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# Conformational Analysis of Seven-Membered Heterocycles. The 1,3-Dioxacycloheptanes—Proton and Carbon-13 Magnetic Resonance

MICHAEL H. GIANNI,* JOSE SAAVEDRA, AND JAMES SAVOY

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*Received June 5, 1973*

Configurational assignments are made for *cis*- and *trans*-4,7-dimethyl-1,3-dioxacycloheptane with the aid of proton and carbon-13 nmr spectroscopy. Five sets of steric interactions are defined which, when found in combinations of two, present effective pseudorotational and/or rotational barriers. Equilibrium studies for *cis*- and *trans*-2-*tert*-butyl-4-methyl-1,3-dioxacycloheptane and *cis*- and *trans*-2-*tert*-butyl-5-methyl-1,3-dioxacycloheptane give $-\Delta G°$ of 0.45 ± 0.05 and 0.0 ± 0.05 kcal/mol, respectively. These values are in good agreement with values for 1,3-dimethylcycloheptane and 1,4-dimethylcycloheptane and reflect the availability of numerous low-energy conformations for each of the isomers.

Conformational analysis of seven-membered carbocyclics has received considerable recent attention.[1-7] Computer calculations by Hendrickson[1] have provided a detailed account of the symmetry and energetics of cycloheptane conformations. A study of coupling constants for cis and trans 2-substituted cycloheptanols[8] indicated that there were no conformational preferences for substituents and that the differences in coupling constants were due only to differences in configuration of the isomers. Thermochemical data[9] for *cis*- and *trans*-1,3-dimethylcycloheptane and *cis*- and *trans*-1,4-dimethylcycloheptane indicated enthalpy differences close to zero.

The initial results from our conformational studies of substituted 1,3-dioxacycloheptanes[10] are reported here. These compounds were selected for their ease of preparation and their amenability to equilibration studies.[11] They also provided an opportunity to study conformational preferences for alkyl substituents in a pseudorotating, heterocyclic system.

Conformational analysis of cyclohexane and 1,3-dioxacyclohexane is reasonably facilitated by the absence of a low-energy pseudorotational barrier and by the existence of only one chair conformation. A study of Dreiding models reveals that 1,3-dioxacycloheptane has four distinct chair conformations (**1**–**4**) in addition

**1** **2** **3** **4**

to their respective twist–chair conformations. There are two conformations in which the syn-4,7-diaxial proton–proton interactions are absent plus two conformations in which the two-proton eclipsing interactions at C(5,6) are absent. On the basis of steric interactions alone, it would appear that chair conformation **4** is preferred over any of the twist–chair conformations. This is in contrast to the finding that the twist–chair conformation of cycloheptane is more stable than the chair conformation.[3] A comparison of Dreiding models reveals that the distance between the 1,3-diaxial positions for 1,3-dioxacyclohexane and 1,3-dioxacycloheptane are comparable. The distance between the 4,7-diaxial positions for 1,3-dioxacycloheptane is smaller than for 1,3-dioxacyclohexane. This suggests that 1,3-diaxial and 4,7-diaxial Me–H steric interactions should be more severe for both these heterocyclic compounds than for the corresponding carbocyclic compounds.[3,11,12]

**Configurational and Conformational Assignments. *cis*- and *trans*-4,7-Dimethyl-1,3-dioxacycloheptanes.** — The isomers of 4,7-dimethyl-1,3-dioxacycloheptane were separated by gas chromatography. Configurational assignments were made on the basis of proton and carbon-13 magnetic resonance spectra. A study of models indicated that there were seven possible chair conformations for the trans isomer and eight possible

(1) J. B. Hendrickson, *J. Amer. Chem. Soc.*, **89**, 7036 (1967).
(2) J. B. Hendrickson, *J. Amer. Chem. Soc.*, **89**, 7043 (1967).
(3) J. B. Hendrickson, *J. Amer. Chem. Soc.*, **89**, 7047 (1967).
(4) J. D. Roberts, R. Knorr, and C. Ganter, *Angew. Chem., Int. Ed. Engl.* **6**, 556 (1967).
(5) M. Cristl and J. D. Roberts, *J. Org. Chem.*, **37**, 3443 (1972).
(6) E. S. Glazer, R. Knorr, C. Ganter, and J. D. Roberts, *J. Amer. Chem., Soc.*, **94**, 6026 (1972).
(7) H. Friebolin, R. Meck, S. Kabuss, and A. Luttringhaus, *Tetrahedron Lett.*, 1929 (1964).
(8) A. Bauman and H. Mohrle, *Tetrahedron*, **25**, 135 (1969).
(9) G. Mann, M. Muhlstadt, R. Muller, E. Kern, and W. Hadeball, *Tetrahedron*, **24**, 6941 (1968).
(10) H. Friebolin and S. Kabuss, "Nuclear Magnetic Resonance in Chemistry," B. Pesce, Ed., Academic Press, New York, N. Y., 1965, reports nmr studies for 2,2-dimethyl-1,3-dioxacyclohept-5-ene.
(11) E. L. Eliel and M. C. Knoeber, *J. Amer. Chem. Soc.*, **88**, 5347 (1966).
(12) W. Nader and E. L. Eliel, *J. Amer. Chem. Soc.*, **92**, 3050 (1970).

TABLE I

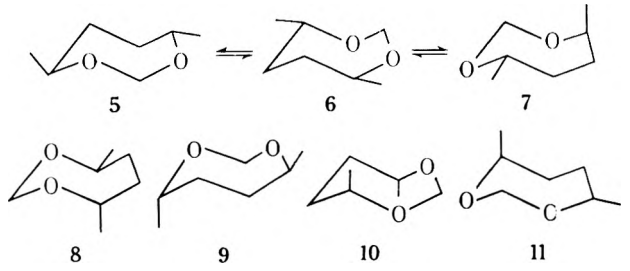
PROTON CHEMICAL SHIFTS FOR SOME 1,3-DIOXACYCLOHEPTANES

| Registry no. | 1,3-Dioxacycloheptanes | H–C(2) | H–C(4,7) | $CH_3$ |
|---|---|---|---|---|
| 41887-61-0 | *cis*-4,7-Dimethyl | 5.16, 5.47 | 6.17 | 8.84 |
| 41887-62-1 | *trans*-4,7-Dimethyl | 5.30 | 6.19 | 8.82 |
| 41887-63-2 | *cis*-2-*tert*-Butyl-4-methyl | 5.89 | 6.23 | 8.82 |
| 41887-64-3 | *trans*-2-*tert*-Butyl-4-methyl | 5.83 | 6.01 | 8.87 |
| 41887-65-4 (cis) 41887-66-5 (trans) | *cis*/*trans*-2-*tert*-Butyl-5-methyl | 5.58 | | 8.81, 9.01 |
| 505-65-7 | 1,3-Dioxacycloheptane | 5.49 | 6.46 | |
| 41887-67-6 | 2-*tert*-Butyl | 5.96 | 6.31 | |

chair conformations for the cis isomer. The conformations for the trans isomer are shown in Chart I.

CHART I

CONFORMERS OF *trans*-4,7-DIMETHYL-1,3-DIOXACYCLOHEPTANE



5 6 7 8 9 10 11

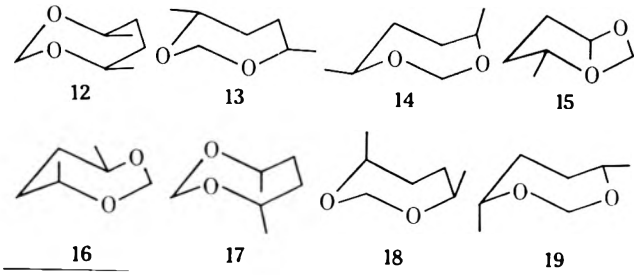
Using Hendrickson's values[3,13] for the steric interaction energies of a single methyl group with the other atoms of cycloheptane as a guide and recalling that 1,3-diaxial Me–H interactions are more severe in this heterocyclic system than in cycloheptane, it was estimated that conformers **8**, **9**, **10**, and **11** did not contribute more than 1% to the conformational array. Therefore they were excluded from further consideration.

Structures **5**, **6**, and **7** represent conformations of *trans*-4,7-dimethyl-1,3-dioxacycloheptane which differ by one pseudorotation. The twist–chair conformation which is obtained in the pseudorotation of **5** to **6** contains a $C_2$ axis which makes the C(2) protons equivalent. This pseudorotation inverts the C(2) protons but the methyl groups remain equatorial. The trans configuration was assigned to the isomer whose C(2) protons gave an $A_2$ nmr spectrum at $\tau$ 5.30. The proton nmr chemical shifts ($\tau$) are listed in Table I.

Chart II shows the conformers of *cis*-4,7-dimethyl-1,3-dioxacycloheptane. Estimation of the steric interaction energies for all conformers indicates that **16**, **17**, **18**, and **19** contribute less than 1% to the conformational array and they were excluded from further consideration. The pseudorotational sequence **12**, **13**, **14**, and **15** is such that the C(2) protons retain their conformational integrity. In each of these conformations the C(2) protons are diastereotopic and should yield an AB nmr spectrum. Therefore, the compound which gave the AB nmr spectrum at $\tau$ 5.16 and 5.47 was assigned the cis configuration.

CHART II

CONFORMERS OF *cis*-4,7-DIMETHYL-1,3-DIOXACYCLOHEPTANE



12 13 14 15 16 17 18 19

The unfavorable Me–H steric interactions found in conformers **8**, **9**, **10**, **11**, **16**, **17**, **18**, and **19** are as follows: A,[14] $syn_O$-diaxial 1,3-Me–H (1.16 Å); B, syn-diaxial 4,7-Me–H (1.88 Å); C, syn-diaxial 4,7-Me–Me (contact); D, syn-diaxial Me–H (contact); E, syn-diaxial 2,5-Me–Me (1.2 Å). Each of these conformers has a minimum of two unfavorable interactions, including at least one of type A. For this system of compounds, it appeared reasonable to exclude those conformations which contain at least two of these interactions from consideration when they appear in a pseudorotational or rotational sequence.[15]

Table II lists the carbon-13 chemical shifts for a series of 1,3-dioxacycloheptanes. Assignments were made by comparison with data for the 1,3-dioxacyclohexanes[16] and 1,3-dioxacyclohept-5-ene. The assignment for C(5,6) was made at 30.05 ppm, as this absorption did not occur in 1,3-dioxacyclohept-5-ene. The methyl assignments were made as indicated, since their absorptions did not occur in the spectrum of the unsubstituted compounds.

The carbon-13 chemical shifts for *trans*-4,7-dimethyl-1,3-dioxacycloheptane are, C(2), 91.95; C(4,7), 72.39;

(13) The Hendrickson values are reprinted here to aid in the estimation of steric interaction energies: 1i (0.5); 2e,2e′ (0.4); 2a,2a′ (3.0); 3e,3e′ (0.3); 3a,3a′ (3.3); 4e,4e′ (0.4); and 4a,4a′ (1.8). These values are not strictly applicable to this system owing to the replacement of two methylene groups by two oxygen atoms.

(14) The symbol $syn_O$ represents a 1,3-diaxial interaction which crosses an oxygen atom (CHOCH).

(15) It is interesting to note that conformer **12** is the rotamer (inversion) of conformer **17**, **13** is the mirror image of the rotamer of **18**, **14** is the mirror image of the rotamer of **19**, and **15** is the mirror image of the rotamer of **16**. If conformers **12**–**15** were inverting, the nmr spectrum for the C(2) protons would show the effects of averaging. The new spectrum could be $A_2$ due to accidental isochronicity or A′B′. The spectrum is not $A_2$. The question remains as to whether the observed spectrum is due to averaging of conformers **12**–**15**, as indicated by the steric interaction energies, or whether it is due to the averaging of conformers **12**–**19**. The chemical shift difference between the AB protons at C(2) for this compound is 17.9 Hz. This value is in good agreement with a value of 18.4 Hz for the chemical shift difference between the C(2) protons of *cis*-4,7-dimethyl-1,3-cyclohept-5-ene, which is conformationally locked so that no inversion is occurring (unpublished data of M. Adams). If in fact the conformers of *cis*-4,7-dimethyl-1,3-dioxacycloheptane were inverting, a difference in the chemical shifts between the C(2) protons would be expected to be small; for example, the nmr spectrum for the C(2) protons of 4-methyl-1,3-dioxacycloheptane gives an $A_2$ pattern. Therefore the assumption that conformers **16**–**19** do not contribute to the conformational array is consistent with the steric interaction energy estimates and the proton nmr spectrum.

(16) A. J. Jones, E. L. Eliel, D. M. Grant, M. C. Knoeber, and W. F. Baily, *J. Amer. Chem. Soc.*, **93**, 4772 (1971).

Table II

Carbon-13 Chemical Shifts for Some 1,3-Dioxacycloheptanes

| Registry no. | 1,3-Dioxacycloheptanes | C(2) | C(4) | C(7) | C(5) | C(6) | $CH_3$ |
|---|---|---|---|---|---|---|---|
| | 1,3-Dioxacycloheptane | 94.67 | 67.24 | | 30.05 | | |
| | *cis*-4,7-Dimethyl | 94.07 | 75.89 | | 33.76 | | 22.36 |
| | *trans*-4,7-Dimethyl | 91.95 | 72.39 | | 36.51 | | 22.58 |
| | *cis*-2-*tert*-Butyl-4-methyl | 108.70 | 76.98 | 70.68 | 28.31 | | 22.32 |
| | *trans*-2-*tert*-Butyl-4-methyl | 106.39 | 71.23 | 66.87 | 29.29 | | 22.51 |
| 2463-48-1 | 4-Methyl | 93.50 | 75.32 | 66.80 | 36.95 | 29.29 | 22.51 |
| | *cis*/*trans*-2-*tert*-Butyl-5-methyl | 109.71 | 76.45 | 68.23 | 34.80 | 37.90 | 18.22 |
| | | 110.19 | 72.45 | 64.59 | | | 17.09 |
| 41887-69-8 | 5-Methyl | 94.65 | 72.40 | 64.84 | 34.95 | 38.44 | 17.27 |

C(5,6), 36.51 ppm. C(4,7) and C(5,6) each gave a single value, which indicated that these chemical shifts were averaged owing to a pseudorotation which was rapid compared with the carbon-13 nmr time scale. The same observation was evident from the cis isomer data. Carbon-13 studies by Eliel[16] and Grant[17] showed a substantial chemical shift difference between axial and equatorial methyl groups, 4.3 ppm for cyclohexane and 3.5 ppm for 1,3-dioxacyclohexane. Therefore the 0.2-ppm difference in chemical shift for the methyl groups of the cis and trans dimethyl isomers could not be considered the difference between axial and equatorial positions. It is clear that the methyl groups experience some averaged conformational atmosphere and that the axial contribution to the carbon-13 chemical shifts is important.

The chemical shift parameters of Eliel,[16] Grant,[17] and Roberts[5] provided a check for the configurational assignments. The trans-4,7-dimethyl isomer had chemical shifts which differed from 1,3-dioxacycloheptane as follows: C(2), +2.81; C(4,5), −5.15; C(5,6), −6.46. Calculated values (obtained by giving equal weight to conformers **5**, **6** and **7**, but excluding **8**–**11**) gave, C(2), +3; C(4,7), −5.2; C(5,6), −8.9.

The chemical shift values for the cis isomer differed from the chemical shift values of the parent as follows: C(2), +0.69; C(4,7), −8.65; C(5,6), −3.71. Calculated values obtained by giving equal weight to conformers **12**–**15**, but excluding **16**–**19**, were, C(2), +1.2; C(4,7), −4.9; C(5,6), −5.6. The parameter[5,17,18] which appeared to be most sensitive to conformation was a paramagnetic shift due to a 1,3-diaxial Me–H interaction. Therefore the calculations for the chemical shifts at C(2) were most sensitive to that interaction. Conformer **7** made the total paramagnetic contribution to the conformational array for the trans isomer. Conformers **14** and **15** made no paramagnetic contribution at C(2) for the cis isomer. The calculated values for C(2) were consistent with the configurational assignments made on the basis of proton nmr. When all conformers were weighted equally for each of the isomers, the cis C(2) value was greater than +7 and the trans value was greater than +6. The calculated chemical shift values also supported the conclusion that the methyl group experienced some averaged (axial–equatorial) conformational atmosphere.

**2-*tert*-Butyl-4-methyl-1,3-dioxacycloheptane.**—Configurational assignments for *cis*- and *trans*-2-*tert*-butyl-4-methyl-1,3-dioxacycloheptane were made on the basis of proton and carbon-13 nmr spectra. Charts III and IV depict the chair conformers of *trans*-2-*tert*-butyl-4-methyl-1,3-dioxacycloheptane and *cis*-2-*tert*-butyl-4-methyl-1,3-dioxacycloheptane, respectively. Conformers with an axial *tert*-butyl group were excluded on the basis of severe steric interactions. Twist-boat and boat conformations were considered to be of sufficiently high energy so as to provide only a minor contribution to the conformational array. Only one twist-boat conformation could have been considered for the cis isomer but it required a paramagnetic carbon-13 chemical shift at C(7), which was not consistent with the spectrum. For the trans isomer the most reasonable twist-boat required a paramagnetic carbon-13 chemical shift at C(4), which was also not consistent with its spectrum.

Chart III

Conformers of *trans*-2-*tert*-Butyl-4-methyl-1,3-dioxacycloheptane

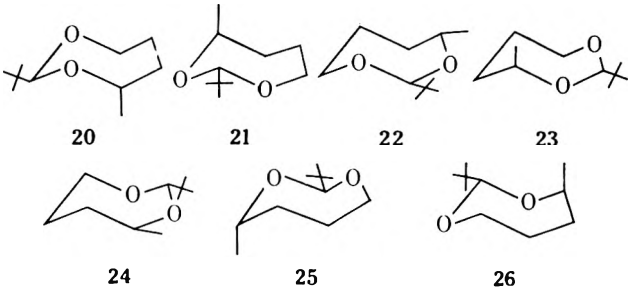
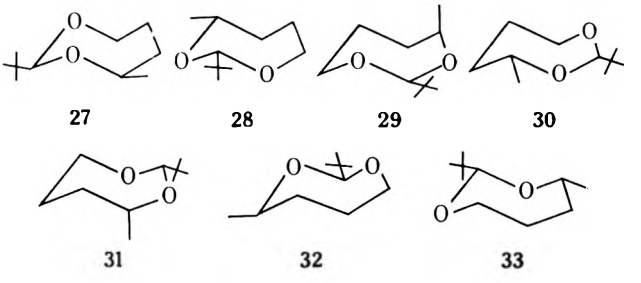



Chart IV

Conformers of *cis*-2-*tert*-Butyl-4-methyl-1,3-dioxacycloheptane




A study of models for the conformers of the trans isomer indicated that conformations **20**, **21**, **23**, and **25** would make little contribution to the conformational array by virtue of the severe steric interactions. For example, conformer **20** showed one syn$_O$-diaxial 1,3-Me–H interaction and one syn-diaxial 4,7-Me–H interaction. Accordingly, only conformers **22**, **24**, and **26** were left to account for the proton and carbon-13 nmr spectra.

(17) D. K. Dalling and D. M. Grant, *J. Amer. Chem. Soc.*, **94**, 5318 (1972).
(18) J. D. Roberts, F. J. Weigert, J. I. Kroschwitz, and H. J. Reid, *J. Amer. Chem. Soc.*, **92**, 1388 (1970).

Conformers **22** and **24** were expected to give low-field chemical shifts for the axial methine C(4) protons because they were directly opposed to an oxygen atom across the ring and conformer **26** had an equatorial proton, which normally absorbs at lower field than an axial proton. The high-field C(4) proton absorption for the cis isomer was consistent with that conformational array, since the proton was axial for five of the conformations and was not found in a position opposed to oxygen.

The carbon-13 data were consistent with this interpretation, since the C(2) absorption for the trans isomer indicated a paramagnetic shift from conformer **26**. Examination of models for the conformers of the cis isomer dictated that none of the conformers could be discarded due to severe steric interactions and none of the conformers would give a paramagnetic shift at C(2). Accordingly, the assignments were made as indicated in the tables with the C(2) chemical shift for the trans isomer at 106.39 ppm. The remaining chemical shifts were found to be consistent with parameters from Eliel, Grant, and Roberts.

**Equilibrium Studies. *cis*- and *trans*-2-*tert*-Butyl-5-methyl-1,3-dioxacycloheptane.**—All attempts to separate the isomers of 2-*tert*-butyl-5-methyl-1,3-dioxacycloheptane were unsuccessful. The carbon-13 nmr indicated that both isomers were present in equal concentration. This isomer mixture was equilibrated (see Experimental Section) until the carbon-13 nmr spectra gave consistent areas[19] for the methyl, C(4), and C(7) peaks. Fortunately, the peaks were of equal area, so that it was not necessary to make unequivocal assignments for each of the absorptions. A $-\Delta G^\circ_{82^\circ}$ of 0.0 ± 0.5 kcal/mol was calculated for the 1:1 mixture.[20]

***cis*- and *trans*-2-*tert*-Butyl-4-methyl-1,3-dioxacycloheptane.**—Equilibrium for the *cis*- and *trans*-2-*tert*-butyl-4-methyl-1,3-dioxacycloheptane was approached from both directions using samples of 95% purity. Relative concentrations of isomers were determined by integration of each of the nmr peaks for the C(2) axial proton and by integration of the appropriate peaks of the gas chromatograms. The cis:trans equilibrium ratio was found to be 1.9:1 and the $-\Delta G^\circ_{355^\circ}$ value was calculated to be 0.45 ± 0.05 kcal/mol.

## Discussion

The low $-\Delta G^\circ$ values for the 2-*tert*-butyl-4-methyl- and 2-*tert*-butyl-5-methyl-1,3-dioxacycloheptane isomerizations indicate that there are numerous low-energy conformations available for each of the systems. The $-\Delta G^\circ$ of 0.45 kcal/mol for 2-*tert*-butyl-4-methyl-1,3-dioxacycloheptane isomerization compares favorably with Eliel's $-\Delta G^\circ$ value of 0.27 kcal/mol for the isomerization of 2-*tert*-butyl-4-methyl-1,3-dioxolane,[21] for which he suggested the availability of numerous low-energy conformations. The $-\Delta G^\circ$ values of 2.9 kcal/mol for 2-*tert*-butyl-4-methyl-1,3-dioxacyclohexane[11] and 1.96 kcal/mol for 1,4-dimethylcyclohexane[22] are high in contrast to those mentioned above, since they are restricted to chair conformations in which the substituent must assume either axial or equatorial positions.

The enthalpy difference between *cis*- and *trans*-1,3-dimethylcycloheptane is approximately zero.[9] Calculation of the enthalpy difference between *cis*- and *trans*-2-*tert*-butyl-4-methyl-1,3-dioxacycloheptane gives a value of 0.14 kcal/mol, assuming that the entropy contribution is due entirely to entropy of mixing ($R \ln {}^7/_3$). All allowable conformers in Charts I and II were given equal weight for this calculation.[23,24]

The $\Delta G^\circ$ value of 0.0 kcal/mol for 2-*tert*-butyl-5-methyl-1,3-dioxacycloheptanes contrasts with a $\Delta G^\circ$ value of −0.84 kcal/mol for 2-*tert*-butyl-5-methyl-1,3-dioxacyclohexanes and a $\Delta G^\circ$ of −1.9 kcal/mol for 1,4-dimethylcyclohexanes. The enthalpy difference for the 1,4-dimethylcyclohexanes is also close to zero. Calculation of the enthalpy difference for the 2-*tert*-butyl-5-methyl-1,3-dioxacycloheptanes, assuming that the entropy contribution is due to mixing ($R \ln {}^7/_5$), gives a value of 0.24 kcal/mol, in good agreement with the value for 1,4-dimethylcyclohexanes.

The data support the concept of numerous low-energy conformations as an explanation for the low $\Delta G^\circ$ values in pseudorotating systems. The suggestion that a combination of any two of the steric interactions is sufficiently severe to prohibit a pseudorotational sequence or severely limit the conformational array is strengthened by the enthalpy calculations.

## Experimental Section

Proton nmr spectra were recorded on a Varian A-60A instrument. Samples were run as 10% solutions in carbon tetrachloride. All chemical shifts are reported in $\tau$ units. The carbon-13 nmr spectra were recorded at 25.15 MHz on a HA-100D nmr spectrometer interfaced to a Digilab NMR-FTS-3 pulse and data system. The samples were neat liquids. The number of data points was 8K or 16K as required to obtain satisfactory resolution. Spectra were recorded with broad band decoupling. All chemical shifts were referenced to internal TMS and reported in parts per million. All *m/e* values were determined on a AEI MS-9 high-resolution mass spectrometer. Separations were

(19) To reduce the probability that areas for the C(2), C(7), and methyl sets of absorptions were not the results of different relaxation rates, the spectra were run at three different pulse rates. The ratios of the areas remained constant.

(20) These equilibrations were run for 8, 24, and 148 hr in order to give reasonable assurance that equilibrium had been reached. These times exceed those required for the equilibration of 2-*tert*-butyl-4-methyl-1,3-dioxacycloheptanes and the 1,3-dioxolanes.

(21) W. E. Willy, G. Bensch, and E. L. Eliel, *J. Amer. Chem. Soc.*, **92**, 5394 (1970).

(22) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965.

(23) The steric interaction energies required to estimate the percentages of each of the conformers are not available. The best (or worst) that can be done is to assume equal concentrations. This assumption is consistent with the values calculated for the C(2) carbon-13 chemical shifts.

(24) A reviewer has expressed concern that the anomeric effect may have a major role in the determination of conformer concentrations [G. Baddely, *Tetrahedron Lett.*, 1645 (1973), and references cited therein]. A study of models indicates that the anomeric effect will disfavor **5** and **7** (Table I). Conformer **5** is probably best represented as a twist-chair, as indicated earlier, but a twist-chair for **7** will severely diminish the required paramagnetic shift at C(2). A twist-boat for **5** makes the anomeric effect less significant while a twist-boat for **7** reduces the anomeric effect but creates new steric interactions at C(4) and C(7). Anomeric effects for **8**, **9**, **10**, and **11** (Table I) are probably small compared with the highly unfavorable steric interactions for both the chair and twist-chair conformations. Conformations **16**, **17**, **18**, and **19** (Table II) have been rejected on the basis of steric effects and the nmr spectra. The twist-chair conformations must be rejected on the same basis, ref 15. The anomeric effect will disfavor **12**, **13**, and **14**. Twist-chair conformations for **12** and **14** relieve the 4,7-diaxial interactions and the anomeric effects would be less significant. However, conformer **14** accounts very well for the paramagnetic shift at C(5). There is no evidence that only one conformer in any of these compounds predominates. It is not clear how important energetically the anomeric effect is in these compounds. The chemical shift parameters would indicate that the anomeric effect is not strong enough to completely disfavor conformations such as **7** and **14**.

carried out on a Hewlett-Packard F & M 5752 gas chromatograph. The infrared spectra were recorded on a Beckman IR-8 instrument and the absorpton values are reported in microns.

1,3-Dioxacycloheptane, 1,3-dioxacyclohept-4-ene,[25] 2-methyl-1,4-butanediol,[26] and 1,4-pentanediol[27] were prepared as described in the literature.

**1,3-Dioxacycloheptanes. General Procedure.**—The preparation of 4-methyl-1,3-dioxacycloheptane is described as a representative example. A mixture of 10.4 g (0.1 mol) of 1,4-pentanediol, 3.0 g (0.1 mol) of paraformaldehyde, 100 ml of benzene, and 50 mg of *p*-toluenesulfonic acid was refluxed using a Dean–Stark distillation trap. The reaction was terminated when 1.8 ml of water was evolved. The mixture was fractionally distilled at atmospheric pressure to give 10.8 g (89%) of the desired product: bp 105–107° (760 Torr); $n^{25}$D 1.4226; ir (neat) 3.41, 8.46, 8.71, 8.90 μ; *m/e* 116 (parent peak).

**4,7-Dimethyl-1,3-dioxacycloheptane.**—The mixture of isomers had bp 65° (760 Torr) and the yield was 37%. The relative concentrations of the isomers were 78% cis and 22% trans. The diastereoisomers were separated by glpc (8 ft 10% Apiezon–Chromosorb column). The trans isomer was the first peak: $n^{25}$D 1.4269; ir 3.43, 3.49, 7.32, 8.68, 8.87, 9.09, and 9.26 μ; $^1$H nmr $CH_2$(5,6) 8.27 ppm; *m/e* 130 (parent peak).

The cis isomer was the second peak: $n^{25}$D 1.4214; ir (neat) 3.38, 3.44, 7.35, 8.68, 8.87, and 9.06 μ; *m/e* 130 (parent peak).

**2-*tert*-Butyl-4-methyl-1,3-dioxacycloheptane.**—The mixture of isomers was distilled at 35° (1 Torr) and the yield was 72%. The isomers were separated by glpc (8 ft 10% Apiezon–Chromosorb column) and the cis isomer was the first peak: $n^{25}$D 1.4291; ir 3.43, 3.49, 6.74, 8.77, 9.15, and 9.52 μ; $^1$H nmr *tert*-butyl 9.15, $CH_2$ (5,6) multiplet 8.30 ppm; $^{13}$C nmr *tert*-butyl (C) 36.64, *tert*-butyl ($CH_3$) 25.10 ppm; *m/e* 116 (P − *tert*-butyl).

The trans isomer was the second peak: $n^{25}$D 1.4304; ir (neat) 3.41, 3.49, 6.73, 8.82, 9.03, 9.21, and 9.47 μ; $^1$H nmr ($CCl_4$) *tert*-butyl 9.15, $CH_2$(5,6) multiplet 8.33 ppm; $^{13}$C nmr *tert*-butyl (C) 36.21, *tert*-butyl ($CH_3$) 25.36 ppm.

**2-*tert*-Butyl-5-methyl-1,3-dioxacycloheptane.**—The mixture of isomers was isolated in 45% yield: bp 44° (1 Torr); $n^{25}$D 1.4323; ir (neat) 3.38, 3.48, 6.79, 6.90, 7.38, 8.33, and 8.93 μ; $^1$H nmr ($CCl_4$) *tert*-butyl 8.92; $^{13}$C nmr *tert*-butyl (C) 36.57, *tert*-butyl ($CH_3$) 25.17; *m/e* 116 (P − *tert*-butyl).

**4-Methyl-1,3-dioxacycloheptane.**—The product was isolated in 89% yield: bp 105° (760 Torr); $n^{25}$D 1.4226; ir (neat) 3.41, 8.46, 8.71, and 8.90 μ; $^1$H nmr ($CCl_4$) Me 8.83, $OCH_2O$ 5.32, CH 6.15, $OCH_2C$ multiplet at 6.26 ppm; *m/e* 116 (parent peak).

**5-Methyl-1,3-dioxacycloheptane.**—The product was isolated in 44% yield: bp 48° (0.3 Torr); $n^{25}$D 1.4266; ir (neat) 3.41, 8.71, 8.90, and 9.43 μ; $^1$H nmr ($CCl_4$) Me 9.33, $OCH_2O$ 5.37, $CH_2$-$OCH_2O$ multiplet 6.49, CH 8.41, $CH_2$ multiplet 8.35 ppm; *m/e* 116 (parent peak).

**Equilibration of *cis*-2-*tert*-Butyl-4-methyl-1,3-dioxacycloheptane.**—A 50-ml three-neck flask equipped with a condenser, thermometer, and drying tube was charged with 0.54 g of *cis*-2-*tert*-butyl-4-methyl-1,3-dioxacycloheptane, 5 mg of *p*-toluenesulfonic acid, and 10 ml of dry benzene. The mixture was heated to reflux for periods of 8, 24, and 148 hr and analyzed by glpc. The response ratio for the glpc was found to be 1.0. The equilibrium ratios were identical with those found by integrating the C(2) proton areas of the nmr spectra. The cis:trans equilibrium ratio was found to be 1.91:1.

**Equilibration of *trans*-2-*tert*-Butyl-4-methyl-1,3-dioxacycloheptane.**—The procedure for this equilibration was the same as described for the cis isomer. The cis:trans equilibrium ratio was 1.9:1.

**Acknowledgment.**—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

**Registry No.**—1,4-Pentanediol, 626-95-9.

(25) K. C. Branncock and G. Lappin, *J. Org. Chem.*, **21**, 1366 (1956).
(26) R. Rossi, P. Diversi, and G. Ingrosso, *Gazz. Chim. Ital.*, **98**, 391 1968).
(27) C. Fuganti and D. Ghiringhelli, *Gazz. Chim. Ital.*, **99**, 316 (1969).

# Nonclassical Condensed Thiophenes. III. Studies in the Benzo[1,2-c:4,5-c']dithiophene System

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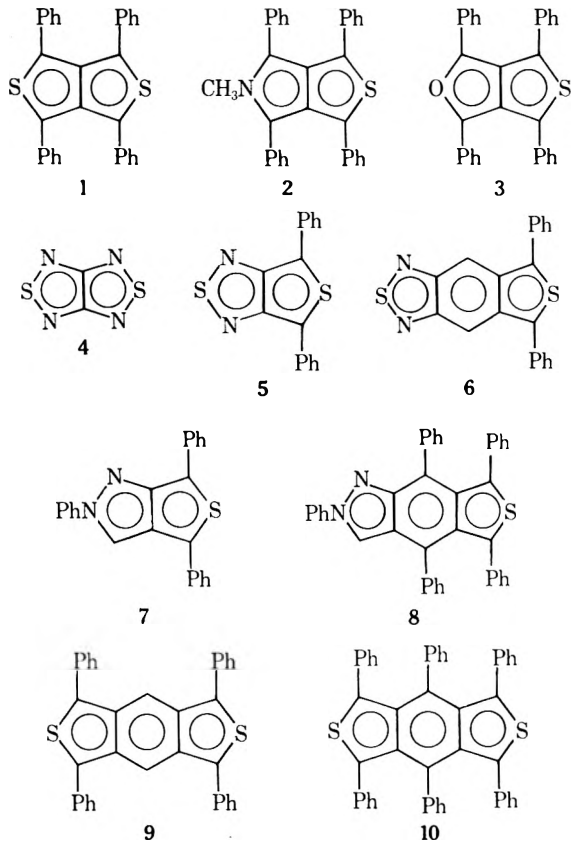
The reaction of phosphorus pentasulfide and xylene with 1,2,4,5-tetrabenzoylbenzene (**13**) and with 1,3,6,7-tetraphenyl-4,5-dibenzoylisothianaphthene (**19**) affords 4,8-dihydro-1,3,5,7-tetraphenylbenzo[1,2-c:4,5-c']dithiophene (**14**) and 4,8-dihydrohexaphenylbenzo[1,2-c:4,5-c']dithiophene (**20**), respectively. Dehydrogenation of **14** and **20** affords diketones **18** and **19**. The intermediacy of **9** and **10** in these transformations is consistent with similar reactions carried out on the recently synthesized compound **10**.

We have reported the synthesis of a number of nonclassical isocondensed thiophenes for which the only uncharged resonance contributors are those structures containing tetracovalent sulfur (**1**–**3**).[1] Other five-membered heterocycles containing tetracovalent sulfur have been reported. In these compounds, at least one sulfur is directly bonded to a heteroatom (**4**–**6**)[2,3] or is in conjugation with a heteroatom whose lone electron pair is not used in π bonding (**7** and **8**).[4] We have now examined an approach to the synthesis of several derivatives (**9** and **10**) of the benzo[1,2-c:4,5-c']dithiophene system which, although unsuccessful, involves the generation of compounds **9** and **10** as reaction intermediates.[5]

Tetrakisbromodurene (**11**)[6] was converted to 1,2,4,5-tetrabenzylbenzene (**12**) by reaction with benzene in the presence of anhydrous ferric chloride.[7] Chromic acid oxidation of **12** afforded the corresponding tetraketone **13** in 70% yield.[8] Treatment of **13** with phosphorus pentasulfide in boiling xylene yielded, as the

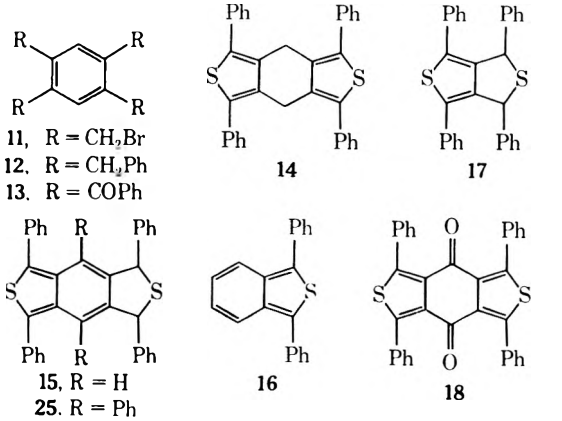
(1) (a) M. P. Cava and G. E. M. Husbands, *J. Amer. Chem. Soc.*, **91**, 3952 (1969), and references cited therein; (b) M. P. Cava and M. A. Sprecker, *ibid.*, **94**, 6214 (1972); (c) for a general review of this work see M. P. Cava, *Int. J. Sulfur Chem.*, in press.
(2) M. Carmack, R. W. Street, and R. Y. Wen, 158th National Meeting of the American Chemical Society, New York, N. Y., Sept 1969, Abstract ORGN-54.
(3) J. D. Bower and R. H. Schlessinger, *J. Amer. Chem. Soc.*, **91**, 6891 (1969).
(4) K. T. Potts and D. McKeough, *J. Amer. Chem. Soc.*, **94**, 6215 (1972).
(5) The isolation of crystalline compound **10** was reported after the writing of the first draft of this paper: K. T. Potts and D. McKeough, *J. Amer. Chem. Soc.*, **95**, 2750 (1973).
(6) W. Reid and H. Boden, *Ber.*, **89**, 2328 (1956).
(7) The preparation of **12** from the less readily available tetrakischlorodurene has been reported: V. G. Dreschler and W. Genill, *J. Prakt. Chem.*, **26**, 24 (1964).
(8) E. Profft, V. G. Dreschler, and H. Oberender, *Chem. Abstr.*, **55**, 2564 (1961).



only isolable product (15%), 4,8-dihydro-1,3,5,7-tetraphenylbenzo[1,2-*c*:3,4-*c*']dithiophene (**14**).

The assigned structure of dithiophene **14** was supported by its spectral properties, which were inconsistent with the anticipated isothianaphthene structure **15**. Compound **15** would be expected to show visible adsorption near 388 nm, which is the observed value for 1,3-diphenylbenzo[*c*]thiophene **16**.[9] The observed uv spectrum for **14**, however, is quite similar to that of 1,3-dihydrotetraphenylthieno[3,4-*c*]thiophene (**17**), which has a similar chromophore. Furthermore, the benzylic protons of **14** appear at $\delta$ 4.05 (four-proton singlet), as compared to the corresponding protons at $\delta$ 5.80 (two proton singlet) observed for the dihydrothienothiophene **17**, a model for the isomeric sulfide **15**.[10]

Attempted dehydrogenation of **14** to the fully aromatic compound **9** by DDQ in boiling *o*-dichlorobenzene resulted in the partial conversion of **14** to di-



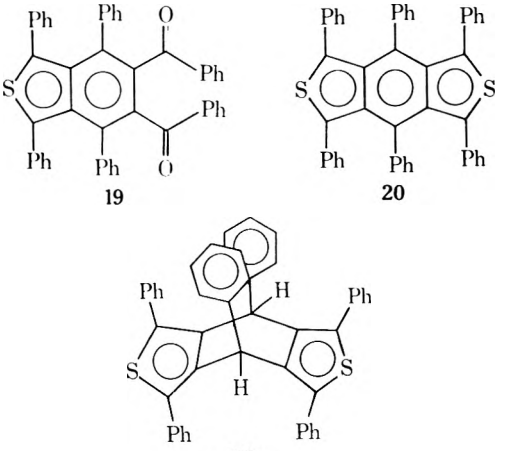
(9) M. P. Cava and J. McGrady, *Chem. Commun.*, 1648 (1968).

(10) M. P. Cava, M. Behforouz, G. E. M. Husbands, and M. Srinivasan, *J. Amer. Chem. Soc.*, **95**, 2561 (1973).

ketone **18**.[11] Similar treatment of degassed solutions of **14** with DDQ and tetracyanoethylene,[12] respectively, resulted only in the isolation of small amounts of starting material.

The reaction of dibenzoylacetylene with thienothiophene **1**[13a] yielded 4,5-dibenzoyltetraphenylisothianaphthene (**19**).[13] When diketone **19** was refluxed for a short time with phosphorus pentasulfide in xylene under nitrogen, the solution exhibited a deep blue color. The blue product, which was apparently benzodithiophene **10**, could not be isolated chromatographically owing to its sensitivity to oxygen. When the original reaction was run for several hours, the blue color slowly faded and the colorless 4,8-dihydrohexaphenylbenzo[1,2-*c*:4,5-*c*']dithiophene (**20**) was formed in 70% yield.[14]

Molecular models indicate that the least hindered configuration of **20** is the *cis*-4,8-diphenyl isomer with the central phenyl groups occupying axial positions as shown in **20a**. The nmr exhibits a singlet at $\delta$ 5.80 (2 H) and two aromatic multiplets at 6.55–6.70 (10 H) and 7.02–7.42 (20 H). The benzylic protons absorb approximately 0.5 ppm downfield from the observed signal in 9,10-dihydro-9,10-diphenylanthracene, indicating that they are deshielded by adjacent phenyl groups.[15] Furthermore, the aromatic adsorptions correspond to four normal and two shielded (axial) phenyl groups, fully consistent with the structure assigned in **20a**.



## Discussion

After the completion of the work described above, other workers reported that the reaction of diketone **19**

(11) DDQ has been used to generate and trap pleiadene as a Diels–Alder adduct: J. W. Loun and A. S. K. Aidoo, *Can J. Chem.*, **49**, 1848 (1971).

(12) Tetracyanoethylene has been used to generate and trap anthracene from 9,10-dihydroanthracene: D. T. Longone and G. L. Smith, *Tetrahedron Lett.*, 205 (1962).

(13) The reaction of tetravalent thiophene derivatives with dienophiles is well documented. See ref 1 and 4.

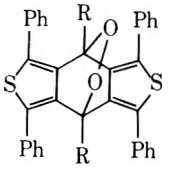
(14) The unsubstituted 4,8-dihydrobenzo[1,2-c:4,5-c']dithiophene has been synthesized by D. W. H. MacDowell and J. C. Wisowaty, *J. Org. Chem.*, **37**, 1712 (1972).

(15) The benzylic protons of 9,10-dihydro-9,10-diphenylanthracene are found at $\delta$ 5.28: W. Theilacker, K. Albrecht, and H. Uffman, *Ber.*, **98**, 428 (1965).

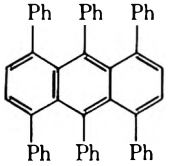
with phosphorus pentasulfide in pyridine afforded **10** as a blue, crystalline solid.[5] We have repeated the preparation of **10** and found that, when **10** was refluxed with phosphorus pentasulfide in xylene, decolorization took place with the formation of the dihydro compound **20**. This reaction is analogous to the reduction of the stable thienothiophene **1** under similar conditions.[10]

The reduction of **9** and **10** could theoretically proceed in either of two ways to yield isothianaphthenes (**25** and **15**) or dithiophenes (**14** and **20**). The formation of the dithiophenes as the only isolable products is a consequence of the greater delocalization energy of two isolated thiophene units as compared with a single isothianaphthene unit.[16] Thus the conversion of diketones **13** and **19** to the reduced dithiophenes provides good evidence for the intermediate formation of benzodithiophenes **9** and **10**.

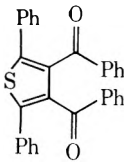
The oxidative dehydrogenation of dihydro compounds **14** and **20** to diketones **18** and **19** is also most readily explained as proceeding *via* benzodithiophenes **9** and **10**. In the tetraphenyl case, dehydrogenation to the fully unsaturated heterocycle **9**, followed by addition of oxygen across the central ring, would yield dione **18** *via* peroxide **21**, a process analogous to the photooxidation of anthracene to anthraquinone.[17] In the hexaphenyl case, the addition of oxygen could proceed reversibly to afford the corresponding peroxide (**22**), as is observed for hexaphenylanthracene (**23**).[18] However, addition of oxygen across either five-membered ring would yield diketone **19** *via* the formation of an unstable thioozonide intermediate.[19] A similar reaction is observed in the oxidation of thienothiophene **1** to the dibenzoylthiophene **24**.[10]



**21**, R = H
**22**, R = Ph



**23**



**24**

With the recent availability of crystalline **10**, we investigated the behavior of this compound under our oxidation conditions. When a benzene solution of **10** was warmed with DDQ in the presence of air, rapid oxidation was observed with the formation of diketone **19**. Indeed, a solution of **10** in xylene was oxidized slowly to **19** by air alone at room temperature.[20]

In view of the high reactivity of the isolable hexaphenyldithiophene **10**, it is not surprising that the less substituted tetraphenyl analog, **9**, would be an even more reactive species. Indeed, an attempted synthesis of **9** from tetrabenzoylbenzene (**13**) and the phosphorus pentasulfide–pyridine reagent gave only a complex mixture of unidentified yellow products under conditions which convert **19** into **10** in virtually quantitative yield.

(16) Dewar has calculated that the resonance energy of thiophene is 6.5 kcal/mol as compared with 9.3 kcal/mol calculated for isothianaphthene: M. J. S. Dewar and N. Trinajstić, *J. Amer. Chem. Soc.*, **92**, 1453 (1970).

(17) A. Schönberg, "Preparative Organic Photochemistry," Springer-Verlag, New York, "N. Y., 1968," p 389.

(18) Y. Lepage and O. Pouchot, *Bull. Soc. Chim. Fr.*, 2342 (1965).

(19) (a) C. N. Skold and R. H. Schlessinger, *Tetrahedron Lett.*, 791 (1970); (b) H. H. Wasserman and W. Streklow, *ibid.*, 795 (1970); (c) J. M. Hoffman, Jr., and R. H. Schlessinger, *ibid.*, 797 (1970).

(20) Both crystalline **10** and its dark blue toluene solution exhibited an esr signal at liquid nitrogen temperatures. A referee has pointed out that this signal (sharp peak, $g = 2.0024$) is almost certainly not that of the thermally excited triplet of **10**, but is most likely due to a small amount of a radical formed by oxidation of the easily oxidized **10**.

## Experimental Section

**General.**—Melting points are uncorrected. Elemental analyses were carried out by Midwest Microlabs, Indianapolis, Ind. Spectra were recorded on a Perkin-Elmer Model 137 ir spectrophotometer, a Perkin-Elmer Model 202 uv–visible spectrophotometer, a Varian Model HA-100D nmr spectrometer, a Perkin-Elmer Model 270B mass spectrometer, and a Varian V-4502 esr spectrometer. Recovered starting materials were identified (ir, tlc) by comparison with authentic samples.

**1,2,4,5-Tetrabenzylbenzene (12).**—A mixture of anhydrous ferric chloride (1.0 g) and **11** (10 g) in benzene (150 ml) was refluxed overnight. Evaporation and chromatography (300 g of neutral grade I alumina, 10% benzene–hexane) yielded **12** as a white, crystalline solid (4.9 g, 48%), mp 132–135° (lit.[7] mp 140°).

**1,2,4,5-Tetrabenzoylbenzene (13).**—The oxidation of **12** to **13** has been previously reported, but without experimental details.[8]

A slurry of **12** (1.79 g, 3.9 mm) and chromium trioxide (3 g, 30 mm) in acetic acid (200 ml) was refluxed for 2 hr. Upon addition of water, a light green powder was recovered. Recrystallization from acetic acid yielded **13** as colorless plates (1.25 g, 70%), mp 259–261° (lit.[8] mp 261–263°).

**1,3,5,7-Tetraphenyl-4*H*,8*H*-benzo[1,2-*c*:4,5-*c'*]dithiophene (14).**—A mixture of tetrabenzoylbenzene (2 g) and phosphorus pentasulfide (2 g) was refluxed ($N_2$) in 200 ml of xylene for 3 hr. The solvent was evaporated *in vacuo* and the residue was dissolved in a small portion of benzene and chromatographed on neutral grade I alumina (100 g) using benzene–hexane (1:10) as the eluent. The resulting yellow solution afforded **14** as colorless prisms (290 mg, 14.5%) after recrystallization from benzene: mp >320°; nmr ($C_4Cl_6$ at 180°) δ 4.05 (s, 4 H), 7.02–7.46 (m, 20 H); uv ($C_2H_4Cl_2$) $\lambda_{max}$ 262 nm (log ε 4.53), 306 (4.50); mass spectrum *m/e* 496 ($M^+$).

*Anal.* Calcd for $C_{34}H_{24}S_2$: C, 82.24; H, 4.87; S, 12.89. Found: C, 82.50; H, 4.98; S, 13.17.

**1,3,5,7-Tetraphenyl-4*H*,8*H*-benzo[1,2-*c*:4,5-*c'*]dithiophene-4,8-dione (18).**—A solution of DDQ (150 mg, 0.5 mmol) and dithiophene **14** (100 mg, 0.2 mmol) was refluxed overnight in 15 ml of *o*-dichlorobenzene. The solvent was removed *in vacuo* and the black residue was dissolved in a small portion of benzene and chromatographed (40 g of grade I neutral alumina). Benzene elution yielded **14** (10 mg, 10%). Chloroform elution afforded an orange solution which upon evaporation and crystallization from benzene yielded yellow crystals of **18** (40 mg, 37.5%): mp >320°; uv ($C_2H_4Cl_2$) $\lambda_{max}$ 275 nm (log ε 4.52), 348 (3.96); ir (KBr) 6.05 μ (C=O); mass spectrum *m/e* 524 ($M^+$).

*Anal.* Calcd for $C_{34}H_{20}S_2O_2$: C, 77.85; H, 3.84. Found: C, 77.60; H, 4.06.

**1,3,4,7-Tetraphenyl-5,6-dibenzoylisothianaphthene (19).**—A solution of thienothiophene **1** (100 mg, 0.23 mmol) and dibenzoylacetylene (61 mg, 0.26 mm) in 25 ml of xylene was refluxed under nitrogen for 6 hr. The xylene was evaporated and a yellow solid was recovered (silica gel ptlc, benzene). Crystallization from benzene yielded yellow needles of **19** (90 mg, 61%): mp 296–297°; uv (dioxane) $\lambda_{max}$ 240 nm (log ε 4.37), 261 (4.58), 280 (4.35), 400 (3.92); ir (KBr) 6.0 μ (C=O); mass spectrum *m/e* 646 ($M^+$).

*Anal.* Calcd for $C_{46}H_{30}SO_2$: C, 85.43; H, 4.68; S, 4.95. Found: C, 85.14; H, 4.81; S, 5.09.

**Hexaphenyl-4*H*,8*H*-benzo[1,2-*c*:4,5-*c'*]dithiophene (20).**—A mixture of isothianaphthene **19** (1.00 g) and $P_2S_5$ (3 g) was refluxed in 100 ml of xylene for 4 hr. The reaction was filtered and the dark residues were extracted with hot benzene. Chromatography (neutral grade I alumina, benzene) yielded white needles of **20** (736 mg, 73.6%): mp 302°; nmr ($CDCl_3$) δ 5.80 (s, S H), 6.55–6.70 (m, 10 H), 7.02–7.42 (m, 20 H); uv ($C_2H_4Cl_2$) $\lambda_{max}$ 233 nm (log ε 4.31), 258 (4.32), 300 (4.34); mass spectrum *m/e* 648 ($M^+$).

*Anal.* Calcd for $C_{46}H_{32}S_2$: C, 85.16; H, 4.97; S, 9.87. Found: C, 84.90; H, 5.12; S, 9.67.

**Reaction of 20 with DDQ.**—A solution of DDQ (71 mg, 0.31 mmol) and 19 (100 mg, 0.155 mm) in 20 ml of *o*-dichlorobenzene was refluxed overnight. The black solution was filtered and evaporated *in vacuo*. Chromatography on grade I neutral alumina yielded 20 (20 mg, 20%) upon benzene elution and 19 (65 mg, 65%) upon chloroform elution.

**Attempted Reaction of 14 with DDQ in the Absence of Oxygen.**—A thoroughly degassed solution of 14 (100 mg, 0.2 mm) and DDQ (150 mg, 0.6 mm) in *o*-dichlorobenzene (15 ml) was heated at 180° overnight in a sealed tube. The dark solution was filtered, reduced in volume (*in vacuo*), and chromatographed on neutral grade I alumina. Benzene elution yielded 14 (20 mg, 28% recovery) as the only isolable compound.

**Reaction of 14 with Tetracyanoethylene in the Absence of Oxygen.**—A degassed solution of 14 (150 mg, 0.3 mmol) and TCNE (96 mg, 0.75 mmol) in *o*-dichlorobenzene (10 ml) was heated in a sealed tube as above. Work-up yielded 14 (110 mg, 73%) as the only product.

**Reaction of 20 with TCNE in the Absence of Air.**—The above procedure carried out using 20 (150 mg, 0.23 mmol) and TCNE (74 mg, 0.58 mmol) resulted in the recovery of 20 (80 mg, 53%).

**Reaction of 20 with DDQ in the Absence of Air.**—Reaction of 20 (100 mg, 0.125 mmol) and DDQ (106 mg, 0.4 mmol) was carried out as above, resulting in the recovery of 28 mg of starting material.

**Reaction of Pure 10 with Phosphorus Pentasulfide and Xylene.**—A mixture of crystalline 10[5] (200 mg), phosphorus pentasulfide (400 mg), and xylene (10 ml) was refluxed for 30 min ($N_2$). Alumina chromatography (benzene) yielded white needles of 20 (145 mg, 73%).

**Oxidation of Pure 10 with DDQ in the Presence of Air.**—A solution of 10 (100 mg) and DDQ (70 mg) in benzene (10 ml) was warmed for 2 min on a steam bath. Chromatography (silica, benzene) yielded diketone 19 (53 mg, 53%).

**Air Oxidation of Pure 10.**—A stream of air was passed through a suspension of 10 (50 mg) in xylene (20 ml) at room temperature for 2 hr with the exclusion of light. Chromatography (silica, benzene) yielded diketone 19 (22 mg, 44%).

**Acknowledgment.**—We thank the National Institutes of Health (for a Predoctoral Fellowship to M. A. Sprecker) and both the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation for partial support of this work.

**Registry No.**—1, 36516-81-1; 10, 41947-66-4; 13, 3867-56-9; 14, 41947-68-6; 18, 41947-69-7; 19, 41947-70-0; 20, 42080-44-4; dibenzoylacetylene, 1087-09-8.

# Seven-Membered Heterocycles. VII. The Synthesis and Properties of 1-Benzothiepin and Its Chlorinated Derivatives[1a,b]

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*Received June 8, 1973*

The reaction of 2,3-dihydro-1-benzothiepin (7) and sulfuryl chloride at low temperatures gave approximately equal amounts of *cis*- (10) and *trans*-4,5-dichloro-2,3,4,5-tetrahydro-1-benzothiepin (11), characterized as their corresponding sulfones 12 and 13, respectively. Chromatography of *cis*-12 or reaction with KOH produced 5-chloro-2,3-dihydro-1-benzothiepin (14). Elimination reactions and nmr spectra were used to assign stereochemistry. When 7 was treated with 1 or 2 equiv of *N*-chlorosuccinimide, 2-chloro- (8) or 2,2-dichloro-2,3-dihydro-1-benzothiepins (19) were formed and converted to their sulfones 18 and 20, respectively. An explanation for the different outcome of these two reactions is presented. The reaction of 8, 19, or 2,4-dichloro-2,3-dihydro-1-benzothiepin (24) with strong base gave 1-benzothiepin (9), 2-chloro-1-benzothiepin (27), and 4-chloro-1-benzothiepin (28). All of these compounds decomposed slowly at room temperature with extrusion of sulfur and formation of naphthalene. The 1-benzothiepins were oxidized to their corresponding sulfones 25, 31, and 32, which were also prepared by dihydrochlorination of the α-chloro sulfones 18, 20, and 2,4-dichloro-2,3-dihydro-1-benzothiepin 1,1-dioxide (33). The thermal stability, mass spectra, and nmr spectra are discussed for both the 1-benzothiepins and their sulfones. The structure of these compounds appears to contain a puckered thiepin ring.

Several literature reports[2-4] have appeared in recent years which described the isolation of substituted 1-benzothiepins 1–6. Most of these compounds 1–4[2,3] were enol derivatives in which the parent enol preferentially tautomerizes to the keto structure. One exception is 6,[4] obtained by mild hydrolysis of 5, which exists in the enol form, most likely owing to intramolecular H bonding with the adjacent methoxycarbonyl group. These 1-benzothiepin derivatives appear to be stable at room temperature but extrude sulfur at elevated temperatures.

In this paper we wish to report the successful synthesis of the parent heterocycle 1-benzothiepin (9) and some of its chlorinated derivatives and their subsequent conversion to the corresponding 1-benzothiepin 1,1-dioxides. These synthetic approaches reflect a general method for producing this class of condensed thiepins.

The key precursor in these synthetic schemes was 2-chloro-2,3-dihydro-1-benzothiepin (8). In a previous publication[5] we examined the use of sulfuryl chloride for the α-chlorination[6] of 2,3-dihydro-1-benzothiepin (7). When these reactants were refluxed in petroleum ether (bp 30–60°) and $NaHCO_3$, the products isolated were sulfur (3–5%), naphthalene (5–10%), and unidentified chlorinated compounds. The origin of sulfur

(1) (a) For part VI in this series see V. J. Traynelis, J. C. Sih, and D. M. Borgnaes, *J. Org. Chem.*, **38**, 2629 (1973). (b) Presented in part before the Organic Division at the 164th National Meeting of the American Chemical Society, New York, N. Y., Aug 1972, and at the 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970. (c) Abstracted from a portion of the Ph.D. Dissertation submitted by Y. Y. in May 1973 and by J. C. S. in Dec 1971 at West Virginia University. (d) Abstracted from a portion of the Ph.D. Dissertation submitted by J. R. L., Jr., in March 1962 at the University of Notre Dame.

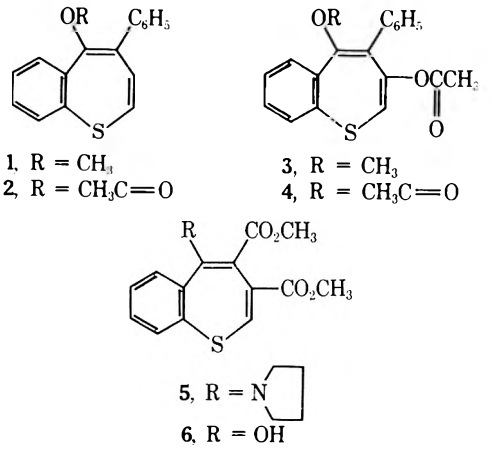
(2) H. Hofmann and H. Westernacher, *Chem. Ber.*, **102**, 205 (1969).

(3) H. Hofmann, B. Meyer, and P. Hofmann, *Angew. Chem., Int. Ed. Engl.*, **11**, 423 (1972).

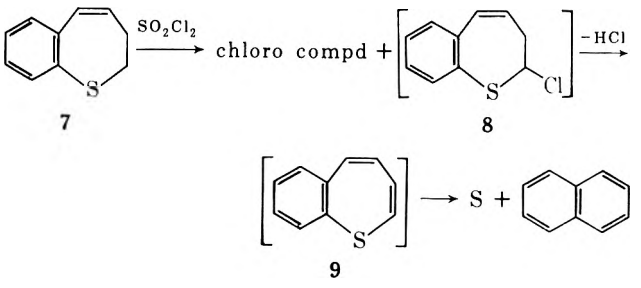
(4) D. N. Reinhoudt and C. G. Kourvenhoven, *Chem. Commun.*, 1233 (1972).

(5) V. J. Traynelis and J. R. Livingston, Jr., *J. Org. Chem.*, **29**, 1092 (1964).

(6) (a) F. G. Bordwell and B. M. Pitts, *J. Amer. Chem. Soc.*, **77**, 572 (1955); (b) L. A. Paquette and L. S. Wittenbrook, *ibid.*, **90**, 6790 (1968).



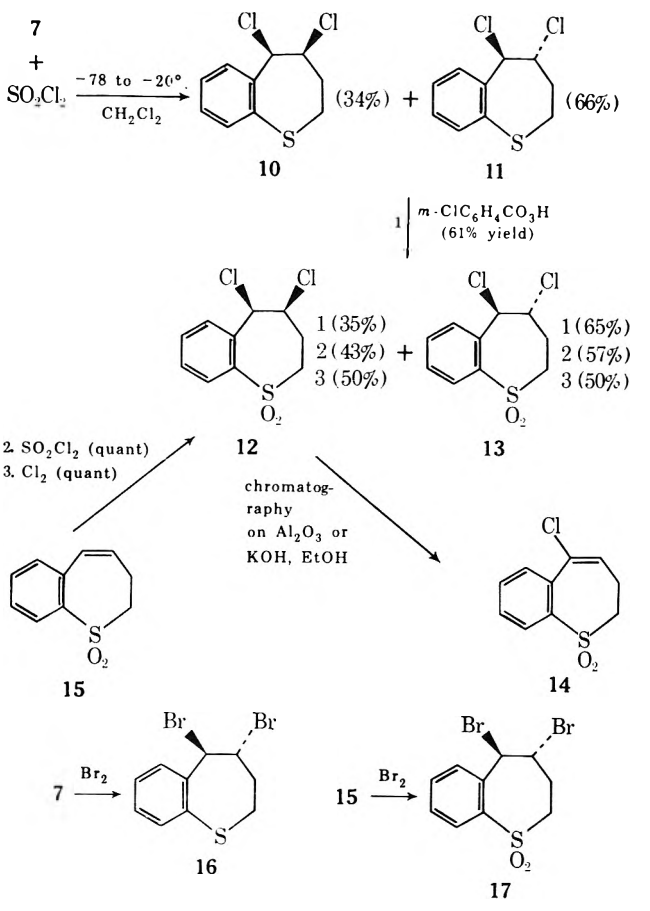

and naphthalene was rationalized by $\alpha$-chlorination of **7** to give **8**, which lost hydrogen chloride to form 1-




benzothiepin (**9**), and subsequent sulfur extrusion in **9** gave sulfur and naphthalene.

The reaction of **7** and sulfuryl chloride was repeated, in which the reagents were mixed at −78° and kept at −20° for 1 week. The major products obtained by this procedure were *cis*- and *trans*-4,5-dichloro-2,3,4,5-tetrahydro-1-benzothiepin (**10** and **11**, respectively) in a ratio of 34:66 cis:trans (determined by nmr analysis). No evidence for the presence of naphthalene was observed. Since these dichloro adducts **10** and **11** were thermally sensitive, they were not separated but the mixture was converted to the corresponding sulfones **12** and **13** (ratio 35:65 cis:trans) for characterization and structural assignment. Column chromatography of the sulfone mixture led to the pure trans isomer **13**, but the cis isomer **12** lost hydrogen chloride and was converted to 5-chloro-2,3-dihydro-1-benzothiepin 1,1-dioxide (**14**). In an independent experiment **12** was exposed to prolonged column chromatography on alumina and gave 91% conversion to **14**. Separation of sulfones **12** and **13** was accomplished by fractional crystallization, and structural assignments for **12**, **13**, and **14** were based on proper elemental analysis and consistent ir and nmr spectra for each.

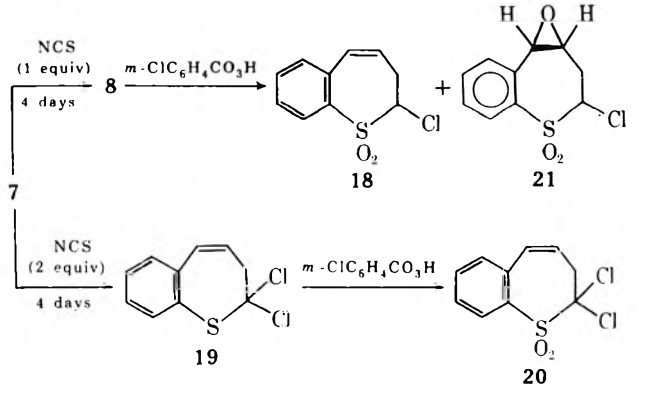
The facile elimination of hydrogen chloride from *cis*-**12** by KOH in ethanol in contrast to the absence of elimination from *trans*-**13** by KOH in ethanol favored the assignment of cis stereochemistry to **12**. These stereochemical assignments are further supported by the coupling pattern of the $C_5$ H, which was a singlet in *cis*-**10** and **12** (dihedral angle between the $C_4$ and $C_5$ hydrogens was approximately 90°) and a doublet in *trans*-**11** and **13** ($J$ = 8 and 7 Hz, respectively, dihedral angle between the $C_4$ and $C_5$ hydrogens was approximately 0° or 180°). Similarly, the nmr spectra of




*trans*-4,5-dibromo-2,3,4,5-tetrahydro-1-benzothiepin (**16**) and its sulfone **17** showed a doublet for the $C_5$ H.

The reaction of **7** and sulfuryl chloride appears to be a simple addition of chlorine to the double bond. Similar cis/trans ratios of chlorine adducts **12** and **13** resulted from the reaction of sulfuryl chloride and chlorine with **15**. Thus the $\alpha$-chlorination of **7** by sulfuryl chloride gave at best a very small amount of **8**[5] and does not provide a useful synthetic pathway to **8**.

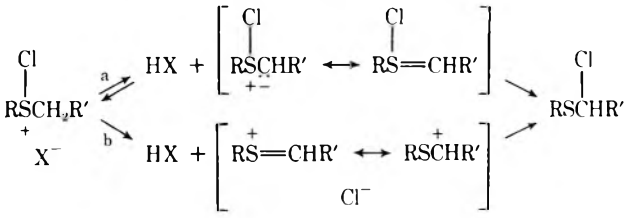
A second approach for the $\alpha$-chlorination of **7** involved reaction with *N*-chlorosuccinimide (NCS).[7] When **7** and 1 or 2 equiv of NCS were allowed to react at room temperature for an extended period of time, 2-chloro- (**8**) or 2,2-dichloro-2,3-dihydro-1-benzothiepin (**19**), respectively, was formed in nearly quantitative yield. Compounds **8** and **19** were each characterized by their ir, nmr, and mass spectral characteristics; how-



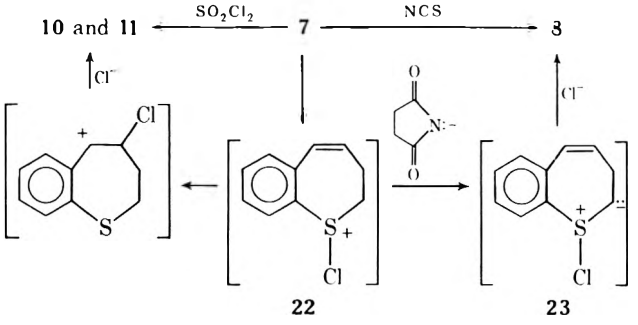

(7) D. L. Tuleen and T. B. Stephens, *J. Org. Chem.*, **34**, 31 (1969).

ever, both were thermally sensitive and were converted to their corresponding sulfones **18** and **20** for further characterization. Sulfones **18** and **20** showed spectral properties consistent with the assigned structures. A second product formed in the oxidation of **8** was assigned the epoxide structure **21** on the basis of elemental analysis and unique nmr and ir spectra.

The observed difference between NCS and sulfuryl chloride in the direction of chlorination of **7** can be rationalized *via* the mechanistic interpretation of Tuleen and Stevens.[7] Path a reflects abstraction of an acidic hydrogen to form an ylide which rearranges to an



$\alpha$-chloro sulfide, while path b represents an ionization to a thiacarbonium ion and chloride ion which recombine to produce the $\alpha$-chloro sulfide. In the reaction of **7** with either NCS or sulfuryl chloride the initial intermediate proposed is the chlorosulfonium ion **22**. Evidence for this species was obtained by hydrolysis to 2,3-dihydro-1-benzothiepin 1-oxide.[8] Formation of $\alpha$-chloro sulfide **8** with NCS parallels path a *via* ylide

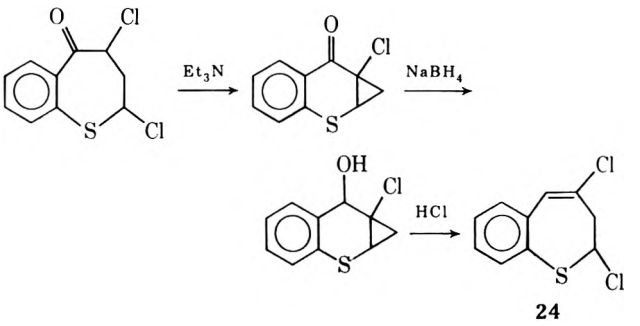


**22** **23**

**23** and may be attributed to the basic succinimidyl anion. However, chloride ion (the anion present in the sulfuryl chloride reaction) is not sufficiently basic to initiate path a and thus **22** should rearrange according to path b. However, in competition with the anticipated path b, which would ultimately form **8**, intermediate **22** can undergo a simple $Cl^+$ transfer to the olefinic center and lead to chlorine adducts **10** and **11**. Apparently the latter pathway, which may be facilitated by a transannular $Cl^+$ transfer, is preferred to the conversion of **22** to **8**.

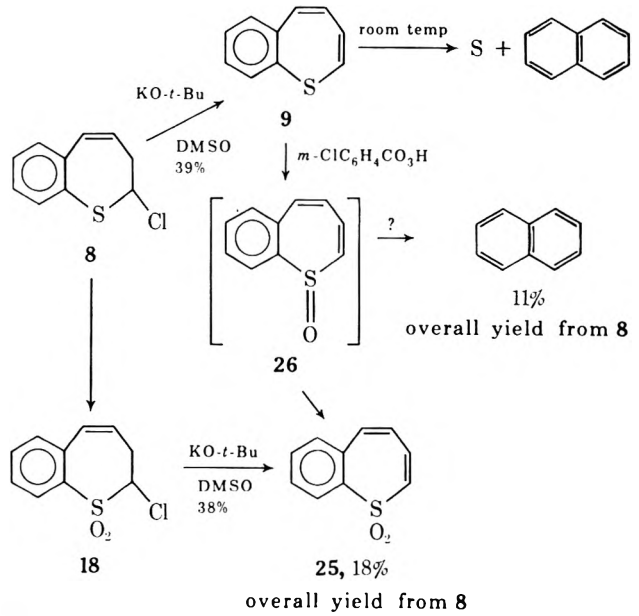
Since 2-chloro-2,3-dihydro-1-benzothiepin (**8**) was now available, we were able to confirm its thermal conversion to sulfur and naphthalene.[5] Although **8** could be refluxed in pentane overnight without change, when **8** was refluxed in $CCl_4$ for 8 days, work-up led to the isolation of naphthalene (29%) and sulfur (14%). These reaction conditions appear more vigorous than those described for the reaction of **7** and sulfuryl chloride; however, in the earlier report[5] sodium bicarbonate was present during reflux of the reaction mixture.

A second avenue for the synthesis of 2-chloro-2,3-dihydro-1-benzothiepins has been described previously and entails the following ring contraction–ring expansion sequence illustrated with the synthesis of 2,4-dichloro-2,3-dihydro-1-benzothiepin (**24**).[1a]



**24**

The reaction of **8** with potassium *tert*-butoxide in DMSO at room temperature for 15 min followed by chromatography on alumina provided a 39% yield of 1-benzothiepin (**9**) as a yellow oil, mp ~15–19°. 1-Benzothiepin decomposed slowly at room temperature (about 3–4 days for complete decomposition) to produce sulfur and naphthalene; however, at Dry Ice temperatures **9** was stable for long periods of time. The structural assignment for **9** was based on the above extrusion reaction and nmr and mass spectral data (to be discussed later), and was confirmed by the oxidation of **9** with *m*-chloroperbenzoic acid to the known 1-benzothiepin 1,1-dioxide (**25**).[9] A second product isolated in the oxidation reaction was naphthalene. The source of naphthalene is most likely from decomposition of 1-benzothiepin, since 1-benzothiepin 1,1-dioxide is thermally quite stable even at temperatures over 200°;[9] however, one cannot exclude the oxidative intermediate, 1-benzothiepin 1-oxide (**26**), as a potential source of naphthalene *via* SO elimination.[10] A third method for



**18** **25**, 18% overall yield from **8**

the synthesis of 1-benzothiepin 1,1-dioxide, which relates back to **8**, involved the dehydrochlorination of 2-chloro-2,3-dihydro-1-benzothiepin 1,1-dioxide (**18**).

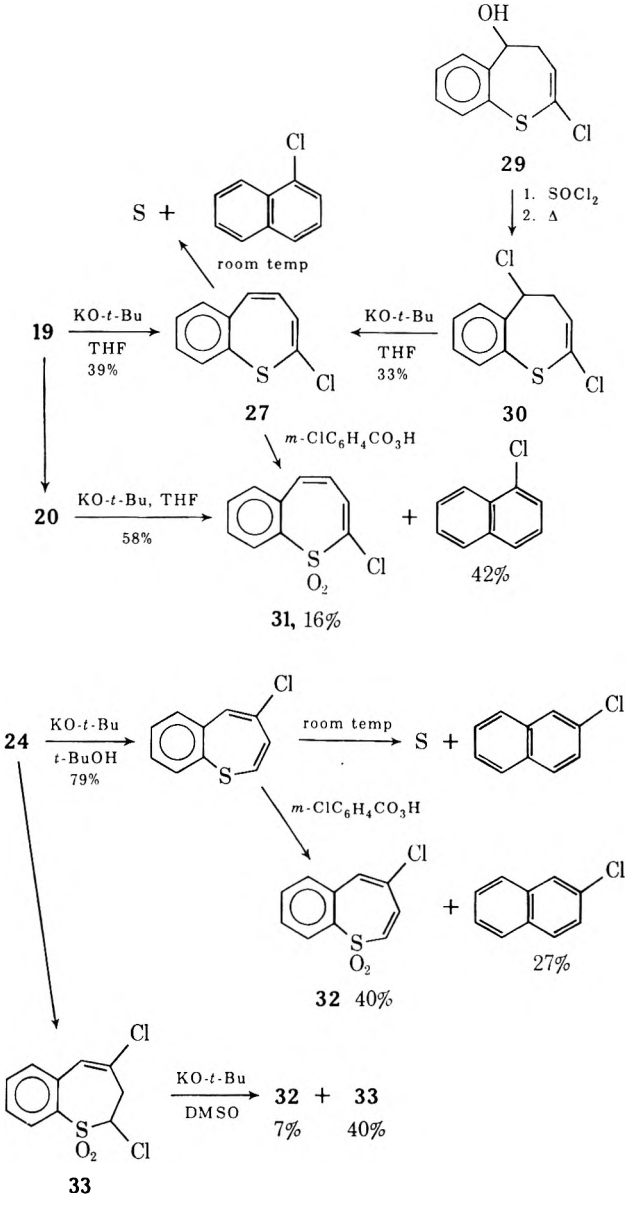
Similarly, the syntheses of 2-chloro-1-benzothiepin

(8) V. J. Traynelis, Y. Yoshikawa,, S. M. Tarka, and J. R. Livingston, Jr., *J. Org., Chem.*, **38**, 3986 (1973).

(9) V. J. Traynelis and R. F. Love, *J. Org. Chem.*, **26**, 2728 (1961).

(10) V. J. Traynelis and D. M. Borgnaes, *J. Org. Chem.*, **37**, 3824 (1972).

(27) and 4-chloro-1-benzothiepin (28) were accomplished by treatment of 2,2-dichloro- (19) and 2,4-dichloro-2,3-dihydro-1-benzothiepin (24), respectively, with strong base. An alternate route to 27 was available by conversion of 2-chloro-5-hydroxy-4,5-dihydro-1-benzothiepin (29)[5] to the 2,5-dichloro derivative 30 followed by dehydrochlorination of 30 with potassium *tert*-butoxide in THF. Structural assignments for 27 and 28 followed the above approach for 9 and included thermal extrusion of sulfur with the formation of α- and β-chloronaphthalene, respectively, nmr and mass spectral data, and the oxidation of 27 and 28 to their corresponding sulfones 31 and 32. The physical and spectral properties of 31 were identical with those reported in the literature.[10] Again the oxidation reaction of the chloro-1-benzothiepins provided the corresponding chloronaphthalenes; however, the yields of the chloronaphthalenes were of such magnitude that one cannot rationalize their total origin from thermal decomposition of 27 or 28 alone. Since the 2- and 4-chloro-1-benzothiepins are also thermally stable, one must again consider the intermediate chloro-1-benzothiepin 1-oxides as potential precursors to the chloronaphthalenes *via* SO extrusion.




An alternate synthesis of 2-chloro- (31) and 4-chloro-1-benzothiepin 1,1-dioxide (32) was accomplished by treatment of 20 and 33 (synthesis described in a prior paper[1a]) with strong base. In the latter case the yield was extremely poor. Thus in summary of the synthetic procedures, the 2-chloro-2,3-dihydro-1-benzothiepins provide an excellent starting point for the synthesis of either 1-benzothiepins or their sulfone derivatives.

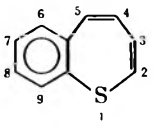
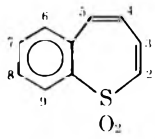
The thermal stability of the 1-benzothiepins 9, 27, and 28 is summarized in Table III. All compounds slowly decompose at room temperature to give sulfur and the corresponding naphthalene, while storage in the cold prolongs the lifetime of these compounds. When these 1-benzothiepins were heated to 60–80°, the sulfur extrusion reaction was very rapid and thus precludes use of elevated reaction temperatures in preparation or purification of these thiepins. Comparison of the thermal stability of the chloro-1-benzothiepins to the parent compound 9 suggests a slight increase in thermal stability when electron-withdrawing groups are present.[4] In contrast to the 1-benzothiepins, their respective sulfones are stable crystalline solids, which in some cases[9] can be heated to 300° for short periods of time. When decomposition does occur, the extrusion of sulfur dioxide and formation of naphthalene is at best minimal.[9]

The mass spectra of 9, 27, and 28 each showed an appreciable intensity for the parent molecule ion (56, 40, and 38%, respectively) and had the corresponding naphthalenes as the base peak. In view of the thermal instability of these 1-benzothiepins the high concentration of the parent molecule ion was somewhat surprising. The naphthalene radical ions can arise by sulfur extrusion of the 1-benzothiepin followed by ionization of the naphthalene or by ionization of the 1-benzothiepins followed by sulfur extrusion. Support for the presence of the latter pathway was found in 1-benzothiepin with the appearance of a metastable peak at *m/e* 102.4. Other important avenues of fragmentation included loss of Cl (in the chloro-1-benzothiepins and chloronaphthalenes) and the loss of CHS (from 1-benzothiepin) or CS and Cl (from the chloro-1-benzothiepins) to form the indenyl radical ion (*m/e* 115). The mass spectral fragmentation of the 1-benzothiepin sulfones 25, 31, and 32 was much simpler than that of the corresponding 1-benzothiepins and showed primarily the parent molecule ion peak and the respective naphthalene radical cations as the base peaks. In the chloro-1-benzothiepin dioxides there was also fragmentation entailing the loss of Cl. Since the 1-benzothiepin dioxides do not thermally extrude sulfur dioxide to any appreciable extent, the origin of the naphthalene base peaks requires sulfur dioxide loss from the parent molecule ion.

Table I shows a comparison of nmr spectral data for the known 1-benzothiepins and their sulfones. The thiepin ring protons appear downfield but are generally located in the olefinic region, except in a few cases where the $C_5$ hydrogen overlaps with aromatic hydrogens. These observations are consistent with the nonaromatic character and nonplanarity of the thiepin ring. The magnitude of the nmr coupling constants across the formal single bonds in fully unsaturated seven-membered cyclic compounds has been correlated to ring

TABLE I

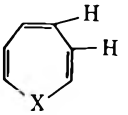
NMR DATA OF 1-BENZOTHIEPINS AND 1-BENZOTHIEPIN DIOXIDES

| Substituent | δ C₂ H | C₃ H | C₄ H | C₆ H |
|---|---|---|---|---|
|  | | | | |
| 1-Benzothiepin | | | | |
| None | 5.81 | 6.12–6.44 | | 6.82–7.31[c] |
| 2-Chloro | | 6.45 | 6.18 | 7.01 |
| 4-Chloro | 5.78 | 6.15 | | 6.8–7.15[a] |
| 5-Methoxy-4-phenyl[b] | 6.04 | 6.40 | | |
| 5-Acetoxy-4-phenyl[b] | 6.08 | 6.43 | | |
| 3,5-Diacetoxy-4-phenyl[b] | 6.0 | | | |
| 3-Acetoxy-5-methoxy-4-phenyl[b] | 5.90 | | | |
| 3,4-Dimethoxycarbonyl-5-(*N*-pyrrolidino)[c] | 7.00 | | | |
|  | | | | |
| 1-Benzothiepin 1,1-Dioxides | | | | |
| None | 6.56–7.00[d] | | | 7.33 |
| 2-Chloro | | 7.10 | 6.70 | 7.56 |
| 4-Chloro | 6.94 | 6.97 | | 7.62–8.41[a] |
| 3,5-Diacetoxy-4-phenyl[b] | 6.75 | | | |

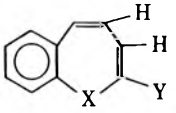
[a] These values represent the $C_5$ H and aromatic hydrogens. [b] See ref 3. [c] See ref 4. [d] These values represent $C_2$ H, $C_3$ H, and $C_4$ H.

TABLE II

COUPLING CONSTANTS IN UNSATURATED SEVEN-MEMBERED RINGS



| X | $J_{H-H}$, Hz | Ref | Angular deviation,[a] deg Stern | Bow |
|---|---|---|---|---|
| $CH_2$[b] | 5.6 | c | 40.5 | 36.5 |
| $SO_2$[d] | 7.0 | *e* | 22.8 | 44.6 |
| $NSO_2C_6H_4Br$-*p*[f] | 5.4 | *g* | 23 | 25[h] |
| C=O[i] | 8.3 | *h* | 0 | 0 |
| C=O, 2-chloro[j] | 9.5 | *h* | 0 | 0 |



| X | Y | $J_{H-H}$, Hz | Ref |
|---|---|---|---|
| $CH_2$ | H | 9.8 | *k* |
| C=O | H | 8.3 | *h* |
| C=O | OH | 9.8 | *h* |
| S (27) | Cl | 6.0 | |
| $SO_2$ (31) | Cl | 7.5 | |

[a] The angles are the deviation of the stern and bow of the boat from the plane of the remaining four carbon atoms. [b] M. Traetteberg, *J. Amer. Chem. Soc.*, 86, 4265 (1964). [c] See ref 13. [d] H. L. Ammon, P. H. Watts, Jr., J. M. Stewart, and W. L. Mock, *J. Amer. Chem. Soc.*, 90, 4501 (1968). [e] See ref 14. [f] I. C. Paul, S. M. Johnson, L. A. Paquette, J. H. Barrett, and R. J. Haluska, *J. Amer. Chem. Soc.*, 90, 5023 (1968). [g] This coupling constant was determined for carboethoxyazepine; see ref 13. [h] See ref 11. [i] K. Kimura, S. Suzuki, M. Kimura, and M. Kubo, *J. Chem. Phys.*, 27, 320 (1957). [j] E. J. Forbes, M. J. Gregory, T. A. Hamor, and D. J. Watkin, *Chem. Commun.*, 114 (1966). [k] See ref 12.

planarity;[11,12] see Table II. The monocyclic systems in Table II show an increase in the coupling constant across the formal single bonds as the ring becomes more planar. The benzocycloheptatrienium ion ($J$ = 9.8 Hz),[12] benzotropone ($J$ = 8.3 Hz),[12] and benzotropolone ($J_{3,4}$ = 9.8 Hz)[11] are proposed as planar structures. In comparison, 2-chloro-1-benzothiepin (**27**) ($J_{3,4}$ = 6.0 Hz) and 2-chloro-1-benzothiepin 1,1-dioxide (**31**) ($J_{3,4}$ = 7.5 Hz) show a marked decrease in the coupling constants and resemble more closely the coupling constants for cycloheptatriene ($J_{2,3}$ = 5.6 Hz)[13] and thiepin 1,1-dioxide ($J_{3,4}$ = 7.0 Hz).[14] Thus one is led to the conclusion that **27** and **31** have a puckered heterocyclic ring most likely in a boat conformation as observed in thiepin 1,1-dioxide. Unfortunately, the nmr spectra (60 MHz) for 1-benzothiepin and its sulfone have a complex multiplet in the region of the $C_3$ H and $C_4$ H absorptions and thus precluded analysis of the coupling constants. However, by analogy to **27**, one would expect 1-benzothiepin to have a boat conformation for the thiepin ring moiety and approach the model used by Hofmann and coworkers[3] in their theoretical treatment of the structure of 1-benzothiepin. Final structural assignments await further physical measurements and X-ray analysis.

## Experimental Section[15]

**Reaction of 2,3-Dihydro-1-benzothiepin with Sulfuryl Chloride.**—Sulfuryl chloride (1.67 g, 12.3 mmol) in $CH_2Cl_2$ (10 ml) was added over a 10-min period to a stirred solution of 2,3-dihydro-1-benzothiepin[9] (2.00 g, 12.3 mmol) in $CH_2Cl_2$ (15 ml) cooled to −78°. After the reaction mixture was stirred at −20° for 1 week, the solvent was removed and gave a mixture of *cis*- (**10**) and *trans*-4,5-dichloro-2,3,4,5-tetrahydro-1-benzothiepin (**11**): nmr ($CDCl_3$) δ 7.70–7.08 (m, 4, aromatic H's), 5.90 [s, 1 (combined weight with $C_5$ H of the trans isomer), $C_5$ H, cis isomer], 5.50 [d, 1 (combined weight with $C_5$ H of the cis isomer), $J_{C_5-C_4}$ = 8 Hz, $C_5$ H, trans isomer], 4.65 [t, 1 (combined weight with $C_4$ H of the trans isomer), $J_{C_4-C_3}$ = 5 Hz, $C_4$ H, cis isomer], 4.34 [double t, 1 (combined weight with the $C_4$ H of the cis isomer), $J_{C_4-C_5}$ = 8, $J_{C_4-C_3}$ = 3.5 Hz, $C_4$ H trans isomer], 3.36–2.07 (m, 4, $-SCH_2CH_2-$, both isomers). Comparison of the $C_5$ H intensities for the cis and trans isomers showed a ratio of 34:66 cis:trans. These halides were thermally sensitive and thus were converted to their sulfones.

After the above mixture of isomers in $CHCl_3$ (10 ml) was added to *m*-chloroperbenzoic acid (5.0 g, 29 mmol) in $CHCl_3$ (30 ml) and the mixture was kept at 0° for 3 days, the reaction mixture was washed with 10% $NaHCO_3$ and $H_2O$ and dried and the solvent was removed. The residue was chromatographed quickly from alumina (Alcoa F-20) using benzene as eluent and gave 2.0 g (61%) of a 35:65 mixture of *cis*- (**12**) and *trans*-4,5-dichloro-2,3,4,5-tetrahydro-1-benzothiepin 1,1-dioxide (**13**). The analysis of the mixture was by nmr using the intensities of the $C_5$ H peaks (δ 6.4 singlet for cis and 5.6 doublet for trans).

(11) D. J. Bertelli, T. G. Andrews, Jr., and P. O. Crews, *J. Amer. Chem. Soc.*, **91**, 5286 (1969).

(12) D. J. Bertelli, J. T. Gerig, and J. M. Herbelin, *J. Amer. Chem. Soc.*, **90**, 107 (1968).

(13) H. Gunther and H. H. Hinrichs, *Tetrahedron Lett.*, 787 (1966).

(14) W. L. Mock, M. P. Williamson, and S. M. Castellano, quoted in A. A. Bothner-By and E. Moser, *J. Amer. Chem. Soc.*, **90**, 2347 (1968).

(15) All melting points and boiling points are uncorrected. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn. Ir spectra were determined on a Beckman IR-8 spectrophotometer, uv spectra were measured on a Bausch and Lomb 505 spectrophotometer, nmr spectra were recorded on a Varian Associates Model HA-60 or Model T-60 spectrometer, and the mass spectra were obtained on a Nuclide Corp. 12-90G high-resolution mass spectrometer.

Column chromatography of 1 g of the sulfone mixture on $Al_2O_3$ (A-540, 120 g) and elution with hexane–$CHCl_3$ (increasing concentration of $CHCl_3$ from 0 to 100%) gave first the trans isomer **13**, mp 165–166°, after two recrystallizations from $CHCl_3$–hexane. Sulfone **13** had identical nmr and ir spectra with those of trans dichloro sulfone **13** described below. The second fraction eluted was recrystallized three times from $CHCl_3$–hexane and was identified as 5-chloro-2,3-dihydro-1-benzothiepin 1,1-dioxide (**14**): mp 131–132°; ir ($CHCl_3$) 1320, 1310, 1155, 1140, 1120 $cm^{-1}$ (>$SO_2$); nmr ($CDCl_3$) $\delta$ 8.19–8.02 (m, 1, $C_9$ H), 7.80–7.30 (m, 3, $C_6$, $C_7$, $C_8$ H's), 6.45 (t, 1, $J_{C_4-C_3}$ = 7.5 Hz, –CCl=CH–), 3.76 (t, 2, $J_{C_2-C_3}$ = 7.0 Hz, $-SO_2CH_2-$), 2.53 (two overlapping t, 2, $J_{C_3-C_4}$ = 7.5, $J_{C_3-C_2}$ = 7.0 Hz, $-SO_2CH_2CH_2-$).

*Anal.* Calcd for $C_{10}H_9ClO_2S$: C, 52.51; H, 3.97; Cl, 15.51. Found: C, 52.40; H, 3.75; Cl, 15.60.

**Reaction of 2,3-Dihydro-1-benzothiepin 1,1-Dioxide with Sulfuryl Chloride.**—After sulfuryl chloride (3.96 g, 29.7 mmol) in $CH_2Cl_2$ (10 ml) was added dropwise to a stirred solution of 2,3-dihydro-1-benzothiepin 1,1-dioxide[9] (5.80 g, 29.7 mmol) in $CH_2Cl_2$ (30 ml) at −5 to −10°, the reaction mixture was stirred for 2 days and poured carefully into 5% $NaHCO_3$ solution, and the $CH_2Cl_2$ layer was separated, washed with $H_2O$, and dried ($MgSO_4$). The solvent was removed and left 7.6 g (99%) of a 43:57 mixture of *cis*- and *trans*-4,5-dichloro-2,3,4,5-tetrahydro-1-benzothiepin 1,1-dioxide. Analysis was made by nmr using the intensities of the $C_5$ H peaks ($\delta$ 6.4 singlet for cis and 5.6 doublet for trans).

Fractional crystallization of the mixture of isomers from $CHCl_3$–hexane gave pure *cis*-**12**, mp 169–170°, ir ($CHCl_3$) 1330, 1320, 1300, 1160, 1130, 1120 $cm^{-1}$ ($-SO_2-$), nmr ($CDCl_3$) $\delta$ 8.15–7.23 (m, 4, aromatic H's), 6.41 (s, 1, $C_5$ H), 4.90 (m, 1, $C_4$ H), 3.47–2.14 (m, 4, $-SO_2CH_2CH_2-$), and pure *trans*-**13**, mp 165–166°, ir ($CHCl_3$), 1330, 1325, 1305, 1160, 1140, 1125 $cm^{-1}$ ($-SO_2-$), nmr ($CDCl_3$) $\delta$ 8.28–8.10 (m, 1, $C_9$ H), 7.73–7.54 (m, 3, $C_6$, $C_7$, $C_8$ H's), 5.59 (d, 1, $J_{C_5-C_4}$ = 7.0 Hz, $C_5$ H), 4.70–4.48 (m, 1, $C_4$ H), 4.08–2.2 (m, 4, $-SO_2CH_2CH_2-$).

*Anal.* Calcd for $C_{10}H_{10}Cl_2O_2S$: C, 45.29; H, 3.80; Cl, 26.74. Found for cis isomer: C, 45.24; H, 3.91; Cl, 26.53. Found for trans isomer: C, 45.45; H, 3.66; Cl, 26.76.

**Addition of Chlorine to 2,3-Dihydro-1 benzothiepin 1,1-Dioxide.**—Chlorine gas was bubbled for 10 min into a solution of 2,3-dihydro-1-benzothiepin 1,1-dioxide[9] (257 mg, 1.32 mmol) in $CH_2Cl_2$ (5 ml) at room temperature and after 10 additional min the excess chlorine was removed under a stream of nitrogen. The solvent was evaporated and gave 352 mg (100%) of a white solid which was shown by nmr to be a 50:50 mixture of *cis*- and *trans*-4,5-dichloro-2,3,4,5-tetrahydro-1-benzothiepin 1,1-dioxide.

**5-Chloro-2,3-dihydro-1-benzothiepin 1,1-Dioxide (14). Method A.**—*cis*-4,5-Dichloro-2,3,4,5-tetrahydro-1-benzothiepin 1,1-dioxide (**12**, 100 mg, 0.38 mmol) was placed on an alumina column (A-540, 20 g) and washed with 250 ml of 1:1 $CHCl_3$–pentane. The recovered solid was starting material.

When **12** was allowed to remain on the column for approximately 9 days, elution from the column as described above gave 78 mg (91%) of crude 5-chloro-2,3-dihydro-1-benzothiepin 1,1-dioxide, mp 122–125°. Recrystallization from $CHCl_3$–pentane gave pure **14**, mp 130–131°, which had an nmr spectrum identical with that of the above sample of **14**.

**Method B.**—A solution of *cis*-4,5-dichloro-2,3,4,5-tetrahydro-1-benzothiepin 1,1-dioxide (160 mg, 0.60 mmol) and KOH (34 mg, 0.62 mmol) in 95% ethanol (18 ml) was stirred at room temperature for 1 hr and the reaction mixture was poured into $H_2O$ (30 ml) and extracted with $CHCl_3$. After the $CHCl_3$ extract was washed with $H_2O$ and dried ($MgSO_4$), the solvent was removed and gave 104 mg (76%) of crude **14**, mp 110–118°. Recrystallization from 95% ethanol gave pure **14**, mp 129–130°, which had an nmr spectrum identical with that of the above sample.

In a second experiment *trans*-4,5-dichloro-2,3,4,5-tetrahydro-1-benzothiepin 1,1-dioxide (160 mg, 0.60 mmol) and KOH (34 mg, 0.62 mmol) in ethanol (18 ml) after 2 hr at room temperature gave 131 mg (82%) of unreacted starting material, mp 163–164°, identified by its nmr.

***trans*-4,5-Dibromo-2,3,4,5-tetrahydro-1-benzothiepin (16).**[16]—Solid pyridinium hydrobromide perbromide[17] (9.95 g, 31 mmol) was added slowly to a solution of 2,3-dihydro-1-benzothiepin[5] (4.8 g, 30 mmol) in $CHCl_3$ (30 ml) at 5°. After the reaction mixture was stirred for 30 min at room temperature, washed with $H_2O$ (50 ml) containing sodium thiosulfate, washed with $H_2O$, and dried ($MgSO_4$), the solvent was removed and the residue (8.13 g, 85%) was recrystallized from ether to give 7.1 g (75%) of *trans*-4,5-dibromo-2,3,4,5-tetrahydro-1-benzothiepin (**16**): mp 107–108°; nmr ($CDCl_3$) $\delta$ 7.58–7.08 (m, 4, aromatic H's), 5.60 (d, 1, $J$ = 6 Hz, $C_5$ H), 4.81 (m, 1, $C_4$ H), 3.27–2.13 (m, 4, $C_2$ H's and $C_3$ H's).

*Anal.* Calcd for $C_{10}H_{10}Br_2S$: C, 37.29; H, 3.13; Br, 49.62. Found: C, 37.40; H, 3.46; Br, 49.39.

***trans*-4,5-Dibromo-2,3,4,5-tetrahydro-1-benzothiepin 1,1-Dioxide (17).**—The procedure described in the literature[9] was repeated and gave 83% *trans*-4,5-dibromo-2,3,4,5-tetrahydro-1-benzothiepin 1,1-dioxide (**17**): mp 197–199° (lit.[9] mp 195–196°); ir ($CHCl_3$) 1325, 1300, 1150, 1120 $cm^{-1}$ ($-SO_2-$); nmr ($CDCl_3$) $\delta$ 8.40–8.07 (m, 1, $C_9$ H), 7.95–7.25 (m, 3, $C_6$, $C_7$, $C_8$ H's), 5.68 (d, 1, $J$ = 5.5 Hz, $C_5$ H), 4.90 (d t, 1, $J_{C_4-C_5}$ = 5.5, $J_{C_4-C_3}$ = 2 Hz, $C_4$ H), 4.15–3.18 (m, 3, $C_2$ H's and $C_3$ $H_b$), 2.70–2.20 (m, 1, $C_3$ $H_a$).

**2-Chloro-2,3-dihydro-1-benzothiepin (8).**—After a mixture of *N*-chlorosuccinimide (5.0 g, 37.4 mmol), 2,3-dihydro-1-benzothiepin[5] (5.1 g, 31.5 mmol), and $CCl_4$ (40 ml) was stirred at ambient temperature for 4 days, the solid was removed by filtration and the solvent was removed under reduced pressure. The residue was exposed to high vacuum and gave 6.19 g (100%) of 2-chloro-2,3-dihydro-1-benzothiepin (**8**): ir (neat) 3030 (m), 2920 (m), 1710 (m), 1465 (m), 1430 (m), 1270 (w), 1190 (w), 1150 (w), 1055 (w), 930 (w), 825 (w), 765 (s), 740 (s), 720 (s), 685 (s), 670 $cm^{-1}$ (s); nmr ($CDCl_3$) $\delta$ 7.70–7.53 (m, 1, $C_9$ H), 7.35–7.04 (m, 3, $C_6$, $C_7$, $C_8$ H's), 6.71 (d, 1, $J_{C_5-C_4}$ = 11 Hz, $C_5$ H), 6.07 (d t, 1, $J_{C_4-C_5}$ = 11, $J_{C_4-C_3}$ = 6.5 Hz, $C_4$ H), 5.62 (d d, 1, $J_{C_2-C_{3a}}$ = 5.3, $J_{C_2-C_{3b}}$ = 10 Hz, –SCHCl–), 2.93 [two d d, 2 (total weight for $C_{3a}$ and $C_{3b}$), $J_{C_{3a}-C_2}$ = 5.3, $J_{C_{3a}-C_4}$ = 6.5, $J_{C_{3a}-C_{3b}}$ = 14 Hz, $-SCHClCH_aH_b-$], 2.50 [two d d, 2 (total weight for $C_{3a}$ and $C_{3b}$), $J_{C_{3b}-C_2}$ = 10, $J_{C_{3b}-C_4}$ = 6.5, $J_{C_{3b}-C_{3a}}$ = 14 Hz, $-SCHClCH_aH_b-$); mass spectrum (70 eV) *m/e* (rel intensity) 196 (4), 161 (31), 160 (43), 147 (29), 134 (100), 128 (71), 119 (29), 117 (27), 115 (31), 106 (34), 105 (36), 91 (77), 77 (44), 63 (21).

Completion of reaction was conveniently followed by nmr. Elemental analysis was performed on the corresponding sulfone (see following experiment).

**2-Chloro-2,3-dihydro-1-benzothiepin 1,1-Dioxide (18).**—2-Chloro-2,3-dihydro-1-benzothiepin (3.39 g, 17.2 mmol) prepared from the reaction of 2,3-dihydro-1-benzothiepin[5] (3.24 g, 20 mmol) and *N*-chlorosuecinimide (3.48 g, 26.2 mmol) was dissolved in $CHCl_3$ (10 ml) and the solution was added dropwise over 15 min to a stirred solution of *m*-chloroperbenzoic acid (8.63 g, 50 mmol) in $CHCl_3$ (40 ml) cooled to −20°. After the reaction mixture was warmed to room temperature and stirred for 1 day, the reaction mixture was filtered and the filtrate was washed with 10% $Na_2CO_3$ solution and $H_2O$ and dried ($MgSO_4$). The solvent was evaporated and gave 3.44 g of a 55:45 mixture of 2-chloro-2,3-dihydro-1-benzothiepin 1,1-dioxide (**18**) and 2-chloro-4,5-oxido-2,3-dihydro-1-benzothiepin 1,1-dioxide (**21**). The analysis of the mixture was made by comparison of the intensities of the nmr peaks for the $C_5$ hydrogen in each compound. Fractional recrystallization from 95% ethanol provided 0.38 g (10%) of pure 2-chloro-2,3-dihydro-1-benzothiepin 1,1-dioxide (**18**): mp 114–115°; ir ($CHCl_3$) 1310, 1145, and 1120 $cm^{-1}$ ($-SO_2-$); nmr ($CDCl_3$) $\delta$ 8.24–8.07 (m, 1, $C_9$ H), 7.76–7.24 (m, 3, $C_6$, $C_7$, $C_8$ H's), 6.66 (d t, 1, $J_{C_5-C_4}$ = 13, $J_{C_5-C_{3a,b}}$ = 1.8 Hz, $C_5$ H), 5.93 (d t, 1, $J_{C_4-C_5}$ = 13, $J_{C_4-C_{3a,b}}$ = 5 Hz, $C_4$ H), 5.13 (t, 1, $J$ = 5 Hz, $-SO_2CHCl-$), 2.45 [two d t, 2 (combined weight for $C_{3a}$ H and $C_{3b}$ H), $J_{C_{3a}-C_4,C_2}$ = 5, $J_{C_{3a}-C_5}$ = 1.8, $J_{C_{3a}-C_{3b}}$ = 19 Hz, $-SO_2CHClCH_aH_b-$], 2.99 [two d t, 2 (combined weight for $C_{3a}$ H and $C_{3b}$ H), $J_{C_{3b}-C_4,C_2}$ = 5, $J_{C_{3b}-C_5}$ = 1.8, $J_{C_{3b}-C_{3a}}$ = 19 Hz, $-SO_2CHClCH_aH_b-$]; mass spectrum (70 eV) *m/e* (rel intensity) 228 (46), 193 (64), 175 (25), 163 (18), 153 (95), 147 (50), 137 (54), 129 (41), 128 (100), 127 (57), 115 (25).

*Anal.* Calcd for $C_{10}H_9ClO_2S$: C, 52.51; H, 3.97; Cl, 15.51. Found: C, 52.85; H, 3.92; Cl, 15.37.

The second product from fractional crystallization with 95% ethanol was further purified by recrystallization from $CHCl_3$ and gave 0.32 g (8%) of 2-chloro-4,5-oxido-2,3,4,5-tetrahydro-1-benzothiepin 1,1-dioxide (**21**): mp 169.5–171°; ir ($CHCl_3$) 3030 (m), 1425 (m), 1330, 1150, 1120 ($-SO_2-$), 950 (w), 870 (w), 800 $cm^{-1}$ (w); nmr ($CDCl_3$) $\delta$ 8.11–7.93 (m, 1, $C_9$ H), 7.80–7.40 (m, 3, $C_6$, $C_7$, $C_8$ H's), 5.03 (d d, 1, $J_{C_2-C_{3a}}$ = 2.5, $J_{C_2-C_{3b}}$ = 5.2 Hz, $-SO_2CHC-$), 4.32 (d, 1, $J_{C_5-C_4}$ = 4.2 Hz, $C_5$ H), 3.71 (two d d, 1, $J_{C_4-C_5}$ = 4.2, $J_{C_4-C_{3a}}$ = 4.4, $J_{C_4-C_{3b}}$ = 9.0 Hz, $C_4$ H),

(16) R. F. Love, Ph.D. Dissertation, University of Notre Dame, 1960.

(17) L. F. Fieser, *J. Chem. Educ.*, **31**, 291 (1954).

2.83 (two d d, 1, $J_{C_{3a}-C_2}$ = 2.5, $J_{C_{3a}-C_4}$ = 4.4, $J_{C_{3a}-C_{3b}}$ = 15.6 Hz, $-SO_2CHClCH_aH_b-$), 1.68 (two d d, 1, $J_{C_{3b}-C_2}$ = 5.2, $J_{C_{3b}-C_4}$ = 9, $J_{C_{3b}-C_{3a}}$ = 15.6 Hz, $-SO_2CHClCH_aH_b-$).

*Anal.* Calcd for $C_{10}H_9ClO_3S$: C, 49.08; H, 3.71; Cl, 14.49; S, 13.10. Found: C, 49.09; H, 3.55; Cl, 14.62; S, 12.85.

The remainder of the product mixture showed the presence of olefin sulfone **18** and epoxide **21** and was not separated further.

**2,2-Dichloro-2,3-dihydro-1-benzothiepin (19).**—Using the procedure described above for the preparation of **8**, the mixture of 2,3-dihydro-1-benzothiepin[5] (4.86 g, 30 mmol) and *N*-chlorosuccinimide (9.6 g, 66 mmol) in $CCl_4$ (40 ml) was stirred with a Hershberg stirrer at room temperature for 4 days and afforded 6.8 (98%) of 2,2-dichloro-2,3-dihydro-1-benzothiepin (**19**) as a brown oil: ir ($CCl_4$) 3060 (w), 1740 (m), 1460 (m), 1425 (m), 1300 (w), 1230 (w), 1200 (w), 1150 (w), 1000 (w), 945 $cm^{-1}$ (w); nmr ($CCl_4$) $\delta$ 7.67–7.08 (m, 4, aromatic H's), 6.90 (d, 1, $J_{C_5-C_4}$ = 11 Hz, $C_5$ H), 6.26 (d t, 1, $J_{C_4-C_5}$ = 11, $J_{C_4-C_3}$ = 7 Hz, $C_4$ H), 3.10 (d, 2, $J$ = 7 Hz, $-SCCl_2CH_2-$); mass spectrum (70 eV) *m/e* (rel intensity) 230 (3), 194 (24), 162 (23), 160 (26), 159 (26), 147 (6), 134 (100), 127 (10), 126 (9), 115 (57). Elemental analysis was performed on the corresponding sulfone (see following experiment).

When the above reaction is performed with ordinary stirring, the reaction time is doubled.

**2,2-Dichloro-2,3-dihydro-1-benzothiepin 1,1-Dioxide (20).**—A solution of 2,2-dichloro-2,3-dihydro-1-benzothiepin (2.31 g, 10 mmol) in $CHCl_3$ (15 ml) was added over 10 min to a stirred solution of *m*-chloroperbenzoic acid (3.46 g, 20 mmol) in $CHCl_3$ (15 ml) maintained at −5° and the reaction mixture was stirred at room temperature overnight. The reaction mixture was processed as described in the preparation of **18** and gave, after recrystallization from $CHCl_3$–hexane, 1.16 g (44%) of 2,2-dichloro-2,3-dihydro-1-benzothiepin 1,1-dioxide (**20**): mp 164–165°; ir ($CHCl_3$) 1330, 1310, 1210, 1155, 1130 $cm^{-1}$ ($-SO_2-$); nmr ($CDCl_3$) $\delta$ 8.33–8.13 (m, 1, $C_9$ H), 7.76–7.20 (m, 3, $C_6$, $C_7$, $C_8$ H's), 6.65 (d t, 1, $J_{C_5-C_4}$ = 13, $J_{C_5-C_3}$ = 2 Hz, $C_5$ H), 5.83 (d t, 1, $J_{C_4-C_5}$ = 11, $J_{C_4-C_3}$ = 5 Hz, $C_4$ H), 3.64 (d d, 2, $J_{C_3-C_4}$ = 5, $J_{C_3-C_5}$ = 2 Hz, $-SO_2CCl_2CH_2-$); mass spectrum (70 eV) *m/e* (rel intensity) 26.4 (19), 262 (26), 245 (7), 227 (16), 209 (24), 181 (33), 162 (42), 153 (100), 137 (59), 128 (56), 127 (53).

*Anal.* Calcd for $C_{10}H_8Cl_2O_2S$: C, 45.80; H, 2.69; Cl, 27.05. Found: C, 45.66; H, 2.92; Cl, 27.08.

**1-Benzothiepin (9).**—A solution of powdered potassium *tert*-butoxide (0.672 g, 6 mmol) in dimethyl sulfoxide (10 ml) was added in several portions to a solution of 2-chloro-2,3-dihydro-1-benzothiepin (0.985 g, 5 mmol) in dimethyl sulfoxide (10 ml) at room temperature. After the reaction mixture was stirred for 15 min at room temperature, the reddish-black solution was poured into $H_2O$ (30 ml) and the aqueous solution was extracted with $CHCl_3$ (30 ml). The extract was washed with $H_2O$, dried ($MgSO_4$), and concentrated *in vacuo* (below room temperature). The residual heavy black oil (0.80 g) was chromatographed on alumina (A-540, 40 g) with Skelly F as the eluent and the combined yellow fractions gave 308 mg (38.5%) of 1-benzothiepin (**9**) as a yellow liquid: solidifies between 15 and 20°; ir ($CHCl_3$) 3060 (m), 3000 (s), 1575 (m), 1470 (s), 1430 (s), 1330 (s), 1290 (w), 1255 (s), 1120 (w), 1060 (m), 1030 (w), 940 (w), 875 (m), 665 $cm^{-1}$ (s); nmr ($CDCl_3$) $\delta$ 7.31–6.82 (m, 5, aromatic H's and $C_5$ H), 6.44–6.12 (m, 2, $C_4$ H and $C_3$ H), 5.81 (d, 1, $J$ = 8.5 Hz, $C_2$ H); mass spectrum (70 eV) *m/e* (rel intensity) 160 (56), 134 (12), 129 (22), 128 (100), 116 (16), 115 (40), 102 (7).

The work-up process must be performed rapidly to avoid thermal decomposition of 1-benzothiepin to naphthalene and sulfur.

**1-Benzothiepin 1,1-Dioxide (25). Method A.**—To a stirred solution of 2-chloro-2,3-dihydro-1-benzothiepin 1,1-dioxide (**18**, 0.19 g, 0.83 mmol) in dimethyl sulfoxide (3 ml) was added at room temperature two portions of powdered potassium *tert*-butoxide (200 mg, 1.16 mmol). After the reaction mixture was stirred for 15 min at room temperature, the dark green solution was poured into $H_2O$ (20 ml) and $CHCl_3$ (20 ml) and the $CHCl_3$ layer was separated, washed with $H_2O$, and dried ($MgSO_4$). The $CHCl_3$ was removed under reduced pressure and left 0.06 g (38%) of crude 1-benzothiepin 1,1-dioxide, mp 131–134°. Recrystallization of the crude product gave pure **25**: mp 140–141° (lit.[9] mp 140–141°); ir ($CHCl_3$) 3015 (w), 1610 (w), 1575 (w), 1545 (w), 1465 (w), 1335, 1305, 1160, 1150, 1120 ($-SO_2-$), 1060 (m), 785 (w), 680 $cm^{-1}$ (w); nmr ($CDCl_3$) $\delta$ 8.27–8.07 (m, 1, $C_9$ H), 7.81–7.53 (m, 3, $C_6$, $C_7$, $C_8$ H's), 7.33 (d, 1, $J$ = 13 Hz, $C_5$ H), 7.00–6.56 (m, 3, $C_2$ H, $C_3$ H, $C_4$ H); mass spectrum (70 eV) *m/e* (rel intensity) 192 (26), 163 (10), 149 (14), 147 (10), 129 (15), 128 (100), 115 (13), 102 (13). A mixture melting point with an authentic sample[9] of **25** was not depressed.

**Method B.**—Crude 1-benzothiepin obtained from the reaction of 2,3-dihydro-1-benzothiepin (5.0 g, 30.9 mmol) and *N*-chlorosuccinimide (4.6 g, 34.4 mmol) followed by dehydrochlorination with potassium *tert*-butoxide (3.7 g, 36 mmol) was dissolved in $CHCl_3$ (30 ml) and the solution was added over a 15-min period to a solution of *m*-chloroperbenzoic acid (12.0 g, 59.1 mmol) in $CHCl_3$ (20 ml) maintained at −50°. The reaction mixture was stirred at −50° for 30 min and allowed to remain at 0° for 3 days. After the reaction mixture was filtered and the solvent was removed, a quick chromatography on alumina of the black, viscous residue (6.1 g) with elution by benzene gave 2.9 g of a black paste. A second chromatography of the 2.9 g of black material on alumina (A-540, 90 g) gave, upon elution with $CHCl_3$–Skelly F (1:1 v/v) first 0.45 g (11% based on 2,3-dihydro-1-benzothiepin) of naphthalene, mp 70–73° (sublimed, mp 79–80°), ir and nmr identical with those of an authentic sample, and second 1.1 g (18% based on 2,3-dihydro-1-benzothiepin) of 1-benzothiepin 1,1-dioxide, mp 134–136°. Recrystallization of the crude product gave pure **25**, mp 140–141°. A mixture melting point with an authentic sample was not depressed and the ir and nmr spectra were identical with those of an authentic sample.

**Pyrolysis of 2-Chloro-2,3-dihydro-1-benzothiepin.**—A solution of 2-chloro-2,3-dihydro-1-benzothiepin (**8**) (1.5 g, 7.6 mmol) in $CCl_4$ (10 ml) was refluxed for 9 days, after which time the nmr spectrum of the reaction mixture showed the absence of **8**. The solvent was removed under reduced pressure and the residual dark oil (1.4 g) was chromatographed on alumina (A-540, 150 g), and elution with Skelly F gave 407 mg of a white solid. A second chromatography of the white solid on alumina (A-540, 50 g) and elution with Skelly F gave 33 mg (14%) of sulfur, mp 112–121°. Recrystallization from ethyl acetate afforded 15 mg (7%) of sulfur, mp 118–120°, which gave no depression in melting point when mixed with an authentic sample. Naphthalene (292 mg, 29%), mp 79–80°, was eluted next. A mixture melting point with an authentic sample was not depressed and the nmr spectra of the two samples were identical.

**2-Chloro-1-benzothiepin (27). Method A.**—A solution of potassium *tert*-butoxide (3.55 g, 31.7 mmol) in tetrahydrofuran (35 ml) was added dropwise over a 40-min period to a stirred solution of 2,2-dichloro-2,3-dihydro-1-benzothiepin (6.9 g, 30 mmol) in tetrahydrofuran (25 ml) at 3°. The mixture was allowed to come to room temperature and stirred vigorously for 4 hr. After the reaction mixture was concentrated (below 25°) under reduced pressure, $H_2O$ (20 ml) was added and the aqueous solution was extracted with Skelly F. The extract was washed with $H_2O$ and dried ($MgSO_4$) and the solution was chromatographed on alumina (A-540, 100 g) using Skelly F as the eluent. The initial yellow-colored fractions were combined and rapid removal of the solvent (below 15°) under reduced pressure gave 2.25 g (39%) of 2-chloro-1-benzothiepin (**27**) as a yellow oil: ir ($CCl_4$) 3070 (m), 3030 (m), 1920 (w), 1810 (w), 1710 (w), 1680 (w), 1610 (w), 1570 (m), 1470 (m), 1430 (m), 1300 (w), 1280 (w), 1260 (w), 1220 (w), 1180 (w), 1120 (w), 1060 (w), 1030 (w), 1000 (w), 960 (w), 910 (s), 860 (m), 820 (m), 710 $cm^{-1}$ (m); nmr ($CDCl_3$) $\delta$ 7.34–7.18 (m, 4, aromatic H's), 7.01 (d, 1, $J$ = 11.5 Hz, $C_5$ H), 6.45 (d, 1, $J$ = 6 Hz, $C_3$ H), 6.18 (d d, 1, $J_{C_4-C_5}$ = 11.5, $J_{C_4-C_3}$ = 6 Hz, $C_4$ H); mass spectrum (70 eV) *m/e* (rel intensity) 196 (16), 194 (40), 164 (38), 162 (100), 159 (29), 128 (16), 127 (31), 126 (17), 115 (31), 105 (17).

**Method B.**—Redistilled thionyl chloride (2.4 g, 0.02 mol) in $CH_2Cl_2$ (10 ml) was added dropwise over 45 min to a refluxing solution of 2-chloro-5-hydroxy-4,5-dihydro-1-benzothiepin[5] (**29**, 3.0 g, 0.013 mol) and the reaction mixture was refluxed for 3 hr. After the $CH_2Cl_2$ was removed, mixed octanes (25 ml) were added and the solution was refluxed for 16 hr. The solvent was removed under reduced pressure and left a residue of 2.6 g (87%) of crude 2,5-dichloro-4,5-dihydro-1-benzothiepin (**30**); ir (neat) showed the absence of OH.

The sample of 2,5-dichloro-4,5-dihydro-1-benzothiepin prepared as described above from **29** (2.00 g, 0.0087 mol) and thionyl chloride (1.60 g, 0.013 mol) was dissolved in THF (10 ml) and to this solution was added dropwise a solution of potassium *tert*-butoxide (0.98 g, 0.0087 mol) in THF (10 ml). After the reaction mixture remained at room temperature for 6 hr, Skelly B (80 ml) was added and the mixture was filtered through Filter-Cel. The material insoluble in THF was dissolved in $H_2O$ and acidified with nitric acid and upon treatment with silver nitrate gave an

81% yield of silver chloride. The Skelly B was removed from the above filtrate and the black residue was chromatographed on alumina (Alcoa F-20, 120 g), Elution with Skelly F gave 551 mg (33%) of 2-chloro-1-benzothiepin as a yellow oil. The infrared spectrum of this material was comparable with that of the sample from method A.

Pyrolysis of this sample produced α-chloronaphthalene (85%) and sulfur (19%); see the last experiment.

**2-Chloro-1-benzothiepin 1,1-Dioxide (31). Method A.**—Powdered potassium *tert*-butoxide (67 mg, 0.65 mmol) was added in one portion to a solution of 2,2-dichloro-2,3-dihydro-1-benzothiepin 1,1-dioxide (132 mg, 0.5 mmol) in tetrahydrofuran (10 ml), and, after the mixture was stirred at room temperature for 3 hr, it was poured into $H_2O$. The aqueous solution was extracted with $CHCl_3$, and the extract was washed with $H_2O$ and dried ($MgSO_4$). The solvent was removed under reduced pressure and left 85 mg of a residue. Recrystallization of the solid from 95% ethanol gave 57 mg (58%) of 2-chloro-1-benzothiepin 1,1-dioxide: mp 139–140° (lit.[18] mp 139.5–140°); nmr ($CDCl_3$) δ 8.28–8.05 (m, 1, $C_9$ H), 7.86–7.70 (m, 3, $C_6$, $C_7$, $C_8$ H's), 7.56 (d, 1, $J$ = 12 Hz, $C_5$ H), 7.10 (d, 1, $J$ = 7.5 Hz, $C_3$ H), 6.70 (d d, 1, $J_{C_4-C_5}$ = 12, $J_{C_4-C_3}$ = 7.5 Hz, $C_4$ H); mass spectrum (70 eV) *m/e* (rel intensity) 228 (16), 226 (35), 181 (6), 164 (45), 162 (100), 127 (47), 126 (27), 115 (14). A mixture melting point with an authentic sample[18] of **31** was not depressed.

Method B.—A solution of 2-chloro-1-benzothiepin (584 mg, 3 mmol) in $CHCl_3$ (5 ml) was added dropwise to a stirred suspension of *m*-chloroperbenzoic acid (2.07 g, 12 mmol) in $CHCl_3$ (20 ml) maintained at −20°. The reaction mixture was allowed to come to room temperature and stirred for 10 hr, and the insoluble *m*-chlorobenzoic acid was filtered. The filtrate was washed with 10% $NaHCO_3$ solution and $H_2O$ and dried ($MgSO_4$). After the solvent was removed under reduced pressure, the residue (780 mg) was chromatographed on alumina (A-540, 120 g). Elution with pentane gave 203 mg (42%) of α-chloronaphthalene, identified by its nmr spectrum, contaminated with some sulfur. Further elution with 20–100% of $CHCl_3$–pentane gave 112 mg (16%) of crude 2-chloro-1-benzothiepin 1,1-dioxide, mp 132–134°, which after recrystallization from 95% ethanol afforded 70 mg (10%) of pure **31**, mp 139–140° (lit.[18] mp 139.5–140°). A mixture melting point with an authentic sample was not depressed and the spectral properties of this sample were identical with those from method A.

**4-Chloro-1-benzothiepin (28).**—A solution of 2,4-dichloro-2,3-dihydro-1-benzothiepin[1a] (500 mg, 2.16 mmol) in *tert*-butyl alcohol (14 ml) was added in one portion to a solution of potassium *tert*-butoxide (246 mg, 2.20 mmol) in *tert*-butyl alcohol (24 ml). After the reaction mixture was stirred for 50 min, the turbid orange solution was poured into $H_2O$ (150 ml), the aqueous solution was extracted with $CHCl_3$, and the extract was washed with $H_2O$ and dried ($MgSO_4$). The solvent was removed under vacuum and gave 330 mg (79%) of 4-chloro-1-benzothiepin (**28**) as a yellow oil: ir ($CHCl_3$) 3070 (w), 3005 (w), 1610 (s), 1470 (s), 1370 (m), 1125 (m), 1005 (s), 945 (w), 890 (s), 855 (m), 840 $cm^{-1}$ (m); nmr ($CDCl_3$) δ 7.5–6.8 (m, 5, aromatic H's and $C_5$ H), 6.15 (d, 1, $J_{C_3-C_2}$ = 9 Hz, $C_3$ H), 5.78 (d, 1, $J_{C_2-C_3}$ = 9 Hz, $C_2$ H); mass spectrum (70 eV) *m/e* (rel intensity) 196 (13), 194 (39), 164 (52), 162 (100), 159 (39), 127 (61), 126 (35), 115 (45), 105 (44). 4-Chloro-1-benzothiepin can be further purified by chromatography on alumina with elution with Skelly F.

When a solution of 2,4-chloro-2,3-dihydro-1-benzothiepin (360 mg, 1.56 mmol) and potassium *tert*-butoxide (180 mg, 1.60 mmol) in *tert*-butyl alcohol (12 ml) was heated at 70° for 90 min and processed as above, chromatography on Alcoa F-20 (20 g) with elution by Skelly F provided 105 mg (40%) of β-chloronaphthalene, mp 56–57°. A mixture melting point with an authentic sample was not depressed.

A reaction of 2,4-dichloro-2,3-dihydro-1-benzothiepin and LiCl in DMF at 65° for 60 min also resulted in the formation of β-chloronaphthalene (22% yield).

**4-Chloro-1-benzothiepin 1,1-Dioxide (32). Method A.**—The reaction mixture of 2,4-dichloro-2,3-dihydro-1-benzothiepin 1,1-dioxide[1a] (1.00 g, 4.41 mmol) and potassium *tert*-butoxide (0.49 g, 4.41 mmol) in DMSO (30 ml) was stirred for 15 min and processed as described in the preparation of 1-benzothiepin 1,1-dioxide (method A) and gave 0.40 g (40%) of crude 2,4-dichloro-2,3-dihydro-1-benzothiepin 1,1-dioxide, mp 174–183°, and 0.17 g (17%) of crude 4-chloro-1-benzothiepin 1,1-dioxide (**32**), mp 139.5–143°. Chromatography of 0.072 g of the latter product on alumina (A-540, 40 g) gave a mixture which was recrystallized from absolute ethanol to give 0.03 g (7% corrected from total crude yield) of pure **32**: mp 154–155°; ir ($CHCl_3$) 1320 and 1150 $cm^{-1}$ ($-SO_2-$); nmr ($CDCl_3$) δ 8.41–8.10 (m, 1, $C_9$ H), 7.90–7.62 (m, 3, $C_6$, $C_7$, $C_8$ H's and $C_5$ H), 6.97 [d, 2 (total weight of $C_2$ H and $C_3$ H), $J_{C_3-C_2}$ = 14 Hz, $C_3$ H], 6.94 [d, 2 (total weight of $C_3$ H and $C_2$ H), $J_{C_2-C_3}$ = 14 Hz, $C_2$ H]; mass spectrum (70 eV) *m/e* (rel intensity) 228 (6), 226 (22), 164 (37), 162 (100), 127 (38).

*Anal.* Calcd for $C_{10}H_7ClO_2S$: C, 52.98; H, 3.11; Cl, 15.64. Found: C, 52.58; H, 3.00; Cl, 15.70.

**Method B.**—A solution of 4-chloro-1-benzothiepin (281 mg, 1.45 mmol) in $CHCl_3$ (3 ml) was added in one portion to a stirred suspension of *m*-chloroperbenzoic acid (560 mg, 3.26 mmol) in $CHCl_3$ (7 ml) at −18°. The reaction mixture was stirred at 10° for 21 hr and filtered, and the $CHCl_3$ filtrate was washed with $Na_2CO_3$ and $H_2O$ and dried ($MgSO_4$). After the solvent was removed under vacuum, the residue (174 mg) was treated with Skelly F (2 × 3 ml) and gave 91 mg (40%) of 4-chloro-1-benzothiepin 1,1-dioxide (**32**), mp 145–155°. Recrystallization of the crude solid from 95% ethanol–benzene gave pure **32**, mp 155–157° dec. The ir spectrum of this sample was identical with that of **32** from method A.

Concentration of the Skelly F washings afforded 63 mg (27%) of β-chloronaphthalene identified by comparison of its ir spectrum with that of an authentic sample.

**Thermal Decomposition of the 1-Benzothiepins. Method A.**—Approximately 1 *M* solutions of 1-benzothiepin, 2-chloro-1-benzothiepin, and 4-chloro-1-benzothiepin in $CCl_4$ were prepared and the decomposition to sulfur and the corresponding naphthalenes was monitored by nmr spectroscopy at room temperature. The disappearance with time of the 1-benzothiepins is recorded in Table III.

TABLE III

THERMAL DECOMPOSITION OF 1-BENZOTHIEPINS[a]

| | Benzothiepin remaining, % | | |
|---|---|---|---|
| Time, days | 1-Benzothiepin | 2-Chloro-1-benzothiepin | 4-Chloro-1-benzothiepin |
| 4.5 hr | 80 | 91 | 80 |
| 1 | 35 | 67 | |
| 2 | 12 | 47 | 22 |
| 3 | 3 | 33 | 15 |
| 4 | 0 | 25 | 5 |
| 5 | | 16 | 0 |
| 9 | | 7 | |
| 11 | | 0 | |

[a] See Thermal Decomposition of 1-Benzothiepin, Method A. When 2-chloro-1-benzothiepin was stored in the cold, very little decomposition occurred over a 3-month period.

After the decomposition of 1-benzothiepin (113 mg, 0.59 mmol) was complete, the solvent was evaporated and the resulting solid was triturated with pentane (2 × 10 ml). The pentane was evaporated and left 0.069 g (78%) of naphthalene, mp 63–65°. The nmr spectrum was identical with that of an authentic sample.

A similar work-up from the decomposition of 2-chloro-1-benzothiepin (0.113 g, 0.59 mmol) gave 0.05 g (68%) of sulfur, mp 118–119°, mmp with authentic sample 118–119°, which precipitated from the residue after removal of $CCl_4$. The pentane solution of the residual oil was dried and upon removal of the solvent gave 0.103 g (93%) of α-chloronaphthalene; ir and nmr spectra were identical with those of an authentic sample.

**Method B.**—2-Chloro-1-benzothiepin (551 mg, 2.83 mmol) was heated neat in a free flame for a few seconds and the pyrolysate was chromatographed on alumina (Alcoa F-20, 60 g). Elution with pentane gave 17 mg (19%) of sulfur, mp 120–121°, mmp with an authentic sample 120–121°, and 389 mg (85%) of α-chloronaphthalene, ir spectrum identical with that of an authentic sample.

A solution of 4-chloro-1-benzothiepin (172 mg, 0.89 mmol) in benzene (15 ml) was refluxed for 30 min, the solvent was removed under vacuum, and the residue (160 mg) was chromatographed on alumina (Alcoa F-20, 20 g). Elution with Skelly F gave 137 mg of β-chloronaphthalene, mp 56–57°. A mixture melting point with an authentic sample was not depressed and the ir spectrum was identical with that of an authentic sample.

(18) V. J. Traynelis and D. M. Borgnaes, *J. Org. Chem.*, **37**, 3824 (1972).

Registry No.—7, 21609-62-1; 8, 41887-72-3; 9, 264-82-4; 10, 41887-74-5; 11, 41887-75-6; 12, 41887-76-7; 13, 41887-77-8; 14, 41887-78-9; 15, 41887-79-0; 16, 41887-80-3; 17, 41887-81-4; 18, 41887-82-5; 19, 41887-83-6; 20, 41887-84-7; 21, 41887-85-8; 25, 41887-86-9; 27, 41887-87-0; 28, 41887-88-1; 29, 41887-89-2; 30, 41887-90-5; 31, 36287-21-5; 32, 41887-92-7.

# Seven-Membered Heterocycles. VIII. 1-Benzothiepin Sulfoxides and a Convenient Synthesis of Sulfoxides[1,2]

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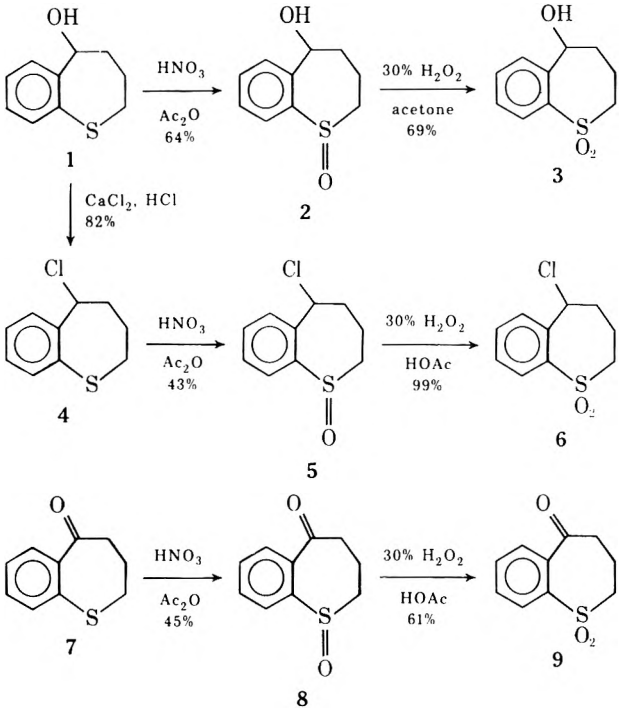
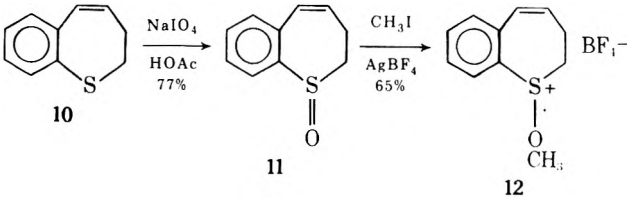
The following sulfoxides were prepared by the oxidation of the corresponding sulfides with a nitric acid–acetic anhydride mixture: 5-hydroxy-2,3,4,5-tetrahydro-1-benzothiepin 1-oxide (**2**, 64% yield), 5-chloro-2,3,4,5-tetrahydro-1-benzothiepin 1-oxide (**5**, 43% yield), and 3,4-dihydro-1-benzothiepin-5(2*H*)-one 1-oxide (**8**, 45% yield). 2,3-Dihydro-1-benzothiepin 1-oxide (**11**) was available by oxidation of the sulfide **10** with sodium metaperiodate or sulfuryl chloride (−78°) followed by hydrolysis. The latter method has been shown to be a general procedure for the synthesis of sulfoxides in high yields. The intermediate in this synthesis appears to be a chlorine sulfide complex which at low temperature is best represented by the tetracovalent sulfur structure **14b**.

In the course of our synthetic studies in the 1-benzothiepin system[1,5-8] we became interested in 1-benzothiepin sulfoxides as potentially useful synthetic intermediates, particularly 2,3-dihydro-1-benzothiepin 1-oxide (**11**). We now wish to report the synthetic methods used to produce these sulfoxides and the development of a new technique which appears to be a general and simple sulfoxide synthesis.

**1-Benzothiepin Sulfoxides.**—The initial sulfoxides prepared were 5-hydroxy-2,3,4,5-tetrahydro-1-benzothiepin 1-oxide (**2**) and 5-chloro-2,3,4,5-tetrahydro-1-benzothiepin 1-oxide (**5**). The reaction entailed oxidation of sulfides **1** and **4** with fuming nitric acid and acetic anhydride as initially reported by Pollard and Robinson[9] and further developed by Bordwell and Boutan.[10] The yields of products were moderate and the structural assignments were based on elemental analyses, spectral data, and the conversion of the sulfoxides to the corresponding sulfones **3** and **6**. A similar reaction sequence was performed in the conversion of ketone **7** to 3,4-dihydro-1-benzothiepin-5(2*H*)-one 1-oxide (**8**) and subsequent oxidation to sulfone **9**.

Attempts to dehydrate alcohol sulfoxide **2** or to dehydrochlorinate sulfoxide **5** were all unsuccessful in leading to 2,3-dihydro-1-benzothiepin 1-oxide (**11**). Synthesis of **11** was initially achieved by sodium metaperiodate oxidation[11] of 2,3-dihydro-1-benzothiepin (**10**). Sulfoxide **11** was an oil with ir and nmr spectra consistent with the assigned structure and was further characterized by conversion to 1-methoxy-2,3-dihydro-1-benzothiepinium tetrafluoroborate (**12**).




**Convenient Synthesis of Sulfoxides.**—A new method for the synthesis of sulfoxides emerged from a study of the chlorination of ketone **7**[7] and 2,3-dihydro-1-benzothiepin (**10**)[1] with sulfuryl chloride. The reaction of sulfides with sulfuryl chloride readily produces α-chloro

(1) For part VII in this series see V. J. Traynelis, Y. Yoshikawa, J. C. Sih, L. J. Miller, and J. R. Livingston, Jr., *J. Org. Chem.*, **38**, 3978 (1973).

(2) (a) Presented in part at the 4th Central Regional Meeting of the American Chemical Society, Pittsburgh, Pa., May 1972. (b) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

(3) Abstracted from a portion of the Ph.D. Dissertation submitted by Y. Y. in May 1973 at West Virginia University.

(4) Abstracted from a portion of the Ph.D. Dissertation submitted by J. R. L., Jr., in March 1962 at the University of Notre Dame.

(5) V. J. Traynelis and J. R. Livingston, Jr., *J. Org. Chem.*, **29**, 1092 (1964).

(6) V. J. Traynelis and D. M. Borgnaes, *J. Org. Chem.*, **37**, 3824 (1972).

(7) V. J. Traynelis, J. C. Sih, Y. Yoshikawa, R. F. Love, and D. M. Borgnaes, *J. Org. Chem.*, **38**, 2623 (1973).

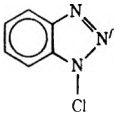
(8) V. J. Traynelis, J. C. Sih, and D. M. Borgnaes, *J. Org. Chem.*, **38**, 2629 (1973).

(9) A. Pollard and R. Robinson, *J. Chem. Soc.*, 3090 (1926).

(10) F. G. Bordwell and P. J. Boutan, *J. Amer. Chem. Soc.*, **79**, 717 (1957).

(11) N. J. Leonard and C. R. Johnson, *J. Org. Chem.*, **27**, 282 (1962).

Table I
Oxidation of Sulfides to Sulfoxides

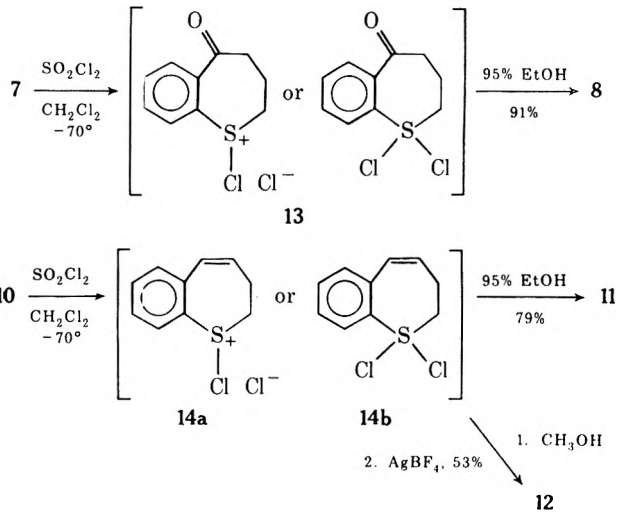
| Sulfoxide | Yield, % | | | | | | |
|---|---|---|---|---|---|---|---|
| | $SO_2Cl_2$ | $NaIO_4$[a] | *t*-BuOCl[b] | $PhICl_2$[c] | DABCO $2Br_2$[d] | NBS[e] |  |
| 2,3-Dihydro-1-benzothiepin 1-oxide (11) | 79 | 77[g] | | | | | |
| 3,4-Dihydro-1-benzothiepin-5(2*H*)-one 1-oxide (8) | 91 | | | | | | |
| Phenyl sulfoxide | 95 | 98 | 94 | 96 | 95 | 93 | |
| Phenyl methyl sulfoxide | 97 | 99 | 90 | 86 | 85[h] | 0[i] | 92 |
| Benzyl sulfoxide | 99 | 96 | 64 | 98 | 70[j] | 86 | |
| *n*-Octadecyl ethyl sulfide | 90 | | | 85[k] | | 76[k] | 87[l] |
| Tetramethylene sulfoxide | 60 | | | | | | 70 |

[a] See ref 11. [b] L. Skattebøl, B. Boulette, and S. Solomon, *J. Org. Chem.*, **32**, 3111 (1967). [c] G. Barbier, M. Cinquini, S. Colonna, and F. Montanari, *J. Chem. Soc.*, 659 (1968). [d] Bromine complex of 1,4-diazabicyclo[2.2.2]octane: S. Oae, Y. Onishi, S. Kozuka, and N. Tagaki, *Bull. Chem. Soc. Jap.*, **39**, 364 (1966). [e] *N*-Bromosuccinimide: R. Harville and S. F. Reed, Jr., *J. Org. Chem.*, **33**, 3976 (1968). [f] W. D. Kingsbury and C. R. Johnson, *Chem. Commun.*, 365 (1969). [g] This work. [h] The yield represents that of *p*-tolyl methyl sulfoxide. [i] W. Tagaki, K. Kikukawa, K. Ando, and S. Oae, *Chem. Ind. (London)*, 1624 (1969). [j] The yield represents that of ethyl benzyl sulfoxide. [k] This yield represents that of *n*-propyl sulfoxide. [l] This yield represents that of isopropyl sulfoxide.

sulfides[12] and has been proposed to proceed by a polar mechanism involving chlorosulfonium salts as initial intermediates.[12a,13] These chlorine sulfide salts or complexes are more commonly generated by the direct reaction of chlorine with sulfides.[14-19] In addition to the ease with which these complexes decompose to α-chloro sulfides, the complexes can also be hydrolyzed to sulfoxides.[14]

Thus the reaction of sulfuryl chloride and sulfides at low temperatures (−40 to −70°) led to chlorine sulfide complexes which were stable at these temperatures, and low-temperature hydrolysis with 95% ethanol converted the complexes to the corresponding sulfoxides. This technique was first applied with 3,4-dihydro-1-benzothiepin-5(2*H*)-one (**7**) to acquire evidence for the intermediate chlorine sulfide complex **13** which was hydrolyzed to sulfoxide **8** in 91% yield. Secondly, the reaction of 2,3-dihydro-1-benzothiepin and sulfuryl chloride, which gave *cis*- and *trans*-4,5-dichloro-2,3,4,5-tetrahydro-1-benzothiepin,[1] was shown to proceed through the chlorine sulfide intermediate **14** by diverting **14** *via* hydrolysis to sulfoxide **11** in 79% yield. In addition further support for intermediate **14** arose from treatment with anhydrous methanol followed by silver tetrafluoroborate to form the methoxysulfonium salt **12**.

These reactions of the chlorine sulfide complexes appeared to have general potential in the synthesis of sulfoxides and methoxysulfonium salts. A series of sulfides including diaryl, aryl alkyl, alkyl, and heterocyclic were subjected to the low-temperature reaction with sulfuryl chloride followed by hydrolysis and were converted to sulfoxides in excellent yields. Table I summarizes these results and compares this method of sulfoxide synthesis to others in the literature.[20,21] The sulfuryl chloride, hydrolysis sequence is effective in the synthesis of sulfoxides in the presence of certain functional groups (carbonyl and olefinic groups were the only ones examined), avoids overoxidation to sulfones, utilizes mild conditions (−78°), employs inexpensive materials, and does not appear to be limited to certain types of sulfides.




The nature of the chlorine sulfide complex in these reactions raises the question of a chlorosulfonium chloride or a tetracovalent dichlorosulfur structure. Lawson and Dawson[14] reported a crystalline chlorine sulfide complex of β,β′-dichloroethyl sulfide isolated below 0° and Meerwein and coworkers[16] prepared dimethylchlorosulfonium salts (hexachloroantimonate, tetrafluoroborate, etc.). In both cases the structures were represented as salt-like. The intermediate proposed in the reaction (at 0° or higher) of sulfuryl chloride and sulfides to form α-chloro sulfides was a chlorosulfonium chloride.[12a,13] However, recent reports in

(12) (a) F. G. Bordwell and B. M. Pitts, *J. Amer. Chem. Soc.*, **77**, 572 (1955); (b) L. A. Paquette and L. S. Wittenbrook, *ibid.*, **90**, 6790 (1968).
(13) D. L. Tuleen and T. B. Stephens, *J. Org. Chem.*, **34**, 31 (1969).
(14) W. E. Lawson and T. P. Dawson, *J. Amer. Chem. Soc.*, **49**, 3119 (1927).
(15) H. Bohme and H. Grand, *Justus Liebigs Ann. Chem.*, **577**, 68 (1952).
(16) H. Meerwein, K. Zenner, and R. Gipp, *Justus Liebigs Ann. Chem.*, **688**, 67 (1965).
(17) R. J. Maner, Ph.D. Dissertation, University of Iowa, 1968.
(18) H. Kwart and H. Omura, *J. Amer. Chem. Soc.*, **93**, 7250 (1971), and references cited therein.
(19) (a) E. J. Corey and C. U. Kim, *J. Amer. Chem. Soc.*, **94**, 7586 (1972); (b) E. J. Corey, C. U. Kim, and M. Takeda, *Tetrahedron Lett.*, 4339 (1972).
(20) C. R. Johnson and J. C. Sharp, *Quart. Rep. Sulfur Chem.*, **4**, 1 (1969).
(21) F. Montanari and M. Cinquini, *Mech. React. Sulfur Compounds*, **3**, 121 (1968).

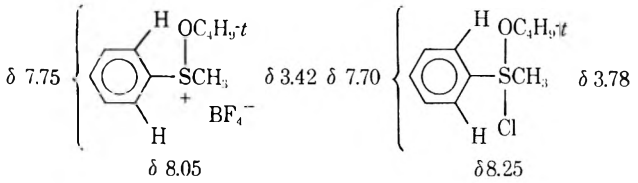
TABLE II

LOW-TEMPERATURE NMR DATA FOR 2,3-DIHYDRO-1-BENZOTHIEPIN (10), 1-METHOXY-2,3-DIHYDRO-1-BENZOTHIEPINIUM TETRAFLUOROBORATE (12), AND 2,3-DIHYDRO-1-BENZOTHIEPIN CHLORINE COMPLEX 14 AT −50°

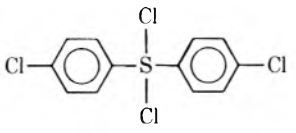
| | δ | | |
|---|---|---|---|
| | 10 | 12 | 14 |
| $C_2$ H | 2.84 (broad s) | 3.6–4.6 (br m) | 4.75 (t, $J$ = 5.5 Hz) |
| $C_3$ H | | 3.0 (br s) | 3.13 (d t, $J$ = 5.5 Hz) |
| $C_4$ H | 5.92 (d t, $J$ = 13 and 3.5 Hz) | 6.01 (br d, $J$ = 12 Hz) | 6.27 (d t, $J$ = 5.5 and 11 Hz) |
| $C_5$ H | 6.45 (d, $J$ = 13 Hz) | 6.32 (d, $J$ = 12 Hz) | 6.57 ($J$ = 11 Hz) |
| $C_6$, $C_7$, $C_8$ H's | 7.10 (m) | 7.43 (m) | 7.40 (m) |
| $C_9$ H | 7.34 (m) | 7.87 (m) | 8.04 (m) |
| $OCH_3$ | | 3.98 (s) | |

the literature[22–25] describe tetracovalent sulfur species which in some cases have been isolated[22] and confirmed by X-ray crystallography[22,23] and in other cases have been detected as reaction intermediates by spectral studies[24] and the nature of the reaction products.[25]

In the oxidation of thioanisole with *tert*-butyl hypochlorite, Johnson and Rigau[24] proposed the intermediacy of a tetracovalent sulfur species **16** on the basis of a low-temperature nmr study. The two ortho hydrogens and methyl hydrogens in **16** appeared significantly at lower field in contrast to analogous hydrogens in the trivalent salt **15**. Similar downfield shifts in the nmr were reported[17] for the ortho hydrogens of bis(*p*-chlorophenyl) sulfide chlorine complex **17** when compared to




15 16




17

the corresponding hydrogen position for the sulfide. The tetracovalent sulfur structure of the complex **17** was supported by an X-ray study.[23]

We have examined the low-temperature (−50°) nmr spectrum of the intermediate **14** from the reaction of sulfuryl chloride with 2,3-dihydro-1-benzothiepin (**10**) and compared this spectrum with those of **10** and 1-methoxy-2,3-dihydro-1-benzothiepinium tetrafluoroborate (**12**) at −50°. The results appear in Table II and the downfield shift of the $C_9$-H and $C_2$-H resonances in **14** compared with the corresponding hydrogens in the methoxysulfonium salt **12** and the sulfide **10** parallel the results reported by Johnson and Rigau.[24] In view of the magnitude of the $C_9$-H and particularly the $C_2$-H shifts in **14** compared with **13**, we favor the assignment of the dichlorosulfurane structure **14b** for the reaction intermediate at −50° in preference to the chlorosulfonium structure **14a**. Similar deshielding affects on the $C_9$ hydrogen, resulting from geometric and electronic change on sulfur, can be observed by increasing the number of oxygen atoms on sulfur in going from 2,3-dihydro-1-benzothiepin (**10**) [$C_9$ H, δ 7.40 (m)] to 2,3-dihydro-1-benzothiepin 1-oxide (**11**) [$C_9$ H, δ 7.88 (m)] and 2,3-dihydro-1-benzothiepin 1,1-dioxide [$C_9$ H, δ 8.10 (m)]. Also consistent with structure **14b** is the multiplicity of the $C_2$ hydrogens (equivalent hydrogens give rise to a triplet) in contrast to **13** where the nonequivalent $C_2$ hydrogens appear as a complex multiplet.

In conclusion the low-temperature reaction of sulfuryl chloride and sulfides forms a chlorine sulfide complex which is readily hydrolyzed to the corresponding sulfoxide in high yield. These intermediates should also find application in the new transformations recently described by Corey and coworkers.[19]

## Experimental Section[26]

**General Oxidative Procedure with Sulfuryl Chloride.**—A solution of sulfuryl chloride in $CH_2Cl_2$ was added dropwise with stirring to an equimolar amount of the sulfide in $CH_2Cl_2$ solution maintained at −70°. After the reaction mixture was stirred for 15–30 min and kept at low temperature, −40 to −78° for 2–24 hr, 95% ethanol was added slowly and the solution was allowed to come to room temperature. The reaction mixture was neutralized with $NaHCO_3$, $Na_2CO_3$, or $K_2CO_3$, the organic layer was separated, washed ($H_2O$), and dried ($MgSO_4$), and the solvent was removed under reduced pressure. The residue which remained was distilled, recrystallized, or characterized without further treatment and shown to be the corresponding sulfoxides.

**2,3-Dihydro-1-benzothiepin 1-Oxide (11). Method A.**[27]—A solution of sodium metaperiodate (104 ml of 0.50 *M*, 0.052 mol) was added to 2,3-dihydro-1-benzothiepin[28] (7.00 g, 0.043 mol) in glacial acetic acid (110 ml) and the reaction mixture was stirred for 31 hr at ice-bath temperature. The solid was filtered and the aqueous solution was extracted with $CHCl_3$. After the extract was washed with 15% $NaHCO_3$ solution and $H_2O$ and dried ($MgSO_4$), the solvent was removed under vacuum and gave 5.84 g (77%) of 2,3-dihydro-1-benzothiepin 1-oxide (**11**) as a yellow oil: ir (neat) 3000 (m), 1645 (m), 1470 (m), 1415 (m), 1070, 1030 (s, >S=O), 750 $cm^{-1}$ (s); nmr ($CDCl_3$) δ 8.00–7.76 (m, 1, $C_9$-H), 7.60–7.10 (m, 3, $C_6$, $C_7$, $C_8$ H's), 6.52 (d, 1, $J_{C_5-C_4}$ = 12.5 Hz, $C_5$-H), 5.97 (d t, 1, $J_{C_4-C_3}$ = 5, $J_{C_4-C_5}$ = 12.5 Hz, $C_4$ H), 3.40 (t, 2, $J_{C_2-C_3}$ = 7.0 Hz, $-SOCH_2CH_2$), 2.64 (d t, 2, $J_{C_3-C_2}$ = 7.0, $J_{C_3-C_4}$ = 5 Hz, $-SOCH_2CH_2-$).

**Method B.**—The above general oxidative procedure was used with 2,3-dihydro-1-benzothiepin[11] (2.0 g, 12 mmol) in $CH_2Cl_2$ (15 ml) at −70° and sulfuryl chloride (1 ml, 12 mmol) in $CH_2Cl_2$ (3 ml) with a reaction time of 3 hr at −70°. Addition of 95% ethanol (10 ml) and work-up as above gave 1.73 (79%) of 2,3-

(22) R. J. Arhart and J. C. Martin, *J. Amer. Chem. Soc.*, **94**, 4997, 5003 (1972); I. C. Paul, J. C. Martin, and E. F. Perozzi, *ibid.*, **94**, 5010 (1972), and related papers.

(23) N. C. Baenziger, R. E. Buckles, R. J. Maner, and T. D. Simpson, *J. Amer. Chem. Soc.*, **91**, 5749 (1969).

(24) C. R. Johnson and J. J. Rigau, *J. Amer. Chem. Soc.*, **91**, 5398 (1969).

(25) T. Durst and K. C. Tin, *Can. J. Chem.*, **49**, 2374 (1971).

(26) All melting points and boiling points are uncorrected. Elemental analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn., or Midwest Microlab Inc., Indianapolis, Ind. Infrared spectra were determined on a Beckman IR-8 or a Perkin-Elmer Model 137-B spectrometer and nmr spectra were obtained on a Varian Associates Model T-60 nmr spectrometer.

(27) This procedure is taken from the Ph.D. Dissertation of J. C. Sih, West Virginia University, Dec 1971.

(28) V. J. Traynelis, W. L. Hergenrother, J. R. Livingston, and J. A. Valicenti, *J. Org. Chem.*, **27**, 2377 (1962).

dihydro-1-benzothiepin 1-oxide as a yellow oil, ir and nmr spectra identical with those of the above sample.

**1-Methoxy-2,3-dihydro-1-benzothiepinium Tetrafluoroborate (12). Method A.**—Silver tetrafluoroborate (1.2 g, 5.8 mmol) and methyl iodide (1.24 g, 11.6 mmol) in $CH_2Cl_2$ (5 ml) were added to a stirred solution of 2,3-dihydro-1-benzothiepin 1-oxide (**11**, 1.0 g, 5.8 mmol) in $CH_2Cl_2$ (15 ml) and the mixture was stirred at room temperature for 3.5 hr. After the reaction mixture was filtered, ether was added to the filtrate until the cloud point and the oil, which separated, crystallized slowly to give 1.0 g (65%) of 1-methoxy-2,3-dihydro-1-benzothiepinium tetrafluoroborate (**12**): mp 106–108°; ir (KBr) 3025 (w), 1470 (m), 1060 (br, s), 775 $cm^{-1}$ (s); nmr ($CDCl_3$) $\delta$ 8.20–8.00 (m, 1, $C_9$ H), 7.84–7.48 (m, 3, $C_6$, $C_7$, $C_8$ H's), 6.64 (d, 1, $J_{C_5-C_4}$ = 12 Hz, $C_5$ H), 6.23 (d t, 1, $J_{C_4-C_5}$ = 12, $J_{C_4-C_3}$ = 5 Hz, $C_4$ H), 4.80–3.67, sharp peak 4.07 (m, 5, $C_2$ H's and $-OCH_3$, 4.07 peak), 3.24–2.87 (m, 2, $C_3$ H's).

*Anal.* Calcd for $C_{11}H_{13}BF_4OS$: C, 47.17; H, 4.68. Found: C, 47.08; H, 4.49.

**Method B.**—After a solution of 2,3-dihydro-1-benzothiepin[28] (0.81 g, 5.0 mmol) and sulfuryl chloride (0.71 g, 5.3 mmol) in $CH_2Cl_2$ (5 ml) was kept at −78° for 2 days, methanol (0.2 ml) in $CH_2Cl_2$ (2 ml) at −78° was added to the reaction mixture and the solution was allowed to come to room temperature (about 90 min). The reaction mixture was again cooled to −50°, silver tetrafluoroborate (2.0 g, 10 mmol) was added, and the mixture was maintained at −78° overnight and then stirred at 5–8° for 5 hr. After the precipitate was filtered and washed with $CH_2Cl_2$, the solvent was removed under reduced pressure from the combined filtrate and washings and left 1.69 g of an oily residue. The oil solidified and was recrystallized from $CH_2Cl_2$–ether to give 0.744 g (53%) of 1-methoxy-2,3-dihydro-1-benzothiepinium tetrafluoroborate (**12**), mp 106–107°. A mixture melting point with the sample from method A was not depressed and their nmr spectra were identical.

**3,4-Dihydro-1-benzothiepin-5(2*H*)-one 1-Oxide (8). Method A.**—An oxidizing mixture was prepared by dropwise addition of red fuming nitric acid (*d* 1.52, 40 ml) to acetic anhydride (20 ml) cooled in an ice bath. This cold solution was added dropwise with stirring over a period of 20 min to a solution of 3,4-dihydro-1-benzothiepin-5(2*H*)-one[29] (10.0 g, 0.056 mmol) in acetic anhydride (40 ml) at ice-bath temperature and the reaction mixture was placed in a refrigerator for 20 hr. After the mixture was poured onto crushed ice (100 g) and neutralized by addition of 20% NaOH solution with vigorous stirring while the temperature was maintained below 30°, sodium bisulfite (5 g) was added and the solution was extracted with $CHCl_3$. The extract was dried ($MgSO_4$) and the $CHCl_3$ was removed under reduced pressure. The residual oil was dried in a vacuum desiccator overnight and extracted with boiling cyclohexane, which, after treatment with Norit, gave 4.85 g (45%) of 3,4-dihydro-1-benzothiepin-5(2*H*)-one 1-oxide (**8**) as white, crystalline needles: mp 70.5–72.5°; ir ($CHCl_3$) 1665 (>C=O), 1050 $cm^{-1}$ (br, >S=O); nmr ($CDCl_3$) $\delta$ 8.10–7.35 (m, 4, aromatic H's), 3.76–2.80 (m, 4, $-SOCH_2CH_2-CH_2CO-$), 2.63–1.94 (m, 2, $-SOCH_2CH_2CH_2CO-$). An analytical sample, mp 72.5–73.5°, was prepared by recrystallization from cyclohexane.

*Anal.* Calcd for $C_{10}H_{10}O_2S$: C, 61.83; H, 5.19. Found: C, 61.53; H, 5.11.

A 2,4-dinitrophenylhydrazone, mp 176.5° after recrystallization from ethanol, was prepared in the usual way.

*Anal.* Calcd for $C_{16}H_{14}N_4O_5S$: C, 51.32; H, 3.78. Found: C, 51.37; H, 4.02.

**Method B.**—The procedure for preparation of **11**, method B, was used to convert 3,4-dihydro-1-benzothiepin-5(2*H*)-one[29] (2.0 g, 11.1 mmol) with sulfuryl chloride (1.55 g, 11.5 mmol) in $CH_2Cl_2$ (12 ml) followed by hydrolysis with 95% ethanol (15 ml) to 1.60 g (74%), recrystallized from cyclohexane, of 3,4-dihydro-1-benzothiepin-5(2*H*)-one 1-oxide, mp 74–75°, ir and nmr identical with those spectra of the above sample.

**3,4-Dihydro-1-benzothiepin-5(2*H*)-one 1,1-Dioxide (9).**—A solution of 3,4-dihydro-1-benzothiepin-5(2*H*)-one 1-oxide (**8**, 0.75 g, 0.004 mol), acetic acid (4 ml), and 30% $H_2O_2$ (2.5 ml) was allowed to stand overnight at room temperature and poured into $H_2O$ and the precipitate was filtered. The solid was recrystallized from ethanol and gave 0.51 g (61%) of 3,4-dihydro-1-benzothiepin-5(2*H*)-one 1,1-dioxide (**9**), mp 153–156° (lit.[29] mp 155–156°). A mixture melting point with an authentic sample was not depressed and the ir spectrum was identical with that of an authentic sample.

**5-Hydroxy-2,3,4,5-tetrahydro-1-benzothiepin 1-Oxide (2).**—The procedure described under 3,4-dihydro-1-benzothiepin-5(2*H*)-one 1-oxide (**8**), method A, was employed for the reaction of red fuming nitric acid (*d* 1.52, 2 ml) in acetic anhydride (12.5 ml) and 5-hydroxy-2,3,4,5-tetrahydro-1-benzothiepin[29] (5.0 g, 0.028 mol) in acetic anhydride (35 ml) for 24 hr at refrigerator temperature. After work-up, the $CHCl_3$ extract, dried ($Na_2SO_4$), was treated with Skelly F and upon cooling in a deep freeze for 2 days gave 3.48 g (64%) of 5-hydroxy-2,3,4,5-tetrahydro-1-benzothiepin 1-oxide (**2**): mp 103–106°; ir ($CHCl_3$) 3350 (OH), 1010 $cm^{-1}$ (>S=O); nmr ($CDCl_3$) $\delta$ 7.87–7.54 (m, 1, $C_9$ H), 7.49–7.28 (m, 3, $C_6$, $C_7$, $C_8$ H's), 5.10 (br d, 1, $C_5$ H), 4.24 (br s, 1, OH), 3.12–1.66 (m, 6, $-SOCH_2CH_2CH_2CHOH-$). An analytical sample, mp 110–113°, was prepared by repeated recrystallization from benzene.

*Anal.* Calcd for $C_{10}H_{12}O_2S$: C, 61.13; H, 6.16. Found: C, 61.25; H, 6.12.

**5-Hydroxy-2,3,4,5-tetrahydro-1-benzothiepin 1,1-Dioxide (3).** A solution of 5-hydroxy-2,3,4,5-tetrahydro-1-benzothiepin 1-oxide (**2**, 0.4 g, 0.002 mol), acetone (2 ml), and 30% $H_2O_2$ (1.75 ml) was allowed to stand overnight, then refluxed for 30 min. The solvent was removed under reduced pressure and the residue was recrystallized from benzene to give 0.30 g (69%) of 5-hydroxy-2,3,4,5-tetrahydro-1-benzothiepin 1,1-dioxide, mp 128–129°. A second recrystallization of **3** from benzene raised the melting point to 136–139° (lit.[29] mp 141–142°). A mixture melting point with an authentic sample was not depressed and the ir spectrum was identical with that of an authentic sample.

**5-Chloro-2,3,4,5-tetrahydro-1-benzothiepin (4).**—Solid 5-hydroxy-2,3,4,5-tetrahydro-1-benzothiepin[29] (9.0 g, 0.05 mol) was added in one portion to a vigorously stirred solution of $CaCl_2$ (25 g) in concentrated HCl (100 ml) and the mixture was heated on a steam bath for 30 min. The reaction mixture was poured onto ice (200 g) and extracted with ether and the extract was dried ($Na_2SO_4$). After the solvent was removed, distillation of the residue gave 8.06 g (82%) of 5-chloro-2,3,4,5-tetrahydro-1-benzothiepin (**4**): bp 79–81° (0.05–0.08 Torr) [lit.[30] bp 105–110° (0.4 Torr)]; $n^{20}D$ 1.6159; ir (neat) 2900 (s), 1450 (s), 1285 (m), 1238 (m), 1035 (m), 910 (m), 876 (m), 820 (m), 760 (s), 741 (s), 718 $cm^{-1}$ (s); nmr ($CDCl_3$) $\delta$ 7.64–7.00 (m, 4, aromatic H's), 5.59 (d d, 1, $J$ = 8.5 and 3.0 Hz, $C_5$ H), 2.72–2.54 (m, 2, $-SCH_2-CH_2-$), 2.48–1.66 (m, 4, $-SCH_2CH_2CH_2-$).

**5-Chloro-2,3,4,5-tetrahydro-1-benzothiepin 1-Oxide (5).**—A solution of 5-chloro-2,3,4,5-tetrahydro-1-benzothiepin (**4**, 5.0 g, 0.25 mol) in acetic anhydride (25 ml) was added to a solution of 70% nitric acid (40 ml) and acetic anhydride (25 ml) prepared as described above and maintained at 0°. After the mixture remained in the refrigerator for 10 hr and was poured onto ice, the solution was neutralized with 20% NaOH solution and the solid was collected and dried. Recrystallization of the crude material from benzene–Skelly B gave 2.02 g (43%) of white needles of 5-chloro-2,3,4,5-tetrahydro-1-benzothiepin 1-oxide (**5**): mp 141–142°; ir ($CHCl_3$) 2980 (m), 1450 (m), 1068 (s), 1030 $cm^{-1}$ (s, >S=O).

*Anal.* Calcd for $C_{10}H_{11}ClOS$: C, 55.94; H, 5.17. Found: C, 55.84; H, 5.13.

**5-Chloro-2,3,4,5-tetrahydro-1-benzothiepin 1,1-Dioxide (6).**—A solution of 5-chloro-2,3,4,5-tetrahydro-1-benzothiepin 1-oxide (**5**, 0.50 g, 0.0023 mol), 30% $H_2O_2$ (2 ml), and acetic acid (10 ml) was allowed to stand for 12 hr at room temperature and then heated on a steam bath for 30 min. The mixture was poured into $H_2O$ (30 ml) and cooled (5° for 24 hr) and the product was filtered. Recrystallization of the solid from cyclohexane gave 0.53 g (99%) of 5-chloro-2,3,4,5-tetrahydro-1-benzothiepin 1,1-dioxide (**6**): mp 97–98.2°; ir ($CHCl_3$) 1300 (br), 1155, and 1120 $cm^{-1}$ (>$SO_2$); nmr ($CDCl_3$) $\delta$ 8.20–7.93 (m, 2, $C_9$ H and $C_6$ H), 7.62–7.30 (m, 2, $C_7$, $C_8$ H's), 5.97 (d d, 1, $J$ = 9 and 2 Hz), 3.36–3.00 (m, 2, $-SO_2CH_2-$), 2.84–1.66 (m, 4, $-SO_2CH_2CH_2CH_2-$). Repeated crystallization of the product from cyclohexane gave an analytical sample, mp 98–99°.

*Anal.* Calcd for $C_{10}H_{11}ClO_2S$: C, 51.93; H, 4.76; S, 13.89; Cl, 15.37. Found: C, 52.14; H, 4.90; S, 13.62; Cl, 15.56.

**Benzyl Sulfoxide.**—The above general oxidative procedure was used with benzyl sulfide (2.00 g, 9.34 mmol) in $CH_2Cl_2$ (12 ml) at −40° and sulfuryl chloride (1.31 g, 9.70 mmol) in $CH_2Cl_2$ (5 ml)

(29) V. J. Traynelis and R. F. Love, *J. Org. Chem.*, **26**, 2728 (1961).

(30) K. Sindelar and M. Protiva, *Collect. Czech. Chem. Commun.*, **33**, 4315 (1968).

with a reaction time of 30 min at −40° and overnight at −78°. Addition of 95% ethanol (15 ml) and work-up as above gave 2.13 g (99%) of crude benzyl sulfoxide, mp 115–120°. The crude product was free of benzyl sulfide and benzyl sulfone by nmr analysis and when the solid was washed with some hexane gave 1.88 g (88%) of pure benzyl sulfoxide: mp 133–134° (lit.[11] mp 135–136°); nmr ($CDCl_3$) δ 7.34 (s, 10, aromatic H's), 3.87 (s, 4, $-CH_2-$). The nmr spectrum was identical with that of an authentic sample.

**Phenyl Sulfoxide.**—Reaction of phenyl sulfide (1.0 g, 5.4 mmol) and sulfuryl chloride (0.80 g, 5.9 mmol) in $CH_2Cl_2$ (9 ml) at −30 to −40° for 90 min produced a yellow precipitate, hydrolysis of which, with 95% ethanol (10 ml) and usual work-up, gave 1.04 g (95%) of crude phenyl sulfoxide, mp 63–67°. The crude material was washed with a small amount of hexane and provided 0.57 g (53%) of pure phenyl sulfoxide: mp 68–70° (lit.[11] mp 69–71°); ir ($CHCl_3$) 1033 $cm^{-1}$ (>S=O) [lit.[11] 1033 $cm^{-1}$ (>S=O)].

**Phenyl Methyl Sulfoxide.**—Thioanisole (1.0 g, 8.1 mmol) in $CH_2Cl_2$ (1 ml) and sulfuryl chloride (1.09 g, 8.0 mmol) in $CH_2Cl_2$ (10 ml) were mixed and kept at −70° for 2 hr. Hydrolysis of the resulting yellow solution with 95% ethanol (15 ml) followed by the usual work-up gave 1.09 g (96%) of phenyl methyl sulfoxide: mp 29–30° (lit.[11] mp 29–30°); ir ($CCl_4$) 1050 $cm^{-1}$ (>S=O) [lit.[11] 1050 $cm^{-1}$ (>S=O)]; nmr ($CDCl_3$) δ 7.70–7.33 (m, 5, aromatic H's), 2.73 (s, 3, $-SOCH_3$). Nmr analysis showed that the product was free of thioanisole and phenyl methyl sulfone.

**Ethyl *n*-Octadecyl Sulfoxide.**—Employing the general oxidation procedure, ethyl *n*-octadecyl sulfide (603 mg, 1.92 mmol) and sulfuryl chloride in $CH_2Cl_2$ (15 ml) were allowed to react at −60° for 24 hr. The reaction mixture was treated with 95% ethanol (10 ml) and standard work-up gave 0.50 g (80%) of ethyl *n*-octadecyl sulfoxide, mp 75–76° (dried by azeotropic distillation of $H_2O$ with benzene), ir ($CHCl_3$) 1010 $cm^{-1}$ (>S=O). An analytical sample, mp 78.5–79.5°, was prepared by recrystallization from ether and dried over $P_2O_5$ at 65° for 2 days. The sulfoxide is hygroscopic.

*Anal.* Calcd for $C_{20}H_{42}OS$: C, 72.66; H, 12.81. Found: C, 72.88; H, 12.79.

**Ethyl *n*-Octadecyl Sulfone.**—A mixture of *m*-chloroperbenzoic acid (0.80 g, 4.6 mmol) and ethyl *n*-octadecyl sulfoxide prepared from ethyl *n*-octadecyl sulfide (1.21 g, 3.8 mmol) and sulfuryl chloride (0.59 g, 4.4 mmol) was stirred in $CHCl_3$ (5 ml) at room temperature for 1 day. After the reaction mixture was filtered and the solvent removed from the filtrate, the residual oil was chromatographed on alumina (A-540) and upon elution with benzene gave 1.2 g (90%) of ethyl *n*-octadecyl sulfone, mp 85–86°, ir ($CHCl_3$) 1300 and 1130 $cm^{-1}$ (>$SO_2$).

*Anal.* Calcd for $C_{20}H_{42}O_2S$: C, 69.30; H, 12.22. Found: C, 69.11; H, 12.18.

**Tetramethylene Sulfoxide.**—Sulfuryl chloride (15.8 g, 0.117 mol) in $CH_2Cl_2$ (5 ml) was added to a solution of tetramethylene sulfide (10 g, 0.114 mol) in $CH_2Cl_2$ (20 ml) and the mixture was allowed to stand at −70° for 3 days. The reaction mixture was treated with 80% ethanol (20 ml) and allowed to warm up to room temperature. The aqueous solution after neutralization of the reaction mixture with potassium carbonate was concentrated prior to extraction with $CHCl_3$. After the $CHCl_3$ extract was dried and the solvent was removed, distillation of the residue (7.1 g) gave 6.0 g (50%) of tetramethylene sulfoxide, bp 48–53° (0.15–0.20 Torr). The product was identified by comparison of nmr and ir spectra with those of an authentic sample.

**Low-Temperature Nmr Measurements.**—The nmr spectra of 2,3-dihydro-1-benzothiepin,[28] 1-methoxy-2,3-dihydro-1-benzothiepinium fluoroborate (12), and the intermediate from the reaction of sulfuryl chloride and 2,3-dihydro-1-benzothiepin were obtained at −50° on a Varian HA-60 nmr spectrometer equipped with a variable temperature probe. The chemical shifts were measured using TMS as an internal standard.

A 0.2-ml aliquot of a 2.5 *M* 2,3-dihydro-1-benzothiepin (10)[28] stock solution in $CDCl_3$ was mixed with 0.1 ml of $CDCl_3$ and cooled to −50°. To this solution was added a 0.2-ml aliquot of 2.5 *M* sulfuryl chloride in $CDCl_3$ mixed with 0.1 ml of $CDCl_3$ precooled to −50°. The resulting yellow solution was shaken vigorously with cooling and placed in the nmr probe at −50°.

The chemical shifts for these compounds are summarized in Table II.

**Registry No.**—2, 41947-71-1; 4, 21609-60-9; 5, 41947-73-3; 6, 41947-74-4; 8, 26524-92-5; 8 2,4-dinitrophenylhydrazone, 41947-76-6; 10, 21609-62-1; 11, 41947-78-8; 12, 41947-79-9; 14, 41947-80-2; 3,4-dihydro-1-benzothiepin-5(2*H*)-one, 21609-70-1; 5-hydroxy-2,3,4,5-tetrahydro-1-benzothiepin, 20500-27-0; ethyl *n*-octadecyl sulfoxide, 41947-83-5; ethyl *n*-octadecyl sulfide, 41947-84-6; sulfuryl chloride, 7791-25-5; ethyl *n*-octadecyl sulfone, 41947-85-7; *m*-chloroperbenzoic acid, 937-14-4.

# Reactions of Thiopyrylium Cations with Amines

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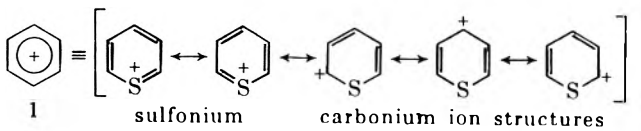
The reactions of parent thiopyrylium cation (1) with various primary amines under mild conditions give ring-opening products, 5- (alkyl- or arylamino-) *N*-alkyl- or -aryl-2,4-pentadienylideniminium salts (4) in good yield. Secondary amines also react with 1 to afford the same type of products. No reaction of 2,4,6-triphenylthiopyrylium cation with aromatic amines took place.

As recently reported[1] SCF MO calculations show that the positive charge in thiopyrylium cation (1) is largest at the sulfur atom (+0.854), but still considerable at the carbon atoms of the α and the γ positions (+0.080 and +0.039, respectively), indicating that 1 can be expressed as a resonance hybrid of sulfonium structures (Kekulé structures) and carbonium ion structures.




Little work has been carried out on the reaction of the parent thiopyrylium cation (1) with nucleophilic reagents. Price, *et al.*,[2] reported that the reaction of 1 and 2,4,6-triphenylthiopyrylium cation (2) with phenyllithium gave thiabenzene derivatives by nucleophilic attack at the sulfur atom. In the case of phosphopyridinium salt, water also reacts preferentially at the heteroatom, rather than carbon.[3] In contrast, we found[4] that the reaction of 2 with a variety of active methylene compounds in the presence of a base yielded substituted benzenes by nucleophilic attack of the carbanions at the α carbon atom. Attempts to isolate

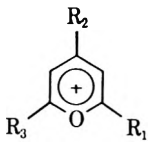
(1) Z. Yoshida, H. Sugimoto, and S. Yoneda, *Tetrahedron*, **28**, 5873 (1972).

(2) (a) M. Polk, M. Siskin, and C. C. Price, *J. Amer. Chem. Soc.*, **91**, 1206 (1969); (b) G. Suld and C. C. Price, *ibid.*, **83**, 1770 (1961); (c) *ibid.*, **84**, 2090 (1962); (d) *ibid.*, **84**, 2094 (1962).

(3) C. C. Price, T. Parasaran, and T. V. Lakshminarayan, *J. Amer. Chem. Soc.*, **88**, 1034 (1966).

(4) Z. Yoshida, S. Yoneda, H. Sugimoto, and T. Sugimoto, *Tetrahedron*, **27**, 6083 (1971).

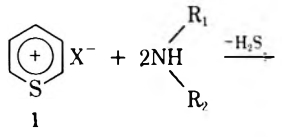
the product in a similar reaction of **1** with active methylene compounds were unsuccessful. A substituted pyrylium cation (**3**) where $R_1$, $R_2$, and $R_3$ denote sub-



**3**

stituents, reacts with ammonia to give pyridine derivatives[5] while the reaction with primary amines affords pyridinium salts.[6] Generally, **3** does not react with secondary amines. This paper deals with the reactions of **1** and **2** toward a variety of amines.

When **1** was treated with aromatic amines in acetonitrile under gentle warming or aliphatic amines in methanol with cooling, the reaction mixture immediately became red or yellow, respectively, with evolution of hydrogen sulfide. The product (**4a**) obtained by the



**1**

$$R_1R_2NCH{=}CHCH{=}CHCH{=}\overset{+}{N}R_1R_2X^-$$

**4a-j**

reaction of thiopyrylium fluoroborate with aniline showed a uv absorption maximum at 486 nm (log $\epsilon$ 4.85) in methanol, suggesting that the product is a highly conjugated one. Elemental analysis ($C_{17}H_{17}N_2BF_4$) indicated that 1 mol of the cation reacted with 2 mol of aniline and hydrogen sulfide was eliminated. The nmr spectrum of **4a** in DMSO-$d_6$ showed two triplets centered at $\delta$ 6.43 (2 H) and 8.03 (1 H) and a broad doublet at $\delta$ 8.65 (2 H) besides the phenyl proton signal ($\delta$ 7.5, 10 H). From comparison of these spectral data with those of the authentic sample prepared by another procedure,[7] the product **4a** was identified as 5-(anilino)-*N*-phenyl-2,4-pentadienylideniminium fluoroborate. The results of the reactions shown below are summarized in Table I. As is seen in Table I, secondary amines as well as primary amines reacted with **1** to afford cyanine-type products (**4**), except *p*-nitroaniline and sulfanilic acid, which did not react with **1** even under vigorous conditions. It is evident that the reactivity of amines with **1** depends upon their basicity. In no cases were pyridinium salts obtained.

Each product (**4**) has three double bonds and the stereochemistry was ascertained from the spectral data. For example, in the spectrum of **4i**, two kinds of equivalent protons ($\alpha$ and $\beta$ protons) revealed a symmetrical structure and all the $J_{H-H}$ values of 12 Hz indicated an all-trans configuration. Further evidence for the trans configuration was obtained by the out-of-plane bending vibrations of vinyl C–H bonds which were observed at 859 and 869 $cm^{-1}$, the latter being shoulder, for **4i**. Similar spectral data for the all-trans configuration of 2,8-dimethylnonatrienyl cation have been reported by Sorensen.[8]

The formation of the ring-opening product **4** might be explained by the reaction course shown in Scheme I.

SCHEME I

A PROBABLE MECHANISM OF THE REACTION OF THIOPYRILIUM CATION WITH AMINE ($R_1R_2NH$)

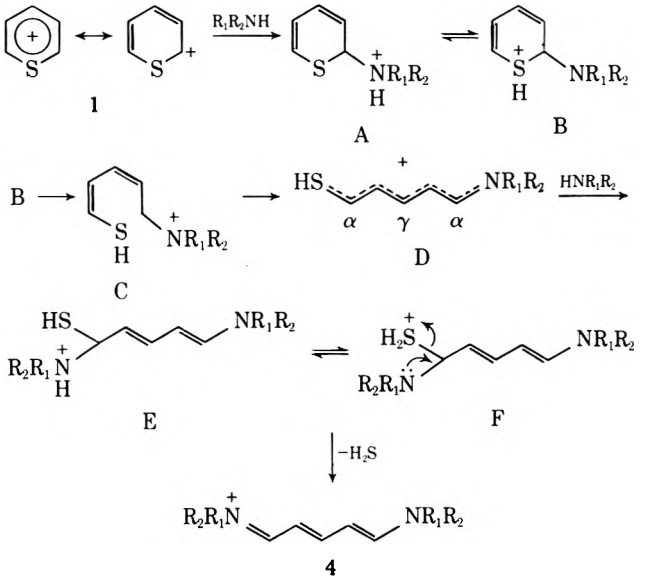


TABLE I

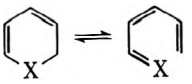
RESULTS OF THE REACTION OF **1** WITH AMINES ($R_1R_2NH$)[a]

| 4 | $R_1$ | $R_2$ | X | Yield, % | Mp (dec), °C |
|---|---|---|---|---|---|
| a | H | Ph | $BF_4$ | 90 | 157–169 |
| b | H | Ph | $ClO_4$ | 71 | 190–192 |
| c | H | *p*-$CH_3$Ph | $BF_4$ | 63 | 138–140 |
| d | H | *p*-$CH_3O$Ph | $BF_4$ | 62 | 165–166 |
| e | H | *p*-HOPh | $BF_4$ | 64 | 180 |
| f | H | *p*-ClPh | $BF_4$ | 54 | 167–170 |
| g | Me | Ph | $BF_4$ | 32 | 84–86 |
| h | H | Me | $BF_4$ | 66 | mp 79 |
| i | Me | Me | $BF_4$ | 65 | mp 128 |
| j | Morpholino | | $BF_4$ | 52 | mp 184–186 |

[a] Satisfactory analytical values (±0.4%) for C, H, and N were reported for all compounds except **4d** (calcd, C, 57.55; found, C, 56.88): Ed.

The initial nucleophilic attack by amine takes place at the $\alpha$ carbon atom, in accord with the reaction indices obtained by the HMO method.[4]

Recently, attention has been focused on the ring opening of $\alpha$-pyrans or $\alpha$-thiopyrans to dienones or dienothiones, respectively, or on their equilibrium as shown below. For $\alpha$-pyran derivatives, Marvell and



collaborators[9] observed that the rate constant for the ring opening to *cis*-$\beta$-ionone (a cis dienone) from 1-oxa-2,5,5,8a-tetramethyl-5,6,7,8-tetrahydronaphthalene (as a model $\alpha$-pyran) is around one-tenth as large as that for the reverse reaction. Furthermore, Becker and Kolk have found that the ring opening of 2,2-diphenyl-

(5) (a) A. Bayer and J. Piccard, *Justus Liebigs Ann. Chem.*, **384**, 208 (1911); (b) *ibid.*, **407**, 332 (1914); (c) A. T. Balaban, *Tetrahedron, Suppl.*, **7**, 1 (1966).

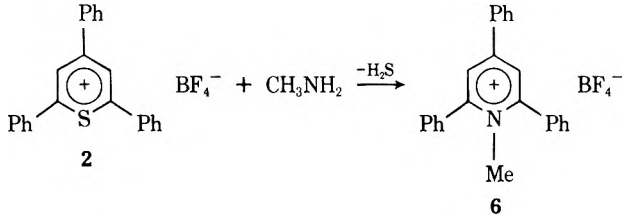
(6) C. Toma and A. T. Balaban, *Tetrahedron, Suppl.*, **7**, 9 (1966).

(7) T. Zincke, *Justus Liebigs Ann. Chem.*, **330**, 361 (1903).

(8) T. S. Sorensen, *J. Amer. Chem. Soc.*, **87**, 5075 (1965).

(9) E. N. Marvell, T. Chadwick, G. Caple, T. Gosink, and G. Zimmer, *J. Org. Chem.*, **37**, 2992 (1972).

2*H*-benzothiopyran is affected only by a photochemical process.[10] In both cases the molecules in question have no polar substituent. However, in the ring opening of the initial adduct (A) of **1** with amines, the ammonium group permits an ionic path rather than a retroelectrocyclic process. This is experimentally suggested from the fact that the reaction proceeds very rapidly and even in the dark. In view of these arguments, the ring opening of the adduct is considered to occur *via* the sulfonium type isomer (B), in which the driving force of the ring opening should come from the electron-withdrawing sulfonium group. The ring opening intermediate might, then, be isomerized from the cis form (C) to the trans form (D). The intermolecular attack of amine at the $\alpha$ carbon adjacent to the sulfur atom followed by the elimination of hydrogen sulfide gives the final cyanine-type product. A marked contrast was found in the reaction of **2** with methylamine, which gives exclusively pyridinium salt and no ring opening product.




The bulky substituents (phenyl groups) may prevent isomerization of the ring opening intermediate for **2**. In addition to this, since the positive charge can delocalize on the phenyl groups, the Coulomb repulsion in the nontrans configuration is considered to be sufficiently lowered.

It is established that **3** ($R_1 = R_2 = R_3 =$ Ph) reacts both with aromatic and aliphatic primary amines; on the other hand, **2** has been found to react only with aliphatic amines. These results indicate that **2** is less reactive toward nucleophilic reagents than **3** ($R_1 = R_2 = R_3 =$ Ph). It is generally accepted that the electron-releasing conjugative effect of oxygen is larger than that of sulfur. For instance, the rate constant of the hydrolysis of $\alpha$-chloromethyl ether was reported to be about 1600 times as large as that of $\alpha$-chloromethyl sulfide.[11] If the nature of the heteroatom plays a major role in the stability and reactivity of **2** and **3** ($R_1 = R_2 = R_3 =$ Ph), then the pyrylium cation should be more stable and less reactive toward nucleophiles than thiopyrylium cation, but this is not the case. These differences must be ascribed to the double bond character of the carbon–heteroatom bond, or, in other words, delocalization of the positive charge. The contribution of carbonium ion structure to a resonance hybrid of pyrylium cation is larger than that of thiopyrylium cation,[1] and this difference may be responsible for the difference in the reactivities of both cations.

## Experimental Section

Ultraviolet spectra were run on a Hitachi EPS-3T recording photometer. Infrared spectra were recorded on a Hitachi grating infrared spectrophotometer. Nmr spectra were determined on a Jeolco C-60H with TMS as an internal standard. Melting points were not corrected.

**Thiopyrylium Fluoroborate (1).**—**1** was prepared according to Degani, Fochi, and Vincenzi[12] and purified by reprecipitation from acetonitrile–ether.

**2,4,6-Triphenylthiopyrylium Fluoroborate (2).**—**2** was prepared by the method of Wizinger and Ultrich.[13]

**5-(Substituted amino)-N-Substituted 2,4-Pentadienylideniminium Salts (4a–j).**—These were prepared by the following procedure. The yields and elemental analyses are listed in Table I.

**General Procedure.**—To a solution of 5.0 mmol of **1** in 10 ml of acetonitrile for arylamines or methanol for alkylamines was added a solution of 20 mmol of arylamine in 10 ml of acetonitrile at 40–50° or a solution of 20 mmol of alkylamine in 10 ml of methanol at ice-cooled temperature. The reaction mixture was immediately colored red or yellow and the evolution of hydrogen sulfide was observed. After stirring was continued for about 1 hr, the dark-red colored reaction mixture was filtered and an excess of ether was added to the filtrate. The precipitate was filtered and recrystallized from methanol to give the product salts. The products were shown to be 5-(substituted amino)-N-substituted 2,4-pentadienyldienylideniminium fluoroborate or perchlorate by their elemental analyses and spectral data. Some of them were identified by the spectral data of the authentic sample.[7,14]

**5-(Phenylamino)-*N*-phenyl-2,4-pentadienylideniminium fluoroborate (4a)** had mp 157–159° dec; $\lambda_{max}$ (MeOH) 486 nm (log $\epsilon$ 4.85); ir (KBr) 1625, 1610, 1545, 1325, 1175, 1015, 880, 855, 765, and 685 $cm^{-1}$; nmr (DMSO-$d_6$) 8.65 (d, 2 H, the protons at the $\alpha$ positions of the pentamethine system), 8.03 (t, 1 H, the proton at the $\gamma$ position), 7.5 (m, 10 H, phenyl protons), and 6.43 (t, 2 H, the protons at the $\beta$ positions).

**5-(Phenylamino)-*N*-phenyl-2,4-pentadienylideniminium perchlorate (4b)** had mp 190–192° dec. The electronic and nmr spectra were entirely the same as those of **4a**. The ir spectrum is also identical with that of **4a** except for the absorption due to the counteranion.

**5-(*p*-Toluidino)-*N*-(*p*-tolyl)-2,4-pentadienylideniminium fluoroborate (4c)** had mp 138–140° dec; $\lambda_{max}$ (EtOH) 490 nm (log $\epsilon$ 4.91) [lit.[8] $\lambda_{max}$ (MeOH) 489 nm (log $\epsilon$ 5.00)]; ir (KBr) 1625, 1560, 1505, 1330, 875, 863, and 816 $cm^{-1}$.

**5-(*p*-Anisidino)-*N*-(*p*-anisyl)-2,4-pentadienylideniminium fluoroborate (4d)** had mp 165–166° dec; $\lambda_{max}$ (EtOH) 498 nm (log $\epsilon$ 4.86) [lit.[8] $\lambda_{max}$ (MeOH) 498 nm (log $\epsilon$ 4.87)]; ir (KBr) 1615, 1560, 1505, 880, 865, and 825 $cm^{-1}$; nmr (DMSO-$d_6$) $\delta$ 8.3 (d, 2 H, $\alpha$ protons), 7.4 (t, 1 H, $\gamma$ proton), 7.2 (m, phenyl protons), and 3.8 (s, 6 H, methyl protons). The protons at the $\beta$ position were not observed, probably because of being included in the aromatic proton region.

**5-(*p*-Chloroanilino)-*N*-(*p*-chlorophenyl)-2,4-pentadienylideniminium fluoroborate (4f)** had mp 167–170° dec; $\lambda_{max}$ (EtOH) 492 nm (log $\epsilon$ 5.05) [lit.[8] $\lambda_{max}$ (MeOH) 492 nm (log $\epsilon$ 5.13)]; ir (KBr) 1625, 1610, 1565, 1495, 1330, 880, 760, 825, and 730 $cm^{-1}$; nmr (DMSO-$d_6$) $\delta$-8.3 (d, 2 H, $\alpha$ protons), 7.4 (m, phenyl protons), and 6.3 (t, 2 H, $\beta$ protons).

**5-(*N*,*N*-Methylphenylanilino)-*N'*,*N'*-methylphenyl-2,4-pentadienylideniminium fluoroborate (4g)** had mp 84–86°; dec; $\lambda_{max}$ (EtOH) 449 nm (log $\epsilon$ 4.88); ir (KBr) 1603, 1530, 1375, 886, 867, 800, 764, and 696 $cm^{-1}$; nmr (DMSO $d_6$) $\delta$ 8.4 (d, 2 H, $\alpha$ protons), 7.5 (m, phenyl protons), 6.5 (t, 2 H $\beta$ protons), 3.6 (s, 3 H, methyl protons), and 3.8 (s, 3 H, methyl protons).[15]

**5-(Methylamino)-*N*-methyl-2,4-pentadienylideniminium fluoroborate (4h)** had mp 79°; ir (KBr) 1600, 1550, 1414, 1350, 1265, 865, 765, and 682 $cm^{-1}$; nmr (DMSO-$d_6$) $\delta$ 7.75 (d, 2 H, $\alpha$ protons), 7.50 (s, 1 H, $\gamma$ proton), 5.70 (t, 2 H, $\beta$ protons), and 3.00 (s, 6 H, methyl protons).

**5-(Dimethylamino)-*N*-dimethyl-2,4-pentadienylideniminium fluoroborate (4i)** had mp 128°; ir (KBr) 1603, 1560, 1393, 1180, 869, and 859 $cm^{-1}$; nmr (DMSO-$d_6$) $\delta$ 7.70 (d, 2 H, $\alpha$ protons), 7.44 (t, 1 H, $\gamma$ proton), 5.91 (t, 2 H, $\beta$ protons), 3.26 (s, 6 H, methyl protons), and 3.09 (s, 6 H, methyl protons).[15]

(10) R. S. Becker, and J. Kolk, *J. Phys. Chem.*, **72**, 997 (1968).

(11) C. C. Price and S. Oae, "Sulfur Bonding," Ronald Press, New York, N. Y., 1962, Chapter 2.

(12) I. Degani, R. Fochi, and C. Vincenzi, *Gazz. Chim. Ital.*, **94**, 203 (1964).

(13) P. Wizinger and P. Ultrich, *Helv. Chim. Acta*, **39**, 207 (1956).

(14) (a) A. T. Balaban, *Tetrahedron, Suppl.*, **7**, 1 (1966); (b) C. Toma and A. T. Balaban, *ibid.*, **7**, 9 (1966); (c) B. E. Grigor'eva, I. K. Ginste, and A. P. Severina, *Zh. Obshch. Khim.*, **26**, 3447 (1956).

(15) That the nmr signals for the methyl groups of **4g** and **4i** appear with differing chemical shifts might be explained as follows. Fluoroborate anion poorly solvated with DMSO-$d_6$ is probably not located at the central position of the cyanine-type cation (**4g** and **4i**) in DMSO-$d_6$ solution. As a result, the small difference (around 0.17–0.20 ppm) in the chemical shift for methyl protons could arise from the effect of the electric field of $BF_4^-$.

**5-Morpholino-*N*,*N*-γ-oxapentamethylene-2,4-pentadienylideniminium fluoroborate** (**4j**) had mp 184–186°; ir (KBr) 1560, 1435, 1295, 1240, 1200, 855, and 805 $cm^{-1}$; nmr (DMSO-$d_6$) δ 7.85 (d, 2 H, α protons), 7.67 (t, 1 H, γ proton), 6.10 (t, 2 H, β protons), and 3.7 (b, 16 H, ethylene).

**Reaction of 2 with Methylamine.**—To an ice-cooled solution of 0.82 g (2.0 mmol) of **2** in 10 ml of methanol was added a solution of 0.62 g (20 mmol) of methylamine in 5.0 ml of methanol. After addition of amine the reaction mixture was refluxed for about 1 hr. The hot reaction mixture was rapidly filtered and the filtrate was allowed to stand at room temperature to give 0.08 g of **6** as white needles: mp 215–216°; yield 10%; nmr (DMSO-$d_6$) δ 8.44 (s, 2 H, β protons), 7.50 (m, 15 H, phenyl), and 3.70 (s, 3 H), methyl protons). The product **6** was determined to be *N*-methyl-2,4,6-triphenylpyridinium fluoroborate by mixture melting point with an authentic sample.[16]

**Registry No.**—1 $BF_4$, 41656-11-5; 1 $ClO_4$, 2567-16-0; **2**, 1582-78-1; **4a**, 41656-13-7; **4b**, 41737-40-0; **4c**, 41656-14-8; **4d**, 41724-27-0; **4e**, 41656-15-9; **4f**, 41656-16-0; **4g**, 41656-17-1; **4h**, 41656-18-2; **4i**, 41656-19-3; **4j**, 41656-20-6; **6**, 2355-56-8; aniline, 62-53-3; *p*-toluidine, 106-49-0; *p*-anisidine, 104-94-9; *p*-hydroxyaniline, 123-30-8; *p*-chloroaniline, 106-47-8; *N*-methylaniline, 100-61-8; methylamine, 74-89-5; dimethylamine, 124-40-3; morpholine, 110-91-8.

(16) A. Baeyer and J. Pickard, *Justus Liebigs Ann. Chem.*, **384**, 208 (1911).

# Cyanide-Induced Dimerization of (4-Pyridyl)pyridinium Chloride. Synthesis of 4,4′-Bipyridine and (4-Pyridyl)viologen Salts[1a]

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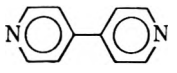
*Received February 5, 1973*

Warming solutions of the title compound (**2**) and sodium cyanide produces 1,1′-di(4-pyridyl)-1,1′-dihydro-4,4′-bipyridine (**3**). After oxidizing **3** in aqueous acid, the resulting solution is heated to afford 4,4′-bipyridine (**1**). This sequence provides a convenient procedure for the synthesis of **1** without simultaneous formation of isomeric side products. The formation of stable (4-pyridyl)viologen cation radicals (**7**) and salts (**6**) from oxidation of **3** is described.

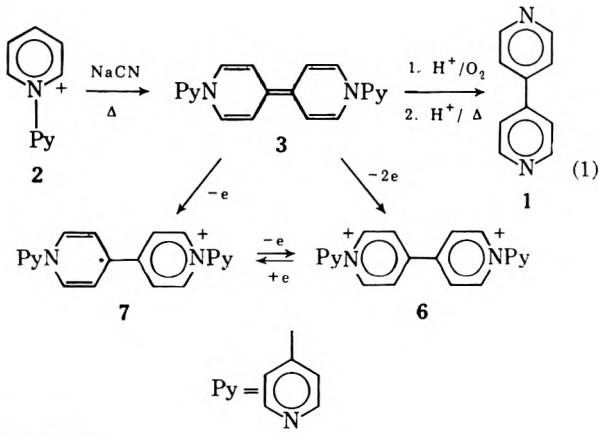
In recent years 4,4′-bipyridine (**1**) has found increasing importance in both organic and organometallic



**1**

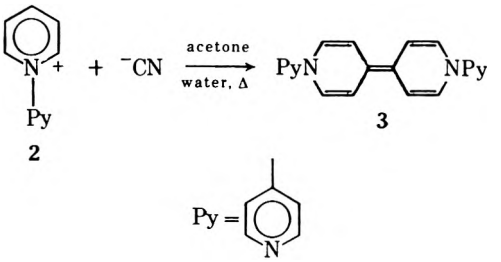
chemistry.[2–4] The synthesis of **1** is usually accomplished by the dimerization of pyridine by metals in inert solvents.[5a] Unfortunately, this procedure suffers from either low yields[5b] or formation of 2,4′- and 2,2′-bipyridine as side products.[5c] In our studies of the cyanide ion induced dimerization of pyridinium salts,[6] we have developed a new, convenient synthesis of **1** which avoids the problem of isomeric side products.

When 1-(4-pyridyl)pyridinium chloride (**2**) and sodium cyanide were heated in aqueous acetone (eq 1),

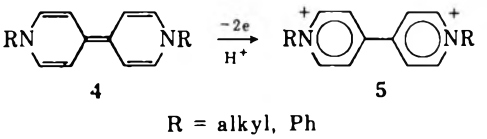


(1)

a 53% yield of 1,1′-di(4-pyridyl)-1,1′-dihydro-$\Delta^{4,4'}$-bipyridine (**3**) was obtained. Previous work[7] had



shown that related dihydrobipyridines (**4**) are readily oxidized to 4,4′-bipyridinium (viologen) salts (**5**) in



acidic solution (*vide infra*). Since it is known that acidic solutions of **2** are susceptible to hydrolysis to afford 4-pyridone and pyridine,[8] it was probable that a similar reaction of (4-pyridyl)viologen (**6**) would give **1**.

(1) (a) Abstracted from the Ph.D. dissertation of R. H. Reuss, Drexel University, 1972. (b) NSF Predoctoral Fellow, 1968–1971. (c) Address all correspondence to this author at Department of Chemistry, Virginia Commonwealth University, Academic Center, Richmond, Va. 23220.

(2) W. R. Boon, *Endeavor*, **26**, 27 (1967).

(3) (a) T. R. Musgrove and C. E. Mattson, *Inorg. Chem.*, **7**, 1433 (1968); (b) R. C. Poller and D. L. Toley, *J. Chem. Soc. A*, 1578 (1967); (c) N. I. Lobanov and A. I. Vlasov, *Russ. J. Inorg. Chem.*, **13**, 395 (1968).

(4) (a) *U. S. Govt. Res. Rep.*, **39** (16), 69 (1964); (b) P. E. Wei, A. H. Corwin, and R. Arellano, *J. Org. Chem.*, **27**, 3344 (1962); (c) J. H. Wang and W. S. Brinigar, *Proc. Nat. Acad. Sci. U. S.*, **46**, 958 (1960); (d) J. R. Barber, and E. S. Gould, *J. Amer. Chem. Soc.*, **93**, 4045 (1971).

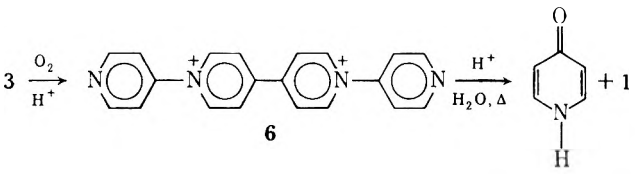
(5) (a) C. D. Schmulbach, C. C. Hinckley, and D. Wasmund, *J. Amer. Chem. Soc.*, **90**, 6600 (1968). (b) Imperial Chemical Industries Limited, Netherlands Patent 6,603,415; *Chem. Abstr.*, **66**, 28674 (1967). (c) R. Setton and L. Hackspill, *C. R. Acad. Sci.*, **244**, 1205 (1957).

(6) (a) L. J. Winters, N. G. Smith, and M. I. Cohen, *Chem. Commun.*, 642 (1970); (b) L. J. Winters, A. L. Borror, and N. G. Smith, *Tetrahedron Lett.*, 2313 (1967).

(7) N. G. Smith, Ph.D. Dissertation, Drexel University, 1970.

(8) R. F. Evans and H. C. Brown, *J. Org. Chem.*, **27**, 1329 (1962).

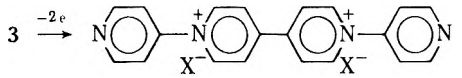
Thus, **3** was oxidized to **6** in acidic media and the resulting solution was heated under reflux to afford **1**.



**6**

Reaction in aqueous hydrochloric acid afforded a 91% yield of **1**. However, a trace of 4-chloropyridine, which is known to polymerize in the solid state,[9] appeared to contaminate the product, since particles of black solid were noted after standing for several days. While use of the stoichiometric amount of nitric acid afforded **1** in 60% yield, excess nitric acid yielded only 33%. The reaction is carried out most conveniently by the aerobic oxidation of **3** to **6** in excess aqueous sulfuric acid, which afforded a 74% yield of **1**.

If desired, it is possible to isolate viologen **6** by oxidation of **3** with aqueous acid and oxygen ($E$ = 1.23 V).[10] Aqueous nitric acid afforded a 75% yield of (4-pyridyl)viologen nitrate dihydronitrate (**6a**), while

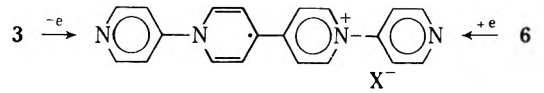


**6a**, X = $NO_3 \cdot 2HNO_3$
**b**, X = Cl
**c**, X = $ClO_4 \cdot HClO_4$
**d**, X = $BPh_4$
**e**, X = Br

hydrochloric acid gave a 52% yield of the chloride salt **6b**. Perchloric acid yielded 75% of a product which contained mostly (4-pyridyl)viologen perchlorate hydroperchlorate (**6c**). The elemental analysis indicated that a small amount of chloride ion was present, which was probably generated by the reduction of perchlorate (1.37 V)[10] by **3**. That the product was predominantly **6c** was demonstrated by the near-quantitative (95%) conversion to the tetraphenylborate salt **6d**.

While the oxidation of **3** could be accomplished readily, certain precautions were necessary. Since base was observed to decompose **6**,[11] it was necessary to either use only the stoichiometric amount of acid, to recover the product from acidic solution, or to cautiously neutralize the excess acid. When iodine or oxygen and hydrochloric (or hydrobromic) acid were used as oxidants, the resulting products tended to decompose in the alcoholic solutions[12] from which they were recrystallized. Metallic oxidizing agents such as $Ag^+$, $Hg^{2+}$, and $Cu^{2+}$ could not be used because of the rapid complex formation between **6** and unreacted metal ion, which was demonstrated by both elemental analysis and qualitative tests for the metal ions. However, no further characterization of these complexes was made.

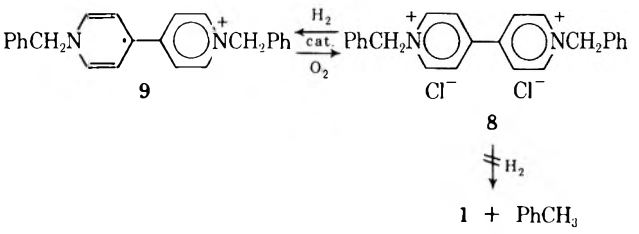
The isolation of the product derived from one-electron oxidation of **3**, (4-pyridyl)viologen cation radical (**7**), was also accomplished. Thus, reaction with bromine afforded bromide **7a** in 99% yield. The structure of **7a** was confirmed by oxidation to the known viologen bromide **6e**.[6b] Alternatively, the viologen salt **6a** was reduced with magnesium to the cation radical nitrate **7b** in 78% yield. While solid samples of **7** were quite



**7a**, X = Br
**b**, X = $NO_3$

stable, showing no evidence of oxidation even after several weeks, solutions of **7** were rapidly air oxidized.

The successful preparation of **1** from viologen **6** prompted us to attempt the hydrogenolysis of benzylviologen chloride (**8**) to **1**. When solutions of **8** were



exposed to a hydrogen atmosphere over platinum or palladium catalysts, a blue solution was observed. Exposure to oxygen caused immediate decolorization and the viologen was recovered unchanged. This behavior is characteristic of the benzylviologen cation radical (**9**).[6a]

## Experimental Section[13]

**1,1′-Di(4-pyridyl)-1,1′-dihydro-$\Delta^{4,4'}$-bipyridine** (**3**).—A solution of 8.92 g (4.6 mmol) of 2 hydrochloride (Aldrich) in 60 ml of water was neutralized (pH 7–8) with concentrated ammonium hydroxide. The solution was transferred with filtration[14] into a 300-ml round-botton flask equipped with a long neck (30 cm × 5 mm). After nitrogen was passed through the solution for 10 min, 3.38 g (6.9 mmol) of sodium cyanide in 20 ml of water, 60 ml of acetone, and a small stirring bar were added. The flask was sealed with a gas–oxygen torch and heated at 90° with stirring. After 42 hr the flask was cooled to room temperature and the red precipitate was collected by suction filtration. The solid was washed with water and acetone and dried under vacuum to afford 3.22 g (53%) of **3**: slow decomposition was observed above 130°; ir (KBr) 1660 $cm^{-1}$ (dihydrobipyridine[7]); mass spectrum (70 eV) $m/e$ (rel intensity) 312 ($M^+$, 74), 234 (100), 157 (17), 156 (16), 78 (28), 51 (51).

*Anal.* Calcd for $C_{20}H_{16}N_4$: C, 76.92; H, 5.13; N, 17.95. Found: C, 76.61; H, 5.22; N, 17.67.

**4,4′-Bipyridine** (**1**).—To a solution of 45 ml of water and 5 ml (excess) of concentrated sulfuric acid was added 1.00 g (3.2 mmol) of **3**. After oxygen was passed through the stirred mixture for 6 hr and the resulting solution was heated under reflux for

(9) A. A. Berlin and E. F. Razvodovskii, *Proc. Acad. Sci. USSR*, **140**, 925 (1961).

(10) "Handbook of Chemistry and Physics," 48th ed, R. C. Weast, Ed., Chemical Rubber Co., Cleveland, Ohio, 1967, p D-86.

(11) It is well known that bases decompose pyridinium salts; see E. M. Kosower, "Molecular Biochemistry," McGraw-Hill, New York, N. Y., 1962, pp 116–219.

(12) Alcohols have been reported to reduce methylviologen: J. A. Farrington, A. Ledwith, and M. F. Stam, *Chem. Commun.*, 259 (1969).

(13) All melting points were determined using a Büchi capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 457 spectrophotometer. Ultraviolet spectra were determined on a Perkin-Elmer 402 spectrophotometer. Nuclear magnetic resonance spectra were recorded using a Varian A-60A spectrometer. The chemical shifts were recorded relative to TMS or DSS as internal standards. The mass spectra were obtained with a RMU-6 mass spectrometer. Elemental microanalyses were performed by Alfred Bernhardt Mikroanalytisches Laboratorium, West Germany.

(14) Neutral solutions of **2** precipitated a red-brown sludge of unknown composition.

40 hr, the reaction was cooled and made basic. Extraction with ether afforded 0.37 g (74%) of 1. The melting point and spectral data were identical with those of commerical samples.

**Preparation of (4-Pyridyl)viologen Salts. A. (4-Pyridyl)viologen Nitrate Dihydronitrate (6a).**—To 50 ml of water containing 0.7 ml (11 mmol) of concentrated nitric acid was added 0.84 g (2.7 mmol) of **3**. Oxygen was passed through the stirred solution for 5 hr. The solution was concentrated under vacuum to give a brown oil which was recrystallized from water–acetone to yield 0.76 g (52%) of **6a**. The mother solution was concentrated to give a second crop of 0.36 g (24%): mp 178° dec; uv max ($H_2O$) 286 nm ($\epsilon$ 24,300); ir (KBr) 1625 $cm^{-1}$ (viologen salts[7]); nmr ($D_2O$) $\tau$ 1.35 (m, 4), 0.65 (m, 8), 0.15 (m, 4).

*Anal.* Calcd for $C_{20}H_{18}N_8O_{12}$: C, 42.71; H, 3.23; N, 19.92. Found: C, 42.60; H, 3.41; N, 19.83.

**B. (4-Pyridyl)viologen Chloride (6b).**—Oxygen was passed through a solution of 0.60 g (6 mmol) of 37% hydrochloric acid and 0.93 g (3 mmol) of **3** in 150 ml of water and 300 ml of acetonitrile. After 24 hr the solution was concentrated under vacuum and the residue was dissolved in 20–30 ml of hot ethanol and 2–3 ml of water. Acetone (10 ml) was added and ether was added to the cloud point. After cooling, 0.60 g (52%) of brown needles of **6b** were obtained: mp 270° dec; ir (KBr) identical with that of **6e** (*vide infra*); uv max ($H_2O$) 287 nm ($\epsilon$ 33,200).

**C. (4-Pyridyl)viologen Perchlorate Hydroperchlorate (6c) and Tetraphenylborate (6d).**—To 140 ml of 50% aqueous nitromethane containing 10 g (70 mmol) of 70% perchloric acid was added 5.18 g of **3**. Oxygen was passed through the stirred solution for 20 hr. After the solution was concentrated and the resulting water-insoluble precipitate was dried under vacuum, 9.20 g (90%) of crude product was isolated. Recrystallization from water gave 7.65 g (75%) of **6c**, ir (KBr) 1615 $cm^{-1}$ (viologen salts[7]).

*Anal.* Calcd for $C_{20}H_{17}Cl_3N_4O_{12}$: C, 39.27; H, 2.80; N, 91.7. Calcd for $C_{20}H_{17}Cl_3N_4O_{11}$: C, 40.32; H, 2.88; N, 9.47. Found: C, 40.07; H, 3.28; N, 9.43.

When 1.10 g (2 mmol, assuming a molecular formula of $C_{20}H_{17}Cl_3N_4O_{11}$) of **6c** was dissolved in 60 ml of water at 45°, neutralized with sodium bicarbonate, and treated with 1.50 g (4.37 mmol) of sodium tetraphenylborate in 10 ml of water, 1.80 g (95%) of **6d** was obtained, mp 205–207° dec, ir (KBr) 1630 $cm^{-1}$ (viologen salts[7]).

*Anal.* Calcd for $C_{68}H_{56}B_2N_4$: C, 85.89; H, 5.94; N, 5.89. Found: C, 85.72; H, 5.96; N, 6.11.

**D. (4-Pyridyl)viologen Bromide (6e).**—Water (20 ml) containing 0.16 g of 50% aqueous hydrogen bromide (1 mmol) was added to 0.39 g (1 mmol) of (4-pyridyl)viologen cation radical bromide (**7a**) and oxygen was passed through the solution overnight. After concentrating to 5–10 ml under vacuum, a few milliliters of ethanol was added, the solution was warmed, and acetone was added to the cloud point. A small amount of black material was removed by filtration. Additional acetone was added to the warmed solution to yield 0.15 g (32%) of **6e**. Concentration of the filtrate afforded another 0.06 g (13%). The ir spectrum was identical with that of an independently prepared sample.[6b]

When 0.19 g (0.49 mmol) of **7a** and 0.08 g (0.50 mmol) of acid were treated as above and filtered to removed insoluble matter, addition of 0.25 g of sodium tetraphenylborate in 10 ml of water afforded 0.37 g (80%) of **6d**.

**Preparation of (4-Pyridyl)viologen Cation Radical Salts. A. (4-Pyridyl)viologen Cation Radical Bromide (7a).**—To 50 ml of acetonitrile which had been outgassed with nitrogen for 10 min was added 0.16 g (1 mmol) of bromine and 0.63 g (2 mmol) of **3**. The mixture was stirred under nitrogen for 10 min and chilled in the refrigerator for 15 min, and the blue precipitate was collected by suction filtration. Drying under vacuum gave 0.78 g (99%) of **7a**, mp 200° dec, ir (KBr) 1640, 1580 $cm^{-1}$.

*Anal.* Calcd for $C_{20}H_{16}BrN_4$: C, 61.24; H, 4.11; N, 14.28. Found: C, 61.03; H, 4.24; N, 14.28.

**B. (4-Pyridyl)viologen Cation Radical Nitrate (7b).**—Potassium carbonate (0.12 g, 0.84 mmol) and 0.47 g (0.84 mmol) of viologen nitrate **6a** were dissolved in 20 ml of water. The solution was outgassed with nitrogen for 20 min and 0.10 g (0.41 mmol) of magnesium was added. After stirring under nitrogen for 2 hr, the resulting blue solid was collected by suction filtration and dried under vacuum to afford 0.24 g (78%) of **7b**, mp 220° dec, ir (KBr) 1640, 1580 $cm^{-1}$.

*Anal.* Calcd for $C_{20}H_{16}N_8O_3$: C, 64.16; H, 4.31; N, 18.71. Found: C, 63.93; H, 4.51; N, 18.47.

**Registry No.**—**1**, 553-26-4; **2**, 22752-98-3; **3**, 41764-90-3; **6a**, 41764-91-4; **6b**, 41764-92-5; **6c**, 41764-93-6; **6d**, 41766-78-3; **7a**, 41764-94-7; **7b**, 41764-95-8.

# Carbon–Nitrogen *vs.* Nitrogen–Nitrogen Bond Formation in Nitrenoid Cyclization Reactions. Pyrolysis of 3-Azido-4-(2-pyridyl)carbostyrils

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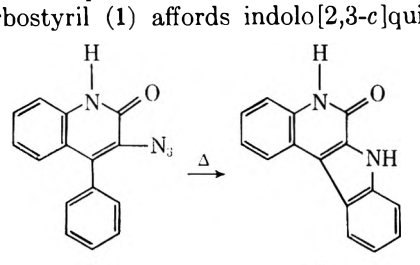
Pyrolysis of 3-azido-4-(2-pyridyl)carbostyrils **7** and **10** afforded mixtures of isomeric tetracyclic products resulting from nitrenoid cyclization reactions. Pyrido[2′,3′:3,2]pyrolo[5,4-*c*]quinolones **9** and **11**, in which the cyclization involved nitrogen–carbon bond formation, were isolated in amounts comparable to those of the pyrido[1′,2′:2,3]pyrazolo[5,4-*c*]quinolones **8** and **12a**, in which the cyclization involved nitrogen–nitrogen bond formation.

Nitrenoid cyclization reactions constitute an important class of reactions for the synthesis of novel heterocyclic compounds.[1] The pyrolysis of 3-azido-4-phenylcarbostyril (**1**) affords indolo[2,3-*c*]quinolone **2** in high yield.[2] In the course of this investigation, we studied the pyrolysis of 3-azido-4-(2-pyridyl)carbostyrils **7**. Related nitrenoid cyclizations of 2-(2-azidophenyl)pyridine,[3] 2-(2-nitrosophenyl)pyridine,[4] and 2-(2-nitrophenyl)pyridine,[3,5] compounds of type **3**, were reported to yield almost exclusively the pyrido[1,2-*b*]indazole (**4**) and not the isomeric δ-carboline **5**.




**1** **2**

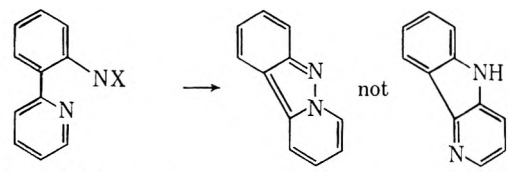
(1) W. Lwowski, Ed., "Nitrenes," Interscience, New York, N. Y., 1970.

(2) (a) J. B. Petersen and K. H. Lakowitz, *Acta Chem. Scand.*, **23**, 971 (1969). (b) We have observed this transformation independently.

(3) R. A. Abramovitch and K. A. H. Adams, *Can. J. Chem.*, **39**, 2516 (1961).

(4) P. J. Bunyan and J. I. G. Cadogan, *J. Chem. Soc.*, 42 (1963).

(5) (a) J. I. G. Cadogan, M. Cameron-Wood, R. K. Mackie, and R. J. G. Searle, *J. Chem. Soc.*, 4831 (1965); (b) J. I. G. Cadogan and R. K. Mackie, *Org. Syn.*, **48**, 113 (1968).




3 (X = $N_2$, O, or $O_2$) 4 5

In view of this we anticipated a preference for nitrogen–nitrogen bond formation in the pyrolysis of **7**. It was surprising to find (see Scheme I) that, in addition to nitrogen–nitrogen bond formation (**8**, **12a**), a substantial amount of carbon–nitrogen bond was formed (**9**, **11**). It is this observation that we particularly wish to record.

3-Azido-4-(2-pyridyl)carbostyrils **7** were prepared by the method described[2] for the preparation of 4-phenyl analog **1**. Pyrolysis of **7a** and **7b** in refluxing toluene afforded, in high yields, mixtures which appeared, by tlc, to contain mainly two products. Recrystallizations of these high-melting, highly insoluble mixtures afforded pyrido[1′,2′:2,3]pyrazolo[5,4-*c*]quinolin-6(5*H*)-ones **8a** and **8b** in 35 and 52% yields, respectively. The second product was not isolated but was presumed to be 5,7-dihydropyrido[2′,3′:3,2]pyrolo[5,4-*c*]quinolin-6-(5*H*)-ones **9**. In order to prove the presence of the isomers **9** in the mixture of pyrolysis products, we peralkylated the crude mixture with 2-diethylaminoethyl chloride in the presence of sodium hydride. The monoalkylated products **12**, formed from **8**, could be readily separated from the dialkylation products of **9**, compounds **13**, which were isolated as dihydrochlorides.

Alternately, the 3-azidocarbostyril **7a** was alkylated first. The 1-(2-diethylaminoethyl) derivative **10** was pyrolyzed, without isolation, to afford a mixture of the two isomeric cyclization products **11** and **12a** which were isolated in 17 and 36% yields, respectively.

Structural assignments are based on nmr, ir, and uv spectral data. The two isomeric heterocyclic nuclei have clearly different uv spectra. The characteristically sharp and strong NH stretching band (3200 $cm^{-1}$) in the ir spectrum of **11** is consistent with that expected for the NH of ring-fused pyrroles.[6]

## Experimental Section[7]

**2-(2-Azidoacetamido-5-bromobenzoyl)pyridine.**—Sodium azide (15.3 g, 236 mmol) was dissolved in a hot solution of 47.0 g (118 mmol) of 2-(5-bromo-2-bromoacetamidobenzoyl)pyridine (**6b**)[8] in 1.6 l. of methanol. The solution was heated to gentle reflux on a steam bath for 20 min. Methanol was evaporated. The residue was extracted with boiling hexane. The hot hexane solution was decanted through a plug of cotton. This process was repeated until only insoluble salts remained. The combined hexane extracts afforded, on cooling and concentration, 31.0 g (73%) of yellow needles: mp 102–103°. (after recrystallizations from hexane, the melting point rose to 103–104°); ir (KBr) 2100 $cm^{-1}$ ($N_3$); nmr (DMSO-$d_6$) δ 3.74 ppm (s, 2 H, $CH_2$); uv max (EtOH) 239 nm (ε 27,600) and 343 (2750).

*Anal.* Calcd for $C_{14}H_{10}BrN_5O_2$: C, 46.69; H, 2.80; N, 19.44. Found: C, 46.71; H, 3.00; N, 19.13.

**3-Azido-4-(2-pyridyl)carbostyril (7a).**—To a hot solution of 79.8 g (0.25 mol) of 2-(2-bromoacetamidobenzoyl)pyridine[11] (**6a**) in 1.2 l. of methanol was added in one portion 32.5 g (0.50 mol) of sodium azide. The mixture was heated on a steam bath to a slow reflux for 20 min. As the solution partially cooled to room temperature, 0.33 mol of benzyltrimethylammonium hydroxide (13.6 ml of a 35% methanolic solution) was added, and the mixture was left to stand at room temperature overnight. The crystals formed (51.0 g, 80%) were collected by filtration and washed thoroughly with methanol. The product was pure by tlc. An analytical sample was prepared by recrystallization from ethanol to give yellow needles: melting point indefinite (decomposition between 100–140° indicated by a change in color from yellow to white); ir (KBr) 2100 ($N_3$) and 1645 $cm^{-1}$ (CO); uv max (EtOH) 230 nm (ε 30,070), 304 (12,490), 326 (10,160), 339 (12,660), and 354 (9420).

*Anal.* Calcd for $C_{14}H_9N_5O$: C, 63.87; H, 3.45; N, 26.60. Found: C, 64.04; H, 3.51; N, 26.49.

**3-Azido-6-bromo-4-(2-pyridyl)carbostyril (7b).** A.—To a warm solution of 3.00 g (8.34 mmol) of 2-(2-azidoacetamido-5-bromobenzoyl)pyridine in 150 ml of methanol was added 1.0 ml of a 35% solution of benzyltrimethylammonium hydroxide in methanol. The solution was allowed to stand at room temperature. After 20 hr, the fibrous yellow solid (2.24 g, 79%) was collected and washed thoroughly with methanol. It was pure by tlc. During melting point determination decomposition was indicated by color change in the range 115–130°, giving a high-melting residue. An analytical sample was prepared by recrystallization from ethanol: uv max (EtOH) 215 nm (ε 23,950), 240 (33,100), 294 (10,800), 304 (12,000), 345 (11,100), 360 (8900).

*Anal.* Calcd for $C_{14}H_8BrN_5O$: C, 49.15; H, 2.36; N, 20.47; Br, 23.35. Found: C, 49.33; H, 2.58; N, 20.37; Br, 23.47.

B.—Alternately, the product was obtained in 97% yield directly from the bromoacetamido precursor **6b**[8] without isolation of the intermediate azide. Thus after 96.0 g (241 mmol) of 2-(2-bromoacetamido-5-bromobenzoyl)pyridine and 31.2 g (480 mmol) of sodium azide were heated in 3.2 l. of methanol for 20 min, 16 ml of 35% solution of benzyltrimethylammonium hydroxide in methanol was added to the partially cooled mixture. In two crops, 80 g of **7b** was collected.

**Pyrido[1′,2′:2,3]pyrazolo[5,4-*c*]quinolin-6(5*H*)-one (8a), 5-(2-Diethylaminoethyl)pyrido[1′,2′:2,3]pyrazolo[5,4-*c*]quinolin-6-(5*H*)-one (12a), and 5,7-Bis(2-diethylaminoethyl)-5,7-dihydropyrido[2′,3′:3,2]pyrolo[5,4-*c*]quinolin-6(5*H*)-one (13a) Dihydrochloride.**—A suspension of 13.2 g (50 mmol) of azidocarbostyril **7a** in 500 ml of toluene was heated under reflux for 3 hr. The crystalline product mixture that separated from solution was collected and washed with toluene (12.5 g). Tlc (silica gel, ether) of this material indicated a clean mixture of two products appearing at $R_f$ 0.08 and 0.35. After drying *in vacuo*, the entire solid mixture was suspended in 1.2 l. of dry dimethylformamide containing 7.20 g of a 50% dispersion of sodium hydride (0.30 mol) in mineral oil. After stirring for 0.5 hr at room temperature, 0.160 mol of 2-diethylaminoethyl chloride (50 ml of a 3.20 *M* solution in toluene) was added and stirring was continued for 3 hr. Excess hydride was decomposed with water; solvents were evaporated. The residue was partitioned between methylene chloride and water. The methylene chloride layer was dried ($Na_2SO_4$) and evaporated. Trituration of the residue with ether afforded 6.50 g of **12a** as a light brown powder, mp 123–125°. Recrystallization from acetonitrile afforded 4.2 g (25%) of colorless prisms: mp 124–126°; ir (KBr), no NH band, 1665 $cm^{-1}$ (CO); uv max (*i*-PrOH) 215 nm (ε 34,600), 228 sh (27,000), 236 (26,600), 249 (35,700), 257 sh (30,000), 266 sh (18,500), 292 sh (6200), 305 (9600), 319 sh (12,900), 330 (14,800), 351 sh (8850), 368 sh (5300); nmr ($CDCl_3$) δ 1.05 (t, $J$ = 7 Hz, 6, 2 $CH_2CH_3$), 2.65 (q, $J$ = 7 Hz, 4, 2 $CH_2CH_3$), 2.80 (m, 2, $CH_2N$), 4.50 (m, 2, $CH_2NCO$), 6.90–7.40 (m, 5, aromatic), 7.80–8.35 (m, 2, aromatic), 8.72 ppm (d, $J$ = 7 Hz, 1, aromatic).

(6) A. R. Katritzky and A. P. Ambler in A. R. Katritzky, Ed., "Physical Methods in Heterocyclic Chemistry," Vol. II, Academic Press, New York, N. Y., 1963, p 208.

(7) All melting points were taken in capillaries heated in oil baths and are corrected. Infrared spectra were determined on a Beckman IR-9 or a Perkin-Elmer 621 grating spectrometer, nuclear magnetic resonance spectra on a Varian A-60 or a Varian HA-100 spectrometer, using tetramethylsilane as internal standard unless specified otherwise, and ultraviolet spectra with a Cary 14M or 15 recording spectrometer. Solvents used were of reagent grade purity. All solvents were evaporated on a Buchi Rotavapor evaporator under water-aspirator pressure using a water bath heated to 30–80°.

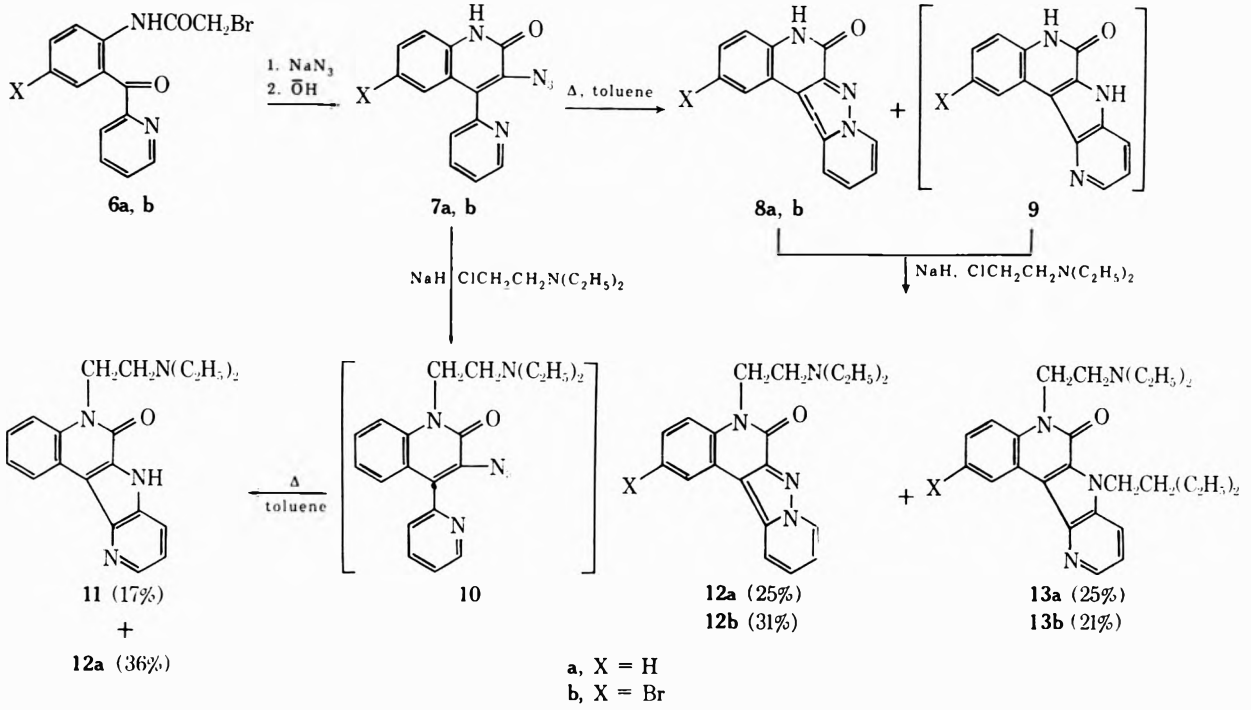
(8) This compound (mp 105–107°) was prepared by the bromoacetylation of 2-(2-amino-5-bromobenzoyl)pyridine,[9,10] following essentially the same procedure as described for **6a** in ref 9.

(9) R. I. Fryer, R. A. Schmidt, and L. H. Sternbach, *J. Pharm. Sci.*, **53**, 264 (1964).

(10) L. O. Randall, W. Schallek, L. H. Sternbach, and R. Y. Ning in "Psychopharmacological Agents," Vol. III, M. Gordon, Ed., Academic Press, New York, N. Y., in press.

(11) This compound (mp 117–119°) was prepared as described in ref 9.

Scheme I




*Anal.* Calcd for $C_{20}H_{22}N_4O$: C, 71.83; H, 6.63; N, 16.76. Found: C, 72.10; H, 6.95; N, 16.84.

The ethereal mother liquors were evaporated to dryness. The residual oil was dissolved in a minimum of ethanol, and to the solution was added an excess of 4 *M* ethanolic hydrogen chloride. The precipitated hydrochloride salt was collected by filtration. Recrystallizations from methanol–ether afforded 6.50 g (25%) of the dihydrochloride salt of **13a** as colorless needles: mp 276–277°; ir (KBr) 1653 $cm^{-1}$ (CO); uv max ($CH_3OH$) 232 nm (ε 38,500), 351 (26,600), 257 (27,100), 274 sh (9320), 310 (13,600), 317 sh (12,500), 334 sh (8400), 348 (10,900), 364 (9320); nmr ($D_2O$, external TMS) δ 1.83 and 1.87 (2 t, *J* = 7 Hz, 6 each, 4 $CH_2CH_3$), 3.88 [m, 12, 2 $CH_2N(CH_2)_2$], 4.91 and 5.48 (2 m, 2 each, $CH_2NCO$ and $CH_2NCCO$), 7.65–8.10 (m, 3, aromatic), 8.18–8.46 (m, 2, aromatic), 8.98 ppm (2 d, *J* = 7 Hz, 1 each, aromatic).

*Anal.* Calcd for $C_{26}H_{35}N_5O \cdot 2HCl \cdot H_2O$: C, 58.85; H, 7.53; N, 13.20. Found: C, 58.78; H, 7.73; N, 13.17.

Alternately, the crude pyrolysis product mixture of **7a** from toluene was recrystallized thrice from dimethylformamide. Compound **8a** was obtained as colorless needles in 35% yield: mp above 325°; ir (Kbr) 3100–3200 (weak bands, amide NH) and 1670 $cm^{-1}$ (CO); uv max (*i*-PrOH, above 240 nm) 253 nm (ε 29,500), 263 sh (17, 700), 304 sh (8400), 318 sh (11,900), 329 (13,750), 350 sh (8400), 368 sh (4700).

*Anal.* Calcd for $C_{14}H_9N_3O$: C, 71.48; H, 3.86; N, 17.86. Found: C, 71.70; H, 3.92; N, 18.00.

**2-Bromopyrido[1′,2′:2,3]pyrazolo[5,4-*c*]quinolin-6(5*H*)-one (8b), 2-Bromo-5-(2-diethylaminoethyl)pyrido[1′,2′:2,3]pyrazolo-[5,4-*c*]quinazolin-6(5*H*)-one (12b), and 2-Bromo-5,7-bis(2-diethylaminoethyl)-5,7-dihydropyrido[2′,3′:3,2]pyrolo[5,4-*c*]quinolin-6(5*H*)-one (13b) Dihydrochloride.**—A suspension of 70.9 g (0.207 mol) of azidocarbostyril **7b** in 3.5 l. of toluene was heated to reflux for 6 hr. The crystalline product mixture that separated from solution was collected and washed with toluene (62.1 g). Tlc (silica gel, ether) of this material indicated a relatively clean mixture of two products appearing at $R_f$ 0.09 and 0.39. This mixture was alkylated in the same manner as described in the preparation of **12a** and **13a**, using 3 l. of dimethylformamide, 24.0 g of 50% dispersion of sodium hydride (1.0 mol) in mineral oil and 0.80 mol of 2-diethylaminoethyl chloride (250 ml of a 3.20 *M* solution in toluene). Crystallization of the product mixture from acetonitrile followed by recrystallizations from the same solvent afforded 26.5 g (31%) of **12b** as colorless needles: mp 194–197°; ir (KBr) 1667 $cm^{-1}$ (CO); uv max (*i*-PrOH) 221 nm (ε 32,350), 233 sh (27,400), 245 sh (33,750), 251 (39,200), 263 sh (25,000), 270 sh (21,200), 317 sh (12,500), 331 (16,450), 350 (11,550), 366 (7750); nmr ($CDCl_3$) δ 1.06 (t, 6, 2 $CH_2CH_3$), 2.69 (q, 4, 2 $CH_2CH_3$), 2.76 (m, 2, $CH_2N$), 4.46 (m, 2, $CH_2NCO$), 7.05–7.55 (m, 4, aromatic), 8.00–8.16 (m, 2, aromatic), 8.75 ppm (d, *J* = 7 Hz, 1, aromatic).

*Anal.* Calcd for $C_{20}H_{21}BrN_4O$: C, 58.12; H, 5.12; N, 13.56. Found: C, 58.25; H, 5.03; N, 13.54.

The acetonitrile mother liquors were combined and evaporated to dryness. The residue was dissolved in a minimum of ethanol and treated with an excess of 4 *M* ethanolic hydrogen chloride. After standing, the precipitated hydrochloride salt was collected and washed with ethanol. After recrystallizations from ethanol, the dihydrochloride salt of **13b** was obtained as yellow needles (25.5 g, 21%): mp 255–258°; ir (KBr) 1650 $cm^{-1}$; uv max ($CH_3OH$) 240 nm (ε 47,500), 253 sh (25,500), 261 (23,600), 270 sh (14,750), 279 (11,100), 303 sh (9750), 311 (12,950), 318 sh (11,300), 336 sh (8950), 349 (12,400), 366 (11,000); nmr ($D_2O$, external TMS) δ 1.86 and 1.90 (2 t, 6 each, 4 $CH_2CH_3$), 3.86 [m, 12, 2 $CH_2N(CH_2)_2$], 4.66 and 5.34 (m, 2 each, $CH_2NCO$ and $CH_2NCCO$), 7.43 (d, *J* = 9 Hz, 1, H-4), 7.75 (d of d, *J* = 2 and 9 Hz, 1, H-3), 7.94 (d of d, *J* = 5 and 9 Hz, 1, H-9), 8.31 (d, *J* = 2 Hz, 1, H-1), 8.54 (d, *J* = 9 Hz, 1, H-8), 8.78 ppm (d, *J* = 5 Hz, 1, H-10).

*Anal.* Calcd for $C_{26}H_{34}BrN_5O \cdot 2HCl$: C, 52.99; H, 6.20; N, 11.96. Found: C, 53.00; H, 6.11; N, 11.81.

Alternately, the crude pyrolysis product mixture of **7a** from toluene was recrystallized from dimethylformamide–ethanol. Compound **8b** was obtained as colorless needles in 52% yield: mp above 350°; ir (KBr) 3175 and 3080 (medium, amide NH) and 1680 $cm^{-1}$ (CO); uv max (EtOH–1.6% DMF) 247 nm (ε 40,000), 257 sh (26,000), 265 sh (21,200), 318 sh (13,400), 330 (17,250), 347 sh (12,400), 363 sh (8000).

*Anal.* Calcd for $C_{14}H_8BrN_3O$: C, 53.58; H, 2.57; N, 13.38; Br, 25.44. Found: C, 53.30; H, 2.59; N, 13.33; Br, 25.06.

**5-(2-Diethylaminoethyl)-7*H*-pyrido[2′,3′:3,2]pyrolo[5,4-*c*]-quinolin-6(5*H*)-one (11) and 5-(2-Diethylaminoethyl)pyrido-[1′,2′:2,3]pyrazolo[5,4-*c*]quinolin-6(5*H*)-one (12a).**—A mixture of 5.20 g (20.0 mmol) of 3-azido-4-(2-pyridyl)carbostyril (**7a**), 1.20 g of a 50% dispersion in oil of sodium hydride (50 mmol), and 50 ml of dimethylformamide was stirred for 0.5 hr. To this mixture was added 10 ml of a 3.20 *M* toluene solution of 2-diethylaminoethyl chloride (32 mmol). After stirring for 3 hr, the excess hydride was decomposed with water and the solvent evaporated. The residue was partitioned between methylene chloride and water. The methylene chloride layer was dried ($Na_2SO_4$) and evaporated to dryness.

The residue was dissolved in 100 ml of toluene and heated to reflux for 5 hr. Evaporation of toluene followed by crystallizations from acetonitrile afforded 1.10 g (17%) of **11** as colorless needles: mp 253–255°; ir (KBr) 3200 (sharp and strong, NH) and

1630 cm$^{-1}$ (CO); uv max (*i*-PrOH) 233 nm (44,750), 250 (28,750) 257 (28,400), 274 sh (10,500), 308 sh (14,300), 314 (15,000), 342 (10,550), 357 (8550).

*Anal.* Calcd for $C_{20}H_{22}N_4O$: C, 71.83; H, 6.63; N, 16.75. Found: C, 71.93; H, 6.87; N, 16.85.

The acetonitrile mother liquors were combined and evaporated to dryness. Trituration of the residue with ether afforded a light brown amorphous solid, which on recrystallizations from acetonitrile gave 2.40 g (36%) of **12a** as colorless prisms, mp 122–125°. This material was found to be identical with **12a** obtained above by tlc and comparison of infrared spectra.

The separation of **11** and **12a** were aided by tlc analyses. On silica gel plates developed in a mixture (1:1) of ethanol and ethyl acetate, **11** appeared at $R_f$ 0.22 and **12a** at $R_f$ 0.08.

**Acknowledgment.**—We thank Dr. R. P. W. Scott and his staff in our Physical Chemistry Department, in particular, Dr. F. Scheidl for elemental analyses, Dr. V. Toome for uv measurements, Mr. S. Traiman for ir spectra, and Dr. T. Williams for nmr spectra.

**Registry No.**—**6a**, 41526-19-6; **6b**, 1694-64-0; **7a**, 41895-15-2; **7b**, 41895-16-3; **8a**, 41895-17-4; **8b**, 41895-18-5; **11**, 41895-19-6; **12a**, 41895-20-9; **12b**, 41895-21-0; **13a** dihydrochloride, 41895-22-1; **13b** dihydrochloride, 41895-23-2; 2-(2-azidoacetamido-5-bromobenzoyl)pyridine, 41895-24-3.

# Reaction of Polyarylated Carbinols. IV. Reactions of 1,2,3,4,5-Pentaphenyl-2,4-cyclopentadien-1-ol with Sodium Amide. Effect of Quenching Temperature on the Products Obtained

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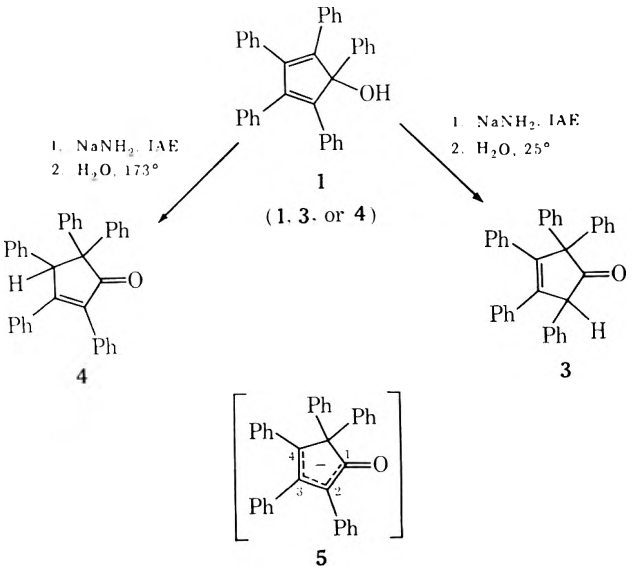
The reaction of 1,2,3,4,5-pentaphenyl-2,4-cyclopentadien-1-ol (**1**) with catalytic and equimolar amounts of sodium amide has been observed and its mechanism investigated. With catalytic amounts of sodium amide the reaction of **1** has been observed to occur *via* the same mechanism previously reported with other bases. With equimolar amounts of sodium amide 1,2,3,4,5-pentaphenyl-2,4-cyclopentadien-1-ol (**1**), 2,2,3,4,5-pentaphenyl-3-cyclopenten-1-one (**3**), and 2,3,4,5,5-pentaphenyl-2-cyclopenten-1-one (**4**) are all observed to produce exclusively **3**, the kinetically controlled product, if quenched with water at room temperature, and **4**, the thermodynamically controlled product, if quenched with water at 173°. A mechanism for production of these products involving initial formation of **3** in each case is proposed. Reaction of the anion formed when **1** is treated with equimolar amounts of sodium amide and quenched with benzoyl and benzyl chloride at both room temperature and at 173° is also discussed.

During our continuing study[1-3] of reactions of polyarylated carbinols we have observed[3] that heating 1,2,3,4,5-pentaphenyl-2,4-cyclopentadien-1-ol (**1**)[4,5] to 173° in isoamyl ether (IAE) in the presence of bases such as sodium hydroxide afforded a mixture of isomeric kinetically and thermodynamically controlled ketones, 2,2,3,4,5-pentaphenyl-3-cyclopenten-1-one (**3**)[6,7] and 2,3,4,5,5-pentaphenyl-2-cyclopenten-1-one (**4**),[6] respectively.

We now wish to report the results of this rearrangement when it is performed in the presence of sodium amide and offer some mechanistic explanation for the differences observed.

Treatment of dienol **1**, ketone **3**, or ketone **4** at 173° in IAE with 1 molar equiv of sodium amide followed by cooling of the anion solution to room temperature and quenching with water produces exclusively ketone **3**, the kinetically controlled product. However, if the anion solution is prepared in exactly the same manner from either dienol **1**, ketone **3**, or ketone **4**, but is quenched at 173° with water, ketone **4**, the thermodynamically controlled product, is exclusively produced.

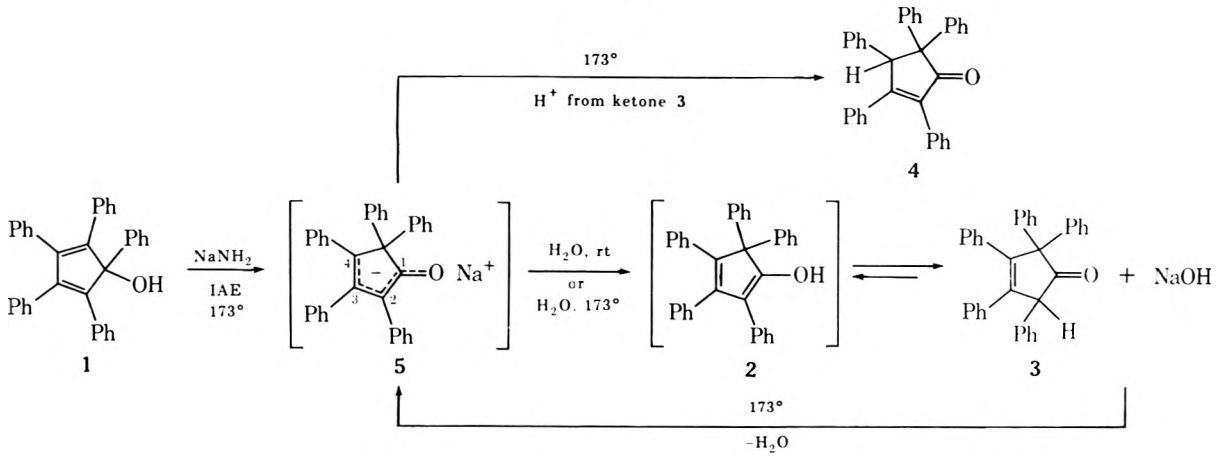
While these results with molar equivalents of sodium amide are different from the results obtained with sodium hydroxide,[3] the results obtained (Table I, Experimental Section) when catalytic amounts of sodium amide are used as base (molar ratio of 10 dienol **1**:1 $NaNH_2$) are identical with those obtained in the reaction of the dienol **1** in IAE with sodium hydroxide as the base.[3] Thus in the reaction of dienol **1** with catalytic amounts of sodium amide, the products formed are obtained by internal quenching and *via* the same mechanism previously described[3] for the sodium hydroxide catalyzed reaction.




This mechanism does not, however, apply in the case where equimolar amounts of sodium amide are employed. Since this quantity of base ensures complete

(1) A. K. Youssef and M. A. Ogliaruso, *J. Org. Chem.*, **37**, 2601 (1972).
(2) A. K. Youssef and M. A. Ogliaruso, *J. Org. Chem.*, **38**, 487 (1973).
(3) A. K. Youssef and M. A. Ogliaruso, *J. Org. Chem.*, **38**, 2023 (1973).
(4) K. Ziegler and B. Schnell, *Justus Liebigs Ann. Chem.*, **445**, 266 (1925).
(5) C. F. H. Allen and J. A. VanAllan, *J. Amer. Chem. Soc.*, **65**, 1384 (1943).
(6) C. Dufraisse, G. Rio, and A. Ranjon, *C. R. Acad. Sci.*, **253**, 2441 (1961).
(7) R. Breslow and H. W. Chang, *J. Amer. Chem. Soc.*, **83**, 3727 (1961).

SCHEME I




conversion of dienol **1** to the intermediate anion **5** and the proton sources, dienol **1** and ketone **3**, available for internal quenching in the case of the sodium hydroxide catalyzed reaction are no longer available in the reaction mixture, the proton source must be the water externally added. In this reaction the quenching temperature controls the site of protonation, either at the oxygen atom, at carbon 2, or at carbon 4, and the results may be explained on the basis of thermodynamically or kinetically controlled product formation.

Reaction of dienol **1** at 173° in IAE with an equimolar amount of sodium amide, cooling the solution containing anion **5** to 120°, and adding water dropwise at this temperature produced ketones **3** and **4** in a 4:6 ratio, respectively. These results agree with expectation that the products formed depended upon thermodynamic and kinetic control.

To establish if the kinetically controlled product, ketone **3**, was the first product formed when the quench was performed at 173° and then rearranged to the thermodynamically controlled product, ketone **4**, under the conditions of the reaction, the following reaction was performed. Dienol **1** was completely converted to anion **5** with molar amounts of sodium amide in IAE at 173° and the reaction was quenched by the addition of water. Immediately upon completion of the water addition a sample was removed and analyzed. The only product shown to be present in this sample by both ir and glpc was ketone **3**. Removal of a second sample from the same reaction mixture after 15 min showed ketone **4** to be the only product present. These observations indicate that the kinetically controlled product, ketone **3**, is formed first and that it is converted to the thermodynamically controlled product, ketone **4**, under the conditions of the reaction.

Attempts to rearrange **3** to **4** thermally were unsuccessful. However, since **3** is converted quantitatively to **4** if the same reaction is performed in the presence of base,[3] then the sodium hydroxide formed when anion **5** is quenched must be catalyzing the rearrangement of **3** to **4** at 173° in IAE completely and quantitatively *within* 15 min. The speed of this isomerization was established independently using a pure sample of **3**.

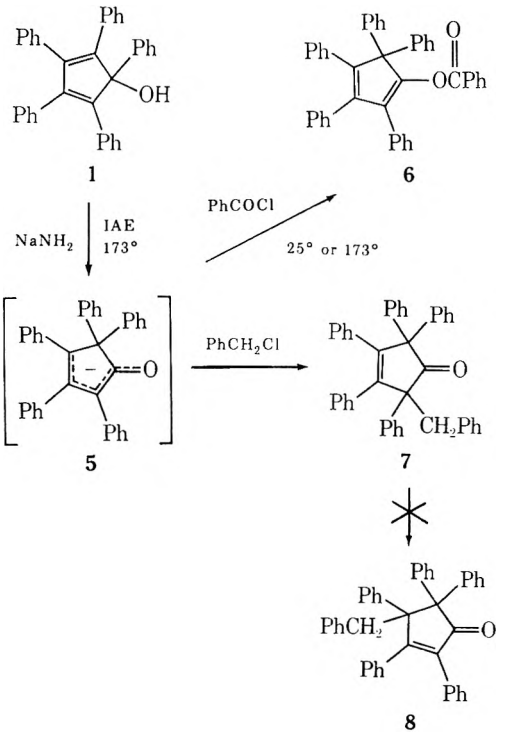
The mechanism proposed for the reaction of dienol **1** with equimolar amounts of sodium amide is illustrated in Scheme I and involves complete conversion of **1** to anion **5**, which upon quenching with water at 173° produces initially the kinetically controlled product, ketone **3**, which then quantitatively rearranges within 15 min to the thermodynamically controlled product, ketone **4**, upon standing in IAE at 173° in the presence of the sodium hydroxide formed. The sodium hydroxide reacts with small amounts of **3** to produce anion **5**, which is then quenched with unreacted **3** to produce **4**. The mechanism proposed for the production of ketone **3** when anion **5** is quenched with water at room temperature involves the same sequence as described above, except that **3** once formed does not undergo rearrangement to **4**. Even though the sodium hydroxide is still produced in this quench, the temperature is not sufficient to cause extensive reaction of the sodium hydroxide with ketone **3** to produce anion **5**.

Additional evidence in support of this proposed mechanism is obtained by quenching anion **5**, formed from dienol **1** at 173° in IAE and an excess of sodium amide, with benzoyl chloride. Using benzoyl chloride as the quenching agent and performing the addition at room temperature should result in the production of the kinetically controlled product, which should resemble structurally ketone **3**. However, since the benzoyl group is a good agent for O- *vs.* C-acylation[8] and since in anion **5** the electron density[3] is greater on oxygen than on $C_2$, it is not surprising that the major product (71%) isolated from this reaction using benzoyl chloride as the quenching agent at room temperature is 1-benzoyloxy-2,3,4,5,5-pentaphenyl-1,3-cyclopentadiene (**6**), the same product which is formed in 70% yield when anion **5** is quenched with benzoyl chloride at 173°.

These results are in direct contrast to the results reported by Dufraisse, *et al.*,[9] who quenched anion **5** with benzyl chloride and bromide. The product which they obtained was 5-benzyl-2,2,3,4,5-pentaphenyl-3-cyclopentadien-1-one (**7**). We have repeated their experiment quenching anion **5** with benzyl chloride at room temperature and at 173° and have obtained good yields (83–92%) of **7**. It is clear that in this case the absence of an allylic hydrogen prevented reaction of **7** with the sodium hydroxide formed and thus prevented **7**, which resembles the kinetically controlled product ketone **3**, from equilibrating to **8**, which resembles the thermodynamically controlled product ketone **4**. Product **7**

(8) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, pp 526–529, 763–765.

(9) C. Dufraisse, G. Rio, and A. Liberles, *C. R. Acad. Sci.*, **256**, 1873 (1963).




can be justified on the basis of the C- *vs.* O-alkylating selectivity of the benzyl group.[8]

From these results it appears that the site of acylation and/or alkylation is governed by both the electron density distribution in anion **5** and, to a greater extent, by the C *vs.* O selectivity of the acylating and/or alkylating agent. Reactions of anion **5** with other acylating and alkylating agents at various temperatures are currently under investigation.

## Experimental Section

**General.**—The glpc analysis of samples was performed on a Bendix Model 2600 gas chromatograph and a Bendix Model 1200 recorder. The glpc was equipped with a 3 ft × 0.25 in. column packed with 3% QF-1 on Chromosorb W (H. P., mesh 100–120) support. Operating conditions were as follows: temperature of inlet 210°; detector 255°; injector 255°; column 210°; and a He carrier gas flow rate of 80 ml/min. Retention times of the dienol **1** was 6.25 min, of ketone **3** 13.75 min, and of ketone **4** 15.75 min. Analysis of the peak areas observed was determined by triangulation.[10] Elemental analyses were performed on a departmental F & M Model 185 C, H, and N analyzer.

**Reaction of 1,2,3,4,5-Pentaphenyl-2,4-cyclopentadien-1-ol (1) with Equimolar Sodium Amide. I. Quenching with Water at 173°.**—Into a 250-ml three-necked round-bottomed flask equipped with a reflux condenser, a magnetic stirrer, a serum cap, and a nitrogen inlet tube was placed 1.0 g (2.16 mmol) of 1,2,3,4,-5-pentaphenyl-2,4-cyclopentadien-1-ol (**1**)[1,3,4] and 50 ml of freshly distilled isoamyl ether (IAE) and the mixture was heated to reflux (173°). At this temperature 84.3 mg (2.16 mmol) of sodium amide was added very cautiously all at once. A vigorous reaction occurred immediately, affording a deep red-orange solution which was allowed to reflux for 15 min. After this time 10 ml of water was added all at once *via* syringe to the reaction mixture, which was then retained at 173° for an additional 30 min. At this point a 5-ml sample was removed for glpc analysis and the rest of the solution was cooled to room temperature. Analysis of the sample removed by glpc using the instrument and conditions described in the general section above showed only one product to be present, 2,3,4,5,5-pentaphenyl-2-cyclopenten-1-one (**4**). The remaining solution, now at room temperature, was poured into 100 ml of water, and the organic layer was separated, washed several times with water, and dried over anhydrous magnesium sulfate. The solvent was removed under vacuum to afford a viscous yellow oil which was crystallized from a mixture of benzene–petroleum ether (bp 30–60°) to give 992 mg (2.14 mmol, 99.1%) of pale yellow crystals of 2,3,4,5,5-pentaphenyl-2-cyclopenten-1-one (**4**), mp 169–170° (lit.[1,3,6] mp 169–170°). The ir,[6] uv,[6] and nmr[1] spectral data for this compound agreed with the literature.

**II. Quenching with Water at Room Temperature.**—The above experiment was repeated as described to the point of allowing the anion solution to reflux for 15 min. At this point the entire reaction mixture was then cooled to room temperature under nitrogen. When the solution attained room temperature, 10 ml of water was added at once *via* syringe to the stirred solution and immediately a 5-ml sample was removed for glpc analysis. Analysis of the sample removed by glpc using the instrument and conditions described in the general section above showed only one product to be present, 2,2,3,4,5-pentaphenyl-3-cyclopenten-1-one (**3**). The remaining solution was worked up as reported above to give 996 mg (2.15 mmol, 99.5%) of white crystals of **3**, mp 194.5–196° (lit. mp 194–195°,[6,7] 194.5–196°[1]). The ir,[1,6,7] uv,[6,7] and nmr[7] for this compound agreed with the literature.

**Reaction of 2,2,3,4,5-Pentaphenyl-3-cyclopenten-1-one (3) with Equimolar Sodium Amide. III. Quenching with Water at 173°.**—This experiment was performed as described above in I to the point of analyzing the sample removed by glpc, except that 1.0 g (2.16 mmol) of 2,2,3,4,5-pentaphenyl-3-cyclopenten-1-one (**3**) was used. The sample removed was subjected to glpc analysis using the instrument and conditions described in the general section and only one product, 2,3,4,5,5-pentaphenyl-2-cyclopenten-1-one (**4**), was shown to be present. The remaining solution, cooled to room temperature, was poured into 100 ml of water and worked up as described in I above to afford 996 mg (2.15 mmol, 99.5%) of white crystals of **4**, melting point and spectral data the same as those described in I above.

**IV. Quenching with Water at Room Temperature.**—This experiment was performed as described in II above, except that 2,2,3,4,5-pentaphenyl-3-cyclopenten-1-one (**3**) was used. The results were the same as reported above in II.

**Reaction of 2,3,4,5,5-Pentaphenyl-2-cyclopenten-1-one (4) with Equimolar Sodium Amide. V. Quenching with Water at 173°.**—This experiment was performed as described in I above except that 1.0 g (2.16 mmol) of 2,3,4,5,5-pentaphenyl-2-cyclopenten-1-one (**4**) was used. Glpc analysis of the sample removed again showed **4** to be the only product present. Work-up of the remaining solution afforded 994 mg (2.14 mmol, 99.1%) of **4** with melting point and spectral data the same as reported in I above.

**VI. Quenching with Water at Room Temperature.**—This experiment was performed as described in II above except that 2,3,4,5,5-pentaphenyl-2-cyclopenten-1-one (**4**) was used. The results were the same as reported above in II.

**Reaction of 1,2,3,4,5-Pentaphenyl-2,4-cyclopentadien-1-ol (1) with Catalytic Sodium Amide.**—Into a 100-ml, three-necked, round-bottomed flask equipped with a reflux condenser, a magnetic stirrer, a serum cap, and a nitrogen inlet tube was placed 50 ml of isoamyl ether (IAE) which was heated to 173°. At this point a mixture of 8.0 mg (0.2 mmol) of sodium amide and 1.0 g (2.16 mmol) of dienol **1** was added all at once. Samples of 1 ml each were taken at various times by inserting a hypodermic syringe through the serum cap. The samples thus removed were placed in separate containers and cooled by means of an ice–water bath. After all the required samples were collected, glpc analysis was carried out using the instrument and conditions described in the general section. Table I reports the per cent composition obtained from the peak areas and these percentages are plotted on the same graph *vs.* time. Qualitative ir analysis of each sample was also performed and for the sample taken after 13 min only two products were observed to be present, the dienol **1** with a hydroxyl peak at 3500 $cm^{-1}$ and ketone **3** with a carbonyl peak at 1760 $cm^{-1}$. Analysis of all samples taken after 53 min and up to 533 min showed three distinct products to be present, dienol **1** (hydroxyl peak at 3500 $cm^{-1}$), ketone **3** (carbonyl peak at 1760 $cm^{-1}$), and ketone **4** (carbonyl peak at 1720 $cm^{-1}$). Fractional crystallization techniques using varying mixtures of benzene–petroleum ether allowed separation and isolation of both ketone **3** and ketone **4** from each of these intermediate samples. Analysis of samples taken after 533 min showed only one peak to be present in both ir and glpc corresponding to ketone **4**.

**Reaction of 1,2,3,4,5-Pentaphenyl-2,4-cyclopentadien-1-ol (1) with Equimolar Sodium Amide. VII. Quenching with Water at**

(10) As described in H. M. McNair and E. J. Bonelli, "Basic Gas Chromatography," Varian Associates, Palo Alto, Calif., 1969, p 154.

TABLE I

ISOMERIZATION REACTION OF 1,2,3,4,5-PENTAPHENYL-2,4-CYCLOPENTADIEN-1-OL IN ISOAMYL ETHER WITH CATALYTIC AMOUNTS OF SODIUM AMIDE

| Reaction time, min | Ratio, % | | |
|---|---|---|---|
| | Dienol 1 | Ketone 3 | Ketone 4 |
| 0 | 100 | 0 | 0 |
| 13 | 87.8 | 12.2 | 0 |
| 53 | 77.8 | 18.4 | 3.8 |
| 113 | 69.8 | 21.5 | 8.7 |
| 143 | 61.0 | 24.3 | 14.7 |
| 173 | 56.7 | 25.7 | 17.6 |
| 203 | 50.4 | 24.6 | 25.0 |
| 233 | 46.5 | 23.3 | 30.2 |
| 263 | 27.7 | 22.2 | 40.1 |
| 323 | 30.2 | 15.8 | 53.9 |
| 383 | 23.5 | 12.0 | 64.5 |
| 443 | 14.6 | 9.4 | 76.0 |
| 503 | 8.6 | 4.7 | 86.7 |
| 533 | 7.0 | 3.6 | 89.4 |

120°.—This experiment was performed with the same amounts of starting material and in the same manner as described in I above to the point of allowing the anion solution to reflux for 15 min. At this point the entire reaction mixture was cooled to 120° and 10 ml of water was added all at once *via* syringe to the reaction mixture, which was then retained at 120° for an additional 30 min. A 5-ml sample was then removed for glpc and ir analysis and the rest of the solution was cooled to room temperature. Analysis by ir of the sample removed showed two strong peaks, one for ketone **3** (carbonyl at 1760 $cm^{-1}$) and one for ketone **4** (carbonyl at 1720 $cm^{-1}$), while glpc analysis of the same sample further established **3** and **4** as the only products present. The remaining solution, now at room temperature, was worked up as described above in I and the residue was subjected to fractional crystallization using varying mixtures of benzene–petroleum ether which allowed separation and isolation of 0.42 g (0.9 mmol, 41%) of ketone **3** and 0.55 g (1.2 mmol, 58%) of ketone **4**. The melting points and spectral data for these compounds agreed with the literature values.

**VIII. Quenching with Water at 90°.**—This experiment was performed in the same manner as described in VII above except that the reaction mixture was cooled to 90° before being quenched with water. Analysis by ir of a sample removed showed one strong peak for ketone **3** (carbonyl at 1760 $cm^{-1}$) and one weak peak for ketone **4** (carbonyl at 1720 $cm^{-1}$), while glpc analysis of the same sample also showed both ketones as the only products present. Work-up of the remaining solution as described above afforded 0.83 g (1.8 mmol, 83%) of ketone **3** and 0.17 g (0.4 mmol, 17%) of ketone **4**.

**Establishment of Ketone 3 as the Initial Product Formed When the Solution Is Quenched at 173°.**—This experiment was performed using the same amounts of starting material and in the same manner as described in I above to the point of allowing the anion solution to reflux for 15 min. At this point a syringe containing 10 ml of water equipped with a needle long enough to extend below the level of the solution in the flask was inserted through the serum cap. On the down stroke of the plunger the 10 ml of water was added all at once to the reaction mixture and immediately a 5-ml sample was removed from the solution by an up stroke of the plunger. Glpc and ir analysis of this sample showed only ketone **3** to be present. A second sample removed from the solution, still at 173°, after 15 min subjected to ir and glpc analysis showed only ketone **4** to be present. Repeating this experiment several times always gave the same results.

**Sodium Hydroxide Catalyzed Isomerization of Ketone 3 to Ketone 4.**—Into a 100-ml, three-necked, round-bottomed flask equipped with a reflux condenser, a magnetic stirrer, and a serum cap was placed 50 ml of IAE which was heated to reflux (173°). At this point a concentrated aqueous solution of sodium hydroxide (85 mg of sodium hydroxide in 2 ml of water) was syringed into the boiling solvent. After the initial spattering subsided, small particles of base were observed to precipitate from the solvent. At this point 1.0 g (2.16 mmol) of 2,2,3,4,5-pentaphenyl-3-cyclopenten-1-one (**3**) was added as a solid all at once to the refluxing base mixture. Samples removed by syringe at 5-min intervals after the addition of **3** was complete showed by ir and glpc that **3** had been quantitatively converted to **4** within 15 min.

**Attempted Thermal Rearrangement of Ketone 4.**—Into a 100-ml, three-necked, round-bottomed flask equipped with a reflux condenser, a magnetic stirrer, and a serum cap was placed 1.0 g (2.16 mmol) of 2,2,3,4,5-pentaphenyl-3-cyclopenten-1-one (**3**) and 50 ml of freshly distilled IAE and the mixture was heated to reflux (173°). In 15-min intervals at the beginning of the reaction, and at 30-min intervals after 2 hr, over an 8-hr period, samples were removed and subjected to ir and glpc analysis. The only product shown to be present in every sample by both ir and glpc was ketone **3**.

**Preparation of 1-Benzoyloxy-2,3,4,5,5-pentaphenyl-1,3-cyclopentadiene (6). Quenching Anion 5 with Benzoyl Chloride. IX. At 173°.**—Into a 100-ml, three-necked, round-bottomed flask equipped with a reflux condenser, a nitrogen inlet tube, a magnetic stirrer, and a dropping funnel were placed 25 ml of freshly distilled IAE and 462 mg (1.0 mmol) of 1,2,3,4,5-pentaphenyl-2,4-cyclopentadien-1-ol (**1**) and the solution was heated to reflux (173°). At this point 39 mg (1.0 mmol) of sodium amide was added and the solution was allowed to reflux for 15 min. To this red-orange solution of anion **5** was added dropwise 140 mg (1.0 mmol) of freshly distilled benzoyl chloride, and the color of the anion solution was observed to completely discharge as the addition of the benzoyl chloride was completed (5 min). The reaction mixture was allowed to reflux for an additional 30 min and cooled to room temperature with stirring, and the solvent was removed under vacuum on the rotoevaporator. This afforded a viscous yellow oil which was crystallized from 95% ethanol to give 390 mg (0.7 mmol, 70%) of white crystals, mp 186–187°, ir ($CCl_4$) 1755 (carbonyl), 1175 $cm^{-1}$ (ester).

*Anal.* Calcd for $C_{42}H_{30}O_2$: C, 89.02; H, 5.34; mol wt, 566. Found: C, 88.88; H, 5.68; mol wt, 566 (mass spectrum).

**X. At Room Temperature.**—This experiment was performed in the same manner as described in IX above except that the reaction mixture was cooled to room temperature with stirring under nitrogen before the benzoyl chloride was added. Removal of the solvent under vacuum on the rotoevaporator afforded a viscous yellow oil which was crystallized from 95% ethanol to yield 400 mg (0.705 mmol, 70.5%) of white, crystalline 1-benzoyloxy-2,3,4,5,5-pentaphenyl-1,3-cyclopentadiene (**6**), melting point, spectral data, and analysis the same as reported above. Concentration of the mother liquor from the crystallization afforded 115 mg (0.248 mmol, 24.8%) of ketone **3** which probably resulted from reaction of some of anion **5** with atmospheric moisture.

**Preparation of 5-Benzyl-2,2,3,4,5-pentaphenyl-3-cyclopenten-1-one (7). Quenching Anion 5 with Benzyl Chloride. XI. At 173°.**—This experiment was performed in the same manner as described in IX above using 1.0 g (2.16 mmol) of **1**, 30 ml of IAE, and 84.3 mg (2.16 mmol) of sodium amide. The refluxing anion solution was quenched with 5 ml of freshly distilled benzyl chloride added dropwise and the resulting solution was allowed to reflux for an additional 1 hr. At this point the solution was cooled to room temperature and poured into 100 ml of water, and the organic layer was separated, dried over magnesium sulfate, and concentrated under vacuum on the rotoevaporator. The resulting viscous yellow oil was crystallized from 95% ethanol to give 1.0 g (1.8 mmol, 83%) of white, crystalline solid, mp 196–197° (lit.[9] mp 197–198°).

**XII. At Room Temperature.**—This experiment was performed in the same manner as described in XI above except that the reaction mixture was cooled to room temperature with stirring under nitrogen before the benzyl chloride was added. Work-up and crystallization as described above afforded 1.1 g (1.99 mmol, 92%) of **7**.

**Acknowledgment.**—We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

**Registry No.**—**1**, 2137-74-8; **3**, 34759-47-2; **4**, 34759-48-3; **6**, 42116-83-6; **7**, 42116-84-7; sodium amide, 7782-92-5.

# Acylation of Indoles by Duff Reaction and Vilsmeier–Haack Formylation and Conformation of *N*-Formylindoles

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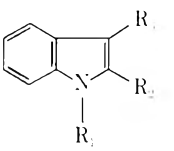
Indoles react with hexamethylenetetramine to give 3-formylindoles. Skatole on formylation with *N,N*-dimethylformamide and phosphorus oxychloride gives 1-formyl-3-methylindole, 2-formyl-3-methylindole, and *o*-formamidoacetophenone. The same reaction with 2,3-dimethylindole gives 2,3-dimethyl-1-formylindole. 1-Formylindole exists in two conformations in $CCl_4$ at 30° while, under the same conditions, 2,3-dimethyl-1-formylindole exists solely in one conformation.

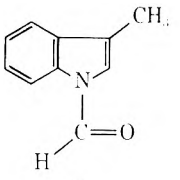
Phenolic compounds are known to undergo Duff reaction with hexamethylenetetramine (HMT) and give the corresponding phenolic aldehydes.[1] It was of interest to study the possibility of formylation of indoles with this reagent. Formylation of indoles by Vilsmeier–Haack reaction and acylation of organometallic derivatives of indoles and 3-substituted indoles are well documented,[2] but extensive investigation of the former reaction with 3-substituted indoles has not been carried out so far.[2a] It was also considered worthwhile to study this reaction on 3-substituted indoles. The results of these studies as well as that of an investigation on the conformational aspect and aldehydic character of *N*-formylindoles are presented in this communication.

The action of HMT on **1** and **2** in hot AcOH resulted in the formation of the indole-3-carboxaldehydes **3** and **4** in 25 and 74% yields, respectively. The yields are lower than those of the Vilsmeier–Haack formylation of indoles. However, the reaction is extremely easy and convenient to perform. It may be mentioned in this connection that no trace of **3** was found in a similar reaction under milder conditions.[3]

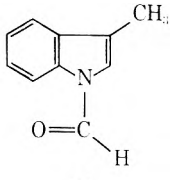
The Vilsmeier–Haack formylation of **5** and **6** was studied and the results are given in Tables I and II.



| Compd | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| 1 | H | H | H |
| 2 | H | $C_6H_5$ | H |
| 3 | H | H | CHO |
| 4 | H | $C_6H_5$ | CHO |
| 5 | H | H | $CH_3$ |
| 6 | H | $CH_3$ | $CH_3$ |
| 7 | H | $COCH_3$ | $CH_3$ |
| 9 | H | CHO | $CH_3$ |
| 12 | $CH{=}NNHC_6H_3(NO_2)_2$ (*o,p*) | H | $CH_3$ |
| 13 | $CH{=}NNHC_6H_3(NO_2)_2$ (*o,p*) | $CH_3$ | $CH_3$ |



8a



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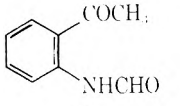
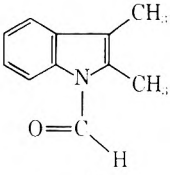


10



11

TABLE I

PRODUCTS FROM THE REACTION OF 5 WITH *N,N*-DIMETHYLFORMAMIDE (DMF) AND $POCl_3$ UNDER DIFFERENT CONDITIONS

| Temp, °C | Time, hr | Yield,[a] % 8 | 9 | 10 | 5 |
|---|---|---|---|---|---|
| 98–100 | 3 | 71 | 22.5 | 0.5 | Nil |
| 28–30 | 3 | 34 | 11 | Nil | 52 |
| 28–30 | 36 | 38 | 15 | 1 | 45 |
| 28–30 | 150 | 41 | 19 | 2.3 | 35 |

[a] Actual yield of the products isolated by column chromatography on silica gel.

The yields of all the products increased considerably at elevated temperature, and the *N*-formyl derivative was the major product.[4–6] However, $BF_3$-catalyzed acetylation of **5** with $Ac_2O$–AcOH in boiling ether for 5 min

TABLE II

PRODUCTS FROM THE REACTION OF 6 WITH DMF AND $POCl_3$ UNDER DIFFERENT CONDITIONS

| Temp, °C | Time, hr | Yield,[a] % 11 | 6 |
|---|---|---|---|
| 98–100 | 6 | 52.1 | 0.55 |
| 28–30 | 48 | 15 | 65 |

[a] See footnote *a*, Table I.

(1) (a) L. N. Ferguson, *Chem. Rev.*, **38**, 230 (1946); (b) C. F. H. Allen and G. W. Leubner, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 866; (c) W. E. Smith, *J. Org. Chem.*, **37**, 3972 (1972).

(2) (a) R. J. Sundberg, "The Chemistry of Indoles," Academic Press, New York, N. Y., 1970, pp 33–39, 412–417; (b) W. A. Remers and R. K. Brown in "The Chemistry of Heterocyclic Compounds," Vol. 25, Part 1, W. J. Houlihan, Ed., Wiley-Interscience, New York, N. Y., 1972, pp 116–120, 133–134; (c) R. A. Heacock and S. Kasparek in "Advances in Heterocyclic Chemistry," Vol. 10, A. R. Katritzky and A. J. Boulton, Ed., Academic Press, New York, N. Y., 1969; (d) D. E. Horning and J. M. Muchowski, *Can. J. Chem.*, **48**, 193 (1970).

(3) H. R. Snyder, S. Swaminathan, and H. J. Sims, *J. Amer. Chem. Soc.*, **74**, 5110 (1952).

(4) It was reported that the yield of **8** remained the same, while that of **9** decreased with increasing temperature of a similar reaction: C. W. Whittle and R. N. Castle, *J. Pharm. Sci.*, **52**, 645 (1963).

(5) A recent report appears to indicate that **8** and **9** were formed in the ratio of 95:5 in the Vilsmeier–Haack formylation of **5**: S. Clementi, P. Linda, and G. Marino, *J. Chem. Soc., Chem. Commun.*, 427 (1972).

(6) **11** was obtained from **6** in 30.4% yield in a slightly different reaction: N. F. Kucherova, V. P. Evdakov, and N. K. Kochetkov, *Zh. Obshch. Khim.*, **27**, 1049 (1957); *Chem. Abstr.*, **52**, 3763 (1958).

afforded only the 2-acetylindole **7** [mp 147°; ir 3320 (NH), 1645 $cm^{-1}$ (C=O)] in 88% yield.[7]

The nitrogen of indole is very weakly basic because of delocalization of its lone pair of electrons to make up the ten-electron $\pi$ system. These electrons of *N*-acylindoles are not fully available for entering into conjugation with the acyl group as in typical amides and formamides. It was, therefore, hoped that *N*-acylindoles would show some carbonyl character. With this view in mind, the *N*-formylindoles **8** and **11** were treated with 2,4-dinitrophenylhydrazine (DNP) in weakly acidic media, and they were, in fact, found to form the DNP derivatives **12** and **13**, exhibiting thereby pronounced carbonyl character of their *N*-formyl groups. However, in the highly acidic medium usually employed in such reactions,[8] the *N*-formyl groups of **8** and **11** were readily cleaved off, and the DNP derivatives could not be isolated from such reaction media. In this connection, it may be pointed out that such carbonyl character of an amido or formamido group does not appear to have been observed before.[9]

Products of the type **10**, which was also prepared by perbenzoic acid oxidation of **5**[10] for direct comparison, do not appear to have been obtained before in the Vilsmeier–Haack formylation of indoles. Perhaps it arises out of aerial oxidation.

From nmr spectral studies, certain *N*-acylindolines were shown to exist in two conformations.[11] Similar investigation on *N*-acylindoles does not appear to have been made so far. Analysis of the nmr spectra of **8** and **11** in $CCl_4$ at 31.5° revealed that under these conditions **8** exists in two different conformations, whereas **11** exists in only one. The aldehydic proton of **11** appeared as a singlet at $\delta$ 9.04, indicating that it exists solely in the conformation shown in its structural formula, because of the buttressing effect of the 2-$CH_3$ group. The same proton of **8** gave rise to two singlets at $\delta$ 8.78 and 9.08 accounting for 75 and 25% of one proton, respectively. Thus, **8** exists in two conformations **8a** and **8b**, **8a** being predominant because of the lack of a buttressing group at the 2 position. The 7-H of **8** and **11** gave rise to a broad doublet at $\delta$ 8.88 ($J$ = 7 Hz, ortho coupling) and a broad hump at $\delta$ 8.12, respectively, due to the deshielding effect of the magnetic anisotropy of the C=O group. The aldehydic proton and the 7-H of **9** appeared as a singlet at $\delta$ 10.02 and as a doublet at $\delta$ 7.70 ($J$ = 7 Hz), respectively.

The uv spectra of the formylindoles and their DNP derivatives are recorded in Table III.

TABLE III
UV SPECTRA OF FORMYLINDOLES AND THEIR DNP DERIVATIVES

| | $\lambda_{max}$, mμ (log $\epsilon_{max}$), in EtOH |
|---|---|
| 1-Formylindole **8** | 240 (4.53), 292 (3.79), 298 (3.78) |
| 1-Formylindole **11** | 247 (4.32), 300 (3.68) |
| 2-Formylindole **9** | 238 (4.17), 312 (4.33) |
| DNP derivative **12**[a] | 256 (4.25), 304 (3.82), 314 (3.84), 392 (4.40) |
| DNP derivative **13**[a] | 227 (4.55), 253 (4.34), 316 (4.07), 391 (4.40), 410 (4.35) |

[a] In THF.

## Experimental Section

Melting points are uncorrected. Light petroleum refers to the fraction boiling at 60–80°. Ir spectra were recorded in Nujol mulls and nmr spectra in $CDCl_3$, if not mentioned otherwise. Chemical shifts are given in $\delta$ values relative to TMS. DMF and $POCl_3$ were distilled immediately before use.

**Indole-3-carboxaldehyde (3).**—A mixture of indole (0.35 g), HMT (1 g), and glacial AcOH (1.5 ml) was heated at 100° for 2.5 hr. Concentrated HCl (2.5 ml) in water (3 ml) was added and heating was continued for 10 min more. Water (15 ml) was added, the mixture was neutralized with $NaHCO_3$, and the resulting solids were collected. A light brown mass was obtained by extracting both the filtrate and the residue with AcOEt. After crystallization from AcOEt–light petroleum and finally from EtOH, it afforded **3** (108 mg, 25%), ir 3175 (NH), 1630 $cm^{-1}$ (C=O), as almost colorless needles, mp 196–198°. Its identity was confirmed by mixture melting point determination and tlc comparison with an authentic sample.

**2-Phenylindole-3-carboxaldehyde (4)** was prepared from 2-phenylindole[12] (2.12 g), HMT (3.65 g), and glacial AcOH (5.5 ml) following the foregoing procedure and obtained after crystallization from EtOH as pale yellow solids (1.80 g, 74%): mp 251–252° (lit.[2d] mp 251–252°); ir 3160 (NH) and 1635 $cm^{-1}$ (s, C=O). Aldoxime: colorless needles (from benzene); mp 182–184° (lit.[3] mp 182–184°); ir 3280, 3460 (NH, OH), 1640 $cm^{-1}$ (w, C=N).

**Formylation of Skatole (5).**—$POCl_3$ (1.25 ml) was added dropwise with stirring to DMF (4.25 ml) at 10–20° over 20 min. **5** (1.64 g) in DMF (1 ml) was added slowly with stirring and the mixture was heated for 3 hr at 98–100°. Excess concentrated aqueous solution of NaOAc was added. The mixture was stirred for 30 min at 28° and extracted with AcOEt (3 × 20 ml). The dried ($MgSO_4$) extract after removal of solvent furnished a pale yellow oil (1.95 g) which was chromatographed on a silica gel column. Elution with light petroleum–ether (19:1) afforded ***N*-formyl-3-methylindole (8, 1.41 g, 71%)** as a colorless oil [lit.[4] bp 98–100° (0.03 mm)]: ir (neat) 1690 $cm^{-1}$ (NCHO); mass spectrum (70 eV) $m/e$ (rel intensity) 159 (70, $M^+$), 131 (20, M − CO), 130 (100, 131 − H). Further elution of the column with light petroleum–ether (17:3) first gave **3-methylindole-2-carboxaldehyde (9, 0.45 g, 22.5%)** as almost colorless needles (from light petroleum): mp 138–140° (lit.[4] mp 139–140°); ir 3340 (NH) and 1648 $cm^{-1}$ (C=O). Latter fractions furnished ***o*-formamidoacetophenone (10, 10 mg, 0.5%)** as almost colorless needles (from cyclohexane): mp 77° (lit.[10] mp 77°); nmr (HA 100 MHz) 8.71 (b d, 1, NCHO, $J$ = 8 Hz), 8.46 (b s, 1, NH), 7.89 (d, 1, ArH ortho to $COCH_3$, $J$ = 8 Hz), 7.86 (d, 1, ArH ortho to NCHO, $J$ = 8 Hz), 7.53 (*ca.* t, 1, ArH para to $COCH_3$, $J$ = 8 Hz), 7.13 (*ca.* t, 1, ArH para to NCHO, $J$ = 8 Hz), and 2.64 (s, 3, $COCH_3$); mass spectrum (70 eV) $m/e$ (rel intensity) 163 (43, $M^+$), 148 (17), 135 (53), 120 (100), 92 (33), 43 (28).

**2,3-Dimethyl-*N*-formylindole (11)** was prepared from **6**[12] (4.5 g), $POCl_3$ (5.45 g), and DMF (10 g), following the foregoing procedure except that the reaction mixture was heated at 98–100° for 6 hr under $N_2$. The crude product on chromatography over silica gel in benzene–light petroleum (1:1) gave unreacted **6** (25 mg) together with **11** (2.80 g, 52.1%) as colorless needles (from cyclohexane), mp 87–88° (lit.[6] mp 84–86°), ir 1700 $cm^{-1}$ (NCHO).

**2,4-Dinitrophenylhydrazone 12 of *N*-Formyl-3-methylindole (8).**—**8** (159 mg) in MeOH (4 ml) was added to a clear, weakly acidic solution of DNP (198 mg) in MeOH (10 ml). After 1 hr, **12** (275 mg) was collected, crystallized from THF, and obtained as orange-red needles: mp 278° dec; ir 3213 (NH), 1613 $cm^{-1}$ (C=N); mass spectrum (70 eV) $m/e$ (rel intensity) 339.2 (16.66, $M^+$), 159.1 (13.43), 131.2 (45.34), 130.2 (100), 103.2 (16.58), 77.1 (25.05).

*Anal.* Calcd for $C_{16}H_{13}N_5O_4$: C, 56.6; H, 3.9; N, 20.6. Found: C, 56.9; H, 3.9; N, 20.5.

(7) (a) A. E. Smith, Ph.D. Thesis, University of Liverpool, 1963; (b) K. M. Biswas, Ph.D. Thesis, University of Liverpool, 1967.

(8) A. I. Vogel, "A Text-Book of Practical Organic Chemistry," 3rd ed, Longmans, Green and Co., New York, N. Y., 1964, pp 344, 722.

(9) The *N*-acetyl group of an acylindole was reported to be inert to DNP and similar other reagents: H. Plieninger and K. Suhr, *Chem. Ber.*, **89**, 270 (1956).

(10) B. Witkop, *Justus Liebigs Ann. Chem.*, **558**, 91 (1947).

(11) R. P. Ryan, W. G. Lobeck, Jr., C. M. Combs, and Y.-H. Wu, *Tetrahedron*, **27**, 2325 (1971), and references cited therein.

(12) Prepared by the method of H. M. Kissman, D. W. Farnsworth, and B. Witkop, *J. Amer. Chem. Soc.*, **74**, 3948 (1952).

2,4-Dinitrophenylhydrazone 13 of 2,3-Dimethyl-*N*-formylindole (11).—Concentrated $H_2SO_4$ (2 drops) was added cautiously to a boiling suspension of DNP (0.1 g) in MeOH (3.5 ml) until a clear solution was obtained, and 11 (86 mg) in MeOH (3 ml) was mixed with it. After the mixture was cooled at 0° for 4 hr, 13 (0.1 g) was collected, crystallized from THF, and obtained as brilliant red, hairy needles: mp 266° dec; ir 1640 $cm^{-1}$ (C=N); mass spectrum (70 eV) *m/e* (rel intensity) 354 (15.90, M + 1), 353 (82.55, $M^+$), 171 (32.01), 145 (47.13), 144 (100), 143 (34.07), 130 (30.68).

*Anal.* Calcd for $C_{17}H_{15}N_5O_4 \cdot {}^1/_2(C_4H_8O)$: C, 58.61; H, 4.92. Found: C, 58.75; H, 5.07.

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Registry No.—1, 120-72-9; 2, 948-65-2; 3, 487-89-8; 4, 25365-71-3; 5, 83-34-1; 6, 91-55-4; 8, 31951-33-4; 9, 5257-24-9; 10, 5257-06-7; 11, 41601-98-3; 12, 41601-99-4; 13, 41602-00-0.

# Effect of *p*-Methoxybenzonitrile on the Course of the Stoichiometric Hydroformylation of Cyclopentene

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The presence of a nitrile, *e.g.*, *p*-methoxybenzonitrile, in the stoichiometric hydroformylation can have a profound effect on both the product distribution and the rate of the reaction. The hydroformylation of cyclopentene under $N_2$ in the presence of excess $HCo(CO)_4$ produces 52% cyclopentane; the addition of nitrile reduces this to 3% and produces aldehyde almost exclusively. The presence of nitrile retards the rate of hydroformylation when the reaction is conducted under $N_2$ but accelerates it under CO. These effects are rationalized on the basis of the available concentration of $HCo(CO)_3$ under the various conditions investigated.

In an earlier publication[1] it was shown that, when the stoichiometric hydroformylation of olefins was carried out in the presence of nitriles, the yield of aldehyde was dramatically increased. Thus, under otherwise identical conditions, the addition of 2 mol of PhCN/mol of $HCo(CO)_4$ resulted in an increase of aldehyde yield from 44 to 90%. This high yield, obtained in the presence of a 20-fold excess of olefin, was unexpected because the formation of each mole of aldehyde requires 2 mol of $HCo(CO)_4$ and there were no suggestions in the literature that the final hydrogenolysis step was so fast relative to the earlier $HCo(CO)_4$-consuming steps. Because of these unusual results, we have investigated the nitrile effect more thoroughly and report herewith the results of such studies. Cyclopentene was chosen as a substrate because of its favorable rate of reaction and because double-bond migration does not affect either olefin or aldehyde composition.

## Experimental Section

Toluene solutions of $HCo(CO)_4$ were prepared and analyzed according to established procedures.[2] Cyclopentane and cyclopentanecarboxaldehyde were obtained from cyclopentene (Phillips Research Grade) by known catalytic hydrogenation and hydroformylation procedures respectively. Glpc analyses were performed on a Pye Series 105, Model 15, gas chromatograph using a 7 ft × 0.25 in. glass column packed with 25% Carbowax on Chromosorb P. Peak areas were measured with a Disc integrator and were corrected for flame ionization detector response by the use of cyclohexane and mesitylene as internal standards. All reactions were performed at constant temperature (±0.1°) under a static atmosphere.

A typical reaction was conducted as follows. A toluene solution of $HCo(CO)_4$, which had been equilibrated at the desired reaction temperature under CO for 10 min, was syringed into a stirred toluene solution of cyclopentene, cyclohexane, mesitylene, and *p*-methoxybenzonitrile, which had been previously equilibrated under the desired reaction conditions for 10 min. To minimize initial concentration variations, sets of reactions were performed with aliquots from $HCo(CO)_4$ as well as olefin standard stock solutions. At appropriate intervals, 0.2-ml reaction mixture aliquots were withdrawn and quenched by addition to 0.2 ml of a 1.6 *M* toluene solution of triphenylphosphine; all cobalt carbonyl compounds precipitate as insoluble phosphine derivatives. The resulting, clear supernatant was then analyzed by glpc. [The reaction of triphenylphosphine with $HCo(CO)_4$ is extremely fast[3] and the resulting insoluble phosphine complex is unreactive as a hydroformylation catalyst under these conditions.[4]]

## Results

Most studies on the stoichiometric hydroformylation have been carried out in the presence of excess olefin. We have followed this practice but, in addition, have also investigated reactions having $HCo(CO)_4$ in excess. The results of both studies are shown in Table I.

The first four reactions reported in Table I were performed in the presence of excess olefin. Reference to these results shows that, in the absence of nitrile, the rate of the reaction is more than 150-fold as fast under $N_2$ as under CO. Although this effect is well documented in the literature, its magnitude has not been previously defined. The presence of nitrile markedly slows the rate under $N_2$ but, surprisingly, accelerates it under CO. The yield of aldehyde in both instances is enhanced, as was expected from earlier work.[1]

Similar, but even more striking, results are obtained when the stoichiometric reaction is carried out with hydrocarbonyl in excess. In the absence of nitrile, the major product is cyclopentane regardless of the atmosphere employed. However, in the presence of nitrile, the major product is cyclopentanecarboxaldehyde; cyclopentane formation is negligible. The remarkable ability of *p*-methoxybenzonitrile to increase selectivity to aldehyde and to increase the rate of olefin consumption is brought out by the data shown in graphical form in Figure 1.

(1) L. Roos and M. Orchin, *J. Org. Chem.*, **31**, 3015 (1966).
(2) M. Orchin, *Advan. Catal.*, **16**, 1 (1966).
(3) R. F. Heck, *J. Amer. Chem. Soc.*, **85**, 657 (1963).
(4) L. Roos, Ph.D. Thesis, University of Cincinnati, Cincinnati, Ohio, 1965.

TABLE I
EFFECT OF *p*-METHOXYBENZONITRILE (ArCN) ON THE HYDROFORMYLATION OF CYCLOPENTENE

| | | | Rate[a] | | Aldehyde, %[b] | | $C_5H_{10}$, %[b] | | $C_5H_8$, %,[b] |
|---|---|---|---|---|---|---|---|---|---|
| $C_5H_8$/Co, *M* | Atm | ArCN | $10^4k$ | Rel | 1 hr | Final | 1 hr | Final | final |
| 12.5[c] | CO | − | 1.7 | 1 | 1 | 3[d] | <1 | <1[d] | |
| 12.5[c] | CO | + | 5.8 | 3 | 10 | 13[e] | <1 | 1[e] | |
| 12.5[c] | $N_2$ | + | 29.6 | 17 | 82 | 84[f] | 2 | 2 | |
| 12.5[c] | $N_2$ | − | 268.5 | 158 | 60 | 60 | 10 | 10 | |
| 0.081[g] | CO | − | 0.3 | 1 | <1 | 13[h] | 2 | 34[h] | 43 |
| 0.066[i] | CO | + | 1.2 | 4 | 24 | 77 | 1 | 2 | 24 |
| 0.066[i] | $N_2$ | + | 3.0 | 9 | 47 | 69 | 3 | 3 | 25 |
| 0.066[i] | $N_2$ | − | 4.3 | 13 | 27 | 32 | 48 | 52 | 18 |

[a] Pseudo-first-order rate constants (reciprocal seconds) computed for about 50% cyclopentene disappearance when $HCo(CO)_4$ was in excess and for ~50% of the theoretical amount of product formation when cyclopentene was in excess. [b] Yields: with cyclopentene in excess based on the initial amount of $HCo(CO)_4$ and stoichiometry of 1 mol of product/2 mol of $HCo(CO)_4$; with $HCo(CO)_4$ in excess based on initial cyclopentene concentration. [c] A toluene solution (10.0 ml), 3.11 *M* in cyclopentene, 0.25 *M* in $HCo(CO)_4$, and 0.25 *M* in *p*-methoxybenzonitrile at 10°. [d] Yield at 83 min; after 308 min, 34% aldehyde and 2% cyclopentane. [e] Interrupted after 83 min. [f] Under these conditions at room temperature olefins generally give essentially quantitative aldehyde yields. [g] Cyclopentene (0.0259 *M*). [h] Incomplete after 432 min. [i] A toluene solution (10.4 ml), 0.0212 *M* in cyclopentene, 0.318 *M* in *p*-methoxybenzonitrile, and 0.32 *M* in $HCo(CO)_4$ at 30°.

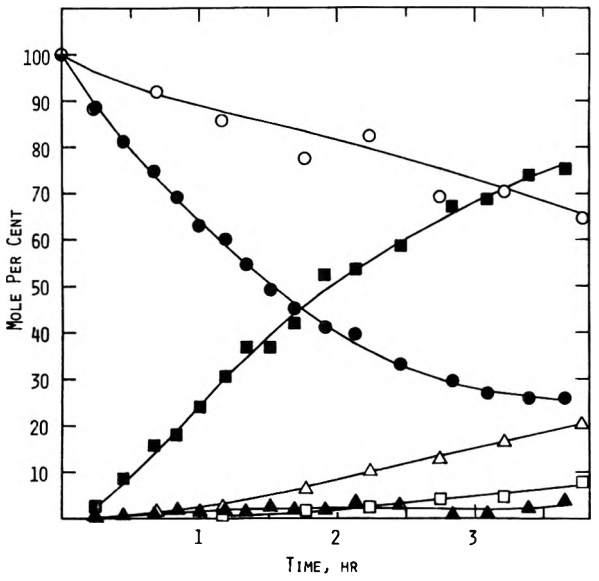


Figure 1.—Stoichiometric hydroformylation of cyclopentene with excess $HCo(CO)_4$ under CO: (○, ●) cyclopentene; (□, ■) cyclopentanecarboxaldehyde; (△, ▲) cyclopentane. Open and solid symbols represent data in the absence and presence of *p*-methoxybenzonitrile, respectively.

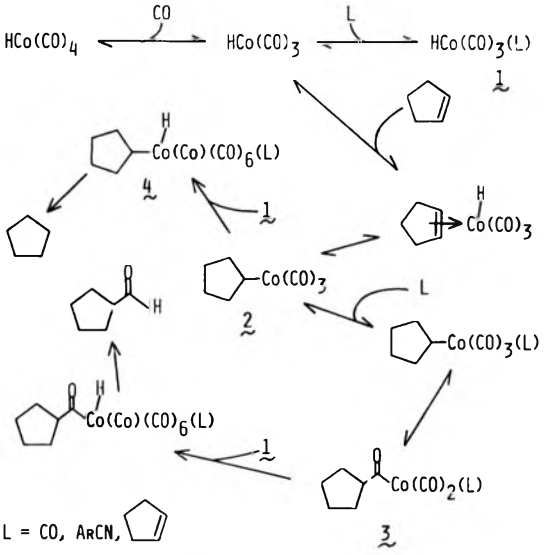


Figure 2.—Stoichiometric hydroformylation and hydrogenation of cyclopentene.

## Discussion

The role of nitrile is conveniently analyzed on the basis of two major effects: the effect on product distribution and the effect on rate. Product dependence will be discussed first.

In the catalytic commercial oxo process, olefin hydrogenation is a minor but important undesirable side reaction.[5] In the stoichiometric reaction, especially under $N_2$ and with low olefin to Co ratios, appreciable hydrogenation occurs.[6] However, from Table I it is seen that the 52% yield of cyclopentane produced under these conditions is reduced to 3% by the addition of nitrile and that practically all of the olefin that is consumed is directed to aldehyde rather than to cyclopentane.

The simplified reaction scheme shown in Figure 2 can be used to rationalize most of our results. The coordinately unsaturated $\sigma$ complex **2** is shown as a common intermediate. The final products may very well be determined by conditions which affect the partitioning of **2** between the pathways that lead to acyl complex **3** and to the oxidative addition intermediate formulated as **4**. At relatively low nucleophile (CO, nitrile, olefin) concentration the pathway to cyclopentane is favored. In the absence of nitrile, such conditions prevail when $HCo(CO)_4$ is in excess or are approached when olefin is in excess. In the presence of either excess $HCo(CO)_4$ or excess olefin, the influence of CO on cyclopentane yield is negligible when nitrile is present. This is understandable in view of the very low solubility of CO in toluene at atmospheric pressure ($\sim 6.7 \times 10^{-3}$ *M*)[7] and hence its small concentration relative to that of nitrile ($320 \times 10^{-3}$ *M*, ArCN/CO ≈ 50). The presence of nitrile enhances selectivity to aldehyde under all conditions and this results from the acceleration of the overall rate of alkyl migration[8] which converts **2** to **3**.

We now proceed to analyze the effect of nitrile on the overall rates of reaction. Although nitrile retards the rate of reaction under $N_2$ (as perhaps might be expected), the fact that it accelerates the rate under CO is difficult to rationalize. Mass balances made in those

(5) L. Marko, *Chem. Ind. (London)*, 260 (1962).
(6) (a) F. Ungvary and L. Markó, *Acta Chim. Acad. Sci. Hung.*, **62**, 425 (1969); G. Karapinka, Ph.D. Thesis, University of Cincinnati, Cincinnati, Ohio, 1962. (b) J. Terapane, Ph.D. Thesis, University of Cincinnati, Cincinnati, Ohio, 1969.
(7) F. Basolo and A. Wojcicki, *J. Amer. Chem. Soc.*, **83**, 520 (1961).
(8) M. Orchin and W. Rupilius, *Catal. Rev.*, **6**, 85 (1972).

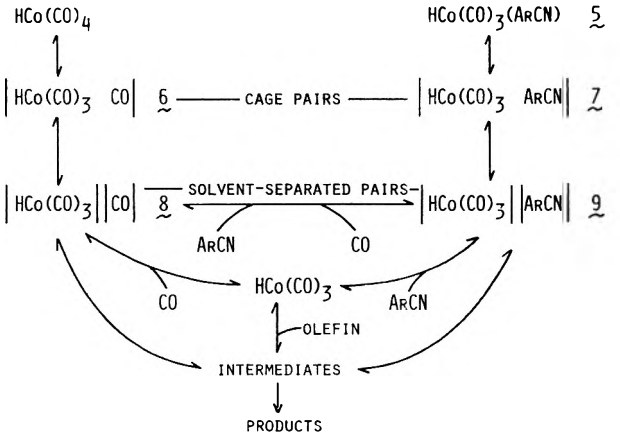


Figure 3.—Solvent cage equilibria.

reactions carried out with excess $HCo(CO)_4$ indicate relatively little accumulation of complexes of any kind (a maximum of 10 mol %), and this accumulation is unaffected by nitrile. These and other considerations lead us to believe that the observed rate differences are not the result of the interaction of nitrile in one of the later or product-determining steps.

The rate of olefin complexation with cobalt hydrocarbonyl as well as subsequent product formation rates should be highly dependent on the concentration of the coordinately unsaturated species $HCo(CO)_3$. The quantity of $HCo(CO)_3$ in equilibrium with $HCo(CO)_4$ under CO at 20° has been estimated to be a few tenths of 1%,[9] and the equilibrium concentration under $N_2$ is considerably greater.[6b] Thus the well-known, rate-retarding effect of CO[10] is explained on the basis of the suppression of $HCo(CO)_3$ formation, and the presence of nitrile under $N_2$ should result in a similar suppression and hence in a reduced rate, as in fact it does.

Consideration of reactant concentration changes in bulk solution would lead one to predict that any increase in total nucleophile concentration would reduce the effective concentration of $HCo(CO)_3$ and hence slow the rate of reaction. This is, of course, the effect of high partial pressures of CO in the catalytic reaction. The presence of phosphines in the catalytic reaction is effective in reducing the rate,[11] and the alkyl phosphines are much more effective than the triphenylphosphine in this respect, in accordance with their difference in nucleophilicity. The rate and product distribution is controlled[12] by equilibrium 1. As a matter of fact, the

$$HCo(CO)_4 + R_3P \rightleftharpoons HCo(CO)_3PR_3 + CO \qquad (1)$$

position of this equilibrium can be estimated by the product distribution.[12] Our problem is to explain the acceleration of the rate of the stoichiometric reaction under CO when nitrile is added. One possibility is that an increase in the concentration of $HCo(CO)_3$ occurs under these conditions. An analysis based on solvent-cage phenomena may be used for this purpose; the appropriate dissociative equilibria are shown in Figure 3. It is likely that the equilibria between **5**, **7**, and **9** favor the solvent-separated pair to a greater extent than the equilibria between $HCo(CO)_4$, **6**, and **8**; *i.e.*, CO is a better ligand than ArCN. The CO originally present in **8** is lost to solution during the formation of **9**, and hence the effective concentration of $HCo(CO)_3$, either as **9** or as free $HCo(CO)_3$, is higher than in the presence of carbon monoxide alone. The magnitude of this ligand or nucleophile effect should be highly sensitive to the ligating ability of the nucleophile. Too strong a ligand, such as triphenylphosphine, results in the formation of a complex which dissociates hardly at all under the conditions of the stoichiometric reaction, and too weak a nucleophile would give negligible association or rate enhancement. This model suggests that the rate of decomposition of $HCo(CO)_4$, which is also highly sensitive to the effective concentration of $HCo(CO)_3$,[9] should display similar behavior in the presence of *p*-methoxybenzonitrile. The results of just a study confirm this prediction and will be reported separately. A second possible explanation involves the effect of nitrile on the dielectric constant of the solution and the sensitivity of one of the rate determining steps to solvent polarity. The migratory insertion of CO in $Mn(CO)_5$ reactions shows such an effect,[13] and further investigation of this possibility is being explored. Finally, in unpublished work[14] we have established that, under catalytic conditions, nitriles (in particular acetonitrile) have essentially no effect on the course of 1-pentene hydroformylation.

**Registry No.**—*p*-Methoxybenzonitrile, 874-90-8; cyclopentene, 142-29-0.

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# Synthesis and Reactivity of an Exo,endo-4,6-Disubstituted Bicyclo[3.1.0]hex-2-ene[1]

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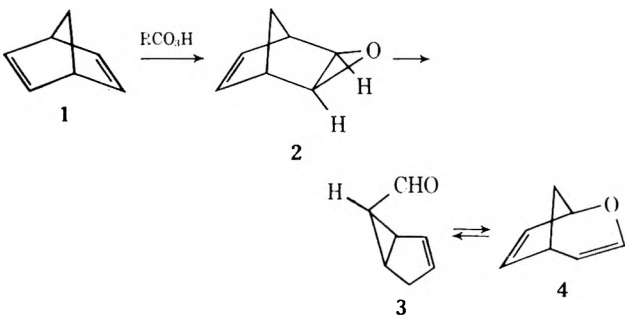
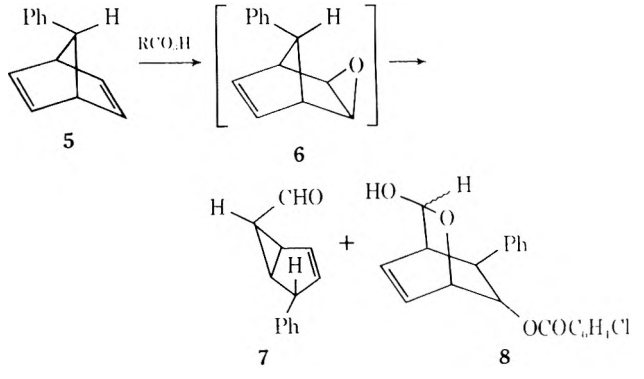
The peracid oxidation of 7-substituted norbornadienes has been found to afford exo-4,endo-6-disubstituted bicyclo[3.1.0]hex-2-enes. The photo- and thermal chemistry of *exo*-4-methylbicyclo[3.1.0]hex-2-ene-*endo*-6-carboxaldehyde (**10**) has been studied. The photolysis of **10** results in photoepimerization by external cyclopropyl bond cleavage whereas the thermolysis proceeds predominantly by a suprafacial homo [1,7] hydrogen shift.

As an extension of our studies on the photochemical Diels–Alder reaction,[3] we became interested in determining the stereochemical consequences attending the thermal and photochemical cycloreversion of the bicyclo[3.1.0]hex-2-ene system. Some recent work in the literature suggests that the thermal rearrangements of bicyclo[3.1.0]hex-2-enes with electron-withdrawing substituents at the 6 position may be proceeding through a [2 + 4] cycloreversion.[4–6] The influence of the electron-withdrawing group at the 6 position of the bicyclohexene ring in the cycloreversion process can be understood in terms of recent discussions of substitutent effects of the cyclopropane ring.[7–9] If there is a $\pi$-electron acceptor, such as a carbonyl group, attached to the cyclopropane ring, then the lowest unoccupied orbital of the $\pi$-electron acceptor can interact with the antisymmetric component of the occupied degenerate Walsh orbital pair in cyclopropane. This interaction removes electron density from the cyclopropane ring and therefore it weakens the bonding between $C_1$ and $C_6$ and $C_5$ and $C_6$ but strengthens the bond between positions 1 and 5. Weakening of the $C_1$–$C_6$ bond would be expected to promote the cycloreversion reaction.

Synthesis of a bicyclo[3.1.0]hex-2-ene with an electron-withdrawing group at the 6 position and a stereochemical marking group at the 4 position, which would thermally decompose at a convenient rate and would also be photochemically reactive, was desired. Of the several possible methods to gain synthetic entry into such a system, the route involving the peracid epoxidation of a 7-substituted norbornadiene was considered most feasible. Meinwald and coworkers[10] have reported the formation of exo epoxide **2** and its rapid rearrangement to bicyclo[3.1.0]hex-2-ene-*endo*-6-carboxaldehyde[11] (**3**). The latter compound was found to exist in mobile equilibrium with 2-oxabicyclo[3.2.1]octa-3,6-diene[13,14] (**4**). The above sequence holds unquestionable promise for the synthesis of an exo,endo-4,6-disubstituted bicyclohexene, since it provides substantial opportunity of controlling the nature of the substituents and their stereochemical relationship. Brown has recently demonstrated that the epoxidation of norbornene proceeds almost exclusively from the exo direction.[15] He has also shown that the presence of a syn-7-methyl group on the norbornene skeleton will retard the rate of epoxidation by a factor of *ca.* 100.[15] Consequently, treatment of a 7-substituted norbornadiene with *m*-chloroperbenzoic acid will be expected to proceed by exo epoxidation of the least hindered double bond. Thermal rearrangement of the initially formed epoxide should be facilitated by back-side participation of the neighboring transannular double bond and give a exo-4,endo-6-disubstituted bicyclo[3.1.0]hex-2-ene.




When 7-phenylnorbornadiene (**5**) was allowed to react with *m*-chloroperbenzoic acid, the expected exo epoxide **6** was not obtained, but rather two new compounds were isolated. The minor component of the mixture was established as *exo*-4-phenylbicyclo[3.1.0]hex-2-ene-*endo*-6-carboxaldehyde (**7**) through a combination of infrared, ultraviolet, and nmr spectroscopy (see Ex-




(1) Photochemical Transformations of Small Ring Carbonyl Compounds. LI. For part L see A. Padwa and G. Lee, *J. Amer. Chem. Soc.*, **95**, 6147 (1973).

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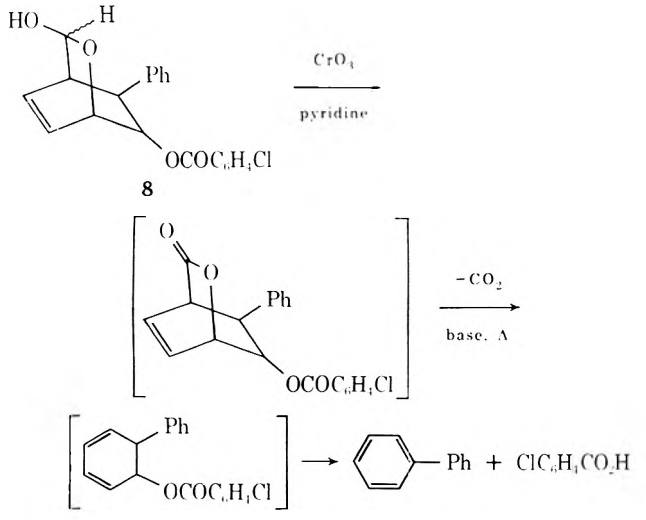
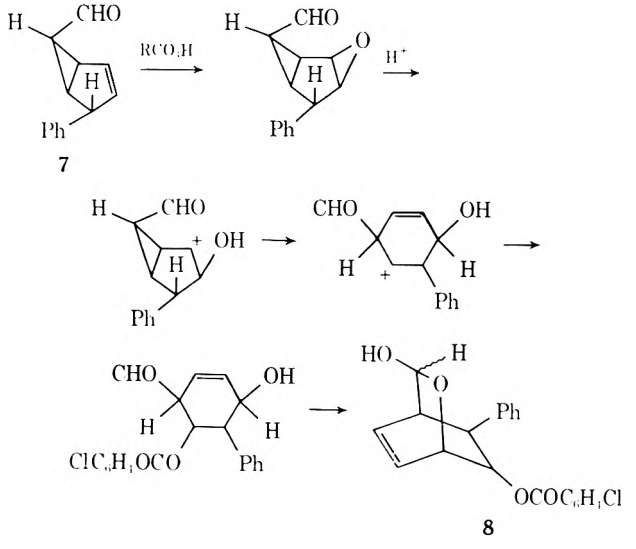
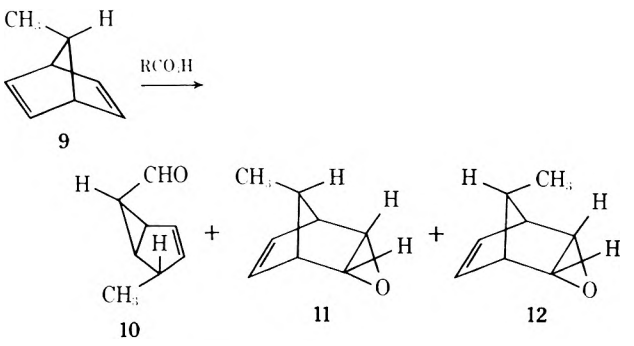
perimental Section). The formation of **7** can best be rationalized as proceeding through the intermediacy of exo epoxide **6** followed by its acid-catalyzed rearrangement to **7**. The major component of the reaction mixture was a white, crystalline solid, mp 153–154°, whose structure is assigned as 2-oxa-3-hydroxy-7-phenyl-8-(*m*-chloro)benzoxybicyclo[2.2.2]oct-5,6-ene (**8**) on the basis of its spectroscopic (see Experimental Section) and chemical data. The elemental analysis of this compound ($C_{20}H_{17}ClO_4$) suggests that it is a further oxidation product of the initially formed bicyclo[3.1.0]hex-2-ene aldehyde (**7**). This suggestion was confirmed by the finding that **7** was smoothly converted to **8** on treatment with *m*-chloroperbenzoic acid. Evidently, the initially formed bicyclohexene **7** undergoes further oxidation at a faster rate than starting material. This explanation accounts for the large amount of starting material that can be recovered when equivalent amounts of peracid were used. Chemical confirmation of the structure of **8** was obtained by its conversion with chromium trioxide in pyridine to biphenyl. This reaction presumably proceeds by loss of carbon dioxide from the initially formed lactone followed by elimination of *m*-chlorobenzoic acid. A reasonable mechanism for the formation of **8** is presented below.



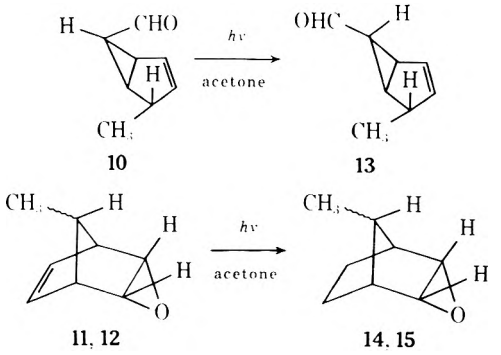




Since the overall yield of *exo*-4-phenylbicyclo[3.1.0]-hex-2-ene-*endo*-6-carboxaldehyde (**7**) was so low, we decided to investigate the peracid oxidation of another 7-substituted norbornadiene. When 7-methylnorbornadiene (**9**) was treated with *m*-chloroperbenzoic acid in methylene chloride at 0°, there was produced a mixture of three isomeric compounds. Preparative-scale vpc




separation of the crude mixture led to the isolation of pure **10**. This product was identified as bicyclohexene **10** (37%) on the basis of its nmr spectrum ($CDCl_3$), which displays a methyl doublet at $\tau$ 8.92 (3 H, $J$ = 7 Hz), cyclopropyl hydrogens at 8.28 (1 H, t, $J$ = 7 Hz), 8.02 (1 H, t, $J$ = 7 Hz), and 7.4 (m) in addition to absorptions due to the olefinic [$\tau$ 4.2 (m, 2 H)] and aldehydic [$\tau$ 0.84 (1 H, d, $J$ = 6 Hz)] hydrogens. The first peak in the vpc chromatogram proved to be a mixture of *endo*-norbornene epoxides (16%). Although the epoxides, **11** and **12**, appeared as a single peak on most vpc columns, we eventually accomplished separation on a 20 ft × 0.25 in. 18% FS-1265 on 60-80 Chromosorb P column at 90°. The endo stereochemical assignment was made by the observation that both epoxides were stable when heated at reflux in benzene which contained a trace of *p*-toluenesulfonic acid.[11]

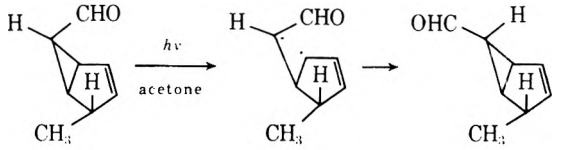
Since the separation of endo epoxides **11** and **12** from bicyclo[3.1.0]hexene **10** was only attained with great difficulty, the initial irradiation experiments were carried out on the initial epoxidized mixture. Photolysis of the epoxidation mixture in acetone with a Pyrex filter gave a mixture of products which were separated by preparative vapor phase chromatography. In addition to unreacted starting material, three new compounds were obtained and subsequently identified as *exo*-4-methylbicyclo[3.1.0]hex-2-ene-*exo*-6-carboxaldehyde (**13**, 35%) and an inseparable 1:1 mixture of the syn and anti isomers of *endo*-2,3-epoxy-7-methylbicyclo[2.2.1]heptane (**14**, **15**). Control experiments on




a pure sample of **10** indicated that it afforded only *exo*-bicyclohexene **13** on irradiation. Similarly, irradiation of the mixture of norbornene epoxides (**11** and **12**) afforded only compounds **14** and **15**. The structure of bicyclohexene **13** was elucidated on the basis of its

spectral properties (see Experimental Section). Structure **13** was further confirmed by the base-catalyzed epimerization of **10** to the thermodynamically more stable exo isomer (**13**). Structures **14** and **15** were established on the basis of both chemical and spectroscopic evidence (see Experimental Section). Reduction of the original epoxidation mixture over 5% palladium on carbon gave a mixture of **14** and **15**. This mixture was spectroscopically identical with the mixture of epoxides obtained from the irradiation.

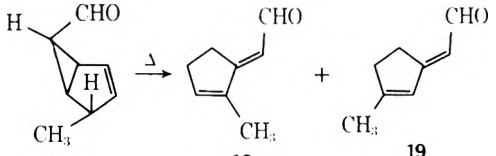
The photochemical isomerization of bicyclohexene **10** to **13** may be rationalized on the assumption that the reaction proceeds *via* diradical **17**, a species derived




10 17 13

by cleavage of the external cyclopropyl bonds. Such a process is not without analogy. Several examples of photosensitized epimerizations in related systems have recently been reported.[16-20] Garin and coworkers,[17] for example, have described the photosensitized epimerization of bicyclo[3.1.0]hex-2-ene-*endo*-6-carboxylic acid and its methyl ester. The photoepimerization reaction was shown to occur by cleavage of the external cyclopropyl bond. The photochemical reduction of norbornene epoxides **11** and **12** to **14** and **15** is not an unprecedented reaction. Kropp[21] and Sauers[22] have shown that various derivatives of norbornene can be reduced when irradiated in the presence of a triplet sensitizer. It would appear that the triplet state of norbornene epoxide (**11** or **12**) is sufficiently long lived to participate in an intermolecular hydrogen atom abstraction.

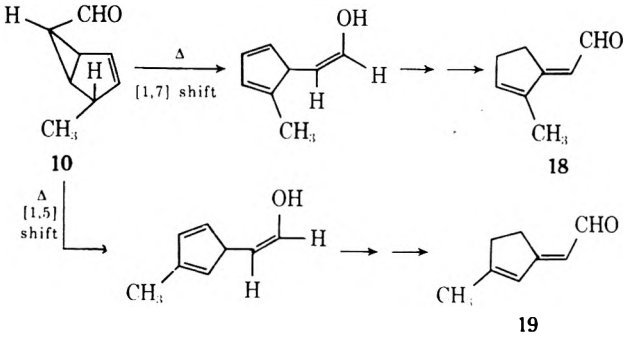
Since bicyclo[3.1.0]hexene **10** did not undergo cycloreversion to a 1,3,5-hexatriene on electronic excitation, we decided to study the thermal chemistry of this system with the hope that we could promote the cycloreversion reaction at elevated temperatures. Heating a benzene solution of **10** at 150° afforded a mixture of two isomeric aldehydes (**18** and **19**). Control experi-




10 18 19

ments showed that the products were stable under the reaction conditions. The structure of the major reaction product **18** (87%) was based on its characteristic spectral data: ir 3.42, 3.68, 6.02, 8.70, and 11.55 μ; uv (cyclohexane) $\lambda_{max}$ 282 nm (ε 16,600); *m/e* 122 ($M^+$); nmr ($CCl_4$, 100 MHz) τ 8.2 (s, 3 H), 7.4 (m, 2 H), 6.96 (m, 2 H), 4.28 (m, 1 H), 3.74 (broad s, 1 H), and 0.25 (1 H, d, $J$ = 6 Hz). Saturation of the signal at τ 4.28 with an external field caused the doublet at τ 0.25 to collapse to a singlet. The minor product of the reaction mixture could not be readily separated from **18** by vapor phase chromatography. While our studies were in progress, a report by Gilbert and Klumpp appeared describing the thermal chemistry of bicyclohexene **10**.[23] These workers assigned structure **19** to the minor reaction component of the thermal mixture. They also identified structure **18** as the major thermal product.

The formation of bicyclohexene **18** from **10** can be rationalized as proceeding *via* a homo [1,7] hydrogen migration as shown below. The minor product is de-




10 18 19

rived by a related suprafacial homo [1,5] hydrogen shift. Although the geometries of the transition states for the homo [1,5] and [1,7] hydrogen shifts are similar, the available data suggests that the activation energy for the [1,7] process is somewhat lower than that for the [1,5] transfer.[23] Both the [1,5] and [1,7] hydrogen transfer processes have lower activation energies than the sought-after thermal cycloreversion process. This same conclusion was reached by Gilbert and Klumpp.[23] The above thermal transformations also shed light on the mechanism of the rearrangement of the closely related bicyclo[3.1.0]hex-2-ene-*endo*-6-carboxaldehyde (**20**).[24] The rate-determining step in the rearrangement of **20** was assumed to involve a homo [1,5] hydrogen shift on the basis of numerous precedents in the literature.[25] From our results, as well as those from Gilbert and Klumpp's group,[23] it would appear as though the thermal rearrangement of **20** actually involves both the π electrons of the carbon–carbon double bond and the σ electrons between C-5 and C-6. This is most reasonable, since it is known that systems possessing the potential for competitive thermal sigmatropic migrations of order [*i*,*j*] favor rearrangement by the higher order pathway.[26-28]

## Experimental Section

All melting points are corrected and boiling points are uncorrected. Elemental analyses were performed by Scandinavian

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Microanalytical Laboratory, Herlev, Denmark, and Alfred Bernhardt Laboratories, Hohenweg, Germany, The infrared absorption spectra were determined on a Perkin-Elmer Infracord spectrophotometer, Model 137. The ultraviolet absorption spectra were measured with a Cary recording spectrophotometer, using 1-cm matched cells. The nuclear magnetic resonance spectra were determined at 60 MHz with the Varian Associates high-resolution spectrometer and at 100 MHz using a Jeolco MH-100 spectrometer.

**Peracid Oxidation of 7-Phenylnorbornadiene.**—A solution of 8.4 g of 7-phenylnorbornadiene[29] and 17.2 g of *m*-chloroperbenzoic acid in 200 ml of methylene chloride was allowed to stand at room temperature for 3 hr. At the end of this time the precipitated *m*-chlorobenzoic acid was removed by filtration and the solution was washed with saturated sodium carbonate and dried over sodium sulfate. The solvent was removed *in vacuo* to give 12.6 g of an orange oil. The crude mixture was dissolved in hexane and passed through a Florisil column. Elution of the chromatographic column with 5% ethyl acetate–hexane gave 0.58 g of recovered starting material. The second peak isolated from the chromatographic column amounted to 0.25 g (3%) of a crystalline solid, mp 67–68°, whose structure is assigned as *exo*-4-phenylbicyclo[3.1.0]hex-2-ene-*endo*-6-carboxaldehyde (**7**): ir (KBr) 5.95, 6.76, 6.92, 8.34, 9.25, 10.21, 10.65, 11.65, 12.51, 13.40, and 14.45 $\mu$; uv (cyclohexane) $\lambda_{max}$ 232, 252, and 258 nm ($\epsilon$ 2000, 670, and 590); nmr ($CCl_4$) $\tau$ 7.8–8.5 (m, 2 H), 6.4 (broad s, 1 H), 6.1 (broad s, 1 H), 4.1 (m, 2 H), 2.7 (m, 5 H), 0.6 (d, 1 H, $J$ = 5 Hz); mass spectrum $m/e$ 184 ($M^+$), 156, 155, 142, 129, 128, 115, and 77 (base).

*Anal.* Calcd for $C_{13}H_{12}O$: C, 84.75; H, 6.57. Found: C, 84.60; H, 6.47.

The remaining component of the reaction mixture consisted of white, crystalline solid (6.8 g), mp 153–154°, which could be separated from aldehyde **7** by fractional crystallization from pentane–ether. This same compound could be prepared in high yield by treating bicyclohexene **7** with *m*-chloroperbenzoic acid. The infrared spectrum of this compound showed bands at 2.90, 5.78, 7.01, 7.82, 7.91, 9.10, 9,80, 10.21, 10.38, 13.40, 13.60, and 14.35 $\mu$. The ultraviolet spectrum (95% ethanol) has maxima at 282 and 290 nm ($\epsilon$ 590 and 510). The nmr spectrum (pyridine $d_5$, 60 MHz) shows broad singlets at $\tau$ 6.65 (1 H), 6.40 (1 H), 5.50 (2 H), 5.10 (1 H), and 3.20 (1 H), and multiplets at 3.70 (2 H) and 2.0–2.9 (9 H); mass spectrum $m/e$ (base, parent − $C_7H_5ClO_2$), 171, 156, 142, 115, 105, and 77.

*Anal.* Calcd for $C_{20}H_{17}O_4Cl$: C, 67.32; H, 4.78. Found: C, 67.27; H, 4.89.

The structure of this material is assigned as 2-oxa-3-hydroxy-7-phenyl-8-(*m*-chloro)benzoxybicyclo[2.2.2]oct-5,6-ene (**8**) on the basis of its spectroscopic properties and by an oxidative elimination to biphenyl. To a solution of 0.16 g of chromium trioxide in 25 ml of pyridine at 0° was added a solution of 0.2 g of **8** in 5 ml of pyridine. The mixture was stirred at room temperature for 3 days. At the end of this time 100 ml of ether was added to the mixture and the resulting ethereal solution was washed with 5% hydrochloric acid. Evaporation of the ether gave 0.14 g of a yellow oil which was placed on a preparative thick layer plate. The plate was developed using a 1:1 pentane–ether mixture and the two major bands were extracted with acetone. The first band amounted to 39 mg and was identified as biphenyl by comparison with an authentic sample. The material in the second band (65 mg) was recovered starting material.

**Peracid Oxidation of 7-Methylnorbornadiene.**—To a stirred suspension of 4.5 g of sodium carbonate and 5.0 g of 7-methylnorbornadiene[29] in 350 ml of methylene chloride at 0° was added a solution of 7.65 g of *m*-chloroperbenzoic acid in 100 ml of methylene chloride. The mixture was stirred at 0° for 3 hr. At the end of this time the mixture was washed with water and dried over sodium sulfate. The solvent was removed *in vacuo* and the residual oil was distilled under reduced pressure to give 2.1 g of a colorless oil, bp 61–63° (20 mm). Analysis of this material by glpc (16% FS-1265 column at 100°) showed that it contained at least two components. The second and largest peak (37%) to be eluted from the vpc column was a colorless liquid whose structure is assigned as *exo*-4-methylbicyclo[3.1.0]hex-2-ene-*endo*-6-carboxaldehyde (**10**) on the basis of the spectroscopic data cited: ir (neat) 3.40, 5.88, 6.85, 8.35, 9.30, 9.40, 9.60, 10.40, 11.50, 12.80, 13.20, and 13.50 $\mu$; uv (cyclohexane) $\lambda_{max}$ 230 and 235 nm ($\epsilon$ 580 and 600); nmr ($CDCl_3$, 100 MHz) $\tau$ 8.92 (d, 3 H, $J$ = 7 Hz), 8.28 (1 H, t, $J$ = 7 Hz), 8.02 (1 H, t, $J$ = 7 Hz), 7.2–7.5 (m, 2 H), 4.20 (m, 2 H), 0.84 (d, 1 H, $J$ = 6 Hz); mass spectrum $m/e$ ($M^+$) 12a, 107, 93, 79, and 77.

The first peak present in the glpc chromatogram could not be easily separated from bicyclohexene **10**. In order to facilitate the separation, the above mixture was treated with silver oxide. A solution of 0.31 g of the above mixture in 12 ml of 25% ethanol containing 1.4 g of silver nitrate was treated with 15 ml of an aqueous solution of sodium hydroxide (0.5 g). The above reaction mixture was allowed to stir for 3 days at room temperature and was then filtered to remove the precipitated silver oxide. The aqueous solution was extracted with ether and the ethereal extracts were dried over sodium sulfate. Evaporation of the solvent gave 0.098 g of a yellow oil which was analyzed by vpc using a 15% FS-1265 column at 100°. The vpc scan showed the complete absence of bicyclo[3.1.0]hex-2-ene-*endo*-6-carboxaldehyde **10**. The oil consisted of a 1:1 mixture of the two endo norbornene epoxides (**11** and **12**) (16%) which could be separated by glpc. Both epoxides could be recovered from a refluxing benzene solution which contained a trace of *p*-toluenesulfonic acid. This provides strong support for the endo epoxide assignment. The first epoxide to be eluted from the column was a colorless oil: ir ($CCl_4$) 3.40, 6.85, 7.27, 7.45, 8.42, 10.10, 11.05, 11.23, and 11.52 $\mu$; nmr ($CCl_4$, 100 MHz) $\tau$ 9.18 (3 H, d, $J$ = 6 Hz), 7.44 (3 H, m), 6.60 (2 H, m), and 4.32 (2 H, m); mass spectrum $m/e$ 122 ($M^+$), 107, 93, and 44 (base). On the basis of the spectra this compound is assigned as *endo*-2,3-epoxy-*syn*-7-methylbicyclo-[2.2.1]hept-5,6-ene (**11**). The second epoxide collected from the glpc chromatogram had very similar spectral properties and is assigned the isomeric structure **12**: nmr ($CCl_4$) $\tau$ 9.00 (3 H, d, $J$ = 6 Hz), 7.58 (3 H, m), 6.58 (2 H, m), and 4.20 (t, $J$ = 2 Hz, 2 H).

The aqueous solution from the above experiment was acidified with hydrochloric acid and extracted with ether. The ether was dried over sodium sulfate and the solvent was removed under reduced pressure to give a white, crystalline solid: mp 76–78° (42%); ir (KBr) 2.9–3.7, 5.84, 6.93, 8.15, 8.62, 10.71, 11.14, 12.90, 13.40, and 14.35 $\mu$; nmr ($CDCl_3$, 100 MHz) $\tau$ 9.0 (3 H, d, $J$ = 7 Hz), 8.32 (2 H, q, $J$ = 8 Hz), 7.56 (1 H, t, $J$ = 7 Hz), 7.00 (1 H, q, $J$ = 7 Hz), 4.30 (2 H, m), and −1.28 (1 H, s); mass spectrum $m/e$ 138 ($M^+$), 123, 105, 93 (base), and 77. On the basis of the data this material is assigned the structure of *exo*-4-methylbicyclo[3.1.0]hex-2-ene-*endo*-6-carboxylic acid.

**Irradiation of *exo*-4-Methylbicyclo[3.1.0]hex-2-ene-*endo*-6-carboxaldehyde (10).**—Since the separation of endo epoxides **11** and **12** from bicyclohexene **10** was only attained with great difficulty, the irradiation was carried out on the initial epoxidized mixtures. A 0.5-g sample of this mixture was irradiated for 4 hr in 200 ml of acetone using a 550-W Hanovia lamp equipped with a Pyrex filter. Vpc analysis of the crude mixture on a 15% FS-1265 column at 100° indicated the presence of three major components. The second component on the chromatogram was identified as recovered bicycloaldehyde **10**. The third peak was a colorless oil (35%) whose structure is assigned as *exo*-4-methylbicyclo[3.1.0]-hex-2-ene-*exo*-6-carboxaldehyde (**13**) on the basis of the chemical and physical data cited: ir ($CCl_4$) 3.25, 3.35, 3.46, 3.67, 5.83, 6.91, 7.45, 9.10, 10.15, 11.87, 13.10, 13.35, and 14.45 $\mu$; nmr ($CCl_4$, 100 MHz) $\tau$ 8.96 (3 H, d, $J$ = 7 Hz), 8.06 (1 H, m), 7.4–7.6 (3 H, m), 4.56 (1 H, m), 4.20 (1 H, m), 0.86 (1 H, d, $J$ = 4 Hz); mass spectrum $m/e$ ($M^+$) 122, 107, 93, 79, and 77.

The exo isomer **13** could also be prepared by the base-catalyzed epimerization of the endo stereoisomer **10**. A 0.1-g sample of the endo isomer **10** and 0.1 g of sodium methoxide in 10 ml of methanol was refluxed for 1 hr. After evaporation of the solvent the oily residue was taken up in ether, washed with water, and dried over sodium sulfate. Removal of the solvent under reduced pressure gave a colorless oil which showed two peaks in the vpc chromatogram. Comparison of retention times and infrared and nmr spectra with that of the exo and endo aldehydes **13** and **10** established the identity of the major components present in the residue.

***endo*-2,3-Epoxy-7-methylbicyclo[2.2.1]heptane.**—The first peak collected from the preparative vpc chromatogram of the photolysis of **10** was a colorless liquid (20%) which proved to be an inseparable mixture of the syn and anti isomers of *endo*-2,3-epoxy-7-methylbicyclo[2.2.1]heptane (**14**, **15**). This was demonstrated by the chemical and spectroscopic data cited: ir ($CCl_4$) 3.45, 6.12, 6.85, 7.0, 7.25, 7.57, 7.70, 8.22, 8.45, 8.62, 9.12, 9.50, 10.2, 10.5, and 11.0 $\mu$; mass spectrum $m/e$ 124 ($M^+$), 109, 95, 93, 80 (base), and 67; nmr ($CCl_4$, 100 MHz) $\tau$ 9.22 (d, $J$ = 7

(29) P. R. Story and S. F. Fahrenholdt, *J. Org. Chem.*, **28**, 1716 (1953).

Hz), 8.88 (d, $J$ = 7 Hz) (combined integration 3 H), 8.60 (broad s, 4 H), 8.12 (broad s, 2 H), 7.76 (q, $J$ = 7 Hz, 1 H), 6.60 (broad s), 6.50 (broad s) (combined integration 2 H). Irradiation of the quartet at $\tau$ 7.76 with an external field collapsed the methyl doublets at $\tau$ 9.22 and 8.88 to singlets and also sharpened up the broad singlets at $\tau$ 6.60 and 6.50. The structure of this mixture was further verified by comparison with a sample independently synthesized as described below.

**Catalytic Hydrogenation of the Crude Epoxidation Mixture Derived from 7-Methylnorbornadiene.**—The crude epoxidation mixture (0.25 g) obtained from the treatment of 7-methylnorbornadiene with *m*-chloroperbenzoic acid was hydrogenated at 15 psig in a Paar shaker over 5% palladium on charcoal for 4 hr. After filtration to remove the catalyst, the solution was concentrated and submitted to preparative vpc. The residue was shown to contain two peaks. The minor peak (35%) in the chromatogram was a colorless oil whose spectral properties were identical with those of the mixture of isomers obtained from the photolysis of **10**. The major peak present in the vpc chromatogram (49%) was a colorless liquid whose structure is assigned as *exo*-8-methyl-2-oxabicyclo[3.2.1]oct-3-ene (**16**) on the basis of the physical data cited: ir ($CCl_4$) 3.45, 6.14, 6.85, 7.0, 7.25, 7.57, 7.7, 8.22, 8.45, 8.62, 9.12, 9.50 (s), 10.45, and 11.0 $\mu$ (s); mass spectrum $m/e$ 124 ($M^+$), 109, 96, 95, 93, 91, 81 (base), and 68; nmr ($CCl_4$, 100 MHz) $\tau$ 9.14 (3 H, d, $J$ = 7 Hz), 8.10 (broad s, 5 H), 7.70 (1 H, q, $J$ = 7 Hz), 5.86 (1 H, broad s), 5.10 (1 H, t, $J$ = 6 Hz), and 4.04 (1 H, d, $J$ = 6 Hz).

**Thermolysis of *exo*-4-Methylbicyclo[3.1.0]hex-2-ene-*endo*-6-carboxaldehyde.**—A 0.75-g sample of bicycylohexene **10** in 5 ml of benzene was heated in a sealed tube at 150° for 4 hr. The solvent was removed under reduced pressure and the residual oil was subjected to preparative thick layer chromatography. The plate was developed with a 25% ether–75% pentane solution. Extraction of the band ($R_f$ 0.33) with methylene chloride followed by evaporation of the solvent gave 0.65 g (87%) of a colorless oil: ir (neat) 3.42, 3.52, 3.68, 6.02 (s), 6.24 (s), 6.45, 6.92, 7.45, 7.8, 7.97, 8.25, 8.70 (s), 9.7 (m), 10.8 (m), 11.55 (s), and 12.1 $\mu$; uv (cyclohexane) $\lambda_{max}$ 282 nm ($\epsilon$ 16,600); mass spectrum $m/e$ 122 ($M^+$), 107, 93 (base), 91, 79, and 77; nmr ($CCl_4$, 100 MHz) $\tau$ 8.2 (s, 3 H), 7.4 (m, 2 H), 6.96 (m, 2 H), 4.28 (m, 1 H), 3.74 (1 H, broad s), 0.25 (1 H, d, $J$ = 6 Hz). When the signal at $\tau$ 4.28 was saturated with an external field, the doublet at 0.25 collapsed to a singlet. On the basis of the data this compound is assigned the structure of unsaturated aldehyde **18**.

Another minor aldehyde (*ca.* 5%) was detected in the crude thermolysis residue but could not be separated from **18**. This compound has since been assigned the structure of **19** by Gilbert, Klumpp, and coworkers.[23]

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**Registry No.**—**5**, 40156-12-5; **7**, 41828-73-3; **8**, 41828-74-4; **9**, 13437-93-9; **10**, 35391-55-0; **11**, 41828-77-7; **12**, 41828-78-8; **13**, 41828-79-9; **14**, 41828-80-2; **15**, 41828-81-3; **16**, 41828-83-5; **18**, 41828-82-4; *exo*-4-methylbicyclo[3.1.0]hex-2-ene-*endo*-6-carboxylic acid, 41828-84-6.

# Electrochemical Preparation and Retrodiene Reaction of 1,4-Bis(methoxycarbonyl)bicyclo[2.2.2]octa-2,5-diene

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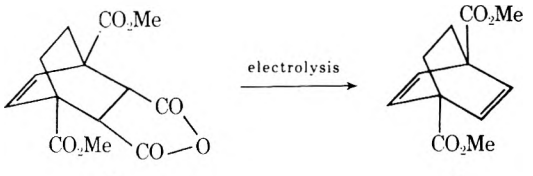
1,4-Bis(methoxycarbonyl)bicyclo[2.2.2]octa-2,5-diene (**1**) was synthesized by electrolytic decarboxylation of the adduct of maleic anhydride and dimethyl cyclohexa-1,3-diene-1,4-dicarboxylate. Addition of a small amount of 4-*tert*-butylcatechol to the electrolysis reaction was found to increase the yield of **1** from 30 to 65%. Replacement of the usual solvent system for this reaction (pyridine, water, triethylamine) with acetonitrile, water, pyridine, triethylamine decreased the reaction time from 12 to 2 hr. Compound **1** readily undergoes a retrodiene reaction to produce ethylene and dimethyl terephthalate. Energy parameters for this reaction are $\Delta H^{\ddagger}$, 26.8 ± 0.3 kcal/mol; $\Delta S^{\ddagger}$, −0.4 ± 0.9 eu. CNDO/2 calculations performed for this reaction indicate that the lowest energy reaction pathway involves loss of an ethylene-like two-carbon fragment from a nearly planar hexadiene ring.

The retro Diels–Alder reaction, particularly when aromatic products are produced, has been extensively used to generate unstable intermediates and relatively inaccessible olefins.[1,2] We would like to report[3] the synthesis of 1,4-bis(methoxycarbonyl)bicyclo[2.2.2]-octa-2,5-diene (**1**) and the activation parameters for the retrodiene decomposition of dihydrobarrelene **1** to dimethyl terephthalate and ethylene. The key step in the synthesis of compound **1** was achieved by electrochemical oxidation of 1,4-bis(methoxycarbonyl)-bicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic anhydride (**2**)




**2** **1**

at low temperature, a technique of considerable potential for the preparation of thermally unstable or chemically labile molecules.

(1) For reviews of the retrodiene reaction see (a) H. Kwart and K. King, *Chem. Rev.*, **68**, 415 (1968); (b) J. Sauer, *Angew. Chem., Int. Ed. Engl.*, **6**, 211 (1966); (c) A. S. Onishchenko, "Diene Synthesis," Oldbourne Press, London, 1964.

(2) For use of the retrodiene reaction to generate unstable intermediates and inaccessible olefins see (a) E. J. Corey and W. L. Mock, *J. Amer. Chem. Soc.*, **84**, 685 (1962); (b) G. D. Peddle, D. N. Roark, A. M. Good, and S. G. McGeachin, *J. Amer. Chem. Soc.*, **91**, 2807 (1969); (c) N. D. Field, *ibid.*, **83**, 3504 (1961); (d) C. M. Wynn and P. S. Klein, *J. Org. Chem.*, **31**, 4251 (1966); (e) W. S. Wilson and R. N. Warrener, *Chem. Commun.*, 211 (1972); (f) U. E. Wiersum and W. J. Myo, *ibid.*, 347 (1972); (g) R. Kreher and J. Seubert, *Z. Naturforsch. B*, **20**, 75 (1965); (h) R. N. Warrener, *J. Amer. Chem. Soc.*, **93**, 2346 (1971).

(3) This work is a continuation of a program concerned with synthesis of bicyclic molecules that are functionally substituted at the bridgehead positions. For previous papers see D. C. Owsley and J. J. Bloomfield, *J. Amer. Chem. Soc.*, **93**, 782 (1971); *J. Org. Chem.*, **36**, 4160 (1971); *Org. Prep. Proced. Int.*, **3**, 61 (1971).

TABLE I
ELECTROLYTIC DECARBOXYLATION OF COMPOUND 2[a]

| Run no. | Initial current, A | Initial voltage, V | Temp, °C | Reaction time, hr | Solvent[b] system | Radical inhibitor (mg, mmol) | Yield of 3, % |
|---|---|---|---|---|---|---|---|
| | | | Effect of *tert*-Butylcatechol | | | | |
| 1 | 0.5 | 150 | 20 | 12 | 1 | None | 30 |
| 2 | 0.5 | 150 | 20 | 12 | 1 | TBC[c] (50, 0.3) | 50 |
| 3 | 2.2 | 70 | 20 | 2 | 2 | None | 32 |
| 4 | 2.4 | 70 | 20 | 2 | 2 | TBC (5, 0.03) | 30 |
| 5 | 2.0 | 70 | 20 | 2 | 2 | TBC (15, 0.09) | 50 |
| 6 | 2.0 | 70 | 20 | 2 | 2 | TBC (50, 0.3) | 67 |
| 7 | 2.0 | 70 | 20 | 2 | 2 | TBC (100, 0.6) | 60 |
| | | | Effect of Type of Radical Inhibitor (*cf.* also run 6) | | | | |
| 8 | 2.5 | 70 | 20 | 2 | 2 | TBH[d] (50, 0.3) | 38 |
| 9 | 2.5 | 70 | 20 | 2 | 2 | PTA[e] (60, 0.3) | 38 |
| 10 | 2.5 | 70 | 20 | 2 | 2 | Binox[f] (128, 0.3) | 47 |
| 11 | 2.5 | 70 | 20 | 2 | 2 | Catechol (33, 0.3) | 53 |
| | | | Effect of Temperature (*cf.* also run 6) | | | | |
| 12 | 2.0 | 70 | −10 | 2 | 2 | TBC (50, 0.3) | 27 |
| 13 | 2.5 | 70 | 30 | 2 | 2 | TBC (50, 0.3) | 65 |
| | | | Effect of Solvent (*cf.* also runs 2 and 6) | | | | |
| 14 | 2.5 | 70 | 20 | 2 | 3 | TBC (50, 0.3) | 0 |

[a] Anhydride 1 (2.94 g, 10 mmol) was used for each reaction. [b] Solvent system 1: triethylamine, 3 ml; pyridine, 117 ml; water, 10 ml. Solvent system 2: triethylamine, 3 ml; pyridine, 10 ml; water, 10 ml; $CH_3CN$, 107 ml. Solvent system 3: triethylamine, 3 ml; $CH_3CN$, 117 ml; water, 10 ml. [c] TBC, 4-*tert*-butylcatechol. [d] TBH, *tert*-butylhydroquinone. [e] PTA, phenothiazine. [f] Binox is the Shell Chemical Co. trade name for 4,4′-methylenebis(2,6-di-*tert*-butylphenol).

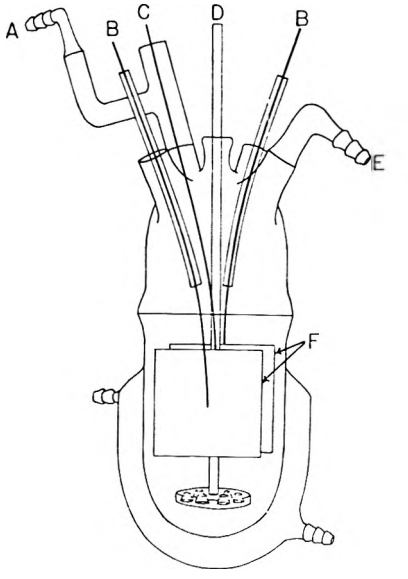



Figure 1.—Electrolysis cell: A, nitrogen gas inlet; B, copper wire lead to electrode; C, thermocouple; D, Vibromixer stirrer; E, gas outlet; F, platinum electrodes.

Bicyclooctadiene 1 was found to undergo a facile retro Diels–Alder reaction (even at room temperature) to give dimethyl terephthalate and ethylene. We have measured the kinetics and activation parameters for this reaction. To our knowledge this is the first time these parameters have been measured for this common type of retrodiene reaction. Finally, some of the bonding and structural changes that occur during the course of the reaction have been estimated by use of semiempirical quantum mechanical techniques.

**Electrolysis Reaction.**—Electrolytic oxidation of 1,2-dicarboxylic acids to olefins, first elucidated by Fichter,[4] has received renewed attention in recent years.[5-7] In particular, the electrolytic method smoothly decarboxylates bicyclic diacids containing proximal olefinic bonds.[5] Lead tetraacetate oxidation,[8] on the other hand, converts this class of compounds to lactones[5,6,9] and polymer.

Laboratory-scale Kolbe oxidations are generally carried out in an open beaker. We have constructed a more sophisticated cell (see Figure 1) from readily available glassware. The cell combines the vigorous agitation provided by a Vibromixer stirrer with a system that monitors and controls the reaction temperature in the area between the electrodes. These two features permit the maintenance of a high current density *and* a low reaction temperature for the oxidation of compound 2.

Previous investigators[5-7] have always used pyridine–water–triethylamine as the solvent system for this reaction. Replacement of most of the pyridine with acetonitrile brought about a dramatic decrease in the internal resistance of the cell which, in turn, permitted the reaction to be run at higher current density and consequently a shorter period of time. Complete removal of pyridine, on the other hand, resulted in conversion of anhydride 2 to a brown oil. (For the effect of solvent on yields and reaction times see runs 2, 6, and 14, Table I.)

Electrolytic decarboxylation of the purified anhydride using typical reaction conditions[5-7] (run 1, Table I) produced the desired material in 30% yield. The remainder of the starting material was converted to an insoluble polymer which coated the reaction vessel and the platinum electrodes. In comparison, crude anhydride (washed with ether but not recrystallized) was cleanly electrolyzed—no insoluble polymer formation—to olefin 1 in about 60% yield. This increase in yield was reproducible and eventually it was discovered that traces of *tert*-butylcatechol (used as a radical inhibitor in the preparation of anhydride 2) eliminated the for-

(4) F. Fichter and H. Stenzel, *Helv. Chim. Acta.*, **22**, 970 (1939).
(5) P. Radlich, R. Klem, S. Spurlock, J. J. Sims, E. E. van Tamelin, and T. Whitesides, *Tetrahedron Lett.*, 5117 (1968), and references cited therein.
(6) H. H. Westberg, and H. J. Dauben, Jr., *Tetrahedron Lett.*, 5123 (1968).
(7) P. G. Gassman H. P. Benecke, and T. J. Murphy, *Tetrahedron Lett.*, 1649 (1969).
(8) C. A. Grob, M. Ohta, E. Renk, and A. Weiss, *Helv. Chim. Acta*, **41**, 1191 (1958).
(9) C. M. Cimarusti and J. Wolinski, *J. Amer. Chem. Soc.*, **90**, 113 (1968).

mation of insoluble polymer. The effect of *tert*-butylcatechol on the yield of olefin **2** is presented in Table I (runs 1–7).

The effect of temperature (runs 6, 12, 13) and type of radical inhibitor (runs 8–11) on the yield of dihydrobarrelene **1** are also listed in Table I. The optimal conditions for this reaction are those of run 6.

**Kinetics.**—A search of the literature revealed that little qualitative and even less quantitative rate data have been reported for the commonly employed retrodiene reaction in which an aromatic molecule is one of the products. Alder and Rickert[10] were first to observe the reaction. They reported that 2,3-bis(ethoxycarbonyl)bicyclo[2.2.2]octa-2,5-diene was converted to ethylene and diethyl phthalate at 200°. More recently Grob and coworkers[11] reported that bicyclo[2.2.2]octadiene (**3**) survived 150° for a brief period of time. Humber and coworkers[12] and Smith and coworkers,[13] on the other hand, were not able to prepare 1,4-bis(ethoxycarbonyl)bicyclo[2.2.2]octa-2,5-diene at reaction temperatures below 150°. Instead, they obtained the retrodiene reaction products, *i.e.*, diethyl terephthalate and ethylene.

Bicyclooctadiene **1** readily cleaves to ethylene and dimethyl terephthalate at temperatures as low as 50°. No other products were detected by gas chromatography, while 99.5 ± 2.5% of the terephthalate was accounted for at the end of each kinetic run by ultraviolet spectroscopy.

The rate of the retrodiene reaction was followed by measuring the increase in uv absorbance of dimethyl terephthalate. Eight points were obtained for each run and conveniently fitted to eq 1 by a weighted non-

$$\frac{A-A_0}{A_\infty-A_0} = e^{-kt} \qquad (1)$$

linear least-squares regression program.[14] Activation parameters were similarly obtained *via* eq 2, where $A_0$,

$$\ln k_r = \ln kT/h - \Delta H^{\ddagger}/RT + \Delta S^{\ddagger}/R \qquad (2)$$

$A$, and $A_\infty$ are the dimethyl terephthalate uv absorbances at zero time, at regular intervals during the reaction, and at infinite time, respectively.

The kinetic data are presented in Table II. For all runs, the deviation of the dependent variable from the calculated regression line was random; the total correlation coefficient squared was 0.9990 for the calculation of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ and ranged from 0.9855 to 0.9994 for the calculation of the first-order rate constants.

**Calculations.**—Of the many methods used to study the mechanism of the Diels–Alder reaction,[15] only secondary deuterium[16] and carbon-13[17] primary kinetic

Table II
Summary of Kinetic Data[a]

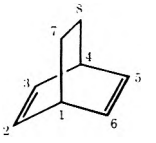
| Temp, °C | Run no. | Initial concn of **2** ($10^4$ *M*) | $f$[b] | $10^6$ $k$,[c] sec$^{-1}$ |
|---|---|---|---|---|
| 50 ± 0.01 | 1 | 1.55 | 0.71 | 4.32 ± 0.12 |
| | 2 | 2.42 | 0.70 | 4.12 ± 0.05 |
| | 3 | 1.42 | 0.86 | 3.96 ± 0.11 |
| 60 ± 0.01 | 4 | 2.19 | 0.92 | 15.0 ± 0.3 |
| | 5 | 2.45 | 0.86 | 14.8 ± 0.2 |
| | 6 | 2.16 | 0.83 | 14.6 ± 0.1 |
| 70 ± 0.01 | 7 | 3.20 | 0.96 | 45.1 ± 2.1 |
| | 8 | 3.59 | 0.84 | 45.7 ± 0.6 |
| | 9 | 3.32 | 0.86 | 50.5 ± 0.5 |
| 80 ± 0.1 | 10 | 2.85 | 0.84 | 161 ± 2 |
| | 11 | 2.80 | 0.98 | 168 ± 1 |
| | 12 | 2.20 | 0.77 | 150 ± 3 |

[a] $H^{\ddagger}$ = 26.8 ± 0.3 kcal/mol; $S^{\ddagger}$ = 0.4 ± 0.9 eu. [b] Maximum extent of reaction followed. [c] Errors are reported as standard deviations.

isotope effect measurements provide information about the structure of the transition state for this type of reaction.[18] The classical argument concerning the Diels–Alder reaction was whether the two $\sigma$ bonds, created during the course of the reaction, were formed simultaneously or stepwise. Kinetic isotope effect measurements[15,16] suggest that the symmetry of bond formation or cleavage closely parallels the symmetry of the reactant(s). Orbital symmetry considerations,[19] predict that the reaction does not proceed through a biradical intermediate.

A search of the literature indicated that neither extended Hückel or CNDO/2 calculations have been carried out for the case of a retrodiene reaction that produces aromatic products. We thus thought it would be of interest to examine the retrodiene reactions of dihydrobarrelene (**3**) and its 1,4-bis(methoxycarbonyl) derivative (**1**) by means of the CNDO/2 method of calculation. In addition, both CNDO/2 and extended Hückel calculations were performed for the cycloaddition of ethylene to butadiene. In this way the two methods of calculation were compared and found to give similar results. These comparison calculations are presented in the Experimental Section.

During the course of the retrodiene reaction of adducts **1** and **3** several events must occur either simul-




**3**

taneously or successively. The cyclodiene portion of the ring must flatten with a subsequent lengthening and shortening of the bonds associated with the ring system; the $C_7$–$C_8$ bond distance must shorten with a flattening of the hydrogens attached to these carbons;

(10) K. Adler and H. E. Rickert, *Justus Liebigs Ann. Chem.*, **524**, 180 (1936).

(11) C. A. Grob, H. Kny, and A. Gagneux, *Helv. Chim. Acta*, **40**, 130 (1957).

(12) L. G. Humber, G. Meyers, L. Hawkins, C. Schmidt, and M. Bonlerice, *Can. J. Chem.*, **42**, 2852 (1964).

(13) G. Smith, C. L. Warren, and W. R. Vaughan, *J. Org. Chem.*, **28**, 3323 (1963).

(14) Program NONLIN written by A. W. Dickinson of the Monsanto Computing Center was used on a CDC 6400 computer.

(15) For reviews on the mechanism of the Diels–Alder reaction see (a) S. Seltzer, *Advan. Alicyclic Chem.*, **2**, 1 (1968); (b) J. Sauer, *Angew. Chem., Int. Ed. Engl.*, **6**, 16 (1967); (c) R. B. Woodward and T. J. Katz, *Tetrahedron*, **5**, 70 (1959).

(16) (a) P. Brown and R. C. Cookson, *Tetrahedron*, **21**, 1993 (1965); (b) S. Seltzer, *J. Amer. Chem. Soc.*, **87**, 1534 (1965); (c) D. E. Van Sickle and J. O. Rodin, *ibid.*, **86**, 3091 (1964).

(17) M. J. Goldstein and G. J. Thayer, Jr., *J. Amer. Chem. Soc.*, **87**, 1933 (1965).

(18) The term "no mechanism" has been used to describe this reaction because numerous kinetic studies have yielded little information about its detailed mechanism: W. von E. Doering and W. Roth, *Tetrahedron*, **18**, 67 (1962).

(19) (a) R. Hoffmann and R. B. Woodward, *J. Amer. Chem. Soc.*, **87**, 2046 (1965); (b) R. Hoffmann and R. B. Woodward, *Accounts Chem. Res.*, **1**, 17 (1968); (c) L. Salem, *J. Amer. Chem. Soc.*, **90**, 543 (1968).

and the $C_1$–$C_7$ and $C_4$–$C_8$ bonds must lengthen. The order in which these events occur can be investigated by varying them singly or simultaneously and observing the resulting effect on the total molecular energies. In order to reduce the dimension of such an energy surface to a few parameters, only those parameters suggested by experimental[16,17,20] and theoretical considerations[21] to be of importance were examined; reasonable estimates were chosen for the others. Absolute molecular energies cannot be obtained using the method employed here; however, the differences in energies obtained should offer insight into the nature of this reaction.

The following six reaction pathways involving symmetric lengthening of bonds $C_1$–$C_7$ and $C_4$–$C_8$ were investigated: 1a, loss of $C_7$–$C_8$ in an ethane conformation from nonplanar cyclohexadiene, and 2a, from planar cyclohexadiene; 1b, loss of $C_7$–$C_8$ in an ethylene conformation from nonplanar cyclohexadiene, and 2b, from planar cyclohexadiene; 1c, loss of $C_7$–$C_8$ in a conformation intermediate to ethane–ethylene from nonplanar cyclohexadiene, and 2c, planar cyclohexadiene. The two unsymmetrical pathways considered were stepwise breaking of bonds $C_1$ $C_7$ and $C_4$–$C_8$ in both the singlet and triplet states. Detailed geometries of the structures used for these series of calculations are presented in the Experimental Section.

The calculations indicated that the lowest energy process involved flattening of the cyclohexadiene ring and loss of the $C_7$–$C_8$ fragment in an ethylene-like conformation (process 1c). These calculations, however, were not pursued far enough to provide the transition state structure for this process.

Substitution of methoxycarbonyl groups at the bridgehead position did not alter the above mechanistic conclusions. Differences, particularly in the activation energy and atomic charges, were observed. The calculated difference in the total energy of the transition states for compounds **3** and **1** was found to be 17 kcal/mol, the latter compound being lower.

## Results and Conclusions

Enthalpy of activation values for the retrodiene reaction vary from 73 (cyclohexane pyrolysis)[22] to 25 kcal/mol (anthracene–tetracyanoethylene adduct)[15a] and entropy of activation values vary from −2.7 to 17.3 eu.[1a] The low enthalpy of activation (26.8 kcal/mol) and entropy of activation (~0 eu) for the retrogression of compound **1** suggest that the transition state occurs early along the reaction coordinate.

At present, there are not sufficient kinetic data on retrodiene cleavage of bicyclo[2.2.2]octadiene systems to allow for correlation of substituent effects with activation energies. Qualitatively, the effects of methoxycarbonyl groups are in accord with the CNDO/2 calculations. These calculations imply that electron-withdrawing groups should facilitate the retro Diels–Alder reaction.[23] The magnitude of these effects should vary, depending on the nature of the substituent and position of attachment. However, it is quite clear that these effects could be of considerable synthetic utility in designing new retro Diels–Alder reactions as routes to unstable intermediates.

## Experimental Section

Melting points are uncorrected; nmr spectra were obtained with a Varian T60; uv spectra were obtained with a Perkin-Elmer 450 spectrometer; microanalyses were carried out at Monsanto's Physical Science Center. A Varian Aerograph 2100 dual column gas chromatograph equipped with flame ionization detectors was used in the single-column mode for gas chromatographic analyses. The signal from the chromatograph was fed to an Infotronics CRS-104 digital integrator and then to a Varian Aerograph Model 30 recorder.

**Electrolysis Cell.**—The electrolyses were carried out in the apparatus shown in Figure 1. Power was supplied by a Sorensen Model RC150-7.5 constant-voltage power supply. The reactions reported in this paper were run in a 100-ml jacketed reaction flask (Kontes K-296100). The reaction flask head was a Kontes K-296170 head to which two 10/30 outer joints had been added to accommodate the electrodes. The temperature of the reaction was monitored between the electrodes with an iron–constantan thermocouple (Aeropak, Model T-91M-12BJ8C) which was insulated with $^1/_{16}$-in.-i.d. Teflon tubing (Fluorocarbon Co., Anaheim, Calif.). The thermocouple was connected to a West-Gardsman temperature controller which controlled a circulating pump. The coolant (1 l. of acetone, 4 l. of methanol) was pumped from a 4-l. dewar flask (mixing bath) through the reaction flask jacket, through a copper coil immersed in Dry Ice–acetone and back to the mixing bath. The square, smooth platinum electrodes (4.45 cm on an edge) were fashioned from 0.076 mm (3 mil) thick platinum foil and were spot welded to 18 gauge platinum wire which was imbedded into 6-mm-o.d. Pyrex glass tubing. Mercury was placed in the tube to provide an electrical contact between the electrode and the copper wire lead. The glass electrodes and the thermocouple were held in place by Teflon thermometer adapters.

**1,4-Bis(methoxycarbonyl)bicyclo[2.2.2]oct-5-ene-2,3-dicarboxylic Anhydride (2).**—Dimethylcyclohexa-1,3-diene 1,4-dicarboxylate (55.7 g, 0.28 mol), which was prepared by the method of Kauer,[24] maleic anhydride (83.9 g, 0.85 mol), 4-*tert*-butylcatechol (1 g, recrystallized from heptane), and 400 ml of o-dichlorobenzene were placed into a three-neck, 1-l. flask equipped with a thermometer, overhead stirrer, and heating mantle. The reaction mixture was heated to 170° for 5 hr, solvent was removed *in vacuo*, and the crude adduct was washed with ether and recrystallized from hexane–chloroform to give 65 g (0.22 mol, 80%) of adduct, mp 183–185° (lit. mp 188.0–188.6).[24]

**1,4-Bis(methoxycarbonyl)bicyclo[2.2.2]octa-2,5-diene. A. Electrochemical Oxidation Reaction.**—Anhydride **2** (2.49 g, 10 mmol) was heated with a mixture of triethylamine (3 ml), pyridine (10 ml), and water (10 ml) until a clear solution was obtained. This solution of hydrolyzed anhydride was washed into the reaction vessel with the remainder of the solvent (pyridine for runs 1 and 2, acetonitrile for runs 3–13). The radical inhibitor was added, the reaction mixture was flushed with nitrogen, and the power was turned on.

Work-up of the reaction mixture involved dilution with 100 ml of water [reactions run in $C_5H_5N$–$H_2O$–$(C_2H_5)_3N$] or reduction of the solvent *in vacuo* to a total volume of 30 ml followed by dilution with 50 ml of water [reactions run in $CH_3CN$, $C_5H_5N$, $(C_2H_5)_3N$, $H_2O$]. The diluted reaction mixture was then extracted with four 25-ml portions of pentane which were combined, washed with 50 ml of 1 *N* HCl, and dried over sodium sulfate. Removal of the pentane *in vacuo* left a white residue which was recrystallized

(20) Primary carbon-13 isotope effects for the reaction of $^{13}$C-labeled dicyanoacetylene with cyclopentadiene were correlated with a transition state in which the total constraints about the acetylenic carbons were approximately $^1/_3$ less (4.8 mdyn/Å) than for ground-state dicyanoacetylene. C. B. Warren, Ph.D. Thesis, Cornell University, 1970; M. J. Goldstein, C. B. Warren, and W. S. Morrison, to be published.

(21) J. W. McIver, Jr., *J. Amer. Chem. Soc.*, **94**, 4782 (1972).

(22) S. R. Smith and A. S. Gordon, *J. Phys. Chem.*, **65**, 1124 (1961).

(23) Recent work by Haberfield suggests that the transition state for the forward Diels–Alder reaction is electron rich relative to the reactants (electron-donor solvents stabilize the reactants; the more electronegative solvents stabilize the transition state). Whether a similar relationship holds for the reverse reaction is not known. P. Haberfield and A. K. Ray, *J. Org. Chem.*, **37**, 3093 (1972).

(24) J. C. Kauer, R. E. Benson, and G. W. Parshall, *J. Org. Chem.*, **30**, 1431 (1965).

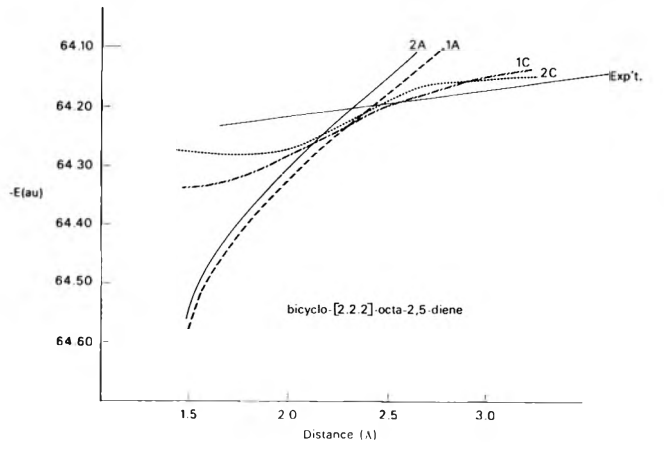



Figure 2.—Total molecular energies as a function of the perpendicular distance between lines connecting atoms $C_1$–$C_4$ and atoms $C_7$–$C_8$ in bicyclo[2.2.2]octadiene for various conformational changes. See the calculation part of the Experimental Section for a description of the conformations studied.

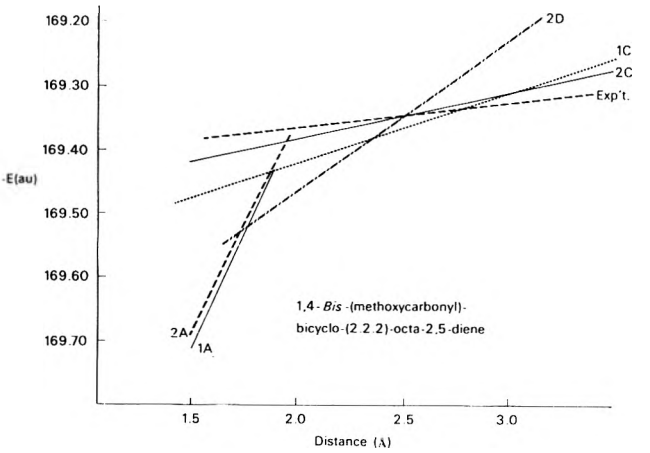



Figure 3.—Total molecular energies as a function of the perpendicular distance between lines connecting atoms $C_1$–$C_4$ and atoms $C_7$–$C_8$ in 1,4-bis(methoxycarbonyl)bicyclo[2.2.2]octa-2,5-diene.

from pentane: mp 88–89°; nmr (DMSO-$d_6$) $\delta$ 6.55 (s, 4, vinyl hydrogen), 3.82 (s, 6, $COOCH_3$), 1.58 (s, 4, methylene hydrogen).

*Anal.* Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35. Found: C, 64.90; H, 6.20.

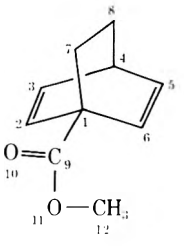
**B. Gas Chromatographic Analyses.**—All gas chromatograms were run at an injection port temperature of 250°. At this temperature, dihydrobarrelene 1 was converted to dimethyl terephthalate and the bistriethylammonium salt of 2 was converted back to anhydride. The reactions listed in Table I were followed by gas chromatography. A 0.20-ml sample of the reaction mixture was withdrawn and spiked with 2 mg of 1-phenylnonane; 0.5 $\mu$l of this solution was injected on a 1.9 m × 2 mm glass U column packed with 3% OV-11 on 100/120 mesh Supelcoport. In two runs, the yields obtained by gas chromatography were compared to the weight of 1 isolated by pentane extraction and found to differ by about 5%. The reaction times listed in Table I were sufficient for the complete disappearance of starting material.

**Kinetics.**—Recrystallized bicyclooctadiene 1 which contained about 3% dimethyl terephthalate was used for the kinetic runs. Analysis of the material by gas chromatography showed no *tert*-butylcatechol in the sample; the nmr showed only dimethyl terephthalate and 1. The kinetics of the reaction were followed by measuring the increase in uv absorbance of the product (dimethyl terephthalate) at all three of its uv max wavelengths, uv max (dodecane) 242 nm ($\epsilon$ 9000), 283 (810), 292 (705). Absorbance varied linearly with concentration to 0.9 absorbance units for $\lambda_{max}$ 242, and to 0.5 absorbance units for $\lambda_{max}$ 283 and 292. Uv measurements were carried out in a 1-cm or 0.1-cm cell depending on the concentration of the solution. All reactions were carried out in olefin-free dodecane.

Typically, a carefully weighed portion of a stock solution of 2 was diluted to 25.0 ml. After the initial absorbance had been measured, 4-ml portions of this solution were placed into six 5-ml vials which were then evacuated, sealed, and placed into a constant-temperature bath. The vials were withdrawn periodically and placed in a dewar flask filled with Dry Ice–acetone. After the run was finished the vials were warmed to room temperature and opened and the terephthalate absorbance was measured. One sample of the reaction mixture was then resealed into a vial and heated to 100° for 3 hr to provide an infinity sample. Comparison of the infinity time concentration of terephthalate to the initial concentration of bicyclic compound 1 showed that 99.5 ± 2.5% of starting material had been converted to product.

**Calculations.**—The structural parameters used in this study were obtained from the structural determinations of bicyclo[2.2.2]octadiene (3),[25] bicyclo[2.2.2]octene-2,3-*endo*-dicarboxylic anhydride,[26] and studies on bicyclo[2.2.2]octane-1,4-dicarboxylic acid.[27] Additional data for the methoxycarbonyl structure used to construct the molecular structure of 1 were obtained from interatomic distances.[28] These values are presented in Table III.

TABLE III
BOND ANGLES AND DISTANCES FOR COMPOUND 1




1

| Methoxycarbonyl | Bond length, Å | Bond angle, deg |
|---|---|---|
| $C_9$–$O_{10}$ | 1.22 | |
| $C_9$–$O_{11}$ | 1.36 | |
| $O_{11}$–$C_{12}$ | 1.46 | |
| $C_{12}$–H | 1.09 | |
| $C_1$–$C_9$–$O_{11}$–$C_{12}$ dihedral angle[a] | | 155 |
| $C_1$–$C_9$–$C_{10}$ | | 120 |
| $C_1$–$C_9$–$O_{11}$ | | 116 |
| $C_9$–$O_{11}$–$C_{12}$ | | 113 |

[a] Methyl points away from molecule.

The events and corresponding geometric changes investigated as a function of the separation distance between $C_1$–$C_4$ and $C_7$–$C_8$ follow.

(1) A bent, nearly planar hexadiene ring with a ring dihedral angle of 168° (also $C_1$–$C_2$–H, 121°) and with bond lengths intermediate between benzene and cyclohexadiene ($C_1$–$C_2$, 1.42 Å; $C_2$–$C_3$, 1.38 Å; $C_2$–H, 1.09 Å) and with either (A) near ethane $C_7$–$C_8$ bond distance (1.553 Å) and experimental methylene bond angles and bond lengths ($C_7$–H, 1.105 Å, H–$C_7$–H, 111.3°); (B) near ethane $C_7$–$C_8$ bond distance and planar ethane hydrogens ($C_7$–H, 1.09 Å; H–$C_7$–H, 122°); (C) near ethylene $C_7$–$C_8$ bond distances (1.39 Å) and planar ethylene hydrogens ($C_7$–H, 1.09 Å; H–$C_7$–H, 122°); (D) near ethylene bond distances (1.39 Å) with nonplanar hydrogens (H–$C_7$–H, 111.3°; $C_7$–H, 1.105 Å).

(2) A planar hexadiene ring with bond distances and angles for the ethyl fragment as reported in cases A–D above.

The results of the calculations for 3 are shown in Figure 2, where the total molecular energies are plotted as a function of the perpendicular distance between two lines joining atoms $C_1$–$C_4$ and $C_7$–$C_8$. Only four of the eight variations outlined above are in-

(25) A. Yokozeki and K. Kuchitsu, *Bull. Chem. Soc., Jap.*, **44**, 1783 (1971).

(26) R. Destro, G. Fillippini, C. M. Gramaccioli, and M. Simonetta, *Tetrahedron Lett.*, **No. 29**, 2493 (1969).

(27) O. Ermer and J. D. Dunitz, *Chem. Commun.*, 567 (1968); *Helv. Chim. Acta*, **52**, 1861 (1969).

(28) "Tables of Interatomic Distances," Special Publication No. 11, The Chemical Society, London, 1958.

cluded; the others either parallel those shown or were conformations of higher energy. At about 3 Å the "benzene–ethylene complex" (experimental ethylene–benzene bond angles and lengths, depicted as Exp't in Figures 2 and 3) has the lowest energy of all the conformations studied. In the stepwise bond-breaking process, the $C_1$–$C_7$ bond length was arbitrarily chosen to be twice as long as the $C_2$–$C_8$ value. Both singlet ($^1S$) and triplet ($^3T$) electronic states were studied.

Similar analyses were performed on compound **1**. The experimental geometry of dihydrobarrelene (**3**) was used to fix the ring geometries. The conformation of the methoxycarbonyl groups used was the one with the carbonyl groups colinear with $C_1$–$C_4$ and the $C_7$–$C_1$–$C_9$–$O_{10}$ dihedral angle equal to 45°. The results of these calculations, shown in Figure 3, parallel those for compound **3**.

To test whether the retrodiene reaction was allowed under the conservation of orbital symmetry concept,[19b] we performed both extended Hückel[19a] and CNDO/2 calculations for ethylene–ethylene and ethylene–butadiene cycloaddition reactions. The two methods gave a slightly different ordering of energy levels but otherwise the same results were obtained. Similar CNDO/2 analyses were performed on both compounds **3** and **1**. The occupied reactant molecular orbitals (MO) were composed predominantly of linear combinations of benzene and ethylene MO's, of which the bonding product MO's were the major contributors, thus confirming the allowableness of the concerted retrodiene reaction of **3** and **1**.

**Registry No.**—**1**, 41894-67-1; **2**, 41894-68-2; dimethyl cyclohexa-1,3-diene-1,4-dicarboxylate, 1659-95-6.

# Electrochemical Reduction of (+)-(2S,4S)-2,4-Dibromopentane

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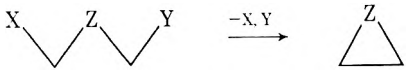
*Received July 16, 1973*

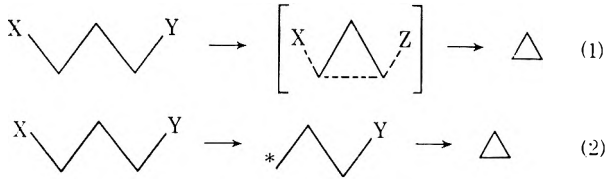
Electrochemical reduction of *meso*- and *dl*-2,4-dibromopentane (**2**) in dimethyl sulfoxide affords in each case roughly equal amounts of *cis*- and *trans*-1,2-dimethylcyclopropanes (**7** and **8**, respectively). The results are interpreted in terms of a stepwise reduction mechanism, *via* a γ-halo carbanion (**13**). (−)-(2*R*,4*R*)-2,4-Pentanediol was prepared by resolution of the racemic diol; the diol was then converted by means of phosphorus tribromide in pyridine into (+)-(2*S*,4*S*)-**2**. Electrochemical reduction of this material afforded (−)-(1*R*,2*R*)-**8** of high optical purity, demonstrating that cyclization of **13** occurs *via* a semi-W transition state. The reduction of *dl* and optically active **2** by a number of chemical reductants was also examined.

There exists a wide variety[2] of reactions which amount to overall 1,3 elimination of two substituents with formation of a carbon–carbon bond, *i.e.*

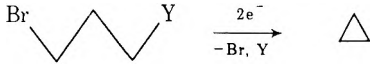



Z = carbon or a heteroatom

Generally, mechanisms proposed for such reactions have fallen into two classes, concerted (eq 1) or stepwise (eq 2). The carbon denoted by an asterisk in



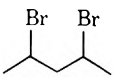

eq 2 may be a carbanion, carbonium ion, carbene, or radical; at any rate, a discrete intermediate intervenes on the way to product, while in the concerted mechanism the bonds to X and Y are both breaking as the new bond is forming. A great deal of recent evidence[3] has demonstrated that a number of such reactions formerly thought to be concerted actually proceed in stepwise fashion. Indeed, there does not now appear to exist any authentic example of a concerted 1,3 elimination.[3] In this light, we were attracted to a number of recent reports that electrochemical reduction of compounds of general structure **1** affords cyclopropanes in good




**1**, Y = Br, Cl, $^+N(CH_3)_3$

yields,[4] and especially to the suggestion that certain of of these reductions—primarily open-chain compounds—proceed by a concerted mechanism.[4]

We describe herein evidence that electrochemical reduction of the open-chain dibromides *meso*- and *dl*-2,4-dibromopentane (**2**) actually proceeds stepwise, *via* an intermediate γ-halo carbanion.[5] Further, we present the first unequivocal demonstration of the stereochemistry of cyclization of an acylic γ-halo carbanion. The study consisted of an analysis of the products, including stereochemistry, of the electrochemical reduction of *meso*- and *dl*-2,4-dibromopentane (**2**) and of (+)-(2*S*,4*S*)-**2**. Reduction of **2** by chemical reductants was also briefly investigated.




**2**

## Results

**Synthesis.**—*meso*- and *dl*-2,4-dibromopentane (**2**) were prepared by an improved modification of the

(1) (a) Excerpted in part from the Ph.D. thesis of W. E. B., Wesleyan University, 1972. (b) A portion of these results have been communicated in preliminary form: A. J. Fry and W. E. Britton, *Tetrahedron Lett.*, 4363 (1971).

(2) A. Nickon and N. H. Werstiuk, *J. Amer. Chem. Soc.*, **89**, 3914 (1967), and many references therein.

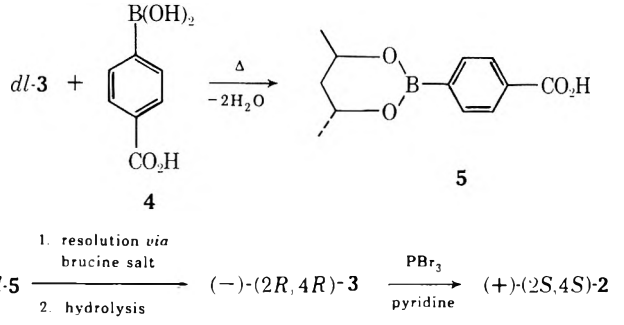
(3) (a) F. C. Bordwell, *Accounts Chem. Res.*, **3**, 281 (1970); (b) L. A. Paquette, *ibid.*, **1**, 209 (1968).

(4) (a) M. R. Rifi, *Collect. Czech. Chem. Commun.*, **36**, 932 (1971); (b) M. R. Rifi, *Tetrahedron Lett.*, 1043, (1969); (c) M. R. Rifi, *J. Amer. Soc.*, **89**, 4442 (1967).

(5) It is well established that electrochemical reduction of alkyl halides involves carbanion intermediates: (a) A. J. Fry and R. G. Reed, *J. Amer. Chem. Soc.*, **94**, 8475 (1972); (b) J. L. Webb, C. K. Mann, and H. M. Walborsky, *ibid.*, **92**, 2042 (1970).

method of Pritchard and Vollmer.[6] This method consists of sodium borohydride reduction of acetylacetone, conversion of the resulting mixture of *meso*- and *dl*-2,4-pentanediol (**3**) to the corresponding sulfite esters, separation of the latter by fractional distillation, and final saponification. Treatment of either *meso*- or *dl*-**3** with phosphorus pentabromide in pyridine afforded the corresponding dibromide **2**, contaminated in each case with a few per cent of the other isomer. The dibromides were purified by preparative vpc before each experiment. Optically active **2** of known absolute configuration was obtained by the method shown in Scheme I. Azeotropic removal of water from a benzene mixture of *dl*-**3** and *p*-carboxyphenylboronic acid (**4**) afforded racemic *trans*-4,6-dimethyl-2-*p*-carboxyphenyl-1,3,2-dioxaborinane (**5**) in quantitative yield. After resolution *via* its brucine salt, optically active **5** was converted into (−)-(2*R*,4*R*)-**3** by vigorous hydrolysis in aqueous sodium hydroxide.[7] The configuration of the diol produced by this sequence follows from the fact that conversion of alcohols to bromides by phosphorus pentabromide in pyridine occurs with inversion of configuration[9] and from the proof of configuration below of the resulting dibromide **2**, which was obtained from **3** in the usual manner. After purification by preparative vpc the dibromide exhibited $[\alpha]^{25}D$ + 102° ($CHCl_3$) and $[\alpha]^{25}_{540}$ 126°. Its absolute configuration was established by partial reduction with triphenyltin hydride in hexane to a mixture of pentane, 2-bromopentane (**6**), and unreacted **2**. After isolation by preparative vpc, **6** exhibited $[\alpha]^{25}D$ + 45.5 ± 2.7°. Since it is known that (+)-**6** has the *S* absolute configuration,[10] (+)-**2** must have the 2*S*,4*S* absolute configuration.

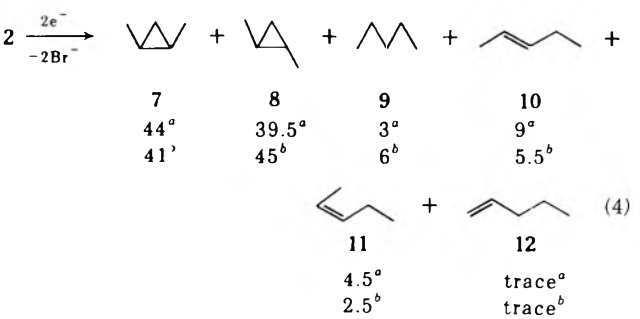
Scheme I




Dibromide **2** must be of high optical purity. Hudson[10b,c] has reported $[\alpha]^{25}D$ −52.6 (neat) and −53.4° (MeOH) for (−)-**6**. Furthermore, the specific rotation of a single neat sample of **6** has been measured as +48.2° at 25° and +49.5° at 20°.[11] Thus the rotation of **6** is both solvent and temperature dependent, and the optical purity of the sample prepared from **2** is consequently somewhat uncertain; assuming that Hudson's material was optically pure, that prepared in the present study must be between 87 and 96% optically pure. Results obtained upon electrochemical reduction of this material (*vide infra*) suggest that its optical purity actually lies near the upper end of this range.

**Electrochemical Data.**—All electrochemical experiments upon *meso*- and *dl*-**2** and upon **6** were carried out in dimethyl sulfoxide (DMSO) containing 0.1 *M* tetraethylammonium bromide (TEAB). Each compound exhibited a single polarographic wave, which appeared at −1.90, −1.91, and −2.09 V (*vs.* sce) for *meso*-**2**, *dl*-**2**, and **6**, respectively. The two dibromides exhibited severe polarographic maxima, which could be eliminated using drop times of 0.5 sec produced by a mechanical drop timer, allowing accurate measurement of the half-wave potential. Because of these maxima, however, diffusion current constants ($I_d = i_d/Cm^{2/3} \cdot t^{1/6}$)[12] could not be computed.

Controlled-potential electrochemical of the diastereomers of **2** was carried out at −2.2 V. The results are summarized in eq 4. These figures represent




[a] Per cent yield using *dl*-**2**. [b] Per cent yield using *meso*-**2**.

relative yields but are identical within experimental error with absolute yields: the absolute yield of the mixture of hydrocarbons **7**–**12** is 100 ± 5%. Coulometry indicated the consumption of 2.0 ± 0.1 Faradays/mol of **2**, as expected.[5]

Vpc analysis of the solution as electrolysis proceeded demonstrated the buildup and decay of three substances of similar retention time fomed in roughly equal proportions. Identification of these materials, which had disappeared by the end of the electrolysis, was impossible since even at their maximum concentration they were present in amounts too small for isolation. The retention time of the largest peak corresponded to that of **6**, a likely intermediate (see Discussion).

Addition of water (1.0 *M*) to the electrolysis medium before reduction of *meso*-**2** resulted in a measurable, but small, effect upon the product composition: **7** (41.5%), **8** (49.5%), **9** (6%), **10** (2.5%), **11** (1%), and **12** (no detectable amount).

The electrochemical reduction of (+)-(2*S*,4*S*)-**2** was carried out in the same manner as that of *dl*- and *meso*-**2**. The hydrocarbon products were extracted from the electrolysis mixture with cold heptane and analyzed by vpc. Because of the small scale upon which electrolyses were carried out, the heptane extracts were analyzed directly by polarimetry without attempting to isolate *trans*-1,2-dimethylcyclopropane (**8**) from the mixture. This procedure is justified by the facts that none of the other products is chiral and that these products account quantitatively for all of the dibromide

(6) J. G. Pritchard and R. L. Vollmer, *J. Org. Chem.*, **28**, 1545 (1963).

(7) This sequence was modeled after a related resolution reported by Agosta.[8]

(8) W. C. Agosta, *J. Amer. Chem. Soc.*, **89**, 3926 (1967).

(9) W. Gerrard, *J. Chem. Soc. C*, 741 (1946).

(10) (a) J. H. Brewster, *J. Amer Chem. Soc.*, **81**, 4575 (1959); (b) H. R. Hudson, *Synthesis*, **1**, 112 (1969); (c) H. R. Hudson, B. A. Chaudri, and D. G. Goodwin, *J. Chem. Soc. C*, 1329 (1970).

(11) Norse Laboratories, private communication, July 1972.

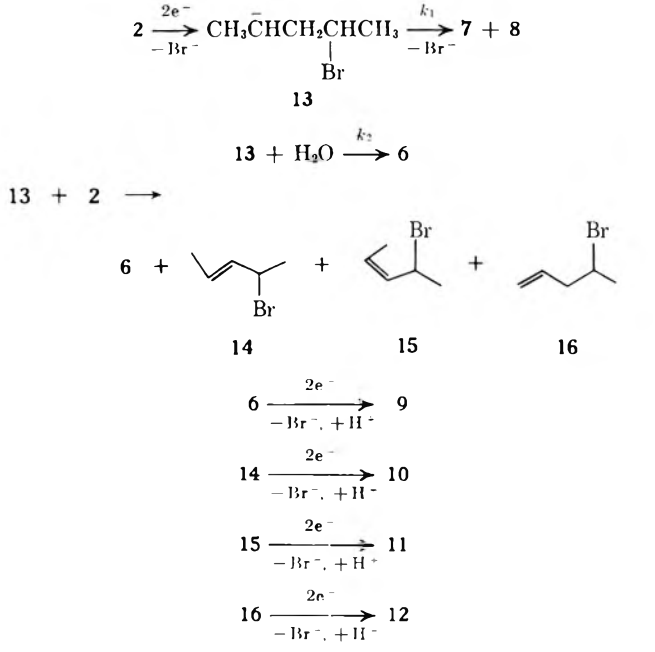
(12) A. J. Fry, "Synthetic Organic Electrochemistry," Harper and Row, New York, N. Y., 1972, pp 71–73.

reduced; *i.e.*, there are no nonvolatile products. After correction (using the results of the vpc analysis) for a small amount of **8** lost by volatilization, the specific rotation of **8** produced in the electrolysis was determined to be $[\alpha]^{25}D$ $-46 \pm 2°$. Doering and Kirmse[13] have shown that (−)-**8** has the 1*R*,2*R* absolute configuration and have presented a convincing argument that the specific rotation of optically pure **8** is ±46°. The high value for the rotation of **8** obtained in the electrolysis is the basis for the conjecture (*vide supra*) that the starting dibromide (+)-**2** was of high optical purity.

## Discussion

Isolation of almost identical mixtures of **7** and **8** from electrolysis of either *dl*- or *meso*-**2** provides essentially definitive proof[14,15] that electrochemical reduction of 1,3-dibromides to cyclopropanes proceeds in stepwise fashion and not concertedly as had previously[4] been claimed. The formation of products **7**–**12** in the reduction may be rationalized by the sequence of reactions shown in Scheme II. The formation of unsaturates

SCHEME II




**10**–**12** and pentane (**9**) strongly implicates a carbanion, presumably **13**, in the reduction. The conclusion appears almost inescapable that this carbanion lies on the reaction pathway for cyclization and that the loss of stereochemical identity occurs at the carbanion stage. Addition of water (1.0 *M*) to the electrolysis medium has only a slight effect upon the total yields of cyclopropanes. This is qualitatively a good indication that cyclization of **13** to **7** and **8** is quite efficient, but it is difficult to attach any quantitative significance to it. The experiment implies that the ratio $k_1/k_2[H_2O] >> 1$ (where $k_1$ is the rate of cyclization of **13** and $k_2[H_2O]$ is the pseudo-first-order rate of protonation of **13**, at $[H_2O] = 1.0$ *M*). It would be interesting to know $k_1$, but, since water is a very poor proton donor in dipolar aprotic solvents such as dimethylformamide (DMF) and DMSO,[17-20] it is not possible to use data measured in other solvent systems to estimate $k_2$.

The results of electrochemical reduction of *meso*- and *dl*-**2** led to the conclusion that reductive cyclization of 1,3-dibromides is not concerted, but stepwise *via* carbanion **13**. Reduction of (+)-(2*S*,4*S*)-**2** then permitted a definitive answer to another question of considerable current interest, *i.e.*, the stereochemistry of cyclization of γ-halo carbanions.[3b,21] Two extreme geometries may be envisaged for the cyclization, semi-W and semi-U,[2] depending upon whether the bromine atom of the γ-halo carbanion is displaced with inversion or retention, respectively. Results from a number of previous studies suggest that the preferred geometry is semi-W; however, all such cases have involved either more or less rigid cyclic systems or γ-halo anions in which the central atom is a heteroatom.[2,3] Either of these factors might affect the course of cyclization in an unsuspected way, hence our interest in the stereochemistry of cyclization of **13**, an all-carbon, open-chain γ-halo carbanion. Scheme III illustrates the stereochemical course of cyclization of **13** by both pathways, recognizing that inversion of configuration at the carbanion carbon and rotation about single bonds must both be taken into account. It is seen that the semi-W path will produce a mixture of *cis*- and (1*R*,2*R*)-*trans*-1,2-dimethylcyclopropanes, while cyclization by the semi-U path affords a mixture of *cis*- and (1*S*,2*S*)-*trans*-cyclopropanes. In the event, the *trans*-1,2-dimethylcyclopropane obtained in the electrolysis was the 1*R*,2*R* enantiomer, of high optical purity (100 ± 5%) (see Results). Thus cyclization of **13**, and presumably γ-halo carbanions in general, does indeed occur preferentially in semi-W fashion, *i.e.*, with inversion as do the more constrained polycyclic and heterocyclic analogs previously studied.

Some comment upon the evidence previously presented[4a,b] in favor of the view that reduction of compounds such as 1,3-dibromopropane is concerted may be appropriate. The claim for concertedness is based upon certain polarographic criteria and upon the failure of water to quench the electrochemical reduction of

(13) W. von E. Doering and W. Kirmse, *Tetrahedron*, **11**, 272 (1960).

(14) Interconversion of *dl*- and *meso*-**2** does not occur at a measurable rate under the electrolysis conditions.

(15) The *caveat* might be raised (and was by a referee of our preliminary communication) that concertedness could be preserved through conversion of *meso*-**2** into **7** and **8** by separate concerted paths (and likewise for *dl*-**2**). This would require the coincidence that the activation energies of two related overall paths of greatly differing stereoelectronic requirements be approximately equal. We regard this possibility as artificial and very unlikely and reject it as unnecessarily complex. We are here invoking the logical principle known as Occam's Razor which, despite recent criticism,[16] appears to remain a useful tool as long as it is recalled that it merely advises one, given several explanations of a set of facts, to select the simplest explanation *consistent with the known facts*. As the phrase in italics here suggests, new facts may at any time compel new and more complex interpretations in a given system.

(16) P. G. Gassman and F. J. Williams, *J. Amer. Chem. Soc.*, **94**, 7733 (1972).

(17) J. R. Jezorek and H. B. Mark, Jr., *J. Phys. Chem.*, **74**, 1726 (1970).

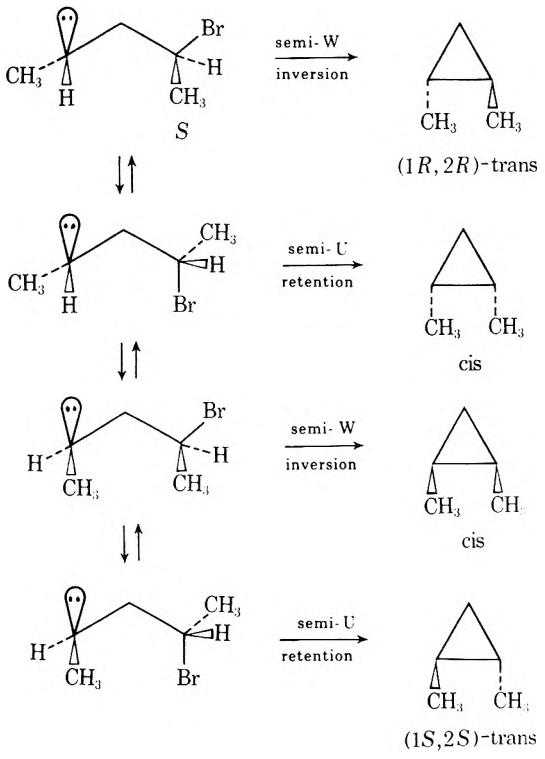
(18) Proton transfer rates appear to be lower in DMSO than in DMF. Thus, on the polarographic time scale the radical anion of 9,10-diphenylanthracene is not protonated in DMSO–phenol solutions,[19] but is readily protonated in DMF–phenol.[20] Furthermore, the only effect of water (2.8 *M*) on the polarographic reduction of 9,10-diphenylanthracene in DMSO is to *lower* the diffusion current because of increased viscosity of water–DMSO solutions over DMSO itself.[19]

(19) L. L. Chung and A. J. Fry, unpublished results.

(20) K. S. V. Santhanam and A. J. Bard, *J. Amer. Chem. Soc.*, **88**, 2669 (1966).

(21) (a) B. M. Trost, W. L. Schinski, F. Chen, and I. B. Mantz, *J. Amer. Chem. Soc.*, **93**, 676 (1971); (b) S. J. Cristol and A. R. Dahl, *ibid.*, **92**, 5670 (1970).

SCHEME III




1,3-dibromopropane to cyclopropane.[4a,b] The latter could well be due simply to rapid cyclization of an intermediate γ-halo carbanion[22] analogous to **13** and indeed this possibility was recognized.[4b]

The arguments from polarographic data adduced in favor of concertedness for certain reductions take the following form. Rifi has said that. . .those dibromides which give cyclic products upon electrolysis[23]. . . have a more positive value [of $E_{1/2}$] than those[24] which give open-chain hydrocarbons. The lower but reproducible value is considered to be an indication of a concerted mechanism in the formation of cyclic compounds,[4b] and, also, . . .how well developed the central (*i.e.*, new carbon–carbon) bond is in the transition state will be reflected in the half-wave potential of the dihalide.[4a] If no other effect could possibly account for the fact, *e.g.*, that 1,3-dibromopropane and 3-bromopropyltriethylammonium bromide are ~0.2 and 0.8 V easier, respectively, to reduce than a 1,5- or 1,6-dibromide, the inferences drawn by Rifi from these data would be both reasonable and justified. In fact, however, there are a number of other factors which can contribute to the observed differences. For example, the inductive effect of one bromine upon the other must be considered. Using the data of Lambert,[25] we calculate that the reduction potential of 1,3-dibromopropane should be more positive than that of 1,5-dibromopentane by 0.17 V; the observed difference is 0.23 V. Rifi has rejected inductive effects as a source of the observed differences because 1-bromo-3-chloropropane is somewhat harder (0.13 V) to reduce than 1,3-dibromopropane, an order opposite to that expected on the basis of inductive effects, and because 3-bromopropyltriethylammonium bromide is easier to reduce than can be accounted for on the basis of inductive effects alone. Neither of these arguments is convincing, however. First, it has recently been discovered that reduction potentials of 1,3-dibromides measured at a mercury cathode are markedly affected by adsorption[26] and may in fact differ by as much as 0.4 V from the same potentials measured at platinum. Thus small differences in expected potentials may be associated with adsorption phenomena. Since alkyl bromides are more strongly adsorbed at mercury than chlorides, one would expect 1,3-dibromopropane to be shifted positive by this adsorption effect more than the corresponding bromo chloride. By the same token, the reduction potential of 3-bromopropyltriethylammonium bromide cannot be directly compared with that of the 1,3-dibromide or indeed any other neutral mono- or dibromide, since it is well known that quaternary ammonium ions undergo strong specific adsorption at a mercury surface.[27] Furthermore, inclusion of a charged electroactive substance in the electrical double layer will shift the position of the outer Helmholtz plane, causing a change in its measured reduction potential (relative to related neutral compounds) of unknown but probably large magnitude.[27] It must also be pointed out that mechanistic conclusions based upon variations in the value of $\alpha$, the electrochemical transfer coefficient, are equally invalid in the face of demonstrable adsorption effects, since the latter phenomenon itself is sufficient to induce significant changes in $\alpha$ even in a series of closely related compounds.

**Chemical Reductants.**—The reduction of *dl*- and (+)-**2** by several chemical reductants was studied briefly, to determine whether reductive cyclization occurs and, if so, its stereochemistry. Reduction of (+)-**2** by sodium naphthalenide in 1,2-dimethoxyethane afforded a mixture of hydrocarbons **7**–**12**, along with some unreacted **2**. After isolation of the volatile fraction and polarometric analysis, the rotation of **8** produced in the reaction was calculated as $-62 \pm 15°$, indicating that cyclization occurs with inversion as it should, since carbanion **13** must be an intermediate in the reduction.[28] The wide error limits on this result are associated with the small scale upon which the reaction was run, with the consequence that measured rotations were small, though real and reproducible.[29] When the optically active dibromide was allowed to react with a large excess of lithium aluminum hydride in ether, pentane was the major volatile product. However, when the mole ratio of (+)-**2** to lithium aluminum hydride was 1:1 the volatile products (total yield 50%) consisted of approximately equal amounts of hydrocarbons **7**–**11**. The optical rotation of the product mixture was zero within experimental error,

(22) This would parallel the difficulty of quenching cyclopropane formation found in the present work and would be consistent with the common observation that water is a poor proton donor in dipolar aprotic solvents.[5a,17,18]

(23) *E.g.*, 1,3-dibromopropane and 3-bromopropyltriethylammonium bromide.

(24) *E.g.*, 1,5-dibromopentane and 1,6-dibromohexane.

(25) F. L. Lambert, *J. Org. Chem.*, **31**, 4184 (1966).

(26) O. R. Brown and E. R. Gonzalez, *J. Electroanal. Chem.*, **43**, 215 (1973).

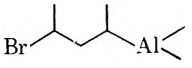
(27) D. M. Mohilner, *Electroanal. Chem.*, **1**, 241 (1966).

(28) (a) J. F. Garst, P. W. Ayers, and R. C. Lamb, *J. Amer. Chem. Soc.*, **88**, 4260 (1966); (b) G. D. Sargent, J. N. Cron, and S. Bank, *ibid.*, **88**, 5363 (1966).

(29) Professor Manfred Schlosser has informed us (private communication, Jan 5, 1973) of his recent proof that reduction of optically active 4,6-dibromononane to *trans*-1,2-dipropylcyclopropane by lithium amalgam[30] also proceeds with inversion.

(30) M. Schlosser and G. Fouquet, *Synthesis*, 200 (1972).

even though, barring unsuspectedly large errors, a small but real rotation should have been observable for the **8** formed in this reaction. The dependence of cyclopropane yield upon hydride concentration could conceivably be explained by formation of an organoaluminum species such as **14**, which could either cyclize




**14**

to **7** and **8** or suffer competitive reduction to **9** by hydride. Alkyllithium intermediates could also account for the observed results.

Reduction of (+)-**2** by triphenyltin hydride has already been mentioned in connection with the proof of absolute configuration of **2**; no more than traces of cyclopropanes were observed. This was also true for the reaction of *dl*-**2** with hexamethylphosphorus triamide[31] which afforded as the major product a single substance whose vpc retention time was identical with that of *trans*-piperylene and which was not investigated further. Reaction of *dl*-**2** with magnesium in ether under nitrogen afforded as the major volatile product (~40% absolute yield) a substance with the same vpc retention time as that of *cis*-2-pentene (**11**). Other products included **8** (20%), **7**, **9**, **10**, and **12**. If the major product is indeed **11**, the preponderance of **11** over **10** is surprising. The reaction may be related to the reported[32] conversion of 1,4-dibromocyclooctanes to cyclooctene upon reaction with magnesium.

## Experimental Section

**Apparatus.**—Polarography was carried out with the aid of a Princeton Applied Research (PAR) Model 170 electrochemistry system. Polarographic drop times were controlled at 0.5 sec with the PAR Model 172 drop timer. Controlled-potential electrolyses were performed using a potentiostat based upon a Kepco KS-120-2.5 programmable power supply. Coulometry was performed by recording the voltage drop across a standard resistor in series with the cell on a Leeds and Northrup Speedomax H recorder equipped with Disc integrator and the digital printer accessory for the integrator. Preparative gc was carried out on a Varian Model 90-P3; analytical gc was carried out on a Varian Model 1200, with flame ionization detector.

***meso*- and *dl*-2,4-Dibromopentane (2).**—The synthesis of the isomeric 2,4 pentanediols (**3**) was a modification of that reported by Pritchard and Vollmer.[6] A solution of 400 g of acetylacetone in 1200 ml of methanol was added dropwise to a stirred solution of 100 g of sodium borohydride and 1.0 g of sodium hydroxide in 1 l. of water, while the reaction temperature was maintained between 0 and 10°. After addition was complete, the resulting solution was concentrated to 1500 ml using a rotary evaporator and was then extracted continuously with ether for 15 hr. After removal of ether, distillation afforded 369 g (90%) of a mixture of *dl*- and *meso*-**3**. The diols were separated and converted into the corresponding bromides (**2**) in ~80% yield by the literature procedure.[6] Each dibromide was contaminated by a few per cent of the other isomer; final purification was carried by preparative vpc (15% Carbowax on Chromosorb G, 0.25 in. by 10 ft column). Retention times under these conditions were as follows: *dl*, 16.5 min; meso, 20.5 min. Analytical vpc upon the preparative vpc-purified samples demonstrated that they do not interconvert under vpc conditions.

***p*-Carboxyphenylboronic Acid (4).**—*p*-Tolylboronic acid was prepared by a modification of the procedure of Johnson and Bean.[33] A solution of 1.17 mol of *p*-tolylmagnesium bromide in 1100 ml of ether was added dropwise to a solution of 122 g of trimethyl borate in 400 ml of ether at −78° under nitrogen. After addition was complete (~4 hr), the solution was stirred for an additional hour under nitrogen. The temperature was then raised to 0° and the reaction mixture was stirred overnight. The resulting yellow solution was then poured into 700 ml of cold 10% sulfuric acid with vigorous stirring, and the ether phase was separated. The methanol from the aqueous phase was removed at the rotary evaporator, and the aqueous solution was then extracted with three 100-ml portions of ether. The combined ether fractions were dried, the ether was distilled, and the resulting solid was recrystallized from water to afford 109.5 g (69%) of *p*-tolylboronic acid: nmr ($CCl_4$) AB quartet at δ 7.65 and 7.05 ($J$ = 8 Hz), singlet at 2.15. A thick yellow oil, possibly di-*p*-tolylboronic acid, was removed by filtration during the recrystallization. *p*-Tolylboronic acid (24 g) was oxidized by potassium permanganate according to the method of Michaelis[34] to afford 18 g (61%) of **4**. The nmr spectrum of **4** in DMSO-$d_6$ consisted of a singlet at δ 7.9 and broad absorption from 4.1 to 6.5.

**(−)-(2*R*,4*R*)-2,4-Pentanediol (3).**—*p*-Carboxyphenylboronic acid (45.0 g) and *dl*-2,4-pentanediol (28.2 g) were added to a flask fitted with a Dean-Stark trap and containing 500 ml of benzene. After 0.5 hr at reflux the theoretical amount of water had been collected. The solution was filtered to remove a small amount of insoluble material. After removal of the solvent (rotary evaporator) and air drying, the yield of *dl-trans*-4,6-dimethyl-2-*p*-carboxyphenyl-1,3,2-dioxaborinane (**5**), a white crystalline material, mp 168–183°, was 71 g (97%). Its nmr spectrum consisted of an AB quartet at δ 8.15 and 7.9 ($J$ = 8 Hz) (4 H), multiplets at 4.3 (2 H) and 1.9 (2 H), a doublet at 1.35 ($J$ = 6 Hz, 6 H), and singlet at −0.8 (1 H). This material (35 g) and 50 g of brucine were dissolved in 1 l. of acetone and the solution was refluxed until all crystalline material had dissolved. Concentration and cooling afforded the brucine salt of **5**, mp 127–140°, $[\alpha]^{25}_{540}$ −12° (benzene). After seven fractional crystallizations from acetone using a high recovery diamond pattern,[35] 20 g (50%) of brucine salt was obtained which had mp 129–132° and $[\alpha]^{25}_{540}$ −3.8°. This material was dissolved in hot acetone and to this solution was added a solution of 4.78 g of *d*-tartaric acid in 40 ml of hot acetone. An immediate white precipitate of brucine tartrate formed and was removed by filtration. After removal of acetone at the rotary evaporator and drying, there was obtained 5.40 g of a mixture consisting of optically active **5** contaminated with a small amount of brucine and 2,4-pentanediol. This mixture was added to 15 ml of 20% sodium hydroxide and refluxed for 5 min. The yellow solution was cooled and a small amount of brown oil (brucine?) floating on the surface was removed by pipet. The solution was then saturated with sodium chloride and extracted with four 15-ml portions of chloroform. The combined chloroform fractions were dried and the solvent was removed to afford 2.0 g of (−)-2,4-pentanediol (**3**, 94.5% overall yield from the brucine salt). A portion of this material was distilled *in vacuo*; it exhibited $[\alpha]^{25}D$ −41.3° ($CHCl_3$).

**(+)-(2*S*,4*S*)-2,4-Dibromopentane (2).**—(−)-2,4-Pentanediol, $[\alpha]^{25}D$ −41.3° ($CHCl_3$), was converted to the corresponding dibromide in the usual manner.[6] After purification by preparative vpc, optically active **2** exhibited $[\alpha]^{25}D$ +102° ($CHCl_3$). Another sample prepared in the same way exhibited $[\alpha]^{25}_{540}$ +126°.

**Proof of Configuration of (+)-2.**—(+)-2,4-Dibromopentane (15 mg) was dissolved in 0.1 ml of heptane. Triphenyltin hydride was injected into this solution in 5-ml portions and the reaction mixture was analyzed at intervals by vpc. The only products were 2-bromopentane (**6**) and pentane (**9**), accompanied by traces of cyclopropanes **7** and **8**. When the concentration of **6** had become greater than that of **2**, the reaction mixture was separated by preparative vpc. Products **6** and **9** were collected as a single fraction. This material was diluted to 1 ml with heptane. Vpc analysis indicated the condentration **6** to be 750 μg/ml. This solution had an observed rotation at the D line of +0.034 ± 0.001°. The specific rotation of this sample of **6** was therefore +45.4 ± 2.7°. Its optical purity and absolute configuration are discussed in the Results section.

**Electrolysis of *meso*- and *dl*-2,4-Dibromopentanes.**—The electrolysis medium, consisting of 15 ml of a 0.1 *M* solution of tetraethylammonium bromide in DMSO contained in a divided cell of

(31) B. B. Jarvis, S. D. Dutkey, and H. L. Amonon, *J. Amer. Chem. Soc.*, **94**, 2136 (1972).

(32) M. S. Baird, C. B. Reese, and M. R. D. Stebles, *Chem. Commun.*, 1340 (1971).

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

(34) A. Michaelis, *Justus Liebigs Ann. Chem.*, **315**, 19 (1901).

(35) R. S. Tipson, in "Technique of Organic Chemistry," Vol. 3, A. Weissberger, Ed., Interscience, New York, N. Y., 1956, Chapter 3.

conventional design[36] maintained at 15°, was purged with nitrogen for 15 min. Preelectrolysis was then carried out at −2.2 V (sce)[37] for 15 min, and 20 μl (35.6 mg) of dibromide was then injected into the cell through a serum cap. Vpc analysis was carried out on a 1/8 in × 20 ft Durapak OPN/Porasil C (Waters Associates) column operated at ambient temperature. Retention times of hydrocarbons under these conditions were as follows: *trans*-1,2-dimethylcyclopropane, 14.7 min; pentane, 15.8 min; *cis*-1,2-dimethylcyclopropane, 16.6 min; 1-pentene, 17.3 min; *trans*-2-pentene, 18.2 min; *cis*-2-pentene, 18.9 min.

**Vpc Analysis of Electrolysis Mixtures.**—It was determined by comparison with standard solutions of the known hydrocarbons that sensitivity factors[39] for pentane, the isomeric pentenes, and the isomeric 1,2-dimethylcyclopropanes in flame ionization vpc are approximately identical (within 2% of each other). Analysis of the gas chromatogram of an aliquot of the electrolysis solution was then carried out by cutting and weighing peaks and comparing the weight of each peak with a calibration chart constructed by injecting a number of standard samples of *trans*-1,2-dimethyl cyclopropane. Integration was by Disc integrator with digital printing accessory when samples to be analyzed by polarimetry were analyzed.

**Noninterconvertability of *meso*- and *dl*-2,4-Dibromopentane under Electrolysis Conditions.**—Into a 0.1 *M* solution of tetraethylammonium bromide in DMSO was injected 100 μl of *dl*-2. This solution was stirred over mercury for 143 min (electrolyses were always complete in much less than 1 hr). Water was added to the solution, the mixture was extracted with pentane, and the pentane was dried and removed *in vacuo*. Vpc and nmr analysis demonstrated the absence of *meso*-2 or other contaminants. Similar observations were made when the electrolyte was tetrabutylammonium perchlorate.

**Electrolysis of (+)-2,4-Dibromopentane.**—Electrolysis was carried out as above. After completion of electrolysis, the solution was extracted with four 5-ml portions of cold heptane. This solution was diluted to a known volume (25 ml) and analyzed by vpc immediately before polarimetry. Vpc analysis indicated a concentration of 0.781 mg/ml. The measured rotation was −0.036 ± 0.001° in a 1-dm tube; therefore, $[\alpha]^{25}D$ was −46 ± 2° for the cyclopropane **8** formed in the reaction.

**Reaction of (+)-2,4-Dibromopentane with Sodium Naphthalenide.**—(+)-2,4-Dibromopentane (44.5 mg) was added to 1 ml of 1,2-dimethoxyethane (distilled from sodium naphthalenide) under a nitrogen atmosphere. Approximately 1.5 × $10^{-4}$ mol of a concentrated solution of sodium naphthalenide in 1,2-dimethoxyethane was injected slowly into the dibromopentane solution. *cis*- and *trans*-2-pentene, pentane, cis-1,2-dimethylcyclopropane, and 1-pentane accounted for 28.5% of the dibromide. *trans*-1,2-Dimethylcyclopropane was produced in 20.5% yield based on the dibromide. Trap to trap distillation of the reaction mixture and polarimetric analysis gave an observed rotation of −0.050° after correction for unreacted starting material (see above). The specific rotation that *trans*-1,2-dimethylcyclopropane produced in this reaction was thus −62 ± 9.5° at the sodium D line.

**Reaction of *dl*-2,4-Dibromopentane with a Large Excess of Lithium Aluminum Hydride.**—Racemic 2,4 dibromopentane (50 mg) was added to a large excess of lithium aluminum hydride in tetrahydrofuran under nitrogen. After 12 hr the solution was analyzed directly by vpc. The major product was pentane, but small amounts of cyclopropanes and pentene isomers were also present.

**Reaction of (+)-2,4-Dibromopentane with a Molar Excess of Lithium Aluminum Hydride.**—(+)-2,4-Dibromopentane [17.8 mg (7.74 × $10^{-5}$ mol)] was added to a solution of 7.7 × $10^{-5}$ mol of lithium aluminum hydride in 0.3 ml of ether under nitrogen. After 10 hr the solution was analyzed by vpc. Approximately equal amounts of *cis*- and *trans*-dimethylcyclopropanes, *cis*- and *trans*-2-pentene, and pentane were present (~10% yield of each). The volatile materials were separated by trap to trap distillation and dissolved in heptane. The concentration of *trans*-dimethylcyclopropane in the heptane solution was determined by vpc. If its specific rotation were −46°, it should have produced a polarimetric rotation of −0.015°; in fact the observed rotation was 0.000 ± 0.0001°.

**Reaction of *dl*-2,4-Dibromopentane with Hexamethylphosphorus Triamide.**—Hexamethylphorous triamide [118 mg (7.18 × $10^{-4}$ mol)] was added to a solution of 89 mg (3.5 × $10^{-4}$ mol) of *dl*-2,4-dibromopentane in 1 ml of benzene under nitrogen. After 12 hr at room temperature the solution was analyzed by vpc. No cyclopropanes were observable. The major product formed in good yield; it had the same retention time as *trans*-piperylene.

**Reaction of *dl*-2 4-Dibromopentane with Magnesium.**—*dl*-2,4-Dibromopentane (18 mg) was added to an excess of magnesium and a crystal of iodine in 0.25 ml of ether under nitrogen. After 10 hr the solution was analyzed by vpc. The major volatile product (~40%) had the same retention time as *cis*-2-pentene (11). Other products included **8** (20%), **7**, **9**, **10**, and **12**.

**Acknowledgments.**—Financial support was provided by the National Science Foundation (GP-12004 and GP-28146). W. E. B. was supported by a National Science Foundation Traineeship (1969–1972). Dr. Walter Moreland and Dr. Thomas Toolan of the Pfizer Chemical Co. generously permitted use of a Perkin-Elmer Model 141 photoelectric polarimeter.

**Registry No.**—(+)-**2**, 42075-31-0; *meso*-**2**, 1825-11-2; *dl*-**2**, 1625-68-9; (−)-**3**, 42075-32-1; *dl*-**3**, 1825-14-5; **4**, 14047-29-1; *dl-trans*-**5**, 42075-35-4; **5** brucine salt, 42199-85-9; (−)-**8**, 20520-64-3.

(36) Reference 12, pp 324–326.

(37) Polarographic and electrolysis potentials were measured with the cadmium amalgam reference electrode of Marple,[38] but are reported relative to sce.

(38) L. W. Marple, *Anal. Chem.*, **39**, 844 (1967). This electrode is *ca.* −0.7 V relative to sce.

(39) H. M. McNair and E. J. Bonelli, "Basic Gas Chromatography," Varian Aerograph, Walnut Creek, Calif., 1968, pp 140–143.

# A Reexamination of the Racemization of 1-Phenylbromoethane in Acetone

ALLAN R. STEIN

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In their original examination of the racemization of 1-phenylbromoethane by lithium bromide in anhydrous acetone which is one of the bulwarks of the SN2 mechanism for the bimolecular nucleophilic substitution at saturated carbon, Hughes and his colleagues reported the rate to be "nonlinear" with lithium bromide concentration. This racemization has been reexamined over a much wider concentration range, at constant ionic strength and as a function of ionic strength. On the basis of the empirical observations, the "nonlinearity" of the rate of racemization with lithium bromide concentration is assigned to ion pairing and aggregation by the lithium bromide. The alternative explanations based on competing uni- and bimolecular processes or the Sneen ion-pair mechanism for nucleophilic substitution at saturated carbon are shown to be untenable.

The recent publication of Beronius, Nilsson, and Holmgren,[2] in which they argue that neglecting ion association when one of the reactants is an ionic species can make a purely bimolecular reaction appear to have a unimolecular component, has prompted this publication of some initial results from a reexamination of the racemization of (+)- and (−)-1-phenylbromoethane. The racemizations of optically active 1-phenylbromoethane and 2-iodooctane were examined by Hughes and his colleagues[3,4] and the observation that the rates of racemization and of halide exchange were the same within experimental error was the basis for the postulation of the SN2 mechanism for the bimolecular nucleophilic displacement at saturated carbon.[5]

Hughes, *et al.*, reported that, for the racemization of optically active 1-phenylbromoethane in acetone containing lithium bromide, the racemization was not exactly first order in halide ion (see Table I). The rate constant calculated assuming a bimolecular reaction, first order in each of 1-phenylbromoethane and lithium bromide, decreased with increasing concentration of the inorganic bromide. Thus, at 30.2° when the concentration of lithium bromide was halved from 0.200 to 0.102 *M*, the empirical second-order rate constant increased by over 20%. The reaction velocity or rate decreased, of course, when the concentration of lithium bromide was halved, but only to 62% rather than 50% of its former value. Similar behavior was reported for the racemization of asymmetric 2-iodooctane.[4,6]

TABLE I

RACEMIZATION OF *d*-1-PHENYLBROMOETHANE IN ACETONE CONTAINING LITHIUM BROMIDE AT 30.2° [a]

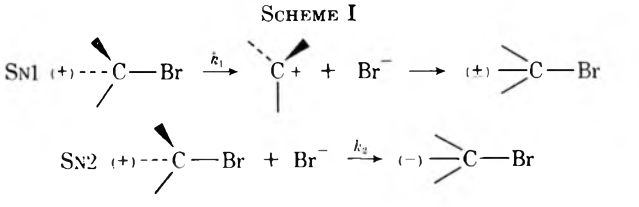
| No. of runs | Concn, *M* RBr | Concn, *M* LiBr | $k$ (× $10^3$ l./msec) | Reaction velocity[b] (× $10^{-5}$ mol/l. sec) |
|---|---|---|---|---|
| 2 | 0.200 | 0.200 | 0.795 | 3.18 |
| 2 | 0.200 | 0.102 | 0.963 | 1.97 |

[a] E. D. Hughes, *et al.*, *J. Chem. Soc.*, 1173 (1936). [b] Reaction velocity (Ni) as calculated by the expression Ni = $(A/2t)$ ln $\alpha_0/\alpha$, where $A$ = concentration of RBr, $t$ the time in seconds, and $\alpha_0$ and $\alpha$ the initial angle of rotation of the plane of polarized light ($t = 0$) and at time $t$, respectively.

There are a number of possible explanations for such a variation of rate constant with the concentration of inorganic bromide. These include (1) unimolecular and bimolecular processes occur simultaneously; (2) the alkyl halide dissociates to an ion pair which may be intercepted by bromide at an early stage or as ion separation occurs; (3) ion pair formation by the lithium bromide. Empirical results are reported which permit a decision among these possibilities but first the three possibilities should be examined in more detail.

If SN1 and SN2 processes are occurring simultaneously (Scheme I), the rate of the former will be independent

SCHEME I




of, and the latter linearly dependent upon, bromide ion concentration. If any other effects of increasing the concentration of lithium bromide (*e.g.*, common ion and salt effects) can be ignored, the uni- and bimolecular components can be separated as shown in Figure 1.[7] Inclusion of a common ion effect on the reaction would result in a decreasing unimolecular component with increasing bromide ion concentration only if the common ion effect operated prior to racemization of the carbonium ion intermediate while the increased ionizing power of the solvent with increasing salt concentration could cause an increase in the unimolecular component despite any common ion effect. Thus instead of a constant contribution to the overall rate of the racemization, the SN1 contribution could increase or decrease (or first decrease, then increase[8]) with increasing lithium bromide concentration. Consequently, some curvature, either convex or concave, in the actual rate *vs.* concentration of bromide ion line could occur, but the racemization rate should be sig-

(1) Address to which correspondence should be sent.

(2) P. Beronius, A.-M. Nilsson, and A. Holmgren, *Acta Chem. Scand.*, **26**, 3173 (1972).

(3) E. D. Hughes, F. Juliusburger, A. D. Scott, B. Topley, and J. Weiss, *J. Chem. Soc.*, 1173 (1936).

(4) E. D. Hughes, F. Juliusburger, S. Masterman, B. Topley, and J. Weiss, *J. Chem. Soc.*, 1525 (1935).

(5) J. L. Gleave, E. D. Hughes, and C. K. Ingold, *J. Chem. Soc.*, 236 (1935).

(6) E. Bergmann, M. Polanyi, and A. L. Szabo, *Z. Phys. Chem., Abt. B*, **20**, 161 (1933); *Trans. Faraday Soc.*, **32**, 843 (1936).

(7) Such mixed kinetics need not be detectable by differences in the rates of racemization and halide exchange, since such differences would only occur if there were significant internal return after racemization in the unimolecular reaction.

(8) S. Winstein, P. E. Klinedinst, and E. Clippinger, *J. Amer. Chem. Soc.*, **83**, 4986 (1961).

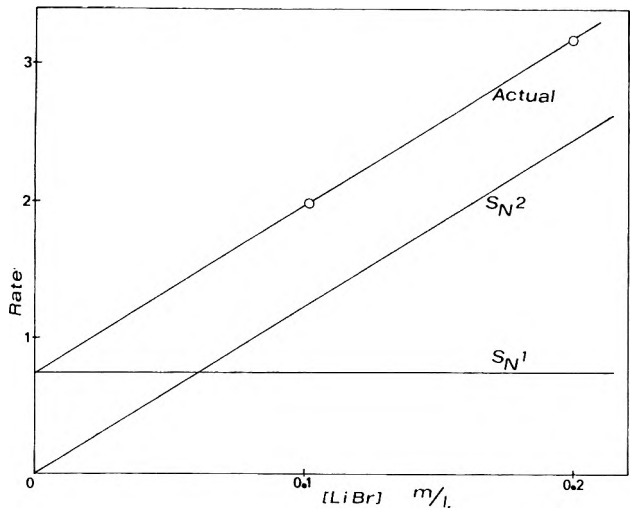



Figure 1.—Schematic representation of the racemization of (+)-1-phenylbromoethane with lithium bromide in anhydrous acetone assuming that both SN1 and SN2 processes are occurring. The actual rate of racemization (rate = $[RBr]/2t \ln \alpha_0/\alpha$) could be considered to have a constant unimolecular component and a bimolecular component linearly dependent upon the concentration of the nucleophile (bromide ion). [Data from E. D. Hughes, *et al.*, *J. Chem. Soc.*, 1173 (1936)].

nificant at zero bromide ion concentration and the intercept or SN1 contribution would be greater, the greater the degree of curvature.

The ion-pair mechanism for nucleophilic substitution at saturated carbon, as proposed by Sneen and Larsen,[9] is summarized in Scheme II. Here it is assumed that there is a single or unified mechanism involving an initially formed ion pair which progressively dissociates as the individual ions are solvated. If the initially formed ion pair is intercepted by the nucleophile, SN2 kinetics and stereochemistry would be expected, while, at the other extreme, combination of a symmetrically solvated carbonium ion with a nucleophile would show SN1 kinetics and stereochemistry. As the average or median site of interception of the dissociating ion pair is shifted to the left, the "unimolecular" character of the reaction decreases and the "bimolecular" character increases. Increasing the concentration of the nucleophile, other things being equal, should have such an effect. Again a positive intercept for the reaction rate *vs.* bromide ion concentration curve would be expected and the rate constant of the reaction should decrease with increasing concentration of lithium bromide. Increasing the ion-supporting ability of the solution, by, for example, adding inert electrolyte, should accelerate the reaction if it involves an equilibrium ionization to even intimate ion pair.

SCHEME II

$$RX \overset{K_1}{\rightleftharpoons} \overset{+}{R}X^- \overset{K_2}{\rightleftharpoons} R^+ \,|\, X^- \overset{K_3}{\rightleftharpoons} R^+ \,\|\, X^- \overset{K_4}{\rightleftharpoons} \overset{K_n}{\rightleftharpoons} R^+ + X^-$$

| intimate ion pair | solvent-separated ion pair | solvated ion pair | | free (dissociated ions) |
|---|---|---|---|---|
| $k_1 \downarrow \bar{Z}$ | $k_2 \downarrow \bar{Z}$ | $k_3 \downarrow \bar{Z}$ | $k_4 \downarrow \bar{Z}$ | $k_n \downarrow \bar{Z}$ |
| RZ | RZ | RZ | RZ | RZ |
| "SN2" | mainly "SN2" | | mainly "SN1" | "SN1" |

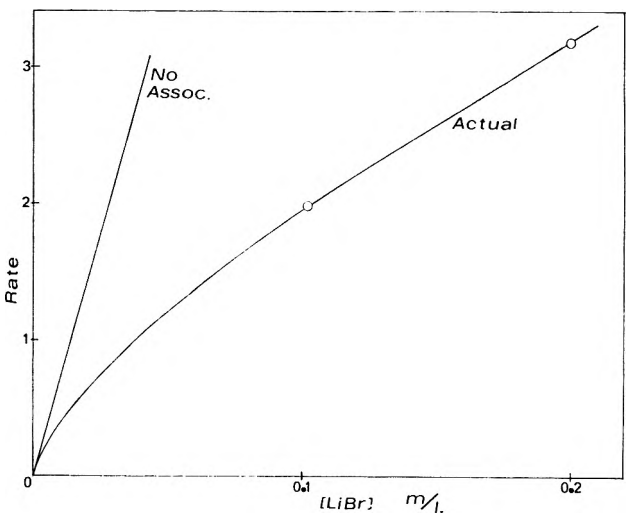



Figure 2.—Schematic representation of the effect of association of lithium bromide on the racemization of (+)-1-phenylbromoethane in anhydrous acetone (rate = $[RBr]/2t \ln \alpha_0/\alpha$). [Data from E. D. Hughes, *et al.*, *J. Chem. Soc.*, 1173 (1936)].

Finally, if association or ion-pair formation on the part of the lithium bromide is occurring, increasing the concentration of lithium bromide would increase the fraction of the salt associated. Since the reactivity of ion pairs and higher aggregates is generally much lower than that of dissociated ions,[10,11] the rate of the reaction would increase less rapidly than expected for a bimolecular reaction as the concentration of lithium bromide is increased. The anticipated behavior is illustrated in Figure 2, again with the limited data of Hughes, *et al.*,[3] included. Here the intercept should be zero (if there is no unimolecular component) and the tangent of the curve at zero bromide ion concentration would represent the rate behavior expected if no association of the added salt occurred.

## Results

Assuming that the reaction of optically active 1-phenylbromoethane [(+)-RX] with bromide ion ($X^-$) is an equilibrium bimolecular process with inversion of stereochemistry [*i.e.*, giving (−)-RX], eq 1 can be written.

$$(+)\text{-RX} + X^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} (-)\text{-RX} + X^- \qquad (1)$$

However, the product will, together with an equal molar quantity of unreacted alkyl halide, give racemic material [(±)-RX], so that a second, instantaneous "reaction," eq 2, can also be written. Since the reaction of racemic product with bromide would have an equal probability of giving either stereoisomer, both the first and second equations can be considered to be irreversible (*i.e.*, racemic material does not spon-

$$(+)\text{-RX} + (-)\text{-RX} \overset{\text{instantaneous}}{\rightleftharpoons} 2\,(\pm)\text{-RX} \qquad (2)$$

(9) R. A. Sneen and J. W. Larsen, *J. Amer. Soc.*, **91**, 362, 6031 (1969).

(10) P. Beronius, L. Pataki, A.-M. Nilsson, and G. Wikander, *Radiochem. Radioanal. Lett.*, **6**, 333 (1971), and references cited therein.

(11) (a) S. G. Smith and M. P. Hanson, *J. Org. Chem.*, **36**, 1931 (1971); (b) G. H. Barlow and H. E. Zangg, *ibid.*, **37**, 2246 (1972), and references cited therein; (c) J. Smid, *Angew. Chem., Int. Ed. Engl.*, **11**, 112 (1972), and references cited therein.

TABLE II
RACEMIZATION OF 1-PHENYLBROMOETHANE IN ANHYDROUS ACETONE CONTAINING LITHIUM BROMIDE AND LITHIUM NITRATE AT 40.38°

| Run no. | Concn of LiBr, mol/l. | Concn of $LiNO_3$, mol/l. | Ionic strength, mol/l. of $Li^+$ | $\Delta \log \alpha_0/\alpha$ / $\Delta t$, sec | $k \times 10^3$, l./mol sec |
|---|---|---|---|---|---|
| 1 | 0.000 | 0.000 | 0.000 | $<0.008 \times 10^{-4}$ | |
| 2 | 0.0025 | 0.000 | 0.0025 | 2.19 | 10.09 |
| 3 | 0.0050 | 0.000 | 0.0050 | 2.95 | 6.79 |
| 4 | 0.0100 | 0.000 | 0.0100 | 4.36 | 5.02 |
| 5 | 0.0200 | 0.000 | 0.0200 | 6.66 | 3.83 |
| 6 | 0.0300 | 0.000 | 0.0300 | 9.17 | 3.52 |
| 7 | 0.0500 | 0.000 | 0.0500 | 12.89[a] | 2.97 |
| 8 | 0.0700 | 0.000 | 0.0700 | 16.74 | 2.75 |
| 9 | 0.1000 | 0.000 | 0.1000 | 21.04[b] | 2.42 (2.39)[e] |
| 10 | 0.0000 | 0.100 | 0.1000 | 0.15[d] | (0.0173)[d] |
| 11 | 0.0050 | 0.0950 | 0.1000 | 1.34 | 3.09 (2.37)[e] |
| 12 | 0.0100 | 0.0900 | 0.1000 | 2.37[c] | 2.73 (2.37)[e] |
| 13 | 0.0300 | 0.0700 | 0.1000 | 6.47 | 2.48 (2.36)[e] |
| 14 | 0.0500 | 0.0500 | 0.1000 | 10.77 | 2.48 (2.41)[e] |
| 15 | 0.0700 | 0.0300 | 0.1000 | 14.79 | 2.43 (2.38)[e] |
| 16 | 0.0100 | 0.0200 | 0.0300 | 3.58 | 4.12 |
| 17 | 0.0100 | 0.0400 | 0.0500 | 2.90 | 3.34 |
| 18 | 0.1000 | 0.0600 | 0.0700 | 2.69 | 3.10 |

[a] Average of two runs. [b] Average of four runs. [c] Average of three runs. [d] Initial rate constant for $NO_3^-$ as the nucleophile. The rate of racemization increases as $Br^-$ is liberated. [e] Values in brackets are corrected for the nonzero intercept which represents the rate of reaction 10 plus the contribution to the rate by the $Br^-$ so liberated.

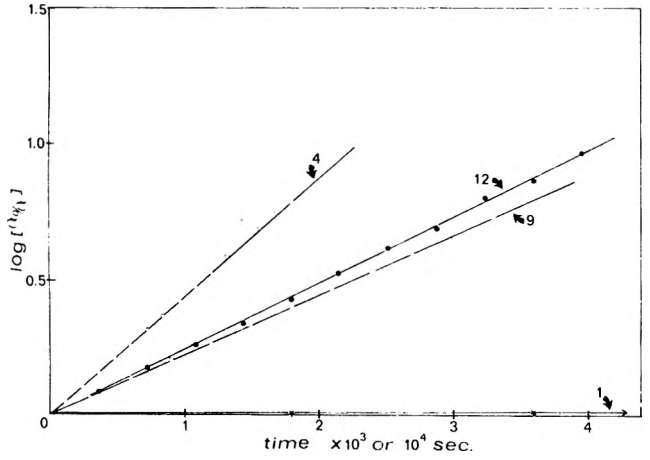



Figure 3.—Typical racemization results for (+)- or (−)-1-phenylbromoethane with lithium bromide in anhydrous acetone at 40.38 ± 0.03°. Curve numbers refer to Table II and the conditions, concentration of lithium bromide, and ionic strength (sum of the concentration of lithium bromide and nitrate) in moles per liter and time scale, are, respectively, run 4, 0.01 *M*, 0.01 *M*, × $10^4$ sec; run 12, 0.01 *M*, 0.10 *M*, × $10^4$ sec; run 9, 0.10 *M*, 0.10 *M*, × $10^3$ sec; run 1, 0.00 *M*, 0.00 *M*, × $10^4$ sec.

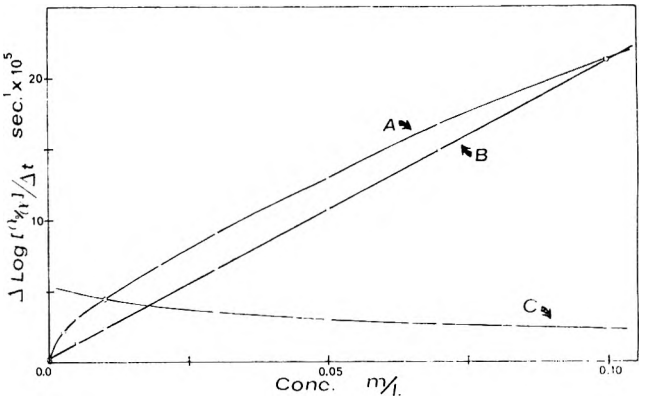



Figure 4.—Racemization rate as a function of concentration of lithium bromide and ionic strength in anhydrous acetone at 40.38°. Curve A: rate *vs.* concentration of lithium bromide. Curve B: rate *vs.* concentration of lithium bromide at constant ionic strength (sum of the concentrations of LiBr and $LiNO_3$ equal to 0.100 *M*). Curve C: rate *vs.* ionic strength with fixed (0.0100 *M*) lithium bromide concentration.

taneously convert to one enantiomer). The observable process can then be represented by eq 3 and 4.

$$(+)\text{-RX} + X^- \xrightarrow{k} (-)\text{-RX} + X^- \quad (3)$$

$$(+)\text{-RX} + (-)\text{-RX} \xrightarrow[\text{aneous}]{\text{instant-}} (\pm)\text{-RX} \quad (4)$$

For eq 3, a rate expression can be written

$$-\frac{d[(+)\text{-RX}]}{dt} = k[X^-][(+)\text{-RX}]$$

However, for every molecule of (+)-RX reacting *via* eq 3, a second molecule is "used up" *via* eq 4, so the overall or actual rate expression can be written

$$\frac{-d[(+)\text{-RX}]}{dt} = 2k[X^-][(+)\text{-RX}]$$

The concentration of the halide ion is a constant throughout, so that on integration the following expression is obtained.

$$\ln [(+)\text{-RX}] = -2k[X^-]t$$

or

$$\log \frac{[RX]_0}{[RX]} = \frac{2k}{2.303}[X]t$$

This last expression was used to evaluate the rate constants reported in Table II. Because the optical purity of the 1-phenylbromoethane varied somewhat from batch to batch and was, in fact, unknown in any case, the angle of rotation, $\alpha$, of plane-polarized light was used directly as a measure of the concentration of the asymmetric material, [(+)-RX]. That this procedure is valid can be seen from Figure 3, where not atypical plots of log $\alpha_0/\alpha$ *vs.* time are shown. The linearity shows the racemization process to be first order with respect to the optically active reactant.

In Figure 4 are plotted some rate data for the racemization of optically active 1-phenylbromoethane at

40.38° in anhydrous acetone. Curves are shown for the rate as a function of concentration of ionic bromide both at constant (curve B) and at varying ionic strengths (curve A). Also shown is the curve for constant concentration of ionic bromide (0.0100 *M*) but with changing ionic strength, *i.e.*, concentration of lithium ion where that concentration is the sum of the concentrations of lithium bromide and of lithium nitrate (curve C).

## Discussion

The shape of the curve for the racemization of 1-phenylbromoethane (curve A, Figure 4) is analagous to that commonly obtained for reactions in nonpolar solvents where the reactant whose concentration is being varied is ionic (see, for example, ref 12). Such a curve with a zero intercept is inconsistent with there being bimolecular and unimolecular processes in competition. (Had SN1 and SN2 racemizations been occurring simultaneously, a result analagous to that shown in Figure 1 would have been expected.) Thus the first of the three possible explanations for the "nonlinearity" with lithium bromide concentration reported by Hughes, *et al.*,[3] can be discarded.

Similarly, the zero intercept for the racemization rate *vs.* the concentration of lithium bromide is inconsistent with the mechanism of Sneen, *et al.*,[9] being the explanation for the nonlinearity. That this second explanation can be discarded is confirmed by the fact that the rate constant of the racemization decreases rather than increases with increasing ionic strength of the solution, an observation inconsistent with an ionization process.

The only one of the three explanations not inconsistent with the empirical observations is the third one, ion-pair formation by the lithium bromide. Analagous conclusions as to the source of apparent nonzero intercepts have been reached by other workers.[2,12,13]

The concentration of dissociated bromide ion will be given by the expression

$$[Br^-] = \frac{K_{dis}[LiBr]}{[Li^+]}$$

where $[Br^-]$ and $[Li^+]$ are, respectively, the concentrations of dissociated bromide and lithium ions, [LiBr] is the concentration of associated lithium bromide, and $K_{dis}$ is the applicable dissociation constant. If a second salt, for example lithium nitrate, is added so that the total concentration of lithium ion (associated plus dissociated) is kept constant as the amount of lithium bromide is varied, the concentration of dissociated lithium ion will remain approximately constant. At the high salt concentrations employed in the weakly ionizing solvent, acetone, a relatively small fraction of the lithium bromide will be dissociated, so that, under the conditions employed at constant total lithium ion concentration, the concentration of dissociated bromide ion should be linearly dependent upon the total amount of lithium bromide present. Consequently, at constant ionic strength a linear correlation between rate of racemization and total concentration of lithium bromide would be anticipated. This is observed and shown as curve B in Figure 4, a further confirmation that the "nonlinear" increase in rate with increasing concentration of lithium bromide observed by Hughes, *et al.*,[3] is caused by association of the salt.

Finally, in conclusion it should perhaps be emphasized that the present study does not disprove the ion pair dissociative mechanism proposed by Sneen and Larsen[9] as an alternative to the Hughes–Ingold SN1–SN2 mechanisms. Rather it has been shown that by far the major source of inconsistency in the earlier results with 1-phenylbromoethane was ion pairing of the ionic reactants. The observed decrease in reaction rate with ionic strength is attributable to a decrease in activity of the bromide ion with increasing concentration of lithium ions. Unfortunately, solubility and dissociation problems precluded the use of other obvious electrolytes to determine whether this is a true salt effect or a cation concentration effect.

## Experimental Section

**Solvent.**—The acetone employed was "Analar" quality solvent (BDH) that was stored for several days over molecular sieves (Davison, Type 4A) and, immediately before preparation of the solutions, was distilled through a short Vigreux column from fresh molecular sieves in oven-dried glassware in a dry nitrogen atmosphere.

**Salts.**—Hydrated lithium nitrate (BDH) was twice recrystallized from anhydrous acetone and dried at room temperature and finally at 200° (0.1 mm) for 36 hr. The salt was stored under dry nitrogen and was reevacuated overnight at 200° immediately before use. Anhydrous, reagent grade (BDH) lithium bromide was dried and stored in an analogous manner. Both salts were off-white, microcrystalline solids.

**(+)- and (−)-1-Phenylbromoethane.**—By the procedure of Downer and Kenyon,[14] 1-phenylethanol (Aldrich) was resolved and the resolved material was converted to (+)- or (−)-1-phenylbromoethane by the procedure of Hughes, *et al.*,[3] with toluene as the solvent. On a 0.05-molar scale, for example, (+)-1-phenylethanol, $[\alpha]^{20}D$ +40° (lit. 44.1°), gave after two distillations at 87° (10.5 mm) an 87% yield of (−)-1-phenylbromoethane, $[\alpha]^{20}D$ −12.6 (lit. 12.8°). Both the (+) and (−) bromides were employed in this study and had molecular rotations of 11.7–12.9°. At high concentrations in $CCl_4$, no hydroxylic absorption was observable in the infrared spectra nor were aliphatic protons of the corresponding alcohol detectable by nmr.

**Rate Studies.**—In anhydrous acetone, 0.1000 *M* stock solutions of LiBr and $LiNO_3$ were prepared. The appropriate quantity of each solution was pipetted into a 10-ml volumetric flask which was made up to volume with anhydrous acetone if appropriate. After equilibration to the bath temperature, 40.38 ± 0.03° throughout this study, 0.1 ml (0.13–0.14 g, $7.3 \times 10^{-4}$ mol) of the optically active 1-phenylbromoethane was added, the solution was shaken and the 0.000-cm jacketed quartz cell (capacity 6.6 ml) of the Perkin-Elmer Model 141 polarimeter was filled. The angle of rotation as a function of time was determined from the Servowriter potentiometric recorder connected to the polarimeter. The initial rotation at the 365-nm wavelength employed was 0.200–0.215° and the infinity value was 0.000 ± 0.003° (owing to instrument zero wandering). Typical results are shown graphically in Figure 3.

**Acknowledgments.**—The author wishes to thank Memorial University of Newfoundland for the financial support that made this research possible and the Department of Chemistry, King's College, University of

(12) P. Beronius, U. Isacsson, and A.-M. Nilsson, *Acta Chem. Scand.*, **24**, 189 (1970).

(13) R. W. C. Broadbank, A. H. E. Harhask, and S. Kanchanalai, *Radioisotop. Phys. Sci. Ind. Proc. Conf., Copenhagen, 1960*, **3**, 179 (1962).

(14) E. Downer and J. Kenyon, *J. Chem. Soc.*, 1156 (1939).

London, for the use of their polarimeter and other laboratory facilities for the kinetic measurements. Finally, the author wishes to sincerely thank Martin Grossel at King's College for so generously sharing his limited laboratory and fumehood space, glassware, solvents, and routine laboratory chemicals and apparatus with a visitor from the "colonies."

**Registry No.**—(+)-1-Phenylbromoethane, 1459-14-9; (−)-1-phenylbromoethane, 3756-40-9.

# Methyl-Substituted Fluorine-Containing Cyclobutenes. Establishment of the HF Coupling Constants between a Vinylic Methyl Group and the Ring Fluorines[1a]

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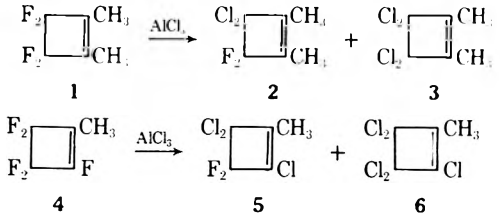
*Received April 27, 1973*

Halogen interchange reactions with aluminum chloride on 1,2-dimethyl-3,3,4,4-tetrafluorocyclobutene and 1-methyl-2,3,3,4,4-pentafluorocyclobutene have been shown to lead to 1,2-dimethyl-3,3-difluoro-4,4-dichlorocyclobutene (**2**) and 1-methyl-3,3-difluoro-2,4,4-trichlorocyclobutene (**5**), respectively. The assignment of the HF coupling constants between the vinylic methyl group and the allylic ring fluorines in the nmr spectra for these materials was aided by compounds produced by alternate synthetic pathways. Thus, 1-methyl-1,2,2-trichloro-3,3-difluorocyclobutane (**7**), prepared by a thermal codimerization technique, served as the starting material for the synthesis of 1-methyl-2-chloro-3,3-difluorocyclobutene (**8**) and 1-methyl-3,3-difluoro-4,4-dichlorocyclobutene (**9**).

Fluorocyclobutenes are known to undergo a facile substitution of the vinylic halide with methyllithium[2a-c] and methyl Grignard reagents[2d] to yield monomethyl- or dimethylperfluorocyclobutenes. Studies on the chemical reactivity of these materials have been concerned with hydrolysis of the ring fluorines,[2c] the halogenation of the vinylic methyl group,[2b] and elimination reactions which occur in the presence of alkoxide ions.[3] This paper reports on a halogen interchange reaction with aluminum chloride to produce methyl-substituted fluorochlorocyclobutenes and chlorocyclobutenes and the assignment of the HF coupling constants between the vinylic methyl group and the allylic ring fluorines in the nmr spectra.

Halogen interchange with aluminum halides has been observed to take place with fluorinated cyclobutenes with particular ease.[4] Application of this convenient technique to 1,2-dimethyl-3,3,4,4-tetrafluorocyclobutene led to the characterization of two major products, 1,2-dimethyl-3,3-difluoro-4,4-dichlorocyclobutene (2) and 1,2-dimethyl-3,3,4,4-tetrachlorocyclobutene (**3**), as indicated in Scheme I. The proton nmr spectrum of 2

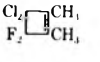
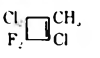
SCHEME I



consisted of a triplet at $\tau$ 8.29 with a coupling constant $J$ = 1.6 Hz and a triplet at $\tau$ 8.17, $J$ = 3.2 Hz, as indicated in Table I along with the nmr data obtained for all of the methyl-substituted fluorocyclobutenes discussed in this report. Since the cross ring allylic fluorines would be expected to deshield the vinylic methyl protons more than do adjacent fluorines,[5] this resonance should occur at a lower field position and the coupling constant for the vinylic methyl protons coupled with cross ring allylic fluorines must be 3.2 Hz, thus

TABLE I

NMR SPECTRA FOR CYCLOBUTENES

| Compd | $\phi$* | $\tau$ | Group | Coupling |
|---|---|---|---|---|
|  | | 8.29 | $CH_3$ | t, $J$ = 1.6 Hz |
| | | 8.17 | $CH_3$ | t, $J$ = 3.2 Hz |
|  | | 8.03 | $CH_3$ | t, $J$ = 3.1 Hz |
| | 110.4 | | Ring $CF_2$ | q, $J$ = 3.1 Hz |
|  | | 7.99 | $CH_3$ | d, t, $J$ = 1.5, 3.2 Hz |
| | | 4.04 | Vinyl H | m, $J$ = 1.5, 2.2 Hz |
| | 104.6 | | Ring $CF_2$ | d, q, $J$ = 2.2, 3.2 Hz |
|  | | 8.09 | $CH_3$ | t, t, $J$ = 3.3, 1.3 Hz |
| | | 7.15 | Ring $CH_2$ | t, q, $J$ = 2.7, 1.3 Hz |
| | 111.3 | | Ring $CF_2$ | t, q, $J$ = 2.7, 3.3 Hz |
|  | | 8.29 | $CH_3$ | t, t, $J$ = 1.6, 2.3 Hz |
| | | 6.92 | Ring $CH_2$ | t, q, $J$ = 2.7, 2.3 Hz |
| | 112.5 | | Ring $CF_2$ | t, q, $J$ = 2.7, 1.6 Hz |

[a] Data obtained from ref 8. Compound prepared from $CH_3Li$ and 1-chloro-2,3,3-trifluorocyclobutene.

(1) (a) Taken in part from the Ph.D. dissertation of T. S. Croft, University of Colorado, 1967. (b) To whom inquires should be sent. Address correspondence to Central Research Laboratories, 3M Co., St. Paul, Minn. 55133.

(2) (a) S. Dixon, *J. Org. Chem.*, **21**, 400 (1956); (b) A. T. Blomquist and P. P. Nicholas, *ibid.*, **32**, 863, 866 (1967); (c) A. T. Blomquist and R. A. Vierling, *Tetrahedron Lett.*, 655 (1961); (d) J. D. Park and R. Fontanelli, *J. Org. Chem.*, **28**, 258 (1963).

(3) J. D. Park and R. J. McMurtry, *J. Org. Chem.*, **32**, 2397 (1967).

(4) (a) J. D. Park and G. G. I. Moore, Abstracts of Papers, 150th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1965, p 5K; (b) W. C. Solomon, L. A. Dee, and D. W. Schults, *J. Org. Chem.*, **31**, 1551 (1966); (c) K. V. Scherer, Jr., and T. J. Meyes, *J. Amer. Chem. Soc.*, **90**, 6253 (1968).

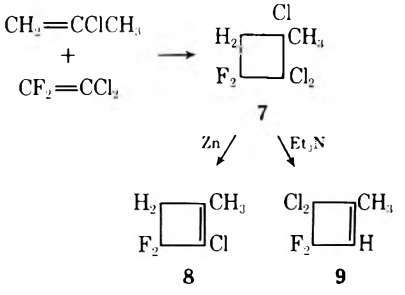
(5) (a) Unpublished results, this laboratory; J. H. Adams, Ph.D. Dissertation, University of Colorado, 1965; (b) J. D. Park, J. R. Dick, and J. H. Adams, *J. Org. Chem.*, **30**, 400 (1965); (c) J. D. Park, G. Groppelli, and J. H. Adams, *Tetrahedron Lett.*, 103 (1967).

larger than the value of 1.6 Hz for adjacent allylic fluorines. This would be consistent with the data of Sharts and Roberts,[6] who reported that the HF coupling constant of a vinylic proton with the cross ring fluorines, through four bonds, was larger than that found with vicinal fluorines, through three bonds.

Scheme I also depicts the products, compounds **5** and **6**, obtained from aluminum chloride and 1-methyl-2,3,3,4,4-pentafluorocyclobutene (**4**), the assignment of the structure of **5** as 1-methyl-3,3-difluoro-2,4,4-trichlorocyclobutene being based upon the coupling constant of 3.1 Hz observed in the nmr spectrum.

To establish definitively the coupling constant of the vinylic methyl group with the cross ring allylic fluorines, the synthesis of 1-methyl-2-chloro-3,3-difluorocyclobutene (**8**) and 1-methyl-3,3-difluoro-4,4-dichlorocyclobutene (**9**) was carried out as shown in Scheme II.

SCHEME II




The thermal codimerization of 1,1-dichloro-2,2-difluoroethylene and 2-chloropropene would be predicted[7] to produce 1-methyl-1,2,2-trichloro-3,3-difluorocyclobutane (**7**), an assignment borne out by the nmr and mass spectra reported in the Experimental Section. Dechlorination of **7** with zinc gave **8** and a dehydrohalogenation induced with triethylamine produced **9**. In both cases, the nmr spectra contained a coupling value of about 3.2 Hz from the cross ring allylic fluorines and the vinylic methyl protons. The magnitude of the coupling value of fluorines $\beta$ to the vinylic methyl group in 1-chloro-2-methyl-3,3-difluorocyclobutene, an isomer of **8**, was 1.6 Hz.[8] These data provide convincing evidence for the coupling and structural assignments.

## Experimental Section

Infrared spectra were taken on a Perkin-Elmer Infracord spectrophotometer. The nuclear magnetic resonance spectra were obtained from a Varian XL-100 spectrometer, utilizing an internal standard of $CFCl_3$ for the determination of $^{19}F$ chemical shifts, reported as $\phi^*$ values,[9] and tetramethylsilane as reference[10] for the proton values. Product analyses and preparative scale separations were carried out on an Aerograph Autoprep Model A-700 utlilizing a column with a fluorosilicone 1265 (QF-1) substrate. A Bausch and Lomb refractometer was used to measure the refractive indices. Densities were determined by weight difference with a calibrated 10-$\mu$l syringe. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. The mass spectrum was taken on a CEC 21 110c mass spectrometer.

**1-Methyl-2,3,3,4,4-pentafluorocyclobutene (4).**—The title compound was prepared following the procedure of Park and Fontanelli,[2d] bp 46–47° (626 mm) [lit.[2d] bp 44–45° (630 mm)].

**1,2-Dimethyl-3,3,4,4-tetrafluorocyclobutene (1).**—The procedure of Dixon[2a] was used to prepare the desired compound: bp 98–98.5° (626 mm); $n^{26}D$ 1.3475 [lit.[2a] bp 100–104° (760 mm); $n^{27}D$ 1.3478].

**Reaction of 1,2-Dimethyl-3,3,4,4-tetrafluorocyclobutene (1) with Aluminum Chloride.**—To an ice-cooled mixture of 11 g of aluminum chloride (B and A reagent powder) and 40 ml of carbon disulfide, under nitrogen atmosphere, was added 21 g of 1,2-dimethyl-3,3,4,4-tetrafluorocyclobutene. After stirring at room temperature for 16 hr, water was added, the black solution was filtered, and the organic layer was dried with anhydrous magnesium sulfate. Distillation gave 10 g of 1,2-dimethyl-3,3-dichloro-4,4-difluorocyclobutene (**2**): bp 139° (629 mm); $n^{27}D$ 1.4334; $d^{25}$ 1.27; molar refractivity, calcd 37.7, found 37.4; ir 1680 $cm^{-1}$ ($CH_3C{=}CCH_3$).

*Anal.* Calcd for $C_6H_6Cl_2F_2$: C, 38.50; H, 3.21; Cl, 37.97; F, 20.32. Found: C, 38.57; H, 3.13; Cl, 38.13; F, 20.25.

Also isolated was 2 g of 1,2-dimethyl-3,3,4,4-tetrachlorocyclobutene (**3**): bp 201.5–202.5° (629 mm); $n^{27}D$ 1.5037; $d^{25}$ 1.40; molar refractivity, calcd 47.2, found 46.2; ir 1630 $cm^{-1}$ ($CH_3C{=}CCH_3$); nmr ($CCl_4$) $\tau$ 8.12 (s, $CH_3$).

*Anal.* Calcd for $C_6H_6Cl_4$: C, 32.73; H, 2.73; Cl, 64.54. Found: C, 32.94; H, 2.73; Cl, 64.49.

Traces of other products were noted by glc but were not isolated in sufficient quantities to be characterized.

**Reaction of 1-Methyl-2,3,3,4,4-pentafluorocyclobutene (4) with Aluminum Chloride.**—The dropwise addition of 25 g of 1-methyl-2,3,3,4,4-pentafluorocyclobutene to a suspension of 23 g of aluminum chloride in 75 ml of carbon disulfide cooled in ice turned the solution black. After 5 hr under a nitrogen flow, the mixture was filtered, the solid being extracted with methylene chloride. The organic layer was dried and distilled to give 10 g of 1-methyl-2,4,4-trichloro-3,3-difluorocyclobutene (**5**): bp 139–139.5° (632 mm); $n^{26}D$ 1.4489; $d^{26}$ 1.50; molar refractivity, calcd 37.82, found 37.35; ir 1670 $cm^{-1}$ ($ClC{=}CCH_3$).

*Anal.* Calcd for $C_5H_3Cl_3F_2$: C, 28.89; H, 1.45; Cl, 51.30; F, 18.32. Found: C, 29.19; H, 1.65; Cl, 50.94; F, 18.38.

A trace was also found of 1-methyl-2,3,3,4,4 pentachlorocyclobutene (**6**): mp 50.5–52.5; bp 203–203.5° (627 mm); ir 1670 $cm^{-1}$ ($ClC{=}CCH_3$); nmr ($CCl_4$) $\tau$ 8.03 (s, $CH_3$).

*Anal.* Calcd for $C_5H_3Cl_5$: C, 24.95; H, 1.25; Cl, 73.84. Found: C, 25.16; H, 1.32; Cl, 73.74.

Traces of other products were also seen in the glc curve of the product but were not characterized.

**Codimerization of 2-Chloropropene and 1,1-Dichloro-2,2-difluoroethylene.**—In a 0.5-l. autoclave, 76 g of 2-chloropropene and 132 g of 1,1-dichloro-2,2-difluoroethylene, along with 1 ml of *d*-limonene to prevent polymerization, were heated to 180° for 12 hr. Distillation of the yellow liquid gave 7 g of 1,2-dichloro-3,3,4,4-tetrafluorocyclobutene, bp 60.5° (628 mm), and 30 g of 1,1,2,2-tetrachloro-3,3,4,4-tetrafluorocyclobutane, bp 124° (628 mm), both identified by comparison with the infrared spectra of authentic samples.[11] Also collected was 31 g of 1-methyl-1,2,2-trichloro-3,3-difluorocyclobutane (**7**): mp 46–49°; bp 148° (628 nm); nmr ($CFCl_3$) $\tau$ 8.09 (d, $J$ = 1.2 Hz, $CH_3$), 6.93 and 7.11 (AB pattern, $J_{AB}$ = 13.8 Hz, ring $CH_2$), with fine structure visible, with 6.93 (d, d, $J$ = 9.5, 15.2 Hz, ring CH) and 7.11 (d, d, $J$ = 11.8, 6.5 Hz, ring CH), $\phi^*$ 98.10 and 102.31 (AB pattern, $J_{AB}$ = 190.0 Hz, $CF_2$) with fine structure visible, with 98.10 (d, d, $J$ = 9.5, 6.4 Hz, CF) and 102.31 (d, d, q, $J$ = 11.6, 15.1, 1.2 Hz, CF); mass spectrum (150°) $m/e$ (ion) in decreasing order of intensity, 76 ($CH_2CClCH_3$), 144 (P − $CF_2CH_2$), 109 (P − $CH_2CF_2$, Cl), 41 ($C_3H_5$), 39 ($C_3H_3$), 132 ($CF_2CCl_2$), 51 ($CF_2H$), 64 ($CF_2CH_2$), 172 (P − HCl), 208 (P).

*Anal.* Calcd for $C_5H_3Cl_3F_2$: C, 28.64; H, 2.39; Cl, 50.08; F, 18.14. Found: C, 28.87; H, 2.50; Cl, 50.71; F, 18.36.

**Reaction of 1-Methyl-1,2,2-trichloro-3,3-difluorocyclobutane (7) with Zinc.**—After a mixture of 10 g of 1-methyl-1,2,2-trichloro-3,3-difluorocyclobutane, 0.5 ml of hydrochloric acid, and 6.5 g of zinc was heated in 1-butanol for 24 hr, distillation gave 4 g of 1-methyl-2-chloro-3,3-difluorocyclobutene (**8**): bp 100° (633 mm); $n^{25}D$ 1.3998; $d^{25}$ 1.18; molar refractivity, calcd 28.2, found 28.2; ir 1670 $cm^{-1}$ ($ClC{=}CCH_3$).

*Anal.* Calcd for $C_5H_5ClF_2$: C, 43.32; H, 3.61; Cl, 25.63; F, 27.80. Found: C, 43.41; H, 3.70; Cl, 25.80; F, 27.39.

(6) C. M. Sharts and J. D. Roberts, *J. Amer. Chem. Soc.*, **79**, 1008 (1957).

(7) (a) J. D. Roberts and C. M. Sharts, *Org. React.*, **12**, 1 (1962); (b) W. H. Sharkey in "Fluorine Chemistry Reviews," Vol. 2, P. Tarrant, Ed., Marcel Dekker, New York, N. Y., 1968, Chapter 1.

(8) Unpublished results, this laboratory: R. O. Michael, Ph.D. Dissertation, University of Colorado, 1969.

(9) G. Filipovich and G. V. D. Tiers, *J. Phys. Chem.*, **63**, 761 (1959).

(10) G. V. D. Tiers, *J. Phys. Chem.*, **62**, 1151 (1958).

(11) A. L. Henne and R. P. Ruh, *J. Amer. Chem. Soc.*, **69**, 279 (1947).

**Reaction of 1-Methyl-1,2,2-trichloro-3,3-difluorobutane (7) with Triethylamine.**—A 10-g sample of 1-methyl-1,2,2-trichloro-3,3-difluorocyclobutane was refluxed with 7.5 g of triethylamine for 91 hr. After washing with hydrochloric acid, separation, and drying, 4 g of starting material was recovered by distillation. Also isolated was 4 g of 1-methyl-3,3-difluoro-4,4-dichlorocyclobutene (9): bp 130° (629 mm); $n^{25}D$ 1.4261; $d^{25}$ 1.34; molar refractivity, calcd 33.0, found, 32.9; ir 1645 $cm^{-1}$ ($HC{=}CCH_3$).

*Anal.* Calcd for $C_5H_4Cl_2F_2$: C, 34.68; H, 2.31; Cl, 41.04; F, 21.96. Found: C, 34.79; H, 2.38; Cl, 41.09; F, 21.83.

**Acknowledgments.**—The authors wish to express their appreciation to Dr. J. J. McBrady and Dr. G. R. Sparrow of the 3M Co., St. Paul, Minn., for having run the $^{19}F$ nmr spectra and the mass spectrum reported in this paper. We also wish to thank AFOSR Chemical Division and the 3M Co., St. Paul, Minn., for their support of this work.

**Registry No.**—**1**, 356-58-1; **2**, 41785-17-5; **3**, 41785-18-6; **4**, 356-59-2; **5**, 41785-19-7; **6**, 41785-20-0; **7**, 41785-21-1; **8**, 41785-22-2; **9**, 41785-23-3; aluminum chloride, 7446-70-0; 2-chloropropene, 557-98-2; 1,1-dichloro-2,2-difluoroethylene, 79-35-6; 1,2-dichloro-3,3,4,4-tetrafluorocyclobutene, 377-93-5; 1,1,2,2-tetrachloro-3,3,4,4-tetrafluorocyclobutane, 336-50-5; zinc, 7740-66-6; triethylamine, 121-44-8.

# Fluorinated Esters Stable to Fluoride Ion

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Some new fluorinated esters, $CF_3CO_2R_f$ [$R_f$ = $(CF_3)_3C$, $C_2F_5(CF_3)_2C$, $(CF_3)_2(CH_3)C$, and $(CF_3)_2CH$], with substituents other than fluorine on the alkoxy $\alpha$ carbon have been prepared using the cesium fluoride catalyzed reactions of trifluoroacetyl fluoride with fluoro alcohols. Unlike the fluorinated esters with fluorine at the alkoxy $\alpha$ carbon atom, these esters are stable in the presence of fluoride ion at 25° or higher temperatures. Their ir, nmr, and mass spectra are reported.

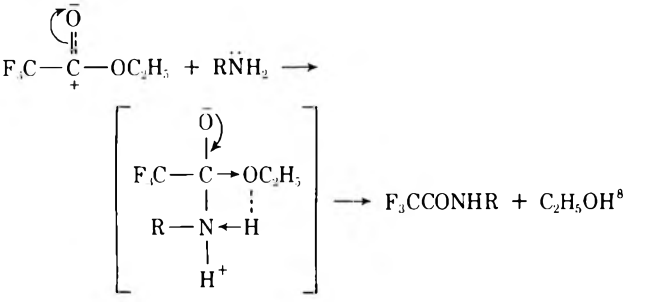
In our earlier studies,[1] we had observed that, while the totally fluorinated esters were stable at 25° and above when pure, they disproportionated readily at $>-78°$ in the presence of fluoride ions. Each of these esters contained a perfluoroalkoxy group with at least one fluorine atom bonded to the $\alpha$ carbon adjacent to the oxygen, $-OCR_f(R_f')F$ ($R_f$ = $CF_3$, $R_f'$ = F; $R_f$ = $R_f'$ = $CF_3$). We now have extended our study to a variety of other esters with different substituents on that carbon to determine their stabilities to attack by fluoride ions.

Contrary to the well-known reactions of acid chlorides with alcohols, the corresponding reactions of acid fluorides have neither been as popular nor as lucrative; *e.g.*, trifluoroacetyl fluoride with ethanol yielded a trace of ethyl trifluoroacetate, $CF_3CO_2C_2H_5$, accompanied by other products.[2] However, we found that a modification of this route provided a good general preparative method for esters.

Although some of the esters described in this paper have been previously reported,[3-7] little spectral characterization was included. Full details of infrared, mass, and $^1H$ and $^{19}F$ nmr spectra are given.

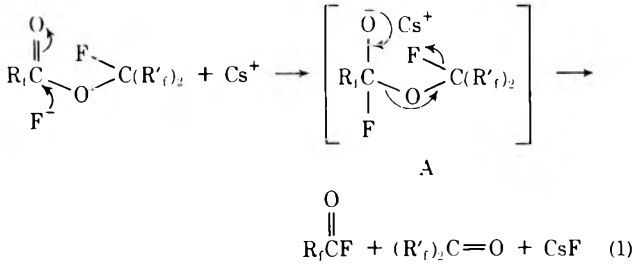
## Results and Discussion

Fluorinated esters of the type $R_fCO_2CF(CF_3)_2$ which contain fluorine on the alkoxy $\alpha$ carbon are unstable in the presence of fluoride ion at $-78°$ or above.[1] However, esters described in this paper that contain substituents other than fluorine at this carbon are very stable in the presence of fluoride ion even at higher temperatures. Since $R_f$ is an electronegative group, it enhances the electrophilic character of the carbonyl carbon atom and thus promotes addition to the carbonyl double bond.



The fluoride ion, which is strongly nucleophilic, can readily attack at the positive carbon of the carbonyl group to form a similar intermediate which will then disproportionate to give the acid fluoride.

Owing to the very strong inductive effect of F, its departure as shown in eq 1 will be favored. However,



A



(1)

the inductive effects of $CF_3$ and particularly of H and $CH_3$ are very much less than that of fluorine.[8b] Thus, these moieties will not be good leaving groups in a complex like A. This explains the greater stability of the

(1) R. A. De Marco, D. A. Couch, and J. M. Shreeve, *J. Org. Chem.*, **37**, 3332 (1972).
(2) W. T. Miller, Jr., and M. Prober, *J. Amer. Chem. Soc.*, **70**, 2602 (1948).
(3) F. J. Pavlik and P. E. Toren, *J. Org. Chem.*, **35**, 2054 (1970).
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(6) E. T. McBee and D. L. Christman, *J. Amer. Chem. Soc.*, **77**, 755 (1955).
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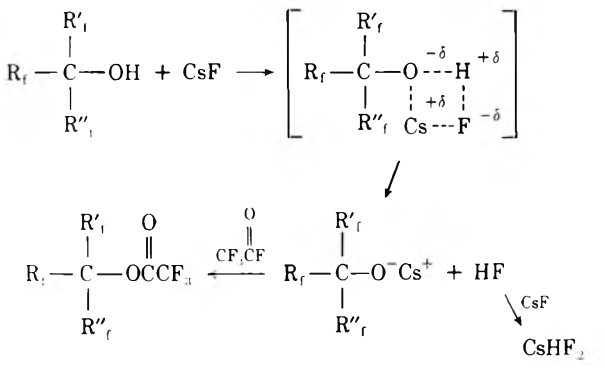
(8) (a) M. M. Joullie and A. R. Day, *J. Amer. Chem. Soc.*, **76**, 2990 (1954); (b) H. P. Braendlin and E. T. McBee, *Advan. Fluorine Chem.*, **3**, 2 (1963).

TABLE I
INFRARED SPECTRA OF $R_fCO_2R_f'$

| Compd | Ir, $cm^{-1}$ |
|---|---|
| $CF_3CO_2C_2H_5$ | 2985 m, 2950 sh, 2890 vw, 1790 vs, 1450 w, br, 1375 m, 1340 m, 1228 vs, 1180 s, 1145 s, 1015 w, 852 vs, 770 w, 725 m |
| $CF_3CO_2CH_2CF_3$ | 2985 w, 2960 w, 1810 vs, 1412 m, 1350 m, 1282 s, 1242 s, 1185 s, 975 m, 900 w, 770 w, 733 m, 650 w, 550 vw, 455 vw |
| $CF_3CO_2C(CF_3)_3$ | 1876 s, 1379 sh, 1346 w, 1295 vs, 1277 sh, 1261 sh, 1211 s, 1136 s, 1078 w, 1012 m, 995 m, 756 m, 733 m, 718 w, 671 w |
| $CF_3CO_2C_5F_{11}$ | 1858 s, 1330 m, 1265 sh, 1258 vs, 1235 sh, 1198 s, 1128 s, 1065 m, 1085 w, 1000 m, 985 sh, 925 sh, 905 sh, 895 m, 750 m, 735 m, 715 m, 665 w–m, 618 w–m, 540 w, 518 s, 445 w |
| $CF_3CO_2C(CF_3)_2H$ | 2975 m, 1825 sh, 1823 s, 1378 s, 1343 m, 1298 s, 1275 m, 1235 s, 1215 m, 1195 s, 1160 sh, 1125 s, 1024 m, 915 s, 824 w, 760 m, 744 m, 710 s, 688 s, 820 m, 474 w, |
| $CF_3CO_2C(CF_3)_2CH_3$ | 2950 w, br, 818 s, 1456 m, 1396 w, 1341 w, 1315 s, br, 1205 s, 1195 m, 1182 sh, 1141 s, 1125 sh, 1093 s, 891 w, 835 w, 760 w, 742 m, 693 m, 645 w, 520 br, w |

fluorinated esters with groups other than fluorine on the alkoxy carbon.

The primary alcohols ethanol and trifluoroethanol reacted at 100° with trifluoroacetyl fluoride in the absence of cesium fluoride to give significant amounts of the respective trifluoroacetates. Secondary and tertiary alcohols, *e.g.*, hexafluoroisopropyl, hexafluoro-2-methylpropyl, perfluoro-*tert*-butyl, and perfluoroisoamyl alcohols, reacted only in the presence of cesium fluoride. Their order of reactivity is roughly represented by $(CF_3)_3COH > (CF_3)_2(C_2F_5)COH > (CF_3)_2C(CH_3)OH \approx (CF_3)_2CHOH$. This can be explained on the basis of the inductive effect of the fluorinated chains and thus the acidity of the alcohols, since the introduction of fluorine or of perfluoroalkyl groups increases the acidity of the alcohols.[9] Based on a comparative study of the $pK_a$ values of the hydrogenated and fluoro alcohols, the secondary fluoro alcohols have the same order of acidity as phenol, and, whereas the primary alcohols are less acidic, the tertiary alcohols compare with carboxylic acids.[10,11] Since ethanol and trifluoroethanol are fairly basic ($pK_a$ = 15.93 and 12.8, respectively),[10] their reactions with trifluoroacetyl fluoride are typical acid–base reactions. However, the other alcohols appear to react through the formation of an alkoxide intermediate. With increasing acidity

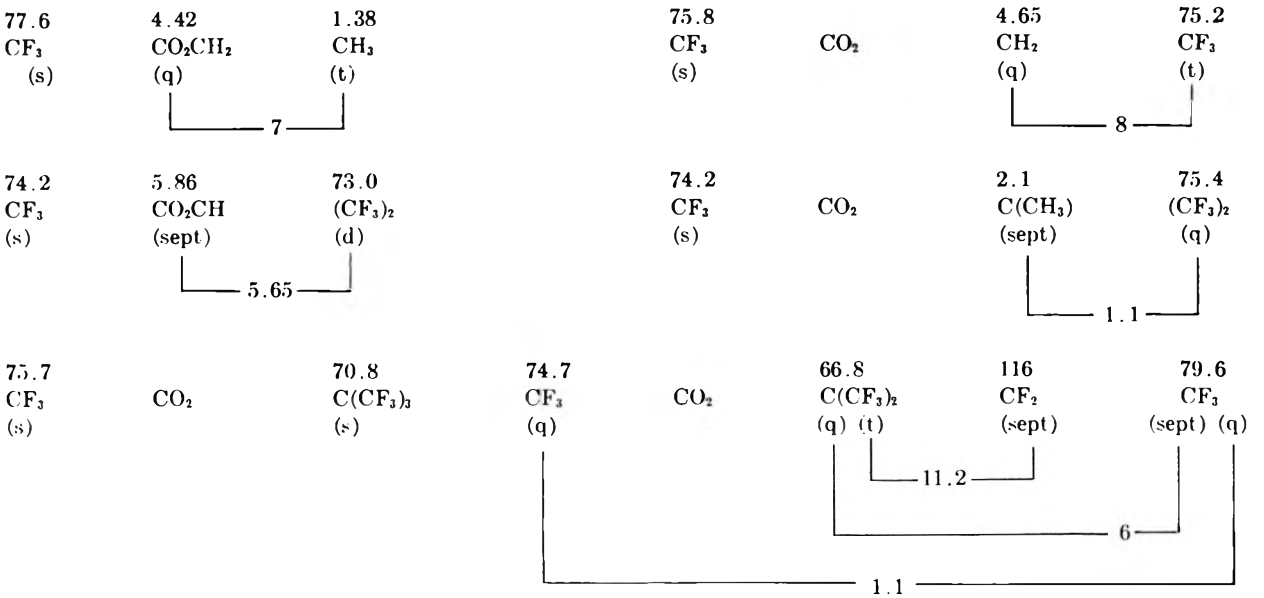


(9) F. Swarts, *Bull. Soc. Chim. Belg.*, **38**, 99 (1929).
(10) J. Murto, *Acta Chem. Scand.*, **18**, 1043 (1964).
(11) S. Kumar De and S. R. Palit, *Advan. Fluorine Chem.*, **6**, 73 (1970).

TABLE II
MASS SPECTRA OF $CF_3CO_2R_f$ (17 eV)

| Registry no. | Compd | *m/e* (assignments, rel intensity)] |
|---|---|---|
| 383-63-1 | $CF_3CO_2C_2H_5$ | 142 (M, 4.8), 141 (M − H, 14.5), 140 (M − 2 H, 3.2), 127 (M − $CH_3$, 29), 113 (M − $C_2H_5$, 9.7), 99 ($C_2H_2F_3O$, 45.1), ($C_2F_3O$, 6.4), 73 (M − $CF_3$, 19.3), 69 ($CF_3$, 16.9), 30 ($CH_2O$, 9.7), 29 ($C_2H_5$, 100), 27 ($C_2H_3$, 11.3) |
| 407-38-5 | $CF_3CO_2CH_2CF_3$ | 177 (M − F, 27.2), 127 (M − $CF_3$, 100), 99 ($C_2H_2F_3O$, 22.8), 97 ($C_2F_3O$, 7.1), 83 ($C_2H_2F_3$, 79.6), 69 ($CF_3$, 17.0) |
| 24165-10-4 | $CF_3CO_2C(CF_3)_3$ | 313 (M − F, 12.5), 263 (M − $CF_3$, 73.9), 235 (M − $CF_3$-CO, 17), 219 [$(CF_3)_3C$, 13.2], 200 ($C_4F_8$, 1.8), 166 ($C_3F_6O$, 2), 164 (?, 3), 162 (?, 4), 147 ($C_3F_5O$, 9.5), 131 ($C_3F_5$, 13), 97 ($CF_3CO$, 85.5), 87 (?, 3), 85 ($CF_3O$, 19.4), 69 ($CF_3$, 100) |
| 42133-36-8 | $CF_3CO_2C_5F_{11}$ | 363 (M − F, 4.4), 313 (M − $CF_3$, 4.4), 285 (M − $CF_3$-CO, 0.8), 269 (M − $CF_3$-$CO_2$, 0.8), 247 ($C_5F_9O$, 1), 181 ($C_4F_7$, 3.8), 131 ($C_3F_5$, 1.8), 119 ($C_2F_5$, 6.8), 100 ($C_2F_4$, 1.6), 97 ($C_2F_3O$, 28.8), 93 ($C_3F_3$, 2), 78 ($C_2F_2O$, 1.8), 69 ($CF_3$, 100), 50 ($CF_2$, 3.8), 47 (CFO, 1.1), 44 ($CO_2$, 1.1), 31 (CF, 2.8) |
| 42031-15-2 | $CF_3CO_2C(CF_3)_2H$ | 245 (M − F, 8.2), 226 (M − 2 F, 4.1), 225 (M − $HF_2$, 49.6), 195 (M − $CF_3$, 48.4), 175 ($C_4F_5O_2$, 1.9), 167 ($C_3HF_6O$, 13.2), 151 ($C_3HF_6$, 42.5), 132 ($C_3HF_5$, 1.9), 130 ($C_3F_5$, 2.8), 129 ($C_3HF_4O$, 2.5), 128 ($C_3F_4O$, 1.9), 113 ($C_2F_3O_2$, 5.7), 101 ($C_2HF_4$, 5.3), 100 ($C_2F_4$, 1.9), 98 ($C_2HF_3O$, 2.2), 97 ($C_2F_3O$, 52.2), 82 ($C_2HF_3$, 5.7), 79 ($C_2HF_2O$, 14.5), 78 ($C_2F_2O$, 9.1), 69 ($CF_3$, 4.1), 63 ($C_2HF_2$, 4.1), 51 ($HCF_2$, 28.9), 50 ($CF_2$, 17.9), 44 ($CO_2$, 6.3), 32 (HCF, 5.7), 31 (CF, 10.8), 29 (HCO, 16.4) |
| 42031-16-3 | $CF_3CO_2C(CF_3)_2CH_3$ | 278 (M, 1.3), 259 (M − F, 2.9), 258 (M − HF, 9.0), 239 [M − (2 F + H), 1.6], 209 (M − $CF_3$, 23.4), 181 (M − $CF_3CO$, 55.1), 165 (M − $CF_3CO_2$, 45.5), 164 ($C_4H_2F_6$, 7.4), 146 ($C_4H_3F_5$, 5.8), 145 ($C_4H_2F_5$, 100), 115 ($C_3H_3F_4$, 19.9), 113 ($CF_3CO_2$, 3.2), 97 ($CF_3CO$, 15.1), 95 ($C_3H_2F_3$, 14.4), 93 ($C_3F_3$, 14.4), 77 ($C_3H_3F_2$, 34.3), 69 ($CF_3$, 44.2), 45 (?, 4.2), 43 ($CH_3$-CO, 72.4) |

TABLE III
NMR SPECTRA[a]




[a] $^1H$ chemical shifts in parts per million (low field of $Me_4Si$); $^{19}F$ chemical shift upfield relative to $CCl_3F$ both as internal indicators. Letters in parentheses: s, singlet; t, triplet; q, quartet; sept, septet. Relative areas of the signals correspond to the assignments in each case.

of the alcohols, the $[R_fCR_f'(R_f'')O^-]$ anion becomes more stable and thus alkoxide formation is favored. This is in line with observed reactivities.

Except for hexafluoroisopropyl trifluoroacetate, $CF_3CO_2CH(CF_3)_2$, all of the esters are stable toward hydrolysis by water at 25°, and all are hydrolyzed at $\leqslant$100°. Since the proton on the alkoxy carbon of the hexafluoroisopropyl group is acidic, nucleophilic attack of water at this point should be very likely, which explains the rapid hydrolysis of this ester.

Infrared spectra of the fluorinated esters are given in Table I. As expected, the carbonyl stretching frequency of ethyl trifluoroacetate is the lowest, and agrees with the previously reported value.[6] Differences between the carbonyl stretching frequencies of $CF_3CH_2O_2CCF_3$, $(CF_3)_2C(CH_3)O_2CCF_3$, and $(CF_3)_2C(H)O_2CCF_3$ are not very large. The carbonyl frequencies for the $(CF_3)_2(C_2F_5)CO_2CCF_3$ and $(CF_3)_3CO_2CCF_3$ esters are significantly higher than for the other four esters. This again indicates that inductive effects of the fluoroalkyl group are more significant than their steric effect. Occurrence of strong bands in the region of 1100–1300 $cm^{-1}$ for C–F stretching modes makes the assignments for $\nu_{C-O}$ difficult.

The mass spectra are given in Table II. Parent peaks were found only for ethyl trifluoroacetate and hexafluoro-2-methylpropyl trifluoroacetate-2. For all other esters, the highest peak observed corresponded to M − F. For the general ester $CF_3CO_2R_f$, a consistent cracking pattern was found. Fragments were observed for each ester corresponding to $CF_3$, $CF_3CO$, (M − $CF_3$), $R_f$, and $R_fO$. This is consistent with the spectra of previously reported fluorinated esters.[1] It is significant to note that the $CF_3CO_2$ fragment is only observed for the esters $CF_3CO_2C_2H_5$, $CF_3CO_2C(H)(CF_3)_2$, and $CF_3CO_2C(CH_3)(CF_3)_2$. This is in line with the previous results.[1]

Nmr spectra of these esters are given in Table III. The spectra are first order and directly interpretable. No spin–spin coupling of the acyl $CF_3$ group with the fluoroalkyl $CF_3$ in $CF_3CO_2CH_2CF_3$ and $CF_3CO_2C(CF_3)_2R$ (R = H, $CH_3$, $CF_3$) occurs. However, consistent with $C_2F_5CO_2C(CF_3)_2F$ and $C_3F_7CO_2C(CF_3)_2F$,[1] the $CF_3$ of the perfluoroethyl group in $CF_3CO_2C(CF_3)_2C_2F_5$ is split by the acyl $CF_3$ group because of through-space coupling.

## Experimental Section

**General Procedures.**—Standard vacuum line techniques were used throughout and rigorous precautions were taken to exclude moisture from all systems. In particular, all glassware was flamed out before each experiment. All reactions were carried out in 200-ml Pyrex bulbs fitted with Teflon (Quickfit) stopcocks. Pressures were measured with a Heise–Bourdon tube gauge. Amounts of volatile materials were determined by PVT measurements assuming ideal gas behavior. In general, the esters were readily separated from more volatile unreacted trifluoroacetyl fluoride by fractional condensation (low-temperature separation based on differences in volatility of components).

Infrared spectra were taken on a Perkin-Elmer 457 spectrometer using a 10-cm Pyrex glass cell equipped with KBr windows and were calibrated against known absorption bands in a polystyrene film. The $^{19}F$ nmr spectra were obtained on a Varian Model HA-100 spectrometer operating at 94.1 MHz using Freon-11 as an internal standard. The $^1H$ nmr were determined on a Varian A-60 spectrometer using tetramethylsilane as an internal standard. Mass spectra were obtained using a Hitachi Perkin-Elmer Model RMU-6E mass spectrometer at 17 and 70 eV. Molecular weights were determined by vapor density measurements. Vapor pressures were obtained by the method of Kellogg and Cady.[12] Equations describing pressure as a function of temperature were obtained by a least-squares fit of the data. Elemental analyses were performed by Laboratorium Beller, Göttingen, Germany.

**Reagents.**—Cesium fluoride (99%) was obtained from ROC/RIC Chemical Co. and was heated at 200° for 24 hr and then powdered. Before use, CsF was activated by forming the salt $(CF_3)_2CFO^-Cs^+$,[13] which was subsequently thermally decomposed at ~100° under dynamic vacuum. This gave a well-dried, finely divided powder. Anhydrous ethanol was obtained from Commercial Solvents Corp. All other chemicals were obtained from PCR, Inc., and used without further purification.

(12) K. B. Kellogg and G. H. Cady, *J. Amer. Chem. Soc.*, **70**, 3986 (1948).
(13) C. T. Ratcliffe and J. M. Shreeve, *Chem. Commun.*, 674 (1966).

TABLE IV

REACTION CONDITIONS AND PRODUCT YIELDS[a]

| $CF_3COF$, mmol | Alcohol (mmol) | Time, day | Ester (mmol) | Mol wt[b] |
|---|---|---|---|---|
| 10.0 | $C_2H_5OH$ (4.0) | 0.5 | $CF_3CO_2C_2H_5$ (3.9) | 142.8 (142.0)[c] |
| 11.0 | $CF_3CH_2OH$ (4.0) | 0.5 | $CF_3CO_2CH_2CF_3$ (3.9) | 195.6 (196.0) |
| 7.0 | $(CF_3)_2CHOH$ (4.0) | 4.0 | $CF_3CO_2C(CF_3)_2H$ (3.4) | 263.1 (264.0) |
| 6.0 | $(CF_3)_2C(CH_3)OH$ (2.0) | 4.0 | $CF_3CO_2C(CF_3)_2CH_3$ (1.6) | 279.3 (278.0) |
| 5.0 | $(CF_3)_3COH$ (1.1) | 2.0 | $CF_3CO_2C(CF_3)_3$ (1.1) | 331.3 (332.0) |
| 0.8 | $(CF_3)_2C(C_2F_5)OH$ (0.6) | 3.0 | $CF_3CO_2C(CF_3)_2C_2F_5$ (0.6) | 380.7 (382.0) |

[a] All reactions were carried out in the presence of CsF at room temperature. [b] Vapor density determined assuming ideal gas behavior by Regnault's method. [c] Calculated value.

TABLE V

ELEMENTAL ANALYSIS AND THERMODYNAMIC DATA

| Ester | Elemental analysis, % C | H | F | Bp °C | $\Delta H_v$, kcal/mol | $\Delta S_v$, eu | Log $P_{mm} = a - b/T$ $a$ | $b$ |
|---|---|---|---|---|---|---|---|---|
| $CF_3CO_2C_2H_5$ | 33.8 (33.8)[a] | 3.6 (3.5) | 39.9 (40.1) | 62 | 8.3 | 24.6 | 8.27 | 1809 |
| $CF_3CO_2CH_2CF_3$ | 24.5 (24.5) | 1.0 (1.0) | 24.5 (24.5) | 57 | 7.6 | 23.1 | 7.92 | 1663 |
| $CF_3CO_2C(CF_3)_2H$ | 22.7 (22.7) | 0.4 (0.4) | 65.5 (64.8) | 48 | 6.8 | 21.2 | 7.51 | 1487 |
| $CF_3CO_2C(CF_3)_2CH_3$ | 25.9 (25.9) | 1.1 (1.1) | 62.0 (61.5) | 65 | 8.0 | 23.6 | 8.04 | 1743 |
| $CF_3CO_2C(CF_3)_3$ | 21.7 (21.7) | | 68.9 (68.7) | 56 | 7.9 | 24.0 | 8.12 | 1724 |
| $CF_3CO_2C(CF_3)_2C_2F_5$ | 21.9 (22.0) | | 69.7 (69.6) | | | | | |

[a] Calculated value.

**Preparative Procedure.**—In a typical reaction a 2.5:1 excess of $CF_3COF$ was condensed into a vessel which contained 4 mmol of the appropriate alcohol and about 5 g of activated CsF. The mixture was left at 25° until the band due to OH stretch (~3600 $cm^{-1}$) disappeared from the infrared spectrum of the mixture. The volatilities of all the esters prepared were much less than that of the trifluoroacetyl fluoride ($CF_3COF$), which facilitated the separation of the esters from the excess unreacted $CF_3COF$ by fractional condensation. Except for hexafluoroisopropyl alcohol, $(CF_3)_2CHOH$, and hexafluoro-2-methylpropanol-2, $(CF_3)_2C(CH_3)OH$, reaction of $CF_3COF$ with the other alcohols went to completion without any difficulty, giving pure esters. The cesium fluoride recovered from these reactions became increasingly more active. $(CF_3)_2CHOH$ and $(CF_3)_2C(CH_3)OH$ reacted more slowly. Some unreacted alcohol always remained in these latter cases and the complete separation from the ester was difficult. However, completion of the reaction could be achieved by condensing the impure ester onto fresh CsF in the presence of excess $CF_3COF$. The solid recovered from these latter reactions had a moist appearance and on heating at 100° evolved the parent alcohol. Reaction conditions and yields of products are given in Table IV. Elemental analyses and thermodynamic data are found in Table V.

**Acknowledgment.**—Fluorine research at the University of Idaho is supported by the National Science Foundation and the Office of Naval Research. We thank Mr. N. R. Zack for mass spectra and Mr. C. Srivanavit for nuclear magnetic resonance spectra. Dr. C. T. Ratcliffe provided samples of $(CF_3)_3COH$ and $(CF_3)_2(C_2F_5)COH$.

# Halomethyl-Metal Compounds. LXV. Generation of Fluorocarboalkoxycarbenes *via* the Organomercury Route[1,2]

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*Received June 29, 1973*

The organomercurials $PhHgCFClCO_2R$ (R = $CH_3$ and $C_2H_5$) and $PhHgCFBrCO_2C_2H_5$ have been prepared by reaction of the respective alkyl dihaloacetate with potassium *tert*-butoxide and phenylmercuric chloride or by mercuration of the respective ethyl trihalovinyl ether with mercuric nitrate in ethanol, followed by redistribution of the mercuration product with diphenylmercury. These mercurials are $FCCO_2R$ transfer agents at temperatures above 125°, reacting with olefins to give *gem*-fluorocarboalkoxycyclopropanes and inserting $FCCO_2R$ into the Si–H bond of triethylsilane. Also described is $FCCO_2Et$ addition to the C=N bond of $PhN{=}CCl_2$.

In a previous investigation[3] we prepared $PhHgCCl_2CO_2CH_3$ and $PhHgCClBrCO_2CH_3$, both $ClCCO_2CH_3$ transfer agents, as well as $PhHgCBr_2CO_2CH_3$, a source of $BrCCO_2CH_3$. In view of our interest in organometallic routes to fluorinated carbenes,[4-9] we have extended these studies to mercury compounds of the type $PhHgCFXCO_2R$ (X = Cl, Br; R = $CH_3$ or $C_2H_5$). The divalent carbon transfer chemistry of the $PhHgCClXCO_2CH_3$ compounds and of $PhHgCBr_2CO_2CH_3$ required rather drastic conditions, but it was expected

(1) Part LXIV: D. Seyferth and Y. M. Cheng, *J. Amer. Chem. Soc.*, **95**, 6763 (1973). (This paper is labeled part XIII by error.)

(2) Preliminary communication: D. Seyferth and R. A. Woodruff, *J. Fluorine Chem.*, **2**, 214 (1972).

(3) D. Seyferth, R. A. Woodruff, D. C. Mueller, and R. L. Lambert, Jr., *J. Organometal. Chem.*, **43**, 55 (1972).

(4) D. Seyferth and S. P. Hopper, *J. Org. Chem.*, **37**, 4070 (1972).

(5) D. Seyferth, H. Dertouzos, R. Suzuki, and J. Y.-P. Mui, *J. Org. Chem.*, **32**, 2980 (1967).

(6) D. Seyferth and K. V. Darragh, *J. Org. Chem.*, **35**, 1297 (1970).

(7) D. Seyferth and G. J. Murphy, *J. Organometal. Chem.*, **49**, 117 (1973).

(8) D. Seyferth and S. P. Hopper, *J. Organometal. Chem.*, **51**, 77 (1973).

(9) D. Seyferth and G. J. Murphy, *J. Organometal. Chem.*, **52**, C1 (1973).

TABLE I

FLUOROCARBOALKOXYCARBENE TRANSFER REACTIONS OF PhHgCFClCO$_2$R

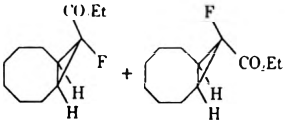
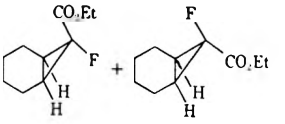
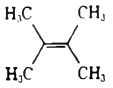
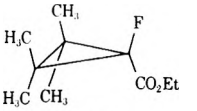
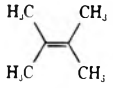
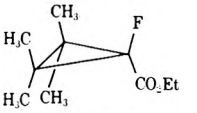
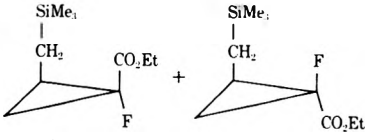
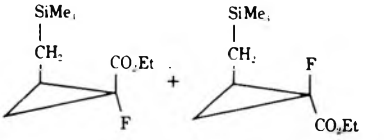
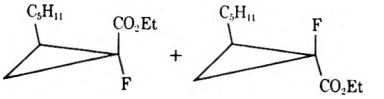
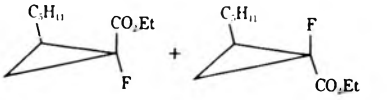
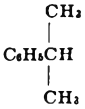
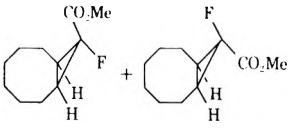
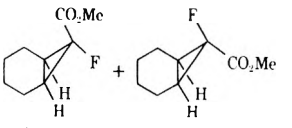
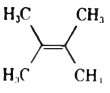
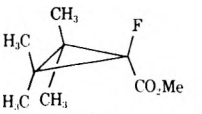
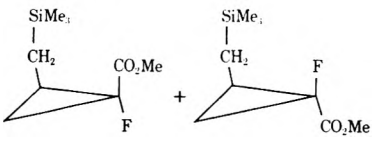
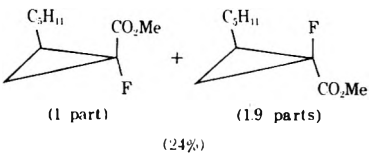
| Substrate (mmol) | Mmol of mercurial | Solvent (ml) | Reaction temp, °C | Reaction time, hr | Yield PhHgCl, % | Recovered starting material, % | Products (% yield based on consumption of starting mercurial) |
|---|---|---|---|---|---|---|---|
| **Reactions of PhHgCFClCO$_2$Et** | | | | | | | |
|  (neat) | 12.0 | Olefin (20) | 144 | 36 | 96 | |  (1 part) (2.45 parts) (85%) |
|  (neat) | 12.0 | Olefin (20) | 132 (sealed tube) | 24 | 79 | 19 |  (1 part) (2.39 parts) (69%) |
|  (36) | 12.0 | Benzene (12) | 135 (sealed tube) | 24 | 26 | 64 |  (22%) |
|  (72) | 12.0 | Benzene (12) | 155 (sealed tube) | 72 | 72 +Hg$^0$ (21) | |  (38%) |
| Me$_3$SiCH$_2$CH=CH$_2$ (neat) | 12.0 | Olefin (20) | 129 (sealed tube) | 36 | 66 +Hg$^0$ (19) | |  (1 part) (1.85 parts) (24%) |
| Me$_3$SiCH$_2$CH=CH$_2$ (neat) | 12.0 | Olefin (20) | 133 (sealed tube) | 62 | 55 +Hg$^0$ (21) | |  (1 part) (1.9 parts) (55%) |
| CH$_2$=CHC$_5$H$_{11}$-*n* (neat) | 12.0 | Olefin (20) | 134 (sealed tube) | 48 | 37 +Hg$^0$ (18) | 9 |  (1 part) (2.5 parts) (15%) |
| CH$_2$=CHC$_5$H$_{11}$-*n* (neat) | 10.3 | Olefin (12) | 145 (sealed tube) | 24 | 33 +Hg$^0$ (14) | 18 |  (1 part) (2.6 parts) (18%) |
| Et$_3$SiH (neat) | 12.0 | Et$_3$SiH (20) | 108–110 | 50 | 25 +Hg$^0$ (54) | | Et$_3$SiCHFCO$_2$Et (71%) |
|  | 24.0 | Cumene (20) | 155 (sealed tube) | 72 | 23 +Hg$^0$ (11) | 37+ | None |
|  (neat) | 12.0 | THF (30) | 155 (sealed tube) | 48 | 0, + Hg$^0$ (54) | | None |

TABLE I
(*Continued*)

| Substrate (mmol) | Mmol of mercurial | Solvent (ml) | Reaction temp, °C | Reaction time, hr | Yield PhHgCl, Yield % | Recovered starting material, % | Products (% yield based on consumption of starting mercurial) |
|---|---|---|---|---|---|---|---|
| Reactions of $PhHgCClFCO_2Me$ | | | | | | | |
|  (22) | 7.2 | Benzene (7.0) | 135 (sealed tube) | 48 | 58 | 38 |  (1 part) (1.8-1.9 parts) (85-88%) |
|  (24) | 8.0 | Benzene (8) | 135 (sealed tube) | 60 | 57 | |  (1 part) (1.9 parts) (47%) |
|  (60) | 10.0 | Benzene (10) | 155 (sealed tube) | 72 | 54 +$Hg^0$ (29) | |  (48%) |
| $Me_3SiCH_2CH{=}CH_2$ (24) | 8.0 | Benzene (8) | 135 (sealed tube) | 60 | 71 | 10 |  (1 part) (1.4 parts) (61%) |
| $CH_2{=}CHC_5H_{11}$-*n* | 8.0 | Benzene (8) | 135 (sealed tube) | 60 | 47 | |  (1 part) (1.9 parts) (24%) |
| $Et_3SiH$ (24) | 8.0 | Benzene (8) | 135 (sealed tube) | 60 | 63 +$Hg^0$ (25) | | $Et_3SiCHFCO_2Me$ (72%) |

that the extrusion of $FCCO_2R$ from $PhHgCFXCO_2R$ compounds should occur more readily. Previous work in these laboratories had shown that thermolytic elimination of fluorocarbenes is much more favorable than elimination of the analogous chloro- or bromocarbenes.[7,8]

## Results and Discussion

**Mercurial Synthesis.**—Phenyl(fluorochlorocarbomethoxymethyl)mercury could be prepared by a variation of our route to phenyl(trihalomethyl)mercury compounds[10] (eq 1). It was found essential to neutralize the reaction mixture at low temperature with dilute HCl. When this step was omitted, no product could be isolated. Application of this procedure to the reaction of phenylmercuric chloride, ethyl bromofluoroacetate, and potassium *tert*-butoxide gave the desired $PhHgCFBrCO_2C_2H_5$ in only 8% yield.

$$PhHgCl + HCClFCO_2CH_3 \xrightarrow[THF/-60°]{1.5\ t\text{-BuOK}} \xrightarrow{HCl\text{-}H_2O} PhHgCClFCO_2CH_3\ (44\%) + t\text{-BuOH} + KCl \quad (1)$$

A second route to such mercurials is based on some results of Knunyants and his coworkers,[11] who reported that halogenated vinyl ethers could be mercurated (eq 2) to give a mixture of products. We found that this mixture, isolated as a heavy oil, could be converted cleanly into the desired product, $PhHgCFClCO_2Et$, by a substituent redistribution reaction with diphenylmercury. After filtration of the phenylmercuric chloride which had formed, phenyl(fluorochlorocarbomethoxymethyl)mercury was isolated in good yield. A similar approach was used in the preparation of $PhHgCFBrCO_2Et$ (Scheme I).

All three of these mercurials are stable, crystalline solids and were found to transfer $FCCO_2R$ to appropriate carbenophiles.

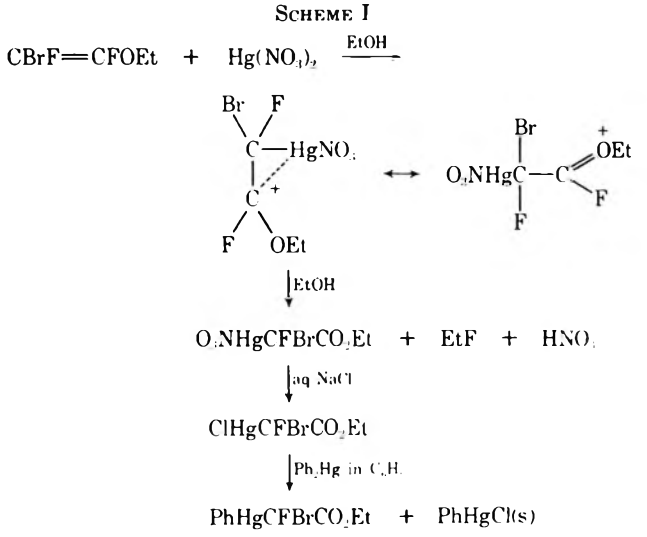
**Divalent Carbon Transfer Chemistry.**—When a cyclooctene solution of $PhHgCFClCO_2Et$ was heated at

$$EtOCF{=}CFCl + Hg(NO_3)_2 \xrightarrow{EtOH} \xrightarrow{aq\ NaCl} Hg(CFClCO_2Et)_2 + ClHgCFClCO_2Et \quad (2)$$

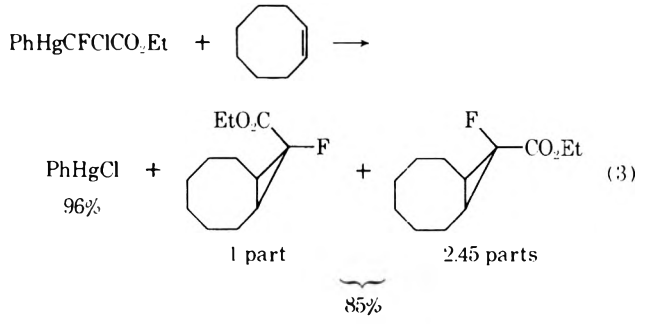
(10) D. Seyferth and R. L. Lambert, Jr., *J. Organometal. Chem.*, **16**, 21 (1969).

(11) V. R. Polishchuk, L. S. German, and I. L. Knunyants, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2024 (1971).

SCHEME I




144° under nitrogen for 36 hr, transfer of $FCCO_2Et$ to the olefin occurred in high yield (eq 3). Precipitation




of phenylmercuric chloride did not occur until the reaction mixture was cooled. Further experiments with other olefins established the generality of this transfer reaction. Rather similar reactivity was exhibited by $PhHgCFClCO_2CH_3$. These reactions are summarized in Table I. Although better product yields were obtained when no diluent such as benzene was used, reactions in which benzene was present also gave reasonably good results. Both of these mercurials inserted their respective divalent carbon species into the Si–H bond of triethylsilane in good yield (eq 4), but attempted

$$PhHgCFClCO_2R + Et_3SiH \longrightarrow Et_3SiCHFCO_2R + PhHgCl \quad (4)$$

$FCCO_2Et$ insertion into C–H bonds known to be quite reactive to $CCl_2$ (cumene and tetrahydrofuran)[12] was not successful.

The reaction conditions required for $FCCO_2R$ transfer from $PhHgCFClCO_2R$ compounds, 2–3 days at 135–145°, were rather severe. Since the elimination of PhHgX from $PhHgCCl_2X$ compounds becomes more facile as X is changed from Cl to Br to I,[13] it was expected and found that $FCCO_2Et$ transfer proceeds more readily from $PhHgCFBrCO_2Et$ than from $PhHgCFClCO_2Et$. Thus a reaction of the former with cyclooctene (1:3 molar ratio) in benzene medium at 125° gave 9-fluoro-9-carboethoxybicyclo[6.1.0]nonane in 74% yield and phenylmercuric bromide in 83% yield after only 20 hr. Other reactions are summarized in Table II. Phenyl(fluorobromocarboethoxymethyl)-mercury also reacted with triethylsilane to insert $FCCO_2Et$ into the Si–H bond, but no C–H insertions (*e.g.*, with cyclooctane and 2,5-dihydrofuran) were observed. Fluorocarboethoxycarbene addition to a C=N bond also was achieved (eq 5).

$$PhHgCFBrCO_2Et + PhN{=}CCl_2 \longrightarrow PhN(CFCO_2Et)C(Cl_2) + PhHgBr \quad (5)$$

It would be of interest to know the nature of the transfer process involved in these reactions, *i.e.*, whether an $FCCO_2R$ carbene intermediate actually is involved, but the results in hand do not allow an answer to this question. Mechanistic implications cannot be derived from product yield comparisons between the various olefins, and, since many of the reactions were carried out in sealed tubes, even crude rate measurements were not possible. With unreactive substrates (*e.g.*, cumene and cyclooctane), starting mercurial recovery was high after heating times which in the case of reactions with olefins gave high phenylmercuric halide yields. However, this observation also does not help to distinguish between a direct transfer process and one involving a carbene intermediate. In the case of a carbene extrusion process, such starting material recovery can be explained in terms of continual regeneration of starting mercurial by insertion of $FCCO_2R$ into the Hg–X bond of the phenylmercuric halide formed in the extrusion step. Dichlorocarbene extrusion from $PhHgCCl_2Br$ is known to be a reversible process.[14] In the present instance, the reversibility of carbene extrusion was implied by the finding that, when the decomposition of $PhHgCFBrCO_2Et$ was carried out in the presence of 1 molar equiv of phenylmercuric chloride, $PhHgCFClCO_2Et$ was formed in 55% isolated yield, together with phenylmercuric bromide (eq 6). This observation is best rationalized

$$PhHgCFBrCO_2Et + PhHgCl \xrightarrow{PhCl,\ 133^\circ} PhHgCFClCO_2Et + PhHgBr \quad (6)$$

in terms of $FCCO_2Et$ insertion into the Hg–Cl bond of phenylmercuric chloride. The organomercury compound formed, being more stable than the starting mercurial, thus accumulates in the reaction mixture.

The absence of C–H insertion reactions in the chemistry of these new mercurials also provides no mechanistic insight. Insertion reactions of bromocarboethoxycarbene occur in only low yield,[15] and the stabilizing effect of fluorine relative to bromine on a singlet state carbene center should increase the selectivity of the $FCCO_2R$ species sufficiently so as to preclude C–H insertion.

In any event, this limited investigation has shown the $PhHgCFXCO_2R$ reagents to be useful $FCCO_2R$ transfer agents, although the reaction conditions, *ca.* 1 day of heating at 125°, are still rather severe. Since they serve to introduce both a fluorine atom and a reactive functional substituent into the product, they may find useful synthetic applications.

(12) D. Seyferth, J. M. Burlitch, K. Yamamoto, S. S. Washburne, and C. J. Attridge, *J. Org. Chem.*, **35**, 1989 (1970).

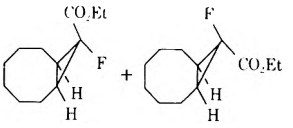
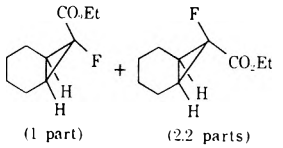
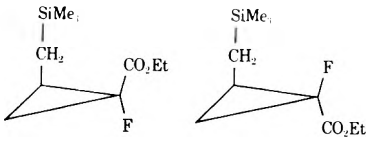
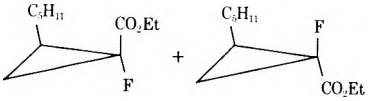
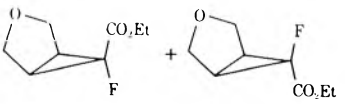
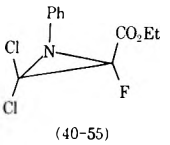
(13) D. Seyferth and C. K. Haas, *J. Organometal. Chem.*, **30**, C38 (1971).

(14) D. Seyferth, J. Y.-P. Mui, and J. M. Burlitch, *J. Amer. Chem. Soc.*, **89**, 4953 (1967).

(15) U. Schöllkopf and M. Reetz, *Tetrahedron Lett.*, 1541 (1969).

TABLE II

FLUOROCARBOETHOXYCARBENE TRANSFER REACTIONS OF PhHgCBrFCO$_2$Et

| Substrate (mmol) | Mmol of mercurial | Solvent (ml) | Reaction temp, °C | Reaction time, hr | Yield PhHgBr, % | Recovered starting material, % | Products (% yield based on starting material consumed) |
|---|---|---|---|---|---|---|---|
|  (21) | 7.0 | Benzene (7) | 125 (sealed tube) | 20 | 83 | |  (1 part) (2.2 parts) (74%) |
|  (21) | 7.0 | Benzene (7) | 125 (sealed tube) | 20 | 80 | |  (1 part) (2.2 parts) (59%) |
| $Me_3SiCH_2CH{=}CH_2$ (18) | 6.0 | Benzene (6) | 135 (sealed tube) | 24 | 86 | |  (1 part) (1.6 parts) (72%) |
| $CH_2{=}CHC_5H_{11}$-*n* (18) | 6.0 | Benzene (6) | 135 (sealed tube) | 24 | 77 | |  (1 part) (2.9 parts) (19%) |
| $Et_3SiH$ (21) | 7.0 | Benzene (7) | 125 (sealed tube) | 20 | 93 | | $Et_3SiCHFCO_2Et$ (74%) |
|  (neat) | 6.0 | Olefin (6) | 125 (sealed tube) | 24 | Mixed with polymer and Hg$^0$ | |  (1 part) (1.3 parts) (*ca.* 15%) |
| $PhN{=}CCl_2$ (6.0) | 6.0 | Benzene (6) | 125 (sealed tube) | 24 | 38 | 36 |  (40-55) |
|  (neat) | 6.0 | Hydrocarbon (6.0) | 135 (sealed tube) | 24 | 68 | | No volatile products |

## Experimental Section

**General Comments.**—All reactions were carried out in flame-dried glassware under an atmosphere of dry nitrogen. Solvents were dried before use. Sealed tube reactions were carried out using a tube oven which was thermostatically controlled to ±2°. Proton nmr spectra were recorded using a Varian Associates T60 or a Hitachi Perkin-Elmer R-20B spectrometer. Chemical shifts are recorded in δ units, parts per million downfield from internal tetramethylsilane. Chloroform or dichloromethane were used as alternative internal standards when necessary. Fluorine nmr spectra were recorded using the R-20B spectrometer with accessory $^{19}$F FR generator (56.446 MHz). Fluorine chemical shifts are reported in parts per million upfield from internal hexafluorobenzene. Infrared spectra were obtained using a Perkin-Elmer Model 257 or 457A grating spectrophotometer. Reactions of the $PhHgCFXCO_2R$ compounds are summarized in Tables I and II. Characterization data for compounds prepared are found in Table III. Two examples of the general techniques used in these reactions are reported in detail. All other reactions followed these procedures, with the exception of those involving $PhN{=}CCl_2$ and PhHgCl as carbenophiles.

**Preparation of the Organomercury Reagents. A. By the Base Procedure.**—A 500-ml, three-necked flask equipped with an addition funnel, paddle stirrer, and Claisen adapter with low-temperature (pentane) thermometer and a nitrogen inlet was charged with 15.65 g (50 mmol) of phenylmercuric chloride, 8.86 g (70 mmol) of methyl fluorochloroacetate,[16] and 100 ml of THF. In the addition funnel was prepared a solution of 7.85 g (70 mmol) of potassium *tert*-butoxide (MSA Research) in 50 ml of THF, precipitated as the alcoholate by addition of 6.6 ml (*ca.* 70 mmol) of *tert*-butyl alcohol.

The reaction mixture was cooled to below −50° in a Dry Ice–

(16) (a) E. R. Larsen, *J. Org. Chem.*, **28**, 1133 (1963). (b) R. S. Corley, J. Lal, and M. W. Kane, *J. Amer. Chem. Soc.*, **78**, 3489 (1956). (c) B. Englund, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, pp 184, 423.

TABLE III

REACTION PRODUCTS

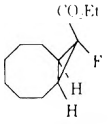
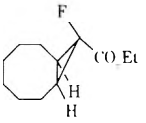
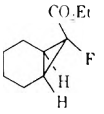
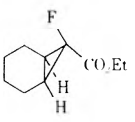
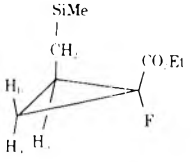
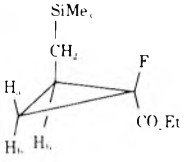
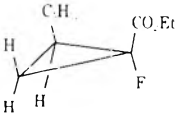
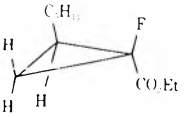
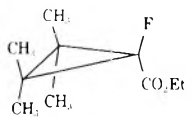
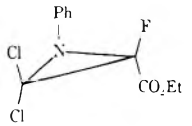
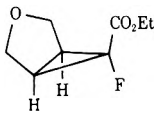
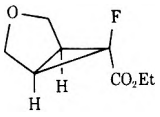
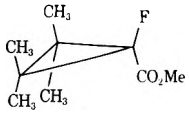
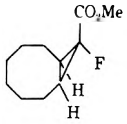
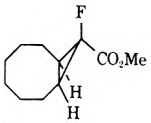
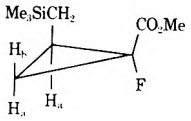
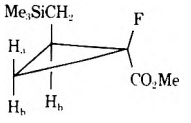
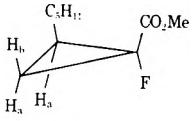
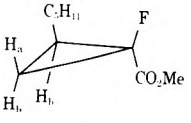
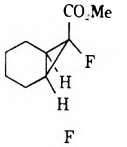
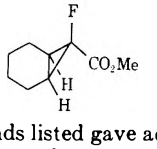
| Registry no. | Structure[a] | $n^{25}D$ | Ir (C=O), cm$^{-1}$ | Nmr ($CCl_4$), δ, ppm | $^{19}F$ nmr, ppm upfield from $C_6F_6$ |
|---|---|---|---|---|---|
| 38204-10-3 |  | 1.4652 | 1732 | 1.13 (t, $J$ = 7 Hz, 3 H, $OCH_2CH_3$)<br>0.75–1.81 (m, 14 H, ring H)<br>4.06 (q, $J$ = 7 Hz, 2 H, $OCH_2CH_3$) | 11.3 (t, $J$ = 23.6 Hz) |
| 38204-09-0 |  | 1.4699 | 1746<br>1729 | 1.13 (t, $J$ = 7 Hz, 3 H, $OCH_2CH_3$)<br>0.93–1.90 (m, 14 H, ring H)<br>4.06 (q, $J$ = 7 Hz, 2 H, $OCH_2CH_3$) | 57.0 (s, br) |
| 38324-35-5 |  | 1.4559 | 1735 | 1.10 (t, $J$ = 7 Hz, 3 H, $OCH_2CH_3$)<br>0.66–1.86 (m, 10 H, ring H)<br>4.03 (q, $J$ = 7 Hz, 2 H, $OCH_2CH_3$) | 10.5 (t, $J$ = 21.5 Hz) |
| 38204-11-4 |  | 1.4580 | 1744<br>1730 | 1.33 (t, $J$ = 7 Hz, 3 H, $OCH_2CH_3$)<br>1.0–2.2 (m, 10 H, ring H)<br>4.22 (q, $J$ = 7 Hz, 2 H, $OCH_2CH_3$) | 53.2 (s, br) |
| 38204-13-6 |  | 1.4299[b] | 1734 | 0.10 (s, 9 H, $Me_3Si$)<br>0.6–1.8 (complex m, 5 H, $SiCH_2$)<br>1.37 (t, $J$ = 7 Hz, 3 H, $OCH_2CH_3$)<br>4.19 (q, $J$ = 7 Hz, 2 H, $OCH_2CH_3$) | 14.6 (t of d, $J_{F-H_a}$ = 18.7 Hz, $J_{F-H_b}$ = 8.5 Hz) |
| 38204-12-5 |  | 1.4302[b] | 1749<br>1733 | 0.14 (s, 9 H, $Me_3Si$)<br>0.7–1.7 (complex m, 5 H, $SiCH_2$)<br>1.36 (t, $J$ = 7 Hz, 3 H, $OCH_2CH_3$)<br>4.18 (q, $J$ = 7 Hz, 2H, $OCH_2CH_3$) | 45.0 (d of t, $J_{F-H_a}$ = 15.2 Hz, $J_{F-H_b}$ = 5.6 Hz) |
| 42086-83-9 |  | 1.4267 | 1733 | 0.40–1.56 (m, 14 H, alkyl and ring H)<br>1.15 (t, $J$ = 7 Hz, 3 H, $OCH_2CH_3$)<br>4.08 (q, $J$ = 7 Hz, 2 H, $OCH_2CH_3$) | 21.7 (complex m) |
| 42086-84-0 |  | 1.4271 | 1751<br>1732 | 0.43–1.43 (m, 14 H, alkyl and ring H)<br>1.10 (t, $J$ = 7 Hz, 3 H, $OCH_2CH_3$)<br>4.01 (q, $J$ = 7 Hz, 2 H, $OCH_2CH_3$) | 46.1 (complex m, approximates a doublet of triplets) |
| 38204-14-7 | $Et_3SiCHFCO_2Et$ | 1.4354 | 1752<br>1719 | 0.42–1.2 (m, 15 H, $Et_3Si$)<br>1.25 (t, $J$ = 7 Hz, 3 H, $OCH_2CH_3$)<br>4.06 (q, $J$ = 7 Hz, 2 H, $OCH_2CH_3$)<br>4.82 (d, $J$ = 47.2 Hz, 1 H, $SiCHFCO_2$–) | 64.0 (d, $J$ = 48 Hz) |
| 42117-05-5 |  | 1.4307 | 1731 | 1.16 (s, 6 H, $Me_2$)<br>1.21 (s, 6 H, $Me_2$)<br>1.33 (t, $J$ = 7 Hz, 3 H, $OCH_2CH_3$)<br>4.18 (q, $J$ = 7 Hz, 2 H, $OCH_2CH_3$) | |
| 42117-06-6 |  | 1.5190 | 1761 | 1.35 (t, $J$ = 7 Hz, 3 H, $OCH_2CH_3$)<br>4.34 (q, $J$ = 7 Hz, 2 H, $OCH_2CH_3$)<br>6.7–7.5 (m, 5 H, Ph) | |

TABLE III
(*Continued*)

| Registry no. | Structure[a] | $n^{25}D$ | Ir (C=O), $cm^{-1}$ | Nmr ($CCl_4$), δ, ppm | $^{19}F$ nmr, ppm upfield from $C_6F_6$ |
|---|---|---|---|---|---|
| 42086-85-1 |  | 1.4408 | 1742 | 1.35 (t, $J$ = 7 Hz, 3 H, $OCH_2CH_3$)<br>2.1 and 2.4 (c of m, $J_{HF}$ = 18 Hz, 2 H, cyclopropyl H)<br>3.6–4.1 (m, 4 H, ring H)<br>4.24 (q, $J$ = 7 Hz, 2 H, $OCH_2CH_3$) | 24.9 (t, $J_{HF}$ = 18 Hz) |
| 42086-86-2 |  | 1.4492 | 1750<br>1736 | 1.37 (t, $J$ = 7 Hz, 3 H, $OCH_2CH_3$)<br>2.25–2.45 (m, 2 H, cyclopropyl H)<br>4.10 (m, 4 H, ring H)<br>4.27 (q, $J$ = 7 Hz, 2 H, $OCH_2CH_3$) | 62.2 (t, $J$ = 3.2 Hz) |
| 42117-08-8 |  | 1.4315 | 1735 | 1.0–1.2 (m, 12 H, $Me_4$)<br>3.75 (s, 3 H, $OCH_3$) | 36.5 (s, br, some fine splitting to Me) |
| 42117-09-9 | $Et_3SiCHFCO_2Me$ | 1.4362 | 1754<br>1727 | 0.44–1.22 (m, 15 H, $Et_3Si$)<br>3.62 (s, 3 H, $OCH_3$)<br>4.84 (d, $J_{HF}$ = 47.5 Hz, 1 H, $SiCHFCO_2$–) | 64.9 (d, $J_{HF}$ = 47.9 Hz) |
| 42086-87-3 |  | 1.4691 | 1737 | 0.93–1.93 (m, 14 H, ring)<br>3.75 (s, 3 H, $OCH_3$) | 14.2 (t, $J_{FH}$ = 21.1 Hz) |
| 42086-88-4 |  | 1.4727 | 1751<br>1735 | 0.93–2.08 (m, 14 H, ring)<br>3.75 (s, 3 H, $OCH_3$) | 60.0 (s, br) width at half height = 11 Hz |
| 42086-89-5 |  | 1.4372 | 1753 (sh)<br>1738 | 0.05 (s, 9 H, $Me_3Si$)<br>0.56–1.70 (m, 5 H, $SiCH_2$-c-$C_3H_5$)<br>3.80 (s, 3 H, $OCH_3$) | 25.4 (t of d, $J_{FH_a}$ = 19, $J_{FH_b}$ = 8.5–10 Hz) |
| 42086-90-8 |  | 1.4330 | 1756<br>1738 | 0.08 (s, 9 H, $Me_3Si$)<br>0.41–1.61 (m, 5 H, $SiCH_2$-c-$C_3H_5$)<br>3.77 (s, 3 H, $OCH_3$) | 48.0 (d of t, $J_{FH_a}$ = 17, $J_{FH_b}$ = 5.3 Hz) |
| 42086-91-9 |  | 1.4242 | 1754 (sh)<br>1740 | 0.61–1.83 (m, 14 H, ring and chain H)<br>3.80 (s, 3 H, $OCH_3$) | 25.3 (complex m, approximates a t of d, $J_{FH_a}$ = 19, $J_{FH_b}$ = 7 Hz) |
| 42086-92-0 |  | 1.4262 | 1756<br>1739 | 0.66–1.66 (m, 14 H, ring and chain H)<br>3.78 (s, 3 H, $OCH_3$) | 50.2 (complex m, approximates a d of t, $J_{FH_a}$ = 18, $J_{FH_b}$ = 5.3 Hz) |
| 42086-93-1 |  | 1.4580 | 1738<br>1732 (sh) | 1.0–2.1 (m, 10 H, ring H)<br>3.80 (s, 3 H, $OCH_3$) | 10.9 (t, $J_{FH}$ = 21.5 Hz) |
| 42086-94-2 |  | 1.4604 | 1752<br>1748<br>1735 | 3.75 (s, 3 H, $CCH_3$) | 54.2 (s, br, width at half height = 13 Hz) |

[a] All compounds listed gave acceptable (±0.3%) carbon and hydrogen analyses. In those cases where two geometrical isomers were formed, the mixture of isomers was analyzed. [b] Refractive index of material *ca.* 95% pure, contaminated with its epimer.

acetone bath, and the solvated butoxide was added over a 15-min period, keeping the temperature below −50° at all times. The resulting clear solution was stirred at −50° for 30 min, then was poured into 500 ml of cold water containing 6 ml (70 mmol) of concentrated HCl, to give a milky white, two-phase system. The mixture was extracted with 500 ml of chloroform. The chloroform was removed on a rotary evaporator to give a white, crystalline residue, which was slurried in 100 ml of chloroform and

filtered to remove phenylmercuric chloride. A 100-ml portion of hexane was added, precipitating a small additional amount of phenylmercuric chloride. The solution was placed in a freezer overnight. Filtration gave, in two crops, 8.9 g (22 mmol, 44%) of $PhHgCFClCO_2CH_3$. Material recrystallized twice from 1:1 chloroform–hexane gave a constant melting point of 115–117°.

The following analytical data support the assigned structure: nmr ($CDCl_3$) $\delta$ 7.41 (m, 5 H, $C_6H_5$) and 3.96 ppm (s, 3 H, $OCH_3$); ir ($CCl_4$) 3080 (w), 1965 (w), 1764 (vs), 1733 (vs), 1483 (w), 1434 (m), 1280 (vs), 1240 (sh), 1070 (m, br), 1028 (w), and 700 $cm^{-1}$ (m).

*Anal.* Calcd for $C_9H_8ClFO_2Hg$: C, 26.81; H, 2.00. Found: C, 26.81; H, 2.05.

Essentially the same procedure was used in the reaction of 30 mmol of phenylmercuric chloride with 6.61 g (35.6 mmol) of ethyl bromofluoroacetate[17] and 35 mmol of *t*-BuOK–*t*-BuOH in 150 ml of THF at −50° for 1 hr. The same work-up procedure gave, upon crystallization from 1:1 chloroform–hexane, 1.10 g (8%) of $PhHgCFBrCO_2Et$: mp 111–114° (two further recrystallizations gave a constant melting point of 113–115°); nmr ($CDCl_3$) $\delta$ 1.35 (t, $J$ = 7 Hz, 3 H, $OCH_2CH_3$), 4.26 (q, $J$ = 7 Hz, 2 H, $OCH_2$–), and 7.15 ppm (m, 5 H, Ph); $^{19}F$ nmr (acetone) 36.9 ppm downfield from internal $C_6F_6$ (s, with Hg satellites, $J_{F-Hg}$ = 565 Hz); ir ($CCl_4$) 3075 (w), 3060 (w), 2989 (m), 2960 (w), 1753 (s), 1722 (vs), 1487 (w), 1465 (w), 1432 (m), 1385 (w), 1368 (w), 1295 (m), 1265 (sh), 1246 (vs, br), 1170 (w), 1091 (m), 1070 (sh), 1058 (s), 1035 (sh), 1026 (sh), 1000 (w), 911 (w), 860 (w), 700 (s), 618 $cm^{-1}$ (m).

*Anal.* Calcd for $C_{10}H_{10}BrFO_2Hg$: C, 26.01; H, 2.18; Br, 17.31. Found: C, 25.93; H, 2.18; Br, 17.57.

**B. By the Olefin Mercuration Procedure. 1. Phenyl(fluorochlorocarboethoxymethyl)mercury.**—A 250-ml three-necked flask equipped with an addition funnel and a magnetic stirring bar was charged with 32.5 g (0.10 mol) of mercuric nitrate (Merck, reagent) and 40 ml of absolute ethanol. From the addition funnel was added 15.0 g (0.118 mol) of ethyl 2-chloro-1,2-difluorovinyl ether.[18] The mercuric nitrate dissolved with heat evolution. The resulting solution was stirred for 1 hr and then was poured into a solution of 27.1 g (0.1 mol) of mercuric chloride in 600 ml of distilled water. A dense white oil separated. Extraction with chloroform followed by drying and removal of solvent gave 35.0 g of a dense, light yellow oil. The oil was diluted to 100.0 ml with benzene.

A solution of 3.54 g (10.0 mmol) of diphenylmercury in 40 ml of benzene in an erlenmeyer flask was "titrated" with the above solution until phenylmercuric chloride no longer precipitated. The end point was reached after addition of 15.0 ml of this solution. Filtration of the resulting mixture gave 3.16 g (10.0 mmol, 100%) of phenylmercuric chloride, mp 254–256°. Solvent was removed from the filtrate to give a white powder which was washed with hexane and suction filtered to give 3.77 g of material, mp 98–105°. Recrystallization two times from methylene chloride–hexane gave material of constant mp 101–105°, which was identified as phenyl(chlorofluorocarboethoxymethyl)mercury (9.05 mmol, 90%) on the basis of the following data: nmr ($CDCl_3$) $\delta$ 1.33 (t, $J$ = 7 Hz, 3 H, $OCH_2CH_3$), 4.35 (q, $J$ = 7 Hz, 2 H, $OCH_2CH_3$), and 7.13–7.47 ppm (m, 5 H, Ph); $^{19}F$ nmr (acetone) 39.9 ppm downfield from internal $C_6F_6$ (s, with Hg satellites, $J_{F-Hg}$ = 578 Hz); ir ($CCl_4$) 3070 (w), 3060 (w), 2985 (m), 2905 (w), 1758 (vs), 1730 (vs), 1432 (w), 1371 (w), 1300 (sh), 1268 (vs), 1239 (s), 1070 (s, br), 1030 (m), 730 (s), 700 (m), 672 (w), and 679 $cm^{-1}$ (w).

*Anal.* Calcd for $C_{10}H_{10}ClFO_2Hg$: C, 28.78; H, 2.42; Cl, 8.50. Found: C, 28.80; H, 2.55; Cl, 8.78.

Based upon the stoichiometry used, the overall yield of the title mercurial was 67 mmol (67%). The originally obtained mercuration product is thought to consist of a mixture of $ClHgCClFCO_2Et$ and $Hg(CClFCO_2Et)_2$, based upon its nmr spectrum, which showed two overlapping quartets assigned to the $CH_2$ resonance of the ethyl group.

**2. Phenyl(fluorobromocarboethoxymethyl)mercury.**—The required starting material, ethyl 2-bromo-1,2-difluorovinyl ether, was prepared in a two-step sequence from bromotrifluoroethylene.

A 250-ml three-necked flask equipped with a magnetic stirrer, a gas addition tube extending to the bottom of the flask, and a Dewar condenser was charged with 100 ml of absolute ethanol and 2.3 g (0.1 mol) of sodium. When the sodium had dissolved, the flask was cooled in an ice bath, and a total of 41.5 g (0.26 mol) of bromotrifluoroethylene was distilled into the stirred sodium ethoxide solution. When bromotrifluoroethylene no longer condensed on the cold finger, the reaction mixture was poured into 250 ml of cold water, separating a dense, yellow liquid. The aqueous layer was extracted with two 25-ml portions of methylene chloride, which were combined with the organic layer, washed with cold water, dried over anhydrous magnesium sulfate, and distilled. A fraction boiling at 102–107.5° (47.5 g, 0.25 mol, 96%) was collected (lit.[17] bp 108°) and identified as 2-bromo-1,1,-2-trifluoroethyl ethyl ether: $n^{25}D$ 1.3707 (lit.[17] $n^{20}D$ 1.375); nmr ($CCl_4$) $\delta$ 1.35 (t, $J$ = 7 Hz, 3 H, $OCH_2CH_3$), 4.07 (q, $J$ = 7 Hz, 2 H, $OCH_2CH_3$), and 6.29 ppm (d of t, $J_{F-H_{gem}}$ = 48 Hz, $J_{F-H_\alpha}$ = 5 Hz, 1 H, $CHFBrCF_2$–); ir (thin film) 3000 (m), 2949 (w), 2930 (w), 2884 (w), 1485 (w), 1448 (w), 1412 (sh), 1380 (s), 1361 (s), 1307 (s, br), 1276 (s), 1254 (w), 1217 (vs, br), 1195 (s, br), 1149 (w), 1085 (vs, br), 1051 (vs, br), 1025 (sh), 936 (w), 912 (sh), 900 (m), 830 (m), 755 (s), 737 (s), and 681 $cm^{-1}$ (w).

A 250-ml three-necked flask equipped with a paddle stirrer and an addition funnel was charged with 13.4 g (120 mmol) of potassium *tert*-butoxide (MSA Research) and 30 ml of *n*-decane. From the addition funnel was added 20.7 g (100 mmol) of 2-bromo-1,1,2-trifluoroethyl ethyl ether over a 5-min period. A pale yellow color developed, and the mixture became somewhat viscous. The reaction was mildly exothermic. The addition funnel was immediately replaced with a 6-in. Vigreux column and stillhead, an additional 10 ml of *n*-decane was added to aid stirring, and the mixture was heated to distil out volatiles. Two low-boiling fractions (I, 81–83°, and II, 83–90°) were examined by glc and found to contain principally *tert*-butyl alcohol. A third fraction (91–101°) was virtually pure 1-bromo-1,2-difluorovinyl ethyl ether (7.82 g, 42 mmol, 42%), and a fourth fraction, 101–115°, was found to contain the 1-bromo-1,2-difluorovinyl ethyl ether and *n*-decane. Both of the higher boiling fractions were suitable for use in the preparation of bromofluorocarboethoxymethylmercuric chloride. The infrared spectrum of a portion of fraction III was identical with that of an authentic sample of the ether prepared previously and characterized on the basis of the following analytical data: nmr ($CCl_4$) (mixed cis and trans) $\delta$ 1.41 (t, $J$ = 7 Hz, 3 H, $OCH_2CH_3$) and 4.03 and 4.05 ppm [2 t, $J$ = 7 Hz, 2 H (combined), $OCH_2CH_3$]; ir (thin film) 3000 (m), 2919 (w), 1867 (vs), 1743 (s), 1480 (w), 1445 (w), 1395 (w), 1377 (m), 1275 (vs), 1251 (sh), 1196 (s), 1165 (vs), 1110 (m), 1070 (vs), 1048 (sh), 1027 (s), 996 (m), 985 (sh), 880 (s, br), and 690 $cm^{-1}$ (m); $n^{25}D$ (mixture of isomers, as obtained) 1.3961.

*Anal.* Calcd for $C_4H_5BrF_2O$: C, 25.69; H, 2.70; Br, 42.74. Found (mixed isomers): C, 25.61; H, 2.73; Br, 42.93.

The preparation of the mercurial then was accomplished as follows.

A 250-ml three-necked flask equipped with an addition funnel and a paddle stirrer was charged with 13.0 g (40 mmol) of mercuric nitrate and 60 ml of absolute ethanol. From the addition funnel was added 7.8 g (42 mmol) of ethyl 2-bromodifluorovinyl ether over a 5-min period. The mixture became homogeneous, and a yellow color appeared. Cooling was required to moderate the reaction. The solution was stirred for 10 min at 0°, then 2.34 g (40 mmol) of NaCl in 50 ml of water was added. The mixture became cloudy. The mixture was poured into an additional 100 ml of water and extracted with two 200-ml portions of chloroform. Filtration removed a small amount of yellow powder, leaving a colorless, homogeneous solution. The solvent was removed on a rotary evaporator and the oily white residue was taken up in benzene and diluted to 50.0 ml. A 3.54-g (10.0 mmol) portion of diphenylmercury in 40 ml of benzene was "titrated" with the mercurial solution. After addition of 24 ml of the latter, a precipitate of phenylmercuric chloride no longer appeared on addition of 1 drop of the solution. The remaining 26 ml of solution was added to another 10 mmol of diphenylmercury, and the mercurial slurries were combined and filtered to give 6.20 g (19.8 mmol) of phenylmercuric chloride (99%), mp 256°. The filtrate was concentrated on a rotary evaporator, then precipitated by addition of cold hexane, giving 9.0 g (19.5 mmol) of the title mercurial, mp 113–115° (49% based on starting mercuric nitrate).

The spectroscopic properties of this product were identical with those of the material obtained by the base reaction (see above).

**Reaction of Phenyl(fluorochlorocarboethoxymethyl)mercury with Cyclooctene.**—A 100-ml three-necked flask equipped with a reflux condenser, a thermometer, and a magnetic stirring bar was charged with 5.0 g (12.0 mmol) of the mercurial and 20 ml (*ca.*

(17) R. N. Haszeldine, *J. Chem. Soc.*, 4259 (1952).

(18) S. Dixon, *J. Org. Chem.*, **21**, 400 (1956).

150 mmol) of cyclooctene. The mixture was heated to reflux, becoming homogeneous at *ca.* 100°. Heating was continued at 143–145° for 36 hr. On cooling, the flask was filled with a precipitate of phenylmercuric chloride. The mixture was filtered to give 3.63 g (11.6 mmol, 96%) of phenylmercuric chloride, mp 255–261°. Glc examination of the filtrate indicated the presence of two products (MIT isothermal glc, 4 ft SE-30, 142°). A portion of the filtrate was saved for analysis and the remainder was distilled *in vacuo* in two fractions: I, 0.04 mm, to room temperature; II, 0.04 mm, 61–65°. Fraction II was analyzed by glc and found to contain two products: A, minor product, retention time 4.2 min; B, major product, retention time 5.5 min. They were separated by preparative glc (F & M 720, 6 ft DC-200, 180°) and identified as 9-*exo*-fluoro-9-*endo*-carboethoxybicyclo[6.1.0]nonane (A) and 9-*endo*-fluoro-9-*exo*-carboethoxybicyclo[6.1.0]nonane (B) on the basis of the analytical data shown in Table III.

Fraction II (2.07 g) contained no other products; thus the distilled yield of mixed isomers of 9-fluoro-9-carboethoxybicyclo[6.1.0]nonane was 9.67 mmol (80%). Glc yield analysis indicated the overall yield to be 85%. The products were formed in a ratio of 1:2.45 in order of elution on glc.

The assignment of structure for the two isomers is based on the fact that in fluorocyclopropanes, $J_{HF}$ (cis) > $J_{HF}$ (trans).[19] Thus, the $^{19}F$ nmr spectrum of A appeared as a triplet, $J_{HF}$ = 23.6 Hz, at 11.3 ppm upfield from internal hexafluorobenzene, while the corresponding fluorine signal of B appeared as a broadened singlet at 57.0 ppm, with a width at half height of 8.5 Hz.[20] The limit for $J$ in this system thus becomes 4.25 Hz. Precedent for such assignments may be found, for example, in the case of 7-phenyl-7-fluoronorcarane.[21]

**Reaction of Phenyl(chlorofluorocarboethoxymethyl)mercury with Cyclohexene.**—A heavy-walled Pyrex tube (flame dried and flushed with nitrogen) was charged with 5.0 g (12.0 mmol) of the mercurial and 20 ml of cyclohexene. It was evacuated to *ca.* 0.5 mm and sealed. The sealed tube was heated in a tube oven at 133° for 24 hr with occasional agitation. When removed from the oven, the contents of the tube were homogeneous, but on cooling, the tube was filled with a precipitate. Filtration of the reaction mixture gave a white, crystalline solid, mp 255–258°, identified as phenylmercuric chloride (2.97 g, 9.5 mmol, 79%), and traces of elemental mercury. A portion of the filtrate was saved for yield analysis, and the remainder was distilled *in vacuo* in two fractions: I, 0.04 mm, to room temperature; II, 0.04 mm, 37–43°. Glc analysis of fraction II (F & M 5750, 4 ft UCW 98, 145°) showed six products. However, two of these accounted for *ca.* 88% of the fraction. These were separated by preparative glc (F & M 720, 6 ft DC-200, 155°) and identified as the two isomers of 7-fluoro-7-carboethoxybicyclo[4.1.0]heptane on the basis of the analytical data shown in Table III. Crystallization of the pot residue from distillation from hexane gave 0.95 g (*ca.* 19%) of starting mercurial. Glc yield analysis (MIT isothermal glc, SE-30, 142°) indicated the overall yield of 7-fluoro-7-carboethoxybicyclo[4.1.0]heptane to be 69%, based on starting mercurial consumed.

**Reaction of Phenyl(fluorobromocarboethoxymethyl)mercury with *N*-Phenyliminophosgene.**—A reaction of 6 mmol of the mercurial with 1.04 g (6 mmol) of PhN=$CCl_2$ in 6 ml of dry benzene was carried out in a sealed tube at 125° for 24 hr. After the tube had been opened, filtration removed 0.82 g (38%) of phenylmercuric bromide, mp 276–278°, from the light yellow solution. Glc examination of the filtrate showed the presence of PhN=$CCl_2$ (47%) and a higher boiling product. Vacuum distillation removed the solvent and the unconverted PhN=$CCl_2$. The pot residue was dissolved in ether and treated with a small amount of hexane to precipitate 0.6 g (22%) of starting mercurial. The remaining material was chromatographed on a small silicic acid column. The first fraction to elute (using 1:1 v/v hexane–dichloromethane) was a colorless oil which was purified by preparative glc (F & M 700, 6 ft UCW 98, 175°) and identified as 1-phenyl-2,2-dichloro-3-fluoro-3-carboethoxyaziridine (Table III). Its yield, estimated by glc, was *ca.* 50%. The second fraction to elute crystallized upon removal of solvent to give another 0.4 g of PhHgCFBrCO$_2$Et, making a total recovery of 36%.

**Reaction of Phenyl(fluorobromocarboethoxymethyl)mercury with Phenylmercuric Chloride.**—A 50-ml flask equipped with a magnetic stirring bar and a reflux condenser with a nitrogen inlet tube was charged with 2.13 g (4.6 mmol) of the mercurial, 1.45 g (4.6 mmol) of phenylmercuric chloride, and 10 ml of dry chlorobenzene. The mixture was stirred and heated at reflux for 4 hr. As the reflux temperature was reached, the reaction mixture became homogeneous, and as the heating period progressed, gradual precipitation of a flaky white solid was observed. The mixture was cooled and filtered to leave 1.87 g of white solid, mp 271–277°, assumed to be mostly PhHgBr containing some PhHgCl. The filtrate was evaporated. Addition of pentane to the residue and refrigeration produced 1.06 g of white solid, mp 99–101°, identified as PhHgCFClCO$_2$Et (ir and nmr). The absence of significant amounts of PhHgCFBrCO$_2$Et was indicated by the absence of the Br–C stretch at 618 cm$^{-1}$. Recrystallization raised the melting point to 101–105°.

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**Registry No.**—PhHgCFClCO$_2$Et, 38204-06-7; PhHgCFClCO$_2$Me, 42117-02-2; PhHgCBrFCO$_2$Et, 42117-03-3; phenylmercuric chloride, 100-56-1; methyl fluorochloroacetate, 433-52-3; ethyl bromofluoroacetate, 401-55-8; ethyl 2-chloro-1,2-difluorovinyl ether, 401-54-7; 2-bromo-1,1,2-trifluoroethyl ethyl ether, 380-78-9; cyclooctene, 931-88-4; cyclohexene, 110-83-8; 2,3-dimethyl-2-butene, 563-79-1; trimethylallylsilane, 762-72-1; 1-heptene, 592-76-7; triethylsilane, 617-86-7.

(19) K. L. Williamson, Y.-F. Li, F. H. Hall, and S. Swager, *J. Amer. Chem. Soc.*, **88**, 5678 (1966).

(20) The half-height width of a singlet may be taken as the limiting value approached by 2$J$ for the same peak interpreted as a poorly resolved 1:2:1 triplet.

(21) T. Ando, Y. Kotoku, H. Yamanaka, and W. Funusaka, *Tetrahedron Lett.*, 2479 (1968).

# Reactions of Some α- and β-Substituted Styrenes in the Presence of Ethylaluminum Dichloride[1]

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The reaction of 0.1 equiv of EADC under mild conditions on some styrene derivatives gives rise mainly to the formation of indan-type cyclic dimers and in some cases also cyclic trimers. The initially formed carbonium ion can simultaneously also lead by different pathways to products derived from alkylation of the aromatic solvent or to a reduced hydrocarbon. The latter is not a catalytic process as it consumes 1 equiv of the reagent to liberate ethylene.

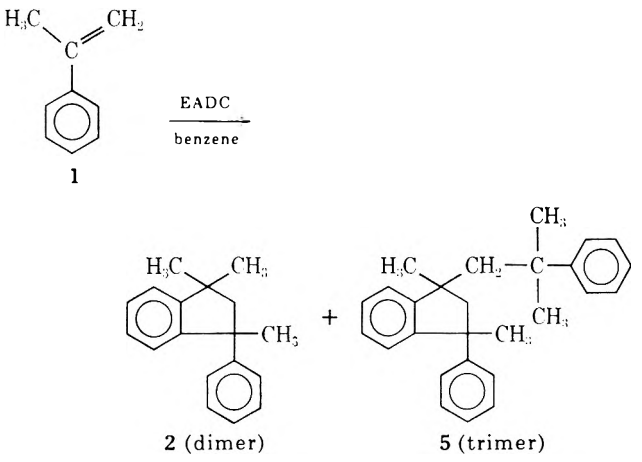
It has been found in our laboratory[2] that EADC acts as a very potent catalyst in the cycloalkylation of benzene, giving rise to cycloalkylbenzenes in almost quantitative conversion in a few minutes at room temperature. In this reaction, the EADC functions in catalytic amounts as a Lewis acid in a typical Friedel–Crafts alkylation.

It has also been known that some styrene derivatives undergo a cyclodimerization reaction to form saturated indan-type derivatives when treated with acids or Lewis acids. Thus Bergmann, *et al.*,[3] showed that by the action of an acid and a Lewis acid on α-methylstyrene (**1**) the saturated dimer 1,1,3-trimethyl-3-phenylindan (**2**) is obtained. Similarly, 1,1-diphenylethylene (**3**) gave 1,3,3-triphenyl-1-methylindan (**4**) as saturated dimer.[4]

In a recent communication,[5] Alberola has shown that styrene and some styrene derivatives like α-methylstyrene, β-methylstyrene, 1,1-diphenylethylene, or 1,1-diphenylpropene-1 undergo a hydroalumination reaction in 70–90% yield when carried out in benzene solution at 80° in the presence of an equivalent amount of diethylaluminum chloride (DEAC). Hydrolysis of the organometallic intermediate gave rise to the corresponding alkane.[6] An intramolecular hydride ion shift from the ethyl group of the reagent accompanied by a release of ethylene was shown to have taken place. Similar results were obtained by the action of ethylaluminum dichloride (EADC).

The above results prompted us to repeat Alberola's experiment on α-methylstyrene. In fact we carried out the reaction on a benzene solution of **1** in the presence of EADC under both "drastic" and "mild" conditions. Under the drastic conditions we tried to follow as closely as possible the conditions used by Alberola, *i.e.*, 1 equiv of EADC under reflux in benzene for 5 hr. Under the mild conditions we allowed only 0.1 equiv of EADC to react for 5 min at room temperature. In both cases the main products obtained by us were the substituted indan-type dimer **2** and trimer 1,3-dimethyl-1-(2′-methyl-2′-phenylpropyl)-3-phenylindan (**5**) as given in Scheme I.

SCHEME I




The reaction of α-methylstyrene with EADC yielded dimers and trimers in different proportions depending on temperature, as shown in Table I.

TABLE I

REACTION OF α-METHYLSTYRENE IN BENZENE IN THE PRESENCE OF EADC AT VARIOUS TEMPERATURES

| Temp, °C | 4[a] | 25[a] | 80[b] |
|---|---|---|---|
| Cyclic dimer[c] **2**, % | 37 | 52 | 73 |
| Cyclic trimer[c] **5**, % | 55 | 28 | 13 |

[a] EADC, 0.1 equiv. [b] EADC, 1 equiv. [c] The yields are calculated from glc curves.

β-Methylstyrene (**6**) similarly gave under mild conditions 46% of the cyclic dimer 1-ethyl-2-methyl-3-phenylindan (**7**) and 17% of the cyclic trimer 1-(3′-phenyl-2′-pentyl)-2-methyl-3-phenylindan (**8**).

Reaction of 1,1-diphenylethylene (**3**) with EADC in benzene yielded under mild conditions 70% of the known cyclic dimer **4** through path A (*vide infra*, Scheme II), 11% of the saturated product 1,1-diphenylethane (**9**) obtained *via* path C, and some higher boiling products. However, under the drastic conditions, the cyclic dimer **4** initially formed underwent a further decomposition reaction to produce a new cyclic product, 1-methyl-3,3-diphenylindan (**10**).

(1) Presented first in Tel-Aviv at the annual meeting of the Israel Chemical Society; *cf.* R. Wolovsky and N. Maoz, Proceedings of the 41st Annual Meeting of the Israel Chemical Society, 1971, p 222.

(2) (a) R. Wolovsky and N. Maoz, *Israel J. Chem.*, **8**, 6p (1970); (b) R. Wolovsky, N. Maoz, and Z. Nir, *Synthesis*, 656 (1970); (c) R. Wolovsky and N. Maoz, Proceedings of the 41st Annual Meeting of the Israel Chemical Society, 1971, p 221.

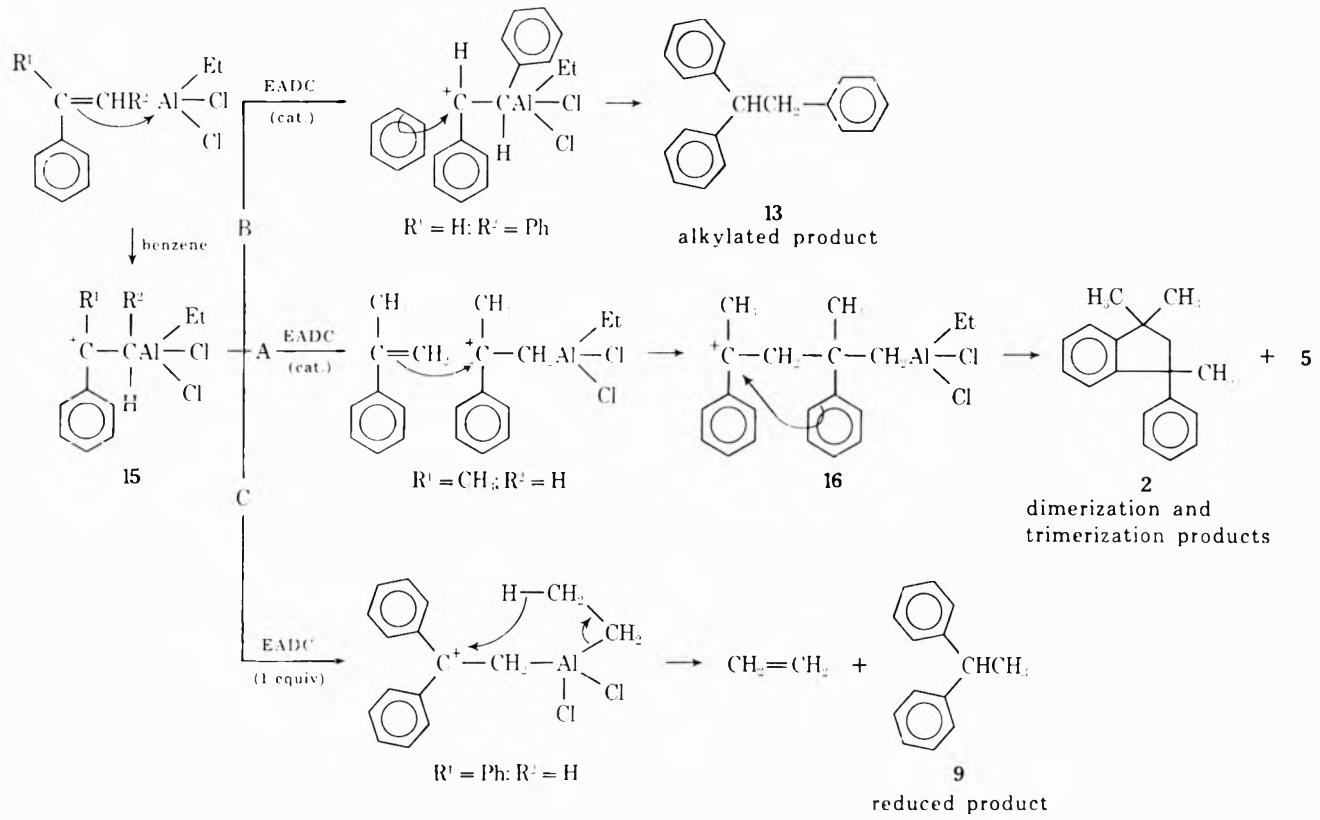
(3) (a) E. Bergmann, H. Taubadel, and H. Weiss, *Chem. Ber.*, **64B**, 1493 (1931); (b) J. C. Petropoulos and J. J. Fischer, *J. Amer. Chem. Soc.*, **80**, 1938 (1958); (c) R. L. McLaughlin, U. S. Patent 3,161,692 (1964); *Chem. Abstr.*, **62**, 9082*d* (1965).

(4) (a) E. Bergmann and H. Weiss, *Justus Liebigs Ann. Chem.*, **480**, 49 (1930); (b) A. G. Evans and D. Price, *J. Chem. Soc.*, 2982 (1959); (c) A. G. Evans and D. Oven, *ibid.*, 4123 (1959); (d) A. G. Evans, E. A. James, and E. D. Oven, *ibid.*, 3532 (1959); (e) A. Uchida, Y. Hamano, Y. Mukai, and S. Matsuda, *Ind. Eng. Chem. Prod. Res. Develop.*, **10**, 372 (1971).

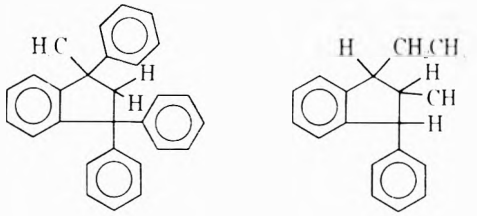
(5) A. Alberola, *Tetrahedron Lett.*, 3471 (1970).

(6) The hydroalumination reaction of butadiene by triisobutylaluminum followed by hydrolysis with methanol to yield 29% of butane in addition to other products was observed in the polymerization reaction under conditions where no solvent was used; *cf.* E. Marcus, D. L. MacPeak, and S. T. Tinsley, *J. Org. Chem.*, **34**, 1931 (1969).

SCHEME II




*trans*-Stilbene (**11**) reacted under mild conditions *via* path A to yield 73% of the cyclic dimer 1-benzyl-2,3-diphenylindan[7] (**12**) as well as 10% of 1,1,2-triphenyl-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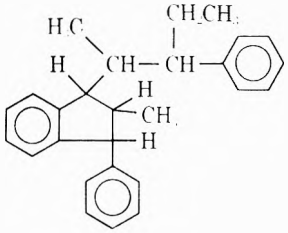
7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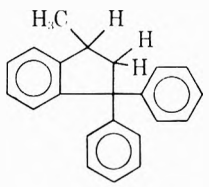
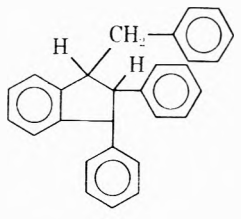

10


12

ethane (**13**) by path B (alkylation of the solvent). *cis*-Stilbene (**14**) reacted similarly to yield 34% of **12** through path A and 47% of **13** *via* path B.

(7) (a) E. Bergmann, D. Winter, and W. Schreiber, *Justus Liebigs Ann. Chem.*, **500**, 122 (1933); (b) G. Montaudo and G. Purrello, *Ann. Chim. (Rome)*, **51**, 865 (1961); *Chem. Abstr.*, **56**, 10021*d* (1962); (c) M. Salzwedel, V. Werner, and D. Schulte-Frohlinde, *Angew. Chem.*, **76**, 989 (1964).

## Experimental Section

**Materials.**—$\alpha$-Methylstyrene, $\beta$-methylstyrene, and *trans*-stilbene were purchased from Fluka, *cis*-stilbene from Koch-Light, and 1,1-diphenylethylene from Eastman. $\alpha$-Methylstyrene was distilled before use; all other starting materials were used as purchased. EADC was obtained from Texas Alkyls as a 20% solution in benzene (1 ml of solution $\cong$1.6 mmole of EADC). Benzene was distilled over sodium before use. All reactions were carried out under a nitrogen atmosphere and the EADC reagent solutions were added with a syringe to the magnetically stirred solutions. The products were checked for their purity by glc.

**Instruments.**—Nmr spectra were taken on a Varian A-60 instrument in $CCl_4$ solution using TMS as an internal standard. The decoupling experiment was carried out on a Bruker HFX-10 instrument operating at 90 MHz. Mass spectra were run on an Atlas CH4 mass spectrometer. A slightly modified Packard Model 7400 series research gas chromatograph, to which an additional heater was added, was used for the glc analyses. A flame ionization detector was used throughout in conjunction with a 1:10 gas splitter for sample collection. Aluminum columns 6 ft $\times$ 0.25 in. o.d. filled with 0.5% OV 17 on Chromosorb W were used; the nitrogen flow rate was 300 ml/min.

**Reaction of $\alpha$-Methylstyrene (1). A. Mild Conditions.**—To a solution of 1.18 g (0.01 mol) of **1** in 30 ml of benzene, 0.64 ml (0.001 mol) of a benzene solution of EADC was added. A red color developed immediately. The reaction mixture was stirred for 5 min at room temperature and terminated by adding a few drops of methanol. The solution was then washed with water and dried over anhydrous sodium sulfate, and the benzene was removed. The remaining oily residue was distilled in a Büchi ball-tube fractionator. The cyclic dimer **2** distilled at 80° (0.1 mm), yielding 0.67 g (57%) of an oil[8] (lit.[9] mp 52°), *m/e* 236, glc retention time 2.3 min (programmed between 60 and 300° at a rate of 30°/min), and the cyclic trimer **5** distilled at 135° (0.1 mm), yielding 0.33 g (28%) of a mixture of isomers, *m/e* 354, retention time 4.5 min.

**B. Drastic Conditions.**—The reaction was carried out as above, but now equimolar quantities of EADC reagent were

(8) R. A. Benkeser, J. Hooz, T. V. Liston, and E. A. Tresillyan, *J. Amer. Chem. Soc.*, **85**, 3984 (1963).

(9) L. M. Adams, R. J. Lee, and F. T. Wadsworth, *J. Org. Chem.*, **24**, 1186 (1959).

used and the mixture was refluxed for 5 hr. The same products as above were obtained but the proportions were different (*cf.* Table I).

*trans*-β-Methylstyrene (6).—To a solution of 1.18 g (0.01 mol) of 6 in 30 ml of benzene, 2 ml (0.0032 mol) of a 20% benzene solution of EADC was added, causing development of a yellowish color. The reaction mixture was stirred for 15 min at room temperature and terminated with methanol as above. The benzene solution was washed, dried, and evaporated. The remaining oil was chromatographed on 150 g of basic Woelm alumina using as eluent increasing proportions of benzene in hexane. There was obtained 0.55 g (47%) of the cyclic dimer[10] 7 as a mixture of isomers, *m/e* 236, retention time 2.4 min (under conditions as above). Then the cyclic trimer 8 (mixture of isomers) was eluted, 0.20 g (17%), *m/e* 354, retention time 4.7 min. Further elution gave mixtures of higher molecular weight products which were not analyzed.

1,1-Diphenylethylene (3). A.—A 1.8-g (0.01 mol) portion of 3 was dissolved in 30 ml of benzene to which 0.8 ml (0.0013 mol) of a 20% benzene solution of EADC was added. A green color developed immediately. After stirring at room temperature for 5 min, the reaction was terminated with methanol and worked up as above, leaving a residue of 1.71 g. Chromatography as above gave fractions which were analyzed by glc and combined accordingly. There was obtained first 0.2 g (11%) of 1,1-diphenylethane[11] (9), *m/e* 182, retention time 1.5 min (when programmed between 100 and 400° at a rate of 40°/min). Second to elute was the cyclic dimer 1,3,3-triphenyl-1-methylindan (4), 1.25 g (70%), *m/e* 360, mp 143° (lit.[4b] mp 143°; also *cf.* ref 13), retention time 2.9 min. Then followed by elution higher molecular weight unidentified products.

B.—To a solution of 1.8 g (0.01 mol) of 3 in 30% ml of benzene was added 7 ml (0.011 mol) of the 20% EADC reagent. The reaction mixture was stirred at room temperature for 5 hr, decomposed with dilute HCl, and worked up as above to give 1.66 g of an oil. The oil was dissolved in chloroform, and, upon addition of hexane, 0.59 g (33%) of the crude dimer 4 was precipitated, mp 137–140°. The remaining 1.07 g was chromatographed as above to render first 0.15 g (8%) of 9, *m/e* 182, retention time 1.5 min, followed by 0.31 g (17%) of the degradation product 1-methyl-3,3-diphenylindan (10), *m/e* 284, retention time 2.2 min, mp 89–90° from ethyl acetate.

*Anal.* Calcd for $C_{22}H_{20}$: C, 92.91; H, 7.09. Found: C, 93.06; H, 7.20.

The third compound to be eluted was the cyclic dimer 4, 0.31 g (17%), mp 143–144°. The last to elute were again higher molecular weight unidentified product mixtures.

C.—The reaction was carried out with 1 equiv of EADC as above but now under reflux for 5 hr. Work-up and chromatography yielded 0.20 g (11%) of 9, 0.27 g (15%) of 10, and 0.34 g (19%) of 4.

1,3,3-Triphenyl-1-methylindan (4).—To a solution of 0.36 g (0.001 mol) of 4 in 6 ml of benzene was added 0.7 ml (0.0011 mol) of the 20% EADC reagent and the mixture was refluxed for 5 hr. Decomposition with dilute HCl and work-up yielded 0.33 g of an oil. Trituration with ethanol recovered 0.2 g (55%) of crystalline starting material 4. Chromatography of the residue yielded 0.11 g (31%) of crystalline 10, mp 88–89°, *m/e* 284, retention time 2.2 min. A mixture melting point with 10 obtained from the reaction of 3 gave no depression. Following from the chromatography there were recovered 3% of 4 and other unidentified products.

*trans*-Stilbene (11).—A solution of 1.8 g (0.01 mol) of 11 in 30 ml of benzene was treated with 0.64 ml (0.001 mol) of a 20% EADC–benzene solution. A red color developed immediately upon the addition of the reagent. Stirring for 5 min at room temperature followed by decomposition with methanol and work-up yielded an oil that was distilled at 0.1 mm in a Büchi ball-tube fractionator to give three fractions. Fraction A, distilling at 80°, gave 0.01 g of starting material 11. Fraction B, distilling at 140°, gave 0.55 g of a mixture of 12, *m/e* 360, retention time 3.0 min, and 13, *m/e* 258, retention time 2.2 min. Fraction C, distilling at 170°, gave 0.95 g of 12 only as a mixture of isomers (lit.[7a] mp 184°), *m/e* 360, retention time 3.0 min. Chromatographic separation of fraction B gave 0.18 g of pure 13 and 0.34 g of pure 12. The overall yields of 13 and 12 were 10 and 72%, respectively.

*cis*-Stilbene (14).—The reaction of 14 was carried out in the same way as that with 11. The yields were 0.93 g (52%) of the alkylation product 13, mp 54–55° from ethanol (lit.[12] mp 54.5°), and 0.68 g (38%) of the cyclic dimer 12 (isomer mixture[13]).

## Discussion

When a certain styrene derivative is allowed to react with EADC in benzene solution, the EADC reagent[14] attacks the double bond to produce first a carbonium ion (15), which may in turn react further in one or more of the pathways A, B, and C outlined in Scheme II, depending on the derivative and conditions used. Path A leads to the formation of cyclic dimers and trimers, path B leads to alkylation products of the solvent (benzene), while path C, consuming the reagent in a noncatalytic reaction, leads after hydrolysis to the reduced product. As illustrated in Scheme II, path A, the monomeric carbonium ion 15 reacts with a second molecule of 1 to produce the dimeric carbonium ion 16. The latter may now react in two ways: (a) it may undergo an intramolecular ring closure to render the indan system 17, which with the aid of a proton released in the cyclization step regenerates the catalyst and forms the dimer 2, or, alternatively, (b) it may first undergo an oligomerization step by the attack of another molecule of α-methylstyrene to form a trimeric carbonium ion[15] 18, followed by cyclization in an irreversible intramolecular attack. The proton liberated in the cyclization reaction regenerates the catalyst, giving rise to the cyclic trimer 5 (Scheme III). The action of catalyst regeneration can take place whether the molecule is in the monomeric or oligomeric stage as well as whether in the carbonium ion, cyclized, or unsaturated form (*vide infra*). Path A thus requires only catalytic amounts of EADC. For similar reasons catalytic amounts are sufficient also for path B.

An additional pool from which protons can temporarily be "borrowed" to regenerate the catalyst (and thus make it more efficient) is the reversible,[16] very fast reaction of the linear dimer or trimer carbonium ions 16 and 18 to form the corresponding unsaturated linear compounds, thereby acting as an auxiliary pool for temporarily available protons.

The irreversible intramolecular formation of the indan type dimer and trimer is very considerably enhanced through the "locking" effect[17] of the substituents on the side chain. The α-substituted side chain in the carbonium ion of the linear dimer or trimer forces a preferred conformation to prevail with the carbonium ion in close proximity to the ortho position of the neighboring aromatic ring. The intramolecular cyclization is thus a more preferred reaction over the competing intermolecular attack of

(10) (a) J. M. Van der Zaden and Th. R. Rix, *Recl. Trav. Chim. Pays-Bas*, **75**, 1166 (1956); (b) *ibid.*, **75**, 1343 (1956).

(11) "Dictionary of Carbon Compounds," Vol. V. Oxford University Press, London, 1965, p 1279.

(12) Reference 11, p 3199.

(13) See ref 7.

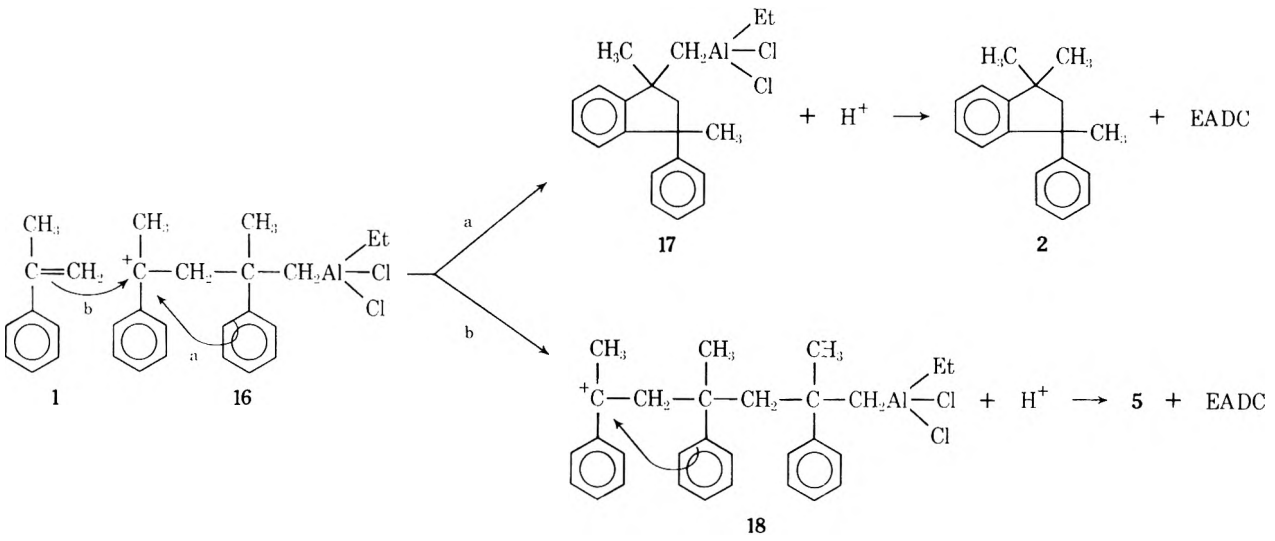
(14) C. G. Overberger, E. M. Pearce, and D. Tanner, *J. Amer. Chem. Soc.*, **80**, 1761 (1958).

(15) The possibility that very small amounts of promoting substances or cocatalysts (*e.g.*, traces of water, protonic acids, or alkyl halides) combine with the EADC to form an ionic complex which provides the cations necessary for the initiation of the reaction cannot be excluded.

(16) L. R. C. Barclay, "Friedel–Crafts and Related Reactions," Vol. II, Part 2, G. A. Olah, Ed., Interscience, New York, N. Y., 1964, p 944.

(17) (a) S. Milstein and L. A. Cohen, *Proc. Nat. Acad. Sci. U. S.*, **67**, 1143 (1970); (b) *J. Amer. Chem. Soc.*, **92**, 4377 (1970); (c) *ibid.*, **94**, 9158 (1972).

SCHEME III



another monomer to give oligomerization. Cyclization rate enhancement due to the *gem*-dimethyl effect in somewhat related systems has been shown[17] to increase cyclization rates by a factor as high as $10^6$.

At a somewhat lower temperature (4°) α-methylstyrene yielded more trimer than dimer (trimer:dimer 1.48), while at higher temperature this relation changes considerably (at 25° trimer:dimer 0.54 and at 80° trimer:dimer 0.18). This result may be a reflection of the difference in the dependence of reaction rates on temperature of the two competing reactions. Cationic polymerizations[18] of α-methylstyrene are known to take place at low temperature (∼−80°); however, at room temperature only dimers and trimers were observed.

Reaction of β-methylstyrene through path A yielded similar results to those of α-methylstyrene but in lower yield. This may be attributed to the fact that the chain is less substituted in the α position to the aromatic ring.

Path B represents alkylation of the aromatic solvent by the olefin. The carbonium ion **15** of *trans*- or *cis*-stilbene, in addition to the dimerization reaction to some extent through path A, reacts to a larger extent with the benzene used as solvent to produce the alkylation product 1,1,2-triphenylethane (**13**) in substantial yield. This reaction requires also only catalytic amount of the reagent (*vide supra*). Path C involves an intramolecular hydride ion shift from the ethyl group of the reagent, leading after hydrolysis to the reduction of the double bond[5] along with the consumption of an equimolar quantity of EADC. This pathway has taken place to some extent in the reaction of 1,1-diphenylethylene along with its main reaction through path A, leading to the corresponding cyclic dimer **4**.

**Nmr Spectra.**[19]—The cyclic dimer of α-methylstyrene possesses an asymmetric carbon atom next to the methylene[20] of the indan ring. The nonequivalence of the geminal protons in the nonplanar five-membered ring is exhibited in their nmr spectrum giving rise to an AB pattern quartet centered at 2.3 ppm with a splitting constant $J$ = 13 Hz. Similarly, and for the very same reason, the cyclic dimer of 1,1-diphenylethylene shows in the nmr for the geminal protons a quartet centered at 3.7 ppm with a splitting constant of $J$ = 14 Hz. The nonequivalent methylene protons in **10**, in addition to their geminal splitting, are also split by the presence of a vicinal proton next to the methylene, giving rise to a somewhat more complex pattern in the region 3.3–2.2 ppm for all three protons. The methyl protons of this compound, however, are split by their geminal proton into a doublet centered at 1.4 ppm with $J$ = 6 Hz. A similar splitting constant of $J$ = 6 Hz was obtained for the methyl doublet also when taken on a 90-MHz instrument. A decoupling experiment was conducted where the methyl doublet collapsed into a singlet upon irradiation at a frequency of 3 ppm.

Compounds **5**, **7**, **8**, and **12** are most probably mixtures of geometrical isomers, a fact that is well reflected in the complexity of their nmr spectra. Of particular mention may be the cyclic dimer of stilbene **12**, where the isomer mixture derived from *trans*-stilbene was different from the mixture derived from *cis*-stilbene. This is also well reflected in the difference in the relative abundance of various peaks in the mass spectrometric fragmentation.

The cyclic nature of the dimers, trimers, and the degradation product **10** obtained in these reactions was based mainly on the proper ratio obtained in their nmr spectra between the aromatic and aliphatic protons.

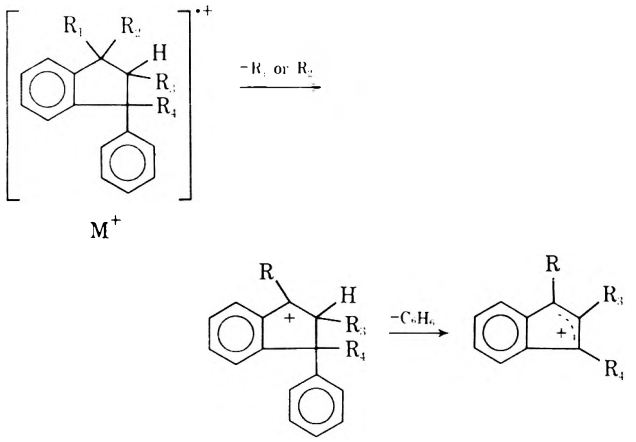
**Mass Spectra.**[19]—The mass spectra of all the 3-phenylindan derivatives taken exhibit a common general fragmentation pattern. The common step in the fragmentation of the molecular ion is rupture of a substituent in position 1, leaving a positive charge stabilized at the benzylic position 1, while a phenyl substituent at position 3 is still attached to the indan nucleus. This is followed by a loss of a neutral molecule $C_6H_6$ (phenyl from position 3 and hydrogen from position 2) to give an indan carbonium ion which is now stabilized by two benzylic positions, 1 and 3.

**Degradation of 4 to 10.**—In the reaction of 1,1-diphenylethylene with 1 equiv of EADC on prolonged

(18) (a) F. S. Dainton and R. H. Tomlinson, *J. Chem. Soc.*, 151 (1953); (b) D. C. Pepper, *Quart. Rev., Chem. Soc.*, **8**, 88 (1954); (c) "Friedel–Crafts and Related Reactions," Vol. II, Part 2, G. A. Olah, Ed., Interscience, New York, N. Y., 1964, p 1293.

(19) See paragraph at end of paper regarding supplementary material.

(20) R. M. Silverstein and G. C. Bassler, "Spectroscopic Identification of Organic Compounds," 2nd ed, Wiley, New York, N. Y., 1967, p 129.



reaction time, in addition to the dimerization and reduction products **4** and **9** obtained through paths A and C, there was formed also compound **10**. This compound is a product of a secondary reaction of the cyclic dimer **4** obtained through path A. To prove this point, pure **4** was submitted to the reaction under the drastic conditions to yield **10** as the major product[21]

(21) Adams[9] reported a somewhat similar degradation of **2** to 1,1,3-triphenylindan when **2** was heated with $AlCl_3$ at 110° for 6 hr.

(*ca.* 73% of the fraction that underwent reaction). Based on the nmr data (splitting of the methyl) we conclude that, in the degradation process of **4** to **10**, the substitution of phenyl by hydrogen occurred on the phenyl in position 1 next to the methyl rather than one of the two geminal phenyls in position 3 (see above).

**Acknowledgment.**—This project has been supported in part by a grant from the National Council for Research and Development (Israel).

**Registry No.**—**1**, 98-83-9; **2**, 3910-35-8; **3**, 530-48-3; **4**, 19303-32-3; **5**, 41906-71-2; **6**, 637-50-3; **7**, 30170-60-6; **8**, 41906-72-3; **9**, 612-00-0; **10**, 30098-24-9; **11**, 103-30-0; **12**, 41906-73-4; **13**, 1520-42-9; **14**, 645-49-8; EADC, 563-43-9.

**Supplementary Material Available.**—A figure with the nmr spectra of compounds **2**, **4**, and **10** as well as two tables summarizing the nmr and mass spectral data for all the products discussed will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20× reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-4040.

# A General Synthesis of 3-(Substituted benzoyl)-3-Substituted Alkanoic Acids

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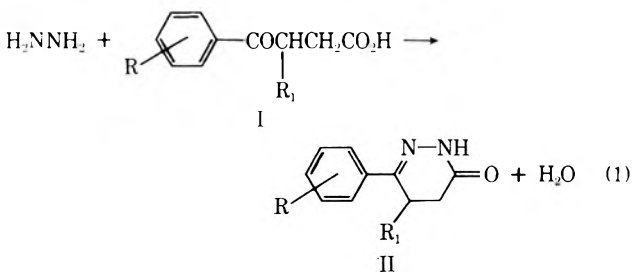
*Received June 28, 1973*

A general method for the preparation of 3-(substituted benzoyl)-3-substituted alkanoic acids is described. The key feature of the method is the conversion of a quaternary salt (V) derived from the Mannich base of a phenone into the corresponding γ-keto nitrile (VI), hydrolysis of which furnishes the acid. The transformation of V into VI by cyanide proceeds in two stages: (1) β elimination, and (2) conjugate hydrocyanation of the resulting enone. The efficiency of the method is compared to (1) the preparation of γ-keto esters by alkylation of enamines with ethyl bromoacetate and (2) the reduction of β-benzoylcrotonic acids obtained by condensation of phenones with glyoxalic acid.

We required a general synthesis of 3-(substituted benzoyl)-3-substituted propionic acids (I) in order to evaluate a series of pharmacologically interesting 6-(substituted phenyl)-5-substituted 4,5-dihydro-3-(2*H*)-pyridazinones (II),[1] which are readily prepared by reaction of I with hydrazine (eq 1).[1,2] Many of the procedures



described in the literature for the preparation of I rely on anionic condensations between ketones and esters,[3] and do not appear applicable to those reactants having substituents containing active hydrogens (see below). Those acid catalyzed procedures, *e.g.*, Friedel–Crafts condensations, compatible with substituents possessing active hydrogens usually give mixtures containing the isomeric 3-(substituted benzoyl)-2-substituted propionic acid.[1,4] In this paper we describe a method of apparent generality for the preparation of I; moreover, its effectiveness is compared with that of two other procedures.

The general method is based on an improved synthesis of γ-keto nitriles (VI), the hydrolysis of which readily furnish I (see Scheme I).[5,6] The preparation of certain γ-keto nitriles by treatment of Mannich bases with aqueous alkali cyanide has been reported by Knott,[6] and we have used a modification of this procedure to prepare the requisite intermediates. Thus, ketones III were converted into Mannich bases IV using the procedure of Back,[7] and reaction of the crude IV with methyl iodide furnished the quaternary salts

(1) W. V. Curran and A. Ross, *J. Med Chem.*, submitted for publication.

(2) E. A. Steck, R. P. Brundage, and L. T. Fletcher, *J. Amer. Chem. Soc.*, **75**, 1117 (1953), and references cited therein.

(3) (a) W. H. Puterbaugh and R. L. Readshaw, *J. Amer. Chem. Soc.*, **82**, 3635 (1960); (b) W. Cocker, L. O. Hopkins, L. Mabrouk, J. McCormick, and T. B. H. McMurray, *J. Chem. Soc.*, 2230 (1960); (c) M. S. Newman, W. C. Sagar, and C. C. Cochrane, *J. Org. Chem.*, **23**, 1832 (1958); (d) J. A. Marshall and S. F. Brady, *ibid.*, **35**, 4068 (1970); (e) W. E. Bachmann and G. D. Johnson, *J. Amer. Chem. Soc.*, **71**, 3463 (1949).

(4) A. G. Peto in "Friedel–Crafts and Related Reactions," Vol. III, Part 1, G. A. Olah, Ed., Interscience, New York, N. Y., 1964, pp 573, 583.

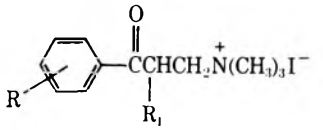
(5) C. F. H. Allen, M. R. Gilbert, and D. M. Young, *J. Org. Chem.*, **2**, 227 (1937).

(6) E. B. Knott, *J. Chem. Soc.* 1190 (1947).

(7) W. Back, *Arch. Pharm. (Weinheim)*, **303**, 491 (1970).

TABLE I

[β-(SUBSTITUTED BENZOYL)ALKYL]TRIMETHYLAMMONIUM IODIDES (V)

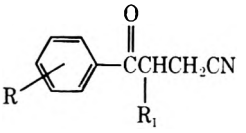


| Compd | R | $R_1$ | Yield,[a] % | Crystn solvent | Mp, °C | Formula[b] |
|---|---|---|---|---|---|---|
| 1 | o-$NO_2$ | H | 64 | Acetone | 152–155 | $C_{12}H_{17}IN_2O_3$[c] |
| 2 | o-$NO_2$ | $CH_3$ | 61 | Acetone | 168–170, 195–200 dec | $C_{13}H_{19}IN_2O_3$[d] |
| 3 | m-$NO_2$ | $CH_3$ | 93 | Acetone | 206–208 | $C_{13}H_{19}IN_2O_3$ |
| 4 | p-Br | $CH_3$ | 93 | Acetone | 184–185 | $C_{13}H_{19}BrINO$ |
| 5 | p-Cl | $CH_3$ | 82 | Acetone | 171–173 | $C_{12}H_{19}ClINO$[e] |
| 6 | p-F | $CH_3$ | 91 | Acetone | 186–187 | $C_{13}H_{19}FINO$[f] |
| 7 | H | $CH_3$ | 92 | Acetone–ether | 149–151 | $C_{13}H_{20}INO$ |
| 8 | p-F | $C_2H_5$ | 71 | Acetone–ether | 164–165 | $C_{14}H_{21}FINO$ |
| 9 | p-NHAc | $CH_3$ | 85 | Acetone | 206–207 | $C_{15}H_{23}IN_2O_2$ |
| 10 | p-F | $C_6H_5$ | 85 | Acetone–ether | 168–170 | $C_{18}H_{21}FINO$[c] |
| 11 | H | $C_6H_5$ | 77 | Acetone–ether | 191–192 | $C_{18}H_{22}INO$ |

[a] Overall for two stages from the corresponding phenone. [b] Satisfactory analytical data (±0.4% for C, H, I, N) were reported for all compounds except as noted. [c] N analysis only. [d] I: calcd, 33.56; found, 34.38. [e] I: calcd, 34.52; found, 34.01. [f] I: calcd, 36.14; found, 36.70.

TABLE II

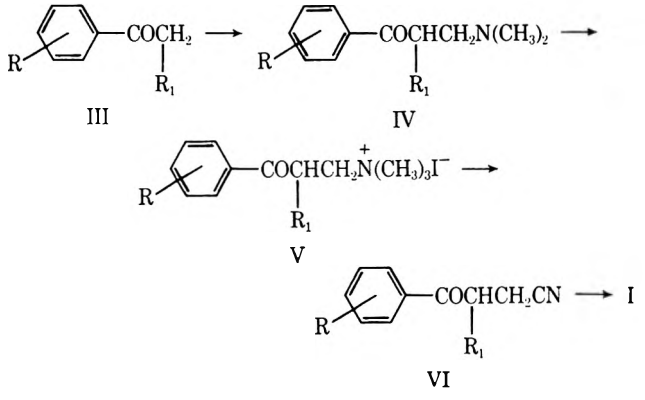
β-(SUBSTITUTED BENZOYL)ALKYLNITRILES (VI)



| Compd | R | $R_1$ | Reaction solvent | Yield, % | Recrystn solvent | Mp, °C | Molecular formula[a] |
|---|---|---|---|---|---|---|---|
| 12 | o-$NO_2$ | H | MeOH | 59 | Acetone–hexane | 73–74 | $C_{10}H_8N_2O_3$ |
| 13 | m-$NO_2$ | $CH_3$ | $H_2O$ | 92 | $Et_2O$ | 63–64 | $C_{11}H_{10}N_2O_3$ |
| 14 | p-NHAc | $CH_3$ | MeOH-$H_2O$ | 92 | Acetone–petroleum ether | 131–132 | $C_{13}H_{14}N_2O_2$ |
| 15 | p-NHAc | $C_2H_5$ | $H_2O$ | 57[b] | Acetone–petroleum ether | 129–130 | $C_{14}H_{16}N_2O_2$ |
| 16 | p-NHAc | n-$C_3H_7$ | $H_2O$ | 40[b] | Acetone–petroleum ether | 103–105 | $C_{15}H_{18}N_2O_2$ |
| 17 | p-F | $C_6H_5$ | MeOH | 91 | $Et_2O$–petroleum ether | 82–85 | $C_{16}H_{12}FNO$[c] |
| 18 | H | $C_6H_5$ | MeOH | 97 | $Et_2O$–petroleum ether | 87–88 | $C_{16}H_{13}NO$ |

[a] Satisfactory analytical data (±0.4% for C, H, N) were reported for all compounds. [b] Overall yield for three stages from the 4′-acetamidophenone, the last characterized intermediate. [c] F: calcd, 7.50; found, 7.72.

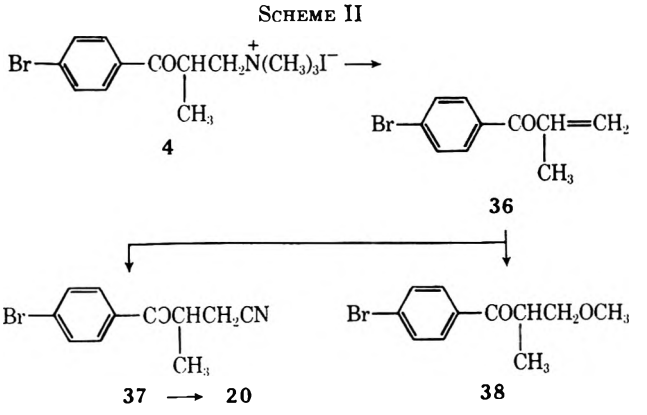
SCHEME I



(V) of Table I. Exposure of V to aqueous or methanolic solutions of potassium cyanide effected smooth, efficient conversion into the γ-keto nitriles (VI) of Table II. Those nitriles that were liquid were converted directly into the γ-keto acids I (see Table III) without purification. The present procedure for the preparation of VI appears to be more efficient and general than that of Knott.

Examination of the reaction of [2-(*p*-bromobenzoyl)-propyl]trimethylammonium iodide (**4**) with potassium cyanide showed that conversion of V into VI proceeds in two stages: (1) β elimination[8] to ketone **36** and (2) conjugate hydrocyanation.[5,9] Thus, reaction of **4** with aqueous cyanide gave 63% of the α,β-unsaturated ketone **36** and 37% of nitrile **37** (Scheme II).

SCHEME II



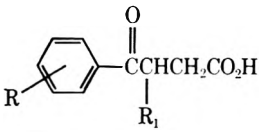
Ketone **36** gives a mixture of the same substances when treated similarly. Methanol is a more effective solvent for the conversion of either the quaternary salt or

(8) S. Patai, S. Weinstein, and Z. Rappoport, *J. Chem. Soc.*, 1741 (1962).

(9) W. Nagata, M. Yoshioka, and S. Hirai, *J. Amer. Chem. Soc.*, **94**, 4635 (1972), and references cited therein.

Table III

β-(Substituted benzoyl)alkanoic Acids (I)

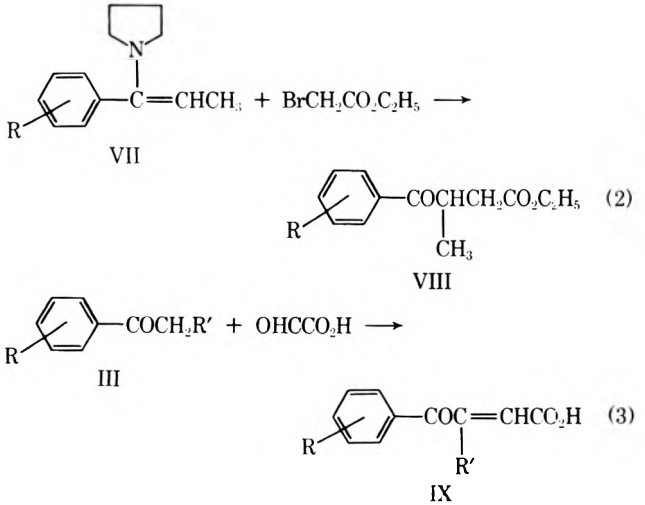


| Compd | R | $R_1$ | Yield, % — Method — A | Yield, % — Method — B | Recrystn solvent | Mp, °C | Molecular formula[a] |
|---|---|---|---|---|---|---|---|
| 19 | o-$NO_2$ | H | 68 | | Ether–petroleum ether | 95–97 | $C_{10}H_9NO_5$ |
| 20 | p-Br | $CH_3$ | 86[b] | 90 | Ether–petroleum ether | 95–96[c] | $C_{11}H_{11}BrO_3$ |
| 21 | p-Cl | $CH_3$ | 82[b] | 78 | Petroleum ether | 79–82[d] | $C_{11}H_{11}ClO_3$ |
| 22 | p-F | $CH_3$ | 87[b] | 94 | Ether–petroleum ether | 57–58 | $C_{11}H_{11}FO_3$ |
| 23 | m-$NO_2$ | $CH_3$ | 87 | | $CH_2Cl_2$–petroleum ether | 89–90 | $C_{11}H_{11}NO_5$ |
| 24 | H | $CH_3$ | 95 | | Ether–petroleum ether | 57–58[e] | $C_{11}H_{12}O_3$ |
| 25 | p-$NH_2$ | $CH_3$ | 73 | | Acetone–benzene | 121–123 | $C_{11}H_{13}NO_3$ |
| 26 | p-F | $C_2H_5$ | 91[b] | 94 | Ether–petroleum ether | 80–81 | $C_{12}H_{13}FO_3$ |
| 27 | p-$NH_2$ | $C_2H_5$ | 82 | | Acetone–petroleum ether | 128–129 | $C_{12}H_{15}NO_3$ |
| 28 | p-$NH_2$ | $C_3H_7$ | 69 | | $CH_2Cl_2$–petroleum ether | 110–111 | $C_{13}H_{17}NO_3$[f] |
| 29 | p-F | $C_6H_5$ | 63 | | Ether–petroleum ether | 114–115 | $C_{16}H_{13}FO_3$ |
| 30 | H | $C_6H_5$ | 91 | 64 | Ethanol–$H_2O$ | 147–149[g] | $C_{16}H_{14}O_3$ |

[a] Satisfactory analyses (±0.4% for C, H, F, N) were reported for all new compounds except as noted. [b] Overall yield from the last crystalline intermediate, the quaternary ammonium salt V. [c] Lit.[14] mp 95.5°. [d] Lit.[3a] mp 81.0–82.5°. [e] Lit.[3b] mp 58°. [f] C: calcd, 66.36; found, 65.79. [g] A dimorph of the reported form having mp 163°: A. M. Cragg, F. M. Dean, and G. Winfield, *J. Chem. Soc.*, 2431 (1959).

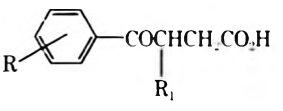
the enone into the nitrile, and the reaction is conveniently monitored by tlc. As reaction proceeds from intermediate **36**, two more polar products, which remain after disappearance of **4** and **36**, appear in the chromatogram. One of these is keto nitrile **37**; nmr spectroscopy of a fraction rich in the second product suggests it to be methoxy ketone **38**. The formation of this product by competitive 1,4 addition of solvent is not a serious factor, for acid hydrolysis of the mixture gave 86% of γ-keto acid **20**.[10]

We also examined the condensation of an enamine with ethyl α-bromoacetate (eq 2)[11] and base-catalyzed condensation of glyoxylic acid with the appropriate ketone (eq 3)[3c,d] as alternative routes to γ-keto acids. Alkylation of the pyrrolidine enamine of propiophenone[12] (VII, R = H) with ethyl bromoacetate gave 61% of ethyl β-benzoylbutyrate (VIII, R = H). However, this procedure proved to be limited, for its application to *o*-acetamidoacetophenone gave only 12% of ethyl β-(*o*-acetamidobenzoyl)propionate. Moreover, the enamine derived from *p*-acetamidopropiophenone and morpholine could not be separated from unreacted ketone, and attempts to utilize this mixture were abortive.



The procedure of eq 3 was somewhat more versatile. Thus, condensation of glyoxylic acid, generated *in situ* by periodate oxidation of tartaric acid,[3c,d] with the appropriate ketone III gave the β-substituted acrylic acids (IX) listed in Table IV; however, the yields of product were disappointing (13–47%). Reduction of the halobenzoyl (**31**, **32**, **34**) and benzoyl (**35**) derivatives with zinc in acetic acid gave 64–94% of the corresponding β-(substituted benzoyl)alkanoic acids (Table III). Yet a similar reduction of the acid **33** did not give β-(*m*-aminobenzoyl)butyric acid. Moreover, the isomeric acid could not be prepared from *p*-acetamidopropiophenone by this sequence, since condensation of the ketone with glyoxylic acid failed. In addition to the above shortcomings, comparison of the overall yield of I by this two-step procedure with that produced by the Mannich sequence demonstrates superiority for the latter method (see Chart I).[13]

Chart I



| Compd | R | $R_1$ | % yield — A[a] | % yield — B[b] |
|---|---|---|---|---|
| 20 | p-Br | $CH_3$ | 80 | 44 |
| 21 | p-Cl | $CH_3$ | 67 | 32 |
| 22 | p-F | $CH_3$ | 79 | 44 |
| 23 | m-$NO_2$ | $CH_3$ | 74 | c |
| 26 | p-F | $C_2H_5$ | 65 | 12 |

[a] Synthesis *via* Mannich reaction. [b] Synthesis *via* glyoxylic acid condensation. [c] Not achieved.

(10) The fate of methoxy ketone **38** under these conditions was not determined; acid-catalyzed elimination of methanol and conversion of the resulting **36** into other nonacidic products is apparent.

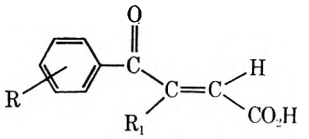
(11) (a) G. Stork, R. Terrell, and J. Szmuszkovicz, *J. Amer. Chem. Soc.*, **76**, 2029 (1954); (b) G. Stork, A. Brizzolava, H. Landesman, J. Szmuszkovicz, and R. Terrell, *ibid.*, **85**, 207 (1963).

(12) P. Y. Sollenberger and R. B. Martin, *J. Amer. Chem. Soc.*, **92**, 4261 (1970).

(13) The direct preparation of certain γ-keto esters and γ-keto nitriles by conjugate addition of benzaldehyde and p-chlorobenzaldehyde to α,β-unsaturated esters and nitriles was described after completion of this work: H. Stetter and M. Schreckenberg, *Angew. Chem. Int. Ed. Engl.*, **12**, 81 (1973).

TABLE IV

β-BENZOYL-β-SUBSTITUTED ACRYLIC ACIDS



| Compd | R | $R_1$ | Yield, % | Recrystn solvent | Mp, °C | Formula[a] |
|---|---|---|---|---|---|---|
| **31** | *p*-Cl | $CH_3$ | 41 | Benzene–heptane | 128 | $C_{11}H_9ClO_3$ |
| **32** | *p*-F | $CH_3$ | 47 | Benzene–heptane | 97–99 | $C_{11}H_9FO_3$ |
| **33** | *m*-$NO_2$ | $CH_3$ | 33 | Benzene–heptane | 137–139 | $C_{11}H_9NO_5$ |
| **34** | *p*-F | $C_2H_5$ | 13 | Ether–hexane | 88–89 | $C_{12}H_{11}FO_3$ |
| **35** | H | $C_6H_5$ | 44 | Benzene–heptane | 120–123[b] | $C_{16}H_{14}O_3$ |

[a] Satisfactory analytical data (±0.4% for C, H, N) were reported for all new compounds. [b] Trans isomer, mp 128°: E. P. Kohler, W. D. Peterson, and C. L. Bickel, *J. Amer. Chem. Soc.*, **56**, 2000 (1934). Cis isomer, mp 140–141°: C. R. Bauer and R. E. Lutz, *J. Amer. Chem. Soc.*, **75**, 5997 (1953).

## Experimental Section

Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Infrared spectra were determined in pressed KBr disks on a Perkin-Elmer Model 21 spectrophotometer, and the ultraviolet spectra were measured in methanol solution with a Cary Model 11 recording spectrometer. Nmr spectra were determined in deuteriochloroform on a Varian HR-100 spectrometer using tetramethylsilane as an internal standard. All evaporations were carried out at reduced pressure. The petroleum ether used was that fraction boiling at 30–60°.

**Preparation of the [(Substituted benzoyl)alkyl]trimethylammonium Iodides (V).**—The following preparation of [2-(*p*-acetamidobenzoyl)propyl]trimethylammonium iodide (**9**) illustrates the general procedure. A solution of 21.0 g (0.257 mol) of dimethylamine hydrochloride in 15.2 ml (0.203 mol) of 37% aqueous formaldehyde was allowed to stand at room temperature for 30 min. To the solution was added 105 ml (1.1 mol) of acetic anhydride and the mixture was swirled until a clear solution resulted and spontaneous gentle boiling began. To the still warm solution was added 32.8 g (0.172 mol) of *p*-acetamidopropiophenone and the mixture was heated on the steam bath for 2 hr. The reaction mixture was evaporated on a water bath at 55–60°. To destroy the excess reagents the residue was treated with 350 ml of acetone and the solution was boiled for 5 min and then evaporated. The residual gum was dissolved in 350 ml of water and washed with three 250-ml portions of methylene chloride. The aqueous solution was stirred in an ice bath with 250 ml of methylene chloride and rendered alkaline by the dropwise addition of 2.5 *N* sodium hydroxide solution. The methylene chloride solution was separated and the aqueous solution was extracted with an additional 250 ml of methylene chloride. The combined organic extracts were washed with saline, dried, and evaporated, leaving 40 g of 4′-(3-dimethylamino-2-methylpropionyl)acetanilide as a liquid which was used without further purification. A solution of this material and 22 ml (0.33 mol) of iodomethane in 400 ml of acetone was stirred at reflux temperature for 18 hr. The mixture was cooled and 51.9 g (85%) of methiodide, mp 206–207°, was collected by filtration. The characterization of this substance and the other Mannich base quaternary salts is given in Table I.

**Preparation of the β-(Substituted benzoyl)alkylnitriles (VI).**—The following preparation of 4′-(3-cyano-2-methylpropionyl)acetanilide (**14**) illustrates the general procedure. To a stirred solution of 88.0 g (1.35 mol) of potassium cyanide in 1.76 l. of water was added a solution of 220 g (0.565 mol) of [2-(*p*-acetamidobenzoyl)propyl]trimethylammonium iodide (**9**) in 440 ml of methanol and 2.2 l. of water. An oil separated and gradually became a white solid during 4 hr of stirring. The solid was collected and washed liberally with water, affording 119 g (92%) of nitrile, mp 127–130°. Characterization of this substance and others prepared in a similar manner is given in Table II. Absence of an entry corresponding to the acids obtained by method B in Table II signifies a liquid product, which was used without attempted purification.

A similar reaction in methanol between 3.40 g of potassium cyanide and 9.00 g of [2-(*p*-bromobenzoyl)propyl]trimethylammonium iodide (**4**) gave, after 3 hr, a binary product mixture ($R_f$ 0.31, 0.54 on silica plates), which was partially separated on a column (5 × 46 cm) prepared from a synthetic magnesia–silica absorbent using heptane–methylene chloride (4:1) as the solvent system. The material (2.12 g) eluted by this solvent was a mixture of **37** and **4′-bromo-3-methoxy-2-methylpropiophenone (38)** as indicated by tlc and the distinctive nmr spectrum: *inter alia* $\delta^{TMS}_{CDCl_3}$ 3.30 (s, $OCH_3$). Further elution of the column with methylene chloride gave 3.40 g (62%) of **3-(*p*-bromobenzoyl)-butyronitrile (37)**, the homogenity of which was indicated by tlc and ir.

**2-Allyl *p*-Bromophenyl Ketone (36).**—A mixture of 29.13 g (0.071 mol) of [2-(*p*-bromobenzoyl)propyl]trimethylammonium iodide (**4**) and 10.5 g (0.162 mol) of potassium cyanide in 650 ml of water was mechanically stirred in a baffle flask for 22 hr. The products were isolated with methylene chloride in the usual manner to give 16.81 g of a liquid that was dissolved in hexane–methylene chloride (4:1) and adsorbed onto a column (5 × 46 cm) prepared from this system and a synthetic magnesia–silica adsorbent. Elution of the column with hexane–methylene chloride (4:1, 5.5 l.) gave 10.1 g (63%) of ketone as white crystals, mp 45–47°. A sample was recrystallized twice from petroleum ether at −78° to give white crystals: mp 50–51°; uv max 258 nm (ε 12,800); ir max 6.04, 6.14, 6.28 μ; nmr $\delta^{TMS}_{CDCl_3}$ 2.06 (d, 2, *J* = 0.8 Hz, $CH_3$), 5.58 (d, 1, *J* = 0.8 Hz, HC=$CCH_3$), 5.90 (d, 1, *J* = 0.8 Hz, HC=$CCH_3$), 7.58 (s, 4, aryl H).

*Anal.* Calcd for $C_{10}H_9BrO$: C, 53.37; H, 4.03. Found: C, 53.39; H, 3.93.

Elution of the column with 3 l. of methylene chloride gave 6.87 g (37%) of **3-(*p*-bromobenzoyl)butyronitrile (37)** as a colorless liquid, ir max 4.50, 5.95, 6.31 μ.

**3-(*p*-Bromobenzoyl)butyronitrile (37).**—A solution of 8.70 g (39.6 mmol) of 2-allyl *p*-bromobenzoyl ketone (**36**) and 5.80 g (89 mmol) of potassium cyanide in 150 ml of methanol was stirred at room temperature for 3 hr to give 9.55 g (96%) of product as a liquid, the ir spectrum of which was identical with that prepared from quaternary salt **4** and acid hydrolysis of which gave 7.71 g (75%) of **3-(*p*-bromobenzoyl)butyric acid (20)**, mp 93–96°.

Use of water as the reaction medium and chromatography of the crude product as described above gave 38% of ketone **36** and 46% of nitrile **37**.

**Preparation of the β-(Substituted benzoyl)alkanoic Acids (I). Method A.**—A solution of 23.2 g (0.10 mol) of 4′-(3-cyano-2-methylpropionyl)acetanilide (**14**) and 230 ml of 6 *N* hydrochloric acid was stirred at reflux temperature for 1 hr. The solution was evaporated and the residue was triturated with acetone, affording, in two crops, 28 g of a mixture of amino acid hydrochloride and ammonium chloride. A 1.22-g sample of this material was dissolved in 12 ml of water and the solution was brought to pH 4 by the dropwise addition of 1.0 *N* sodium hydroxide solution. The ice-cooled solution deposited 690 mg of 3-(*p*-aminobenzoyl)-butyric acid (**25**) as white crystals, mp 119–123°. The characterization of this substance is given in Table III.

Those compounds of Table III lacking an amino group were isolated by extraction of cooled acid solution with $CH_2Cl_2$, removal of solvent, and recrystallization.

**Method B.**—A mixture of 31.40 g (0.116 mol) of β-(*p*-bromobenzoyl)crotonic acid[14] and 15.2 g of zinc dust in 168 ml of glacial acetic acid and 68 ml of water was stirred at steam-bath tempera-

(14) R. E. Lutz and R. J. Taylor, *J. Amer. Chem. Soc.*, **55**, 1168 (1933).

ture for 30 min. The mixture was filtered into 1 l. of water to precipitate an oil that crystallized on rubbing. Filtration gave 26.41 g of solid, mp 88–93°. Extraction of the filtrate with ether and recrystallization of the material from $CH_2Cl_2$–petroleum ether gave an additional 1.66 g (90%) of material, mp 82–86°, having suitable purity for further use. The preparation and characterization of other acids prepared by this procedure is given in Table IV.

1-(1-Phenylpropenyl)pyrrolidine.—This enamine was prepared by the procedure outlined by Stork.[11] A solution of 13.4 g (0.10 mol) of propiophenone, 11.6 ml (0.14 mol) of pyrrolidine, and 100 mg of *p*-toluenesulfonic acid in 30 ml of benzene was heated under reflux with water removal by a Dean–Stark trap for 23 hr. The mixture was evaporated *in vacuo* and the residual gum was dissolved in 30 ml of benzene. To the solution was added 11.6 ml of pyrrolidine and 100 mg of *p*-toluenesulfonic acid and the mixture was again heated under reflux with water collection for 18 hr. The solvent was removed and the residue was distilled to give 9.60 g (51%) of enamine, bp 83–85° (0.6 mm), ir max 5.94 μ. Sollenberger and Martin[12] report bp 139.5–140° (13 mm).

Ethyl β-Benzoylbutyrate.—To a boiling solution of 3.74 g (20 mmol) of the above enamine in 30 ml of ethanol was added dropwise a solution of 3.3 ml (30 mmol) of ethyl bromoacetate in 10 ml of ethanol. The solution was heated at reflux for 90 min and then for an additional 60 min with 20 ml of water. The alcohol was evaporated and the residue was diluted with water. The product was isolated with methylene chloride and vacuum distilled to give 2.53 g (61%) of ester, bp 108–116° (0.6 mm), ir max 5.76, 5.95, 6.29 μ. This product was characterized further by its conversion into the known 4,5-dihydro-5-methyl-6-phenyl-3(2*H*)-pyridazinone, mp 151–153° (lit.[1] mp 147–149°), by reaction with hydrazine in ethanol containing a catalytic amount of acetic acid.

Ethyl β-(*o*-Acetamidobenzoyl)propionate.—Application of the above transformations to 17.7 g (0.10 mol) of *o*-acetamidoacetophenone gave 3.11 g (12%) of product as an orange oil following chromatography on a synthetic magnesia–silica adsorbent: ir max 3.10, 5.78, 5.88, 6.06, 6.30, 6.58 μ. This material was converted directly into the 4,5-dihydro-3(2*H*)-pyridazinone without further purification.

Preparation of the β-Benzoyl-β-Substituted Acrylic Acids (IX).—The following preparation of β-(*p*-bromobenzoyl)crotonic acid illustrates the general procedure. A solution of 36.00 g (0.24 mol) of tartaric acid in 72 ml of water was added to a mechanically stirred, ice-cooled mixture of 51.36 g (0.24 mol) of sodium metaperiodate in 300 ml of water containing 4.8 ml of concentrated sulfuric acid. Stirring was continued at ice-bath temperature for 5 min and then at room temperature for 25 min, whereafter 50.95 g (0.24 mol) of *p*-bromopropiophenone, a solution of 36.00 g of sodium hydroxide in 660 ml of water, and 600 ml of ethanol were added in the indicated sequence. The resulting mixture was stirred at room temperature for 15 hr, whereafter it was heated at steam-bath temperature for 1 hr. The cooled mixture was diluted with water sufficient to dissolve the solids. The solution was extracted with ether to remove 8.11 g (16%) of *p*-bromopropiophenone. Dissolved ether was removed from the aqueous solution under reduced pressure, and the concentrate was rendered acid to Congo Red paper by addition of 3 *N* hydrochloric acid solution. The precipitated solid was collected and recrystallized with the aid of activated carbon from benzene–heptane to give 31.40 g (49%) of tan crystals, mp 140–143° (lit.[14] mp 144.5–145.0°). The preparation of other β-benzoyl-β-substituted acrylic acids is summarized in Table IV.

**Acknowledgment.**—We thank Dr. D. S. Allen, Jr., for helpful discussions, and we are indebted to Messrs. W. Fulmor and L. Brancone and their associates for the spectral data and microanalyses, respectively.

**Registry No.**—**1**, 42075-08-1; **2**, 42075-09-2; **3**, 42075-10-5; **4**, 42075-11-6; **5**, 42075-12-7; **6**, 42075-13-8; **7**, 31035-03-7; **8**, 42075-15-0; **9**, 42075-16-1; **10**, 42075-17-2; **11**, 31035-04-8; **12**, 42075-19-4; **13**, 42075-20-7; **14**, 42075-21-8; **15**, 42075-22-9; **16**, 42075-23-0; **17**, 42075-24-1; **18**, 13866-36-9; **19**, 42075-26-3; **22**, 42075-27-4; **23**, 42075-28-5; **25**, 42075-29-6; **26**, 42071-57-8; **27**, 42071-58-9; **28**, 42071-59-0; **29**, 42071-60-3; **30**, 6307-19-3; **31**, 42071-62-5; **32**, 42071-63-6; **33**, 42071-64-7; **34**, 42071-65-8; **36**, 42071-66-9; 1-(1-phenylpropenyl)pyrrolidine, 31889-28-8; ethyl β-benzoylbutyrate, 40394-84-1; ethyl β-(*o*-acetamidobenzoyl)-propionate, 42071-69-2.

# Conformational and Configurational Studies of Some Diethyl 2,3-Diarylsuccinates Using Nuclear Magnetic Resonance

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The diethyl 2,3-diarylsuccinates, I-H, II-H, I-Cl, I-OMe, I-$NH_2$, and I-$NO_2$ have been synthesized and their nmr spectra examined. I-H, II-H, I-Cl, I-OMe, and I-$NO_2$ have been equilibrated with their respective stereoisomers. In each case the threo isomer predominated at equilibrium and the equilibrium constant increased with the electron-withdrawing power of the substituent. The $J_{HCCH}$ obtained for the benzylic protons in I-$NO_2$ and II-$NO_2$ (12 Hz) and other characteristics of the nmr spectra indicate that predominant conformers for the erythro and threo isomers are IA and IIA, respectively.

As a result of stereochemical questions raised by our earlier work on the thermal decomposition of *meso*-di-*tert*-butylperoxy 2,3-diphenylsuccinate,[1] we have synthesized a series of *erythro*-diethyl 2,3-diarylsuccinates (I-H, I-Cl, I-OMe, I-$NH_2$ and I-$NO_2$) and the threo isomer II-H and examined their nmr spectra in some detail.

Our initial intent was to use the coupling constant for the benzylic protons in conjunction with the Karplus equation[2] to establish the major conformer for each succinate isomer (Figure 1). This relationship has been used with considerable success in cyclic and acyclic systems,[3] although some apparent exceptions have been observed.[4]

The compounds I-H, II-H, I-Cl, I-OMe, and I-$NO_2$ were subjected to base-catalyzed equilibration and the respective equilibrium constants determined. The equilibration of 2,3-diphenylsuccinic acid had been observed as early as 1890 by Anschütz,[5] and the equilibration of the unsubstituted esters was studied in some detail by

(1) L. M. Bobroff, L. B. Gortler, D. J. Sahn, and H. Wiland, *J. Org. Chem.*, **31**, 2678 (1966).

(2) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); *J. Amer. Chem. Soc.*, **85**, 2870 (1963).

(3) A review of the literature pertaining to acyclic systems can be found in C. A. Kingsbury, *J. Org. Chem.*, **35**, 1319 (1970), and the preceding papers in the series.

(4) (a) D. C. Best, G. Underwood, and C. A. Kingsbury, *Chem. Commun.*, 627 (1969), and references therein. (b) W. T. Borden, Harvard University, 1971, private communication. Both diastereomers of 2,2-dimethyl-4-phenyl-3-pentanol have a $J_{HCCH}$ for the methine protons of about 3.5 Hz.

(5) R. Anschütz and P. Bendix, *Justus Liebigs Ann. Chem.*, **259**, 61 (1890).

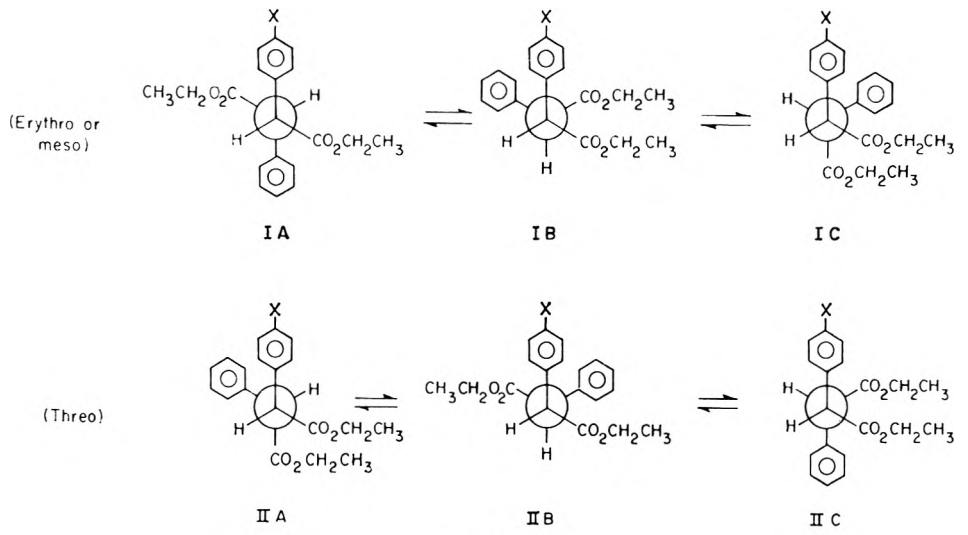
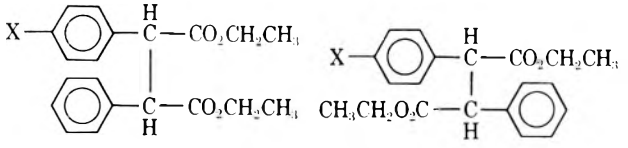



Figure 1.



I (erythro or meso)
I-H, X = H
I-Cl, X = Cl
I-OMe, X = OMe
I-$NH_2$, X = $NH_2$
I-$NO_2$, X = $NO_2$

II (threo)
II-H
II-Cl
II-OMe
II-$NO_2$

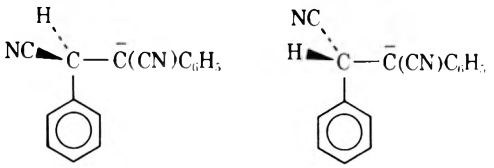
Wren and Still.[6] No equilibrium constants were determined in these earlier studies.

This work has enabled us to establish the absolute configurations of the substituted diarylsuccinates and to assign the major conformer for each isomer.

## Results and Discussion

**Synthesis of the Esters.** —Most of the esters were prepared through the condensation of the appropriate para-substituted benzaldehyde and benzyl cyanide followed by addition of hydrogen cyanide to yield the mono-para-substituted 2,3-diphenylsuccinonitrile. The procedure developed by Davis[7] permits the condensation and addition to proceed together. The dinitrile was hydrolyzed and the resulting acid was esterfied. The *p*-nitro ester, however, could not be made directly using either *p*-nitrobenzaldehyde or *p*-nitrobenzyl cyanide. This direct synthesis apparently fails because of difficulty in adding HCN to the 2-phenyl-3-*p*-nitrophenylacrylonitrile. An indirect synthesis starting with *p*-acetamidobenzaldehyde yielded small quantities of the *p*-nitro ester.

The fact that only one diastereomer, I-H, I-Cl, I-OMe, I-$NH_2$ and I-$NO_2$, was obtained in each synthesis is an interesting, if not surprising, phenomenon. The stereoselective addition of hydrogen cyanide to (*Z*)-2,3-diphenylacrylonitrile is known,[7b] but is difficult to rationalize on mechanistic grounds. The addition surely goes through the anions IIIa and IIIb[8] which



IIIa IIIb

should, on protonation, yield a mixture of diastereomers. We strongly suspect that the erythro dinitriles are far less soluble than the threo isomers and precipitate as they are formed; *i.e.*, the product ratio is determined by the solubility of the products. We are currently investigating this problem.

**Absolute Configuration of the Diastereomers.** —The fact that I-H, I-Cl, I-OMe, I-$NH_2$, and I-$NO_2$ were all obtained in essentially the same way, *i.e.*, from a selectively produced dinitrile, is one basis for assigning stereochemistry to these isomers. Compound I-H is well characterized[6a] as the *meso*-diethyl 2,3-diphenylsuccinate. The other I compounds, by analogy, can be assigned the same absolute configuration.

We have also used the chemical shift of the methyl protons to determine the stereochemistry of the various isomers. Compound I-H has a methyl triplet in the nmr centered at $\delta$ 0.88 ($CDCl_3$). The equally well characterized[6a] threo isomer, II-H, has a methyl triplet centered at $\delta$ 1.16. Compound I-OMe has two methyl triplets[9] centered at $\delta$ 0.90 and 0.93. Compound II-OMe, observed only in a mixture with I-OMe, has a single methyl triplet at $\delta$ 1.18.[10] Two upfield triplets are also observed for I-Cl, I-$NH_2$, and I-$NO_2$ (Table I). Compound II-Cl has a single downfield triplet, and II-$NO_2$ has two closely spaced downfield triplets (chemical shift difference of about 0.8 Hz).

All of the I compounds, then, have methyl absorption

(6) (a) H. Wren and C. J. Still, *J. Chem. Soc.*, **107**, 444 (1915); (b) *ibid.*, **111**, 513 (1917); (c) *ibid.*, **111**, 1019 (1917).

(7) (a) R. B. Davis, *J. Amer. Chem. Soc.*, **80**, 1752 (1958); (b) N. Rabjohn, Ed., "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, pp 392–395.

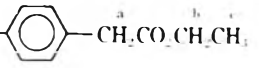
(8) C. A. Fyfe, *Can. J. Chem.*, **47**, 2331 (1969); D. J. Kroeger and R. Stewart, *J. Chem. Soc. B*, 217 (1970).

(9) When the 60- and 100-MHz spectra were compared, we found the resonance positions of the two triplets changed with respect to one another but the coupling constants remained the same. We are, therefore, dealing with two triplets and not the splitting of a single triplet.

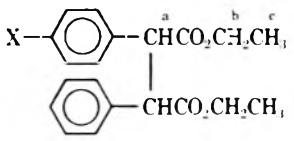
(10) The nmr data for II-OMe, II-Cl, and II-$NO_2$ were obtained from spectra of mixtures.

TABLE I

NMR DATA.[a] PROTON CHEMICAL SHIFTS, δ[b]

Ethyl Phenylacetates 

| Registry no. | X | a | b | c |
|---|---|---|---|---|
| 101-97-3 | H | 3.51 (s) | 4.06 (q, 6.5) | 1.13 (t, 6.5) |
| 14062-18-1 | OMe | 3.48 (s) | 4.08 (q, 7) | 1.17 (t, 7) |
| 14062-24-9 | Cl | 3.50 (s) | 4.08 (q, 6.5) | 1.17 (t, 6.5) |
| 5445-26-1 | $NO_2$ | 3.74 (s) | 4.18 (q, 6.5) | 1.25 (t, 6.5) |

Diethyl 2,3-Diarylsuccinates, 

| Compd | a | b | c |
|---|---|---|---|
| I-H | 4.38 (s) | 3.84 (q, 7) | 0.88 (t, 7) |
| II-H | 4.22 (s) | 4.14 (q, 7) | 1.16 (t, 7) |
| I-OMe | 4.31 (s) | 3.88 (q, 7)[c] | 0.90 (t, 7) |
| | | | 0.93 (t, 7) |
| II-OMe | 4.18 (s) | 4.14 (q, 7) | 1.18 (t, 7) |
| I-Cl | 4.34 (s) | 3.84 (q, 7)[d] | 0.90 (t, 7) |
| | | 3.88 (q, 7) | 0.94 (t, 7) |
| II-Cl | 4.20 (s) | 4.15 (q, 7) | 1.18 (t, 7) |
| I-$NH_2$ | 4.31 (s) | 3.85 (q, 7) | 0.88 (t, 7) |
| | | 3.87 (q, 7) | 0.92 (t, 7) |
| I-$NO_2$ | 4.34 (d, 12) | 3.86 (q, 7)[d] | 0.92 (t, 7) |
| | 4.51 (d, 12) | 3.88 (q, 7) | 0.96 (t, 7) |
| II-$NO_2$ | 4.17 (d, 12) | 4.11 (q, 7) | 1.20 (t, 7) |
| | 4.42 (d, 12) | | 1.21 (t, 7) |

[a] Solvent, $CDCl_3$; internal standard, TMS. [b] When the signal is not a singlet, the value is that for the center of the pattern. The splitting pattern followed by the coupling constant in hertz is given in parentheses after the chemical shift: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. [c] Broad bands. Probably more than one quartet. $CH_3O$ absorbs at δ 3.77 for I-OMe and δ 3.67 for II-OMe. [d] With higher resolution further splitting of the quartets was observed (see Figure 2). The methylene protons are diastereotopic and the pattern is probably that for an $ABX_3$ spin system.

at upfield positions (less than δ 1.0), and all of the II compounds have methyl absorption at downfield positions (above δ 1.0). This suggests that all of the I compounds have the erythro configuration, and all of the II compounds have the threo configuration.

The upfield and downfield chemical shifts and the appearance of double and single triplets can be explained in terms of the predominant conformer and will be discussed in detail below.

**Equilibration of the Diastereomers.**—The equilibration of the diastereomers, I ⇄ II, was effected by refluxing an ethanol solution of the erythro isomer containing a small quantity of sodium ethoxide until the ratio of the two isomers no longer changed. In one experiment we started with the threo isomer, II-H, and the result was the same. Before analysis, the mixture of isomers was isolated and then redissolved in $CDCl_3$. The equilibrium constants were calculated from the integration of the methyl proton region of the spectra (see Figure 2B). The results of our measurements are tabulated in Table II.

The analyses were reproducible to ±5%, and had an accuracy of about ±10% determined using synthetic mixtures of I-H and II-H. In cases where the threo methyl triplet overlapped with the erythro methyl triplet(s), the integrals of the outside peaks were compared (see Figure 2). This comparison favors a $K_{threo/erythro} > 1$ because the methyl signal is not completely symmetrical and the downfield peaks, those closest to the methylene signal, are larger than the upfield peaks. The nonsymmetry of the triplets is minimal, however, because of the large chemical shift differences between methyl and methylene (*ca.* δ 3). Any errors from this source are already included in the accuracy errors mentioned above. The areas under the benzylic proton signals could not be measured since they overlapped the methylene peaks, but a visual comparison yielded the same qualitative result, $K_{threo/erythro} > 1$, as that obtained from integration of the methyl signals.

TABLE II

EQUILIBRIUM CONSTANTS FOR I ⇄ II IN ETHANOL AT 78°

| Compd[a] | $K_{threo/erythro}$[b] |
|---|---|
| I-OMe | 1.25 |
| I-H | 1.35 |
| II-H | 1.37 |
| I-Cl | 1.5 |
| I-$NO_2$ | 2.5 |

[a] Compound with which equilibration was started. [b] Equilibrium constants have an accuracy of ±10%.

Although the $K$ values could be off by as much as 10%, the trend of the equilibrium constants is obvious. The more electronegative the substituent, the larger the equilibrium constant. If, indeed, IA and IIA (Figure 1) are the predominant conformers (see below), the major factor determining the position of equilibrium must be the decreasing repulsion of the gauche aryl groups as the substituent becomes more electronegative. Such a decrease in aryl repulsion would favor conformer IIA and the $K$ value would increase. The total repulsion must be a composite of steric and electronic effects, $R_{total} = R_{steric} + R_{electronic}$, and the electronic factor must decrease significantly, or perhaps change sign, as one aryl group becomes more electrophilic. The correlation with the Hammett σ function is not linear, but this is not surprising. The change in $K$, however, is in the direction we would expect for an "acid–base," or charge-transfer, like π interaction between the two aryl groups.

On examination of a model of II we find that, when the aryl groups are gauche, the least steric interaction is obtained when the π orbitals are facing each other. The rings are not parallel, but the 1 carbon atoms, those attached to the benzylic carbons, are about 3 Å apart, well within the van der Waals overlap distance of 3.7 Å.[11] The 4 carbons, those in the para positions, however, are 5 to 6 Å apart. Some distortion of the bond angles and bond distances may be necessary to maximize the attractive forces.

**Conformational Analysis.**—Our initial objective was the determination of the major ground-state conformer for the diethyl 2,3-diarylsuccinates using the Karplus relationship. The only compounds for which an AB coupling constant could be obtained for the two benzylic hydrogens were I-$NO_2$ and II-$NO_2$ (see Figure 2). The coupling constant for each isomer is 12.0 Hz. This coupling constant must be close to the maximum expected for trans protons in this system. Bothner-By[12]

(11) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1962, p 28. The half thickness of an aromatic ring is given as 1.85 Å.

(12) A. A. Bothner-By and C. Naar-Colin, *J. Amer. Chem. Soc.*, **84**, 743 (1962).

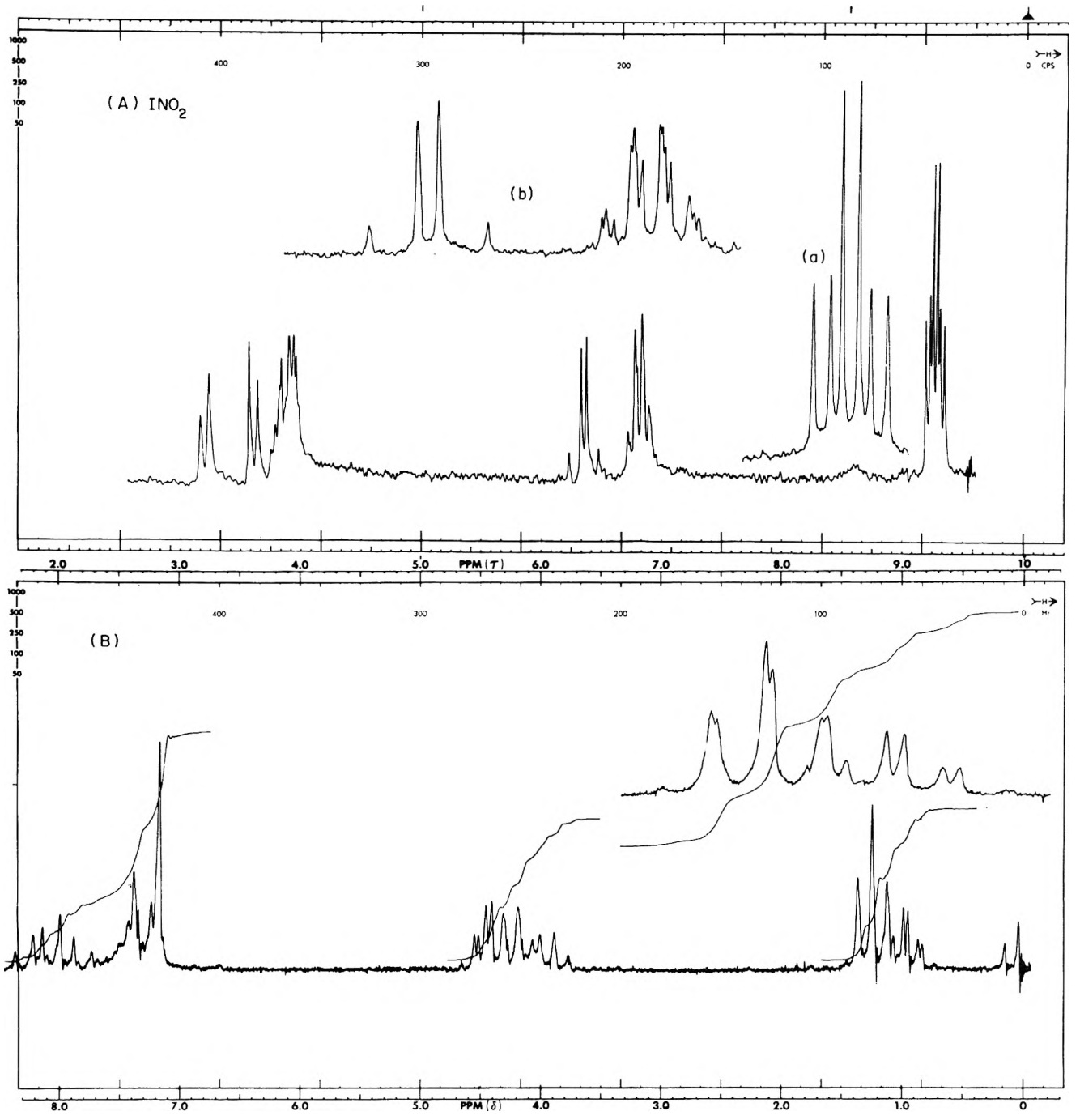



Figure 2.—(A) $INO_2$, 100 MHz, sweep width 1000 Hz, $CDCl_3$. Inserts: (a) methyl triplets, sweep width 250 Hz; (b) benzylic protons (an AB quartet) and methylene multiplet (two quartets, each with $J$ = 7 Hz; each quartet is further split into a doublet, $J$ = 0.6 and 1.5 Hz), sweep width 250 Hz. (B) Equilibrium mixture of $INO_2$ and $IINO_2$, 60 MHz, sweep width 500 Hz, $CDCl_3$. Insert: methyl signals, sweep width 100 Hz.

uses values of 3 and 13 Hz for $J_g$ and $J_t$ in his analysis of the 2,3-diphenylbutanes, and values of 1 and 11 Hz for the 2,3-dibromobutanes since electronegative groups tend to decrease the size of the coupling constant. We can assume, then, that $J_t$ for our system must lie between 11 and 13 Hz (12 Hz is obviously the lower limit). If this assumption is correct, conformers IA and IIA must account for over 90% of their respective isomers, at least for the *p*-nitro compounds.

The fact that only I-$NO_2$ and II-$NO_2$ had an observable coupling constant for the benzylic protons is not surprising. The insensitivity of the chemical shift of benzylic protons to changes in the para substituent can be observed in the ethyl phenylacetates (Table I) with only the *p*-nitro compound showing a significant shift from the unsubstituted ester. A similar insensitivity of the chemical shift of benzylic protons to substituent has been observed by Indictor and coworkers in a study of 2-aryl-1,3-dioxolanes and heteroatomic analogs.[13] Here, too, the *p*-nitro group is anomalous.

As we argued in the previous section, the trend in the equilibrium constants is consistent with a preponderance of conformers IA and IIA. This suggests that a similar conformer distribution exists for all of the compounds, not just the *p*-nitro compounds.

(13) N. Indictor, J. W. Horodniak, H. Jaffe, and D. Miller, *J. Chem. Eng. Data*, **14**, 76 (1969).

In the section concerned with the stereochemistry of the diastereomers we observed that the methyl signals for erythro isomers were always upfield with respect to the methyl signals of their threo counterparts. This result is best explained by a carbethoxy–aryl gauche interaction where the methyl lies over the aromatic $\pi$ cloud and is shielded by the induced diamagnetic field above and below the plane of the ring.[14] In the erythro isomers there is at least one carbethoxy–aryl gauche interaction in each of the conformers, and, in IA, the supposed predominant conformer, there are two such interactions. In IIA, the major conformer for the threo compounds, there are no carbethoxy–aryl gauche interactions and the chemical shift for these methyl protons is about the same as that for the ethyl phenylacetates (Table I). If there were significant contributions from IIB and IIC we would expect to see some upfield shift of the methyl signal.

For each of the substituted compounds in series I, two methyl groups were observed. This is reasonable since the methyl groups are magnetically nonequivalent in each of the conformers, assuming, of course, that the carbethoxy groups interact differently with phenyl and substituted phenyl. The fact that only one methyl triplet is observed for II-Cl and II-OMe can be explained only by the predominance of conformer IIA. In this conformation, the carbethoxy groups are essentially in the same magnetic environment. If IIA is the predominant conformer, the chemical shifts for the methyl signals should differ no more than do the methyl signals in the ethyl phenylacetates (Table I). In an nmr spectrum of a mixture of ethyl phenylacetate and ethyl *p*-chlorophenylacetate taken at 60 MHz, the methyl groups were indistinguishable. The methyl in ethyl *p*-nitrophenylacetate is shifted significantly from that of the unsubstituted compound ($\delta$ 1.25 *vs.* 1.13), and this probably explains the appearance of the two closely spaced triplets in II-$NO_2$.

Interaction of the carbethoxy group with the phenyl or substituted phenyl attached to the same carbon must be minimal. If such interactions were more important than the gauche interactions, we would expect the spectra of the diastereomers to be more alike.

All of the evidence, then, demands that IIA be the predominant conformer for the compounds in series II. The arguments are not so overwhelming for IA, but the size of the benzylic proton coupling constant, energy considerations, especially the three large group interactions in IB and IC *vs.* two such interactions in IA, and some of the spectral evidence, leaves little doubt that this is the predominant conformer in series I.

## Experimental Section

**Preparation of the Erythro Nitriles.**—2,3-Diphenylsuccinonitrile, 2-*p*-methoxyphenyl-3-phenylsuccinonitrile, and 2-*p*-chlorophenyl-3-phenylsuccinonitrile were prepared using procedure A of R. B. Davis.[7]

***erythro*-2-*p*-Acetamidophenyl-3-phenylsuccinonitrile.**—A solution of 30.6 g (0.63 mol) of sodium cyanide in 50 ml of water was heated until the solid dissolved. Absolute methanol (200 ml) was added, the solution was heated to reflux, and 25 ml (0.21 mol) of freshly distilled benzyl cyanide was added all at once. Solid *p*-acetamidobenzaldehyde (41 g, 0.25 mol) was added to the stirred, refluxing solution over 45 min. The *p*-acetamidobenzaldehyde did not go completely into solution. An additional 15 ml (0.13 mol) of freshly distilled benzyl cyanide was added to the reaction mixture followed by the addition of 150 ml of absolute methanol. Following these additions, the solution was refluxed for 1.5 hr. During this period it turned green. The solution was cooled in an ice bath. The precipitate, a yellow solid, was collected and washed with cold 75% methanol–water, with water, and again with 75% methanol–water. The crude solid weighed 26.6 g (37%). Recrystallization from glacial acetic acid yielded a colorless solid, mp 265–268°.

**Preparation of the Erythro Acids.**—2,3-Diphenylsuccinic acid, 2-*p*-methoxyphenyl-3-phenylsuccinic acid, and 2-*p*-chlorophenyl-3-phenylsuccinic acid were prepared by hydrolysis of the corresponding dinitriles using the procedure of Wawzonek.[15] Melting points of the various acids after recrystallization from acetic acid follow: unsubstituted acid, mp 248–249° (lit.[16] mp 252°); *p*-methoxy acid, mp 225–227° (lit.[17] mp 227°); *p*-chloro acid, mp 247–254° (lit.[18] 249–250°).

***threo*-2,3-Diphenylsuccinic Acid.**—This acid was prepared by a modification of the method of Corey and Casanova.[19] A 3-g portion of *erythro*-2,3-diphenylsuccinic acid that had been recrystallized from acetic acid was heated to 300° in a Wood's metal bath. After 5 min, the white acid had been completely converted to a yellow oil. The oil was cooled and triturated with a minimal amount of ether while warming over a steam bath. The ether solution was dried over magnesium sulfate, filtered, and some of the solvent evaporated. The crude anhydride was collected by suction filtration and recrystallized from ether. The faint yellow crystals, 1.3 g (48%), of *threo*-2,3-diphenylsuccinic anhydride had a melting point of 113–114° (lit.[5] mp 115–116°).

The anhydride (5 g, 0.02 mol) was dissolved by heating in a minimal amount of 20% sodium carbonate. After the solution was filtered, the threo acid was precipitated by acidification. The acid (5 g, 0.019 mol, 95%) was collected and recrystallized from ethanol. The acid melted at 178°, resolidified, and melted again at 220–224°. This behavior is essentially that reported in the literature,[20] mp 183°, 220–221°.

***erythro*-2-*p*-Aminophenyl-3-phenylsuccinic Acid.**—A solution of 15.9 g (0.055 mol) of *erythro*-2-*p*-acetamidophenyl-3-phenylsuccinonitrile in 60 ml of acetic acid, 40 ml of sulfuric acid, and 40 ml of water was refluxed for 3 days. After cooling to room temperature, the solution was diluted with an equal volume of water and neutralized to pH 6 with 6 *N* sodium hydroxide. The solid was collected by suction filtration and washed thoroughly with water to dissolve solid salts. The water-insoluble solid, presumably the zwitterionic amino acid (5.6 g, 0.02 mol, 36%), did not melt.

**Preparation of the Erythro Esters. Diethyl 2-*p*-Aminophenyl-3-phenylsuccinate (I-$NH_2$).**—A solution of 5.6 g (0.02 mol) of *erythro*-2-*p*-aminophenyl-3-phenylsuccinic acid in 125 ml of ethanol and 5 ml of concentrated sulfuric acid was refluxed for 3 days. The solution was cooled to room temperature and neutralized with 20% sodium carbonate, and the ethanol was removed at reduced pressure. Ether and additional aqueous base were added to the mixture remaining. The layers were separated and the water layer was washed three times with ether. The combined ether layers were dried over magnesium sulfate and filtered, and the ether was evaporated. The solid was recrystallized from ethanol, yielding 1 g (0.003 mol, 15%) of colorless I-$NH_2$: mp 136.5–137°; nmr ($CDCl_3$) $\delta$ 6.4–7.7 (m, 9, aromatic), 4.31 (s, 2, benzylic), 3.83 (q, $J$ = 7 Hz, $-OCH_2-$), 3.87 (q, $J$ = 7 Hz, $-OCH_2-$), broad $-NH_2$ signal, center *ca.* 3.63, overlapped methylene signals (total integral for $-OCH_2-$ and $-NH_2$ was 6), 0.88 (t, $J$ = 7 Hz, $-CH_3$), 0.92 (t, $J$ = 7 Hz, $-CH_3$) (total integral for two methyl triplets was 6).

*Anal.* Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 69.70; H, 6.77; N, 4.48.

Using essentially the same procedure, the following esters were prepared: I-H, mp 139–140° (lit.[6a] mp 140–141°); II-H, mp 78–82° (lit.[6a] mp 82–83.5°); I-OMe, mp 101–102° (lit.[17] mp 102°); and I-Cl, mp 112–113° (from known acid and nmr perfect for diester).

(14) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969, p 97.

(15) S. Wawzonek, *J. Amer. Chem. Soc.*, **62**, 745 (1940).

(16) W. Roser, *Justus Liebigs Ann. Chem.*, **247**, 152 (1888).

(17) J. A. McRae and A. S. Townsend, *Can. J. Res.*, **11**, 628 (1934).

(18) F. J. Villani and N. Sperber, U. S. Patent 2,852,526 (1958); *Chem. Abstr.*, **53**, 8163*i* (1958).

(19) E. J. Corey and J. Casnova, Jr., *J. Amer. Chem. Soc.*, **85**, 165 (1963).

(20) K. L. Reimer, *Chem. Ber.*, **14**, 1803 (1881).

*erythro*-**Diethyl 2-*p*-Nitrophenyl-3-phenylsuccinate (I-$NO_2$).**—The *p*-amino ester, I-$NH_2$, was oxidized to I-$NO_2$ using the procedure of Emmons:[21] mp 105–106° (from ethanol) (lit.[22] mp 101°); nmr ($CDCl_3$) δ 7.1–8.3 (m, 9, aromatic), 4.34 (d) and 4.51 (d) (2, benzylic), 3.86 (q) and 3.88 (q) (4, $-OCH_2-$), 0.92 (t) and 0.96 (t) (6, $-CH_3$).

**Equilibration Procedure.**—To a solution of 0.12 g ($3.24 \times 10^{-4}$ mol) of I-$NO_2$ in 20 ml of absolute ethanol was added 1 ml ($3.24 \times 10^{-5}$ mol of NaOEt) of a solution prepared from 7.4 mg of sodium dissolved in 10 ml of absolute ethanol. Upon addition of the base, the yellow ester solution turned light brown. The solution was heated at reflux under nitrogen for 24 hr. The reaction was terminated by acidification of the solution with dilute HCl and then pouring it into a beaker of ice. The brown color disappeared when the acid was added. The water–ethanol was milky white at this point. The ethanol was evaporated and the remaining aqueous mixture was washed three times with ether. The ether extracts were combined, dried over magnesium sulfate, and filtered. Evaporation of the ether left 113.9 mg of an oily, yellow solid. This material was analyzed as described in the discussion of the equilibrations.

Equilibrations of I-H, II-H, I-Cl, and I-OMe were carried out using the same procedure. However, no color changes accompanied these equilibrations and these esters were easily collected by suction filtration of the melted ice solution as opposed to the extraction procedure described above.

The nmr spectra were taken using Varian A-60 and Varian HA-100 spectrometers. $CDCl_3$ containing TMS was used as the solvent in all cases.

(21) W. D. Emmons, *J. Amer. Chem. Soc.*, **76**, 3470 (1954).
(22) J. Hoch and D. Legay, *C. R. Acad. Sci., Ser. C*, **255**, 2975 (1962).

**Acknowledgment.**—Our thanks to the National Science Foundation for its support of this research. K. B., S. H., E. H., and R. L. were National Science Foundation Undergraduate Research Participants (GY-7540).

**Registry No.**—I-H, 13638-89-6; I-OMe, 41915-54-2; I-Cl, 41915-55-3; I-$NH_2$, 41915-56-4; I-$NO_2$, 41915-57-5; II-H, 41915-58-6; II-OMe, 41939-32-6; II-Cl, 41915-59-7; II-$NO_2$, 41915-60-0; *erythro*-2-*p*-acetamidophenyl-3-phenylsuccinonitrile, 41915-61-1; benzyl cyanide, 140-29-4; *p*-acetamidobenzaldehyde, 122-85-0; *erythro*-2-*p*-methoxyphenyl-3-phenylsuccinic acid, 41915-62-2; *erythro*-2-*p*-chlorophenyl-3-phenylsuccinic acid, 41915-63-3; *threo*-2,3-diphenylsuccinic acid, 41915-64-4; *erythro*-2,3-diphenylsuccinic acid, 41915-65-5; *erythro*-2-*p*-aminophenyl-3-phenylsuccinic acid, 41915-66-6.

# Catalytic Mechanism of Intermolecularly Carboxylate-Assisted Acyl Transfer[1,2]

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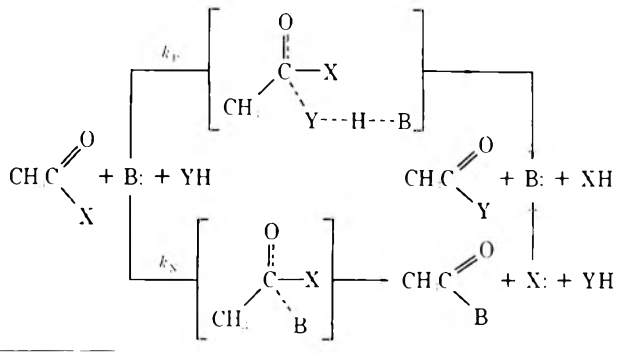
*Received March 30, 1973*

The methanolysis of *p*-nitrophenyl benzoate in methanolic buffers of sodium phenylacetate and phenylacetic acid is general base catalyzed and leads to both methyl benzoate (in 17–54% yield, depending on the buffer-component concentrations) and methyl phenylacetate (in corresponding 83–46% yield). This shows that at least a part of the catalyzed reaction occurs by a nucleophilic mechanism to generate benzoic phenylacetic anhydride, which then rapidly methanolyzes. Synthesis of this anhydride and its methanolysis shows the yield of methyl phenylacetate, under conditions of the kinetic study, to be 96.5 ± 0.6%. The data cited above show that the yield of this product from the phenylacetate-catalyzed part of the ester methanolysis is identical with that from the anhydride methanolysis, demonstrating that the sole mechanism of general-base catalysis in this system is the nucleophilic mechanism. This further supports the view that alcoholysis reactions prefer nucleophilic rather than protolytic general catalysis, in comparison to hydrolysis reactions.

The discrimination of the protolytic ($k_P$) and nucleophilic ($k_N$) mechanisms (Scheme I) of general base catalyzed acyl transfer processes,[5] which are usually kinetically indistinguishable, is of interest not only from standpoint of solution chemical dynamics, but also because of the role of such catalysis in the action of enzymes[6] and in medicinal chemistry.[7] For example, it appears that the imidazole ring of the active-site His-57 of α-chymotrypsin can function either as a protolytic catalyst or as a nucleophilic catalyst in the acylation of the nearby Ser-195 hydroxyl group, with the choice of catalytic mechanism depending on the structure of the substrate.[8] Very good leaving groups favor the nucleophilic mechanism, as is expected from the comprehensive investigation of Gold, Oakenfull, and Riley.[9] These workers studied the acetate-catalyzed hydrolysis of a series of aryl acetates, trapping the acetic anhydride intermediate formed in nucleophilic catalysis with aniline, and found that leaving groups more reactive than *p*-nitrophenoxide give preferential nucleophilic catalysis and less reactive leaving groups give preferential protolytic catalysis: *p*-nitrophenoxide itself produced 56% nucleophilic and 44% protolytic catalysis. The direct application of these results to enzymic systems such as α-chymotrypsin and the other "serine

SCHEME I




(1) Catalysis in Ester Cleavage. V. For part IV, see S. S. Minor and R. L. Schowen, *J. Amer. Chem. Soc.*, **95**, 2279 (1973).
(2) This research was supported by a grant from the National Institutes of Health and was carried out in part at the Computation Center of the University of Kansas. Further details may be found in A. E. Williams, M. S. Thesis in Chemistry, University of Kansas, 1972.
(3) Education Professions Development Act Fellow, 1970–1972.
(4) Holder of a Research Career Development Award of the National Institute of General Medical Sciences.
(5) (a) S. L. Johnson, *Advan. Phys. Org. Chem.*, **5**, 237 (1967); (b) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y., 1969; (c) M. L. Bender, "Mechanisms of Homogeneous Catalysis from Protons to Proteins," Wiley-Interscience, New York, N. Y., 1971.
(6) R. M. S. Smellie, Ed., "Chemical Reactivity and Biological Role of Functional Groups in Enzymes," Academic Press, New York, N. Y., 1970.
(7) R. D. Gandour and R. L. Schowen, *Ann. Rep. Med. Chem.*, **7**, 279 (1972).
(8) C. D. Hubbard and J. F. Kirsch, *Biochemistry*, **11**, 2483 (1972).
(9) V. Gold, D. G. Oakenfull, and T. Riley, *J. Chem. Soc. B*, 515 (1968).

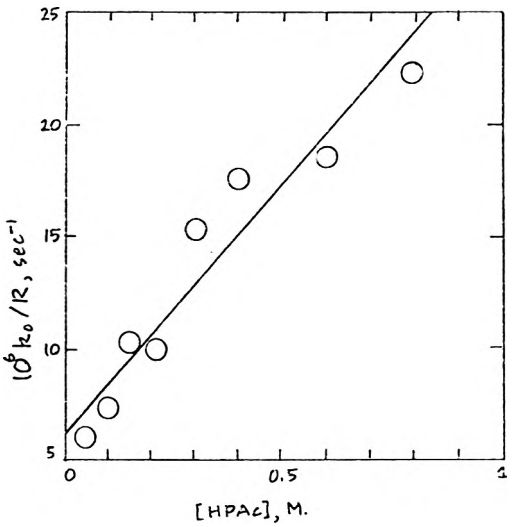



Figure 1.—Graphical test of eq 3. Data are from Table I.

hydrolases" is complicated by the fact that the acyl transfer is to an alcoholic function (the hydroxyl of serine) in the enzymic reactions but to water in the model reaction. Since the acyl acceptor is present in the transition state, at least for protolytic catalysis, its structure could easily affect the relative rate of the two forms of catalysis. Indeed, Behn discovered that acetyl transfer from *p*-nitrophenyl acetate to methanol gave less than 14% of protolytic catalysis, in contrast to 44% in the aqueous reaction, and suggested a steric destabilization of the protolytic transition state by the methyl group of the acyl acceptor.[10] We now report the dissection of nucleophilic and protolytic routes in another methanolytic reaction, determined using a different substrate, catalyst, and analytical technique from those of Behn.

## Results

**Kinetics.**—The methanolysis of *p*-nitrophenyl benzoate (eq 1) in buffers of phenylacetic acid and sodium

$$C_6H_5CO_2C_6H_4NO_2 + CH_3OH \longrightarrow C_6H_5CO_2CH_3 + HOC_6H_4NO_2 \quad (1)$$

phenylacetate yielded the first-order rate constants of Table I. If the reaction is general base catalyzed with only terms in phenylacetate and methoxide ions being important in the rate law, then eq 2 should hold. We

$$k_0 = k_B[\text{NaPAc}] + k_M[\text{NaOCH}_3] \quad (2)$$

define the buffer ratio $R$ by $R \equiv [\text{NaPAc}]/[\text{HPAc}]$ and note that $[\text{NaOCH}_3] = KR$. Substitution of these relations into eq 2 produces eq 3, which shows that a plot

$$k_0/R = k_B[\text{HPAc}] + k_MK \quad (3)$$

of $k_0/R$ *vs.* [HPAc] should be linear with slope of $k_B$ and intercept $k_MK$ if the assumptions are correct. Figure 1 exhibits the requisite linearity, whence $k_B = 2.28 \pm 0.33 \times 10^{-5}\ M^{-1}$ sec$^{-1}$ and $k_MK = 6.0 \pm 1.2 \times 10^{-6}$ sec$^{-1}$.

**Products.**—Scheme II shows the relationship of reaction products to reaction mechanism. Methyl benzoate (MB) is formed by the reaction of substrate with methoxide ion ($k_M$), through protolytic catalysis by

(10) R. L. Schowen and C. G. Behn, *J. Amer. Chem. Soc.*, **90**, 5839 (1968).

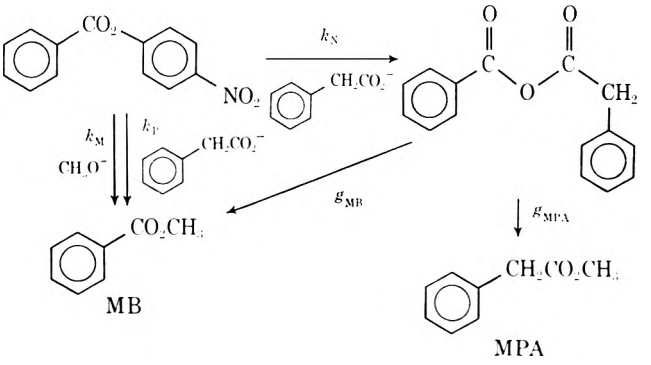
TABLE I

FIRST-ORDER RATE CONSTANTS FOR THE METHANOLYSIS OF 0.01 *M* *p*-NITROPHENYL BENZOATE IN METHANOLIC BUFFERS OF SODIUM PHENYLACETATE (NaPAc) AND PHENYLACETIC ACID (HPAc) AT 45.00 ± 0.05° ($\mu$ = 0.300 *M*)[a]

| [NaPAc], *M* | [HPAc], *M* | $10^6 k_0$,[b] sec$^{-1}$ |
|---|---|---|
| 0.100 | 0.050 | 11.8 ± 0.1 |
| 0.100 | 0.100 | 6.1 ± 0.1 |
| 0.100 | 0.200 | 4.2 ± 0.1 |
| 0.100 | 0.400 | 3.4 ± 0.1 |
| 0.200 | 0.100 | 16.7 ± 1.8 |
| 0.200 | 0.200 | 11.2 ± 0.1 |
| 0.200 | 0.400 | 10.7 ± 0.1 |
| 0.200 | 0.800 | 5.6 ± 0.1 |
| 0.300 | 0.150 | 20.5 ± 0.8 |
| 0.300 | 0.300 | 15.3 ± 0.3 |
| 0.300 | 0.600 | 9.2 ± 0.1 |

[a] Ionic strength maintained by added lithium perchlorate. [b] Error limits are standard deviations.

SCHEME II




phenylacetate ($k_P$) and from that fraction $g_{MB}$ of anhydride formed along the nucleophilic catalysis route ($k_N$) which undergoes attack at the benzoyl carbonyl group. Methyl phenylacetate (MPA) can be formed only from that fraction $g_{MPA}$ of the anhydride formed along the nucleophilic catalysis route which undergoes attack at the phenylacetyl carbonyl group. The fraction $f_{MPA}$ of methyl phenylacetate formed as product in the methanolysis of *p*-nitrophenyl benzoate under any set of circumstances will then be given by the ratio of the rate of nucleophilic catalysis times $g_{MPA}$ to the total rate (eq 4). If $k_0$, $f_{MPA}$, and $g_{MPA}$ could

$$f_{MPA} = k_N[\text{NaPAc}]g_{MPA}/k_0 \quad (4)$$

all be determined at a given sodium phenylacetate concentration, $k_N$ could then be calculated from eq 4.

To determine $g_{MPA}$, benzoic phenylacetic anhydride was synthesized and methanolyzed in dummy reaction solutions from which only *p*-nitrophenyl benzoate was omitted. The product composition was then determined gas chromatographically as explained in the Experimental Section. For two quite different sets of conditions ([HPAc] = 0.400 *M*, [NaPAc] = 0.200 *M*, [$LiClO_4$] = 0.100 *M* and [HPAc] = 0.150 *M*, [NaPAc] = 0.300 *M*), the same result was obtained: $g_{MPA} = 0.965 \pm 0.006$. This was therefore accepted as the general value of $g_{MPA}$.

The products from methanolysis of *p*-nitrophenyl benzoate were similarly determined, as shown in Table II. Each experiment in Table II may be matched with one in Table I to obtain the corresponding value of $k_0$ and thus we can calculate five values of $k_N$ from eq 4.

TABLE II

PRODUCT COMPOSITION IN THE METHANOLYSIS OF 0.01 *M* *p*-NITROPHENYL BENZOATE IN METHANOLIC BUFFERS OF SODIUM PHENYLACETATE (NaPAc) AND PHENYLACETIC ACID (HPAc) AT 45.00 ± 0.05° ($\mu$ = 0.300 *M*)[a]

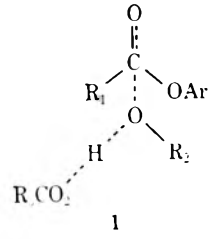
| [NaPAc], *M* | [HPAc], *M* | $(c_{MPA}/c_{MB})$[b] | $f_{MPA}$[c] |
|---|---|---|---|
| 0.100 | 0.200 | 0.85 ± 0.03 | 0.46 ± 0.02 |
| 0.100 | 0.400 | 1.94 ± 0.09 | 0.66 ± 0.04 |
| 0.200 | 0.400 | 1.98 ± 0.07 | 0.66 ± 0.03 |
| 0.200 | 0.800 | 4.81 ± 0.19 | 0.83 ± 0.04 |
| 0.300 | 0.600 | 1.88 ± 0.07 | 0.65 ± 0.03 |

[a] Ionic strength maintained by added lithium perchlorate. [b] Ratio of concentration of methyl phenylacetate to methyl benzoate, determined as described in the Experimental Section. Error limits are standard deviations. [c] Fraction of methyl phenylacetate in product.

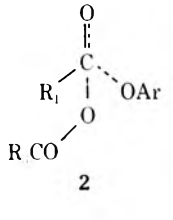
In the order of the entries in Table II, we calculate $10^5$ $k_N$ ($M^{-1}$ sec$^{-1}$) = 2.00, 2.33, 3.66, 2.40, 2.07. Discarding the value of 3.66, we have $k_N$ = 2.20 ± 0.17 × $10^{-5}$ $M^{-1}$ sec$^{-1}$. This is equal to the value of $k_B$ (2.28 ± 0.33 × $10^{-5}$ $M^{-1}$ sec$^{-1}$) determined above, which shows the mechanism of catalysis to be solely nucleophilic.

## Discussion

As before,[10] we presume the activated-complex structures along the protolytic and nucleophilic routes to be **1** and **2**, respectively. In the previously studied



**1**



**2**

acetate catalysis of *p*-nitrophenyl acetate ($R_1$ = $R_3$ = $CH_3$) solvolysis, the shift from nearly equal free energies of **1** and **2** in hydrolysis ($R_2$ = H)[9] to a lower relative free energy for **2** in methanolysis ($R_2$ = $CH_3$)[10] is interpreted most simply as a steric destabilization of **1** relative to **2** by the methyl group. Two changes were made in transforming to the system used in the present study: $R_3$ was changed from $CH_3$ to $C_6H_5CH_2$ and $R_1$ from $CH_3$ to $C_6H_5$. At first glance, $R_1$ should have little effect on the relative free energies of **1** and **2**, while the change in $R_3$ to a more electron-withdrawing group should favor **1**, in which the center of negative charge is closer to $R_3$. Since only catalysis *via* **2** is observed, this effect is apparently insufficient to overcome the steric destabilization of **1** by the methyl at $R_2$.

It is of course possible that **1** is more crowded near $R_1$ and is therefore destabilized by $C_6H_5$ *vs.* $CH_3$, thus cancelling the tendency at $R_3$. Indeed this reaction is about 23-fold slower than the acetate-catalyzed reaction of the acetate ester at the same temperature (we calculate $k_N$ = 4.73 × $10^{-4}$ $M^{-1}$ sec $^{-1}$ from Behn's data[10]): the question is, how much of this factor comes from the weaker basicity of the catalyst? To estimate this contribution, we assume the difference in p$K_a$ of acetic and phenylacetic acids to be the same in methanol and water ($\Delta$p$K_a$ = 0.47, or a factor of 3). If **2** strongly resembles the tetrahedral intermediate, then this factor of 3 should roughly represent the expected factor in rate, since the $R_3CO_2^-$ moiety in **2** would resemble that in $R_3CO_2H$. As **2** more closely resembles the anhydride product, however, the rate factor should increase to a limit[11] of $3^{1.72}$ or 6.3. Thus the residual effect to be attributed to the phenyl group is between 23/3 ~ 4. Since some of this surely arises from destruction of reactant-state conjugation between phenyl and carbonyl, on activation, it seems unlikely that phenyl exerts a decisive differential steric effect in determining the lower free energy of **2** in the present case.

The conclusion is that nucleophilic catalysis of acyl transfer to alcohlic functions is preferred over protolytic catalysis, when compared to acyl transfer to water. Other things being equal, this conclusion leads us to expect nucleophilic catalysis in the chymotrypsin active site as observed by Hubbard and Kirsch[8] for activated esters. Needless to say, other things are radically not equal in active sites of serine acyltransferases, but our findings indicate that, when an enzyme undergoes protolytically accelerated acyl transfer to serine, its catalytic power must by capable of overcoming an extra barrier not apparent from model studies in aqueous solution.

## Experimental Section

**Materials.**—All commercially obtained materials were used with no additional purification unless otherwise specified. Absolute methanol (anhydrous, Mallinckrodt) was purified according to the method of Lund and Bjerrum.[12] Methyl phenylacetate, prepared by refluxing of phenylacetic acid (Matheson Coleman and Bell, recrystallized) in methanol for 1 hr, had bp 213–214° (lit.[13] bp 215°). *p*-Nitrophenyl benzoate was prepared by the reaction of benzoyl chloride (Mallinckrodt, redistilled) and *p*-nitrophenol (Matheson Coleman and Bell, practical grade, recrystallized once from 0.5 *N* HCl) in cold pyridine (Baker Analyzed Reagent) for 15 min. The slightly yellow crystals obtained were recrystallized from an ethanol–methanol (1:7, v/v) mixture, yielding white crystals, mp 140–141° (lit.[14] mp 140–142°). Thallium(I) phenylacetate was prepared by adding 12.47 g (0.05 mol) of thallium(I) ethoxide, 98% (Aldrich), all at once to a stirred solution of 7.49 g (0.055 mol) of phenylacetic acid in ether under dry nitrogen. The white crystals were recrystallized from aqueous ethanol, mp 156–157°.

**Benzoic phenylacetic anhydride**, apparently not previously described, was prepared by allowing 10 g (0.029 mol) of an ether suspension of thallium(I) phenylacetate to react with 4.13 g (0.029 mol) of benzoyl chloride at 35° for 5 hr.[15] After the thallium chloride was filtered from the solution and the ether was evaporated, benzoyl chloride was removed by distillation at a pressure of 0.1 mm. The residue was washed quickly with 10 ml of 5% aqueous sodium bicarbonate solution and then with 10 ml of water, dried over Drierite for 30 min, and dissolved in warm benzene. Enough petroleum ether (bp 20–40°) was added to cause cloudiness and the solution was left in the refrigerator for about 10 hr. The white crystals, mp 62–63°, showed ir and nmr spectra and elemental composition (*Anal.* Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03. Found: C, 76.07; H, 5.25.) consistent with the presumed structure. Samples were prepared immediately before use to avoid disproportionation.

**Kinetic Procedure.**—Reaction rates were determined by following the increase in absorption at 395 nm, owing to the formation of *p*-nitrophenol, with a Gilford Multiple Sample Absorbance Recorder (Model 2000).

**Product Recovery by Multiple-Contact Pseudocountercurrent Extraction.**—The product esters were separated from the reaction

(11) J. Gerstein and W. P. Jencks, *J. Amer. Chem. Soc.*, **86**, 4655 (1964).
(12) H. Lund and I. Bjerrum, *Ber.*, **64**, 210 (1931).
(13) A. I. Vogel, *J. Chem. Soc.*, 654 (1948).
(14) M. L. Bender, F. J. Kezdy, and B. Zerner, *J. Amer. Chem. Soc.*, **85**, 3017 (1963).
(15) E. C. Taylor, G. W. McLay, and A. McKillop, *J. Amer. Chem. Soc.*, **90**, 2422 (1968).

mixture by the pseudo-CCD technique described by Wiberg.[16] A reaction-solution aliquot of 30 ml was distributed in equal parts into four separatory funnels, each containing 250 ml of water. Four successive 50-ml portions of cyclohexane were passed down the series of funnels and combined at the end. The cyclohexane solution was then washed with 5% sodium bicarbonate solution and with water, dried over Drierite, and concentrated to 1 ml by flash distillation. After filtration through glass wool, the solution was analyzed for ester composition by gas chromatography.

**Product Analysis by Gas Chromatography.**—A Model 90-P3 Aerograph gas chromatograph, equipped with a thermal detector and a Model 8000–2600 Barber-Coleman recorder, was used with a 10 ft × 0.25 in. column of 60–80 mesh Varian Aerograph Chromosorb W regular solid support coated with 15% by weight diethylene glycol succinate (column temperature 190°, helium carrier gas flow 45 ml/min). Area integrations of the chromatogram peaks were obtained by tracing the peaks using Clearprint technical paper (no. 1000PH) and a light tracing pencil and then cutting out the traces and weighing them on a Mettler analytical balance (type H16).

**Calibration.**—Buffer solutions similar to those for the methanolysis of *p*-nitrophenyl benzoate and benzoic phenylacetic anhydride were used for acquiring the calibration data. These buffers, containing no substrate, were heated for 4 hr at 45.00° in a constant-temperature bath, after which methyl benzoate (0.0010–0.0050 *M*), methyl phenylacetate (0.0050–0.0090 *M*), benzoic acid (0.0050 *M*), and *p*-nitrophenol (0.0100 *M*) were added to simulate the products of an actual methanolysis. The samples of esters were weighed out in small combustion boats and the entire boat was put into the calibration solution. All other samples were added by volumetric pipettes from stock solutions. The esters were then separated and analyzed by gas chromatography as described in the above paragraphs. Esterification of buffer under reaction conditions led to high values of the methyl phenylacetate:methyl benzoate ratio. Therefore a plot of peak area ratio *vs.* actual product composition had to be prepared and used to calculate true reaction-product distributions.

**Registry No.**—*p*-Nitrophenyl benzoate, 959-22-8; benzoic phenylacetic anhydride, 41085-80-7; thallium(I) phenylacetate, 41085-81-8; benzoyl chloride, 98-88-4.

(16) K. B. Wiberg, "Laboratory Technique in Organic Chemistry," McGraw-Hill, New York, N. Y., 1960, p 187.

# Stable Carbocations. CLVII.[1] Protonation of 2,4,6-Trimethoxytoluene and 2,4,6-Trimethoxy-*m*-xylene in Superacid Solutions

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Protonation of 2,4,6-trimethoxytoluene and -*m*-xylene in $FSO_3H$–$SO_2$ and in HF–$SbF_5$–$SO_2ClF$ solution is reported. The structure of the formed arenium ions and methylated oxocyclohexenyl dications is based on their pmr spectroscopic study. The relative stability of these ions is discussed in terms of resonance, inductive, and steric effects.

A series of stable arenium ions have been observed previously in superacid media.[3] Among them, methylbenzenium ions,[4a] fluorobenzenium ions,[1,4b] halomethylbenzenium ions,[5] and hydroxy- and alkoxybenzenium ions[6] have been reported. Recently, we have succeeded even in the direct observation of the parent benzenium ion[7] and naphthalenium ion.[8]

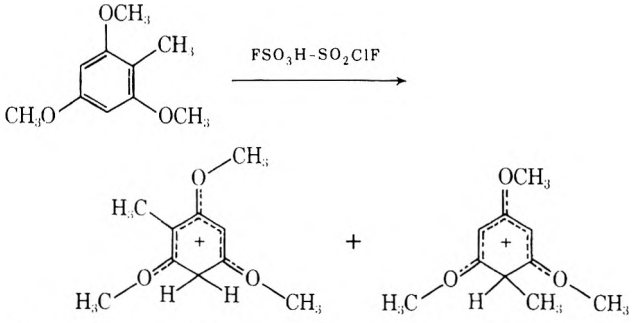
Protonation of arenes generally takes place at a ring position to which hydrogen is attached. Carbons bearing substituents, however, also can be protonated to give stable arenium ions, as first shown by Vaughan and his associates[9] in case of some methoxy-1,2,3-trimethylbenzenes and *o*-xylenes.

We now wish to report further such examples of arenium ions and methylated cyclohexenyl dications obtained by protonation of 2,4,6-trimethoxytoluene and 2,4,6-trimethoxy-*m*-xylene in $FSO_3H$–$SO_2$ and HF–$SbF_5$–$SO_2ClF$ solution.

(1) Part CLVI: G. A. Olah and Y. K. Mo, *J. Org. Chem.*, **38**, 3221 (1973).
(2) Postdoctoral Research Associate, 1969–1971.
(3) For a review, see D. M. Brouwer, E. L. Mackor, and C. MacLean in "Carbonium Ions," Vol. 2, G. A. Olah and P. v. R. Schleyer, Ed. Wiley-Interscience, New York, N.Y., 1970, p 864.
(4) (a) G. A. Olah, *J. Amer. Chem. Soc.*, **87**, 1103 (1965); (b) G. A. Olah and T. E. Kiovsky, *ibid.*, **89**, 5692 (1967).
(5) (a) G. A. Olah and T. E. Kiovsky, *J. Amer. Chem. Soc.*, **90**, 2583 (1968); (b) D. M. Brouwer, *Recl. Trav. Chim. Pays-Bas*, **87**, 335, 342 (1968).
(6) (a) G. A. Olah and Y. K. Mo, *J. Amer. Chem. Soc.*, **94**, 5341 (1972); (b) *J. Org. Chem.*, **38**, 353 (1973); (c) A. J. Kresge, S. G. Mylonakis, Y. Sato, and V. P. Vitullo, *J. Amer. Chem. Soc.*, **93**, 6181 (1971).
(7) (a) G. A. Olah, R. H. Schlosberg, D. P. Kelly, and Gh. D. Mateescu, *J. Amer. Chem. Soc.*, **92**, 2546 (1970); (b) G. A. Olah, R. H. Schlosberg, R. D. Porter, Y. K. Mo, D. P. Kelly, and Gh. D. Mateescu, *ibid.*, **94**, 2034 (1972).
(8) G. A. Olah, Gh. D. Mateescu, and Y. K. Mo, *J. Amer. Soc.*, **95**, 1865 (1973).
(9) M. P. Hartshorn, K. E. Richards, J. Vaughan, and G. J. Wright, *J. Chem. Soc. B*, 1624 (1971).

## Results and Discussion

Protonation of 2,4,6-trimethoxytoluene in $FSO_3H$–$SO_2ClF$ gave a mixture of two benzenium ions (**1** and **2**). The pmr spectrum of the solution (Figure 1) is

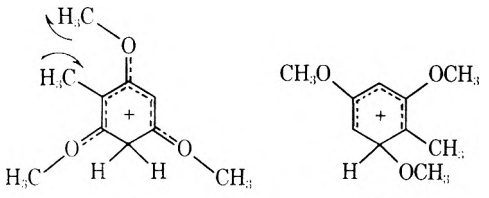



| Temp, °C | 1, % | 2, % |
|---|---|---|
| −70 | 80 | 20 |
| −50 | 77 | 23 |
| −30 | 73 | 27 |
| −20 | 72 | 28 |

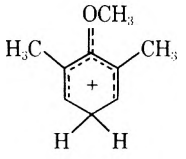
well resolved and shows in the methyl proton region (of benzenium ions) a singlet at $\delta$ 1.85 and a doublet at $\delta$ 1.59 ($J$ = 7.5 Hz). In the vinyl region, there are two singlets at $\delta$ 6.10 and 6.27. If protonation take place at the unsubstituted position of 2,4,6-trimethoxytoluene, only one methyl and one vinylic proton absorption should be observed. These data suggest the

formation of ion 2 (*via* protonation of the methyl-bearing carbon). Furthermore, a quartet at δ 3.63 is also observed for the methine proton of ion 2. It is interesting to note that the methylene proton (δ 3.90) of ion 1 is more deshielded than the methine proton of ion 2. There are only two methoxy absorptions appearing at δ 4.03 and 4.26 in a ratio of 2:1 indicating the coincidence of the *o*-$OCH_3$ and of the *p*-$OCH_3$ in ions 1 and 2. In addition, the ratio of 1 and 2 is temperature dependent, *i.e.*, a higher ratio is observed at lower temperature. These data indicate that 1 is thermodynamically more stable than 2.

One may suggest three possible mechanisms for the reversible interconversion process (1 ⇌ 2). First, it could proceed by intermolecular exchange between the precursor and the benzenium ion; second, it could involve an unstable intermediate such as **1b** and a 1,2-hydrogen shift (intramolecular); and, finally, it could involve hydrogen transfer with the acid solvent $FSO_3H$–$SO_2$, which is present in large excess.



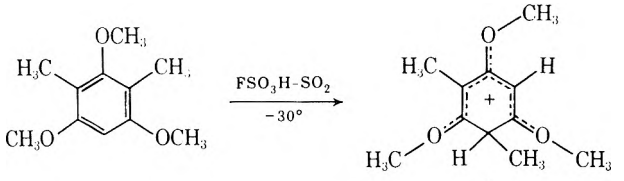
1a 1b



3

It is known that the pmr spectrum of C-protonated anisole (4-methoxybenzenium ion) is temperature dependent, indicating the rotation of C=O partial double bond at higher temperature.[6] However, the pmr of both ion 1 and 2 (present in the same solution) is temperature independent. It is therefore suggested that the ion formed from 2,4,6-trimethoxytoluene has structure 1 rather than that of **1a** or of equibrating of ions 1 ⇌ **1a**. Ion **1a** is expected to be less stable than ion 1 owing to prevailing steric effects. This kind of steric effect has been demonstrated when 2,6-dimethylanisole was not found to be C-protonated to give 3,5-dimethyl-4-methoxybenzenium ion **3**.[6] On the other hand, the C=O partial double bond of ion 2 may be rapidly rotating even at −80°, since its double bond character is less pronounced than that of the 4-methoxybenzenium ion (or there is less charge introduced into the *p*-$CH_3O$ group).

Protonation of 2,4,6-trimethoxy-*m*-xylene in $FSO_3H$–$SO_2$ solution at −30° gave exclusively ion **4**. The




4

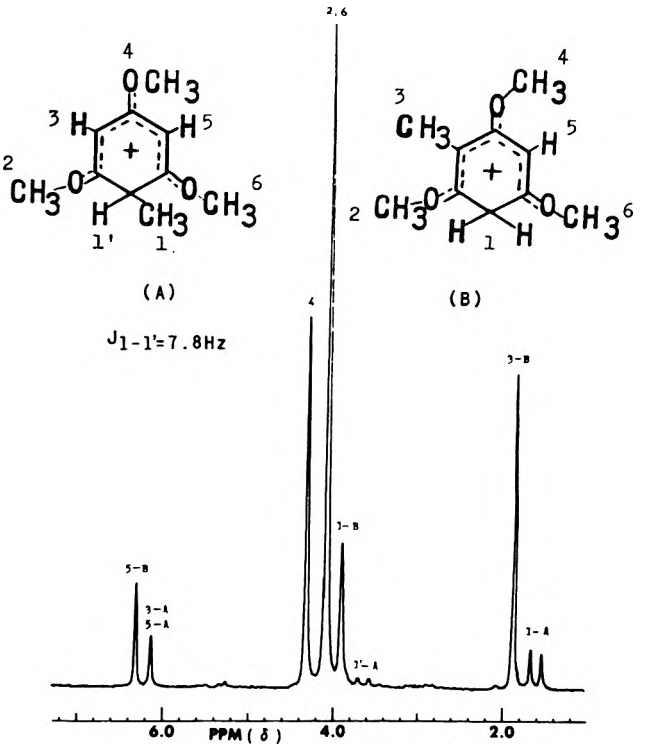
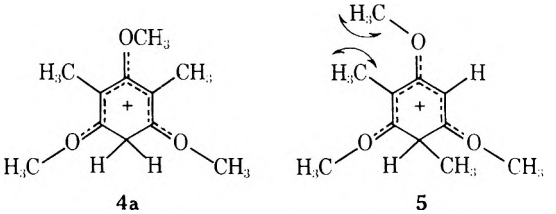



Figure 1.—Pmr spectrum of 1-methyl-2,4,6-trimethoxybenzenium ion (A) and 3-methyl-2,4,6-trimethoxybenzenium ion (B).

isomeric ion **5** was not observed at the temperature range −80 to −20°, indicating considerable stability difference between ions **4** and **4a**.

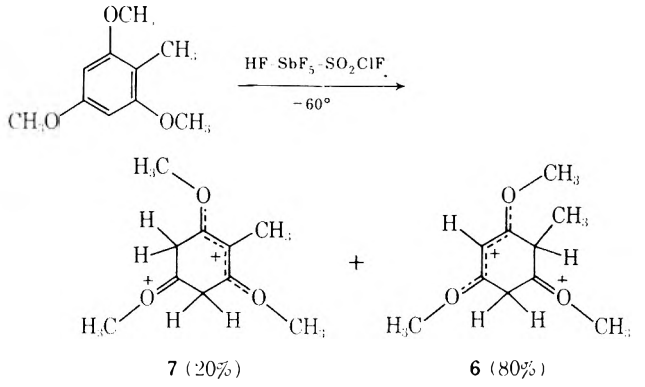


4a 5

In the pmr spectrum of ion **4** the methyl group which is attached to the $sp^3$ carbon shows a doublet at δ 1.62 ($J$ = 7.5 Hz). It is coupled to the methine proton which displays a quartet at δ 3.89 ($J$ = 7.5 Hz). The other methyl proton absorption is a slightly deshielded singlet at δ 1.86. The three methoxy groups of ion **4** are significantly deshielded and situated in different environments. Consequently, they are no longer equivalent and their signals appear at δ 4.11, 4.17, and 4.32 as three singlets. The most deshielded absorption (δ 4.32) is evidently assigned to the *p*-$OCH_3$. Because of the obvious steric effect, the structure of the ion obtained from protonation of 2,4,6-trimethoxy-*m*-xylene in $FSO_3H$–$SO_2$ solution must have the structure **4** and not **5**. Consequently, we can assign the more deshielded methoxy singlet at δ 4.17 to the 2-$OCH_3$ because of the anisotropy effect of the *p*-$OCH_3$.[6] Finally, it is interesting to note that the vinylic proton of **5** is more shielded (δ 6.16) than the ring protons of its precursor (δ 6.23), indicating that there is essentially no charge introduced into the meta position upon protonation.

In stronger superacidic $FSO_3H$–$SbF_5$–$SO_2ClF$ and HF-$SbF_5$–$SO_2ClF$ solution, 2,4,6-trimethoxytoluene was

diprotonated to give the methylated oxocyclohexenyl dications 6 and 7 in a ratio of 4:1. The ratio of these

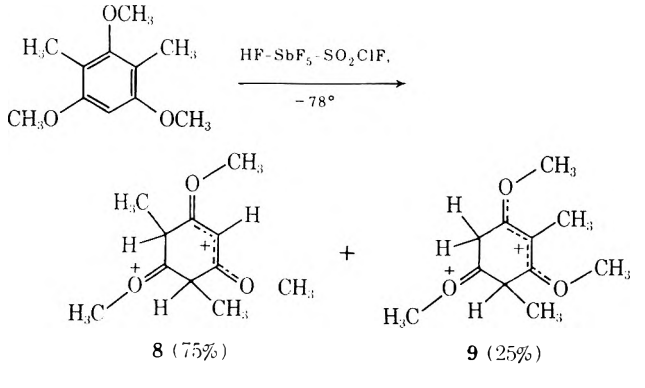



7 (20%) 6 (80%)

ions is temperature independent. The pmr spectrum of the solution is different from that of 2,4,6-trimethoxytoluene when protonated in $FSO_3H$–$SO_2$ (each corresponding absorption is further deshielded). It shows in the methyl proton region (of benzenium ions) a doublet at $\delta$ 2.21 ($J$ = 6 Hz, $CH_3$, of 7) and a singlet at $\delta$ 2.41 ($CH_3$ of 6). The methine proton absorption of 6 is a quartet at $\delta$ 4.20. There is a singlet absorption at $\delta$ 7.06 which can be assigned to the vinylic proton of dication 7. The $CH_3$—$^+O$=C proton absorptions of 6 and 7 are two close singlets at $\delta$ 5.50 and 5.70 (also in a ratio of 4:1). The methoxy groups attached to the terminal allylic carbons in dications 6 and 7 show a coincidental singlet at $\delta$ 4.91. The methylene protons of 6 and 7 also show a coincidental slightly broadened singlet at $\delta$ 5.0.

Methylated oxocyclohexenyl dications 6 and 7 were formed when ions 1 and 2 in $FSO_3H$–$SO_2$ solution were added to $SbF_5$–$SO_2ClF$ or HF–$SbF_5$–$SO_2ClF$ solution at −78°. This result evidently shows that the formation of 6 and 7 takes place through additional protonation at the meta carbons of 1 and 2. Dication 6 is the only product ion when 2 is further protonated at the unsubstituted meta positions. Both dication 6 and 7 can be formed when 1 is further protonated at C-3 and C-5, respectively. The ratio of ions 1 and 2 is 4:1 at −70°. Thus, the ratio of protonation at C-3 and C-5 is becoming 3:1, although the former protonation is sterically unfavorable. This result may be accounted for by the unusual stability of dication 6.

Similarly, when 2,4,6-trimethoxy-*m*-xylene was protonated in HF–$SbF_5$–$SO_2ClF$ solution, two methylated oxocyclohexenyl dications 8 and 9 (in a ratio of 3:1)




8 (75%) 9 (25%)

were obtained. The pmr spectrum of the solution is different from that when 2,4,6-trimethoxy-*m*-xylene was protonated in $FSO_3H$–$SO_2$ solution (each corresponding absorption peak is further deshielded). It is less resolved presumably owing to the viscosity of the medium. The methyl group attached to the central allylic carbon shows a deshielded singlet at $\delta$ 2.42. The other methyl group of dication 9 and the two symmetrical methyl groups of dication 8 show a multiplet pmr absorption at $\delta$ 2.2–2.3. The formation of dication 8 can easily be recognized by the vinylic proton singlet absorption at $\delta$ 7.01. The $CH_3$—$^+O$=C of 8 and 9 show two close singlet absorptions at $\delta$ 5.64 (75%) and 5.50 (25%), respectively. The other methoxy groups and the methylene protons show a slightly broadened singlet absorption at $\delta$ 5.0. The methine protons of 8 and 9 show a multiplet at $\delta$ 4.2–4.4. Finally, it is interesting to note that the additional protonation of 5 (to form 8 and 9) occurring at the meta carbon bearing a methyl group is again 3:1 with respect to the other unsubstituted meta carbon.

The study of protonation of 2,4,6-trimethoxytoluene and -*m*-xylene in superacid solutions led to the formation of the observed novel benzenium ions and methylated oxocyclohexenyl dications, indicating the importance of steric and resonance effects on the stability of arenium ions. Geminally substituted arenium ions may play an important role in electrophilic reactivity of polyalkoxybenzenes.

## Experimental Section

**Materials.**—2,4,6-Trimethoxytoluene was commercially available material from Aldrich Chemical Co. and used without further purification. 2,4,6-Trimethoxy-*m*-xylene was prepared according to the method reported for the preparation of 1,3-dimethoxy-2-methylbenzene.[10] 2,4,6-Trimethoxytoluene (0.1 mol) was added to 200 ml of an ether solution of phenyllithium (0.1 mol). After the solution was kept for 2 days at room temperature in the dark, dimethyl sulfate (0.12 mol) was added to the solution. It was refluxed for 2 hr, then poured onto ice–water. The product was extracted with ether and isolated as a white solid, mp 60°, with correct analysis and nmr spectrum.

Fluorosulfuric acid (Allied Chemical Co.) was doubly distilled and antimony pentafluoride (Allied Chemical Co.) was triply distilled before used. HF was obtained form J. T. Baker Chemical Co. The preparation of superacid solutions has been described previously.[11]

**Preparation of the Ions and Their Nmr Study.**—Solutions of the ions for nmr studies were prepared by adding 0.2 g of the aromatic to 2 ml of $FSO_3H$–$SO_2ClF$ (HF–$SbF_5$–$SO_2ClF$) solution which had been cooled at −78°. The well-stirred solutions were allowed to slightly warm till clear, slightly yellow solutions were obtained.

A Varian Associates Model A-56-60A nmr spectrometer equipped with a variable-temperature probe was used to obtain all spectra. External capillary tetramethylsilane was used for proton reference.

**Acknowledgment.**—Support of our work by the donors of the Petroleum Research Fund, administered by the American Chemical Society, and by the National Science Foundation is gratefully acknowledged.

**Registry No.**—1, 42077-30-5; 2, 42077-31-6; 4, 42077-32-7; 6, 42200-04-4; 7, 42077-33-8; 8, 42077-34-9; 9, 42077-35-0; 2,4,6-trimethoxytoluene, 14107-97-2; 2,4,6-trimethoxy-*m*-xylene, 1521-61-5.

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# Ring Expansions. I. Diazomethane and Tiffeneau–Demjanov Ring Expansions of Norcamphor and Deyhydronorcamphor[1]

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The ring expansion of norcamphor (1) with diazomethane in methanol leads to a complex mixture of homologous ketones. When 1 was allowed to react with less than a stoichiometric amount of diazomethane, bicyclo[3.2.1]-octan-2-one (3) and bicyclo[3.2.1]octan-3-one (4) were formed in the ratio of 70:30. Ring expansion of *exo*-2-aminomethylbicyclo[2.2.1]heptan-*endo*-2-ol (12) gave ketones 3 and 4 in the ratio of 62:38 while ring expansion of *endo*-2-aminomethylbicyclo[2.2.1]heptan-*exo*-2-ol (15) yielded 3 and 4 in the ratio of 91:9. Comparison of these results indicates a predominance of exo attack of diazomethane on 1. Similarly, the reaction of less than a stoichiometric amount of diazomethane in methanol with dehydronorcamphor (2) yielded bicyclo[2.1.1]oct-6-en-2-one (7) and bicyclo[3.2.1]oct-6-en-3-one (8) in the ratio of 53:47. Ring expansion of *exo*-2-aminomethylbicyclo[2.2.1]hept-5-en-*endo*-2-ol (18) yielded ketones 7 and 8 in the ratio of 50:50. Ring expansion of *endo*-2-aminomethylbicyclo[2.2.1]hept-5-en-*exo*-2-ol (21) afforded 7 and 8 in the ratio of 77:23. Predominant exo attack of diazomethane on 2 is indicated by these results. Competition experiments indicated that 2 was two times as reactive as 1 toward diazomethane in methanol. The migratory aptitudes for the compounds examined in this study are compared to other *exo*- and *endo*-2-norbornylcarbinyl systems.

Cyclic ketones can be transformed into their higher homologs by reaction with diazoalkanes[2] and by the Tiffeneau–Demjanov[3] rearrangement of amino alcohols derived from the cyclic ketone. If the diazoalkane ring expansion is carried out in an alcoholic solvent[4] the intermediates in both types of ring expansion reactions is a β-hydroxy diazonium ion.

The extensive investigations of Gutsche[5] on the ring expansion of unsymmetrical cyclic ketones by the diazoalkane method have elucidated the importance of electronic and steric factors in governing the migratory aptitude of the ring carbon atoms. Steric factors also play an important role in determining the stereochemistry of attack of the diazoalkane as well as the amount of epoxide formation accompanying ring expansion.[6]

The stereochemistry of attack of diazomethane on *trans*-2-decalone[7] and 5*A*-3-oxo steroids[8] has been determined. Comparison of the ratio of isomeric ketone products obtained in these systems, when ring expanded with diazomethane, to the ratio obtained from the epimeric amino alcohols indicated predominant equatorial attack of diazomethane. The stereochemistry of attack and the migratory aptitudes in the diazoethane ring expansion of 4-alkylcyclohexanones[9] and methylcyclopropanones[10] have been examined. The product ratios obtained in these studies were explained in terms of steric approach control and conformational interactions in the intermediates.

Only recently has the diazomethane ring expansion of bridged bicyclic ketones been investigated. The reaction of norcamphor with diazomethane was first reported by Sauers.[11] In a more extensive study Pietra[12] determined the relative reactivities of a series of bicyclo[*n*.2.1]alkanones toward diazomethane as well as the migratory aptitudes for norcamphor and bicyclo[3.2.1]octan-2-one. The migratory aptitudes in the ring expansion of bicyclo[2.1.1]hexan-2-one and its monomethylated derivatives have also been reported.[13] The effect of unsaturation on the stereochemistry of attack and the product ratios obtained in the reaction of diazomethane with 7-ketonorbornene and 7-ketonorborane has been examined by Bly.[14] In order to assess the importance of stereochemistry in determining the migratory aptitudes in the ring expansion of bridged bicyclic ketones we have studied the Tiffeneau–Demjanov ring expansion of the epimeric β-amino alcohols of norcamphor (1) and dehydronorcamphor (2). The ketonic product ratios obtained in these ring expansions are compared with the product ratios obtained in the diazomethane ring enlargement of 1 and 2.

## Experimental Section[15]

**Preparation of *exo*-2-Aminomethylbicyclo[2.2.1]heptan-*endo*-2-ol (12).**—A 300-ml pressure reaction vessel (Autoclave Engineers, Inc.) was flushed with nitrogen and cooled externally by a Dry Ice–acetone bath. The vessel was charged with 3.0 g (25 mmol) of epoxide 11[16] in 10 ml of anhydrous ether and 4.8 g (0.12 mol) of sodium amide[17] in 65 ml of liquid ammonia. The apparatus was sealed and allowed to warm to room temperature.

(1) This work was supported in part by a grant from the donors of the Petroleum Research Fund, administered by the American Chemical Society, and a Marquette University Committee on Research Grant.

(2) (a) C. D. Gutsche, *Org. React.*, **8**, 364 (1954); (b) C. D. Gutsche and D. Redmore, "Carbocyclic Ring Expansion Reactions," Academic Press, New York, N. Y., 1968.

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(15) All boiling and melting points are uncorrected. The infrared spectra were recorded on a Beckman IR-12 spectrophotometer and a Perkin-Elmer spectrophotometer. The nuclear magnetic resonance spectra were recorded on a Varian A-60A nmr spectrometer. Quantitative gas–liquid phase chromatographic analyses were obtained using an F & M Model 700 gas chromatograph equipped with a Leeds and Northrup Speedomax H nonintegrating recorder, and preparative separations were performed on an F & M Model 770 automatic preparative gas chromatograph; both instruments were equipped with thermal conductivity detectors. Microanalyses were performed by Chemalytics, Inc., Tempe, Ariz. Mass spectra were run on a Hitachi RMU-6A spectrometer at Purdue University, Lafayette, Ind.

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(17) C. R. Hauser, J. T. Adams, and R. Levine, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 291.

After 24 hr,[18] the apparatus was recooled in a Dry Ice–acetone bath and opened, and the ammonia was allowed to evaporate upon warming to room temperature. The resulting slurry was quenched with a saturated ammonium chloride solution and extracted with five 150-ml portions of ether. The combined ether extract was dried ($MgSO_4$) and concentrated. The residue was flash vacuum distilled in a short-path distillation apparatus to yield 2.77 g of crude amino alcohol, bp 104° (0.05 mm). The crude product was vacuum sublimed (50–60°, 0.02 mm) three successive times to yield 1.5 g (44%) of amino alcohol, mp 108.5–111° dec. The amino alcohol was extremely hygroscopic and was therefore characterized through its hydrochloride and benzamide derivatives.

A hydrochloride was prepared using the method of Parham:[19] mp 259–260° dec; ir (Nujol) 3493, 1623, 1600, 1212, 1023, 1000, 1163, 795, and 708 $cm^{-1}$; nmr ($CF_3CO_2H$) δ 1.27–2.33 (unresolved pattern, 9 protons), 2.44 (broad s, 2, bridgehead protons), 3.47 (q, 2, $J$ = 6 Hz, $CH_2NH_3^+$), 7.0 (broad, 3, $NH_3^+$).

*Anal.* Calcd for $C_8H_{16}ONCl$: C, 54.08; H, 9.01; N, 7.88; Cl, 19.97. Found: C, 54.11; H, 8.82; N, 7.47; Cl, 19.82.

A benzamide derivative was prepared in the usual manner,[20] mp 150–151°.

*Anal.* Calcd for $C_{15}H_{19}O_2N$: C, 73.44; H, 7.80; N, 5.36. Found: C, 73.13; H, 7.68; N, 5.71.

**Preparation of *endo*-2-Aminomethylbicyclo[2.2.1]heptan-*exo*-2-ol (15).**—A 3.31-g (26.7 mmol) sample of epoxide 17[16] in 10 ml of anhydrous ether was allowed to react with a freshly prepared solution of 5.2 g (0.134 mol) of sodium amide in 65 ml of liquid ammonia in the manner described in the synthesis of 12. The crude product was vacuum sublimed (50–60°, 0.01 mm) and desiccated over phosphorus pentoxide to yield 2.32 g (62%) of amino alcohol: mp 60–130°; ir (Nujol) 3315, 3280, 2950, 1640, and 1375 $cm^{-1}$. The amino alcohol was extremely hygroscopic and therefore was characterized as its benzamide derivative:[20] mp 132–132.5°; nmr ($CDCl_3$) δ 7.6 (m, 5, phenyl), 6.9 (broad s, 1, NH), 3.6 (d, $J$ = 5.5 Hz, 2, $CH_2N$), 3.13 (s, 1, OH), 2.4–0.85 (unresolved pattern, 10 protons).

*Anal* Calcd for $C_{15}H_{19}O_2N$: C, 73.44; H, 7.80; N, 5.36. Found: C, 73.57; H, 7.77; N, 5.68.

**Preparation of *exo*-2-Aminomethylbicyclo[2.2.1]hept-5-ene-*endo*-2-ol (18).**—A 3.0-g (25 mmol) sample of epoxide 14[16] in 10 ml of anhydrous ether was allowed to react with a solution of 4.8 g (0.12 mol) of sodium amide in 65 ml of liquid ammonia as described previously. After normal work-up the crude product was flash vacuum distilled in a short-path distillation apparatus, bp 60–105° (0.02 mm), to yield 2.74 g of crude product. Vacuum sublimation (50–60°, 0.01 mm) and vacuum desiccation (20 mm) over phosphorus pentoxide afforded 2.45 g (72%) of 18: mp 108–109° dec; ir (Nujol) 3360 (s, OH), 3280, 3300 (broad doublet, primary $NH_2$), 1215, and 1050 $cm^{-1}$ (CN); nmr ($CCl_4$) δ 6.25 (ABX multiplet, 2, CH=CH), 2.8 (broad s, 4, bridgeheads and $CH_2N$), 2.00 (broad s, 3, OH and $NH_2$), 0.85–1.85 (unresolved pattern, 4 protons). A benzamide derivative was prepared in the usual manner,[20] mp 152–153°.

*Anal.* Calcd for $C_{15}H_{17}O_2N$: C, 74.04; H, 7.04; N, 5.78. Found: C, 73.77; H, 6.85; N, 5.95.

**Preparation of *endo*-2-Aminomethylbicyclo[2.2.1]hept-5-en-*exo*-2-ol (21).**—A 3.0-g (25 mmol) sample of epoxide 20[16] in 10 ml of anhydrous ether was allowed to react with 4.8 g (0.123 mol) of sodium amide in 65 ml of liquid ammonia as described previously. Work-up and flash vacuum distillation in a short-path distillation apparatus yielded 3.8 g, bp 80–101° (0.02 mm), of crude product. Vacuum sublimation (50–60°, 0.01 mm) and vacuum desiccation (20 mm) over phosphorus pentoxide yielded 2.8 g (82%) of 21: mp 72–74° dec; ir (Nujol) 3345, 1380, 1180, 1130, 1075, 810, and 710 $cm^{-1}$; nmr ($CDCl_3$) δ 6.1 (ABX multiplet, 2, CH=CH), 2.85 (broad, m, 1, bridgehead proton), 2.6 (broad s, 3, $CH_2N$ and OH), 2.1–1.0 (unresolved pattern, 7 protons). A benzamide derivative was prepared in the usual manner,[20] mp 107–107.5°.

*Anal.* Calcd for $C_{15}H_{17}O_2N$: C, 74.04; H, 7.04; N, 5.78. Found: C, 73.69; H, 6.98; N, 5.88.

**Ring Expansion of Amino Alcohol 12. A.**—A 500-mg (3.55 mmol) sample of 12 dissolved in 5 ml of water containing 266 mg (4.43 mmol) of acetic acid was stirred magnetically and cooled in an ice–water bath. To this, a solution of 310 mg (4.4 mmol) of sodium nitrite in 5 ml of water was added dropwise over a period of 15 min. The mixture was stirred for an additional 1 hr at ice-bath temperature, heated at reflux for another 1 hr, and then allowed to cool to room temperature. The solution was neutralized with sodium bicarbonate solution and extracted with five 100-ml portions of ether, and the combined ether extracts were dried ($MgSO_4$) and concentrated. The crude product was vacuum sublimed (50–60°, 20 mm) yielding 207 mg (47%) of a mixture which was shown by glpc analysis[21] to consist of two components which were collected individually and identified as follows. The first component (retention time 5.5 min, relative abundance 37.7%) was identical in all respects (ir, nmr, and retention time) with an authentic sample of bicyclo[3.2.1]octan-3-one (4), mp 139–140° (lit.[22] mp 139°). The second component (retention time 6.8 min, relative abundance 62.3%) was identical in all respects (ir, nmr, and retention time) with an authentic sample of bicyclo[3.2.1]octan-2-one (3), mp 120–122° (lit.[23] mp 121–123.5°).

**B.**—A 266-mg (1.5 mmol) sample of 12 HCl dissolved in 10 ml of water containing 112 mg (1.87 mmol) of acetic acid was stirred magnetically and cooled in an ice–water bath. To this, a solution of 129 mg (1.87 mmol) of sodium nitrite was added dropwise over a period of 15 min. The mixture was stirred for an additional 1 hr at ice-bath temperature, heated at reflux for 1 hr, and then allowed to cool to room temperature. Normal work-up afforded 160 mg (86%) of a mixture which was shown by glpc analysis[21] to consist of 61.3% ketone 3 and 38.7% ketone 4, by their glpc retention times and spectral properties.

**Ring Expansion of Amino Alcohol 15.**—A 500-mg (3.55 mmol) sample of 15 was ring expanded according to procedure A used for 12. Work-up and sublimation (50–60°, 20 mm) afforded 230 mg (53.5%) of a mixture which by glpc analysis was shown to consist of 9% ketone 4 and 91% ketone 3, by their glpc retention times and spectral properties.

**Ring Expansion of Amino Alcohol 18.**—A 1.2-g (8.64 mmol) sample of amino alcohol 18 was ring expanded according to the procedure outlined above for amino alcohol 12. Normal work-up and sublimation (50–60°, 20 mm) yielded 490 mg (46%) of a mixture which was shown by glpc analysis[21] to consist of two components which were collected individually and identified as follows. The first component (retention time 9 min, relative abundance 50%) was identified as bicyclo[3.2.1]oct-6-en-2-one (7): mp 74–75.5°; nmr ($CCl_4$) δ 6.05 (ABX multiplet, 2, CH=CH), 3.05–1.6 (unresolved pattern, 8 protons); ir ($CCl_4$) 1725, 1455–1425, and 720 $cm^{-1}$; mass spectrum (70 eV) $m/e$ 122. The second component (retention time 9.8 min, relative abundance 50%) was identical in all respects (ir, nmr, and retention time) with an authentic sample of bicyclo[3.2.1]oct-6-en-3-one[24] (8), mp 98–99.5° (lit.[24] mp 99–100.5°).

**Ring Expansion of Amino Alcohol 21.**—A 1.2-g (8.64 mmol) sample of amino alcohol 21 was ring expanded according to the procedure outline above for amino alcohol 12. Normal work-up and sublimation (50–60°, 20 mm) yielded 510 mg (49%) of a mixture which was shown gy glpc[21] analysis to consist of 77.3% ketone 7 and 22.7% ketone 8.

A part of the mixture from this experiment was combined with a sample of the ketone mixture obtained from the ring expansion of 18. The mixture (600 mg, 4.9 mmol) was hydrogenated in 25 ml of absolute ethanol at 50 psi (Parr hydrogenation apparatus) using 6.7 mg of 5% palladium on charcoal as catalyst. After the hydrogen uptake had ceased, the solution was filtered and concentrated and the residue was sublimed (50–60°, 20 mm) to give 494 mg (81%) of a mixture which was shown by glpc analysis[21] to contain ketones 3 and 4, by their glpc retention times and spectral properties. Thus, the assigned structures for the unsaturated ketones obtained in the ring expansion of amino alcohols 18 and 21 were further confirmed.

**Reaction Products of Bicyclo Ketones with Diazomethane. A. Norcamphor (1).**—To a solution of 500 mg (4.55 mmol) of nor-

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(19) W. E. Parham and L. J. Czuba, *J. Amer. Chem. Soc.*, **90**, 4030 (1968).

(20) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1935, p 260.

(21) A 13 ft × 0.25 in. aluminum column packed with 20% diethylene glycol succinate (DEGS) on 45–60 mesh Chromosorb W-AW was employed at a temperature of 170° and a helium flow rate of 110 ml/min.

(22) C. W. Fefford and B. Waegell, *Tetrahedron Lett.*, 1981 (1963).

(23) K. Alder and W. E. Windemuth, *Chem. Ber.*, **71**, 2404 (1938).

(24) N. A. LeBel and R. N. Liesmer, *J. Amer. Chem. Soc.*, **87**, 4301 (1965).

camphor (1) in 5 ml of 3% methanolic potassium carbonate solution was added dropwise 500 mg (3.8 mmol) of nitrosomethylurethane.[25] After an induction period, the reaction started, as evidenced by a rise in temperature. The solution was cooled to maintain the temperature between 20 and 25°. After the addition was complete, the solution was stirred for an additional 30 min, filtered, and concentrated by distillation. The residue was analyzed by glpc.[21] The reaction was repeated under the above conditions except that the amount of nitrosomethylurethane used was varied. Each run was analyzed by glpc.[21]

In another experiment 2.04 g (18.6 mmol) of 1 in 10 ml of methanol was allowed to react as described above with 8.05 g (61 mmol) of nitrosomethylurethane in the presence of anhydrous sodium carbonate. The concentrated residue was shown by glpc analysis[26] to consist of eight components which were collected individually and identified as follows. The first component (retention time 5.3 min, relative abundance 4.2%) was identical in all respects (ir, nmr, and retention time) with norcamphor (1). The second component (retention time 7.5 min, relative abundance 24.8%) and the third component (retention time 8.8 min, relative abundance 1.4%) were collected together and assigned structures 4 and 3, respectively, by their glpc retention times and spectral properties. The fourth component (retention time 11.6 min, relative abundance 20.5%) was assigned structure 5: ir ($CCl_4$) 1700 $cm^{-1}$ (C=O, seven-membered cyclic ketone[27]); mass spectrum (70 eV) *m/e* 138; mp 80–83.5° (lit.[28] mp 95–96°). The fifth component (retention time 14.2 min, relative abundance 25.6%) was assigned structure 6: ir ($CCl_4$) 1700 $cm^{-1}$ (C=O, seven-membered cyclic ketone[27]); mass spectrum (70 eV) *m/e* 138; mp 102–108° (lit.[28] mp 122–123°); semicarbazone mp 191–192° (lit.[28] mp 193–195°). The sixth component (retention time 18 min, relative abundance 3.4%) and the seventh component (retention time 18 min, relative abundance 3.4%) were collected together and are believed to be bicyclo[5.2.1]decan-3-one and bicyclo[5.2.1]decan-4-one, respectively: ir ($CCl_4$) 1695 $cm^{-1}$ (C=O, eight-membered cyclic ketone[27]); mass spectrum (70 eV) *m/e* 152; mp 60–62°. The eighth component (relative abundance 1.5%) was not identified.

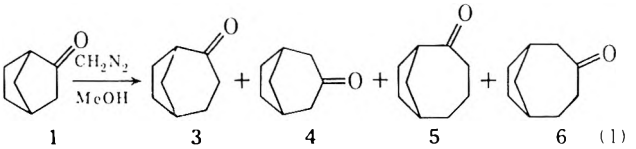
**B. Dehydronorcamphor (2)** (500 mg, 4.63 mmol) was ring expanded exactly as described for 1 (part A), and the reaction was repeated with varying amounts of nitrosomethylurethane. Each run was analyzed by glpc.[26]

In a separate experiment, 2.0 g (18.4 mmol) of 2 in 5 ml of methanol was allowed to react as described above (part A) with 8.0 g (61 mmol) of nitrosomethylurethane in the presence of anhydrous sodium carbonate. The concentrated residue was shown by glpc analysis[26] to consist of eight components which were collected individually and identified as follows. The first component (retention time 4.3 min, relative abundance 6.1%) was identical in all respects with dehydronorcamphor (2). The second component (retention time 6.6 min, relative abundance 4.9%) and the third component (retention time 7 min, relative abundance 34.8%) were collected together and assigned structures 7 and 8, respectively, by their glpc retention times and spectral properties. The fourth component (retention time 9.3 min, relative abundance 28.3%) and the fifth component (retention time 10 min, relative abundance 9%) were collected together and identified as 10 and 9, respectively. The structural assignments were made by converting the mixture of olefinic ketones into their known[28] saturated analogs 6 and 5 by catalytic hydrogenation. The sixth, seventh, and eighth components, formed in the ratio of 13.6:5.5:2.5, were shown to exhibit carbonyl absorption in the ir but were not further characterized.

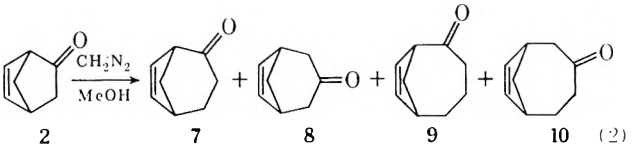
**Competition Reaction of 1 and 2 with Diazomethane.**—To a solution of 200 mg (1.85 mmol) of 2 and 200 mg (1.82 mmol) of 1 in 5 ml of methanol containing anhydrous sodium carbonate was added 0.2 g (1.5 mmol) of nitrosomethylurethane as described previously. The solution was analyzed by glpc.[7] The mixture was found to contain 41.9% 6, 47.5% 1, and ring-expanded products. The relative reactivity of ketones 1 and 2 is therefore approximately 1:2.2.[29]

## Results

Norcamphor (1) and dehydrononorcamphor (2) were allowed to react with varying amounts of diazomethane, generated from nitrosomethylurethane, in methanol at 25°. The reaction mixtures were analyzed by gas–liquid partition chromatography (glpc). The reactions resulted in mixtures of ring-expanded bicyclic ketones, the exact amount of each depending upon the molar amount of diazomethane used. The results are summarized in eq 1 and 2 and listed in Tables I and II.



(1)



(2)

TABLE I

REACTION OF NORCAMPHOR (1) WITH DIAZOMETHANE[a]

| Mole ratio of 1:urethane | Unreacted 1, % | Product, % 3 | 4 | 5 | 6 | Higher ketones |
|---|---|---|---|---|---|---|
| 1:0.41 | 80.3 | 8.8 | 6.0 | 3.1 | 2.1 | |
| 1:0.82 | 59.6 | 10.6 | 12.8 | 10.1 | 7.1 | |
| 1:1.64 | 38.6 | 9.5 | 18.6 | 19.2 | 11.3 | 3.2 |
| 1:2.46 | 21.6 | 9.1 | 23.0 | 20.6 | 14.2 | 11.4 |
| 1:3.28 | 19.6 | 3.9 | 26.5 | 21.3 | 17.4 | 12.0 |

[a] See Experimental Section for exact reaction conditions.

TABLE II

REACTION OF DIAZOMETHANE WITH DEHYDRONORCAMPHOR (2)[a]

| Mole ratio of 2:urethane | Unreacted 2, % | Product, % 7 | 8 | 9 | 10 | Higher ketones |
|---|---|---|---|---|---|---|
| 1:0.41 | 83.0 | 5.8 | 8.1 | 1.8 | 1.9 | |
| 1:0.82 | 63.7 | 9.0 | 16.5 | 4.6 | 6.2 | |
| 1:1.64 | 36.5 | 7.1 | 28.4 | 9.9 | 14.6 | 3.8 |
| 1:2.46 | 29.8 | 5.6 | 34.6 | 7.0 | 16.2 | 6.9 |
| 1:3.28 | 10.2 | 5.1 | 42.0 | 6.4 | 23.2 | 13.0 |

[a] See Experimental Section for exact reaction conditions.

The structures of ketones 3, 4, and 8 were established by comparison of their retention times and spectral properties with those of the authentic compounds.[22–24] The structures of 5 and 6 were established by spectral comparison and melting points of collected samples with those reported by Hartmann.[28] Finally, the structures of 7, 9, and 10 were assigned by conversion of these olefinic ketones by catalytic hydrogenation to 3, 5, and 6, respectively.

The relative reactivity of 1 and 2 toward diazomethane was estimated by allowing an equimolar mixture of the two to react with a less than stoichiometric amount of diazomethane. The composition of the reaction mixture was determined by glpc analysis.

(25) W. W. Hartman and R. Phillips, "Organic Syntheses" Collect. Vol. II, Wiley, New York, N. Y., 1943, p 464.

(26) Same column as in ref 21 used at 180° and a helium flow rate of 120 ml/min.

(27) R. T. Conley, "Infrared Spectroscopy," Allyn and Bacon, Boston, Mass., 1966, p 141.

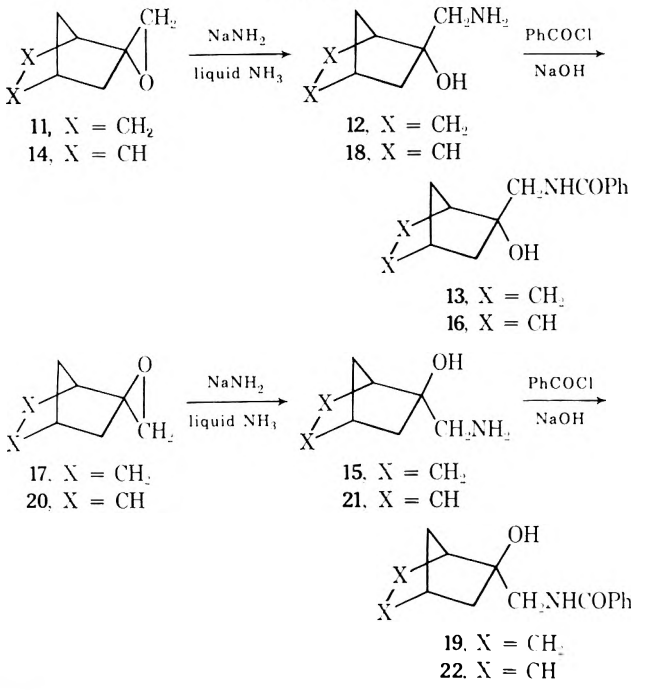
(28) M. Hartmann, *Justus Liebigs Ann. Chem.*, **724**, 102 (1969).

(29) T. S. Lee in "Technique in Organic Chemistry," Vol. VIII, S. L. Friess and A. Weissberger, Ed., Interscience, New York, N. Y., 1953, p 100.

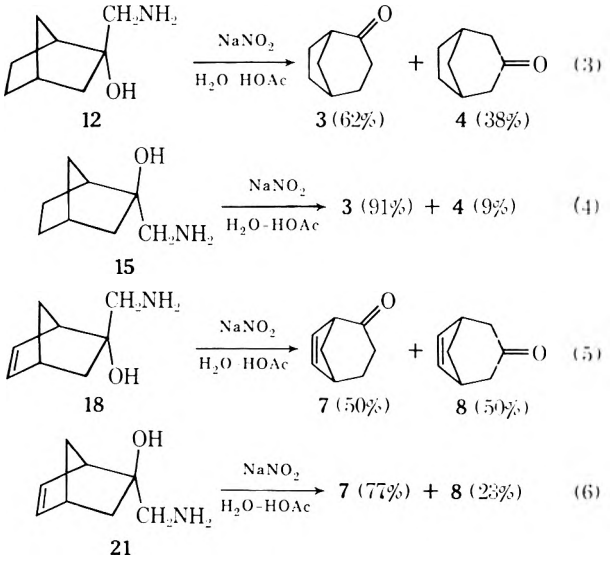
From these data it was calculated[29] that **2** was about two times as reactive as **1**.

The amino alcohols **12**, **18**, **15**, and **21** were prepared from the known epoxides **11**, **14**, **17**, and **20**[16] as outlined in Scheme I and characterized as their

Scheme I




benzamide derivatives. The amino alcohols were ring expanded by the Tiffeneau–Demjanov method and the ketonic mixtures obtained were analyzed by glpc. The relative percentages of the ketones obtained in each case are summarized in eq 3–6. No epoxides

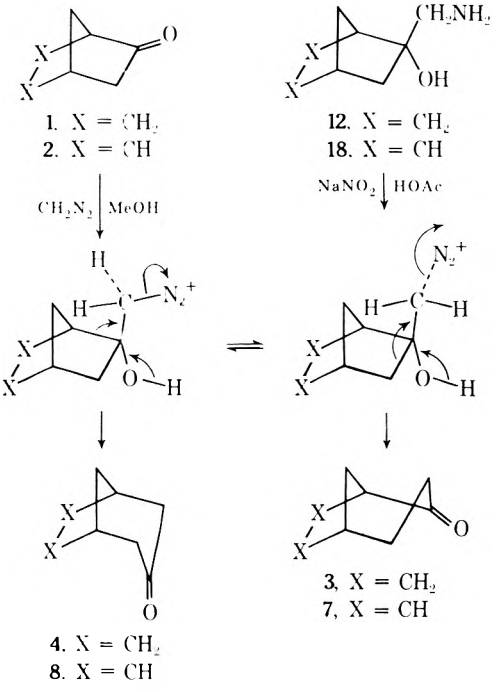



were detected as products in any of the amino alcohol or diazomethane ring-expansion reactions.[30] The yields of sublimed products obtained in the amino alcohol ring expansions studied were between 46 and 54%; no other volatile products were detected by glpc analysis. The hydrochloride of amino alcohol **12** was also ring expanded under identical reaction conditions, yielding **3** and **4** in the ratio of 61:39 in 86% yield. Thus, although the yield of ketonic products obtained increased, the ratio of products obtained remained constant. We therefore believe, despite the relatively low yields obtained in the amino alcohol ring expansions, that the ratio of ketones obtained in each case is an accurate measure of the relative migratory aptitudes of the methine and methylene carbons in these derivatives.

## Discussion

**Ring Expansion of Norcamphor.**—The reaction of norcamphor (**1**) with nucleophiles such as Grignard reagents, metal hydrides, and mixed hydrides[31] yields predominantly (>90%) the product of exo attack, an endo alcohol. The neutral nucleophiles dimethyloxosulfonium methylide and dimethylsulfonium methylide also attack **1** on its exo face to yield an endo epoxide.[16] One would therefore predict that the neutral nucleophile diazomethane would also react with **1** in an exo fashion. As shown in Scheme II, the intermediate

Scheme II



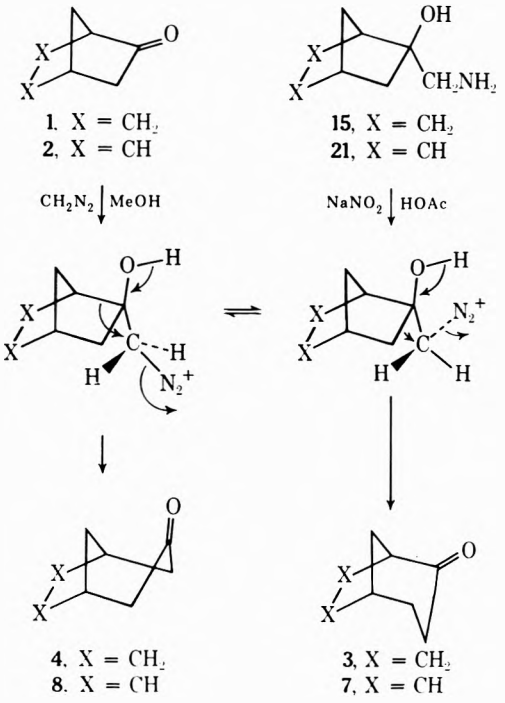

diazonium ion produced by exo attack of diazomethane on **1** can also be formed from the treatment of **12** with nitrous acid. The ratio of ketones **3** and **4** formed in the deamination of **12** should serve as the expected ratio of products that would be formed in the exo attack of diazomethane on **1**. Similarly, the product ratio obtained in the deamination of amino alcohol **15** should serve as the expected product ratio for endo attack of diazomethane on **1** (Scheme III). Comparison of the deamination results for **12** and **15** (eq 2 and 3) with the initial product ratio (70:30)[32] of ketones **3** and **4** formed when **1** was allowed to react with a less than stoichiometric amount of diazomethane indicates a predominance of exo attack (75%) of diazomethane on **1**.

(30) Authentic samples of the most probably epoxide rearrangement products were shown to be stable to the glpc analysis conditions and could have been detected if present in amounts greater than 1%.

(31) See Table I, ref 16.

(32) Estimated from the data in Table I.

SCHEME III




The ring expansion product ratios from amino alcohols **12** and **15** allow a comparison of the migratory aptitudes of the methine and methylene carbons in these systems with those observed in other 2-norbornylcarbinyl systems. The pertinent data are summarized in Table III. As can be seen from the data, b

TABLE III

MIGRATORY APTITUDES IN THE REARRANGEMENT OF *exo*- AND *endo*-2-NORBORNYLCARBINYL SYSTEMS

I II

| | X | Y | a migration, % | b migration, % |
|---|---|---|---|---|
| I | OBs[a] | H | 7 | 93 |
| I | $NH_2$[b] | H | 18 | 82 |
| I (12) | $NH_2$[c] | OH | 38 | 62 |
| II | OBs[c] | H | 0 (1)[a] | ~100 (70) |
| II | $NH_2$[d] | H | <1 | ~100 |
| II (15) | $NH_2$[c] | OH | 9 | 91 |

[a] Data taken from ref 11. [b] Taken from ref 33b. [c] This work. [d] J. A. Berson and P. Reynolds-Warnhoff, *J. Amer. Chem. Soc.*, **86**, 595 (1964).

or methylene migration is favored over a or methine migration in both the *exo*- and *endo*-2-norbornylcarbinyl systems. The preference for methylene migration in the exo systems, which is unexpected from electronic considerations and an unfavoral boat-like transition state, has been considered previously.[33] Sauers and Beisler[33] proposed that torsional nonbonded interactions between the substituents on C-2 and C-3 are relieved in the methylene migration transition state and that such strain relief is not rendered in the methine migration transition state. We would like to propose an alternative explanation based on the principle of least motion.[34] Methylene migration can proceed by a rotation around the C-3–C-4 bond which involves the motion of relatively few atoms in the molecule. However, methine migration requires the motion of the bridgehead carbon and thus most of the other atoms in the rigid bicyclic system. Thus, least motion favors methylene migration.

The selectivity of methylene over methine migration is reduced in going from the solvolytic brosylate system to the amine deamination. This is generally found to be the case,[35,36] because of the compressed energy scale in the energetically favorable loss of molecular nitrogen in the deamination. We see from the data for amino alcohol **12** that the selectivity is further reduced in deamination of an amino alcohol. Thus, the facile loss of nitrogen is further enhanced by the fact that a hydroxy carbonium ion, rather than a secondary carbonium ion, is produced as an intermediate.

In the *endo*-2-norbornylcarbinyl systems methylene migration predominates to even a greater extent. In the endo system the factors which favored methylene migration in the exo series are further reinforced by a conformationally favorable chairlike transition state. The trends in selectivity are maintained and are slightly enhanced.

**Ring Expansion of Dehydronorcamphor.**—The reaction of dehydronorcamphor (**2**) with a wide variety of nucleophiles occurs predominantly from the exo side with one notable exception.[16] The neutral nucleophile dimethyloxosulfonium methylide attacks **2** preferentially from its endo side to produce a 29:71 mixture of epoxides **14** and **20**, respectively.[16] Bly attributed this selectivity to an electronic stabilization of the endo attack transition state through an interaction of the double bond in **2** with the developing zwitterion.[16] Bly attempted to test the generality of this behavior of neutral nucleophiles toward **2** by studying the reaction of **2** with diazomethane in 10% methanolic ether.[37] In this solvent system, however, the diazomethane reacted exclusively with the double bond of **2** to produce ketopyrazolines.

Our results for the reaction of **2** with diazomethane in pure methanol indicate that in the more polar solvent the diazomethane reacts exclusively with the carbonyl double bond, resulting in ring expansion. As shown in Scheme II, the diazonium ion produced by exo attack of diazomethane on **2** can also be formed from the diazotization of amino alcohol **18**. The ratio of ketones formed in the deamination of **18** should therefore serve as the expected ratio of products that would result from an exo attack of diazomethane on **2**. Applying a similar argument, a model system for the endo attack of diazomethane on **2** is the deamination of amino alcohol **21**. This is shown in Scheme III. Comparison of the deamination results for **18** and **21** (eq 5 and 6) with the initial product ratio (53:47)[38]

(33) (a) R. R. Sauers and J. A. Beisler, *J. Org. Chem.*, **29**, 210 (1964); (b) J. A. Berson and D. Willner, *J. Amer. Chem. Soc.*, **86**, 609 (1964).

(34) (a) J. Hine, *J. Org. Chem.*, **31**, 1236 (1966); (b) J. Hine, *J. Amer. Chem. Soc.*, **88**, 5525 (1966); (c) S. I. Miller, *Advan. Phys. Org. Chem.*, **6**, 185 (1968); (d) O. S. Tee, *J. Amer. Chem. Soc.*, **91**, 7144 (1969).

(35) E. H. White, "The Chemistry of the Amino Group," S. Patai, Ed., Wiley, New York, N. Y., 1968, Chapter 8.

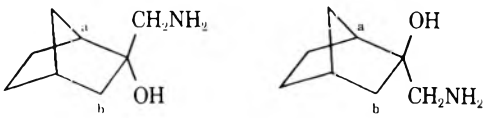
(36) J. A. Berson, J. W. Foley, J. M. McKenna, H. Junge, D. S. Donald, R. T. Luibrand, N. G. Kundu, W. J. Libby, M. S. Poonian, J. J. Gajewski, and J. B. E. Allen, *J. Amer. Chem. Soc.*, **93**, 1299 (1971).

(37) R. S. Bly, F. B. Culp, Jr., and R. K. Bly, *J. Org. Chem.*, **35**, 2235 (1970).

(38) Estimated from the data in Table II.

TABLE IV

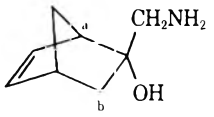
MIGRATORY APTITUDES IN THE DEAMINATION OF *exo*- AND *endo*-2-NORBORNENYLCARBINYL AND *exo*- AND *endo*-2-NORBORNYLCARBINYL SYSTEMS



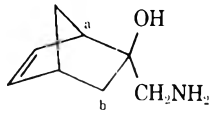

12




15




18



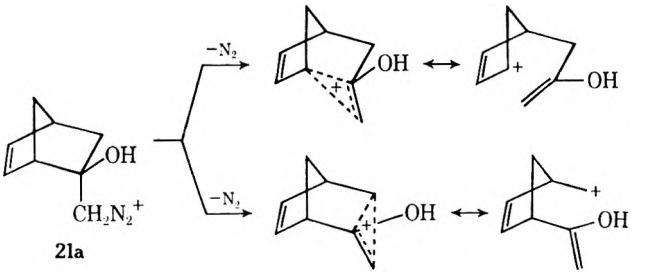

21

| Compd | a migration, % | b migration, % |
|---|---|---|
| 12 | 38 | 62 |
| 18 | 50 | 50 |
| 15 | 9 | 91 |
| 21 | 23 | 77 |

of ketones **7** and **8** formed in the reaction of **2** with a less than equivalent amount of diazomethane indicates a predominance of exo attack (86%) of diazomethane on **2**. The increase in exo attack of diazomethane on **2** as compared to **1** may be attributed to a greater steric repulsion on the endo face of **2** toward the attack of diazomethane as compared to **1**. Definitely, there is not a favorable interaction between the diazomethane and the double bond in **2** as in the attack of dimethyloxosulfonium methylide on **2**.

A quantitative comparison of methine *vs.* methylene migratory aptitudes observed in the deamination of **18** and **21** with other 2-norbornenyl carbinyl systems cannot be made because, although other systems have been studied,[39] the multiple rearrangements involved led to product mixtures which did not reflect kinetic product control. We can, however, compare the results for the amino alcohols ring expanded in this study. The results are summarized in Table IV. It is seen that the amount of methine migration increases in going from the norbornylcarbinyl to the norborenylcarbinyl system in both the exo and endo carbinyl substrates. Thus, although rearrangement did not occur, the double bond did have the effect of promoting methine migration.

If we look at the transition state for methine migration in **21** we see that one resonance form of this




21a

carbon-bridged species would be stabilized by the double bond, whereas methylene migration would not gain such a stabilizing influence. This could then account for the increased methine migration observed. This represents the first time that such an effect has been observed in a norbornenylcarbinyl system which is uncomplicated by rearrangements.

**Registry No.**—**1**, 497-38-1; **2**, 694-98-4; **7**, 34956-68-8; **11**, 16282-11-4; **12**, 41915-37-1; **12** hydrochloride, 40344-79-4; **12** benzamide derivative, 41915-39-3; **14**, 16282-09-0; **15**, 41915-41-7; **15** benzamide derivative, 41915-42-8; **17**, 16282-10-3; **18**, 41915-44-0; **18** benzamide derivative, 41915-45-1; **20**, 16282-08-9; **21**, 41915-47-3; **21** benzamide derivative, 41915-48-4; diazomethane, 334-88-3.

(39) R. R. Sauers, R. A. Parent, and H. M. How, *Tetrahedron*, **21**, 2907 (1965).

# *Notes*

## Ring Expansions. II. Diazoethane Ring Expansion of Norcamphor

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The reaction of diazoethane with methyl-substituted cyclopropanones has been studied by Turro.[1] The mechanisms of these reactions were discussed in terms of the stereoelectronics of the ring expansions and the role of conformational equilibria on the product distributions. It was concluded that conformational restrictions play an important role in the diazoethane ring expansions and that, owing to the exothermicity of the reactions, a synchronous addition–rearrangement mechanism may be operative. Thus, the product ratios could be explained on the bases of the energy content of the transition states favored by steric approach considerations. Marshall and Partridge[2] had earlier studied the ring expansion of 4-alkylcyclohexanones with diazoethane. Steric approach control of the diazoethane and conformational interactions in the intermediates were the important factors controlling the product distributions found in their work also.

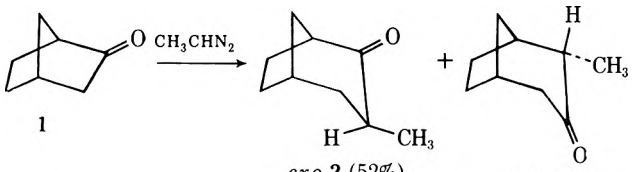
We would like to report our results on the diazoethane ring expansion of norcamphor (**1**). The product ratios obtained can be explained in terms of steric approach control of the diazoethane on the exo face of norcam-

(1) N. J. Turro and R. B. Gagosian, *J. Amer. Chem. Soc.*, **92**, 2036 (1970).

(2) J. A. Marshall and J. J. Partridge, *J. Org. Chem.*, **33**, 4090 (1968).

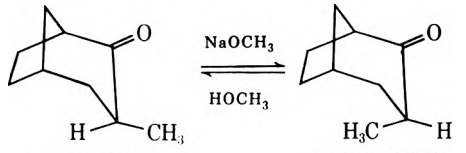
phor, the migratory aptitude of the methine and methylene carbons in the product-forming intermediates, and conformation equilibria in the intermediates.

The ring expansion of norcamphor (**1**) was carried out in methanol by generation *in situ* of diazoethane from *N*-ethyl-*N*-nitrosourethane.[3] The reaction of **1** with a fourfold excess of diazoethane yielded two ring-expansion products in 59% yield. The two ketones were isolated by preparative glpc. One ketone was identified as *exo*-3-methylbicyclo[3.2.1]octan-2-one (*exo*-**2**) by comparison of its spectral properties and the melting point of its 2,4-dinitrophenylhydrazone derivative with those reported by Sisti.[4] The other ketone was identified as *endo*-2-methylbicyclo[3.2.1]octan-3-one (*endo*-**3**) by comparison of its spectral properties with those of a sample prepared by the methylation of bicyclo[3.2.1]-octan-3-one (see Experimental Section). The reaction of **1** with less than 1 equiv of diazoethane yields *exo*-**2** and *endo*-**3** in the ratio of 1.1:1, as shown below.



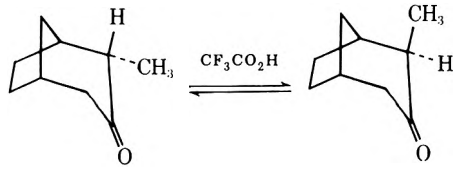

**1** *exo*-**2** (52%) *endo*-**3** (48%)

The exo and endo isomers of 3-methylbicyclo[3.2.1]-octan-2-one (**2**) were also prepared by methylation of bicyclo[3.2.1]octan-2-one with tritylsodium and methyl iodide in dioxane. The two isomers were separated by preparative glpc and independently isomerized to a thermodynamic mixture with 3% sodium methoxide in methanol. The results are shown below.




*exo*-**2** (70%) *endo*-**2** (30%)

In a similar manner bicyclo[3.2.1]octan-3-one was methylated and a mixture of the exo and endo isomers, which could not be separated by glpc, was collected by preparative glpc and the mixture was equilibrated by heating with trifluoroacetic acid. The isomer ratio was determined by nmr integration of the doublet methyl absorptions. The following mixture was obtained.




*endo*-**3** (67%) *exo*-**3** (33%)

Thus, the methyl ketones obtained in the ring expansion of **1** with diazoethane are the thermodynamically more stable isomers.

These results for the ring expansion of **1** with diazoethane indicate that methylene and methine migration occur to an almost equal extent. The similar reaction of diazomethane with **1** results in a 70:30 ratio of methylene to methine migration.[5] This reaction was found to occur with preferential exo attack (75%) of diazomethane on **1**.[5]

The rate-limiting step in the diazoalkane ring expansion is the addition of the diazoalkane to the ketone,[6] and therefore the steric approach of the diazoethane on **1** as well as steric interactions in the rotameric forms of the product-determining intermediates should control which carbon–carbon bond migrates. Thus, Scheme I outlines a reasonable reaction pathway for reaction of diazoethane with **1**. Only exo attack intermediates are considered on the assumption that endo attack of diazoethane would be sterically less accessible than endo attack of diazomethane on **1**, which occurred to the extent of 25%.

Exo attack of diazoethane with the methyl group "out" would lead to rotameric intermediates A and B, of which A would be sterically most favored. Ring expansion from A affords *endo*-**3**, which is one of the observed products. Expansion of B gives *exo*-**2**, the other observed ring-enlarged product. The ring-enlarged products which would result from the methyl "in" intermediates C and D are not observed. Thus, steric approach control strongly favors initial formation of intermediate A. Although methylene migration was favored in the ring expansion of **1** with diazomethane, the ring expansion of **1** with diazoethane led to equal amounts of methylene and methine carbon migration. This is reasonable if ring expansion occurs by the back-side displacement of nitrogen by the migrating carbon atom,[7] for conformer B, which allows methylene migration, should be sterically less favorable than A owing to the position of the methyl group opposed to the C-7 methylene. These results therefore are explainable in terms of a ring-expansion mechanism in which the diazoalkane approaches the ketone in the sterically most favorable fashion leading to a β-hydroxy diazonium ion as an intermediate. This intermediate is then partitioned to products through its various rotameric forms, most probably with a trans relationship between the migrating carbon and the expelled nitrogen molecule. If a synchronous mechanism were operative, with structures A–D of Scheme I representing transition states, one would have expected some *endo*-**2** as a product because structure D should be sterically more favorable than B and this would balance, at least in part, the small energy difference (0.5 kcal) between the *exo*-**2** and *endo*-**2** products.

## Experimental Section[8]

**Ring Expansion of Norcamphor (1).**—To a solution of 2.0 g (18.2 mmol) of **1** in 10 ml of 3% methanolic $K_2CO_3$ was added 8.7

(3) W. W. Hartmann and R. Phillips, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 464.

(4) A. J. Sisti, *J. Org. Chem.*, **35**, 2670 (1970).

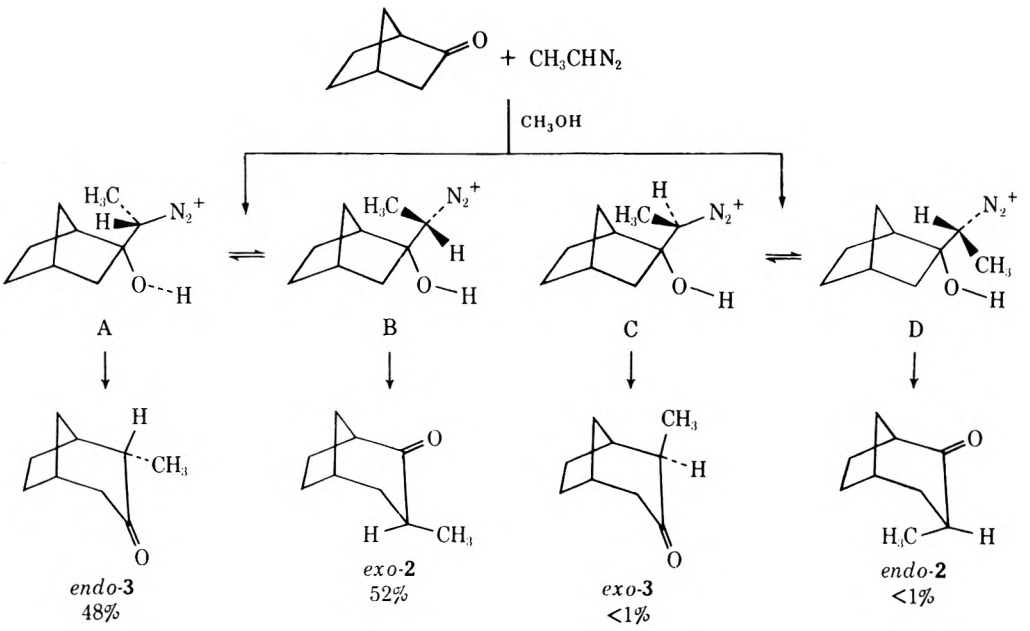
(5) M. A. McKinney and P. P. Patel, *J. Org. Chem.*, **38**, 4059 (1973).

(6) J. N. Bradley C. W. Cowell, and H. Ledwith, *J. Chem. Soc.*, 4334 (1964).

(7) C. D. Gutsche and D. Redmore, "Carbocyclic Ring Expansion Reaction," Academic Press, New York, N. Y., 1968.

(8) All melting points and boiling points are uncorrected. Nuclear magnetic resonance spectra were obtained on a Varian A-60A spectrometer, using TMS as the internal standard and $CCl_4$ as the solvent. Infrared spectra were recorded on a Beckman IR-12 spectrometer. Mass spectra were obtained using a CEC 21-104 mass spectrometer. Gas chromatographic analyses were performed on an F & M Model 700 gas chromatograph equipped with a thermal conductivity detector and a Disc integrator. Microanalysis was performed by Chemalytics, Inc., Tempe, Ariz.

SCHEME I




g (59.6 mmol) of *N*-ethyl-*N*-nitrosourethane[3] at such a rate so as to maintain the temperature of the reaction mixture between 20 and 25°. The reaction solution was concentrated and analyzed by glpc.[9] The chromatogram indicated three components, which were collected individually and identified as follows.

Fraction 1 (40%, retention time 6.4 min) was identified as unreacted 1.

Fraction 2 (33%, retention time 9.6 min) had nmr $\delta$ 0.93 (d, $J$ = 7 Hz, 3, $CH_3$), 1.1–2.8 (m, 11 hydrogens); ir (neat) 1715 $cm^{-1}$ (C=O); mass spectrum (70 eV) $m/e$ 138. A semicarbazone derivative was prepared in the usual manner,[10] mp 203–204° dec from ethanol–water.

*Anal.* Calcd for $C_{10}H_{17}N_3O$: C, 61.51; H, 8.77; N, 21.53. Found: C, 61.61, H, 8.80; N, 21.56.

This compound was assigned the structure *endo*-2-methylbicyclo[3.2.1]octan-3-one (*endo*-**3**) by comparison of its nmr spectrum with that of the thermodynamically most stable product obtained from the methylation of bicyclo[3.2.1]octan-3-one (see below).

Fraction 3 (25%, retention time 10.4 min) was identified as *exo*-3-methylbicyclo[3.2.1]octan-2-one (*exo*-**2**): nmr $\delta$ 0.94 (d, $J$ = 6 Hz, $CH_3$), 2.4 (b s, 1 bridgehead H, C-5), 2.7 (b s, 1 bridgehead H, C-1); ir ($CCl_4$) 1713 $cm^{-1}$; 2,4-DNP derivative mp 146–147° (lit.[4] mp 144–145.5°).

In another experiment a solution of 0.5 g of 1 in 5 ml of 3% methanolic $K_2CO_3$ was allowed to react with 0.27 g (1.86 mmol) of *N*-ethyl-*N*-nitrosourethane as described above. The solution was concentrated and glpc analysis[9] showed that *exo*-**2** and *endo*-**3** were formed in the ratio 1.1:1 in 1–2% yield.

*exo*- and *endo*-**3-Methylbicyclo[3.2.1]octan-2-one (2).**—To a solution of 2.0 g (16 mmol) of bicyclo[3.2.1]octan-2-one in 6 ml of dry dioxane was added a solution of 0.15*M* tritylsodium[11] in ether under a nitrogen atmosphere. The addition was continued until a deep red color persisted, the mixture was stirred for 5 min, and then 11.5 g (80.6 mmol) of freshly distilled methyl iodide was added as rapidly as possible. The reaction mixture was stirred overnight, diluted with water, and extracted with five 100-ml portions of petroleum ether, and the extracts were combined and dried ($Na_2SO_4$). The solution was concentrated and short-path distillation gave 0.55 g (25%, corrected for 30% unreacted starting material), bp 68–71° (2.25 mm), of methylated product. The ketones were separated by preparative glpc[12] and identified as follows.

The first fraction (21%, retention time 6.3 min) was identified as *endo*-3-methylbicyclo[3.2.1]octan-2-one (*endo*-**2**): nmr $\delta$ 1.09 (d, $J$ = 5 Hz, $CH_3$), 1.67–2.17 (m, 9 hydrogens), 2.47 (b s, 1, bridgehead, C-5), 2.72 (b s, 1 bridgehead, C-1); ir ($CCl_4$) 1713 $cm^{-1}$ (C=O).

Fraction 2 (49%, retention time 7 min) was identified as *exo*-3-methylbicyclo[3.2.1]octan-2-one (*exo*-**2**): nmr $\delta$ 0.94 (d, $J$ = 6 Hz, $CH_3$), 1.23–2.25 (m, 9 hydrogens), 2.4 (b s, 1, bridgehead, C-5), 2.7 (b s, 1, bridgehead, C-1); ir ($CCl_4$) 1713 $cm^{-1}$ (C=O); 2,4-DNP derivative mp 146–147° (lit.[4] mp 144–145.5°). This component was identical in all respects with one of the products of the diazoethane ring expansion of 1.

Fraction 3 (25%, retention time 8 min) was identical in all respects with unreacted bicyclo[3.2.1]octan-2-one.

**Isomerization of *exo*-2 and *endo*-2.**—A 200-mg sample of *endo*-**2** was dissolved in 2 ml of 3% sodium methoxide in methanol and the solution was heated under reflux in a nitrogen atmosphere for 24 hr. The solution was cooled and diluted with 15 ml of ice–water, extracted with a pentane–methylene chloride mixture, washed to neutrality with water, dried ($Na_2SO_4$), and concentrated using a 10-in. Vigreux column. The residue was analyzed by glpc[12] and shown to consist of a 31:69 mixture of *endo*-**2** and *exo*-**3**, respectively.

In another experiment a 200-mg sample of *exo*-**2** was isomerized in a similar manner and glpc[12] analysis after work-up showed a 30:70 mixture of *endo*-**2** and *exo*-**3**, respectively.

*exo*- and *endo*-**2-Methylbicyclo[3.2.1]octan-3-one (3).**—A 1.2-g sample of bicyclo[3.2.1]octan-3-one was methylated as described previously for bicyclo[3.2.1]octan-2-one. Work-up of the reaction mixture gave 1.04 g of product, bp 59–61° (1 mm). The product mixture was analyzed by glpc[13] and shown to consist of three components.

Fraction 1 (14%, retention time 4.5 min)[14] was identical in all respects with bicyclo[3.2.1]octan-2-one.

Fraction 2 (61%, retention time 6 min) was shown by nmr analysis (integration of doublet methyl absorptions) to be a 24:76 mixture of *exo*-**3** and *endo*-**3**, respectively: nmr $\delta$ 0.95 (d, $J$ = 6.5 Hz, endo $CH_3$), 1.12 (d, $J$ = 7 Hz, exo $CH_3$), 1.4–2.7 (m, 11 hydrogens; ir (neat) 1718 $cm^{-1}$ (C=O); mass spectrum (70 eV) $m/e$ 138. The major component of this mixture had a doublet methyl absorption in the nmr which matched the abforption obtained for one of the ring-expansion products obtained from 1 and diazoethane.

Fraction 3 (25%, retention time 7.7 min) was not fully characterized, but nmr, ir, and mass spectral analysis showed it to be a mixture of dimethylbicyclo[3.2.1]octan-3-ones.

(9) A 13 ft × 0.25 in. aluminum column packed with 20% diethylene glycol succinate (DEGS) on 60–80 mesh Chromosorb W was used at 140° with a 120 ml/min He flow rate.

(10) D. J. Pasto and C. R. Johnson, "Organic Structure Determination," Prentice-Hall, Englewood Cliffs, N. J., 1969, p 390.

(11) W. B. Renfrow, Jr., and C. R. Hauser, "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 607.

(12) Same column as in ref 9 at 175° and a 70-ml/min He flow rate.

(13) A 6 ft × 0.25 in. aluminum column packed with 20% SE-30 on 60–80 mesh Chromosorb W was used at 160° with a 50-ml/min He flow rate.

(14) All attempts to resolve this mixture on other glpc columns were unsuccessful.

Isomerization of *exo*-**3** and *endo*-**3**.[15]—A 50-mg sample of fraction 3 from above was heated to 110° in trifluoroacetic acid for 60 hr under nitrogen, diluted with water, neutralized with solid $NaHCO_3$, extracted with ether, dried ($Na_2SO_4$), and concentrated. Nmr analysis showed a 33:67 mixture of *exo*-**3** and *endo*-**3** respectively.

**Registry No.**—**1**, 497-38-1; *exo*-**2**, 41828-85-7; *endo*-**2**, 41828-86-8; *endo*-**3**, 41828-87-9; *endo*-**3** semicarbazone, 41828-88-0; *exo*-**3**, 41828-89-1; *N*-ethyl-*N*-nitrosourethane, 614-95-9; bicyclo[3.2.1]octan-2-one, 5019-82-9; methyl iodide, 74-88-4; bicyclo-[3.2.1]octan-3-one, 5019-82-9.

(15) Attempted isomerization with sodium methoxide in methanol led to a complex reaction mixture, apparently owing to aldol condensations.

## Preparation of 4-Phenyl Medium- and Large-Sized Ring Ketones

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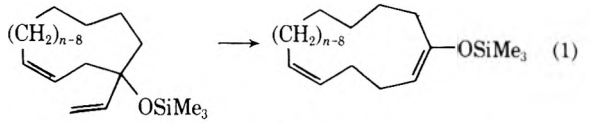
*Received May 21, 1973*

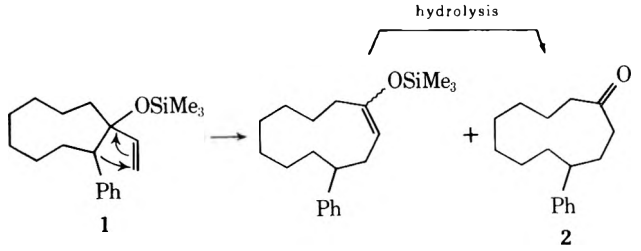
Previous studies in these laboratories[1] have described the siloxy-Cope rearrangement as a ring expansion for medium-sized rings (*e.g.*, eq 1). The present




(1)

$n$ = 8, 9, 10

work shows that 2-phenyl-1-trimethylsiloxy-1-vinylcyclononane (**1**) undergoes a related rearrangement




cis and trans

which represents a general ring expansion route to 4-phenyl medium- and large-sized ring ketones. Other synthetic approaches to such compounds are quite limited.[2]

Cyclooctanone was converted by a previously described procedure[3] to 2-phenylcyclononanone. The reaction of this ketone with vinylmagnesium bromide gave only very low conversion and that with vinylmagnesium chloride gave serious side reactions. However, the reaction with vinyllithium gave a 60% conversion to the vinyl alcohol. The incomplete reaction presumably arises because enolate anion formation competes with the desired reaction. The conversion can be increased by allowing the crude mixture to react again (*ca.* 75% conversion). Alternatively, the unreacted ketone can be readily removed by chromatography and recycled. Trimethylsilylation of the alcohol gives complete conversion to **1**.

Heating **1** in sealed ampoules in the 210–280° temperature range gave enol ethers corresponding to a [1,3] sigmatropic shift and also the corresponding ketone **2**. Hydrolysis of the mixture gave **2** in 80% overall yield from **1**.

The structure of **2** was assigned from the nmr spectrum and from decoupling experiments carried out on samples in which the chemical shifts had been separated with $Eu(fod)_3$. Thus sufficient shift reagent was added so that the $\alpha$-proton multiplet moved to $\delta$ 5.0, the benzylic proton (a broad triplet) to $\delta$ 4.5, and three of the $\beta$ protons to $\delta$ 3.9.[4] Decoupling established that the benzylic proton was coupled to the $\beta$ protons, which were in turn coupled to the $\alpha$ protons, thus establishing the position of the phenyl on the ring.

Kinetic measurements were made (Table I); however, the data were somewhat erratic and gave activation parameters that are unreasonable for a simple process ($E_a$ = 25.4 and log $A$ = 5.5). Presumably a major part of the reaction involves some sort of surface catalysis or radical chain process. This process apparently causes formation of ketone during the pyrolysis, which is not normal for this type of reaction. Major amounts of ketone were formed with this system even when the ampoules were carefully dried.

TABLE I

AMPOULE PYROLYSIS OF 2-PHENYL-1-TRIMETHYLSILOXY-1-VINYLCYCLONONANE (1)

| Temp, °C | Time, hr | % 2[a,b] | % nonvolatile[b] |
|---|---|---|---|
| 213 | 11.75 | 42 | |
| | 24 | 58 | |
| 225 | 6 | 44 | |
| | 12 | 63 | |
| 260 | 6 | 30 | |
| | 12 | 66 | |
| | 18 | 74 | |
| 280 | 6 | 59 | 12 |
| | 12 | 74 | 17 |
| 310 | 0.67 | 58 | 41 |
| 330 | 0.67 | 52 | 48 |

[a] Measured after hydrolysis of the pyrolysis mixture. [b] Yield and nonvolatile were determined by gc using an internal standard.

Although the reaction is not kinetically well behaved, it is high yield and clean in the sense that it leads to a single product after hydrolysis. The success of the reaction depends on the balance between the change in ring strain and the favorable energy change associated with formation of the enol (*ca.* 4.5 kcal/mol[5]). By analogy with the related systems shown in eq 1, the reaction should be feasible for rings larger than eight membered.

(1) (a) R. W. Thies, *Chem. Commun.*, 237 (1971); (b) R. W. Thies, *J. Amer. Chem. Soc.*, **94**, 7074 (1972); (c) R. W. Thies, M. T. Wills, A. W. Chin, L. E. Schick, and E. S. Walton, *ibid.*, **59**, 5281 (1973); (d) R. W. Thies and J. E. Billigmeier, 161st National Meeting of the American Chemical Society, Los Angeles, Calif, March 28–April 12, 1971, Abstract 162.

(2) For syntheses of 4-phenylcyclooctanone see A. C. Cope and R. B. Kinnel, *J. Amer. Chem. Soc.*, **88**, 752 (1966); A. C. Cope and R. B. Kinnel, *ibid.*, **89**, 5995 (1967); A. C. Cope, M. A. McKervey, and N. M. Weinshenker, *ibid.*, **89**, 2932 (1967).

(3) A. J. Sisti, *J. Org. Chem.*, **33**, 453 (1968). For an alternative method, see E. Müller and R. Heischkeil, *Tetrahedron Lett.*, 1032 (1962).

(4) The remainder of the spectra consists of the phenyl protons at $\delta$ 7.2 and 7.6, a two-proton multiplet containing the remaining $\beta$ proton at $\delta$ 3.2, and a large multiplet at $\delta$ 2.9–1.8.

(5) S. J. Rhoads and E. E. Waali, *J. Org. Chem.*, **35**, 3358 (1970).

### Experimental Section

**General.**—Spectra were recorded on Beckman IR-8, Varian HA-100, Atlas CH7, and CEC 110B instruments.[6] Varian-Aerograph 1200 and A90P instruments were used for glc with columns (A) 0.01 in. × 25 ft UCONLB550X capillary, (B) 0.125 in. × 7 ft 2.5% KOH–2.5% Carbowax 4000 on 80/100 Chromosorb W, and (C) 0.25 in. × 4 ft 20% SF96 on Chromosorb. Analyses were performed at Galbraith Laboratories.

**2-Phenyl-1-trimethylsiloxy-1-vinylcyclononane** (1).—A solution of 1 g (4.7 mmol) of 2-phenyl-1-cyclononanone[3] in 5 ml of dry THF was added under nitrogen at room temperature to 15 ml of 1 *M* vinyllithium in THF (diluted Ventron solution). The reaction was stirred for 15 min and was then quenched with 5 ml of saturated ammonium chloride and extracted with pentane. The pentane solution was washed with water and dried over magnesium sulfate. Analysis by gc (column A at 135°) showed a 60% conversion (other runs with longer reaction times did not give significantly greater conversion). The alcohol was purified by chromatography on SilicAR, eluting with pentane to remove a substantial amount of nonpolar material and then with 3% ether–pentane, which gave unreacted ketone (36%) and the desired alcohol[7] (45% yield) as a low-melting solid: ir ($CS_2$) 2.8, 3.42, 14.4 μ; nmr ($CCl_4$) δ 7.12 (s, 5), 5.82, 4.74, 4.68 (ABC pattern, $J$ = 12, 17 Hz, 3), 2.8 (m, 1), 1.0–1.8 (m, 15).

The alcohol was converted to the trimethylsilyl derivative by stirring with Tri-Sil Concentrate (Pierce Chemical Co.) and dimethyl sulfoxide as described previously.[1b] The product was purified by preparative gas chromatography on column C at 160°, which gave 1 as a semisolid: ir (neat) 3.42, 6.75, 6.90, 8.04, 9.42, 11.15, 12.0, 13.3, 14.35 μ; nmr ($CCl_4$) δ 7.2 (m, 5), 5.52, 4.92, 4.84 (ABC pattern, $J$ = 17, 10, 2 Hz, 3), 2.8 (m, 1), 1.2–2.2 (m, 14), 0.12 (s, 9); mass spectrum $m/e$ 316.221 (calcd for $C_{20}H_{32}OSi$, $m/e$ 316.222).

**4-Phenylcycloundecanone** (2).—Ampoules were prepared and sealed as described previously.[1b]. The ampoules were heated in an aluminum block oven which was regulated with a Cole Palmer Model 1300 temperature controller. Most runs utilized 10 mg of gc-purified sample in a 10-ml ampoule. A run using a 0.8-ml ampoule and 0.2 g of sample that had only been purified by vacuum transfer gave similar results when heated for 16 hr at 280° except that the amount of ketone formed during pyrolysis was much higher (64% *vs.* 13%) and the yield was only 60%. Analysis of the product mixture before hydrolysis using a glc–mass spectrometer combination (column B) showed two rearranged trimethylsilyl compounds and a third component which was identified as 2.

Hydrolysis of the mixture as described earlier[1b] gave only one product, 2: ir (neat) 3.42, 5.88, 6.70, 6.90, 13.25, 14.35 μ; nmr ($CCl_4$) δ 7.5 (m, 5), 2.4–2.9 (m, 5), 1.3–2.1 (m, 14).

*Anal.* Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.89. Found: C, 83.23; H, 9.67.

**Acknowledgment.**—We thank the Research Corporation for Cottrell Research Grant support.

**Registry No.**—1, 42031-17-4; 2, 42031-18-5; 2-phenyl-1-cyclonanone, 14996-80-6.

(6) We thank the University of Oregon for the use of their CEC mass spectrometer.

(7) Two diastereomers are possible. The alcohol used showed only one peak on gc (columns A and B). The later chromatography fractions (not used) showed minor amounts of another alcohol with a slightly longer retention time.

## Di- and Trimethyl-2-cyclohexenones

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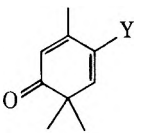
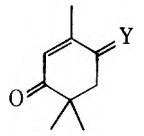
*Received June 13, 1973*

In connection with a problem of terpene synthesis 4-methoxy-3,6,6-trimethyl-2,4-cyclohexadienone (**1a**) was needed as starting material as a consequence of which the following reactions were investigated.

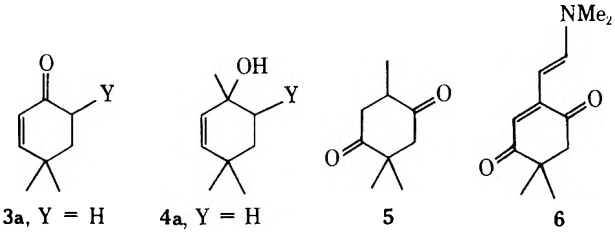


**1a**, Y = OMe
**b**, Y = H



**2a**, Y = $H_2$
**b**, Y = H, Br
**c**, Y = H, OAc
**d**, Y = O
**e**, Y = H, OMe

Treatment of 3,6,6-trimethyl-2-cyclohexenone (**2a**),[1] prepared by the interaction of methylmagnesium iodide with 4,4-dimethyl-2-cyclohexenone (**3a**)[2] followed by chromic acid oxidation of the resultant carbinol (**4a**), with *N*-bromosuccinimide yielded bromo ketone **2b**, which suffered facile dehydrobromination producing dienone **1b** but could be converted into the keto ester **2c** on exposure to silver acetate. Lithium aluminum hydride reduction of **2c**, followed by manganese dioxide oxidation of the intermediate diol, gave the diketone **2d**. Unfortunately, neither ketalation of the latter or its dihydro derivative **5** under a variety of conditions[3] nor enol ether formation of **2d** succeeded.



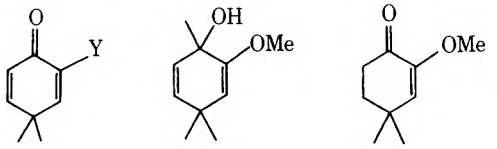
**3a**, Y = H
**b**, Y = Br
**c**, Y = OMe
**d**, Y = OAc
**e**, Y = OH

**4a**, Y = H
**b**, Y = OMe

**5**

**6**

An alternative route toward the desired product was based on an attempt to introduce the methoxyalkene function into the framework of cyclohexenone **3a**. While selenium dioxide oxidation of the latter yielded dienone **7a**,[4] treatment of **3a** with cupric bromide afforded **3b**,[4] whose exposure to methanolic silver nitrate led to the keto ether **3c**. Interaction of the latter with methylmagnesium iodide and the resultant carbinol **4b** with chromic acid produced the ether **2e**. Unfortunately, various attempts to dehydrogenate **2e** failed.



**7a**, Y = H
**b**, Y = OH
**c**, Y = OMe

**8**

**9**

(1) J. M. Conia and F. Rouessac, *Bull. Soc. Chim. Fr.*, 1925 (1963).

(2) (a) E. L. Eliel and C. A. Lukach, *J. Amer. Chem. Soc.*, **79**, 5986 (1957); (b) E. D. Bergmann and R. Corett, *J. Org. Chem.*, **23**, 1507 (1958); (c) J. M. Conia and A. Le Craz, *Bull. Soc. Chim. Fr.*, 1937 (1960); (d) F. G. Bordwell and K. M. Wellman, *J. Org. Chem.*, **28**, 1347 (1963); (e) J. W. Lewis and R. L. Meyers, *J. Chem. Soc. C*, 753 (1971).

(3) Treatment of **2d** with bis(dimethylamino)methoxymethane afforded the condensation product **6** [*cf.* R. F. Borch, C. V. Grudzinskas, D. A. Peterson, and L. D. Weber, *J. Org. Chem.*, **37**, 1141 (1972)].

(4) F. G. Bordwell and K. M. Wellman, *J. Org. Chem.*, **28**, 2544 (1963).

Finally, alkaline hydrolysis of keto ester **3d**, previously prepared by the lead tetraacetate oxidation of 4,4-dimethyl-2-cyclohexenone (**3a**),[2d] yielded ketol **3e**. Oxidation of the latter with bismuth oxide, followed by base-induced O-methylation, led to cyclohexadienones **7b** and **7c**, consecutively. Interaction of the methoxy ketone **7c** with methyllithium afforded carbinol **8**, whose Collins oxidation[5] gave the desired methoxy ketone **1a**. Since selenium dioxide oxidation of keto ether **9**, a recently reported product of the ready condensation of isobutyraldehyde and methoxymethyl vinyl ketone,[6] leads to dienone **7c**, its aforementioned transformation into **1a** makes available a facile, four-step synthesis of the dienone **1a**.

### Experimental Section

Melting points, determined on a Reichert micro hot stage, are uncorrected. Infrared spectra were obtained on a Perkin-Elmer Model 137 spectrophotometer. Unless otherwise noted, proton magnetic resonance spectra of deuteriochloroform solutions containing tetramethylsilane ($\delta$ 0 ppm) as internal standard were taken on a Varian Associates Model A-60 spectrometer.

**3,3,6-Trimethyl-2-cyclohexenone (2a).**—A solution of methylmagnesium iodide, from 2.9 g of magnesium, 8.1 ml of methyl iodide, and 100 ml of ether, was added dropwise over a 1-hr period to an ice-cold solution of 10.0 g of 4,4-dimethyl-2-cyclohexenone (**3a**) in 50 ml of ether. The mixture was refluxed for 1 hr and stirred at room temperature for 14 hr. Saturated ammonium chloride solution (200 ml) was added, the mixture was shaken, and the organic layer was separated and evaporated. A suspension of 10.0 g of chromium trioxide in 200 ml of acetic acid was added dropwise to a solution of the residual carbinol **4a** (12 g) in 50 ml of acetic acid and the mixture was kept at room temperature for 16 hr. It then was diluted with water and extracted with ether. The extract was washed with sodium bicarbonate solution and water and evaporated. Chromatography of the residue (7.0 g) on neutral alumina (activity I) and elution with 1:1 pentane–ether yielded 4.7 g of liquid **2a**: bp 87–89° (16 Torr) [lit.[1] bp 86–88° (15 Torr)]; ir (neat) 5.98 (s, C=O), 6.09 $\mu$ (m, C=C); pmr ($CCl_4$) $\delta$ 1.03 (s, 6, $Me_2$), 1.6–2.5 [m, 4, $(CH_2)_2$], 1.92 (broad s, 3, olefinic Me), 5.63 (q, 1, $J$ = 2 Hz, olefinic H); literature[1] spectra identical.

**3,6,6-Trimethyl-2,4-cyclohexadienone (1b).**—A solution of 10.0 g of **2a** and 13.0 g of *N*-bromosuccinimide in 250 ml of carbon tetrachloride was refluxed under nitrogen for 20 min. The mixture then was cooled and filtered. Evaporation of the filtrate yielded 17.0 g of unstable, oily bromo ketone **2b**: ir (neat) 5.96 (s, C=O), 6.12 $\mu$ (m, C=C); pmr $\delta$ 1.11 (s, 3, Me), 1.22 (s, 3, Me), 1.2–1.5 (m, 2, $CH_2$), 2.13 (t, 3, $J$ = 2 Hz, olefinic Me), 4.88 (m, 1, BrCH), 5.87 (p, 1, $J$ = 2 Hz, olefinic H). A mixture of 5.0 g of the latter and 10 g of calcium carbonate in 70 ml of *N*,*N*-dimethylacetamide was refluxed under nitrogen for 30 min. It was cooled and filtered and the filtrate was diluted with water and extracted with ether. The extract was evaporated and the residual oil (2.5 g) was chromatographed on silica gel. Elution with 5:1 hexane–ether gave 2.0 g of oil whose distillation afforded colorless liquid **1b**: bp 66–67° (4.7 Torr); ir (neat) 6.00 (s, C=O), 6.33 $\mu$ (m, C=C); pmr $\delta$ 1.19 (s, 6, $Me_2$), 2.07 (d, 3, $J$ = 2 Hz, olefinic Me), 5.88 (m, 1, H-2), 6.04 (dd, 1, $J$ = 10, 2 Hz, H-4), 6.30 (d, 1, $J$ = 10 Hz, H-5).

*Anal.* Calcd for $C_9H_{12}O$: C, 79.37; H, 8.88. Found: C, 79.17; H, 8.83.

**4-Acetoxy-3,6,6-trimethyl-2-cyclohexenone (2c).**—A solution of 12.0 g of bromo ketone **2b** and 15.0 g of silver acetate in 50 ml of acetic acid was stirred at room temperature for 24 hr. The mixture was filtered and the filtrate was diluted with water and extracted with ether. The extract was washed with sodium bicarbonate solution and with water, dried over sodium sulfate, and evaporated. Distillation of the residue (8.9 g) gave 3.9 g of oil whose chromatography on alumina (activity IV) and elution with 10:1 hexane–ether gave liquid keto ester **2c**: uv (EtOH) $\lambda_{max}$ 229 nm ($\epsilon$ 13,900); ir (neat) 5.75 (s, C=O), 5.97 $\mu$ (s); pmr $\delta$ 1.17 (s, 6, $Me_2$), 1.95 (t, 3, $J$ = 1 Hz, olefinic Me), 1.9–2.2 (m, 2, $CH_2$), 2.13 (s, 3, acetyl Me), 5.75 (m, 1, oxymethine), 5.84 (m, 1, olefinic H).

*Anal.* Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.61; H, 8.27.

**2,5,5-Trimethyl-2-cyclohexene-1,4-dione (2d).**—A solution of 17.9 g of keto ester **2c** in 250 ml of dry ether was added to a suspension of 16.4 g of lithium aluminum hydride in 750 ml of ether and the mixture was kept at room temperature for 3 hr. A sodium sulfate slurry saturated with water was added and the mixture was shaken and filtered. Evaporation of the filtrate gave 13.1 g of oily enediol: ir (neat) 2.97 (s, OH), 6.02 $\mu$ (w, C=C). A mixture of 12.9 g of the latter and 150 g of activated manganese dioxide in 350 ml of ether was stirred at room temperature under nitrogen for 20 hr. It was filtered and the filtrate was evaporated. Crystallization of the residual solid (6.7 g) from hexane and sublimation yielded yellow, crystalline **2d**: mp 85°; uv (EtOH) $\lambda_{max}$ 242 nm ($\epsilon$ 15,200); ir (Nujol) 5.94 (s, C=O), 6.13 $\mu$ (m); pmr $\delta$ 1.24 (s, 6, $Me_2$), 2.01 (d, 3, $J$ = 2 Hz, olefinic Me), 2.77 (s, 2, $CH_2$), 6.52 (m, 1, olefinic H).

*Anal.* Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found: C, 71.23; H, 8.17.

**2,2,5-Trimethyl-1,4-cyclohexanedione (5).**—A mixture of 0.70 g of diketone **2d** and 10 g of zinc dust in 40 ml of acetic acid was stirred at room temperature for 10 min. It was filtered and the filtrate was diluted with water and extracted with ether. Evaporation of the extract yielded 0.51 g of a solid whose crystallization from hexane and sublimation gave colorless, crystalline diketone **5**: mp 52–54°; ir (Nujol) 5.85 $\mu$ (s, C=O); pmr $\delta$ 1.17 (s, 6, $Me_2$), 1.19 (d, 3, $J$ = 6 Hz, Me), 2.61 (s, 2, $H_2$-3), 2.6–2.8 (m, 3, H-5 and $H_2$-6).

*Anal.* Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.26; H, 8.97.

**2-(*trans*-β-Dimethylaminovinyl)-5,5-dimethyl-2-cyclohexene-1,4-dione (6).**—A solution of 200 mg of diketone **2d** and 4.0 ml of bis(dimethylamino)methoxymethane in 10 ml of benzene was refluxed under nitrogen for 18 hr. It was poured into water and extracted with ether. The exatract was evaporated and the residue (210 mg) was chromatographed on alumina (activity III). Elution with hexane led to recovery of 160 mg of starting ketone, while elution with 20:1 hexane–ether gave 30 mg of solid whose sublimation yielded orange, crystalline **6**: mp 96–98°; uv (EtOH) absorption at 448 nm; ir (Nujol) 5.88 (s, C=O), 6.06 (s, C=O and C=C), 6.18 (s), 6.44 $\mu$ (s); pmr $\delta$ 1.21 (s, 6, $Me_2$), 2.73 (s, 2, $CH_2$), 2.98 (s, 6, $NMe_2$), 4.93 7.40 (d each, 1 each, $J$ = 14 Hz, vinyl methines), 6.14 (s, 1, H-3).

*Anal.* Calcd for $C_{12}H_{17}O_2N$: mol wt, 207.1259. Found: mol wt, 207.1261 (mass spectrum).

**4,4-Dimethyl-6-methoxy-2-cyclohexenone (3c).**—A suspension of 29.4 g of cupric bromide in 150 ml of methanol was added dropwise during a 1-hr period to a refluxing solution of 8.0 g of ketone **3a** in 100 ml of methanol and the refluxing was then continued for 4 hr The cooled solution was filtered, the precipitate was washed with ether, and the combined organic solutions were reduced to a volume of 100 ml under vacuum at room temperature. Water was added and the mixture was extracted with ether. Evaporation of the extract and distillation of the residue yielded 11.1 g of oil whose redistillation gave a colorless liquid which crystallized on standing. Crystallization from hexane gave bromo ketone **3b**: bp 77–79° (0.2 Torr); mp 44–45° (lit.[4] mp 47.5°); ir (film) 5.91 (s, C=O), 12.25 $\mu$ (m, CBr) (lit.[4] 5.92 and 12.20 $\mu$, respectively); pmr $\delta$ 1.23 (s, 3, Me), 1.26 (s, 3, Me), 2.40 (d, 1, $J$ = 11 Hz, H-5), 2.42 (dd, 1, $J$ = 8, 2 Hz, H-5), 4.87 (dd, 1 $J$ = 11, 8 Hz, BrCH), 5.92 (d, 1, $J$ = 11 Hz, H-2), 6.72 (dd, 1, $J$ = 11, 2 Hz, H-3). A mixture of 8.0 g of **3b**, 7.7 g of silver nitrate, and 0.1 ml of 70% perchloric acid in 75 ml of methanol was stirred at room temperature for 2 hr. It was filtered and the filtrate was concentrated to 30 ml under vacuum at room temperature. Water was added and the mixture was extracted with ether. The extract was evaporated and the residue (6.5 g) was chromatographed on alumina (activity II) and eluted with 5:1 hexane–ether. Distillation of the eluate (1.3 g) afforded liquid keto ether **3c**: bp 55° (0.25 Torr); ir (neat) 5.95 (s, C=O), 6.21 $\mu$ (w, C=C); pmr $\delta$ 1.20 (s, 3, Me), 1.27 (s, 3, Me), 1.90 (d, 1, $J$ = 12 Hz, H-5), 2.02 (d d, 1, $J$ = 7, 2 Hz, H-5), 3.52 (s, 3, OMe), 3.89 (dd, 1, $J$ = 12, 7 Hz, H-6), 5.75 (d, 1, $J$ = 10 Hz, H-2), 6.61 (dd, 1, $J$ = 10, 2 Hz, H-3).

*Anal.* Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.31; H, 9.21.

(5) R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).

(6) E. Wenkert, N. F. Golob, S. S. Sathe, and R. A. J. Smith, *Syn. Commun.*, **3**, 205 (1973).

**4-Methoxy-3,6,6-trimethyl-2-cyclohexenone (2e).**—A solution of methylmagnesium iodide, from 360 mg of magnesium and 1 ml of methyl iodide in 50 ml of ether, was added dropwise over a 0.5-hr period to an ice-cold solution of 1.55 g of keto ether **3c** in 25 ml of dry ether and the mixture was stirred at room temperature for 14 hr. Saturated ammonium chloride solution (100 ml) was added and the ether solution was separated and evaporated. A suspension of 1.27 g of chromium trioxide in 20 ml of acetic acid was added to a solution of the residual carbinol stereoisomer mixture **4b** (1.62 g) in 10 ml of acetic acid and the mixture was kept at room temperature for 4 hr. It then was poured into water and extracted with ether. Evaporation of the extract, chromatography of the residue (0.97 g) on alumina (activity IV), and elution with hexane yielded an oil whose distillation gave 780 mg of ketone **2e**: bp 75° (0.5 Torr); uv (EtOH) $\lambda_{max}$ 232 nm ($\epsilon$ 9900); ir (neat) 5.98 (s, C=O), 6.12 $\mu$ (m, C=C); pmr $\delta$ 1.12 (s, 3, Me), 1.16 (s, 3, Me), 1.0–2.3 (m, 2, $CH_2$), 1.99 (t, 3, $J$ = 2 Hz, olefinic Me), 3.43 (s, 3, OMe), 3.98 (m, 1, OCH), 5.74 (m, 1, olefinic H).

*Anal.* Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.51; H, 9.69.

**Dienones 7.**—A mixture of 500 mg of ketone **3a** and 1.3 g of selenium dioxide in 4 ml of water and 20 ml of dioxane was refluxed for 30 hr. It was filtered and the filtrate was diluted with water and extracted with ether. The extract was evaporated and the residue (390 mg) was chromatographed on alumina (activity IV). Elution with 20:1 pentane–ether gave 70 mg of liquid 4,4-dimethyl-2,5-cyclohexadienone (**7a**), ir and pmr identical with those cited in the literature.[4,7]

A solution of 9.6 g of keto ester **3d**[2d] in 125 ml of 0.5 $N$ aqueous potassium hydroxide and 125 ml of methanol was kept at room temperature under nitrogen for 10 min. It was brought to pH 6 with acetic acid and evaporated under vacuum at room temperature. Extraction of the residue with ether, evaporation of the extract, and distillation of the residue gave 5.0 g of liquid 4,4-dimethyl-6-hydroxy-2-cyclohexenone (**3e**): bp 50° (0.2 Torr); ir (neat) 2.86 (m, OH), 5.92 (s, C=O), 6.15 $\mu$ (m, C=C); pmr $\delta$ 1.19 (s, 3, Me), 1.27 (s, 3, Me), 1.89 (d, 1, $J$ = 13 Hz, H-5), 2.12 (dd, 1, $J$ = 7, 2 Hz, H-5), 4.38 (dd, 1, $J$ = 13, 7 Hz, H-6), 5.92 (d, 1, $J$ = 10 Hz, H-2), 6.68 (dd, 1, $J$ = 10, 2 Hz, H-3). A mixture of 2.8 g of the latter and 9.3 g of bismuth trioxide in 40 ml of acetic acid was kept at 100° for 10 min. It then was cooled, diluted with ether, and filtered. The precipitate was washed thoroughly with ether and the combined washings and filtrate were washed with saturated sodium bicarbonate solution and with water and evaporated. Distillation of the residue yielded 1.5 g of liquid 4,4-dimethyl-2-hydroxy-2,5-cyclohexadienone (**7b**): bp 53–54° (0.3 Torr); uv (EtOH) $\lambda_{max}$ 238 nm ($\epsilon$ 6300), 283 (2440); ir (neat) 2.92 (m, OH), 6.06 (br s, C=O), 6.23 $\mu$ (w, C=C); pmr $\delta$ 1.31 (s, 6, $Me_2$), 5.98 (d, 1, $J$ = 2 Hz, H-3), 6.18 (d, 1, $J$ = 10 Hz, H-6), 6.82 (dd, 1, $J$ = 10, 2 Hz, H-5).

*Anal.* Calcd for $C_8H_{10}O_2$: C, 69.55; H, 7.30. Found: C, 69.31; H, 7.50.

A mixture of 1.4 g of **7b**, 2.2 g of anhydrous potassium carbonate, and 5 ml of methyl iodide in 70 ml of dry acetone was stirred at room temperature for 18 hr. It was filtered and the filtrate was evaporated. Chromatography of the residue (1.6 g) on alumina (activity II) and elution with 10:1 hexane–ether yielded 720 mg of oil whose distillation produced liquid 4,4-dimethyl-2-methoxy-2,5-cyclohexadienone (**7c**): bp 81° (0.3 Torr); uv (EtOH) $\lambda_{max}$ 238 nm ($\epsilon$ 9200), 283 (3100); ir (neat) 6.05 (s, C=O), 6.15 (s, C=C), 6.26 $\mu$ (s); pmr $\delta$ 1.31 (s, 6, $Me_2$), 3.62 (s, 3, OMe), 5.71 (d, 1, $J$ = 2 Hz, H-3), 6.18 (d, 1, $J$ = 10 Hz, H-6), 6.79 (dd, 1, $J$ = 10, 2 Hz, H-5).

*Anal.* Calcd for $C_9H_{12}O_2$: C, 71.03; H, 7.95. Found C: 70.75; H, 7.96.

A mixture of 26.8 g of keto ether **9**[6] and 23.2 g of selenium dioxide in 192 ml of glacial acetic acid and 1.5 l. of dry *tert*-amyl alcohol was refluxed under nitrogen for 24 hr. It was filtered and the filtrate was concentrated at atmospheric pressure and finally evaporated fully under vacuum. A methylene chloride solution of the residual oil was washed with 5% sodium hydroxide solution and saturated brine solution, dried over potassium carbonate, and evaporated. Distillation of the residue gave 20.4 g of dienone **7c**, physical properties identical with those of the above sample.

**4-Methoxy-3,6,6-trimethyl-2,4-cyclohexadienone (1a).**—A solution of 180 ml of ethereal 1.5 $M$ methyllithium was added to a stirring solution of 20.4 g of **7c** in 300 ml of ether under nitrogen at such rate as to assure gentle refluxing. After 14 hr water was added and the organic solution was separated, dried over potassium carbonate, and evaporated. The residual ketol **8** (22.3 g) [ir (neat) 2.90 (m, OH), 5.95 (m, C=C), 6.11 $\mu$ (m); pmr $\delta$ 1.05 (s, 3, Me), 1.11 (s, 3, Me), 1.37 (s, 3, carbinol Me), 3.57 (s, 3, OMe), 4.54 (s, 1, $\beta$-methoxy olefinic H), 5.53 (broad s, 2, olefinic Hs)] was used in the next reaction without further purification. Dry chromium oxide (13.5 g) was added to a stirring solution of 21.3 g of pyridine, distilled from barium oxide, in 350 ml of methylene chloride. After 15 min 2.78 g of **8** in 5 ml of methylene chloride was added to the mixture and stirring was continued for 15 min. The mixture was poured into ether and washed with 5% sodium hydroxide solution and 10% cupric sulfate solution. The organic solution was dried over magnesium sulfate and evaporated. Distillation of the residue gave 1.77 g of liquid ketone **1a**: bp 55° (0.2 Torr); ir (neat) 6.01 (s, C=O), 6.10 (s, C=C), 6.32 $\mu$ (s); pmr $\delta$ 1.19 (s, 6, $Me_2$), 2.03 (s, 3, olefinic Me), 3.57 (s, 3, OMe), 5.04 (s, 1, H-5), 5.85 (s, 1, H-2).

*Anal.* Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.49. Found: C, 72.45; H, 8.42.

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**Registry No.**—**1a**, 42116-94-9; **1b**, 23438-76-8; **2a**, 23438-77-9; **2b**, 42116-96-1; **2c**, 42116-97-2; **2d**, 38770-37-5; **2e**, 42116-99-4; **3a**, 1073-13-8; **3b**, 40441-34-7; **3c**, 42117-25-9; **3d**, 42117-26-0; **3e**, 42117-27-1; **5**, 42117-27-2; **6**, 42087-03-6; **7b**, 42117-29-3; **7c**, 42117-30-6; **8**, 42117-31-7; **9**, 42117-32-8; methyl iodide, 74-88-4; bis(dimethylamino)methoxymethane, 1186-70-5.

(7) E. W. Garbisch, *J. Org. Chem.*, **30**, 2109 (1965); G. Legler and B. Quiring, *Tetrahedron*, **23**, 2683 (1967); H. E. Zimmerman, E. W. Binkley, J. J. McCullough, and G. A. Zimmerman, *J. Amer. Chem. Soc.*, **89**, 6589 (1967).

## An Improved Method for the Synthesis of Aliphatic Sulfinic Acids

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Despite their importance as polymerization activators[1] and as proposed intermediates in photochemical smog systems,[2] no simple one-step method appears to be available for the synthesis of aliphatic sulfinic acids in high yields and purity. For example, in the most important preparation,[3] the reduction of sulfonyl chlorides with zinc, iron, aluminium, or magnesium, the yields are reduced and the work-up is complicated by further reduction to disulfides and mercaptans.

Another favored method,[3] the treatment of organometallic compounds (RMgX and RLi) with sulfur dioxide, though preferable in cases where the sulfonyl chloride is unstable, suffers similarly from complications arising from competing side reactions. During the course of a study of the photochemical reactions of excited sulfur dioxide with hydrocarbons[4] we found it necessary to devise a synthesis capable of yielding

(1) C. S. Marvel and R. S. Johnson, *J. Org. Chem.*, **13**, 822 (1948).

(2) P. A. Leighton, "Photochemistry of Air Pollution," Academic Press, New York, N. Y., 1961, p 298.

(3) For reviews see W. E. Truce and A. M. Murphy, *Chem. Rev.*, **48**, 69 (1951); M. Quaedvlieg in "Enzyklopädie der organischen Chemie," E. Müller, Ed., Fourth ed, Band 9, Georg Thieme Verlag, Stuttgart, 1955, p 343.

(4) R. D. Penzhorn, L. Stieglitz, W. G. Filby, and K. Günther, *Chemosphere*, **3**, 111 (1973).

aliphatic sulfinic acids in gram amounts. We have observed that the direct oxidation of aliphatic mercaptans with *m*-chloroperoxybenzoic acid (MCPBA) (2 equiv) in methylene dichloride yields sulfinic acids in a high state of purity and in good yield. The experimental procedure is extremely simple and was applicable, in our hands, to all paraffinic isomers in the homologous series from ethyl to butyl. Preliminary experiments have also demonstrated that the reaction proceeds cleanly in the case of the analogous system thiophenol → benzenesulfinic acid.

From the stoichiometry the reaction appears to proceed *via* the intermediate sulfinic acid RSOH, which must then undergo a preferential rapid oxidation to sulfinic acid.

$$RSH \xrightarrow{[O]} RSOH \xrightarrow{[O]} RSO_2H$$

This reasoning is supported by our failure to observe disulfides in the reaction products by combined mass spectral–glc analysis. The latter are reported to be disproportionation products of sulfinic acids.[5]

$$2RSOH \longrightarrow RSH + RSO_2H$$

$$RSOH + RSH \longrightarrow RSSR + H_2O$$

Additionally we observed no trace of sulfonic acid in the freshly isolated sulfinic acids. Presumably *m*-chloroperoxybenzoic acid is too mild to further oxidize the sulfinic acid.

### Experimental Section

Mercaptan (0.05 mol) was dissolved in methylene dichloride (10 ml) and cooled to −30° in a deep freeze. Similarly, MCPBA (0.1 mol) was dissolved in methylene dichloride (200 ml) and cooled to −30°. At 0.5-hr intervals MCPBA slurry (10 ml) was pipetted slowly with vigorous stirring (exothermic) into the mercaptan solution and the flasks were returned to the deep freeze. This procedure is necessary in order to prevent an excess of MCPBA building up in the presence of sulfinic acid. Neglect of the latter point leads to formation of sulfonic acid, which is difficult to separate in the purification stage. The reaction can be monitored for excess oxidant by removing a spot of reaction mixture and testing with acidified potassium iodide solution. After addition of all the oxidant solution the reaction flask was allowed to stand overnight at −30°, before filtration of the precipitated *m*-chlorobenzoic acid (MCBA). Removal of the last traces of the latter proved difficult. Our most successful method consisted of cooling the original solution to *ca.* −80° by immersing in liquid nitrogen and then rapidly filtering. Two repeats of this process gave an end product showing no MCBA peaks in its ir spectrum. After removal of the MCBA the procedure consisted solely of evaporating the solvent in a rapid nitrogen stream. The sulfinic acids remained as pale yellow oils or solids. A short period (30 min) in an evacuated desiccator ($P_2O_5$) removed the last traces of moisture. The yields ranged from 80 to 85%.

In a typical run *n*-butyl mercaptan (0.05 mol, 4.5 g) gave 4.95 g (81.5%) of *n*-butanesulfinic acid after purification: ir[6,7] ($CHCl_3$) 3000 (s), 2520 (s), 1470 (s), 1335 (s), 1130 (s, broad), 1075 (s, broad), 1015 (m, shoulder), 960 $cm^{-1}$ (m, shoulder); mass spectrum[6] (70 eV) *m/e* (rel intensity, assignment) 137 (2.1, M + 1), 136 (4.3, M), 105 (16.4, $C_4H_9SO$), 80 (60, $CH_4SO_2$), 65 (24, $SO_2H$), 57 (100, $C_4H_9$).

*Anal.* Calcd for $C_4H_9SO_2H$: C, 39.39; H, 8.2; S, 26.22. Found: C, 39.1; H, 8.4; S, 26.08.

Evacuated samples maintained at low temperature (−30°) could be preserved for months without any noticeable decomposition (mass spectrum–glc). Samples warmed in either vacuum or air, however, rapidly undergo decay, turning to a deep orange yellow and precipitating white crystals.[8] For the purpose of long-term storage we have found it preferable to prepare the silver salts and store these under vacuum and low temperature. The latter can then be used at wish as a source of fresh sulfinic acid.

**Registry No.**—*m*-Chloroperoxybenzoic acid, 937-14-4; *n*-butyl mercaptan, 109-79-5; *n*-butanesulfinic acid, 5675-04-7.

(5) M. Kharasch, S. J. Potempa, and H. L. Wehrmeister, *Chem. Rev.*, **39**, 269 (1946).

(6) F. Wudl, D. A. Lightmer, and D. J. Cram, *J. Amer. Chem. Soc.*, **89**, 4099 (1967).

(7) S. Detoni and D. Hadzi, *J. Chem. Soc.*, 3163 (1955).

(8) W. G. Filby, unpublished observations.

## Phosphorus Pentoxide–Methanesulfonic Acid. A Convenient Alternative to Polyphosphoric Acid

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Polyphosphoric acid (PPA) has been utilized extensively in organic synthesis. It is one of the most effective reagents for carrying out alkylation and acylation reactions on aromatic and olefinic systems. PPA is often the favored reagent for a variety of synthetic transformations such as dehydrations, the Fischer–Indole synthesis, the Beckmann rearrangement, the Schmidt rearrangement, and many others.[1-3] As has been widely recognized, however, polyphosphoric acid has certain unfortunate physical properties. It is extremely viscous and is virtually impossible to stir effectively or manipulate conveniently at temperatures below 60–90°. It is difficult to handle on a large scale, even at elevated temperatures. Some organics are only sparingly soluble in PPA, and, in any case, rates of dissolution are low. Hydrolysis of PPA in work-up procedures is always tedious.

To escape the difficulties encountered with polyphosphoric acid, we have developed a new reagent composed of a 1:10 solution by weight of phosphorus pentoxide in methanesulfonic acid.[4] This reagent, prepared by simply dissolving phosphorus pentoxide in methanesulfonic acid, is a mobile, colorless liquid that can be poured and stirred (even magnetically) without difficulty. Organic compounds dissolve readily in this medium. Unlike the related phosphorus pentoxide–trifluoromethanesulfonic acid reagent reported earlier from this laboratory,[5] the material is inexpensive, readily available, and safe to handle. Work-ups of phosphorus pentoxide–methanesulfonic acid reaction mixtures are easy and clean. The reagent can be destroyed conveniently with approximately three times

(1) F. D. Popp and W. E. McEwen, *Chem. Rev.*, **58**, 321 (1958).

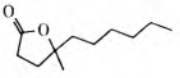
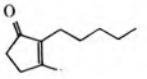
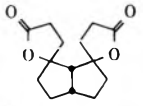
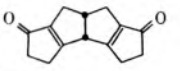
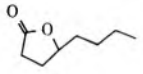
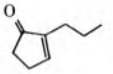
(2) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. I, Wiley, New York, N. Y., 1967, pp 894–905.

(3) F. Uhlig and H. R. Snyder, *Advan. Org. Chem.*, **1**, 35 (1960).

(4) The 1:10 ratio of components merely represents the limit of ready solubility of phosphorus pentoxide in methanesulfonic acid at room temperature. More concentrated reagents can easily be prepared at elevated temperatures. However, neither these nor more dilute solutions were investigated in any detail.

(5) *Cf.* P. E. Eaton and R. H. Mueller, *J. Amer. Chem. Soc.*, **94**, 1014 (1972).

TABLE I
USE OF PHOSPHORUS PENTOXIDE–METHANESULFONIC ACID IN THE PREPARATION OF CYCLOPENTENONES AND AMIDES

| Registry no. | Compound | Reaction conditions | Registry no. | Product | Typical isolated yield, % | Literature yield with PPA, % |
|---|---|---|---|---|---|---|
| 7011-83-8 |  | 33 hr, 25°, 1:80[a] | 1128-08-1 |  | 92 | 92[b] |
| 36269-13-3 |  | 96 hr, 45°, 1:75<br>5 hr, 80°, 1:75<br>114 hr, 35°, 1:20 to 1:100[c] | 36269-14-4 |  | 75–85[d] | 65–70[e] |
| 104-50-7 |  | 24 hr, 60°, 1:40 | 24105-07-5 |  | 33[f] | |
| | | | 31863-60-2 |  | 24 | 52[g] (combined products) |
| 501-52-0 | Phenylpropionic acid | 6 hr, 50°, 1:75 | 83-33-0 | 1-Indanone | 87 | 93[h] |
| 574-66-3 | Benzophenone oxime | 48 hr, 50°, 1:25 | 93-98-1 | Benzanilide | 95 | 99[i] |
| | | 1 hr, 100°, 1:25 | | | 90 | |
| 100-64-1 | Cyclohexanone oxime | 1 hr, 100°, 1:25 | 105-60-2 | ϵ-Caprolactam | 96 | 89[i] |
| 629-31-2 | Heptaldoxime | 1 hr, 100°, 1:25 | 628-62-6 | Heptamide | 90[j] | 92[k] |

[a] Weight ratio, substrate:reagent. [b] Reference 7b. [c] The yield did not vary significantly over this range. At 1:10 the yield fell off substantially. In general, moderate temperature and a high ratio of reagent to reactant give the cleanest reactions. [d] Crystallized from isopropyl alcohol; mp 209–210°. [e] Reference 5. [f] Distilled at 58° (3 Torr) and separated by glpc (6 ft × 0.25 in., 10% Carbowax 20M on 60/80 Chromosorb W, 100°). [g] Reference 7e. [h] References 7f and 7g. [i] Reference 8a. [j] No trace of nitrile was detected in the crude reaction product. [k] Reference 8b.

its weight of water or with saturated aqueous sodium bicarbonate solution.[6]

Table I illustrates the utility of the phosphorus pentoxide–methanesulfonic acid reagent for two types of transformations classically performed in polyphosphoric acid, namely, the preparation of cyclopentenones *via* the intramolecular acylation of olefin acids or their lactones[7] and the preparation of amides *via* the Beckmann rearrangement.[8] In all cases, the isolated yield using 1:10 phosphorus pentoxide–methanesulfonic acid compares favorably with the best yield reported for the same transformation carried out in polyphosphoric acid. In fact, the reaction of each substrate in the new reagent seems to mimic that in polyphosphoric acid in terms of relative rate, product distribution, and yield. No doubt, phosphorus pentoxide–methanesulfonic acid could be substituted usefully in other reactions brought about by PPA.[9] Logically, the two reagents can be expected to have similar chemical limitations.[10]

The important reactant in the phosphorus pentoxide–methanesulfonic acid reagent is not certain; most probably it is a very active mixed anhydride. Although methanesulfonic anhydride is clearly present in the phosphorus pentoxide–methanesulfonic acid mixture, as observed by nmr, appropriate methanesulfonic anhydride–methanesulfonic acid solutions are less effective in carrying out these transformations; the reaction rates are slower, and product yields are generally poorer. Pure methanesulfonic acid will not promote the reactions considered here under comparable conditions.

(6) Quenching on ice is generally not recommended, as methanesulfonic anhydride, present in the mixture, precipitates and is only slowly hydrolyzed by cold water. The anhydride (mp 66–67°) is easily extracted into organic solvents and can be a bothersome contaminant. The hydrolysis of the anhydride is rapid at room temperature, requiring only 5–10 min. Quenching with aqueous sodium bicarbonate solution assures almost instantaneous hydrolysis of the anhydride, but this practice is less convenient, as extensive foaming occurs.

(7) (a) K. Biemann, G. Büchi, and B. H. Walker, *J. Amer. Chem. Soc.*, **79**, 5558 (1957); (b) C. Rai and S. Dev, *J. Indian Chem. Soc.*, **34**, 173 (1957); (c) T. M. Jacob and S. Dev, *ibid.*, **36**, 429 (1959); (d) T. M. Jacob, P. A. Vatakencherry, and S. Dev, *Tetrahedron*, **20**, 2815, 2821 (1964); (e) M. F. Ansell and S. S. Brown, *J. Chem. Soc.*, 2955 (1958); (f) R. C. Gilmore, Jr., *J. Amer. Chem. Soc.*, **73**, 5879 (1951); (g) G. Metz, *Synthesis*, 612 (1972).

(8) (a) E. C. Horning and V. L. Stromberg, *J. Amer. Chem. Soc.*, **74**, 2680 (1952); (b) *ibid.*, **74**, 5151 (1952).

(9) Following our recommendation, R. L. Cargill and T. E. Jackson, *J. Org. Chem.*, **38**, 2125 (1973) (footnote 17), have utilized methanesulfonic acid containing phosphorus pentoxide to effect the intermolecular acylation of cyclohexene with acrylic acid.

(10) J. K. Groves, *Chem. Soc. Rev.*, **1**, 73 (1972).

## Experimental Section

Methanesulfonic acid (technical grade, Eastman Organic Chemicals) must be distilled before use for clean work-ups and good yields. Distillation under vacuum is recommended to avoid thermal decomposition that begins at temperatures of about 140–150°. The material used distilled at 108° (0.25 Torr) as a clear, colorless liquid containing less than 1 mol % methanesulfonic anhydride as determined by nmr. γ-Octanoic lactone and phenylpropionic acid were obtained from Aldrich Chemical Co.; the former was used directly, but the latter was recrystallized from heptane prior to use. All oximes were prepared according to literature procedures and were recrystallized to constant melting point.

**Preparation of 1:10 Phosphorus Pentoxide–Methanesulfonic Acid Solution.**—In a typical experiment, freshly distilled methanesulfonic acid (360 g) was placed in a 500-ml, three-necked flask fitted with an efficient mechanical stirrer (important) and a calcium chloride drying tube. Phosphorus pentoxide (36 g, weighed out in a drybox) was added in one portion and generally dissolved in 1–2 hr. The reagent could be used immediately or could be stored in a stoppered flask for later use. Slight yellowing occurred on long storage, but this did not effect the efficacy of the reagent to any noticeable degree.

**Preparation of Dihydrojasmone.**—The following procedure is typical for the preparation of cyclopentenones from lactones using the 1:10 phosphorus pentoxide–methanesulfonic acid reagent. A 4.91-g portion of γ-methyl-γ-decanolactone[11] was added in small portions to 410 g of rapidly stirred 1:10 phosphorus pentoxide–methanesulfonic acid. The homogeneous reaction

(11) P. E. Eaton, G. F. Cooper, R. C. Johnson, and R. H. Mueller, *J. Org. Chem.*, **37**, 1947 (1972).

mixture was stirred at 25° for 33 hr. The yellow solution was transferred to a 500-ml separatory funnel and added dropwise to 1 l. of water. The aqueous mixture was stirred rapidly for 5–10 min to ensure hydrolysis of methanesulfonic anhydride and was then extracted with chloroform (4 × 300 ml). The extract was washed once with dilute aqueous sodium bicarbonate (200 ml) and once with water, dried over magnesium sulfate, and concentrated. The fragrant oil remaining was distilled at 90–91° (2 Torr) to give 4.08 g (92%) of dihydrojasmone in 97% purity as judged by glpc (10 ft × 0.125 in., 15% OV-101 on 60/80 Chromosorb G, 200°). The semicarbazone was prepared, mp 176–177° (lit.[12] mp 175–176°).

**Preparation of ε-Caprolactam.**—The following is a typical preparation of amides from oximes using 1:10 phosphorus pentoxide–methanesulfonic acid. A 2.0-g portion of cyclohexanone oxime was added in small portions to 50 g of rapidly stirred 1:10 phosphorus pentoxide–methanesulfonic acid. Each batch of oxime was added only after the previous one had dissolved; the whole process required about 5 min. The colorless reaction mixture was then heated with stirring to 100°. One hour later the yellow solution was quenched in aqueous saturated sodium bicarbonate (200 ml) and extracted with chloroform (3 × 100 ml). The extract was dried with magnesium sulfate and evaporated. The crude product was crystallized from ether–hexane to give 1.92 g (96%) of ε-caprolactam as colorless crystals, mp 68–69° (lit.[8a] mp 65–68°).

**Acknowledgment.**—This work was supported generously by the National Science Foundation and the National Cancer Institute of the National Institutes of Health. G. R. C. is grateful to the National Institute of Allergy and Infectious Diseases of the NIH for a postdoctoral fellowship.

**Registry No.**—Phosphorus pentoxide–methanesulfonic acid, 39394-84-8.

(12) H. Staudinger and L. Ruzicka, *Helv. Chim. Acta*, **7**, 245 (1924).

## An Improved Aromatization of α-Tetralone Oximes to *N*-(1-Naphthyl)acetamides[1]

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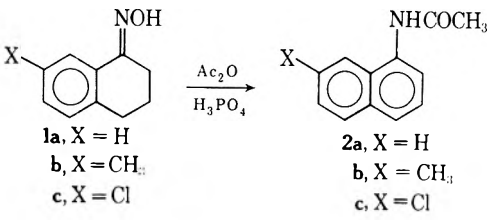
*Received July 12, 1973*

The conversion of oximes of substituted cyclohexenones to aromatic amines has been carried out frequently by heating in acetic acid–acetic anhydride containing dissolved hydrogen chloride or hydrogen bromide. This reaction, originally discovered by Semmler,[2] has been applied to methylated cyclohexenones,[3] tetralones,[4,5] and 1- and 4-keto-1,2,3,4-tetrahydrophenanthrenes,[5] although the yields rarely exceeded 50%. Because of the potential value of this type of intramolecular oxidation–reduction reaction for the synthesis of intermediates needed for the synthesis of polycyclic aromatic compounds, we decided to seek an improved method for carrying out such reactions.

We have found that on heating the oxime in acetic anhydride and anhydrous phosphoric acid at 80° for 30 min the yield of amine lies in the 82–93% region. By this method we have converted the oximes of α-tetralone (**1a**), 7-methyl-α-tetralone (**1b**), 7-chloro-α-tetralone (**1c**), and 4-keto-1,2,3,4-tetrahydrophenanthrene (**3**) into the corresponding acetylamino compounds (and/or amines) in 82, 91, 93, and 82% yields, respectively.




**1a**, X = H
**b**, X = $CH_3$
**c**, X = Cl

**2a**, X = H
**b**, X = $CH_3$
**c**, X = Cl

In one attempt to treat the oxime of 6-methoxy-α-tetralone under the new conditions, such a mixture of products was obtained (including nuclear acetylated material) that no further study of this compound was made.

### Experimental Section

α-Tetralone (**1a**) and 6-methoxy-α-tetralone were purchased from the Aldrich Chemical Co., Milwaukee, Wis. 7-Methyl-α-tetralone (**1b**) was prepared as described.[6] 7-Chloro-α-tetralone[4a] (**1c**) was best prepared by heating a solution of 45 g of γ-(*p*-chlorophenyl)butyric acid[7] in 360 g of 115% polyphosphoric acid[8] at 90° for 30 min. The neutral fraction of the reaction products was crystallized from ether–petroleum ether (bp 35–60°) to yield 36.9 g (90%) of **1c**, mp 94.5–96.0°, pure enough for conversion to the oxime. Attempts to cyclize γ-(*p*-chlorophenyl)butyric acid with anhydrous hydrogen fluoride afforded **1c** in very low yield.

The oximes were prepared by refluxing a solution of the tetralone (0.1 mol), hydroxylamine hydrochloride (0.12 mol), pyridine (10 ml), and absolute ethanol (100 ml) for 4 hr. The oximes, after recrystallization from ether–petroleum ether, were obtained in 95–98% yield. The oxime **1c** was light sensitive.

**Aromatization of Oximes.**—In a typical experiment, 17.5 g (0.1 mol) of 7-methyl-α-tetralone oxime,[9] mp 100–101°, was added to a well-mixed solution of acetic anhydride (204 g, 2.0 mol) and anhydrous phosphoric acid (196 g, 2.0 mol).[10] The mixture was held at 80° for 30 min and the resulting light brown solution was poured in 1.5 l. of ice water. The solid was collected and washed with water to yield 12.8 g of *N*-(7-methyl-1-naphthyl)acetamide[6] (**2b**), mp 176–178°, after drying. The aqueous filtrate was made basic with sodium hydroxide and treated with 50 ml of acetic anhydride. The amide thus formed (5.2 g) was added to the first portion. The combined yield was 91%.

In a similar way **1a**,[11] mp 100.5–101.5°, **1c**,[4a] mp 124–125°, and **3**,[12] mp 174–175°, were converted into *N*-(1-naphthyl)acetamide (**2a**), mp 153–155°, *N*-(7-chloro-1-naphthyl)acetamide (**2c**), mp 196–197°, and *N*-(4-phenanthryl)acetamide,[12] mp 192–194°, in 82, 93, and 82% yields, respectively. In all cases, both amide and amine hydrochloride were formed. The yields reported include the amide formed from the amine as described.

*Anal.* Calcd for $C_{12}H_{10}ClNO$ (**2c**): C, 65.6; H, 4.6; N, 6.4; Cl, 16.2. Found: C, 65.8; H, 4.7; N, 6.4; Cl, 16.0.

In the case of **1c**, the reaction on 0.1 mol was carried out as described but with only one quarter of the amounts of acetic

(1) This research was supported by Grant No. CA-07394 from the National Institutes of Health.

(2) W. Semmler, *Ber.*, **25**, 3352 (1892). See also L. Wolff, *Justus Liebigs Ann. Chem.*, **322**, 351 (1902).

(3) F. M. Beringer and I. Ugelow, *J. Amer. Chem. Soc.*, **75**, 2635 (1953).

(4) (a) O. Schrader, *et al.*, *Ber.*, **63**, 1308 (1930); (b) A. Hardy, E. R. Ward, and L. A. Day, *J. Chem. Soc.*, 1979 (1956); (c) W. Adcock and M. J. S. Dewar, *J. Amer. Chem. Soc.*, **89**, 386 (1967).

(5) W. Langenbeck and K. Weissenborn, *Ber.*, **72**, 724 (1939). See also F. M. Beringer, L. L. Chang, A. N. Fenster, and R. R. Rossi, *Tetrahedron*, **25**, 4339 (1969).

(6) L. Ruzicka and E. Morgeli, *Helv. Chim. Acta*, **19**, 377 (1936).

(7) S. Skraup and E. Schwamberger, *Justus Liebigs Ann. Chem.*, **462**, 135 (1928).

(8) We thank the FMC Corp., New York, N. Y., for a generous gift of 115% polyphosphoric acid.

(9) R. Huisgen and V. Vossius, *Monatsh. Chem.*, **88**, 517 (1957).

(10) Anhydrous phosphoric acid was prepared as described by R. E. Ferrel, H. S. Olcott, and H. Fraenkel-Conrat, *J. Amer. Chem. Soc.*, **70**, 2101 (1948).

(11) F. S. Kipping and A. Hill, *J. Chem. Soc.*, **75**, 150 (1899).

(12) J. W. Krueger and E. Mosettig, *J. Org. Chem.*, **3**, 340 (1938).

anhydride and phosphoric acid reagent. The same yield of **2c** was obtained.

**Registry No.**—1a oxime, 3349-64-2; 1b, 5462-81-7; 1c oxime, 42071-42-1; 2a, 42071-43-2; 2b, 42071-44-3; 2c, 42071-45-4; 3, 781-23-7; *N*-(4-phenanthryl)acetamide, 42071-47-6; γ-(*p*-chlorophenyl)butyric acid, 4619-18-5.

## New Reactions of 3-Vinylindoles. II. Synthesis of 1,2-Dimethyl-3-(2-indolylcarbonyl)piperidine

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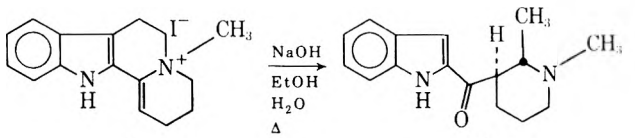
In 1968, we reported[2] that 5-methyl-2,3,4,6,7,12-hexahydroindolo[2,3-*a*]quinolizinium iodide (**1**) is converted on prolonged heating in aqueous ethanolic sodium hydroxide into 1,2-dimethyl-3-(2-indolylcarbonyl)piperidine (**2**), the product of a remarkable structural transformation.



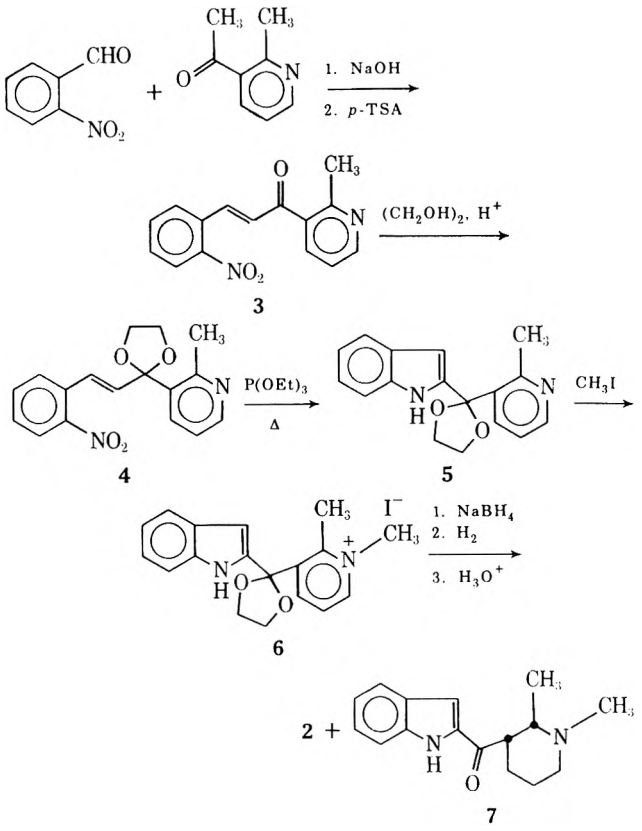

**1** **2**

Our original assignment was based on degradative studies, model reactions, and mechanistic considerations.[2] The complexity of the **1** → **2** rearrangement and the potential importance of the observed nucleophilic reactions of the intermediate 3-vinylindoles demanded further investigation of this transformation.

We now wish to describe an independent synthesis of 2-acylindole **2** which confirms the originally proposed structure. Our synthesis of **2** is outlined in Scheme I. An aldol condensation[3] between 2-methyl-3-acetylpyridine[4] and 2-nitrobenzaldehyde gives the unsaturated ketone **3** (17%) after dehydration of the intermediate ketol. Ketalization with ethylene glycol affords the nitrostyrene ketal **4** (97%) which on heating with triethyl phosphite[3] gives indole ketal **5** (52%).[5] Treating **5** with methyl iodide yields pyridinium salt **6** (~100%), which on successive exposure[6] to sodium borohydride, hydrogen, and aqueous acid gives a mixture of 2-acylindoles **2** and **7** (36% from **6**).[7]

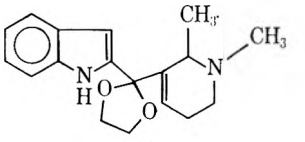
The mixture of 2-acylindoles could be separated by column chromatography into a major (92%) and a minor (8%) compound. The minor 2-acylindole is identical with the 2-acylindole obtained from **1**.

SCHEME I




**3** **4** **5** **6** **7**

Furthermore, the major 2-acylindole is completely converted into the minor 2-acylindole under the basic reaction conditions. On this basis, we assign the major 2-acylindole to the presumed less stable cis configuration **7** and the minor 2-acylindole to the more stable trans configuration **2**. In our original work[2] we made no attempt to assign stereochemistry to the single 2-acylindole obtained from **1**. If the intermediate tetrahydropyridine from **6** is **8**, as seems likely,[8] then it is reasonable to suppose that catalytic hydrogenation will proceed on the side away from the allylic methyl group to give mainly the cis configuration[9] **7**, after regeneration of the carbonyl group.[10]



**8**

### Experimental Section

Melting points were determined in open capillaries with a Mel-Temp Laboratory Devices apparatus and are uncorrected. Infrared spectra were measured with Perkin-Elmer 137 or 337 instruments. Nmr spectra were obtained with a Perkin-Elmer R-24 spectrometer. Woelm alumina was used for column chromatography and silica gel G (Merck) was used for thin layer chromatography (tlc). The tlc solvent system generally used was EtOAc–$Et_3N$ (~95:5) and plates were developed with a spray of 3% $Ce(SO_4)_2$–10% $H_2SO_4$ followed by a brief heat treat-

(1) Recipient of a Public Health Service Research Career Development Award (1 KO4-GM 23756) from the National Institute of General Medical Sciences.

(2) L. J. Dolby and G. W. Gribble, *Tetrahedron*, **24**, 6377 (1968).

(3) R. J. Sundberg, H. F. Russell, W. V. Ligon, Jr., and L.-S. Lin, *J. Org. Chem.*, **37**, 719 (1972).

(4) A. Dornow and W. Schacht, *Chem. Ber.*, **82**, 117 (1949).

(5) Attempts to cyclize **3** with triethyl phosphite give either no reaction or, on prolonged heating, no recognizable products.

(6) Attempts to hydrogenate **6** directly to the piperidine ketal are unsatisfactory.

(7) The crude reaction product also appears to contain the alcohols[2] (14%) corresponding to **2** and **7**, probably resulting from partial deketalization during $NaBH_4$ reduction.

(8) R. E. Lyle and P. S. Anderson, *Advan. Heterocycl. Chem.*, **6**, 45 (1966).

(9) The catalytic hydrogenation of 1,2,3-trimethylpyridinium iodide gives 99% cis product: M. Tsuda and Y. Kawazoe, *Chem. Pharm. Bull.*, **18**, 2499 (1970).

(10) The small amount of **2** obtained probably does not arise by acid-catalyzed epimerization during the deketalization, because treating **7** under acidic conditions (aqueous ethanolic HCl, reflux, 2 hr) does not convert it to **2**.

ment at 110°. Organic solutions were dried with anhydrous granular $K_2CO_3$ and concentrated *in vacuo* with a Buchler rotary evaporator. Microanalyses were performed by PCR, Inc., Gainesville, Fla., and Micro-Tech Labs Inc., Skokie, Ill. Mass spectra were determined by Mr. J. W. Suggs and Mr. H. E. Ensley at Harvard University.

**3-(2-Nitrophenyl)-1-(2-methyl-3-pyridyl)-2-propen-1-one (3).**—To a solution of 12 g (0.079 mol) of 2-nitrobenzaldehyde (Aldrich), 3.0 g (0.075 mol) of NaOH, 30 ml of $H_2O$, 30 ml of EtOH, and 25 ml of $Et_2O$ at 0–5° was added with stirring over 1 hr 10 g (0.074 mol) of 2-methyl-3-acetylpyridine.[4] A yellow precipitate formed during the addition, and near the end of the addition 25 ml of $Et_2O$ was added. The mixture was stirred at 0–5° for 2 hr and then stored in a refrigerator at 5° for 24 hr. The solid was collected by filtration and dissolved in 300 ml of benzene. The benzene solution was washed with water and refluxed with 0.9 g of *p*-toluenesulfonic acid (Dean-Stark trap) for 4 hr. The solution was filtered, washed with aqueous $NaHCO_3$ and then $H_2O$, dried, and concentrated to give a dark solid. Chromatography over activity III basic alumina gave, with benzene elution, 3.4 g (17%) of **3** as a white solid, mp 133–135°. Recrystallization from MeOH–$Et_2O$ gave colorless needles, mp 140–142°.

Pertinent spectral data for **3** are as follows: ir ($CHCl_3$) 2990, 1660, 1520, 1440, 1340, 1290, and 975 $cm^{-1}$; nmr ($CDCl_3$) δ 2.69 (s, 3), 7.7 (m, 8), and 8.6 ppm (m, 1).

*Anal.* Calcd for $C_{15}H_{12}N_2O_3$: C, 67.16; H, 4.51; N, 10.44. Found: C, 67.20; H, 4.60; N, 10.34.

**2-[2-(2-Nitrophenyl)vinyl]-2-(2-methyl-3-pyridyl)-1,3-dioxolane (4).**—A mixture of 6.85 g (0.0255 mol) of ketone **3**, 5.4 g (0.028 mol) of *p*-toluenesulfonic acid, 4.8 ml of ethylene glycol, and 120 ml of benzene was refluxed (Dean-Stark trap) with stirring. After 3 hr, more ethylene glycol (7 ml) and *p*-toluenesulfonic acid (1.7 g) were added and reflux was continued for 23 hr. The solution was allowed to cool and poured into water. The mixture was basified with 2 *N* NaOH and the benzene layer was separated. The aqueous layer was extracted with fresh benzene and the combined benzene extracts were washed with 1 *N* NaOH and then $H_2O$, dried, and concentrated to give 7.74 g (97%) of **4** as a yellow solid. Recrystallization from $Et_2O$–hexane gave large, colorless prisms, mp 91–93°.

Pertinent spectral data for **4** are as follows: ir ($CHCl_3$) 2980, 1520, 1440, 1340, 1050, and 969 $cm^{-1}$; nmr ($CDCl_3$) δ 2.70 (s, 3), 4.05 (m, 4), 6.67 (AB q, 2, $J$ = 15 Hz), 7.4 (m, 4), 7.9 (m, 2), and 8.24 ppm (d of d, 1).

*Anal.* Calcd for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.16; N, 8.97. Found: C, 65.48; H, 5.02; N, 8.89.

**2-(2-Indolyl)-2-(2-methyl-3-pyridyl)-1,3-dioxolane (5).**—To a refluxing, stirred solution of 30 ml of triethyl phosphite (distilled and passed through activity I basic alumina prior to use) under $N_2$ was added a solution of 1.57 g (0.00503 mol) of **4** in 40 ml of triethyl phosphite over a period of 3.5 hr. After addition, the mixture was refluxed for 5 hr and then allowed to stand overnight at 25°. The mixture was concentrated to near dryness (vacuum pump) and the residue was dissolved in 100 ml of $Et_2O$. The solution was stirred and saturated with HCl gas at 0° until the formation of insoluble material was judged complete. The ether was decanted off, and the residue was washed with ether and then treated with $CHCl_3$ and 2 *N* NaOH (ice cooling). Further extraction with $CHCl_3$ gave, after washing, drying, and concentration, a dark oil. Chromatography over activity III basic alumina gave, with benzene elution, 0.73 g (52%) of **5** as oily crystals. Recrystallization from benzene and then $CHCl_3$–hexane gave pure **5** as colorless, fluffy needles, mp 182–183°. A larger run with 7.75 g of **4** gave **5** in 38% yield.

Pertinent spectral data for **5** are as follows: ir ($CHCl_3$) 3495, 2980, 1290, 1170, 1080, and 1430 $cm^{-1}$; nmr ($CDCl_3$) δ 2.55 (s, 3) 3.85 (m, 4), 6.10 (broad s, 1), 7.1 (m, 5), 7.86 (d of d, 1), and 8.27 ppm (d of d, 1).

*Anal.* Calcd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.75; N, 9.99. Found: C, 73.01; H, 5.69; N, 10.11.

**1,2-Dimethyl-3-[2-(2-indolyl)-1,3-dioxolan-2-yl]pyridinium Iodide (6).**—A mixture of 1.37 g (0.00489 mol) of **5** and 10 ml of methyl iodide in 30 ml of benzene was stirred at 25° for 2 hr and then at 50° for 2 hr. After 3 days at 25°, the precipitate was collected and washed with benzene and then $Et_2O$ to give 2.1 g (~100%) of **6** as a light yellow powder. Recrystallization from MeOH–$Et_2O$ gave pure **6** as tiny, colorless needles, mp 214–216°.

*Anal.* Calcd for $C_{18}H_{19}N_2O_2I$: C, 51.20; H, 4.54; N, 6.63. Found: C, 51.02; H, 4.56; N, 6.48.

***cis*- and *trans*-1,2-Dimethyl-3-(2-indolylcarbonyl)piperidine (2 and 7).**—To a stirred solution of 0.5 g of $NaBH_4$ in 30 ml of 70% aqueous EtOH at 0–5° was added 0.56 g (0.0013 mol) of **6** over 1 min. After addition, more EtOH (5 ml) was added and the mixture was stirred at 0–5° for 1 hr and then at 25°. An additional 0.5 g of $NaBH_4$ and 15 ml of 50% EtOH were added after 4 hr at 25°. After stirring for 22 hr, the mixture was extracted with $CH_2Cl_2$. The extract was washed, dried, and concentrated to give 0.42 g of a yellow foam. The yellow foam was hydrogenated in 30 ml of EtOH with 0.15 g of 10% Pd/C at 25° (1 atm). Filtration and concentration gave 0.42 g of an amber oil. The amber oil was refluxed for 1 hr with 20 ml of 80% aqueous ethanol and 10 drops of concentrated HCl. The mixture was basified with 2 *N* NaOH, concentrated to near dryness, and extracted with $CH_2Cl_2$. The extract was washed, dried, and concentrated to give 0.30 g (88% crude from **6**) of a yellow-brown solid. Chromatography over activity III basic alumina gave, with benzene elution, 0.009 g (3%) of **2** as a yellow solid and 0.114 g (33%) of **7** as a white solid. Further elution with benzene and benzene–$CHCl_3$ gave 0.046 g of an amber gum which appeared to be a mixture of the alcohols derived from **2** and **7**.

Recrystallization from MeOH–$Et_2O$–hexane gave pure **2** as tiny prisms, mp 169–170° (lit.[2] mp 167–168°). This synthetic material was completely identical (tlc, infrared, mass spectrum) with a freshly recrystallized sample (mp 172–174°) of **2** as obtained[2] from **1**.

Recrystallization from MeOH–$Et_2O$–hexane gave pure **7** as tiny cubes of fluffy needles, mp 184–185°. This material was distinguishable from **2** in the fingerprint region of the infrared spectrum, and **7** exhibited a higher $R_f$ (0.73) and a lighter brown-colored spot on tlc than did **2** ($R_f$ 0.69). **7** showed nearly the same mass spectrum as **2**.

Pertinent spectral data for **7** are as follows: ir ($CHCl_3$) 3520, 3370, 2970, 1650, 1520, 1340, 1130, and 1110 $cm^{-1}$; nmr ($CDCl_3$) δ 0.88 (d, 3, $J$ = 6 Hz), 2.38 (s, 3), 7.3 ppm (m, 5). A mixture nmr spectrum of **2** and **7** clearly showed separate methyl resonances for the two epimers.

*Anal.* (**7**) Calcd for $C_{16}H_{20}N_2O$: C, 74.97; H, 7.86; N, 10.93. Found: C, 74.93; H, 7.92; N, 10.97.

**Conversion of 7 into 2.**—A mixture of 15 mg of a mixture of **2** and **7** (~50:50 by tlc) was refluxed under $N_2$ with 1.2 ml of 10% aqueous NaOH and 1.5 ml of 50% aqueous EtOH for 5 hr. Extraction with $CH_2Cl_2$ gave, after the usual work-up, 15 mg of a yellow solid showing only **2** by tlc, mp 167–169°. Recrystallization from MeOH–$Et_2O$–hexane gave pure **2** (tlc, infrared). A similar reaction with 44 mg of pure **7** gave 37 mg (84%) of **2**. The epimerization appears to be complete in 30 min by tlc and no **7** can be detected by tlc or nmr.

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**Registry No.**—**2**, 42031-20-9; **3**, 42031-21-0; **4**, 42031-22-1; **5**, 42031-23-2; **6**, 42031-24-3; **7**, 42031-25-4; *o*-nitrobenzaldehyde, 552-89-6; 2-methyl-3-acetylpyridine, 1721-12-6.

## Secondary Orbital Interactions Determining Regioselectivity in the Diels–Alder Reaction

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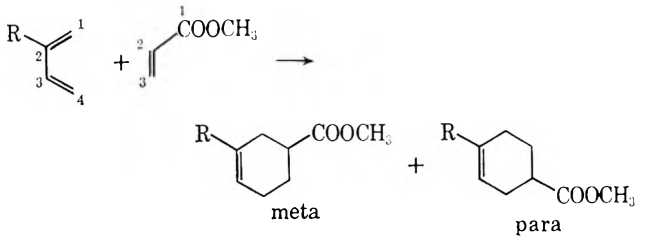
Recently, there has been considerable interest in the prediction of the preferred regioisomers of the Diels–

Alder reaction between unsymmetrically substituted dienes and dienophiles from molecular orbital calculations.[1,2] Houk[2] has proposed two generalizations for predicting the preferred regioisomers from terminal frontier coefficient magnitudes and frontier orbital energies. We have also examined these reactions using the frontier coefficient magnitudes and frontier orbital energies from INDO[3] calculations to determine the effect of secondary orbital interactions on the regioselectivity of these reactions.

The conformations[4] used in these calculations were the cisoid planar for the dienes and the transoid planar for the dienophiles. We found that the interpretations from the INDO calculated eigenvectors and eigenvalues were independent of small changes[6] in bond angles, bond distances, and rotational conformations. Thus, there was no justification of the use of computer time for an extensive optimization of the structures of these dienes; so standard bond angles and bond lengths[7,8] were used.

Employing Houk's generalizations and terminal coefficient magnitudes and orbital energies from the INDO calculations, the experimentally preferred regioisomers[5,9] were predicted for the cases **1a–1e** in which




**1a**, R = $CH_3$
**b**, R = Cl
**c**, R = CN
**d**, R = $C_6H_5$
**e**, R = $OCH_3$

there were considerable differences between the magnitudes (Table I) of the C-1 and C-4 HOMO coefficients of the dienes. However, it was found that the terminal carbons of the 1-substituted 1,3-butadienes studied have almost equal HOMO coefficients (Table II) implying, a 1:1 ratio of ortho and meta isomers

TABLE I
ISOMER RATIOS AND $P_z$ COEFFICIENTS OF HOMO FOR 2-SUBSTITUTED 1,3-BUTADIENES

| Substituent[a] | Ratio of para:meta | $P_z$ coefficients[b] C-1 | C-2 | C-3 | C-4 |
|---|---|---|---|---|---|
| $CH_3$ | 2.3:1[c] | 0.614 | 0.420 | 0.348 | 0.506 |
| $OCH_3$ | *d* | 0.650 | 0.345 | 0.223 | 0.369 |
| $C_6H_5$ | 4.0:1[c] | 0.572 | 0.341 | 0.214 | 0.335 |
| Cl | 6.7:1[c] | 0.546 | 0.346 | 0.266 | 0.397 |
| CN | 5.3:1[c] | 0.595 | 0.405 | 0.342 | 0.490 |

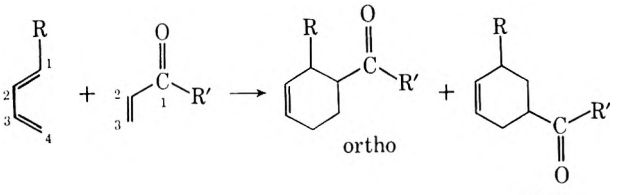
[a] Registry numbers are, respectively, 78-79-5, 3588-30-5, 2288-18-8, 126-99-8, 5167-62-4. [b] These are absolute values. The other atomic orbital coefficients are zero for HOMO. [c] Reference 9. [d] Para isomer was the only product isolated for 1-ethoxy-1,3-butadiene.[5]

TABLE II
ISOMER RATIOS AND $P_z$ COEFFICIENTS OF HOMO FOR 1-SUBSTITUTED 1,3-BUTADIENES

| Substituent[a] | Ratio of ortho:meta | $P_z$ coefficients[b] C-1 | C-2 | C-3 | C-4 |
|---|---|---|---|---|---|
| $CH_3$ | 9:1[c] | 0.531 | 0.456 | 0.350 | 0.534 |
| COOH | 8.8:1[d] | 0.483 | 0.384 | 0.314 | 0.460 |
| $C_6H_5$ | 39:1[d] | 0.408 | 0.443 | 0.230 | 0.416 |
| $p$-$NO_2C_6H_4$ | *e* | 0.424 | 0.426 | 0.247 | 0.419 |

[a] Registry numbers are, respectively, 504-60-9, 626-99-3, 1515-78-2, 20264-89-5. [b] These are absolute values. The other atomic orbital coefficients are zero. [c] Reference 9. [d] Reference 5. [e] The ortho isomer was the only product isolated (71%).[10]

which is contrary to experimental evidence. In these cases (**2a–d**) it is well known[5,9,10] that the ortho isomer




**2a**, R = $CH_3$; R' = $OCH_3$
**b**, R = $C_6H_5$; R' = $OCH_3$
**c**, R = COOH; R' = OH
**d**, R = $p$-$NO_2C_6H_4$; R' = OH

dominates. We have found that the preferred regioisomers can still be predicted by considering the secondary orbital interactions between the C-2 and C-3 positions of the diene and the position C-1 of the dienophile in the endo transition state.[11] In these cases the C-2 HOMO coefficients are significantly larger than their corresponding C-3 coefficients (Table II). Thus, the stabilization of the endo transition is greater when C-1 of the dienophile is near the secondary position C-2 of the diene, yielding the ortho isomer.

By similar analysis, the secondary orbital interactions in the endo transition state of the 2-substituted 1,3-butadienes favor the meta isomer instead of the experimentally preferred para isomer. This indicates the greater importance of the terminal orbital interactions in determining regioselectivity.

Consideration was also given to the substituent effect on the HOMO–LUMO splitting on the diene. For all cases but the reaction of 1-carboxy-1,3-butadiene with acrylic acid, the HOMO diene–LUMO dienophile inter-

(1) O. Eisenstein, J.-M. Lefour, and N. T. Anh, *Chem. Commun.*, 969 (1971).
(2) K. N. Houk, *J. Amer. Chem. Soc.*, **95**, 4092 (1973).
(3) J. A. Pople and D. L. Beveridge, "Approximate Molecular Orbital Theory," McGraw-Hill, New York, N. Y., 1970; CNDO/2 calculations were used for 2-chloro-1,3-butadiene.
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(5) J. Sauer, *Angew. Chem., Int. Ed. Engl.*, **6**, 16 (1967).
(6) Small changes in bond angles and bond distances effect the magnitudes of the coefficients and orbital energies only in the third decimal place.
(7) J. A. Pople and M. Gordon, *J. Amer. Chem. Soc.*, **89**, 4253 (1967).
(8) J. Donohue and K. N. Trueblood, *Acta, Crystallogr.*, **9**, 900 (1956): geometry of nitro group.
(9) T. Inukai and T. Kojima, *J. Org. Chem.*, **36**, 924 (1971).
(10) G. A. Ropp and E. C. Coyner, *J. Amer. Chem. Soc.*, **72**, 3960 (1950).
(11) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969), and references therein.

actions are greater than the HOMO dienophile–LUMO diene interactions.[12] In this reaction the magnitudes of the two interactions are nearly the same; thus both interactions effect the regioselectivity. We found that the HOMO C-1 and C-4 coefficients of the diene predict a slight dominance of the meta product while the LUMO C-1 and C-4 coefficients favor the ortho product.[13] This dichotomy is resolved by the larger C-2 coefficients in both molecular orbitals which results in the ortho product dominating.

In conclusion, secondary orbital interactions do have a significant effect on the regioselectivity of the Diels–Alder reaction between unsymmetrically substituted dienes and dienophiles. In the cases where the C-1 and C-4 frontier coefficients of the dienes are of nearly equal magnitudes, they can be used to predict the preferred regioisomers.

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(12) In the cases of **1b** and **1c**, the HOMO dienophile–LUMO diene interactions will have a significant effect on the regioselectivity. These interactions favor the para isomer as does the HOMO diene–LUMO dienophile interactions.

(13) The C-3 positions in HOMO and LUMO of methyl acrylate and acrylic acid have greater coefficients than their corresponding C-1 and C-2 positions.

## The Inductive Effect of Cyclopropane[1]

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As a result of studies of solvolyses of cyclopropane-substituted systems[3] we have been interested in determining the effect of nonconjugated cyclopropane[4] on the electronic environment at a reaction site involving electron-deficient carbon.

In surveying the literature it is readily apparent that the consensus is that cyclopropane is inductively electron withdrawing. This conclusion arises from consideration of dipole measurements[5] and measurements of infrared spectra and amine basicities,[6] the increased s character (hybridization) of the exocyclic cyclopropyl bonds,[7] the strain of the cyclopropyl group which should make it a negative pole and thus electron withdrawing[8] in the inductive sense, and from consideration of solvolysis data in which there is no conjugative interaction of the cyclopropyl group with the reactive site.[3a,9] Most striking is the recent finding that cyclopropane is a meta director in electrophilic substitution.[10] The general trend observed in most substituent effect studies is one of increasing electronegativity of a substituent with increasing s character, which is also paralleled by increases in $\sigma^*$[7b] values. Thus determination of the $\sigma^*$ value for cyclopropane should give a good measure of the inductive effect of the cyclopropyl group, uncomplicated by other effects.

As one of the best correlations of inductive effects is that of the ionization constants with $\sigma^*$ values ($\rho^* = +1.721 \pm 0.025$ in $H_2O$ at 25°[11]) for aliphatic carboxylic acids, our goal became the synthesis of cyclopropaneacetic acid. Cyclopropaneacetic acid has been prepared by a variety of procedures, but each is either lengthy or gives a low yield. It was anticipated that the Willgerodt reaction of methyl cyclopropyl ketone using the Kindler modification[12] might be useful, although this had been tried previously[13] using the Carmack method[14] Using the Kindler modification we achieved only an 8% yield of cyclopropaneacetic acid, but this was sufficient for our studies.

The ionization constants of acetic acid, isovaleric acid, vinylacetic acid, and cyclopropaneacetic acid were measured in water at 25° from pH titration curves. The measured $pK_a$ values are listed and compared with some literature[15] values in Table I, along with the cor-

TABLE I

IONIZATION CONSTANTS OF ALIPHATIC ACIDS

$$RCH_2CO_2H + H_2O \underset{25°,\ H_2O}{\overset{K}{\rightleftharpoons}} RCH_2CO_2^- + H_3O^+$$

| R | $pK_a$ lit. | $pK_a$ expt | $pK_a$ av | $\sigma^*_{RCH_2}$ [a] |
|---|---|---|---|---|
| H | 4.76 | 4.75 | 4.76 | 0.000 |
| | | 4.76 | | |
| | | 4.76 | | |
| $CH_3CHCH_3$ | 4.78 | 4.80 | 4.79 | −0.125[b] |
| | | 4.78 | | |
| | | 4.74 | | |
| c-$C_3H_5$ | | 4.73 | 4.74 | +0.011 |
| | | 4.75 | | |
| | | 4.74 | | |
| $CH_2$=CH | 4.35 | 4.37 | 4.36 | +0.226[b] |
| | | 4.36 | | |
| $C_6H_5$ | 4.31 | | | +0.260[c] |

[a] $\rho^* = +1.721 \pm 0.025$, ref 7b, p 606. [b] Calculated from measured and literature $pK_a$ values. [c] Calculated from literature values.

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(2) Visiting Faculty Associate from the Catholic University of Chile, Valparaiso, Chile.

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(11) Reference 7b, p 606.

(12) (a) K. Kindler, *Justus Liebigs Ann. Chem.*, **187**, 431 (1923); (b) D. Asinger, W. Schofer, K. Halcour, A. Saus, and H. Triem, *Angew. Chem., Int. Ed. Engl.*, **3**, 19 (1964).

(13) L. I. Smith and S. McKenzie, *J. Org. Chem.*, **15**, 74 (1950).

(14) M. Carmack and M. A. Spielman, *Org. React.*, **3**, 83 (1946).

(15) G. Kortüm, W. Vogel, and K. Andrussow, "Dissociation Constants of Organic Acids in Aqueous Solution," Butterworths, London, 1961, pp 241, 246.

TABLE II
SUBSTITUENT CONSTANTS FOR CYCLOPROPANE

| $\sigma_i$ | Value | % $\mathcal{R}$[a] |
|---|---|---|
| $\sigma^*$ | +0.017[b] | 5 |
| $\sigma_{CH_2X}^*$ | +0.011[c] | 5 |
| $\sigma_I$ | +0.01,[d] −0.08[e] | 0 |
| $\sigma_m^+$ | −0.04,[f] −0.06[g] | 33 |
| $\sigma_m$ | −0.07,[h] −0.102,[i] −0.14[j] | 22 |
| $\sigma_R^\circ$ | −0.13[e] | 84 |
| $\sigma^\circ$ | −0.21[k] | 41 |
| $\sigma_p$ | −0.19,[l] −0.21,[h] −0.23,[i] −0.24[l] | 53 |
| $\sigma_p^+$ | −0.410,[m] −0.439,[n] −0.45,[f] −0.462[g] | 66 |

[a] Defined in ref 17. [b] T. L. Brown, J. M. Sandri, and H. A. Hart, *J. Phys. Chem.*, 61, 698 (1951). [c] This work. [d] Reference 9a. [e] R. G. Pews, *J. Amer. Chem. Soc.*, 89, 5605 (1967). [f] R. C. Hahn, T. F. Corbin, and H. Shechter, *ibid.*, 90, 3404 (1968). [g] D. H. Man and J. B. Stothers, *Can. J. Chem.*, 45, 225 (1967). [h] J. Smejkal, J. Jones, and J. Farkas, *Collect. Czech. Chem. Commun.*, 29, 2950 (1964). [i] J. A. Landgrebe and W. Becker, *J. Amer. Chem. Soc.*, 90, 395 (1968). [j] T. F. Corbin, Ph.D. Dissertation, Ohio State University, 1956. [k] R. G. Pews and N. D. Ojha, *J. Amer. Chem. Soc.*, 91, 5769 (1969), [l] R. Levina, P. A. Gimbitskii, L. P. Guseva, and P. K. Agasyan, *Zh. Obshch. Khim.*, 34, 146 (1964); *Chem Abstr.*, 60, 10519a (1964). [m] L. B. Jones and V. K. Jones, *Tetrahedron Lett.*, 1493 (1966). [n] L. B. Jones and S. S. Eng, *ibid.*, 1431 (1968).

responding derived $\sigma^*_{CH_2}$ values. The substituent constant thus found for nonconjugated cyclopropane, $\sigma^*_{CH_2} = +0.011$, is little different from that for hydrogen, indicating a very weak electron withdrawal by cyclopropane as compared with vinyl or phenyl, as has also been reported recently by Martin and Ree for a conjugated but nonbisected geometry of a cyclopropylcarbinyl system.[9a] This indicates that hybridization ($sp^2$ for cyclopropane, vinyl and phenyl $\sigma$ bonding orbitals) is *not* the dominant factor in determining the electronegativity and the inductive effect of the cyclopropyl group. Recent arguments[16] indicate that the low reactivity of the 1-nortricyclyl system is caused by angle strain deformations in the carbonium ion and not by an inductive withdrawal by cyclopropane. The experimental finding of a small, weak electron-withdrawing effect, as opposed to the larger effects observed for vinyl and phenyl, tends to support that argument.

The known substituent constants which have been determined for cyclopropane in various types of reaction environments are listed in Table II with the corresponding values of % $\mathcal{R}$,[17] a measure of the sensitivity of resonance effects of particular substituent constants. The changes of the substituent constant values for cyclopropane in different reaction types is seen to be proportional to the corresponding changes in % $\mathcal{R}$. This clearly demonstrates the response of electron donation by cyclopropane toward increasingly more electron-deficient centers, superimposed on a small, weak electron-withdrawing effect of the cyclopropyl group.

(16) S. A. Sherrod, R. G. Bergman, G. J. Gleicher, and D. G. Morris, *J. Amer. Chem. Soc.*, 94, 4615 (1972).

(17) C. G. Swain and E. C. Lupton, Jr., *J. Amer. Chem. Soc.*, 90, 4328 (1968).

## Experimental Section

**Cyclopropaneacetic Acid.**—Cyclopropaneacetic acid was prepared by the Willgerodt reaction.[12] Cyclopropyl methyl ketone (8.4 g, 0.10 mol), piperidine (13.0 g, 0.15 mol), and sulfur (4.8 g, 0.15 mol) were heated at reflux for 2.4 hr and the resulting black reaction mixture was poured onto ice. The solution was extracted with ether and washed with ice-cold 10% hydrochloric acid followed by saturated aqueous sodium bicarbonate solution and then by water. The solution was dried over anhydrous sodium sulfate, filtered, and concentrated. The residual product could not be crystallized and was hydrolyzed with 1.2 equiv of 10% aqueous potassium hydroxide without further purification. The alkaline solution was acidified, extracted with ether, dried over sodium sulfate, concentrated, and distilled, giving 0.8 g (8%) of cyclopropaneacetic acid, bp 89–94° (14 mm), $n^{25}D$ 1.440 [lit.[18] bp 90° (15 mm), $n^{25}D$ 1.4320). The infrared and nmr spectra were consistent with the assigned structure.

**Acidity Determination.**—Samples of the acids, generally in the range of 5–10 mg, were weighed to 0.1-mg accuracy into 50-ml beakers to which 25 ml of water (redistilled from sodium hydroxide to remove carbon dioxide) was added. The pH of the solution was measured with a Beckman glass electrode (40498) and a Beckman calomel electrode (39970), both immersed in the solution to a depth sufficient to cover the bulb of the glass electrode. The electrodes were connected to a Sargent Model DR pH meter with which a relative accuracy of ±0.005 pH could be obtained. The pH meter was standardized using a buffer of pH 4.64 (M/10 NaOAc/HOAc). Increments ranging from 0.02 to 0.2 ml of sodium hydroxide (carbonate-free, 0.1176 *N*, standardized against potassium biphthalate) were added from a microburet (5.00 ml) graduated in 0.002 ml. After each addition the solution was stirred mechanically for 1 min and the pH was measured. The determination of the end point was made by the rate of change in the slope of the titration curve. At the conclusion of the titration, the electrode was checked against the standard buffer and was always found to be within 0.01 pH unit of the nominal value. The pH values at 25, 50, and 75% neutralization were read off the titration curves and from each a value of $pK_a$ was calculated using eq 1, in which the concentrations of the

$$pK_a = pH - \log \frac{[RCOO^-]}{[RCOOH]} \quad (1)$$

anion ($RCOO^-$) and undissociated acid (RCOOH) have been calculated taking into account the change in concentration of the acid and the anion due to dissociation of the acid. Sample data from one titration curve and calculations are shown in Table III for cyclopropaneacetic acid in water solution at 25°.

TABLE III[a]

| Neutralization, % | NaOH, ml (0.1176 *N*) | NaOH × $10^{-5}$, mol | pH | $H^+$[b] × $10^{-5}$, mol | $RCOO^-$[c] × $10^{-5}$, mol | RCOOH[d] × $10^{-5}$, mol | $pK_a'$[e] |
|---|---|---|---|---|---|---|---|
| 25 | 0.3412 | 4.01 | 4.26 | 0.139 | 3.72 | 12.33 | 4.738 |
| 50 | 0.6825 | 8.02 | 4.74 | 0.046 | 8.06 | 7.98 | 4.737 |
| 75 | 1.0237 | 12.04 | 5.22 | 0.157 | 12.06 | 4.00 | 4.741 |

[a] Titration end point 1.365 ml, original volume of solution 25.0 ml. [b] $H^+$, $RCOO^-$, and RCOOH refer to moles of hydrogen ion, cyclopropaneacetate ion, and undissociated acid present in the titration vessel. $H^+$ is derived from the observed pH and the total volume of solution. [c] $RCOO^-$ = moles of NaOH added plus moles of $H^+$. [d] RCOOH = moles of acid used ($16.05 \times 10^{-5}$) minus $RCOO^-$. [e] From eq 1.

**Registry No.**—Cyclopropane, 75-19-4; cyclopropylacetic acid, 5239-82-7; cyclopropyl methyl ketone, 765-43-5.

(18) J. H. Turnbull and E. S. Wallis, *J. Org. Chem.*, 21, 663 (1954).

## Ring Inversion Barrier in 5,5-Difluoro-1,3-dioxane

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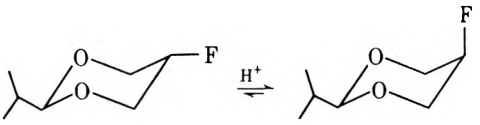
In recent publications[2,3] we have reported that the equilibrium between the 2-isopropyl-5-fluorodioxanes (**1** ⇄ **2**) favors the axial (cis) isomer (Scheme I) and

SCHEME I

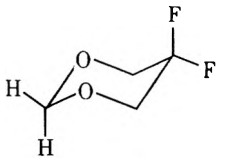


**1** **2**

| Solvent | $\Delta G°$, kcal/mol |
|---|---|
| $CCl_4$ | −0.36 |
| $(C_2H_5)_2O$ | −0.62 |
| $C_6H_6$ | −0.83 |
| $CHCl_3$ | −0.87 |
| $CH_3CN$ | −1.22 |

this result has been confirmed qualitatively by comparison of the $^{19}F$ nmr spectra of the equatorial and axial models, **1** and **2**, with the corresponding spectrum of the conformationally mobile 5-fluoro-1,3-dioxane (**3**); the $^{19}F$ chemical shift of **3** is much closer to that of **2** than to that of **1**.[4] The situation is in contrast to that with the chlorine and bromine analogs of **1** and **2**, for which the equatorial isomer is favored;[2,3] it is reminiscent of that existing in the 1,2-haloethanes, where the gauche isomer predominates for the 1,2-difluoro compound, whereas in 1,2-dichloro- and 1,2-dibromoethane the anti isomer is favored, at least in the gas phase.[5,6]

Because of recent interest[7-9] in possible attractive interactions between heteroatoms, we desired to obtain independent evidence that the greater stability of **2** as compared with **1** was due to a fluorine–oxygen attraction. To that end, we determined the inversion barrier in 5,5-difluoro-1,3-dioxane (**4**); we argued that ground-state stabilization in **4** by fluorine–oxygen attraction should reflect itself in an enhanced barrier to inversion, since we had hoped that the transition state



**4**

would not be affected in a major way by the fluorine substituents at C-5.[10]

The barrier in **4** was measured by low-temperature proton nmr observing coalescence of the AB pattern at C-2. To check our experimental technique, especially the accuracy of the temperature measurement, we also repeated the measurement of the known[11-14] barriers in 1,3-dioxane (**5**) itself and in the 5,5-dimethyl homolog (**6**). The data are summarized in Table I. Our data for **5** and **6** are within the range of those determined by other groups; clearly, the barrier for **4** is appreciably lower than that for **5** and **6**.

By way of further confirmation of the lower barrier for **4** we also measured the coalescence of the $^{19}F$ nmr spectrum. Because of the large relative chemical shift of the geminal fluorines ($\phi_a$ 113.2 ppm, $\phi_e$ 115.2 ppm) the spectrum at coalescence was extremely broad, but the coalescence could nevertheless be determined to occur at −84°, corresponding to $\Delta G^{\ddagger}$ = 8.2 kcal/mol. Because of the discrepancy of 0.6 kcal/mol between the activation barriers determined by $^1H$ and $^{19}F$, we simulated the line shape of the proton spectrum in the vicinity of the coalescence temperature by the program QUABEX[15] varying the rate constant from that computed by the approximative equation 1 (which had

$$k = \frac{\pi}{\sqrt{2}}\sqrt{\Delta\nu_{AB}^2 + 6J_{AB}^2} \quad (1)$$

been used to calculate the data in Table I). The line fit at coalescence for $k$ = 55.2 sec$^{-1}$ (for which $\Delta G^{\ddagger}$ = 8.8 kcal/mol) was the best obtainable but was not perfect, probably because of neglect of the long-range coupling constant $J_{H_{2e}F_{5e}}$. We can thus not claim the highest accuracy for our data, but it is nevertheless clear that the barrier of 8.5 ± 0.3 kcal/mol for **4**, far from being enhanced as we might have expected, is lower than that of **5** by about 1 kcal/mol and lower than that of **6** by about 2 kcal/mol.

Several possible explanations suggest themselves. (1) Rather than there being a stabilization in **2**, there might be a destabilization in **1** (Scheme I). This could best be explained by the existence of four gauche-vicinal hydrogen atoms in **1** but only two such atoms in **2**. It would thus amount to postulating a repulsive F–H gauche interaction. In view of other recent findings,[16] such an explanation would appear exceedingly

(1) Address correspondence to Department of Chemistry, University of North Carolina, Chapel Hill, N. C. 27514

(2) E. L. Eliel and M. K. Kaloustian, *Chem. Commun.*, 290 (1970).

(3) R. J. Abraham, H. D. Banks, E. L. Eliel, O. Hofer, and M. K. Kaloustian, *J. Amer. Chem. Soc.*, **94**, 1913 (1972).

(4) S. Mager and E. L. Eliel, *Rev. Roum. Chim.*, in press. A low-temperature nmr study of **3** has been reported [L. D. Hall and R. N. Johnson, *Org. Magn. Resonance*, **4**, 369 (1972)] and leads to the same conclusion.

(5) R. J. Abraham and R. H. Kemp, *J. Chem. Soc. B*, 1240 (1971), and Table III in ref 3.

(6) Since these equilibria involve highly polar substituents and the conformers differ greatly in dipole moment, there is a strong solvent dependence. There is no question that the gauche isomer of $FCH_2CH_2F$ predominates in the liquid phase, but the gas-phase preference rests on an older infrared determination [P. Klaboe and J. R. Nielsen, *J. Chem. Phys.*, **33**, 1764 (1960)] and should probably be put on a firmer experimental basis, especially since quantum mechanical calculations suggest the anti isomer to be more stable.[7]

(7) L. Radom, W. A. Lathan, W. J. Hehre, and J. A. Pople, *J. Amer. Chem. Soc.*, **95**, 693 (1973).

(8) L. Phillips and V. Wray, *Chem. Commun.*, 90 (1973).

(9) N. D. Epiotis and W. Cherry, *Chem. Commun.*, 278 (1973); N. D. Epiotis, *J. Amer. Chem. Soc.*, **95**, 3087 (1973).

(10) The barrier in 1,1-difluorocyclohexane is about 0.5–0.9 kcal/mol lower than that in cyclohexane; *cf.* G. Binsch, *Top. Stereochem.*, **3**, 158 (1968). Of this difference, 0.15–0.28 kcal/mol may be ascribed to ground-state compression by axial fluorine; *cf.* J. A. Hirsch, *Top. Stereochem.*, **1**, 200 (1967); F. J. Jensen, C. H. Bushweller, and B. H. Beck, *J. Amer. Chem. Soc.*, **91**, 344 (1969).

(11) H. Friebolin, S. Kabuss, W. Maier, and A. Lüttringhaus, *Tetrahedron Lett.*, 683 (1962).

(12) H. Friebolin, H. G. Schmid, S. Kabuss, and W. Faist, *Org. Magn. Resonance*, **1**, 67 (1969).

(13) J. E. Anderson and J. C. D. Brand, *Trans. Faraday Soc.*, **62**, 39 (1966).

(14) E. Coene and M. Anteunis, *Bull. Soc. Chim. Belg.*, **79**, 37 (1970).

(15) G. Binsch, *Top. Stereochem.*, **3**, 180 (1968).

(16) *Cf.* R. D. Norris and G. Binsch, *J. Amer. Chem. Soc.*, **95**, 182 (1973).

TABLE I

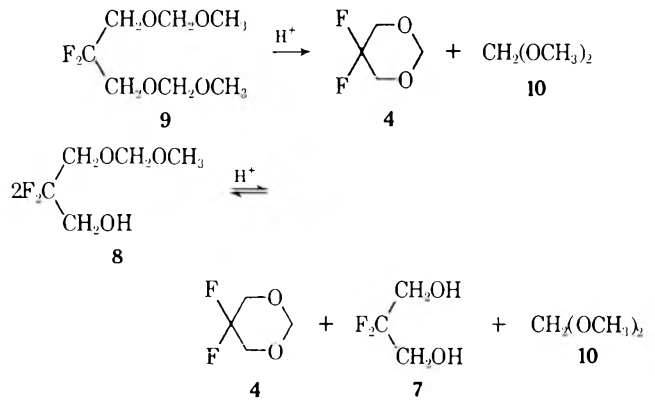
RING INVERSION BARRIERS

| Compd | 4 | 5 | 5 | 5 | 5 | 5 | 6 | 6 | 6 | 6 | 6 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| $\Delta G^{\ddagger}$, kcal/mol | 8.8 | 9.6 | 9.7 | 9.9 | 9.0 | 9.7 | 10.7 | 11.2 | 11.1 | 10.5 | 10.5 |
| Ref | *a* | *a* | 11 | 12 | 13 | 14 | *a* | 11 | 12 | 13 | 14 |

[a] This work. Coalescence temperatures: **4**, −96°; **5**, −80°; **6**, −57°.

implausible. (2) The stabilization of **2** over **1** might be caused largely by differential solvation; no corresponding differential solvation occurs between **4** and the transition state for its inversion. This explanation has a fair measure of plausibility, in as much as it has been calculated[3] that, in the gas phase, **1** should actually be *more stable* than **2** by 0.5 kcal/mol.[17] (3) Our *a priori* assumption that comparison of the inversion barrier of the difluoro compound **4** with that of the parent dioxane **5** should not be dominated by a lowering of the transition-state energy might be incorrect. This factor probably contributes, since the relative effect of introducing a geminal difluoro group on the barrier height varies from system to system. For example, the inversion barrier of 518 $cm^{-1}$ (1.48 kcal/mol) in puckered cyclobutane[18] drops to less than half, 241 $cm^{-1}$ (0.69 kcal/mol), in 1,1-difluorocyclobutane[19] and the already very small analogous barrier in oxetane (15.3 $cm^{-1}$)[20] disappears completely in (planar) 3,3-difluorooxetane.[21] A combination of **2** and **3** may well be responsible for our findings. Unfortunately, since the relative importance of the two factors is not known, the barrier measurement in **4**, as it turns out, throws no light on the equilibrium shown in Scheme I.

2,2-Difluoro-1,3-propanediol (**7**) was obtained by lithium aluminum hydride reduction of diethyl difluoromalonate.[22] Acid-catalyzed condensation of **7** with dimethoxymethane, unlike similar condensations of other 1,3-diols, gave rise not only to the dioxane **4** but also to the mixed formals $CH_3OCH_2OCH_2CF_2CH_2OH$ (**8**) and $CH_3OCH_2OCH_2CF_2CH_2OCH_2OCH_3$ (**9**) (see Experimental Section). When **9** was distilled over polystyrenesulfonic acid, it was smoothly converted to




**4** and dimethoxymethane (**10**). Compound **8**, under these circumstances, yielded starting material **7** in addition to **4** and **10**, as might be expected from the stoichiometry.

Condensation of **7** with isobutyraldehyde yielded 2-isopropyl-5,5-difluoro-1,3-dioxane (**11**). The $^1H$ and $^{19}F$ nmr chemical shifts for both **4** (at room temperature and below the coalescence point) and **11** are recorded in the Experimental Section. Not unexpectedly[23,24] the axial and equatorial fluorine signals in **11** are not the same as those in **4** at low temperature, nor do they average to the room-temperature fluorine signal in **4**.

### Experimental Section

The fluorine nmr spectra were recorded on a Varian XL-100-12 instrument at 94.1 MHz, the proton spectra on a Varian A-60A instrument at 60 MHz. $^{19}F$ chemical shifts are reported in the $\phi$ scale.[25] Microanalyses were performed by Midwest Microlab, Indianapolis, Ind.

**2,2-Difluoro-1,3-propanediol** (**7**).—Lithium aluminum hydride (12 g, 0.32 mol) was partially dissolved in anhydrous ether with good stirring and 40 g (0.20 mol) of diethyl difluoromalonate in 400 ml of ether was added slowly, maintaining gentle reflux. The solution was boiled for 2 hr and cooled, 7.5 ml of water was added cautiously to destroy excess hydride, and the mixture was poured into 500 ml of 10% sulfuric acid. The solution was saturated with ammonium sulfate and extracted four times with 500-ml portions of ether. The ether was dried over magnesium sulfate, filtered, and concentrated; the residue was dissolved in a 1:1:1 mixture of benzene, ethyl acetate, and Skellysolve F (petroleum ether, bp 30–60°). Cooling and further addition of Skellysolve F produced crystals which were collected and washed with Skellysolve F, mp 51–52° (lit.[26] mp 54.5°), yield 14.3 g (63%). Additional material may be obtained by concentration and vacuum distillation of the mother liquor. The proton nmr spectrum, $\delta$ 3.83 ppm (in $D_2O$ from $Me_3SiCH_2CH_2CH_2SO_3^-Na^+$), showed a rather small H–F vicinal coupling constant, $J$ = 14 Hz, confirmed by the $^{19}F$ spectrum, $\phi$ 117.7 ppm.

**2-Isopropyl-5,5-difluoro-1,3-dioxane** (**11**).—A solution of 0.3 g (2.7 mmol) of diol **7**, 2.25 g (31 mmol) of isobutyraldehyde, and 0.05 g of *p*-toluenesulfonic acid in 30 ml of Skellysolve F was boiled at reflux with a Dean–Stark trap until no more water was given off (15 hr). After neutralization with 0.05 g of sodium acetate (stirring for 30 min), the solution was filtered, the residue was washed with 20 ml of ether, and the combined filtrates were washed twice with 10 ml of water, dried over magnesium sulfate, and concentrated. The residue was purified by glpc using a 15 × 0.25 in. 20% Carbowax 20M on Chromosorb A (45–60 mesh) column at 164° with a 260-ml/min flow of helium, retention time 168 sec. Material of mp 32° was obtained in 55% yield.

*Anal.* Calcd for $C_7H_{12}F_2O_2$: C, 50.59; H, 7.28. Found: C, 50.99; H, 7.55.

$^{19}F$ nmr spectrum: $\phi_a$ 114.1, $\phi_e$ 118.3 ppm, $J_{F_aF_e}$ = 252, $J_{F_aH_{4(6)e}}$ = 27, $J_{F_aH_{4(6)e}}$ = 11, $J_{F_eH_{4(6)a}}$ = 5, $J_{F_eH_{4(6)e}}$ = 0.7, $J_{F_aH_{2a}}$ = 0.7 Hz. $^1H$ nmr spectrum: 0.94 (d, $J$ = 6 Hz, 6 H), 1.53–2.15 (m, 1 H), 3.28–4.1 (AB split by fluorines, $J_{gem}$ = 12 Hz, 4 H), 4.24 ppm (d, $J$ = 4.8 Hz, 1 H).

**5,5-Difluoro-1,3-dioxane** (**4**).—A solution of 2 g (18 mmol) of diol **7** in 20 ml of dimethoxymethane was boiled for 4 hr in the presence of a catalytic amount of Amberlyst-15 (beaded polystyrenesulfonic acid). Excess dimethoxymethane was distilled,

(17) Preliminary experimental results by N. C. Craig tend to confirm this prediction.

(18) F. A. Miller and R. J. Capwell, *Spectrochim. Acta, Part A*, **27**, 947 (1971).

(19) A. C. Luntz, *J. Chem. Phys.*, **50**, 1109 (1969).

(20) S. I. Chan, T. R. Borgers, J. W. Russell, H. L. Strauss and W. D. Gwinn, *J. Chem. Phys.*, **44**, 1103 (1966).

(21) G. L. McKown and R. A. Beaudet, *J. Chem. Phys.*, **55**, 3105 (1971).

(22) H. Gershon, J. A. A. Renwick, W. K. Wynn, and R. D'Ascoli, *J. Org. Chem.*, **31**, 916 (1966).

(23) *Cf.* E. L. Eliel and R. J. L. Martin, *J. Amer. Chem. Soc.*, **90**, 682 (1968).

(24) See also S. L. Spassov, D. L. Griffith, E. S. Glazer, K. Nagarajan, and J. D. Roberts, *J. Amer. Chem. Soc.*, **89**, 88 (1967).

(25) G. Filipovich and G. V. D. Tiers, *J. Phys. Chem.*, **63**, 761 (1959). The reference substance is $CCl_3F$.

(26) L. S. Boguslavskaya, V. S. Etlis, K. V. Yarovykh, and A. B. Bulovyatova, *Zh. Org. Khim.*, **7**, 1338 (1971).

the residue was transferred to a small distillation flask, and fresh Amberlyst was added. The residue was heated for 3–4 hr at 135° and the material which distilled was collected. To the residue, fresh dimethoxymethane (20 ml) and Amberlyst was added, the solution was boiled for 3 hr, and the above procedure was repeated. At the end, the bath temperature was increased to 150°. The combined distillates were purified by glpc on the column mentioned above at 110°, with 330-ml/min He flow, retention time 6 min: yield 0.52 g (23%); mp 19°; $n^{20}D$ 1.3752.

*Anal.* Calcd for $C_4H_6F_2O_2$: C, 38.71; H, 4.87. Found: C, 38.78; H, 4.88.

$^{19}F$ nmr spectrum (−124°): $\phi_a$ 113.2, $\phi_e$ 115.2, $\phi_{av}$ (room temperature) 114.7 ppm; $J_{F_aF_e} = 253$, $J_{F_aH_{4(6)a}} = 25$, $J_{F_4H_{4(6)e}} = 10.9$ Hz. $^1H$ nmr spectrum (−112°): $\delta_{H_{2e}}$ 5.11, $\delta_{H_{2a}}$ 4.77 ppm, $J_{H_{2e}H_{2a}} = -5.75$ Hz; (room temperature) 3.92 (t, $J$ = 11 Hz, 4 H), 4.89 ppm (d, $J$ = 1.2 Hz, 2 H).

When the original residue after distillation of excess dimethoxymethane and **4** was subjected to gas chromatography in the above column at 190° with a 310-ml/min He flow, two compounds were obtained, **8**, retention time 6 min, and **9**, retention time 11 min. Proton nmr spectra and elemental analyses were in accord with the structures assigned. *Anal.* Calcd for $C_5H_{10}F_2O_3$ (**8**): C, 38.46; H, 6.45. Found: C, 38.88; H, 6.56. *Anal.* Calcd for $C_7H_{14}F_2O_4$ (**9**): C, 42.00; H, 7.05. Found: C, 42.55; H, 7.25.

When **9** was heated over Amberlyst in a distilling flask, it was converted entirely into **4** and dimethoxymethane, as evidenced by gas chromatographic analysis of both the distillate and the residue. In contrast, similar treatment of **8**, while giving the same distillate (**4** and dimethoxymethane), left a residue containing some unchanged **8** as well as $HOCH_2CF_2CH_2OH$ (**7**).

**Barrier Measurement.**—The nmr spectrum of **4** was measured in a solvent mixture of 80% acetone-$d_6$ and 20% trichlorofluoromethane with some TMS.[27] For the low-temperature runs, the temperature was measured by letting the probe, refrigerated by a stream of precooled nitrogen, come to equilibrium and replacing the sample with a copper–constantan thermocouple located inside an nmr tube. A period of 10 min was allowed to allow either the sample tube or the thermocouple tube come to temperature equilibrium with the probe. Temperature readings were reproducible to ±2°. The proton signals (AB pattern for the H-2's) were located at 283 ($\nu_1$), 289 ($\nu_2$), 304.5 ($\nu_3$), and 310 Hz ($\nu_4$), indicating a coupling constant of −5.75 ± 0.25 Hz, and the chemical shifts reported above were calculated by the usual equation, $\Delta\nu_{AB} = (\nu_4 - \nu_1)^{1/2}(\nu_3 - \nu_2)^{1/2} = 20.46$ Hz. The coalescence temperature was found to be −96° by varying the temperature first in intervals of 5° and then, near the coalescence temperature, in intervals of 2°. The rate constant was calculated from the computed chemical shifts and the coalescence temperature by the equation given in the discussion and was found to be 55.2 $sec^{-1}$ at −96°. The activation energy $\Delta G^{\ddagger}$ was calculated to be 8.8 kcal/mol by application of the Eyring equation, $k = \mathbf{k}T/h)e^{-\Delta G^{\ddagger}/RT}$ or $\Delta G^{\ddagger} = -RT \ln hk/\mathbf{k}T$. To simulate the spectrum in the vicinity of the coalescence point we used the program QUABEX,[15] which in addition to $\nu_A$, $\nu_B$, and $J_{AB}$ requires the relaxation time $T_2$ as input; $T_2$ was taken at $1/\pi W$ where $W$ is the width (in hertz) at half height of the peak. Spectra were calculated by a Univac 1107 computer and plotted by a Calcomp 750 plotter.

The fluorine data were handled similarly. Chemical shifts and coupling constants have been reported above at low temperature. Coalescence to a very broad spectrum occurred at approximately −84°, at which temperature the rate constant was calculated to be 1437 $sec^{-1}$ and the activation energy 8.2 kcal/mol.

Rate constants and activation energies for **5** and **6** were determined similarly from the H-2 proton spectra.

**Acknowledgment.**—We are grateful to Mr. Donald Schifferl for recording the low-temperature $^1H$ and $^{19}F$ spectra. One of us (S. M.) is indebted to the University Babes Bolyai, Cluj, Romania, for an academic leave. This work was supported by NSF Grant GP-24,910.

**Registry No.**—**4**, 36301-44-7; **5**, 505-22-6; **6**, 766-15-4; **7**, 428-63-7; **8**, 42116-92-7; **9**, 42116-93-8.

(27) We used the most polar solvent available which would not freeze at the low temperature required in the nmr experiment, since, as indicated in Scheme I, the axial preference of fluorine is greatest in the most polar solvents. From results on 5-methoxy-1,3-dioxane [O. Hofer in E. L. Eliel, *Angew. Chem., Int. Ed. Engl.*, **11**, 739 (1972), Table VIII] acetone should favor the axial isomer **2** more than ether and benzene but less than acetonitrile.

## An Exceptionally Facile Reaction of α,α-Dichloro-β-keto Esters with Bases

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*Received July 27, 1973*

α,α-Dichloro-β-keto esters react rapidly with even relatively weak nucleophiles such as sodium bicarbonate, potassium acetate, and diethylamine to give products according to eq 1.

$$MeCOCCl_2COOEt + MeCOONa \xrightarrow{EtOH} MeCOOEt + CHCl_2COOEt \quad (1)$$

To our knowledge, such a facile fragmentation of an α,α-disubstituted β-keto ester derivative with a base (eq 1) is unprecedented.[1] This reaction proceeds under extremely mild conditions. For example, when a solution of ethyl α,α-dichloroacetoacetate in ethanol is stirred at 25° for 30 min in the presence of a catalytic quantity of sodium acetate, ethyl acetate and ethyl dichloroacetate are produced in nearly quantitative yield. The results on other representative reactions are summarized in Table I.

The present reaction appears to be an example of retro acetoacetic ester consensation.[2] The characteristics noteworthy of this novel fragmentation process are (1) there is no reaction between the dichloro compound and the alcohol in the absence of required base; (2) when ethyl α,α-dichloroacetoacetate and sodium acetate are stirred together in a solvent such as benzene, chloroform, or dimethyl sulfoxide, the formation of acetic anhydride is not detected (ir, glpc) (however, upon the addition of an alcohol to this reaction mixture, the expected products are produced rapidly); and (3) when ethyl α,α-dichloroacetoacetate is stirred with potassium benzoate or ethyl α,α-dichlorobenzoylacetate is stirred with potassium acetate in a solvent such as chloroform or dimethyl sulfoxide in order to achieve a redistribution according to eq 2, the starting materials are recovered unchanged in both cases.

$$C_6H_5COCCl_2COOEt + KOCOCH_3 \rightleftharpoons H_3CCOCCl_2COOEt + C_6H_5COOK \quad (2)$$

Although a study of the precise mechanism of this reaction has not been undertaken, it would appear likely that the present fragmentation proceeds *via* an attack of the nucleophile on the reactive carbonyl moiety of the dichloro compound.[3]

(1) For a recent report on a related reaction which results in the ring opening of certain α,α-dihalospirocyclobutanones with bases, see B. M. Trost and M. J. Bodganowicz, *J. Amer. Chem. Soc.*, **95**, 2038 (1973).

(2) For a discussion of the principles involved in the acetoacetic ester condensation, see H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, New York, N. Y., 1972, Chapter 11.

(3) For a discussion of the reactivity of α- and β-keto halides, see (a) E. W. Trachtenberg and T. J. Whall, *J. Org. Chem.*, **37**, 1494 (1972), and references cited therein; (b) R. G. Pews and R. A. Davis, *J. Chem. Soc., Chem. Commun.*, 269 (1973).

TABLE I

REACTION OF α,α-DICHLORO-β-KETO ESTERS WITH REPRESENTATIVE BASES[a]

| Registry no. (ester) | α,α-Dichloro-β-keto ester | Registry no. (base) | Base | Reaction time, min | Products identified (mmol) |
|---|---|---|---|---|---|
| 6134-66-3 | $MeCOCCl_2COOEt$ | 7542-12-3 | $NaHCO_3$ | 30 | MeCOONa (8)[b] |
| | | | | | $HCCl_2COOEt$ (10) |
| | | 127-08-2 | $KOCOCH_3$ | 15 | MeCOOEt (10) |
| | | | | | $HCCl_2COOEt$ (10) |
| | | 532-32-1 | $NaOCOC_6H_5$ | 15 | $C_6H_5COOEt$ (8) |
| | | | | | MeCOOEt (1) |
| | | 141-52-6 | NaOEt | 1 | MeCOOEt (9) |
| | | | | | $HCCl_2COOEt$ (10) |
| | | 109-89-7 | $Et_2NH$ | 1 | $MeCONEt_2$ (8) |
| | | | | | $HCCl_2COOEt$ (9) |
| 42071-71-6 | $C_6H_5COCCl_2COOEt$ | | $KOCOCH_3$ | 15 | $C_6H_5COOEt$ (8) |
| | | | | | MeCOOEt (1) |
| | | | | | $HCCl_2COOEt$ (9.5) |
| | | | NaOEt | 1 | $C_6H_5COOEt$ (8) |
| | | | | | $HCCl_2COOEt$ (9) |
| | | | $Et_2NH$ | 1 | $C_6H_5CONEt_2$ (8.5) |
| | | | | | $HCCl_2COOEt$ (9.5) |

[a] A mixture of α,α-dichloro-β-keto ester (10 mmol), ethanol (10 ml), and the appropriate base (10 mmol) was stirred at 25°. The reaction mixture was then analyzed by glpc (5% DC 550 on Chromosorb W) using an internal standard. [b] Yield by isolation.

The α,α-dichloro-β-keto esters required in the present study were synthesized by the chlorination of the corresponding β-keto esters with sulfuryl chloride.[4] Our improved procedure, described herein, now provides these dichloro keto esters in virtually quantitative yields. The formation of any side products in these chlorinations is negligible (glpc, nmr), thus permitting the direct use of these powerful lacrymators without further purification.

The novel fragmentation reaction reported here demonstrates the potential of readily available α,α-dichloro-β-keto esters as acyl transferring agents. Also, this reaction could be useful in organic structural elucidation where the degradation of a β-keto acid (ester) moiety can now be achieved under very mild conditions to give readily identified fragments of defined functionality.[5]

### Experimental Section[6]

**Preparation of α,α-Dichloro-β-keto esters.**—*Caution:* α,α-Dichloro-β-keto esters are powerful lacrymators. The preparation of these compounds should be conducted in a well-ventilated hood.

The synthesis of ethyl α,α-dichloroacetoacetate is representative of this procedure. Ethyl acetoacetate (6.5 g, 50 mmol) was placed in a round-bottom flask and sulfuryl chloride (14.9 g, 110 mmol) was added to it in 0.5 hr keeping the reaction temperature below 35° with occasional cooling. After the reaction mixture was stirred for an additional 0.5 hr at 25°, glpc analysis showed a quantitative yield of the desired product. The residual sulfuryl chloride was removed under vacuum, and the crude compound thus obtained (98% pure) was used in the subsequent reactions: nmr ($CDCl_3$, TMS) δ 1.33 (t, 3 H, J = 7 Hz), 2.80 (s, 3 H), and 4.39 (q, 2 H, J = 7 Hz).

Ethyl α,α-dichlorobenzoylacetate was prepared by a similar procedure in 98% yield: nmr ($CDCl_3$, TMS) δ 1.15 (t, 3 H, J = 7 Hz), 4.31 (q, 2 H, J = 7 Hz), 7.56, and 7.96 (m, 5 H).

(4) D. P. Wyman, P. R. Kaufman, and W. R. Freeman, *J. Org. Chem.*, **29**, 2706 (1964). For a recent discussion on the mechanism of ketone halogenation, see K. E. Teo and W. W. Warnhoff, *J. Amer. Chem. Soc.*, **95**, 2728 (1973).

(5) For a recent application of this concept in the structural determination of certain α,α-dihalocyclobutanones, see L. Ghosez, R. Montaigne, A. Roussel, H. Vanlierde, and P. Mollet, *Tetrahedron*, **27**, 615 (1971).

(6) Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Glpc analyses were performed on a DC-550, 5% on Chromosorb W, 5 ft × 0.25 in. column. Nmr spectra were recorded on a Varian A-60 instrument.

**Reaction of α,α-Dichloro-β-keto Esters with Bases.**—A typical reaction is described here. To a stirred mixture of potassium acetate (22.1 g, 225 mmol) and ethanol (90 ml), ethyl α,α-dichloroacetoacetate (43.0 g, 225 mmol) was added in 0.5 hr. The reaction was slightly exothermic (25° → 35°), and, after an additional 15 min, glpc analysis showed it to be complete. The composition of the reaction mixture was determined (Table I), and then water (400 ml) was added to it. After extraction with methylene chloride and drying, distillation gave 32.6 g (92%) of ethyl dichloroacetate: bp 152–156°; nmr ($CDCl_3$, TMS) δ 1.33 (t, 3 H, J = 7 Hz), 4.32 (q, 2 H, J = 7 Hz), and 5.95 (s, 1 H).

The reactions with other bases were performed in an identical manner.

**Reaction of Ethyl α,α-Dichloroacetoacetate with a Catalytic Quantity of Potassium Acetate.**—This experiment was performed according to the general procedure described above, except that only 5 mol % of potassium acetate per mole of dichloro ester was used. The reaction required 30 min for completion at 35°.

**Reaction of Ethyl α,α-Dichloroacetoacetate with Potassium Acetate in Benzene.**—A mixture of ethyl α,α-dichloroacetoacetate (4.98 g, 25 mmol), potassium acetate (2.45 g, 25 mmol), and benzene (25 ml) was stirred at 25° for 12 hr. Ir and glpc analysis of the benzene solution revealed the absence of any acetic anhydride. Upon the addition of ethanol (5 ml) to this reaction mixture, a rapid reaction occurred giving ethyl acetate (24 mmol) and ethyl dichloroacetate (24 mmol).

**Acknowledgments.**—The author wishes to thank Dr. R. K. Blackwood for stimulating discussions and Mr. H. J. Slater for expert technical assistance.

## Lithiotriphenylphosphinioacetonide as a Convenient Reagent for the Introduction of the Acetonyl Synthon

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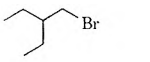
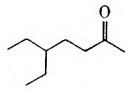
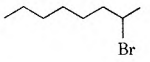
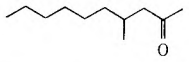
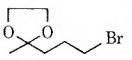
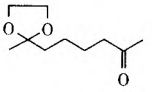
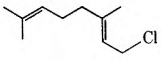
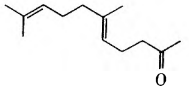
*Received April 3, 1973*

We wish to report that lithiotriphenylphosphinioacetonide (2) prepared from readily available acetyl-

TABLE I

PREPARATION OF KETONES FROM ALKYL HALIDES

| Entry | Registry no. (alkyl halide) | Alkyl halide | Reaction scale, mmol RX[a] | Phosphorane hydrolysis time, hr[b] | Registry no. (ketone) | Ketone | Isolated yield, % |
|---|---|---|---|---|---|---|---|
| 1 | 100-44-7 | $PhCH_2Cl$ | 100 | 40[c] | 2550-26-7 | $PhCH_2CH_2\overset{O}{\overset{\|}{C}}CH_3$ | 76[d,e] |
| 2 | 110-53-2 | $CH_3(CH_2)_3CH_2Br$ | 100 | 8[f] | 111-13-7 | $CH_3(CH_2)_4CH_2\overset{O}{\overset{\|}{C}}CH_3$ | 82 |
| 3 | 693-58-3 | $CH_3(CH_2)_7CH_2Br$ | 100 | 22 | 6175-49-1 | $CH_3(CH_2)_8CH_2\overset{O}{\overset{\|}{C}}CH_3$ | 93 |
| 4 | 3814-34-4 |  | 79 | 12 | 40238-93-5 |  | 78 |
| 5 | 557-35-7 |  | 68[g] | 18 | 42071-54-5 |  | 39 |
| 6 | 24400-75-7 |  | 66 | 24 | 26118-50-3 |  | 58[h] |
| 7 | 4490-10-2 |  | 40 | 12 | 689-67-8 |  | 85 |

[a] Typical runs (see Experimental Section) used a ratio of ylide:BuLi:RX of 1.08:1.05:1.00 with a reaction time of approximately 1 hr at 0° for the alkylation step. [b] Hydrolyses were conducted by heating a solution of crude phosphorane **3** in EtOH–$H_2O$ at 75–85°. The pH of these solutions was 8–10 owing to the slight excess of ylide anion **2** employed in the alkylation step. [c] Reduction of the hydrolysis time to 8 hr resulted in a 44% yield of ketone. [d] A yield of 92% (glpc) was obtained on a 1-mmol scale. [e] The intermediate phosphorane **3** was isolated in 97% yield. [f] A yield of 71% (glpc) was obtained when the hydrolysis was conducted for 20 hr after the solution was adjusted to pH 7 by the addition of HOAc. [g] The alkylation reaction was conducted at 0° for 3 hr followed by 12 hr at 25° followed by 50° for 1 hr. [h] New compound, bp 110–112° (3 mm). *Anal.* Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.78; H, 9.75.

methylenetriphenylphosphorane[1] (**1**) is a convenient reagent for the introduction of the acetonyl group by nucleophilic displacements on alkyl halides. Analogous to the formation of dianions from enolates,[2] we and others[3] have found that treatment of **1** with strong bases such as lithium diisopropylamide or butyllithium in THF at −78° gives rise to the stable, highly colored ylide anion **2**. Ylide anion **2** is highly nucleophilic and is alkylated by a variety of alkyl halides to give the substituted β-ketophosphorane **3** in high yield.[5] That

$$\underset{\mathbf{1}}{CH_3\overset{O}{\overset{\|}{C}}CH{=}PPh_3} \qquad \underset{\mathbf{2}}{LiCH_2\overset{O}{\overset{\|}{C}}CH{=}PPh_3} \qquad \underset{\mathbf{3}}{RCH_2\overset{O}{\overset{\|}{C}}CH{=}PPh_3}$$

the anion is efficiently formed and readily alkylated is illustrated by the treatment of **1** with butyllithium at −78° for 15 min in THF followed by alkylation with benzyl chloride at 0° (20 min) giving after work-up the substituted phosphorane **3**[6] (R = benzyl) in 97% isolated yield. Most significantly we have found that **2** is efficiently alkylated by ordinary alkyl bromides.[5] Completion of the alkylation reaction is conveniently signaled by the disappearance of the intense color of **2**.

While the newly formed phosphoranes are useful in Wittig-type olefination reactions[4,7] we have found that the simple hydrolysis[1] of these acylphosphoranes in combination with the facile alkylation of ylide anion **2** allows a mild, high-yield method for the introduction by nucleophilic substitution of the acetonyl synthon in the manner classically accomplished by the acetoacetic ester synthesis. Examples are shown in Table I. While alkylations of acetoacetic ester salts often proceed slowly and in moderate yields with other than active halides,[8] alkylations of ylide anion **2** proceed rapidly at 0° with no evidence of other than monoalkylation of **2**, and isolation of the intermediate **3** is not required. In addition, completion of the ketone

$$\mathbf{2} \xrightarrow{RX} \mathbf{3} \xrightarrow{H_2O} RCH_2\overset{O}{\overset{\|}{C}}CH_3 + Ph_3PO$$

(1) F. Ramirez and S. Dershowitz, *J. Org. Chem.*, **22**, 41 (1957).

(2) T. M. Harris and C. M. Harris in "Organic Reactions," Vol. 17, W. G. Dauben, Ed., Wiley, New York, N. Y., 1969, Chapter 2.

(3) After the completion of this work there appeared a report describing the preparation of this anion in a similar manner and the use of subsequently prepared substituted phosphoranes in Wittig-type olefination reactions (ref 4.

(4) J. D. Taylor and J. F. Wolf, *Chem. Commun.*, 876 (1972).

(5) Taylor and Wolf[4] have reported that **2** is alkylated at low temperatures by active halides such as benzyl bromide and allyl bromide and by a single alkyl halide, butyl iodide, to give substituted acylphosphoranes in moderate yields.

(6) H. J. Bestmann and B. Arnason, *Chem. Ber.*, **95**, 1513 (1962).

(7) A. Maereker in "Organic Reactions," Vol. 14, R. Adams, Ed., Wiley, New York, N. Y., 1965, p 270.

(8) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif. 1972, pp 510–546.

synthesis *via* the acetoacetic ester method often requires removal of the carboalkoxy control group under conditions requiring either high and low pH or hydrogenolysis of special esters if these conditions are to be avoided,[8] while the hydrolysis of **3** is accomplished by heating with ethanol–water under neutral or slightly basic conditions. As seen in Table I, halides containing groups threatened by acidic conditions (entries 6 and 7) are readily converted to the corresponding acetone derivative. Secondary bromides are less satisfactory for this process, however, presumably owing to their increased susceptibility to E2 elimination under the influence of highly basic nucleophiles.[9]

### Experimental Section

*n*-Butyllithium was obtained from Matheson Coleman and Bell as a 1.6 *N* solution in hexane. Reagent grade tetrahydrofuran was distilled from $LiAlH_4$ immediately prior to use for small-scale reactions but used without purification for large-scale reactions. Starting materials were obtained from commercial sources or prepared by literature procedures. Alkyl bromides were distilled prior to use. All products were characterized by spectral and glpc comparison with authentic samples when available and through the melting points of their semicarbazone derivatives. New compounds gave satisfactory elemental analyses which were performed by the Analytical Laboratory of the University of Idaho.

The following experimental procedure is representative of the method developed for the preparation of methyl ketones from alkyl halides. Any variations in conditions are given in Table I.

**2-Dodecanone from 1-Bromononane.**—In 800 ml of dry THF under a nitrogen atmosphere was placed 34.4 g (0.108 mol) of acetylmethylenetriphenylphosphorane[1] (**1**). The solution was cooled by means of a Dry Ice–acetone bath and with stirring there was added 67 ml of 1.6 *N* butyllithium in hexane (0.105 mol) beyond the point where the red color of the ylide anion persisted. The intensely colored solution was stirred at −78° for 15 min, whereupon 20.7 g (0.100 mol) of 1-bromononane was added and the Dry Ice bath was replaced by an ice–water bath. The solution was stirred at 0° for 1 hr, whereupon the color of the ylide anion was nearly discharged. The solvent was removed under reduced pressure and the residue was dissolved in 300 ml of ethanol followed by the addition of water approaching the cloud point (approximately 200 ml). The resulting solution was heated (steam bath) for 22 hr and then poured into brine solution and extracted with two portions of pentane. Distillation of the oil obtained after removal of the solvent gave 17.1 g (93%) of 2-dodecanone, bp 77–78° (0.6 mm) [lit.[10] bp 120° (12 mm)].

The following procedure illustrates the preparation and isolation of the intermediate substituted phosphorane **3** obtained by alkylation of **2**.

**3-Phenylpropionylmethylenetriphenylphosphine (3, R = Benzyl).**—A solution containing 3.18 g (10.0 mmol) of **1** in 100 ml of THF was treated with 10.5 mmol of *n*-butyllithium at −78° as described above. The resulting solution containing anion **2** was then treated with 1.33 g (10.5 mmol) of benzyl chloride and the resulting mixture was stirred at 0° for 20 min. The mixture was warmed to room temperature whereupon the color of **2** was discharged. The reaction mixture was poured into an ice–water mixture with vigorous stirring and the product, 3.94 g (97%), was collected by filtration. Recrystallization from ethyl acetate gave 3.30 g (82%) of pure **3** (R = benzyl), mp 150–152° (lit.[6] mp 148–150°).

**Acknowledgment.**—We thank the Research Corporation and Washington State University for their supports through grants-in-aid.

Registry No.—**1**, 1439-36-7; **2**, 38938-34-0.

(9) J. Hine, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1956, p 180.

(10) T. Shenton and J. C. Smith, *Chem. Ind. (London)*, 1510 (1958).

## Stereoselectivity in the Base-Catalyzed Decarboxylation of 5,5-Dicarboxy-2-isopropyl-1,3-dioxane

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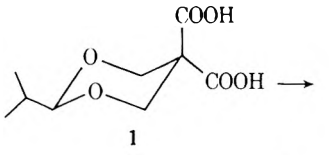
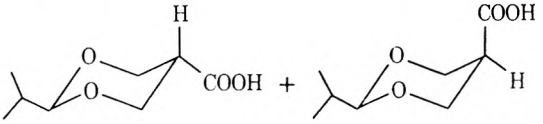
*Received July 3, 1973*

Some years ago Zimmerman and Giallombardo studied the stereochemical consequences of base-catalyzed decarboxylation of 4-phenylcyclohexane-1,1-dicarboxylic acid.[1] They found that *cis*-4-phenylcyclohexanecarboxylic acid comprises 57% of the product regardless of whether the solvent is 2,4,6-trimethylpyridine or nonbasic 1,3,5-trimethylbenzene. In striking contrast to these results, the product composition in the decarboxylation of solutions of 5,5-dicarboxy-2-isopropyl-1,3-dioxane (**1**) in pyridine and aniline derivatives depends critically on the solvent.




**1**




**2** **3**

Solutions of **1** (0.1–0.2 *M*) dissolved in the desired pyridine or aniline base were decarboxylated at constant temperature. The predominant product was **2** with every base except 2,6-dimethylpyridine. The results are given in Table I.

TABLE I
PRODUCT COMPOSITION IN THE DECARBOXYLATION OF 5,5-DICARBOXY-2-ISOPROPYL-1,3-DIOXANE

| Solvent | % 3 at 100.0° | % 3 at 125.0° |
|---|---|---|
| Pyridine | 41.4 ± 0.1 | |
| 2-Methylpyridine | 35.9 | |
| 2,6-Dimethylpyridine | 56.3 | 56.3 ± 0.1 |
| 3,5-Dimethylpyridine | 33.4 | 33.3 |
| Aniline | 24.2 | 27.5 |
| *N*-Methylaniline | 16.9 | |
| *N*,*N*-Dimethylaniline | 11.7 | 17.6 |

One possible mechanism for this reaction is the concerted loss of carbon dioxide and protonation, occurring with either retention or inversion of configuration. The product composition is determined by which carboxyl group departs. To test this mechanism, the kinetics of the reaction were studied using four bases at 100.0, 110.0, and 125.0°. The rate constants were all pseudo first order, and are given in Table II. If the composition of the product is determined exclusively by which diastereotopic carboxyl group is displaced, the product composition may be used to partition each rate constant into a rate constant for loss of

(1) H. E. Zimmerman and H. J. Giallombardo, *J. Amer. Chem. Soc.*, **78**, 6259 (1956).

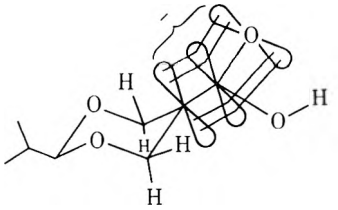
TABLE II
PSEUDO-FIRST-ORDER RATE CONSTANTS FOR DECARBOXYLATION OF 5,5-DICARBOXY-2-ISOPROPYL-1,3-DIOXANE

| Solvent | Temp, °C | $10^4 k$, $sec^{-1}$ |
|---|---|---|
| 2,6-Dimethylpyridine | 100.0 | 5.24 |
| | 110.0 | 17.0 |
| | 125.0 | 29.0 |
| 3,5-Dimethylpyridine | 100.0 | 3.97 |
| | 110.0 | 20.6 |
| | 125.0 | 52.2 |
| Aniline | 100.0 | 7.78 |
| | 110.0 | 15.0 |
| | 125.0 | 39.4 |
| *N,N*-Dimethylaniline | 100.0 | 16.4 |
| | 110.0 | 27.4 |
| | 125.0 | 49.1 |

an axial carboxyl group and a rate constant for loss of an equatorial carboxyl group. For 2,6-dimethylpyridine at 100.0°, using the data of Tables I and II, the individual rate constants are $(0.563)(5.24 \times 10^{-4}) = 2.95 \times 10^{-4}$ $sec^{-1}$ and $(0.437)(5.24 \times 10^{-4}) = 2.29 \times 10^{-4}$ $sec^{-1}$. The individual rate constants were calculated for each basic solvent at 100.0 and 125.0°. Arrhenius plots were then used to predict the rate constants at 110.0°, which were compared with the experimental values. The predicted rate constants at 110.0° for 2,6- and 3,5-dimethylpyridine are 36 and 34% too low, respectively; these findings are inconsistent with the proposed mechanism.

The calculated rate constants at 110.0° in the solvents aniline and *N,N*-dimethylaniline both agree with the experimental values within 5%. The entropies of activation, calculated from the individual rate constants, are −26.0 and −23.3 eu $mol^{-1}$ in aniline and −26.5 and −42.4 eu $mol^{-1}$ in *N,N*-dimethylaniline. These very large negative values are inconsistent with the proposed mechanism.

A second possible mechanism is that proposed by Fraenkel, Belford, and Yankwich[2] for the decarboxylation of malonic acid in quinoline. The rate-determining step is the nucleophilic attack by the basic solvent on the hydrogen bond donating or hydrogen bond accepting[3] carboxy group of the intramolecularly hydrogen bonded species. The departure of carbon dioxide is thereby facilitated, and an enediol intermediate is produced. The composition of the product is determined by which of the two faces of the intermediate is more accessible to attack by the conjugate acid of the basic solvent.[4] The upper face of the intermediate is less hindered to attack by all the conjugate acids of the bases investigated in this study, with the exception of 2,6-dimethylpyridine. Apparently the bulk of the two methyl groups results in substantial steric interaction in approach from either side.



Comparison of the results using pyridine derivatives with those using aniline derivatives shows that the latter are more selective as proton donors. This is presumably a consequence of the more congested environment of the $sp^3$-hydridized nitrogen in the anilinium ions compared to the $sp^2$-hydridized nitrogen in the pyridinium ions. As expected, as methyl groups are substituted for hydrogen, steric interference becomes more important, and selectivity increases.

The apparent difference between the cyclohexane and 1,3-dioxane systems is puzzling, and the decarboxylation of 4-*tert*-butylcyclohexane-1,1-dicarboxylic acid is being studied in a number of basic solvents.

## Experimental Section

Gas chromatographic analyses were obtained using a Hewlett-Packard research chromatograph, Model 7620A. The nmr spectra were recorded on an Hitachi Perkin-Elmer R-24 nmr spectrometer. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

*trans*-**5-Carboxy-2-isopropyl-1,3-dioxane** (**2**).—A mixture of 20.0 g (92 mmol) of 5,5-dicarboxy-2-isopropyl-1,3-dioxane[5] and 20 ml of *N,N*-dimethylaniline was maintained at 100° for 2 hr. The reaction mixture was cooled in an ice–salt bath, and was acidified by the dropwise addition of concentrated HCl. This mixture was extracted three times with 200-ml portions of diethyl ether, and the combined ether extracts were dried over anhydrous $MgSO_4$. After filtration, the solution was concentrated on the rotary evaporator, and the last traces of ether were removed at 0.1 Torr. The residue was recrystallized from benzene to give 14.2 g (90%) of **2**: mp 141.0–141.5°; nmr ($CDCl_3$) δ 0.94 (d, 6 H, $J$ = 10 Hz), 1.43–2.00 (m, 1 H), 2.85–3.32 (m, 1 H), 3.51–4.49 (several peaks, 5 H), 10.12 (s, 1 H).

*Anal.* Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.21; H, 8.10.

*cis*-**5-Carboxy-2-isopropyl-1,3-dioxane** (**3**).—The decarboxylation of **1** was effected using dimethylformamide as the solvent.[6] Recrystallization of the crude product from benzene–petroleum ether gave crystals: mp 127.0–127.5°; nmr ($CDCl_3$) δ 0.91 (d, 6 H, $J$ = 10 Hz), 1.47–2.14 (m, 1 H), 2.24–2.50 (m, 1 H), 3.68–4.75 (several peaks, 5 H), 11.42 (s, 1 H).

*Anal.* Calcd for $C_8H_{14}O_4$: C, 55.16; H, 8.10. Found: C, 55.11; H, 8.07.

**Decarboxylation Studies.**—A sample of 0.3–0.4 g of **1** was weighed on an analytical balance (to the nearest 0.1 mg) into a small, thin-walled glass ampoule. The ampoule was sealed and placed into a 50-ml round-bottom flask, fitted with a condenser that was attached to a three-way stopcock. One arm of the stopcock was connected to a buret for measuring the evolved carbon dioxide, and the third arm was open to the atmosphere. To the flask was added 10.0 ml of the freshly distilled solvent. Dry carbon dioxide gas was bubbled slowly through the solvent for 10 min to ensure saturation.

The reaction flask was immersed in the constant-temperature bath, and the three-way stopcock was turned so that the system was open to the atmosphere until equilibrium had been established. The stopcock was then turned so that the gas buret was connected to the system. Room temperature and the barometric pressure were recorded. The reaction was initiated by fracturing the ampoule by the impact with a falling Teflon-coated magnet. The reaction vessel was shaken vigorously for 30 sec. The volume of carbon dioxide was measured at regular intervals for at least four half-lives.

After the reaction mixture was cooled, a sample of 1 ml of the solution was added to 5 g of crushed ice. Concentrated HCl was added dropwise until the mixture was acid to litmus paper. When the ice had melted, the solution was transferred to a test

(2) G. Fraenkel, R. L. Belford, and P. E. Yankwich, *J. Amer. Chem. Soc.*, **76**, 15 (1954).

(3) L. W. Clark, *J. Phys. Chem.*, **73**, 438 (1969).

(4) This explanation of the results is consistent with the finding of H. E. Zimmerman and P. S. Mariano, *J. Amer. Chem. Soc.*, **90**, 6091 (1968), that the proton donor in the ketonization of the enol of 1-acetyl-4-phenylcyclohexane, and in the tautomerization of the aci form of 4-phenyl-1-nitrocyclohexane, attacks preferentially from the less hindered, equatorial direction.

(5) E. L. Eliel and H. D. Banks, *J. Amer. Chem. Soc.*, **94**, 171 (1972).

(6) E. L. Eliel, personal communication, Nov 29, 1971; S. Mager and E. L. Eliel, *Rev. Roum. Chim.*, in press.

tube and was extracted with three 1-ml portions of diethyl ether by means of a Pasteur pipet. The combined extracts were dried over a mixture of equal parts of anhydrous $MgSO_4$ and anhydrous $Na_2CO_3$. The dried extract was decanted into a test tube, and excess diazomethane was added.[7] Excess diazomethane was removed by means of a stream of nitrogen, and 50- to 100-$\mu$l samples of the solution were analyzed by glpc (6-ft 10% Carbowax 20M on Chromosorb W, 80–100 mesh at 150°, He flow 60 ml/min). A correction factor for the extraction and analysis was determined using a synthetic mixture of pure **2** and **3**. Control experiments demonstrated that epimerization of the products did not occur under the conditions of the decarboxylation.

**Acknowledgment.**—It is a pleasure to acknowledge support of this research by the donors of the Petroleum Research Fund, administered by the American Chemical Society.

**Registry No.**—**1**, 35113-49-6; **2**, 42031-28-7; **3**, 42031-29-8.

(7) H. Schlenk and J. L. Gellerman, *Anal. Chem.*, **32**, 1412 (1960).

## Carboxylation Reactions Using the Reagent Lithium 4-Methyl-2,6-di-*tert*-butylphenoxide

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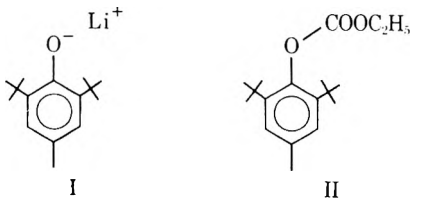
*Received July 5, 1973*

This research was initiated in order to develop a system for the carboxylation of weakly acidic substances such as ketones by the use of a base which is protected sterically from attack on carbon dioxide but able to deprotonate the substrate for carboxylation. The base chosen for initial studies was the 4-methyl-2,6-di-*tert*-butylphenoxide ion (I). It was found that the lithium salt I was readily generated from the phenol in ethereal solution by treatment with 1 equiv of *n*-butyllithium. Although solutions of I in ether did take up carbon dioxide, the rate of absorption was quite slow. It was determined, for example, that exposure of I in ethereal solution to carbon dioxide at 760 mm for 12 hr followed by quenching with triethyloxonium fluoroborate gave only 15% of the carbonated derivative II together with much recovered phenol.



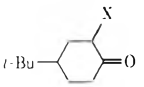
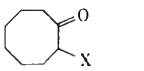

I II

The carbonation of a number of substrates was then investigated using mixtures of substrate, phenoxide base I, and carbon dioxide. Table I summarizes the results obtained for three ketones, a terminal acetylene, and a sulfone. No carbonation was observed for isoamyl acetate, *N*-acetylpiperidine, phenylacetamide, or 1-nonyne. Methyl phenylacetate, phenylacetonitrile, and $\gamma$-butyrolactone underwent carbonation to some extent with yields in the range 20–50%.

In summary, the above data would suggest that the reagent I can be used to promote the carboxylation of ketones, but that it is ineffective toward less acidic substrates. The reagent I has also been applied to dithiocarboxylation reactions using carbon disulfide as reactant.[1]

TABLE I

REACTION OF SUBSTRATES WITH CARBON DIOXIDE AND LITHIUM 4-METHYL-2,6-DI-*tert*-BUTYLPHENOXIDE[a]

| Substrate registry no. | Substrate, X = H; product, X = COOH | Product registry no. | Yield, % | Reaction time, hr |
|---|---|---|---|---|
| 98-53-3 |  | 42031-70-9 | 89 | 16 |
| 502-49-8 |  | 25731-69-7 | 77 | 16 |
| 98-86-2 | $C_6H_5COCH_2X$ | 614-20-0 | 75 | 24 |
| 536-74-3 | $C_6H_5C{\equiv}CX$ | 637-44-5 | 74 | 16 |
| 3112-85-4 | $C_6H_5SO_2CH_2X$ | 3959-23-7 | 65 | 24 |

[a] Reaction conditions: 760 mm of $CO_2$, 4 equiv of I/equiv of substrate, ether solvent.

### Experimental Section

**2-Carboxy-4-*tert*-butylcyclohexanone.**—This preparation can be used to illustrate the general procedure applied to the substrates listed in Table I. Lithium 4-methyl-2,6-di-*tert*-butylphenoxide (4 mmol) was generated by slow addition of 4 mmol (2 ml, 2 *M* in hexane) of *n*-butyllithium to 4.2 mmol (924 mg) of 4-methyl-2,6-di-*tert*-butylphenol in 25 ml of ether at −78° under argon. The resulting white precipitate dissolved completely when the mixture was allowed to warm up to room temperature. The flask containing this reagent was then attached to a hydrogenation apparatus, which was prefilled with excess carbon dioxide, and 0.9 mmol (139 mg) of 4-*tert*-butylcyclohexanone in 1 ml of ether was added. The resulting mixture was well stirred for 16 hr (the solution became turbid after 90 min). The mixture was diluted with 20 ml of ice water at 0° and extracted with ether. The aqueous layer was acidified to pH 3–4 using 0.1 *M* aqueous hydrochloric acid at 0° and extracted with two portions of ether. The ethereal extract was dried over sodium sulfate and concentrated *in vacuo* to give a thick oil (89% yield) which slowly crystallized in a cold room at 5°. Thin layer chromatographic analysis of this product revealed no impurities. The infrared spectrum ($CHCl_3$ solution) exhibited bands at 3400–2800, 1715 (m), 1660 (s), and 1598 $cm^{-1}$ (m), indicating a predominance of the enol form. The product lost carbon dioxide upon warming with formation of 4-*tert*-butylcyclohexanone.

**Acknowledgment.**—This work was assisted financially by a grant from the National Science Foundation.

**Registry No.**—Carbon dioxide, 124-38-9; lithium 4-methyl-2,6-di-*tert*-butylphenoxide, 42031-71-0.

(1) E. J. Corey and R. H. K. Chen, *Tetrahedron Lett.*, in press.

## Synthesis of Methyl 3-Hydroxybenzo[*b*]thiophene-2-carboxylate Esters by Nitro Displacement

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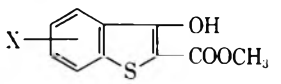
*Received July 27, 1973*

The first synthesis of methyl 3-hydroxybenzo[*b*]-thiophene-2-carboxylate was reported by Friedlander.[1]

(1) P. Friedlander, *Justus Liebigs Ann. Chem.*, **351**, 390 (1906).

TABLE I

METHYL 3-HYDROXYBENZO[b]THIOPHENE-2-CARBOXYLATES



| Registry no. | X | Mp, °C | Yield, % | Crystn solvent[a] | Temp, °C; time, hr |
|---|---|---|---|---|---|
| 13134-76-4 | H | 109–110[b] | 61 | A | 0, 0.5; 25, 2.5 |
| 33851-22-8 | 6-Cl | 147–149 | 75 | B | 0, 0.5; 25, 1 |
| 33851-23-9 | 7-Cl | 133–134 | 80 | B | 0, 0.5; 25, 2 |
| 42087-77-4 | 4-$NO_2$ | 185–186.5 | 85 | B | 0, 0.5 |
| 42087-78-5 | 7-$NO_2$ | 226–228 | 73 | B | 0, 0.5 |
| 42087-79-6 | 7-$OCH_3$ | 118–119 | 50 | A | 0, 0.5; 25, 3 |

[a] A, alcohol–water; B, alcohol. [b] Lit.[1] mp 104°.

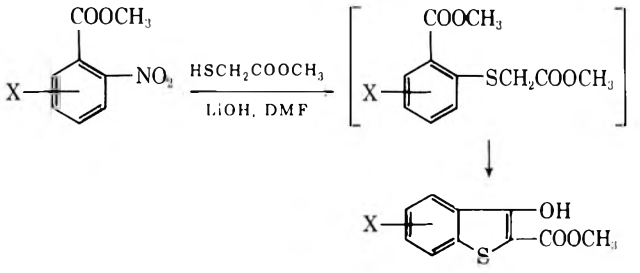
TABLE II

MICROANALYTICAL DATA

| X | Empirical formula | Calcd, % C | H | N | S | Found, % C | H | N | S |
|---|---|---|---|---|---|---|---|---|---|
| H | $C_{10}H_8O_3S$ | 57.68 | 3.87 | | 15.40 | 57.91 | 3.94 | | 15.51 |
| 6-Cl | $C_{10}H_7ClO_3S$ | 49.48 | 2.91 | | 13.21 | 49.31 | 2.82 | | 13.16 |
| 7-Cl | $C_{10}H_7ClO_3S$ | 49.48 | 2.91 | | 13.21 | 49.70 | 2.87 | | 13.31 |
| 4-$NO_2$ | $C_{10}H_7NO_5S$ | 47.43 | 2.79 | 5.53 | 12.66 | 47.47 | 2.77 | 5.52 | 12.76 |
| 7-$NO_2$ | $C_{10}H_7NO_5S$ | 47.43 | 2.79 | 5.53 | 12.66 | 47.59 | 2.74 | 5.47 | 12.61 |
| 7-$OCH_3$ | $C_{11}H_{10}O_4S$ | 55.45 | 4.23 | | 13.46 | 55.67 | 4.14 | | 13.59 |

The compound was formed by base-catalyzed cyclization of the bis methyl ester of *o*-[(carboxymethyl)thio]-benzoic acid, which was obtained in three steps from *o*-mercaptobenzoic acid. There are many modifications of this general synthesis, and these have been reviewed.[2] The free acids are readily decarboxylated to form benzo[*b*]thiophen-3(2*H*)-ones (thioindoxyls), which are precursors to thioindigo dyes. In a previous communication,[3] the author reported a direct synthesis of methyl 3-aminobenzo[*b*]thiophene-2-carboxylates from *o*-nitrobenzonitriles and methyl benzo[*b*]thiophene-2-carboxylates from *o*-nitrobenzaldehydes. This synthesis has now been extended for the conversion of methyl *o*-nitrobenzoates to methyl 3-hydroxybenzo[*b*]thiophene-2-carboxylates (Scheme I).

SCHEME I




Under the conditions of the reaction, the nitro group, activated by the adjacent carbomethoxyl function, is readily displaced by methyl thioglycolate anion (lithium salt) in DMF, and this is followed by a base-catalyzed cyclization as in the Friedlander synthesis. The conditions are mild and the yields, which are based upon crystallized products, are high (Table I). The major side reaction appears to be hydrolysis of the starting ester, and this can probably be overcome by rigorous drying of the DMF and lithium hydroxide. Other examples of the synthetic utility of activated nitro displacement will be the subject of further communications.

### Experimental Section[4]

**Materials.**—All benzoic acids utilized are commercially available from the Aldrich Chemical Co. The methyl esters were prepared by standard procedures in the literature.

**General Procedure for Methyl 3-Hydroxybenzo[*b*]thiophene-2-carboxylates.**—To a well stirred, cold solution (ice bath) containing 30 mmol of the substituted methyl *o*-nitrobenzoate and 4.0 ml of methyl thioglycolate in 60 ml of DMF was added slowly, portionwise, 2.5 g of lithium hydroxide. The mixture was stirred in the cold for 0.5 hr and then at room temperature for the time period shown in Table I. It was poured into ice water and the solution was acidified. The crude product was collected and crystallized from the appropriate solvent (Table I). Microanalytical data are summarized in Table II.

**Acknowledgments.**—The author wishes to thank Mr. Paul Unger and associates for spectral measurements and Mr. George Maciak and associates for microanalytical data.

**Registry No.**—Methyl *o*-nitrobenzoate, 606-27-9; methyl 4-chloro-2-nitrobenzoate, 42087-80-9; methyl 3-chloro-2-nitrobenzoate, 42087-81-0; methyl 2,6-dinitrobenzoate, 42087-82-1; methyl 2,3-dinitrobenzoate, 42087-83-2; methyl 3-methoxy-2-nitrobenzoate, 5307-17-5; methyl thioglycolate, 2365-48-2.

(2) (a) H. D. Hartough and S. L. Meisel, "The Chemistry of Heterocyclic Compounds," A. Weissberger, Ed., Interscience, New York, N. Y., 1954, pp 67, 138; (b) B. Iddon and R. M. Scrowston, *Advan. Heterocycl. Chem.*, **11**, 229 (1970).

(3) J. R. Beck, *J. Org. Chem.*, **37**, 3224 (1972).

(4) Melting points were determined on a Mel-Temp apparatus and are uncorrected.

## Synthesis and Properties of 3,3,6,6-Tetramethyl-1-oxacycloheptane-4,5-dione

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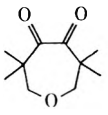
*Received May 21, 1973*

Our interest in charge-transfer phenomena in heteroatom containing medium ring ketone[1a] and α-dione[1b,c] substrates has led us to synthesize oxa α-dione **1**[2] in order to compare its uv spectra, mass spectral frag-

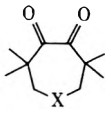
(1) (a) P. Y. Johnson and G. A. Berchtold, *J. Org. Chem.*, **35**, 584 (1970); (b) P. Y. Johnson, *Tetrahedron Lett.*, 1991 (1972); (c) P. Y. Johnson and I. Jacobs, *Chem. Commun.*, 925 (1972).

(2) Since submitting this manuscript a second report of the synthesis of **1** has been published. See A. Krebs and G. Eurgdorfer, *Tetrahedron Lett.*, 2063 (1973).

mentation pattern, and photochemical reactions with its sulfur, **2**,[1b,3] nitrogen, **3**,[4] and carbon, **4**,[3,5] analogs.



**1**



**2**, X = S
**3a**, X = *N*-*t*-Bu
**b**, X = *N*-phenyl
**4**, X = $CH_2$

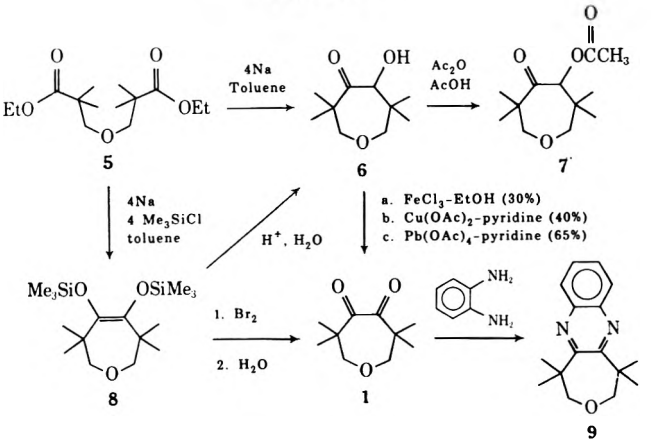
Initial attempts to synthesize oxa dione **1** by an acyloin ring closure procedure from the appropriate 3,3′-oxa diester, **5**,[6] were only partially successful. While the acyloin product, hydroxy ketone **6**, could be obtained in high yield (~85%) using either the normal[7a] or the chlorotrimethylsilane modification[7b] of the acyloin reaction, we were unable to oxidize it to **1** in greater than 50% yield using procedures which worked well in our hands for similar molecules. The following procedures were employed: $FeCl_3$–ethanol, 24-hr reflux (~30% **1** + **6**); $Cu(OAc)_2$–pyridine, 15 hr at 25° (~40% **1** + **6**); and $Pb(OAc)_4$–pyridine, 160 hr at 25° (~50% **1** + **6**). In all cases vpc analysis showed no further reaction with increased time. The addition of more oxidant and/or solvent did not seem to improve the yields of these reactions. The differences between the oxidation of **6** and its sulfur analog **2**[1b,8] cannot be accounted for.[9] Acyloin **6** was, however, oxidized by $Pb(OAc)_4$–pyridine in 65% yield when the reaction was run at reflux temperatures for 12 hr under a nitrogen atmosphere.

Hydroxy ketone **6** was converted to its acetate derivative, **7**, by standard procedures. The decomposition noticed (see Experimental Section, procedure A) during the distillation of **6**, leaving a viscous, nondistillable oil, was not noticed during the distillation of acetate **7**.

The desired oxa α-dione **1** was also obtained in 70% yield using a simplification of a procedure involving the bromine oxidation of the disiloxene intermediate, **8**, which was generated in the chlorotrimethylsilane modification of the acyloin reaction.[10] We found it to be experimentally easier to oxidize the disiloxene intermediate in the original reaction flask than to try to isolate it first as is the reported procedure. In our case, bromine was added to the cooled reaction mixture until a red color persisted. Usually slightly more than 1 equiv of bromine was required, probably owing to reaction of the bromine with traces of unreacted sodium.

Oxa dione **1** was characterized as its quinoxaline derivative **9**. The reactions described are shown in Scheme I.

SCHEME I




In contrast to α-diones **2**[1b] and **3**,[4] **1** showed no absorption band in its uv spectra attributable to charge transfer interaction. On the contrary, its uv spectrum was similar to that of its carbon analog **4**[5] [**4**, uv max (EtOH) 337 nm (ε 33), 292 (34), shoulder 288 (28); **1**, uv max (EtOH) 326 nm (ε 26), 292 (26), shoulder 283 (20)].

The lack of apparent charge-transfer interaction (uv spectra) leads us to believe that the photolysis of **1** will not parallel that of **2**.[1b]

## Experimental Section

Melting points were taken on a calibrated Mel-Temp apparatus. Infrared spectra were taken on a Perkin-Elmer 337 spectrometer; nmr spectra were recorded on a Varian A-60 spectrometer using TMS as an internal standard. Mass spectra were obtained on a Hitachi RMU6D mass spectrometer. Ultraviolet spectra were recorded on a Cary 14 instrument. Vpc analyses were performed using program temperature control on a Hewlett-Packard 5750 gas chromatograph equipped with 8 ft × 0.25 in. 10% Carbowax on Chrom-P and 8 ft × 0.25 in. 10% SE-30 on Chrom-P stainless steel columns. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.

**3,3,6,6-Tetramethyl-5-hydroxy-1-oxacycloheptan-4-one (6).**—Hydroxy ketone **6** was synthesized from diester **5** using both the normal (A) and the chlorotrimethylsilane modification (B) of the acyloin reaction.

**Procedure A.**—Into a dry Morton flask set up for high-speed stirring under $N_2$ was added 400 ml of toluene and 13.34 g (0.58 mol) of sodium. The mixture was refluxed and 39.6 g (0.145 mol) of diester **5** in 100 ml of toluene was added to it over several hours. After 2 hr additional reflux, the mixture was cooled to 0° and the reaction was quenched with aqueous $NH_4Cl$ [7.8 g (0.145 mol) in 200 ml of water]. The organic layer was separated, washed with $H_2O$, dried with $MgSO_4$, filtered, and evaporated to give 27 g (~100%)[11] of a crude oil. Vpc analysis of the crude oil showed it to be mostly desired hydroxy ketone **6** (based on the mass spectrum of a collected sample) and some starting diester. Attempts to solidify this oil by cooling it or by cooling it in the presence of acetic acid[8] or ethanol failed. Finally, distillation of the oil gave a low yield, 7.4 g (28.0%), of **6**, bp 92–96° (0.2 mm), which solidified upon standing. Recrystallization from low petroleum ether (bp 30–60°) gave **6** as a white solid: mp 58.5–59.5°; ir ($CCl_4$) 3450, 2952, 2935, 2865, 1700, 1470, 1385, 1360, 1262, 1123, 1048 $cm^{-1}$; nmr ($CCl_4$) δ 0.69 (s, 3), 0.91 (s, 6), 1.27 (s, 3), 3.2–3.7 (m, 5), 4.19 (d, 1, $J$ = 5 Hz, collapses to singlet in $D_2O$); mass spectrum (70 eV) $m/e$ (rel intensity) 186 (trace, $M^+$), 158 (7), 131 (11), 114 (16), 103 (59), 101 (18), 85 (15), 73 (30), 72 (23), 71 (30), 59 (10), 57 (30), 56 (100), 55 (17), 43 (24), 41 (37); uv $\lambda_{max}$ (EtOH) 261 nm (ε 43). When the reaction was run in the same manner as described above but the crude oil was kept under high vacuum for 24 hr in order to remove

(3) A second report on the photolysis of the sulfur, **2**, and the carbon, **4**, analogs of **1** has been published. See J. Kooi, H. Wynberg, and R. M. Kellogg, *Tetrahedron*, **29**, 2135 (1973).

(4) P. Y. Johnson and I. Jacobs, unpublished results.

(5) N. J. Leonard and P. M. Mader, *J. Amer. Chem. Soc.*, **72**, 5388 (1950).

(6) (a) J. Zitsman and P. Y. Johnson, *Tetrahedron Lett.*, 4201 (1971); (b) P. Y. Johnson and J. Zitsman, *J. Org. Chem.*, **38**, 2346 (1973).

(7) (a) K. Y. Finley, *Chem. Rev.*, **64**, 573 (1964); (b) J. J. Bloomfield, *Tetrahedron Lett.*, 587 (1968).

(8) Ae De Groot and H. Wynberg, *J. Org. Chem.*, **31**, 3954 (1966).

(9) For a large list of oxidants employed in the oxidation of α-hydroxy ketones and a discussion of their usefulness for reaction with hindered systems, see G. E. Gream and S. Worthley, *Tetrahedron Lett.*, 3319 (1968), and references cited therein.

(10) For a review of this procedure, see J. Strating, S. Reiffers, and H. Wynberg, *Synthesis*, 209 (1971).

(11) In our hands the yields of these and other acyloin reactions have been found to fall 10–20% when a *Morton flask* is not used.

all of the reaction solvents, it was found to solidify after standing at 0° for 24 hr. Recrystallization from low petroleum ether twice gave pure **6** (85%),[11] mp 59–59.5°.

**Procedure B.**—The reaction was run as above but 4 equiv of chlorotrimethylsilane were added to the reaction mixture dropwise along with diester **5**. After the additional 1 hr of reflux the reaction mixture was cooled. No attempt was made to isolate the disiloxene intermediate **8**, but rather aqueous $NH_4Cl$ was added to the reaction mixture. The organic–aqueous mixture was stirred for 1 hr and the organic layer was treated as described in procedure A. The yield of **6** was 80–85% over several runs.

**3,3,6,6-Tetramethyl-5-acetoxy-1-oxacycloheptan-4-one (7).**—Hydroxy ketone **6** (2.5 g, 0.014 mol) was refluxed in 10 ml of acetic acid and 10 ml of acetic anhydride for 12 hr and cooled. Water was added and the mixture was stirred for 30 min. It was then extracted with ether which was washed with 10% $K_2CO_3$, dried, and evaporated to give an oil which did not solidify. Short-path distillation of the oil gave 2.6 g of liquid which solidified upon standing. Recrystallization from ethanol gave 2.4 g (78%) of pure acetate **7**: bp 91–93° (1.00 mm); mp 69.5–71°; ir ($CCl_4$) no OH, 2960, 2940, 2860, 1749, 1725, 1380, 1365, 1250, 1120 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 0.85 (s, 3), 0.91 (s, 3), 0.98 (s, 3), 1.18 (s, 3), 2.08 (s, 3), 3.3–3.8 (m, 4), 5.32 (s, 1); mass spectrum (70 eV) *m/e* (rel intensity) 228 (1, $M^+$), 185 (3), 173 (31), 157 (7), 145 (8), 131 (17), 115 (10), 113 (8), 86 (9), 85 (38), 73 (15), 72 (15), 57 (24), 56 (59), 55 (14), 43 (100), 41 (32); uv $\lambda_{max}$ (EtOH) 273 nm ($\epsilon$ 40).

*Anal.* Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83. Found: C, 62.99; H, 8.71.

**3,3,6,6-Tetramethyl-1-oxacycloheptane-4,5-dione (1).**—Dione **1** was synthesized according to procedure B described above for the synthesis of **6** with the following changes. To the cooled reaction mixture containing disiloxene **8** was added about 1 equiv of $Br_2$ in $CCl_4$ over 10 min with cooling. Additional $Br_2$ was added until its characteristic red color persisted. After the mixture was allowed to warm to 25° over 30 min, aqueous $NH_4Cl$ was added and stirring was continued for 1 hr. The organic layer was separated, washed with a minimum amount of 10% sodium bisulfite, 10% $K_2CO_3$, and 10% HCl, dried, filtered, and evaporated to give an oil which was distilled to give 60–70% (several runs) of pure dione **1**: bp 52–54° (0.1 mm) and 62–63° (0.5 mm) (this oxa dione was a low-melting solid when pure); ir ($CCl_4$) 2955, 2940, 2855, 1720 (shoulder 1700), 1395, 1365, 1200, 1187, 1108 $cm^{-1}$; nmr ($CCl_4$) $\delta$ 1.10 (s, 12), 3.51 (s, 4); mass spectrum (70 eV) *m/e* (rel intensity) 184 (12, $M^+$), 101 (56), 73 (19), 59 (11), 57 (19), 56 (100), 55 (22), 43 (11), 42 (11), 41 (44); uv $\lambda_{max}$ (EtOH) 283 nm ($\epsilon$ 20), 292 (26), 326 (26).

**3,3,6,6-Tetramethyl-1-oxacycloheptane-4,5-dione (1) Using $Pb(OAc)_4$.**—Hydroxy ketone **6**, 3.16 g (0.017 mol), and lead tetraacetate, 9.04 g (0.020 mol), were refluxed in 35 ml of pyridine, under nitrogen, for 12 hr. The reaction mixture was cooled and poured into 120 ml of cold 6 *N* HCl and the resulting solution was extracted with ether. The ether was washed with 10% aqueous $K_2CO_3$, dried over anhydrous $K_2CO_3$, and evaporated to give an oily liquid. Distillation gave 1.90 g (65%) of pure dione **1** as a pale yellow, oily liquid which solidified to a low-melting solid on cooling, mp 41.5–43.5°.

Dione **1** was characterized as its quinoxaline derivative, **9**, which was synthesized by standard procedures, mp (EtOH) 74–75°.

*Anal.* Calcd for $C_{16}H_{20}N_2O$: C, 74.96; H, 7.86; N, 10.93. Found: C, 74.98; H, 7.74; N, 10.94.

**Acknowledgment.**—We wish to thank the National Institutes of Health for partial support of this work.

**Registry No.**—**1**, 42031-65-2; **5**, 34506-36-0; **6**, 42031-67-4; **7**, 42031-68-5; **8**, 42133-38-0; **9**, 42031-69-6.

# Communications

See Editorial, *J. Org. Chem.*, **37**, No. 13, 4A (1972).

## A Synthesis of Rosenonolactone from Podocarpic Acid

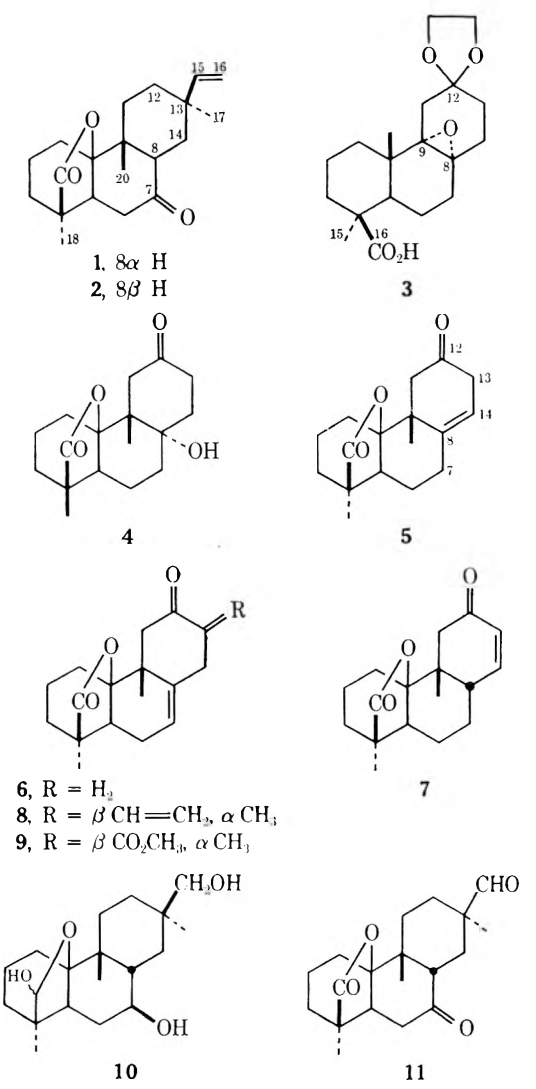
*Summary:* The 10 → 9 methyl group shift, with concomitant lactonization, effected by Lewis acid treatment of 12,12-ethylenedioxy-8α,9α-epoxypodocarpan-16-oic acid (**3**), provides the basis for a new synthesis of rosenonolactone (**1**).

*Sir:* The greater thermodynamic stability of rosane compounds over that of pimarane derivatives[1] has been exploited in a biogenetically modeled synthesis[2] of rosenonolactone (**1**) from isocupressic acid. We report a similar synthesis which, in contrast, however, is completely stereoselective and introduces the lactone function directly during the isomerization step. The brevity of the following sequence, which begins with abundantly available podocarpic acid, offers a particularly attractive route to rosane compounds.

The $\Delta^8$-ethylene acetal[3] derived from 12-oxopodocarp-9(11)-en-16-oic acid[4] was oxidized in quantitative yield by *m*-chloroperoxybenzoic acid to the α-epoxide **3**. When a dilute solution of the epoxide in nitromethane[5] was treated with 2 molar equiv of boron trifluoride etherate for 0.5 hr, the hydroxy lactone **4** (55% yield) was the only neutral product isolated. With 12 equiv of reagent a 2:2:1 mixture (59% yield) of the 8(14)-en-12-one **5**, the $\Delta^7$ isomer **6**, and hydroxy ketone **4** was obtained.[6] Olefin **5** was rapidly isomerized by ethanolic HCl to the α,β-unsaturated lactone **7**,[7] whereas olefin **6** was recovered unchanged.

The elaboration of a rosadiene derivative from ketone **6** was completed simply by C-methylation of its 13-ethylidene derivative,[8] affording a single stereoisomer (**8**, 65% overall yield) in which the vinyl group could be assigned the β configuration from Eu(dpm)$_3$-induced shifts in the nmr spectra of the derived ($NaBH_4$) 12α and 12β alcohols. A correlation of these compounds with rosenonolactone (**1**) to confirm the stereochemical assignments was thwarted by complications arising from the labile vinyl group and an alternative sequence was therefore initiated.

Methoxycarbonylation (NaH, $CH_3OCO_2CH_3$) of ketone **6** followed by *in situ* methylation (MeI) gave a single stereoisomer (**9**, 80% yield) which was converted to its ethylene dithioacetal derivative (33% yield) under carefully controlled conditions (rigorously dried reagents, brief reaction times with recycling of recovered ketone).[9] Desulfurization (W2 Raney nickel) was accompanied by partial double-bond migration (3:2 mixture of $\Delta^7$ and $\Delta^{8(14)}$ olefins) but the triol **10** could be obtained cleanly (40% yield) from hydroboration of the mixture. Ketoaldehyde **11** from oxidation by excess Collins' reagent[10] reacted selectively with




methylenetriphenylphosphorane to give isorosenonolactone (**2**, 80% yield)[11] which, on equilibration in HCl–$CCl_4$, gave a 1:1 mixture with rosenonolactone (**1**). Synthetic **1** was indistinguishable (melting point, mixture melting point, and tlc, ir, and nmr spectra)

(1) T. McCreadie and K. H. Overton, *J. Chem. Soc. C*, 312 (1971).

(2) T. McCreadie, K. H. Overton, and A. J. Allison, *J. Chem. Soc. C.*, 317 (1971).

(3) See paragraph at end of paper regarding supplementary material.

(4) R. H. Bible and R. B. Burtner, *J. Org. Chem.*, **26**, 1174 (1961).

(5) Reduced yields of lactonic products were obtained in benzene, acetonitrile, or ether; the acetal function survived in the last solvent.

(6) Several analogous epoxy acids were treated similarly with equivalent results.

(7) Resonances in the nmr spectrum of **7** at δ 5.87 (H-13, d, $J_{13,14}$ = 10 Hz) and 6.93 ppm (H-14, dd, $J_{13,14}$ = 10 Hz, $J_{8,14}$ = 6 Hz) clearly indicated that the C-8 hydrogen substituent was quasiequatorial with respect to ring C. Therefore **7** possesses the trans,syn,cis configuration as assigned, since the cis,syn,cis isomer merits no consideration and trans,syn,trans or cis,-syn,trans backbones would confer a quasiaxial conformation (in both rings) on C-8 substituents.

(8) R. E. Ireland and P. W. Schiess, *J. Org. Chem.*, **28**, 6 (1963).

(9) The lactone function was degraded to the $\Delta^{5(10)}$ olefinic acid at a rate marginally slower than that of thioacetal formation. *Cf.* N. Kiriyama, Y. Yamamoto, and Y. Tsuda, *Chem. Commun.*, 37 (1971).

(10) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

(11) A. Harris, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 1799 (1958).

from an authentic sample.[12] The surprisingly efficient lactonization–migration step[13] is an intriguing aspect of this synthesis and is the subject of current investigation. The utility of this approach in preparing further analogs of rosenonolactone, *e.g.*, the 11β-hydroxy derivative, Rosein III,[9] is also under examination.

**Supplementary Material Available.**—Complete experimental details on all compounds described in this communication will appear following these pages in the microfilm edition of this volume of the journal. Photocopies of the supplementary material from this paper only or microfiche (105 × 148 mm, 20 × reduction, negatives) containing all of the supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D. C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-4090.

(12) We are grateful to Professor R. W. Rickards, Australian National University, for this compound.

(13) *Cf.* W. Herz and H. J. Wahlborg, *J. Org. Chem.*, **30**, 1881 (1965).

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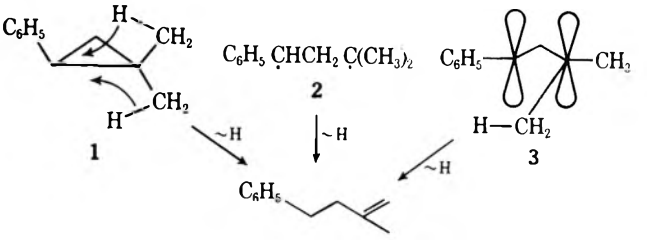
## The Photoisomerizations of 2-Methylphenylcyclopropanes. Isotope Effects and Stereochemistry

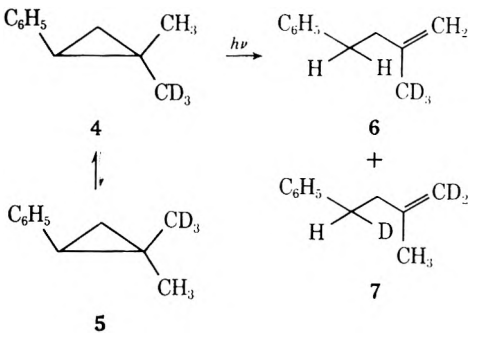
*Summary:* A deuterium-labeling study on 2,2-dimethylphenylcyclopropane has resulted in the determination of secondary and rather small primary isotope effects for the photochemical reaction and has shown that hydrogen migration in this system takes place preferentially from the methyl group trans to the benzene ring.

*Sir:* The photochemistry of phenylcyclopropanes has been the subject of intensive investigation recently.[1-6] In particular the isomerizations of 2-alkylphenylcyclopropanes to 4-phenyl-1-butenes[7-11] are of interest since they could represent an example of the allowed [$_{\sigma}2_s + {}_{\sigma}2_s$] concerted[12] photochemical cycloaddition. Alternatively the reaction could proceed *via* preliminary opening to a classical diradical (**2**) or a π cyclopropane-like[13] intermediate (**3**) resulting from disrotatory or conrotatory opening of **1** with subsequent hydrogen migration affording the observed product. *A priori* one expects equivalent migration from *cis*- and *trans*-methyl groups *via* the $_{\sigma}2 + {}_{\sigma}2$ route with steric factors possibly causing a slight preponderance of migration from the *trans*-methyl group, whereas, if **2** is the intermediate, stereochemical information on the initial locus of the migrating hydrogen must be lost. Preferred disrotatory opening to **3** for electronic or steric reasons requires migration from the *trans*-methyl group, whereas migration from the *cis*-methyl group would result from conrotatory opening. Stereochemical information is thus of value in elucidating the mechanism of this rearrangement.




In principle the problem could be solved by examining the relative rates of rearrangement of *cis*- and *trans*-2-methylphenylcyclopropane; however, this system is complicated by the fact that the ground-state conformations and energies of the isomers differ significantly[14] and photochemical cis → trans isomerization[4] is so fast that it completely dominates terminal olefin formation.

The problem can be solved by examining the products from photolysis of labeled materials such as **4**. The cis to trans migration ratio is simply the 6:7 ratio




obtained on photolysis of **4**,[15] and this ratio is amenable to mass spectroscopic analysis; *i.e.*, whereas **6** affords a normal tropylium ion at *m/e* 91, the tropylium ion from **7** ($C_7H_6D$) appears at *m/e* 92. The 6:7 ratio is obtained from the suitably corrected[16] *m/e* 91/92 peak intensity ratio (H/D). As expected geometrical isomerization (*i.e.*, **4** → **5**) is slower in this system than in the 2-methylphenylcyclopropanes and the experimental 6:7 ratios from **4** were obtained by determining

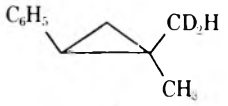
(1) W. von E. Doering and M. Jones, *Tetrahedron Lett.*, 791 (1963).
(2) G. S. Hammond and R. S. Cole, *J. Amer. Chem. Soc.*, **87**, 3256 (1965).
(3) E. W. Valyocsik and P. Sigal, *J. Org. Chem.*, **36**, 66 (1971).
(4) K. Salisbury, *J. Amer. Chem. Soc.*, **94**, 3707 (1972).
(5) G. W. Griffin, *Angew. Chem., Int. Ed. Engl.*, **10**, 537 (1971).
(6) S. S. Hixson, *J. Amer. Chem. Soc.*, **93**, 5293 (1971).
(7) H. Kristinsson and G. W. Griffin, *J. Amer. Chem. Soc.*, **88**, 378 (1966).
(8) H. Kristinsson and G. W. Griffin, *Tetrahedron Lett.*, 3259 (1966).
(9) P. H. Mazzocchi, R. S. Lustig, and G. W. Craig, *J. Amer. Chem. Soc.*, **92**, 2169 (1970).
(10) J. Meinwald and D. A. Seely, *Tetrahedron Lett.*, 3739 (1970).
(11) L. Ulrich, H. J. Hansen, and H. Schmid, *Helv. Chem. Acta*, **53**, 1323 (1970).
(12) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).
(13) R. Hoffmann, *J. Amer. Chem. Soc.*, **90**, 1475 (1968). Hoffmann's calculations suggest that there is no distinct energy minimum in the singlet or triplet excited states of the trimethylene diradical.
(14) J. J. Rocchio, Ph.D. Thesis, University of Maryland, 1970.
(15) Details of the synthesis of the labeled compounds used will be presented elsewhere.
(16) An empirical correction factor was calculated from *m/e* 91/92 ratios obtained from synthetic mixtures of 2-methyl-4-phenyl-1-butene and 2-methyl-4-phenyl-4-*d*-1-butene. Scrambling of deuterium from the methyl and vinyl positions to the benzylic position in the mass spectrum was also considered. Examination of the mass spectra of suitable model compounds showed that this was not a major process. The error limits reflect our estimation of the magnitude of this process.

this ratio at various conversions and extrapolating back to zero conversion. The formation of **6** and **7** is also subject to primary and secondary isotope effects and knowledge of these values is necessary to make the data applicable to compound **1**. If we define $\pi$ as the primary, $\alpha$ and $\beta$ as secondary type I and type II isotope effects, respectively, and $x$ as the fraction migration from the *cis*-methyl group, an expression relating the corrected $m/e$ 91/92 (H/D) to the **6**:**7** ratio can be written; *i.e.*, hydrogen migration to give **6** occurs from the cis side ($x$) and is subject to three secondary type II effects ($\beta^3$), while **7** results *via* trans migration ($1 - x$) and is subject to a primary ($\pi$) and a pair of secondary type I effects ($\alpha^2$) (eq 1).

$$H/D = \frac{x/\beta^3}{(1-x)/\pi\alpha^2} = \frac{x\pi\alpha^2}{(1-x)\beta^3} \quad (1)$$

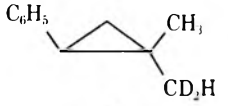
Similarly for systems **8** → **11** + **12** equations 2–5 can be written. These equations allow a solution for

$$H/D = \frac{\pi\beta^2 x + (1-x)3\pi\alpha^2}{2x\alpha\beta^2} \quad \text{for} \quad \text{(2)}$$



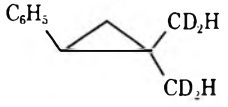
**8**

$$H/D = \frac{3x\pi\alpha^2 + (1-x)\pi\beta^2}{2\alpha\beta^2(1-x)} \quad \text{for} \quad \text{(3)}$$



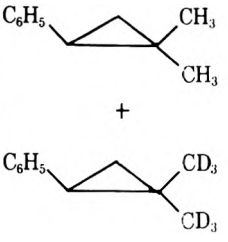
**9**

$$H/D = \frac{\pi}{2\alpha} \quad \text{for} \quad \text{(4)}$$



**10**

$$H/D = \pi\alpha^2\beta^3 \quad \text{for} \quad \text{(5)}$$



$x$, $\pi$, $\alpha$, and $\beta$[17] and substitution of the experimental H/D values (Table I) affords isotope effect values: $\pi = 1.96 \pm 0.22$; $\alpha = 1.10 \pm 0.05$; $\beta = 1.04 \pm 0.09$.[18,19]

The calculated value of $x$ is $0.373 \pm 0.054$; *i.e.*, there is a distinct preference for migration from the methyl group trans to the benzene ring. The 63:37 ratio of trans to cis migration is significant and clearly rules out **2** as a viable intermediate. In addition, processes which proceed with exclusive disrotatory *or* conrotatory opening to an intermediate such as **3** are also excluded by these results.

TABLE I

| System | 4 | 8 | 9 | 10 | 11 + 12 |
|---|---|---|---|---|---|
| H/D[a] | 1.23 ± 0.12 | 5.68 ± 0.97 | 2.49 ± 0.25 | 0.893 ± 0.089 | 2.67 ± 0.27 |

[a] Corrected $m/e$ 91/92 intensity ratio.

The data are consistent with mechanisms which either result from a mixture of disrotatory and conrotatory openings to **3** followed by hydrogen migration or a reaction which proceeds *via* a $[{}_\sigma 2_s + {}_\sigma 2_s]$ transition state, or its equivalent,[20] subject to a slight steric discrimination.

It is inviting to attempt to interpret the isotope effects determined. Whereas the secondary effects are of the expected magnitude and direction for the hybridization changes involved,[21] the primary effect is low. In fact the magnitude of this effect is in the range predicted for a four-centered transition[22] state like that which would be involved in a $[{}_\sigma 2_s + {}_\sigma 2_s]$ process. However, the lack of appropriate models for isotope effects in photochemical systems would make mechanistic interpretation of these data dangerous. Experiments on the stereochemistry at the migration terminus further elucidate the mechanism of this reaction.[23]

**Acknowledgment.**—We wish to thank the Research Corporation and the Center of Materials Research of the University of Maryland for partial support of this work.

(17) S-H. Dai and W. R. Dolbier, Jr., *J. Amer. Chem. Soc.*, **94**, 3953 (1972). These authors use a similar method to calculate isotope effects.

(18) The validity of the use of eq 5 can be questioned; *i.e.*, these are intermolecular isotope effects as opposed to intramolecular effects in the other cases. In the case of **11** + **12** we could be seeing an effect which arises on formation of the reactive excited state. The use of five equations for the four unknowns allows a solution for $x$ independent of eq 5. Furthermore the fact that the calculated values constitute a solution, well within experimental error, of eq 1–4 suggests that there is little, if any, isotope effect on formation of the reactive excited state.

(19) The inclusion of the secondary type 2 effect is actually mechanistically prejudicial suggesting that $C_1$–$C_3$ bond cleavage occurs in the rate-determining step in the reaction. We have no evidence on this point. Inclusion of a value $\beta = 1.00$ results in little change in the calculated values for $\pi$ and $\alpha$ ($\pi = 2.11$, $\alpha = 1.05$) and the value for $x$ is unchanged.

(20) We cannot at present differentiate a $[{}_\sigma 2_s + {}_\sigma 2_s]$ process from one in which 1,2 bond cleavage has occurred *via* simple expansion of the $C_1$–$C_3$–$C_2$ bond angle followed by hydrogen migration.

(21) A. Streitwieser, R. Jagow, R. Fahey, and S. Suzuki, *J. Amer. Chem. Soc.*, **80**, 2326 (1958).

(22) R. A. More O'Ferrall, *J. Chem. Soc. B*, 785 (1970).

(23) P. H. Mazzocchi and R. S. Lustig, *J. Amer. Chem. Soc.*, **95**, 7178 (1973).

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## Exceptionally High Regioselectivity in the Hydroboration of Representative Olefins with 9-Borabicyclo[3.3.1]nonane in a Simplified Rapid Procedure

*Summary:* Hydroboration–oxidation of olefins with stoichiometric amounts of 9-borabicyclo[3.3.1]nonane in refluxing tetrahydrofuran proceeds rapidly and gives the anti-Markovnikov alcohols in high isomeric purity, often >99.5%. The regioselectivity obtained surpasses that obtained with other hydroborating agents, especially in the case of internal olefins.

*Sir:* The hydroboration of even highly substituted olefins with stoichiometric quantities of 9-borabicyclo-

TABLE I
PRODUCT DISTRIBUTION IN THE HYDROBORATION–OXIDATION OF REPRESENTATIVE OLEFINS WITH 9-BBN, $BH_3$, AND $Sia_2BH$ IN THF AND WITH $ClBH_2$–$OEt_2$

| Olefin | Product | Product distribution, %[a] 9-BBN–THF | $BH_3$–THF[b] | $Sia_2BH$–THF[c] | $H_2BCl$–$OEt_2$[d] |
|---|---|---|---|---|---|
| 1-Hexene | 1-Hexanol | 99.9 | 94 | 99 | >99.5 |
| | 2-Hexanol | <0.1 | 6 | 1 | <0.5 |
| 3,3-Dimethyl-1-butene | 3,3-Dimethyl-1-butanol | 99.7 | 94 | | |
| | 3,3-Dimethyl-2-butanol | <0.3 | 6 | | |
| 2-Methyl-1-pentene | 2-Methyl-1-pentanol | 99.8 | | | |
| | 2-Methyl-2-pentanol | <0.2 | | | |
| Styrene | 2-Phenylethanol | 98.5 | 81[e] | 98 | 96 |
| | 1-Phenylethanol | 1.5 | 19[e] | 2 | 4 |
| *cis*-4-Methyl-2-pentene | 4-Methyl-2-pentanol | 99.8 | 57[f] | 97 | 60 |
| | 2-Methyl-3-pentanol | 0.2 | 43[f] | 3 | 40 |
| *cis*-4,4-Dimethyl-2-pentene | 4,4-Dimethyl-2-pentanol | 99.9 | 58[f] | | 79 |
| | 2,2-Dimethyl-3-pentanol | 0.1 | 42[f] | | 21 |
| 2-Methyl-2-butene | 3-Methyl-2-butanol | >99.8 | 98 | | 99.7 |
| | 2-Methyl-2-butanol | <0.2 | 2 | | 0.3 |
| 1-Methylcyclopentene | *trans*-2-Methylcyclopentanol | >99.8 | 98.5 | | >99.8 |
| | 1-Methylcyclopentanol | Trace | 1.5 | | <0.2 |
| Norbornene | *exo*-2-Norbornanol | 99.5 | 99.5 | | >99.8 |
| | *endo*-2-Norbornanol | 0.5 | 0.5 | | 0.2 |

[a] Total yields were 95 ± 5%. [b] Reference 2a,b. [c] Reference 4. [d] Reference 3. [e] Reference 2c. [f] Trans olefin.

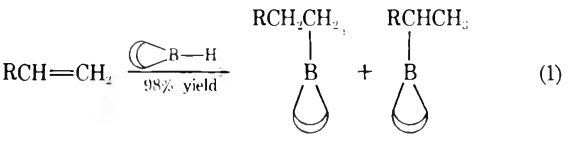
[3.3.1]nonane[1] (9-BBN) proceeds rapidly in refluxing tetrahydrofuran (THF). Oxidation of the intermediate *B*-R-9-BBN derivatives establishes that the regioselectivity realized with 9-BBN under these conditions is exceptionally high, both for terminal and for internal olefins. Moreover, 9-BBN is thermally stable and can be stored at room temperature almost indefinitely, either as the solid or as the THF solution. Consequently, hydroboration with 9-BBN using this procedure offers convenience and major improvements in product purities, both for the synthesis of the *B*-R-9-BBN derivatives and for the anti-Markovnikov hydration of carbon–carbon double bonds.

The use of hydroboration–oxidation with $BH_3$–THF for the anti-Markovnikov hydration of olefins[2] suffers from the formation of significant amounts of the minor isomer in the hydroboration stage. The use of monochloroborane–ethyl etherate ($H_2BCl$–$OEt_2$) was recently found to give very pure (>99.5%) primary alcohols from terminal olefins.[3] However, little regioselectivity was obtained with internal olefins. Hydroboration with disiamylborane ($Sia_2BH$) offers higher regioselectivity, but the reagent reacts only very sluggishly with internal and cyclic olefins.[4]

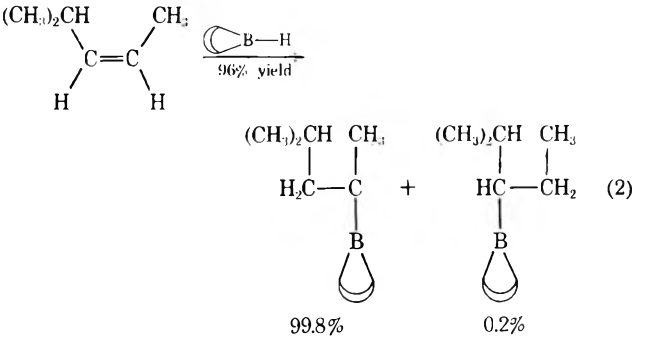
It appeared that 9-BBN might overcome these difficulties. Unfortunately, the rate of reaction of 9-BBN with olefins, especially the more substituted compounds, is relatively slow. Consequently, the procedure adopted used a large excess (100%) of 9-BBN to facilitate the reaction.[1] The presence of such an excess was especially undesirable for hydroborations in which it was desired to use the *B*-R-9-BBN derivatives for further syntheses.[5]

We have now established that it is possible to achieve the hydroboration of even highly substituted olefins with the stoichiometric quantity of 9-BBN in refluxing THF. First, the reaction time is relatively short. Unexpectedly, under these conditions isomerization of the *B*-R-9-BBN derivatives is not significant.[6] Finally, the regioselectivity observed is remarkably high, much higher than that noted previously.[1]

For example, 1-hexene undergoes hydroboration to give only 0.1% minor isomer (eq 1). Even more remarkable, internal olefins, such as *cis*-4-methyl-2-pentene, reveal a remarkable preference for placing the boron adjacent to the less bulky substituent (eq 2).



(1)



(2)

The following procedure for the hydroboration–oxidation of *cis*-4-methyl-2-pentene with 9-BBN is representative.[7]

A dry, nitrogen-flushed, 50-ml flask with an injection port was charged with 5.0 mmol of 9-BBN[8] (0.61 g) in a

(1) E. F. Knights and H. C. Brown, *J. Amer. Chem. Soc.*, **90**, 5280 (1968).
(2) (a) H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **82**, 4708 (1960); (b) H. C. Brown, "Hydroboration," W. A. Benjamin, New York, N. Y., 1962; (c) H. C. Brown and R. L. Sharp, *J. Amer. Chem. Soc.*, **88**, 5851 (1966); (d) G. Zweifel, N. R. Ayyangar, and H. C. Brown, *ibid.*, **85**, 2072 (1963).
(3) H. C. Brown and N. Ravindran, *J. Org. Chem.*, **38**, 182 (1973).
(4) H. C. Brown and G. Zweifel, *J. Amer. Chem. Soc.*, **83**, 1241 (1961).
(5) (a) H. C. Brown and M. M. Rogić, *J. Amer. Chem. Soc.*, **91**, 2146 (1969); (b) H. C. Brown and R. A. Coleman, *ibid.*, **91**, 4606 (1969).
(6) A detailed study of the isomerization of *B*-R-9-BBN derivatives is underway with Hiroaki Taniguchi.
(7) For an excellent discussion of applicable technique, see D. F. Shriver, "The Manipulation of Air-Sensitive Compounds," McGraw-Hill, New York, N. Y., 1969, Chapter 7.
(8) 9-BBN is now available from the Aldrich Chemical Co., Milwaukee, Wis.

nitrogen-filled glove bag. Dry THF (10 ml) was then added *via* syringe. The solution was heated to reflux and the reaction initiated by adding 2.5 ml of 2 *M cis*-4-methyl-2-pentene in THF (5.0 mmol). The mixture was stirred under reflux for 1 hr[9] and then cooled to room temperature. The intermediate organoboranes were oxidized by adding, successively, 3 ml of ethanol, 1 ml of 6 *N* NaOH, and 2 ml of 30% $H_2O_2$. Complete oxidation was ensured by maintaining the reaction mixture at 50° for 1 hr. The aqueous phase was saturated with potassium carbonate to give a dry THF solution of the product. The absolute and relative product yields were determined by glpc using dodecane as an internal standard. (The reliability of the instrument in determining the minor component was checked by analyzing known synthetic mixtures of the two products in the proportions expected from the reaction.) 4-Methyl-2-pentanol was obtained in 96% yield, together with 0.2% 2-methyl-3-pentanol.

The results are summarized in Table I together with comparable data for hydroborations with $BH_3$–THF, $H_2BCl$–$OEt_2$, and $Sia_2BH$.

(9) One hour in refluxing THF proved adequate for all olefins examined except the most sluggish, such as 1-methylcyclohexene and 2,3-dimethyl-2-butene. In these cases, 8 hr under reflux proved adequate to complete the hydroboration.

The origin of the exceptionally high regioselectivity obtained with 9-BBN is not clear. The facile reaction of 9-BBN with highly substituted olefins seems to indicate that the reagent is sterically less demanding than $Sia_2BH$. However, the bicyclic structure of 9-BBN is rigid and steric crowding in the transition state cannot be relieved by internal rotation in the borane moiety. Thus 9-BBN may be more sensitive to subtle differences in steric environment than the acyclic dialkylborane, $Sia_2BH$.

In any case, it is clear that hydroboration with 9-BBN furnishes a convenient route to the synthetically useful *B*-alkyl-9-BBN derivatives, as well as furnishing the anti-Markovnikov alkylborane moiety in extremely high isomeric purity. This development, together with the stability and commercial availability of the reagent,[8] greatly simplifies the synthesis of regiospecifically and stereochemically pure derivatives.

(10) Graduate Research Assistant on a grant, GP-31385, provided by the National Science Foundation.

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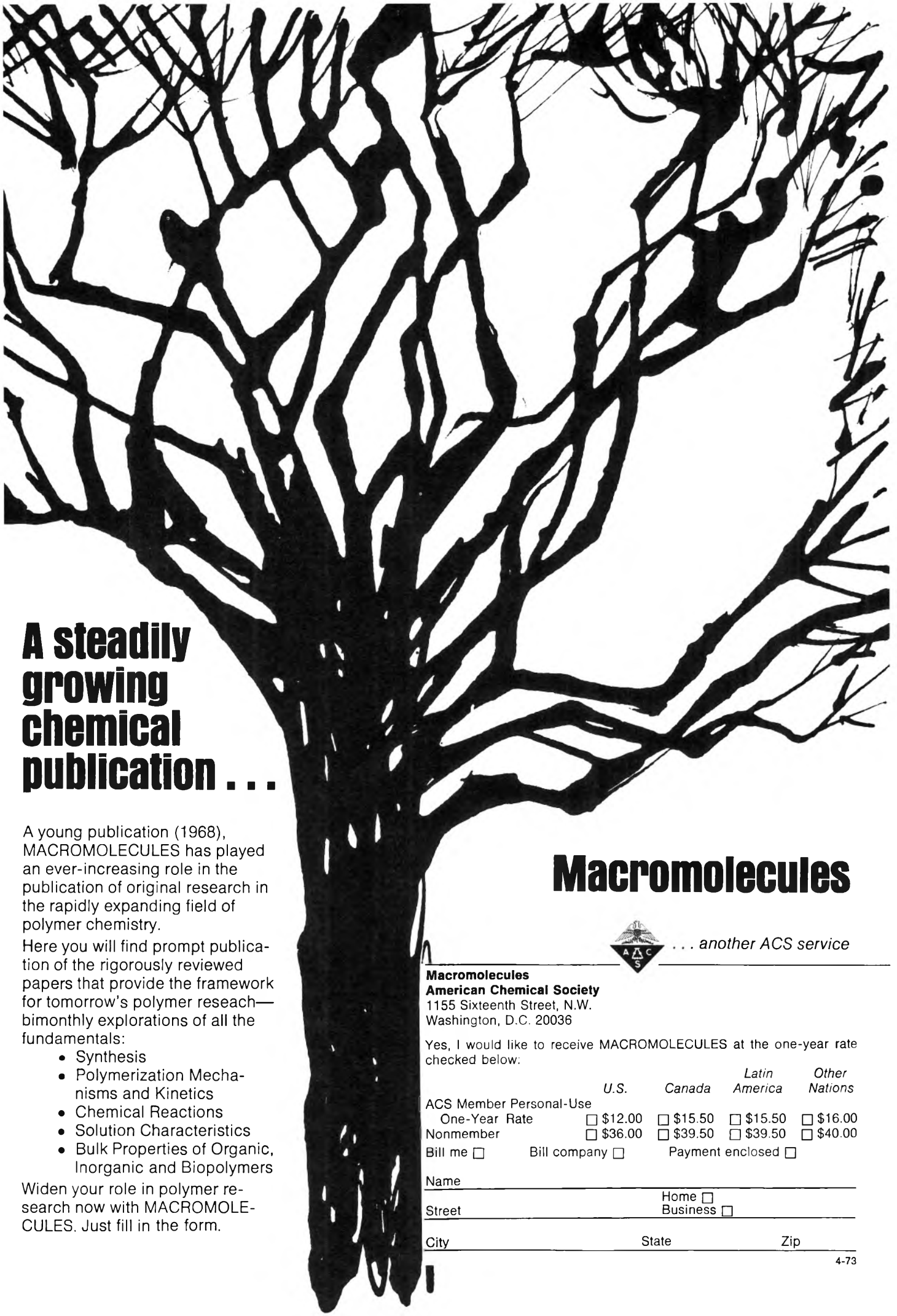

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2) K. B. Sharpless and R. F. Lauer, *J. Org. Chem.*, **37**, 3973 (1972).
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5) K. B. Sharpless and R. F. Lauer, unpublished results.
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8) D. L. J. Clive, *J. Chem. Soc., Chem. Commun.*, 695 (1973).


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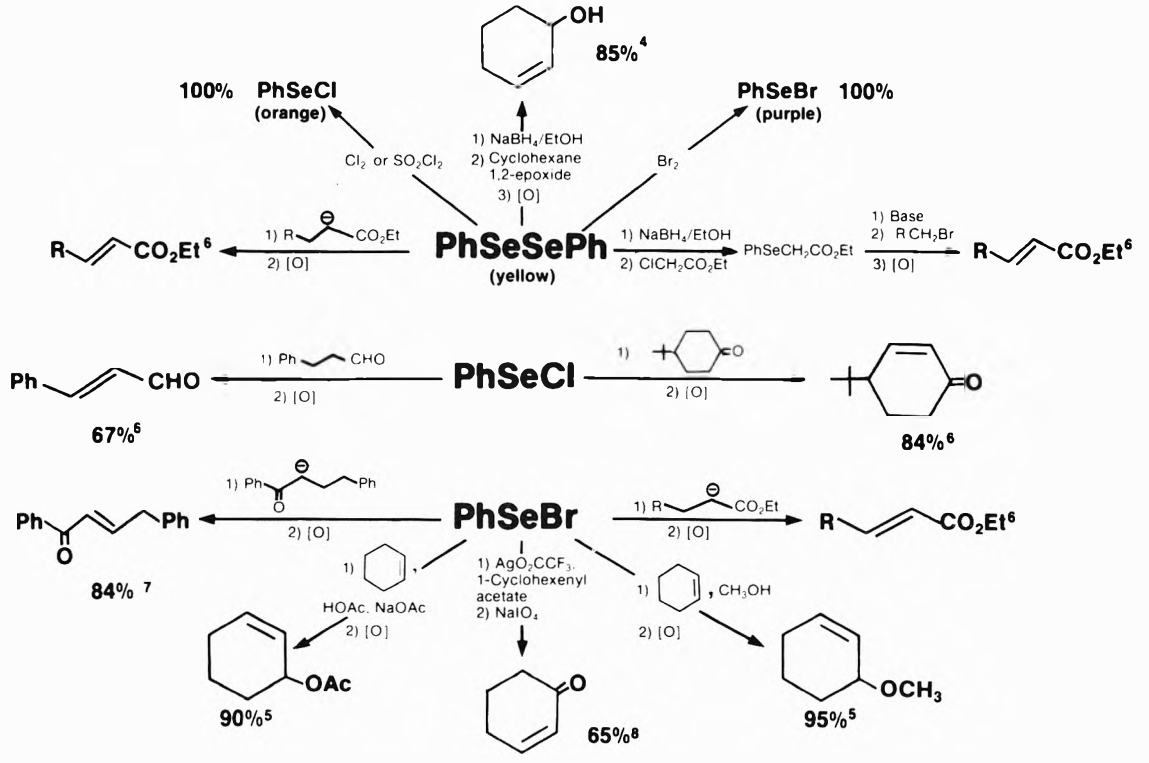


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