] C, 87.7; H, 4.9; F, 7.1.

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(8) All melting points are uncorrected. Analyses marked[a] and[s] were done by the Galbraith and Schwarzkopf Laboratories respectively. The term "worked up in the usual way" means that an ether-benzene extract of the organic products was washed with acid and/or alkali as required, saturated sodium chloride solution, and filtered through a layer of anhydrous magnesium sulphate; the solvents were removed and the residue treated as described.

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[CONTRIBUTION FROM THE RADIUM INSTITUTE OF THE UNIVERSITY OF PARIS]

Potential Leukopenia-Inducing Amines. I. 6-Amino-12-ethylchrysene

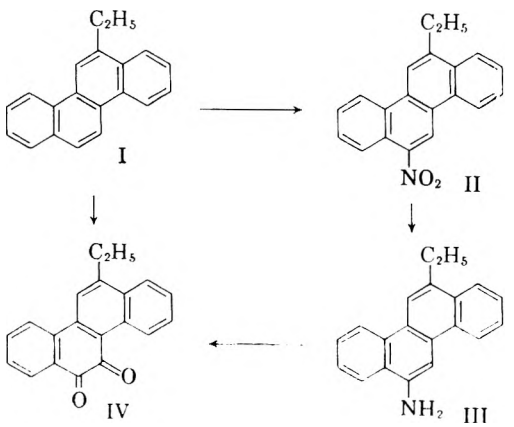
PHILIPPE MABILLE AND N. P. BUU-HOÏ

Received August 10, 1959

6-Amino-12-ethylchrysene has been synthesized by two different methods, both starting from 6-ethylchrysene, and the structure of this amine has been determined. This work establishes the orientation of substituents in the nitration and Friedel-Crafts reactions of a 6-alkylchrysene.

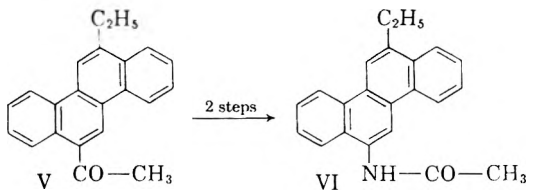
6-Aminochrysene is known to be a leukopenia-promoting agent with a pronounced atrophying effect on the spleen.[1] Experimentally, it inhibits the growth of spontaneous adenocarcinoma of the breast[2] and retards the development of L 1210 leukemia[3] in mice. These considerations prompted the search for compounds possessing similar biological activities, and particularly those which would have greater lipoid solubility than 6-aminochrysene itself. In the latter respect, alkyl homologs of 6-aminochrysene appeared promising, and 12-ethyl-6-aminochrysene (III) was therefore prepared, by two different methods.

First method. 6-Ethylchrysene (I), easily prepared by Wolff-Kishner reaction of 6-acetylchrysene, underwent reaction with nitric acid in mild conditions, to give a monosubstitution product, 12-ethyl-6-nitrochrysene (II); this was readily reduced by sodium hydrosulfite in ethanol medium to 6-amino-12-ethylchrysene, whose structure was established by oxidation with sodium bichromate in acetic acid medium to 12-ethylchrysene-5,6-quinone (IV), a compound that could also be obtained



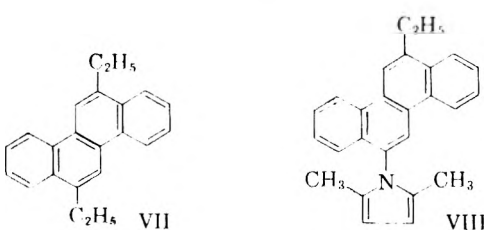
by direct oxidation of 6-ethylchrysene with the same reagent. From the standpoint of pure organic chemistry, this experiment demonstrates the greater resistance to oxidation of an alkylated *meso*-phenanthrene zone as compared with a non-substituted region.

Second method. The Friedel-Crafts acetylation of 6-ethylchrysene (a reaction which was shown by Funke and Ristic[4] to yield an acetyl-6-ethylchrysene whose structure they did not investigate) afforded 6-acetyl-12-ethylchrysene (V), as was proven by the Beckmann rearrangement of its oxime to 6-acetamino-12-ethylchrysene (VI), identical with the



product from the acetylation of the amine obtained by the first method. As it is known that the positions 5 and 11 in chrysene resist substitution because of particularly strong steric encumbrance at those two sites,[5] this second experiment establishes the orientation of substituents in Friedel-Crafts acylations of 6-alkylchrysenes. Hence, the 6,x-diethylchrysene prepared by Funke and Ristic by a Clemmensen reduction of the acetylation product of 6-ethylchrysene,[4] was 6,12-diethylchrysene (VII), which we now prepared in excellent yield by the Wolff-Kishner method.

As was to be expected, 6-amino-12-ethylchrysene has a considerably lower melting point than 6-aminochrysene, and is also far more soluble in lipoids. Its condensation with hexane-2,5-dione[6] readily yielded 6-(2,5-dimethyl-1-pyrryl)-12-ethylchrysene (VIII).



The results of biological studies will be reported at a later date.

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EXPERIMENTAL

Preparation of 6-acetylchrysene. The preparation of 6-acetylchrysene has frequently been reported in the literature,[7] the most satisfactory method being that of Carruthers,[8] where the use of methylene chloride as solvent ensures a smoother reaction than with carbon disulfide. So as to enhance the yield and to obtain an isomer-free ketone, we modified Carruthers' technique as follows. To a stirred mixture of 80 g. of aluminum chloride and 40 ml. of acetyl chloride in 2 l. of methylene chloride, 100 g. of chrysene (suspended in 700 ml. of methylene chloride) was added portionwise during 45 min. at a temperature ranging from 3° to 9°, and the mixture was then stirred for 3 hr. at room temperature. It was then refluxed for 2 hr., left to stand overnight at room temperature, then refluxed again for 1.5 hr. After decomposition with ice and hydrochloric acid, the methylene chloride solution was washed with 5% aqueous sodium hydroxide, then with water, dried over sodium sulfate, and the solvent removed by distillation. Crystallization of the residue from acetone afforded 95 g. of 6-acetylchrysene, lemon yellow needles, m.p. 144°.

Preparation of 6-ethylchrysene. A mixture of 54 g. of 6-acetylchrysene, 50 g. of 98% hydrazine hydrate, and 40 g. of potassium hydroxide in 1250 ml. of diethylene glycol was gently refluxed for 13 hr. with removal of water. When cooled, water was added, then dilute hydrochloric acid, and the solid precipitate was collected and recrystallized from ethanol-acetone. Yield: 47 g. (91.6%) of colorless needles, m.p. 129–130°; lit.[9] m.p. 126°.

12-Ethyl-6-nitrochrysene (II). To a suspension of 20 g. of ethylchrysene in 750 ml. of acetic acid, 16.5 ml. of fuming nitric acid (d = 1.49; dissolved in 250 ml. of acetic acid) was added at 33–35° with stirring. Within 5 to 10 min. a yellow precipitate had formed, and after 30 min. cooling in an iced water-bath, this was collected, washed with acetic acid, and recrystallized from 1 l. of acetone. Yield: 14.5 g. (61.7%) of silky pale yellow needles, m.p. 203°.

Anal. Calcd. for $C_{20}H_{15}NO_2$: C, 79.7; H, 5.0; N, 4.7. Found: C, 79.5; H, 5.0; N, 4.8. From the mother liquors of recrystallization of the nitro compound was isolated 2.2 g. of a product which crystallized from ethanol in shiny colorless leaflets, m.p. 184°, giving a blue coloration in sulfuric acid. The constitution of this byproduct is unknown.

12-Ethyl-6-aminochrysene (III). To a solution of 0.5 g. of the foregoing nitro-derivative in 400 ml. of hot ethanol, 1 g. of sodium hydrosulfite (dissolved in a few ml. of water) was added with stirring. Discoloration occurred, and after 15 min. a mineral precipitate was filtered off and the filtrate diluted with water, giving the amine which was washed with water, dried, and recrystallized twice from hexane, to yield 0.3 g. of cream-colored needles, m.p. 159° (the solvated product melted partly at 140–144°). The solution in ethanol gave an intense blue fluorescence.

Anal. Calcd. for $C_{20}H_{17}N$: C, 88.5; H, 6.3; N, 5.2. Found: C, 88.7; H, 6.3; N, 5.2.

6-Acetyl-12-ethylchrysene (V). To a solution of 24 g. of 6-ethylchrysene and 120 ml. of acetyl chloride in 400 ml. of dry carbon disulfide, 24 g. of finely powdered aluminum chloride was added, with stirring, during 15 min. and at room temperature. The mixture was left to stand for 13 hr., then refluxed for 5 hr. After decomposition with ice and hydrochloric acid, the solvent was distilled, and the solid precipitate was collected. This was treated with 80 ml. of acetone (for removal of the resins), and left overnight in the refrigerator, after which the crystalline mass that had formed was collected and recrystallized from ethanol (800 ml.), to give pale yellow needles, m.p. 131–132°. Evaporation of the acetonic mother liquors and crystallization of the residue from ethanol gave a further crop of the same ketone (total yield: 14.4 g.). Funke and Ristic[4] gave m.p. 131° for their product.

The corresponding *oxime*, prepared by heating for 24 hr. a mixture of 11 g. of the above ketone, 5.2 g. of hydroxylamine hydrochloride, and 2.2 g. of sodium hydroxide in 800 ml. of ethanol, crystallized from ethanol-benzene in beige needles (9.7 g.), m.p. 218–219°.

Anal. Calcd. for $C_{22}H_{19}NO$: C, 84.3; H, 6.1; N, 4.5. Found: C, 84.2; H, 6.3; N, 4.5.

6-Acetamino-12-ethylchrysene (VI). Into a suspension of 9.4 g. of the foregoing oxime in 500 ml. of anhydrous ether and 50 ml. of benzene, was shaken, at room temperature and in small portions, 10 g. of finely powdered phosphorus pentachloride. Shaking was continued for 1.5 hr., by which time the oxime had undergone complete dissolution and rearrangement. After decomposition with ice and evaporation of the solvent, the precipitate obtained was recrystallized from toluene, yielding 3.5 g. of *12-ethyl-6-acetaminochrysene*, as colorless needles, m.p. 249°, which could be sublimed.

Anal. Calcd. for $C_{22}H_{19}NO$: C, 84.3; H, 6.1; N, 4.5. Found: C, 84.4; H, 6.2; N, 4.7.

A solution of 1.3 g. of this compound in a mixture of 300 ml. of ethanol and 100 ml. of hydrochloric acid was heated at reflux for 1 hr., and the solution was concentrated until a precipitate began to form. After 2 hr. in the refrigerator, the precipitate of *12-ethyl-6-aminochrysene hydrochloride* was collected, washed with ethanol and benzene, and dried; it melted at 200–203°, with decomposition above 175°. Treatment with potassium hydroxide in ethanol yielded the free *base*, m.p. 159° after crystallization from benzene; the melting point was not depressed on admixture with a sample prepared by reduction of 12-ethyl-6-nitrochrysene.

12-Ethylchrysene-5,6-quinone (IV). A suspension of 1 g. of 12-ethyl-6-acetaminochrysene in 15 ml. of acetic acid was refluxed for 30 min. with 4 g. of sodium bichromate. After cooling and dilution with water, the precipitate formed was collected, washed with water, and recrystallized from acetic acid, to furnish 0.7 g. of orange-red needles, m.p. 183–184° (the solvated product melted partly at 175–176°), giving a blue-violet coloration in sulfuric acid.

Anal. Calcd. for $C_{20}H_{14}O_2$: C, 83.9; H, 4.9. Found: C, 83.7; H, 4.8.

The same compound was obtained by oxidation of the free amine, or, with a lower yield, of 6-ethylchrysene.

The corresponding *phenazine*, prepared with *o*-phenylenediamine in acetic acid, crystallized from acetic acid in yellowish leaflets, m.p. 204–205°, giving an olive green coloration in sulfuric acid.

Anal. Calcd. for $C_{26}H_{18}N_2$: C, 87.1; H, 5.1; N, 7.8. Found: C, 87.0; H, 5.3; N, 7.9.

6-(2,5-Dimethyl-1-pyrryl)-12-ethylchrysene (VIII). A mixture of 0.3 g. of 12-ethyl-6-aminochrysene and 1 g. of hexane-2,5-dione was refluxed for 15 min. The solid obtained on cooling crystallized from ethanol after treatment with charcoal, to give shiny colorless needles (0.2 g.), m.p. 174–175°.

Anal. Calcd. for $C_{26}H_{23}N$: C, 89.4; H, 6.6. Found: C, 89.3; H, 6.8.

6,12-Diethylchrysene (VII). This *hydrocarbon*, prepared from 0.7 g. of 12-ethyl-6-acetylchrysene, 0.7 g. of hydrazine hydrate, and 0.7 g. of potassium hydroxide in 30 ml. of diethylene glycol, crystallized from ethanol in colorless leaflets (0.4 g.), m.p. 152°; lit.,[4] m.p. 145°.

Acknowledgment. This work was conducted with the financial aid of The Anna Fuller Fund, New Haven, Connecticut; the authors express their gratitude to Professor William U. Gardner and the Trustees of the Fund.

PARIS (VE), FRANCE

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

The Epoxy Acids of *Chrysanthemum coronarium* and *Clarkia elegans* Seed Oils

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Coronaric acid, the constituent epoxy acid of *Chrysanthemum coronarium* seed oil, is characterized as *cis*-9,10-epoxy-*cis*-12-octadecenoic acid. The epoxy acid of *Clarkia elegans* seed oil is identified as vernolic acid.

Vernolic acid, the principal fatty acid of *Vernonia anthelmintica* seed oil, was the first epoxy fatty acid found to occur naturally. Gunstone[2] proved its structure to be *cis*-12,13-epoxy-*cis*-9-octadecenoic acid. Vernolic acid was also found by Bharucha and Gunstone in the oil of *Cephalocroton cordofanus*,[3] and by Hopkins and Chisholm in oils of *Vernonia colorata*,[4] *Hibiscus esculentus* (okra),[4] and *Hibiscus cannabinus*.[5] The screening of a considerable number of previously uninvestigated species suggested that epoxy acids are constituents of numerous seed oils in the composite family.[6] The discovery of a second epoxy fatty acid as a constituent of a vegetable oil was reported in a preliminary communication from this laboratory.[7] This new epoxy acid, coronaric acid (I), was found in *Chrysanthemum coronarium* (garland chrysanthemum) seed oil and was tentatively identified as *cis*-9,10-epoxy-*cis*-12-octadecenoic acid. A third epoxy acid, 15,16-epoxy-9,12-octadecadienoic acid, was shown by Gunstone and Morris[8] to be a constituent of *Camelina sativa* seed oil. This paper will present conclusive evidence for the structure suggested tentatively for coronaric acid. It will also show that the epoxy acid in *Clarkia elegans* seed oil[9] is vernolic acid. The epoxy acids in both of these oils were accompanied by mixtures of fatty acids of the common types (see Experimental.)

Structural work on coronaric acid (Ia) was carried out on different samples of *Chrysanthemum coronarium* seed oil containing 0.15 to 0.85%[6] oxirane oxygen as determined by Durbetaki's procedure.[10] The epoxy acid was not isolated as such, but was converted by acetolysis and saponification to an unsaturated dihydroxy acid (II); the latter was isolated by solvent partitioning with aqueous methanol–petroleum ether. The procedure followed was that used by Gunstone in his work with *Vernonia anthelmintica* oil.[2] Chemical determination of oxirane oxygen in *Chrysanthemum coronarium* oil was in agreement with infrared evidence and indicated the presence of an epoxy group, but no appreciable hydroxyl. Therefore, II was undoubtedly derived from Ib.

The unsaturated dihydroxy acid (II), m.p. 57–58°, was shown by infrared spectrum and quantitative hydrogenation to have one *cis* double bond. Its melting point was markedly depressed by admixture with *threo*-12,13-dihydroxy-*cis*-9-octadecenoic acid (X) prepared from *Vernonia anthelmintica* seed oil. Hydrogenation of II produced saturated dihydroxy acid III, m.p. 93–93.5°, whose melting point was markedly depressed by admixture with *threo*-12,13-dihydroxyoctadecanoic acid (m.p. 96–97°). No depression of melting point was evident, however, on admixture with *threo*-9,10-dihydroxyoctadecanoic acid. Thus it was indicated that *C. coronarium* oil contains an epoxy acid which is different from, and isomeric with, vernolic acid.

The unsaturated dihydroxy acid, II, was subjected to periodate cleavage, using Gunstone's procedure for cleaving compound X. Two C_9 aldehydes, compound IV and V, resulted; these were separated by steam distillation and characterized as 2,4-dinitrophenylhydrazones. The derivative o IV had $\lambda_{max}^{C_2H_5OH}$ 375 mμ, strongly suggesting α,β-unsaturation.[11] The 2,4-dinitrophenylhydrazone of V was isolated as an ethyl ester and had $\lambda_{max}^{C_2H_5OH}$ 356 mμ. II was also cleaved by the permanganate-periodate procedure of Lemieux and von Rudloff.[12] A model experiment was first carried out with X; the nonvolatile acid obtained was nonandioic acid, showing that no double bond migration occurred in

(1) This is a laboratory of the Northern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture. Article not copyrighted.

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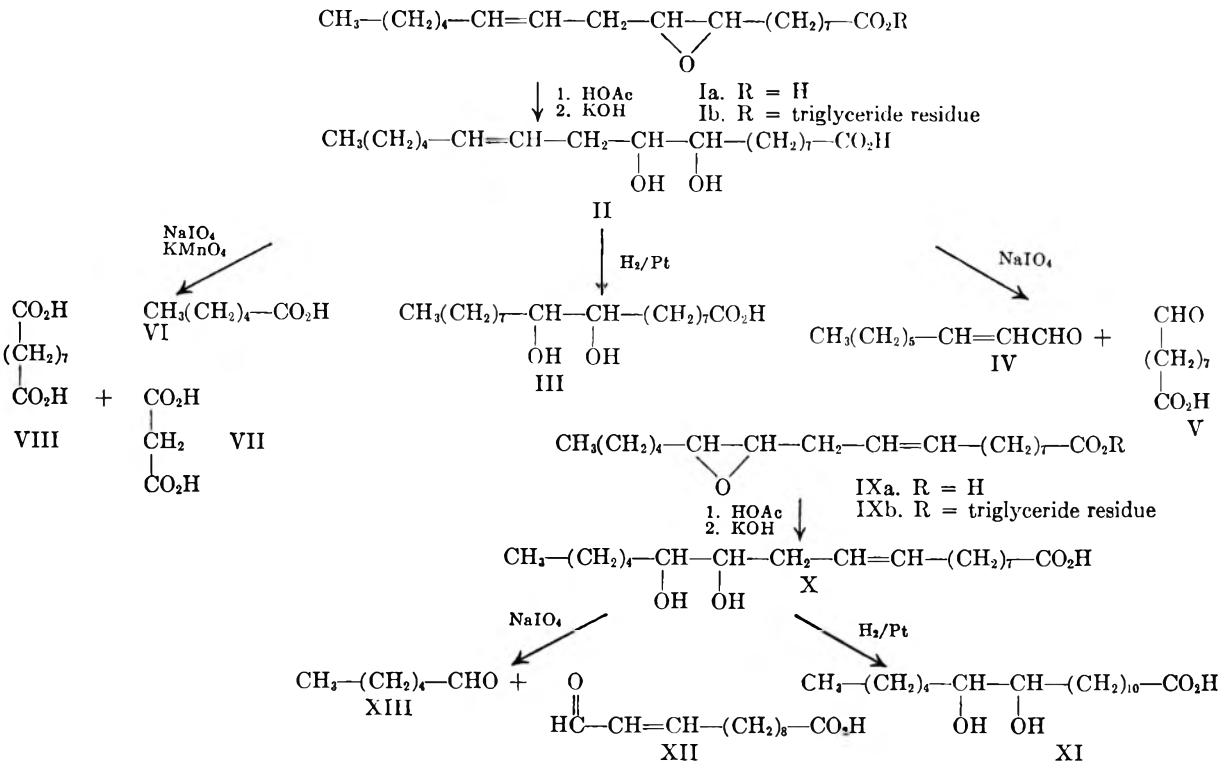
(12) R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, 33, 1701 (1955); E. von Rudloff, *J. Am. Oil Chemists' Soc.*, 33, 126 (1956).



this oxidation and that the same method presumably could be used with II. Permanganate-periodate oxidation of II yielded hexanoic and nonandioic acids, which were separated by steam distillation and characterized as *p*-bromophenacyl esters. The middle fragment, malonic acid, was not isolated. These degradations clearly established the structure of coronaric acid (I) as *cis*-9,10-epoxy-*cis*-12-octadecenoic acid. They also showed that when II was oxidized with periodate under acidic conditions, its double bond migrated into conjugation, following the reaction observed by Gunstone in the case of X.[2]

The assignment of a *cis* configuration to the 9,10-epoxy group of coronaric acid (Ia) followed from the fact that a dihydroxy acid of the *threo*-series was produced by acetolysis of the epoxide ring followed by alkaline hydrolysis of the resulting 9,10-dihydroxy monoacetate.[13–16] However, Bharucha and Gunstone[14] found that X obtained from *Vernonia* oil was optically active and that the saturated dihydroxy acid derived from X apparently was optically active also. They reasoned that derivation of an optically active glycol from IXb resulted from formation of unequal amounts of the two isomers obtainable by opening the oxirane ring. Coronaric acid is probably also optically active, although we did not have sufficient material to check this point experimentally. The specimen used for determining the mixed melting point with III was DL-*threo*-9,10-dihydroxyoctadecanoic acid prepared by epoxidation of oleic acid; it had a melting point very similar to that of III. It may be noted that McGhie and coworkers[16] resolved DL-*threo*-9,10-dihydroxyoctadecanoic acid into its enantiomorphic forms, and found that these optical isomers had m.p. 99.5° and $[\alpha]_D \pm 23°$.

The DL form of II was apparently reported by McKay and Bader,[17] who prepared a compound which they termed "*cis*-9,10-dihydroxy-12-octadecenoic acid." In view of configurational reassignments by Swern,[13] however, this acid should be considered a *threo*-glycol. McKay and Bader obtained it only as an oil.

A sample of *Clarkia elegans* oil containing 0.54% oxirane oxygen[9] was obtained for isolation work. The infrared spectrum of this oil indicated no free hydroxyl. The epoxy acid was converted to an unsaturated dihydroxy acid and thus isolated; the latter was shown by mixed melting point determinations, hydrogenation, and oxidative cleavage to be identical with X isolated from *Veronia anthelmintica* oil by Gunstone's procedure.[2] The mother liquors from crystallization of X that was isolated from *Clarkia elegans* were carefully chromatographed, but no evidence for the presence of a dihydroxy acid other than X was found. The substituent epoxy acid of *Clarkia elegans* seed oil therefore is vernolic acid.

(13) D. Swern, *J. Am. Chem. Soc.*, **70**, 1235 (1948).
(14) K. E. Bharucha and F. D. Gunstone, *J. Chem. Soc.*, **1956**, 1611.
(15) W. J. Gensler and H. N. Schlein, *J. Am. Chem. Soc.*, **78**, 169 (1956).
(16) J. F. McGhie, W. A. Ross, and D. J. Polton, *Chem. & Ind. (London)*, **1956**, 353.
(17) A. F. McKay and A. R. Bader, *J. Org. Chem.*, **13**, 75 (1948).

Vernolic acid, coronaric acid, and the 15,16-epoxylinoleic acid in *Camelina sativa* oil have a striking feature in common: All three may be considered common fatty acids of the type having methylene-interrupted unsaturation, but with one double bond replaced by an epoxide ring. It appears possible that these epoxy acids may be derived biogenetically from linoleic or linolenic acid through the action of unknown epoxidases which preferentially attack one or the other of the available double bonds.[17a] Epoxy acids may be of rather wide occurrence in the plant kingdom, having now been found in seed oils of genera distributed among several plant families—the Compositae (includes *Vernonia* and *Chrysanthemum*), Euphorbiaceae (*Cephalocroton*), Malvaceae (*Hibiscus*), Cruciferae (*Camelina*), and now in one of the Onagraceae (*Clarkia*).

In recent years, epoxy acids prepared chemically have attained a position of industrial importance. Consequently, natural sources of such acids may be of considerable future significance.

EXPERIMENTAL[18]

Isolation of threo-9,10-dihydroxy-12-octadecenoic acid (II) *from Chrysanthemum coronarium oil.* Coarsely ground seeds of *Chrysanthemum coronarium* were extracted overnight in a Soxhlet apparatus with 30–60° petroleum ether. The bulk of the solvent was evaporated on a steam bath under a nitrogen atmosphere, and the remainder was removed *in vacuo* with a rotating evaporator. Part of the isolation work was carried out on oil containing 0.85% oxirane-oxygen;[19] oil containing only 0.15% oxirane-oxygen was used for the rest.[19] (These percentages corresponded to a content of 2.8 to 15.8% monoepoxy C_{18} acids.) The infrared spectrum of the oil showed a low-intensity maximum at 11.85 μ (epoxy), but no appreciable hydroxyl content. Acids accompanying the epoxy acid in this oil were apparently predominantly of the common types: 11% saturated, 24% monoethenoid, and 59% nonconjugated diethenoid.[6]

Acid-free *C. coronarium* oil (32.5 g.) was refluxed with glacial acetic acid (300 ml.) for 3 hr. under an atmosphere of nitrogen. Most of the acetic acid was removed by distillation; the residue was diluted with water, then extracted with ether. The oil obtained by evaporation of the ether extract (29.6 g.) had a negligible oxirane-oxygen content,[19] and was saponified by refluxing with 2*N* ethanolic potassium hydroxide (150 ml.) under nitrogen for 30 min. The resulting mixture was diluted with water and extracted with ether to remove unsaponifiables. The alkaline liquor, on acidification and extraction with ether, yielded 27.1 g. of free acids.

Free acids thus obtained (22.0 g.) were fractionated by solvent partitioning between aqueous methanol and petroleum ether following Gunstone's scheme.[2] The combined methanol fractions yielded 0.815 g. of dihydroxy acid concentrate; additional concentrate was prepared similarly. A 2.85-g. portion of such concentrate was purified by recrystallization from acetone (28 ml.) at −45°. A yellow solid (1.91 g.) was obtained which was similarly recrystallized from 19 ml. of acetone. A 1.52-g. yield of II, m.p. 53–57°, resulted. On admixture with *threo*-12,13-dihydroxy-9-octadecenoic acid (X) a melting point of 42–52° was observed. The specimen of X (lit.[2] m.p. 53–54°) used in this mixed melting point determination was prepared in this laboratory from *Vernonia anthelmintica* seed oil, following Gunstone's procedure. The infrared spectrum of II showed absorption at 2.95 μ (medium intensity); no *trans* C=C absorption.

Anal. Calcd. for $C_{18}H_{34}O_4$: C, 68.7; H, 10.9. Found: C, 68.6; H, 10.6; absorbs 0.95 mol. of hydrogen (*cf.* following paragraph for conditions).

Hydrogenation of threo-9,10-dihydroxy-12-octadecenoic acid (II). A 0.364-g. portion of II was hydrogenated at atmospheric pressure and room temperature, using platinum oxide catalyst in ethanol solution. Crude III was obtained having m.p. 83–91°. Recrystallization from chloroform yielded 0.245 g. of III, m.p. 93–93.5°; no depression of melting point was observed on admixture with authentic *threo*-9,10-dihydroxyoctadecanoic acid (lit.[20] m.p. 93–94°). A marked depression of melting point (83–93°) was evident, however, on admixture with *threo*-12,13-dihydroxyoctadecanoic acid (XI) (lit.[20] m.p. 95–96°). The specimen of XI used for mixed melting point determination was prepared in this laboratory by hydrogenation of X and had m.p. 96–97°.

Periodate oxidation of II. A 1.01-g. portion of II dissolved in 50 ml. of ethanol was combined with 0.8 g. of sodium periodate in 38 ml. of 1*N* sulfuric acid. The resulting solution was kept at 40° for 15 min., then chilled, diluted with 100 ml. of water, and extracted with ethyl ether four times. The combined ether extracts were dried over sodium sulfate; most of the ether was removed by distillation. The residual liquid, which contained considerable ethanol, was diluted with water to give Solution A, which was extracted repeatedly with petroleum ether to remove the volatile aldehyde. The combined petroleum ether extracts were distilled to remove most of the volatile solvent and the residue was steam-distilled. The cloudy distillate was extracted four times with ethyl ether (combined, dried ether extracts = Solution C).

Solution A, having been previously extracted with petroleum ether, was extracted repeatedly after steam distillation with ethyl ether (combined extracts = Solution B).

2,4-Dinitrophenylhydrazone of volatile aldehyde (IV). Solution C was distilled to remove the volatile solvent. A 2,4-dinitrophenylhydrazone of IV was prepared from the residue according to the procedure of Shriner, Fuson, and Curtin.[21] The crude product obtained was 0.584 g. of orange solid, m.p. 84–92°. After two recrystallizations from ethanol, the substance had m.p. 119–121° (lit.[22] m.p. for 2-nonenal-2,4-dinitrophenylhydrazone, 124–124.5°). The visible spectrum showed λ_{max} 375 mμ (ϵ 28,650; conjugated carbonyl derivative[11]).

(17a) NOTE ADDED IN PROOF: Since this paper was submitted, *cis*-9,10-epoxyoctadecanoic acid has been found in *Tragopogon porrifolius* seed oil [M. J. Chisholm and C. Y. Hopkins, *Chem. and Ind. London*, 1154 (1959)] and also in wheat stem rust lipids [A. P. Tulloch, B. M. Craig, and G. A. Ledingham, *Can. J. Microbiol.*, **5**, 485 (1959)]. This saturated epoxy acid is related to oleic acid in the same manner that the unsaturated ones are related to linoleic or linolenic acid.

(18) Melting points were determined with a Fisher-Johns block and are uncorrected. Infrared spectra were measured with a Perkin-Elmer model 21 rock salt spectrophotometer. Visible spectra were determined in ethanol solution with a Beckman DU spectrophotometer. The mention of trade names or products does not constitute an endorsement by the Department of Agriculture over those not named.

(19) There is considerable variability among samples in the oxirane-oxygen content of the oil of *C. coronarium*. Seed from a source other than used in this investigation had a negligible oxirane-oxygen content.

(20) W. F. Huber, *J. Am. Chem. Soc.*, **73**, 2731 (1951).

(21) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *Systematic Identification of Organic Compounds*, 4th Ed., John Wiley & Sons, New York, 1956.

(22) C. J. Martin, A. I. Shepartz, and B. F. Daubert, *J. Am. Chem. Soc.*, **70**, 2601 (1948).

Anal. Calcd. for $C_{15}H_{20}N_4O_4$: C, 56.2; H, 6.3; N, 17.5. Found: C, 56.2; H, 6.1; N, 17.7.

2,4-Dinitrophenylhydrazone of nonvolatile aldehyde (V). Solution B was distilled to remove most of the solvent; 0.377 g. of crude aldehyde (V) was obtained as a light-colored oil. This oil was steam-distilled to remove any volatile impurities. The residual aqueous liquor was saturated with sodium chloride and extracted repeatedly with ethyl ether. The combined ether extracts were dried over sodium sulfate; 0.271 g. of aldehydoacid (V) was obtained. A 2,4-dinitrophenylhydrazone was prepared from V according to the procedure of Shriner, Fuson, and Curtin.[21] A crude yield (0.323 g.) of poorly crystalline yellow solid was obtained as an ethyl ester, m.p. 47–52°, and was recrystallized from ethanol. A sample having m.p. 54–56° was obtained (lit.[23] m.p. 63–64°); its spectra showed λ_{max} 356 (ϵ 18,320; no conjugation[11]) and an infrared maximum at 5.73 μ (ester).

Anal. Calcd. for $C_{17}H_{24}N_4O_6$: C, 53.7; H, 6.4; N, 14.7. Found: C, 54.0; H, 6.4; N, 15.1.

Periodate-permanganate oxidation of threo-12,13-dihydroxy-9-octadecenoic acid (X). The general procedure of Lemieux and von Rudloff[12] was followed. A 0.314-g. portion (1 mmol.) of X, 0.416 g. (3 mmol.) of potassium carbonate, 2.60 g. of sodium periodate (12 mmol.), and 0.02 g. (0.13 mmol.) of potassium permanganate were combined in 400 ml. of water. The mixture was allowed to stand 24 hr. at room temperature with occasional stirring; the suspended solid gradually disappeared during this time. The mixture was acidified with 10% sulfuric acid and extracted with ether. Evaporation of the ether after drying over sodium sulfate yielded 0.163 g. of mixed acids. This mixture was steam-distilled. After the distillation, the aqueous residue was extracted with ether. On evaporation, the dried ether extract yielded 0.089 g. of acid, m.p. 97–104°. Recrystallization from petroleum ether–chloroform yielded 0.060 g., m.p. 105–106°. No depression of melting point was observed on admixture with authentic nonandioic acid. The other cleavage products were not characterized.

Periodate-permanganate oxidation of II. The oxidation of II was carried out in the same manner as that of X. A 0.302-g. portion of II was oxidized; 0.291 g. of mixed acids were obtained. On steam-distilling this, 0.053 g. of volatile acid (VI) was obtained from the distillate and 0.167 g. of nonvolatile acid (VII), m.p. 96–103°, from the residual liquor. Recrystallization of the latter from ethyl acetate–petroleum ether produced a sample having m.p. 103.5–105°; no depression of melting point was observed on admixture with authentic nonandioic acid (VIII). The *bis-p*-bromophenacyl ester of the dicarboxylic acid was prepared, m.p. 129–130.5°; mixed m.p. with the authentic derivative of nonandioic acid, 130–131.5°.[21]

The steam-volatile acid was dissolved in 4.2 ml. of 0.1*N* sodium hydroxide. The resulting solution was made slightly acidic by addition of 0.15 ml. of 0.1*N* hydrochloric acid, and was refluxed 1 hr. with 5 ml. of 95% ethanol and 0.114 g. of *p*-bromophenacyl bromide. Most of the ethanol was removed under reduced pressure, and the residue was extracted with ether. The ether extracts were dried over sodium sulfate and evaporated, yielding 0.111 g. of crude *p*-bromophenacyl ester, m.p. 47–59°. Two recrystallizations from 80% ethanol and two from hexane yielded a sample with m.p. 67–69°. The mixed melting point of this material with authentic *p*-bromophenacyl hexanoate (m.p. 70.5–71°) was 68.5–71°. On admixture with *p*-bromophenacyl heptanoate (m.p. 69–70°), the melting point was depressed to 61–64°.

Isolation of threo-12,13-dihydroxy-9-octadecenoic acid (X) *from Clarkia elegans oil.* Coarsely ground seeds of *Clarkia elegans* were extracted overnight in a Soxhlet apparatus with 30–60° petroleum ether. A 36.7% yield of oil was obtained containing 0.73% oxirane-oxygen.[9] Acids accompanying the epoxy acid in this oil were apparently predominantly of the common types: 14% saturated, 20% monoethenoid, and 57% nonconjugated diethenoid.[9] Its infrared spectrum showed no appreciable hydroxyl content. A 91.6-g. portion of acid-free oil was treated with acetic acid and saponified as described for *C. coronarium*. After acetolysis, the oil had a negligible oxirane-oxygen content. A yield of 83.9 g. of free acids and 1.1 g. of unsaponifiable matter was obtained. The dihydroxy acids were concentrated, following Gunstone's solvent partitioning scheme.[2] A dihydroxy acid concentrate of 7.9 g. was obtained. Fraction D[2] (5.7 g.) was recrystallized twice from acetone (4 ml.) at −40°. A solid (0.101 g.), m.p. 49–51.5°, was obtained; further recrystallization increased the m.p. to 50–52°. No depression of melting point was observed on admixture with authentic X prepared from *Vernonia anthelmintica* oil. The infrared spectrum of the solid, m.p. 49–51.5°, indicated no *trans*-unsaturation. Mother liquor from the recrystallization of the dihydroxy acid concentrate was evaporated and the residue chromatographed on neutral alumina, collecting numerous fractions. No evidence was found for a dihydroxy acid other than X.

Anal. Calcd. for $C_{18}H_{34}O_4$: Neut. equiv., 314. Found: Neut. equiv., 313; absorbs 1.0 mol. of hydrogen.

Hydrogenation of threo-12,13-dihydroxy-9-octadecenoic acid (X). The dihydroxy acid (X) from *Clarkia* oil was hydrogenated as described for II. Crude XI was obtained, m.p. 90–95°, and was recrystallized from ethyl acetate. A sample, m.p. 94–96.5°, was obtained; no depression of melting point was observed on admixture with X (prepared from authentic IX from *Vernonia anthelmintica* seed oil), m.p. 96–97°.

Periodate oxidation of X. The dihydroxy acid (X) from *Clarkia* oil (0.803 g.) was subjected to periodate cleavage and separated in much the same manner as with II.

A yield of 0.642 g. of nonvolatile aldehyde (XII) was obtained; 0.413 g. of this was converted to a 2,4-dinitrophenylhydrazone by the method of Shriner, Fuson, and Curtin.[21] Orange crystals (0.625 g.) of a crude derivative were obtained; the melting point of this material after recrystallization from ethanol was 63–68.5°. By a combination of recrystallizations from ethanol and chromatography on alumina (eluting with benzene), 0.096 g. of the derivative was obtained, m.p. 81–83° (lit.[2] m.p. for 11-formyl-10-undecenoic acid 2,4-dinitrophenylhydrazone, 81.5–83°); λ_{max} 375 mμ (ϵ 26,290; conjugated carbonyl derivative[11]).

The steam-volatile aldehyde (XIII) obtained was similarly converted to a 2,4-dinitrophenylhydrazone (0.235 g.), m.p. 84–93°, and similarly purified; 0.053 g., m.p. 102.5–104°, was obtained. No depression of melting point was observed on admixture with authentic *n*-hexanal-2,4-dinitrophenylhydrazone (lit.[21] m.p. 104°). The identity of XIII with *n*-hexanal was confirmed by paper chromatography, using the solvent system heptane/methanol.[24] The observed R_f value was 0.80 for the 2,4-dinitrophenylhydrazones of both XIII and authentic *n*-hexanal when run simultaneously.

Permanganate oxidation of X. Oxidation of X (0.636 g.) was carried out with potassium permanganate in acetic acid solution, essentially as described by Begemann and coworkers.[25] After completion of the oxidation, most of the acetic acid was removed by distillation. The residue was dissolved in dilute sulfuric acid and decolorized with sodium sulfite. The resulting aqueous solution was extracted with ether and dried over sodium sulfate. The acids obtained by evaporation of solvent were separated by steam distillation; 0.101 g. of steam-volatile and 0.417 g. of crude nonvolatile acid were obtained. The latter was recrystallized from water and then from petroleum ether–ethyl acetate; 0.055 g., m.p. 102–105° resulted. This melting point was undepressed on admixture with authentic nonandioic acid. The nonvolatile

(23) J. T. Scanlan and D. Swern, *J. Am. Chem. Soc.*, 62, 2305 (1940).

(24) D. F. Meigh, *Nature*, 170, 579 (1952).

(25) P. H. Begemann, I. G. Keppler, and H. A. Boekenoogen, *Rec. trav. chim.*, 69, 439 (1950).

acid was also characterized as a *p*-bromophenacyl ester, prepared as described by Shriner, Fuson, and Curtin.[21] A 0.091-g. portion of the acid yielded 0.043 g. of *p*-bromophenacyl ester, m.p. 129–131°, undepressed on admixture with authentic *p*-bromophenacyl nonandioate. The volatile acid (0.101 g.) was similarly converted to a *p*-bromophenacyl ester, 0.011 g. after two recrystallizations from 50% ethanol, m.p. 68–70°, undepressed on admixture with authentic *p*-bromophenacyl hexanoate. The malonic acid fragment (VII) was not isolated.

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Some Neutral Components of Cigarette Smoke[1]

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The paraffin wax fraction of cigarette smoke has been shown to contain the fifteen normal alkanes from docosane to hexatriacontane and branched alkanes having between 21 and 32 carbon atoms, inclusive. About one third of this paraffin mixture consists of hentriacontane and tritriacontane. Also present in the neutral fraction of smoke are squalene, isosqualene, stigmasterol, β-sitosterol, and probably γ-sitosterol.

Carcinogenicity tests on mice[3] of fractions of cigarette smoke indicated that the fractions designated as K and M[4] were the most active. We have previously described, in part, the chemical composition of these materials; the present paper reports our further studies on the neutral components of M and related fractions.

An earlier paper from our laboratory[4] had presented indicative proof of the presence of hentriacontane and tritriacontane in the smoke of blended American cigarettes. A later report by Cuzin *et. al.*[5] stated that no evidence was found for the presence in smoke (or tobacco leaf) of alkanes of more than 32 carbons.[6] A reinvestigation of our material was accordingly undertaken. A purified paraffin mixture of M'[4] was prepared as before and its x-ray diffractogram was compared with those of synthetic samples of hentriacontane, tritriacontane, and pentriacontane; the respective values for the long-spacings were 42.7 Å, 41.8 Å, 44.1 Å, and 46.7 Å.[7] These results confirmed those obtained earlier by us in that the value for the wax from smoke fell between those of the C_{31} and C_{33} hydrocarbons; we were later able to obtain a mass spectrometric analysis which clearly showed this wax to be composed largely of equal amounts of the C_{31} and C_{33} *normal* alkanes, some C_{32} homolog, and small amounts of other alkanes (Table I).

TABLE I

MASS SPECTRA OF PARAFFIN MIXTURE FROM M'

No. of Carbons	% Normal	% Branched
30	2	
31	38	1
32	14	
33	39	1
34	5	

To obtain a broader analysis of the higher-alkane distribution in cigarette smoke, a sample of MM[4] was exhaustively extracted with concentrated

(1) Portions of this paper were presented at the Seventh International Cancer Congress, London, July 1958 and at the Meeting-in-Miniature of the New York Section of the American Chemical Society, April 1959; *cf.* also A. I. Kosak and J. S. Swinehart, *Chem. and Ind. (London)*, 1007 (1958).

(2) Abstracted from a part of the Ph.D. thesis of J.S.S., New York University, April 1959.

(3) W. E. Smith, N. Nelson, L. Orris, and A. I. Kosak, unpublished data.

(4) A. I. Kosak, J. S. Swinehart, and D. Taber, *J. Natl. Cancer Inst.*, **17**, 375 (1956).

(5) J. L. Cuzin, L. V. Thoi, and M. S. Morec, paper presented at the second International Tobacco Science Congress, Brussels, June 1958.

(6) The x-ray diffraction data listed by these workers for their highest molecular weight fraction was the same as that which we had reported and the difference is one of interpretation. They ascribed their *d*-value of 42.7 Å to dotriacontane. We felt that the *d*-value of this magnitude more probably represented a mixture of *odd*-numbered alkanes for four reasons: first, the paraffins of other plant waxes consist principally of this class of alkanes; second, a mixture of normal alkanes will have the same long-spacing as that of a single hydrocarbon whose molecular weight equals that of the average of the mixture, if the hydrocarbons of the mixture do not differ from each other by more than four carbon atoms [S. H. Piper, A. C. Chibnall, S. J. Hopkins, A. Pollard, J. A. B. Smith, and E. F. Williams, *Biochem. J.*, 25, 2072 (1931)]; third, the "blurred" diffraction lines (Piper *et al.*, *loc. cit.*); fourth, evidence for the occurrence of tritriacontane in tobacco leaf [A. C. Chibnall, S. H. Piper, A. Pollard, E. F. Williams, and P. N. Sahai, *Biochem. J.*, 28, 2189 (1934)].

(7) The values for the synthetic materials are in good agreement with those reported by D. R. Kreger in J. Bouman, *Selected Topics in X-Ray Crystallography*, Amsterdam, 1951, p. 316.

TABLE II

PARAFFIN CONTENT OF MM

No. Carbons	Fraction 1, %		Fraction 2, %		Fraction 3, %		Fraction 4, %		Fraction 5, %		% of Total Alkanes in MM[a]	
	Normal	Branched	Normal	Branched	Normal	Branched	Normal	Branched	Normal	Branched	Normal	Branched
21		3										0.16
22	2	4									0.11	0.21
23	9	4									0.49	0.21
24	17	4									0.92	0.21
25	18	3	2								2.5	0.16
26	11	2	1	2							1.4	1.63
27	9	2	8	1							6.6	0.87
28	6	1	2	18		1		1			1.8	13.9
29	5		8	3				1			6.3	2.31
30			4	19	1	7	3	3	1	1	3.3	15.33
31			26	1	24	1	9	1	5		22.9	0.90
32			4	1	13	3	4		4	1	4.8	1.13
33					46		71		53		9.7	
34					4		7		13		1.2	
35									21		0.97	
36									1		0.05	
% of total paraffins	4.2	1.2	41.7	34.2	9.6	1.3	3.0	0.2	4.5	0.1	63.0	37.0

[a] These values are approximate since Fraction 1 contained 10–20% olefinic or naphthenic material of formula C_{n-2} with discrete peaks at C_{20} (m/e = 278) and C_{24} (m/e = 334) and Fraction 5 contained 2–3% of C_nH_{2n-6} material with peaks at C_{26}, C_{28}, and C_{40}.

sulfuric acid and was then separated by chromatography on alumina into five fractions which were also examined in the mass spectrometer. Table II indicates that hentriacontane is the principal component, and that considerable quantities of branched-chain alkanes are also present. Somewhat similar distributions of alkanes have been found in other plant waxes, marine sediments, and soil extracts.[8,9]

After removal of the paraffin hydrocarbons from a sample of fraction M[4] by chromatography on silica gel, a viscous oil was eluted whose infrared spectrum indicated it to be a mixture of polyolefins and long-chain ketones. Most of the ketonic material was removed by further chromatography on acid-washed and on basic alumina, and subsequent distillation yielded a cut boiling at 215–221°/1 mm., constituting about 0.02% of the total smoke condensate, whose infrared spectrum was that of squalene plus bands at the 6.07μ (w) and 11.25μ (m) regions where isosqualene absorbs strongly.[10] This material was hydrogenated over 5% rhodium on alumina catalyst and absorbed 6.1 mol. of hydrogen; the value expected for squalene is 6.0 mol. Upon treatment of the smoke component with hydrogen chloride in anhydrous acetone a hexahydrochloride was formed[11] which was identical with that produced from a freshly distilled sample of squalene under the same conditions. Identity was established by mixture melting point, infrared absorption, and x-ray diffraction pattern.

The presence of isoqualene was confirmed by chromatographing on paper the mixture isolated from smoke, "regenerated squalene" (which contains isosqualene) obtained from squalene hexahydrochloride,[10] and squalene. The results are presented in Table III. The isosqualene spot derived from the smoke component (R_f 0.82) was decidedly weaker than the squalene spot (R_f 0.68) from the same source, which is consistent with the spectroscopic data.

TABLE III

PAPER CHROMATOGRAPHY OF SQUALENE SAMPLES

Material	R_f Value
Squalene[a]	0.70
Regenerated squalene[b]	0.68, 0.84
Material from smoke[b]	0.64,[c] 0.69, 0.82, 0.91[c]
Acid-treated squalene[d]	0.69

[a] Average of four runs. [b] Three runs. [c] These spots were weak and diffuse. [d] One run.

(8) *E.g.* G. Wanless, W. King, and J. J. Ritter, *Biochem. J.*, 59, 687 (1955); E. D. Evans, G. S. Kenny, M. G. Meinschein, and E. E. Bray, *Anal. Chem.*, 29, 1859 (1957); W. E. Meinschein and G. S. Kenny, *Anal. Chem.*, 29, 1153 (1957).

(9) Dr. W. Carruthers has informed us that he and Dr. R. A. W. Johnston have also detected branched-chain alkanes in cigarette smoke as well as in green and fermented tobacco leaves. We are indebted to Dr. Carruthers for making his results available to us before publication.

(10) W. G. Dauben, H. C. Bradlow, N. K. Freeman, D. Kritchevsky, and M. Kirk, *J. Am. Chem. Soc.*, 74, 4321 (1952).

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No changes were noted in the infrared spectrum of a sample of squalene which had been agitated with 12% hydrochloric acid for 12 hr. nor did any new paper chromatographic spot appear. This precludes the possibility that the isosqualene found was an artifact produced during the acid extraction step employed in the primary fractionation[4] (see Table III).

Three steroids, stigmasterol,[12-14] β-sitosterol,[13] and γ-sitosterol,[13] have been reported to be in cigarette smoke. It is extremely difficult to isolate *pure* individual components from small amounts of mixtures of related sterols whose melting points and rotations are in the same range,[15] *e.g.*, the sitosterols. Proof of identity of such phytosterols is often complicated by the fact that C_{27}-C_{29} sterols with the same number of double bonds, identical oxygen functions, and similar but not identical structures often have identical infrared spectra.[16] We have isolated two steroids from fraction M in addition to the previously reported stigmasterol.[12] By a comparison of the melting points, rotations, and infrared spectra of these compounds and their esters with those of β- and γ-sitosterol, we have assigned the latter two structures to the smoke sterols, confirming the work of Carruthers and Johnston.[13] We have obtained what we believe to be positive evidence for the identities of β-sitosterol and stigmasterol by x-ray diffraction powder techniques[17] which showed the patterns of the isolated sterols to be identical with those of the respective authentic samples.

EXPERIMENTAL[18]

15-Tritriacontanone was synthesized in 72% yield from 1-bromohexadecane and margaroyl chloride *via* the organocadmium intermediate[4]; m.p. 73.4–76.8°. Chromatography on alumina and two recrystallizations from ethanol raised the m.p. to 79.7–81.7° [lit.[19] m.p. 78.8–79.2°].

18-Pentatriacontanone was prepared by the method of Kipping[20] in 40% yield; m.p. 88.5–89.4° [lit.[21] m.p. 88.7–89.0°].

Tritriacontane and pentatriacontane. A mixture of 1.1 g. of ketone (15-tritriacontanone or 18-pentatriacontanone), 17 ml. of 70% hydrazine hydrate, and 65 ml. of diethylene glycol was maintained at 110° for 1 hr.; 6.5 g. of potassium hydroxide was then added and the mixture was heated at reflux for 8 hr. The mixture was cooled to 110° and the above steps were repeated four times with the addition of 10 ml. of hydrazine hydrate and 5 g. of potassium hydroxide in each stage; after the last addition, the reaction was heated at reflux for 72 hr.[22] The acidified reaction product was extracted with three 200-ml. portions of benzene, the solvent evaporated, and the residue was recrystallized from ethanol to give tritriacontane (30%), m.p. 71.4–71.7° [lit.[23] m.p. 71.5–71.6°] and pentatriacontane (26%), m.p. 74.2–74.6° [lit.[24] m.p. 74.4–74.5°].

X-Ray diffraction data for paraffins. The diffraction maxima (angles in degrees) were: paraffin wax from smoke,[25] 1.05, 2.07, 3.11, 4.13, 5.15, 6.07; hentriacontane[4] 1.06, 2.10, 3.16, 4.24, 5.29; tritriacontane: 2.95, 4.03, 5.04, 6.04, 7.03; pentatriacontane: 1.87, 2.85, 3.82, 4.77, 5.74, 6.70, 7.64, 8.56. Substitution of these values in Bragg's equation gave respective average values for *d* of 42.7 Å, 41.8 Å, 44.1 Å, 46.5 Å.

Fractionation of MM waxes for mass spectrographic study. A solution of 16 g. of MM in 140 ml. of petroleum ether (30–60°) was extracted successively with thirty 50-ml. portions of concentrated sulfuric acid, two 6-ml. portions of 5% aqueous sodium carbonate, and three 60-ml. portions of water. The residue was chromatographed on 5.5 kg. of basic alumina, and petroleum ether (30–60°) was passed through the column. Fraction 1 (0.6 g.), fraction 2 (8.4 g.), m.p. 50.0–61.0°, fraction 3 (1.2 g.), m.p. 58.0–67.5°; fraction 4 (0.38 g.), m.p. 62.0–68.9°; fraction 5, eluted with benzene, (0.51 g.), m.p. 64.0–70.3°.

Isolation of squalene. In a typical run, 25 g. of fraction M was chromatographed on 2800 g. of silica gel. The column was eluted successively with 30–60° petroleum ether (1.6 l.), 1:4 benzene–petroleum ether (2.3 l.), and 2:3 benzene–petroleum ether (2.8 l.). Evaporation of the solvent from the last eluate left 5 g. of viscous, orange oil, 2.2 g. of which was chromatographed on 1800 g. of Merck acid washed alumina and eluted with 2 l. of petroleum ether. The product thus obtained from several runs (9.3 g.) was put through a column of 800 g. of basic alumina and the petroleum ether eluate (300 ml.) consisted of 4.2 g. of light yellow oil which still showed some infrared absorption in the carbonyl region. It was distilled and gave 0.31 g. of colorless oil, b.p. 215–221°/1 mm., whose infrared spectrum resembled that of squalene with the addition of peaks at 6.07 μ and 11.25 μ.

Squalene hexahydrochloride was prepared by the method of Heilbron *et al.*[11] both from the isolated squalene mixture (m.p. 109.5–112.0°) and from a sample of squalene (m.p. 111.0–112.8°); mixture melting point 109.8–112.5°.

X-Ray diffraction data for squalene hexahydrochlorides. The values cited are for the *d*-spacing in Å and the corresponding intensity (I/I_1); squalene hexahydrochloride: 5.9 (0.40); 5.1 (0.70); 4.7 (1.00); 4.2 (0.18); 4.1 (0.13); 3.5 (0.07); 3.0 (0.09); hexahydrochloride of smoke component: 5.9 (0.38); 5.1 (0.70); 4.7 (1.00); 4.2 (0.20); 4.1 (0.16); 3.5 (0.08); 3.0 (0.18).

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Reduction of isolated squalene mixture. A solution of 3.5 mg. (0.0088 mmol.) of polyolefin in prereduced petroleum ether containing 5% rhodium on alumina catalyst absorbed 1.2 ml. of hydrogen (standard conditions).

Paper chromatography of squalene and related materials. Squalene, regenerated squalene,[10] the squalene mixture from smoke, and acid-treated squalene were spotted on Whatman No. 1 filter paper impregnated with "Quilon" (stearato chromic chloride[10,26]; the chromatogram was developed with methanol, and iodine vapor[27] was used for detection. R_f values were measured to the leading edge of the spot.

Isolation of sterol mixture from M. After the removal of polyolefins during silica gel chromatography of a 40 g. sample of M, the column (3.2 kg.) was eluted successively with 3 l. of benzene, 2.4 l. of 1:20 ethyl ether–benzene, 5 l. of 1:10 ethyl ether–benzene, 6 l. of 1:8 ethyl ether–benzene and 6 l. of 1:6 ethyl ether–benzene. The last solution yielded 0.21 g. of light orange oil which gave a positive Liebermann-Burchard test; crystallization from 1:1 benzene–methanol gave colorless crystals, m.p. 145.2–149.8°. The combined material from several runs was chromatographed on acid-washed alumina, and the column was eluted with petroleum ether, benzene, 4% ethyl ether in benzene, 12% ethyl ether in benzene, and 25% ethyl ether in benzene. The steroids were recovered from the last fraction; this procedure was repeated twice. The steroids were recrystallized from 4:1 methanol-ethanol and then from 4:1 petroleum ether–benzene to give colorless crystals, m.p. 158.4–162.8°. (In some runs it was found desirable to chromatograph the mixture once more on basic alumina at this point.) The yield of mixed steroids was of the order of 0.25% based on M.

Isolation and identification of β-sitosterol. This material was subjected to an extensive (more than 900 theoretical plates) fractional recrystallization from 1:1 benzene-methanol. Some of the filtrates from the previous recrystallizations were combined with various filtrates in the fractional recrystallization. From the filtrate side of the fractional recrystallization, sterol I was obtained, which after treatment with Darco and two recrystallizations from 95% ethanol gave rhombic platelets, m.p. 135–136°, $[\alpha]_D^{24}$ −38° (*c* 0.745). A mixture melting point of sterol I and β-sitosterol showed no depression. The acetate and benzoate of sterol I were made: acetate m.p. 127–128°, $[\alpha]_D^{25}$ −41.5° (*c* 0.823); benzoate m.p. 146–147°, $[\alpha]_D^{24}$ −14.7 (*c* 1.284); the reported constants for β-sitosterol are[28]: m.p. 137.0–137.5°, $[\alpha]_D^{24}$ −37°; for β-sitosteryl acetate: m.p.[29,30] 126.0–127.5°; $[\alpha]_D^{24}$ −42°[30]; for β-sitosteryl benzoate[28]: m.p. 146–147°, $[\alpha]_D^{24}$ −13.8°. The infrared spectra of the isolated sterol and its derivatives were identical with those of the corresponding sitosterol family.

Isolation and identification of stigmasterol. From the less soluble side of the fractional recrystallization, sterol II was obtained and recrystallized from ethanol to give colorless platelets, m.p. 169.5–170.5°, $[\alpha]_D^{24}$ −44.6°; a mixture melting point with an authentic sample of stigmasterol[31] was undepressed. The acetate of sterol II was prepared, m.p. 142.4–143.8°, $[\alpha]_D^{24}$ −53.6° (*c* 0.781), and the benzoate, m.p. 161.1–161.6°, $[\alpha]_D^{24}$ −24.2° (*c* 0.821). The reported constants for stigmasterol are: m.p. 170–171°,[32] $[\alpha]_D^{24}$ −45.8°[33]; for stigmasteryl acetate,[32] m.p. 144°, $[\alpha]_D^{20}$ −55.6°; for stigmasteryl benzoate,[34] m.p. 160.5–161.5°, $[\alpha]_D^{24}$ −24.5°.

Reduction of sterols. Sterols I and II and stigmasterol were separately reduced in acetic acid solution using a 5% rhodium on alumina catalyst (Baker and Co.). The moles of hydrogen taken up, respectively, per mole of steroid were 1.07, 2.14, and 2.10. The stanols and their acetates and benzoates were all identical as shown by melting points, mixture melting points, rotations, and infrared absorption spectra.

X-Ray diffraction data for sterols I and II. The values are in Å followed by intensity, I/I_1, in parentheses. Sterol I: 8.6 (0.10), 7.5 (0.10), 7.0 (0.13), 6.7 (0.16), 6.3 (0.12), 5.8 (0.75), 5.5 (1.00), 5.4 (0.87), 5.1 (0.37), 5.0 (0.24), 4.8 (0.26), 4.6 (0.18), 4.5 (0.17), 4.2 (0.19), 4.1 (0.14), 3.7 (0.12), 3.5 (0.12), 3.3 (0.08), 3.2 (0.07); for β-sitosterol: 8.6 (0.09), 7.4 (0.09), 7.0 (0.14), 6.7 (0.17), 6.3 (0.11), 5.8 (0.78), 5.5 (1.00), 5.4 (0.87), 5.1 (0.34), 5.0 (0.33), 4.8 (0.32), 4.6 (0.31), 4.5 (0.17), 4.2 (0.19), 4.1 (0.15), 3.7 (0.13), 3.5 (0.11), 3.3 (0.08), 3.2 (0.08); for sterol II: 7.4 (0.39), 6.7 (0.25), 6.2 (0.32), 5.9 (0.93), 5.1 (0.88), 4.8 (1.00), 4.6 (0.49), 4.3 (0.28), 4.0 (0.27), 3.9 (0.28), 3.6 (0.17), 3.5 (0.19), 2.7 (0.10), 2.3 (0.14), 2.3 (0.14), 2.2 (0.22); for stigmasterol: 7.4 (0.39), 6.7 (0.35), 6.2 (0.34), 5.9 (1.00), 5.1 (0.77), 4.8 (0.95), 4.6 (0.33), 4.3 (0.27), 4.0 (0.28), 3.9 (0.24), 3.6 (0.17), 3.5 (0.23), 2.7 (0.11), 2.4 (0.12), 2.3 (0.15), 2.2 (0.28).

Isolation of γ-sitosterol. The group of fractions closest to the four which yielded sterol I in the extended fractional recrystallization, yielded 0.47 g. of a sterol mixture which was acylated by refluxing with 32 ml. of acetic anhydride and 0.01 g. of sodium acetate. The mixed acetates were subjected to a 100-plate triangular fractional recrystallization from 1:2 benzene-ethanol. The six least soluble fractions were combined and yielded 3.4 mg. of a colorless compound, m.p. 142.3–143.6°, $[\alpha]_D^{23}$ −44.4° (*c* 0.31). This compound was hydrolyzed by refluxing with an aqueous ethanolic solution of potassium hydroxide under nitrogen to give sterol III which, after two recrystallizations from ethanol, melted at 145.0–146.4°, $[\alpha]_D^{22}$ −42.4° (*c* 0.014); the literature values for γ-sitosterol and its acetate are[35]: m.p. 147–148°, $[\alpha]_D$ −43°; m.p. 143–146°, $[\alpha]_D$ −46°.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, A. AND M. COLLEGE OF TEXAS AND THE TEXAS ENGINEERING EXPERIMENT STATION]

Spectrophotometric Studies of Some 2,4-Dinitrophenylhydrazones. III.[1] Taft and Hammett Relationships

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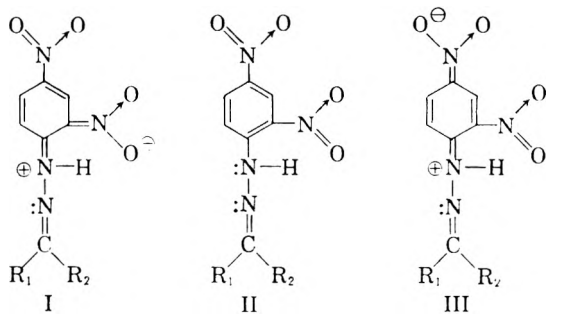
The ultraviolet and visible spectra of 21 *m*- and *p*-substituted aromatic 2,4-dinitrophenylhydrazones (DNP's) and 23 α-substituted acetaldehyde and acetone DNP's in chloroform and in alcoholic base have been determined. The difference in the absorption frequencies of these solutions, *i.e.*, $\nu_{max}^{CHCl_3} - \nu_{max}^{NaOH}$, for the aromatic DNP's were related to the Hammett substituent constants by Eq. 4: $\Delta\nu = 4835$ cm.$^{-1} + 2233\sigma$ with $r = 0.977$ and $s = 274$. The aliphatic derivatives were related to Taft's σ^*-values by Eq. 6: $\Delta\nu = 4474$ cm.$^{-1} + 843.9\Sigma\sigma^*$ with $r = 0.951$ and $s = 203$. By minimizing the squares along the substituent constant axis, new values were calculated for *p*-$(CH_3)_2N$ (−1.154), *p*-OH → *p*-$O^{\ominus}$ (−0.013 and −0.267) and *m*-OH → *m*-$O^{\ominus}$ (−0.014) in the aromatic series and in the aliphatic series, new constants were determined for F_3C (+2.595 ± 0.160), Et_2NCH_2 (−0.066) and cyclo-C_3H_5 (−0.475). The relationship between $\Delta\nu$ and ΔF is discussed.

The shift of absorption maxima which a substituent causes in the ultraviolet absorption spectra of monosubstituted benzenes has been shown to be proportional to the difference of the Hammett substituent constants[3] in the *m*- and *p* -positions ($\Delta\sigma$).[4] More recently, the similar displacement which occurs for the disubstituted benzenes has been correlated with the Hammett substituent constants,[3] the Brown-Okamoto σ^+-values,[5] and the Taft resonance parameters[6] although for substituents with like electrical properties (*m*-orienting *vs.* m-orienting, etc.), no straightforward relationship was apparent.[7] Moreover no unique equation was found to express the relationship between substituent constants and the wave-length displacement in substituted anilines, phenols, and nitrobenzenes combined.

The ultraviolet spectra of 2,4-dinitrophenylhydrazones (DNP's) can be described in terms of increased contributions of the canonical forms I and III relative to II in the structure of the photo-excited state of the molecule compared to the



I II III

ground state. The position of the absorption should be related to the electronegativities of R_1 and R_2 which would affect the electron density of the nitrogens and, in turn, the stability of the excited states. Earlier, the absorption maximum λ_{max} was empirically described as the sum of λ_{R1}, λ_{R2}, and λ_{DNP} where each term represents the "contribution" in millimicrons of the indicated moieties of the derivative.[8] However, the relationship was not applicable to substituent constants.

This communication reports a spectrophotometric examination of the chloroform and the alcoholic sodium hydroxide solutions of (a) 21 substituted aromatic DNP's, (b) 23 α-substituted acetaldehyde and acetone DNP's, and (c) the relationship of these spectra to the Hammett[3] and Taft[9] substituent constants, respectively. New constants are reported for several substituents.

EXPERIMENTAL

The procedure for preparing the derivatives and their spectra has been described.[1a]

The melting points and spectral data are contained in Tables I and II. The estimated accuracy of the wave lengths, reported to the nearest mμ, is ±0.5 mμ.

The DNP of ethyl glyoxylate in basic solution gave two peaks $\lambda_1 = 369$ mμ, $\epsilon = 1.83 \times 10^4$; $\lambda_2 = 446$ mμ, $\epsilon = 1.42 \times 10^4$. The longer wave-length absorption increased with the passage of time and shifted to 450 mμ while the shorter wave-length absorption disappeared. Since this probably

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TABLE I

PHYSICAL CONSTANTS OF SUBSTITUTED AROMATIC 2,4-DINITROPHENYLHYDRAZONES

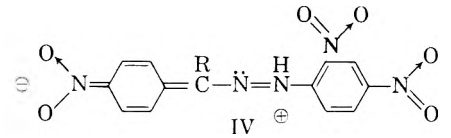
No.	2,4-Dinitrophenylhydrazone of	M.P. (Uncorr.)	$\lambda_{max}^{CHCl_3}$ mμ	ε × 10^{-4}	λ_{max}^{NaOH} mμ	ε × 10^{-4}	$\Delta\nu^a$	σ^b
1	*p*-NO_2-acetophenone	257–258[c]	382	3.48	540	3.75	7659	+1.270
2	*p*-NO_2-benzaldehyde	319–320[d]	381	3.69	537	4.52	7625	+1.270
3	*m*-NO_2-acetophenone	227–228[e]	363	2.74	473	2.87	6406	+0.710
4	*m*-NO_2-benzaldehyde	285–286d[d]	369	3.12	481	3.27	6310	+0.710
5	*p*-Cl-acetophenone	235–236[d]	377	2.95	465	2.87	5020	+0.227
6	*p*-Cl-benzaldehyde	264–265[e]	375	3.30	468	3.70	5299	+0.227
7	*m*-MeO-benzaldehyde	218–219[f]	369	3.08	469	3.39	5778	+0.115
8	Acetophenone	247–248[d]	377	2.76	461	2.66	4833	0.000
9	Benzaldehyde	238–239[d]	378	3.03	462	3.19	4810	0.000
10	*p*-OH-benzaldehyde	271–272d[d]	387	2.85	475	2.91	4788	−0.013[g]
11	*m*-OH-benzaldehyde	256–257[h]	377	2.99	460	3.12	4786	−0.014[g]
12	*p*-CH_3CONH-benzaldehyde	—[i]	390	—	480	—	4808	−0.015
13	*m*-NH_2-acetophenone	265–266[j]	381	2.89	460	2.57	4508	−0.161
14	*m*-NH_2-benzaldehyde	270–271d[k]	381	2.90	467	3.29	4834	−0.161
15	*p*-CH_3-acetophenone	257–258[d]	380	2.75	458	2.45	4481	−0.170
16	3,4-$(CH_3)_2$-acetophenone	251–252[l]	385	2.86	458	2.53	4140	−0.239
17	*p*-OH-acetophenone	258–259d[m]	387	2.73	462	2.54	4195	−0.267[g]
18	*p*-MeO-acetophenone	227–228[d]	392	2.74	460	2.56	3771	−0.268
19	*p*-MeO-benzaldehyde	251–252[n]	387	3.05	470	3.19	4563	−0.268
20	*p*-NH_2-acetophenone	258–259d[o]	403	2.68	461	2.61	3122	−0.660
21	*p*-$(CH_3)_2N$-benzaldehyde	233–234[d]	434	3.02	478	3.88	2120	−1.154[g]

[a] $\Delta\nu = \nu_{max}^{CHCl_3} - \nu_{max}^{NaOH}$. [b] σ-values taken from ref. 3 (b). [c] Calcd. for $C_{14}H_{11}N_5O_6$: N, 20.3. Found: N 20.8. [d] Ref. 8. [e] N. D. Cheronis and J. B. Entrekin, *Semimicro Qualitative Organic Analysis*, Interscience Publishers, Inc., New York, N. Y., 1957, pp. 582–587. [f] J. B. Bowen and E. M. Wilkinson, *J. Chem. Soc.*, 750 (1950). [g] Calcd. from Eq. 5. [h] I. Heilbron, *Dictionary of Organic Compounds*, Oxford University Press, New York, N. Y., 1953, Vol. II. [i] Data taken from K. Yamaguchi, S. Fukushima, T. Tabata, and M. Ito, *J. Pharm. Soc. (Japan)*, **74**, 1335 (1954). No extinction coefficients reported. Acetone used as neutral solvent, 1% alcoholic sodium hydroxide as basic solvent. [j] Calcd. for $C_{14}H_{13}N_5O_4$: N 22.2. Found: 22.5. [k] Calcd. for $C_{13}H_{11}N_5O_4$: N 23.3. Found: N 23.4. [l] Calcd. for $C_{16}H_{16}N_4O_4$: N 17.1. Found: 16.8. [m] Ref. e, pp. 663–668. [n] Ref. 1(a). [o] W. Borsche and H. Groth, *Ann.*, **549**, 238 (1941).

represents the hydrolysis of the ester, only the original long wave-length maximum is reported in Table II.

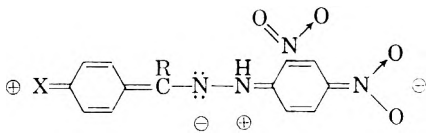
RESULTS and DISCUSSION

A. *Aromatic derivatives.* The *p*-substituted DNP's absorbed at longer wave lengths in chloroform solution than benzaldehyde DNP (377 mμ) or acetophonone DNP (378 mμ), and, as the substituent constants decreased, the extinction coefficients also decreased and became more nearly equal (Table I). Despite the large positive σ-value of the *p*-NO_2 group which would be expected to decrease the weights of I and III and cause absorption at shorter wave lengths, the derivatives so substituted absorbed at 381–382 mμ, probably due to the contribution of IV to I, II, and III which further stabilizes the excited state.



IV

The less electronegative groups can stabilize the excited state by V and, as the availability of the electrons in the substituent increases,



V

the contribution of V to the hybrid must also increase, thus accounting for the absorption maxima of the *p*-NH_2- and *p*-$(CH_3)_2N$-substituted derivatives (Table I).

The excitation energy of the *m*-substituted DNP's is considerably higher than that of the *p*-substituted DNP's with the same group. Although *p*-quinoid structures can be written for the latter derivatives, the *m*-substituent cannot contribute in a similar manner to the stability of the excited state. Hence, the inductive effect described elsewhere[10] lessens the contribution of I and III to the hybrid unless the substituent is extremely electron rich (as in *m*-NH_2 groups).

In basic solution, the acidic *N*-hydrogen is removed and the excited state is stabilized since no separation of charge is required.[1b] Those groups with positive σ-values absorbed at the longest wave length due to the increased weight of the anion of IV. Conversely, the anion of V can contribute only slightly more to the excited state than

(10) Ref. 3b, p. 230.

TABLE II

PHYSICAL CONSTANTS FOR R_1—CO—R_2 2,4-DINITROPHENYLHYDRAZONES

No.	R_1	R_2	M.P. (Uncorr.)	$\lambda_{max}^{CHCl_3}$ mμ	$\epsilon \times 10^{-4}$	λ_{max}^{NaOH} mμ	$\epsilon \times 10^{-4}$	$\Delta\nu$[a]	σR_1*[b]	σR_2*[b]	$\Sigma\sigma$*
1	F_3C	H	149–150[c]	329	2.17	436	2.84	7459	+2.755[d]	+0.490	+3.245
2	F_3C	CH_3	135–136[e]	338	2.10	437	2.57	6703	+2.435[d]	0.000	+2.435
3	$C_2H_5O_2C$	H	126–127[f]	349	3.20	446	2.25	6231	+1.900[g]	+0.490	+2.390
4	$ClCH_2$	H	156–157[h]	345	2.31	435 (500)[i]	2.23 (1.30)[i]	5997	+1.050	+0.490	+1.540
5	$C_6H_5OCH_2$	H	129–130[f]	348	2.41	433 (500)	2.46 (1.44)	5641	+0.850	+0.490	+1.340
6	$ClCH_2$	CH_3	125–126[j]	351	2.46	431 (517)	2.50 (1.55)	5288	+1.050	0.000	+1.050
7	H	H	164–165[k]	345	2.09	430 (500)	1.73 (1.05)	5730	+0.490	+0.490	+0.980
8	$C_6H_5CH_2$	H	121–122[k]	355	2.42	430 (510)	2.25 (1.23)	4913	+0.215	+0.490	+0.705
9	$C_6H_5(CH_2)_2$	H	154–155[k]	355	2.22	433 (515)	2.22 (1.24)	5074	+0.080	+0.490	+0.570
10	CH_3	H	146–147[l]	355	2.22	431 (519)	2.19 (1.28)	4967	0.000	+0.490	+0.490
11	CH_3CH_2	H	—[m]	356	2.25	431 (520)	2.25 (—)	4888	−0.100	+0.490	+0.390
12	$CH_3(CH_2)_2$	H	—[m]	358	2.10	426 (520)	2.04 (—)	4459	−0.115	+0.490	+0.375
13	$(CH_3)_2CH$	H	—[m]	357	2.18	428 (523)	2.51 (—)	4647	−0.190	+0.490	+0.300
14	$C_6H_5CH_2$	CH_3	154–155[n]	360	2.46	434 (527)	2.23 (1.34)	4736	+0.215	0.000	+0.215
15	$C_6H_5(CH_2)_2$	CH_3	129–130[j]	364	2.40	440 (526)	2.54 (1.38)	4646	+0.080	0.000	+0.080
16	CH_3	CH_3	125–126[k]	362	2.15	432 (530)	2.12 (1.28)	4325	0.000	0.000	0.000
17	Et_2NCH_2	CH_3	85.0–85.5[f]	362	2.43	430 (525)	2.21 (1.37)	4368	−0.066[d]	0.000	−0.066
18	CH_3CH_2	CH_3	—[m]	365	2.16	430 (532)	2.17 (—)	4141	−0.100	0.000	−0.100
19	$(CH_3)_2CH$	CH_3	—[m]	363	2.27	430 (532)	2.21 (—)	4292	−0.190	0.000	−0.190
20	CH_3CH_2	CH_3CH_2	—[m]	365	2.18	430 (530)	2.16 (—)	4141	−0.100	−0.100	−0.200
21	cyclo-C_6H_{11}	cyclo-C_6H_{11}	151.0–151.5[o]	370	2.41	438 (535)	2.14 (1.30)	4196	−0.150	−0.150	−0.300
22	$(CH_3)_2CH$	$(CH_3)_2CH$	87–88[p]	365	2.45	435 (535)	2.17 (1.33)	4408	−0.190	−0.190	−0.380
23	cyclo-C_3H_5	CH_3	155–156[q]	370	2.42	434 (525)	2.36 (1.42)	3986	−0.475[d]	0.000	−0.475

[a] $\Delta\nu = \nu_{max}^{CHCl_3} - \nu_{max}^{NaOH}$. [b] σ*— values taken from ref. 9. [c] F. Brown and W. K. R. Musgrave, *J. Chem. Soc.*, 5049 (1952). [d] Calcd. from Eq. 7. [e] R. N. Hazeldine, *J. Chem. Soc.*, 3565 (1953). [f] L. A. Jones, C. K. Hancock, and R. B. Seligman, unpublished data. [g] Calcd. from $\sigma^*_{CH_3O_2C} + \sigma^*_{Et}$ in Ref. b. [h] F. Weygand, G. Eberhardt, H. Linden, F. Schafer, and I. Eigen, *Angew. Chem.*, **65**, 525 (1953). [i] Data in parenthesis indicate secondary maxima. [j] Ref. 8. [k] Ref. 1(a). [l] W. M. D. Bryant, *J. Am. Chem. Soc.*, **60**, 2814 (1938). [m] Data taken from Ref. 1(a). No extinction coefficients were reported for the secondary maxima in basic solution. [n] F. Ramirez and A. F. Kirby, *J. Am. Chem. Soc.*, **75**, 6026 (1953). [o] Calcd. for $C_{19}H_{24}N_4O_4$: N 15.1. Found: N 15.1. [p] Calcd. for $C_{13}H_{18}N_4O_4$: N 19.0. Found: N 18.9. [q] M. F. Hawthorne, *J. Org. Chem.*, **21**, 1523 (1956).

originally since energy is still required for charge separation. The *m*-substituted DNP's absorbed in the same region as the unsubstituted derivatives, indicating the inductive effect does not favor stabilization of the excited state.

Quantitative treatment. As indicated in Table I (and also Table II), neither the chloroform solution data nor the alcoholic sodium hydroxide solution data are independently related to the substituent constants suggesting that a change of "mechanism" may be involved. Since no mechanistic change can be present in these spectra, the substituents themselves must contribute to the stability of the excited states in different ways as previously shown in IV and V.

However, using the statistical treatment described by Jaffé,[3b] the difference in the absorption frequencies in chloroform and alcoholic base, $\nu_{max}^{CHCl_3} - \nu_{max}^{NaOH}$, of the benzaldehyde DNP's[11] were related to the Hammett substituent constants[12] by the equation

$$\Delta\nu = 4764 \text{ cm.}^{-1} + 2500\sigma \quad (1)$$

with a correlation coefficient r of 0.929 and standard deviation s equal to 590. The *p*-$(CH_3)_2$N-benzaldehyde DNP showed serious deviation, the experimental and calculated $\Delta\nu$-values being 2120 and 3264 cm.$^{-1}$, respectively, or a 54% deviation. Omitting this derivative from the calculations, Eq. 2 was obtained with $r = 0.971$ and $s = 268$. The decrease in the standard deviation

$$\Delta\nu = 5041 \text{ cm.}^{-1} + 1970\sigma \quad (2)$$

was statistically significant although only a slight increase in the correlation coefficient was obtained.

Repeating the statistical treatment using the substituted acetophenone DNP's gave

$$\Delta\nu = 4698 \text{ cm.}^{-1} + 2344\sigma \quad (3)$$

with $r = 0.993$ and $s = 178$. Comparison of equations 1 and 3 showed the slopes and intercepts to be similar, despite the serious deviation of the *p*-$(CH_3)_2$N-substituted derivative. Hence, all of the data for the 17 substituted aromatic DNP's were statistically combined to give

$$\Delta\nu = 4835 \text{ cm.}^{-1} + 2233\sigma \quad (4)$$

with $r = 0.977$ and $s = 274$. A plot of the experimental $\Delta\nu$-values *versus* the substituent constants and the line described by Eq. 4 are shown in Fig. 1.

(11) The substituted phenols were omitted in these calculations since —OH → —O$^-$ in basic solution.

(12) For the *p*-NO_2 group, the σ^- value of +1.270 (same as σ* but redefined in reference given) was used since an appreciable difference in conjugation of the substituent and the reaction site exists between the ground and the excited states of the molecule. This is the condition given by H. H. Jaffé, *J. Org. Chem.*, 23, 1790 (1958).

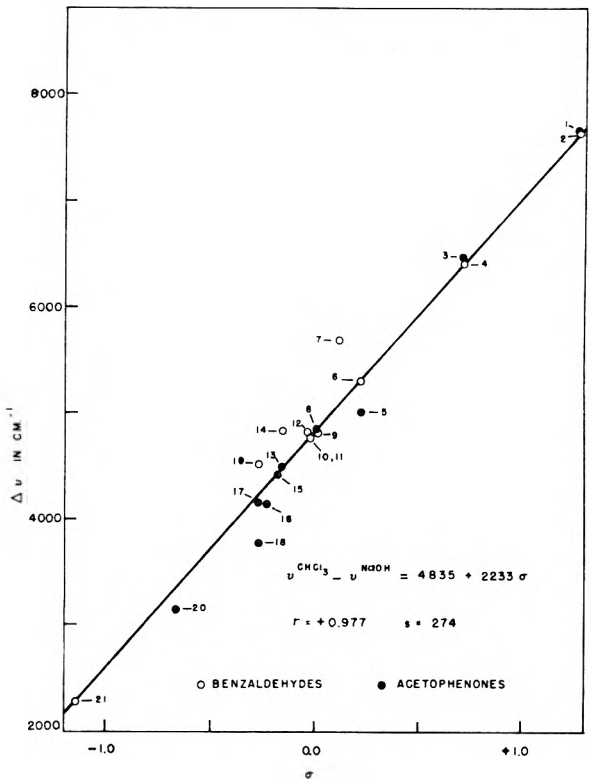


Fig. 1. Relationship between the experimental $\Delta\nu$-values and σ-values. Numbers refer to the compounds in Table 1.

By minimizing the squares of the deviations along the σ-axis,[3b] Eq. 5 was obtained

$$\sigma = 4.274 \times 10^{-4}\Delta\nu - 2.059 \qquad (5)$$

Substitution of the $\Delta\nu$-value for the p-$(CH_3)_2N$-benzaldehyde DNP in Eq. 5 yielded a σ- value of -1.154. Jaffé[3b] has presented evidence that the substituent constant for the p-$N(CH_3)_2$ group should have a range of values dependent on the nature of the side chain, in this case the $=N-NH-C_6H_3(NO_2)_2$ group of I, II, III, and V. It is apparent that this moiety is strongly electron withdrawing and the resonance stabilization of the excited state is considerably affected by the increased electron density of the p-$N(CH_3)_2$ group. The most negative value for the substituent constant previously reported is -0.972[3b] and the value -1.154 determined here is within the precision of the Hammett equation.

The substituent constant for the p-OH → p-$O^{\ominus}$ group was calculated from Eq. 5 to be -0.013 and -0.267 for the benzaldehyde and acetophenone derivatives, respectively. It should be noted that the formation of this ion in basic solution involves the loss of *two* protons whereas other derivatives lose only one, possibly accounting for the large differences observed. The m-OH → m-$O^{\ominus}$ σ-value was calculated to be -0.014 from Eq. 5 suggesting that the inductive effect encountered from m-substituents has little effect on the stability of the excited state. However, the limitations observed above for the p-OH → p-$O^{\ominus}$ group would probably apply also.

Some discussion concerning the deviations of the DNP's of p-Cl- and p-MeO-acetophenone and m-MeO-benzaldehyde from the straight line in Fig. 1 appears warranted. The methoxy substituents are noted for their substituent constant deviations and have been discussed in some detail.[13] However, in addition to the usual reasons for these deviations, the problem of *syn*- and *anti*-isomers must also be considered. In a previous work,[14a] the *syn*- and *anti*-isomers of 2-furaldehyde DNP were prepared and their spectra obtained in chloroform and alcoholic sodium hydroxide solutions. The *syn*-DNP yielded a $\Delta\nu$-value of 5237 cm.$^{-1}$, while the *anti*-form gave a $\Delta\nu$-value of 4542 cm.$^{-1}$, indicating that the isomeric modifications can have considerable effect on the spectra. These results suggest that the deviations noted for m- and p-OH → $O^{\ominus}$, p-Cl, and m- and p-MeO substituted aromatic DNP's may be due to *syn*- and *anti*-modifications as well as substituent constant deviations. As will be shown, the isomeric modifications are not as important in the aliphatic series.

B. *Aliphatic derivatives.* Since no resonance (except hyperconjugation) can be involved within the substituents R_1 and R_2 of I, II, and III for the aliphatic DNP's, the excitation energy must depend on the ability of these substituents to aid in the shift of electron density towards the nitro groups. Table II shows that, as the substituents became less positive, the absorption maxima of these derivatives in chloroform shifted to the red although little change in the extinction coefficients was apparent. The bathochromic shift of 5 to 11 mμ noted in the comparison of correspondingly substituted aldehyde and acetone DNP's has been previously attributed to hyperconjugation of the methyl groups.[4]

The absorption maxima in basic solution were located between 426 and 446 mμ, and, as in the chloroform solution spectra, the extinction coefficients were quite similar. DNP's with more positive substituents did not exhibit the secondary absorption maxima previously reported to be characteristic of the aliphatic derivatives.[14a] In those cases where the secondary maxima were observed, changes in the absorption wave lengths or the extinction coefficients were not appreciable. Hyperconjugation affected the maxima to a lesser extent than in chloroform although the secondary maxima were more sensitive to this effect as indicated in Table II.

Quantitative treatment. A statistical treatment of the $\Delta\nu$-values and σ^*-values[9] (Table II) gave

(13) Ref. 6, p. 578.

(14) H. C. Barany and M. Pianka, *J. Chem. Soc.*, 2217 (1953).

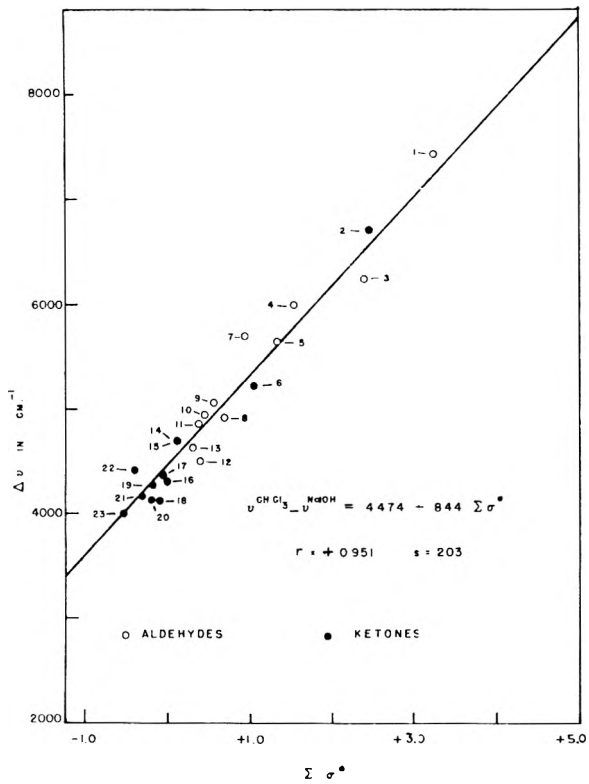


Fig. 2. Relationship between the experimental $\Delta\nu$-values and $\Sigma\sigma$-values. Numbers refer to the compounds in Table II

$$\Delta\nu = 4474 \text{ cm.}^{-1} + 843.9\Sigma\sigma^* \quad (6)$$

with $r = 0.951$ and $s = 203.4$. The regression line and the experimental $\Delta\nu$-values and $\Sigma\sigma^*$-values are shown in Fig. 2.

The squares of the deviations along the $\Sigma\sigma^*$-axis were minimized[3b] and Eq. 7 this obtained:

$$\Sigma\sigma^* = 1.071 \times 10^{-3}\Delta\nu - 4.744 \quad (7)$$

The experimental $\Delta\nu$-values obtained for the F_3C-substituted DNP's yielded, when substituted in Eq. 7, σ^*-values of +2.756 and +2.436 (Table II) for the F_3C-group. The average value of $+2.595 \pm 0.160$ is in reasonable agreement with the σ^*-value of +2.79 calculated by the method of Brown.[15]

In a similar manner a σ^*-value of −0.066 was calculated for the Et_2NCH_2 group.

On the basis of its apparent ability to conjugate with aromatic systems,[16] carbonyl groups,[17] and double bonds,[18] the cyclopropyl group has been placed between a vinyl and a saturated group from ultraviolet studies. The effects on chemical reactions resulting from conjugation of this group with carbonyl groups,[19] double bonds,[20] and carbonium ions[21] further supports an electron release which has been attributed to a possible hyperconjugative release mechanism.[19b,21c] Substitution of the spectral data for methylcyclopropyl ketone DNP in equation 7 gives a σ^*-value of −0.475 in agreement with the above results.

Conversely, some ultraviolet studies have shown that the cyclopropyl group does not give the expected bathochromic shift[22,16b] and, further, the pK_a's of a series of *m*- and *p*-substituted hydrocinnamic and *trans*-2-phenylcyclopropanecarboxylic acids were similar but radically different from those of the *trans*-cinnamic acids.[22] The electronegativity of the three-membered ring has been predicted[23] and, in support of these data, a σ^*-value of +0.11 has been determined.[15]

The value determined here appears reasonable since (1) the spectra in chloroform and in alcoholic sodium hydroxide solutions were similar in *all* respects to the other aliphatic derivatives (Table II) and (2) the σ^*-values of alicyclic rings decrease in value as the ring size decreases.[9] That no ring opening occurred in basic solution is apparent by comparison of the spectra of olefinic derivatives in basic solution.[1a] It seems likely that in view of the conflicting experimental evidence, the cyclopropyl group may have dual substituent constants dependent on the electron demands of adjacent groups and/or the type of reaction involved.

C. *Theoretical discussion.* The instantaneous color developed by DNP's in basic solution has been shown to disappear with the passage of time and the rate appears to be a function of R_1 and R_2 in I.[1a] The reaction proceeds with the evolution of nitrogen and the end products are, for the most part, polymers.[24] The over-all reaction can be represented by

$$\text{DNP} + \text{OH}\ominus \xrightarrow{\text{fast}} \text{DNP}\ominus \xrightarrow[\text{r.d.}]{\text{OH}} \text{products}$$

where the rate-determining step occurs *after* the formation of the anion or intermediate. From these data, Fig. 3 can be said to represent the free energy requirements of the reactions involved.

(15) T. L. Brown, *J. Am. Chem. Soc.*, 80, 6489 (1958).

(16) (a) R. P. Mariella, L. F. A. Peterson, and R. C. Ferris, *J. Am. Chem. Soc.*, 70, 1494 (1948). (b) L. I. Smith and E. R. Rogier, *J. Am. Chem. Soc.*, 73, 3840 (1951).

(17) H. E. Smith and R. H. Eastman, *J. Am. Chem. Soc.*, 79, 5500 (1957).

(18) I. R. Klotz, *J. Am. Chem. Soc.*, 66, 88 (1944).

(19) (a) R. W. Kierstead, R. P. Linstead, and B. C. L. Weedon, *J. Chem. Soc.*, 3616 (1952). (b) For a review see E. Vogel, *Fortschr. Chem. Forsch.*, 3, 431 (1955).

(20) R. van Volkenburgh, K. W. Greenlee, J. M. Derfer, and C. E. Boord, *J. Am. Chem. Soc.*, 71, 172 (1949); *J. Am. Chem. Soc.*, 71, 3595 (1949).

(21) (a) J. D. Roberts and R. H. Mazur, *J. Am. Chem. Soc.*, 73, 2509 (1951); *J. Am. Chem. Soc.*, 73, 3542 (1951). (b) C. G. Bergstrom and S. Siegal, *J. Am. Chem. Soc.*, 74, 145 (1952). (c) H. Hart and J. M. Sandri, *J. Am. Chem. Soc.*, 81, 320 (1959).

(22) See E. N. Trachtenburg and G. Odian, *J. Am. Chem. Soc.*, 80, 4018 (1958), for an excellent discussion.

(23) (a) A. D. Walsh, *Trans. Faraday Soc.*, 45, 179 (1949). (b) C. A. Coulson and W. E. Moffitt, *Phil. Mag.*, 40, 1 (1949).

(24) C. K. Hancock and L. A. Jones, unpublished data.

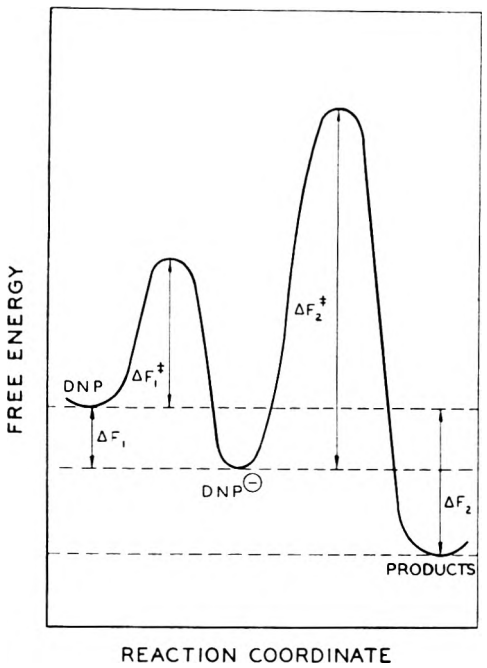


Figure 3

The $\Delta F_1\ddagger$ in Fig. 3 cannot be determined due to the very rapid formation of $DNP^{\ominus}$ and the lower free-energy of this intermediate implies a stability greater than that of the reactant in basic solution as well as a high concentration, in accord with the experimental results. The $\Delta F_2\ddagger$ values are being determined by kinetic studies at the present time.

The ΔF_1 term represents the difference in free-energy content of the product (in this case, $DNP^{\ominus}$) and the reactant states and, as such, is proportional to the ionization constant. The relationship of this free-energy term and the Hammett equation has been discussed.[25] However, in the present investigation, the absorption spectra of the reactant (DNP in chloroform) and the product (DNP in alcoholic base) were determined and the difference $\nu_{max}^{CHCl_3} - \nu_{max}^{NaOH}$ related to the Hammett substituent constants. With these $\Delta\nu$- values, the change in energy $E^{NaOH} - E^{CHCl_3}$ was calculated to range from -21.9 kcal./mol. (p-NO_2 compound) to -6.05 kcal./mol. (p-$(CH_3)_2N$ compound). Since the ΔF_1 values would also be negative, it is apparent that the energy differences (and hence the $\Delta\nu$-values), being *linearly related* to the Hammett substituent constants, must also be linearly related to ΔF_1. Comparison of the $\Delta\nu$- values and some pK_a's of DNP's[26] suggests that $\Delta\nu$ is the more sensitive measure of the free-energy changes involved.

The same arguments may be applied to the Taft relationship found for aliphatic DNP's. In addition, the condition "that all effects other than polar must remain nearly constant within the given reaction series"[27] for the Taft equation to hold applies here also. Hence, the hyperconjugation found in ketone DNP's disappears in the determination of $\Delta\nu$, indicating the effect is of the same order of magnitude in the DNP and $DNP^{\ominus}$ spectra. Further, the spectral data previously obtained for the mono-DNP's of aliphatic 1,2-dicarbonyl compounds[1b] could not be used since the $\Delta\nu$-values contain not only the polar effect of R—CO— but also the effect of hydrogen bonding with the *N*-hydrogen which abnormally lowers the ground state in chloroform solution but disappears in basic solution.[1b] In addition, the removal of the *N*-hydrogen in basic solution permits resonance interaction of the substituent with the 2,4-dinitrophenyl group, obscuring any polar effects.

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(25) Ref. 6, p. 563-565.

(26) C. J. Timmons, *J. Chem. Soc.*, 2613 (1957).

(27) Ref. 6, p. 611.

[CONTRIBUTION FROM RESEARCH AND DEVELOPMENT DIVISION, CONSOLIDATION COAL COMPANY]

Ring Alkylation of Aromatic Thiols[1]

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A procedure has been developed for ring alkylation of thiophenols based on boron trifluoride–catalyzed reaction with isobutylene or by disproportion of the appropriate *t*-butyl sulfide with the parent thiol. The *t*-butyl derivatives of thiophenol, *o*-thiocresol, and 2,6-dimethylthiophenol have been prepared. Substitution occurs exclusively *para*. Therefore, thiophenols substituted in the *para* position, *e.g.*, *p*-thiocresol, do not yield any ring-substituted product. Reaction of thiophenol with propylene produced *o*-isopropylthiophenol in low yield. Ethylation of thiophenol did not occur using this technique.

Ring alkylation of aromatic thiols with olefins is difficult because of the reactivity of the thiol group and the stability of resulting alkyl sulfides. The resistance of sulfides to cleavage[4] by acid catalysts was compared with their oxygen analogs by Tarbell. The aluminum chloride–catalyzed ring alkylation of thiophenol, *o*-thiocresol, and *o*-ethyl thiophenol with *t*-butyl alcohol or *t*-amyl mercaptam was claimed in a recent patent.[5] The properties of the resulting alkyl derivatives were not described.

We have succeeded in the ring alkylation of thiophenol, *o*-thiocresol, and 2,6-thioxylenol with isobutylene or by disproportionation of the appropriate *t*-butyl sulfide with the parent thiol. Boron trifluoride was used as a catalyst. Substitution occurs exclusively *para*.[5] Reaction of thiophenol with propylene produced isopropylthiophenol in low yield. The isopropylthiophenol appears to be entirely *ortho*-substituted. Ethyl thiophenols could not be synthesized by this technique.

EXPERIMENTAL

Starting materials. Thiophenol (99% minimum purity) was purchased from Evans Chemetics, Inc.

o-Thiocresol and *p*-thiocresol were purchased from Eastman Kodak Co. (White Label) and used without further purification.

2,6-Thioxylenol was synthesized by the procedure of Bartkus *et al.*,[6] thiol content 99%.

The *t*-butyl thioethers were synthesized by the procedure of Ipatieff *et al.*,[7] using equal weights of 75% sulfuric acid and thiophenol with a slight molar excess of isobutylene. The reaction was carried out in an autoclave. Essentially quantitative yields of thioethers were obtained. The crude thioether was purified by distillation, a center cut being retained for further synthesis.

The reactants and catalyst were added at room temperature to a 300-ml. Aminco rocking autoclave or a 2 l. stirred Parr autoclave depending on the scale of operation. After the reaction was completed, the catalyst was neutralized. The thiols were extracted with aqueous sodium hydroxide in a nitrogen atmosphere. The sodium hydroxide extract was neutralized with sulfuric acid. The organic layer was washed with water and azeotropically dried with toluene. The dried product was fractionated *in vacuo* on a 25 × 120 cm. Vigreux distillation column. The caustic insoluble fraction was analyzed by distillation.

DISCUSSION OF RESULTS

An interesting facet of this study was the observation that boron fluoride does not form stable complexes with aromatic thiols. A saturated solution of boron trifluoride in thiophenol at room temperature contains less than 2% boron fluoride. Reaction of a saturated solution with isobutylene will occur in an open system for a short time. The excess olefin sweeps out the boron trifluoride, and the reaction stops. Simultaneous addition of boron fluoride and olefin permits reactions to be carried out at 1 atm. The use of a pressure vessel is much more efficient in minimizing the amount of boron trifluoride required.

A series of experiments was carried out in which equimolar amounts of *t*-butyl phenyl sulfide and thiophenol were treated with 10% boron trifluoride in an autoclave. The temperature was varied from 80 to 140°. Yields of 4-*t*-butyl thiophenol varied from 58% to 81% based on sulfide charged. The major by-product is 4-*t*-butylphenyl *t*-butyl sulfide. A reaction temperature of 80° for 4 hr. appears optimum based on the recovery of 4-*t*-butyl thiophenol in 81% yield. No *o*-*t*-butyl thiophenol could be detected by precision fractionation. In order to show that an open *para* position was required for ring alkylation, *t*-butyl-*p*-tolyl sulfide was treated with *p*-thiocresol at 80°. No reaction occurred; the starting material was recovered unchanged. Reaction of the *t*-butyl thioether of 2,6-thioxylenol with an equimolar amount of 2,6-thioxylenol produced 4-*t*-butyl-2,6-dimethylthiophenol in 55% yield.

Direct *t*-butylation of thiophenol was explored. The results are shown in Table I. At 80°, the yield of 4-*t*-butyl thiophenol was 64%. The principal by-products are the *t*-butyl sulfide and the *t*-butyl sulfide of 4-*t*-butyl thiophenol. Higher molecular weight sulfides and diphenyl disulfide make up the higher boiling fraction. The results, while incomplete, suggest that under optimum conditions the same yield of 4-*t*-butyl-thiophenol could be obtained by direct alkylation as shown previously for the disproportionation of *t*-butyl phenyl sulfide. Direct alkylation of o-thiocresol at 80° produced a 44% yield of the 4-*t*-butyl derivative.

An authentic sample of 4-*t*-butyl thiophenol was synthesized by reaction of *t*-butylbenzene with chlorosulfonic acid. The resulting sulfonyl chloride was reduced using zinc and sulfuric acid. The crude thiol was distilled on a high efficiency fractionating column to produce a heart cut analyzing 97% *t*-butylthiophenol by silver nitrate titration.

(1) Presented before the Organic Division at the 134th National Meeting of the American Chemical Society, Chicago, Ill., September 1958.

(2) Present address: American Cyanamid Co., Stamford, Conn.

(3) Present address: American Machine and Foundry Co., Springdale, Conn.

(4) D. S. Tarbell and D. P. Harnish, *J. Am. Chem. Soc.*, **74**, 1862 (1952).

(5) K. L. Kreuz, U. S. Pat. **2,753,378** (July 3, 1956).

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(7) V. N. Ipatieff, H. Pines, and B. S. Friedman, *J. Am. Chem. Soc.*, **60**, 2731 (1938).

TABLE I

SYNTHESIS OF ALKYLATED THIOPHENOLS BY DIRECT ALKYLATION

Experiment	Temp., °C.	Time, Hr.	BF_3, Wt. %	Mol. Ratio Thiol/ Olefin	Conversion of Thiol, %	Yields, Mol. % Converted Thiol: Alkyl thiol	Alkyl aryl sulfide	Alkyl aryl alkyl sulfide
1	120	2	5	2.0	33	58	12	12
2	80	6	5	1.4	71	64	5	10
3 (*o*-thiocresol)	80	6	10	0.8	71	44	—	—
4 (propylene	80	5	6	1.1	48	19	32	—
5 (propylene)	140	4	9	1.2	76	14	40	9
6 (*p*-thiocresol-propylene)	80	2	10	0.5	45	25	14	21

TABLE II

PROPERTIES AND ANALYSES OF ALKYL THIOPHENOLS AND DERIVATIVES

Compound	Derivative	B.P., °C.	M.P., °C.[a]		Analysis: Calculated C	Calculated H	Calculated S	Found C	Found H	Found S
4-*t*-Butyl thiophenol		120 (20)[b]		$C_{10}H_{14}S$	72.23	8.48	19.28	72.10	8.40	19.77
	2,4-Dinitrophenyl sulfide		130.2–131.5	$C_{16}H_{16}O_4N_2S$	57.82	4.85		57.99	5.65	
4-*t*-Butyl, 2-methyl thiophenol		117 (10)		$C_{11}H_{16}S$	73.27	8.95	17.78	73.16	8.91	16.79
	2,4-Dinitrophenyl sulfide		140.5–142.5	$C_{17}H_{18}O_4N_2S$	58.94	5.24		58.60	5.25	
4-*t*-Butyl, 2,6-dimethyl thiophenol		126 (10)	44–46	$C_{12}H_{18}S$	74.17	9.33		74.28	9.36	
	2,4-Dinitrophenyl sulfide		192–193	$C_{18}H_{20}O_4N_2S$	59.98	5.60	8.90	60.24	5.72	8.00
t-Butyl-*p*-*t*-butylphenyl sulfide		132 (10)	49.5–51	$C_{14}H_{22}S$	75.31	9.97	14.41	75.23	10.01	14.25
2-Isopropyl, 4-methyl thiophenol		115 (20)		$C_{10}H_{14}S$	72.23	8.48		72.42	8.28	
2-Isopropylthiophenol		100 (20)		$C_9H_{12}S$	71.00	7.95	21.05	70.64	8.25	20.20

[a] All melting points corrected. [b] Distillation pressure, mm.

The boiling point agreed with the published value of Strating and Backer.[8] The infrared spectrum in the 5 to 6 μ region corresponds to a *para*-substituted benzene. Air oxidation of the thiol in the presence of ammonia produced the disulfide m.p. 88.5–89.5°, in agreement with the literature value.[9] In addition, a 2,4-dinitrophenyl sulfide was prepared by reaction with 2,4-dinitrochlorobenzene. The melting points of the disulfide and dinitrophenyl sulfide produced from the butylated thiophenol were identical to the respective values of the authentic samples. The mixed melting points of the appropriate pairs were undepressed.

Direct alkylation of thiophenol with propylene produced low yields of isopropyl thiophenol. (Cf. Experiments 4 and 5, Table I). Increasing the reaction temperature to 140° did not improve the yield. Substitution appears to be entirely *ortho*. The identity of the isopropyl thiophenol was established by comparison of the infrared spectrum with the spectra of authentic samples[10] of *ortho*- and *para*-isopropyl thiophenol.

While *t*-butylation of *p*-thiocresol was unsuccessful, propylation of *p*-thiocresol did yield 2-isopropyl-4-methylthiophenol in 25% yield.

The properties and analyses of the alkylated thiophenols and characterizing 2,4-dinitrophenyl sulfides are shown in Table II.

Acknowledgment. The authors are indebted to Miss Elizabeth Depp of our laboratory for the preparation of the authentic sample of 4 *t*-butyl thiophenol and its 2,4-dinitrophenyl derivative.

LIBRARY, PA.

(8) J. Strating and N. J. Backer, *Rec. trav. chim.*, 69, 638 (1950).

(9) N. J. Backer and E. Westerhuis, *Rec. trav. chim.*, 71, 1071 (1952).

(10) The authentic samples were prepared by Dr. R. J. Laufer, of our laboratory, by reacting the appropriate cumidines with potassium ethyl xanthate followed by reduction with lithium aluminum hydride.

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

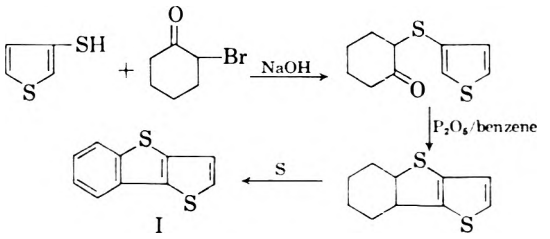
The Synthesis of Thienothianaphthene Derivatives by Ring Formation with Sulfur[1]

WILLIAM E. PARHAM AND BRIAN GADSBY

Received October 8, 1959

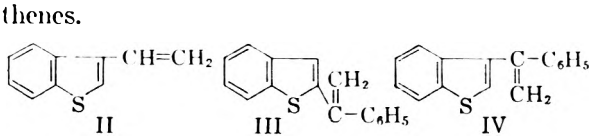
The syntheses of 3-phenylthieno[3,2-b]thianaphthene and 3-phenylthieno[2,3-b]thianaphthene from thianaphthene are described. Their structures are confirmed by synthesis, using alternate unambiguous routes.

Tilak and co-workers[2] in a series of recent papers have prepared two of the three possible thiophthenes, together with a number of their benzo derivatives. Their synthetic routes are based on the reaction of an α-bromoketone with a 2-, or 3-, mercapto-thiophene or -thianaphthene, cyclodehydration of the resulting β-ketosulfide, and finally dehydrogenation to a fully aromatised structure, equation 1.



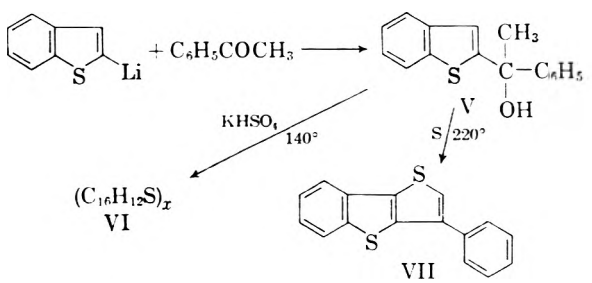
Horton[3] has described the reaction of sulfur, at 340°, with hydrocarbons as a means of thiophene ring formation, while Harper[4] has evidence for the production of two sulfur-containing rings at the same time by treating a diaryl olefin with sulfur at 200°.

It was of interest to investigate the scope of the use of sulfur as a means of producing, by an alternative route, ring structures related to those prepared by Tilak *et al.*[2] The preparations of II, III and IV were therefore undertaken with a view to their conversion to the corresponding thienothianaphthenes.



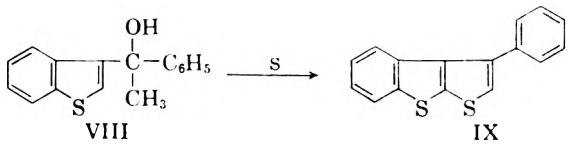
3-Vinylthianaphthene (II), prepared by dehydration of 2(3′-thianaphthenyl)ethanol,[5] on treatment with sulfur at 220° for four hours yielded, on distillation, a bright orange oil. Chromatography of the oil on alumina gave only a series of orange-yellow oils, instead of the expected crystalline thieno[2,3-b]thianaphthene.[2b]

1-Phenyl-1(2′-thianaphthenyl)ethylene III was obtained as a colorless oil, slowly polymerising at room temperature to a brown gum, by dehydration under mild conditions (iodine-benzene) of the tertiary alcohol V. The latter was prepared, in high yield, by the reaction of acetophenone with 2-thianaphthenyl lithium (cf. Shirley and Cameron[6]).



The dehydration of V with potassium bisulfate under more vigorous conditions produced only a white amorphous solid (VI) of indefinite melting point.

In view of the instability of the olefin III further investigations were confined to the alcohol V. The latter was treated with sulfur under varying conditions of time and temperature. Under the least vigorous conditions (220° for four hours) 3-phenylthieno[3,2-b]thianaphthene (VII) was isolated as a white crystalline solid. The latter was characterized as its mono-nitro derivative.



The isomeric tertiary alcohol VIII was prepared by reaction of the Grignard reagent derived from 3-bromothianaphthene with acetophenone. Direct treatment of the alcohol with sulfur gave a 33% yield of the expected 3-phenylthieno[2,3-b]thianaphthene (IX).

The fact that ring closure in both cases occurred to form a thienothianaphthene derivative rather than the corresponding thianaphthenylthianaphthene was confirmed by the synthesis in each case of

(1) This work was supported by the Office of Ordnance Research, U. S. Army, Contract No. DA-11-022-Ord-571.

(2) (a) V. V. Ghaisas and B. D. Tilak, *J. Sci. Ind. Research* 16B, 345 (1957), cf. Chemical Abstracts 52, 5370 (1958). (b) R. B. Mitru, L. J. Pandya, and B. D. Tilak, *J. Sci. Ind. Research*, 348, cf Chemical Abstracts 52, 5371 (1958). (c) V. V. Ghaisas and B. D. Tilak, *Proc Ind. Acad. Sci.* 22, 184 (1953).

(3) A. W. Horton, *J. Org. Chem.*, 14, 760 (1949).

(4) E. T. Harper, Ph.D. thesis, University of Minnesota 1959.

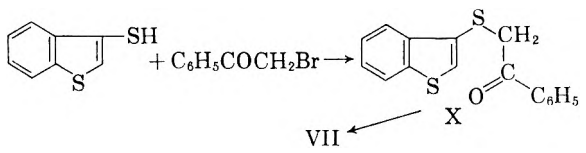
(5) W. Davies, Q. N. Porter, and J. R. Wilmshurst, *J. Chem. Soc.*, 3366 (1957).

(6) D. A. Shirley and M. D. Cameron, *J. Am. Chem. Soc.*, 74, 664 (1952).

TABLE I

Experiment	Temp.	Time (hr.)	% Yield of VII	By-products
1	310	16	0	Polymeric material of indefinite m.p.
2	245	15	7.5	—
3	200–250	16	17	18% of $(C_{16}H_{10}S)_x$
4	220	1.5	16	—
5	200	16	0	yellow oils

an authentic specimen. This was achieved by a route similar to that of Tilak *et al.*[2] 3-Mercaptothianaphthene,[2a] prepared from 3-iodothianaphthene, was treated with phenacyl bromide and the resulting β-ketosulfide (X) was treated with phosphorus pentoxide in refluxing benzene to yield 3-phenylthieno[3,2-b]thianaphthene, identical in every respect with that derived from V.



Similarly, the reaction of 2-mercaptothianaphthene, prepared from 2-thianaphthenyl lithium,[2b] with phenacyl bromide, and subsequent cyclodehydration of the derived β-ketosulfide gave 3-phenylthieno[2,3-b]thianaphthene, identical in every respect with the product obtained from VIII.

EXPERIMENTAL[7]

The reaction of 3-vinylthianaphthene with sulfur. A mixture of 3-vinylthianaphthene[5] (6.5 g., 0.039 mol.) and sulfur (2.6 g., 0.081 mol.) was heated at 220° for 3 hr. The resulting black oil was distilled to give a bright orange distillate (2 g.), b.p. 110–130°/0.5 mm. Elution of the latter from 100 g. of alumina with petroleum–benzene gave only unreacted sulfur and a series of red-yellow oils.

Methylphenyl-2-thianaphthenylcarbinol V. Thianaphthene (17.9 g., 0.133 mol.), dissolved in dry ether (40 ml.), was added at −10° to a solution of butyllithium, prepared from butyl bromide (29.5 g., 0.217 mol.) and lithium (3.61 g., 0.535 mol.), in ether (100 ml.), followed by the addition of a solution of acetophenone (16.0 g., 0.33 mol.) in ether (40 ml.) at room temperature. The mixture was stirred for 1 hr. and then hydrolyzed by pouring onto iced ammonium chloride. The ethereal extracts (2 × 100 ml.) were combined, dried over magnesium sulfate and distilled to give methylphenyl-2-thianaphthenylcarbinol, (26.15 g., 77%) b.p. 168–170°/0.1 mm. n_D^{27} 1.6466. The distillate slowly crystallized and an analytical sample, recrystallized from petroleum, melted at 56.5–58°.

Anal. Calcd. for $C_{16}H_{14}OS$: C, 75.57; H, 5.55; S, 12.62. Found: C, 75.64; H, 5.60; S, 12.90.

The dehydration of methylphenyl-2-thianaphthenylcarbinol. (a) *With iodine–benzene.* A solution of methylphenyl-2-thianaphthenylcarbinol (1.0 g., 4 m. mol.) and iodine (0.2 g.) in benzene (200 ml.) was boiled under reflux for 2 hr., washed with a 10% aqueous solution of sodium sulfite (two 20-ml. portions), dried magnesium sulfate and the solvent was then evaporated to leave a dark brown oil (0.5 g.). The latter was eluted from a column of alumina (40 g.) with petroleum and the solvent evaporated to leave the olefin as a colorless mobile oil (0.3 g.) (n_D^{25} 1.6809). The infrared spectrum had a strong band at 895 cm.$^{-1}$, indicative of a terminal methylene group.

Anal. Calcd. for $C_{16}H_{12}S$: C, 81.34; H, 5.12; S, 13.54. Found: C, 81.15; H, 5.14; S, 13.37.

(b) *With potassium bisulfate.* A mixture of the carbinol V (5.0 g.) and freshly fused potassium bisulfate (1.0 g.) was heated on an oil bath at 140° for 20 min. The cold residue was extracted with ether (two 50-ml. portions) and the combined extracts were washed with 10% aqueous sodium carbonate (50 ml.) and a saturated sodium chloride solution (50 ml.), dried potassium carbonate, and the solvent then evaporated to leave a viscous oil (4.7 g.). The latter was distilled to give a semi-solid glass (b.p. *ca.* 185°/4 mm.). The distillate was extracted with petroleum and recrystallized from the same solvent to give a white amorphous solid (0.45 g.) m.p. 170–180°. Further recrystallization of this solid had no effect on the melting point.

Anal. Calcd. for $C_{16}H_{12}S$: C, 81.34; H, 5.12; S, 13.54. Found: C, 81.19; H, 5.68; S, 13.11.

The reaction of methylphenyl-2-thianaphthenylcarbinol with sulfur. The carbinol V (5.0 g., 0.02 mol.) and sulfur (2.0 g., 0.062 mol.) were mixed and heated in an atmosphere of nitrogen, under the conditions stated in Table I.

The residual dark oil was dissolved in the minimum quantity of benzene and placed on a column of alumina (150 g.). Unchanged sulfur was eluted first with 10% benzene-petroleum ether, followed in later fractions by 3-phenylthieno-[3,2-b]thianaphthene melting at 90–100°. Recrystallization of these fractions from benzene–petroleum gave a solid m.p. 103.5–104.5°. A mixed melting point with an authentic sample of 3-phenylthieno[3,2-b]thianaphthene (see later) showed no depression.

Experiment 2 was modified in that the carbinol V (10.0 g.) was treated with a solution of iodine in benzene, as described above, and the crude product (7.4 g.) was then treated with sulfur (3.0 g.).

In experiment 3, elution of the chromatographic column with a 30% benzene-petroleum mixture, after removal of 3-phenylthieno[3,2-b]thianaphthene asd escribed, yielded 0.95 g. (18%) of a white solid (m.p. 200–201.5°) corresponding to the formula $(C_{16}H_{10}S)_x$.

Anal. Calcd. for $C_{16}H_{10}S$: C, 82.04; H, 4.30; S, 13.66. Found: C, 81.87; H, 4.29; S, 13.47.

Methylphenyl-3-thianaphthenylcarbinol (VIII). A solution of 3-bromothianaphthene (40.25 g., 0.188 mol.) and methyl iodide (26.8 g., 0.188 mol.) in ether (150 ml.) was added to a stirred suspension of magnesium (9.2 g., 0.376 mol.) in ether (50 ml.) and the mixture was boiled under reflux for 1.5 hr. Acetophenone (45 g., 0.376 mol.), dissolved in ether (100 ml.) was then added slowly. The mixture was stirred at room temperature for 30 min. and then hydrolyzed by pouring onto ice-ammonium chloride. The ethereal layer was separated and the aqueous phase extracted with ether (two 200-ml. portions). The combined ethereal solutions were dried magnesium sulfate, the solvent was evaporated under reduced pressure and the mixture then heated on a steam bath at 1.5 mm. pressure for 30 min. The solid obtained on cooling the residue was recrystallized from benzene-petroleum to yield methylphenyl-3-thianaphthenylcarbinol (29.4 g., 61.5%) m.p. 118.5–120.5°.

Anal. Calcd. for $C_{16}H_{14}O$: C, 75.57; H, 5.55; S, 12.62. Found: C, 75.77; H, 5.59; S, 12.60.

(7) Petroleum denotes petroleum ether of b.p. 60–68°.

The reaction of methylphenyl-3-thianaphthenylcarbinol with sulfur. A mixture of methylphenyl-3-thianaphthenylcarbinol (5.0 g., 0.02 mol.) and sulfur (2.0 g., 0.062 mol.) was heated at 240° for 4 hr. The residual oil was dissolved in a minimum of methylene chloride and placed on a column of alumina (previously activated by heating at 200° for 4 hr.). Development of the column with petroleum (500 ml.) separated unchanged sulfur. Elution with a 10% solution of methylene chloride-petroleum (350 ml.) yielded a colorless oil (2.05 gm.) which subsequently became crystalline. Recrystallization of this solid from petroleum ether and finally from methanol gave 3-phenylthieno[2,3-b]thianaphthene (1.73 g., 33%) as needles m.p. 75–77.5°. An analytical sample melted at 76.5–77.5°.

Anal. Calcd. for $C_{16}H_{10}S_2$: C, 72.18; H, 3.79; S, 24.04. Found: C, 72.53; H, 3.64; S, 24.09.

Phenacyl-3-thianaphthenyl sulfide (X). Phenacyl bromide (16.1 g., 0.081 mol.) was added, during 10 min., to a solution of 3-mercaptothianaphthene[22] (13.2 g., 0.08 mol.) dissolved in 20 g. of 20% aqueous sodium hydroxide and cooled to 20°. The mixture was stirred for a further 2 hr., diluted with water and then extracted with ether (three 100-ml. portions). The ethereal extracts were dried (magnesium sulfate) and the solvent evaporated. The residue was recrystallized from ethanol to yield phenacyl-3-thianaphthenyl sulfide (13.75 g., 57%) m.p. 82–85°. An analytical sample melted at 85.5–86.5°.

Anal. Calcd. for $C_{16}H_{12}OS_2$: C, 67.60; H, 4.26; S, 22.51. Found: C, 67.62; H, 4.38; S, 22.51.

The *2,4-dinitrophenylhydrazone* (orange needles from ethyl acetate) melted at 183–183.5°.

Anal. Calcd. for $C_{22}H_{16}N_4O_4S_2$: C, 56.90; H, 3.47; N, 12.07. Found: C, 57.04; H, 3.47; N, 11.77.

3-Phenylthieno[3,2-b]thianaphthene (VII). Phosphorus pentoxide (50 g.) was added to a solution of phenacyl-3-thianaphthenyl sulfide (12.65 g., 0.045 mol.) in benzene (200 ml.) and the mixture was separated and the residue washed with further benzene (two 100-ml. portions). The solvent was evaporated from the combined benzene solutions to leave a light yellow semi-crystalline residue. The latter was dissolved in a minimum quantity of benzene and placed on a column of alumina (150 g.). Elution of the column with 30% benzene–petroleum (400 ml.) yielded 3-phenylthieno[3,2-b]thianaphthene (3.70 g., 35%) m.p. range 93–100°. An analytical sample melted at 104–105°.

Anal. Calcd. for $C_{16}H_{10}S_2$: C, 72.18; H, 3.79; S, 24.04. Found: C, 72.12; H, 3.91; S, 23.94. λ_{max}^{241} ϵ30,110, λ_{max}^{269} ϵ16,490, λ_{max}^{293} ϵ10,090; $\lambda_{inf.}^{306}$ ϵ7,223, λ_{max}^{319} ϵ5,042.

The product was found to be identical (mixed melting point—no depression, infra-red spectrum) with the product derived from methylphenyl-3-thianaphthenylcarbinol.

Further elution of the column with 70% benzene-petroleum yielded some unchanged phenacyl-3-thianaphthenyl sulfide (1.50 g.) m.p. 80–84°.

2-Nitro-3-phenylthieno[3,2-b]thianaphthene. To a solution of 3-phenylthieno[3,2-b]thianaphthene (2.45 g., 9.2 m. mol.) in acetic anhydride (25 ml.) at −10° was added 2 ml. of a solution prepared from nitric acid (3 ml. d. 1.42) and acetic anhydride (10 ml.). The mixture was stirred at 0° for 40 min. then poured onto ice and ammonium bicarbonate and the resulting yellow solid extracted with benzene. The benzene extract was evaporated to leave a yellow solid. The latter was placed on a column of alumina (150 g.). Elution of the column with 60% benzene–petroleum (1200 ml.) yielded 2-nitro-3-phenylthieno[3,2-b]thianaphthene as a bright yellow solid, m.p. 215–216°. An analytical sample (needles from benzene-petroleum) melted at 215.5–217°.

Anal. Calcd. for $C_{16}H_9NO_2S_2$: C, 61.74; H, 2.91; N, 4.50. Found: C, 61.78; H, 3.05; N, 4.40.

Phenacyl-2-thianaphthenyl sulfide (XI). Phenacyl bromide (17.1 g., 0.086 mol.) was added, during 10 min., to a solution of 2-mercaptothianaphthene[2b] (14.2 g., 0.086 mol.) and sodium hydroxide (3.5 g.) in water (20 ml.), cooled to 20°. The mixture was stirred for 1 hr., diluted with water and extracted with ether (three 100-ml. portions). The ethereal extracts were dried (magnesium sulfate) and the solvent evaporated. The solid residue was recrystallized from methanol to give phenacyl-2-thianaphthenyl sulfide as white needles (15.6 g., 64%), m.p. 53–55.5°. An analytical sample melted at 55–56°.

Anal. Calcd. for $C_{16}H_{12}OS_2$: C, 67.60; H, 4.26; S, 22.51. Found: C, 67.90; H, 4.13; S, 22.77.

3-Phenylthieno[2,3-b]thianaphthene (IX). Phosphorus pentoxide (40 g.) was added to a solution of phenacyl-2-thianaphthenyl sulfide (10.0 g.) in chlorobenzene (150 ml.) and the mixture boiled under reflux for 3 hr. The chlorobenzene layer was separated, and the residue was cautiously dissolved in water and then extracted with benzene (two 100-ml. portions). The combined organic solutions were washed with water, dried and (magnesium sulfate), solvent was evaporated on a steam bath at reduced pressure to leave a brown crystalline residue. The latter was dissolved in a minimum of benzene, placed on a column of activated alumina (200 g.), and eluted with 15% benzene–petroleum to yield 3-phenylthieno[2,3-b]thianaphthene (4.90 g., 52%), m.p. 74–77°. Recrystallization of the product from methanol gave the pure material of m.p. 76.5–77.5°.

The above product was found to be identical (mixed melting point—no depression, infrared spectrum) with the product obtained from methylphenyl-3-thianaphthenylcarbinol VIII.

MINNEAPOLIS 14, MINN.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Polyalkylene Disulfides and Polysulfides Containing Silicon[1]

P. V. BONSIGNORE, C. S. MARVEL, AND SAHADEB BANERJEE[2]

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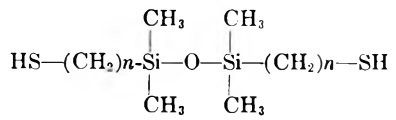
The catalytic air oxidation of 1,3-di(2-mercaptoethyl)tetramethyldisiloxane and 1,3-di(3-mercaptopropyl)tetramethyldisiloxane to form high molecular weight polydisulfides has been carried out in a soap emulsion system. Higher temperatures of oxidation were found to result in significantly higher molecular weights for the polymers. Treatment of these polydisulfides with sulfur resulted in the formation of rubbery polypolysulfides. Some oxidations were carried out using mixtures of 1,3-di(3-mercaptopropyl)tetramethyldisiloxane and 1,4-dimercaptobutene-2 (a new compound), but the soluble polymers isolated appeared by analysis and infrared spectrum to be exclusively homopolymers of the dimercaptodisiloxane monomer.

In the search for useful elastomeric materials possessing good low temperature properties and good solvent resistance, the investigation of the class of polymeric disulfides containing disiloxane linkages was a logical choice.[3,4] As previous work in this laboratory had shown the efficacy of catalytic air oxidation of α,ω-alkylene dimercaptans in an emulsion system for the formation of high molecular weight polymeric disulfides,[5] appropriate α,ω-alkylene dimercaptans containing disiloxane linkages were synthesized. The dimercaptans used in this investigation were 1,3-di-(2-mercaptoethyl)-tetramethyldisiloxane (I) and 1,3-di-(3-mercaptopropyl)-tetramethyldisiloxane (II). Both monomers were obtained by the addition of thiolacetic acid to the corresponding diolefinic disiloxanes, followed by saponification of the resultant dithioacetates. Monomer II was synthesized by the procedure of Marvel and Cripps.[6] It was found in the synthesis of monomer I, by the addition of thiolacetic acid to 1,3-divinyltetramethyldisiloxane, that the use of twice freshly distilled thiolacetic acid was required to avoid the formation of the monoaddition product even though excess thiolacetic acid was used. No such difficulty was experienced in the addition of thiolacetic acid to 1,3-diallyltetramethyldisiloxane to form the dithioacetate of monomer II.



I. $n = 2$
II. $n = 3$

Catalytic air oxidations were carried out using a standardized emulsion recipe developed by Marvel and Olson.[5] The effect of the temperature at which the oxidation of the dimercaptan was carried out on the molecular weight of the resultant polymeric disulfides was investigated. It was found that higher temperatures favored higher molecular weights with the exception that above 80° the product of the oxidation of I tended to undergo secondary reactions with the formation of crosslinked insoluble polymer (see Table I).

TABLE I

CATALYTIC AIR OXIDATION[a] OF 1,3-DI(2-MERCAPTOETHYL)-TETRAMETHYLDISILOXANE (I)

Temp.	Yield[b] %	Inherent Viscosity[c]	Remarks
Room	70	0.37	Mobile, tacky liquid
42	74	0.46	Viscous, tacky liquid
56	55	0.69	Tacky, semisolid[e]
80	62	0.77	Rubbery, semisolid[f]
89	85[d]	—	Crumbly, factice-like solid

[a] In an emulsion system, the recipe of which is given in the experimental section. [b] Yield after one reprecipitation from chloroform by methanol. [c] Viscosity of ~0.5% solution in chloroform. [d] Crude yield, insoluble in the usual solvents, *i.e.*, chloroform, benzene, dioxane-chloroform mixtures. [e] *Anal.* Calcd. for $(C_8H_{20}OS_2Si_2)_x$: S, 25.39; Si, 21.74. Found: S, 23.77; Si, 21.76. [f] *Anal.* Calcd. for $(C_8H_{20}OS_2Si_2)_x$: C, 38.05; H, 7.98; S, 25.39. Found: C, 38.23; H, 7.73; S, 21.87.

TABLE II

CATALYTIC AIR OXIDATION[a] OF 1,3-DI(3-MERCAPTOPROPYL)TETRAMETHYLDISILOXANE (II)

Temp.	Yield[b] %	Inherent Viscosity[c]	Remarks
Room	72	0.33	Mobile, tacky wax
56	78	0.56	Cohesive, tacky liquid[d]
80	82	0.67	Rubbery, viscous liquid
89	75	0.78	Rubbery semisolid[e]

[a] In an emulsion system for seven days, the recipe of which is given in the experimental section. [b] After one reprecipitation from chloroform by methanol. [c] Viscosity of ~0.5% solution in chloroform. [d] *Anal.* Calcd. for $(C_{10}H_{24}OS_2Si_2)_x$: S, 22.86; Si, 20.02. Found: S, 22.65; Si 20.09. [e] *Anal.* Found: S, 23.54; Si, 19.95

(1) The work reported herein was supported by Contract No. DA-19-129-QM-1262 with the U. S. Quartermaster Corps. Dr. J. C. Montermoso of the Quartermaster Research and Engineering Center, U. S. Army, Natick, Massachusetts, was the project supervisor.

(2) Visiting Scientist from the Indian Institute of Technology, Kharagpur, India, under the sponsorship of the U. S. State Department International Cooperation program and in part supported by NSF grant G-2626.

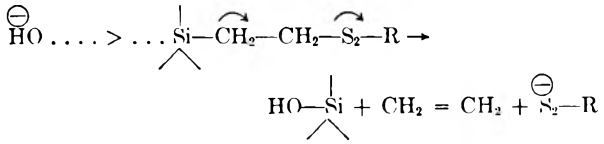
(3) For an example of the known solvent resistance of polydisulfide elastomers, see J. J. Prendergast, *Rubber Age*, **84**, No. 4, January 1959.

(4) For an example of the good low temperature properties and very low second order transition temperatures of silicone elastomers, see C. E. Weir, W. H. Leser and L. A. Wood, *J. Research, Natl. Bur. Standards*, **44**, 367 (1950).

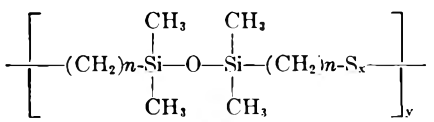
(5) C. S. Marvel and L. E. Olson, *J. Am. Chem. Soc.*, **79**, 3089 (1957).

(6) C. S. Marvel and H. N. Cripps, *J. Polymer Sci.*, **9**, 53 (1952).

A possible explanation for the tendency of the polydisulfide of monomer I to undergo secondary reactions and of its consistently low analytical values for sulfur lies in the presence of a *beta*-substituted ethyl group attached to silicon atoms in the polymer chain. As this substituent, the disulfide group can be stabilized as an anion, cleavage by hydroxide ion (in the alkaline emulsion system), especially at higher temperatures, will be facilitated[7] yielding silanols capable of further condensations.



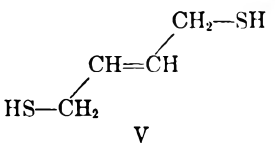
All of these polymeric disulfides (IIIa, IIIb) were essentially liquids which exhibited cold flow to a



IIIa. $n = 2$, x = 2
b. $n = 3$, x = 2
IVa. $n = 2$, x = 3.5–5.7
b. $n = 3$, x = 3.5–5.7

greater or less degree depending on their inherent viscosities. These polymeric disulfides could be treated with two gram atom equivalents of sulfur per base mole of disulfide links at 150° to form polysulfides,[8] IVa and IVb. These polypolysulfides were tough, rubbery, cohesive, non-tacky solids which no longer exhibited cold flow. Preliminary evaluations indicate them to be definitely elastomeric with good low temperature properties, but their solvent resistance was not satisfactory.[9] They are much more difficultly soluble in the usual organic solvents for the polydisulfides, III, *i.e.*, chloroform and benzene, but will dissolve eventually in a mixture of chloroform and dioxane, indicating the lack of any appreciable crosslinkages. It is interesting that the polypolysulfide IVb with x = 2.7 and y = 5.2 has been prepared in an alternate manner by Nasiak and Post[10] who added hydrogen polysulfide to allyldimethylethoxysilane in bulk and heated the resultant adduct to complete the condensation. Their polymer was reported to have a molecular weight of 1505 (by cryoscopic measurement in benzene) and an inherent viscosity of 0.15 (0.4% in chloroform).

As these polydisulfides and polypolysulfides are essentially linear and soluble, an attempt was made to introduce reactive sites along the polymer chain which could serve for eventual crosslinking to increase the solvent resistance and perhaps the elastomeric nature of these polymers. For this purpose 1,4-dimercaptobutene-2 (V) was synthesized. It was



V

obtained by the saponification of the di-isothiuronium salt formed from 1,4-dibromobutene-2. The *trans* structure is assigned on the basis of strong absorption in the infrared spectrum of 962 cm.$^{-1}$ (C–H out-of-plane deformation for *trans* disubstituted ethylenic double bond)[11a] and the absence of absorption in the region 1620–1680 cm.$^{-1}$.[11b]

In an attempt to prepare copolymers, mixtures of 2.5, 5.0, and 10% of V with monomer II were subjected to air oxidation in the emulsion system for seven days at 89°. The polymers which were isolated consisted of a chloroform soluble fraction and a completely insoluble fraction (chloroform, benzene, chloroform-dioxane, dimethylsulfoxide, dimethylsulfoxide-chloroform) (see Table III).

The infrared spectra of samples 1, 2 and 3, as well as the analytical data, indicates that the soluble polymers isolated were exclusively the homopolymer IIIb formed by oxidation of monomer II. It is difficult to explain the complete exclusion of monomer V from incorporation into a soluble copolymer with II. Premature crosslinking by addition of a terminal mercaptan group of a polymer chain across the internal double bond of a polymer chain containing an unsaturated dimercaptan unit would seem to be ruled out by the observations of Marvel and Cripps.[12]

EXPERIMENTAL

1,3-Di(2-thioacetoxyethyl)tetramethyldisiloxane. In a 500-ml. three necked flask equipped with stirring and reflux condenser was placed a solution of 76 g. (1.0 mol.) of thiolacetic acid (Matheson, Coleman and Bell, reagent grade, twice freshly distilled) in 250 ml. of cyclohexane (distilled from calcium hydride). A small amount of benzoyl peroxide was added and 1,3-divinyltetramethyldisiloxane (56 g., 0.30 mol.)[13] prepared by the acid hydrolysis of vinyldimethylethoxysilane (Penninsular ChemResearch, Inc.) in 75% yield, b.p. 136–137°, n_D^{25} 1.4103, was added quite rapidly. The temperature of the reaction rose quickly to

(7) See, for example, P. D. George, M. Prober, and J. R. Eliot, *Chem. Revs.*, **56**, 1118 (1956). 3-Chloroethylsilanes are quantitatively cleaved by base at room temperature with the elimination of ethylene and chloride ion.

(8) J. C. Patrick and S. M. Martin, *Ind. Eng. Chem.*, **28**, 1148 (1936).

(9) Private communication, Dr. Juan C. Montermoso, QC

(10) L. D. Nasiak and H. K. Post, *J. Org. Chem.*, **24**, 492 (1959).

(11) a. "The Infrared Spectra of Complex Molecules," L. J. Bellamy, John Wiley & Sons, Inc., New York (1956), p. 40. b. "The Infrared Spectra of Complex Molecules," L. J. Bellamy, John Wiley & Sons, Inc., New York (1956), p. 34, " . . . . no C=C stretching vibration will appear in the infrared from compounds with a *trans* double bond at the center of symmetry."

(12) C. S. Marvel and H. N. Cripps, *J. Polymer Sci.*, **8**, 313 (1952).

(13) W. Kantor, C. Osthoff, and D. T. Hurd, *J. Am. Chem. Soc.*, **77**, 1685 (1955).

TABLE III

CO-OXIDATION[a] OF 1,4-DIMERCAPTOBUTENE-2 (V) AND 1,3-DI(3-MERCAPTOPROPYL)TETRAMETHYLDISILOXANE (II)

Sample Run	II ml.	V ml.	Chloroform Soluble[b] %	η^c	Analyses[d] Found Si	Found S	Insoluble %
1	10.0	0.25	82	0.73	20.14	23.23	12
2	10.0	0.50	74	0.95	20.09	22.65	16
3	10.0	1.00	52	0.60	20.23	22.77	33

[a] In an emulsion system for seven days at 89°. [b] After one reprecipitation from chloroform into methanol. [c] Inherent viscosity (~0.5% in chloroform). [d] ANAL. Calcd. for $(C_{10}H_{24}OS_2Si_2)_n$ (IIIb): S, 22.86; Si, 20.02 for $(C_4H_6S_2)_n$ (Polymer from V). S, 54.25. If complete statistical incorporation of V into the polymer had taken place, for sample 3: S, 28.7; Si, 16.2.

about 65°. Reflux was applied for 8 hr. and then solvent and excess thiolacetic acid were removed by heating on a steam bath. Distillation of the residue gave 95 g. of product (93.3% yield) boiling at 146–150°/1.5 mm. Redistillation gave pure 1,3-di-(2-thioacetoxyethyl)-tetramethyldisiloxane, 85 g. (83% yield), b.p. 149–150°/1.6 mm., n_D^{25} 1.4839.

Anal. Calcd. for $C_{12}H_{26}O_3S_2Si_2$: C, 42.56; H, 7.74; S, 18.94; Si, 16.59. Found: C, 42.82; H, 7.40; S, 18.93; Si, 16.59.

1,3-Di-(2-mercaptoethyl)-tetramethyldisiloxane (*I*). To a solution of 85 g. of 1,3-di-(2-thioacetoxyethyl)-tetramethyldisiloxane (0.251 mol.) in 250 ml. of ethanol (nitrogen atmosphere) was added a solution of 50 g. (1.25 mol.) of sodium hydroxide in 100 ml. of water. The solution was allowed to reflux on a steam bath for 4 hr. after which the alcohol was removed by distillation. The alkaline reaction mixture was cooled and kept below 20° in an ice bath while ~30% sulfuric acid was added until the reaction was acid to nitrazine paper. The liberated mercaptan was extracted with 3 × 100 ml.-portions of methylene chloride. The combined methylene chloride extracts were washed with dilute sodium bicarbonate solution and dried over calcium chloride. After removal of the solvent, distillation gave 52.5 g. (82%) of product, b.p. 96–100°/1.5–1.7 mm. Redistillation yielded 48 g. (75%) of 1,3-di-(2-mercaptoethyl)-tetramethyldisiloxane, b.p. 94°/1.0 mm., n_D^{25} 1.4781.

Anal. Calcd. for $C_8H_{22}OS_2Si_2$: C, 37.74; H, 8.71; S, 25.19; Si, 22.07. Found: C, 37.28; H, 8.70; S, 25.36; Si, 21.82.

The infrared spectrum showed strong absorption at 1250 cm.$^{-1}$ (>Si(CH$_3$)$_2$ rocking vibration) and broad strong absorption at 1050–1090 cm.$^{-1}$ (Si-O stretching) and weak absorption at 2560 cm.$^{-1}$ (SH stretching vibration).

1,4-Dimercaptobutene-2. To a solution of *trans*-1,4-dibromobutene-2,[14] m.p. 53°, 162 g. (0.76 mol.) in 500 ml. of ethanol, was added rapidly a solution of 120 g. (1.52 mol.) of thiourea dissolved in about 300 ml. of 50% ethanol. Vigorous refluxing took place. Reflux was continued for 3 hr. and the solution was then cooled to 0°. There was obtained 178 g. (64% yield) of the di-isothiuronium salt, m.p. 225–227° (dec.).

In a 2-l. flask was placed a solution of 170 g. (0.46 mol.) of the di-isothiuronium salt dissolved in 800 ml. of water. While maintaining a nitrogen atmosphere, potassium hydroxide, 450 g. (~7.0 mol.) in 450 ml. of water, was added in one portion and the reaction was maintained at reflux temperature for 5 hr. At the end of this time, the solution was cooled and kept below 25° while 50% sulfuric acid was added until the reaction mixture was acid to Congo Red paper. The liberated dimercaptan was extracted with 3 × 200-ml. portions of methylene chloride. The combined extracts were washed with dilute sodium bicarbonate solution and dried over calcium chloride. Removal of the solvent and distillation of the residual oil gave only one small narrow boiling fraction, 7.5 g., b.p. 80–85°/18 mm. Redistillation gave 7.0 g. (13.4%) of 1,4-dimercaptobutene-2, b.p. 83°/17 mm., n_D^{25} 1.5608.

(14) C. Provost, *Compt. rend.*, 186, 1209 (1928).

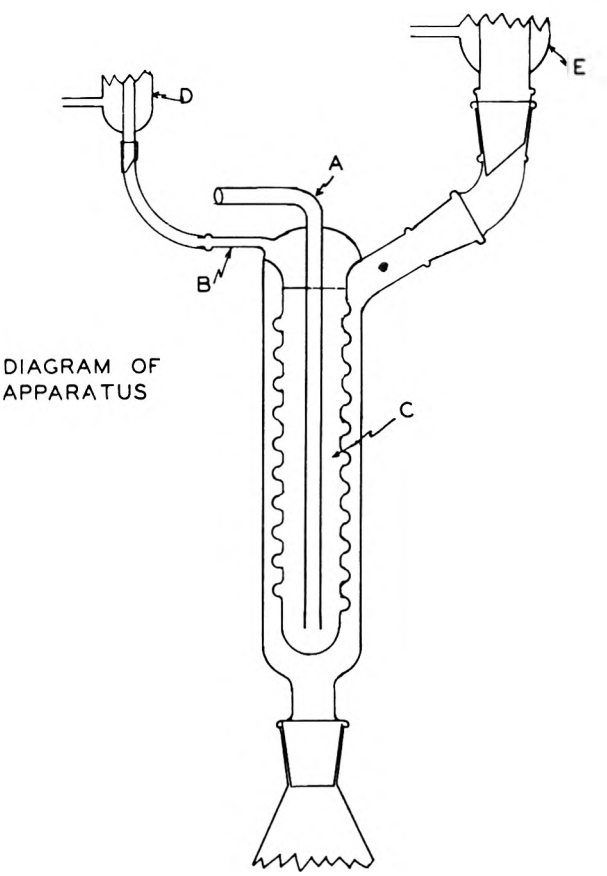


Fig. 1. Apparatus for oxidative polymerization at higher temperatures

Anal. Calcd. for $C_4H_8S_2$: C, 39.95; H, 6.70; S, 53.35. Found: C, 40.30; H, 6.41; S, 52.80.

Polymerization by Catalytic Air Oxidation. All oxidative polymerizations were carried out in a standardized emulsion recipe developed by Marvel and Olson.[6] The recipe is as follows:

Potassium hydroxide	8.0 g.
Lauric acid, C.P.	3.0 g.
Water	100 ml.
Selenous acid	50 mg.
Dithiol	10 ml.
Antifoam A (Dow-Corning)	1 drop

A convenient constant temperature reaction vessel for oxidations at higher temperatures was available in the conventional Friedrich's type condenser which is illustrated in Fig. 1. A unit batch of the emulsion containing the dithiol to be oxidized, C, *ca.* 115 ml., was placed in the water con-

denser portion of the Friedrich's condenser. Filtered compressed air was bubbled through the inlet tube A at the rate of about 3–5 drops per second. The air outlet tube B was connected by means of "Tygon" tubing to an auxiliary vertical water condenser D which prevented the loss of water vapor from the heated solution. The dithiol emulsion undergoing oxidation was kept at constant elevated temperatures by refluxing vapors which were returned by condenser E. Liquids of suitable boiling points which were used as constant temperature baths were methylene chloride, 42°; acetone, 56°; ethanol (absolute), 78.4°; isopropyl acetate, 88.5°. Filtered compressed air was bubbled through the emulsions at a rate of between three to five drops per second for seven days. At the end of this time, the polymers were isolated by pouring the latex into about 1500 ml. of rapidly stirred methanol. The precipitated polymers were extracted with chloroform from a Soxhlet extractor whereupon most of the polymers went completely into solution (except some of IIIa prepared at 80° and above). The volume of chloroform solution was reduced to about 50 ml. and an equal volume of low boiling petroleum ether (b.p. 30–60°) was added to thin the viscosity and allow for better reprecipitation into about 1500 ml. of rapidly stirred methanol. The precipitated polymer was collected and dried in a vacuum oven at 60° for 24 hr.

a. *Polydisulfide of 1,3-Di-(2-mercaptoethyl)-tetramethyldisiloxane* (I). Analytical values for sulfur content of the soluble polydisulfides IIIa tended to be low in sulfur. Discrepancies became wider at the higher temperatures of formation.

b. Polydisulfide of 1,3-Di-(3-mercaptopropyl)-tetramethyldisiloxane. All the polydisulfides IIIb were completely soluble in chloroform. No variation was shown in analytical composition among polymers prepared over the temperature range investigated.

Preparation of Polypolysulfides. IIIa: To a solution of 6.0 g. (0.024 base mol.) of the polydisulfide of 1,3-di-(2-mercaptoethyl)-tetramethyldisiloxane (η = 0.428) in 100 ml. of chloroform was added a solution of 3.0 g. (0.094 g.-atom) of sulfur dissolved in carbon disulfide. The solvents were removed and the residue was maintained at 150–160° for 4 hr. (Note: Invariably hydrogen sulfide fumes were evolved to a greater or lesser degree as shown by lead acetate paper.) At the end of this time a high vacuum was applied for an additional hour to sublime out unreacted sulfur. On cooling the melt a solid dark brown rubbery polymer, 7.3 g. (95%), was obtained which was incompletely soluble in chloroform. The soluble portion (~10%) had an inherent viscosity of 0.145 (0.5% in chloroform).

Anal. Calcd. for $(C_8H_{20}OSi_2S_{3.49})_x$: C, 31.99; H, 6.78; Si, 18.71; S, 37.26. Found: C, 29.73; H, 6.04; Si, 19.80; S, 36.27.

IIIb: In an analogous manner, 9.0 g. (0.032 base mol.) of the polydisulfide from 1,3-di-(3-mercaptopropyl)-tetramethyldisiloxane (η = 0.627) was heated with 2.383 g. (0.075 g.-atom) of sulfur at 150–155° for 4 hr. followed by high vacuum for an additional hour. The polymer, 11.23 g. (93%), when cool was a dark rubbery solid, incompletely soluble in chloroform. The soluble portion had an inherent viscosity of 0.153 (0.5% in chloroform).

Anal. Calcd. for $(C_{10}H_{24}OSi_2S_{3.66})_x$: C, 35.97; H, 7.25; Si, 16.83; S, 35.16. Found: C, 34.57; H, 7.00; Si, 17.89; S, 34.44.

URBANA, ILLINOIS

[CONTRIBUTION FROM THE GENERAL ELECTRIC COMPANY RESEARCH LABORATORY]

Alkylation of β-Cyanoethyltrichlorosilane and Preparation of β-Cyanoethyl(methyl)polysiloxanes

GLENN D. COOPER AND MAURICE PROBER

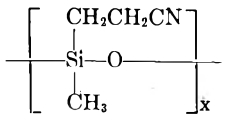
Received August 3, 1959

The reaction of equimolar amounts of β-cyanoethyltrichlorosilane, methylmagnesium bromide, and pyridine produced a mixture of the mono-, di-, and tri-methylated compounds. With methylzinc iodide (methyl iodide + zinc–copper couple) only β-cyanoethyltrimethylsilane was obtained, while dimethylcadmium gave only β-cyanoethyl(methyl)dichlorosilane. Hydrolysis of the dichlorosilane yielded β-cyanoethyl(methyl)polysiloxane oils. These oils do not undergo appreciable silicon-carbon cleavage either with bases or acids, in contrast to the α-cyano substituted polysiloxanes.

Many of the properties of the alkylpolysiloxanes, for example, their abnormally low boiling points and viscosity-temperature coefficients, are due to the low barrier to rotation about the Si—O bond and the consequent very low intermolecular forces in these molecules.[1] These properties can be altered significantly by the introduction of polar substituents into the hydrocarbon groups attached to the silicon atoms of the siloxane chains. The cyano group is among the more polar of these substituents and it has been shown that cyanomethyl groups attached to silicon bring about a large increase in the intermolecular forces, as measured by the activation energies for viscous flow and entropies of vaporization of a number of model silanes and siloxanes.[2] The cyanomethyl group, however, is readily cleaved from silicon by water, particularly in the presence of either acid or base.

$$\equiv SiCH_2CN + H_2O \longrightarrow \equiv SiOH + CH_3CN$$

This type of hydrolytic cleavage is characteristic of organosilicon compounds with electron-withdrawing groups on the carbon atom adjacent to silicon. It would be expected that compounds having a nitrile group on the β carbon would have approximately the same polar characteristics as the α substituted compounds, but might be more resistant to silicon-carbon cleavage. To test this hypothesis a β-cyanoethyl substituted polysiloxane,



(1) E. G. Rochow, *Chemistry of the Silicones*, 2nd edition, p. 115, John Wiley and Sons, New York, N. Y. (1951).

(2) M. Prober, *J. Am. Chem. Soc.*, 77, 3224 (1955).

has been prepared and its properties examined.[3]

Alkylation of β-cyanoethyltrichlorosilane. For the purposes of this investigation an organosilicon compound having two hydrolyzable groups attached to silicon was required. It was anticipated that the reaction of methylmagnesium bromide with β-cyanoethyltrichlorosilane, which can readily be obtained by the addition of trichlorosilane to acrylonitrile,[4-7] would provide a convenient preparation of β-cyanoethyl(methyl)dichlorosilane.[8] It was found that recovery of the nitriles was facilitated and the yields improved when the reaction was carried out in the presence of one mole of a tertiary amine for each mole of methylmagnesium bromide. The recovery of β-cyanoethyl compounds from the reaction in ether of equimolar amounts of Grignard reagent, pyridine, and β-cyanoethyltrichlorosilane was 61%. Only 60% of this was the monomethyl compound, however, the remainder being made up of unreacted β-cyanoethyltrichlorosilane (16%), β-cyanoethyldimethylchlorosilane (21%) and β-cyanoethyltrimethylsilane (3%).

Although the Grignard reagent may be used for the preparation of β-cyanoethyl(methyl)dichlorosilane, the tendency toward replacement of more than one of the chlorine atoms reduces the yield and gives a mixture of products from which the monomethyl compound can be separated only with difficulty. Organozinc reagents show an even greater tendency to polymethylation; the only products isolated from the reaction of equimolar amounts of methyl iodide and β-cyanoethyltrichlorosilane in the presence of a zinc-copper couple were β-cyanoethyltrimethylsilane (33%, based on methyl iodide) and unreacted starting material.

By far the best reagent found for the monomethylation of β-cyanoethyltrichlorosilane was dimethylcadmium. Pure dimethylcadmium reacted smoothly with the chlorosilane in refluxing toluene, depositing yellow plates of methylcadmium chloride which were replaced as the reaction proceeded by a fine white precipitate of cadmium chloride. The reaction of one mole of the chlorosilane with an equivalent amount (0.5 mole) of dimethylcadmium gave a 90% yield of β-cyanoethyl(methyl)dichlorosilane. Even when a two-fold excess of dimethylcadmium was used the monomethylated compound was the major product. The high yields and ease of separation of the product more than compensate for the additional step involved in the preparation of the cadmium reagent.

These results, although only qualitative, demonstrate a surprising difference in the effect of substitution of methyl for chlorine in β-cyanoethyltrichlorosilane (and presumably other polychlorosilanes) on reactivity towards organometallic reagents of different metals. β-Cyanoethyl(methyl)-dichlorosilane reacts much less readily with dimethylcadmium than does β-cyanoethyltrichlorosilane, while the reverse is true with the organozinc reagent; methyl substitution appears to have relatively little effect on reactivity toward the Grignard reagent.

β-Cyanoethyl(methyl)polysiloxanes. Hydrolysis of β-cyanoethyl(methyl)dichlorosilane by stirring an ether solution with ice yielded β-cyanoethyl-(methyl)polysiloxane as a viscous oil, which was insoluble in diethyl ether, ethanol, toluene, and other hydrocarbon solvents, but was readily soluble in dimethylformamide. This solubility behavior, which is the reverse of that observed with dimethylpolysiloxanes, indicates that the intermolecular forces were substantially increased, as expected, by the incorporation of the polar β-cyanoethyl group. This is supported by the relatively high activation energy for viscous flow of the cyanoethyl oil (6.9 Kcal. as compared with 3.8 Kcal. for linear dimethylpolysiloxanes.)[9]

Hydrolysis of β-cyanoethyl(methyl)dimethoxysilane with water[10] did not yield the expected β-cyanoethyl(methyl)silanediol. A solid product, m.p. 60–70° was obtained, apparently a mixture of siloxanediols, $HO[Si(CH_3)(CH_2CH_2CN)O]_nH$, which had a silanol content of 9.3%, corresponding to an average value of n = 3.

Hydrolytic stability of β-cyanoethyl(methyl)polysiloxane. The stability of the silicon-carbon bond in the β-cyanoethyl(methyl)polysiloxane oil toward hydrolytic cleavage was tested by refluxing samples of the oil for 24 hr. with 5% sodium hydroxide and sulfuric acid solutions. The solutions were acidified with sulfuric acid, diluted to 200 ml. with water, distilled, and the first 100 ml. of distillate was titrated for propionic acid, which would be formed if the silicon-carbon bond were cleaved either before or after hydrolysis of the nitrile group. For comparison, equivalent samples of propionitrile were treated under the same conditions. There was no detectable silicon-carbon cleavage in the sample of the oil which was refluxed with acid. A very small

(3) The preparation of a polysiloxane of this type by the hydrolysis of β-cyanoethyl(methyl)dichlorosilane was recently reported, but no properties were given.

(4) M. Prober and G. D. Cooper, Fr. Patent 1,116,726 (1956).

(5) S. Nozakura and S. Konotsune, *Bull. Chem. Soc. Japan*, 29, 322, 326 (1956).

(6) R. A. Pike and D. L. Bailey, Abstracts of the 134th meeting of the American Chemical Society, 49P, September 1958.

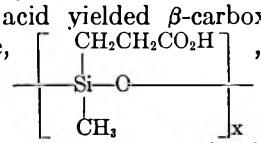
(7) J. C. Saam and J. L. Speier, *J. Org. Chem.*, 24, 427 (1959).

(8) In a paper which appeared after our work was completed the preparation of this compound in low yields by the pyridine-catalyzed addition of methyldichlorosilane to acrylonitrile was reported. [A. D. Petrov and V. M. Vdovin, *Isvest. Akad. Nauk. SSSR, Otdel. Khim. Nauk.*, 1957, 1490]. More recently its preparation in 22% yield *via* the Grignard reaction was also reported (ref. 7).

(9) Ref. 1, p. 113.

(10) S. W. Kantor, *J. Am. Chem. Soc.*, 76, 2712 (1953).

amount of cleavage (less than 0.10%) occurred in the sample which was refluxed with base, but it is not known whether this represents cleavage of the nitrile or of the amide or acid formed on hydrolysis. A comparable α-cyano substituted compound, cyanomethylheptamethylcyclotetrasiloxane, was completely cleaved by refluxing for 24 hr. with 5% sodium hydroxide solution, and 38% cleaved with 5% hydrochloric acid.[2]

β-Carboxyethyl(methyl)polysiloxanes. Hydrolysis of β-cyanoethyl(methyl)polysiloxane by warming with 96% sulfuric acid yielded β-carboxyethyl(methyl)polysiloxane,  , a colorless, extremely viscous oil, readily soluble in dilute sodium hydroxide solution.

EXPERIMENTAL

β-Cyanoethyltrichlorosilane was prepared by the addition of trichlorosilane to acrylonitrile.[4] *β-Cyanoethyltrimethoxysilane* was prepared in 83% yield by the reaction of the chlorosilane with methanol and pyridine in benzene; b.p. 112–113°/17 mm., n_D^{20} 1.4142.

Anal. Calcd. for $C_6H_{13}O_3NSi$: C, 41.1; H, 7.5. Found: C, 41.4; H, 7.4.

Reaction of β-cyanoethyltrichlorosilane with methylmagnesium bromide and pyridine. Methylmagnesium bromide (3.0 mol.) in 1.5 l. of diethyl ether was added over a 3-hr. period to a stirred solution of 565 g. (3.0 mol.) of β-cyanoethyltrichlorosilane and 273 g. (3.0 mol.) of pyridine in 2 l. of ether. After completing the addition the mixture was refluxed for 1.5 hr. and then stirred overnight at room temperature. The mixture was filtered and the filtrate was distilled. There was obtained 409 g. of crude chlorosilanes boiling at 78–80°/4.5 mm. A 90% aliquot of this material was converted to the ethoxy compounds for easier separation. Rectification of the product yielded 5.3 g. (0.04 mol.) of β-cyanoethyltrimethylsilane, b.p. 77–80°/30 mm., 55.4 g. (0.35 mol.) of β-cyanoethyldimethylethoxysilane (I), b.p. 106–108°/30 mm., 187.2 g. (1.00 mol.) of β-cyanoethyl(methyl)diethoxysilane (II), b.p. 123–125°/30 mm., and 57.2 g. (0.26 mol.) of β-cyanoethyltriethoxysilane, b.p. 135–137°/29 mm.

Anal. Calcd. for (I): Si, 15.0. Found: Si, 15.0. Calcd. for (II): Si, 17.9. Found: Si, 18.4.

When the reaction was carried out under the same conditions, but in the absence of pyridine, filtration of the reaction mixture was very difficult and the filtrate consisted of two phases, one of which was an extremely viscous oil, presumably a complex of the cyano compounds with the magnesium halide produced in the reaction. The yield of β-cyanoethyl(methyl)dichlorosilane was only 14%.

In another experiment 4.4 mol. of methylmagnesium bromide in 1 l. of ether was added over a 3-hr. period to a solution of 377 g. (2.0 mol.) of β-cyanoethyltrichlorosilane and 348 g. (4.4 mol.) of pyridine. The mixture was stirred for 3 hr. and then filtered and the filtrate was distilled. There was obtained 58 g. (0.46 mol.) of β-cyanoethyltrimethylsilane, b.p. 92–93°/46 mm., and 87 g. (0.59 mol.) of β-cyanoethyldimethylchlorosilane, b.p. 119–120°/42 mm., n_D^{20} 1.4442.

Anal. Calcd. for $C_5H_{10}NClSi$: Cl, 24.0. Found: Cl, 24.4.

Reaction of β-cyanoethyltrichlorosilane with dimethylcadmium. A solution of 131 g. (0.92 mol.) of dimethylcadmium, prepared by the method of Krause,[11] and 320 g. (1.7 mol.) of β-cyanoethyltrichlorosilane in 600 ml. of toluene was refluxed under nitrogen. A precipitate of yellow plates began to form after about 30 min. and was replaced as the reaction proceeded by a fine white precipitate of cadmium chloride. After 9 hr. the solution was filtered and the filtrate distilled, yielding 288 g. (90%) of β-cyanoethyl(methyl)dichlorosilane, b.p. 87°/7 mm., n_D^{20} 1.4568–1.4574. Rectification of 530 g. of this material in a 100-plate column yielded 500 g. of material having b.p. 128.5°/50 mm., n_D^{20} 1.4571, d_4^{20} 1.2015; lit.[5] n_D^{22} 1.4560, d_4^{25} 1.206.

Anal. Calcd. for $C_4H_7NCl_2Si$: C, 28.6; H, 4.2; Cl, 42.2; mol. refr., 38.46.[12] Found: C, 28.7; H, 4.3; Cl, 42.4; mol. refr., 38.12.

In one experiment the reaction mixture was filtered after 1 hr. and the precipitate was washed with toluene and dried in vacuum. It consisted of large, slightly yellow plates, which turned purple very rapidly upon exposure to air. Hydrolysis of a sample in dilute sulfuric acid yielded 75% of the amount of methane calculated for methylcadmium chloride.

A solution of 89 g. (0.625 mol.) of dimethylcadmium and 113 g. (0.6 mol.) of β-cyanoethyltrichlorosilane in 400 ml. of benzene was refluxed for 12 hr. Fractional distillation of the filtrate yielded 69 g. (69% of β-cyanoethyl(methyl)dichlorosilane, b.p. 104.5/17 mm., n_D^{20} 1.4568, along with 22 g. (21%) of β-cyanoethyltrichlorosilane, b.p. 95°/17 mm.

β-Cyanoethyl(methyl)dimethoxysilane was prepared by the reaction of the β-cyanoethyl(methyl)dichlorosilane with methanol and pyridine in benzene; b.p. 89–90°/8 mm., n_D^{20} 1.4192, d_4^{20} 0.9862.

Anal. Calcd. for $C_6H_{13}O_2NSi$: C, 45.3; H, 8.2; mol. refr., 40.72. Found: C, 45.6; H, 8.1; mol. refr., 40.80.

β-Cyanoethyl(methyl)diacetoxysilane was prepared by the reaction of the chloro compound with acetic anhydride: b.p. 133°/5 mm., n_D^{20} 1.4326, d_4^{20} 1.1193.

Anal. Calcd. for $C_8H_{13}O_4NSi$: C, 44.6; H, 6.1; mol. refr., 49.98. Found: C, 44.3; H, 6.3; mol. refr., 49.93.

β-Cyanoethyl(methyl)polysiloxane. A solution of 47 g. of β-cyanoethyl(methyl)dichlorosilane in 350 ml. of diethyl ether was stirred for 2 hr. with 50 g. of ice. The oil layer was separated from the three-phase system, dried over sodium sulfate and then heated for 1.5 hr. at 175° and 1.5 mm. pressure. The only volatile product was a small amount of water. Before heating the oil had a moderately strong silanol absorption band at 2.89 microns, which was almost completely absent after heating. The colorless, viscous oil, presumably a mixture of cyclic and linear silanol chain-stopped polysiloxanes, weighed 26 g. (85% of theoretical). It was insoluble in ether, ethanol, hexane, and toluene, but was readily soluble in dimethylformamide.

Anal. Calcd. for $(C_4H_7ONSi)_x$: C, 42.5; H, 6.2; N, 12.4. Found: C, 41.5; H, 5.9; N, 12.3.

A solution of 10 g. of the oil in 20 ml. of 96% sulfuric acid was warmed for 1 hr. on a steam bath and then poured into 100 ml. of water. The oil which separated upon standing was washed thoroughly with water and then was heated for 1 hr. at 150°, yielding β-carboxyethyl(methyl)polysiloxane as a stiff gum, readily soluble in 10% sodium hydroxide solution.

Sample	Moles Propionic Acid in Distillate
Cyanoethyl oil + 5% sodium hydroxide	5×10^{-6}
Propionitrile + 5% sodium hydroxide	1.1×10^{-2}
Cyanoethyl oil + 5% sulfuric acid	0
Propionitrile + 5% sulfuric acid	1.2×10^{-8}

(11) E. Krause, *Ber.*, 50, 1813 (1917).

(12) Molar refractions were calculated from the bond refraction values of E. L. Warrick, *J. Am. Chem. Soc.*, 68, 2455 (1946). The value for the C≡N bond was taken as 4.73 ml., which is the average of values obtained for eight compounds in this laboratory.

Anal. Calcd. for $(C_4H_8O_2Si)_x$: C, 36.3; H, 6.1; neut. equiv., 132. Found: C, 33.9; H, 6.2; neut. equiv., 130.

Stability of β-cyanoethyl(methyl)polysiloxane oil to silicon-carbon cleavage. Two grams (0.018 equivalent) of the β-cyanoethyl oil was refluxed with 50 ml. of 5% sodium hydroxide solution. Ammonia was evolved and the polymer had completely dissolved within 0.5 hr. After 24 hr. the solution was acidified with sulfuric acid (no odor of hydrogen cyanide), diluted to 200 ml., distilled, and the first 100-ml. portion of the distillate was titrated for propionic acid. Another 2-g. portion was refluxed for 24 hr. with 50 ml. of 5% sulfuric acid, diluted, distilled, and titrated. For comparison, 1-g. (0.018 mol.) samples of propionitrile were treated in the same manner.

SCHENECTADY, N. Y.

[CONTRIBUTION FROM MATERIALS LABORATORY, WRIGHT AIR DEVELOPMENT CENTER]

Organosilicon Compounds. I. Synthesis of Some Long-Chain Tetraalkylsilanes[1]

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The preparation of several series of unsymmetrical tetraalkylsilanes and one series of mixed symmetrical tetraalkylsilanes by the reaction of the appropriate *n*-alkylchlorosilane with *n*-alkyllithium compounds is described. Certain of the physical properties of the products are presented and discussed. Many of the silanes synthesized exhibit extremely wide liquidus range and may be considered representative of a new class of thermally stable fluids.

A number of symmetrical tetraalkylsilanes of the type R_4Si[2-10] have been reported since Friedel and Crafts[11] first prepared tetraethylsilane in 1863. In connection with a program to develop high-temperature fluids, however, it was of interest to investigate the synthesis and properties of unsymmetrical and mixed symmetrical tetraalkylsilanes of the type $RSiR'_3$ and $R_2SiR'_2$ to determine the structural requirements for optimum liquidus range. Compounds representative of these two types have been previously prepared by the reactions of the Grignard reagents with alkylchlorosilanes,[12-15] by alkyllithium compounds with trialkylsilanes[16] and alkyllithium compounds with alkylalkoxysilanes.[17]

$$4-n\ RMgX + R'_nSiCl_{4-n} \longrightarrow R_nR'SiR\ 4-n + 4-n\ MgXCl$$

$$RLi + R'_3SiH \longrightarrow RSiR'_3 + LiH$$

$$4-n\ RLi + R'_nSiCl_{4-n} \longrightarrow R'_nSiR_{4-n} + 4-n\ LiCl$$

In an effort to extend the synthesis of both unsymmetrical ($RSiR'_3$) and mixed symmetrical ($R_2SiR'_2$) tetraalkylsilanes as classes, it was thought desirable to modify and combine the general methods of Bygden[12] and Gilman[16] in order to use the more reactive organolithium compounds (as compared to Grignard reagents) for obtaining increased yields with alkylchlorosilanes. Two series of long-chain tetraalkylsilanes of the type, $RSiR'_3$, and one series of the type, $R_2SiR'_2$, were thus prepared by the reaction of an appropriate *n*-alkylchlorosilane with various *n*-alkyllithium compounds.

$$n\text{-}C_{12}H_{25}SiCl_3 + 3\text{-}RLi \longrightarrow n\text{-}C_{12}H_{25}SiR_3 + 3LiCl$$

$$n\text{-}C_{18}H_{37}SiCl_3 + 3\text{-}RLi \longrightarrow n\text{-}C_{18}H_{37}SiR_3 + 3LiCl$$

$$(n\text{-}C_{12}H_{25})_2SiCl_2 + 2\text{-}RLi \longrightarrow (n\text{-}C_{12}H_{25})_2SiR_2 + 2LiCl$$

For the present study, *n*-dodecyl and *n*-octadecyl were chosen as typical examples of long-chain moieties while normal alkyl groups of from one to eighteen carbon atoms in length (with the exception of $n\text{-}C_{13}H_{27}$, $n\text{-}C_{15}H_{31}$, and $n\text{-}C_{17}H_{35}$) were selected for the other alkyl substituents.

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(1) Presented in part before the Division of Organic Chemistry at the 126th National Meeting, American Chemical Society, New York, N. Y., September 1954.

(2) C. Friedel and J. M. Crafts, *Bull. soc. chim.*, 6, 356 (1865).

(3) C. Page, *Ber.*, 14, 1872 (1881).

(4) C. L. Tseng and T. Y. Chao, *Science Repts. Natl. Univ. Peking*, 1, 21 (1936).

(5) W. C. Schumb, J. Ackerman, and C. M. Saffer, *J. Am. Chem. Soc.*, 60, 2486 (1938).

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(7) A. Petrov and E. A. Chernyshev, *Bull. Akad. Nauk S.S.S.R.*, 99, 1082 (1952).

(8) H. Gilman and R. K. Ingham, *J. Am. Chem. Soc.*, 77, 1680 (1955).

(9) H. Gilman and D. Miles, *J. Org. Chem.*, 21, 254 (1956).

(10) S. D. Rosenberg, J. J. Walburn, T. D. Stankovich, A. E. Balint, and H. E. Ramsden, *J. Org. Chem.*, 22, 1200 (1957).

(11) C. Friedel and J. M. Crafts, *Ann.*, 127, 28 (1863).

(12) A. Bygden, *Ber.*, 44B, 2640 (1911); *Ber.*, 45B, 707 (1912); *Inaugural Dissertation, Uppsala* (1916); *Chem. Abstr.*, 14, 974 (1920).

(13) F. C. Whitmore, L. H. Sommers, P. A. DiGiorgio, W. A. Strong, R. E. Van Strien, D. L. Bailey, H. K. Hall, E. W. Pietrusza, and G. T. Kerr, *J. Am. Chem. Soc.*, 68, 475 (1946).

(14) L. H. Tyler, L. H. Sommers, and F. C. Whitmore, *J. Am. Chem. Soc.*, 69, 981 (1947).

(15) A. D. Petrov and E. A. Chernyshev, *Doklady Akad. Nauk, S.S.S.R.*, 86, 737 (1952).

(16) H. Gilman and S. P. Massie, Jr., *J. Am. Chem. Soc.*, 68, 1128 (1946); R. N. Meals, *J. Am. Chem. Soc.*, 68, 1880 (1946).

(17) E. Larsson and E. van Gilse van der Pals, *Svensk Kem. Tidskr.*, 63, 179 (1951); *Chem. Abstr.*, 46, 2516 (1952).

Di(*n*-dodecyl)dimethyl- and di(*n*-dodecyl)diethylsilane were prepared by a reverse procedure to that utilized for the synthesis of the other di(*n*-dodecyl)dialkylsilanes. Thus, dimethyldichloro- and diethyldichlorosilanes were treated with *n*-dodecyllithium to give the corresponding tetraalkylsilanes in excellent yields. Although not a tetraalkylsilane, one aryl derivative, di(*n*-dodecyl)diphenylsilane, was similarly obtained from diphenyldichlorosilane and the alkyllithium.

When isopropyllithium was treated with *n*-dodecyltrichlorosilane under more vigorous conditions than those which were normally used for the preparation of the other tetraalkylsilanes, a mixture of products was obtained and the desired *n*-dodecyltri(isopropyl)silane could not be isolated.[18] Similarly, the reaction of cyclohexyllithium with *n*-dodecyltrichlorosilane failed to yield the expected cyclohexyl derivative.[19]

The yields, physical properties and analytical data for the two series of unsymmetrical tetraalkyl silanes are presented in Table I. The yields of 65–96% were somewhat lower than those obtained for the synthesis of symmetrical tetraalkylsilanes,[20] but were definitely superior to those obtained for unsymmetrical tetraalkylsilanes by the Grignard method.[12,13] In the case of the mixed symmetrical tetraalkylsilanes, the yields, as shown in Table II, ranged for 61–90% and were similarly superior to those obtained by other workers for related compounds of this type.[12,15,17]

EXPERIMENTAL

Materials. The *n*-alkyllithium compounds were prepared from Distillation Products, Inc. White Label *n*-alkyl bromides with the exception of those synthesized from 1-bromononane and 1-bromohendecane. The 1-bromononane was obtained in 59% yield by a Hundsdiecker reaction from capric acid while the 1-bromohendecane was prepared from *n*-undecanol and phosphorus tribromide in 61% yield.

n-Dodecyltrichlorosilane. The method used was a modification of that used by Whitmore.[13] To 79 g. (3.3 mol.) of magnesium turnings in 1250 ml. of anhydrous ethyl ether was added dropwise with stirring 777 g. (3.0 mol.) of *n*-bromododecane. The reaction was initiated by the addition of a small amount of previously prepared ethylmagnesium bromide. The mixture was stirred for an additional hour after all of the halide had been added. The yield of *n*-dodecylmagnesium bromide was 74.2% as determined by acid titration.

To a stirred solution of 382.5 g. (2.25 mol.) of redistilled silicon tetrachloride in 2 l. of anhydrous ethyl ether was added dropwise the Grignard reagent prepared above. The mixture was refluxed 12 hr. and the magnesium salts were filtered. After removal of the ether by distillation, additional salts were precipitated and filtered. The residue was fractionated *in vacuo* through a 24-in. column, packed with glass helices, to give 453 g. (66.5%) of *n*-dodecyltrichlorosilane, b.p. 82°/0.15 mm., n_D^{25} 1.4522. This compares with the 29% yield (no refractive index) obtained by Whitmore[13] for this compound.

n-Octadecyltrichlorosilane. This compound was prepared in 51% yield by the same method used for the synthesis of *n*-dodecyltrichlorosilane. The physical properties were found to be in agreement with those obtained for the compound prepared by other procedures.

Di(n-dodecyl)dichlorosilane. The dialkyldichlorosilane starting material was prepared by a procedure similar to that described for the preparation of disubstituted dihalosilanes.[21] To 182 g. (1.07 mol.) of silicon tetrachloride in 1200 ml. of anhydrous ethyl ether contained in a 5-l., 3 necked round bottomed flask fitted with a condenser, stirrer, and dropping funnel was added dropwise a 2200 ml. ethereal solution containing 2.85 moles of *n*-dodecylmagnesium bromide. The Grignard reagent was added with stirring over a period of 7 hr. and then gently refluxed overnight with continued stirring. The mixture was then filtered with suction and the salts were washed several times with anhydrous ethyl ether. The washings were added to the filtrate. After removal of the ether, the residue was fractionally distilled through a 12-in. column packed with glass helices. There was obtained 78.8 g. (16.8%) of the product, di(*n*-dodecyl) dichlorosilane, as a colorless liquid, b.p. 192° (0.23 mm.), n_D^{25} 1.4600. If after one half the Grignard reagent is added, 1 hr. is allowed to elapse before the remainder is added dropwise, the yield of product can be increased to 40–50%.

n-Dodecyltrialkyl (I) *and n-Octadecyltrialkylsilanes* (II). The method for the preparation of both series is illustrated by the synthesis of *n*-dodecyltri(*n*-propyl)silane. To a solution of 0.82 mol. of *n*-propyllithium (prepared by the same general method[22] used for the *n*-dodecyllithium previously described) in 550 ml. of anhydrous ether and maintained under a nitrogen atmosphere, 75.8 g. (0.25 mol.) of freshly distilled *n*-dodecyltrichlorosilane in 100 ml. of anhydrous ether was added dropwise with stirring. A constant reflux temperature of 34–35° was maintained throughout the addition which was complete in 90 min. The reaction mixture was refluxed for 24 hr. and the unreacted lithium filtered off. The filtrate was poured over 600 g. of cracked ice and the resulting solution was neutralized with 3*N* hydrochloric acid. The ether layer was phase separated, the water layer extracted three times with ethyl ether, and the combined ether layer and extracts were dried over anhydrous calcium sulfate. Following removal of the solvent by distillation, fractionation of the yellow liquid residue through a 30-cm. short-path Vigreux column gave 66.2 g. (81.1%) of *n*-dodecyltri(*n*-propyl)silane, b.p. 88° (0.09 mm.), n_D^{25} 1.4504, d_4^{25} 0.8069. See Table I for analysis.

Di(n-dodecyl)dialkylsilanes (*III*). The method for the preparation of this series is illustrated by the synthesis of di(*n*-dodecyl)di(*n*-hexyl)silane. To a solution of 0.7 mol. of *n*-hexyllithium (prepared by the general procedure of Gilman and co-workers,[22] and the yield determined by the double titration method[23]) in 200 ml. of anhydrous ethyl ether was added dropwise with stirring 78.0 gm. (0.18 mol.) of di(*n*-

(18) Gilman and Clark, *J. Am. Chem. Soc.*, 69, 1499 (1947), reported they were unable to prepare tetra(isopropyl)silane from silicon tetrachloride and isopropyllithium.

(19) This result was not entirely unexpected since Nebergall and Johnson [W. H. Nebergall and O. H. Johnson, *J. Am. Chem. Soc.*, 71, 4022 (1949)] were unable to replace the chlorine in tricyclohexylsilane with methyl and ethyl groups. This failure was apparently due to steric effects arising from the crowding of three cyclohexyl groups around the silicon atom. In the case of germanium, unlike silicon, alkyltricyclohexylgermanes may be prepared [O. H. Johnson and W. H. Nebergall, *J. Am. Chem. Soc.*, 71, 1721 (1949)], presumably because of the increased size of the germanium atom.

(20) H. Gilman and R. N. Clark, *J. Am. Chem. Soc.*, 68, 1675 (1946); *cf. J. Am. Chem. Soc.*, 69, 967 (1947).

(21) K. W. Palmer and F. S. Kipping, *J. Chem. Soc.*, 1020 (1930).

(22) H. Gilman *et al.*, *J. Am. Chem. Soc.*, 71, 1499 (1949).

(23) H. Gilman and A. H. Haubein, *J. Am. Chem. Soc.*, 66, 1515 (1944).

TABLE I

UNSYMMETRICAL TETRAALKYLSILANES, $RSiR'_3$

R	R′	Formula	Yield, %	B.P.	Mm.	n_D^{25}	d_4^{25}	Analyses[a] MR$_D$ Caled.	MR$_D$ Found	Carbon, % Caled.	Carbon, % Found	Hydrogen, % Caled.	Hydrogen, % Found	Silicon, % Caled.	Silicon, % Found
n-$C_{12}H_{25}$	CH_3	$C_{15}H_{34}Si$	75	69	0.19	1.4350	0.7782	81.32	81.32	74.29	74.35	14.13	13.87	11.58	11.31
n-$C_{12}H_{25}$	C_2H_5	$C_{18}H_{40}Si$	96	95	0.20	1.4495	0.8038	95.26	95.06	75.96	76.07	14.17	13.98	9.87	9.59
n-$C_{12}H_{25}$	n-C_3H_7	$C_{21}H_{46}Si$	81	88	0.09	1.4504	0.8069	109.2	108.8	77.21	77.06	14.19	13.90	8.60	8.49
n-$C_{12}H_{25}$	n-C_4H_9	$C_{24}H_{52}Si$	79	98	0.05	1.4530	0.8095	123.1	123.1	78.17	79.09	13.22	13.73	7.62	7.30
n-$C_{12}H_{25}$	n-C_5H_{11}	$C_{27}H_{58}Si$	91	152	0.05	1.4548	0.8144	137.1	136.8	78.93	79.03	14.23	13.97	6.84	7.23
n-$C_{12}H_{25}$	n-C_6H_{13}	$C_{30}H_{64}Si$	87	165	0.07	1.4565	0.8170	151.0	150.8	79.56	79.82	14.24	13.95	6.20	6.38
n-$C_{12}H_{25}$	n-C_7H_{15}	$C_{33}H_{70}Si$	92	212	0.10	1.4584	0.8187	165.0	165.1	80.07	80.15	14.26	14.35	5.67	5.94
n-$C_{12}H_{25}$	n-C_8H_{17}	$C_{36}H_{76}Si$	95	221	0.15	1.4595	0.8224	178.9	178.7	80.50	80.60	14.26	14.30	5.23	5.22
n-$C_{12}H_{25}$	n-C_9H_{19}	$C_{39}H_{82}Si$	77	235	0.10	1.4600	0.8245	192.9	192.4	80.88	81.59	14.27	14.41	4.85	4.29
n-$C_{12}H_{25}$	n-$C_{10}H_{21}$	$C_{42}H_{88}Si$	95	240	0.03	1.4613	0.8255	206.8	206.6	81.20	81.37	14.28	14.53	4.52	4.81
n-$C_{12}H_{25}$	n-$C_{11}H_{23}$	$C_{45}H_{94}Si$	65	268	0.06	1.4619	0.8268	220.8	220.5	81.48	82.31	14.28	14.00	4.23	3.84
n-$C_{12}H_{25}$	n-$C_{12}H_{25}$	$C_{48}H_{100}Si$	90	280	0.13	1.4630	0.8276	234.7	234.4	81.73	81.83	14.30	14.31	3.98	4.21
n-$C_{12}H_{25}$	n-$C_{14}H_{29}$	$C_{54}H_{112}Si$	75	305	0.15	1.4638	0.8294	262.6	262.6	82.14	82.24	14.30	14.41	3.56	3.73
n-$C_{18}H_{37}$	n-C_6H_{13}	$C_{36}H_{76}Si$	79	209	0.04	1.4599	0.8263	178.9	178.0	80.50	80.71	14.26	14.20	5.23	5.22
n-$C_{18}H_{37}$	n-C_8H_{17}	$C_{42}H_{88}Si$	87	250	0.10	1.4618	0.8284	206.8	206.0	81.20	81.47	14.28	14.24	4.52	4.94
n-$C_{18}H_{37}$	n-$C_{10}H_{21}$	$C_{48}H_{100}Si$	93	283	0.10	1.4632	0.8294	234.7	234.3	81.73	81.65	14.30	14.45	3.98	4.12
n-$C_{18}H_{37}$	n-$C_{12}H_{25}$	$C_{54}H_{112}Si$	85	296	0.05	1.4640	0.8304	262.6	262.4	82.14	82.25	14.30	14.32	3.56	3.60
n-$C_{18}H_{37}$	n-$C_{14}H_{29}$	$C_{60}H_{124}Si$	81	323	0.10	1.4648	0.8321	290.5	290.1	82.48	82.50	14.31	14.26	3.22	3.18

[a] Analyses by Schwarzkopf Microanalytical Laboratories, Woodside, N. J.

TABLE II

DI(n-DODECYL)DIALKYLSILANES, $(n\text{-}C_{12}H_{25})_2SiR_2$

R	Empirical Formula	Yield, %	B.P.	Mm.	n_D^{25}	d_4^{25}	Analyses[a] MR$_D$ Caled.	MR$_D$ Found	Carbon, % Caled.	Carbon, % Found	Hydrogen, % Caled.	Hydrogen, % Found	Silicon, % Caled.	Silicon, % Found
CH_3	$C_{26}H_{56}Si$	88.5	177	0.12	1.4507	0.8064	132.4	132.4	78.69	78.75	14.27	14.12	7.08	7.19
C_2H_5	$C_{28}H_{60}Si$	83.0	197	0.17	1.4563	0.8159	141.7	141.6	79.15	79.22	14.24	14.09	6.61	6.80
n-C_3H_7	$C_{30}H_{64}Si$	88.2	208	0.50	1.4572	0.8181	151.0	150.8	79.55	79.52	14.24	14.00	6.20	6.00
n-C_4H_9	$C_{32}H_{68}Si$	81.5	185	0.05	1.4579	0.8192	160.3	160.2	79.91	80.19	14.26	13.96	5.84	5.63
n-C_5H_{11}	$C_{34}H_{72}Si$	75.0	202	0.08	1.4585	0.8204	169.6	169.4	80.22	80.29	14.26	13.95	5.52	5.56
n-C_6H_{13}	$C_{36}H_{76}Si$	61.0	209	0.04	1.4594	0.8212	178.9	178.9	80.50	80.61	14.26	14.00	5.23	5.39
n-C_7H_{15}	$C_{38}H_{80}Si$	82.8	228	0.15	1.4599	0.8211	188.2	188.2	80.76	80.74	14.27	14.11	4.97	5.18
n-C_8H_{17}	$C_{40}H_{84}Si$	73.0	256	0.12	1.4605	0.8261	197.5	197.3	80.99	14.27	14.27	14.17	4.74	4.74
n-C_9H_{19}	$C_{42}H_{88}Si$	77.3	263	0.06	1.4609	0.8250	206.8	206.6	81.20	81.27	14.28	14.34	4.52	4.76
n-$C_{10}H_{21}$	$C_{44}H_{92}Si$	75.5	259	0.25	1.4615	0.8259	216.1	215.9	81.39	81.44	14.28	14.15	4.33	4.71
n-$C_{12}H_{23}$	$C_{46}H_{96}Si$	80.0	260	0.04	1.4619	0.8266	225.4	225.2	81.57	81.72	14.29	14.26	4.15	4.24
n-$C_{12}H_{25}$	$C_{48}H_{100}Si$	79.8	280	0.13	1.4622	0.8276	231.7	234.4	81.73	81.83	14.29	14.31	3.98	4.21
n-$C_{14}H_{29}$	$C_{52}H_{108}Si$	79.0	290	0.05	1.4635	0.8309	253.3	252.6	82.01	81.95	14.30	14.12	3.69	4.27
n-$C_{18}H_{37}$	$C_{60}H_{124}Si$	86.5	355	0.10	1.4648	0.8337	290.5	290.1	82.52	82.48	14.30	14.12	3.20	3.87

[a] Analyses by Schwarzkopf Microanalytical Laboratories, Woodside, N. J.

dodecyl)dichlorosilane in 100 ml. of anhydrous ethyl ether over a period of 2 hr. After the addition was completed the mixture was stirred for an additional hour and then refluxed overnight (*ca.* 20 hr.). The excess lithium particles were filtered off with suction and the filtrate was poured slowly over ice to decompose the excess alkyllithium. The solution was then neutralized with 3*N* hydrochloric acid and the ether layer phase separated. The water layer was extracted three times with 100 ml. of ethyl ether and the extracts, together with the ether layer, were dried over anhydrous calcium sulfate. After removal of the ether by distillation, fractionation of the liquid residue through a 30-cm. short-path Vigreux column gave 59.1 gm. (61.0%) of the product, b.p 209° (0.04 mm.), n_D^{28} 1.4594, d_4^{25} 0.8212. See Table II for analysis

Di(n-dodecyl)diphenylsilane. This aralkyl derivative, as well as the corresponding dimethyl and diethyl derivatives, was prepared by the reverse reaction of that used for the preparation of the di(*n*-dodecyl)dialkylsilanes. Thus, 127.0 g. (0.5 mol.) of diphenyldichlorosilane was added dropwise to an ether solution of 1.4 mol. of *n*-dodecyllithium (prepared by the same procedure used for the *n*-hexyllithium described above) over a period of 4 hr. The mixture was stirred for an additional hour and the unreacted lithium metal and salts were removed by suction filtration. The filtrate was treated in the same manner as described in the preparation of the di(*n*-dodecyl)di(*n*-hexyl)silane. The product was obtained, upon fractional distillation through a glass helices-packed column, as a colorless liquid, weighing 17.4 g. (79.1%), b.p. 216° (0.05 mm.). n_D^{25} 1.5053. d_4^{25} 0.9023.

Anal. Calcd. for $C_{36}H_{60}Si$: Si, 5.39; MR_D, 171.45. Found, Si, 5.68; MR_D, 171.30.

Acknowledgment. The authors gratefully acknowledge the technical assistance of Dr. Marvin Rausch in this investigation.

WRIGHT-PATTERSON AIR FORCE BASE, OHIO

[CONTRIBUTION FROM MATERIALS LABORATORY, WRIGHT AIR DEVELOPMENT CENTER]

Organosilicon Compounds. II. 1,1-Disubstituted Silacyclohexanes

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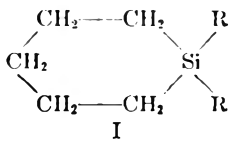
1,1-Disubstituted-silacyclohexanes were prepared by the reaction of 1,1-dichlorosilacyclohexane with an alkyl- or aryllithium compound Attempts to effect cyclization of 1,5-dilithiopentane and a dialkyl(or diaryl)dichlorosilane were unsuccessful. Certain physical properties of the 1,1-dialkylsilacyclohexanes are presented.

In the first paper of this series,[1] the preparation and properties of two classes of long-chain tetraalkylsilanes were reported as part of a program on thermally stable fluids in which various properties of different types of organosilanes were correlated with molecular structure. The present paper describes the synthesis and properties of a series of cyclic organosilicon compounds, the 1,1-disubstituted-silacyclohexanes. In this class of compounds, represented by I, silicon is contained in a six-



I

membered ring in which two alkyl or aryl groups are attached to the heterocyclic atom.

A review of previous attempts to prepare cyclic organosilicon compounds is contained in a paper by West.[2] The first 1,1-disubstituted-silacyclohexane to be prepared was reported by Bygden[3] more than forty years ago. He synthesized 1,1-dimethylsilacyclohexane by reacting methylmagnesium bromide with 1,1-dichlorosilacyclohexane, which was prepared from the Grignard reagent of 1,5-dibromopentane and silicon tetrachloride.

$$BrMg(CH_2)_5MgBr + SiCl_4 \longrightarrow (CH_2)_5SiCl_2 + 2MgBrCl$$

$$(CH_2)_5SiCl_2 + 2CH_3MgBr \longrightarrow (CH_2)_5Si(CH_3)_2 + 2MgBrCl$$

This compound was also prepared by West[2] in somewhat greater yield (72%) by the reaction of 1-chloro-1-methylsilacyclohexane with the Grignard reagent obtained from methyl iodide. The only other compound of this type described in the literature is the diethyl derivative of I, 1,1-diethylsilacyclohexane.[4] This was apparently prepared through a Wurtz type reaction in which a mixture of 1,5-dibromopentane and diethyldichlorosilane was treated with sodium metal. However, no details of the synthetic procedure used, yield

$$Br(CH_2)_5Br + (C_2H_5)_2SiCl_2 + 2Na \longrightarrow (CH_2)_5Si(C_2H_5)_2 + 2NaCl$$

obtained, or physical properties of the product were reported.

Bygden[3] also attempted the preparation of the diethyl derivative by the reaction of the Grignard reagent of 1,5-dibromopentane and diethyldichlorosilane but failed to obtain a pure product.

In the present work, a series of alkyl derivatives of I was prepared in good yield by the reaction of 1,1-dichlorosilacyclohexane with an alkyllithium in a 1 to 2 molar ratio:

$$(CH_2)_5Si(Cl)_2 + 2RLi \longrightarrow I + 2LiCl$$

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TABLE I

1,1-DISUBSTITUTED-SILACYCLOHEXANES, $(CH_2)_5SiR_2$

R	Formula	Yield, %	B.P.	Mm.	n_D^{25}	d_4^{25}	Analyses[a]							
							MR_D		Carbon, %		Hydrogen, %		Silicon, %	
							Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
CH_3	$C_7H_{16}Si$	74.2	131–133	760	1.4390	0.7994	42.04	42.29	65.53	65.89	12.57	12.40	21.89	21.62
C_2H_5	$C_9H_{20}Si$	77.1	184	760	1.4565	0.8346	51.30	50.96	69.13	69.25	12.89	12.68	17.97	17.69
n-C_3H_7	$C_{11}H_{24}Si$	80.1	78	3.5	1.4590	0.8338	60.56	60.46	71.64	71.63	13.12	13.14	15.23	14.94
n-C_4H_9	$C_{13}H_{28}Si$	85.8	52	0.10	1.4614	0.8365	69.82	69.74	73.49	73.33	13.28	13.41	13.22	12.96
n-C_5H_{11}	$C_{15}H_{32}Si$	81.3	79	0.12	1.4623	0.8370	79.08	78.87	74.91	75.16	13.41	13.38	11.68	11.27
n-C_6H_{13}	$C_{17}H_{36}Si$	74.9	101	0.13	1.4631	0.8376	88.34	88.31	76.02	76.01	13.51	13.40	10.46	10.47
n-C_7H_{15}	$C_{19}H_{40}Si$	80.1	120	0.12	1.4638	0.8386	97.60	97.56	76.93	77.20	13.59	13.67	9.47	9.33
n-C_8H_{17}	$C_{21}H_{44}Si$	92.4	147	0.20	1.4645	0.8387	106.9	106.9	77.68	77.84	13.66	13.47	8.65	9.10
n-C_9H_{19}	$C_{23}H_{48}Si$	79.2	158	0.18	1.4650	0.8397	116.1	116.1	78.32	78.85	13.72	13.22	7.96	7.96
n-$C_{10}H_{21}$	$C_{25}H_{52}Si$	83.1	202	0.80	1.4656	0.8402	125.4	125.4	78.85	79.05	13.77	13.70	7.38	7.29
n-$C_{11}H_{23}$	$C_{27}H_{56}Si$	86.3	196	0.20	1.4661	0.8410	134.6	134.6	79.32	79.62	13.81	13.77	6.88	6.70
n-$C_{12}H_{25}$	$C_{29}H_{60}Si$	93.1	198	0.10	1.4667	0.8416	143.9	144.0	79.72	79.78	13.84	13.62	6.43	7.05
n-$C_{14}H_{29}$	$C_{31}H_{64}Si$	87.5	215	0.02	1.4679	0.8425	162.4	162.6	80.39	80.51	13.90	13.14	5.70	5.74
n-$C_{16}H_{33}$	$C_{33}H_{68}Si$	91.4	257	0.07	1.4685	0.8431	180.9	181.2	80.93	81.12	13.95	13.53	5.12	5.09
n-$C_{18}H_{37}$	$C_{35}H_{72}Si$	89.7	282	0.07	1.4689	0.8435	199.5	199.8	81.36	81.44	13.99	13.92	4.62	4.72
i-C_5H_{11}	$C_{15}H_{32}Si$	79.0	61	0.05	1.4600	0.8335	79.08	79.02	74.91	75.06	13.41	13.52	11.68	11.23
$(C_2H_5)_2CHCH_2$	$C_{17}H_{36}Si$	80.0	96	0.10	1.4621	0.8503	88.34	86.84	76.02	76.16	13.51	13.53	10.46	10.31
C_6H_5	$C_{17}H_{20}Si$	83.2	122	0.12	1.5820	1.0319	81.46	81.64	80.89	80.75	7.99	8.19	11.13	11.06

[a] Analyses by Schwarzkopf Microanalytical Laboratories, Woodside, New Jersey.

In the above equation R represents *n*-alkyl groups of from one to eighteen carbon atoms (with the exception of C_{13}, C_{15}, and C_{17}). In addition, two branched-chain derivatives, 1,1'-diisoamylsilacyclohexane and 1,1-di(2-ethylbutyl)silacyclohexane, were prepared from isoamyllithium and 2-ethylbutyllithium, respectively. An aryl derivative, 1,1-diphenylsilacyclohexane was obtained from the corresponding reaction with phenyllithium. The synthesis of all these compounds was carried out by the addition of the 1,1-dichlorosilacyclohexane to an ethereal solution of the alkyllithium derivative, followed by hydrolysis of unreacted organolithium and fractionation of the product. The alkyllithium compounds were prepared by standard procedures[5] from the alkyl bromides (with the exception of methyllithium[6] which was obtained from the iodide).

In an attempt to prepare 1,1-disubstituted-silacyclohexanes by an alternate procedure, 1,5-dilithiopentane was treated with dimethyldichlorosilane and di-*n*-dodecyldichlorosilane, as well as with diphenyldichlorosilane. In each of these cases, although there was some spectral evidence for ring closure and for the formation of a small amount of the desired cyclic silane derivative, the main products were extremely high-boiling liquids or tacky solids. These are apparently linear polymeric materials resulting from the reaction of a dialkyl (or diaryl)-dichlorosilane with an ω-lithioamyldialkyl (or aryl) chlorosilane, formed by the equimolar reaction of dialkyl (or diaryl) dichlorosilane with 1,5-dilithiopentane. Further work aimed at studying this polymer formation, as well as preparing the cyclic dialkylsilanes by modification of the ring closure method, is in progress in this Laboratory.

The yields, physical characteristics, and analytical data for the 1,1-disubstituted-silacyclohexanes prepared in the present study are shown in Table I. The yields of 75–93% were somewhat greater than that obtained by West[2] for the preparation of 1,1-dimethylsilacyclohexane and are definitely superior to the yield obtained by Bygden[3] for the latter compound using the Grignard method.

EXPERIMENTAL

1,1-Disubstituted-silacyclohexanes. The method for the preparation of this series is illustrated by the synthesis of 1,1-di(*n*-octyl)silacyclohexane. To a solution of 0.89 mole of *n*-octyllithium (prepared by the general procedure of Gilman and co-workers,[5] the yield determined by the double titration method of Gilman and Haubein[7]) in 550 ml. of anhydrous ethyl ether and maintained under a nitrogen atmosphere, 59.7 g. (0.3 mol.) of 1,1-dichlorosilacyclohexane (prepared by interaction of the Grignard reagent of 1,5-dibromopentane and silicon tetrachloride)[2] dissolved in 50 ml. of anhydrous ether was added dropwise with stirring. A temperature of 0–10° was maintained throughout the addition which was complete in 80 min. The reaction mixture was allowed to warm up to room temperature and then refluxed for 18 hr. The contents of the flask were filtered to remove unreacted lithium metal and the filtrate poured over cracked ice. A 3% hydrochloric acid solution was added to the mixture until the water layer was just slightly acidic. The water layer was extracted with three 100-ml. portions of ethyl ether and the combined ether layer and washings dried over anhydrous calcium sulfate. Following removal of the solvents by distillation, fractionation of the yellow liquid residue through a 30-cm. short-path Vigreaux column gave 86.4 g. (87.5%) of the 1,1-dialkylsilacyclohexane, b.p. 147° (0.20 mm.), n_D^{25} 1.4645, d_4^{25} 0.8391. See Table I for the analysis.

Attempted preparation of cyclopentamethylenedimethylsilane. As a typical example of experiments conducted in an effort to synthesize 1,1-disubstituted-silacyclohexanes by ring closure of 1,5-dilithiopentane and dialkyldichlorosilanes, the attempted preparation of 1,1-dimethylsilacyclohexane by this method is described. To 20.7 g. (3.0 g. atoms) of lithium ribbon and 200 ml. of anhydrous ethyl ether, under a dry nitrogen atmosphere, was added 150.9 g. (0.656 mol.) of 1,5-dibromopentane while the temperature was maintained between −10° to −20°. After all of the dihalide had been added, the reaction mixture was allowed to come to room temperature. Titration of an aliquot sample of the mixture indicated a yield of 64% of the dilithium compound.[7] To the 0.42 mole of 1,5-dilithiopentane in the flask was then added dropwise with stirring 51.6 g. (0.4 mole) of dimethyldichlorosilane (Anderson Laboratories, Inc.) dissolved in 100 ml. of anhydrous ether. The reaction was exothermic and precipitation of lithium chloride was observed almost immediately. The mixture was refluxed for 20 hr when the excess lithium metal was removed by filtration. The filtrate was poured over cracked ice and neutralized with 3 *N* hydrochloric acid. The ether layer was separated and the water layer extracted three times with 100-ml. portions of ether. The ether layer and washings were combined and dried over anhydrous calcium sulfate. After the ether was removed by distillation, the liquid residue was fractionated through a 30-cm. column packed with glass helices. Four fractions were obtained, none of which boiled at a constant temperature. The refractive index of fraction 2, n_D^{25} 1.4371, is in approximate agreement with that obtained by West[2] for cyclopentamethylenedimethylsilane. However, only a minute quantity of this fraction was obtained and the bulk of the reaction product was an extremely high-boiling (non-distillable) polymeric material which could not be readily characterized.

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WRIGHT-PATTERSON AIR FORCE BASE, OHIO

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF BUFFALO]

Studies in Organosilicon Chemistry. XXXVIII. Further Studies in Sila-Organic Polysulfides

QUINTIN W. DECKER[1a] AND HOWARD W. POST

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Chlorination of methyltrichlorosilane results in the formation of chloromethyltrichlorosilane from which triethylchloromethylsilane and tri-*n*-propylchloromethylsilane can be prepared by the action of the proper Grignard reagent. Sodium hydrosulfide reacts with each of the last two compounds to form the corresponding mercaptans. These mercaptans, as well as trimethylsilylmethyl mercaptan, form addition compounds (2:1 mole ratio) with mercuric chloride. Sodium sulfide reacts with trimethylchloromethylsilane and triethylchloromethylsilane to form the respective sulfides. Each sulfide adds methyl iodide giving the corresponding sulfonium iodide while bis(trimethylsilylmethyl) sulfide adds mercuric iodide in a 1:1 mole ratio. The action of iodine on sodium trimethylsilylmethyl mercaptide and on sodium triethylsilylmethyl mercaptide results in the formation of the corresponding disulfides. Infrared absorption spectra are presented for triethylchloromethylsilane, tri-*n*-propylchloromethylsilane, trimethylsilylmethyl mercaptan, triethylsilylmethyl mercaptan, tri-*n*-propylsilylmethyl mercaptan, bis(trimethylsilylmethyl) sulfide, bis(triethylsilylmethyl) sulfide, bis(trimethylsilylmethyl)-methylsulfonium iodide, bis(triethylsilylmethyl)methylsulfonium iodide, bis(trimethylsilylmethyl) disulfide, and bis-(triethylsilylmethyl) disulfide. Ultraviolet absorption spectra have been examined for bis(trimethylsilylmethyl) disulfide and for bis(triethylsilylmethyl) disulfide.

The investigation was directed toward the preparation and study of mercaptans, sulfides, and polysulfides containing the trialkylsilylmethyl unit and certain of their derivatives, partly by the use of procedures already investigated and partly by methods which are new. A short bibliography has already appeared in a recent contribution by Minklei, Decker, and Post,[1b] summarizing work carried out by Gilman and co-workers[2-6] and by Burkhard,[7] Noller and Post,[8] Cooper[9] and by Marvel and Cripps.[10]

Sodium trimethylsilylmethyl mercaptide has been treated with iodine with the subsequent formation of bis(trimethylsilylmethyl) disulfide. Bis-(trimethylsilylmethyl) methylsulfonium iodide has been synthesized by the addition of methyl iodide to bis(trimethylsilylmethyl) sulfide. Mercuric iodide adds to the last named compound to form an additional product in 1:1 molar ratio. Trimethylsilylmethyl mercaptan also forms a 2:1 molar ratio addition compound with mercuric chloride. These reactions are presented in completion of the work previously reported by Minklei, Decker, and Post.[1b] The corresponding ethyl homologs have also been prepared.

By similar procedures tri-*n*-propylchloromethylsilane and tri-*n*-propylsilylmethyl mercaptan have been prepared as well as the 2:1 addition product of the latter with mercuric chloride.

These compounds, with the exception of the mercuric halide addition products, were examined using an infrared spectroscope to provide a basis for comparing and establishing structures and to support their chemical identification.

The infrared bands have been analyzed and a comparison has been made with data found in Bellamy.[11]

A Baird Atomic recording spectrophotometer was used to record all spectral measurements. Liquid samples were examined using fixed thickness cells. When the samples were solid they were prepared as Nujol mulls and examined between rock salt plates without a spacer. No compensating solvents or plates were used in the reference beam.

The ultraviolet absorption spectra were determined for bis(trimethylsilylmethyl) disulfide and bis(triethylsilylmethyl) disulfide. These spectra were measured with a Beckman Model D K-2 spectrophotometer, using iso-octane as the solvent. The concentration of the solutions which were examined was about 0.002*M*.

Bis(trimethylsilylmethyl) disulfide showed a minimum at 244 mμ and a maximum at 262 mμ. For bis(triethylsilylmethyl) disulfide the figures were 244 mμ and 257 mμ, respectively. These properties essentially agree with previously published data

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TABLE I

PHYSICAL PROPERTIES

	B.P	Mm.	n_D^{25}	D_4^{25}	Yield, %
$(C_2H_5)_3SiCH_2Cl$	116	100	1.4452[a]	0.9020	65.0
$(n\text{-}C_3H_7)_3SiCH_2Cl$	117	20	1.4502[b]	0.8899	28.3
$[(CH_3)_3SiCH_2S]_2$	82	1	1.4874[c]	0.9147	57.8
$(C_2H_5)_3SiCH_2SH$	110	50	1.4678	0.8750	50.7
$[(C_2H_5)_3SiCH_2]_2S$	111	0.8	1.4771	0.8802	76.0
$[(C_2H_5)_3SiCH_2S]_2$	122	0.02	1.5020	0.9334	53.3
$(n\text{-}C_3H_7)_3SiCH_2SH$	89	3	1.4676	0.8614	66.7

[a] Literature: n_D^{20} 1.4480.[13] [b] Literature: n_D^{20} 1.4530.[14] [c] Literature: n_D^{25} 1.4906.[1]

TABLE II

MELTING POINTS, SULFUR COMPOUNDS

	M.P.	Yield, %
$([(CH_3)_3SiCH_2]_2SCH_3)^+(I)^-$	147	90
$[(CH_3)_3SiCH_2]_2S,HgI_2$	63	20
$([(CH_3)_3SiCH_2SH]_2\cdot Hg)^{++}2(Cl^-)$	142	—
$([(C_2H_5)_3SiCH_2]_2SCH_3)^+(I)^-$	145	69
$([(C_2H_5)_3SiCH_2SH]_2\cdot Hg)^{++}2(Cl^-)$	105	—
$([(n\text{-}C_3H_7)_3SiCH_2SH]_2\cdot Hg)^{++}2(Cl^-)$	135	—

same solvent was added until precipitation ceased. The precipitate, di-(trimethylsilylmethyl mercaptan) mercuric chloride, was filtered, washed with ethanol and dried in air, m.p. 142°.

Anal. Calcd. for $C_8H_{24}Cl_2HgS_2Si_2$: Si, 10.9; C, 18.8; H, 4.7. Found: Si, 10.6; C, 18.2; H, 4.6.

Bis(trimethylsilylmethyl)methylsulfonium iodide. Following the general method of Cooper,[15] bis(trimethylsilylmethyl) sulfide 6.2 g. (0.03 mol.) was thoroughly mixed with methyl iodide 8.6 g. (0.06 mol.) and allowed to stand in the dark for 20 hr. A precipitate formed within 10 min. and was ultimately filtered, washed with dry cyclohexane, and dried in air, to yield an orange-yellow powder, 9.4 g. (0.2 mol.); m.p. 147°; yield 90.0%.

Anal. Calcd. for $C_9H_{25}IS\,Si_2$: Si, 16.1; S, 9.2; I, 36.4. Found: Si, 15.9; S, 9.0; I, 36.2.

Bis(trimethylsilylmethyl) sulfide mercuric iodide. Following the method of Linnemann[16] bis(trimethylsilylmethyl) sulfide 2.1 g. (0.01 mol.) was thoroughly mixed with mercuric iodide 4.0 g. (0.009 mol.) and allowed to stand 12 hr. The mixture was added to 25 cc. of hot ethanol, brought to a boil, filtered, and the filtrate cooled in ice. The resulting crystals, bis(trimethylsilylmethyl) sulfide mercuric iodide,

TABLE III

CHARACTERISTIC INFRARED ABSORPTION BANDS[a]

Compounds	CH (stretching)	CH (def.) C—CH_3	CH (def.) —$(CH_3)_3$	CH (def.) —CH_2—	Ethyl Group	Propyl Group	Si—CH_3, Si—C	Si—CH_2—	S—H	C—Cl
$(C_2H_5)_3SiCH_2Cl$	3.4	7.1	—	6.8	9.8 10.4	—	13.0	8.1	—	13.6
$(n\text{-}C_3H_7)_3SiCH_2Cl$	3.4	7.1	—	6.8	—	9.9 11.1	13.0	8.3	—	13.4
$(CH_3)_3SiCH_2SH$	3.4	7.1	7.2	—	—	—	11.7	8.0	3.9	—
$(C_2H_5)_3SiCH_2SH$	3.4	7.1	—	6.8	9.8 10.3	—	13.5	8.1	3.9	—
$(n\text{-}C_3H_7)_3SiCH_2SH$	3.4	7.1	—	6.8	—	9.9 11.1	13.3	8.3	3.9	—
$[(CH_3)_3SiCH_2]_2S$	3.4	7.1	7.2	—	—	—	11.7	8.0	—	—
$[(C_2H_5)_3SiCH_2]_2S$	3.4	7.1	—	6.8	9.8 10.3	—	13.5	8.1	—	—
$([(CH_3)_3SiCH_2]_2SCH_3)^+(I)^-$	3.5[b]	7.1[b]	7.3[b]	6.9[b]	—	—	11.8	8.0	—	—
$([(C_2H_5)_3SiCH_2]_2SCH_3)^+(I)^-$	3.5[b]	7.0[b]	7.2[b]	6.8[b]	9.8 10.1	—	13.2	8.0	—	—
$[(CH_3)_3SiCH_2S]_2$	3.4	7.1	7.2	—	—	—	11.9	8.1	—	—
$[(C_2H_5)_3SiCH_2S]_2$	3.4	7.1	—	6.8	9.8 10.3	—	13.4	8.1	—	—

[a] Measured in microns. [b] Nujol interference.

on alkyl polysulfides not containing a silicon structure.[12]

EXPERIMENTAL

Di-(trimethylsilylmethyl mercaptyl) mercuric chloride. Trimethylsilylmethyl mercaptan (0.5 cc.) was added to 2 cc. of ethanol, and a 10% solution of mercuric chloride in the

(12) Q. W. Decker and H. W. Post, *J. Org. Chem.*, **22**, 145 (1957).

(13) V. Ponomarenko and V. Mironov, *Doklady Akad. Nauk S.S.S.R.*, **94**, 485 (1954).

(14) V. Mironov, *Doklady Akad. Nauk S.S.S.R.*, **108**, 266 (1956).

(15) G. D. Cooper, U. S. Patent **2,719,165**, Sept. 27, 1955.

(16) E. Linnemann, *Ann.*, **120**, 61 (1861).

were filtered, washed with absolute ethanol, and dried in air 2.0 g. (0.003 mol.); m.p. 63°; yield, 20.0%.

Anal. Calcd. for $C_8H_{22}I_2HgSSi_2$: Si, 8.5; S, 4.85. Found: Si, 8.5; S, 4.8.

Bis(trimethylsilylmethyl) disulfide. The general procedures here were taken from the work of McAllan *et al.*[17] Sodium hydroxide 4.7 g. (0.117 mol.) and potassium iodide 0.32 g. (0.0019 mol.) were placed in a 500 cc. three-neck flask equipped with a reflux condenser, a mercury-sealed mechanical stirrer, and dropping funnel. With stirring, 20 cc. of water was added until all solids dissolved. Trimethylsilylmethyl mercaptan 14.0 g. (0.117 mol.) in 200 cc. of dioxane was added slowly with stirring and cooling. After the addition was complete and the system had returned to room temperature, iodine was added 14.8 g. (0.058 mol.) in small portions, with stirring. After about 75% of the iodine had been added, discoloration of the system ceased and the remainder was added in one portion. After 2 hr. of refluxing, the mixture was once again colorless, and after cooling, was poured into 500 cc. of water, the crude product separated and was dried overnight over calcium chloride. Darkening of the crude product was observed, which could have been caused by a reversal of the reaction, so the product was placed over solid sodium hydroxide for several hours, decanted, and fractionated. Bis(trimethylsilylmethyl) disulfide 8.0 g. (0.033 mol.) was isolated, b.p. 82° (1 mm.); n_D^{25} 1.4874, lit.,[1] 1.4906; D_4^{25} 0.9147, lit.,[1] 0.9203; yield 57.8%.

Anal. Calcd. for $C_8H_{22}S_2Si_2$: M.R., 74.4; Mol. Wt., 238.57. Found: M.R., 75.04; Mol. Wt., 237.9 (cryoscopic in benzene).

Triethylchloromethylsilane. This procedure also was adapted from the results of Mironov.[14] Ethylmagnesium bromide 159.6 g. (1.2 mol. in about 1000 cc. of anhydrous ether) was treated with an ethereal solution of 73.5 g. (0.4 mol.) of chloromethyltrichlorosilane at a rate sufficient to induce refluxing about 2 hr. The system was refluxed for an additional 5 hr. after all of the chlorosilane compound had been added. Most of the ether was then removed and the crude reaction mixture refluxed at 85° for 10 hr. Chilled dilute hydrochloric acid was added to the reaction mixture and the aqueous layer separated and extracted twice with 200 cc. of ether. Distillation of the combined organic layers removed the solvent. The residue was dried over calcium chloride for 12 hr. and fractionated giving triethylchloromethylsilane, 43.0 g. (0.26 mol.); b.p. 116° (100 mm.); n_D^{25} 1.4452, n_D^{20} 1.4480 (lit.)[14]; D_4^{25} 0.9020, D_4^{20} 0.9101 (lit.)[14]; yield 65.0%.

Anal. Calcd. for $C_7H_{17}ClSi$: M.R., 48.9. Found: M.R., 48.7.

Triethylsilylmethyl mercaptan. This compound was prepared following a modified method previously recorded by Cooper.[18] Potassium hydroxide 9.5 g. (0.17 mol.) and 75 cc. of absolute ethanol were placed in a 250 cc. three-neck flask, with stirrer, dropping funnel and reflux condenser protected by a calcium chloride tube and were saturated with hydrogen sulfide for 3 hr. Triethylchloromethylsilane 19.0 g. (0.12 mol.) in 25 cc. of absolute ethanol was added during 1 hr. with stirring and refluxing. Hydrogen sulfide was bubbled through the system during the addition and refluxing period which was an additional hr. The precipitate was centrifuged and the organic layer decanted. The solid was washed twice with ethanol and again centrifuged for 2 min. The organic layer and washings were freed from solvent by distillation and the residue dried over calcium sulfate for 4 hr. Fractionation yielded 9.5 g. (0.06 mol.) of triethylsilylmethyl mercaptan, b.p. 110° (50 mm.); n_D^{25} 1.4678; D_4^{25} 0.8750; yield 50.7%.

Anal. Calcd. for $C_7H_{18}SSi$: Si, 17.3; S, 19.6; M.R., 51.55. Found: Si, 17.4; S, 19.5; M.R., 51.60.

Bistriethylsilylmethyl sulfide was also isolated, 1.7 g. (0.006 mol.) about a 10% yield, b.p. 149° (4 mm.).

Di(triethylsilylmethyl mercaptyl) mercuric chloride. This compound, m.p. 105°, was prepared by the same method as that used in the preparation of di(trimethylsilylmethyl mercaptyl) mercuric chloride.

Anal. Calcd. for $C_{14}H_{36}Cl_2HgS_2Si_2$: Si, 9.4; C, 28.2; H, 6.1. Found: Si, 8.9; C, 27.5; H, 5.8.

Bistriethylsilylmethyl sulfide. This compound also was prepared by a modification of the method reported by Cooper.[9] Triethylchloromethylsilane 16.5 g. (0.1 mol.) was added with stirring, to 130 cc. of ethanol in a flask equipped as in the preparation of the corresponding mercaptan. Sodium sulfide 7.0 g. (0.009 mol.) in 25 cc. of warm water was added over 1 hr. with heating and stirring, and the system was stirred and refluxed for 4 hr. To facilitate separation of the organic layer, the mixture was poured into 400 cc. of water and the water layer extracted with 300 cc. of ether. Combined organic layer and extractions were distilled to remove solvent and the residue dried overnight over 5 g. of calcium chloride. Fractionation yielded 11.0 g. (0.04 mol.) of bis(triethylsilylmethyl) sulfide, 76.0% yield; b.p. 111° (0.08 mm.); n_D^{25} 1.4771; D_4^{25} 0.8802.

Anal. Calcd. for $C_{14}H_{34}SSi_2$: Si, 19.3; S, 11.0; M.R., 93.0. Found: Si, 19.3; S, 10.8; M.R., 93.4.

Bis(triethylsilylmethyl)methylsulfonium iodide. This compound was prepared in a manner similar to the corresponding trimethyl homolog; however, it was necessary to cool the reaction mixture in Dry Ice to induce precipitation. The product was filtered and washed three times with dry cyclohexane, 3.0 g. (0.0069 mol.); m.p. 145°; yield 69.0%.

Anal. Calcd. for $C_{15}H_{37}ISSi_2$: Si, 13.0; S, 7.4; I, 29.3. Found: Si, 13.0; S, 7.3; I, 29.0.

Bis(triethylsilylmethyl) disulfide. The method described previously for the preparation of bis(trimethylsilylmethyl) disulfide was followed here, using 6.0 g. (0.15 mol.) of sodium hydroxide, 0.5 g. (0.003 mol.) of potassium iodide, 12.0 g. (0.074 mol.) of triethylsilylmethyl mercaptan and 9.4 g. (0.037 mol.) of iodine. Bis(triethylsilylmethyl) disulfide was collected, 6.5 g. (0.02 mol.); b.p. 122° (0.02 mm.); n_D^{25} 1.5020; D_4^{25} 0.9334; yield 53.3%.

Anal. Calcd. for $C_{14}H_{34}S_2Si_2$: Si, 17.4; S, 19.9; M.R., 101.6. Found: Si, 17.3; S, 20.0; M.R., 102.0.

Tri-n-propylchloromethylsilane. The procedure followed closely that which lead to the synthesis of triethylchloromethylsilane, using 176.8 g. (1.2 mol.) of *n*-propylmagnesium bromide and 73.5 g. (0.4 mol.) of chloromethyltrichlorosilane. The crude reaction mixture was refluxed and stirred for 15 hr. at 35°. The temperature of this mixture then was increased to 105° for 30 hr., after the majority of the ether had been removed. Fractionation of the crude mixture yielded 23.3 g. (0.113 mol.) of tri-*n*-propylchloromethylsilane, b.p. 117° (20 mm.), 222–225° (749 mm.), lit.[14] 222° (733 mm.); n_D^{25} 1.4502, n_D^{20} (lit.[14]) 1.4530; D_4^{25} 0.8899, D_4^{20} (lit.[14]) 0.8919; yield 23.3%.

Anal. Calcd. for $C_{10}H_{23}ClSi$: Si, 13.55; Cl, 17.4; M.R., 62.8. Found: Si, 13.4; Cl, 17.3; M.R., 62.5.

Tri-n-propylsilylmethyl mercaptan. The compound was prepared in a manner similar to triethylsilylmethyl mercaptan, with 5.6 g. (0.10 mol.) of potassium hydroxide, hydrogen sulfide, and 15.0 g. (0.072 mol.) of tri-*n*-propylchloromethylsilane, giving 9.8 g. (0.048 mol.) of tri-*n*-propylsilylmethyl mercaptan, b.p. 89° (3 mm.); n_D^{25} 1.4676; D_4^{25} 0.8614; yield 66.7%.

Anal. Calcd. for $C_{10}H_{24}SSi$: Si, 13.7; S, 15.7; M.R., 65.5. Found: Si, 13.6; S, 15.5; M.R., 65.9.

Di(tri-n-propylsilylmethyl mercaptyl) mercuric chloride.

(17) D. McAllan, T. Cullum, R. Dean, and F. Fidler, *J. Am. Chem. Soc.*, **73**, 3627 (1951).

(18) G. D. Cooper, *J. Am. Chem. Soc.*, **76**, 2500 (1954).

This compound, m.p. 135°, was prepared using a procedure analogous to the preparation of the two preceding mercuric chloride addition compounds.

Anal. Calcd. for $C_{70}H_{48}Cl_2HgS_2Si_2$: S, 8.2; C, 35.3; H, 7.1. Found: Si, 7.9; C, 34.4; H, 6.6.

Hydrogen sulfide, solvents, and other reagents were purchased from the usual sources. *Spectro grade iso-octane* was purchased from Phillips Petroleum Company. All were found to possess satisfactory physical constants. Molecular refractions were calculated using the data of Warrick.[19]

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(19) E. L. Warrick, *J. Am. Chem. Soc.*, 68, 2455 (1946).

[CONTRIBUTION FROM THE CHEMICAL DIVISION, DENVER RESEARCH INSTITUTE, UNIVERSITY OF DENVER]

Alkylpolyphenyls. I. 4′-Alkyl-*m*-terphenyls[1]

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A series of 4′-alkyl-*m*-terphenyls have been prepared for potential use as high temperature hydraulic fluids and lubricants. An improved synthesis of 4′-bromo-*m*-terphenyl has been developed.

In connection with a study on the preparation of potential hydraulic fluids and lubricants of high thermal stability and wide liquid range, the authors have prepared a number of alkylbiphenyls and alkylterphenyls. Compounds of the alkylpolyphenyl type were chosen for investigation as it was expected that the well established thermal stability of such "chain-type" aromatic structures as biphenyl and the terphenyls might also be found to some extent in their derivatives.

Although biphenyl and the terphenyls are rather high melting compounds, it is known, especially from the study of biphenyl derivatives, that the introduction of an alkyl group into the nucleus greatly extends the liquid range of the compound. While numerous alkylbiphenyls are known, only a very few alkyl terphenyls have been reported; however the information available for the biphenyls is sufficient to make certain correlations concerning the substitution of alkyl groups on the terphenyl nucleus.

A study of the alkylbiphenyls revealed that substitution of an alkyl group at any position in the molecule lowered the melting point of the parent compound, substitution in the 2- or 3-position producing much greater lowering than substitution in the 4-position. This same depression was postulated for substitution in the terminal nucleus of the terphenyl molecule and was confirmed by the few examples reported in the literature. It was further postulated that substitution in the inner ring of a terphenyl molecule should depress the melting point; however, a literature survey revealed only one such compound, 5′-methyl-*m*-terphenyl,[3] and this compound, perhaps because of its molecular symmetry, had a melting point of 130°, somewhat higher than that (87°) of *m*-terphenyl. It was also evident that increased symmetry of the substituted alkyl group would lead to an increased melting point for the corresponding alkyl derivative. For example, melting points have been reported for certain 2-alkylbiphenyls as follows: *n*-propyl, −11.26°[4]; isopropyl, 24.46°[4]; *n*-butyl, −9.65° and −13.71°[4]; isobutyl, glass;[5] *sec*-butyl, 8.12°[5]; and *tert*-butyl, 31–34°.[6] This trend has been confirmed by our work which shows that the normal alkyl derivatives generally have lower pour points than the branched alkyl derivatives.

In considering the terphenyls, the *ortho* and *meta* isomers are much more attractive starting materials, from the standpoint of providing derivatives of wide liquid range, than is the *para* isomer due to the much lower melting points of the first two isomers.

Among the alkylpolyphenyls which have been prepared in this laboratory are 2-, 3-, and 4-monoalkylbiphenyls; 2- and 3-monoalkyl-*o*-terphenyls; 2-, 3-, 4-, and 4′-monoalkyl-*m*-terphenyls and 2-, 3-, and 4-monoalkyl-*p*-terphenyls. Other alkylterphenyls have been prepared by the Friedel-Crafts reaction, which by its inherent nature usually gave products of indefinite composition. While the 2- and 3-substituted alkyl derivatives will be described in a subsequent publication, the 4′-alkyl-*m*-terphenyls are discussed in this communication.

The 4′-alkyl-*m*-terphenyl series was selected for the investigation of inner ring substitution due to the availability of 4′-bromo-*m*-terphenyl as a starting material. The bromination of *m*-terphenyl to give 4′-bromo-*m*-terphenyl has been re-

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(2) Denver Research Institute Fellow 1956–57.

(3) C. Gastaldi and F. Cherchi, *Gazz. Chim. Ital.*, **45**, 11, 251 (1915); *Chem. Abstr.*, 10, 1637 (1916).

(4) I. A. Goodman and P. H. Wise, *J. Am. Chem. Soc.*, 72, 3076 (1950).

(5) I. A. Goodman and P. H. Wise, *Natl. Advisory Comm. Aeronaut. Tech. Note*, 2260, 29 pp. (1951); *Chem. Abstr.*, 45, 7986 (1951).

(6) J. I. G. Cadogan, D. H. Hey, and G. H. Williams, *J. Chem. Soc.*, 3352 (1954).

ported by Olgiati,[7] Cook and Cook,[8] and Bradsher and Swerlick.[9] Bradsher and Swerlick also prepared this compound from 4′-amino-*m*-terphenyl by the Sandmeyer method. The various procedures reported gave products which melted at 31°,[7] 36.5–37°,[9] or which did not solidify.[8] Bradsher and Swerlick also showed the presence of 4-bromo-*m*-terphenyl in the product prepared by the Cook and Cook method.

We first prepared 4′-bromo-*m*-terphenyl by the methods of Olgiati, and Cook and Cook, obtaining similar results to those reported. A change in procedure and more important, the purification of the product by fractional distillation through a glass-helices-packed column gave material which ultimately melted at 58°. This disagreement with the published values led us to the purification of 4′-bromo-*m*-terphenyl prepared by both the Olgiati, and Cook and Cook methods, and from both methods we obtained material agreeing with the melting point claimed by us for 4′-bromo-*m*-terphenyl. We have also studied the composition of various samples of 4′-bromo-*m*-terphenyl by gas chromatography methods which show that unless the product is carefully purified, it will contain impurities which will cause low melting points. Preparations by the Olgiati method contain *m*-terphenyl as the principal impurity, whereas preparations by the Cook and Cook method in addition, contain a higher boiling impurity, apparently the 4-bromo isomer first noted by Bradsher and Swerlick.

We also found that conditions existing during the solidification of 4′-bromo-*m*-terphenyl affected the melting point. At times products were obtained which melted over a range (for example 40–53°). Remelting and seeding with a crystal of 57° melting product gave complete solidification with a melting point of 53–54°.

Bradsher and Swerlick reported that in one preparation of 4′-bromo-*m*-terphenyl (from 4′-amino-*m*-terphenyl by the Sandmeyer method) the product first obtained melted at 40–42° and after recrystallization from ether-ethanol solution, the product attained a constant melting point of 36.5–37°. They stated that the initial high melting point was probably due to a small quantity of high melting impurity. We have not repeated this preparation. We have not been able to lower the melting point of any sample of 4′-bromo-*m*-terphenyl by recrystallization.

The preparation of a 4′-alkyl-*m*-terphenyl from 4′-bromo-*m*-terphenyl was accomplished by converting the bromide into the corresponding lithium or magnesium bromide compound, adding the desired aldehyde or ketone, dehydrating the resulting alcohol, and finally selectively hydrogenating the alkenyl-*m*-terphenyl to the desired 4′-alkyl-*m*-terphenyl.

Of the 4′-alkyl-*m*-terphenyls prepared, all had pour points (most of the derivatives did not crystallize) or melting points considerably below that of the parent hydrocarbon. This lowering of pour point combined with elevated boiling points has given compounds of wide liquid range.

The thermal stability of these compounds was studied by heating in a nitrogen atmosphere, distilling in air, and determining vapor pressure using either a Smith-Menzies type[10] or a Greene type[11] isoteniscope. A typical compound, 4′-*n*-heptyl-*m*-terphenyl showed a 4.7% weight loss when heated in a nitrogen atmosphere for 24 hr. at 370°. It could be distilled in air with only a slight change in refractive index. Vapor pressure measurements[12] showed the first deviation from the straight line plot of log pressure *vs.* 1/T at 262°. This temperature is considered to be the point of initial thermal decomposition. For comparison, di-2-ethylhexyl sebacate showed an initial thermal decomposition point of 290°. Other 4′-alkyl-*m*-terphenyls showed slightly higher initial decomposition points. The 4′-alkyl-*m*-terphenyls, as well as other alkylpolyphenyl compounds have shown good radiation stability.[12]

EXPERIMENTAL[13]

4′-Bromo-m-terphenyl. (a) *By the method of Olgiati. m*-Terphenyl, m.p. 87°, 138 g. (0.6 mole) was brominated in carbon disulfide solution as described by Olgiati.[7] Fractional distillation of the crude product through a column[14] gave 50-g. forecuts containing both *m*-terphenyl and 4′-bromo-*m*-terphenyl, and 75 g. of 4′-bromo-*m*-terphenyl, m.p. 54.5–56°, 40% yield. From a different preparation in which recrystallization instead of distillation was used, a product similar to that described by Olgiati was obtained.

(b) *By the method of Cook and Cook.* Molten *m*-terphenyl (Santowax M) was brominated at 90–95° as described by Cook and Cook.[8] Distillation using a 20 × 200 mm. Vigreux column gave fractions which either did not solidify or which developed small amounts of white crystals on prolonged standing. Similar results were noted by Cook and Cook. Fractionation of a portion of this product through a column[14] gave two fractions of interest, both of which were solidified by seeding with 4′-bromo-*m*-terphenyl (m.p. 57°): 1. indefinite m.p. 30–45° and 2. m.p. 50–53°, which on recrystallization from absolute ethanol gave a m.p. of 54–55°. These fractions are further described in the section on gas chromatography.

(7) L. Olgiati, *Ber.*, **27**, 3385 (1894).

(8) W. A. Cook and K. H. Cook, *J. Am. Chem. Soc.*, **55**, 1212 (1933).

(9) C. K. Bradsher and I. Swerlick, *J. Am. Chem. Soc.*, **72**, 4189 (1950).

(10) A. Smith and A. W. C. Menzies, *J. Am. Chem. Soc.*, **32**, 1412 (1910).

(11) H. Greene, *Anal. Chem.*, **28**, 428 (1956).

(12) A detailed discussion of the use of vapor pressure measurements to determine thermal stability and radiation stability of alkylpolyphenyls will be subjects covered in future publications from this laboratory.

(13) All melting points and boiling points are uncorrected. Microanalyses by Huffman Microanalytical Laboratories, Wheatridge, Colo.

(14) 600 × 25mm., vacuum jacketed, packed with 1/8″ multiturn glass helices.

(c) *By direct bromination in ethylene dichloride.* To a stirred solution of 1380 g. (6 mole) of *m*-terphenyl (Santowax M)[15] and 1100 ml. of ethylene dichloride, heated to about 80°, were added several ml. of bromine, several iron nails (freshly cleaned with hydrochloric acid) and several drops of water (to promote the formation of hydrogen bromide). As soon as the bromine vapors disappeared, the reaction mixture was cooled to room temperature. A total of 815 g. (5.1 moles) of bromine[16] was added over a period of 16 hr. The reaction mixture was cooled in an ice-water bath and filtered to remove about 75 g. of a red-brown solid. Recrystallization of this material from ethanol gave white plates, m.p. 235–236° which did not depress the melting point of 4-bromo-*p*-terphenyl, which was prepared by the bromination of *p*-terphenyl. The filtrate was steam distilled to remove ethylene dichloride and hydrogen bromide. The steam distillation residue was washed several times with water by decantation and dried by heating under reduced pressure. The crude bromide was purified by distillation through a column.[14] Two distillations were used, the first to separate the product into a low boiling yellow forecut, containing some *m*-terphenyl, 50 g.; *m*-terphenyl, 150 g.; intermediates, 60 g.; crude 4′-bromo-*m*-terphenyl, 1280 g.; and higher boiling residue, 150 g. Careful refractionation of the crude 4′-bromo-*m*-terphenyl through the same column gave the following fractions: 1. *m*-terphenyl, 40 g., m.p. 87°, b.p. 162°/1.3 mm.; 2. intermediate fractions containing both *m*-terphenyl and 4′-bromo-*m*-terphenyl, 215 g., b.p. 162–183/1.5 mm.; 3. 4′-bromo-*m*-terphenyl, 970 g., b.p. 183°/1.5 mm., m.p. 55–56°; and 4. higher boiling material and residue, 55 g.

The composition of the residue is still under investigation. It has however, been shown to contain 4-bromo-*p*-terphenyl. This compound was isolated from the ethanol extraction of the distilled residue as white plates, m.p. 236–237° which did not depress the melting point of known 4-bromo-*p*-terphenyl. This compound was also converted into the lithium derivative by *n*-butyllithium and hydrolyzed to give a product which, after recrystallization from ethanol, melted at 213° and did not depress the melting point of a known sample of *p*-terphenyl (m.p. 215°).

The principal product, 4′-bromo-*m*-terphenyl, was obtained as an almost colorless, viscous, liquid which slowly solidified. It usually melted over a 1° range between the temperatures of 53 and 57°; however, sometimes a sample was obtained which started to melt as low as 35°. This could be converted into the higher melting material. Specifically, a sample of 4′-bromo-*m*-terphenyl melting at 45–52° was remelted and seeded with a small crystal of this compound melting at 57°. The resulting solid had a melting point of 52–54°. Recrystallization of 4′-bromo-*m*-terphenyl, m.p. 56–57°, twice from absolute ethanol, once from hexane, and finally from absolute ethanol gave a product which melted at 58°. This is somewhat higher than the values reported in the literature, 31°,[7] 36.5–37°.[9]

During the course of this investigation and related work approximately 40 kg. of 4′-bromo-*m*-terphenyl have been prepared by this method.

Anal. (m.p. 58°). Calcd. for $C_{18}H_{13}Br$: C, 69.92; H, 4.24; Br, 25.85. Found: C, 69.86; H, 4.29; Br, 25.90.

Anal. (m.p. 54–55°). Found: C, 70.45; H, 4.09; Br, 25.50.

(d) *Analysis by gas chromatography.*[17] Various samples of 4′-bromo-*m*-terphenyl (I) were analyzed using a 4-ft. column packed with polyethylene, a carrier gas of helium and temperatures of 305–320°. Samples were shown to contain, in addition to I, the following impurities: *m*-terphenyl (II), and an unidentified product higher boiling than I (possibly 4-bromo-*m*-terphenyl) (III), in the amounts indicated. Percentages were estimated from the areas beneath each peak. I prepared by Olgiati method, 11% of II, 2% of III. I prepared by Olgiati method and purified by fractional distillation, m.p. 54.5–56°, trace of II and 0.5% of III. I prepared by Cook and Cook method, purified by fractional distillation and melting 30–45°, 7.5% of II, and 3.5% of III. I, Cook and Cook as preceding and m.p. 50–53°, trace of II and 9% of III. I, m.p. 52–53°, 0.4% of II and 1.7% of III. I, m.p. 58°, no trace of either II or III. I, to which 1.99% of II had been added, 2.2% of II.

4-Bromo-p-terphenyl. *p*-Terphenyl (Santowax P) was brominated in a manner similar to that described for *m*-terphenyl, with the exception that bromination was carried out in refluxing ethylene dichloride. The product was purified by distillation and recrystallization from benzene and from ethanol, m.p. 234°; lit.[1] 228°, 230–232°.[18]

4′-Alkyl-m-terphenyls. These compounds were prepared from 4′-bromo-*m*-terphenyl by the same method which is described in general terms below with specific results being given in Tables I and II.

(a) *Alkyl-4′-m-terphenylylcarbinols.* To a stirred solution of 4′-bromo-*m*-terphenyl dissolved in diethyl ether (300 ml. per mole of bromide), cooled to 0°, was added an ethereal solution containing the exact molar equivalent of *n*-butyllithium (molarity determined by the double titration method)[19] at a rate of 2 moles per hr. A yellow-white precipitate formed after about one third of the *n*-butyllithium solution had been added. To the 4′-*m*-terphenylyllithium so formed was added the molar equivalent of the desired aldehyde or ketone to form an alkyl- or dialkyl-4′-*m*-terphenylylcarbinol. With the exception of 5-nonanone, 6-undecanone, and 7-tridecanone, which were prepared by the oxidation of the corresponding alcohols, and *n*-dodecanal which was prepared by the dehydrogenation of *n*-dodecanol, all aldehydes and ketones were commercially available, but were purified by distillation prior to use. For several preparations, 4′-*m*-terphenylylmagnesium bromide in diethyl ether or tetrahydrofuran was used; however the reaction in diethyl ether proceeded slowly and the reaction in tetrahydrofuran was sometimes (but not always) difficult to initiate. We have prepared 4′-*m*-terphenylylmagnesium bromide in tetrahydrofuran in 89% yield. We feel that this reagent has not been fully exploited.

The alcohols so prepared were usually purified by distillation. For those alcohols which were not purified by distillation, the lower boiling products were removed by distillation to approximately the boiling point of the alcohol.

(b) *4′-Alkenyl-m-terphenyls.* The alkyl- or dialkyl-4′-*m*-terphenylylcarbinol was dehydrated by heating with 5% by weight of anhydrous copper sulfate for a period of 1 to 2 hr., during which time the reaction temperature reached a maximum of 250° and approximately 80% of the theoretical amount of water was condensed and collected. The crude 4′-alkenyl-*m*-terphenyl was filtered to remove solid materials and purified by distillation. The *cis* and *trans* isomers were not separated.

(c) *4′-Alkyl-m-terphenyls.* The 4′-alkenyl-*m*-terphenyl was selectively hydrogenated to the 4′-alkyl-*m*-terphenyl in a rocking autoclave using Raney nickel catalyst, pressures of 1000 to 1500 p.s.i. and temperatures up to 80°. If only a small amount of the 4′-alkenyl-*m*-terphenyl was available, hexane was used as a solvent. The 4′-alkyl-*m*-terphenyls were purified by distillation through a 20 × 200 mm. Vigreux column. All 4′-alkyl-*m*-terphenyls were prepared in 20- to 40-g. quantities with the exception of the heptyl and

(15) Both Santowax M and *m*-terphenyl, obtained by the distillation or recrystallization of Santowax M were used as starting materials to give similar final products.

(16) In this run a deficiency of bromine was used in an effort to reduce polybromination. In later runs, the theoretical amount was used without causing an objectionable increase in polybromination.

(17) We thank Mr. George E. Bonner, Jr., for the gas chromatography analyses.

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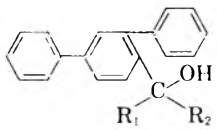
TABLE I

ALKYL-*m*-TERPHENYLYLCARBINOLS AND ALKENYL-*m*-TERPHENYLS



		Alkyl-*m*-terphenylylcarbinol			Alkenyl-*m*-terphenyl			
R_1	R_2	Yield, %	B.P.	Mm.	Yield, %	B.P.	Mm.	n_D^{25}
C_2H_5	H	60	181	0.3	87	174	0.5[a]	
n-C_4H_9	H	60	203–207	0.25	78	186–188	0.3	
n-C_5H_{11}	H	79	234–237	0.8	52	200–210	0.7	
n-C_6H_{13}	H	85	214	0.4	66	170–174	0.3	1.6144[b]
n-C_8H_{17}	H	72	229	0.65[c]	94	218–222	0.6	1.6088[d]
n-$C_{10}H_{21}$	H	67	241	0.5[e]	81	235	0.6	1.5965
n-$C_{11}H_{23}$	H	45	Not distilled		77	238–242	0.4[f]	
Cyclohexyl	H	[g]			54	192–194	0.35[h]	
C_2H_5	C_2H_5	83	180–183	0.35	80	172	0.45	
n-C_3H_7	*n*-C_3H_7	60	194–199	0.6	79	166	0.15	1.6114
n-C_4H_9	*n*-C_4H_9	63	214	0.5	90	176	0.15	1.5985
n-C_5H_{11}	*n*-C_5H_{11}	50	Not distilled		73	193	0.3	1.5857
n-C_6H_{13}	*n*-C_6H_{13}	82	Not distilled		87	200	0.1	1.5779
C_2H_5	*n*-C_4H_9	42	185–192	0.4	66	170–174	0.3	1.6144
CH_3	*n*-C_6H_{13}	69	225–230	1.2	90	182–189	0.3	1.6037
CH_3	*n*-$C_{15}H_{31}$	81	Not distilled[i]		87	240–242	0.1	1.5570

[a] M.p. 102°. [b] *Anal.* Calcd. for $C_{25}H_{26}$: C, 91.97; H, 8.03. Found: C, 92.00; H, 8.00. [c] n_D^{25} 1.5882. [d] *Anal.* Calcd. for $C_{27}H_{30}$: C, 91.47; H, 8.53. Found: C, 91.58; H, 8.47. [e] n_D^{25} 1.5763. [f] M.p. 44–46°. [g] Carbinol dehydrated during preparation. [h] M.p. 85–88°. [i] M.p. 48–50°.

TABLE II

4′-ALKYL-*m*-TERPHENYLS

Alkyl Group	B.P.	Mm.	n_D^{20}	Pour Point[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
n-C_3H_7-	153	0.3	1.6204	−7	$C_{21}H_{20}$	92.60	92.78	7.40	7.33
n-C_5H_{11}-	202–204	1.2	1.6050[b]	−15	$C_{23}H_{24}$	91.95	91.91	8.05	8.16
n-C_7H_{15}-	194–195	0.4	1.5921	−23	$C_{25}H_{28}$	91.41	91.35	8.59	8.60
n-C_9H_{19}-	212–214	0.55	1.5781	−26	$C_{27}H_{32}$	90.95	90.70	9.05	9.10
n-$C_{12}H_{25}$-	232	0.4	1.5675[b]	−23	$C_{30}H_{38}$	90.39	90.35	9.61	8.60
Cyclohexyl-[c]	196	0.5		75–77[d]	$C_{24}H_{24}$	92.26	92.33	7.74	7.47
$(C_2H_5)_2CH$-	164	0.3	1.6203	16	$C_{23}H_{24}$	91.95	92.10	8.05	7.60
$(n\text{-}C_3H_7)_2CH$-	185	0.6	1.6109	−12	$C_{25}H_{28}$	91.41	91.48	8.59	7.95
$(n\text{-}C_4H_9)_2CH$-	182	0.3	1.5953	−2	$C_{27}H_{32}$	90.95	91.63	9.05	8.39
$(n\text{-}C_5H_{11})_2CH$-	194	0.3	1.5749	−7	$C_{29}H_{36}$	90.48	90.44	9.52	9.26
$(n\text{-}C_6H_{13})_2CH$-	199	0.15	1.5641[b]	10	$C_{31}H_{40}$	90.23	90.18	9.77	9.62
$(C_2H_5)(n\text{-}C_4H_9)CH$-	168–170	0.3	1.5938	7	$C_{25}H_{28}$	91.41	91.51	8.59	8.49
$(CH_3)(n\text{-}C_6H_{13})CH$-	184	0.25	1.5944	−7	$C_{26}H_{30}$	91.17	91.16	8.83	8.55
$(CH_3)(n\text{-}C_{15}H_{31})CH$-	241–242	0.2		45[d]	$C_{35}H_{58}$	89.68	89.50	10.34	10.28

[a] Pour points were determined in °F. to the nearest 5° and converted into °C. for consistency with this table. [b] n_D^{20}. [c] Two other *n*-alkyl derivatives were prepared but are not included in this table due to unsatisfactory analyses: *n*-hexyl-, b.p. 206–210°/1 mm., n_D^{25} 1.6141, p.p. −4°; *n*-undecyl-, b.p. 219°/0.5 mm., n_D^{20} 1.5590, p.p. −32°. [d] Melting point.

nonyl derivatives which were prepared in kilogram quantities.

(d) *Viscosities of 4′-alkyl-m-terphenyls.* The following viscosity data were obtained: viscosity c.s. at 100°F., 210°F., and ASTM slope 100–210°F. For *n*-heptyl- 64.89, 6.18, 0.85; *n*-nonyl- 72.88, 6.70, 0.84; *n*-undecyl- 64.43, 7.62, 0.77; (1-amylhexyl)- 245.76, 10.13, 0.92; and (1-butylamyl)- 394.68, 11.76, 0.99.

Thermal stability tests. (a) *By heating in inert atmosphere.* A 5-g. sample of the 4′-alkyl-*m*-terphenyl was placed in a sample tube, and fitted with a condenser and receiver to collect any low boiling material which might be formed. The sample tube was evacuated, filled with nitrogen, and kept under a slight positive pressure of nitrogen for the duration of the test. The sample tube was heated in an Aroclor bath at 370° for 24 hr. The following 4′-alkyl-*m*-terphenyls were tested: *n*-hexyl-, *n*-heptyl-, (1-methylheptyl)-, *n*-dodecyl-, (1-methylhexadecyl)-, and (1-hexylheptyl)-. All samples showed slight darkening at the end of the heating period and respective weight losses as follows: 4.7%, 7.2%, 8.0%, 0.8%, 3.8%, and 8.7%.

(b) *By distilling at atmospheric pressure in air.* Small samples of selected 4′-alkyl-*m*-terphenyls were distilled in air at 630 mm. All samples showed some decomposition, which was particularly evident for compounds with more than seven carbon atoms in the alkyl group. On distilling 4′-heptyl-*m*-terphenyl, n_D^{25} 1.5905, the first distillate was obtained at 368° with the major portion distilling at 396–400°. The distillate was light yellow in color, n_D^{25} 1.5925, and had a slight odor similar to that usually associated with aliphatic olefins. On distilling 4′-*n*-dodecyl-*m*-terphenyl, a fraction boiling at 140–164° was collected. It had an "ali-

phatic olefin" odor. Infrared spectra analysis showed the presence of a compound with terminal C=C stretching. The residue distilled to 367°. Other derivatives tested included the following: *n*-hexyl-, (1-methylheptyl)-, and (1-hexylheptyl)-.

(c) *By measurement of vapor pressure.* Vapor pressures were determined by use of the isoteniscope.[10,11] The sample was placed in the isoteniscope and degassed at pressure of 1×10^{-4} mm. or less. In the Smith-Menzies-type isoteniscope, enough liquid was distilled to form a manometer in the capillary tube; this is, of course, unnecessary when using the Greene-type isoteniscope. The isoteniscope was heated in a furnace at a rate of ~2° per min. Vapor pressure measurements were made by observing the nitrogen pressure in the system which (1) for the Smith-Menzies-type is required to balance the liquid height in the two arms of the isoteniscope manometer, and (2) for the Greene-type is required to force the liquid from the capillary tube to a level equal with the surrounding liquid. The logarithm of the vapor pressure was plotted against the reciprocal of the absolute temperature for each vapor pressure determination. Through the resulting points, two straight lines could be drawn, the first through points representing lower temperatures at which the sample was undecomposed; and the second, of steeper slope, through points representing higher temperatures at which some decomposition products were present. The intersection of these lines is taken as the point of initial thermal decomposition. The following decomposition temperatures were obtained for 4′-alkyl-*m*-terphenyls: *n*-amyl- 278°, *n*-heptyl- 262°, (1-methylheptyl)- 276°, and (1-methylhexadecyl)- 310°.

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Notes

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Method for the Cleavage of Osmate Esters

JOHN S. BARAN

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Osmate esters obtained in the oxidation of alkenes with osmium tetroxide have been cleaved with reagents such as strong aqueous base and mannitol,[1] refluxing aqueous alcoholic sodium sulfite[2] or bisulfite,[3] and hydrogen sulfide.[4] This communication describes a method for the smooth transformation of osmate esters to *cis*-glycols under mild conditions which avoid the often troublesome separation of product from osmium or its inorganic derivatives.

In this modified technique an osmate ester which is prepared in pyridine is stirred at room temperature for 5 to 30 minutes with a solution of sodium bisulfite and aqueous pyridine. The clear orange solution which results contains the *cis*-glycol and a soluble osmium salt. Extraction of the aqueous pyridine solution with chloroform yields a colorless chloroform and pyridine solution which contains only the *cis*-glycol. By this method 3β-hydroxyandrost - 5 - en - 17 - one, 17 - vinyltestosterone, and ouabagenin tetraacetate have been oxidized to glycols in crude yields of 86, 72, and 81%, respectively.

EXPERIMENTAL

General procedure. A 3.9-mmol. sample of the alkene to be oxidized was dissolved in 15 ml. of pyridine and stirred with 1.0 g. (3.94 mmol.) of osmium tetroxide for an appropriate time. To this mixture was added with stirring a solution of 1.8 g. of sodium bisulfite, 30 ml. of water, and 20 ml. of pyridine. The ratio of sodium bisulfite, and water, and pyridine in the final mixture should be about 2:30:35. When a clear orange solution was obtained (5 to 30 min.), it was extracted thoroughly with chloroform. The chloroform extract was dried over potassium carbonate or sodium sulfate and evaporated to dryness *in vacuo* to yield the product.

3β,5α,6α-Trihydroxyandrostan-17-one.[5] A solution of 1.14 g. (3.9 mmol.) of 3β-hydroxyandrost-5-en-17-one, 1.0 g. (3.94 mmol.) of osmium tetroxide and 15 ml. of pyridine was stirred for 2 hr. The mixture was then stirred for 5 min. with a solution of 1.8 g. of sodium bisulfite, 30 ml. of water, and 20 ml. of pyridine. The orange solution which was obtained was extracted with one 150-ml. and two 50-ml. portions of chloroform. The combined organic extract was dried over potassium carbonate and evaporated to dryness *in vacuo*. The crude crystalline product was triturated with ethyl acetate, collected by filtration, and dried. It weighed 1.05 g. (86%) and melted at 240–243°.

17,20ε,21-Trihydroxy-17α-pregn-4-en-3-one.[6] A solution of 3 g. (9.65 mmol.) of 17-vinyltestosterone, 3.0 g. (11.8 mmol.) of osmium tetroxide and 60 ml. of pyridine was stirred in the dark for 20 hr. To the mixture was added with stirring a solution of 5.6 g. of sodium bisulfite, 90 ml. of water, and 45 ml. of pyridine. The solution was then extracted thoroughly with chloroform. The chloroform extract was washed with water, dilute hydrochloric acid, water, and aqueous sodium bicarbonate, dried over sodium sulfate, and evaporated to dryness *in vacuo*. Crystallization of the residue from methanol yielded 2.5 g. (72%) of product which melted at 186–193°.

1β,3β,5β,11α,14,19,20ε,22ε-Octahydroxycardanolide-1,3,11,-19-tetraacetate. A solution of 2.2 g. (3.25 mmol.) of ouabagenin-1,3,11,19-tetraacetate,[7] 1.0 g. (3.94 mmol.) of osmium tetroxide and 20 ml. of pyridine was stirred for 1 day. The mixture was then stirred for 30 min. with a solution of 1.8 g. of sodium bisulfite, 30 ml. of water, and 15 ml. of pyridine. The solution was extracted thoroughly with chloroform. The chloroform extract was washed with water, dilute hydrochloric acid, water, and aqueous sodium bicarbonate, dried over sodium sulfate, and evaporated to dryness *in vacuo*. Crystallization of the residue from ethyl acetate yielded a crude product which melted at 285–290° and weighed 1.7 g (81%). An analytical sample prepared by crystallization of the crude product from methanol melted at about 318°.

Anal. Calcd. for $C_{31}H_{44}O_{14}$: C, 58.11; H, 6.92. Found: C, 57.86; H, 7.07.

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Aliphatic Nitriles from Alkyl Chlorides

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The preparation of nitriles by the reaction of primary alkyl halides with alkali metal cyanides is an old and well known procedure. However, alkyl chlorides, except for benzyl- or allyl-type compounds, have not been used very frequently because of excessive reaction times required with the aqueous alcohol solvent usually used for this type reaction.[1] Other solvent systems, such as ethylene glycol monomethyl ether[2] or polyethylene glycol,[3]

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TABLE I

REACTION OF ALKYL CHLORIDES WITH SODIUM CYANIDE IN DMSO

	Reaction Time, Min.	Product	Yield, %	B.P., Mm.	n_D^{25}
1,2-Dichloroethane	20	Succinonitrile	56	114 (3.4)	—
1,3-Dichloropropane	30	Glutaronitrile	67	101–102 (1.5)	1.4339
1,4-Dichlorobutane	30	Adiponitrile	88	115 (0.7)	1.4369
1,5-Dichloropentane	30	Pimelonitrile	75	149 (1.0)	1.4398
1-Chlorobutane	20	Valeronitrile	93	139	1.3949
1-Chloropentane	20	Capronitrile	97	80 (48)	1.4050
1-Chlorohexane	20	Heptanenitrile	91	96–97 (50)	1.4125
1-Chlorodecane	20	Hendecanenitrile	94	87–88 (1.2)	1.4314
2-Chlorobutane	180	2-Cyanobutane	69	125–126	1.3873
2-Chlorooctane	60	2-Cyanooctane	70	88 (12)	1.4179

have recently been disclosed which permitted the use of primary chlorides in the preparation of nitriles in reasonable reaction times, but no mention has been made of the use of secondary chlorides.

It has now been found that both primary and secondary alkyl chlorides react with sodium cyanide in dimethyl sulfoxide solvent to give high yields of the corresponding nitrile in shorter reaction times than have been obtained with bromides or iodides in aqueous alcohol solvent. Both mono- and di-primary alkyl chlorides react in thirty minutes or less while secondary chlorides require one to 3 hours depending on the boiling point of the chloride. The yield of secondary nitrile by this method far exceeds the 25–30% yield generally given for the displacement of secondary halides by cyanide.[1] Table I shows the reaction times and the yields of nitriles from a number of representative chlorides.

EXPERIMENTAL

Starting materials. Dimethyl sulfoxide, obtained from the Stepan Chemical Co., was dried over calcium hydride before use. Reagent grade sodium cyanide was dried at 110° overnight and stored in a tightly stoppered bottle. Failure to dry the sodium cyanide sometimes caused the reaction mixtures to become very dark in color. The alkyl halides were all Eastman Kodak Co. White Label grade and were used as received.

Procedure for primary chlorides. Dry sodium cyanide (30 g.) was added to 150 ml. of dimethyl sulfoxide in a flask fitted with a stirrer, reflux condenser, dropping funnel, and thermometer. The thick slurry was heated on a steam bath to 90° and the steam bath was then removed. The halide (0.5 mol. of monochloride or 0.25 mol. of dichloride) was slowly added to the stirred mixture causing the temperature to increase immediately. The rate of addition was such that the temperature of the reaction did not go above about 160°. After all the halide was added (about 10 min.) the mixture was stirred for 10 min. more, or until the temperature dropped below 50°. In the preparation of mononitriles, the reaction mixture was then poured into water and the product extracted with chloroform or ethyl ether. The extract was washed several times with saturated sodium chloride solution, dried over calcium chloride, and the product distilled.

With the dinitriles a slightly different procedure was used due to their water solubility. After the reaction had cooled, 150 ml. of chloroform was added to the flask and this mixture was then poured into saturated salt solution. Enough water was added to dissolve precipitated salt and the chloroform layer was separated. The aqueous layer was extracted once with chloroform. The combined extracts were then washed twice with salt solution, dried, and distilled.

Secondary chlorides. With a low-boiling chloride such as 2-chlorobutane, a stirred slurry of 30 gm. of sodium cyanide in 150 ml. of dimethyl sulfoxide was heated to 90° with a heating mantle and 0.5 mol. of the chloride was slowly added over a period of 30 min. The temperature of the refluxing reaction mixture slowly increased as nitrile was formed. Refluxing continued as the temperature slowly rose to 150° after 3 hr. reaction time. The flask was then cooled and the reaction mixture worked up in the same way as for the primary nitriles. With 2-chlorooctane, the sodium cyanide–dimethyl sulfoxide slurry was heated to 130° and 0.5 mol. of the chloride added. The reaction mixture was maintained at 135–145° for 1 hr., then cooled, and the product isolated.

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Reactions of Ethyl Isobutenyl Ether

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The ready availability of ethyl isobutenyl ether[1] prompted our investigation of some of its reactions.

The acid-catalyzed addition of ethyl orthoformate[2] to ethyl isobutenyl ether gave dimethylmalonaldehyde tetraethyl acetal in good yield. Although the dimethylmalonaldehyde bis(2,4-dinitrophenylhydrazone) could be obtained in the usual manner from the acetal, repeated attempts to obtain the free aldehyde by hydrolysis failed; either the acetal was recovered or the hydrolytic cleavage products of the aldehyde, formic acid, and isobutyraldehyde were obtained.

The acid-catalyzed addition of diethyl acetals to ethyl isobutenyl ether occurred smoothly,

(1) (a) M. G. Voronkov, *J. Gen. Chem. U.S.S.R.*, (Eng. Transl.), **20**, 2060 (1950). (b) J. L. E. Erickson and M. Z. Woskow, *J. Org. Chem.*, **23**, 670 (1958).

(2) F. G. Young, U. S. Patent **2,556,312** (1949).

giving 1,1,3-triethoxy-2,2-dimethylalkanes in good yields. Because of the greater stability of ethyl isobutenyl ether, a much smaller excess of the acetal is required for optimum yields than when the vinyl ethers are used.[3] The 1,1,3-triethoxy-2,2-dimethylalkanes were easily hydrolyzed to the corresponding 3-ethoxy-2,2-dimethylalkanals which, in turn, were easily reduced to the 3-ethoxy-2,2-dimethyl-1-alkanols.

Ethyl isobutenyl ether underwent the Diels-Alder reaction with acrolein to give 2-ethoxy-3,4-dihydro-3,3-dimethyl-2H-pyran.[4]

Hydroformylation of ethyl isobutenyl ether gave two isomeric aldehydes. The major product was the expected 2-ethoxy-3-methylbutyraldehyde. The minor product was 4-ethoxy-3-methylbutyraldehyde, which must have arisen from a rearrangement of the double bond of the isobutenyl group.

EXPERIMENTAL

Ethyl isobutenyl ether. The method used was essentially that of Voronkov,[1a] except that phosphoric acid was used as the catalyst.[5] Distillation of isobutyraldehyde diethyl acetal (441 g., 3 mol.) from 0.2 g. of 85% phosphoric acid through a 1-ft. Vigreux column at a rate that maintained a head temperature of 72–84° (flask temperature 113–150°) gave 408.5 g. of distillate. The distillate was washed once with a 500-ml. portion and twice with 250-ml. portions of 0.5% aqueous potassium carbonate solution to remove the ethyl alcohol. The remaining organic phase was dried over potassium carbonate and distilled to give 252 g. (84%) of ethyl isobutenyl ether, b.p. 91–92°, n_D^{20} 1.4081 (lit.[1a] b.p. 94°, n_D^{20} 1.4053; lit.[1b] b.p. 92–94°, n_D^{25} 1.4060).

Dimethylmalonaldehyde tetraethyl acetal. Ethyl isobutenyl ether (150 g., 1.5 mol.) was added over a 1-hr. period to ethyl orthoformate (296 g., 2 mol.) containing 5 ml. of boron trifluoride etherate. The temperature was maintained at 20–25° by cooling. The mixture was stirred for an additional 1.5 hr. and the catalyst was then neutralized by addition of excess potassium carbonate solution. The organic phase was separated and distilled to give, after removal of unreacted starting materials, 268 g. (72%) of dimethylmalonaldehyde tetraethyl acetal, b.p. 52°/2 mm., n_D^{20} 1.4192, and 20 g. of residue.

Anal. Calcd. for $C_{13}H_{28}O_4$: C, 62.9; H, 11.4. Found: C, 62.9; H, 11.5.

The acetal gave the very insoluble bis(2,4-dinitrophenylhydrazone), which was recrystallized from acetone; m.p. 260–261°.

Anal. Calcd. for $C_{17}H_{16}N_8O_8$: C, 44.4; H, 3.5. Found: C, 44.3; H, 3.7.

Products from addition of isobutyraldehyde diethyl acetal to ethyl isobutenyl ether. A. Ethyl isobutenyl ether (140 g., 1.4 mol.) was added over a 2.5-hr. period to isobutyraldehyde diethyl acetal (307 g., 2.1 mol.) containing 1.5 ml. of boron trifluoride etherate at 35–40°. Stirring was continued for 1 hr., and the catalyst was then neutralized by addition of excess potassium carbonate solution. The organic phase was separated and distilled to give, after removal of unused starting materials, 218 g. (63.5%) of 1,1,3-triethoxy-2,2,4-trimethylpentane, b.p. 53–54°/0.5–1 mm., n_D^{20} 1.4259.

Anal. Calcd. for $C_{14}H_{30}O_3$: C, 68.3; H, 12.3. Found: C, 68.1; H, 12.0.

B. A solution of 24 ml. of concentrated sulfuric acid in 1 l. of water was stirred for 16 hr. with 1,1,3-triethoxy-2,2,4-trimethylpentane (360 g., 1.46 mol.) at room temperature. The organic phase was taken up in ether and distilled to give 232.5 g. (92.5%) of 3-ethoxy-2,2,4-trimethylvaleraldehyde, b.p 66–67°/7.5 mm., n_D^{20} 1.4262.

Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.7; H, 11.7. Found: C, 69.4; H, 11.7.

The 2,4-dinitrophenylhydrazone melted at 102–103°.

Anal. Calcd. for $C_{16}H_{24}N_4O_5$: C, 54.5; H, 6.9. Found: C, 54.4; H, 6.9.

C. Hydrogenation of the 3-ethoxy-2,2,4-trimethylvaleraldehyde over Raney nickel at 125° and 100 atm. gave 3-ethoxy-2,2,4-trimethyl-1-pentanol, b.p. 47–48°/0.5 mm., n_D^{20} 1.4370, in 92% yield.

Anal. Calcd. for $C_{10}H_{22}O_2$: C, 68.9; H, 12.7. Found: C, 69.1; H, 12.6.

Products from addition of acetaldehyde diethyl acetal to ethyl isobutenyl ether. A. In a manner similar to that described above, acetaldehyde diethyl acetal and ethyl isobutenyl ether gave 1,1,3-triethoxy-2,2-dimethylbutane, b.p. 77°/7 mm., n_D^{20} 1.4182, in 76% yield.

Anal. Calcd. for $C_{12}H_{26}O_3$: C, 66.0; H, 12.0. Found: C, 65.8; H, 11.9.

B. 3-Ethoxy-2,2-dimethylbutyraldehyde, b.p. 62–64°/23 mm., n_D^{20} 1.4133, was obtained in 87% yield.

Anal. Calcd. for $C_8H_{16}O_2$: C, 66.6; H, 11.2. Found: C, 66.5; H, 11.2.

The 2,4-dinitrophenylhydrazone melted at 116–118°.

Anal. Calcd. for $C_{14}H_{20}N_4O_5$: C, 51.8; H, 6.2. Found: C, 51.6; H, 6.3.

C. 3-Ethoxy-2,2-dimethyl-1-butanol, b.p. 128–130°/160 mm., n_D^{20} 1.4262, was obtained in 90% yield.

Anal. Calcd. for $C_8H_{18}O_2$: C, 65.7; H, 12.4. Found: C, 65.9; H, 12.5.

Products from addition of benzaldehyde diethyl acetal to ethyl isobutenyl ether. A. 1,1,3-Triethoxy-2,2-dimethyl-3-phenylpropane, b.p. 89–91°/0.5 mm., n_D^{20} 1.4770, was obtained in 77% yield using a 1:1 ratio of acetal to ether.

Anal. Calcd. for $C_{17}H_{28}O_3$: C, 72.8; H, 10.1. Found: C, 72.9; H, 10.0.

B. 3-Ethoxy-2,2-dimethylhydrocinnamaldehyde, b.p. 64°/0.5 mm., n_D^{20} 1.4950, was obtained in 92% yield.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.7; H, 8.8. Found: C, 75.6; H, 8.8.

The 2,4-dinitrophenylhydrazone melted at 134°.

Anal. Calcd. for $C_{19}H_{22}N_4O_5$: C, 59.1; H, 5.7. Found: C, 59.3; H, 5.9.

C. 3-Ethoxy-2,2-dimethyl-3-phenyl-1-propanol, b.p. 88°/1.3–1.4 mm., n_D^{20} 1.5022, was obtained in 89% yield.

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 75.0; H, 9.7. Found: C, 75.5; H, 9.8.

2-Ethoxy-3,4-dihydro-3,3-dimethyl-2H-pyran. A mixture of ethyl isobutenyl ether (252 g., 2.52 mol.) and acrolein (168 g., 3 mol.) containing 0.2 g. of hydroquinone was heated for 3 hr. at 180° in an autoclave. Distillation of the reaction mixture gave, after removal of unreacted starting materials and a small amount of acrolein dimer, 212 g. (54%) of 2-ethoxy-3,4-dihydro-3,3-dimethyl-2H-pyran, b.p. 158°, n_D^{20} 1.4344.

Anal. Calcd. for $C_9H_{16}O_2$: C, 69.2; H, 10.3. Found: C, 69.3; H, 10.2.

The dihydropyran gave, by the usual procedure, the bis(2,4-dinitrophenylhydrazone) of 2,2-dimethylglutaraldehyde, m.p. 237–239°.

Anal. Calcd. for $C_{19}H_{20}N_8O_8$: C, 46.7; H, 4.1. Found: C, 46.6; H, 4.1.

Hydroformylation of ethyl isobutenyl ether. A mixture of ethyl isobutenyl ether (136 g., 1.36 mol.) in 500 ml. of benzene and 10 g. of cobalt carbonyl was placed in an autoclave. Hydrogen was admitted to the autoclave to a pressure of 30 atm., and then hydrogen–carbon monoxide was admitted to a pressure of 100 atm. The temperature was raised to 130° and held for 1 hr. The reaction mixture was

(3) R. I. Hoaglin and R. Hirsch, *J. Am. Chem. Soc.*, **71**, 3468 (1949); U. S. Patent **2,564,760** (1957).

(4) R. I. Longley, Jr., and W. S. Emerson, *J. Am. Chem. Soc.*, **72**, 3079 (1950).

(5) A. Duhamel, *Bull. soc. chim. France*, 156 (1956).

then steam-distilled. The organic phase was separated and then fractionated. Two well defined fractions were obtained. The first fraction (46 g., 27%), b.p. 137–138°, n_D^{20} 1.4029, was 2-ethoxy-3-methylbutyraldehyde.

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.6; H, 10.8. Found: C, 64.8; H, 10.9.

The 2,4-dinitrophenylhydrazone melted at 125–126°.

Anal. Calcd. for $C_{13}H_{18}N_4O_5$: C, 50.3; H, 5.8. Found: C, 50.1; H, 5.8.

The second fraction (21 g., 12%), b.p. 160–162°, n_D^{20} 1.4132, was 4-ethoxy-3-methylbutyraldehyde.

Anal. Calcd. for $C_7H_{14}O_2$: C, 64.6; H, 10.8. Found: C, 64.9; H, 10.9.

The 2,4-dinitrophenylhydrazone, m.p. 48–50°, was very soluble and therefore difficult to purify.

Anal. Calcd. for $C_{13}H_{18}N_4O_5$: C, 50.3; H, 5.8. Found: C, 49.7; H, 6.1.

The structures of the two aldehydes were assigned on the basis of their nuclear magnetic resonance spectra. These spectra were in full agreement with the assigned structures and preclude the other possible isomer, ethoxypivalaldehyde.

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Studies of Configuration. VI. *cis*- and *trans*-4-Methoxycyclohexanol[1,2]

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The isomeric mixture of the 4-methoxycyclohexanols is well known, having been prepared frequently by hydrogenation of hydroquinone monomethyl ether.[3] However, there are only three reports concerning individual isomers. In 1941, Ruggli, Leupin, and Businger[4] reported that 4-methoxycyclohexyl tosylate could be separated into a solid, m.p. 87°, and a liquid. They suggested the *trans*-configuration for the solid 4-methoxycyclohexaneacetic acid prepared by treatment of the tosylate with sodio diethylmalonate, but made no assignment to the 4-methoxycyclohexyl tosylate.

Almost simultaneously with our preliminary report on the solvolysis of the *cis*- and *trans*-4-methoxycyclohexyl tosylates, Henbest and Nichols[5] reported the 3,5-dinitrobenzoate of the *trans*-isomer.

We have reported the separation of the isomers through the acid phthalates and a preliminary correlation of the configuration with the known 1,4-dihydroxycyclohexane by partial methylation. In view of the very interesting behavior of the two isomers, it seemed essential to present a definitive proof of configuration. Such is the purpose of the present report.

The known *cis*-4-hydroxycyclohexanecarboxylic acid[6] (I) was converted by methylation with methyl iodide and silver oxide following the procedure used by Noyce and Denney[7] to methyl *cis*-4-methoxycyclohexanecarboxylate (II). Ample evidence is available to show that this reaction proceeds without jeopardizing the stereochemical integrity of the system. The ester II was hydrolyzed to *cis*-4-methoxycyclohexanecarboxylic acid (III), m.p. 54.5–55.7°. This material was shown to be identical, by mixed melting point and comparison of infrared spectra, with the isomer of 4-methoxycyclohexanecarboxylic acid assigned the *cis*-configuration by Noyce and Weingarten.[8] Thus, confirmation of the previous assignment on the basis of rearrangement behavior is obtained.

Treatment of *cis*-4-methoxycyclohexanecarboxylic acid with methyllithium afforded the ketone *cis*-4-methoxy-1-acetylcyclohexane (IV). This reaction has been shown by Dauben and Hoerger[9] to proceed without any inversion or epimerization adjacent to the carbonyl group. Treatment of the ketone with perbenzoic acid afforded *cis*-4-methoxycyclohexylacetate (V), a reaction shown to proceed with retention of configuration by Turner.[10] Hydrolysis of the acetate afforded *cis*-4-methoxycyclohexanol (VI), which was characterized by infrared spectra and preparation of derivatives. Each of the steps proceeded in satisfactory yield.

The second method which was used was the partial methylation of the known *trans*-1,4-dihydroxycyclohexane.[11] Unfortunately, the yield of the monomethyl ether was low (10%) and the more definitive sequence above was carried through.

The chemical transformations are summarized in Chart I, and the properties of derivatives of *cis*- and *trans*-4-methoxycyclohexanol are given in Table I.

(1) A portion of this work has been published in preliminary form [D. S. Noyce and B. R. Thomas, *J. Am. Chem. Soc.*, **79**, 755 (1957)].

(2) Supported in part by the National Science Foundation (G-2387).

(3) For recent examples, see F. Hunziker, F. X. Mullner, and H. Schaltegger, *Helv. Chim. Acta*, **38**, 1943 (1955); D. Papa, F. J. Villani, and H. F. Ginsberg, *J. Am. Chem. Soc.*, **76**, 4446 (1954).

(4) P. Ruggli, O. Leupin, and A. Businger, *Helv. Chim. Acta*, **24**, 339 (1941).

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Chart I

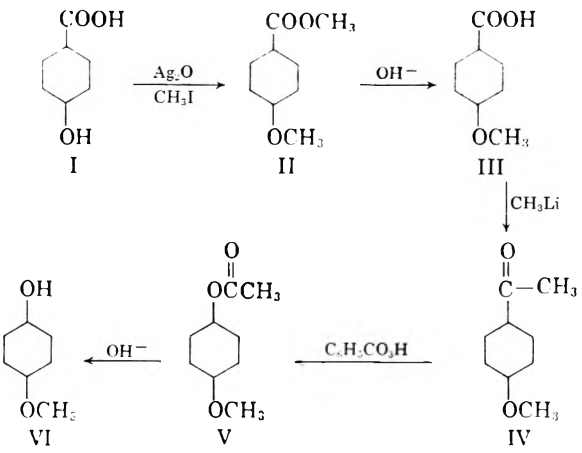

TABLE I

MELTING POINTS OF 4-METHOXYCYCLOHEXANOL DERIVATIVES

	M.P., °C.	
	cis-	*trans-*
3,5-Dinitrobenzoate	116.2–116.5	125.5–126.5
p-Toluene sulfonate	87.8–88.2	66.4–67.2
Acid phthalate	61–65	148.6–149.0

It is to be noted that the tosylate of the *cis*-isomer is the higher melting of the pair.

Another very interesting observation made during the course of this work is that the lithium aluminum hydroxide reduction of 4-methoxycyclohexanone affords 70% of the *cis*-isomer. Further study is in progress in this area.

EXPERIMENTAL[12]

cis-4-Hydroxycyclohexanecarboxylic acid (I). *p*-Hydroxybenzoic acid in acetic acid was hydrogenated over 5% rhodium-on-alumina at an initial hydrogen pressure of 45 p.s.i. After removal of the catalyst by filtration, the remaining solution was distilled at atmospheric pressure to afford a main fraction b.p. 235–245°. This fraction was redistilled to afford the lactone of *cis*-4-hydroxycyclohexanecarboxylic acid, b.p. 120–123° (11 mm.). Crystallization from benzene-pentane afforded the pure lactone, m.p. 127.2–128.0° (lit.[6] 126–128°).

The lactone was dissolved in a minimum amount of water and heated on a steam bath. The *cis*-4-hydroxycyclohexanecarboxylic acid (I) obtained by continuous ether extraction was crystallized from acetonitrile, m.p. 150.1–151.2° (lit.[6] 152°).

Methyl cis-4-methoxycyclohexanecarboxylate (II) was prepared by the procedure of Noyce and Fessenden[13] from 4.0 g. of *cis*-4-hydroxycyclohexanecarboxylic acid, 50 g. of freshly prepared silver oxide (anhydrous), and 150 ml. of methyl iodide. The crude ester was fractionally distilled at reduced pressure to afford 2.8 g. (58%) of methyl *cis*-4-methoxycyclohexanecarboxylate, II, b.p. 99–99.5° (10.5 mm.), n_D^{22} 1.4503.

cis-4-Methoxycyclohexanecarboxylic acid (III). The ester (2.35 g.) was heated under reflux with 15 ml. of water and 50 ml. of aqueous 1*N* sodium hydroxide for 3 hr. The acidified solution was continuously extracted with ether. The dried ether extracts were concentrated, and the residue crystallized from pentane (charcoal). The *cis*-4-methoxycyclohexanecarboxylic acid obtained had a m.p. 54.5–55.7° and weighed 1.33 g. (62%). When mixed with a sample of *cis*-4-methoxycyclohexanecarboxylic acid, m.p. 54.8–55.8°, prepared by Noyce and Weingarten,[8] the m.p. was 54.5–55.7°.

cis-4-Methoxy-1-acetylcyclohexane (IV). To a solution of 9.5 g. of *cis*-4-methoxycyclohexanecarboxylic acid in anhydrous ether was added dropwise 300 ml. of a freshly prepared 0.52 molar methyllithium solution in anhydrous ether.[14] After addition was complete, the cloudy solution was stirred for an additional 20 min., and then poured onto 100 g. of ice. The crude ketone was distilled to afford 6.4 g. (69%) of *cis*-4-methoxy-1-acetylcyclohexane, b.p. 99–102° (12 mm.), n_D^{27} 1.4576.

The dinitrophenylhydrazone was prepared in aqueous ethanol and crystallized from 50% ethanol, m.p. 104.2–105.4°.

Anal. Calcd. for $C_{15}H_{20}O_5N_4$: C, 53.56; H, 5.98; N, 16.73. Found: C, 53.7; H, 5.95; N, 16.70.

Conversion of cis-4-methoxy-1-acetylcyclohexane to cis-4-methoxycyclohexyl acetate (V). *cis*-4-Methoxy-1-acetylcyclohexane, 5.3 g., was treated with a 50% excess of freshly prepared perbenzoic acid in chloroform,[15] and allowed to stand at room temperature for 14 days. The solution was diluted with ether, washed with dilute sodium hydroxide and water, and dried over magnesium sulfate. Fractionation afforded *cis*-4-methoxycyclohexyl acetate (V), b.p. 98–100° (12.5 mm.) n_D^{28} 1.4438. The yield was 3.0 g. (52%).

cis-4-Methoxycyclohexanol (VI). Hydrolysis of V, 3.0 g., with 1*N* sodium hydroxide was followed by continuous extraction with ether. Fractionation of the dried ether extract afforded 1.3 g. (57%) of *cis*-4-methoxycyclohexanol, b.p. 98–99° (11 mm.) n_D^{27} 1.4641.

cis-4-Methoxycyclohexyl 3,5-dinitrobenzoate was prepared in the usual manner and crystallized from hexane, m.p. 115.6–116.2°.

Separation of isomers of 4-methoxycyclohexanol. 4-Methoxycyclohexyl hydrogen phthalate was fractionally crystallized from benzene. Three crystallizations afforded the *trans*-4-methoxycyclohexyl hydrogen phthalate, m.p. 148.6–149.0°.

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.71; H, 6.49.

From the mother liquors a low melting form, m.p. 61–65°, was obtained, which subsequent investigation showed to be primarily *cis*-4-methoxycyclohexyl hydrogen phthalate.

Anal. Found: C, 64.66; H, 6.45.

The *p-toluenesulfonates* were prepared in the usual manner, m.p. *cis*-, 87.8–88.2°; *trans*-, 66.4–67.2°. The *p*-toluenesulfonates may also be separated by fractional crystallization of the mixed isomers from petroleum ether.

Anal. Calcd. for $C_{14}H_{20}O_4S$: C, 59.13; H, 7.09; S, 11.27. Found (*cis*-): C, 59.25; H, 7.18; S, 11.16. Found (*trans*-): C, 59.03; H, 7.13; S, 11.18.

The 3,5-dinitrobenzoates were prepared in the usual manner from the regenerated alcohol. *cis-4-Methoxycyclohexyl 3,5-dinitrobenzoate* was crystallized from hexane, m.p. 116.2–116.5°. *trans-4-Methoxycyclohexol 3,5-dinitrobenzoate* was crystallized from methanol, m.p. 125.5–126.5°.

Anal. Calcd. for $C_{14}H_{16}O_7N_2$: C, 51.85; H, 4.95; N, 8.64. Found (*cis*-): C, 52.03; H, 4.73; N, 8.65. Found (*trans*-): C, 51.61; H, 4.93; N, 8.79.

trans-4-Methoxycyclohexanol from trans-1,4-cyclohexanediol. Treatment of 5 g. of *trans*-1,4-cyclohexanediol with an eightfold excess of methyl iodide and silver oxide using methanol as a solvent afforded 0.6 g. (10%) of *trans*-4-

(12) Melting points are corrected; boiling points are uncorrected. Analyses are by the Microanalytical Laboratory of the University of California.

(13) D. S. Noyce and J. S. Fessenden, *J. Org. Chem.*, **24**, 715 (1959).

(14) D. A. Van Dorp and J. A. Arens, *Rec. trav. chim.*, **65**, 338 (1946).

(15) G. Braun, *Org. Syntheses*, **Coll. Vol. I**, 431 (1941).

methoxycyclohexanol (VII), b.p. 90–95° (10 mm.) n_D^{25} 1.4650.

The distillation residue afforded 2 g. of recovered *trans*-1,4-cyclohexanediol on crystallization from acetone, m.p. 141–142°.

The *p*-toluene sulfonate and 3,5-dinitrobenzoate of VII were prepared, m.p. 65–66° and 126–127°, respectively.

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Conformational Analysis. VII. The Dipole Moment of 2-Bromocyclooctanone[1,2]

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Recently a conformational analysis of the 2-bromocyclooctanone molecule (I) was reported.[3] This molecule was predicted to exist as a mixture of the five conformational species III–VI[4] depicted in Fig. 1. (There are two species having the gross geometry of III which differ in dihedral angle.) The percentage compositions of the equilibrium mixtures of III–VI (see Table I) in the solvents *n*-heptane benzene, and dioxane were calculated from theoretical considerations and these values predicted rather small changes in the position of the conformational equilibrium with respect to the effective dielectric constant of the medium. A small influence of solvent upon the equilibrium composition was detected by experimental measurements of the absorption intensities of the infrared and ultraviolet carbonyl absorption maxima of I in various media and these spectral data were qualitatively consistent with the theoretical predictions. The exact extent of the agreement between theory and experiment was somewhat obscured, however, by the fact that at present there is no theory available which could be used to quantitatively predict the results of the spectral measurements. On the other hand, the determination of the dipole moment of I in benzene solution did provide an accurate physical measurement which could be directly compared to a calculated value. The experimental value of 3.36 D was in excellent agreement with the predicted dipole moment of 3.28 D for the compound in this solvent.

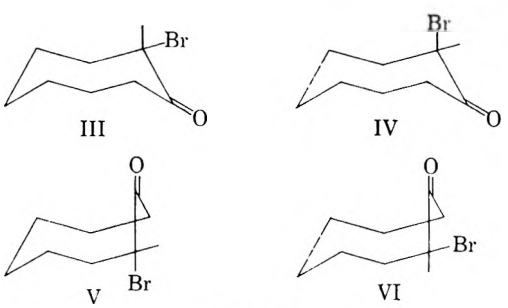

Figure 1

TABLE I

CALCULATED PERCENTAGE CONFORMATIONAL ISOMER COMPOSITION OF 2-BROMOCYCLOOCTANONE

Conformational Isomer	Dihedral Angle	Solvent (D_{effco}) *n*-Heptane (4.83)	Benzene (6.44)	Dioxane (10.3)
IIIa	40°	16	19	22
IIIb	63°	26	27	28
IV	166°	2	1	1
V	132°	47	41	34
VI	12°	9	12	15

The present study was undertaken to extend the dipole moment data for 2-bromocyclooctanone to the solvents *n*-heptane and dioxane and thus to provide a more extensive experimental test of the theoretical analysis. The dipole moments of I were obtained from dielectric constant measurements and had the values 3.29 D and 3.42 D in the solvents *n*-heptane and dioxane, respectively. These values, along with the experimental dipole moment of I in benzene solution and the dipole moments calculated from the estimated compositions for each solvent of Table I, are listed in Table II.

TABLE II

DIPOLE MOMENT OF 2-BROMOCYCLOOCTANONE AT 25°

Solvent	μ Calcd.	μ Observed
n-Heptane	3.13	3.29
Benzene	3.28	3.36
Dioxane	3.41	3.42

The qualitative prediction that only small changes in the conformational composition of the equilibrium mixture of IIIa–VI would result from the changing effective dielectric constant is substantiated by the small differences observed between the magnitudes of the dipole moment in each solvent. The deviations between the calculated and observed moments as the solvent is varied appear to be systematic, but are certainly as small as could be hoped for. The variation of the dipole moment of 2-bromocyclooctanone with solvent is to be compared with the similar corresponding changes in the moment of 2-bromocyclohexanone.[5]

(1) Sponsored by the Office of Ordnance Research, U. S. Army.

(2) Paper VI, *J. Org. Chem.*, **25**, in press (1959).

(3) J. Allinger and N. L. Allinger, *J. Am. Chem. Soc.*, **81**, 5736 (1959).

(4) For reference, the numbers assigned to these isomers in Paper V (ref. 3) have been retained herein.

(5) The dipole moments of 2-bromocyclohexanone in *n*-heptane, benzene, and dioxane, respectively, are 3.37, 3.50, and 3.64 D. [W. D. Kumler and A. C. Huitric, *J. Am. Chem. Soc.*, **78**, 3369 (1956)].

EXPERIMENTAL

The *n*-heptane solvent was freed from olefinic contaminant by passage through a silica gel chromatographic column and then dried by distillation from sodium metal. The dioxane solvent was purified according to the method of Fieser.[6]

Dipole moment study. The dipole moment of 2-bromocyclooctanone in *n*-heptane and dioxane solution was determined at 25°. The data were treated by the method of Halverstadt and Kumler,[7] and the actual calculations were performed by applying automatic computing methods with an IBM 650 computer as described earlier.[8]

The molar refractivity was calculated from standard values of atomic refractivities[9] and had the value 44.720 cc. Atomic polarization was neglected. The data are summarized in Table III.

TABLE III

DIPOLE MOMENT DATA FOR 2-BROMOCYCLOOCTANONE AT 25°

N_2	d_{12}	ϵ_{12}
Dioxane Solvent		
0.0071283	1.031228	2.3191
0.0041682	1.029428	2.2697
0.0027629	1.028583	2.2465
0.0016669	1.027949	2.2283
0.0008651	1.027463	2.2143
0.0000000	1.026897	2.2013
α = 16.5874 β = 0.6039 ϵ_1 = 2.2007		
d_1 = 1.026921 $P_{2\infty}$ = 284.60 μ = 3.426D		
n-Heptane Solvent		
0.0079180	0.683125	1.9706
0.0059871	0.681701	1.9547
0.0041774	0.680434	1.9409
0.0024350	0.679182	1.9261
0.0012521	0.678316	1.9174
0.0000000	0.677423	1.9069
α = 8.0093 β = 0.7188 ϵ_1 = 1.9070		
d_1 = 0.677422 $P_{2\infty}$ = 266.67 μ = 3.295D		

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N-Bromocaprolactam

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In the course of investigating the halogenation of caprolactam we had occasion to prepare the heretofore unknown *N*-bromocaprolactam. We have found that *N*-bromocaprolactam is useful as a brominating agent in much the same manner as *N*-bromosuccinimide,[1] *N*-bromophthalimide[2] and *N*-bromo-5,5-dimethylhydantoin.[3] We have also found that the new *N*-bromo derivative functions in many instances as an oxidizing agent in the same manner as *N*-bromoacetamide.[4] Whereas the known *N*-bromo-derivatives usually require a peroxide catalyst and/or actinic light to initiate bromination, *N*-bromocaprolactam can be employed without the aid of a catalyst.

The *N*-bromocaprolactam can be prepared following the procedure of Oliveto[5] for the synthesis of *N*-bromoacetamide. However, the product obtained by this method is usually difficult to crystallize, and in most cases can be purified only after several recrystallizations from water. We have found that a relatively pure *N*-bromocaprolactam can be obtained by a modified procedure, which involves adding liquid bromine to an aqueous solution of caprolactam followed by the addition of 50% aqueous potassium or sodium hydroxide until the bromine color is discharged, and treating the resultant solution with common salt to precipitate the *N*-bromocaprolactam, which after several ice water washes, melts at 64–66°.

EXPERIMENTAL

N-Bromocaprolactam. Into a flask equipped with an agitator, thermometer, and dropping funnel was placed a mixture of 271.2 g. (2.4 mol.) of caprolactam and 90 ml. of water. The reaction mixture was cooled to about 0° by an ice-salt bath, following which 320 g. (2.0 mol.) of liquid bromine was added dropwise over a 30-min. period. After the addition was complete, 270 ml. of a 50% aqueous potassium hydroxide solution (previously cooled to 10°) was added dropwise maintaining the temperature of the reaction mixture below 10° throughout the addition. The resultant yellow solution was stirred at ice temperatures for an additional 2 hr., following which 80 g. of sodium chloride was added, effecting precipitation of the *N*-bromocaprolactam. The product was filtered, washed thoroughly with ice water, and dried at room temperature *in vacuo*. There was obtained 288 g. (75%) of *N*-bromocaprolactam; m.p. 64–66°.

Anal. Calcd. for $C_6H_{10}NOBr$: Br, 41.6; N, 7.3. Found: Br, 41.2; N, 7.0.

4-Bromoacetanilide. Into a flask equipped with an agitator and reflux condenser was placed a solution of 13.5 g. (0.1 mol.) of acetanilide in 100 ml. of chloroform. Then while stirring, 19.2 g. (0.1 mol.) of *N*-bromocaprolactam was added all at once. After a short induction period (*ca.* 15 min.), the reaction mixture began to reflux, after which the solution was stirred at room temperature for 2 hr. The solid residue obtained after evaporating the solvent was washed with cold water to remove the caprolactam formed during

(1) K. Ziegler, W. Schumann, and E. Winkelmann, *Ann.*, **551**, 120 (1942).

(2) A. Wohl and K. Jaschinowski, *Ber.*, **54**, 476 (1921).

(3) J. F. Salellas and O. O. Orazi, *Anales asoc. quim. argentina*, **39**, 175–183 (1951).

(4) A. Wohl, *Ber.*, **52**, 51 (1919).

(5) E. P. Oliveto and C. Gerold, *Org. Syntheses*, **31**, 17 (1951).

the reaction. There was obtained 18 g. (84%) of 4-bromoacetanilide; m.p. 165°; lit.[6a] 167°.

5-Bromoisatin. A suspension of 16.2 g. (0.11 mol.) of isatin in 100 ml. of carbon tetrachloride was treated with 21.2 g. (0.11 mol.) of *N*-bromocaprolactam. The reaction mixture was heated to reflux to initiate bromination, following which it was stirred at room temperature overnight. The insoluble product was filtered, washed with carbon tetrachloride to insure the removal of residual caprolactam, and finally dried. There was obtained 19 g. (77%) of 5-bromoisatin; m.p. 254–256°; lit.[7] m.p. 255–256°.

Cyclohexanone. Into a flask equipped with a stirrer and reflux condenser were placed 5 g. (0.05 mol.) cyclohexanol, 75 ml. benzene, and 10 ml. pyridine. While agitating, 9.6 g. (0.05 mol.) of *N*-bromocaprolactam was added all at once. After a short induction period (*ca.* 15 min.), an exothermic reaction occurred, causing the benzene to reflux. The mixture was then allowed to stir without further application of heat for 18 hr. The solid pyridine hydrobromide was filtered. The filtrate was washed with a dilute aqueous solution of sodium hydrosulfite to decompose any unreacted *N*-bromocaprolactam, following which the organic layer was washed successively with two 50-ml. portions of 2*N* sulfuric acid, two 50-ml. portions of distilled water, and finally dried over anhydrous sodium sulfate. After removing the benzene by distillation, there was obtained 4 g. (82%) of cyclohexanone. The ketone was identified by converting it to its 2,4-dinitrophenylhydrazone; m.p. 159°; lit.[6b] 162°.

Benzophenone. To a solution of 9.2 g. (0.05 mol.) of benzhydrol in 75 ml. of benzene was added 10 ml. of pyridine, following which 9.6 g. (0.05 mol.) of *N*-bromocaprolactam was added all at once. The solution was refluxed for 1 hr. to initiate the reaction, following which the mixture was stirred at room temperature for 18 hr.

The product was isolated as in the previous experiment. There was obtained 8 g. (88%) of benzophenone; 2,4-dinitrophenylhydrazone; m.p. 239–240°; lit.[6c] 239°.

Acknowledgment. The authors are indebted to Mr. M. D. Edelman for his helpful suggestions during the course of this investigation.

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(6) R. L. Shriner and R. C. Fuson, *The Systematic Identification of Organic Compounds*, J. Wiley and Sons, Inc., New York, 1948, (a) p. 232, (b) p. 262, (c) p. 264.

(7) Ng. Ph. Buu-Hoï, *Rec. trav. chim.*, **73**, 197–202 (1954).

Oxidation of Hindered Phenols. Preparation of Bis(1,3,5-tri-*t*-butyl-2,5-cyclohexadiene-4-one) Peroxide

HARRY S. BLANCHARD

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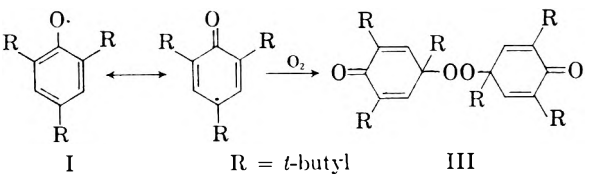
Cook and Woodworth[1] have reported the quantitative preparation of the stable 2,4,6-tri-butylphenoxy radical (I) by oxidation of 2,4,6-tri-*t*-butylphenol (II) with alkaline ferricyanide. Moreover, they found that I could be converted to bis-(1,3,5-tri-*t*-butyl-2,5-cyclohexadiene-4-one) peroxide (III) if the oxidation of II were carried out in the presence of air or oxygen. In this manner they were able to prepare III in a crude yield of 81% utilizing a reaction time of a few hours. We have found that III can be prepared quickly in a state of high purity and in essentially quantitative yield by oxidizing II with silver oxide in the presence of oxygen. Interestingly enough, although the yield of III is nearly quantitative, the solutions never absorb the theoretical amount of oxygen. Thus, in a typical experiment, when 0.01 mol. of II was oxidized in 100 ml. of benzene with 0.022 mole of silver oxide, 0.0035 mol. of oxygen was absorbed. This corresponds to only 70% of the theoretical quantity of oxygen, although 0.0049 mol. (98%) of III was isolated. This finding suggests that some of the oxygen which ultimately ends up in the peroxide must come directly from the silver oxide.



I R = *t*-butyl III

Silver oxide is known to undergo a rather facile thermal decomposition to silver metal and oxygen although the reaction is very slow below 160°.[2] However, as the decomposition is catalyzed by light as well as by silver metal itself, it is perhaps not unreasonable that some of the oxygen does come from the oxide. Moreover, as silver metal is a catalyst for the decomposition, it may not be unreasonable to suggest that I can also function as a catalyst for this decomposition. In this connection, Witsiepe[3] has recently investigated the use of silver oxide in preparing stable phenoxy radicals, including I. He found that II could be converted quantitatively to I only when freshly prepared silver oxide was employed under rather special conditions. Most of the present work was carried out utilizing a sample of commercial silver oxide. However, the same results were also obtained when we employed a sample of silver oxide freshly prepared according to Witsiepe's directions. In view of these results we would suggest that silver oxide is a poor choice as a reagent when the object is to prepare I itself. Along these same lines Müller and co-workers[4] found that when II was oxidized with lead dioxide, the yield of I was not quantitative, apparently because of reaction of I with the lead dioxide. In view of the present results it would seem likely that here too there is a direct reaction

(1) C. D. Cook and R. C. Woodworth, *J. Am. Chem. Soc.*, **75**, 6242 (1953).

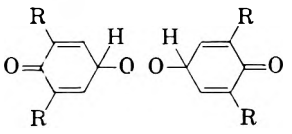
(2) H. Remy, "Treatise on Inorganic Chemistry," Elsevier Publishing Co., New York, 1956, p. 398.

(3) W. K. Witsiepe, *The Effect of t-Butyl Groups and Phenyl Groups on the Dissociation of Phenoxy Radicals*, University Microfilms, Publication No. 20,540, Ann Arbor, Michigan, 1956, pp. 61–65.

(4) E. Müller, K. Ley, and W. Keidaisch, *Ber.*, **87**, 1605 (1954).

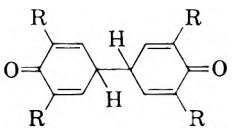
between I and lead dioxide probably resulting in III.

As we were also interested in obtaining bis(1-hydro-3,5-di-*t*-butyl-2,5-cyclohexadiene-4-one) peroxide (IV), we briefly examined the oxidation of 2,6-di-*t*-butylphenol (V) with silver oxide and also with alkaline potassium ferricyanide. Recently



IV R = *tert*-butyl

Kharash and Joshi[5] oxidized V with alkaline ferricyanide in the absence of air and isolated 3,5,3′,5′-tetra-*t*-butyl-1,1′-dihydro-2,5,2′,5′-biscyclohexadiene-4,4′-dione (VI), along with the known of 2,6,-2′,6′-tetra-*t*-butyldiphenoquinone. This interesting keto tautomer was reported by Kharasch and



VI R = *t*-butyl

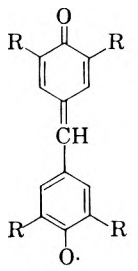
Joshi to be stable in non-polar solvents, but to tautomerize immediately to the bisphenol in hydroxylic solvents such as alcohols.

We found that V is oxidized by silver oxide to essentially the same mixture as reported by Kharasch and Joshi. Moreover, this same mixture results even when the oxidation is run in the presence of oxygen. We could find no evidence for a reaction between the phenoxy radical intermediates and oxygen. Further, we were somewhat surprised by the fact that VI itself did not react directly with oxygen yielding the corresponding diphenoquinone, particularly in the presence of the silver oxide.

As VI rearranges to the corresponding bisphenol in polar solvents, it seemed of interest to examine the oxidation in methanol and ethanol. Here we found, as expected, that a good yield of the tetra-*t*-butyldiphenoquinone resulted, apparently via the rearrangement of VI to the bisphenol and further oxidation of this to the diphenoquinone.

Because we were unable to prepare IV via the silver oxide route, it seemed of interest to oxidize V under Kharasch's and Joshi's conditions, except in the presence of oxygen. To this end we oxidized V with alkaline potassium ferricyanide in the presence of oxygen. However, as in the silver oxide oxidations oxygen had no effect on this reaction, and the same mixture of VI and the tetra-*t*-butyldiphenoquinone was obtained in the presence as well as in the absence of oxygen.

Recently, Müller and co-workers[6] presented convincing evidence that the oxidative coupling of V proceeds via the corresponding phenoxy radical. In view of this it seems somewhat surprising that oxygen is such an inefficient scavenger for these radicals. By way of comparison, carbon radicals are scavenged very effectively by oxygen even in the presence of efficient phenolic type inhibitors.[7] It should be pointed out that certain phenoxy radicals such as VII have been shown to be unreactive toward oxygen.[8] However, such phenoxy radicals as VII possess unique resonance stabiliza-



VII R = *t*-butyl

tion, a characteristic difficult to ascribe to the phenoxy radical resulting from oxidation of V. Rather, one must conclude either that the intermediate 2,6-di-*t*-butylphenoxy radicals prefer to undergo a coupling reaction or that V itself is a very efficient scavenger for the corresponding 2,6-di-*t*-butylphenoxy radical, resulting in the observed products.

EXPERIMENTAL

Materials. 2,4,6-Tri-*t*-butylphenol (II) was prepared by the procedure of Stillson, Sawyer, and Hunt.[9] It was purified by recrystallization from ethanol, m.p. 131–132° (lit.[6] m.p. 130–131°. 2,6-Di-*t*-butylphenol (V) (Eastman Kodak) was purified by several recrystallizations from *n*-hexene, m.p. 36–37°. Silver oxide (Eastman Kodak) was used without further purification. The freshly prepared silver oxide was made according to the directions of Witsiepe.[3]

Bis(1,3,5-tri-t-butyl-2,5-cyclohexadiene-4-one) peroxide (II). In a typical experiment 2.62 g. (0.01 mol.) of 2,4,6-tri-*t*-butylphenol in 100 ml. of benzene containing 5 g. (0.022 mol.) of commercial silver oxide was agitated at room temperature with oxygen. Adequate mixing was obtained by the use of a Fisher "Vibro-Mixer." After 0.5–1 hr., the solids were removed by filtration and the benzene evaporated at room temperature. In this manner 2.7 g. (98%) of a very pale green solid was isolated, m.p. 148–149° (lit.[1] m.p. 148–149°). Recrystallization from ethanol had no effect on the melting point. Several experiments were run in which the oxygen absorption was followed by means of a gas burette. In every instance including the use of freshly prepared silver oxide, only 60–70% of the theoretical quantity of oxygen was absorbed while the yield of III varied between 90–100%.

3,5,3′,5′-Tetra-t-butyl-1,1′-dihydro-2,5,2′,5′-bis-cyclohexadiene-4-one (VI). a. *Silver oxide in benzene.* In a typical experiment 4.12 g. (0.02 mol.) of 2,6-di-*t*-butylphenol in 300

(5) M. S. Kharasch and B. S. Joshi, *J. Org. Chem.*, **22**, 1439 (1957).

(6) K. Ley, E. Müller, R. Mayer, and K. Scheffler, *Ber.*, **91**, 2670 (1958).

(7) C. E. Boozer, G. S. Hammond, C. E. Hamilton, and J. N. Sen, *J. Am. Chem. Soc.*, **77**, 3233 (1955).

(8) M. S. Kharasch and B. S. Joshi, *J. Org. Chem.*, **22**, 1435, 1957; G. M. Coppinger, *J. Am. Chem. Soc.*, **79**, 501 (1957).

(9) G. H. Stillson, D. W. Sawyer, and C. K. Hunt, *J. Am. Chem. Soc.*, **67**, 303 (1945).

ml. benzene was stirred for 2 hr. with 9.3 g. (0.04 mol.) of commercial silver oxide. The solids were removed by filtration and the red colored filtrate evaporated in a rotary film evaporator at 15–20 mm. The dark residue was transferred with the aid of petroleum ether to a filter funnel and the solids washed with petroleum ether leaving very light lemon colored crystals, 2.8 g., m.p. 151–152° (lit.[5] m.p. 151–152°) mixed m.p. 151–152°. The filtrate was evaporated leaving 1 g. of a dark brown solid, m.p. 243°, which was identified by infrared comparison as 2,6,2′,6′-tetra-*t*-butyldiphenoquinone. This same mixture resulted when the reaction was carried out in the presence of oxygen.

b. *Alkaline ferricyanide in benzene.* The experiment reported by Kharasch and Joshi[5] was repeated in both a nitrogen atmosphere as well as in an oxygen atmosphere. In the case of the experiments with oxygen, mixing was accomplished with a Fisher "Vibro-Mixer." The reactions were worked up as described by Kharasch and Joshi and in each instance the same mixture of VI and the tetra-*t*-butyldiphenoquinone was obtained regardless of the presence or absence of oxygen. Thus oxygen appears to have no effect on this reaction.

2,6,2′,6′-Tetra-t-butyldiphenoquinone. In a typical experiment 2.06 g. (0.01 mol.) of 2,6-di-*t*-butylphenol in 200 ml. of methanol or ethanol was stirred with 4.7 g. (0.02 mol.) of silver oxide for 1 hr. The solids were removed by filtration and washed with hot benzene, the benzene being combined with the filtrate. The filtrate was then concentrated to approximately one quarter of its original volume and the red solids (2.0 g., 97%) which had separated were collected by filtration, m.p. 246° (lit.[5] for the diphenoquinone, 245°). The material was further identified by infrared comparison with an authentic sample.

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Improved Synthesis of Salts and Esters of Nitroacetic Acid

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The esters of nitroacetic acid are usually prepared from nitromethane by means of a two-step synthesis. The dipotassium salt of nitroacetic acid is made *via* the self-condensation of two molecules of nitromethane in the presence of strong, aqueous alkali[2] and the salt is then esterified directly by acidification in the presence of the appropriate alcohol.[3] The best yields reported by previous investigators were about 57% of relatively pure salt for the first step and 60% for the esterification, or an over-all yield of nitroacetate ester of 34%, based on nitromethane.[3]

In an effort to improve these yields, a study of both the salt formation and the esterification procedures was undertaken in this laboratory. The first step contains an inherent disadvantage in that the salts of nitroacetic acid are unstable in aqueous base solution, decomposing to give the alkali metal salt of nitromethane and the corresponding alkali carbonate.[4,5] Consequently, there

$$KO_2N{=}CHCOOK + KOH \longrightarrow K^+CH_2NO_2^- + K_2CO_3$$

is an upper limit to the yield of dipotassium nitroacetate which can be obtained by the self-condensation of nitromethane in aqueous potassium hydroxide. It appeared that if the amount of water in the reaction system could be minimized, the decomposition of the nitroacetate salt could be lessened and higher yields obtained.

The ultraviolet absorption spectra of nitroacetate ion and its precursors, nitromethane and methazonate ion, have been determined under a variety of conditions[5] and the effect of *p*H on the position and intensity of the methazonate absorption band has been investigated.[6] An analytical method based on the ultraviolet absorption spectra of the various entities was developed for the determination of nitroacetate in mixtures. This method is described further in the Experimental section.

Application of the optical analytical method to the study of the reaction of nitromethane with potassium hydroxide in various alcohols showed that when the condensation is carried out in *n*-butanol, yields of dipotassium nitroacetate of from 80–90% can be obtained. Results found using various solvents are listed in Table I.

TABLE I

Effect of Solvent on the Reaction of Nitromethane with Potassium Hydroxide

Mole Ratio of KOH/CH_3NO_2, 4/1

Solvent	Max. Reaction Temp.	Reflux Time, Hr.	Yield, % Nitroacetate (±2%)	Yield, % Methazonate
50% aq. KOH	118	25 min.	51	0
CH_3OH	73	38.3	0	17[a]
C_2H_5OH	95	23.25	0	81
C_4H_9OH[b]	118	20	84	3
n-Hexanol	142	20	83	0

[a] Recovered some material which had a λ_{max} of 288 mμ in 1*N* KOH. [b] When potassium butoxide was substituted for potassium hydroxide, no dipotassium nitroacetate was formed, but high yields (90–100%) of potassium methazonate were recovered.

Further studies of the reaction in butanolic potassium hydroxide gave the results shown in Table II.

The crude solids obtained from the reaction mixtures are always contaminated with varying amounts of alkali, alcohol, and unconverted potassium methazonate. However, they may be recrystal-

(1) Present address: Hampden-Sydney College, Hampden-Sydney, Va.

(2) W. Steinkopf, *Ber.*, **42**, 3925 (1909).

(3) H. Feuer, H. B. Hass, and K. S. Warren, *J. Am. Chem. Soc.*, **71**, 3078 (1949).

(4) W. Steinkopf, *Ber.*, **42**, 2026 (1909).

(5) A. Hantzsch and K. Voigt, *Ber.*, **45**, 85 (1912).

(6) C. M. Drew, J. R. McNesby, and A. S. Gordon, *J. Am. Chem. Soc.*, **77**, 2622 (1955).

TABLE II

EFFECT OF REFLUX TIME ON REACTION OF NITROMETHANE AND POTASSIUM HYDROXIDE IN BUTANOL

Mole Ratio KOH/CH_3NO_2, 4/1

Reflux Time, Hr.	Yield, % Nitroacetate (±2%)	Yield, % Methazonate
6	63	33
9.5	71	31
12.4	80	5
15	84[a,b]	5
17	83[c]	4
20	84	3
33.25	77	0

[a] Average of three experiments. [b] For six experiments with discontinuous heating at reflux for 15 hr. (mixture allowed to stand at room temperature overnight; heating resumed next morning), the average yield of nitroacetate was 90%. [c] Average of two experiments.

lized from hot aqueous alkali to give average overall yields of relatively pure dipotassium nitroacetate of 71–77% based on nitromethane.

Preparation of methyl nitroacetate. The previously recommended procedure for the conversion of dipotassium nitroacetate to methyl nitroacetate requires reaction with concentrated sulfuric acid at from −50 to −60° for 24 hours, followed by standing at room temperature for 144 hours before isolation of the product, in order to obtain 60% yields of ester.[3] It has now been found that yields of 60–66% methyl nitroacetate can be obtained if the acidification is carried out at from −5 to −10° for 17 hours and the reaction mixture is allowed to stand at room temperature for 2 hours prior to workup. In agreement with Feuer *et al.*,[3] it was found that the omission of anhydrous sodium sulfate or use of less than 2 moles of sulfuric acid per mole of dipotassium nitroacetate gave much lower yields of ester.

In addition, the procedure used by Feuer *et al.*[3] for the isolation of methyl nitroacetate was modified. We obtained considerably better yields of the ester by extracting the excess sulfuric acid with water before distillation rather than by neutralization of the acid with aqueous sodium carbonate. This averts losses of the ester to the aqueous layer as the salt (K_a of ethyl nitroacetate is 1.4×10^{-6}).[7]

EXPERIMENTAL[8]

Spectral analysis.[9] Reference samples of dipotassium nitroacetate, methazonic acid, and nitroacetonitrile were prepared, and their absorption maxima and specific extinction coefficients were determined in water and 1*N* potassium hydroxide. The results are given in Table III. On standing in 1*N* potassium hydroxide for two weeks, the absorption maximum of nitroacetonitrile shifted from 288 mμ to 278 mμ, indicating gradual conversion to dipotassium nitroacetate. In water, no shift in the absorption maximum was observed after two weeks' standing, but the specific extinction coefficient decreased markedly. It is to be noted that the λ_{max} of methazonic acid in potassium hydroxide solution shifts from 298 mμ at a *p*H of 10 to 310 mμ in 1*N* potassium hydroxide.[10]

TABLE III

ULTRAVIOLET ABSORPTION OF DIPOTASSIUM NITROACETATE AND ITS PRECURSORS

Compound	Solvent	λ_{max}, mμ	$k = \frac{D^a}{c}$
Dipotassium nitroacetate	Water	None[b]	—
	1*N* KOH	276	60.6
Methazonic acid	Water	298	80.0
	Dil. KOH (*p*H 10)	298	115.3
	1*N* KOH	310	197.3
	1*N* KOH	276[c]	45.0
Nitroacetonitrile (initial)	Water	288	140
	1*N* KOH	288	132
(After standing 2 weeks)	Water	288	87
	1*N* KOH	278	112

[a] Specific extinction coefficient; $D = kcl$ where l is in cm., c in g./l. [b] λ_{max} at 276 fades within seconds. [c] This value is not λ_{max} but the absorption of methazonate at this λ.

The values of the specific extinction coefficients are somewhat uncertain since they depend on the purity of the samples used for calibration.

The crude reaction products were analyzed by determining the concentration of potassium methazonate at 298 mμ in aqueous solutions having a *p*H of 10.0, followed by correcting the absorbance of the sample in 1*N* potassium hydroxide at 276 mμ for the absorbance of the methazonate and subsequent calculation of the dipotassium nitroacetate concentrations. No evidence for the presence of nitroacetonitrile was observed. Preparation of synthetic mixtures of methazonate, nitroacetonitrile, and nitroacetate and subsequent analysis indicated that the accuracy of the method was 2% for nitroacetate when the amount of methazonate present was less than 10% of the total material.

Apparatus and method. Spectral measurements were made using a Beckman Model DK recording spectrophotometer.

(7) H. Ley and A. Hantzsch, *Ber.*, **39**, 3149 (1906).

(8) All melting and boiling points are reported uncorrected.

(9) We are indebted to Mr. C. T. Desmond of these laboratories for the development of the ultraviolet spectral method.

(10) Other investigators[6] have noted that methazonate salts exhibited only one very pronounced ultraviolet absorption peak with λ_{max} at 298 mμ, and that absorption of methazonate ion at 298 mμ obeys Beer's law only at a *p*H of 10.5 or higher. At *p*H 11 to 11.5, they found a value of ε for ammonium methazonate in sodium hydroxide of 17,840. They made no mention of a λ_{max} shift at higher *p*H values. In this laboratory, the ε value for methazonic acid in 1*N* potassium hydroxide at λ_{max} = 310 mμ was 28,086; at λ_{max} = 298, *p*H = 10, ε was 16,407. Recent evidence has shown that methazonic acid forms a disodium salt.[11] λ_{max} at 298 is undoubtedly due to the monopotassium salt (I), while that observed at 310 mμ may be due to the dipotassium salt (II).

$O_2NCH_2CH{=}NOK$ (I) $\qquad$ $K{-}ON{=}CH{-}CH{=}NO_2K$ (II)

(11) D. J. Morgan, *J. Org. Chem.*, **23**, 1069 (1958).

The *p*H values were measured with a Leeds-Northrup *p*H meter having a Leeds-Northrup Standard 1199-30 calomel reference electrode and a Leeds-Northrup Standard 1199-31 glass electrode. Measurements were referred to standards prepared from Coleman Buffer tablets.

The dilutions used were approximately 1×10^{-2} g./l. They were allowed to stand for 1 hour after preparation before the absorbance was measured to allow for complete hydrolysis of dipotassium nitroacetate in the aqueous solutions of *p*H 10. The glassware used for the sample dilutions was caustic-free.

Methazonic acid. This compound was prepared by a modification of the method of Reid and Köhler.[12] In the reaction flask were placed 40 g. (1 mole) of sodium hydroxide and 80 ml. of water. After the resulting solution had cooled to 48°, 40 g. (0.653 mole) of distilled nitromethane was added, with vigorous stirring, at a rate designed to keep the reaction temperature between 45 and 50°. The addition took 1.5 hour.

The deep amber-colored solution was then cooled to 0° and acidified by the dropwise addition of 85 ml. of concentrated hydrochloric acid. The reaction temperature was maintained at 0 to +5° throughout this addition, which took 44 min. Upon reaching an acid *p*H value, the solution changed color from amber to bright yellow, and a solid precipitated. This solid was collected by immediate filtration, pressed on a clay plate, and taken up in 200 ml. of ethyl ether. The ether solution was dried over anhydrous calcium chloride overnight, filtered, and evaporated to dryness *in vacuo* without heating. The resulting bright orange solid weighed 17.0 g., representing a 50% yield of crude methazonic acid. A portion of the solid was recrystallized from hot chloroform to give yellow needles; m.p. 70–72°.[13,14]

Anal. Calcd. for $C_2H_4O_3N_2$: N.E. 104.07. Found: N.E. 105.3.

The material is very unstable. It decomposes to a red resin within 3 days even when stored below 0°.

Nitroacetonitrile. This material was made by the procedure of Ried and Köhler,[12] using 14.7 g. (0.141 mole) of recrystallized methazonic acid, 17.1 g. (0.145 mole) of freshly distilled thionyl chloride (b.p. 75°/atm.) and 80 ml. of absolute ethyl ether. There was obtained 3.7 g. (31% yield) of pale yellow nitroacetonitrile. This liquid, which could have contained some methazonic acid as an impurity, was used as a standard for the determination of nitroacetonitrile in crude nitroacetate samples.

Dipotassium nitroacetate. The analytical standard was prepared by the method of Feuer, Hass, and Warren.[3] A yield of 47.5% of fairly high purity material was obtained in two crops. A sample was recrystallized from the minimum amount of hot 50% aqueous potassium hydroxide, washed with methanol, and dried *in vacuo* at 100°.

Anal. Calcd. for $C_2HNO_4K_2$: K, 43.15; N, 7.73. Found: K, 42.8; N, 7.29.

Reactions in alcoholic potassium hydroxide. The studies of the effect of various conditions on the reaction of nitromethane with potassium hydroxide were carried out using similar procedures. Generally, the reactions were carried out in 1-, 2-, or 5-l. flasks fitted with air-driven, high speed stirrers. The reaction flasks were also fitted with reflux condensers, dropping funnels, and thermowells.

Potassium butoxide was prepared by adding freshly cut slivers of potassium to an excess of distilled *n*-butanol with vigorous stirring under a nitrogen purge. The resulting solutions were heated at 96° for 2 hours to insure complete reaction, and the reaction with nitromethane was carried out in the same system.

A representative reaction procedure is described below. Results of the various studies are given in the tables.

In a 2-l. creased flask was placed 705 g. of a 15.9% solution of potassium hydroxide in *n*-butanol. Nitromethane (31 g., 0.5 mole) was added dropwise with vigorous stirring over a 25-minute period. The temperature rose from 30 to 49° during the addition. The mixture was then warmed to reflux in a 58-minute period and heated at reflux (117 to 120°) for 15 hours.

The reaction mixture was cooled, and the pale yellow solid product was removed by filtration (sintered glass filter) washed with methanol, crushed, and dried in a vacuum desiccator for 8 hr. The material was powdered and dried in a vacuum oven at 60°/1 mm. for 7.5 hr. The dried material (66.3 g.) was off-white, and contained 62% (by ultraviolet analysis; 41.1 g., 0.226 mole) of dipotassium nitroacetate and 1% (0.66 g., 0.006 mole) of potassium methazonate, corresponding to yields of 91% and 2%, respectively, based on nitromethane.

Recrystallization of crude dipotassium nitroacetate. There was dissolved 472 g. of crude reaction product, which contained 319 g. of dipotassium nitroacetate, in hot 50% aqueous potassium hydroxide. The mixture was cooled in an ice bath to yield two crops of silky white needles. The solid was collected by filtration, washed with methanol, and dried in the vacuum oven at 90°/1 mm. for 5 hours. The crops weighed 230 g. and 41 g., respectively, and had purities of 100% and 98% as dipotassium nitroacetate. This represented a recovery of 85%.

Methyl nitroacetate. To 90.5 g. (0.5 mole) of 100% pure dipotassium nitroacetate in a jacketed kettle there were added 600 ml. (471 g., 14.69 moles) of methanol and 15 g. (0.11 mole) of anhydrous sodium sulfate. The flask contents were cooled to −11° by circulating brine through the outer jacket while stirring the cream-colored slurry. One hundred g. of 98% sulfuric acid was added dropwise to the stirred mixture over a period of 2.1 hours. The resulting white slurry was stirred at −5 to −11° for 17 hours, then for 2.3 hours at room temperature. The precipitated white solid was filtered, washed with methanol, and discarded. The excess methanol was stripped at room temperature from the amber-colored filtrate at reduced pressure. The oily residue was shaken with 150 ml. of methylene chloride and 100 ml. of water. The resulting layers (a light yellow, organic layer, and a deep amber water layer) were separated and the organic layer was washed with 100 ml. of water. The aqueous washings were combined, extracted with 50 ml. of ether, and discarded. The combined organic layers were dried over anhydrous sodium sulfate and the solvent was distilled through a 30 × 180 mm., glass ring-packed column at atmospheric pressure. Vacuum distillation of the residue from a smaller flask *via* the same column (heated) gave 39.3 g. (0.33 mole, 66% yield) of methyl nitroacetate, boiling at 46–47°/0.8 mm.; n_D^{20} 1.4260 (lit.[3] gives b.p. 93–94°/15 mm., n_D^{20} 1.4245).

Anal. Calcd. for $C_3H_5O_4N$: N, 11.77; neut. equiv. 119. Found: N, 11.98; neut. equiv. 119.

Acknowledgments. We are indebted to Mr. J. E. Free for the determination of the spectral data and to Mr. J. S. Bodenschatz for the elemental analyses. The assistance of Mr. R. G. Lowther with the experimental work is gratefully acknowledged.

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(12) W. Reid and E. Köhler, *Ann.*, **598**, 145 (1956).

(13) Melting point taken in sealed, evacuated capillary.

(14) O. Schultze, *Ber.*, **29**, 2287 (1896) reported a m.p. of 78–80° for methazonic acid; W. Dunstan and E. Goulding, *J. Chem. Soc.*, **77**, 1264 (1900) reported a m.p. between 60 and 70°, depending on the rate of heating.

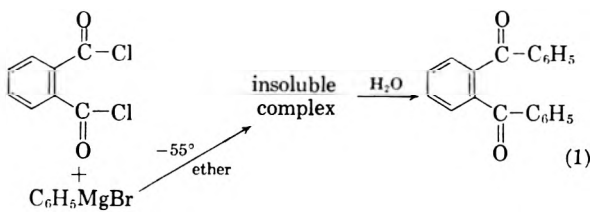
Preparation of o-Dibenzoylbenzene and o-Dibenzylbenzene

FREDERICK R. JENSEN

Received July 14, 1959

o-Disubstituted benzene derivatives are frequently difficult to prepare, and often cannot be synthesized by conventional methods. No convenient methods have been reported for the preparation of the useful compounds, *o*-dibenzoylbenzene and *o*-dibenzylbenzene. Since it was desired to obtain substantial quantities of these compounds, a number of methods for their preparation were investigated. The most satisfactory methods found are reported here.

Although the yield is poor (32%) in the method given for the preparation of *o*-dibenzoylbenzene, the procedure involves a simple reaction using cheap, commercially available starting materials. The reaction was carried out by adding phenylmagnesium bromide to a solution of phthaloyl chloride in ether at −55° (Equation 1). The product forms an ether insoluble complex with magnesium bromide. The side products are largely removed

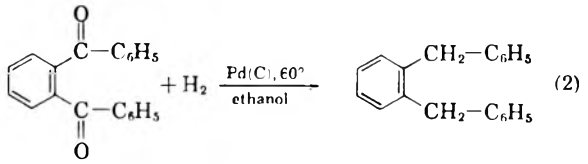


(1)

by decanting the ether solution from the complex. Addition of water liberates the *o*-dibenzoylbenzene from the complex.

The preparation of *o*-dibenzoylbenzene from phthaloyl chloride and phenylmagnesium bromide (unreported yield) has been carried out previously,[1] but the preparation could not be repeated satisfactorily. Cason and Reist[2] have shown that succinyl dichloride gives reactions with ethylmagnesium bromide characteristic of the unsymmetrical form at room temperature and the symmetrical form at low temperature. It had been hoped that *o*-dibenzoylbenzene could be prepared by the reaction of diphenylcadmium with phthaloyl chloride,[3] but the principal product of the reaction was diphenylphthalide.

It was found that *o*-dibenzylbenzene can be conveniently prepared by reducing *o*-dibenzoylbenzene with hydrogen in the presence of palladium on charcoal (Equation 2). *o*-Dibenzylbenzene has usually been obtained previously from the complex



(2)

mixture resulting from the reaction of benzyl chloride and diphenylmethane in the presence of aluminum chloride.[4]

EXPERIMENTAL

o-Dibenzoylbenzene. A solution containing 1.11 mol. phenylmagnesium bromide and 1000 ml. ether was prepared in the usual manner. This solution (without cooling) was added over a period of 15 min. to a stirred mixture of 107.6 g. (0.53 mol.) phthaloyl chloride (Eastman Organic Chemical Co., practical grade) and 1000 ml. anhydrous ether, which was cooled in a Dry Ice–trichloroethylene bath. The temperature in the reaction vessel was about −55°. During the addition, a solid separated from the solution. (A powerful stirred was found necessary to keep the mixture agitated.) After the addition was complete, the low temperature bath was removed and the mixture was allowed to warm to room temperature while being stirred.

The ether solution was decanted from the solid, 2000 ml. technical ether was added to the complex, and then the solid complex was decomposed by adding 1000 ml. water containing 5 ml. acetic acid. The ether solution was separated, and then washed with 500-ml. portions of water, 5% sodium bicarbonate solution, and water. Ether was added as necessary to keep the product in solution. After drying the solution with magnesium sulfate, the bulk of the ether was removed. *o*-Dibenzoylbenzene separated in almost pure form, in a yield of 45.7 g. (32%), m.p. 146–147°. The crystals contained a very small amount of highly colored material which was difficult to remove. This product was found to be suitable for most purposes. Recrystallization from ethanol was found to be convenient, but the product was yellow with m.p. 147.6–148.5°. Pure *o*-dibenzoylbenzene, m.p. 147.6–148.8° (lit.,[5] m.p. 148°), was obtained by clarifying and recrystallizing the compound in heptane-acetone.

Anal. Calcd. for $C_{20}H_{14}O_2$: C, 83.92; H, 4.89. Found: C, 84.08; H, 5.07.

o-Dibenzylbenzene. A mixture of 23 g. (0.081 mol.) *o*-dibenzoylbenzene (m.p. 146–147°), 4 g. palladium (5%) on charcoal and 200 ml. absolute ethanol was placed in a Parr low-pressure hydrogenation unit. After heating the reaction vessel to 60°, the hydrogenation was started using an initial pressure of 44 p.s.i. In 10 hr., the calculated amount of hydrogen was taken up, and the hydrogenation was stopped. Since the hydrogen uptake continued slowly beyond the calculated amount, the yield was diminished if the reaction was allowed to continue.

The reaction mixture was heated to boiling and then filtered while hot. After allowing the mixture to cool to room temperature, the solution was placed in a refrigerator at 6°. The crystals were collected, and recrystallized from absolute ethanol to give 13.9 g. (0.054 mol.) *o*-dibenzylbenzene (66%) as white needles with m.p. 78.7–79.4° (lit.,[3] m.p. 78°).

Anal. Calcd. for $C_{20}H_{18}$: C, 92.98; H, 7.07. Found: C, 92.73; H, 6.86.

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(1) E. Clar, F. John, and B. Hawran, *Ber.*, **62**, 944 (1929).

(2) J. Cason and E. Reist, *J. Org. Chem.*, **23**, 1668 (1958).

(3) J. Cason, *Chem. Revs.*, **40**, 15 (1947).

(4) C. Radziewanowski, *Ber.*, **27**, 3235 (1894).

(5) E. P. Kohler, *Am. Chem. J.*, **40**, 227 (1908).

Convenient Synthesis of Vinylcyclohexane-α-*d*

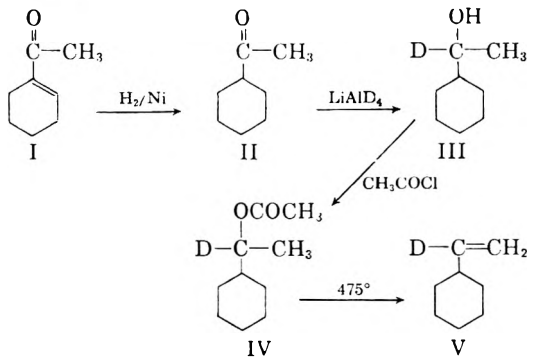
C. G. Overberger, A. Katchman,[1,2] and J. E. Mulvaney

Received September 4, 1959

A recent note[3] on the preparation of methyl cyclohexyl ketone has prompted us to report some results we have obtained in the course of preparing the monomer vinylcyclohexane-α-*d* (V).

A convenient laboratory preparation of the deuterated vinylcyclohexane (V) utilized ketone (II) as the starting material.[4] Vinylcyclohexane has previously been reported by Van Derby and Kooyman, prepared by preparation of methyl cyclohexylcarbinol by reaction of cyclohexylmagnesium bromide and acetaldehyde, followed by acetylation and pyrolysis. The ketone (II) had also been prepared by oxidation of 1-cyclohexylethanol[5,6] and more recently by the catalytic reduction of methyl cyclohexen-3-yl ketone.[3]

The ketone (II) was readily accessible from the reduction of methyl cyclohexen-1-yl ketone[5,7] (I). Reduction was carried out in an 86% yield by



hydrogenation at room temperature with Raney Nickel W-2[8] as the catalyst. Reduction with lithium aluminum deuteride gave the deuterated alcohol (III) in 91.5% yield which was smoothly acetylated to the deutero acetate (IV) in a 95.3% yield. Pyrolysis of the acetate (IV) gave the desired deuterated monomer (V) after careful fractionation (71%). Fractionations were followed by vapor phase chromatography to insure purity of the monomer. Vinylcyclohexane[4] (V. D = H) was prepared in analogous fashion using lithium aluminum hydride for the reduction of the ketone (II).

EXPERIMENTAL

Methyl cyclohexyl ketone (II). A mixture of methyl cyclohexen-1-yl ketone,[6] 17.5 g. (0.138 mol.), 75 ml. of methanol and 1 g. of W-2 Raney Nickel catalyst[7] in a rocking autoclave pressurized to 500 lbs./in.^{2} was shaken at room temperature for 20–30 min. after which no further hydrogen was absorbed. The catalyst and methanol were removed and distillation of the residual oil furnished 15.2 g. (86%), b.p. 66° (12 mm.), n_D^{26} 1.4491, of methyl cyclohexyl ketone (reported[6] b.p. 182.5–184.5° (676 mm.), $n_D^{25.9}$ 1.44955).

1-Cyclohexylethanol-1-d (III). To a solution of 3.3 g. (6.078 mol.) of lithium aluminum deuteride[9] in 300 ml. of absolute ethyl ether was added dropwise 37.9 g. (0.3 mol.) of II in 100 ml. of absolute ethyl ether. Upon completion of the addition, the mixture was refluxed for 1 hr. and then decomposed with water. The ether was removed and the residual oil was distilled yielding 35.5 g. of carbinol (91.5%), b.p. 65° (3.9 mm.), n_D^{25} 1.4632.

Anal. Calcd. for $C_8H_{15}DO$: C, 74.35; H + D, 13.26. Found: C, 74.31; H + D, 13.23, 0.891 deuterium atom/mol.[10]

1-Cyclohexylethyl-1-d acetate (IV). 1-Cyclohexylethanol-1-*d*, 33.0 g. (0.26 mol.), (III), was added dropwise to 30 g. of acetyl chloride at a rate to maintain reflux and the mixture was refluxed for 2 additional hr. Excess acetyl chloride was removed and the residual oil was distilled to yield 41.6 g. (95.3%), b.p. 67° (4.3 mm.), n_D^{25} 1.4445, of acetate.

Anal. Calcd. for $C_{10}H_{17}DO_2$: C, 70.13; H + D, 11.18. Found: C, 70.29; H + D, 11.28; 0.942 deuterium atom/mol.[9]

Vinylcyclohexane-α-d (V). 1-Cyclohexylethyl-1-*d* acetate, 34.5 g. (0.20 mol.), (IV), was pyrolyzed[11] by dropping the liquid at a rate of 8–12 drops per min. through a 12″ tube packed with Pyrex glass Raschig rings at 475° under a nitrogen atmosphere. The pyrolyzate was washed with aqueous sodium bicarbonate and water and dried over anhydrous sodium sulfate. Distillation in a seventy-five plate concentric tube column yielded 17.8 g. (80%), boiling at 127–129°, n_D^{25} 1.4459, of crude olefin. Careful distillation yielded 12.7 g. (71%), boiling at 127.5–128°, n_D^{25} 1.4441, of vinylcyclohexane-α-*d*. The product was pure as determined by vapor phase chromatography. It absorbed strongly at 11.0 μ in the infrared which indicated that it was a terminal olefin.

Anal. Calcd. for $C_8H_{13}D$: C, 86.40; H + D, 13.60. Found: C, 86.13; H + D, 13.62; 0.889 deuterium atom/mol.[10]

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(2) Hooker Chemical Company, Post Doctoral Fellowship, 1957–59.

(3) W. K. Johnson, *J. Org. Chem.*, 24, 864 (1959).

(4) J. R. Van Derby and E. C. Kooyman, *Rec. trav. Chem.*, 71, 837 (1952).

(5) O. Wallach, *Ann.*, 360, 26 (1908).

(6) S. van Woerden, *Rec. trav. Chem.*, 45, 124 (1926).

(7) J. H. Saunders, *Org. Syntheses*, Coll. Vol. III, 22 (1955).

(8) R. Mozingo, *Org. Syntheses*, Coll. Vol. III, 181 (1955).

(9) Purchased from Metal Hydrides, Inc., Beverly, Mass.

(10) Deuterium analyses were performed by Professor D. B. Denney of Rutgers, the State University of New Jersey, by means of a mass spectrograph.

(11) C. G. Overberger and D. Tanner, *J. Am. Chem. Soc.*, 77, 369 (1955).

Preparation and Properties of 1-Phenyl-4-methyl-2-penten-1-one

Kurt Kulka, Robert J. Eiserle, James A. Rogers, Jr., and Fred W. Richter

Received March 23, 1959

The recent availability of isobutyraldehyde in commercial quantities through the oxo process[1]

(1) H. J. Hagemeyer and G. C. DeCroes, *The Chemistry of Isobutyraldehyde and its Derivatives*, Tennessee Eastman Co., Kingsport, Tenn., 3 (1953).

prompted us to prepare a sample of isobutylideneacetophenone for investigation of its organoleptic properties. The reaction of isobutyraldehyde with acetophenone under alkaline conditions yielded a small amount of unreacted acetophenone, a liquid boiling at 130° at 8 mm. and, as the main product, a solid. The latter, white, odorless crystals, melted at 144.5–145° after repeated recrystallizations from a methanol-benzene mixture.

The liquid was not the aldol since water was not produced upon heating in the presence of iodine or oxalic acid, but the starting material was recovered. A carbon-hydrogen ratio determination of the liquid and the solid compounds gave identical results. Consequently, we investigated the possibility that the solid and the liquid reaction products were geometrical isomers, or that the double bond in the side chain of either compound was out of conjugation with the carbonyl group.

The structure of the liquid isomer was proven by its reduction products which were previously reported in the literature. Thus catalytic hydrogenation with Raney nickel in methanol solution at 50 p.s.i. yielded 1-phenyl-4-methyl-pentan-1-one and 1-phenyl-4-methylpentan-1-ol. By potassium borohydride reduction and also by Meerwein, Ponndorf-Verley reduction the unsaturated alcohol 1-phenyl-4-methyl-2-penten-1-ol was obtained. This alcohol was reduced by catalytic hydrogenation with Raney nickel in methanol solution at 50 p.s.i. to 1-phenyl-4-methylpentane. As these compounds were previously obtained by more complicated synthesis such as Grignard reactions, the above reductions are novel and simple ways for their preparation.

Attempted reduction of the solid compound at 50 p.s.i. in various solvent systems, with various catalysts including Raney nickel, Adams platinum oxide and palladium on charcoal were unsuccessful. Bromination in carbon tetrachloride and in hexane solution did not proceed satisfactorily. Hydrogen bromide was given off and resins were formed. The absence of a double bond in the solid compound became obvious and suggested the possibility that it was a dimer having the uncommon cyclobutane structure similar to that in truxillic acid which is formed by the dimerization of cinnamic acid. Molecular weight determinations of the liquid as well as the solid reaction products by a modified Rast method gave evidence that the liquid was the monomer and the solid a dimer of 1-phenyl-4-methyl-2-penten-1-one.

Prior to this paper, the crystalline dimer was erroneously defined as the monomer by Thoms and Kahre[2]; the actual monomer was not reported.

It was of interest to prepare these compounds by other syntheses. Isobutyraldehyde was treated with malonic acid in pyridine solution using piperidine as the catalyst to obtain 4-methyl-2-pentenoic acid which was converted to its acid chloride. The acid chloride was treated with benzene in a Friedel-Crafts synthesis to give mainly the liquid monomer and a small amount of the solid dimer. Knoevenagel reaction of benzoylacetic acid with isobutyraldehyde in pyridine solution, using piperidine as the catalyst, gave only the liquid monomer after decarboxylation.

Depolymerization of the dimer to the monomer was accomplished by vacuum distillation in the presence of a catalytic amount of sodium acetate. Dimerization of the liquid monomer was carried out under identical conditions as in the previously described condensation, *i.e.*, in methanol solution using potassium hydroxide as the catalyst. It was further observed that the liquid on standing in a stoppered brown bottle over a prolonged period of time was partly dimerized.

The degree of reactivity of these two compounds is best demonstrated by the fact that it took 480 hr. for the solid and only 24 hr. for the liquid to react completely with hydroxylamine hydrochloride at room temperature. Molecular weight determinations of these two oximes by a modified Rast method showed the first to be the oxime of a dimer and the latter to be the oxime of the monomer.

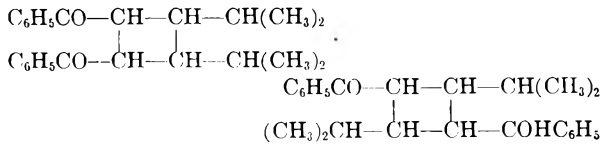
The next higher member of this series of branched-chain, unsaturated ketones (1-phenyl-5-methyl-2-hexen-1-one) was obtained from the reaction of acetophenone with isovaleraldehyde under identical (alkaline) conditions. In this reaction only the liquid monomer was formed.

Infrared curves of 1-phenyl-4-methyl-2-penten-1-one (monomer and dimer) were run on a Perkin-Elmer Model 21 spectrophotometer with sodium chloride prism. The liquid ketone gave the normal spectrum for a conjugated unsaturated actophenone except for a splitting of the monosubstituted phenyl peak in the 750 cm.$^{-1}$ range. The recrystallized solid ketone melted film run on a hot stage cell showed aromatic carbon-carbon double bond and carbonyl stretching bands and monosubstituted phenyl ring peaks. It lacked aliphatic carbon-carbon double bond stretching peaks, indicating saturation of the *trans* double bond. A medium intensity peak at 880 cm.$^{-1}$ can be assigned to the cyclobutane ring which according to Reid and Sack[3] is the expected range for 1,2,3,4-tetrasubstituted cyclobutane compounds.

Thus the spectrum and previously reported experimental findings indicate the structure of our solid to be either of the two structures following:

(2) H. Thoms and H. Kahre, *Arch. Pharm.*, **263**, 251 (1925).

(3) E. B. Reid and M. Sack, *J. Am. Chem. Soc.*, **73**, 1985 (1951).



EXPERIMENTAL

All boiling points and melting points are uncorrected.

Dimer of 1-phenyl-4-methyl-2-penten-1-one (I). During 1.5 hr. at a temperature of 50°, 72.1 g. isobutyraldehyde was added to a well agitated solution of 120.7 g. acetophenone, 17 g. potassium hydroxide (reagent grade), 125 ml. methanol, and 125 ml. water. On continuing agitation at 48–50° a white solid formed. After 3.5 hr. the reaction mass was cooled to room temperature neutralized with acetic acid, and filtered on a Buchner funnel. The separated solid was washed with 100 ml. methanol and dried; it weighed 107 g. (61% yield). After 3 recrystallizations from a mixture of 70% methanol and 30% benzene, it gave a constant melting point of 144.5–145°, the dimer of 1-phenyl-4-methyl-2-penten-1-one (I). The liquid organic filtrate combined with the above methanol was fractionated through a 40-cm. Vigreux column yielding 10.5 g. unreacted acetophenone and 38 g. of a liquid boiling 133–134° at 8 mm. n_D^{20}: 1.5385, which on redistillation boiled at 130° at 8 mm. n_D^{20}: 1.5385. This liquid was identified as the *monomer of 1-phenyl-4-methyl-2-penten-1-one* (II). The distillation residue (12.2 g.) after recrystallization from a methanol-benzene mixture was found to be identical with I having a melting point of: 144.5–145°.

Anal. Calcd. for I: $C_{24}H_{18}O_2$: C, 82.2; H, 8.1. Found: C, 81.6; H, 7.8.

Anal. Calcd. for II: $C_{12}H_{14}O$: C, 82.2; H, 8.1. Found: C, 83; H, 7.86.

Molecular weight determination of I. The modified Rast procedure described by Becker[4] for the semimicro molecular weight determination was applied in principle. When the solution of the organic compound in camphor, prepared as advised by Becker, was used, erroneous and nonreproducible results were obtained, probably due to partial depolymerization of the dimer. The compound to be analyzed was, therefore, thoroughly mixed with the camphor. As five consecutive experiments gave almost identical results, we consider this abbreviation of the procedure to give sufficiently accurate results. Calculated molecular weight: 348, Found: 344 (average).

Determination of the carbonyl content of I *and* II *using hydroxylamine hydrochloride.* The method described by Guenther[5] was employed: Thus 0.5421 g. of I was treated at room temperature with 35 ml. of 0.5*N* hydroxylamine hydrochloride solution, and the liberated hydrochloric acid titrated with 0.5*N* sodium hydroxide solution. The following ketone contents were obtained: After 24 hr.: 32.3%; after 384 hr.: 93.3% and after 480 hr.: 99.9%. In the same way 0.5384 g. of II was treated as I, but gave after 24 hr. a ketone content of 98.2%.

Dioxime of I. The dioxime was prepared according to a procedure described by Vavon and Anziani:[6] Thus 8.9 g. of I, 10 g. hydroxylamine hydrochloride, 70 g. ethanol, 30 g. water, and 3.6 g. sodium hydroxide (reagent grade) were refluxed for 24 hr. The solution was poured into 100 ml. water, the precipitated crystals collected on a Buchner funnel, and recrystallized 4 times from 80% ethanol to a constant m.p. of 184–185°.

Anal. Calcd. for $C_{24}H_{30}N_2O_2$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.13; H, 8.06; N, 7.39.

Oxime of II. The above procedure was followed with the exception that the solution was permitted to stand at room temperature (25–30°) for 24 hr. The oxime, recrystallized 4 times from 80% ethanol, had an m.p. of 57°.

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.15; H, 7.99; N, 7.40. Found: C, 76.12; H, 8.02; N, 7.41.

Depolymerization of I *to* II. A mixture of 50 g. of I and 1.5 g. anhydrous sodium acetate (reagent grade) was heated in a vacuum of 8 mm. At 185° the mixture became completely liquid, and the depolymerization was considered complete. On distillation without a column, 41 g. were collected, boiling from 130–135° at 8 mm. n_D^{20}: 1.5392. On redistillation through a 40-cm. Vigreux column, the ketone (II) boiled at 130° at 8 mm.; n_D^{20}: 1.5385.

Dimerization of II *to* I. At a temperature of 50°, 70 g. of I was agitated for 45 min. with a solution of 6 g. potassium hydroxide in 70 g. methanol and 70 g. water. The solid was collected on a Buchner funnel and recrystallized twice from methanol. The resulting white crystals had an m.p. of 143–144°. A mixed melting point with the original ketone (I) showed no depression.

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(4) E. I. Becker, *Chemist Analyst*, **40**, 80 (1951).

(5) E. Guenther, *The Essential Oils*, Vol. I, D. Van Nostrand Co., N. Y., 1948, p. 286.

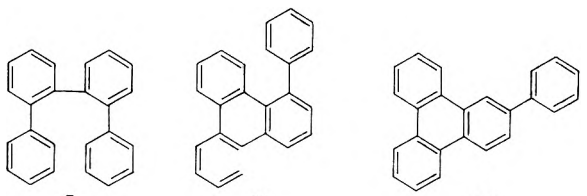
(6) G. Vavon and P. Anziani, *Bull. soc. chim.*, **5**, 2026 (1937).

Synthesis of 2-Phenyltriphenylene and 2,6,10-Trimethyltriphenylene

D. DAVID LAWSON AND CHARLES M. BUESS

Received August 10, 1959

Hansch and Geiger[1] recently prepared a phenyltriphenylene by cyclodehydrogenation of 2,2′-diphenylbiphenyl (I). Although 1-phenyltriphenylene (II) might be expected from this reaction, the authors considered rearrangement to the 2-isomer (III) very likely. In the course of related work in



I II III

this laboratory, 2-phenyltriphenylene was prepared by an unequivocal method, an adaptation of the Rapson synthesis as improved by Barker, Emmerson, and Periam.[2] The sample was compared with one kindly supplied by Dr. Corwin Hansch and the physical properties including infrared spectra were found to be identical. The melting point of a mixture sample was not depressed. It may therefore be concluded that the phenyl group does migrate under the cyclodehydrogenation conditions employed in ref. 1.

(1) C. Hansch and C. F. Geiger, *J. Org. Chem.*, **23**, 477 (1958).

(2) C. C. Barker, R. G. Emmerson and J. D. Periam, *J. Chem. Soc.*, 1077 (1958).

The ultraviolet spectrum of 2-phenyltriphenylene does not exhibit as much fine structure as that of triphenylene or its alkyl derivatives.[2-4]

In the course of our study a sample of 2,6,10-trimethyltriphenylene was prepared by dehydrogenation of the product obtained by self-condensation of 4-methylcyclohexanone under conditions employed in the Mannich triphenylene synthesis.[5] Although the spectrum of this compound was reported recently,[2] no details of its preparation were given. The procedure employed by us is therefore included here.

EXPERIMENTAL

2-(1'-Cyclohexenyl)-1-p-biphenylylcyclohexanol. To a solution of 0.80 moles of *n*-butyllithium[6] was added in 5 to 10 g. portions 167 g. of 4-bromobiphenyl while the temperature was held below 0°. The mixture was then warmed to 5° and stirred for 30 min. (until all the 4-bromobiphenyl had dissolved). A solution of 133 g. of 2-(1'-cyclohexenyl)-cyclohexanone in 200 ml. of ether was added while the temperature was held just below 5° with external cooling. The mixture was allowed to warm to room temperature and stand overnight. The ethereal solution was treated with 1*N* hydrochloric acid, separated, and dried over anhydrous sodium sulfate. Ether and volatile material was removed by distillation, eventually on a steam bath at water pump pressure. The residual crude oil (170 g.) was used directly in the next step.

2-(1',2'-Epoxycyclohexyl)-1-p-biphenylylcyclohexanol. To a solution of 160 g. of the crude oil above in 400 ml. of ether cooled to −40° was slowly added 1.25 l. of the ether solution of perphthalic acid.[7] After 3 hr. at −40° the mixture was allowed to warm to +5° and was kept at that temperature for 16 hr. The resulting precipitate was separated; it contained only a small amount of desired product which remained after extraction with aqueous sodium bicarbonate. The ethereal solution was dried and the ether was evaporated. The oily residue was extracted with 250 ml. of ethanol at 5° and the residue was collected and washed with more cold ethanol. Yield: 82 g.; 35% based on 4-bromobiphenyl; m.p. 147–148°.

Anal. Calcd. for $C_{24}H_{28}O_2$: C, 82.72; H, 8.10. Found: C, 81.46; H, 8.17.

2-Phenyltriphenylene. A solution of 70 g. of the epoxide in 400 ml. of acetic acid and 350 ml. of 48% hydrobromic acid was refluxed for 20 hr. The reaction mixture was poured into 3 l. of water, the product was extracted with benzene, and the benzene solution was washed with aqueous sodium bicarbonate and dried over sodium sulfate. The crude oil (5,6,7,8,9,10,11,12-octahydro-2-phenyltriphenylene) obtained after evaporation of the benzene was mixed with 15 g. of 5% palladium on charcoal and dehydrogenated at 300° for 6 hr. under nitrogen. The cooled product was extracted with 250 ml. of benzene. The benzene was evaporated and the residue slowly crystallized. Oily products were extracted with 200 ml. of petroleum ether (63–69°). Yield: 6.0 g.; m.p. 180–185°. The sample was further purified by chromatography in benzene on alumina and by recrystallization from 3:1 ethanol-benzene. M.p. 182–185° (lit.[1] 183–184°), small needles.

Anal. Calcd. for $C_{24}H_{16}$: C, 94.70; H, 5.30. Found: C, 94.82; H, 5.14. Ultraviolet maxima in 95% ethanol: 261.5 mμ (log ε, 4.91); 268.5 mμ (log ε, 4.96); 301 mμ (inflection, log ε, 4.37).

2,6,10-Trimethyltriphenylene. A mixture of 450 g. of 4-methylcyclohexanone with 1.4 l. of methanol containing 246 g. of concentrated sulfuric acid was refluxed for 12 hr. After dilution with 2.5 l. of methanol, crystals of 1,2,3,4,5,6,7,8,9,10,11,12-dodecahydro-2,6,10-trimethyltriphenylene separated. These were collected and washed with acetone. Yield: 20 g.; 5%; m.p., 194–196° (lit.[3] 195°).

The dodecahydro compound was dehydrogenated like the 2-phenyl analog and the product was recrystallized from ethanol. Yield: 90%; m.p. 188–189° (lit.[3] 190°).

Acknowledgment. We are indebted to Cyclo Chemical Corporation, Los Angeles, Calif., for partial support of this work.

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(3) R. C. Hinton, F. G. Mann, and I. T. Millar, *J. Chem. Soc.*, 4704 (1958).

(4) Analogous effects are recorded in R. A. Friedel and M. Orchin, *Ultraviolet Spectra of Aromatic Compounds*, John Wiley and Sons, New York, 1951, p. 19.

(5) C. Mannich, *Ber.*, 40, 153 (1907).

(6) H. Gilman, J. A. Beel, C. G. Brannen, M. W. Bullock, G. E. Dunn, and L. S. Miller, *J. Am. Chem. Soc.*, 71, 1499 (1949).

(7) H. Bohme, *Org. Syntheses*, Coll. Vol. III, 619 (1955).

A Fifth Route to 1,2,3-Triphenylazulene[1a]

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1,2,3-Triphenylazulene was synthesized by Assony and Kharasch,[1b] in one step, in 25% yield, by the reaction of diphenylacetylene with 2,4-dinitrobenzenesulfenylchloride, and also in very low over-all yield by a nine-step synthesis from cycloheptanone. Battiste and Breslow[2] have recently synthesized the azulene by dehydration of a diphenylcyclopropenecarboxylic acid derivative, and Büchi[3] reports its formation by irradiation of solutions of diphenylacetylene.

This note reports the synthesis of this unique hydrocarbon by a fifth route, based on the azulene synthesis which was briefly communicated by Ziegler and Hafner[4,5] and by Hafner and Kaiser.[6]

The essential steps in the synthesis, which involves reaction of 1,2,3-triphenylcyclopentadiene with *N*-methylpyridinium iodide, have been formulated by Ziegler and Hafner[4,5] and Hafner and Kaiser[6] for other cases.

(1) (a) This work was carried out as an assigned project, suggested by Mr. Earl M. Evleth, in the organic synthesis course conducted by Professor Norman Kharasch in the fall of 1958. The interest and assistance of Mr. Evleth and Dr. Kharasch are gratefully acknowledged. (b) S. J. Assony, and N. Kharasch, *J. Am. Chem. Soc.*, 80, 5978 (1958).

(2) M. Battiste and R. Breslow, Division of Organic Chemistry, American Chemical Society, Abstracts of papers presented at the Boston meeting, April 5, 1959.

(3) G. Büchi and E. W. Robb, personal communication to N. Kharasch, April (1959); *Chimia*, 12, 282 (1958).

(4) H. Hafner, *Angew Chem.*, 70, 419 (1958).

(5) K. Hafner, *Angew Chem.*, 67, 301 (1950).

(6) K. Hafner and H. Kaiser, *Ann.*, 618, 140 (1958).

The triphenylazulene was obtained in 20% overall yield and was shown to be identical with the product of Assony and Kharasch by its melting point, mixture melting point, and infrared spectrum.

EXPERIMENTAL

1,2,3-Triphenylcyclopentadiene (III) was prepared in 55% yield from 1,2,3-triphenylcyclopentadiol, by the method of Paulson.[7]

1,2,3-Triphenylazulene. To 1,2,3-triphenylcyclopentadiene (2 g., 0.007 mol.) was added 20 ml. diphenyl ether and sodium methoxide (0.3 g., 0.007 mol.). The mixture was heated to 70° under nitrogen. Generation of the triphenylcyclopentadienyl anion was indicated by the intense red color of the reaction mixture. Pyridium methiodide (2.0 g., 0.01 mol.) was added to the solution, causing a distinct darkening of the reaction mixture. The solution was refluxed 1 hr., when evolution of methylamine was noted. The reaction mixture was chromatographed on a column of alumina (20 × 2.5 cm.) using low boiling mixed alkanes as solvent and eluting with a 50%, by volume, mixture of benzene and mixed alkanes. A blue band developed, which, after elution and aspiration of the eluate to dryness, yielded a blue solid (0.5 g., 20%). Recrystallization from nitromethane gave the characteristic blue compound melting at 215.5°.

A mixture-melting point of the product and that prepared *via* the sulfenyl chloride–diphenylacetylene route showed no depression and the infrared spectra of the two samples, run consecutively, also exhibited no observable differences.

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(7) P. L. Paulson, *J. Am. Chem. Soc.*, **75**, 2187 (1957).

A New Route to 2,5-Dimethoxyphenylacetic Acid

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The mechanism of the amination of various halobenzenes in the presence of sodium amide and liquid ammonia has been elucidated by Roberts and co-workers.[1] Such aminations of halobenzenes which are nonactivated for nucleophilic substitution appear to involve a "benzyne" intermediate. With an explanation of the course of these reactions came a renewed interest in the further characterization of similar reactions and in the synthetic possibilities of such reactions. Thus Bunnett and Brotherton prepared a number of dialkylanilines by the reaction of bromobenzene with sodium amide and dialkylamines[2] and studied some reactions of "benzyne" and "α-naphthalyne";[3] Hrutfiord and Bunnett recognized the utility of such reactions in the synthesis of heterocyclic and homocyclic compounds.[4] Scardiglia and Roberts have extended earlier studies from their laboratory to include reactions of nonactivated aryl halides with various nucleophilic agents induced by alkali amides in liquid ammonia.[5] Additionally extensive characterization of similar reactions has been carried out by Huisgen and co-workers.[6] Recently Leake and Levine have reported the phenylation of ketones by reaction with phenyl halides and alkali amides.[7]

It seemed that an improved synthesis of 2,5-dimethoxyphenylacetic acid might be achieved by reactions presumably involving a "benzyne" intermediate. 2,5-Dimethoxyphenylacetic acid may be readily converted to homogentisic acid (2,5-dihydroxyphenylacetic acid), a compound of considerable biochemical interest. Studies of the nature and mode of formation of homogentisic acid in animals have provided many of the fundamental data on the intermediary metabolism of tyrosine and phenylalanine. A strong indication that homogentisic acid is an intermediate in the oxidative degradation of phenylalanine and tyrosine was first obtained from isotopic experiments.[8-11]

An improved synthesis of homogentisic acid was desirable. In the best published synthesis of this compound the synthesis of the intermediate 2,5-dimethoxyphenylacetic acid presents serious limitations to the synthesis of homogentisic acid itself since the over-all yield of the intermediate is 30–40% and reactions and work-up procedures are lengthy.[12] It seemed of considerable interest to attempt the synthesis of this intermediate using 2,5-dimethoxybromobenzene with appropriate nucleophiles under conditions where formation of a "benzyne" intermediate might be expected, *i.e.*, in the presence of a metal amide and liquid ammonia. Attempts to use diethyl malonate as a potential nucleophile with potassium amide and liquid ammonia were unsuccessful. However the

(1) J. D. Roberts, H. E. Simmons, Jr., L. A. Carlsmith, and C. W. Vaughan, *J. Am. Chem. Soc.*, **75**, 3290 (1953); J. D. Roberts, D. A. Semenow, H. E. Simmons, and L. A. Carlsmith, *J. Am. Chem. Soc.*, **78**, 601 (1956).

(2) J. F. Bunnett and T. K. Brotherton, *J. Org. Chem.*, **22**, 832 (1957).

(3) J. F. Bunnett and T. K. Brotherton, *J. Org. Chem.*, **23**, 904 (1958).

(4) B. F. Hrutfiord and J. F. Bunnett, *J. Am. Chem. Soc.*, **80**, 2021 (1958).

(5) F. Scardiglia and J. D. Roberts, *Tetrahedron*, **3**, 197 (1958).

(6) H. Konig and R. Huisgen, *Chem. Ber.*, **92**, 429 (1959); see also earlier publications in this series.

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(9) B. Schepartz and S. Gurin, *J. Biol. Chem.*, **180**, 663 (1949).

(10) A. B. Lerner, *J. Biol. Chem.*, **181**, 281 (1949).

(11) R. G. Ravdin and D. I. Crandall, *J. Biol. Chem.*, **189**, 137 (1951).

(12) H. Wolkowitz and M. S. Dunn, *Biochemical Preparations*, Vol. 4, W. W. Westerfeld, ed., J. Wiley and Sons, Inc., New York, 1955, p. 6.

isolation of 2,5-dimethoxyaniline in 12% yield indicated that a "benzyne" intermediate had indeed formed. To minimize the competing reaction, sodium amide in liquid ammonia[13] was used in subsequent experiments in slight molar excess to the bromo compound plus nucleophile.

An attempt to use ethyl acetate as a potential nucleophile was also unsuccessful. Examination of Fisher-Hirschfelder-Taylor models suggested that the formation of the products expected from reaction with diethyl malonate or ethyl acetate would be unlikely for steric reasons.

α-Sodio sodium acetate[14] was also tried as a nucleophile at the boiling points of the inert solvents *p*-xylene and tetrahydrofuran as well as at room temperature with 2,5-dimethoxybromobenzene itself as a suspending medium. The α-sodio sodium acetate appeared to be partially soluble in each of these reaction media but in no case could the product of interest be isolated.

When acetonitrile was tested as a potential nucleophile, the reaction mixture after work-up yielded 2,5-dimethoxyphenylacetic acid. While synthesis of this compound *via* the nitrile results in yields of approximately 10%, the reaction takes little time and work-up procedures are short. Thus the synthesis appears to hold promise for the synthesis of homogentisic acid labeled in the side chain for metabolic studies. In addition the reactions constitute a novel route to 2,5-dimethoxyphenylacetic acid.

EXPERIMENTAL

Materials. 2,5-Dimethoxybromobenzene (I) was prepared in approximately 60% yield by the methylation of bromohydroquinone employing conventional reaction conditions with dimethyl sulfate and sodium hydroxide. The product was obtained as a colorless oil which was identified by boiling point, analysis for C, H, and Br, and infrared analysis.[15]

Attempted reaction of I with diethyl malonate. Isolation of 2,5-dimethoxyaniline (II). To approximately 300 ml. of liquid ammonia (−77°) and 0.28 g. of ferric nitrate·9 H_2O, approximately 2 g. of potassium was added and the mixture stirred for 15 min. to form the catalyst (metallic iron) for the preparation of potassium amide. Additional potassium (43.4 g., 1.14 mol.) was then added with stirring. After evolution of hydrogen was complete, 19.2 g. of diethyl malonate (0.12 mol.) was added dropwise with stirring, followed by 21.7 g. of 2,5-dimethoxybromobenzene (0.1 mol.) and the temperature of the reaction mixture raised to approximately −30° for 1 hr. Enough 10% ammonium chloride was then carefully added to convert amide ion to ammonia and the ammonia was then distilled out of the reaction mixture at reduced pressure. The reaction mixture was extracted with diethyl ether, and the ether removed by distillation to leave a dark brown oil. The oil was fractionated by distillation under reduced pressure and partial characterization of minor fractions gave no indication that diethyl(2,5-dimethoxyphenyl)malonate had been formed. The major fraction which distilled at about 1 mm. from 80–90° and crystallized in the condenser was collected. This solid was further purified by sublimation to yield 1.8 g. (12%) of white, crystalline II, which melted at 74–76° (literature m.p. 80°[16]) and behaved as a typical amine.

Anal. Calcd. for $C_8H_{11}NO_2$: C, 62.72; H, 7.24; N, 9.15. Found: C, 62.59; H, 7.23; N, 9.27.

The infrared spectrum supported the structure of the product.

Reaction of I *with acetonitrile. Preparation of 2,5-dimethoxyphenylacetic acid* (III). Reaction conditions were similar to those described above except that to one flask (−30°) containing 150 ml. of ammonia and 3.84 g. of sodium (0.17 mol.), 6.93 g. of acetonitrile (0.17 mol.) was added followed by the addition of 17.8 g. of 2,5-dimethoxybromobenzene (0.083 mol.). The contents of a second flask (−30°) containing initially 250 ml. of ammonia, 3.84 g. of sodium (0.17 mol.), and a catalytic amount of ferric nitrate·9 H_2O were then slowly flushed into the first flask. After complete transfer, which took approximately 30 min., the reaction mixture was covered with anhydrous diethyl ether and ammonium chloride added to liberate ammonia. To the reaction mixture more diethyl ether was added, and the ether was then removed from the ether extract by distillation, leaving a brown oil. This oil was then submitted to hydrolysis in twice its volume of concentrated hydrochloric acid for 4 hr. During hydrolysis a viscous oil separated, and after hydrolysis this oil was dissolved in 10% sodium carbonate. Acidification of the bicarbonate solution to *p*H 2 yielded a tan crystalline compound which was isolated in 15% yield (2.38 g). Purification of the tan product by sublimation and recrystallization resulted in 50–70% recovery of the tan product as a white, crystalline compound (III). III melted at 121.0–121.5° (literature m.p., 122–123°[12]) and the infrared spectrum supported the proposed structure.

Anal. Calcd. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17. Found: C, 61.19; H, 6.13.

Acknowledgment. The authors wish to thank Professor J. F. Bunnett for acquainting them with the synthetic possibilities of reactions presumably involving a "benzyne" intermediate.

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(13) Sodium amide is less soluble in ammonia at −30° than is potassium amide.

(14) We wish to thank Ethyl Corp., New York, for a generous gift of this compound.

(15) Elemental analyses were performed by Weiler and Strauss, Microanalytical Laboratory; infrared analyses were made by the Division of Industrial Research, Washington State University.

(16) A. Blackhall and R. H. Thomson, *J. Chem. Soc.*, 3916 (1954).

Epoxidation of Cinnamaldehyde by Alkaline *tert*-Butyl Hydroperoxide

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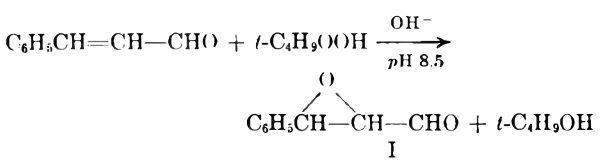
An attempt was made to form an epoxide of cinnamaldehyde with alkaline hydrogen peroxide using the technique recently described for the epoxidation of acrolein and α-methylacrolein.[1] As the

(1) G. B. Payne, *J. Am. Chem. Soc.*, **81**, 4901 (1959); E. Weitz and A. Scheffer, *Ber.*, **54**, 2327 (1921) obtained only acidic product from the attempted alkaline epoxidation of cinnamaldehyde.

major product appeared to be an organic peroxide rather than the desired epoxy aldehyde, the reaction was carried out with *tert*-butyl hydroperoxide as oxidant rather than hydrogen peroxide.



Cinnamaldehyde and *tert*-butyl hydroperoxide were allowed to react in *methanol* solution at 35–40° for five to six hours while dilute sodium hydroxide was added continuously to neutralize acidic by-product and maintain a *p*H of about 8.5. β-Phenylglycidaldehyde (I) was readily obtained in 73% yield by Claisen-distillation of the crude product.

While this epoxidation of cinnamaldehyde by means of alkaline *tert*-butyl hydroperoxide appears to be the first such reaction with an α,β-unsaturated aldehyde, the corresponding reaction with α,β-unsaturated ketones has recently been described.[2] In that work, *benzene* was the solvent and no attempt was made to operate with controlled *p*H. When such a procedure was used with cinnamaldehyde, the crude product was mainly an organic peroxide (possibly *via* Michael addition); it was not further investigated.

EXPERIMENTAL

Epoxidation of cinnamaldehyde. To a 1-l., 5-neck, round bottom flask equipped with mechanical stirrer, dropping funnels, thermometer, and standard electrodes connected to a Beckman *p*H meter, were added 400 ml. of methanol and 71.2 g. (0.60 mol.) of *tert*-butyl hydroperoxide (Lucidol, 75.9% by iodometric titration). The meter *p*H was adjusted to 10.5 ± 0.2 (true *p*H of about 8.5 by indicator paper) by the addition of *N* sodium hydroxide and maintained there as 66 g. (0.50 mol.) of freshly distilled cinnamaldehyde was added at 35–40° over 1 hr. After another 4.5 hr., iodometric titration indicated that 0.48 mol. of hydroperoxide had been consumed and the reaction had essentially stopped; 20 ml. of alkali (4 mol. %) was utilized in maintaining the desired *p*H.

After dilution with 1.5 l. of water and extraction by three 200-ml. portions of chloroform, the combined extracts were washed, dried, concentrated to low volume under vacuum and finally Claisen-distilled. There was thus obtained 54 g. (73% yield) of β-phenylglycidaldehyde, b.p. 66–68° (0.2 mm.), n_D^{25} 1.5447. The infrared spectrum showed aldehyde carbonyl absorption at 5.76 μ and epoxide absorption at 8.14 and 11.50 μ.

Anal. Calcd. for $C_9H_8O_2$: C, 73.0; H, 5.4; carbonyl value, 0.68 equiv./100 g.; oxirane oxygen, 10.8. Found: C, 72.9; H, 5.7; carbonyl value, 0.69 equiv./100 g.; oxirane oxygen, 6.7.[3]

The *2,4-dinitrophenylhydrazone* was prepared from 3.0 g. of epoxy aldehyde by adding the latter to a hot solution of 4.0 g. of 2,4-dinitrophenylhydrazine and 2 ml. of acetic acid in 300 ml. of ethanol. After boiling for 1 min., the solution was cooled quickly to 60° and filtered. After standing overnight at room temperature, the derivative was recovered by filtration and washed well with ethanol. The weight of material melting at 138–139° was 3.3 g.

Anal. Calcd. for $C_{15}H_{12}N_4O_5$: N, 17.0. Found: N, 16.9.

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(2) N. C. Yang and R. A. Finnegan, *J. Am. Chem. Soc.*, **80**, 5845 (1958).

(3) Hydrochloric acid in dioxane; see J. L. Jungnickel, E. D. Peters, A. Polgar, and F. T. Weiss, "Organic Analysis, Vol. 1," Interscience Publishers, Inc., New York, 1953, p. 135; in a blank experiment, styrene oxide itself gave an oxirane oxygen value of only 88% of theory.

Diels-Alder Diene Synthesis With 1,1,1-Trichloro-3-nitropropene[1]

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Although many examples of the Diels-Alder reaction for aromatic substituted nitroolefins, such as β-nitrostyrene and substituted β-nitrostyrenes, have been published,[2] few have been reported for non-aromatic nitroolefins. Nitroethene,[3,4] 1-nitro-1-propene,[3] 1-nitro-1-pentene,[3] 1-nitro-1-heptene,[5] 1-nitro-1-octene,[5] 2-nitropropene,[6,7] 2-nitro-1-butene[6] and 2-nitro-2-butene[7] react with cyclopentadiene to yield the normal Diels-Alder adduct in 33 to 72% yield. Both aromatic and non-aromatic nitroolefins react with anthracene[8] in yields up to 62%. Substituents on the nitroolefins reduce the yield[8] or appear to cause the reaction to proceed with greater difficulty.[5]

The present study was undertaken to learn the effect of the sterically bulky, electron attracting trichloromethyl group in 1,1,1-trichloro-3-nitropropene[9] (I) upon the Diels-Alder reaction. The dienes used were butadiene-1,3 (IIa), isoprene (IIb), pentadiene-1,3 (IIc), 2,3-dimethylbutadiene-1,3 (IId), cyclopentadiene (IIe), 2-chlorobutadiene-1,3,furan and 2,5-dimethylfuran. The latter two compounds were chosen because they react with less facility or fail to react in the Diels-Alder re-

(1) Supported in part by a grant from Research Corporation to whom the authors are grateful. Taken in part from the Masters thesis of W. W.

(2) For example: W. C. Wildman, R. B. Wildman, W. T. Norton, and J. B. Fine, *J. Am. Chem. Soc.*, **75**, 1912 (1953).

(3) K. Alder, H. Rickert, and E. Windemuth, *Ber.*, **71**, 2451 (1938).

(4) W. C. Wildman and C. H. Hemminger, *J. Org. Chem.*, **17**, 1641 (1952); J. D. Roberts, C. C. Lee and W. H. Saunders, Jr., *J. Am. Chem. Soc.*, **76**, 4501 (1954).

(5) W. E. Noland, R. E. Counsell, and M. H. Fisher, *J. Org. Chem.*, **21**, 911 (1956).

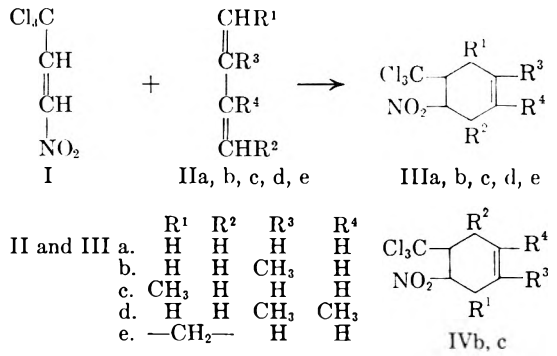
(6) D. V. Nightingale, M. Maienthal, and J. A. Gallagher, *J. Am. Chem. Soc.*, **75**, 4852 (1953).

(7) W. E. Noland and R. E. Bambury, *J. Am. Chem. Soc.*, **77**, 6386 (1955).

(8) W. E. Noland, H. I. Freeman, and M. S. Baker, *J. Am. Chem. Soc.*, **78**, 188 (1956).

(9) F. Brower and H. Burkett, *J. Am. Chem. Soc.*, **75**, 1082 (1953).

action. For example, both are reported not to react with β-nitrostyrene.[10]



The dienes listed, except the two furans and 2-chlorobutadiene-1,3, reacted with I to yield adducts in 65 to 88% yield. Attempts with the furans included standing at room temperature for thirty days without solvent, refluxing without solvent and refluxing in acetic acid. In each case both the furan and I were recovered and there was no residue. In all of the attempts with the 2-chlorobutadiene, I was completely or nearly completely recovered. The remainder of the reaction mixture was a non-distillable, resinous material. This reaction was tried, without solvent, in xylene and in acetic acid; with temperatures between room temperature and that of refluxing xylene; and with reaction times from four hours to nineteen days. In most of the attempts hydroquinone was added to inhibit polymerization.

Although no experiments were performed to prove the position of the double bond in the products, the infrared spectrum for each product was consistent with that expected for the normal Diels-Alder product.[11]

Two position isomers are possible for the products from both IIb and IIc. Treatment of the adduct from IIb with palladium on charcoal produced 4-methyl-2-nitrobenzoic acid. Heating the same material with concentrated sulfuric acid produced *m*-toluic acid. Evidently, the product contained both isomers, IIIb and IVb. No attempt was made to separate them. Although the presence of isomeric compounds in the product from IIc was not investigated, it probably contained both IIIc and IVc.

Whereas the reaction with IIe was exothermic and essentially complete at 35–50° within a few hours, that using IIa was quite slow. Table I indicates the percent yield isolated from reactions carried out at room temperature for different lengths of time. Maximum yields were obtained only when the reaction time was over two weeks. As the reaction was not exothermic for any of the other compounds, each was allowed to react at room temperature for at least two weeks before distilling.

TABLE I

PERCENT YIELD VS. REACTION TIME FOR BUTADIENE

Time (days)	Yield, %
0.25	1.7
0.5	3.5
1	7.8
3	19.5
6	37
8	50
11	65
15	78

EXPERIMENTAL

Dienes. 2-Chlorobutadiene-1,3 was distilled from a chloroprene-xylene mixture obtained from E. I. du Pont de Nemours.[12] The 1,3-butadiene (special purity grade), isoprene (polymerization grade), and pentadiene-1,3 were supplied by the Phillips Petroleum Company.[12] The 2,3-dimethylbutadiene-1,3 was supplied by the Borden Company.[12] Cyclopentadiene was obtained by the thermal depolymerization of dicyclopentadiene from the Enjay Company.[12]

2-Nitro-1,2,3,6-tetrahydrobenzotrichloride (IIIa). For each run 32.5 g. (0.6 mol.) of 1,3-butadiene and 80 g. (0.45 mol.) of I were sealed in a heavy-walled bottle. After the length of time given in Table I each mixture was distilled under reduced pressure. The yield of product was taken to be that distilling at *ca.* 109–112°/1 mm. The crude product from a run allowed to stand for 18 days was carefully fractionated, yielding 71 g. (67%) of a very pale yellow oil, b.p. 110–111°/1 mm., d_{20}^{20} 1.4801, n_D^{20} 1.5317.

Anal. Calcd. for $C_7H_8Cl_3NO_2$: N, 5.73; Cl, 43.52. Found: N, 5.74; Cl, 43.70.

4-Methyl-2-nitro-1,2,3,6-tetrahydrobenzotrichloride (IIIb) *and 5-methyl-2-nitro-1,2,3,6-tetrahydrobenzotrichloride* (IVb). A solution of 15 g. (0.22 mol.) of isoprene (IIb) and 39 g. (0.22 mol.) of I was placed in a stoppered flask. After 25 days the mixture was fractionated, yielding 48 g. (84.5%) of pale yellow oil, b.p. 117–118°/1 mm., d_{20}^{20} 1.4119, n_D^{20} 1.5271.

Anal. Calcd. for $C_8H_{10}Cl_3NO_2$: N, 5.42; Cl, 41.14. Found: N, 5.49; Cl, 41.23.

Evidence for IIIb in the product from isoprene. A mixture of 20 g. of the product from isoprene and 5 g. of 10% palladium on charcoal was heated in a flask at 190° until no more gas was evolved. The cooled residue was pulverized and extracted with three 40-ml. portions of ether. Evaporation of the ether left a brown sticky residue. Distillation gave 2.0 g. of a liquid, which solidified. Sublimation afforded a pale yellow product, m.p. 161–163°. The reported[13] melting point for 4-methyl-2-nitrobenzoic acid is 161°. The product was converted,[14] via the acid chloride, m.p. 158–160°, to the amide, m.p. 150–152°. The reported[13] melting points are 157° and 153°, respectively.

Evidence for IVb in the product from isoprene. The product (14 g.) was dissolved with cooling in 50 ml. of concentrated sulfuric acid. After standing at room temperature for 4 hr. and heating on the steam bath for 5 hr., the mixture was cooled and poured onto 125 g. of ice. After filtering, the

(10) C. F. H. Allen and A. Bell, *J. Am. Chem. Soc.*, 61, 521 (1939).

(11) The authors are indebted to Dr. Harold Boaz of Eli Lilly and Company for help in interpreting the spectra.

(12) The authors are grateful to these companies for complementary samples.

(13) C. Joachim, *Ann.*, 266, 210 (1891).

(14) S. M. McElvain, "The Characterization of Organic Compounds," The MacMillan Company, New York, N. Y., 1945, p. 193.

resulting solid was extracted with 225 ml. of boiling water in six portions. Chilling in ice and filtering left a brown crystalline solid. This was extracted with boiling 90–100° ligroin, decanting from the insoluble dark oil. Cooling and filtering yielded 0.8 g. of white crystals, m.p. 110.5–111.5°. The reported melting point for *m*-toluic acid is 111–112°. This product was converted,[14] *via* the acid chloride, to the amide, m.p. 93–94° (lit.[14] 94°).

3-Methyl-2-nitro-1,2,3,6-tetrahydrobenzotrichloride (IIIc) *and/or 6-methyl-2-nitro-1,2,3,6-tetrahydrobenzotrichloride* (IVc). A mixture of 15 g. (0.22 mol.) of pentadiene-1,3 and 39 g. (0.22 mol.) of I was allowed to stand in a stoppered flask for 14 days. Fractionation afforded 26 g. (65%) of pale yellow liquid, b.p. 110–111.5°/1 mm., d_{20}^{20} 1.3626, n_D^{20} 1.5232.

Anal. Calcd. for $C_8H_{10}Cl_3NO_2$: N, 5.42; Cl, 41.14. Found: N, 5.32; Cl, 41.34.

4,5-Dimethyl-2-nitro-1,2,3,6-tetrahydrobenzotrichloride (IIId). A mixture of 18 g. (0.22 mol.) of 2,3-dimethylbutadiene-1,3 and 39 g. (0.22 mol.) of I was allowed to stand in a stoppered flask at room temperature for 14 days. Fractionation gave 41 g. (69%) of pale yellow liquid, b.p. 118–119°/1 mm., d_{20}^{20} 1.4225, n_D^{20} 1.5253.

Anal. Calcd. for $C_9H_{12}Cl_3NO_2$: N, 5.14; Cl, 39.05. Found: N, 5.17; Cl, 39.21.

3,6-Endomethylene-2-nitro-1,2,3,6-tetrahydrobenzotrichloride (IIIe). To 78 g. (0.44 mol.) of cold I was added 31 g. (0.44 mol.) of cold freshly-prepared cyclopentadiene in 3-ml. portions with swirling and cooling in an ice bath so that the temperature was maintained at 35–50°. When the mixture was no longer exothermic, the container was stoppered and allowed to stand at room temperature. Fractionation yielded 98 g. (87.5%) of pale yellow liquid, b.p. 113.5–115°/1 mm., d_{20}^{20} 1.4831, n_D^{20} 1.5334.

Anal. Calcd. for $C_8H_8Cl_3NO_2$: N, 5.50; Cl, 41.45. Found: N, 5.40; Cl, 41.04.

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Reactions of Allene. I. Diels-Alder Adducts

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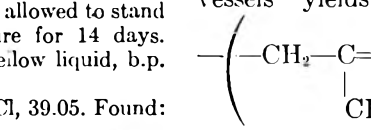
The Diels-Alder reaction between simple olefins and dienes is known[1] The same reaction between dienes and activated double bonds has received much attention.[2] However, the Diels-Alder reaction between dienes and compounds possessing cumulated double bonds has received very limited study.[3]

In this laboratory the Diels-Alder reactions between allene, which contains cumulated double bonds, and several conjugated dienes were studied. These Diels-Alder adducts were sought as intermediates for other studies now in progress in this laboratory. We wish to report at this time some results on cyclopentadiene and hexachlorocyclopentadiene.

Cyclopentadiene reacted with allene yielding four isolable products (II and III were not previously known): 5-methylenebicyclo[2.2.1]-2-heptene (I);[4] 1,2,3,4,4a,5,8 8a-octahydro-2-methylene-1,4,5,8 - dimethanonaphthalene (II); 1,2,3,4,4a,5,-5a,6,9.9a,10,10a-dodecahydro-2-methylene-1,4,5,-10,6,9-trimethanoanthracene (III); and a polymer (IV). The structures of the cuts corresponding to compounds II and III have not been proved but are probably as named. The characterization of IV has not been made, but collected data does not refute Lebedev and Merezhkovskii's[5] presumption that the polymerization of allene in metallic vessels yields a polymer of the structure



—. Average molecular weight coupled with percent unsaturation would indicate that the average value of n is 11.5 in the particular sample of polymer reported here. Three different elemental analyses gave total carbon and hydrogen of about 95–97%. Mass spectroscopy analyses showed water present in the polymer. The infrared absorption at 11.45 μ is indicative of terminal unsaturation at the polymer chain end. While higher adducts such as four or five diene molecules to one of allene may have been formed in this reaction, they were in such low concentration that they were not isolated by distillation of the reaction mixture.

Hexachlorocyclopentadiene (V) reacted with allene yielding only one isolable product which was previously unknown: 1,2,3,4,7,7-hexachloro-5-methylenebicyclo [2.2.1]-2-heptene (VI). As would be expected, V reacted with allene at a lower temperature than cyclopentadiene and the yield of VI was higher than for I. No higher molecular weight adducts or polymer was isolated or indicated.

EXPERIMENTAL[6]

Allene. Fractional distillation of Dow methylacetylene–propadiene mixture (30% allene and 70% methylacetylene) at atmospheric pressure through a 60-inch glass, helices packed column yielded allene, b.p. −34.8° to −33.9°, having 98+% purity which was stored in steel cylinders until used.

Cyclopentadiene was prepared as 99+% pure material, b.p. 41–43°, by pyrolysis of Enjay dicyclopentadiene. The

(1) L. M. Joshel and L. W. Butz, *J. Am. Chem. Soc.*, **63**, 3350 (1941).

(2) H. L. Holmes, "Organic Reactions," John Wiley and Sons, Inc., New York, 1948, Vol. IV, 60.

(3) von O. Diels and W. Friedrichsen, *Ann.*, **513**, 145 (1934); O. Wickterle and J. Rocek, *Chem. Listy*, **47**, 1768 (1953); *Coll. Czechoslov. Chem. Comm.*, **19**, 282 (1954).

(4) This compound was made by dehydrobromination of the Diels-Alder adduct between allyl bromide and cyclopentadiene and was presented by P. von R. Schleyer and R. E. O'Connor before the Division Organic Chemistry, American Chemical Society, Chicago, Ill., September, 1958, Paper No. 66.

(5) S. V. Lebedev and B. K. Merezhkovskii, *J. Russ. Phys. Chem. Soc.*, **45**, 1249.

(6) Boiling points are uncorrected. Elemental analyses were carried out by Galbraith Laboratory, Knoxville, Tennessee. Yields are calculated on charged reactant as noted.

material was stored at −20° for periods not longer than one month before use.

Hexachlorocyclopentadiene was received as a sample from Hooker Electrochemical Company (C-56) and was used as such.

5-Methylenebicyclo[2.2.1]-2-heptene (I). A 2960 ml. stainless steel autoclave was cooled to −78° while purging with dry nitrogen and was then charged with 330 g. (5.0 mol.) cyclopentadiene and 200 g. (5.0 mol.) allene (determined by passage through a calibrated flow meter). The autoclave was capped, placed in a rocker, and heated to 200° over a 1.25-hr. period. At 200° the autogeneous pressure reached 620 p.s.i. and began dropping. During the next 5 hr. the temperature was maintained between 200 and 230° with a subsequent drop in pressure to 280 p.s.i. (210°). When the autoclave had cooled to room temperature, it was vented (while warming) through a trap at −78° to collect 55.4 g. of unreacted allene. The straw yellow liquid (479.2 g.) in the autoclave was distilled rapidly through a 3-inch tube containing a side arm at a total take off yielding 200.9 g. liquid, b.p. 26–100°/160 mm. This crude product was redistilled through a 10-inch glass spiral column at atmospheric pressure yielding 186 g. (48.6% yield based on allene) I, b.p. 115–120°, n_D^{25} 1.4834–1.4840. A heart cut, b.p. 73.0°/172 mm., n_D^{25} 1.4838, n_D^{20} 1.4860, d_4^{20} 0.889, from the redistillation of combined I from several runs was used for analyses. The infrared spectrum showed principal bands at 5.72, 6.03, 6.38, 11.44, 13.8, and 14.6 μ. Mass spectroscopy analyses support the structure of I.

Anal. Calcd. for C_8H_{10}: C, 90.6; H, 9.4. Found: C, 90.5; H, 9.5.

Mol. refr. calcd.: 33.8. Found 34.1. Mol. wt. calcd.: 106.2. Found (ebulioscopic): 114.

A sample of I, b.p. 73.0/160 mm., absorbed 4 equivalents of hydrogen in 4 hr. at 175–185° and 1500 p.s.i. over Harshaw 0104 Ni/Kieselguhr catalyst. Distillation gave a 95% yield of 2-methylbicyclo[2.2.1]heptane,[7] b.p. 124.5–125.0°, n_D^{25} 1.4516, n_D^{20} 1.4541.

1,2,3,4,4a,5,8,8a-Octahydro-2-methylene-1,4,5,8-dimethanonaphthalene (II). The residues from the rapid distillation and from the redistillation above were combined and distilled through a 10-inch glass spiral column yielding 74.8 g. (12.1% yield based on allene) II, b.p. 92–98°/7.0 mm., n_D^{25} 1.5312–1.5330, d_4^{20} 1.020. A heart cut, b.p. 92.0°/6 mm., n_D^{25} 1.5319, n_D^{20} 1.5338, d_4^{20} 1.012, from redistillation of combined II from several runs was used for analyses. The infrared spectrum showed principal bands at 5.72, 6.03, 6.38, 11.44, 13.2, and 13.6 μ.

Anal. Calcd. for $C_{13}H_{16}$: C, 90.6; H, 9.3. Found: C, 90.10; H, 9.88.

Mol. refr. calcd.: 52.5. Found: 52.8. Mol. wt. calcd.: 172. Found: 170.

1,2,3,4,4a,5,5a,6,9,9a,10,10a-Dodecahydro-2-methylene-1,4,5,10,6,9-trimethanoanthracene (III). Continued distillation of the above residues at reduced pressure yielded 10.9 g. (9.3% yield based on allene) III, b.p. 71–76°/0.07 mm., n_D^{25} 1.5444. A heart cut, b.p. 74.5°/0.07 mm., n_D^{25} 1.5442, n_D^{20} 1.5463, d_4^{20} 1.048, was used for analyses. The infrared spectrum of III showed principal bands at 5.72, 6.03, 6.38, 11.44, 13.29, and 13.4 μ.

Anal. Calcd. for $C_{18}H_{22}$: C, 90.71; H, 9.33. Found: C, 90.0; H, 8.6. Mol. ref. calcd.: 71.6. Found: 71.9. Mol. wt. calcd.: 238.0. Found: 218.

Polymer. The 31.5 g. of residue from the above distillation cooled to a hard glass which was dissolved in 100 ml. boiling benzene. The cooled solution was slowly poured into 3 l. of methanol and the resulting brown precipitate was filtered, mixed with 300 ml. methanol, beaten 1 min. in a Waring blendor, filtered, and air dried 3 days yielding 30 g. (15.0% yield based on allene) of cream colored powder. This polymer softened at 81° and melted at 162–165°.

Anal. Calcd. for $(C_6H_8)_n$: C, 90.0; H, 10.0. Found: C, 86.5; H, 9.2. Mol. wt. calcd. for n = 11.5: 920. Found: 903 ± 1%. % Unsatn. calcd. for $(C_6H_8)_{11.5}$: 30. Found (Bromination): 29.

The infrared spectrum of a Nujol mull of this polymer has bands at 6.04, 11.45, and 12.57 μ.

1,2,3,4,7,7-Hexachloro-5-methylenebicyclo[2.2.1]-2-heptene (VI). A 2960 ml. stainless steel autoclave was charged as above with 1173.8 g. (4.3 mol.) hexachlorocyclopentadiene (V) and 208.7 g. (5.2 mol.) allene. After capping and placing in a rocker, the autoclave was heated to 150° while rocking. At 150° the autogeneous pressure reached 245 p.s.i. and remained constant during the next 6 min. while the temperature continued to rise to 176° without external heating. The heat of reaction produced a maximum rise in temperature to 200° while the pressure dropped to 190 p.s.i. over the next 23 min. The temperature then began dropping. Over a 2.25-hr. period the temperature had risen from 150° to a maximum 230° and dropped to 170° while the pressure dropped from 245 p.s.i. to a constant 150 p.s.i. After the autoclave had cooled to room temperature it was vented through a trap (−78°) yielding 7.8 g. allene. Gaseous hydrogen chloride was also liberated during venting. The black liquid (1347.1 g.) remaining in the autoclave was subjected to reduced pressure for 1 hr. to remove absorbed hydrogen chloride. Rapid distillation of the residual liquid through a 4-inch Vigreaux column yielded 1098.7 g. yellow liquid, b.p. 74 (0.5 mm.) −80° (0.08 mm.), and 185 g. black charred residue. Redistillation of the 1098.7 g. of distillate through a 24-inch glass helices packed column yielded 1021.9 g. (76% yield based on hexachlorocyclopentadiene charged) VI, b.p. 72° (0.08 mm.) −85° (0.25 mm.), n_D^{25} 1.5590. A heart cut, b.p. 90°/0.3 mm., n_D^{25} 1.5592, n_D^{20} 1.5611, d_4^{20} 1.605, was used for analyses. Infrared spectrum showed principal bands at 6.02, 6.23, 10.95, 13.5, 13.8, and 15.38 μ.

Anal. Calcd. for $C_7H_4Cl_6$: C, 30.73; H, 1.29: Cl, 68.0. Found: C, 30.44; H, 1.66; Cl, 67.97. Mol. refr. calcd.: 63.0. Found: 63.0. Mol. wt. calcd.: 312.9. Found: 326.

Acknowledgment. We wish to acknowledge the able assistance of Mr. W. D. Beck in carrying out several of the autoclave reactions and Mr. D. H. Wolfe for his help in hydrogenating one of the products.

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(7) These properties agree with the values, b.p. 126.9–127.3° and n_D^{20} 1.4540, reported by G. Calingaert, H. Soross, and H. Shapiro, *Ind. Eng. Chem.*, **36**, 1055 (1944).

The Chemistry of β-Bromopropionyl Isocyanate. II. Use in Identification of Alcohols[1]

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The reaction of β-bromopropionyl isocyanate (I) with alcohols has been examined to determine the utility of I in making solid urethanes for the

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identification of alcohols. It has been found useful for this purpose.

Solid β-bromopropionylcarbamates ($BrCH_2CH_2CONHCO_2R$) were obtained from the reaction of compound I with most common alcohols: *e.g.*, methyl, *i*-propyl, *t*-butyl, propargyl, and allyl alcohols; benzohydrol and triphenylcarbinol; and several glycols. Long chain alcohols (cetyl and stearyl) and cholesterol formed solid urethanes without difficulty; the β-bromopropionylcarbamates appear to be among the most easily obtained derivatives of the long chain alcohols. The most important difficulty with compound I was the tendency of some secondary alcohols to form oils (in Table I, those alcohols which formed oils instead of solid urethanes are noted). Glycerol did not appear to react with compound I, apparently because of immiscibility with the chloroform solvent.

Compound I offers two advantages over the more conventional aryl isocyanates. First, it may be prepared as needed from the stable, easily stored *N*-bromosuccinimide.[2] Compound I is not isolated from the rearrangement; the alcohol is added to the solution in which the rearrangement was conducted. Secondly, the reaction product of compound I with water is β-bromopropionamide,[2,3] which can be removed in most instances by crystallization.[4] Thus terpin hydrate and pinacol hydrate gave normal diurethanes without removel of the water of hydration. 95% Ethanol also gave a satisfactory derivative. With the more soluble derivatives, particularly those of secondary alcohols, better results were obtained with dry alcohols. Compound I is more reactive than the aryl isocyanates, and forms carbamates with even the longer chain alcohols very rapidly. A study of quantitative differences in reactivity will be undertaken shortly.

The usual range of melting points is encountered with the β-bromopropionylcarbamates. Some have melting points too near to be of value in differentiation; the long chain urethanes are particularly poor in this respect.[5]

Reasonable care should be exercised in the use of compound I. Although it did not appear to be more toxic than phenyl or α-naphthyl isocyanates, 10% solutions of compound I in chloroform did produce rashes when allowed to come into contact with skin. No investigation of the toxicity of compound I or its derivatives was undertaken.

TABLE I. TABLE OF DERIVATIVES

Alcohol[a]	M.P. of β-Bromo-propionylcarbamate,[b] °C.	Nitrogen, %[c] Calcd.	Found
Methyl	137–139	[d]	
Ethyl	111–113	6.25	6.49[e]
n-Propyl	95–97	5.89	6.37
iso-Propyl	103–104	5.89	5.92
n-Butyl	90–92[f]	5.57	5.38[e]
iso-Butyl	80–82	5.57	5.61[e]
sec-Butyl	Oil		
tert-Butyl	97–99	5.57	5.18[e]
n-Amyl	81–83[f]	5.27	5.18[e]
2-Pentanol	85–87	5.27	4.96[e]
3-Pentanol	Oil		
iso-Amyl	87–88	5.27	5.03[e]
tert-Amyl	101–103	5.27	5.44[e]
n-Hexyl	72–74	5.01	4.60
n-Heptyl	75–77	4.77	4.37[e]
2-Octanol	Oil		
n-Decyl	86–88	4.17	4.46
n-Dodecyl	87–89	3.85	3.95
n-Tetradecyl	92–93	3.57	3.23
Cetyl	92–94[f]	3.34	3.53
Stearyl	97–98	3.12	2.76
Allyl	99–100	5.94	5.77
Propargyl	117–118	5.99	6.36
Cyclohexyl	82–84	5.04	5.44
Benzyl	125–127	4.91	5.24
p-Methoxybenzyl	113–115	4.44	4.24[e]
α-Phenylethyl	Oil		
β-Phenylethyl	86–88	4.67	4.71
γ-Phenylpropyl	76–77	4.47	4.33
β-Chloroethyl	125–127	5.45	5.49
β-Hydroxypropionitrile	152–154	11.37	11.62
Cinnamyl	132–133	4.49	4.19[e]
Cholesterol	238–240 (sl. dec.)[g]	2.49	2.76[e]
Terpin hydrate	162–163[g]	5.14	4.78
Furfuryl[h]	123–127 (dec.)		
Tetrahydrofurfuryl	96–98	5.08	4.68
2-Ethoxyethyl	90–92[f]	5.23	4.88[e]
Ethylene glycol	162–163	6.72	6.65
Diethylene glycol	162–164[g]	6.07	5.77
Isoborneol	122–124	4.19	3.82[e]
Benzohydrol	137–139	3.89	3.85
Triphenyl carbinol	82–84	2.94	3.20
Diacetone alcohol	109–110[f]	4.86	4.99[e]
Pinacol hydrate	200–201	5.98	5.62
meso-2,3-Butanediol	128–130	6.28	6.31[e]
1,1,1-Trichloro-2-2-methyl-2-propanol	137–138	3.94	4.29
1-Methoxy-2-propanol	102–104	5.23	5.33
2-Methoxyethanol	95–97	5.52	5.58
3-Hydroxy-2-butanone	105–107	5.26	5.49[e]
Geraniol	65–67	4.22	3.90[e]
Benzoin	135–137	3.59	3.25
2,2-Dimethylpropanediol	170–172	6.09	5.72[e]

[a] Alcohols were obtained from commercial sources and were used as obtained. [b] Melting points were measured on a Fischer-Johns block and were not corrected. [c] Dumas nitrogen by C. F. Geiger, 312 Yale St., Ontario, Calif. [d] Calcd. for $C_5H_8O_3NBr$: C, 28.60; H, 3.84; N, 6.67; Br, 38.05. Found: C, 28.7; H, 3.8; N, 6.5; Br, 38.0. Analyses by Analytical Laboratories, The Dow Chemical Co., Midland, Mich. [e] Determined by authors using Kjeldahl method. [f] Crystallized from benzene. [g] Crystallized from tetrahydrofuran. [h] Decomposed on standing at room temperature. No analysis performed.

(2) H. W. Johnson, Jr., and D. E. Bublitz, *J. Am. Chem. Soc.*, **80**, 3150 (1958).

(3) J. C. Martin and P. D. Bartlett, *J. Am. Chem. Soc.*, **79**, 2533 (1957).

(4) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Identification of Organic Compounds*, 4th ed., John Wiley & Sons, New York, N. Y., 1956, p. 207.

(5) See the melting points of the phenylurethanes and α-naphthylurethanes of lauryl, myristyl, and cetyl alcohols in ref. 4, p. 282, for other examples of similar behavior in this series.

EXPERIMENTAL

β-Bromopropionyl isocyanate. The rearrangement of *N*-bromosuccinimide was carried out as indicated previously.[2] The *N*-bromosuccinimide should be crushed to break up lumps of material for maximum rate. We have carried out the rearrangement on scales which ranged from 0.2 to 50 g. *N*-bromosuccinimide without difficulty.

Reaction of compound I *with alcohols.* In preparative scale reactions a solution of chloroform containing 5 g. of rearranged *N*-bromosuccinimide was allowed to react with 0.7 mol. equivalent of the alcohol. The solution was cooled in an ice bath. If a precipitate appeared, the solution was filtered, and the precipitate was recrystallized from methanol. If the derivative did not precipitate, the solution was evaporated on a steam bath using an air jet. The residue was induced to crystallize with Dry Ice, and the material was recrystallized.

On a smaller scale, 0.5 g. *N*-bromosuccinimide was rearranged in 5 ml. chloroform (dried over calcium chloride), *ca.* 0.5 ml. allyl chloride, and a trace of benzoyl peroxide. The solution was refluxed 30 min. beyond the time required for the *N*-bromosuccinimide to dissolve, and cooled to room temperature. Then 0.2–0.4 ml. of the alcohol was added, and the solution was cooled or evaporated as required. A slight excess of the isocyanate appears desirable to give the most easily crystallized urethanes. With secondary alcohols less trouble was encountered with oils if the reaction mixture were worked up reasonably quickly (less than 2 hr.) rather than allowing the mixture to stand overnight.

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A New Base-Catalyzed Aromatization Reaction[1]

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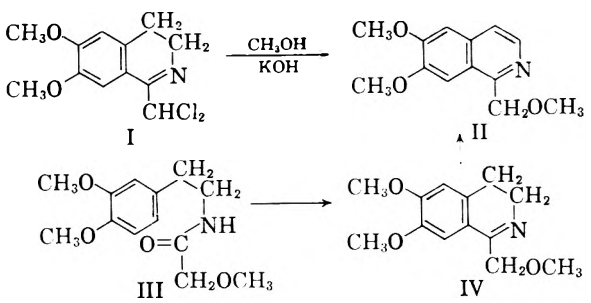
We have had occasion to study the effect of 5% methanolic potassium hydroxide solution on 1-dichloromethyl-6,7-dimethoxy-3,4-dihydroisoquinoline (I). The crystalline product, obtained in excellent yield, was shown to be halogen-free, and the infrared absorption spectrum was without significant absorption in the 5.83–5.90 region (aromatic aldehyde). The composition of the new compound did not correspond with that of a simple

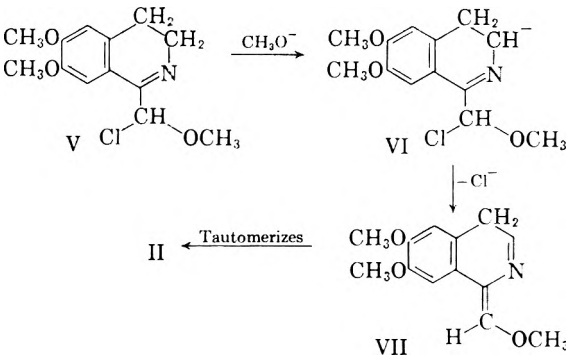


(1) This research was supported by a research grant (H-2170) from The National Heart Institute of The National Institutes of Health.

acetal, but gave best agreement with the empirical formula $C_{13}H_{15}NO_3$.

Of the compounds which could have the observed composition the previously unknown 1-methoxymethyl-6,7-dimethoxyisoquinoline (II) appeared most likely, and an unequivocal synthesis was undertaken *via* the Bischler-Napieralski cyclization of *N*-homoveratrylmethoxyacetamide (III). Dehydrogenation of the cyclization product (IV) yielded 1-methoxymethyl-6,7-dimethoxyisoquinoline identical in every respect with the product obtained by the action of methanolic potassium hydroxide on 1-dichloromethyl-6,7-dimethoxy-3,4-dihydroisoquincline (I).

Since this type of aromatization reaction does not appear to have been reported before, speculation concerning a possible mechanism is in order. A logical sequence of events would involve a simple



nucleophilic displacement of chlorine by methoxide ion to yield V. This would be followed by the abstraction of a proton to yield some of the anion (VI). The loss of a chloride ion from anion VI would, through the sequential shift of electrons lead to structure VII, which would be expected to tautomerize to 1-methoxymethyl-6,7-dimethoxyisoquinoline (II).

The new aromatization reaction occurs in 80–94% yield and is thus of preparative as well as theoretical interest.

EXPERIMENTAL[2]

1-Dichloromethyl-6,7-dimethoxy-3,4-dihydroisoquinoline (I). A mixture containing 12 g. of *N*-homoveratryl-1,1-dichloroacetamide,[3] 100 ml. of dry toluene and 30 ml. of phosphorus oxychloride was refluxed for about 2 hr. when the majority of the solvent was removed under vacuum and the residue carefully decomposed with water and dilute hydrochloride acid. After the acidic solution had been extracted with ether to remove any neutral material, the aqueous solution was made basic and the dihydroquinoline derivative extracted with ether or benzene. The product afforded 7.0 g. (64%) of colorless plates from ligroin, m.p. 90–90.5°. A dilute hydrochloric acid solution of the product was not fluorescent.

Anal. Calcd. for $C_{12}H_{13}Cl_2NO_2$: N, 5.13; Cl, 25.65. Found: N, 5.22; Cl, 25.80.

(2) Except as noted all melting points were determined on the Fisher-Johns block and are uncorrected. The analyses were carried out by Drs. Weiler and Strauss, Oxford, England.

(3) A. P. Phillips, *J. Am. Chem. Soc.*, **74**, 6125 (1952).

1-Methoxymethyl-6,7-dimethoxy-3,4-dihydroisoquinoline (IV). A mixture containing 15 g. of *N*-homoveratrylmethoxyacetamide[4] (III), 150 ml. of dry toluene and 30 ml. of phosphorus oxychloride was refluxed and worked up as in the preparation of I. The product, 6 g. (43%), was isolated by distillation, b.p. 150–160° (0.7 mm.). The analytical sample boiled at 149° (0.7 mm.).

Anal. Calcd. for $C_{13}H_{17}NO_3$: C, 66.30; H, 7.24; N, 5.96. Found: C, 65.96; H, 7.29; N, 5.97.

1-Methoxymethyl-6,7-dimethoxyisoquinoline (II). (a) *By action of methanolic potassium hydroxide on* I. A 1-g. sample of the dichloromethylisoquinoline (I) was refluxed with 10 ml. of 5% methanolic potassium hydroxide solution for 1 hr. (steam bath). The dichloro compound (I) dissolved, and precipitation of potassium chloride was soon observed. At the end of the hour the weight of the inorganic salt corresponded closely with that expected if 2 mol. equivalents of potassium chloride had formed. The filtrate was diluted with water and extracted repeatedly with benzene. The solution was treated with Norit, dried, concentrated and diluted with petroleum ether. The product which separated in 80–94% yield melted at 110–120°, and showed a negative test for halide. Recrystallized from ligroin it melted at 122.5–123.5°. A solution of the product in dilute hydrochloric acid gave a bright yellow fluorescence.

(b) *By dehydrogenation of 1-methoxymethyl-6,7-dimethoxy-3,4-dihydroisoquinoline* (IV). Dehydrogenation of the dihydroisoquinoline IV with 10% palladium charcoal catalyst was effected by heating at 160–175°. The product, b.p. 160–165° (1 mm.), obtained in 60% yield, solidified and on crystallization from ligroin, had m.p. 122–123°. This material did not depress the melting point of the product obtained by Procedure (a).

Anal. Calcd. for $C_{13}H_{15}NO_3$: C, 66.95; H, 6.44; N, 6.02. Found: C, 67.30; H, 6.52; N, 6.39.

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(4) This material, m.p. 40–43°, was prepared by the reaction of methoxyacetyl chloride [R. Leimu, *Ber.*, **70**, 1040 (1937)] with homoveratrylamine.

Study of the Double Fries Rearrangement. II. Rearrangement of Diesters of 4,4′-Biphenol

RESAN PAKKAL,[1] FORREST D. THOMAS, II, AND W. CONARD FERNELIUS

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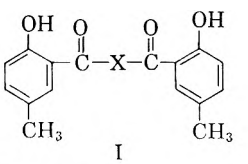
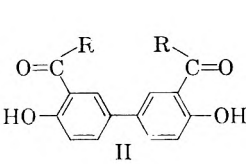
The preparation of a series of bis(*o*-hydroxyketones) of type I where X represents $(CH_2)n$ or *m*- or *p*-phenylene has been reported.[2]



I



II

(1) Appointment supported by the International Cooperation Administration under the Visiting Research Scientists Program administered by the National Academy of Sciences of the United States of America.

(2) F. D. Thomas II, M. Shamma, and W. Conard Fernelius, *J. Am. Chem. Soc.*, **80**, 5864 (1958).

A similar series of type II where the bis-functional starting material was a biphenol rather than a dicarboxylic acid was also desired. Although there has been a moderate amount of work on the Fries rearrangement of esters of polyhydroxybenzenes,[3] only two studies report the rearrangement of diesters of 4,4′-biphenol[4] to give 3,3′-diacetyl-4,4′-biphenol[4a,b] and 3,3′-dipropanoyl-4,4′-biphenol,[4a] whereas attempts to prepare 3,3′-dilauroyl-4,4′-biphenol were unsuccessful.[4b]

In the present study a number of esters of 4,4′-biphenol was prepared by treating the phenol with a series of acid halides in chlorobenzene solution. Each of these esters, when subjected to the Fries rearrangement under conditions previously described,[2] gave the corresponding 3,3′-diacyl-4,4′-biphenols in yields ranging from 19 to 92%.

Infrared spectra. The infrared spectra of the bis(*o*-hydroxyketones) show no absorption in the region of 2.77–2.79 μ (3610–3584 cm.$^{-1}$) characteristic of the free phenolic hydroxyl group, but they do exhibit one rather sharp absorption band in the region of 3.32–3.46 μ (3012–2890 cm.$^{-1}$). This corresponds to the broad absorption bands extending from 2.8–3.6 μ (3571–2778 cm.$^{-1}$) reported by Martin[5] for salicylaldehyde and *o*-hydroxyacetophenone which were attributed to the absorption of the hydroxyl group hydrogen bonded to the carbonyl group and, in part, to the carbon-hydrogen stretching frequency. Gordy[6] noted that the characteristic carbonyl group absorption of acetophenone at 5.96 μ (1678 cm.$^{-1}$) was shifted, in the case of *o*-hydroxyacetophenone, to 6.17 μ (1621 cm.$^{-1}$), due probably, to hydrogen bonding with the *o*-hydroxyl group. In a similar manner, each of the bis(*o*-hydroxyketones) exhibited one sharp absorption peak in the 6.10–6.14 μ (1639–1629 cm.$^{-1}$) region which could also be attributed to the absorption of the carbonyl group hydrogen-bonded to the *o*-hydroxyl group.

EXPERIMENTAL[7]

A. *4,4′-Biphenol esters.* All of the esters of 4,4′-biphenol were prepared from the same molar proportions and in the same general way as described for 4,4′-biphenol diacetate. Pertinent information is assembled in Table I.

4,4′-Biphenol diacetate. A solution of acetyl chloride (8.6 g., 0.11 mol.) in 25 ml. of dry chlorobenzene was added dropwise to a solution of 4,4′-biphenol (9.3 g., 0.05 mol.) and 25

(3) A. H. Blatt, *Organic Reactions*, Vol. I, Chap. 11, John Wiley and Sons, Inc., New York, N. Y., 1942, pp. 342–369. See Table E., pp. 364–366.

(4) (a) R. W. Stoughton, R. Baltzly, and A. Bass, *J. Am. Chem. Soc.*, **56**, 2007 (1934). (b) N. Boon-Long, *J. Pharm. Assoc. Siam*, **1**, No. 4, 5 (1948). [*Chem. Abstr.*, **43**, 5017h (1949)].

(5) A. E. Martin, *Nature*, 166, 474 (1950).

(6) W. Gordy, *J. Chem. Phys.*, **8**, 516 (1940).

(7) All melting points are uncorrected. Analyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn. The 4,4′-biphenol was a gift of the Dow Chemical Company.

TABLE I

4,4′-Biphenol Esters

Diester, 4,4′-biphenol	Yield, %	M.P.	Recrystn. Solvents	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Diacetate	61.8	161–162.5[a]	Benzene	71.10	70.97	5.22	5.37
Dipropanoate	77	148–149	Ethanol	72.47	72.57	6.08	5.95
Dibutanoate	62.5	123–123.5	Ethanol	73.60	73.73	6.79	6.70
Dipentanoate	21	118–119	Ethanol	74.55	74.37	7.34	7.35
Dihexanoate	73	116–117	Ethanol	75.37	75.37	7.90	8.13
Diheptanoate	21.8	118–118.5	Ethanol	76.06	75.83	8.35	8.48
Dioctanoate	63	121.5–123	Ethanol	76.67	76.52	8.74	8.54
Dinonanoate	65	120–121.5	Ethanol	77.21	77.07	9.07	9.03
Didodecanoate	70	122.5–124[b]	1:1 Dioxane-ethanol	78.50	78.33	9.88	9.84
Dibenzoate	77	251–252[c]	Dioxane	79.17	79.09	4.60	4.65

[a] Reported m.p. 159–160[4b]; 159–160[8a]; 160–161[8b]; 160.5–161.5[8c]; 163–164[9d]. [b] Reported m.p 119.5–120.5.[4b] [c] Reported m.p. 240–241[4b]; 250.5–251.5[8d]; 241[9a]; 257[9b].

TABLE II

3,3′-Diacyl-4,4′-biphenols

3,3′-Diacyl-4,4′-biphenols	Yield, %	M.P.	Recrystn. Solvents	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Infrared Bands, μ 3.32–3.46	Infrared Bands, μ 6.10–6.14
3,3′-Diacetyl	19.2	215–216[b]	1:1 Ethanol-dioxane	71.10	71.07	5.22	5.36	3.35	6.10
3,3′-Dipropanoyl	58	143–144[c]	Ethanol	72.47	72.54	6.08	6.00	3.37	6.10
3,3′-Dibutanoyl	89	125–126	1:1 Ethanol-dioxane	73.60	73.72	6.79	6.72	3.33	6.10
3,3′-Dipentanoyl	92.2	70–80.5	Ethanol	74.55	74.30	7.39	7.45	3.32	6.10
3,3′-Dihexanoyl	53.3	92.5–93.5	Ethanol	75.37	75.33	7.90	7.78	3.44	6.11
3,3′-Diheptanoyl	52.4	93–94	Ethanol	76.06	75.88	8.35	8.27	3.45	6.12
3,3′-Dioctanoyl	88	88.5–90	Ethanol	76.67	76.74	8.74	8.65	3.45	6.11
3,3′-Dinonanoyl	72	72–73	Ethanol	77.21	77.13	9.07	8.99	3.46	6.12
3,3′-Didodecanoyl	85	87–88	2:1 Ethanol-dioxane	78.50	78.46	9.88	9.64	3.45	6.12
3,3′-Dibenzoyl	30[a]	184–185	1:1 Ethanol-dioxane	79.17	79.28	4.60	4.62	3.35	6.14

[a] Reaction mixture heated for 3 days. [b] Reported m.p. 219–219.5[4a]; 219–220.[4b] [c] Reported m.p. 140–141.[4a]

ml. of dry chlorobenzene in a 200-ml. round bottom flask fitted with a thermometer and reflux condenser attached to a Gilman trap filled with sulfuric acid. The exit of the Gilman trap led to a water trough which served to absorb the hydrogen chloride evolved during the reaction. The flask was heated to 80° by means of a heating mantle during which time the vigorous evolution of hydrogen chloride was observed. The solution was heated at 80° overnight and then cooled. The light brown crystalline material which formed was recrystallized from benzene to give 8.35 g. (61.8%) of a white crystalline material, m.p. 161–162.5°.

B. *3,3′-Diacyl-4,4′-biphenols.* All runs were made with the same molar proportions and in the same general manner as described for 3,3′-diacetyl-4,4′-biphenol. The apparatus was the same as just described for the preparation of 4,4′-biphenol diacetate. Pertinent information is assembled in Table II.

3,3′-Diacetyl-4,4′-biphenol. A mixture of 4,4′-biphenol diacetate (5.2 g., 0.02 mol.), aluminum chloride (6.7 g., 0.05 mol.) and 50 ml. of dry chlorobenzene was heated at reflux for 24 hr. During this time hydrogen chloride was evolved and a dark yellow precipitate formed. The yellow mixture was cooled in an ice bath and 50 ml. of 3*N* hydrochloric acid was added dropwise with vigorous stirring. The chlorobenzene was then removed by steam distillation and the light brown solid remaining in the distillation flask was collected and recrystallized from 1:1 ethanol-dioxane to give 1.0 g. (19.2%) of light yellow fibrous needles, m.p. 215–216°.

C. *Infrared spectra.*[10] The infrared spectra of all the bis(*o*-hydroxyketones) were obtained in chloroform solution using sealed liquid absorption cells of approximately 0.1 mm. thickness. A Perkin-Elmer Model 21 double beam spectrophotometer with sodium chloride optics was used. Important absorption bands are listed in Table II.

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(8) (a) H. Schmidt and G. Schultz, *Ann.*, **207**, 320 (1881). (b) J. van Alphen, *Rec. trav. chim.*, **50**, 415 (1931). (c) A. Weissberger and J. W. Williams, *Z. physik. Chem.*, [B] **3**, 367 (1929). (d) A. L. Wilds, C. H. Shunk, and C. H. Hoffman, *J. Am. Chem. Soc.*, **76**, 1733 (1954).

(9) (a) J. Moir, *J. Chem. Soc.*, **91**, 1305 (1907). (b) D. Vorlander, *Z. physik. Chem.*, [A] **105**, 211 (1923).

(10) The infrared spectra were run by Mrs. Ann. V. Baker of this laboratory.

Reduction of Phthalyl and Succinyl Dichlorides with Tri-*n*-butyltin Hydride. Cyclization of γ-Oxoacyl Chlorides[1]

HENRY G. KUIVILA

Received July 27, 1959

Recently van der Kerk, Noltes, and Luijten have reported that benzaldehyde is obtained by the reduction of benzoyl chloride with triphenyltin hydride (equation 1, R = phenyl).[2]

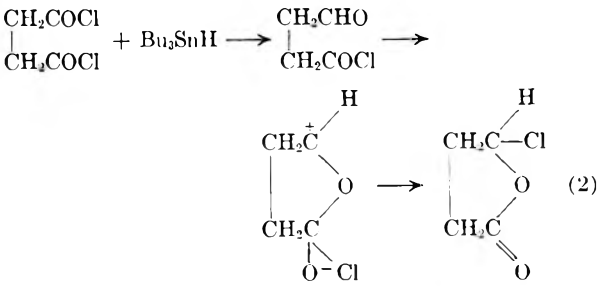
$$R_3SnH + C_6H_5COCl \longrightarrow R_3SnCl + C_6H_5CHO \quad (1)$$

We have found that a similar result is obtained with the more conveniently prepared tri-*n*-butyltin hydride. This reaction proceeds exothermically when the reactants are mixed at room temperature. Aldehydes, on the other hand, are reduced only under much more drastic conditions. Thus, a new convenient synthesis of aldehydes from acid chlorides is suggested. As part of an examination of the scope of such reductions phthalyl and succinyl chlorides have been examined as substrates.

When 1 mole of tri-*n*-butyltin hydride was added to a mole of succinyl dichloride without solvent, an exothermic reaction ensued. The reaction product, after 2 hr. at about 40°, was distilled yielding about 80% of crude product, which upon redistillation provided a product corresponding in neutral equivalent and chloride analysis to the replacement of one of the chlorines by hydrogen. The infrared spectrum showed a carbonyl band at 1810 cm.$^{-1}$, but none in the region 1635–1730 cm.$^{-1}$, nor any C—H band in the region 2700–2800 cm.$^{-1}$. The product is therefore not an aldehyde. The location of the carbonyl band is not shifted by the dilution of the chloride with 2 mol. of tri-*n*-butyltin chloride. Similar mixtures involving the tin halide and succinyl dichloride or γ-butyrolactone have carbonyl absorptions at 1785–1790 cm.$^{-1}$ or 1775 cm.$^{-1}$, respectively.

When 2 moles of hydride were used, the nature of the infrared spectrum after 2 hr. of reaction time was essentially the same as when 1 mole was used. The only difference was in broadening of the band at 1810 cm.$^{-1}$, which was due to the Sn—H band of unreacted hydride which occurs at this same frequency. Clearly the second chloride is far more difficult to reduce than the first.

The reduction product is undoubtedly γ-chloro-γ-butyrolactone, whose formation can be rationalized by the reaction sequence (2).



(2)

As there is no indication of the presence of aldehyde, the second step must be essentially irreversible. Furthermore, the cyclization must occur fairly rapidly, for the second mole of hydride does not lead to the formation of succindialdehyde, which would be expected to form fairly readily in view of the speed of reduction of the first acid chloride group.

Analogous reactions have been observed in the reaction of succinyl chloride with reagents such as diethylcadmium by Cason and Reist.[3] The products obtained are ethyl γ-ketocaproate (when diethyl ether is the solvent) and γ-ethyl-γ-caprolactone; no 3,6-octanedione is obtained. The products found can be accounted for on the basis of cyclization of initially formed γ-ketocaproyl chloride; the diketone would be formed by reaction of this (acyclic) acid chloride with another mole of diethylcadmium. An alternative mechanism proceeding through a cyclic acylonium ion can also account for the facts.[3a]

A cyclic structure has been assigned to γ-ketocaproyl chloride[5b] on the basis of the presence of a single carbonyl band at 1805 cm.$^{-1}$. Similarly,[4] four 2-benzoylbenzoyl chlorides had single carbonyl bands in the region 1790–1800 cm.$^{-1}$. These latter bands represent upward shifts of about 20 cm^{-1} from the 3-phenylphthalides. The shift from α-butyrolactone (1775 cm.$^{-1}$) to the chloro compound involves a shift of 35 cm.$^{-1}$ to a higher frequency. These examples supplement those reported earlier[5] in which electron withdrawing substituents in the γ-position cause shifts in the carbonyl bands of γ-lactones to higher frequencies.

On the basis of the examples discussed above it seems reasonable to conclude that the cyclic γ-chloro-γ-lactones are more stable thermodynamically than the acyclic tautomers, the γ-oxoacid chlorides. Furthermore the cyclization can be brought about with as weak a Lewis acid as tri-*n*-butyltin chloride, and might possibly not require a catalyst at all.

Experiments similar to those conducted with succinyl dichloride were also carried out with phthalyl dichloride. Presumably because of the

(1) It is a pleasure to acknowledge support of this work by the Office of Ordnance Research. Thanks are also due to the Metal and Thermit Corporation for samples of tri-*n*-butyltin chloride.

(2) G. J. M. van der Kerk, J. G. Noltes, and J. G. A. Luijten, *J. Appl. Chem.*, **7**, 356 (1957).

(3) (a) J. Cason and E. J. Reist, *J. Org. Chem.*, **23**, 1668 (1958); (b) J. Cason and E. J. Reist, *J. Org. Chem.*, **23**, 1492 (1958).

(4) W. Graf, E. Girod, E. Schmid, and W. G. Stoll, *Helv. Chim. Acta*, **42**, 1085 (1959).

(5) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley, Inc., New York, 1958, p. 187.

presence of carbonyl impurities, the spectra of the products were not amenable to reliable interpretation. However, when 2 moles of tri-*n*-butyltin hydride were allowed to react with the acid chloride, a 55% yield of phthalide crystallized from the reaction mixture. Its formation undoubtedly results from the reduction of 3-chlorophthalide formed by way of a sequence such as (2). The ready reduction of the phthalide in the second step occurs because the chlorine is now benzylic, and therefore more susceptible to reduction than that in γ-chloro-γ-butyrolactone.

EXPERIMENTAL

Reaction between succinyl dichloride and tri-n-butyltin hydride. To 2.92 g. (18.9 mmol.) of succinyl dichloride which had been freshly distilled was added 5.50 g. (18.9 mmol.) of tri-*n*-butyltin hydride.[6]

The reactants were allowed to stand, with occasional cooling to keep the temperature below about 40°, for 2 hr. Distillation from a modified Claisen flask provided two fractions: b.p. 49–62°/0.3–0.4 mm., 1.84 g. (80%) and b.p. 102–127°/0.4 mm., 6.06 g. (98% crude tri-*n*-butyltin chloride). The first fraction was redistilled yielding a main fraction b.p. 45°/0.4 mm., 1.00 g. of γ-chloro-γ-butyrolactone.

Anal. Calcd. for $C_4H_5O_2Cl$: Cl, 29.4; neut. eq., 60.3. Found: Cl, 28.1, 28.0; neut. eq., 60.5.

Reaction between phthalyl dichloride and tri-n-butyltin hydride. A mixture of 11.0 g. (37.8 mmol.) of tri-*n*-butyltin hydride and 4.54 g. (8.9 mmol.) of phthalyl dichloride was cooled in a water bath occasionally during the first hour after preparation in order to keep the temperature below 50°. It was then allowed to stand for 5 days; 0.47 g. of crystals which had appeared were filtered off and washed with 10 ml., of petroleum ether, b.p. 30–60°. The filtrate was diluted with 20 ml. more of petroleum ether, whereupon another 0.91 g. of crystals appeared. The product melted at 72–74°, undepressed upon mixture with authentic phthalide, and had an infrared spectrum identical with that of phthalide.

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(6) G. J. M. van der Kerk, J. G. Noltes, and J. G. A. Luijten, *J. Applied Chem.*, **7**, 366 (1957).

Proton Nuclear Resonance Spectroscopy. X. Rapid Tautomerization of Formazans[1,2]

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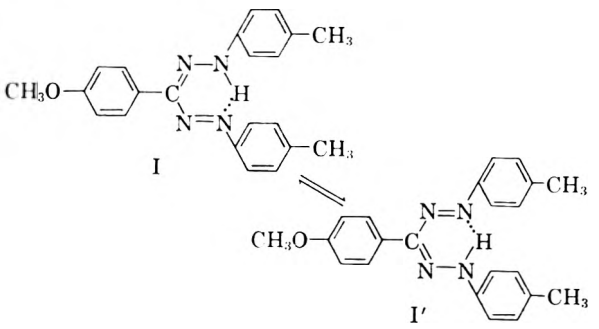
Received August 24, 1959

Early workers, studying the problem of tautomerism in unsymmetrically substituted formazans, reported the isolation of two tautomers[4]; however, subsequent studies[5–7] showed that only one form could be isolated. The cyclic hydrogen-bridged structure was proposed[6] in view of the chelating ability of formazans, and the failure to isolate two forms of the chelates prepared from unsymmetrical formazans. In all such studies the requirement of unsymmetrical substitution introduces the possibility of severe steric, electronic, and solvent effects upon the position of tautomeric equilibrium.

Nuclear spin resonance (NSR) spectroscopy affords a sensitive method for the detection of rapid equilibration: it is especially suitable for the study of symmetrical systems,[8] for example, 1,5-di-(4-methylphenyl)-3-(4-methoxyphenyl) formazan



(I). For such purposes it is necessary to choose cases for which all the observed NSR peaks can be assigned with confidence; for the formazan (I) the detailed assignment is given in Table I.

TABLE I

ASSIGNMENT OF NSR SHIELDING VALUES[a] FOR FORMAZAN (I)

Proton Group	Shielding Value, τ (p.p.m.)[a]	Relative No. of Protons
For the 4-Methoxyphenyl Group:		
2-H	2.10[b] J =	2
3-H	3.20[b] 8.9c/s	2
4-CH_3O	6.218 ± 0.002	3
For the 4-Methylphenyl Groups:		
2-H	2.59[b] J =	4
3-H	2.93[b] 8.5c/s	4
4-CH_3	7.684 ± 0.002	6

[a] For the definition of τ see ref. 10; the formazan, I, concentration was 8% (wt./vol.) in CCl_4. [b] "Nonequivalent doublet" (AB-type) analyzed according to ref. 8, p. 119; the coupling constant J refers to spin interaction between 2- and 3-H.

Whenever NSR assignment may be desired, it is important to avoid unsubstituted phenyl groups, and to synthesize, instead, an appropriate *para*-substituted analog; it may not be widely

(1) Contribution No. 165; Central Research Department, Minnesota Mining and Manufacturing Co., St. Paul, Minn.

(2) A portion of a dissertation submitted in partial fulfillment of the requirements for the Ph.D. degree at Kansas State University, 1959.

(3) Pan American Petroleum Foundation Fellow, 1957–58.

(4) M. Busch and R. Schmidt, *J. Prakt. Chem.*, **131**, 182 (1931).

(5) D. Jerchel and W. Woticky, *Ann.*, **605**, 191 (1957).

(6) L. Hunter and C. B. Roberts, *J. Chem. Soc.*, 820–3 (1941).

(7) R. Kuhn and D. Jerchel, *Ber.*, **74**, 941 (1941).

(8) J. A. Pople, W. G. Schneider, and H. J. Bernstein, *High Resolution Nuclear Magnetic Resonance*, McGraw-Hill, Inc., New York, 1959, p. 438 and p. 223.

recognized that *only infrequently* do phenyl groups give analyzable NSR patterns. *Para*-substituents having spin $^1/_2$ (F^{19}, P^{31}) introduce some complexity and should be avoided; all others (including D) appear quite satisfactory.

A further advantage is gained in the present instance by the use of "*para*-sensitive" groups such as methyl and methoxy (formyl, acetyl, and dimethylamino also are good) which give sharp NSR peaks, the exact spectral location of which is dependent upon the electrical nature of the structure attached *para* to them.[9] Thus, the 3-position in the formazan appears to be slightly electron-withdrawing, the methoxy shift being −0.048 p.p.m. relative to anisole,[10] while the *average* of the 1- and 5- positions is slightly electron-donating as judged by the positive methyl shift, +0.021 p.p.m., compared to toluene.[10]

The two apparently different *p*-tolyl groups of I in fact yield identical spectral patterns; if a symmetrical, "mesomeric" structure be ruled out, the observed equivalence requires rapid tautomerization, with an estimated lower limit for the rate constant being *ca.* 10^3 sec.$^{-1}$.[8] An alternative explanation, based on rapid intermolecular NH exchange, is excluded, as it would require a sharp NH peak (not seen), the effects of spin-spin interaction and quadrupole broadening by N^{14} being averaged to zero by such exchange.[11]

EXPERIMENTAL

The NSR equipment and techniques used were previously described.[10,12]

1,5-Di-(4-methylphenyl)-3-(4-methoxyphenyl)-formazan (I). A solution of 2.4 g. (0.01 mol.) of *p*-anisaldehyde-*p*-tolylhydrazone in 300 ml. 95% ethanol at 0° was treated with a diazonium salt solution prepared from 1.07 g. (0.01 mol.) *p*-toluidine, 2.5 ml. (0.03 mol.) 12*N* HCl and 0.76 g. (0.11 mol.) sodium nitrite, at 0°. The *p*H of the diazonium salt solution was adjusted to 6.5 by means of sodium acetate, and it was added dropwise to the vigorously stirred hydrazone solution. After 15 min. a yellow solid was filtered from the solution and allowed to stand until its color was deep red; it was twice recrystallized from ethanol, 2.6 g. (73%) being recovered as deep red needles, m p. 172–175° (uncorr.).

Anal. Calcd. for $C_{22}H_{22}ON_4$: N, 15.64%. Found: N, 16.08%.

Acknowledgment. We thank George Filipovich and Donald Hotchkiss for excellent maintenance and operation of the NSR spectrometer.

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(9) G. V. D. Tiers, Presented at the Symposium on Nuclear Resonance Spectroscopy, Joint SAS-ASTM E-13 Meeting, New York, 1958.

(10) G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

(11) Ref. 8, p. 102 and p. 226.

(12) G. V. D. Tiers and F. A. Bovey, *J. Phys. Chem.*, **63**, 302 (1959).

The Tetrazole-Azidoazomethine Equilibrium. III. Reduction of Pyridotetrazoles[1]

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Received August 24, 1959

The presence of an equilibrium between pyridotetrazole (I) and 2-azidopyridine (III) with electron withdrawing substituents in the pyridine ring was established by spectrophotometric detection of both azido and tetrazolo groups in solutions of certain examples. With no substituent or with electron donating substituents, azide concentration, if present, was not detected.[2] The marked stability of pyridotetrazole in strong acid[3] may be explained by an electromeric displacement toward the electron seeking tetrazole ring. An electromeric displacement toward the pyridine ring, on the other hand, would decrease the stability of the tetrazole ring in I relative to its tautomer III, and might be realized in alkaline solutions.[4] A confirmation of the two possible electronic displacements has been found in catalytic hydrogenation of pyridotetrazole in acidic, basic and neutral media and by reduction of 7-methyl-8-nitropyridotetrazole with stannous chloride in hydrochloric acid.

A detailed catalytic reduction of the tetrazole ring has not been reported heretofore.[5] Its resistance to catalytic hydrogenation was demonstrated in the reduction of I over a noble metal to di- and tetrahydropyridotetrazole[6] (II) and in the reduction of 5-phenyltetrazole in acetic acid over platinum to 5-cyclohexyltetrazole.[7] In the present work, reduction of pyridotetrazole (I) over palladium in the presence of acetic acid to tetramethylenetetrazole (II) in nearly quantitative yield, together with a trace of 2-aminopyridine (IV) has been realized. A dihydropyridotetrazole is not detected. In con-

(1) Financial support by E. Bilhuber, Inc., Orange, New Jersey, and by Research Grants H-2295 and CY-2895 from the National Institutes of Health is gratefully acknowledged.

(2) J. H. Boyer and E. J. Miller, Jr., *J. Am. Chem. Soc.*, **81**, 4671 (1959) (Part I); J. H. Boyer and H. W Hyde, *J. Org. Chem.*, in press.

(3) Pyridotetrazole is recovered unchanged from concentrated sulfuric acid at 120° (J. H. Boyer, W. J. McCarville, D. I. McCane, and A. T. Tweedie, *J. Am. Chem. Soc.*, **75**, 5298 (1953).

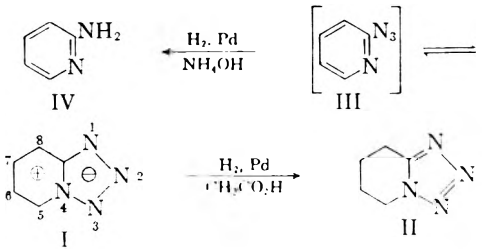
(4) Preliminary observations suggested an instability of pyridotetrazole and its derivatives in bases.[3]

(5) Ring cleavage of tetrazolium salts may occur upon catalytic reduction over palladium [D. Jerchel and R. Kuhn, *Ann.*, **568**, 185 (1950)]. R. O. Roblin, Jr., J. H. Williams, P. S. Winnek, and J. P. English, *J. Org. Chem.*, **62**, 2002 (1940) state that 5-*p*-nitrobenzenesulfonamidotetrazole is reduced over palladium to sulfanilylguanidine, but they do not give the experimental procedure.

(6) Kereszty and Wolf, German pat. **613,123** [*C. A.* **29**, 5604 (1935)]; U. S. pat. **2,008,536** [*C. A.* **29**, 5994 (1935)]. The solvent is not specified in the abstracts.

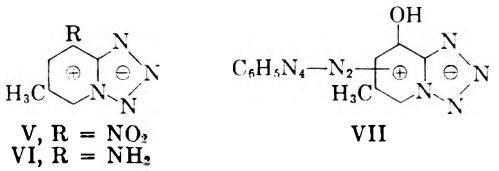
(7) B. Elpern and F. C. Nachod, *J. Am. Chem. Soc.*, **72**, 3379 (1950).

trast, reduction in the presence of ammonium hydroxide gives 2-aminopyridine (IV) in moderate yield with no tetramethylenetetrazole and a similar reduction in ethanol gives lower yields of both II and IV.



Stannous chloride in hydrochloric acid transforms 6-methyl-8-nitropyridotetrazole (V) into 6-methyl-8-aminopyridotetrazole (VI). Apparently tetrazole destabilization as a result of the presence of the electron attracting nitro group is ineffective in the presence of an opposing electromeric shift demanded by the acid environment.

A derivative tentatively assigned the structure of an azo compound (VII) is obtained upon treatment of diazotized VI with boiling water.



EXPERIMENTAL[8]

Tetramethylenetetrazole. A solution of 10.65 g. (0.09 mol.) of pyridotetrazole in 5.40 g. (0.09 mol.) of glacial acetic acid and 200 ml. of 95% ethanol was treated with hydrogen (initial pressure of 2 atm.) over 1.25 g. of 10% palladium on charcoal. Hydrogen pressure decreased to a constant value after about 4 hr. The solution, separated from catalyst, was evaporated to dryness *in vacuo*. Addition of *n*-hexane to dried and decolorized chloroform extracts of the residue precipitated 8.6 g. (85%) of tetramethylenetetrazole as colorless needles, m.p. 117–118° after recrystallization from a mixture of chloroform and *n*-hexane (lit.[6] m.p. 115–116°).

Anal. Calcd. for $C_5H_8N_4$: C, 48.38; H, 6.49; N, 45.14. Found: C, 48.65; H, 6.54; N, 45.39.

A trace of 2-aminopyridine in the filtrate was detected as the picrate, melting point and mixture melting point 215–216° (lit.[9] m.p. 216–217°).

The reduction was repeated with the substitution of 0.09 mol. of ammonium hydroxide for 0.09 mol. of glacial acetic acid. Addition of hexane to a chloroform solution of the product did not precipitate tetramethylenetetrazole. Addition of a saturated ethanolic solution of picric acid gave 7.81 g. of *2-aminopyridine* picrate, melting point and mixture melting point 216–217° after recrystallization. Based upon quantitative picrate formation this represents a 29.4% yield of 2-aminopyridine.

In another reduction, neither acid nor base was added to the ethanol solvent. A 15.8% yield of 2-aminopyridine was isolated as its picrate derivative and a 35.0% yield of tetramethylenetetrazole was obtained.

Preparation of 6-methyl-8-aminopyridotetrazole. A solution of 11.3 g. (0.05 mol.) of stannous chloride dihydrate and 15 ml. of concentrated hydrochloric acid was cooled to 5°. The temperature rose to about 60° with the addition of 1.69 g. (0.01 mol.) of 6-methyl-8-nitropyridotetrazole[10] in one portion. The solution was vigorously stirred for about 5 min. until a clear solution resulted and was then stirred in an ice bath for 1 hr. and filtered. The filtrate was treated dropwise with a solution of 40% sodium hydroxide to precipitate the amine as a fine solid, 0.92 g. (61%), m.p. 214–215° (dec.) after recrystallization from boiling water and drying *in vacuo* overnight at 80°.

Anal. Calcd. for $C_6H_7N_5$: C, 48.31; H, 4.73; N, 46.95. Found: C, 48.43; H, 4.90; N, 46.86.

Preparation of 6-methyl-8-acetamidopyridotetrazole. A solution of 0.3 g. (0.002 mol.) of 6-methyl-8-aminopyridotetrazole and 2 g. of acetic anhydride was heated for a few minutes, and cooled. The precipitate, 0.32 g. (84%), m.p. 238–239°, was recrystallized from ethanol.

Anal. Calcd. for $C_8H_9N_5O$: C, 50.25; H, 4.74; N, 36.63; O, 8.37. Found: C, 50.45; H, 4.72; N, 36.83; O, 8.53.

Preparation of 6-methyl-8-hydroxy 5(or 7)-(8′-azo-6′-methyl-pyridotetrazolo)-pyridotetrazole. A solution of 0.3 g. (0.002 mol.) of 6-methyl-8-aminopyridotetrazole, 3 g. of water and 3.6 g. (0.36 mol.) of concentrated sulfuric acid was chilled to 0–5° in an ice-salt bath with stirring. Dropwise addition of a solution of 0.15 g. (0.0022 mol.) of sodium nitrite was accompanied by an evolution of gas. After stirring for 5 to 10 min. the diazotization mixture was added slowly to 10–20 ml. of boiling water. A crude red solid after recrystallization from *N,N*-dimethylformamide gave 0.05 g. (48.4%) of 6-methyl-8-hydroxy 5(or 7)-8′-azo-6′-methyl-pyridotetrazole)-pyridotetrazole, m.p. 230° (explosive dec.) and 0.20 g. of starting material, m.p. 214–215°.

Anal. Calcd. for $C_{12}H_{10}N_{10}O$: C, 46.49; H, 3.25; N, 45.18; O, 5.16. Found: C, 46.70; H, 3.29; N, 44.61; O, 5.87.

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(8) Semimicro analyses by Alfred Bernhardt, Max Planck Institut Mülheim (Ruhr), Germany. Melting points are not corrected.

(9) W. Marckwald, *Ber.*, **27**, 1317 (1894).

(10) J. H. Boyer and W. Schoen, *J. Am. Chem. Soc.*, **78**, 423 (1956).

Hofmann Degradation of 3a-(3,4-Methylenedioxyphenyl)-1-methyloctahydroindole

P. F. HIGHET AND W. C. WILDMAN

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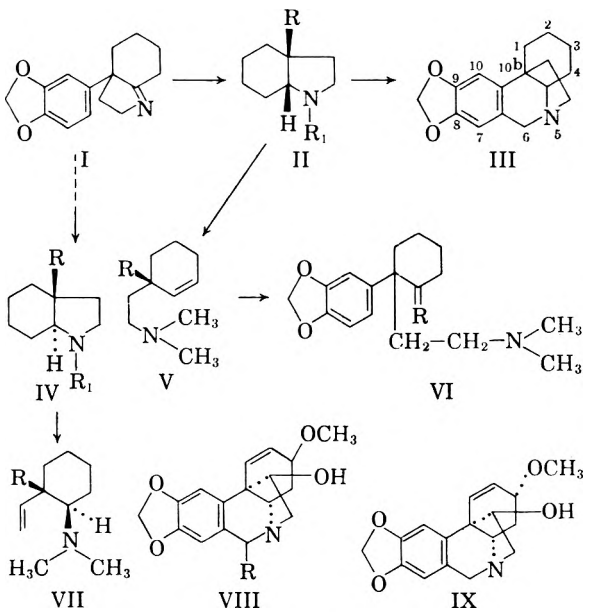
The synthesis of (±)-crinane (III) demonstrated that several Amaryllidaceae alkaloids are derivatives of 5,10b-ethanophenanthridine.[1,2] A key intermediate in this synthesis was the hexahydroindole (I) which was reduced by catalytic methods to an octahydroindole of unknown stereochemistry. It was reasoned[3] that catalytic hydrogenation of I should proceed by the addition of hydrogen to the enamine from the side opposite that occupied

(1) W. C. Wildman, *Chem. & Ind. (London)*, 1090 (1956).

(2) W. C. Wildman, *J. Am. Chem. Soc.*, **80**, 2567 (1958).

(3) N. Sugimoto and H. Kugita, *Pharm. Bull.*, **5**, 378 (1957).

by the methylenedioxyphenyl group. Such a process would lead to a *trans*-octahydroindole (IVa, R_1 = H). Sodium borohydride reduction of I gave the same octahydroindole as was obtained by catalytic reduction. Since this type of reduction would be expected to lead to the more stable *cis*



Series: (a). R = 3,4-methylenedioxyphenyl
(b). R = H

isomer (IIa, R_1 = H), independent evidence for the stereochemistry of the C:D ring junction was sought. Although structural studies on the alkaloids haemanthamine (VIII, R = H),[4] haemanthidine (VIII, R=OH)[5] and crinamine (IX)[4] provided degradative evidence that rings C and D of these bases were *cis* fused, independent proof based on the synthesis of III was sought for the nature of this ring fusion.

The recent studies by Booth and King[6] prompted us to examine the stereochemistry of the hydrogenation product of I by the Hofmann degradation. Hofmann degradation of *cis*-octahydro-1-methylindole (IIb, R_1 = CH_3) leads to 3-(β-dimethylaminoethyl)-cyclohexene (Vb)[7-9] while the corresponding *trans* compound (IVb, R_1 = CH_3) affords *trans*-1-dimethylamino-2-vinylcyclohexane (VIIb).[6] It seemed likely that the mode of elimination found for these simple indoles should prevail in the analogous precursor of crinane (IIa or IVa, R_1 = CH_3). By this reasoning, if the octahydroindole formed by the reduction of I were *cis* fused (IIa, R_1 = H), Va would result from the Hofmann degradation of IIa (R_1 = CH_3), while a *trans* fusion (IVa, R_1 = H) would give rise to VIIa under similar conditions.

Preliminary attempts to prepare the requisite starting material by methylation of the octahydroindole with formaldehyde and formic acid were unsuccessful. The only product isolated by this method was (±)-crinane (III), formed by a Pictet-Spengler type of cyclization to the activated aromatic nucleus. The desired *N*-methyl derivative was prepared successfully by reductive methylation of the secondary amine in the presence of formaldehyde, palladium-on-charcoal, and hydrogen. Quaternization of the product with methyl iodide and pyrolysis of the derived methohydroxide gave a product which was proved to be Va by spectral evidence and by the synthesis of the dihydro derivative (VI, R = H_2).

The methine (Va) showed no bands in the infrared spectrum attributable to a terminal methylene group but showed absorption at 3015 and 702 $cm.^{-1}$ characteristic of an unsubstituted cyclohexene. Catalytic hydrogenation of Va afforded a dihydro derivative (VI, R = H_2) which showed neither of these bands. Finally, VI (R = H_2) was synthesized in an unambiguous manner. Alkylation of 2-(3,4-methylenedioxyphenyl)-cyclohexanone[2] with β-dimethylaminoethyl chloride in the presence of sodamide gave an aminoketone (VI, R = O). Wolff-Kishner reduction of this gave a product identical with that obtained from catalytic reduction of Va.

These data support the assignment of a *cis* C:D ring fusion in (±)-crinane and the Amaryllidaceae alkaloids based on this nucleus. It is evident that the catalytic and chemical reduction product of I is IIa (R_1 = H) and that the course of the Hofmann degradation of IIa (R_1 = CH_3) parallels that of the simpler analog IIb (R_1 = CH_3). Conformational considerations consistent with the observed reaction path have been discussed earlier.[10]

EXPERIMENTAL[11]

Attempted methylation of IIa (R_1 = H) *with formic acid and formalin.* A solution of 654 mg. of IIa (R_1 = H) in 5 ml. of formic acid and 3 ml. of formalin was refluxed for 23 hr. The mixture was made basic with concentrated sodium hydroxide and extracted four times with ether. The ethereal solution was washed twice with water and twice with brine.

(4) H. M. Fales and W. C. Wildman, *Chem. & Ind.* (London), 561 (1958); *J. Am. Chem. Soc.*, **82**, 197 (1960).

(5) S. Uyeo, H. M. Fales, R. J. Highet, and W. C. Wildman, *J. Am. Chem. Soc.*, **80**, 2590 (1958).

(6) H. Booth and F. E. King, *J. Chem. Soc.*, 2688 (1958).

(7) J. McKenna, *Chem. & Ind. (London)*, 406 (1954).

(8) B. Bailey, R. D. Haworth, and J. McKenna, *J. Chem. Soc.*, 967 (1954).

(9) F. E. King, J. A. Barltrop, and R. J. Walley, *J. Chem. Soc.*, 277 (1945).

(10) F. E. King and H. Booth, *J. Chem. Soc.*, 3798 (1954).

(11) All melting points were observed on a Köfler microscope hot stage and are corrected. Infrared spectra were determined with either a Perkin-Elmer model 21 or a Beckman model IR-7 spectrophotometer. Analyses were performed by Mr. J. F. Alicino, Metuchen, N. J.

The solvent was removed under reduced pressure to give 678 mg. of an oil whose infrared spectrum resembled that of crinane. Two recrystallizations from ether gave 323 mg. of material melting at 108–111°; mixture melting point with (±)-crinane, 106–110°.[2,12]

Cis-3a-(3,4-methylenedioxyphenyl)-1-methyloctahydroindole (IIa, $R_1 = CH_3$). An ethanolic solution of 234 mg. of IIa ($R_1 = H$) was stirred under hydrogen at room temperature and atmospheric pressure in the presence of 230 mg. of 10% palladium-on-charcoal and 5 ml. of formalin. In 45 min. the mixture absorbed 20.3 ml. of hydrogen (85%). The product was filtered, concentrated and chromatographed on Merck alumina. Elution with chloroform gave 231 mg. of oil which was dissolved in acetone and treated with methyl iodide. Addition of ether precipitated 258 mg. of material, m.p. 169–175°. Four recrystallizations of the *methiodide* from chloroform–ethyl acetate gave colorless prisms, m.p. 198.5–199.5°.

Anal. Calcd. for $C_{17}H_{24}NO_2I$: C, 50.88; H, 6.03; N, 3.49. Found: C, 50.91; H, 6.04; N, 3.53.

The *picrate* was prepared in ethanol and recrystallized from acetone-ethanol and from acetone-ether to give prisms, m.p. 196–198°.

Anal. Calcd. for $C_{16}H_{21}NO_2 \cdot C_6H_3N_3O_7$: C, 54.09; H, 4.95; N, 11.47. Found: C, 53.99; H, 4.88; N, 11.57.

Hofmann degradation of IIa ($R_1 = CH_3$). A solution of 194 mg. of the methiodide of IIa ($R_1 = CH_3$) in 1:1 ethanol-water was treated with silver oxide that had been freshly prepared from 93 mg. of silver nitrate. The mixture was scratched and stirred for a few minutes, then centrifuged. The solid material was washed twice with water and once with methanol. The combined supernatant liquid was evaporated to dryness at 40–50° under reduced pressure, then heated for 25 min. at a temperature gradually increasing from 125 to 165°. The resulting residue, 130 mg., was partitioned between 0.1*N* hydrochloric acid and ether. The aqueous layers were made basic with ammonium hydroxide and extracted four times with ether. The ether extracts were washed with water and brine and concentrated under reduced pressure to give 97 mg. of oil. This was chromatographed on 10 g. of Merck alumina. Benzene elution produced 8 mg. of fore run, followed by 38 mg. of Va, then 20 mg. of material whose infrared spectrum suggested it to be slightly impure Va. Elution with 1–5% ethyl acetate gave 20 mg. of material trailing in many fractions.

The infrared spectrum (carbon tetrachloride) of Va purified in this manner showed absorption at 3012 and 702 cm.$^{-1}$. The ultraviolet absorption spectrum (ethanol) showed maxima at 234 (ϵ 4240) and 287 mμ (ϵ 4240).

1-(β-Dimethylaminoethyl)-1-(3,4-methylenedioxyphenyl)-cyclohexane (VI, R = H_2). A solution of 38 mg. of Va in ethanol was hydrogenated at room temperature and atmospheric pressure in the presence of 40 mg. of pre-equilibrated 10% palladium-on-charcoal. Absorption of hydrogen ceased after the uptake of 3.55 ml. (theor. 3.2 ml.) in 29 min. The mixture was filtered, and the solvent was removed under reduced pressure to give 40 mg. of a clear oil. The infrared spectrum (carbon tetrachloride) showed no absorption at 3012 or 702 cm.$^{-1}$. The ultraviolet absorption spectrum (ethanol) showed maxima at 235 (ϵ 4120) and 288 mμ (ϵ 3980).

The *picrate* was prepared in ethanol to yield 48 mg. of material, m.p. 108–131°. Three recrystallizations from ethanol gave 27 mg. of short prisms, m.p. 133.5–135°. On standing in a vial for 3 months, the melting point was found to be 174–176°. The infrared spectrum (chloroform) of this material was identical with that obtained by synthesis from VI (R = O), (*vide infra*).

Anal. Calcd. for $C_{17}H_{25}NO_2 \cdot C_6H_3N_3O_7$: C, 54.75; H, 5.59; N, 11.11. Found: C, 55.10; H, 5.54; N, 11.16.

2-(β-Dimethylaminoethyl)-2-(3,4-methylenedioxyphenyl)-cyclohexanone (VI, R = O). To a stirred suspension of sodamide (prepared from 690 mg. of sodium) and 20 ml. of benzene was added dropwise a solution of 2.22 g. of 2-(3,4-methylenedioxyphenyl)-cyclohexanone[2] in dry benzene. A dark brown color appeared. The mixture was refluxed for 3 hr. At the end of this time a solution of β-chloroethyldimethylamine (prepared from 10.9 g. of the amine hydrochloride) was added. The reaction mixture was refluxed for 16 hr., chilled, and treated first with ethanol, then with water. The layers were separated, and the aqueous portion was extracted twice with benzene. The benzene solution was extracted once with dilute hydrochloric acid and twice with water, then concentrated under reduced pressure to give 0.917 g. of neutral material with an infrared spectrum identical with that of the starting ketone.

The acidic solution was made basic with sodium hydroxide and extracted four times with benzene to give 1.966 g. of an oil which was chromatographed on 100 g. of alumina. Elution with 10–50% ethyl acetate in benzene and finally with ethyl acetate gave 770 mg. of a clear oil. Infrared spectra of the various chromatographic fractions showed only minor differences.

The *hydrochloride* was formed by saturating an ethanolic solution of the amine with gaseous hydrogen chloride. Three recrystallizations from ethanol–ethyl acetate gave fine white needles, m.p. 245–249° (dec.).

Anal. Calcd. for $C_{17}H_{24}NO_3Cl$: C, 62.66; H, 7.42; N, 4.30. Found: C, 62.70; H, 7.38; N, 4.37.

1-(β-Dimethylaminoethyl)-1-(3,4-methylenedioxyphenyl)-cyclohexane (VI, R = H_2). A solution of 488 mg. of VI (R = O), 2.9 g. of potassium hydroxide and 5 ml. of hydrazine hydrate in 17 ml. of diethylene glycol was refluxed for 6.5 hr. at 150–160°. The mixture was diluted with water, acidified with hydrochloric acid and extracted twice with benzene. The aqueous layer was filtered, made basic with sodium hydroxide and extracted four times with chloroform. The chloroform was evaporated under reduced pressure to leave 256 mg. of oil. The infrared spectrum of this oil showed that reduction was not complete.[13] Chromatography of the oil on 20 g. of alumina and elution with 10% ethyl acetate gave 77 mg. of a clear oil which showed no carbonyl absorption.

The *picrate* was prepared in ethanol and recrystallized three times from ethanol to give elongated prisms, m.p. 173–174°. A mixture melting point with the higher melting polymorphic picrate of VI (R = H_2) which had been obtained from the reduction of Va was 173.5–174.5°.

Anal. Calcd. for $C_{17}H_{25}NO_2 \cdot C_6H_3N_3O_7$: C, 54.75; H, 5.59; N, 11.11. Found: C, 54.97; H, 5.51; N, 11.25.

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(12) (±)-Crinane was reported[2] to melt at 97–99°. A re-examination of this material showed that it is a low melting polymorph of the (±)-crinane reported above. The higher melting form may be isolated either by sublimation of the material melting at 97–99° or by seeding a melt with the higher melting polymorph at 105°. The infrared spectra ($CHCl_3$) of the two forms are identical.

(13) More forcing conditions for the Wolff-Kishner reduction of compounds similar to VI (R = O) have led to ill-defined products lacking the methylenedioxy group, so this method of attempting to improve the yield of VI (R = H_2) was not used. However, it was established that lengthening the reaction time caused no improvement in yield.

Dissociation Constants of 2-Substituted Pyridines

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Received June 5, 1959

As part of a research program on pyridine chemistry, the dissociation constants of several 2-substituted pyridines were measured.

EXPERIMENTAL

The half-neutralization method was used and all *p*H measurements were made at 25 ± 0.2°. At least 2 solutions of different concentrations, half neutralized with hydrochloric acid were made for each compound, and four *p*H measurements were made on each solution; this was repeated with a fresh sample of the same solution. All measurements were made on solutions freshly made up from the pyridines immediately after their purification.

All distillations were done on an all-glass column packed with Fenske rings. This column had twelve theoretical plates when tested at atmospheric pressure with benzene–carbon tetrachloride.

Since $BH^+ \rightleftarrows B + H^+$

$K_a = a_B \cdot a_{H^+}/a_{BH^+} = c_B \cdot \gamma_B \cdot a_{H^+}/c_{BH^+} \cdot \gamma_{BH^+}$

We assume $\gamma_B = 1.00$ and $c_B = c_{BH^+}$

then $pK_a = pH + \log \gamma_{BH^+}$

The Debye-Huckel limiting law was used in the form $\log \gamma = -0.509\sqrt{\mu}/(1 + \sqrt{\mu})$

No difference in results could be found using carbon dioxide–free water or ordinary distilled water. It was found that carbon dioxide in the air did not change the measured *p*H values even for the weakest acids.

The values in Table I indicate the expected trend in +I effect:

$$(CH_3)_3C > CH_3 > H > CH_2C_6H_5 > CH = CH_2 > Br > Cl$$

The author is grateful to the Research Corporation for financial assistance. Thanks are due Mr. Alexander Kaczmarczyk for making the measurements.

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TABLE I

Compound	Fraction Used: B.P., °C.	Fraction Used: Pressure, mm. Hg	n_D^{20}	Conc. of Solutions mol./l.	pK_a at 25° (thermodynamic)
2-Amylpyridine	211	760	1.4848	0.00500, 0.00560	6.00 ± 0.02
2-Hexylpyridine	87	6	1.4850	0.0010	5.95 ± 0.02
2-Methylpyridine	128	760	1.4940	0.142, 0.101	5.94 ± 0.01 (lit. 5.96[a]; 6.02[b])
Pyridine[c]	115	760	1.5033	0.100, 0.005	5.25 ± 0.01 (lit. 5.23[a]; 5.25[b])
2-Benzylpyridine	123–126	5	1.5732	0.00580, 0.00184	5.13 ± 0.01
2-Vinylpyridine	42–44	10	1.5386	0.0220, 0.0128	4.98 ± 0.01
2-Bromopyridine[d]	66	10	1.5658	0.0928, 0.102	0.71 ± 0.01
2-Chloropyridine[d]	170.5	760	1.5262	0.109, 0.114	0.49 ± 0.02
					Standard deviations given

[a] A. Gero and J. Markham, *J. Org. Chem.* 16, 1835 (1951). [b] R. Pearson and F. Williams, *J. Am. Chem. Soc.* 75, 3073 (1953). [c] Prepared by several methods: (1) redistilled from reaction of sodium and pyridine; (2) redistilled from pyrolysis of pyridine at 700–800; (3) from zinc chloride addition compound. [d] Since this base is very weak the assumption of $C_B = C_{BH^+}$ is not valid. This pK_a was estimated from $C_{H^+} = a_{B^+}/\gamma_{B^+}$ (using $\gamma_{H^+} = \gamma_{BH^+}$ from Debye-Hückel), $C_{BH^+} = C_{HCl} - C_{H^+}$ and $C_B = C_B^0 - C_{BH^+}$ (where C_{HCl} is concentration of added hydrochloric acid and C_B^0 is initial concentration of the pyridine). Then $pK_a = pH + \log \gamma_{BH^+} + \log C_{BH^+}/C_B$.

1,3,5,7-Tetramethyl-2,4,6,8-tetracarbethoxyporphyrin[1]

WINSLOW S. CAUGHEY, ALSOPH H. CORWIN, AND RANBIR SINGH

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Corwin and Sydow[2] showed that it is possible to produce the copper complex of 1,3,5,7-tetramethyl-2,4,6,8-tetracarbethoxyporphyrin by the condensation of the appropriate bromomethene in the presence of cuprous chloride. Because of the importance of having a number of porphyrins with electron-attracting substituents available for study, we have attempted to improve upon the synthesis of this compound.

We have found that it is possible to prepare the free porphyrin directly without the necessity for an extra step to remove the metal. This is done by the substitution of silver powder for cuprous chloride in the condensation. The reaction is carried out in boiling terphenyl. Subsequent preparation of the silver complex has shown that silver is removed thermally under the reaction conditions, thus accounting for the occurrence of the free porphyrin under the conditions used. The mechanism of this unusual reaction is under investigation.

EXPERIMENTAL

1,3,5,7-Tetramethyl-2,4,6,8-tetracarbethoxyporphyrin. Ten grams of 3,5,4′-trimethyl-4,3′-dicarbethoxy-5′-bromodipyrrylmethene hydrobromide, 5 g. of silver powder and 15 g. of *p,p′*-terphenyl were mixed thoroughly. The mixture was heated in small amounts by a Bunsen burner flame until it started to give a thick smoky ring. This required approximately 10 seconds. After cooling, the material hardened together as a black mass. It was scraped off with a spatula,

(1) Porphyrin Studies XVI. Paper XV, A. H. Corwin and S. D. Bruck, *J. Am. Chem. Soc.*, 80, 4736 (1958).

(2) A. H. Corwin and V. L. Sydow, *J. Am. Chem. Soc.*, 75, 4484 (1953).

extracted with ethylene dichloride, and filtered. The filtrate was concentrated and chromatographed on a column of Fisher's alumina. It was developed with ethylene dichloride until it was washed free from yellow material. Later, the porphyrin was eluted with chloroform. After distilling the chloroform, the porphyrin was purified by extracting with 30% hydrochloric acid. Finally it was crystallized from a mixture of chloroform and methanol. Yield, 2.1% of analytically pure porphyrin.

Anal. Calcd. for $C_{36}H_{38}O_8N_4$: C, 66.06; H, 5.81. Found: C, 66.09; H, 6.35. Spectrum in chloroform: λ 653 mμ (log ε, 3.3377); λ 596 mμ (log ε, 3.7009); λ 557 mμ (log ε, 3.7467); λ 522 mμ (log ε, 4.1196).

Silver complex. Twenty milligrams of the porphyrin was dissolved in 1 ml. of pyridine and a concentrated solution of 50 mg. of silver acetate in pyridine was added. The mixture was heated on a steam bath until it gave a pure silver complex spectrum. (Two bands) The solvent was distilled nearly to dryness under reduced pressure. The residue was washed several times with hot water and dried in a desiccator. The dry material was crystallized from a mixture of benzene and methanol. Yield, 17 mg.

Anal. Calcd. for $C_{36}H_{36}O_8N_4Ag$: C, 56.84; H, 4.76. Found: C, 57.19; H, 4.77. Spectrum in chloroform: 592, 552. In pyridine, 595, 559.

Demetallation of the silver complex. In the presence of excess silver powder the following observations were made: (a) No demetallation in boiling benzene or naphthalene. (b) Heating the silver complex in terphenyl under the conditions used for the synthesis brought about complete demetallation as judged spectroscopically with the Hartridge reversion spectroscope. The demetallation can also be brought about in this solvent by heating in a Wood's metal bath for about 2 min., the time required for the test tube to reach the boiling temperature of the terphenyl. Experiments were performed in the presence and absence of added silver and demetallation took place equally well either way.

Acknowledgments. This research was supported in part by a grant from the Petroleum Research Fund administered by the American Chemical Society. Grateful acknowledgment is hereby made to the donors of said fund. We also appreciate support received from the National Institutes of Health under Grant A-2877, B. B. C.

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Antihypertensive Agents. III. Dialkylaminoalkoxypiperidines and Related Compounds

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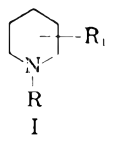
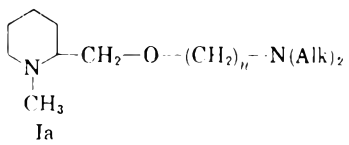
Received June 25, 1959

In a previous paper[1] selective effectiveness as hypotensive agents with bistertiary amines of the type I, R = CH_3, R_1 = 2—$CH_2O(CH_2)_nN(Alk)_2$, n = 2 and 3, *i.e.* (Ia), had been noted. In this report the effectiveness of 3- and 4-position analogs of Ia was evaluated. The structure (I), R_1 = 3—$O(CH_2)_nN(Alk)_2$ which retains the two-carbon



I



Ia

chain between the piperidine nitrogen and the ether oxygen, characteristic of Ia, was also studied. In addition, replacement of R = CH_3 in Ia by R = $C_6H_5CH_2CH_2$— was investigated. This type of group replacement has been particularly effective in enhancing analgesic properties.[2] The compounds prepared are described in Table I.

The only compound showing even moderate hypotensive activity as the bistertiary amine was compound 7, which is related to Phillips[3] 1-methyl-3-(4′-dimethylaminobutyl)piperidine.

EXPERIMENTAL[4]

N-Alkyl-3-piperidinols. Reductive alkylation of *N*-alkyl-3-piperidinols[5] using formaldehyde and acetaldehyde, respectively, gave *N*-methyl-3-piperidinol (73%), b.p. 103–104° (40 mm.),[6] and *N*-ethyl-3-piperidinol (51%), b.p. 126–128° (40 mm.).[7]

3-(Hydroxymethyl)-1-methylpyridinium bromide. A solution of 56.8 g. (0.52 mol.) of 3-pyridinemethanol in 500 ml. of acetonitrile was cooled to −5° during the addition of 95 g. (1.0 mol.) of methyl bromide. After storage at 20° for 20 hr., 101 g. of product was separated and recrystallized (isopropanol–isopropyl ether) to give 89 g. (84%), m.p. 92–94°.

Anal. Calcd. for $C_7H_{10}BrNO$: C, 41.2; H, 4.9; N, 6.9. Found: C, 40.7; H, 5.2; N, 6.9.

1-Methanol-3-piperidinemethanol hydrobromide was prepared in 70% yield (using the method previously described[1] for the 2-hydroxymethyl analog), m.p. 113–115° (ethanol–methyl ethyl ketone).

Anal. Calcd. for $C_7H_{16}BrNO$: C, 40.0; H, 7.7; N, 6.7. Found: C, 40.3; H, 7.9; N, 6.6.

1-Ethyl-4-piperidinemethanol. A solution of 89.1 g. (0.82 mol.) of 4-pyridinemethanol and 133 g. (1.2 mol.) of ethyl bromide in 800 ml. of acetonitrile was heated under reflux for 24 hr. Removal of the solvent and seeding gave a solid which after trituration with ether yielded 170 g. of crude 4-(hydroxymethyl)-1-ethylpyridinium bromide.

The crude quaternary salt was hydrogenated directly by the method described above[1] and converted to the piperidine base with 40% sodium hydroxide. The reaction mixture was salted with potassium carbonate, extracted with ether, dried (anhydrous magnesium sulfate) and distilled to yield 4-hydroxymethyl-1-ethylpiperidine (31%) b.p. 90–92° (0.15 mm.).

Anal. Calcd. for $C_8H_{17}NO$: C, 67.1; H, 12.0; N, 9.8. Found: C, 66.7; H, 12.0; N, 9.5.

2-Hydroxymethyl-1-phenethylpyridinium bromide. 2-Pyridinemethanol (22 g., 0.2 mol.) and 40.7 g. (0.22 mol.) of phenethyl bromide were dissolved in 250 ml. of acetonitrile

(1) S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Chem. Soc.*, **80**, 2743 (1958).

(2) E. L. May and N. B. Eddy, *J. Org. Chem.*, **24**, 294 (1959).

(3) A. P. Phillips, *J. Am. Chem. Soc.*, **76**, 2211 (1954).

(4) Descriptive data shown in the table are not reproduced in the Experimental section.

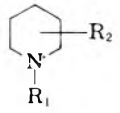
(5) S. L. Shapiro, H. Soloway, and L. Freedman, *J. Am. Pharm. Assoc., (Sci. Ed.)*, **46**, 333 (1957).

(6) S. Tchelitcheff, U. S. Patent **2,489,546** (Nov. 29, 1949), reports b.p. 79° (15 mm.).

(7) J. H. Biel, H. L. Friedman, H. A. Leiser, and E. P. Sprengeler, *J. Am. Chem. Soc.*, **74**, 1485 (1952), report b.p. 93–95° (15 mm.).

TABLE I

DIALKYLAMINOALKOXYALKYLPIPERIDINES



No.	R_1	R_2	Yield,[a] %	M.P.[b,c(a)] or B.P. (Mm.)	Formula	Analyses[d] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Activity
1[e]	CH_3—	3-$O(CH_2)_2N(CH_3)_2$	11	100–103 (9)								0
2	$2CH_3I$[f]		60	294–297[c(b)]	$C_{12}H_{28}IN_2O$	30.6	30.8	6.0	6.1	6.0	6.0	1+
3	C_2H_5—	3-$O(CH_2)_2N(CH_3)_2$	17	102–106 (8)	$C_{11}H_{24}N_2O$	66.0	65.6	12.1	12.3			0
4	CH_3—	3-$O(CH_2)_3N(CH_3)_2$	50	142–144 (35)	$C_{11}H_{24}N_2O$	66.0	65.8	12.1	11.8	14.0	13.5	0
5	$2CH_3I$[f]		85	214–216	$C_{13}H_{30}I_2N_2O$	32.2	32.2	6.2	6.2	5.8	5.7	1+
6	$2C_2H_5I$[g]		71	171–174	$C_{15}H_{34}I_2N_2O$	35.2	34.9	6.7	7.0			0
7	C_2H_5—	3-$O(CH_2)_3N(CH_3)_2$	38	116–118 (6)	$C_{12}H_{26}N_2O$					13.1	13.1	2+
8	$2CH_3I$[f]		52	197–200	$C_{14}H_{32}I_2N_2O$	33.8	33.8	6.5	6.5	5.6	5.2	3+
9[h]	CH_3—	3-$CH_2O(CH_2)_2N(C_2H_5)_2$	10	113 (2)								0
10	C_2H_5—	4-$CH_2O(CH_2)_2N(C_2H_5)_2$	40	106 (0.9)	$C_{14}H_{30}N_2O$	69.4	69.1	12.5	12.6	11.6	11.6	0
11	$C_6H_5CH_2CH_2$—	2-$CH_2O(CH_2)_2N(C_2H_5)_2$	4	120–124 (0.08)	$C_{20}H_{34}N_2O$	75.4	75.3	10.8	10.2			0

[a] Yields are based on distilled or recrystallized product. [b] Melting points are not corrected and were obtained on a Fisher-Johns melting point block. [c] (a) Recrystallizing solvent is ethanol unless otherwise shown; (b) methanol. [d] Analyses by Weiler and Strauss, Oxford, England. [e] Characterized as the methiodide (Compound 2). [f] Compound is the dimethiodide of bisamine immediately above. [g] Compound is the diethiodide of bisamine immediately above. [h] B. Elpern, U. S. Patent 2,773,876 (Dec. 11, 1956) reports b.p. 113–118° (3.2 mm.).

and heated under reflux for 22 hr. The solvent was removed to give 19 g. (32%), m.p. 150–154°. Recrystallization (ethanol) gave m.p. 158–159°.

Anal. Calcd. for $C_{15}H_{16}BrNO$: C, 57.2; H, 5.5; N, 4.8. Found: C, 57.4; H, 5.7; N, 5.1.

1-Phenethyl-2-piperidinemethanol hydrobromide. A mixture of 14 g. (0.048 mol.) of 2-hydroxymethyl-1-phenethylpyridinium bromide in 250 ml. of ethanol and 1.3 g. of 5% rhodium on carbon afforded complete uptake of hydrogen[1] after 3 hr. The catalyst was removed and the filtrate concentrated to dryness. Crystallization (ethanol-ether) gave 10 g., m.p. 153–154° and recrystallization (ethanol-ether) gave m.p. 157–158°.

Anal. Calcd. for $C_{14}H_{22}BrNO$: C, 56.0; H, 7.4; N, 4.7. Found: C, 56.3; H, 7.1; N, 4.9.

3-(3-Dimethylaminopropoxy)-1-ethylpiperidine (Compound 7). Sodium hydride (3.1 g., 0.13 mol.) was stirred under 50 ml. of dry toluene while a solution of 15.4 g. (0.12 mol.) of 1-ethyl-3-piperidinol in 50 ml. of toluene was added over 40 min. Stirring was continued at 20° for 2 hr. and then under reflux for 2 hr. This solution was treated over 1 hr. with the filtered solution prepared from 38.4 g. (0.24 mol.) of 3-dimethylaminopropyl chloride hydrochloride dissolved in water, made basic with 40% sodium hydroxide, extracted with 150 ml. of toluene and dried (magnesium sulfate). Reflux was continued for 6 hr. When cool, the mixture was filtered and the residue distilled to yield 9.8 g. (38%) of product, b.p. 116–118° (6 mm.).

3-(3-Dimethylaminopropoxy)-1-ethyl-1-methylpiperidinium iodide methiodide (Compound 8). Addition of 3.2 g. (0.015 mol.) of 3-(3-dimethylaminopropoxy)-1-ethylpiperidine in 10 ml. of acetonitrile to a cooled solution of 4.7 g. (0.033 mol.) of methyl iodide in 15 ml. of acetonitrile caused an immediate exothermic reaction. After 20 hr. the precipitated product (4.7 g.) was separated.

Acknowledgment. The authors wish to thank Dr. G. Ungar and his staff for the pharmacological results of the screening of the compounds and Mrs. T. Ast for technical assistance.

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6-Alkylacridizinium Derivatives[1]

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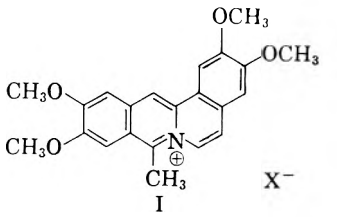
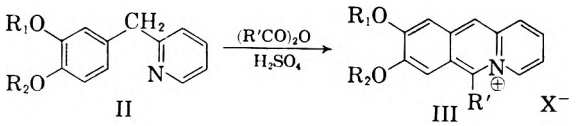
Received July 30, 1959

Probably the first reported compound containing the fully aromatic quinolizinium[2] nucleus was the Coralyn (I) of Schneider and Schroeter,[3,4] described in 1920. Coralyn, an 8-methyl-2,3,10,11-tetramethoxybenz[a]acridizinium salt was obtained in 90% yield by the action of sulfoacetic acid (acetic anhydride containing a small amount of sulfuric acid) on papaverine.



I

It seemed likely that 2-(3,4-dialkoxybenzyl)-pyridines (II) might be made to undergo a similar acylative cyclization, affording the first simple 6-alkylacridizinium salts III.



II III

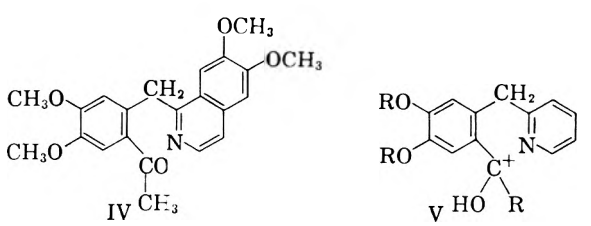
The requisite benzylpyridines (II) were prepared by reaction of 2-pyridyllithium with the appropriate aldehyde, followed by reduction of the crude carbinol. The acylative cyclization was carried out at 100° by means of sulfuric acid in a large excess of the appropriate anhydride, and the results are summarized in Table I.

TABLE I

6-ALKYL-8,9-ALKOXYACRIDIZINIUM SALTS (III)

R_1	R_2	R′	% Yield (as)	Ultraviolet Absorption Maxima, mμ (Perchlorate)		
CH_3	CH_3	CH_3	—[c]	368	382	401
C_2H_5	C_2H_5	CH_3	74[b](ClO_4)	370	384	404
C_2H_5	C_2H_5	C_2H_5	48[c]	370	385	405
—CH_2—		CH_3	25(Pic.)[d]			

[a] A 31% yield of sulfoacetate, m.p. 255–262° (dec.), was recorded, but this salt was never obtained in a state of analytical purity. [b] Product melting at 252–256° (dec.). [c] A part of the yield (25%) was obtained as the perchlorate m.p. 260–264° (dec.), the remainder (23%) as picrate, m.p. 188–192°. [d] No perchlorate of this compound was prepared.



IV V

Schneider and Schroeter[3] adduced evidence to show that the acetylative cyclization of papaverine occurred *via* acetopapaverine (IV). Probably the acylative cyclization of the 2-(3,4-dialkoxybenzyl)pyridine likewise occurs *via* a carbonyl derivative, or more exactly, *via* the conjugate acid V. The Coralyn synthesis can be regarded not only as the prototype of the Woodward synthesis of

(1) Taken in part from a thesis submitted in partial fulfillment of the requirements for the Ph.D. Degree, Duke University, 1958. This research was supported by a research grant (NSF-G2364) of The National Science Foundation.

(2) *Chemical Abstracts* nomenclature.

(3) W. Schneider and K. Schroeter, *Ber.* **53B**, 1459 (1920).

(4) W. Schneider and O. Boger, *Ber.*, **54B**, 2021 (1921).

TABLE II

6-ALKYLACRIDIZINIUM SALTS, III

R_1	R_2	R′	M.P., °C.	Formula	C Calcd.	C Obsd.	H Calcd.	H Obsd.	N Calcd.	N Obsd.
				Picrates						
CH_3	CH_3	CH_3	239–241 (dec.)[a]	$C_{22}H_{13}N_4O_9$	54.80	55.02	3.76	3.91	11.62	12.04
C_2H_5	C_2H_5	CH_3	205–206[b]	$C_{24}H_{22}N_4O_9 \cdot {}^1/_2H_2O$	55.00	54.81	4.46	4.72	10.79	10.65
C_2H_5	C_2H_5	C_2H_5	197–199[c]	$C_{25}H_{24}N_4O_9$	57.25	57.43	4.62	4.92	10.69	10.50
—CH_2—		CH_3	235–236[d]	$C_{21}H_{14}N_4O_9$	54.09	54.03	3.03	3.19	12.01	11.99
				Perchlorates						
CH_3	CH_3	CH_3	288–291[e]	$C_{16}H_{16}ClNO_6$	54.10	54.39	4.57	4.59	3.86	4.32
C_2H_5	C_2H_5	CH_3	272–274[f]	$C_{18}H_{20}ClNO_6 \cdot 3/2H_2O$	52.98	53.13	5.67	5.72	3.44	3.68
C_2H_5	C_2H_5	C_2H_5	269–270[g]	$C_{19}H_{22}ClNO_6$	57.69	57.31	5.56	5.66	3.56	3.75

[a] Needles from acetone. [b] Well formed needles from acetone-ethanol. [c] Flakes from acetone-ethanol. [d] Granules from ethanol. [e] All of the perchlorates formed needles which melted with decomposition. [f] From acetone-water. [g] From acetone-ethanol.

quinolizinium derivatives,[5–8] but also a further example of aromatic cyclodehydration,[9] one involving electrophilic attack on aromatic nitrogen rather than the usual carbon.

EXPERIMENTAL[10]

2-(3′,4′-Methylenedioxybenzyl)pyridine (II) ($R_1 - R_2 =$ —O—CH_2O—) was prepared essentially as in the case of the known 2-(3,4-dimethoxybenzyl)pyridine[11] (II, $R_1 = R_2 = OCH_3$). To a solution of butyllithium prepared from 30.5 g. of *n*-butyl chloride, and maintained at a temperature of −50°, 40 g. of 2-bromopyridine was added in dry ether. The reaction mixture was stirred for 15 min., and then 42.7 g. of piperonal in dry ether was added. The temperature of the mixture was maintained at 0° for 1 hr. longer, and then allowed to come to room temperature. The reaction mixture was poured into dilute acid, the acid layer separated and made basic, and the resulting oil taken up in ether. The ethereal solution was washed, dried and concentrated and the crude residue was used directly for the reduction. A solution of the residue in 300 ml. of benzene was cooled and treated with 38 g. of thionyl chloride, the temperature being kept below 25°. After the mixture had stood for an additional hour, it was made basic with sodium hydroxide solution. The benzene layer was separated, wahed, dried and concentrated. The residue was dissolved in 250 ml. of glacial acetic acid and while this was heated on the steam bath during a 6 hr. period, 36 g. of zinc powder was added in small portions. The excess zinc was removed by filtration, the acetic acid was evaporated under reduced pressure, and the residue made alkaline with sodium hydroxide. The oil which separated was taken up in ether, and the ethereal extract washed, dried and concentrated. The residue was fractionated yielding 13.2 g. (28%) of an oil, b.p. 185–196° (3 mm.).

A *picrate* was prepared for analysis as fine yellow granules from ethanol, m.p. 143–145°.

Anal. Calcd. for $C_{19}H_{13}N_4O_9$: C, 51.70; H, 2.97; N, 12.70. Found: C, 52.00; H, 3.59; N, 12.66.

2-(3′,4′-Diethoxybenzyl)pyridine (II, $R_1 = R_2 = OC_2H_5$). Essentially the same procedure was used except that the aldehyde was 3,4-diethoxybenzaldehyde. The yield of 2-(3′,4′-diethoxybenzyl) pyridine, b.p. 170–180°(3 mm.) was 12.5%.

The *picrate*, prepared for analysis, crystallized from ethanol as bright yellow clusters, m.p. 157–158°.

Anal. Calcd. for $C_{22}H_{22}N_4O_9$: C, 54.40; H, 4.56; N, 11.51. Found: C, 54.36; H, 4.84; N, 11.79.

Acetylative cyclization of the benzylpyridine derivatives. One gram of the benzylpyridine derivative (II) was dissolved in 20 ml. of acetic or propionic anhydride containing 0.8 ml. of concentrated sulfuric acid. The mixture was heated on the steam bath for 2 hr., after which it was cooled, and the salt precipitated by addition of ether. The organic solvents were separated from the salt either by filtration or decantation. The crude sulfoacetate salt was dissolved in water, and perchloric acid added to precipitate the product as a *perchlorate* salt which was crystallized from an acetone-ethanol mixture.

The *picrate* was prepared by addition of an alcoholic solution of picric acid to an aqueous solution containing the crude sulfoacetate salt. The results are summarized in Table II.

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(5) R. B. Woodward and B. Witkop, *J. Org. Chem.*, **71**, 379 (1949).

(6) R. B. Woodward and W. M. McLamore, *J. Org. Chem.*, **71**, 379 (1949).

(7) A. Richards and T. S. Stevens, *Chem. and Ind.* **1954**, 905.

(8) A. Richards and T. S. Stevens, *J. Chem. Soc.*, 3067 (1958).

(9) *Cf.*, C. K. Bradsher, *Chem. Revs.*, **38**, 447 (1946).

(10) All melting points were taken on a Fisher-Johns hot stage and are uncorrected. All analyses were by Micro Tech Laboratories, Skokie, Illinois.

(11) N. Sugiomoto, *J. Pharm. Soc. Japan*, **76**, 1045 (1956).

Benzo[*b*]quinolizidine Derivatives[1]

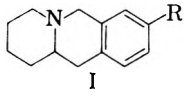
C. K. BRADSHER AND NANCY L. YARRINGTON

Received August 18, 1959

It was shown earlier[2] that benzo[*b*]quinolizidine derivatives (I, R = H) can be produced by the catalytic reduction of the acridizinium nucleus. As part of a study of the relation between structure

(1) This investigation was supported by a research grant (H-2170) from the National Heart Institute of the National Institutes of Health.

(2) C. K. Bradsher and L. E. Beavers, *J. Am. Chem. Soc.*, **77**, 4812 (1955).



I

and hypotensive activity, we have prepared a few benzo[*b*]quinolizidine derivatives. It has been found that sodium borohydride may be used for the reduction of acridizinium bromide to I (R = H).

EXPERIMENTAL[3]

2-Aldoximino-1-(3-methoxy)benzylpyridinium bromide. To a flask containing 5 ml. of dimethyl formamide, 4.88 g. of pyridine 2-aldoxime and 8.04 g. of *m*-methoxybenzyl bromide were added. The flask was warmed gently on the steam bath until solution was complete, then stoppered and allowed to stand for 24 hr. at room temperature. The colorless crystals were triturated with ethyl acetate and collected. The yield was 11.41 g. (88%), m.p. 178–182°. The analytical sample melted at 180–182°.

Anal. Calcd. for $C_{14}H_{15}BrN_2O_2$: C, 52.03; H, 4.68; N, 8.67. Found: C, 52.44; H, 4.84; N, 8.55.

8-Methoxyacridizinium perchlorate. To a solution containing 1 g. of the oximino quaternary salt in 8 ml. of absolute alcohol, 6 ml. of concentrated hydrochloric acid was added, and the mixture refluxed for 5 hr. After vacuum evaporation of the solvents the residual yellow solid was washed with ethyl acetate and then dissolved in a small quantity of water. The perchlorate was precipitated by addition of perchloric acid. Recrystallization of the product from methanol yielded 0.41 g. (44%) of yellow platelets, m.p. 222–224° (lit.[4] 218–219°).

8-Hydroxyacridizinium bromide. The oximino quaternary salt (5.9 g.) was placed in 30 ml. of 48% hydrobromic acid and the mixture refluxed for 45 min. The mixture was vacuum evaporated and the residue crystallized from a concentrated ethanol solution. The yield was 3.9 g. (97%),[5] m.p. 246–248° (lit.[4] 250–252°).

8-Methoxybenzo[b]quinolizidine (I, R = OCH_3) *hydroperchlorate.* To a suspension of 5.2 g. of 8-methoxyacridizinium perchlorate in 300 ml. of methanol, 100 mg. of platinum oxide was added and hydrogenation was carried out at room temperature and atmospheric pressure until the theoretical amount of hydrogen had been absorbed. The solution was filtered, concentrated, and cooled; 4.4 g. (83%) of colorless crystals, m.p. 175–177° was obtained.

Anal. Calcd. for $C_{14}H_{20}ClNO_4$: C, 52.92; H, 6.35; N, 4.41. Found: C, 53.10; H, 6.07; N, 4.50.

8-Methoxybenzo[b]quinolizidine (I, R = OCH_3) was recrystallized from ethanol, m.p. 50–51°.

Anal. Calcd. for $C_{14}H_{19}NO \cdot {}^1/_3H_2O$: C, 75.30; H, 8.88; N, 6.27. Found: C, 75.58; H, 8.69; N, 6.15.

8-Hydroxybenzo[b]quinolizidine (I, R = OH) *hydrochloride.* The reduction of 1.7 g. of the 8-hydroxyacridizinium salt was carried out as in the case of the methyl ether. Concentration of the methanol solution yielded 1.51 g. (88%), decomposes 268–290°. The analytical sample consisted of colorless prisms, decomposes 276–318°.

Anal. Calcd. for $C_{13}H_{18}ClNO$: C, 65.13; H, 7.57; N, 5.81. Found: C, 65.37; H, 7.69; N, 5.70.

8-Hydroxybenzo[b]quinolizidine (I, R = OH) was obtained as a colorless powder, m.p. 230–231°.

Anal. Calcd. for $C_{13}H_{17}NO$: C, 76.82; H, 8.43; N, 6.90. Found: C, 76.51; H, 8.35; N, 7.04.

The *methiodide* was prepared in 92% yield by refluxing a methanol solution of the base for 1 hr. with excess methyl iodide. It formed colorless needles from ethanol, m.p. 274–275°.

Anal. Calcd. for $C_{14}H_{20}INO$: C, 48.72; H, 5.84; N, 4.06. Found: C, 48.56; H, 5.91; N, 4.25.

Benzo[b]quinolizidine (I, R = H) *methiodide.* (a) *From the hydrobromide.* Benzo[b]quinolizidine hydrobromide[2] was converted to the free base by action of ammonia, and the crude base obtained by ethereal extraction was methylated with methyl iodide. The product was obtained from ethanol as colorless irregular crystals, m.p. 290–291°.

(b) *From the sodium borohydride reduction product.* To a solution of 2 g. of acridizinium bromide in 45 ml. of water an aqueous suspension 0.68 g. of sodium borohydride was added. The mixture was heated on the steam bath until the evolution of hydrogen ceased and a red oil separated. The oil was taken up in ether, the solution dried and concentrated, and the residue heated with methyl iodide on the steam bath for 2 hr. The product melted at 267–268° and the melting point did not change on recrystallization. When a sample of the product was dissolved in ethanol and seeded with a single crystal of product obtained by Procedure a, the entire material crystallized in irregular clusters, m.p. 290–291°. The infrared spectrum of this material was identical with that of the product obtained by Procedure a.

Anal. Calcd. for $C_{14}H_{20}IN$: C, 51.07; H, 6.12; N, 4.25. Found[6]: C, 51.27, 50.97; H, 5.85, 5.96; N, 4.13, 4.55.

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(3) All melting points were taken on a Fisher-Johns hot stage and are uncorrected. All analyses were performed by Drs. Weiler and Strauss, Oxford, England.

(4) C. K. Bradsher and J. H. Jones, *J. Am. Chem. Soc.*, **79**, 6033 (1957).

(5) Only a 37% yield of 8-hydroxyacridizinium was reported earlier [ref. (4)] for the cyclization of crude 1-(3-methoxybenzyl)-2-formylpyridinium bromide.

(6) Values are for the product of Procedure *a* and for the low-melting form (m.p. 267–268°) obtained by Procedure *b*.

9(11)-Dehydrocortical Steroids. Synthesis of 9(11)-Anhydro-17α-hydroxycorticosterone Acetate and 9(11)-Anhydrocorticosterone Acetate

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The elimination of the 11β-hydroxyl group from the steroidal nucleus to give 9(11)-dehydro compounds is easily accomplished because of the favorable conformation of the 11β-hydroxyl group and the 9α-hydrogen atom (di-axial-trans).[1] Reichstein and his co-workers[2] have reported the conversion of 11β-hydroxylated cortical steroids without a 17α-hydroxyl function to 9(11)-anhydro derivatives using phosphorus oxychloride and pyridine or refluxing acetic-hydrochloric acid mixtures. In the

(1) W. A. Cranshaw, H. B. Henbest, and E. R. Jones, *J. Chem. Soc.*, **73** (1954); H. L. Herzog, C. C. Payne, and E. B. Hershberg, *J. Am. Chem. Soc.*, **76**, 930 (1954).

(2) (a) C. W. Shoppee, *Helv. Chim. Acta*, **23**, 740 (1940); (b) C. W. Shoppee and T. Reichstein, *Helv. Chim. Acta*, **24**, 351 (1941); (c) P. Hegner and T. Reichstein, *Helv. Chim. Acta*, **26**, 715 (1943); (d) C. W. Shoppee and T. Reichstein, *Helv. Chim. Acta*, **26**, 1316 (1943).

case of the steroidal hormones where an α,β-unsaturated ketone is present, the usual reagents for dehydration lead to complications. Graber, Haven, and Wendler[3] have reported the preparation of 17α-hydroxy-21-acetoxy-4,9(11-)pregnadiene-3-20-dione, [9(11)-anhydro-17α-hydroxycorticosterone acetate], by an indirect method from 11β-hydroxy-20-cyano-21-acetoxy-17(20)-pregnen-3-one. The dehydration of this latter compound was effected with phosphorus oxychloride and pyridine. In compounds where the Δ^4-3-ketone structure is absent, these latter authors[3] have shown that dehydration with phosphorus oxychloride-pyridine proceeds without complications to give the anhydro compound in good yields—e.g., 11β,17α-dihydroxy-21-acetoxypregnane-3,20-dione gives 17-α-hydroxy-21-acetoxy-9(11)-pregnene-3,20-dione in 73% yield.

The preparation of 9-halo derivatives of 11β,17α-dihydroxy-21-acetoxy-4-pregnen-3,20-dione (hydrocortisone acetate) demanded a ready supply of the 9(11)-anhydro compound, 17α-hydroxy-21-acetoxy-4,9(11)-pregnadien-3,20-dione, and a direct method of dehydration of the readily available hydrocortisone acetate was sought. Two reagents, methanesulfonyl chloride and methyl chlorosulfite, were found which bring about this dehydration smoothly and in good yield. One of these reagents was mentioned briefly without details in the preparation of 17α-hydroxy-21-acetoxy-1,4,9(11)-pregnatrien-3,20-dione from 11β,17α-dihydroxy-21-acetoxy-1,4-pregnadien-3,20-dione (prednisolone acetate)[4] and we are prompted to communicate our experience with this dehydration.

Initially, hydrocortisone acetate in pyridine reacted with methanesulfonyl chloride at room temperature in the course of 24 hr. to give a 30% yield of the 9(11)-anhydro compound. Further study of this reaction lead to optimum conditions whereby the dehydration was carried out with methanesulfonyl chloride in pyridine-dimethylformamide solution at 80–85° to give 75–80% yield of product.

The method appears to be generally applicable and has been employed in the dehydration of corticosterone acetate.

A more vigorous dehydrating agent was methyl chlorosulfite.[5] This reagent effected dehydration of hydrocortisone acetate in tetrahydrofuran-pyridine solution at −10 to −5° over a period of 4 hr. or in dimethylacetamide solution at 20–25° over a period of 30 min. The yield with this reagent was 65–89% of theory. It is of interest that in the dehydration of cholesterol to cholestadiene with methyl chlorosulfite reported by Berti[5] the methyl sulfonyl ester was first obtained and isolated and the dehydration was achieved only by heating at 185–270° under 20 mm. vacuum. In the present work despite our efforts to isolate the intermediate esters no trace of these intermediates could be isolated.

(3) R. P. Graber, A. C. Haven, Jr., and N. L. Wendler, *J. Am. Chem. Soc.*, **75**, 4722 (1953).

(4) J. Fried, K. Florey, E. F. Sabo, J. E. Herz, A. R. Restino, A. Borman, and F. M. Singer, *J. Am. Chem. Soc.*, **77**, 4181 (1955).

(5) Berti, *J. Am. Chem. Soc.*, **76**, 1214 (1954).

EXPERIMENTAL

17α-Hydroxy-21-acetoxy-4,9(11)-pregnadien-3,20-dione. (a) Methanesulfonyl chloride method. To a slurry of 10 g. (0.0247 mol.) of 11β,17α-dihydroxy-21-acetoxy-4-pregnen-3,20-dione (hydrocortisone acetate) in 50 ml. of dry dimethylformamide[6] and 8.8 ml. of dry pyridine was added dropwise with stirring 6.43 g. (4.4 ml., 0.0564 mol.) of methanesulfonyl chloride. The reaction mixture was stirred and the temperature maintained at 80–85° for 1 hr. after all the methanesulfonyl chloride had been added. At the end of the reaction period the temperature was brought to 25–30° and the mixture was diluted with 200 ml. of methanol. After cooling (ice bath) for 1/2 hr. the product was filtered and washed with methanol. Recrystallization from methylene chloride–methanol afforded 7.4 g. (77.5%) of product, m.p. 228–238°; infrared identical with an authentic sample. An analytical sample melted 232.5–236.5° (lit.[3] m.p. 231.5–234.5°).

Anal. Calcd. for $C_{23}H_{30}O_5$: C, 71.47; H, 7.38. Found: C, 71.08; H, 7.93.

(b) Methyl chlorosulfite method. Four grams (0.01 mol.) of 11β,17α-dihydroxy-21-acetoxy-4-pregnene-3,20-dione (hydrocortisone acetate) was dissolved in 20 cc. of dry dimethylacetamide. To this solution was added with stirring 11 g. (0.084 mol.) of methyl chlorosulfite.[5] During the addition the temperature was kept between 20–25° by external cooling. During the course of the addition the mixture set to a semi-solid mass. When the addition of the methyl chlorosulfite was complete (30 min.), 70 ml. of methanol was added and the mixture was aged in an ice bath for 1/2 hr. The product was filtered and washed with methanol, 2.5 g. (65%), m.p. 205–225°. Recrystallized from chloroform-methanol, the product melted 237–240°. Identity was established by infrared comparison and mixed melting point.

A 4-g. sample (0.01 mol.) of 11β,17α-dihydroxy-21-acetoxy-4-pregnene-3,20-dione was dissolved by heating in 150 ml. of dry tetrahydrofuran and the solution was cooled to −10°. Dry pyridine (8 ml.) was added. To the cooled solution was added with stirring 11.5 g. (0.088 mol.) of methyl chlorosulfite.[5] The temperature was kept between −10 and −5° during the addition of the reagent. The reaction mixture was then allowed to come to room temperature over a period of 4 hr and the product was precipitated by the addition of 150 ml of ice water. The product was filtered after aging 1/2 hr. and washed with cold water, yield 3.45 g. (89%), m.p. 226–230°. The identity of the substance was confirmed by mixed melting point and comparison of the infrared spectrum.

21-Acetoxy-4,9(11)-pregnadien-3,20-dione. A 4-g. sample (0.013 mole) of 11β-hydroxy-21-acetoxy-4-pregnene-3,20-dione (corticosterone acetate) was dissolved in 20 ml. of dry dimethylformamide. To this solution was added 1.6 ml. of dry pyridine and 2 ml. of methanesulfonyl chloride. The reaction mixture stood at room temperature 3 days. At the end of this time 60 ml. ice water was added. The precipitated product was filtered, washed with water, and twice recrystallized from methanol, m.p. 153–157° (lit.[2d] m.p. 159–160°); infrared 5.75 μ (OAc), 5.82 μ (>C=O), 6.01 μ, 6.19 μ (—C=C—C=O), no OH band.

(6) The steroid initially all goes into solution and then reprecipitates as a dimethylformamide complex.

Anal. Calcd. for $C_{23}H_{30}O_4$: C, 74.50; H, 8.16. Found: C, 74.71; H, 8.22.

Acknowledgment. The authors are indebted to Dr. N. Trenner and Mr. R. Walker for the infrared spectra and to Mr. R. N. Boos and staff for the analytical data reported.

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16-Hydroxylated Steroids. XIII.[1] 9α-Fluoro-11β,16α-dihydroxy-4-androstene-3,17-dione

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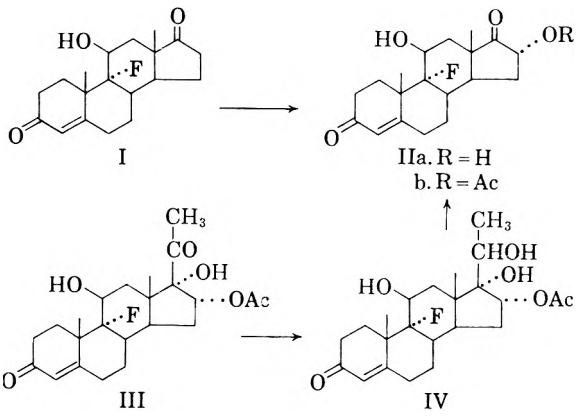
The research program of this laboratory on the preparation of 16-hydroxylated steroids has been extended to include C19-steroids. We wish to report on the synthesis of 9α-fluoro-11β,16α-dihydroxy-4-androstene-3,17-dione (IIa).[2]

9α-Fluoro-11β-hydroxy-4-androstene-3,17-dione (I)[3] on microbiological hydroxylation with *Streptomyces roseochromogenus* (Lederle AE 409)[4] afforded 9α-fluoro-11β,16α-dihydroxy-4-androstene-3,17-dione (IIa). The structure of the fermentation product was established as follows:

Compound IIa exhibited a positive Blue Tetrazolium test indicative of the 16,17-ketol moiety.[5] Acetylation gave the monoacetate IIb, in turn, synthesized from 16α-acetoxy-9α-fluoro-11β,17α-dihydroxy-4-pregnene-3,20-dione (III).[6] Reduction of III in methanol at 0° with sodium borohydride gave 16α-acetoxy-9α-fluoro-11β,17α,20-trihydroxy-4-pregnen-3-one (IV).[7] The latter on the basis of elemental analyses was apparently obtained in a pure state. However, its ultraviolet absorption spectrum, $\lambda_{max}^{methanol}$ 240 mμ (ε 11,000), revealing a low molecular extinction coefficient,[8] indicated that reduction in part of the C3-carbonyl and/or the C4-5-double bond had occurred.[9] The material as such in methanol was treated with an aqueous solution of sodium periodate at room temperature to give after partition chromatography 16α-acetoxy-9α-fluoro-11β-hydroxy-4-androstene-3,17-dione (IIb), identical in all respects with the acetylated fermentation product.

Bioassay. Rosemberg and Dorfman[10] have recently cited 9α-fluoro-11β-hydroxy-4-androstene-3,17-dione (I) as the first instance of a highly active sodium retaining substance in the C19-series. These same investigators have now found in a preliminary assay that 9α-fluoro-11β,16α-dihydroxy-4-androstene-3,17-dione (IIa) was inactive in the electrolyte assay (saline load, six hours) on adrenalectomized rats at 6, 25, and 100 μg. dose levels.[11]

Flow Sheet



EXPERIMENTAL

All melting points are uncorrected.

9α-Fluoro-11β,16α-dihydroxy-4-androstene-3,17-dione (IIa). Forty 500 ml. flasks were charged with 100 ml. each of the following medium: corn steep liquor (30 g.), glucose (30 g.), soybean oil (5 g.), and calcium carbonate (5 g.) in 1 l. of distilled water. Each flask, after the addition of 25 mg. of 9α-fluoro-11β-hydroxy-4-androstene-3,17-dione (I) dissolved in 1 ml. of methanol, was inoculated with 4 ml. of a 48 hr. (28°) mycelial growth of *Streptomyces roseochromogenus* (Lederle AE 409). The fermentation was carried out for 78 hr. at 28° with shaking (rotary shaker, 240 RPM).

The pooled fermentation mixture was filtered, and the filtrate was extracted twice with 4 l.-portions of chloroform. The combined extracts were washed with water, treated with animal charcoal, dried and evaporated. The crude residue was subjected to partition chromatography on 300

(1) Paper XII, S. Bernstein, R. Littell, J. J. Brown, and I. Ringler, *J. Am. Chem. Soc.*, **81**, 4573 (1959).

(2) G. H. Thomas and R. W. Thoma, U. S. Patent **2,853,502** (Sept. 23, 1958), have also described the preparation of IIa by microbiological 16α-hydroxylation.

(3) S. Bernstein and R. H. Lenhard, *J. Am. Chem. Soc.*, **77**, 6665 (1955); J. Fried and E. F. Sabo, *J. Am. Chem. Soc.*, **79**, 1130 (1957).

(4) J. Fried, R. W. Thoma, D. Perlman, J. E. Herz, and A. Borman, *Recent Progr. Hormone Research*, **9**, 149 (1955); R. W. Thoma, J. Fried, S. Bonanno and P. Grabowich, *J. Am. Chem. Soc.*, **79**, 4818 (1957).

(5) A. S. Meyer and M. C. Lindberg, *Anal. Chem.*, **27**, 813 (1955).

(6) S. Bernstein, J. J. Brown, L. I. Feldman, and N. E. Rigler, *J. Am. Chem. Soc.*, **81**, 4956 (1959).

(7) The reduction of the C20-carbonyl group presumably provided the 20β-hydroxyl group; see, D. K. Fukushima and E. D. Meyer, *J. Org. Chem.*, **23**, 174 (1958).

(8) L. Dorfman, *Chem. Revs.*, **53**, 47 (1953).

(9) F. Sondheimer, M. Velasco, E. Batres and G. Rosenkranz, *Chem. & Ind.* (London), 1482 (1954); J. Norymberski and G. F. Woods, *J. Chem. Soc.*, 3426 (1955).

(10) E. Rosemberg and R. I. Dorfman, *Proc. Exptl. Biol. and Med.*, **99**, 336 (1958).

(11) We wish to thank the Worcester Foundation group for carrying out this assay, the details of which will be reported by them elsewhere.

g. of Celite[12] with a ternary system consisting of 1 part water, 5 parts dioxane, and 4 parts cyclohexane. The fraction collected from 2.3–3.9 hold-back volumes (HBV) (maximum product at 3.3) (1 HBV = 485 ml.) was evaporated to afford 604 mg. of crude IIa. Two crystallizations from acetone gave pure IIa, m.p. 262–270° with previous softening and browning and with decomposition at 271°; $\lambda_{max}^{methanol}$ 237 mμ (ε 17,400); ν_{max}^{KBr} 3510, 3400, 3250, 1754, 1657, 1640–1615 (inflection) cm.$^{-1}$; $[\alpha]_D^{25}$ +157° (methanol); positive Blue Tetrazolium test.

Anal. Calcd. for $C_{19}H_{25}O_4F$ (336.39): C, 67.83; H, 7.49; F, 5.65. Found: C, 67.64; H, 7.65; F, 5.86.

16α-Acetoxy-9α-fluoro-11β,17α,20-trihydroxy-4-pregnen-3-one (IV). A solution of 350 mg. of 16α-acetoxy-9α-fluoro-11β,17α-dihydroxy-4-pregnene-3,20-dione (III) in 50 ml. of methanol was cooled to 0° and treated with 47 mg. of sodium borohydride. After remaining at 0° for 1 hr., the solution was acidified with 0.2 ml. of glacial acetic acid and evaporated. The residue was dissolved in ethyl acetate and washed with saturated sodium bicarbonate solution and water. The dried extract was evaporated and the residue crystallized from acetone-petroleum ether to afford 254 mg. of crude IV, m.p. 215–219.5° with previous softening. Two additional crystallizations from the same solvent pair gave 228 mg., m.p. 214.5–217.5° with previous softening; $\lambda_{max}^{methanol}$ 240 mμ (ε 11,000); ν_{max}^{KBr} 3430, 1725, 1666, 1625, 1277, and 1253 cm.$^{-1}$; $[\alpha]_D^{25}$ −19° (acetone).

Anal. Calcd. for $C_{23}H_{33}O_6F$ (424.49): C, 65.07; H, 7.84; F, 4.48. Found: C, 64.99; H, 8.17; F, 4.19.

This material was used as such in the subsequent side chain degradation.

16α-Acetoxy-9α-fluoro-11β-hydroxy-4-androstene-3,17-dione (IIb). A. Forty milligrams of IIa in 2 ml. of pyridine was treated with 1 ml. of acetic anhydride, and the mixture was allowed to stand at room temperature overnight. The crude acetate was subjected to partition chromatography on 31 g. of Celite[12] with the system four parts petroleum ether (b.p. 90–100°), three parts ethyl acetate, four parts methanol, and two parts water. The fraction collected from 3.5–5.5 hold-back volumes (maximum product at 4.7) (1 HBV = 38 ml.) was evaporated, and the residue was crystallized from acetone-petroleum ether (b.p. 35–60°) to afford pure IIb, m.p. 248–250°. Its infrared spectrum was identical with that obtained in preparation B.

B. A solution of 380 mg. of impure 16α-acetoxy-9α-fluoro-11β,17α,20-trihydroxy-4-pregnen-3-one (IV) in 20 ml. of methanol was treated with 7.6 ml. of an aqueous solution of sodium periodate (0.1*M*). After standing at room temperature for 19 hr., the solution was poured into ice water, and the resultant precipitate was filtered and washed with water to afford 178 mg. of crude product, m.p. 227.5–236° with previous softening. Three crystallizations from acetone-petroleum ether (b.p. 60–70°) gave 129 mg. of material having a constant melting point (233–239°). Paper strip chromatography indicated approximately 75% of pure IIb together with 25% of a more polar contaminant. A 110 mg. portion of the above 129 mg. was subjected to partition chromatography on Celite[12] using a solvent system consisting of three parts of petroleum ether (b.p. 90–100°), two parts of ethyl acetate, three parts of methanol and two parts of water. The eluate from the second hold-back volume (1 HBV = 320 ml.) was evaporated and the residue crystallized from acetone-petroleum ether to afford 78 mg. of pure IIb, m.p. 246.5–249° with previous softening. One additional crystallization did not alter the melting point; $\lambda_{max}^{methanol}$ 238 mμ (ε 16,300); ν_{max}^{KBr} 3510, 1770, 1755, 1662, 1630, 1245, and 1220 cm.$^{-1}$; $[\alpha]_D^{25}$ +121° (chloroform). Paper strip chromatography indicated an homogeneous compound.

Anal. Calcd. for $C_{21}H_{27}O_5F$ (378.43): C, 66.73; H, 7.19; F, 5.02. Found: C, 67.16; H, 7.54; F, 4.75.

Acknowledgment. We wish to thank Louis M. Brancone and associates for the analyses, William Fulmor and associates for the infrared and ultraviolet absorption spectra and optical rotation data, and Robert H. Blank for the paper chromatographic analyses.

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(12) 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 a mixture of methanol and ethyl acetate. Finally, it was dried at room temperature. Celite is the trademark of Johns-Manville Company for diatomaceous silica products.

Steroidal Hormone Relatives. VIII. A Synthetic Approach to 6-Aza-equilenin[1,2]

J. H. Burckhalter and John A. Durden, Jr

Received October 3, 1959

Estrogens are carcinogenic to experimental animals which have an inherited sensitivity to the development of mammary carcinoma, and many clinicians will not employ them in the treatment of women who have a familial history of malignancy.[3] Yet, estrogens,[3] as well as androgens,[4] may be used in the treatment of inoperable breast cancer, and estrogenic materials are effective in the palliation of prostatic carcinoma and its metastases and may also be useful against lung and skin metastases.[3] Such facts have led us to propose that the aza analogs of the steroids might be of considerable interest as possible carcinolytic agents.[5] Perhaps an azasteroid would fit the enzyme site of the parent hormone in such a manner that only a carcinolytic effect would result.

The favorable effect of estrogens upon the blood levels of cholesterol and presumably upon the course of atherosclerosis[6] raises the question of whether or not an azaestrogen would retain the antiatherogenic effect of the parent hormone without exhibiting the undesirable estrogenic effect. It is possible that a nonestrogenic azasteroid would

(1) Abstracted from a portion of the Ph.D. thesis of John A. Durden, Jr., University of Kansas, 1957.

(2) This investigation was supported in part by Grant CY-3573, from the National Cancer Institute, U. S. Public Health Service.

(3) *New and Nonofficial Drugs*, J. P. Lippincott Co., Philadelphia, Pa., 1959, p. 504.

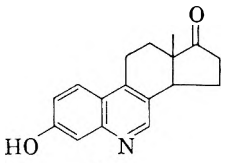
(4) *New and Nonofficial Drugs*, J. P. Lippincott Co., Philadelphia, Pa., 1959, p. 542.

(5) Application for Research Grant to the National Institutes of Health, February 26, 1957.

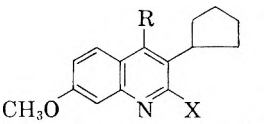
(6) H. W. Eder in *Hormones and Atherosclerosis*, G. Pincus, Ed., Academic Press, Inc., New York, N. Y., 1959, Chapter 24.

fit an enzyme site important to cholesterol synthesis in such a manner that the generation of cholesterol would be inhibited.

These considerations have induced us to undertake various syntheses designed to lead to a number of azasteroids. Recent publications from other laboratories have prompted a preliminary report of incomplete work toward a total synthesis of 6-azaequilenin (I).[7]



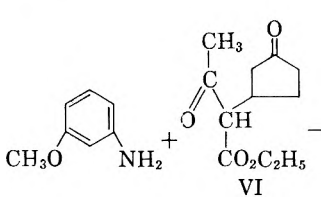
I



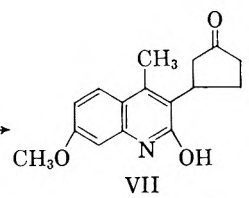
	R	X
II.	CH_2CH_3	OH
III.	CH_3	OH
IV.	CH_2	Cl
V.	CH_3	H

Model compound II was made by means of the Knorr quinoline synthesis[11] which entailed heating a mixture of *m*-anisidine and ethyl α-cyclopentylpropionylacetate[12] to give an anilide which was closed by sulfuric acid to 3-cyclopentyl-7-methoxy-4-ethylcarbostyril (II). The same reactions involving *m*-anisidine and ethyl α-cyclopentylacetoacetate[12a] gave α-cyclopentylacetoaceto-*m*-anisidide. Treatment of the anisidide with sulfuric acid gave 3-cyclopentyl-7-methoxy-4-methylcarbostyril (III). Reaction of III with phosphorus oxychloride gave the gummy 2-chloroquinoline (IV) which, through hydrogenolysis using palladium on charcoal, afforded 3-cyclopentyl-7-methoxylepidine (V) as the hydrochloride.

A closer approach to I was through the synthesis of 3-(3-oxocyclopentyl)-7-methoxy-4-methylcarbostyril (VII). Ethyl α-(3-oxocyclopentyl)-acetoacetate (VI) was synthesized by the Michael condensation using 2-cyclopentenone[13] and acetoacetic ester. From *m*-anisidine and VI in the Knorr reaction, the carbostyril (VII) was obtained. VII formed a 2,4-dinitrophenylhydrazone.



VI



VII

Carbostyrils II, III, and VII have very similar infrared spectra, with lactam peaks (1650 cm.$^{-1}$)[14] but only VIII has carbonyl absorption (1740 cm.$^{-1}$) which is due exclusively to the terminal ring ketonic grouping. The lepidine (V) showed no lactam absorption.

Attempts are currently being made to improve the yield of VII; and other studies are in progress toward the synthesis of 6-azaequilenin and other azasteroids.

EXPERIMENTAL

3-Cyclopentyl-7-methoxy-4-ethylcarbostyril (II). A mixture of 14 g. (0.067 mol.) of ethyl α-cyclopentylpropionylacetate[12] and 10 g. (0.067 mol.) of *m*-anisidine was heated at reflux temperature with a Bunsen burner for 5 min. After the mixture had been cooled, 40 ml. of concentrated sulfuric acid was added very slowly with stirring. During the treatment a solid separated, the mixture became very hot and the the solid redissolved while a vigorous ebullition took place. After standing 40 min. at room temperature, the reaction mixture was heated on the steam bath for 20 min. before it was poured with stirring into ice water. A purple solid separated. The suspension was made neutral with sodium hydroxide and a solid was collected on a filter and subsequently recrystallized from alcohol with charcoal treatment to yield 2 g. (11% yield) of a white solid, II, m.p. 200–201°. Further recrystallization from alcohol elevated the melting point to 204–205°.

Anal. Calcd. for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80. Found: C, 75.30; H, 7.70.

α-Cyclopentylacetoaceto-m-anisidide. A mixture of 19.8 g. (0.1 mol.) of ethyl α-acetylcyclopentylacetate[12a] and 12.3 g. (0.1 mol.) of *m*-anisidine[15] was heated at reflux temperature under an air condenser for 4 min. with a Bunsen burner. During this period, fumes came from the condenser. The contents of the flask were poured into a beaker, and cooling in an ice bath gave a solid which was collected on a filter. The product was triturated with Skelly B to yield 14 g. (51%) of white anisidide, m.p. 130–133°. Recrystallization from benzene-Skelly B elevated the melting point to 133–134.5°. $\lambda_{max}^{CHCl_3}$ 1680 cm.$^{-1}$ (C=O sec. amide I); 1600 cm.$^{-1}$ (sec. amide II); 1530 cm.$^{-1}$ (sec. amide II); 1280 cm.$^{-1}$ (sec. amide III).

Anal. Calcd. for $C_{16}H_{21}NO_3$: C, 69.63; H, 7.69. Found: C, 69.53; H, 7.68.

3-Cyclopentyl-7-methoxy-4-methylcarbostyril (III). A mixture of 14.7 g. (0.07 mol.) of ethyl α-cyclopentylaceto[12a] and 9.1 g. (0.07 mol.) of *m*-anisidine[15] was heated at reflux under an air condenser with an open flame for 3 min. and was then

(7) Several steroid analogs with a five-membered heterocyclic B ring have been synthesized.[8] A 3-aza-A-homocholestanone has been prepared through partial synthesis from cholestanone,[9] and a synthetic approach has been made toward a 14-aza-D-homosteroid.[10]

(8) G. V. Bhide, M. R. Pai, N. L. Tikotkar, and B. D. Tilak, *Tetrahedron*, **4**, 420 (1958); G. V. Bhide, N. L. Tikotkar, and B. D. Tilak, *Chemistry and Industry*, 1319 (1957); R. B. Mitra and B. D. Tilak, *J. Sci. Ind. Research (India)*, **15B**, 497, 573 (1956) [*Chem. Abstr.*, **51**, 5784, 8719 (1957)]; R. J. Collins and E. V. Brown, *J. Am. Chem. Soc.*, **79**, 1103 (1957).

(9) C. W. Shoppee and J. C. P. Sly, *J. Chem. Soc.*, 3458 (1958).

(10) N. A. Nelson, J. E. Ladbury, and R. S. P. Hsi, *J. Am. Chem. Soc.*, **80**, 6633 (1958).

(11) R. C. Elderfield, *Heterocyclic Compounds*, John Wiley and Sons, Inc., New York, N. Y., 1952, Vol. 4, p. 30.

(12) Prepared by the methods of (a) H. Rydon, *J. Chem. Soc.*, 1544 (1939), and (b) F. Challenger and B. Fishwick, *J. Inst. Petrol.*, **39**, 220 (1953) [*Chem. Abstr.*, **48**, 9355 (1954)].

(13) M. Rosenblum, *J. Am. Chem. Soc.*, **79**, 3179 (1957), and K. Alder and R. Flock, *Chem. Ber.*, **89**, 1735 (1956).

(14) *Cf.* J. A. Gibson, W. Kynaston, and A. S. Lindsay, *J. Chem. Soc.*, 4340 (1955), who have shown that carbostyrils exist as 2-quinolones whose spectra confirm the amido form in neutral or acidic media. Also, G. W. Ewing and E. A. Steck, *J. Am. Chem. Soc.*, **68**, 2181 (1946), have used ultraviolet spectra to demonstrate the amido structure.

(15) F. Reverdin and A. de Luc, *Ber.*, **47**, 1537 (1914).

allowed to cool at room temperature. The mixture was then added slowly to 15 ml. of sulfuric acid preheated to 60°, at such a rate that the temperature did not rise above 90°. When addition was complete the temperature of the reaction mixture was held at 90° for 20 min. and then allowed to fall to 60° when the mixture was poured with vigorous stirring over ice. The solid which separated was collected on a filter and then recrystallized from 500 ml. of alcohol with charcoal treatment to give 5.4 g. (30% yield) of a white solid (III), m.p. 216–218°. After further recrystallization it melted at 218–219°.

Anal. Calcd. for $C_{16}H_{19}NO_2$: C, 74.79; H, 7.44. Found: C, 74.83; H, 7.25.

α-Cyclopentylacetoaceto-*m*-anisidide which had been isolated was also converted in about 50% yield by treatment with sulfuric acid to III.

3-Cyclopentyl-7-methoxylepidine hydrochloride monohydrate (V). A mixture of 5.43 g. (0.021 mol.) of III and 5 ml. of phosphorus oxychloride was heated on a steam bath for about 30 min. until complete solution had almost taken place. The reaction mixture was heated at gentle reflux for 15 min. with a Bunsen burner and then it was poured into water with stirring. A solid separated which was collected on a filter and subsequently dissolved in chloroform. The solution was washed with water, and then dried over a sodium sulfate–sodium carbonate mixture. The drying agent was removed by filtration and the chloroform was removed *in vacuo* to leave a residual gum. The residue was dissolved in 40 ml. of glacial acetic acid. After the addition of 2 g. of anhydrous sodium acetate and 1 g. of 5% palladium on charcoal, hydrogenation was carried out at 35 lb. pressure with heat supplied to the flask by an infrared lamp. When the theoretical amount of hydrogen had been absorbed, the catalyst was removed and the volume of the filtrate was reduced. The residue was made basic with alkali. Extraction with ether and drying over a sodium hydroxide–sodium sulfate mixture gave an ether solution which was treated with hydrogen chloride gas to produce a solid. Recrystallization from alcohol gave 4 g. (70% yield) of off-white crystalline V, m.p. 210–211°.

Anal. Calcd. for $C_{16}H_{19}NO \cdot HCl \cdot H_2O$: C, 64.96; H, 7.50. Found: C, 65.05; H, 7.50.

Ethyl α-(3-oxocyclopentyl)acetoacetate (VI). A solution of 1.15 g. (0.05 atom) of sodium metal in 100 ml. of absolute alcohol was reduced in volume to dryness and the residue taken up in 4 ml. of absolute alcohol. Then a mixture of 22 g. (0.27 mol.) of 2-cyclopentenone[13] and 59.5 g. (0.46 mol.) of ethyl acetoacetate was added to the alcoholic solution with shaking. An exothermic reaction occurred. After 30 min. at room temperature, the reaction mixture was warmed at 45° for 2 hr. and then left at room temperature overnight. The reaction mixture was made neutral with 3.5 ml. of glacial acetic acid, diluted with 200 ml. of ether, and extracted twice with water. The ether extract was dried over sodium sulfate. Removal of the drying agent and distillation gave 38 g. (67% yield) of clear liquid (VI), b.p. 135° (1.5 mm.); n_D^{23} 1.4650. $\lambda_{max}^{CHCl_3}$ 1718 cm.$^{-1}$ (C=O); 1740 cm.$^{-1}$ (5-membered ring C=O); 1742 cm.$^{-1}$ (ester C=O); 1625 cm.$^{-1}$ (ester C=O chelated to enolic OH?).

Anal. Calcd. for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.32; H, 7.79.

3-(3-Oxocyclopentyl)-7-methoxy-4-methylcarbostyril (VII). A mixture of 5 g. (0.023 mol.) of ester VI and 2.9 g. (0.024 mol.) of *m*-anisidine was heated at reflux temperature over an open flame for 2.75 min. The thick red oil was poured into a beaker and allowed to cool. The oil was then chilled in ice and treated slowly with 23 ml. of concentrated sulfuric acid with stirring. The acid solution was left in ice for about 30 min., warmed on the steam bath for 10 to 15 min. and then poured with vigorous stirring over ice whereupon a gum separated. The suspension was made basic with sodium hydroxide solution so that the mixture became warm and the gum turned slightly crystalline. The mixture was neutralized with 10% hydrochloric acid and chilled in the ice bath for 3 hr. The solid was collected on a filter. Recrystallization from a 20:1 ethyl acetate–alcohol mixture gave a white solid (VII), m.p. 177–178°, 1 g. (15% yield).

Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32. Found: C, 70.56; H, 6.32.

The *2,4-dinitrophenylhydrazone* of VII was prepared and recrystallized from acetic acid,[16] m.p. 275–277° (dec.).

Anal. Calcd. for $C_{22}H_{21}N_5O_6$: C, 58.53; H, 4.69. Found: C, 58.13; H, 4.66.

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(16) By Mr. D. G. Mikolasek.

The Color of 8-Mercaptoquinoline

J. E. BANFIELD

September 22, 1959

The absorption spectrum of 8-mercaptoquinoline in ethanol and in 50% ethanol has been reported by Badger and Buttery[1] and observations concerning its thermochromic solution in chloroform containing a little ethanol were made. These workers considered that the C=C—C=S chromophore was not involved.

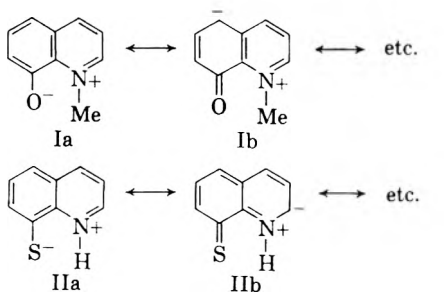
Very recently the absorption spectrum of 8-hydroxy-1-methylquinolinium anhydro salt (and of related compounds) in a number of solvents has been reported[2] together with some observations of the colors. Thus the hydrated 8-hydroxy-1-methylquinolinium hydroxide was orange, and this on dehydration changed to violet-red. The solution of the anhydro salt in water was red, in nonpolar solvents was violet, and the addition of hydroxylic solvents to the chloroform solution resulted in a progressive hypsochromic shift. End absorption in the visible was recorded for the acidic solution. A lucid explanation of these facts in terms of the resonance contributors (Ia), (Ib), *etc.*, the modification of these by hydrogen bonding at the oxygen atom, and of protonation of the oxygen atom has been presented.[2]

The generally similar shape of the spectra and the relative positions of the long wave length maxima of the 8-hydroxy-1-methylquinolinium anhydro salt (484 mμ)[2] and of the 8-mercaptoquinoline (500 mμ)[1] in ethanol together with some findings made during another investigation prompt us to record these observations in support of a parallel explanation of the properties of 8-mercaptoquinoline in terms of the resonance contributors (IIa), (IIb), *etc.* Thus the concentrated solution of 8-mercaptoquinoline in pyridine was an intense blue-violet which was changed by the addi-

(1) G. M. Badger and R. G. Buttery, *J. Chem. Soc.*, 3236 (1956).

(2) J. P. Saxena, W. H. Stafford, and Winifred L. Stafford, *J. Chem. Soc.*, 1579 (1959).

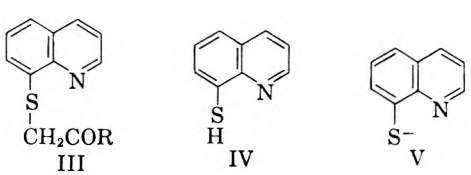
tion of ethanol to a reddish blue color; on the other hand, dilution of the concentrated solution with pyridine caused the color to be very greatly diminished.



The preparation of two *S*-alkyl type derivatives of 8-mercaptoquinoline is now reported. The reaction of phenacyl chloride with 8-mercaptoquinoline in pyridine solution gave 8-quinolyl phenacyl sulfide (III, R = C_6H_5); 8-quinolyl acetonyl sulfide (III, R = CH_3) was similarly prepared from chloroacetone and the thiol. Both of these compounds were colorless, either in the solid state or as their solution in organic solvents.

S-benzoyl 8-quinolyl sulfide, as reported previously,[3] was colorless. This compound gave a colorless solution in ethanol unchanged by the addition of water; however, this aqueous ethanolic solution gradually developed a red color, the more rapidly on warming. Thus it seems likely that the long wave-length absorption reported[1] for the benzoyl derivative in 50% ethanol should be attributed to the partial hydrolysis of this thiol ester, in which case the objection to the C=C—C=S chromophore for this substance is invalid.

Alkaline solutions of 8-mercaptoquinoline were colorless or nearly so, and the acidic solution was yellow confirming earlier observations.[3]



The above observations together with the change in the red color of the dihydrate to the pale violet color of the liquid 8-mercaptoquinoline[1] find a ready explanation in structure II. The existence in ionizing solvents of 8-mercaptoquinoline in the purple zwitterionic form is not unexpected in view of the greater acidity of thiol compounds as compared with hydroxyl compounds, this zwitterionic form being presumably modified in hydroxylic solvents and in the solid red dihydrate by hydrogen bonding. In nonpolar solvents the zwitterionic form would be relatively less stable (compare the *N*-heteroaromatic hydroxy compounds[4]) and the colorless nature of such solutions[1] finds explanation in the predominance of the tautomeric form (IV), the pale violet color of the pure liquid thus indicates an autoprotolytic equilibrium between IV and II. The effect of dilution of the pyridine solution can be attributed to a solvolytic equilibrium involving pyridinium ions and the anion (V), the latter entity accounting also for the lack of color of the aqueous alkaline solution of the thiol.

(3) A. Edinger, *Ber.*, **41**, 937 (1908).
(4) S. F. Mason, *J. Chem. Soc.*, 5016 (1957).

EXPERIMENTAL

S-Benzoyl 8-mercaptoquinoline was prepared by Edinger's method[3] and had m.p. 110° (lit.[3] 110°); preparation of this compound under nitrogen was found advantageous.

8-Quinolyl acetonyl sulfide. Chloroacetone was added to a solution of 8-mercaptoquinoline in pyridine and the solution was set aside overnight under nitrogen. The next day the mixture was stirred into water and the mixture was set aside for several days to crystallize. The solid was collected and purified by low temperature recrystallization from ethanol. The product was 8-quinolyl acetonyl sulfide, m.p. 54–54.5°.

Anal. Calcd. for $C_{12}H_{11}NOS$: C, 66.35; H, 5.10; N, 6.45. Found: C, 66.28; H, 4.97; N, 6.11.

8-Quinolyl phenacyl sulfide. Phenacyl chloride in pyridine was added to an equimolecular amount of 8-mercaptoquinoline in pyridine and the mixture was kept for 24 hr. under nitrogen and then poured into water to yield a solid. This solid was recrystallized from ethanol to give 8-quinolyl phenacyl sulfide m.p. 133°.

Anal. Calcd. for $C_{17}H_{13}NOS$: C, 73.12; H, 4.69; N, 5.02. Found: C, 73.01; H, 4.70; N, 4.76.

Acknowledgment. The author is indebted to Dr. W. Zimmermann and his staff for the microanalyses.

NOTE ADDED IN PROOF: Substantially similar conclusions concerning the color of 8-mercaptoquinoline have been reached by A. Albert and G. B. Barlin [*J. Chem. Soc.*, 2384 (1959)] in a paper which appeared after the submission of this note.

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Hydrogenolytic Cleavage of Menthofuran[1]

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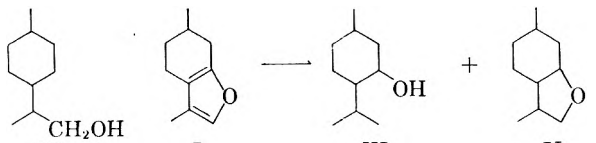
Received March 23, 1959

Recently, Wienhaus[2] carried out the catalytic hydrogenation of menthofuran (I) over platinum black in acetic acid, reporting tetrahydromenthofuran (II) as the sole product. It is known, however, that in the presence of Adams' catalyst furan compounds are not only hydrogenated to tetrahydrofurans, but often subjected to hydrogen-

(1) Abstracted partly from the Master thesis submitted by W. Tagaki, March 1, 1956, and presented at the monthly meeting of Kansai Branch of the Agricultural Chemical Society of Japan, Kyoto, January 26, 1957.
(2) H. Wienhaus and H. Dewein, *Ber.*, **91**, 256 (1958).

olysis also.[3] Thus, it appears that the hydrogenolysis of I may result either in the formation of menthol (III) or *p*-menthane-9-ol (IV).



IV I III II

IIIa. (+)-*neo*menthol
IIIb. (+)-*neoiso*menthol

Independently of Wienhaus,[2] we have carried out the catalytic hydrogenation of I using Adams' catalyst and acetic acid and have found that cleavage occurs to the extent of about 20% to give a mixture of menthols. The remaining 80% of the product was II formed by ring hydrogenation. The cleaved product was converted quantitatively to the 3,5-dinitrobenzoate. By chromatography of this ester on an alumina column it was found that the cleavage product was entirely composed of (+)-*neo*menthol (IIIa) and (+)-*neoiso*menthol (IIIb) without any *p*-menthane-9-ol, (IV). The direction of hydrogenolytic cleavage of I observed here agrees with that reported by Shuikin and Belsky[4] who used a different catalyst.

Variation of the hydrogenation temperature between 20° and 60° did not affect the extent of ring cleavage, but did change the ratio of IIIb to IIIa, as shown in Table I, from 2:1 at 20° to 1.2:1 at 60°. This result is of interest from both the stereochemical and preparative point of view, since *neoiso*menthol is considered to be the most unstable isomer[5] and is more difficult to prepare than any of the other isomeric menthols.

The formation of IIIa and IIIb in the hydrogenation substantiates the common observation regarding *cis*- addition of hydrogen to ethylenic bonds in the presence of catalysts, since in both IIIa and IIIb the hydroxyl and *iso*propyl groups are *cis* to each other. The corresponding *trans*-isomers, (−)-menthol and (+)-*iso*menthol were not obtained in the catalytic hydrogenation. On the other hand, the stereochemistry of the major product II is not certain. An attempt to correlate the steric configuration of II with that of isomeric menthol by cleaving the ether bond with acetyl chloride failed, resulting in IV. As discussed by Smith and Fuzek,[3] II is probably not an intermediate in the transformation of I into III, since II no longer reacted with hydrogen under the same experimental conditions. We are now making an effort to establish the stereochemistry of II and the result will be reported.

EXPERIMENTAL[6]

Menthofuran (I) synthesized by the method reported by Pallaud and Berna[7] showed the following constants; $[\alpha]_D^{21}$ + 93° (*c*, 9.63 in methanol), b.p. 91.5–92.5° (18 mm.).

Catalytic hydrogenation. Only the procedure at 20° is described. The reductions at 40° and 60° were carried out by the same procedure using the same amount of sample and reagent. The amount of hydrogen uptake and the content of menthol (measured by acetylation) in the product were not much affected by temperature.

TABLE I[a]

COMPOSITION (%) OF THE CRUDE MENTHYL 3,5-DINITROBENZOATE

T,[b] °C.	F-I: M.P. 150–155°	F-II: M.P. 85–145°	F-III: M.P. 95–99°	R[c]	F-III/F-I[d]
20	26	4	52	9	2.0
40	29	8	49	9	1.7
60	38	5	45	4	1.2
	32	3	64	—	2.0

[a] The bottom line represents the analysis of an authentic mixture (2:1) of (+)-*neoiso*menthyl- (m.p. 99–100°) and (+)-*neo*menthyl 3,5-dinitrobenzoate (m.p. 154–155°). [b] Hydrogenation temperature. [c] Resinous substance. [d] The accuracy was ±0.1 in duplicate analysis.

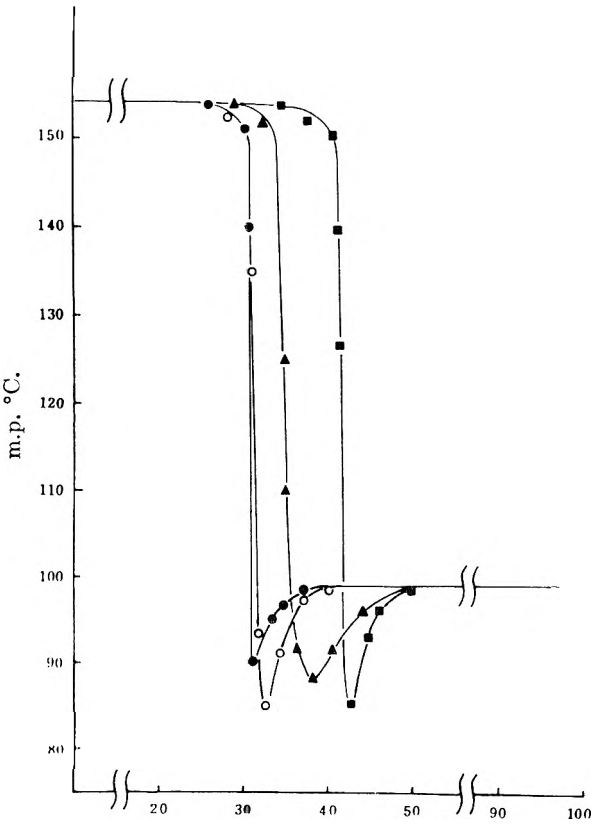


Fig. 1. Alumina chromatography of Menthyl 3,5-dinitrobenzoate (See Table I): ●, authentic mixture; ○, 20°; ▲, 40°; ■, 60°

(3) H. A. Smith and J. F. Fuzek, *J. Am. Chem. Soc.*, **71**, 415 (1949), and the references there cited.

(4) N. I. Shuikin and I. F. Belsky, *Proc. Acad. Sci. U.S.S.R.* (*English Translation*), **116**, 905 (1957).

(5) E. L. Eliel, *Experimentia*, **9**, 91 (1953).

(6) All melting and boiling points are uncorrected.

(7) R. Pallaud and J. Berna, *Ind. Parfum.*, **8**, 154 (1953); *Chem. Abstr.*, **47**, 10179 (1953).

The hydrogenation temperature was controlled by the circulation of water through the jacket surrounding the hydrogenation flask. In the flask were placed freshly distilled menthofuran (I), 3.210 g., (0.0214 mol.), platinum oxide (60 mg.), and acetic acid (30 ml.). At the beginning of the shaking, the hydrogenation mixture should be colorless.[8] After 4 hr., the absorption of hydrogen ceased at 1120 ml. (0.466 mol.; measured at 20°). From the hydrogenation mixture a colorless oil (3.000 g.) was obtained, b.p. 88–100° (18 mm.) which contained 20.1% menthol mixture.

The hydrogenation product was treated with 3,5-dinitrobenzoyl chloride in pyridine and then steam-distilled. The undistilled residue solidified to give the crude 3,5-dinitrobenzoate (0.829 g.). From the distillate, tetrahydromenthofuran (II) was obtained, b.p. 91–92° (20 mm.). α_D^{17} −20.8° (homogeneous), d_4^{25} 0.9286, n_D^{25} 1.4610, MR (calcd.) 45.62, (obsd.) 45.58.

Anal. Calcd. for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.90; H, 11.81.

The crude 3,5-dinitrobenzoate (100 mg.) was purified by passing an *n*-hexane solution of the 3,5-dinitrobenzoate through a layer of alumina (1 g.). The removal of *n*-hexane from the effluent gave colorless needles (86 mg.), while a resinous substance (9 mg.) adsorbed on the alumina was eluted with ether.

The purified 3,5-dinitrobenzoate (20.0 mg.) was chromatographed on an alumina column (alumina 15 g.; height 15 cm.) using *n*-hexane mixed with 5% ether as developing solvent. The effluent was collected in small fractions and the solvent was removed from each fraction. After the melting points had been determined, as shown in Fig. 1, the fractions were combined into three parts: Fraction I 6.0 mg. (m.p. 150–154°), Fraction II 1.0 mg. (m.p. 85–145°), and Fraction III 12.1 mg. (m.p. 95–99°). From the results obtained by the above preliminary purification and by chromatography, the composition of crude ester was calculated as shown in Table I.

When recrystallized from methanol, Fraction I and Fraction III melted at 154–155° and 99–100° respectively, and were shown to be (+)-*neo*menthyl- and (+)-*neoiso*menthyl 3,5-dinitrobenzoate, by mixed melting point determinations with authentic samples. Fraction II was a mixture of these two isomers.

Acknowledgment. The authors wish to express their sincere thanks to Prof. Sankichi Takei for his constant encouragement, and to Mr. Hiroo Ueda for supplying the authentic samples.

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(8) R. B. Woodward and R. H. Eastman, *J. Am. Chem. Soc.*, **72**, 399 (1950).

Differentiation of Glyceraldehyde from Other Trioses by Means of 2,4-Dinitrophenylhydrazine[1]

SAMUEL C. SMITH, P. M. ALTHOUSE, AND J. W. SHIGLEY

Received August 11, 1959

In an effort to identify some oxidation products of glycerides by 2,4-dinitrophenylhydrazone derivatives it was discovered that the literature is rather vague concerning the 2,4-dinitrophenylhydrazone of glyceraldehyde.

Neuberg,[2] using a saturated solution of 2,4-dinitrophenylhydrazine in 2*N* hydrochloric acid at 0°, prepared glyceraldehyde 2,4-dinitrophenylhydrazone which melted at 166–167°. Neuberg and Collatz[3] reported the 2,4-dinitrophenylosazone of glyceraldehyde to melt at 265° (dec.). Later, Neuberg and Strauss[4] reported that the bishydrazone (osazone) of methyl glyoxal can be obtained quantitatively from dihydroxyacetone and glyceraldehyde with 2,4-dinitrophenylhydrazine in hydrochloric acid. This 2,4-dinitrophenylosazone melted at 298°.[5]

In the present investigation two methods were used to study the dinitrophenylhydrazones and osazones of glyceraldehyde, dihydroxyacetone, and pyruvaldehyde (methyl glyoxal). The results appear in Table I.

Infrared spectra of the products melting at 164–166° were all similar with peaks at: 3.05, 6.15–6.20, 6.28, 7.45, 8.18, 8.70–8.90, 9.15–9.35, 10.28, 10.75–10.90, 11.73–11.95, and 12.00 μ. Infrared spectra of the products melting at 297–299° were all similar with peaks at: 3.08, 6.19, 6.27, 6.32, 6.65, 7.40–7.50, 7.60, 7.95, 8.23–8.28, 8.73, 9.20, 9.47, 10.68, 10.92, 11.90–12.00, and 13.43–13.70 μ.

The results show that glyceraldehyde 2,4-dinitrophenylhydrazone can be prepared in hydrochloric acid at 5°, but the 2,4-dinitrophenylosazone of pyruvaldehyde forms at other temperatures. In the case of dihydroxyacetone and pyruvaldehyde, however, the 2,4-dinitrophenylosazone of pyruvaldehyde forms at all the temperatures tried. This osazone which melts from 250–298° can be recrystallized from dioxane or pyridine to melt at 297–299°.

These data show that by the use of 2,4-dinitrophenylhydrazine in 2*N* hydrochloric acid at 5° glyceraldehyde can be differentiated from the other trioses.

EXPERIMENTAL

Preparation of dinitrophenylhydrazones and osazones. Two methods were used to study the dinitrophenylhydrazones and osazones of glyceraldehyde (Nutritional Biochemicals #6559), dihydroxyacetone (Nutritional Biochemicals #4386), and pyruvaldehyde (methyl glyoxal), (K&K #2995L 30% soln.). The first was that of Brady and Elsmie[6] in which a saturated solution of 2,4-dinitrophenylhydrazine in 2*N* hydrochloric acid was added to an aqueous solution of the triose. The second method was that of Allen[7] as modified

(1) This Communication has been authorized for publication on October 15, 1958, as Paper No. 2302 in the Journal Series of the Pennsylvania Agricultural Experiment Station.

(2) I. S. Neuberg, *Biochem. Z.*, 255, 1 (1932).

(3) C. Neuberg and H. Collatz, *Biochem. Z.*, 223, 494 (1930).

(4) C. Neuberg and E. Strauss, *Arch. Biochem.*, 11, 457 (1946).

(5) E. Simon and C. Neuberg, *Biochem. Z.*, 232, 479 (1931).

(6) O. L. Brady and G. V. Elsmie, *Analyst*, 51, 77 (1926).

(7) C. F. H. Allen, *J. Am. Chem. Soc.*, 52, 2955 (1930).

TABLE I

PROPERTIES OF VARIOUS PRODUCTS PREPARED FROM TRIOSES WITH 2,4-DINITROPHENYLHYDRAZINE

Method Temperature	HCl 5°	HCl 20°	HCl 35°	H_2SO_4 5°	H_2SO_4 20°	H_2SO_4 35°
PPt. color						
Gly[a]	Yellow	Yellow-orange	Orange	Orange	Orange	Orange
DHA[b]	Orange	Orange	[e]	[e]	Orange	[e]
Pyr[c]	Orange	[e]	[e]	[e]	Orange	[e]
Solubility in hot (1:1) 50% C_2H_5OH/C_2H_5OAc						
Gly	Complete	*ca.* 50%	*ca.* 50%	Trace	Trace	Trace
DHA	Trace	Trace			Trace	
Pyr	Trace				Trace	
M.p. material recrystallized by above						
Gly	166	166	164	—	—	—
DHA	—	—			—	
Pyr	—				—	
M.p. residue from solubility tests						
Gly	—	284[d]	289	298	298	298
DHA	253[d]	280[d]			284[d]	
Pyr	299				289[d]	

[a] Gly, glyceraldehyde. [b] DHA, dihydroxyacetone. [c] Pyr, pyruvaldehyde. [d] Recrystallized from dioxane to melt at 298°. [e] Not performed.

by Brady[8] in which 2,4-dinitrophenylhydrazine was dissolved in a small amount of concentrated sulfuric acid and the solution diluted with ethanol. This solution was added to an alcoholic solution of the triose. Each procedure was run at 5°, 20°, and 35°. The solutions were held at the required temperature for 2 hr. before mixing, and then allowed to react for 12 hr. Only the first crops of precipitate were retained.

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(8) O. L. Brady, *J. Chem. Soc.*, 1931, 756.

The Identification of $C_{12}H_8N_4O$, an Oxidation Product from α-Pyridil Monohydrazone[1]

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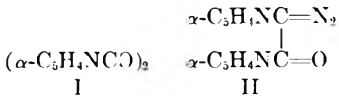
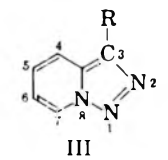
Received August 17, 1959

Treatment of α-pyridil (I) with tosyl hydrazide and the resulting derivative with aqueous alkali gives a product, $C_{12}H_8N_4O$, incorrectly identified as "azipyridil" (II).[2] Chemical and physical evidence require the formulation to be that of 1-α-picolinoylpyridotriazole (III, R = α−C_5H_4NCO).



I II



III

In acid solution pyridotriazole (III. R = H) and, at higher temperatures, 1-phenylpyridotriazole (III. R = C_6H_5) react with carboxylic acids to form esters of corresponding α-pyridylcarbinols.[3] In its resistance to attack by carboxylic acids, III (R = α-C_5H_4NCO) further demonstrates lack of triazole ring reactivity towards acids when electron withdrawing groups are at the 1-position. In boiling aniline, III (R = α − C_5H_4NCO) undergoes degradation of the triazole ring and the product,[2] di(α-pyridyl) acetanilide, suggests an intermediate formation of II. Transformation of III (R = α − C_5H_4NCO) into II apparently occurs more readily in the presence of iodine or bromine, each of which gives rise to the formation of α,α-dihaloketones as nitrogen is liberated.[2]

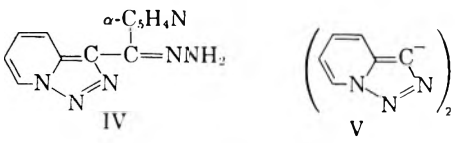
Hydrazine hydrate combines with III (R = α − C_5H_4NCO) to bring about the formation of the corresponding hydrazone (IV) and, if air is present, its oxidation product 1,1′-bipyridotriazole(V).[4]

(1) Partial support of this work under a National Institutes of Health Grant No. CY-2895 is gratefully acknowledged.

(2) B. Eistert and W. Schade, *Chem. Ber.*, 91, 1411 (1958).

(3) J. H. Boyer and L. T. Wolford, *J. Am. Chem. Soc.*, 80, 2741 (1958).

(4) J. H. Boyer, R. Borgers and L. T. Wolford, Jr., *J. Am. Chem. Soc.*, 79, 678 (1957).



IV V

Infrared absorption data for III have been obtained from potassium bromide discs and from chloroform solution. Lack of absorption from 3.5 to 6.0 mμ clearly indicates the absence of an aliphatic diazo group in both the solid state and in solution at ordinary temperature.

EXPERIMENTAL[5]

1-α-Picolinoylpyridotriazole (III, R = C_5H_4NCO). According to the directions of Eistert and Schade[2] for the preparation of azipyridil, 1-α-picolinoylpyridotriazole (III. R = C_5H_4NCO), m.p. 151° was obtained in 66% yield.

Infrared absorption for 1-α-picolinoylpyridotriazole from (a) a potassium bromide disc (cm.$^{-1}$, % transmission): 3086, 18.5; 3040, 18.0; 1658, 7.1; 1634, 12.5; 1587, 28.6; 1572, 28.0; 1511, 7.4; 1479, 30.0; 1427, 15.2; 1416, 10.6; 1355, 29.9; 1328, 33.9; 1309, 42.2; 1271, 26.2; 1245, 27.1; 1225, 10.3; 1159, 21.7; 1151, 27.4; 1110, 39.1; 1091, 17.5; 1052, 34.9; 1010, 41.5; 993, 27.0; 940, 7.9; 890, 23.4; 812, 41.6; 768, 4.5; 752, 20.0; 742, 17.2; 723, 43.7; 703, 26.0; 673, 16.1; 648, 46.6; and (b) a chloroform solution (cm.$^{-1}$, absorptivity): 3425, 0.03; 2967, 0.15; 2445, 0.03; 1653, 0.82; 1634, 0.70; 1585, 0.34; 1572, 0.26; 1499, 0.33; 1471, 0.11; 1412, 0.40; 1359, 0.19; 1325, 0.21; 1274, 0.28; 1145, 0.36; 1107, 0.17; 1091, 0.42; 1045, 0.05; 1008, 0.31; 995, 0.36; 964, 0.06; 939, 0.70; 886, 0.50.

1-α-picolinoylpyridotriazole 3,5-dinitrobenzoate. A solution of 2.25 g. (0.01 mol.) of 1-α-picolinoylpyridotriazole and 2.12 g. (0.01 mol.) of 3,5-dinitrobenzoic acid in 75 ml. of *o*-xylene was heated at 110° for 2 hr. Upon cooling the crude salt, *1-α-picolinoylpyridotriazole 3,5-dinitrobenzoate*, m.p. 154–159° (dec.) separated in 75% yield. It recrystallized from ethyl acetate–ethanol as pale yellow needles, m.p. 158–159 (dec.).

Anal. Calcd. for $C_{19}H_{12}N_6O_7$: C, 52.30; H, 2.77; N, 19.28; O, 25.66. Found: C, 52.40; H, 2.69; N, 18.98; O, 25.68.

After treating 1.0 g. (0.002 mol.) of this salt with 10 ml. of 10% sodium hydroxide with stirring for 10 min., a solid was removed by filtration. Upon acidifying the filtrate, 0.4 g. (90%) of 3,5-dinitrobenzoic acid, m.p. and mixture m.p. 204–205°, was obtained. The solid phase from the alkaline reaction mixture was identified as 1-α-picolinoylpyridotriazole, melting point and mixture melting point 151°, 0.5 g. (90%).

Attempts to alkylate 3,5-dinitrobenzoic acid with 1-α-picolinoylpyridotriazole in tetralin at 160° led to an unidentified oil.

1,1′-Bipyridotriazole. A solution of 1.0 g. (0.005 mol.) of 1-α-picolinoylpyridotriazole and 0.16 g. (0.05 mol.) of hydrazine (as 95% aqueous hydrazine) in 30 ml. of *n*-butyl alcohol was refluxed for 2 hr. Colorless needles, 0.2 g. (17% of *1,1′-bipyridotriazole*, m.p. 245° (dec.), separated upon cooling, and after recrystallization from ethanol melted at 254–255° (dec.).

Anal. Calcd. for $C_{12}H_8N_6$: C, 61.02; H, 3.41; N, 35.55. Found: C, 61.09; H, 3.34; N, 35.60.

A mixture melting point determination with a sample prepared from a dihydrazone of α-pyridil and silver oxide[4] showed no depression. The previously reported[4] m.p. 272–274° (dec.) is in error.

Upon concentration of the solvent a second product separated from the reaction mixture in *n*-butyl alcohol as pale yellow needles, 0.6 g. (51%), m.p. 172–176°. Recrystallization from ethanol gave the *hydrazone of 1-α-picolinoylpyridotriazole*, m.p. 174–175°.

Anal. Calcd. for $C_{12}H_{10}N_6$: C, 60.49; H, 4.19; N, 35.28. Found: C, 60.53; H, 4.08; N, 35.64.

When the reaction between 1-α-picolinoylpyridotriazole and hydrazine was carried out under nitrogen, the hydrazone derivative was obtained in 90% yield with no trace of 1,1′-bipyridotriazole.

Acknowledgment. We are indebted to Mr. R. T. O'Connor, Southern Regional Research Laboratory for infrared absorption data.

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(5) Semimicro elemental analyses by Alfred Bernhardt, Mülheim (Ruhr) Germany. Melting points are uncorrected.

The Electrochemical Reduction of Michler's Ketone[1]

R. M. ELOFSON

Received September 15, 1959

In connection with another project, it became necessary to reduce Michler's ketone to the corresponding pinacol (*p,p*-dimethylaminodiphenylcarbinol) and to rearrange this material to the pinacolone. After rather unsuccessful attempts to prepare the pinacol by other means it was decided to reduce Michler's ketone electrochemically. The ensuing experiments resulted in some interesting results of theoretical and practical significance for electrochemical preparations and are reported herewith.

The reduction of ketones at a variety of cathodes to form pinacols has been widely used.[2a–4] Escherlich and Moest[5] found that Michler's ketone yields the pinacol with a copper electrode while both pinacol and hydrol are formed in almost equal amounts at a nickel cathode. The chief advantage of any given electrode under the usual conditions of uncontrolled cathode potentials is to limit the cathodic potential to the hydrogen overvoltage of the metal. It was therefore deemed simplest to use the method of Allen and Corwin[6] where the reduction is conducted at a controlled potential mercury cathode.

From polarographic results,[7] it is known that in acid solutions of *p*H 1.3 benzophenone is reduced

(1) Contribution No. 109 from the Research Council of Alberta.

(2) (a) K. Elbs and K. Brand, *Z. Electrochem.*, **8**, 783 (1902). (b) J. Tafel, *Z. Electrochem.*, **17**, 972 (1911).

(3) S. Swann, Jr., N. J. Leonard, and F. C. Howard, *Trans. Electrochem. Soc.*, **67**, 6 pp. preprint (1936).

(4) N. J. Leonard, S. Swann, Jr., and C. Fuller, *J. Am. Chem. Soc.*, **75**, 5127 (1953).

(5) F. Escherlich and M. Moest, *Z. Electrochem.*, **8**, 849 (1902).

(6) M. J. Allen and A. H. Corwin, *J. Am. Chem. Soc.*, **72**, 114 (1950).

(7) R. Pasternak *Helv. Chim. Acta*, **31**, 753 (1948).

TABLE I

ELECTROLYSES OF MICHLER'S KETONE[a]

Cathode[b] Potential, V.	Ketone Concn.	Acid Concn.	Stirring[c]	Yield Pinacol	Other Products
0.90	0.125*M*	1.5*N*	Rapid	70%	Hydrol
1.40	0.125*M*	1.5*N*	Rapid	5%	Hydrol
0.90	0.125*M*	1.5*N*	Slow	14%	Ether and viscous oil
1.05	0.125*M*	1.5*N*	Slow	None	Ether 90%, tar
1.40	0.125*M*	1.5*N*	Slow	None	Ethane 8%, ether 30%
1.50	0.125*M*	1.5*N*	None	None	Ethane 26%, ether tar
1.20	0.5*M*	1.5*N*	Rapid	85%	Hydrol 4%
1.20	0.5*M*	2.5*N*	Rapid	64%	Ether
1.35	0.5*M*	1.5*N*	Rapid	38%	Hydrol and tar
1.40	0.5*M*	2.2*N*	Rapid	45%	Ether 45%, tar
0.95	0.125 *I*	0.75 in 50% isopropyl alcohol	Rapid	74%	Recovered ketone
1.05	0.125*M*	Same	Rapid	77%	Ether
1.05	0.125*M*	Same	Slow	None	48% ether, tar

[a] 200-ml. solution. [b] Cathode area, 50 cm.^{2} [c] Temp., 20–25°.

in one electron step. In controlled potential electrolyses Pasternak showed that only benzopinacol is isolated, whereas at *p*H 4.3 a mixture of benzpinacol and benzhydrol was produced and at *p*H 8.6 mainly benzhydrol was produced. Polarographic investigation of Michler's ketone showed that in 1.5*M* hydrochloric acid a one-electron reduction occurred at a half-wave potential of −0.72 volt in solutions of $7.5 \times 10^{-4}M$ to 1×10^{-2} *M*. This indicated that electrolyses conducted with cathodic potentials of −0.90V should result in good yields of pinacol. However, the work of Allen and Corwin[3] indicated that higher yields of pinacol and lower yields of the hydrol were obtained in the reduction of *p*-aminoacetophenone with potentials as high as −1.5 volts despite the fact that polarographic results indicated that a potential of −1.1 volt would be adequate.

The results of a number of reductions of Michler's ketone under varied conditions are summarized in Table I. High pinacol yields are favored by higher concentrations of ketones, comparatively low voltages and rapid stirring. Increasing the acid concentration from 1.5*N* to 2.5*N* resulted in a decreased pinacol yield and favored formation of the ether. Lower acid concentration which might be beneficial were not investigated because of solubility considerations. While the effect of diluting the electrolyte with isopropyl alcohol seemed to increase the specificity of the reduction at −0.95 volt, the results at −1.05 volts indicate quite clearly that the same factors were operative in producing side reactions. Very high cathodic potentials with no stirring resulted in appreciable yields of the ethane. Because of the possibility of pinacol-pinacolone rearrangement, the temperature was maintained in the 20–25° range although Allen, Fearn, and Levine[8] found that high temperatures favored pinacol formation.

Isomerization of the pinacol to the pinacolone. First attempts to prepare the pinacol resulted in the isolation of some pinacolone as contaminating material. It was determined that this material arose from isomerization of the pinacol hydrochloride when this material was isolated according to the method of Allen and Corwin. In subsequent experiments the electrolyzed solution was neutralized with sodium bicarbonate, the precipitated pinacol extracted with chloroform and precipitated with benzene, care being exercized not to heat any of the solutions. That isomerization of the pinacol did not take place during the electrolysis was indicated by the fact that no pinacolone was detected with the latter isolation technique. However, some isomerization of the pinacol occurred when heated on the steam cone for 2 hr. in 2*N* hydrochloric acid although 50% of the starting material was recovered unchanged. On the other hand, warming the pinacol to 50° for 15 min. in glacial acetic acid resulted in complete destruction of the pinacol and a higher yield of pinacolone. Heating for longer periods resulted in extensive decomposition of the pinacolone. The facile rearrangement of the pinacol in acetic acid but not in hydrochloric acid is presumably due to the fact that the free amine groups in acetic acid solution labilize the system toward the pinacol-pinacolone rearrangement.[9] On the other hand, in hydrochloric acid these amino groups exist as cations which stabilize the system towards rearrangement.

From the polarographic results it is certain that the primary electrode process is a rapid one electron reduction of Michler's ketone to form a ketyl radical. The results reported in Table I demon-

(8) M. J. Allen, J. E. Fearn, and H. A. Levine, *J. Chem. Soc.*, 2220 (1952).

(9) W. E. Bachmann and H. R. Steinberger, *J. Am. Chem. Soc.*, **56**, 170 (1934).

TABLE II

DIAGNOSTIC BANDS[a] OF MICHLER'S KETONE AND REDUCTION PRODUCTS[b]

Ketone	1361 (st)	1321 (st)	1289 (st)	1230	1183 (st)	1169	1064	947	927 (st)	833 (st)	819	768 (st)	682
Hydrol	3570	1349 (st)	1227	1182	1162 (st)	1058	1018	999	948	813 (st)	797 (st)		750
Pinacol	3540	1348 (st)	1227	1206	1156		1058	1032	948	813 (st)	797 (st)		757
Pinacolone	1665 (st)	1349 (st)	1242	1163	1060	1027	948	822	805 (st)	765	747		674 (st)
Ether	1348 (st)	1226	1184	1162 (st)	1131	1000 (Broad)		948	816 (st)	800	756		
Ethane (Nujol)	1620	1521	1354	1236	1206	1168	1123	1064	950	805	793		752

[a] Cm.$^{-1}$ [b] Carbon disulfide solution.

strate that this radical forms a complex[10a] with the electrode which has been formulated by Brewster[10b] according to Equation 1:

$$Ar_2C{=}O \xrightarrow[Hg^-]{H^+} Ar_2COH \quad (Hg) \qquad (1)$$

Under the influence of stirring, the free radical is apparently freed from the surface of the electrode and dimerization occurs to form the pinacol according to Equation 2:

$$2Ar_2COH\ (Hg) \longrightarrow 2Ar_2\dot{C}OH \longrightarrow Ar_2COH - Ar_2COH \qquad (2)$$

This mechanism explains why high yields of pinacol are only obtained with rapid stirring. Slow stirring or dilute solutions, both of which inhibit dimerization, may present an opportunity for further reduction. In particular, higher cathodic potentials encourage reduction to the hydrol, which is easily converted to the ether in acid solutions, and to the ethane. This occurs very easily in the case of Michler's ketone. These results are at variance with the results of Corwin for *p*-aminoacetophenone where high pinacol yields were favored by higher cathodic potentials.

A recent paper by Mandell, Powers, and Day[11] has produced convincing evidence of a rate controlling reaction for the second step of the reduction of phenyl ketones in alkaline solutions. The existence of a stereospecific reaction indicated the existence of a complex between the ketyl radical and the mercury surface. The effect of stirring reported here gives independent substantiation to the existence of such a complex and demonstrates that the mechanism is operative in acid solution.

EXPERIMENTAL

The electrolyses were carried out in a 600-ml. beaker with a layer of mercury, stirred by a magnetic stirrer, as cathode. The beaker was cooled to 20–25° by means of a copper water bath through which tap water flowed. The anolyte was 1.5*N* hydrochloric acid containing hydrazine as an anodic depolarizing agent. The anolyte compartment was made from an alundum thimble 4.5 × 16 cm. outside dimensions soaked in sodium silicate followed by sulfuric acid accorded to Allen and Corwin. The cathode potential was controlled manually.

After completion of electrolyses as indicated by a fall of the current to a low value, or evolution of hydrogen, or both the solution was poured into a sodium bicarbonate solution, extracted with chloroform, and the chloroform solution dried over sodium sulfate, and reduced in volume at reduced pressure to produce a 10% solution. To the dried chloroform solution was added three volumes of benzene and the solution cooled in the refrigerator. The pinacol, filtered off and

(10) (a) No attempt is made herein to define the actual nature of such a complex. Presumably it is not an adsorption complex because the polarographic results indicate a normal diffusion wave. (b) J. H. Brewster, *J. Am. Chem. Soc.*, **76**, 6361 (1954).

(11) L. Mandell, R. M. Powers, and R. A. Day, Jr., *J. Am. Chem. Soc.*, **80**, 6284 (1958).

dried melted at 192–193° when carried out under optimum conditions. Reduction of volume to a small volume and addition of ethyl alcohol precipitates the ether. Identification of material was largely by means of infrared analyses in carbon disulfide solution. Diagnostic bands of isolated compounds are listed in Table II.

Preparation of pinacolone. A 2-g. sample of pinacol was dissolved in 40 ml. acetic acid and warmed to 50° on steam cone for 15 min. The acetic acid solution was poured into water, neutralized with sodium carbonate, and extracted with benzene. The benzene extract was dried over sodium sulfate, reduced in volume and diluted with petroleum ether 40–60°. Yield of crude pinacolone m.p. 220° 1.6 g. After recrystallization from benzene–petroleum ether, it melted at 230–232°.

Acknowledgment. The author is indebted to Dr. R. B. Sandin for many helpful discussions and to Mr. Wm. Dammeyer for infrared analyses.

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Chondroitin Sulfate Modifications. II.[1] Peracetylated Sodium Chondroitin Sulfate A

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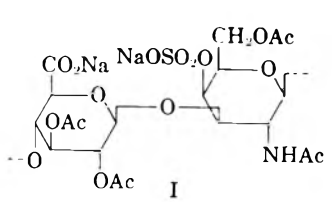
Received September 29, 1959

The acetylation of the acidic polysaccharides, pectin[3] and hyaluronic acid,[4] as effected with pyridine and acetic anhydride in formamide, has been reported. We find that this acetylating system can be applied to sodium chondroitin sulfate A under conditions in which the reaction is entirely homogeneous. It is essential that all moisture be excluded. The polysaccharide salt is peracetylated without desulfation and the product (I), after purification by precipitation methods and dialysis, can be isolated as a white, fluffy powder on freeze-drying. This polymeric peracetate is remarkable in being readily soluble in water, formamide and 1:1 water-ethanol. It is insoluble in acetone, chloroform, ethanol, and ether. It may be readily de-*O*-acetylated to yield the original material and can thus be of use in the purification of the polysaccharide.



I

(1) Part I, *J. Am. Chem. Soc.*, **82**, in press (1960).

(2) National Science Foundation Research Associate under Grant NSF G584 to The Ohio State University.

(3) J. F. Carson, Jr., and W. D. Maclay, *J. Am. Chem. Soc.*, **67**, 787 (1945).

(4) Z. Hadidian and N. W. Pirie, *Biochem. J.*, **42**, 266 (1948); R. W. Jeanloz and E. Forchielli, *J. Biol. Chem.*, **186**, 495 (1950).

EXPERIMENTAL

Peracetylated sodium chondroitin sulfate A (I). An amount of 3.8 g. of sodium chondroitin sulfate A, purified essentially as described previously,[5] was finely pulverized and dried over phosphoric anhydride at 70° and 0.05 mm. for 24 hr. This dry powder was dissolved in 24 ml. of dry, freshly distilled formamide by shaking overnight in a sealed flask. To this solution was added, with agitation, 24 ml. of dry, freshly distilled pyridine followed by 10 ml. of acetic anhydride. The sealed solution was shaken at room temperature for 12 hr. when a further quantity of 13 ml. of acetic anhydride was added, and shaking was continued for a total of 24 hr., during which time the color of the solution became a medium red-brown. The solution was then poured with stirring into 500 ml. of ethanol at 0° and then 400 ml. more ethanol was added to yield a white, flocculent precipitate which was collected by filtration and washed with ethanol. The product was further purified by pouring its solution in 100 ml. of water into 500 ml. of ethanol. Precipitation was effected on the addition of 3–5 ml. of a saturated aqueous sodium chloride solution. This procedure was twice repeated and the final product was dissolved in 100 ml. of water and dialyzed for 2 days against distilled water. Recovery of the product as a fluffy, white, amorphous solid was effected by freeze-drying; yield 3.5 g. (72%), $[\alpha]_D^{30}$ −25° (*c* 1.14, water).

This material was insoluble in acetone, chloroform, ether, ethanol, and methanol but was soluble in water, formamide and 1:1 (by vol.) water-ethanol. It was nonreducing toward Benedict solution and exhibited a positive sulfate test only after hydrolysis with dilute hydrochloric acid. The ninhydrin test for the free amino group was negative; positive tests were obtained for uronic acid and hexosamine. Infrared absorption spectral examination showed the strong acetate ester peak at 1740 cm.$^{-1}$ The prominent bands at 3500 cm.$^{-1}$ and 1670 cm.$^{-1}$ may be attributed to the water of hydration.[6]

Anal. Calcd. for $C_{12}H_{12}NaO_6(NHCOCH_3)(OCOCH_3)_{3.25}(OSO_2ONa\cdot 2H_2O)_{0.75}$: C, 38.38; H, 4.52; N, 2.18; Na, 6.28; CH_3CO, 28.52. Found: C, 37.83; H, 4.53; N, 2.34; Na, 6.14; CH_3CO,[7] 28.05.

De-O-acetylation of peracetylated sodium chondroitin sulfate A. An amount of 600 mg. of the above-described peracetylated sodium chondroitin sulfate A was added at 0° to a filtered solution of 3.0 g. of barium hydroxide octahydrate in 50 ml. of water, and the resultant solution was maintained at 0–5° for 1.5 hr. The solution was then carbonated, filtered, and barium ion was removed exactly with sulfuric acid. The centrifuged, neutral solution was dialyzed against distilled water for 48 hr. and its solid content was recovered as a white powder by freeze-drying; yield 300 mg. (64%), $[\alpha]_D^{32}$ −16° (*c* 1.08, water). The product exhibited a negative ninhydrin reaction for the free amino group.

Anal. Calcd. for $C_{12}H_{10}NaO_6(NHCOCH_3)(OH)_{3.25}(OSO_2ONa\cdot 2H_2O)_{0.75}$: N, 2.77; ash (as sulfate), 24.62; CH_3CO, 8.52. Found: N, 2.50; ash, 24.42; CH_3CO,[7] 8.15.

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(5) M. L. Wolfrom and K. Onodera, *J. Am. Chem. Soc.*, **79**, 4739 (1957). In footnote 23 of this reference the product is designated incorrectly as sodium chondroitin sulfate C. Our preparation contained 0.8 sulfate group per disaccharide unit.

(6) S. A. Barker, E. J. Bourne, and D. H. Whiffen, *Methods of Biochem. Anal.*, **3**, 213 (1956).

(7) A. Chaney and M. L. Wolfrom, *Anal. Chem.*, **28**, 1614 (1956).

Formation of Linear Polymers from Diene Monomers by a Cyclic Polymerization Mechanism. IV. Synthesis and Polymerization Studies of Some Doubly-Unsaturated, Unsymmetrical Monomers[1]

MARTIN D. BARNETT[2a,b] AND GEORGE B. BUTLER

Received August 7, 1959

Current interest in the polymerization of symmetrical dienes by an alternating intramolecular-intermolecular mechanism has led to extensive studies in this field.[3] Previous work[3] in these Laboratories has successfully extended the scope of this reaction to unsymmetrical dienes. We now wish to report the synthesis and results of the polymerization studies of a number of unsaturated derivatives of crotyl and vinylacetic acid, additional examples of unsymmetrical, doubly-unsaturated monomers.

EXPERIMENTAL[4]

Monomers. The *esters of crotonic acid* were prepared by refluxing a benzene solution (200 ml.) of *trans*-crotonic acid (0.5 mol.), the appropriate alcohol (0.55 mol.), and *p*-toluenesulfonic acid (1.0 g.) under a Dean-Stark trap until water evolution ceased (*ca.* 24 hr.). The reaction mixtures were worked up as previously described.[3]

The *esters of vinylacetic acid* were prepared by the dropwise addition of vinylacetyl chloride[5] (0.2 mol.) to a stirred solution of the appropriate alcohol (0.22 mol.) and pyridine (0.21 mol.) in 125 ml. of dry ether. The temperature of the reaction mixture was maintained at 0–5° throughout the addition, after which the cooling bath was removed and the mixture stirred an additional 4 hr. One hundred milliliters of water was added, and the ether layer washed with saturated sodium bicarbonate solution, water, and dried over anhydrous sodium sulfate. Distillation afforded the desired ester.

N-Allylcrotonamide was prepared by the dropwise addition of a solution of 0.5 mol. of crotonyl chloride in 50 ml. of dry ethylene dichloride to a cooled (0°), stirred solution of 1.01 mol. of allyl amine in 400 ml. of dry ethylene dichloride.[6] When addition was complete the mixture was allowed to warm to room temperature and stirred overnight. The work-up was identical with that of the above vinylacetates.

TABLE I

PHYSICAL PROPERTIES OF MONOMERS

$CH_3CH{=}CHC(=O)X$ (I)

$CH_2{=}CHCH_2C(=O)X$ (II)

Compound	Yield, %	B.P., °/Mm.	n_D^{22}	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Ia. X = $-OCH_2CH{=}CH_2$[a]	—	63–64°/22	1.4452	—	—	—	—
Ib. X = $-OCH_2CH{=}CHCH_3$[b]	33	84–86°/22	1.4484	68.54	68.77	8.63	8.77
Ic. X = $-OCH_2C(CH_3){=}CH_2$	41	77.3–77.5°/22	1.4491	68.54	68.49	8.63	8.79
Id. X = $-OCH_2C{\equiv}CH$	37	79.5–80.5°/25	1.4583	67.73	67.53	6.41	6.50
Ie. X = $-NCH_2CH{=}CH_2$[c]	83	90–91°/0.8	1.4911	67.16	67.32	8.86	8.91
IIa. X = $-OCH_2CH{=}CH_2$	48	58–58.5°/27	1.4313	66.64	66.76	7.99	8.15
IIb. X = $-OCH_2CH{=}CHCH_3$	56	78–79°/27	1.4374	68.54	68.25	8.63	8.81
IIc. X = $-OCH_2C(CH_3){=}CH_2$	53	73–74°/27	1.4351	68.54	68.42	8.63	8.88

[a] V. P. Golendeev, *J. Gen. Chem.* (*U.S.S.R.*), 10, 1408 (1940) [*Chem. Abstr.*, 35, 3607[5] (1941)] reports b.p. 88–89°/70 mm., n_D^{20} 1.4465. [b] F. C. Frostick, Jr., B.Phillips, and P. S. Starcher, *J. Am. Chem. Soc.*, 81, 3350 (1959), report b.p. 85–87°/25 mm., n_D^{30} 1.4495. [c] N: Calcd., 11.19. Found, 11.15.

The infrared spectra (liquid films) of the monomers were consistent with their assigned structures. Physical data are recorded in Table I.

Polymerizations were carried out in bulk under dry nitrogen using 5–10 g. samples of monomer and 2% by weight of the appropriate initiator [benzoyl peroxide or azobisisobutyronitrile]. The solid polymers were isolated and purified as previously described.[3] Benzoyl peroxide-initiated polymerizations were run at 100°; those using azobisisobutyronitrile were maintained at 75°. Data concerning the polymerizations is summarized in Table II.

(1) This research was supported by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command, under Contract Number AF 18(603)-116. Reproduction in whole or in part is permitted for any purpose of the United States Government.

(2a) Post-doctoral fellow, 1958–1959; (b) Present address: Department of Chemistry, Marshall College, Huntington, W. Va.

(3) The previous paper in this series [M. D. Barnett, A. Crawshaw, and G. B. Butler, *J. Am. Chem. Soc.*, 81, 5946 (1959)] contains many pertinent references.

(4) All boiling points are uncorrected. Infrared spectra were recorded using a Perkin-Elmer Model 21 double beam spectrophotometer. Analyses were carried out by Galbraith Laboratories, Knoxville, Tenn., or by Weiler and Strauss, Oxford, England.

(5) G. H. Jeffery and A. J. Vogel, *J. Chem. Soc.*, 658 (1948).

(6) W. S. Weaver and W. M. Whaley, *J. Am. Chem. Soc.*, 69, 515 (1947).

TABLE II

POLYMERIZATION STUDIES

Monomer	Polymer (Approximate Values) % Residual Alcohol Bond	% Residual Acid Bond	% Cyclization	Approximate % Conversion	Gel Time (hr.)	Inherent Viscosity (g. polymer/100 ml. solution)	Observations
Ia[a]	15	60	25	10	110	0.046 (0.198)	—
Ib	—	—	—	—	—	—	No polymer with 2% Bz_2O_2[d] at 100° for 45 days or 2% AIBN[e] at 75° for 14 days
Ic[b]	11	58	31	10	[c]	0.039 (0.207)	—
Id	—	—	—	—	—	—	No solid polymer with 2% Bz_2O_2 at 100° for 29 days
Ie	—	—	—	—	—	—	No polymer with 2% Bz_2O_2 at 100° for 14 days or 2% AIBN at 75° for 14 days
IIa	—	—	—	—	—	—	No solid polymer with 2% Bz_2O_2 at 100° for 22 days or 2% AIBN at 25° for 11 days
IIb	—	—	—	—	—	—	No polymer with 2% Bz_2O_2 at 100° for 25 days or 2% AIBN at 75° for 12 days
IIc	—	—	—	—	—	—	No solid polymer with 2% Bz_2O_2 at 100° for 25 days or 2% AIBN at 75° for 12 days

[a] Calcd. for $(C_7H_{10}O_2)_n$: C, 66.64; H, 7.99. Found: C, 66.37; H, 7.90. [b] Calcd. for $(C_8H_{12}O_2)_n$: C, 68.54; H, 8.63. Found: C, 68.37; H, 8.29. [c] No gelation after 32 days at 100° using 2% Bz_2O_2. [d] Benzoyl peroxide. [e] Azobisisobutyronitrile.

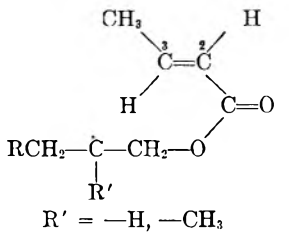
Residual unsaturation was determined as previously described[3] (Table II).

Inherent viscosity measurements were carried out in glacial acetic acid at 30.0° using a modified Ubbelohde viscometer (Table II).

Results and discussion. As indicated in Table II only allyl crotonate (Ia) and β-methallyl crotonate (Ic) gave solid, titratable polymers. Crotyl crotonate (Ib), crotyl vinylacetate (IIb) and *N*-allylcrotonamide (Ie) gave no polymeric material; allyl vinylacetate (IIa), β-methallyl vinylacetate (IIc) and propargyl crotonate (Id) afforded only viscous oils which resisted crystallization.

The relatively low degree of cyclization in poly(allyl crotonate) and poly(β-methallyl crotonate) is not surprising in view of the great difference in reactivities between the alcohol and acid bonds. This effect of differences in bond reactivities as reflected in linear *vs.* cyclopolymerization has been noted earlier.[3]

In addition to the anticipated absorption in the C=C stretching (1640–1655 cm.$^{-1}$) and carbonyl (1725–1740 cm.$^{-1}$) regions the infrared spectra (solid film from carbon tetrachloride) of the solid polymers showed a strong band at 1770–1772 cm.$^{-1}$ characteristic of a 5-membered lactone ring.[7] These findings were surprising, for although molecular models indicated somewhat less steric hindrance to attack of the initially-formed free radical at C_2 of



the acid (5-membered lactone ring) rather than at C_3 (6-membered lactone ring), attack at C_3 should be favored by virtue of the resonance-stabilized radical formed at C_2.

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(7) H. K. Hall and R. Zbinden, *J. Am. Chem. Soc.*, **80**, 6428 (1958).

Preparation of Hexaphenylcyclotrisiloxane by the Reaction of Diphenyldichlorosilane with Zinc Oxide

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In recent papers,[1] the senior author has described some methods which involve direct synthesis of

(1) T. Takiguchi, *J. Org. Chem.*, **23**, 1216 (1958); T. Takiguchi, *J. Chem. Soc. Japan (Ind. Chem. Sect.)*, **61**, 478 (1958); T. Takiguchi, *J. Chem. Soc. Japan (Ind. Chem. Sect.)*, **62**, 148 (1959); T. Takiguchi, *J. Org. Chem.*, **24**, 861 (1959).

hexaphenylcyclotrisiloxane (hereafter called trimer) from diphenyldichlorosilane (DPDS).

It has now been found that the trimer can be obtained readily by the reaction of DPDS with zinc oxide: When one mol. of DPDS was added to one and one half to two mol. of zinc oxide in inert solvents, reaction occurred exothermally. Trimer was obtained from the reaction product in a yield of 96 % (mean). Zinc chloride was determined as zinc hydroxide by neutralization with aqueous base.

Stoichiometry supports the following equation:

$$ZnO + (C_6H_5)_2SiCl_2 \longrightarrow ZnCl_2 + 1/3[(C_6H_5)_2SiO]_3$$

Other anhydrous reagents[2] (cupric oxide, lead oxide, silver oxide, manganese dioxide, cupric sulfate, ferric sulfate, zinc sulfate, nickel sulfate, ferric oxalate, cupric carbonate basic, etc.) were found to react with DPDS in substantially similar manner.

EXPERIMENTAL

Reagents. Purified-grade diphenyldichlorosilane was received from the Shin-etsu Chemical Industrial Co. Reagent-grade zinc oxide was finely powdered after prolonged drying. Methyl acetate was purified according to the ordinary method.

Procedure. A typical procedure is as follows: When a solution of diphenyldichlorosilane in methyl acetate (50 g., 0.2 mol., of DPDS, dissolved in 100 ml. of methyl acetate) was added portion-wise to a shaking flask which contained 24 g., 0.3 mole, of zinc oxide and 200 ml. of methyl acetate, an exothermic reaction occurred gradually. After the addition of DPDS was complete, the reaction mixture was gently refluxed for about 10 min., the color change of crystal violet[3] was used to determine completion of the reaction.

Benzene (200 ml.) was added to the reaction mixture to dissolve the silicon-containing product, and the resulting mixture, cooled to room temperature, was filtered by suction. The filtrate was shaken with about 400 ml. of distilled water to remove zinc chloride.

The top layer was separated, ethanol (200 ml.) was added to it, and the solution was evaporated to dryness on a water bath. A white crystalline mass melting at 177–180° and mixed with a small amount of oily liquid, was obtained. Further purification was effected by recrystallization from ethyl acetate, whereby 38 g. (97%) of pure trimer melting at 188–189° was obtained as elongated hexagonal plates.

Anal. Calcd. for $C_{36}H_{30}Si_3O_3$: Si, 14.16; OH/mol., 0.00; mol. wt., 594. Found: Si, 14.8; OH/mol., 0.0 (Karl Fischer titration[4]); mol. wt., 580–600 (Rast).

The x-ray powder pattern of the trimer obtained showed the major part to be orthorhombic trimer[5] and a minor amount to be triclinic trimer.[5]

From the bottom layer, 19 g. (96%) of zinc hydroxide was obtained by aqueous treatment with ammonium hydroxide using phenolphthalein as an indicator.

Although some other oxides and sulfates were also found to produce trimer and chlorides, respectively, most effective results (highest yield of trimer, greatest simplicity in procedure) were achieved by using zinc oxide as a reactant, whereby the marked dehydrating effect of the chloride resulted in almost a quantitative formation of the trimer.

The authors thank the Shin-etsu Chemical Industrial Co. for the supply of pure diphenyldichlorosilane.

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(2) Thorough investigations will soon appear in *J. Chem. Soc. Japan (Ind. Chem. Sect.)*.

(3) T. Takiguchi, *J. Chem. Soc. Japan (Ind. Chem. Sect.)*, **62**, 527 (1959); T. Takiguchi, *J. Am. Chem. Soc.*, **81**, 2359 (1959).

(4) H. Gilman and L. Miller, *J. Am. Chem. Soc.*, **70**, 2367 (1951).

(5) J. F. Hyde, L. K. Frevel, H. S. Nutting, P. S. Petrie, and M. A. Purcell, *J. Am. Chem. Soc.*, 69, 488 (1947).

Synthesis of Tetra(perfluoroalkoxy)silanes

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Received September 10, 1959

The first reported synthesis of a tetraalkoxysilane was made by von Ebelman.[1] Since that time many tetraalkoxysilanes have been reported in literature.[2,3,4,5] Reaction 1 is most generally used for the preparation of these compounds:[6,7]

$$4SiCl_4 + 10\ ROH \longrightarrow ROSiCl_3 + (RO)_2SiCl_2 + (RO)_3SiCl + (RO)_4Si + 10HCl \quad (1)$$

A modification of the method of Helferich and Hausen[8] was employed to make a number of previously unreported tetra(perfluoroalkoxy)silanes. The method consisted of reacting tetrachlorosilane and a 10% molar excess of perfluorinated alcohols in an anhydrous medium at −10°. Hydrogen chloride produced during the reaction was removed by refluxing and by purging the reaction mixture with dry inert gas. The desired silanes were recovered by vacuum distillation.

Molar excesses of alcohol were used, not only to promote the formation of the tetra-substituted silanes, but also to prevent any reaction between silicon tetrachloride and the tetra-substituted silanes during refluxing or distillation.[9]

$$SiCl_4 + Si(OR)_4 \longrightarrow 2Cl_2Si(OR)_2 \quad (2)$$

Before distillation, the crude mixture of silanes was percolated through a column of activated, dry silica gel to remove the acidic materials which

(1) J. von Ebelman, *Ann.*, **57**, 334 (1846).

(2) H. W. Post, "The Chemistry of the Aliphatic Orthoesters," Reinhold Publishing Corp., New York, N. Y. (1943) p. 120.

(3) C. A. Burkhard, E. G. Rochow, H. S. Booth, and J. Hart, *Chem. Revs*, **41**, 97 (1947).

(4) K. A. Andrianov, "Organic Silicon Compounds" (Kremniyorganicheskiye Soedineniyz) (W. A. D. C. Trans.). State Scientific Technical Publishing House for Chemical Literature, Moscow (1955).

(5) J. R. Wright, R. O. Bolt, A. Goldschmidt, and A. D. Abbott, *J. Am. Chem. Soc.*, **80**, 1733 (1958).

(6) H. W. Post, "Silicones and Other Organic Silicon Compounds," Reinhold Publishing Corp., New York, N. Y. (1949), p. 122.

(7) C. R. Morgan, W. F. Olds, and A. L. Rafferty, *J. Am. Chem. Soc.*, **73**, 5193 (1951).

(8) B. Helferich and J. Hausen, *Ber.*, **57**, 759 (1924).

(9) C. Friedel and J. Crafts, *Ann.*, **127**, 28 (1863).

TABLE I

PROPERTIES OF TETRA(PERFLUOROALKOXY)SILANES

R	B.P./Mm. Hg	$(RO)_4Si$ F.P.[a]	d_4^{20a} and	$d_4^{71.1}$	n_D^{20}	Viscosity, cp.[a] 20.0 and	71.1
$CF_3—CH_2—$[b]	155.5–157/743	−25	1.5107	1.4089	1.30206	2.2089	1.240
$HCF_2CF_2CH_2—$	117–118/4	< −68	1.5927	1.5100	1.33174	18.92	3.583
$CF_3(CF_2)_2CH_2—$	96–97/4	< −68	—	1.5740	1.30088	7.613	1.931
$H(CF_2—CF_2)_2CH_2—$	156–159/2.5	< −68	1.8150	1.6440	1.32622	42.75	5.820
$H(CF_2—CF_2)_3CH_2—$	201–204/3	< −68	—	1.7181	—	108.8	12.23
$H(CF_2—CF_2)_4CH_2—$	235–240/2.5[c]	—	—	—	—	—	—

[a] Freezing points, densities, and viscosities were determined by T. M. Verdura. [b] Pennsalt Chemicals Corp. Booklet DC-1254, *Trifluoroethanol*, b.p. 60–61/25 mm. [c] Material decomposed during distillation.

are deleterious to hydrolytic stability. The mechanism that has been postulated[10] for this hydrolyzation is as follows:

$$\equiv SiOR + H_2O \longrightarrow ROH + \equiv SiOH \longrightarrow {}^1/_2 \equiv SiOSi\equiv + {}^1/_2H_2O \quad (3)$$

The corresponding alcohol and polymeric siloxanes are produced, leading to the precipitation of insoluble polymers or, ultimately, of silica.

All the compounds listed in Table I, except tetra (1,1-dihydrotrifluoroethoxy)silane, are new compounds.

EXPERIMENTAL[11]

Starting materials. Tetrahydrofuran (Eastman Kodak Co., white label) was refluxed over calcium hydride until no more bubbles evolved upon further calcium hydride addition. The tetrahydrofuran was then distilled from the calcium hydride through a 1/2 by 12 inch Vigreux column, and the portion distilling at 64–64.5° collected. Water content was less than 0.003% by test with Karl Fischer reagent.[12] *Tetrachlorosilane* (Tech. Grade) was purified by distillation. *1,1-Dihydrotrifluoroethanol* (Pennsalt Chemicals Corp.) was distilled from anhydrous calcium sulfate (Drierite), and the portion distilling at 72–72.5° collected. *1,1-Dihydroheptafluorobutanol* (Minnesota Mining & Mfg. Co.) was distilled, and the portion distilling at 74–74.6° collected. The *trihydroperfluoroalcohols*[13] (du Pont) were used as received. The inert gases used for purging of the reaction mixtures were dried by passage through Linde molecular sieve, Type 4A.

Apparatus. The all-glass apparatus used in the preparations and distillations was protected from atmospheric moisture by Drierite-filled tubes.

Tetra (1,1-dihydrotrifluoroethoxy)silane. While 220.1 g. (2.2 mol.) of 1,1-dihydrotrifluoroethanol was rapidly stirred, 84.9 g. (0.50 mol.) of tetrachlorosilane was added over a period of 1 hr. After the addition was completed, the solution was refluxed for 2 hr., while hydrogen chloride was evolved at a decreasing rate. The reaction mixture was cooled to 25° and percolated through an anhydrous silica gel column, using dry tetrahydrofuran as eluant. The product was then distilled through a 1/2 by 12 inch Vigreux column, and the clear fraction boiling at 155.5–157° (743 mm.) was collected.

Tetra (1,1,3-trihydrotetrafluoropropoxy)silane. The preparation of this compound will illustrate the method used for the preparation of the remaining compounds listed in Table I. A solution of 290.5 g. (2.2 mol.) of 1,1,3-trihydrotetrafluoropropanol in an equal volume of tetrahydrofuran was cooled to −14°. While this solution was vigorously stirred, a solution of 84.9 g. (0.5 mol.) of tetrachlorosilane in an equal volume of tetrahydrofuran was added over a 1-hr. period. During the addition the solution temperature was maintained below −10°. The solution was then refluxed for 2 hr. with the generation of copious amounts of hydrogen chloride. The heat source was removed and the solution purged with a dry inert gas for 2 hr. Tetrahydrofuran and excess alcohol were removed under vacuum at room temperature, and the residue vacuum distilled through a 1/2 by 12 inch Vigreux column. The clear colorless fluid distilling at 117–118° (4 mm.) was collected.

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(10) R. Aelion, A. Loebel, and F. Eirich, *J. Am. Chem. Soc.*, **72**, 5705 (1950).

(11) All temperature readings are uncorrected.

(12) J. Mitchell and D. M. Smith, "Chemical Analysis," Interscience Publishers, New York, N. Y. (1948), Vol. 5, Chap. 4.

(13) The author wishes to thank A. C. Haven of du Pont who supplied samples of alcohols.

Communications TO THE EDITOR

The Wolff-Kishner Reaction with α-Oximinoketones

Sir:

The Wolff-Kishner reaction is usually a very reliable and useful method for converting a carbonyl group to methylene. However, when applied to α- or β-substituted ketones and aldehydes,[1] some other structural change may occur as well. We have found that α-oximinoketones, when subjected to this reaction, may lead to a number of products, including in one instance normal reduction to the methylene group.

When 1,2-indanedione 2-oxime (I) was exposed to the usual Wolff-Kishner reaction conditions (hydrazine, potassium hydroxide, diethylene glycol, 190°) a 73% yield of indano[1.2]-v-triazole (II) resulted (m.p. 140–141°. *Anal.* Found: C, 68.8; H, 4.4; N, 26.8). The hydrazone of I (m.p. 240–

I II

242°, *Anal.* Found: C, 61.9; H, 5.2; N, 24.1) gave the same product when exposed to the action of alkali in diethylene glycol. This appears to be a possible method for preparing v-triazoles in which the nitrogen is unsubstituted.[2] However, the reaction is far from general.

When α-oximinoacetophenone was treated under the same conditions, the only product isolated was phenylacetic acid (in 70% yield). From 2,3-butanedione 2-oxime, 2,3-butanedione 3-hydrazone-2-oxime was obtained in 65% yield with no evidence of any triazole formation. And from 2,3-octanedione 3-oxime a 90% yield resulted of the normal reduction product, 3-octanone oxime (b.p. 115°/14 mm., n_D^{25} 1.4492; reported[3] b.p. 92°/5 mm., n_D^{20} 1.4517. *Anal.* Found: C, 67.4; H, 11.7; N, 9.5).

The mechanism of this reaction and its application to α-oximinoketones in general is under further study.

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(1) D. Todd, *Org. Reactions*, IV, 378 (1948); R. B. Turner, R. Anliker, R. Heibling, J. Meier, and H. Heusser, *Helv. Chim. Acta*, **38**, 411 (1955); R. Fischer, G. Lardelli, and O. Jeger, *Helv. Chim. Acta*, **34**, 1577 (1957).

(2) A number of *N*-phenyltriazoles have been obtained by the action of acids or acetic anhydride on oxime-phenylhydrazones [F. R. Benson and W. L. Savell, *Chem. Revs.*, **46**, 1 (1950)]. Also, M. Ruccia and D. Spinelli, [*Gazz. chim. ital.*, **89**, 1654 (1959)] have considered the reaction with hydrazone-oximes.

(3) F. Asinger, G. Geiseler, and P. Laue, *Ber.*, **90**, 485 (1957).

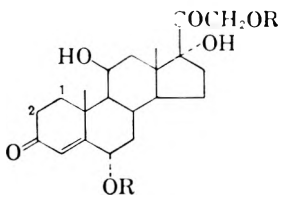
(4) Frank Shu Scientific Fellow of the China Institute in America.

C6-Hydroxylated Steroids. I. Preparation of 6α- and 6β-Hydroxyhydrocortisone and 6α-Hydroxyprednisolone

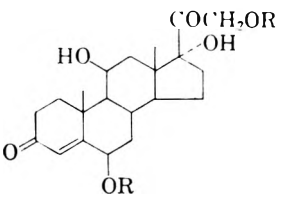
Sir:

We wish here to describe the first chemical preparation of 6α- and 6β-hydroxyhydrocortisone (Ia, IIa) and 6α-hydroxyprednisolone (Ic).[1]

6β-Hydroxyhydrocortisone (IIa) has been established as a metabolite of hydrocortisone in animal and human studies.[2a] Burstein and Dorfman[2b] have speculated that 6α-hydroxyhydrocortisone (Ia) may also be a metabolite of hydrocortisone in the guinea pig.



I a. R = H
b. R = Ac
c. Δ¹, R = H
d. Δ¹, R = Ac



II a. R = H
b. R = Ac

The 5α,6α-epoxide III of hydrocortisone bisethylene ketal[3] on treatment with either perchloric

(1) F. Sondheimer, O. Mancera, and G. Rosenkranz, *J. Am. Chem. Soc.*, **76**, 5020 (1954), have described the preparation of 6β-hydroxycortisone. Also the 6α-hydroxy analogs of cortisone and prednisone have been prepared, J. A. Edwards, J. Iriarte, C. Djerassi, and H. J. Ringold, forthcoming publication, as cited by A. Bowers and co-workers, *J. Am. Chem. Soc.* **81**, 5233 (1959).

(2) (a) S. Burstein, R. Dorfman, and E. Nadel, *Arch. Biochem. and Biophys.*, **53**, 307 (1954); (b) S. Burstein and R. Dorfman, *J. Biol. Chem.*, **213**, 581 (1955), and (c) E. Colle, R. A. Ulstrom, J. Burley, and R. Gunville, Abstracts of the 41st Meeting of the Endocrine Society, Atlantic City, N. J., June 4–6, 1959. See also, (d) M. Hayano and R. Dorfman, *Arch. Biochem. and Biophys.*, **50**, 218 (1954).

(3) R. Littell and S. Bernstein, *J. Am. Chem. Soc.*, **78**, 984 (1956).

or sulfuric acid in aqueous acetone gave 5α,6β,-11β, 17α,21-pentahydroxypregnane-3,20-dione (IV) [m.p. 273–274° dec., $[\alpha]_D^{25}$ +35° (pyridine). *Anal.* Found: C, 63.44; H, 8.46]. Acetylation of IV at room temperature gave a separable mixture of 21-monoacetate V [m.p. 280–282°, $[\alpha]_D^{25}$ +35° (pyridine). *Anal.* Found: C, 62.62; H, 8.00], and the 6,21-diacetate VI [m.p. 145–155°,[4] $[\alpha]_D^{25}$ +6° (pyridine). *Anal.* Found: C, 62.46; H, 7.81]. Acetylation at 100° provided exclusively the 6,21-diacetate VI.[5]

Treatment of the 6,21-diacetate VI in methylene chloride with hydrogen chloride at 0° provided a mixture of 6α-hydroxyhydrocortisone 6,21-diacetate (Ib) and 6β-hydroxyhydrocortisone 6,21-diacetate (IIb) separated by chromatography on magnesium silicate. This gave the 6α,21-diacetate Ib [m.p. 128–130°, $\lambda_{max}^{CH_3OH}$ 236 mμ (ε 12,800), $[\alpha]_D^{25}$ +107° (chloroform). *Anal.* Found: C, 64.72; H, 7.69] and the *impure* 6β,21-diacetate IIb. When the reaction was performed in methylene chloride containing ethanol only the thermodynamically more stable 6β,21-diacetate Ib was obtained. Saponification of Ib with potassium carbonate gave 6α-hydroxyhydrocortisone (Ia) as a solvate [m.p. 220–222°, $\lambda_{max}^{CH_3OH}$ 241 mμ (ε 13,300), $[\alpha]_D^{25}$ +122° (pyridine). *Anal.* Found: C, 64.42; H, 7.96]. Impure 6β,21-diacetate IIb on saponification followed by partition chromatography on diatomaceous earth provided 6β-hydroxyhydrocortisone (IIa) [m.p. 241–243°, $\lambda_{max}^{CH_3OH}$ 234–235 mμ (ε 12,000), $[\alpha]_D^{25}$ +90° (methanol)].[2b,d] Acetylation gave the 6β,21-diacetate IIb [m.p. 148–150°, $\lambda_{max}^{CH_3OH}$ 235–236 mμ (ε 12,100), $[\alpha]_D^{25}$ +89° (methanol)].[2b,d;6]

Finally, 6α-hydroxyhydrocortisone 6,21-diacetate (Ib) on selenium dioxide dehydrogenation in *t*-butyl alcohol and acetic acid[7] gave 6α-hydroxyprednisolone 6,21-diacetate (Id) [m.p. 146–148°, $\lambda_{max}^{CH_3OH}$ 241–242 mμ (ε 13,900), $[\alpha]_D^{25}$ +80° (chloroform). *Anal.* Found: C, 65.08; H, 7.48]. Saponification gave 6α-hydroxyprednisolone (Ic) as a solvate [m.p. 248–250°, $\lambda_{max}^{CH_3OH}$ 242 mμ (ε 13,800), $[\alpha]_D^{52}$ +88° (methanol). *Anal.* Found: C, 66.28; H, 7.97].

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(4) All attempts to obtain a sample with a sharp m.p. were unsuccessful. However, the compound was shown to be homogeneous by paper strip chromatographic analysis. In fact, all compounds reported herein were similarly shown to be homogeneous.

(5) The 6,21-diacetate VI usually proved difficult to obtain in a crystalline form, and generally was used as an oil in subsequent transformations. The oil was demonstrated by paper chromatographic analysis to be practically homogeneous.

(6) The infrared absorption spectra of IIa and b were identical with those of the Worcester samples. We are indebted to Dr. S. Burstein for these comparisons.

(7) C. Meystre, H. Frey, W. Voser, and A. Wettstein, *Helv. Chim. Acta*, **39**, 734 (1956); S. Szpilfogel, T. Posthumus, M. De Winter, and D. Van Dorp. *Rec. Trav. Chim.*, **75**, 475 (1956).