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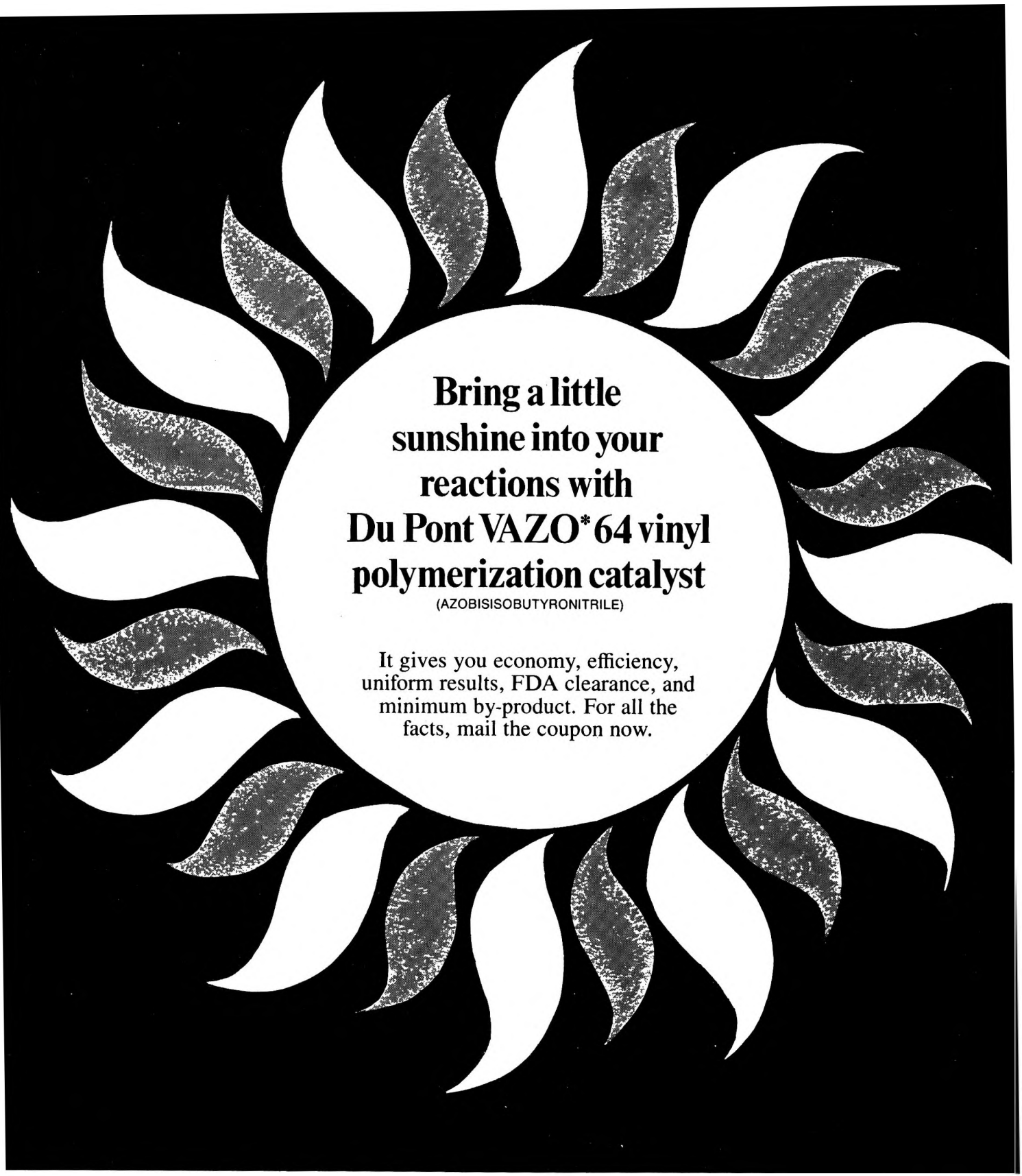

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VOLUME 35, NUMBER 10 OCTOBER 1970

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THE JOURNAL OF Organic Chemistry®

VOLUME 35, NUMBER 10

OCTOBER 1970

A New Synthesis of 3-Alkyl-2-cyclopenten-2-ol-1-ones

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Received March 12, 1970

A new synthesis of 3-methyl-2-cyclopenten-2-ol-1-one (**3**) and 3-ethyl-2-cyclopenten-2-ol-1-one (**4**) is described. Dieckmann cyclization of dimethyl adipate and alkylation in *N*,*N*-dimethylformamide gave keto esters **1a** and **1b**; chlorination in acetic acid produced dichloro keto esters **2a** and **2b** which were hydrolyzed and decarboxylated to afford **3** and **4** in 65–70% overall yields. This route has been demonstrated to be a convenient, general method for the preparation of other 3-alkyl-substituted 2-cyclopenten-2-ol-1-ones.

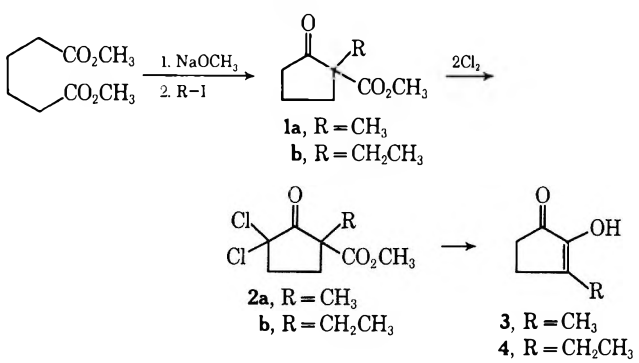
For some time 3-methyl-2-cyclopenten-2-ol-1-one (**3**) has been recognized, as a flavor constituent, for example, in coffee aroma[2] and maple flavor,[3] and the material has found commercial use when incorporated as a flavorant in various food items. It has been reported[2] as well that the homolog, 3-ethyl-2-cyclopenten-2-ol-1-one (**4**), is also a constituent of coffee aroma. In addition, it has been observed[4] that the ethyl compound **4** possesses organoleptic qualities superior to those of **3**.

Besides being available from natural sources, **3** has been synthesized by a variety of methods reported in the literature.[5] The preparation of **4** also has been reported.[5a,6] These methods have not been entirely satisfactory, particularly for larger scale preparations, owing to low overall yields and/or inaccessibility of starting materials.

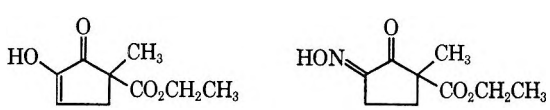
In this paper, we describe a convenient method for the preparation of 3-methyl-2-cyclopenten-2-ol-1-one and the more potent 3-ethyl-2-cyclopenten-2-ol-1-one, which is adaptable as a general method for the preparation of a variety of other alkyl-substituted 2-cyclopenten-2-ol-1-ones. Starting with dimethyl adipate, the route proceeds as outlined in Scheme I in excellent overall yield.

The Dieckmann cyclization of dimethyl adipate was conducted in *N*,*N*-dimethylformamide (DMF) solution and afforded the sodium enolate of 2-carbomethoxycyclopentanone which was alkylated with methyl or ethyl iodide giving **1a** and **1b** in high yield (85%).

SCHEME I



Sato, *et. al.*,[5b] have employed the corresponding ethyl ester of **1a**, 2-methyl-2-carbethoxycyclopentanone, as an intermediate in the synthesis of **3**. They were able to introduce the requisite α-carbonyl group with selenium dioxide to afford **5**, or with *n*-butyl nitrite to give oxime **6**. In both cases, the yields were low, as was the yield of **3** from the subsequent hydrolysis of **5** or **6**.



5 **6**

The possibility that a *gem*-dichloro group α to the carbonyl of **1a** and **1b** might serve as the necessary ketone precursor appeared attractive, especially from the standpoint of ease of preparation. Indeed, **2a** and **2b** were obtained in quantitative yield from the chlorination of **1a** and **1b** in acetic acid.

The hydrolysis of **2a** to **3** in 10% sulfuric acid was complete in 6 hr, but, under the same conditions, **2b** was

(1) Biochemical Research Laboratory, 3M Co., St. Paul, Minn.

(2) M. A. Gianturco, A. S. Giammarino, and R. G. Pitcher, *Tetrahedron*, **19**, 2051 (1963).

(3) V. J. Filipic, J. C. Underwood, and C. O. Willits, *J. Food Sci.*, **30**, 1008 (1965).

(4) (a) A. Torres and C. R. Stephens, unpublished results. (b) A. O. Pittet, P. Rittersbacher, and R. Muralidhara, presented to the Annual Meeting of the American Association of Cereal Chemists, Chicago, Ill., April 27–May 1, 1969.

(5) (a) K. Tonari, I. Ichimoto, H. Ueda, and C. Tatsumi, *J. Agr. Chem. Soc. Jap.*, **44**, 46 (1970). (b) K. Sato, S. Suzuki, and Y. Kojima, *J. Org. Chem.*, **32**, 339 (1967), and references therein. (c) K. Sato, Y. Kojima, and H. Sato, *ibid.*, **35**, 2374 (1970).

(6) M. A. Gianturco and P. Friedel, *Tetrahedron*, **19**, 2039 (1963).

unaffected. Extended periods of reflux served only to decompose this material to a black tar. After experimentation with various conditions, high yields (~80%) of **4** were obtained when **2b** was hydrolyzed in large volumes of 5% hydrochloric acid containing 15% acetic acid. Under these conditions, 12 hr were required for complete reaction. Although no attempt was made to optimize conditions for the hydrolysis of **2a** to **3**, good results were obtained with the use of 5% hydrochloric acid containing 5% acetic acid (~70% overall yield).

Surprisingly, 3-ethyl-2-cyclopenten-2-ol-1-one proved to be notably less stable on standing than the methyl homolog **3**. In *ca.* 6–8 hr after isolation, samples of the material (mp 42–44°) kept at room temperature had partially decomposed, forming viscous brown oils which contained a small amount of a new, more polar substance when examined by tlc. The nature of this decomposition reaction remains unexplained, but, fortunately, a facile method for preserving the product was found. In concentrated (80%) ethanol solution, **4** suffered no significant change over extended periods of time.[7]

Several other 3-alkyl-2-cyclopenten-2-ol-1-ones were prepared by this procedure as an indication of the generality of the method. These compounds, several of which were previously unreported, are listed in Table I with their physical constants and microanalyses. The yields reported are overall yields from dimethyl adipate to recrystallized products. In these experiments, the intermediates were not purified, and no attempts were made to optimize conditions in the final hydrolysis step.

TABLE I

3-Alkyl-2-cyclopenten-2-ol-1-one	Bp, °C (0.1 mm)	Mp, °C	—Calcd, %— C	H	—Found, %— C	C	Yield, %
Propyl[a]	75–80	54–56	68.54	8.63	68.71	8.75	30
Isobutyl	92–93	90–92	70.10	9.15	69.85	9.24	30
Benzyl[b]		98–100	76.57	6.43	76.28	6.61	26

[a] Lit.[5a] bp 107–109 (8 mm), mp 56–58°. [b] Alkylation with benzyl chloride.

Experimental Section

Melting points and boiling points are uncorrected. Vapor phase chromatographic (vpc) analyses were performed on a Varian Aerograph 90P-3 instrument using a 5-ft SE-30 column. The following spectrometers were used: nmr, Varian A-60 (TMS as internal standard); ir, Perkin-Elmer Model 21; uv, Cary Model 14. Microanalyses were performed by the analytical services group of these laboratories.

2-Methyl-2-carbomethoxycyclopentanone (1a).—To a stirred mixture of 56.4 g (1.06 mol) of sodium methoxide in 250 ml of dry *N,N*-dimethylformamide was added rapidly 174.0 g (1.0 mol) of dimethyl adipate. The clear brown solution was stirred and heated under vacuum (165 mm) while methanol and dimethylformamide were allowed to distil from the reaction. In ~45 min, the head temperature was constant at 105–108°, and the solution was cooled to ~35–40° under nitrogen. A solution of methyl iodide (170.4 g, 1.2 mol) in 150 ml of dimethylformamide was added with stirring to the solution while the temperature was maintained at ~40–55° with external cooling. After addition was complete, a heavy precipitate of sodium iodide formed and the temperature rose to 60–65°. The pasty mass was stirred rapidly with cooling until the pH had dropped to neutral (~45 min). An equal volume of dry ether was added, the solid was filtered and washed well with ether, and the ether and dimethylformamide of the combined filtrate and washings were evaporated on a rotary evaporator giving a brown oil. This was taken up in ether, washed with water, dried, and evaporated to afford a light yellow oil (~150 g). Distillation gave pure **1a** as a colorless oil (132.2 g, 85% yield), bp 85–90° (5 mm) [lit.[8] bp 100–106° (13 mm)].

2-Ethyl-2-carbomethoxycyclopentanone (1b).—The procedure was identical with that for the preparation of **1a** above except that 187.0 g (1.2 mol) of ethyl iodide was used in place of methyl iodide. Work-up gave 155 g of crude product which was distilled to afford 144.6 g (85%) of **1b**: bp 114–117° (17 mm); ir ($CHCl_3$) 5.70, 5.75 μ; nmr ($CDCl_3$) δ 3.68 (s, 3, CO_2CH_3), 2.00 (m, 8), 0.88 (t, 3, J = 7 Hz, CH_2CH_3).

Anal. Calcd for $C_9H_{14}O_3$: C, 63.51; H, 8.29. Found: C, 63.39; H, 8.53.

Dichloro Keto Ester 2a.—Chlorine was bubbled rapidly into a stirred solution of 132.2 g (0.85 mol) of **1a** in 1 l. of glacial acetic acid. The temperature of the exothermic reaction was held at 45–50° by means of a water bath. After 130 g (1.8 mol) of chlorine had been added, the addition was stopped and the solution stirred until the vpc of an aliquot indicated complete conversion to the dichlorinated material (~1 hr). Evaporation of the acetic acid gave a colorless oil which was distilled to afford **2a** (186.7 g, 98%): bp 90–95° (0.3 mm); ir ($CHCl_3$) 5.60, 5.75 μ; nmr ($CDCl_3$) δ 3.73 (s, 3, CO_2CH_3), 2.75 (m, 2), 2.15 (m, 2), 1.51 (s, 3, CH_3).

Anal. Calcd $C_8H_{10}Cl_2O_3$: C, 42.69; H, 4.48. Found: C, 42.88; H, 4.50.

Dichloro Keto Ester 2b.—The procedure was identical with that for the preparation of **2a** above. From 144.6 g (0.85 mol) of **1b** there was obtained 196.0 g (97%) of pure **2b**: bp 100–106° (0.3 mm); ir ($CHCl_3$) 5.55, 5.70 μ; nmr ($CDCl_3$) δ 3.72 (s, 3, CO_2CH_3), 2.70 (m, 2), 2.00 (m, 4), 0.92 (t, 3, J = 7 Hz, CH_2CH_3).

Anal. Calcd for $C_9H_{12}Cl_2O_3$: C, 45.21; H, 5.06. Found: C, 44.94; H, 5.05.

3-Methyl-2-cyclopenten-2-ol-1-one (3).—A mixture of 186.7 g (0.83 mol) of **2a**, 1800 ml of 5% HCl, and 100 ml of glacial acetic acid was stirred and heated under reflux until carbon dioxide evolution ceased (~6 hr). The yellow solution was cooled to ~15°, neutralized to pH ~5 with concentrated NaOH solution, and extracted with seven 500-ml portions of ethyl acetate. The combined extracts were washed with saturated sodium bicarbonate solution until basic and the organic layer was evaporated to dryness to afford a yellow solid. Recrystallization from ethyl acetate gave 63.8 g (58.4 g plus 5.4 g from a second crop) of pure **3** (68% yield, 57% overall yield from dimethyl adipate). The product had mp 104.5–106° and was identical in all respects with the authentic material: uv max (H_2O) 256 mμ (ε 12,400); nmr ($CDCl_3$) δ 6.98 (s, 1, **OH**), 2.39 (s, 4), 2.00 (s, 3, **CH_3**) [lit.[5b] mp 105–106°; uv max (EtOH) 257 mμ (ε 13,350); nmr δ 6.33 (s), 2.37 (s), 1.97 (s)].

In another preparation in which the intermediates were not purified by distillation, slightly higher overall yields were obtained. Thus 174.0 g (1.0 mol) of dimethyl adipate gave 71.0 g of **3** (63% yield) of mp 102–104°.

3-Ethyl-2-cyclopenten-2-ol-1-one (4).—A mixture of 196.0 g (0.83 mol) of **2b**, 3600 ml of 5% HCl, and 600 ml of glacial acetic acid was stirred and heated under reflux until the vpc of an aliquot showed the complete disappearance of **2b** (~12 hr). The clear brown solution was cooled to room temperature and extracted with five 700-ml portions of ethyl acetate. The combined extracts were evaporated to dryness to give a brown oil. Distillation afforded 81.9 g (79% yield, 65% overall yield from dimethyl adipate) of **4**: bp 73–75° (0.3 mm); uv max (CH_3OH) 258 mμ (ε 13,200); nmr ($CDCl_3$) δ 7.15 (s, 1, **OH**), 2.46 (m, 6), 1.17 (t, 3, J = 7 Hz, CH_2CH_3) [lit.[6] bp 65–68° (1 mm); uv max (EtOH) 259 mμ (ε 10,100)]. According to vpc, the product was >99% pure. Recrystallization from cold (−78°) hexane gave 70.0 g (2 crops) of white, crystalline **4** of mp 42–44°. This material was dissolved in 14 g of 95% ethanol immediately after drying to avoid decomposition.

Anal. Calcd for $C_7H_{10}O_2$: C, 66.64; H, 7.99. Found: C, 66.37; H, 8.06.

Slightly higher overall yields were realized in another preparation in which the intermediates were not purified by distillation.

(7) The author is indebted to Mr. Anibal Torres of these laboratories for making this observation.

(8) R. Mayer and P. Held, *Chem. Ber.*, **93**, 2750 (1960).

From 174.0 g (1.0 mol) of dimethyl adipate there was obtained 87.0 g (70% yield) of distilled 3-ethyl-2-cyclopenten-2-ol-1-one of >99% purity according to vpc.

Registry No.—**1b**, 25684-00-8; **2a**, 25684-01-9; **2b**, 25684-02-0; **3**, 80-71-7; **4**, 21835-01-8; Table I—propyl, 25684-04-2; isobutyl, 25684-05-3; benzyl, 25684-06-4.

Acknowledgment.—The author wishes to express his sincere appreciation to Mr. Philip A. Twomey for his competent technical assistance, and to Dr. John J. Beereboom for his interest and many helpful discussions. The author is also indebted to Dr. Charles R. Stephens who suggested the problem.

Diels–Alder Reaction of Acetoxy-1,3-dienes with Dimethyl Acetylenedicarboxylate and Chloromaleic Anhydride. A Synthesis of Benzene Derivatives

JOSEPH WOLINSKY* AND ROBERT B. LOGIN[1]

Department of Chemistry, Purdue University, Lafayette, Indiana 47907

Received January 29, 1970

Acyclic acetoxy-1,3-dienes, generated *in situ* from α,β-unsaturated aldehydes and ketones, undergo the Diels–Alder reaction with dimethyl acetylenedicarboxylate or chloromaleic anhydride to yield phthalic acid derivatives. Cyclic acetoxy-1,3-dienes and dimethyl acetylenedicarboxylate give bicyclo[2.2.2]octadiene derivatives. Heating the bicyclo[2.2.2]octadiene derivatives above 200° yields dimethyl acetoxyphthalates.

Acetoxy-1,3-dienes, preformed[2,3] or generated *in situ*,[4,5] readily participate in the Diels–Alder reaction. This paper describes a convenient one-step synthesis of phthalate derivatives by the reaction of acetoxy-1,3-dienes with dimethyl acetylenedicarboxylate or chloromaleic anhydride. This procedure complements and extends the methods for direct construction of benzene rings developed by Blanc[6] and Hill.[7]

Heating an acyclic α,β-unsaturated aldehyde or ketone in isopropenyl acetate, containing a catalytic amount of *p*-toluenesulfonic acid, with 1.5 equiv of dimethyl acetylenedicarboxylate affords a dimethyl phthalate derivative in good yield. Scheme I shows a pathway for the production of phthalate derivatives and lists representative examples used to demonstrate the scope of this reaction.

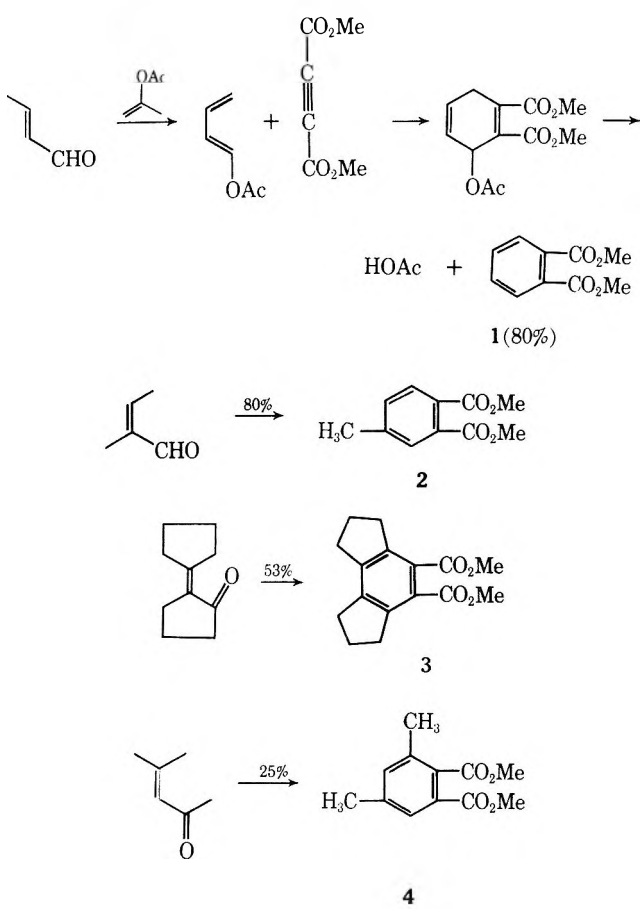
When chloromaleic anhydride is used as the dienophile the corresponding phthalic anhydride derivative is obtained (see Scheme II). The intermediate chloro acetate produced in this reaction must eliminate 1 equiv of acetic acid and hydrogen chloride to give the aromatic system.

Cyclic acetoxy-1,3-dienes were found to undergo the Diels–Alder reaction with dimethyl acetylenedicarboxylate, but not with chloromaleic anhydride. Dimedone gave a white, crystalline adduct **9** whose nmr spectrum exhibited singlets at 0.99, 1.11, 2.08, 2.11, and 3.78 ppm assigned to a *gem*-dimethyl group, two acetate groups, and two methoxy groups, respectively. The methylene group appeared as an AB-type quartet at 1.69 and 2.05 with a coupling constant of 12 Hz, while the bridgehead proton is observed at 3.48 and is coupled (J = 2 Hz) with the vinyl proton at 6.21 ppm.

Hydrolysis of adduct **9** gave keto acetate **10** and keto alcohol **11** which were readily separated by column chromatography. The C-7 methylene group of keto acetate **10** appeared as an AB pattern (J = 12 Hz) in which the upfield signal centered at 1.82 ppm was split into a doublet of doublets *via* long-range coupling (J = 2 Hz) through a "W" arrangement[8] with the endo proton at C-2, whose nmr signal was located at 2.72 ppm.

The structure of keto alcohol **11** was established by its conversion to keto acetate **10** by prolonged heating with acetic anhydride containing a catalytic amount of *p*-toluenesulfonic acid. The unique feature of the nmr

SCHEME I



* Author to whom correspondence should be addressed.

(1) David Ross Fellow, 1968–1969.

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(4) C. M. Cimarusti and J. Wolinsky, *J. Amer. Chem. Soc.*, **90**, 113 (1968).

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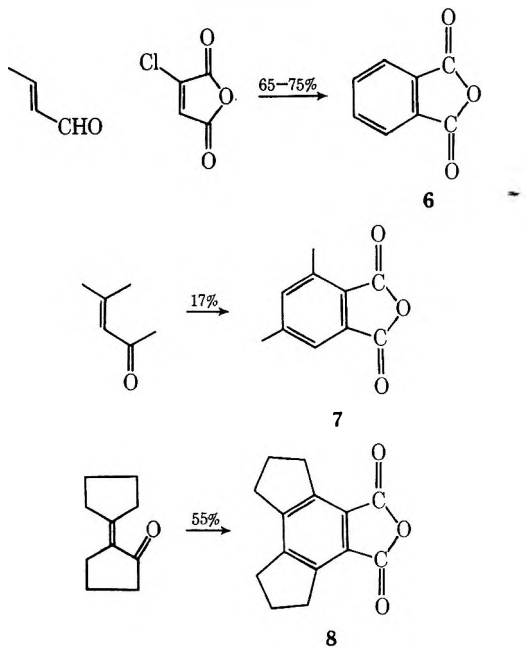
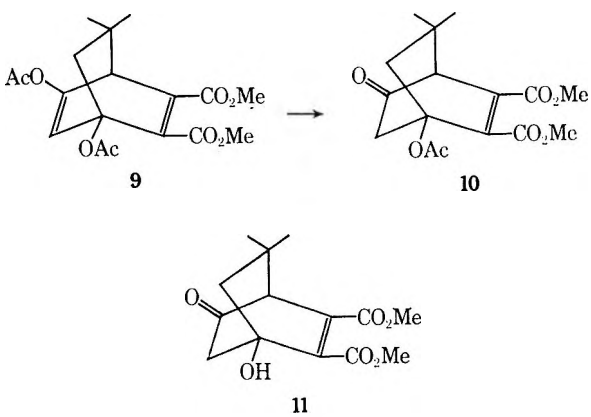
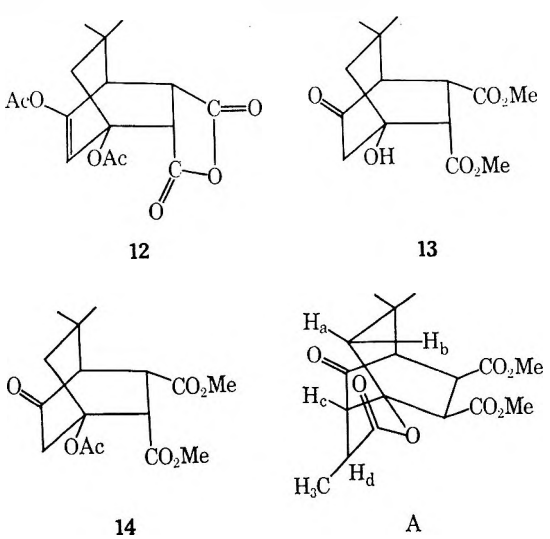
SCHEME II



spectrum of **11** was the appearance of a singlet for the C-7 methylene group at 1.69 ppm, instead of the multiplet shown by keto acetate **10**.



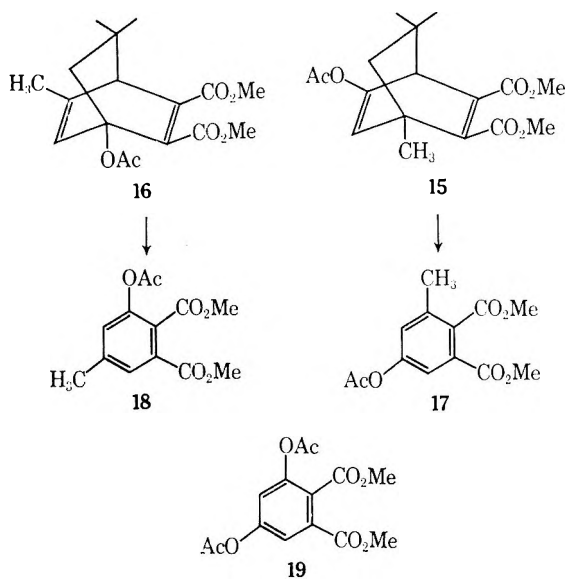
Hydrolysis of **12**[4] with hydrochloric acid in methanol gave the saturated keto alcohol **13** which was transformed into keto acetate **14** on heating with acetic anhydride containing *p*-toluenesulfonic acid. Again



it was found that the C-7 methylene signals of the acetate **14** and alcohol **13** are quite different. Acetate **14** displayed an AB-type doublet in which the high-field signal appeared as a doublet of doublets due to long range "W" type of coupling (J = 1.5 Hz), while the corresponding methylene signal in alcohol **13** appeared as a broad singlet.

A possible explanation for these observations is that the acetate group adopts a preferred conformation in which it is as far as possible from the carbonyl of the neighboring ester group. In this conformation A the protons labeled H_c and H_a are shifted downfield by the anisotropic effect of the carbonyl group, whereas protons H_b and H_d remain in their normal upfield location.

Isophorone reacted with dimethyl acetylenedicarboxylate to give a mixture of adducts **15** and **16** in a ratio of 23:77 on the basis of nmr analysis. Adducts **9** and the mixture of **15** and **16** undergo the Alder–Rickert reaction[9] when heated above 200° to give dimethyl acetoxyphthalate derivative **19** and a mixture of **17** and **18** in quantitative yield.



Experimental Section[10]

Dimethyl Phthalate.—A mixture of 1.82 g of crotonaldehyde, 5.5 g of dimethyl acetylenedicarboxylate, and 25 mg of *p*-toluenesulfonic acid in 30 ml of isopropenyl acetate was refluxed for 54 hr. The volatile reagents were removed under diminished pressure; the residue was added to saturated sodium bicarbonate solution and extracted with ether. The ether solution was washed with saturated salt solution and dried ($MgSO_4$). Distillation afforded 4 g (80%) of dimethyl phthalate, bp 140–145° (10 mm) [lit.[11] bp 137° (6 mm)].

Dimethyl 4-Methylphthalate.—A mixture of 2.02 g of tiglaldehyde and 5.12 g of dimethyl acetylenedicarboxylate was refluxed for 43 hr under the conditions described above and gave 4.0 g (80%) of dimethyl 4-methylphthalate, bp 125–137° (1 mm), n^{17}D 1.5100 (lit.[12] n^{26}D 1.5125).

Dimethyl Dicyclopentanophthalate (3).—The reaction of 2.74 g of 2-cyclopentylidenecyclopentanone with 3.9 g of dimethyl acetylenedicarboxylate, after heating 41 hr, gave on cooling 280 mg of **3**. Work-up of the reaction mixture in the usual manner and column chromatography on neutral alumina and elution with 25% ethyl acetate–hexane gave 2.38 g of **3**. A pure sample

(9) K. Alder and H. F. Rickert, *Justus Liebigs Ann. Chem.*, **524**, 180 (1936).

(10) Boiling and melting points are uncorrected. Microanalyses were performed by Dr. C. S. Yeh and associates.

(11) G. S. Gardner, and J. E. Brewer, *Ind. Eng. Chem.*, **29**, 179 (1937).

(12) A. Eschenmoser and H. Schinz, *Helv. Chim. Acta*, **33**, 171 (1950).

of **3** was obtained by recrystallization from methanol and showed mp 125–126° (lit.[13] mp 127°).

Dimethyl 3,5-Dimethylphthalate (4).—Heating 2.21 g of mesityl oxide with 4.8 g of dimethyl acetylenedicarboxylate under the usual conditions and chromatography of the crude product on neutral alumina gave, on elution with 30% ethyl acetate–hexane, 0.64 g (25%) of phthalate **4**: mp 54–55° (lit.[14] mp 54°); nmr ($CDCl_3$) 2.29 and 2.32 (s, 6, Me–), 3.83 and 3.88 (s, 6, –OMe), 7.2 and 7.6 (s, broad, 2, Ar H). A second fraction of 0.8 g was isolated and exhibited ir ($CHCl_3$) 5.75 and 6.19 μ; nmr ($CDCl_3$) 2.33 (s), 3.5–4.0 (m), 5.0–5.9 (m); tlc indicated a complicated mixture.

Phthalic Anhydride.—A solution of 6.9 g of crotonaldehyde, 13.2 g of chloromaleic anhydride, and 20 mg of *p*-toluenesulfonic acid in 30 ml of isopropenyl acetate was refluxed for 16 hr and yielded on work-up and chromatography on silica gel a 70% yield of phthalic anhydride, mp 129° (lit.[15] mp 127–128°).

3,5-Dimethylphthalic Anhydride (7).—A mixture of 1.67 g of mesityl oxide and 3.4 g of chloromaleic anhydride was refluxed for 60 hr under the usual conditions. The volume of the resulting solution was reduced to ~25 ml and ether was added causing 1.1 g of polymeric material to separate. The ether solution was concentrated and the resulting mixture was chromatographed on 100 g of silica gel. Elution with hexane–ether and recrystallization from hexane gave 0.5 g (17%) of anhydride **7**, mp 115–116° (lit.[16] mp 114.5–115.5°).

3,4,5,6-Dicyclopentanophthalic Anhydride (8).—The reaction of 7.5 g of 2-cyclopentylidenecyclopentanone with 13 g of chloromaleic anhydride under the usual conditions gave, on cooling and addition of ether, 9 g (55%) of solid which was recrystallized from acetic anhydride and showed mp 265–266° (lit.[13] mp 266°).

Dimethyl 1,3-Diacetoxy-8,8-dimethylbicyclo[2.2.2]oct-2,5-diene-5,6-dicarboxylate (9).—A solution of 7.0 g of dimedone and 10 g of dimethyl acetylenedicarboxylate was refluxed for 24 hr in the usual manner and work-up gave 20.4 g of a viscous orange oil. A 2-g portion of this oil was chromatographed on 80 g of silica gel and eluted with hexane–ether–ethyl acetate to give 0.835 g of adduct **9**. Several recrystallizations from hexane gave an analytical sample: mp 96.5–98°; ir ($CHCl_3$) 5.7, 6.05, and 6.15 μ; nmr ($CDCl_3$) 0.99 and 1.11 (s's, 6, CH_3CCH_3), 1.65 and 2.05 (AB-type q, 2, J = 11 Hz, $-CH_2-$), 2.08 and 2.11 (s's, 6, $-OCOCH_3$), 3.48 (d, 1, J = 2 Hz, –CH), 3.78 (s, 6, $-OCH_3$), 6.21 (d, 1, J = 2 Hz, C=C–H); mass spectrum (75 eV) m/e (rel intensity), no molecular ion, 310 (9), 279 (14), 268 (57), 237 (14), 226 (85), 195 (47), 194 (100), 136 (42), 69 (52), 57 (22), 56, 55 (24), 43 (96), and 41 (87).

Anal. Calcd for $C_{18}H_{22}O_8$: C, 59.01; H, 6.05. Found: C, 59.19; H, 6.32.

Hydrolysis of Adduct 9.—A solution of 1 g of adduct **9** in 40 ml of 50% aqueous methanol containing 10 ml of 0.1 *N* hydrochloric acid was refluxed for 2 hr. The mixture was poured into salt solution and extracted with ether. The ether extracts were dried ($MgSO_4$) and evaporated to give 900 mg of an oil. The oil was chromatographed on 75 g of silica gel. Elution with 10% ether–hexane gave 0.36 g of keto acetate **10** which was recrystallized from benzene–hexane and displayed mp 106–108°; ir ($CHCl_3$) 5.75 and 6.05 μ; nmr ($CDCl_3$) 1.02 and 1.15 (s's, 6, CH_3CCH_3), 2.04 (s, 3, $OCHCH_3$), 1.82 (d, of d, 1, J = 12 Hz and J = 2 Hz, C^7-H), 2.35 (d, 1, J = 12 Hz, C^7-H), 2.72 (d, 1, J = 2 Hz, C^2-H), 2.78 (s, 1, –CH), 3.32 (s, 1, C^4-H), 3.78 and 3.80 (s's, 6, $-OCH_3$); mass spectrum (75 eV) m/e (rel intensity) 293 (22) (p − 31), 264 (52), 250 (53), 249 (79), 235 (83), 219 (26), 217 (90), 208 (81), 206 (39), 203 (39), 194 (39), 193 (60), 175 (27), 91 (25), and 43 (100).

Anal. Calcd for $C_{16}H_{20}O_7$: C, 59.25; H, 6.22. Found: C, 59.41; H, 6.22.

Further elution of the chromatography column gave 0.41 g (50%) of keto alcohol **11** which crystallized after standing for several months. An analytical sample was obtained by recrystallization from ethyl acetate–hexane and showed mp 78–79°; ir ($CHCl_3$) 5.8 and 6.12 μ; nmr ($CDCl_3$) 1.0 and 1.11 (s's, 6, $-CCH_3$), 1.69 (s, 2, $-C^7-H_2$), 2.33 (s, 2, $-C^2-H_2$), 3.31 (s, 1, $-C^4$-H), 3.78 and 3.85 (s's, 6, $-OCH_3$); mass spectrum (75 eV) m/e (rel intensity) 282 (4), 264 (8), 251 (20), 249 (28), 240 (63), 235 (53), 209 (80), 208 (100), 194 (41), 193 (64).

Anal. Calcd for $C_{14}H_{18}O_6$: C, 59.57; H, 6.43. Found: C, 59.70; H, 6.21.

When 10 g of adduct **9** was refluxed for 48 hr in 100 ml of methanol containing 2 ml of concentrated hydrochloric acid there was obtained 7.4 g (100%) of an oil identical with keto alcohol **11**. This oil also crystallized on prolonged standing. A 2.4 g sample of keto alcohol **11** was refluxed for 72 hr in 30 ml of acetic anhydride containing 100 mg of *p*-toluenesulfonic acid. On work-up an oil was obtained which gradually crystallized. Recrystallization from benzene–hexane (Norit) gave 2.5 g of keto acetate **10**, mp 106–108°.

Dimethyl 1-Hydroxy-8,8-dimethylbicyclo[2.2.2]octan-3-one-5,6-dicarboxylate (13).—A solution of 2.85 g of adduct **12**[4] in 50 ml of methanol containing 2 ml of concentrated hydrochloric acid was refluxed for 20 hr. Water (30 ml) was added and the solution heated another 5 hr. Work-up gave 1.60 g of **13** which was recrystallized from ethyl acetate–hexane and showed mp 105–107°; nmr ($CDCl_3$) 1.0 and 1.21 (s's, 6, CH_3CCH_3), 1.05 (d, 2, $-C^7-H_2$), 2.01 and 2.32 (d of d, 1, J = 19 Hz, J = 2 Hz, exo-C^2-H), 2.1 (d, 1, J = 3 Hz, $-C^4$-H), 2.89 and 3.09 (d of d, 1, J = 12 Hz, C^8-H), 3.0 and 3.32 (d, 1, J = 19 Hz, endo-C^2-H), 3.49 (d, 1, J = 3 Hz, $-C^5$-H), 3.59 and 3.61 (s's, 6, $-OCH_3$), and 4.42 ppm (s, 1, –OH); mass spectrum (75 eV) m/e (rel intensity) 284 (37), 253 (44), 224 (16), 221 (25), 169 (60), 145 (45), 140 (87), 125 (100), 113 (69), 95 (38), 83 (40), 81 (29), and 69 (33).

Anal. Calcd for $C_{14}H_{20}O_6$: C, 59.14; H, 709. Found: C, 59.00; H, 6.85.

Dimethyl 1-Acetoxy-8,8-dimethylbicyclo[2.2.2]octan-3-one-5,6-dicarboxylate (14).—A solution of 600 mg of **13** in 20 ml of acetic anhydride containing 10 mg of *p*-toluenesulfonic acid was refluxed for 24 hr and after cooling was added to 50 ml of saturated sodium bicarbonate solution. The resulting mixture was extracted with ether. The ether solution was dried and evaporated to give 600 mg of **14** which was recrystallized from hexane and showed mp 116–118°. This sample of acetate **14** did not depress the melting point of an authentic sample of **14**.[4]

Dimethyl 1-Acetoxy-3,8,8-trimethylbicyclo[2.2.2]octa-2,5-diene-5,6-dicarboxylate (16) and Dimethyl 3-Acetoxy-1,8,8-trimethylbicyclo[2.2.2]octa-2,5-diene-5,6-dicarboxylate (15).—The reaction of 9.4 g of isophorone and 14.7 g of dimethyl acetylenedicarboxylate conducted for 48 hr in the usual manner gave 28.1 g of an orange oil. Column chromatography failed to separate **15** and **16** which were indicated to be present in a 77:23 ratio by nmr analysis: ir ($CHCl_3$) 5.8, 6.02, 6.15; nmr ($CDCl_3$) 0.95, 1.02, and 1.05 (s's, CH_3), 1.84 (d, J = 1.8 Hz, $C=CCH_3$), 2.07 and 2.10 (s's, $OCOCH_3$), 3.71 (s, $-OCH_3$), 5.72 (d, J = 2 Hz, C=CH), and 6.0 (m, –C=CH).

Anal. Calcd for $C_{17}H_{22}O_6$: C, 63.34; H, 6.88. Found: C, 62.95; H, 6.89.

Heating a sample of this mixture above 200° gave a quantitative yield of a mixture of **17** and **18**: ir ($CHCl_3$) 5.61 and 5.75 μ; nmr ($CDCl_3$) 2.23, 2.26, 2.33, and 2.8 (s's, $-OCOCH_3$, CH_3Ar), 3.85 and 3.9 (s, $-OCH_3$), 7.17 and 7.58 (m, Ar H); mass spectrum (75 eV) m/e (rel intensity) 266 (11), 235 (18), 225 (11), 224 (84), 193 (74), 192 (100), 162 (18), 134 (68), 133 (13).

Anal. Calcd for $C_{13}H_{14}O_6$: C, 58.64; H, 5.30. Found: C, 58.41; H, 5.02.

Dimethyl 3,5-Diacetoxphthalate (19).—Heating a sample of adduct **9** above 200° gave a quantitative yield of phthalate **19**: mp 77.5–80.5°; ir ($CHCl_3$) 5.62 and 5.75 μ; nmr ($CDCl_3$) 2.25 and 2.28 (s's, 6, $OCOCH_3$), 3.88 and 3.90 (s's, 6, $-OCH_3$), 7.22 and 7.62 (AB q, J = 2 Hz, Ar H). The mass spectrum of **19** was essentially identical with that of adduct **9**.

Anal. Calcd for $C_{14}H_{14}O_8$: C, 54.20; H, 4.55. Found: C, 54.45; H, 4.82.

Registry No.—**9**, 25864-63-5; **10**, 25864-64-6; **11**, 25864-65-7; **13**, 25864-66-8; **15**, 25864-67-9; **16**, 25864-68-0; **17**, 25864-69-1; **18**, 25864-70-4; **19**, 25907-95-3; dimethyl acetylenedicarboxylate, 762-42-5; chloromaleic anhydride, 96-02-6.

(13) D. S. Greidinger and D. Ginsburg, *J. Org. Chem.*, **22**, 1406 (1957).

(14) K. Alder, R. Munders, W. Krane, and P. Wirtz, *Justus Liebigs Ann. Chem.*, **627**, 59 (1959).

(15) L. Carius, *ibid.*, **148**, 62 (1868).

(16) H. Pines and R. H. Kozlonski, *J. Amer. Chem. Soc.*, **78**, 3776 (1956).

Stereochemistry of the Addition of *t*-Butyl Hydroperoxide to Cyclopentadiene

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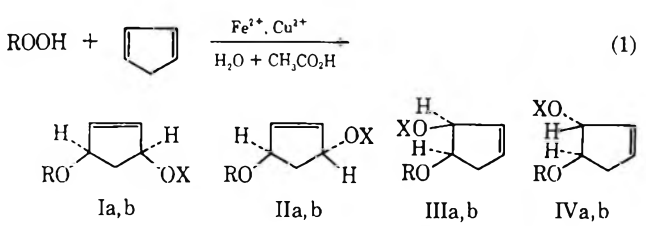
The isomeric addition products of the reaction of *t*-butyl hydroperoxide to cyclopentadiene are reported. The major isomeric adducts were isolated by preparative gas chromatography. Characterization of the adducts was accomplished by the use of nmr and ir spectroscopy, and the major products were shown to be the *cis*- and *trans*-1,4 adducts, with little of the corresponding 1,2 adducts detected. An analysis of the nmr spectra and stereochemical assignments is given and the reaction is discussed.

Addition reactions of cyclic conjugated dienes, other than Diels–Alder reactions, have not been extensively studied.[1] Structural analyses of product geometries are necessary as a first step in understanding the mechanisms of these reactions. Bromination studies of cyclopentadiene in petroleum ether and in chloroform were reported some years ago,[2] and it was shown that *cis*-3,5-dibromocyclopentene (*cis*-1,4 adduct) was an important direct product of these reactions. The *trans*-1,4 adduct was also obtained, but in impure form. Electrophilic addition of *t*-butyl hypochlorite to cyclopentadiene in reactive hydroxylic solvents has been reported to give mainly the *trans*-1,4 adducts, although isomeric mixtures were obtained.[3]

As part of a study of addition reactions to cyclic dienes, the reaction of *t*-butyl hydroperoxide to cyclopentadiene in aqueous acetic acid in the presence of ferrous sulfate and cupric acetate was carried out. The stereochemical course of this addition reaction is reported in this paper. Adduct structures which could be expected to be formed in this reaction are shown in eq 1. A complex mixture of eight components includ-



a, X = H; b, X = $-COCH_3$; R = $(CH_3)_3C-$

ing both alcohol and acetate adducts is possible. It was therefore desirable to simplify such mixtures by converting acetate groups to alcohols without affecting the stereochemical configurations of the adducts.

(1) For a discussion, see A. Liberles, "Introduction to Theoretical Organic Chemistry," Macmillan, New York, N. Y., 1968, pp 413–415.

(2) W. G. Young, H. K. Hall, Jr., and S. Winstein, *J. Amer. Chem. Soc.*, **78**, 4338 (1956).

(3) R. Riemschneider and R. Nehring, *Justus Liebigs Ann. Chem.*, **660**, 41 (1962); R. Riemschneider and R. Nehring, *Monatsh. Chem.*, **92**, 744 (1961).

Results and Discussion

Cyclopentadiene was allowed to react with *t*-butyl hydroperoxide in aqueous acetic acid in the presence of ferrous sulfate and cupric acetate. The temperature was kept below 15°. Details of the reaction are given in the Experimental Section. An infrared spectrum of the crude product clearly indicated the presence of both alcohol and acetate adducts. In order to simplify analysis of the mixture, it was reduced with lithium aluminum hydride, thus converting the acetate to alcohol adducts and lowering the number of potential isomers to four. This reduction has an additional advantage since the alcohols should be less prone to rearrangement during subsequent separation procedures than the corresponding acetates. The yield of crude adducts based on the hydroperoxide used and on the amount of adduct obtained after reduction was about 65%.

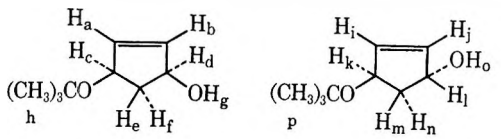
Distillation of the reduced adduct mixture followed by gas chromatographic analysis revealed the presence of four components, two present in major amounts and two in only minor amounts. The major components were isolated in pure form by preparative gas chromatography and shown to be the *cis*- and *trans*-1,4 adducts, Ia and IIa, respectively. The *cis*-1,4 adduct Ia represented 33% and the *trans*-1,4 adduct IIa, 53% of the total mixture (normalized to 100%). Thus the predominant product of the reaction was that corresponding to 1,4 addition to the diene.

Structural assignments of the *cis*- and *trans*-1,4 adducts, Ia and IIa, were made from their 100-MHz nmr spectra. Spectral parameters for isomer Ia, based on a first-order analysis, are listed in Table I.

In the nmr spectrum of isomer Ia, protons H_e and H_f are a pair of double triplets reflecting the large geminal and the two equivalent *cis* (or *trans*) vicinal coupling constants. The higher field proton H_e was assigned to that proton *cis* to the two ring substituents on the basis of the large diamagnetic shift it experiences due to the anisotropy of the two eclipsed C–O bonds and by its smaller *trans* vicinal coupling with the methine protons H_c and H_d. Conversely, the downfield methylene proton H_f experiences a paramagnetic shift and exhibits the larger *cis* vicinal coupling with the adjacent methine

Table I

Nmr Spectral Parameters for Isomers Ia and IIa



Ia IIa

Isomer	δ, ppm (J[a])					
	$H_{a,b}$	$H_{c,d}$	H_e	H_f	H_g	H_h
Ia	5.78[b]	4.44 m[c]	1.44 dt	2.60 dt	4.15 s	1.19 s

Isomer	δ, ppm (J[d])				
	$H_{i,j}$	$H_{k,l}$	$H_{m,n}$	H_o	H_p
IIa	5.78[e]	4.79	1.88	4.44 s	1.17 s

[a] $J_{a,b}$ = 5.8 Hz; $J_{e,f}$ = 13.5; $J_{c,f} = J_{d,f}$ = 7.2; $J_{c,e} = J_{d,e}$ = 5.0. [b] Center of multiplet, ($|\delta_{H_a} - \delta_{H_b}|$ = 0.15 ppm). [c] Center of multiplet. [d] $|J_{m,l} + J_{m,k}| = |J_{n,l} + J_{n,k}|$ = 10.0 Hz. [e] Center of multiplet, ($|\delta_{H_i} - \delta_{H_j}|$ = 0.04 ppm).

protons.[4] These stereochemical assignments based on chemical shifts of the methylene protons are in accord with data on *cis*- and *trans*-cyclopentene-3,5-diols and dibenzoates.[5] This data showed that the methylene proton *cis* to a C–O bond is at higher field relative to the *trans* proton. In the *trans*-diol or dibenzoate, the methylene proton signal appears at an intermediate position since the protons are both *cis* and *trans* to C–O bonds. Further supporting data for these assignments may be found in a comparison of chemical shifts in the nmr spectra of acenaphthalene and its hydroxy and acetoxy derivatives.[6]

The methine protons H_c and H_d have essentially the same chemical shift and show a symmetrical pattern of four broadened peaks centered at 4.44 ppm. The olefinic protons H_a and H_b are not equivalent and appear as a typical AB pattern with, however, each AB peak further split owing to weak coupling with the methine protons H_c and H_d. No appreciable coupling of the olefinic protons occurs with H_e and H_f, as is evident from the sharpness of the latter signals.

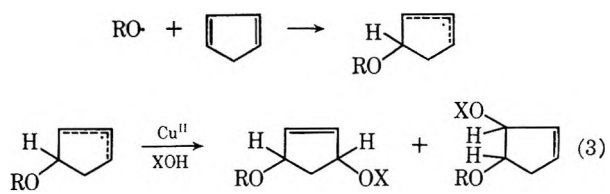
In the *trans* isomer IIa, the methylene protons H_m and H_n are accidentally chemically equivalent as are the methine protons H_k and H_l. These protons appear as a deceptively simple AA′XX′ pattern[7] and the chemical shifts and sum of the *cis* and *trans* coupling constants are listed in Table I. In contrast to the *cis* isomer Ia the olefinic protons H_i and H_j show no appreciable coupling with the other ring protons. This difference is probably due to conformational effects in the two isomers. The methylene protons H_m and H_n have chemical shifts intermediate between those observed for the methylene protons of isomer Ia, since each methylene proton is both *cis* and *trans* to a C–O bond.[5,6]

One of the minor components was isolated by preparative gas chromatography. Further gas chromatographic analysis of this component indicated that it was about 95% pure and contained 5% of the second minor component. This latter component, which constituted 7% of the total adduct mixture could not be separated. The minor component isolated constituted about 6% of the total mixture. Analysis by nmr suggested that it was a 1,2 adduct but its exact isomeric composition was not determined. The infrared spectrum was very similar to those of the major adducts, providing further evidence for its isomeric nature.

In the presence of ferrous ion, *t*-butyl hydroperoxide decomposes to *t*-butoxy radicals[8] (eq 2) which add to

$$(CH_3)_3C{-}OOH + Fe^{II} \longrightarrow (CH_3)_3C{-}O\cdot + Fe^{III}OH \quad (2)$$

the diene[9] to give intermediate allylic radicals. The intermediate radicals are oxidized by cupric ion[10,11] and in the presence of a reactive hydroxylic solvent the latter is incorporated in the adduct (eq 3).



(3)

cis + *trans*

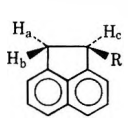
R = $(CH_3)_3C$–; X = H or CH_3CO–

Cupric ion oxidation of the allylic radicals may involve formation of an allylic carbonium ion which is then attacked by solvent, or may involve a transition state with considerable cationic character (electron transfer).[10,11] Contrary to additions of *t*-butyl hydroperoxide to acyclic dienes[10] in which the predominant adduct formed corresponds to 1,2 addition, with cyclopentadiene the 1,4 adducts are by far the predominant products. No thermal isomerization during distillation or gas chromatographic analysis occurred since the separated *t*-butoxy adducts were subjected to further gas chromatographic analysis without rearrangement. Since the reaction was carried out under mild conditions similar to those used in acyclic systems[10] where the thermodynamically less stable adducts were formed, it seems likely that kinetic control was in effect. Further work will be carried out in order to more fully define the mechanism of this addition reaction. The absence of appreciable amounts of the 1,2 adducts may be due to steric hindrance to solvation of the cation by the *t*-butoxy group in the transition state leading to 1,2 adduct.

(4) In cyclopentene systems *cis* vicinal coupling is generally regarded as larger than *trans*. For instance, J_{cis} is 7.4 Hz while J_{trans} is 4.6 Hz in cyclopentene, which is known to be puckered. See G. W. Ratjens, Jr., *J. Chem. Phys.*, **36**, 3401 (1962). The difference in coupling constants is magnified in the more planar *cis*-3,5-dibromocyclopentene, J_{cis} = 6.9 Hz and J_{trans} = 1.5 Hz. See H. J. Jakobsen, *Tetrahedron Lett.*, No. 21, 1991 (1967).

(5) H. Z. Sable, W. M. Ritchey, and J. E. Nordlander, *Carbohyd. Res.*, **1**, 10 (1965).

(6) In the acenaphthalene derivatives V_a and V_b, a proton *cis* to the C–O bond experiences an upfield shift while the *trans* proton is shifted considerably downfield relative to V: C. K. Fay, S. Sternhell, and P. W. Westerman, unpublished work; L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Elmsford, N.Y., 1969, p 233.



	R	^4H_a	^4H_b
V	H	3.36	3.36
V_a	OH	3.70	3.14
V_b	$OCOCH_3$	3.72	3.26

(7) See, for example, E. D. Becker, *J. Chem. Educ.*, **42**, 591 (1965).

(8) A. Tobolsky and R. Mesrobian, "Organic Peroxides," Interscience, New York, N. Y., 1954, p 95.

(9) M. S. Kharasch, F. S. Arimoto, and W. Nudenberg, *J. Org. Chem.*, **16**, 1556 (1951).

(10) J. K. Kochi, *J. Amer. Chem. Soc.*, **84**, 2785 (1962).

(11) For reviews of Kochi's work, see also J. K. Kochi, *Rec. Chem. Progr.*, **27**, No. 4, 207 (1966); J. K. Kochi, *Science*, **155**, 415 (1967).

This explanation is tentative at this stage. The observation of predominant 1,4 addition is in accord with the electrophilic addition of *t*-butyl hypochlorite to cyclopentadiene, a reaction which also involves a cationic intermediate.[3]

Experimental Section

t-Butyl hydroperoxide (Monomer–Polymer Laboratories) was distilled (helix-packed column), and the fraction, bp 38–39° (20 mm), was used. Gas chromatographic analyses were carried out with a Hewlett–Packard 5750 instrument using a 10-ft 10% Carbowax 20M column at 165°. Gas chromatographic separations were carried out with a Hewlett–Packard 5798A preparative attachment unit. The nmr spectra were run in carbon tetrachloride solution on a Varian HA-100 instrument. Elemental analysis was carried out by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y.

Reaction of *t*-Butyl Hydroperoxide with Cyclopentadiene.—A solution of ferrous sulfate ($FeSO_4 \cdot 7H_2O$, 0.25 mol) in 125 ml of distilled water was added dropwise over 90 min to a well-stirred mixture of cupric acetate (monohydrate, 0.25 mol), *t*-butyl hydroperoxide (22.5 g, 0.25 mol), freshly distilled cyclopentadiene (20 g, 0.30 mol), and 275 ml of glacial acetic acid. The temperature of the reaction mixture was kept below 15° during this addition. The reaction mixture was stirred for 30 min with continued ice-bath cooling, then poured into 1 l. of ice water. The product was extracted with methylene chloride, and the extract was washed with sodium bicarbonate and water and dried over anhydrous magnesium sulfate. The product was a clear yellow liquid, 35.3 g. An ir spectrum was consistent with an alcohol and acetate adduct mixture showing O—H str, also acetate C=O str (1742 cm^{-1}) and C—O str (1250 cm^{-1}), as well as strong ether absorption (1075 cm^{-1}).

Reduction of *t*-Butyl Hydroperoxide Adduct Mixture.—The crude adduct mixture (30.0 g) was reduced with lithium aluminum hydride (3 g) in diethyl ether. The reaction mixture was hydrolyzed under alkaline conditions[12] giving 21.3 g of product. The crude reduction product (20.1 g) was distilled at reduced pressure (0.7 mm) through an annular Teflon spinning-band column and the following fractions collected: (1) bp 53–64°, 2.2 g; (2) bp 56–66°, 8.1 g; (3) bp 66–66.5°, 5.3 g; (4) bp 48–56° (0.1 mm), 0.3 g; residue 2.4 g. Fractions 1 and 2 had ir spectra consistent with the expected adducts but showed weak carbonyl absorption (C=O str, 1730 cm^{-1}) indicating the presence of some unreduced acetate adduct. An ir of fraction 3 was consistent with the expected alcohol adduct (O—H str, 3390 cm^{-1}, ether C—O str, 1053 cm^{-1}, both very strong). Fraction 4 was identical with 3. Analysis of each fraction was done by gc. Fraction 3 was an isomeric adduct mixture, and this was further verified by elemental analysis.

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found (fraction 3): C, 69.44; H, 10.61.

Pure isomers shown to be *cis*- and *trans*-1,4 adducts Ia and IIa were separated from fraction 3 by preparative gc and these were shown by further analytical gc to be homogeneous and to correspond exactly to the two peaks present in the gc of fraction 3. The structure of each of these adducts was confirmed by nmr as discussed (*vide supra*). The ir spectra of the separated 1,4 adducts Ia and IIa were very similar and consistent with the expected adduct structures. *trans* adduct IIa showed O—H str at 3390 cm^{-1}, ether C—O 1053 cm^{-1}, =CH str 3067 cm^{-1}. Similar bands were present in the spectrum of Ia.

Anal. Calcd for $C_9H_{16}O_2$: C, 69.19; H, 10.32. Found (*trans* adduct): C, 69.19; H, 10.49.

There was insufficient *cis* adduct for C, H analysis. Further gc analysis of a weighed mixture of Ia and IIa showed that the area per cent calculated by the peak height width at half-height method agreed with the weight per cent as expected for similar isomers.

Registry No.—*t*-Butyl hydroperoxide, 75-91-2; 1,3-cyclopentadiene, 542-92-7; Ia, 25594-22-3; IIa, 25594-23-4.

Acknowledgment.—The authors would like to thank Professor L. M. Jackman of Pennsylvania State University for his constructive suggestions. A portion of the work was done under a City University Doctoral Faculty Research Grant (H. H.).

(12) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 584.

Oxidative Cleavage of Cyclopropanes. VII. Kinetics of the Cleavage of Some Bicyclo[*n*.1.0]alkanes and Spiro[*n*.2]alkanes by Thallium Triacetate[1,2]

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The rates of cyclopropane ring cleavage of spiro[5.2]octane, spiro[4.2]heptane, and fluorene-9-spirocyclopropane by thallium triacetate in acetic acid at 17.95° have been determined. Bicyclo[5.1.0]octane, bicyclo[4.1.0]heptane, and bicyclo[3.1.0]hexane cyclopropane ring cleavages were studied at 29.30 and 50.05°. The kinetics of the cleavage reactions were overall second order, first order in each reactant. Stability of the incipient carbonium ion is the rate-controlling feature in the case of the spiroalkanes. However, steric features of each molecule are noted in the spiroalkanes and the steric factor becomes preeminent in the case of the bicycloalkanes.

The rates of cyclopropane ring cleavage by mercury(II) acetate,[3] thallium(III) acetate,[4] and lead(IV) acetate[5] have been determined in acetic acid using arylcyclopropanes as reference substrates. In addition to establishing an order of reactivity of $Tl(OAc)_3 > Hg(OAc)_2 > Pb(OAc)_4$ these studies have yielded information concerning the selectivity of the metal acetates as reflected by the magnitude of ρ^+. The ρ^+ values for $Tl(OAc)_3$, $Hg(OAc)_2$, and $Pb(OAc)_4$ are -4.3, -3.2, and -1.7, respectively. Therefore not only is $Tl(OAc)_3$ the most reactive of the metal acetates studied, it also is the most selective. While the mechanistic interpretation of these data has only been partially successful it is clear that from an experimental viewpoint $Tl(OAc)_3$ is a reagent that should be studied further in a variety of oxidation reactions of organic molecules.

Our kinetic studies of the oxidative cleavage of cyclo-

(1) Paper VI: A. South, Jr., and R. J. Ouellette, *J. Amer. Chem. Soc.*, **90**, 7064 (1968).

(2) This research was supported by Grant GP6778 from the National Science Foundation.

(3) R. J. Ouellette, R. D. Robins, and A. South, Jr., *ibid.*, **90**, 1619 (1968).

(4) Paper VI.[1]

(5) R. J. Ouellette, D. Miller, A. South, Jr., and R. D. Robins, *ibid.*, **91**, 971 (1969).

propanes have dealt exclusively with arylcyclopropanes in which only one of the two nonequivalent bonds is cleaved. This selective cleavage controlled by the stability of the incipient cationic center generated in the electrophilic attack of the metal was a convenient first approach. However, there are other cyclopropanes in which the relative rates of attack of the electrophile at two possible sites may be more comparable. Under such conditions it should be possible to evaluate the effect of other structural features such as ring strain of the cyclopropane and steric accessibility to the electrophile on the rate of reaction. Two classes of compounds were chosen as likely candidates with which to study rate-controlling features other than that which results in stability of a cationic center. These classes are the spiro[*n*.2]alkanes and the bicyclo[*n*.1.0]alkanes represented by general structures **1** and **2**, respectively.

1 **2**

In the case of the spiro[*n*.2]alkanes a single bond would be expected to cleave as a reflection of the great difference in stability between a primary and a tertiary cation. In short a strong tendency toward Markovnikov addition should result. Any difference in the rate of cleavage of the ring bond will reflect in part the relative stability of the tertiary cationic center on a ring of variable size. Other features such as ring strain and steric accessibility of the bonds should be evident once the cationic stability factor has been corrected for on the basis of appropriate reference reactions. In the case of the bicyclo[*n*.1.0]alkanes the product studies indicate that both of the possible ring bonds are cleaved.[6] Furthermore, the ratio of the products resulting from cleavage of each bond is a function of ring size. From the product studies previously reported it is possible to calculate rates for individual cleavages of the two bonds from the observed rate constants. Thus structural features controlling the rates of external and internal bond cleavage can be evaluated.

Results

We have shown that the oxidation reactions of thallium triacetate can be followed by quenching in excess aqueous 5% potassium iodide solution and then back-titrating the triiodide formed with standard sodium thiosulfate.[4,7] When the excess potassium iodide solution is added to the reaction mixture, a yellow heterogeneous mixture is obtained which turns dark upon addition of the starch indicator. This mixture is then titrated with standardized sodium thiosulfate to a pure yellow heterogeneous mixture of thallous iodide.

Thallium triacetate forms a double salt with thallous acetate which arises from the decomposition of the organothallium intermediate.[4] The formation of the double salt causes a rapid decrease in the rate of cleavage of cyclopropanes.

$$Tl(OAc)_3 + TlOAc \rightleftharpoons Tl_2(OAc)_4$$

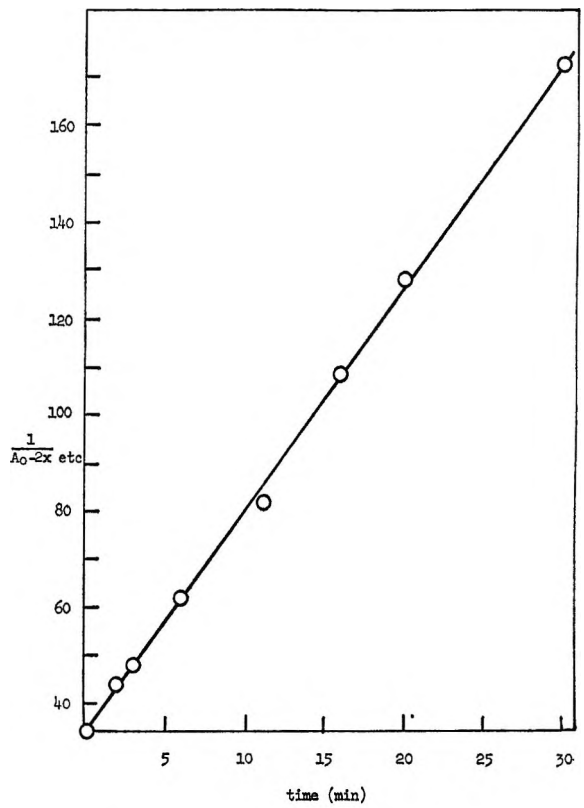


Figure 1.—Graph of typical kinetic run.

The titrimetric analytical method gives directly only the total concentration of thallium(III) species present. This does not correspond to the concentration of thallium triacetate in solution. Therefore, in order to facilitate analysis of the rate of cleavage of cyclopropanes by *free thallium triacetate*, we have employed the method previously described.[4] For the case in which the concentration of thallium triacetate (A) is twice that of cyclopropane, the rate of cleavage and formation of products (X) is equal to the change in oxidative titer of the solution as indicated by the following rate law and integrated expression.

$$dx/dt = k[A_0 - 2X][A_0/2 - X]$$

$$\frac{1}{A_0 - 2X} = kt + 1/A_0$$

The observed rate constants for the rates of oxidation of the series of cyclopropanes studied are listed in Table I. The reported values are the average of at least duplicate runs. Individual rate constants deviate from the average values by no more than 2%. The typical run illustrated in Figure 1 for spiro[5.2]octane at 29.3° has a correlation coefficient of 0.9996.

Discussion

Both spiro[5.2]octane and spiro[4.2]heptane react much faster than any of the bicyclo[*n*.1.0]alkanes studied. This large difference must reflect the stability of the tertiary cationic center developed in the case of the spiro[*n*.2]alkanes compared with the secondary cationic center developed in the bicyclo[*n*.1.0]alkanes. On the basis of the earlier studies with arylcyclopropanes in which $\rho^+ = -4.3$ was determined the results reported herein for the differences between the two classes of bicycloalkanes were expected.

(6) R. J. Ouellette, A. South, Jr., and D. L. Shaw, *J. Amer. Chem. Soc.*, **87**, 2602 (1965).

(7) R. J. Ouellette, G. Kordosky, C. Levin, and S. Williams, *J. Org. Chem.*, **34**, 4104 (1969).

TABLE I

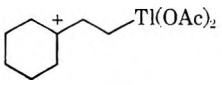
SECOND-ORDER RATE CONSTANTS AND ACTIVATION PARAMETERS

Compd	$k_{17.85°}$ (l./mol min)	$k_{29.80°}$ (l./mol min)	$k_{50.05°}$ (l./mol min)	$\Delta H^{\pm}$ (kcal/mol)	$\Delta S^{\pm}$ (cal/deg)
Spiro[5.2]octane (a)[a]	1.57	4.45		15.5	−4.5
Spiro[4.2]heptane (b)	3.62×10^{1}				
Fluorene-9-spirocyclopropane (c)	1.65×10^{-1}				
Bicyclo[5.1.0]octane (d)		5.26×10^{-4}	7.09×10^{-3}	23.7	4.9
Bicyclo[4.1.0]heptane (e)		5.39×10^{-2}	2.68×10^{-1}	14.4	−16.8
Bicyclo[3.1.0]hexane (f)		2.15×10^{-2}	1.16×10^{-1}	15.2	−16.1

[a] Identification for registry number.

The spiro[4.2]heptane reacts faster than the spiro[5.2]octane by a factor of 23.1. However this value must be corrected for differences in the symmetry of the molecules. In spiro[4.2]heptane two cyclopropane bonds are equivalent with respect to the five-membered ring which must be planar or very nearly so. Even if the five-membered ring were nonplanar the difference in the steric environment of the two cyclopropane bonds attached to the ring cannot be large. Furthermore, rapid interconversion by pseudorotation will result in the equivalence of the two bonds on a time average basis. By contrast the two cyclopropane bonds attached to the six-membered ring in spiro[5.2]octane are nonequivalent. One of the bonds is in a pseudoaxial position in which case the axial protons should hinder the approach of the thallium triacetate. The pseudoequatorial bond is much more open to electrophilic attack. While the six-membered ring undergoes chair–chair interconversion rapidly and the two cyclopropane ring bonds become equivalent on a time average basis, there is still only one pseudoequatorial bond accessible at a time. The ratio of the attack at the pseudoequatorial to pseudoaxial bond cannot be calculated from the system studied to date but could be derived from related decalin derivatives. However the maximum rate constant for pseudoequatorial bond attack can be no greater than the observed rate constant and would not be expected to be less than one-half of the observed rate constant. By using a statistical factor of two to obtain the relative rate of attack of an individual bond of spiro[4.2]heptane relative to a pseudoequatorial bond of spiro[5.2]octane the rate factor should be 23.1/2 or 11.5.

The relative stability of the cyclohexyl cation intermediate **3** compared with the cyclopentyl cation **4** should



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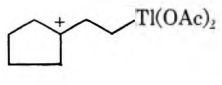

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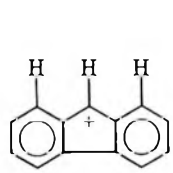
be reflected in solvolysis reaction rates. While data on the appropriate 1-ethylcycloalkyl derivatives are not available, the unsubstituted cyclohexyl and cyclopentyl data are available for the tosylates in acetic acid.[8] Cyclopentyl tosylate solvolyzes 16 times as fast as cyclohexyl tosylate, a value consistent with the rate factor observed in the ring cleavage reaction. Therefore, carbonium ion stability is the dominant rate-controlling feature in these two compounds.

The fluorene-9-spirocyclopropane[9] reacts much slower than either of the other two related compounds. From the available solvolysis data on cyclopentyl-[10] and 9-fluorenylmercuric perchlorates[11] in acetic acid it is known that the rates stand in the order of 1 to 0.65 respectively. Therefore, while ring cleavage rate of the spiro[4.2]heptane would be expected to be larger than that of fluorene-9-spirocyclopropane the observed ordering of 1 to 0.005 is clearly indicative of structural features other than carbonium ion stability. There are significant differences between the cation **5** generated in solvolysis of the mercury compound and that from cyclopropane cleavage, **6**. The larger steric bulk of the



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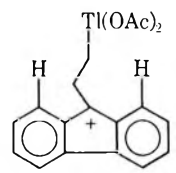

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methylene group attached to the 9 position in intermediate **6** should decrease its stability, raise the energy of the transition state, and slow the rate of the reaction. It should be recalled that $\rho^{+} = -4.3$ was observed in the cleavage of arylcyclopropanes and therefore the transition state is located far along the reaction coordinate and strongly reflects product stabilities.

In the bicyclo[*n*.1.0]alkanes the rates of reaction reflect many factors for the cleavage can occur at either an internal or external bond. In both cases the incipient cation is secondary. Since there are two external bonds and one internal bond a statistical factor of two should favor external bond cleavage. It has been established that 91% of the reaction of bicyclo[4.1.0]heptane occurs *via* attack of an external bond whereas 46.5% external bond cleavage occurs in bicyclo[3.1.0]hexane.[6] The deviations from the statistically expected 66.7% in both compounds indicates the importance of structural differences.

Each of the observed rate constants must be separated into specific rate constants for internal and external bond cleavage.

$$k_{obsd} = k_{int} + k_{ext}$$

The ratio of the internal to external rate constants must be equal to the ratio of the amounts of the products derived from the two paths after taking into account the statistical correction. The calculated k_{int} and k_{ext} for bicyclo[4.1.0]heptane are 0.25×10^{-1} and 1.21×10^{-1} l./mol min at 50°, respectively, and the k_{int} and k_{ext} for bicyclo[3.1.0]hexane are 0.65×10^{-1} and 0.27×10^{-1} l./mol min at 50°, respectively.

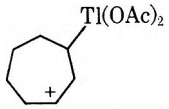
(8) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Book Co., New York, N. Y., 1962, p 95.

(9) The authors gratefully acknowledge the generosity of Professor G. Fraenkel in providing us with this compound.

(10) R. J. Ouellette, Ph. D. Thesis, University of California, 1962.

(11) B. G. van Leuwen and R. J. Ouellette, *J. Amer. Chem. Soc.*, **90**, 7056 (1968).

The ratio of the specific rates for internal bond cleavage of bicyclo[4.1.0]heptane to that of bicyclo[3.1.0]-hexane is 0.38. Since a cycloheptyl cation (**7**) results from the former compound and a cyclohexyl cation (**8**)



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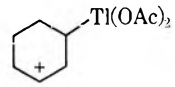

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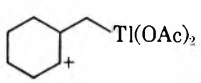
results from the latter compound this rate ratio does not reflect carbonium ion stabilities. An opposite order of reactivities is observed in cycloalkyl tosylate solvolysis with the cycloheptyl derivative solvolyzing 31 times as fast as the cyclohexyl derivative.[8] Therefore some structural feature must give rise to a rate factor difference of 82 to produce the order observed. In bicyclo[3.1.0]hexane the five-membered ring contains eclipsed hydrogens which are moved to staggered orientations in intermediate **8**. In the bicyclo[4.1.0]heptane the change in the hydrogen–hydrogen interaction in proceeding to intermediate **7** is much smaller. The energy difference which must be involved in reversing the expected rates based on carbonium ion stabilities is only 2.6 kcal/mol, a value well within that possible for removing the eclipsing interactions in the five-membered ring.

The ratio of the external bond cleavage rates for bicyclo[4.1.0]heptane to bicyclo[3.1.0]hexane is 4.4. On the basis of carbonium ion stabilities of the intermediates **9** and **10** a ratio of 0.06 would be expected.[8]



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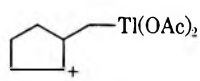

10

In order to account for the difference between the expected ratio and the observed ratio a rate factor of 70 favoring the cleavage of bicyclo[4.1.0]heptane over that of bicyclo[3.1.0]hexane must be accounted for. Examination of models reveals no outstanding differences in the steric accessability of the external bonds of the two compounds. However there are many hydrogen–hydrogen interactions in bicyclo[4.1.0]heptane which contains a nonchair six-membered ring. These interactions are eliminated in intermediate **9** where staggered vicinal hydrogens are present. In bicyclo-[3.1.0]hexane the eclipsed hydrogens in the reactant remain nearly eclipsed in the intermediate **10**. An energy factor of 2.5 kcal/mol does not seem an unreasonable quantity to expect for the change to the chair conformation which occurs in the cleavage of bicyclo[4.1.0]-heptane.

The rate of cleavage of bicyclo[5.1.0]octane is much slower than either of the other two bicyclo[*n*.1.0]alkanes studied. On the basis of carbonium ion stabilities as indicated from solvolysis data this compound should cleave the most rapidly. There appears to be little difference in the steric accessability of the cyclopropane bond as evidenced by inspection of molecular models. However, there is a substantial shielding of the back of the C-1 carbon by the methylene group at C-3. LaLonde[12] observed in the acid cleavage of 2,3-methano-*trans*-decalin that the products are the result of *trans*-diaxial attack. Analogous attack in bicyclo[5.1.0]-octane would be seriously retarded. Solvation of the cationic center from the back side as the electrophile attacks the cyclopropane ring bond may be difficult to achieve and hence slow the rate. The activation parameters for bicyclo[5.1.0]octane are dramatically different from those for the other compounds and may reflect this solvation difference. Other structural features of a more subtle nature may be operative as a result of differences in conformations of the seven-membered ring in the reactant and the transition state.

Experimental Section

Purification of Acetic Acid.—The acetic acid which was used for the kinetics and reaction of cyclopropanes with thallium triacetate was purified by refluxing a solution of 1.5 l. of glacial acetic acid containing 30 ml of acetic anhydride and about 3 g of *p*-toluenesulfonic acid for 18 hr. The acetic acid was distilled through a 60-cm glass-helix-packed column. The fraction with bp 117.5–118° was retained.

Kinetic Analysis.—The kinetic solutions were prepared by weighing an amount of the cyclopropane into a volumetrically measured amount of purified acetic acid. From the weight of sample, the desired amount of thallium triacetate was calculated, weighed out, and added to the solution. The concentration of the cyclopropane was ~0.015 *M* and that of thallium triacetate was ~0.030 *M*.

The methods of sampling were dependent upon the rate of the reaction. For slow reactions, in which evaporation could occur, 2-ml aliquots were sealed in test tubes. For reactions with a moderate rate, where evaporation was not a problem, aliquots were pipetted directly from the reaction flask. For fast reactions, aliquots of each reactant were pipetted into opposite sides of a partition flask and allowed to equilibrate at the bath temperature, and the solutions were mixed by shaking so as to allow passage over the partition barrier.

The method of analysis consisted of quenching the aliquot in excess 5% aqueous potassium iodide solution, addition of a starch–iodide indicator to the yellow heterogeneous mixture, and titration of the resulting dark mixture to a pure yellow mixture with standard aqueous sodium thiosulfate.

Registry No.—Thallium triacetate, 2570-63-0; Table I—a, 185-65-9; b, 185-49-9; c, 167-02-2; d, 286-43-1; e, 286-08-8; f, 285-58-5.

(12) R. T. LaLonde and M. A. Tobias, *J. Amer. Chem Soc.*, **85**, 3771 (1963).

Electrophilic Addition of Molecular Bromine to a Stereochemically Defined Cyclopropane

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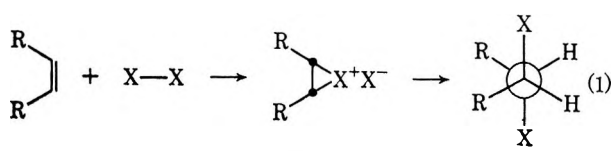
The polar addition of molecular bromine to bicyclo[3.1.0]hexane has been carried out at −30 to −50° in chloroform with the exclusion of light. Addition is predominantly to the internal, more substituted cyclopropane bond. The major products (83%) are *cis*- and *trans*-1,3-dibromocyclohexane and *trans*-1,2-dibromocyclohexane. Minor products have also been studied. The reaction lacks the stereospecificity that characterizes halogen additions to analogous alkenes, such as cyclohexene. These results are discussed primarily in terms of the nonbridged, secondary carbonium ion. There is no evidence that requires a 1,3-bridged bromonium ion.

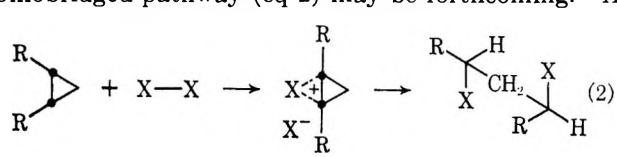
The mechanisms of halogen additions to alkenes are among the most thoroughly studied in organic chemistry.[2] In contrast, studies of halogen additions to cyclopropane rings have only recently been initiated.[3,4] Stereochemical methods in particular have not been fully utilized in developing the mechanistic foundations for this type of reaction. The work of Deno and Lincoln[3b] identified the important mechanistic pathways but did not include stereochemistry. The halogenation of bicyclo[2.1.0]pentane, as studied by LaLonde,[3a] proceeded by an isomerization pathway that precluded a stereochemical discussion of the initial addition.

Our present approach is to examine halogen additions to cyclopropane rings, with special attention to the stereochemical concomitants. One result from stereochemical studies of additions to alkenes was the suggestion that the reaction proceeds to a symmetrical or unsymmetrical bridged halonium ion intermediate, which may be destroyed by stereochemically well defined pathways (eq 1).[5] By analogous experiments



(1)

with cyclopropanes, evidence concerning a possible homobridged pathway (eq 2) may be forthcoming. A



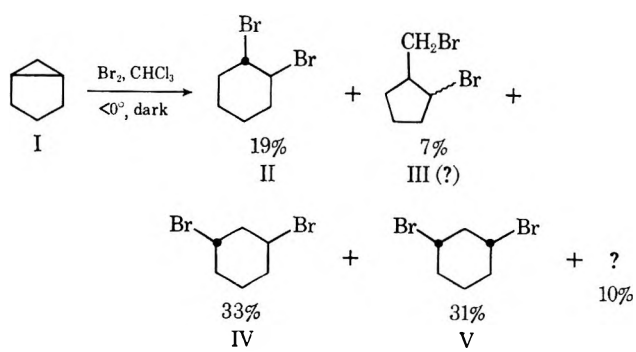
(2)

similar bridged structure for protonated cyclopropanes has received considerable attention recently, and acceptance of such intermediates is now widespread.[6] In the present paper, we discuss the reaction of molecular bromine with bicyclo[3.1.0]hexane, a system that may be capable of revealing the stereochemical pathways for electrophilic addition to the three-membered ring.

Results and Discussion

Bicyclo[3.1.0]hexane was allowed to react in chloroform with an equimolar quantity of bromine at −50° in the dark (see Experimental Section). The solvent was removed by vacuum distillation below 0°, and the reaction mixture was examined immediately by vpc. If the mixture was heated to reflux, the product proportions remained constant. Each component was collected by preparative vpc and identified by comparison of its spectral and chromatographic properties with those of authentic material. The three major components (see below) were subjected to the reaction conditions and found to be stable even above 0°. No isomerization could therefore have occurred during solvent removal.

The products and their percentages (the mean of four runs with a standard deviation of about 1.5%) are given below. Compounds II, IV, and V were identified unequivocally by comparison with the spectra of known materials.[7] Compound III was identified as to formula by its mass spectrum (parent peak triplet at *m/e* 240/242/244). Its nmr spectrum contains a sharp doublet (J = 6 Hz) at δ 3.6, indicative of a $BrCH_2$ group coupled to a methine proton. The structure proof is not, however, complete. Much of the unidentified 10% consists of several shorter retention time materials, possibly alkenes. 1,1-Dibromocyclohexane, *cis*-1,2-dibromocyclohexane, and *trans*-1,4-dibromocyclohexane were synthesized and found not to be in



(1) (a) Fellow of the Alfred P. Sloan Foundation, 1968–1970. This work was supported by the National Science Foundation (Grant GP-9257), and by the Petroleum Research Foundation, administered by the American Chemical Society (Grant 2970-A4, 5). (b) National Science Foundation Undergraduate Research Participant, 1967–1969.

(2) For reviews, see (a) G. Heublein, *Z. Chem.*, **9**, 281 (1969); (b) W. R. Dolbier, Jr., *J. Chem. Educ.*, **46**, 342 (1969); (c) R. C. Storr in "Organic Reaction Mechanisms, 1968," B. Capon and C. W. Rees, Ed., Interscience, London, 1969, pp 156–161.

(3) For addition of bromine, see (a) R. T. LaLonde, *J. Amer. Chem. Soc.*, **87**, 4217 (1965); (b) N. C. Deno and D. N. Lincoln, *ibid.*, **88**, 5357 (1966); (c) A. J. Gordon, *J. Chem. Educ.*, **44**, 461 (1967).

(4) For additions of other electrophiles, see among others (a) R. J. Ouellette, A. South, Jr., and D. L. Shaw, *J. Amer. Chem. Soc.*, **87**, 2602 ((1965); (b) R. T. LaLonde, J.-y. Ding, and M. A. Tobias, *ibid.*, **89**, 6651 (1967); (c) H. Hart and R. H. Schlosberg, *ibid.*, **88**, 5030 (1966); **90**, 5189 (1968); (d) V. I. Sokolov, N. B. Rodina, and O. A. Reutov, *J. Org. Chem. USSR*, **3**, 2038 (1967).

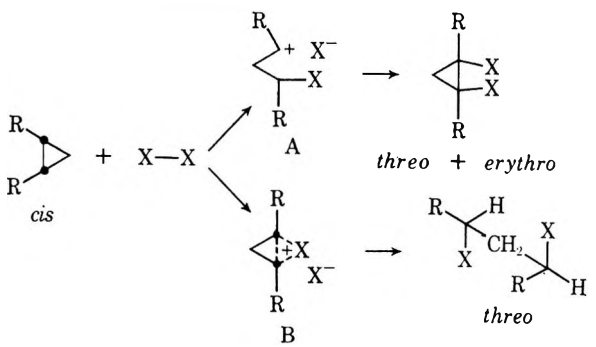
(5) The mechanistic alternatives and refinements have been discussed in ref 2a.

(6) For a review, see C. J. Collins, *Chem. Rev.*, **69**, 543 (1969).

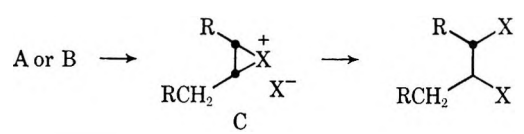
(7) B. Franzus and B. E. Hudson, Jr., *J. Org. Chem.*, **28**, 2238 (1963).

the reaction mixture. One peak amounting to 1% of the mixture was identical in retention time with *cis*-1,4-dibromocyclohexane, but a rigorous identification could not be made.

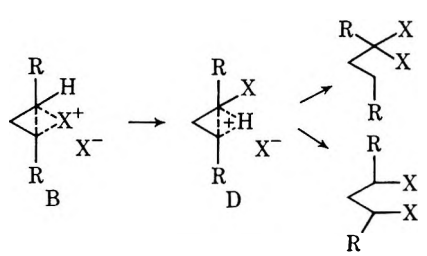
The reactions of cyclopropane rings with electrophiles may be discussed in terms of either nonbridged A or bridged B ions that can yield 1,3 products.[8] The nonbridged pathway should be nonstereospecific, but the opening of the bridged ion B should occur stereospecifically *trans*, *e.g.*, a *cis* starting material should yield a *threo* product, *trans*-1,3-dibromocyclohexane in the present example.



Hydride shifts in either A or B may produce a 1,2-bromine bridge C,[3a] which would be opened stereo-



specifically to a *trans*-1,2 product. Conceivably, the 1,3-bromine bridge could also rearrange to a proton-bridged species[3b] D, which could give 1,1- and 1,3-substituted products.



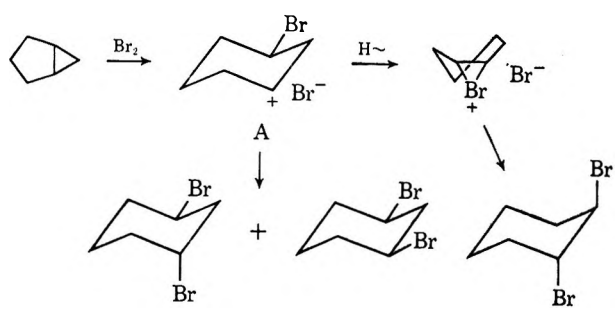
The above discussion of these mechanisms has assumed that bromine addition is favored at the more substituted cyclopropane bond, since higher substitution might better stabilize a partial or full positive charge. Addition to the less substituted bond would yield, by the same set of mechanisms, another series of products, in which the R groups are on adjacent carbon atoms.

It remains to discuss the observed products from bromination of bicyclo[3.1.0]hexane in terms of the above intermediates A–D, in hopes that certain mechanisms may be proved or disproved. Since the three principal products possess six-membered rings, at least 83% of the reaction must occur on the more substituted cyclopropane bond. The small amount of the suspected cyclopentane III may be produced by initial attack on one of the less substituted bonds.

About 19% of the reaction, corresponding to the proportion of *trans*-1,2-dibromocyclohexane (II), must pass through intermediate C [R,R, $(CH_2)_3$; X, Br]. This same intermediate is also proposed for the polar bromination of cyclohexene, in which *trans*-1,2-dibromocyclohexane is produced stereospecifically and exclusively. It is therefore a dead end intermediate in the present reaction. No further rearrangements may proceed from it. Since C can be produced either from A or B, its formation gives no information concerning the initial intermediate.

Because the 1,3-dibromocyclohexanes form almost two-thirds of the reaction mixture, pathways to their formation are more important than in the bicyclo[2.1.0]pentane case,[3a] in which the 1,2 product is formed almost exclusively. The presence of both the *cis*- and the *trans*-1,3-dibromocyclohexane excludes the bridged ion B from being the only intermediate that yields 1,3 products. The nonbridged mechanism A is very appealing, since IV and V are formed in almost equal amounts. A mechanism involving only bridged species demands the improbable necessity that half of B react to form the *trans* compound, and the other half rearrange to D to form the *cis* compound stereospecifically.[9] At present we favor the nonbridged mechanism (Scheme I) since IV and V are produced in similar

SCHEME I



amounts. None of the data presently at hand require the intermediacy of bromine-bridged ions, although such intermediates cannot be entirely rejected. Deno and coworkers[10] have presented evidence that methylcyclopropane forms a nonbridged ion on protonation. Rearrangement of substituted cyclopropanes to secondary carbonium ions on electrophilic attack may in general preclude any stereoselectivity such as is found in the analogous reactions of substituted alkenes.

Experimental Section

Nmr spectra were taken on Varian Models A-60 and T-60 spectrometers and the Bruker 90-MHz HFX-10.[11] Infrared spectra were recorded on Beckman IR-5 and IR-10 spectrophotometers. Mass spectra were obtained from a CEC model 21-104 analytical mass spectrometer. Gas chromatographic experiments were carried out on F & M Model 700 and Varian Aerograph Model 1520B instruments. Analytic and preparative

(8) Two complications are neglected. First, the bridged intermediate could be unsymmetrical. Second, the initial step in either case might be the formation of a charge-transfer complex. The latter situation is much less likely for cyclopropanes than with alkenes. *Cf.* B. C. Menon and R. E. Pincock, *Can. J. Chem.*, **47**, 3327 (1969).

(9) The opening of D should always be stereospecific, with a *cis*-D yielding an *erythro* product, *cis*-1,3-dibromocyclohexane in the present case.

(10) N. C. Deno D. LaVietes, J. Mockus, and P. C. Scholl, *J. Amer. Chem. Soc.*, **90**, 6460 (1968); N. C. Deno, W. E. Billup, D. LaVietes, P. C. Scholl, and S. Schneider, *ibid.*, **92**, 3700 (1970).

(11) We thank the National Science Foundation for a grant that made the purchase of this instrument possible.

experiments utilized 0.25 in × 6 ft columns containing 10% Carbowax 20M on Chromosorb G, DMCS treated.

Bicyclo[3.1.0]hexane (I) was prepared by the Simmons–Smith reaction on cyclopentene.[12]

trans-**1,2-Dibromocyclohexane** (II) was prepared by the method of Snyder and Brooks.[13]

1-Bromocyclohexene.—The method of Stevens and Valicenti was used to prepare this compound from 2,3-dibromocyclohexene.[14]

1,1-Dibromocyclohexane.—1-Bromocyclohexene (2.0 g) was dissolved in 40 ml of anhydrous ether in a round-bottomed flask equipped with a Dry Ice condenser and a gas-inlet tube. The flask was immersed in an ice bath, 0.1 g of $FeCl_3$ was added, and anhydrous hydrogen bromide was bubbled into the solution for 2 hr. The reaction mixture was washed with four 25-ml portions of water and one 25-ml portion of 10% sodium carbonate, and dried over anhydrous sodium carbonate. 1,1-Dibromocyclohexane (2.1 g) was isolated by distillation [bp 72–81° (7 mm)].[15]

cis-**1,2-Dibromocyclohexane.**—1-Bromocyclohexene (2.5 g) in 250 ml of pentane was irradiated for 1 hr in a Hanovia ultraviolet apparatus, as anhydrous hydrogen bromide was bubbled through the solution. The excess HBr was removed by washing with water and 10% sodium carbonate, and the dried pentane solution was distilled to give 1.7 g of pure *cis*-1,2-dibromocyclohexane [bp 104–105° (9 mm)].[15]

3-Bromocyclohexene was prepared from cyclohexene and N-bromosuccinimide.

1,3-Dibromocyclohexanes (*trans*, **IV**; *cis*, **V**).—3-Bromocyclohexene (1.6 g) was placed in a flask containing 6 ml of 48% aqueous hydrobromic acid. The flask was stoppered, heated to 65°, and allowed to stir for 7 hr. From the organic phase, the *cis*- and *trans*-1,3-dibromocyclohexanes were obtained by preparative gas chromatography. Their nmr spectra agreed with those of Franzus and Hudson.[7]

A mixture of *cis*-1,3-, *trans*-1,3-, *cis*-1,4-, and *trans*-1,4-dibromocyclohexane was prepared from the reaction of cyclohexane-1,3-diol with PBr_3 following the method of Franzus and Hudson.[7]

Reaction of Bromine with Bicyclo[3.1.0]hexane.—The brominations were performed in a dark room under red light; the flasks were covered with aluminum foil. Bicyclo[3.1.0]hexane (1.0 g) in 10 ml of chloroform (Baker analyzed reagent grade) and bromine (0.5 g) in 10 ml of chloroform were cooled in separate flasks to −50°. The bromine solution was added slowly to the cyclopropane compounds, and the reaction mixture was then allowed to stand at −30° for about 5 min. The solvent was removed under aspirator pressure below 0°, and the residue was analyzed directly by gas chromatography. The nmr spectrum of the immediate reaction mixture did not change with time.

Registry No.—Bromine, 7726-95-6; I, 285-58-5.

(12) H. E. Simmons and R. D. Smith, *J. Amer. Chem. Soc.*, **81**, 4256 (1959).

(13) H. R. Snyder and L. A. Brooks, "Organic Syntheses," Coll. Vol. II, A. H. Blatt, Ed., Wiley, New York, N. Y., 1943, pp 171–172.

(14) C. L. Stevens and J. A. Valicenti, *J. Amer. Chem. Soc.*, **87**, 838 (1965).

(15) H. L. Goering and L. L. Sims, *ibid.*, **77**, 3465 (1955).

Alumina-Catalyzed Reactions of Hydroxyarenes and Hydroaromatic Ketones. VI. Mediation of Alcohols in the Reduction Rearrangement of Hexamethylcyclohexadienones[1a]

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Received March 4, 1970

At 320° on alumina 2,3,4,5,6,6-hexamethyl-2,4-cyclohexadienone (1) in a solvent of methanol, 1-propanol, 2-propanol, or benzene is converted into hexamethylbenzene as the main identified product (24–88 mol %). 2,3,4,4,5,6-Hexamethyl-2,5-cyclohexadienone (in methanol) gives quantitative conversion into hexamethylbenzene under the same conditions. Mechanisms of the reactions are interpreted in terms of surface processes of Meerwein–Ponndorf–Verley reduction and subsequent dienol–benzene rearrangement. Partial demethylation of 1 on the catalyst accounts directly for the formation of by-products (pentamethylbenzene and pentamethylphenol) and indirectly for the occurrence of the main reaction in benzene.

Recently, Ramana and Pillai[2] reported catalysis by sodium-containing alumina of hydrogen-transfer reactions between alcohols (of three of more carbon atoms) and carbonyl compounds in a manner formally similar to the Meerwein–Pondorff–Verley (MPV) reduction and the Oppenauer oxidation. Studies in our laboratory[3–5] with the naphthalene ring system have also shown that methanol plus alumina serve for conversions such as (1) 1-tetralone into 1,2-dihydronaphthalene and (2) 1-oxo-2,2-dimethyl-1,2-dihydronaphthalene and 2-oxo-1,1-dimethyl-1,2-dihydronaphthalene into 1,2-dimethylnaphthalene. It was proposed that reactions 1 and 2 (as well as conversions of naphthols to di- and polymethylnaphthalenes) proceed through a step of the MPV type, whereby hydride transfer occurs from a surface methoxide group to the carbonyl carbon atom to produce a chemisorbed hydronaphthoxide, plus formaldehyde (or other oxidation products).[3–6] In case 1, the transformation is completed by loss of a proton and an oxide ion from the hydronaphthoxide to the alumina surface. In case 2, an attendant process of methyl migration (neopentyl-type rearrangement) is involved.

In further study of reduction–rearrangement such as occurs in case 2 we now report reactions of 2,3,4,5,6,6-hexamethyl-2,4-cyclohexadienone (1)[7] and its cross-conjugated isomer 2,3,4,4,5,6-hexamethyl-2,5-cyclohexadienone (2)[8] with excess alcohol when passed through a bed of Houdry hard alumina (designated catalyst C,[9] containing ~0.4% sodium ion) at 320 and 420°. For 1 at 320° (experiments 1, 3, 4) the major product was hexamethylbenzene (4), irrespective of whether methanol, 1-propanol, or 2-propanol was used as the alcohol (see Table I). This result is consistent

(1) (a) This investigation was supported by Research Grant No. CA-5969 from the National Cancer Institute, U. S. Public Health Service. For part V, see ref 5. (b) Research Assistant, 1964–1967.

(2) D. V. Ramana and C. N. Pillai, *Can. J. Chem.*, **47**, 3705 (1969).

(3) J. Shabtai, L. H. Klemm, and D. R. Taylor, *J. Org. Chem.*, **33**, 1489 (1968).

(4) L. H. Klemm, J. Shabtai, and C. E. Klopfenstein, *ibid.*, **35**, 1069 (1970).

(5) J. Shabtai, L. H. Klemm, and D. R. Taylor, *ibid.*, **35**, 1075 (1970).

(6) (a) L. H. Klemm, J. Shabtai, and D. R. Taylor, *ibid.*, **33**, 1480 (1968); (b) *ibid.*, **33**, 1494 (1968).

(7) H. Hart, P. M. Collins, and A. J. Waring, *J. Amer. Chem. Soc.*, **88**, 1005 (1966).

(8) H. Hart and D. W. Swatton, *ibid.*, **89**, 1874 (1967).

(9) This designation for the Houdry alumina catalyst was used in previous papers in this series.[3–6]

TABLE I

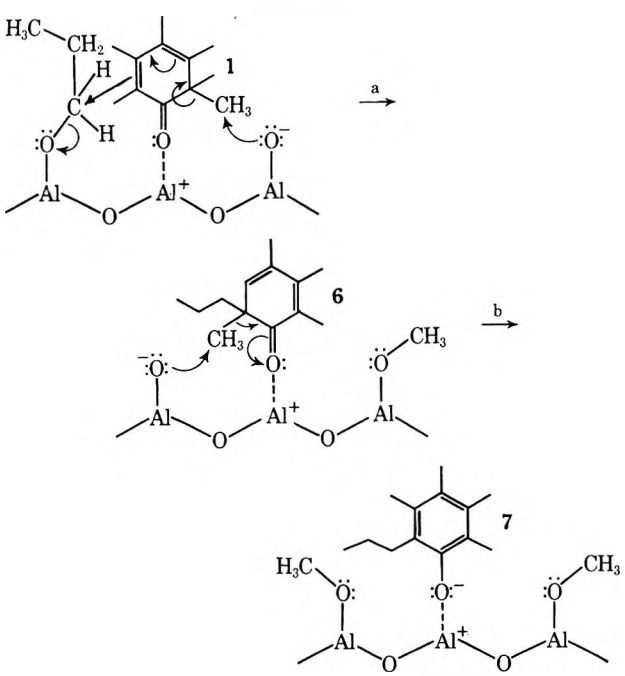
ALUMINA-CATALYZED REACTIONS OF HEXAMETHYLCYCLOHEXADIENONES WITH ALCOHOLS[a]

Expt no.	Substrate	Reaction temp, °C	Alcohol used	Conversion,[c] %	Product selectivity,[d] % Pentamethylbenzene (3)	Hexamethylbenzene (4)	Pentamethylphenol (5)	Unidentified[e]
1	1	320	MeOH	100	1.5	87.7	4.0	(8.7)
2	1	420	MeOH	100	4.0	85.5	5.8	(7.1)
3	1	320	*n*-PrOH	95	0.7	24.2	4.4	(53.3)[f]
4	1	320	*i*-PrOH	97	2.1	57.0	1.2	(14.4)
5	1	320	None[b]	94	3.6	44.1	16.0	(10.4)
6	2	320	MeOH	100	Trace	100		Trace
7	2	420	MeOH	89	Trace	67		Trace[g]

[a] See Experimental Section for reaction conditions. [b] Benzene was used in place of an alcohol. [c] Conversion = 100 × mol of substrate converted/mol of substrate charged. [d] Product selectivity = 100 × mol of specific product formed/mol of substrate converted. [e] Percentage by weight of total product based on gas chromatography and the assumption of an equal factor of instrumental response/gram for each component. [f] This portion contains at least 19 components of longer retention time than 4. Spectral investigation of the mixture showed the presence of both phenolic and C_{Ar} C_3H_7 groups. [g] Acetone-insoluble products were also formed.

with the intervention of a step of the MPV type. However, the yield of **4** was higher with methanol than with 1- or 2-propanol (a favorite hydride donor in MPV reactions in solution).[10] The low yield of **4** with 1-propanol (experiment 3) results from alkyl exchange between **1** and surface 1-propoxide, as evidenced by the complex mixture of products formed and the presence of C_{Ar} C_3H_7 groups therein (*cf.* footnote *f*, Table I). A mechanism for alkyl exchange to give an adsorbed ketone (**6**) or an absorbed pentaalkylphenoxide ion (**7**) is depicted in Scheme I, where step a is shown as a concerted process which involves reaction at both C-2 and C-6. Formation of **6** by a two-step process, of demethylation at C-6 to give adsorbed pentamethylphenoxide (**5a**) and then propylation at C-2 or C-6, is also possible. 2-Propoxide, on the other hand (experiment 4), functions as a hydride donor without effecting alkyl exchange. Probably, steric hindrance to isopropylation at a ring carbon atom already bearing a methyl substituent is too great to permit formation of the corresponding requisite pentamethylisopropylcyclohexadienone intermediate under reaction conditions.[11]

SCHEME I



On the basis of the proposed surface MPV and alkyl-exchange mechanisms one might predict that **1** would be inert in the presence of a tertiary alcohol as solvent. Since tertiary alcohols dehydrate very readily under the reaction conditions used, however, this experiment was not attempted. Instead, a solution of **1** in benzene alone (believed to be inert) was passed through the reactor (experiment 5) under otherwise identical conditions.[12] Even in this absence of an attendant hydride donor, however, **1** was converted into **4** in significant yield. Accompanying the formation of **4** was a somewhat larger yield of the by-product pentamethylbenzene (**3**) and a markedly higher yield of the by-product pentamethylphenol (**5**) than occurred in experiments 1, 3, and 4. Both by-products result from monodemethylation of the substrate, as indicated in Scheme II, step a. The resultant adsorbed pentamethylphenoxide ion (**5a**) could abstract a proton from the catalyst surface (step d) to give **5**.

Surface methoxide formed by demethylation of **1** is available for further reductive processes. Thus, it can transfer hydride to other molecules of adsorbed **1** in the MPV manner (Scheme II, step b) with the ultimate formation (step c) of **4** plus formaldehyde (as well as its oxidation products formate and/or carbon monoxide).[13] Additionally, surface methoxide (or other alkoxide bearing an α-hydrogen atom) may cause reduction of ion **5a** to **3**, as indicated in Scheme III. Here it is suggested that a surface hydroxide group first transfers a proton to the ambident ion **5a** (step a) to give the adsorbed tautomer of pentamethylphenol (**5b**). Reduction of **5b** to adsorbed alkoxide **9** is again depicted as involving a surface MPV reaction (step b). Loss of a proton plus an oxide ion from **9** to the catalyst surface (step c) would then yield pentamethylbenzene (**3**).

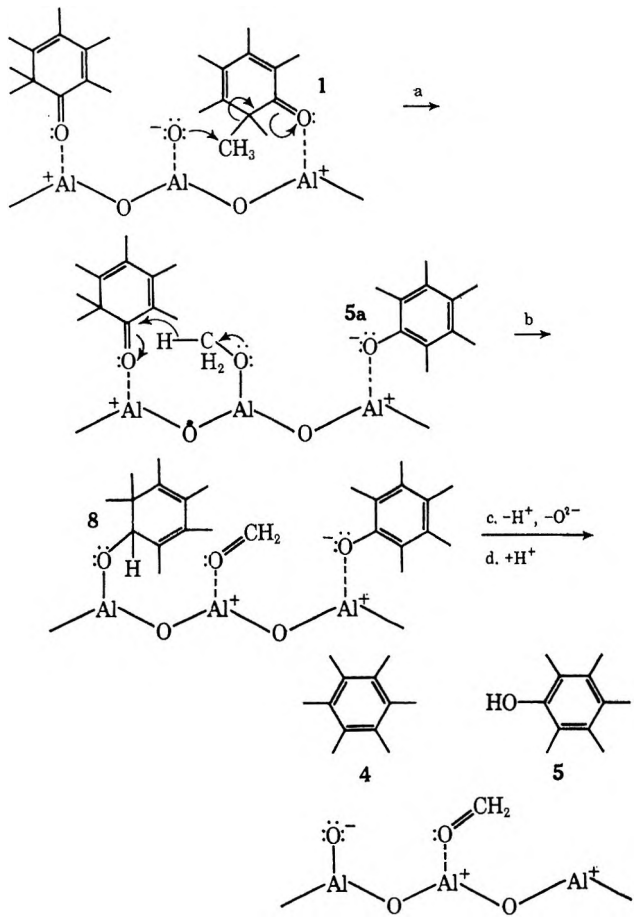
(10) A. L. Wilds, *Org. React.*, **2**, 178 (1944). H. Plieninger and G. Keilich [*Chem. Ber.*, **91**, 1891 (1958)] found that cyclohexadienones were readily converted into cyclohexadienols in this manner.

(11) Indirect evidence from this laboratory indicates that phenol will dialkylate at C-2 with 1-propanol but will only monoalkylate at C-2 with 2-propanol: L. H. Klemm and D. R. Taylor, unpublished results.

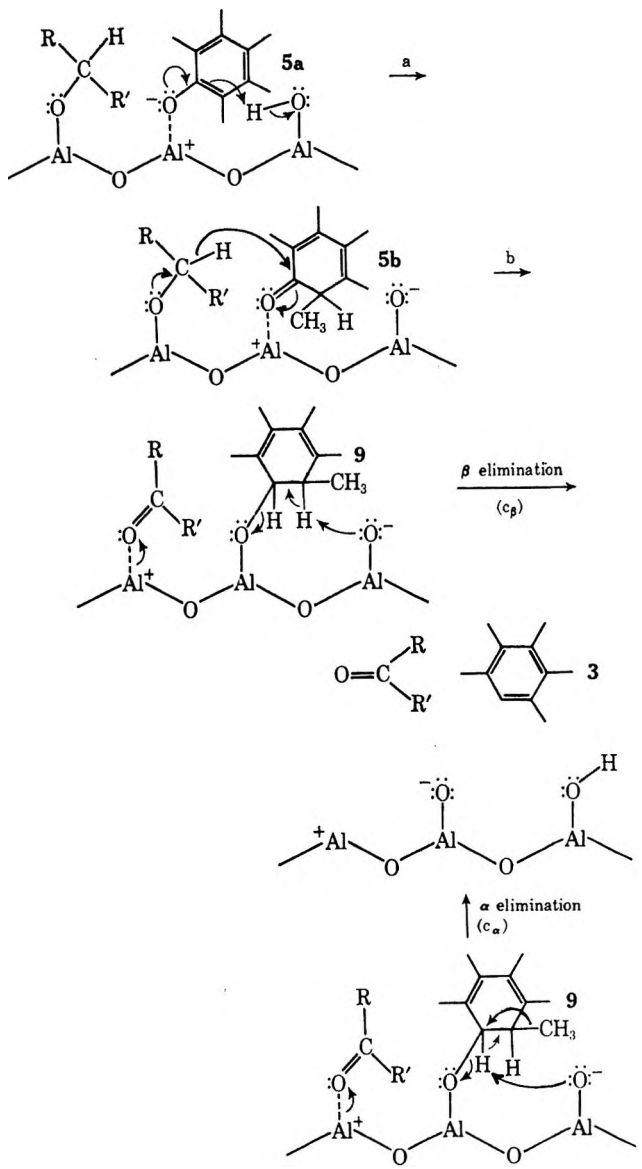
(12) It should be noted that apparent activity of the catalyst may vary depending on the solvent used, since the catalytic surface will be in a steady-state condition (involving adsorbed substrates) during the reaction proper. It is presumed that benzene will not be dissociatively chemisorbed (as has been postulated in the case of alcohols).[5,6]

(13) A material balance for formation of **3**, **4**, and **5** from **1** (in experiment 5) shows that more oxygen atoms are released than could be converted into water and carbon monoxide by the methyl groups released. Although an experimental determination of the fate of the "excess oxygen" has not been made, it seems plausible that it may be present in carbon dioxide or in the unidentified products.

SCHEME II



SCHEME III



Step c in Scheme III may be envisioned as occurring by α, β, or γ elimination. β elimination has been suggested previously[5] in the methanol–alumina conversion of 1-tetralone to 1,2-dihydronaphthalene. It is particularly attractive here because it has an overall simplicity as a concerted process, it involves the formation of a pseudocyclic eight-membered transition state (expected to be preferred on an alumina surface),[5] and it should be facilitated by *cis* geometry in **9** (which would allow *trans* elimination). If, as seems reasonable, steps a and b in Scheme III involve attack of H^+ and H^-, respectively, from the catalyst surface onto flatwise adsorbed substrate, **9** would, indeed, be the *cis* isomer. γ elimination (not shown in Scheme III) has been proposed previously[4] for conversion of adsorbed 2,2-dimethyl-1,2-dihydro-1-arenoxides to 1,2-dimethylarenes (*cf.* **8** → **4**, Scheme II, step c). Neither β nor γ elimination would be expected to give methyl migration in the conversion of **9** to **3**. On the other hand, α elimination (whether concerted or not) could result in methyl migration, as shown in Scheme III, step c_α.

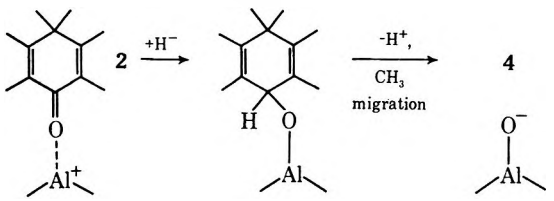
Experiments reported here do not allow an evaluation of the relative extents of α, β, and γ elimination in the pentamethylphenol system. However, the presence of 19% of the 1 isomer in the monomethylnaphthalene fraction from reaction of 1-naphthol with methanol at 350° over Houdry alumina[6a] is consistent with the occurrence of some α elimination under closely similar conditions. In the same series of experiments,[6a] the composition of this fraction attained 47% of 1-methylnaphthalene for a more acidic alumina and a reaction temperature of 420°. On the other hand, only small amounts (<10%) of 2 isomer were found in the monomethylnaphthalene fraction from reaction of 2-naphthol with methanol in the presence of alumina catalysts of various acidities[4] at temperatures up to 420°. A reduction–elimination mechanism of the type shown in Scheme III is also suggested for the direct deoxygenation (*via* an adsorbed keto form) of 1- and 2-naphthols to naphthalene.[6a]

Reaction of 2,3,4,4,5,6-hexamethyl-2,5-cyclohexadienone (**2**) with methanol in the presence of catalyst C at 320° (experiment 6) gave quantitative formation of hexamethylbenzene (**4**). Failure to detect any pentamethylphenol or more than a trace of pentamethylbenzene in the total product implies that neither demethylation of **2** to adsorbed pentamethylphenoxide ion nor rearrangement (*e.g.*, by concerted demethylation at C-4 and methylation at C-2) of **2** to **1** occurs as an intermediate process.[14] Moreover, methylation at C-2 without attendant demethylation at C-4 seems highly unlikely. In fact, a concerted intramolecular migration of the methyl group from C-4 to C-1 in a surface

(14) In fact R. F. Childs, *J. Chem. Soc. D*, 946 (1969), found that **1** rearranges to **2** under strongly acidic conditions.

dienol–benzene rearrangement[15] may be implicated (Scheme IV).

SCHEME IV



Increasing the reaction temperature from 320 to 420° for **1** in the presence of methanol gave little change in the yield of **4** but did increase the extent of demethylation (experiments 1 and 2). On the other hand, a similar change in reaction temperature for **2** (experiments 6 and 7) produced a much lower yield of **4**, without accompanying appearance of demethylation products **3** and **5**. Since unidentified chromatographic peaks were not observed in the regular range, it is presumed that **2** undergoes extensive decomposition at the higher temperature.

It is noteworthy that cases of demethylation have been found in hydroaromatic ketones of the naphthalene series, as well as in the presently reported benzene series. Thus, 1-oxo-2,2-dimethyl-1,2-dihydronaphthalene (analogous to **1**) underwent limited conversion to 2-methylnaphthalene at 350–420° in the presence of alumina–methanol, while the isomeric compound 1-oxo-4,4-dimethyl-1,4-dihydronaphthalene (analogous to **2**) gave no monomethylated products under similar conditions. At 275° reduction–rearrangement occurred with 1,1-dimethyl-2-oxo-1,2-dihydronaphthalene without attendant demethylation.[4] Investigation of this compound at higher temperatures was not made. With catalyst C[9] and methanol at 325–420°, monomethylated compounds constituted 52–82 mol % of the total identified product from 2,2-dimethyl-1-tetralone.[5] With more acidic alumina (catalyst A), however, monomethylated products were less prevalent (3–6 mol %), probably because of a much more facile rearrangement on this catalyst. Catalyst A, likewise, gave 4–7 mol % monodemethylated product (presumed to be 1,3,6-trimethylnaphthalene) from 2,2,4,7-tetramethyl-1-tetralone.[5] It is thus apparent that (at least for the second methyl group) the methylation–demethylation process is reversible at C-2 in the temperature range of 320–420° for the 1-naphthol, the 1-tetralone, and the phenol systems, but it is not reversible at C-4 under these conditions. It is suggested that the general mechanism shown in step a, Scheme II (and its reverse), applies to these cases. For the 1-oxo-2,2-dimethyl-1,2-dihydro systems involved, demethylation and MPV reduction (plus skeletal rearrangement) are competing reactions. Demethylation is fostered by using basic alumina catalysts and low (or zero) ratios of methanol to substrate in the influent.

(15) H. Plieninger and G. Keilich, *Angew. Chem.*, **68**, 618 (1956). For mechanistic characteristics of this reaction in the 2-allyl-2-methyl-2,4-cyclohexadien-1-ol and 4-allyl-4-methyl-2,5-cyclohexadien-1-ol systems, see H. J. Hansen, B. Sutter, and H. Schmid, *Helv. Chim. Acta*, **51**, 828 (1968).

Experimental Section

The apparatus and procedure were similar to those reported earlier.[6] In each experiment a solution of 1 g of substrate (**1**[7] or **2**[8]) in the appropriate alcohol [molar ratio, alcohol:substrate (40:1)] or (for experiment 5 only) in benzene (15 ml) was added at a rate of 15 drops/min in a stream of dry nitrogen gas (41 ml/min) to a vertically mounted, externally heated 53 cm × 2.7 cm (o.d.) Pyrex reactor tube, packed to a height of 28 cm with 45 g of fresh Houdry HA-100 alumina (cylindrically extruded 0.125-in. pellets, containing ~0.4% sodium ion, pre-activated *in situ* by passing 25 ml of solvent and a slow stream of nitrogen through the reactor at the reaction temperature). After completion of the reaction proper the catalyst was flushed (hot) with 25 ml of solvent, allowed to cool, and extracted with boiling acetone. Combined effluents and washings were evaporated to remove solvents and extracted with ether. The ether extract was washed with water, dried, and evaporated. The residue was analyzed by gas chromatography (by comparison with authentic samples) using columns of 10% DC-550 silicone fluid on Chromosorb W (8 ft × 0.375 in. at 160–200°) and of Bentone 34–silicone on Chromosorb (to separate hexamethylbenzene and **1**, not resolved on the former column).

Registry No.—**1**, 3854-96-4; **2**, 14790-04-6.

Synthesis of 2-Alkylidene Ketones. Chemistry of Boron Difluoride Complexes of 2-Formyl Ketones[1]

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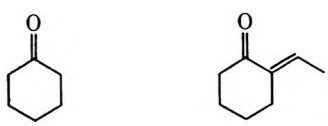
The chemistry of the long-known and readily prepared boron difluoride complexes of 1,3-dicarbonyl compounds had not been investigated except for hydrolysis. The reaction of such BF_2 complexes of 2-formyl ketones (*e.g.*, **4**) with organometallic reagents has been found to constitute an effective synthesis of 2-alkylidene ketones. For example, **4** reacts with 1 equiv of methyllithium to yield, after treatment with acid, 81% 2-ethylidenecyclohexanone. Other syntheses of 2-alkylidene ketones have been compared with this new procedure. In particular, reinvestigation of the reaction of 2-formyl ketones with Grignard reagents has shown this to be a comparably effective method of preparation of 2-alkylidene ketones.

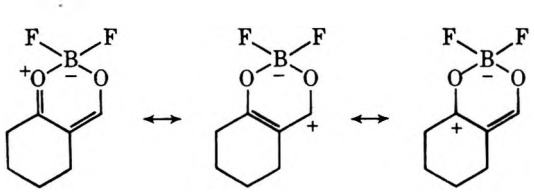
Preparation of 2-alkylidene ketones by direct aldol condensation of an aldehyde with a ketone (as in **1** → **2**) is usually not a practical synthetic method.[2] Less direct but more effective procedures devised for the synthesis of 2-alkylidene ketones have included the use



1 **2**

of enamine intermediates,[3] the reaction of 2-aminomethylene ketones with Grignard reagents,[4] and the reaction of enolates generated by zinc reduction of 2-bromo ketones with aldehydes.[5] Of particular relevance to the research described herein is the report by Dreiding and Nickel[6] of the preparation of **2** by direct reaction of the 2-formyl ketone[7] **3**, as well as its O-isopropyl derivative, with organometallic reagents.

The long-known[8] and readily prepared (see below) boron difluoride complexes of 1,3-dicarbonyl compounds (*e.g.*, **4**) seemed to offer an attractive alternative method for the synthesis of 2-alkylidene ketones, if the electrophilicity at the exocyclic carbon implied in contributing structure **4b** could be manifested by its attachment to a carbanionic nucleophile. Accordingly, an investigation of the reactions of BF_2 complexes of 2-formyl ketone, with organometallic reagents was undertaken.

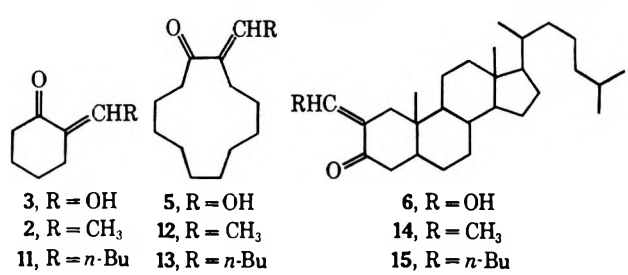


a **b** **c**

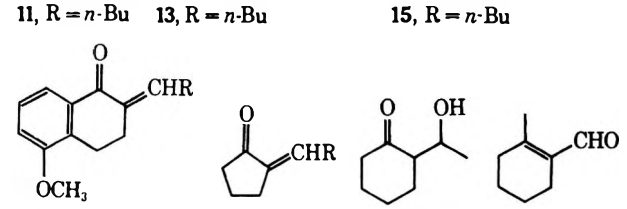
4

No examples of BF_2 complexes derived from 2-formyl ketones had been reported at the outset of the study, but their preparation proved facile, as might have been anticipated on the basis of the isolation of such complexes from 1,3 diketones. These are most frequently encountered as intermediates in boron trifluoride catalyzed acylation of ketones with anhydrides.[9] Hydrolysis to the parent 1,3-dicarbonyl compound was the only chemistry of these species which had been studied.

The best procedure for preparation of the desired BF_2 complexes consists in treatment of a methylene chloride solution of the 2-formyl ketone with 1.5–2.0 equiv of boron trifluoride etherate at room temperature. In this manner, nicely crystalline BF_2 complexes were obtained in 70–86% yield from 2-formylcyclohexanone (**3**), 2-formylcyclododecanone (**5**), 2-formylcholestan-3-one (**6**), and 2-formyl-5-methoxy-1-tetralone (**7**). The complex from 2-formylcyclopentanone (**8**) was liquid and relatively unstable, and could not be purified, but it displayed the same spectral properties and chemistry as the others. These complexes have distinctive infrared and ultraviolet absorption; the complexes from 2-formyl derivatives of unconjugated ketones all show absorption at ~6.2 and 6.7 μ and at 310–311 mμ (in cyclohexane), with ϵ ~14,000. They are stable in aprotic solvents, such as hexane, benzene, methylene



3, R = OH **5**, R = OH **6**, R = OH
2, R = CH_3 **12**, R = CH_3 **14**, R = CH_3
11, R = *n*-Bu **13**, R = *n*-Bu **15**, R = *n*-Bu



7, R = OH **8**, R = OH **9** **10**
16, R = CH_3 **18**, R = CH_3
17, R = *n*-Bu **19**, R = *n*-Bu

(1) This research was presented at the 159th National Meeting of the American Chemical Society, Houston, Texas, Feb 22–27, 1970.

(2) A. T. Nielsen and W. J. Houlihan, *Org. React.*, **16** (1968), provide references to specific examples and on p 38 the conclusion that "yields are low" in this type of reaction.

(3) L. Birkofer, S. M. Kim, and H. E. Engels, *Ber.*, **95**, 1495 (1962).

(4) *E.g.*, (a) L. I. Zakharkin and V. V. Korneva, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2206 (1964); (b) P. N. Weintraub, *Chem. Ind. (London)*, 1497 (1966); (c) R. E. Ireland and P. W. Schiess, *J. Org. Chem.*, **28**, 6 (1963).

(5) T. A. Spencer, R. W. Britton, and D. S. Watt, *J. Amer. Chem. Soc.*, **89**, 5727 (1967).

(6) A. S. Dreiding and S. N. Nickel, *ibid.*, **76**, 3965 (1954).

(7) The term 2-formyl ketone is used [as it was by E. W. Garbisch, *ibid.*, **85**, 1696 (1963)] to designate the enolic mixtures often referred to, and shown structurally in this paper, as 2-hydroxymethylene ketones.

(8) G. T. Morgan and R. B. Tunstall, *J. Chem. Soc.*, **125**, 1963 (1924).

(9) C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. React.*, **8**, 98 (1954); R. D. Youssefyeh, *J. Amer. Chem. Soc.*, **85**, 3901 (1963); H. Musso and K. Figge, *Justus Liebigs Ann. Chem.*, **668**, 1, 15 (1963); T. F. Crimmins and C. R. Hauser, *J. Org. Chem.*, **32**, 2615 (1967).

(10) No indication of consumption of organometallic reagent by reaction with the BF_2 moiety to give alkylboron compounds [*cf.* E. Krause and R. Nitsche, *Ber.*, **54**, 2784 (1921)] was ever observed.

chloride, or carefully dried ether or tetrahydrofuran. Protic solvents such as ethanol effect rapid conversion to the original 2-formyl ketone and chromatography is not suitable for purification.

When the boron difluoride complex **4** in benzene solution was treated with 1 equiv[10] of methyllithium in ether, followed by hydrolysis with aqueous ammonium chloride, the major product was β-hydroxy ketone **9**, accompanied by some enone **2**. In order to facilitate isolation of product and determination of yields by vapor phase chromatography (vpc), the crude reaction products were subsequently routinely treated with *p*-toluenesulfonic acid in benzene to effect complete dehydration to enone. If the intermediate ketol were the desired product, however, it presumably could be obtained.

After this acid-catalyzed dehydration, the product from **4** was 2-ethylidenecyclohexanone (**2**) (81% by vpc analysis), containing only small amounts of other substances. The 2-ethylidenecyclohexanone obtained possessed exclusively the *trans* geometry (see Experimental Section) as shown in **2**, but at least some of the other 2-alkylidene ketones synthesized were obtained as mixtures of *cis* and *trans* isomers. No attempt was made to separate or, in most cases, determine ratios of geometrical isomers. No products, such as **10**, resulting from attack at the endocyclic electrophilic position (*cf.* **4c**) were isolated from **4** or any other BF_2 complex studied, although minor products were not identified. Use of more than 1 equiv of methyllithium did not affect the product composition.

The results from all the reactions of boron difluoride complexes with organometallic reagents are shown in Table I. Methyllithium was distinctly superior to methylmagnesium iodide in the two cases where comparison was made. The generality of the 2-alkylidene ketone synthesis was demonstrated by the preparation of comparable yields of 2-pentylidene ketones with 1 equiv of *n*-butyllithium, except in the case of the 2-formyl-5-methoxy-1-tetralone BF_2 complex, which gave an anomalous and unexplained low yield of **17**.

Clearly, the BF_2 complexes provide an effective pathway to 2-alkylidene ketones. It was not clear, however, that this pathway represented an improvement over the direct reaction of the 2-formyl ketone with an organometallic reagent. The previous brief study[6] of this direct route reported 61 and 25% of **2** from **3** using methylmagnesium iodide and methyllithium, but these somewhat lower yields were of distilled products and, since we had learned in the course of the present work that distillation of the 2-alkylidene ketones lowered the yields, a reinvestigation seemed imperative.

The results of the reactions of the same set of 2-formyl ketones (**4**–**8**) directly with methyllithium or methylmagnesium iodide, followed by acid-catalyzed dehydration of intermediate ketols, are also shown in Table I. The yields with the Grignard reagent are in all instances comparable with those of the BF_2 complexes with methyllithium. As found by Dreiding,[6] methyllithium is relatively less effective in direct reaction with 2-formyl ketones.

The reaction of a Grignard reagent with a 2-formyl ketone thus should probably be the first method tried for synthesis of a given 2-alkylidene ketone. However, this procedure requires at least 2 equiv of organometallic reagent, the first reacting with the acidic proton of the enolized 1,3-dicarbonyl system to yield the magnesium enolate which then reacts with the second equivalent. Use of a protecting group such as boron difluoride is advisable when conservation of organometallic reagent is desired.

One of the indirect routes may also provide the maximum yield in a particular case. As an example of the unpredictability of the best method for synthesis of a specific 2-alkylidene ketone, the low yields of 2-alkylidenecholestan-3-ones in all of the procedures involving 2-formyl ketones may be cited. In addition to the examples recorded in Table I, the reaction of 2-pyrrolidinomethylenecholestan-3-one with methylmagnesium iodide affords **14** in a comparably disappointing yield (30%).[4b] Preparation of 2-alkylidenecholestan-3-ones is best accomplished (*e.g.*, 90% yield of **14**) *via* the zinc enolate derived from 2-bromocholestan-3-one.[5] These contrasting results, for which there is no obvious explanation, emphasize the desirability of having a variety of methods available for the synthesis of 2-alkylidene ketones.

Further investigation of the chemistry of boron difluoride complexes of various 1,3-dicarbonyl compounds with organometallic and other reagents is in progress.

Experimental Section[11]

Preparation of 2-Formyl Ketones.—Preparation of 2-formyl ketones was carried out by condensing the parent ketone with ethyl formate by reported procedures in the cases of 2-formylcyclohexanone (**3**),[12] 2-formylcyclododecanone (**5**),[13] 2-formylcholestan-3-one (**6**),[14] and 2-formylcyclopentanone (**8**).[15]

2-Formyl-5-methoxy-1-tetralone (7).—A 50% mineral oil dispersion of sodium hydride (1.90 g, 0.035 mol) was added to a stirred solution of 5-methoxy-1-tetralone[16] (3.26 g, 0.0185 mol) in freshly distilled ethyl formate (50 ml) held at 0°. Anhydrous methanol (0.75 ml) was then added and the mixture was stirred at room temperature under purified nitrogen for 18 hr. The resulting suspension was poured onto water (100 ml) and the organic layer was separated and extracted with two 100-ml portions of 2 *N* sodium hydroxide solution. Acidification of the combined aqueous extracts with cold 50% v/v aqueous hydrochloric acid and ether extraction afforded, after removal of the solvent at reduced pressure, 2-formyl-5-methoxy-1-tetralone (**7**) (3.78 g, 99.7%) as a yellow oil which crystallized on standing. Crystallization from hexane gave an analytical sample: mp

(11) Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Melting points were taken in an open capillary and are corrected. Ultraviolet (uv) spectra were determined on a Unicam SP800 spectrometer, using the solvents indicated. Infrared (ir) spectra were determined on a Perkin-Elmer Model 137 recording spectrophotometer. Nuclear magnetic resonance (nmr) spectra were determined on a Varian Associates DA-60-IL spectrometer. Vapor phase chromatography (vpc) was carried out on a Wilkens A-700 chromatograph using a 5 ft × 0.25 in. copper column packed with 60–80 mesh Chromosorb W coated with 7.5% Carbowax 20M. The column was operated at 150° at a helium gas flow rate of 60 ml/min. Vpc identification of compounds was performed by peak enhancement with authentic samples. Vpc yields were determined by triangulation of peak areas. Minor products were not identified, so response factors were not determined; neither were internal standard compounds used to determine yields. Analytical thin layer chromatography (tlc) was carried out on 250-μ-thick layers of Merck silica gel G. Preparative tlc was carried out on 1.25-mm-thick layers of Merck silica gel $PF_{254+366}$.

(12) C. Ainsworth, "Organic Syntheses," Coll. Vol. IV, Wiley, New York, N. Y, 1963, p 537.

(13) V. Prelog, L. Ruzicka, and O. Metzler, *Helv. Chim. Acta*, **30**, 1883 (1947).

(14) C. Djerassi, N. Finch, R. C. Cookson, and C. W. Bird, *J. Amer. Chem. Soc.*, **82**, 5488 (1960).

(15) W. S. Johnson and W. E. Shelberg, *ibid.*, **67**, 1752 (1945).

(16) Aldrich Chemical Co., Milwaukee, Wis.

TABLE I

FORMATION OF 2-ALKYLIDENE KETONES BY REACTION OF 2-FORMYL KETONES AND THEIR BORON DIFLUORIDE COMPLEXES WITH ORGANOMETALLIC REAGENTS

	Reactions of BF_2 complexes of 2-formyl ketones, % yield[a] (product)			Reactions of 2-formyl ketones, % yield (product)		
2-Formyl ketone	CH_3Li	CH_3MgI	*n*-BuLi	CH_3Li	CH_3MgI	*n*-BuLi
2-Formylcyclohexanone (**3**)	81[b] (**2**)	45[b] (**2**)	85[b] (**11**)	44[b] (**2**)	85[b] (**2**)	49[b] (**11**)
2-Formylcyclododecanone (**5**)	61 (**12**)	35 (**12**)	53 (**13**)	38 (**12**)	58 (**12**)	35 (**13**)
2-Formylcholestan-3-one (**6**)	37 (**14**)		32 (**15**)	25 (**14**)	41 (**14**)	17 (**15**)
2-Formyl-5-methoxy-1-tetralone (**7**)	87 (**16**)		38 (**17**)	89 (**16**)	81 (**16**)	20 (**17**)
2-Formylcyclopentanone (**8**)	62[b] (**18**)		60[b] (**19**)	56[b] (**18**)	75[b] (**18**)	48[b] (**19**)

[a] Yields are of isolated purified material unless indicated otherwise. [b] Yield based on vpc analysis.

67–68°; uv max (95% EtOH) 311 mμ (ε 10,700), 262 (5700), and 230 (10,900); uv max (95% EtOH–NaOH) 354 mμ (ε 14,790), 318 shoulder (6120), and 248 (15,000); ir (KBr) 6.3–6.4 (broad) μ; nmr ($CDCl_3$) δ 2.3–3.0 (m, 4), 3.78 (s, 3, H_3C–O–), 6.83–7.66 (AMX system, 3, H_A 7.58, H_B 7.20, H_X 6.92, J_{AX} = 1.5 Hz, J_{AM} = J_{MX} = 8.0 Hz, aromatic ring protons), 8.17 [s, broad, 1, HC–(OH)=], and 13.67–14.83 ppm (m, 1, H–O–).

Anal. Calcd for $C_{12}H_{12}O_3$: C, 70.58; H, 5.92. Found: C, 70.49; H, 5.97.

Preparation of Boron Difluoride Complexes of 2-Formyl Ketones.—The boron difluoride (BF_2) complexes were prepared by adding 1.5–2 equiv of freshly distilled boron trifluoride etherate to a stirred (~10% w/v) solution of the appropriate 2-formyl ketone in methylene chloride at room temperature under nitrogen. After 1 hr the methylene chloride solution was washed with water until free of excess boron trifluoride and the solvents were removed under reduced pressure. The crystalline products (all cases except 2-formylcyclopentanone) were then recrystallized from hexane or methylene chloride–hexane until constant melting points were obtained. The individual yields and properties of the BF_2 complexes follow.

BF_2 complex of 2-formylcyclohexanone (**4**)[17] was formed in 72% yield: mp 44–45°; uv max (cyclohexane) 311 mμ (ε 14,750); ir (KBr) 6.20 and 6.68 μ; nmr ($CDCl_3$) δ 1.8 (m, 4), 2.5 (m, 4), and 7.9 ppm [s, 1, HC(OBF_2)=]; mass spectrum M^+ at *m/e* 174.

Anal. Calcd for $C_7H_9O_2BF_2$: C, 48.28; H, 5.17; F, 21.84. Found: C, 48.28; H, 5.22; F, 21.75.

BF_2 complex of 2-formylcyclododecanone was formed in 70% yield: mp 66–67°; uv max (cyclohexane) 311 mμ (ε 14,100); ir (KBr) 6.25 and 6.78 μ; nmr ($CDCl_3$) δ 1.1–2.1 (m, 16), 2.2–2.8 (m, 4), and 7.9 ppm [s, broad, 1, HC(OBF_2)=].

Anal. Calcd for $C_{13}H_{21}O_2BF_2$: C, 60.49; H, 8.20. Found: C, 60.53; H, 8.25.

BF_2 complex of 2-formylcholestan-3-one was formed in 86% yield: mp 133–134°; uv max (cyclohexane) 311 mμ (ε 14,100); ir (KBr) 6.18 and 6.69 μ.

Anal. Calcd for $C_{28}H_{45}O_2BF_2$: C, 72.72; H, 9.81. Found: C, 72.84; H, 9.76.

BF_2 complex of 2-formyl-5-methoxy-1-tetralone was formed in 80% yield: mp 167–167.5°; uv max (cyclohexane) 353 mμ (ε 19,800); ir (KBr) 6.53 and 6.70 μ; nmr ($CDCl_3$) δ 2.4–3.2 (m, 4), 3.82 (s, 3, H_3CO–), 7.0–7.85 (AMX system, 3, H_A 7.75, H_M 7.33, H_X 7.10, J_{AX} = 2.0 Hz, J_{AM} = J_{MX} = 8.0 Hz, aromatic protons), and 8.10 ppm [s, 1, HC(OBF_2)=].

Anal. Calcd for $C_{12}H_{11}O_3BF_2$: C, 57.19; H, 4.40. Found: 57.08; H, 4.36.

BF_2 complex of 2-Formylcyclopentanone.—The general procedure outlined above produced a dark oil (65% yield) which could not be solidified or purified by distillation or chromatography. The crude product showed uv max (cyclohexane) 310 mμ and ir (film) 6.18 and 6.65 μ indicating that the BF_2 complex was indeed present and subsequent reactions were carried out with this crude product.

Preparation of 2-Alkylidene Ketones. A. General Method for the Reactions of the BF_2 Complexes of 2-Formyl Ketones with Organometallic Reagents.—Methyllithium (CH_3Li) and *n*-butyllithium (*n*-BuLi), obtained[18] in ether and hexane solutions respectively, were analyzed by the method of Gilman, *et al.*[19] Methylmagnesium iodide (CH_3MgI) was prepared from magnesium and methyl iodide in approximately 1 *M* ethereal solutions and filtered under nitrogen prior to use. To a stirred 10% w/v solution of the BF_2 complex in anhydrous benzene at room temperature under nitrogen was added 1 equiv of the organometallic reagent solution. The reaction was essentially instantaneous and after 15 min the benzene solution was washed with 10% w/v aqueous ammonium chloride and dried ($MgSO_4$). To the resulting mixture was added 15–20 mg of *p*-toluenesulfonic acid and it was then heated under reflux with azeotropic removal of water utilizing a Dean–Stark apparatus. After 2 hr the benzene solution was cooled, washed with water until free of acid, and dried ($MgSO_4$), and the solvents were removed under reduced pressure. Purification of each product is described under its respective heading.

2,4-Dinitrophenylhydrazone (2,4-DNP) derivatives were prepared by adding 1 equiv of a solution of 0.30 g of 2,4-dinitrophenylhydrazine in a mixture of 95% ethanol (10 ml), water (3 ml), and concentrated sulfuric acid (2 ml) to a solution of the 2-alkylidene ketone in 95% ethanol. The mixture was stored overnight at 0° and the precipitate was collected and crystallized to constant melting point from methylene chloride–ethanol mixtures.

B. General Method for the Reactions of 2-Formyl Ketones with Organometallic Reagents.—To a stirred 10% w/v solution of the 2-formyl ketone in anhydrous ether at 0° under nitrogen was added 2–2.2 equiv of the same organometallic reagent solutions used with the BF_2 complexes. After 15 min the ethereal solution was washed with 10% w/v aqueous ammonium chloride and dried ($MgSO_4$), and the solvents were removed under reduced pressure. The residue was then treated with acid in the same manner as the products from the BF_2 complexes. Purification of each product is described under its respective heading and 2,4-DNP's were prepared as outlined above.

2-Ethylidenecyclohexanone (**2**).—Reaction of **4** with CH_3Li afforded a product which was 81% **2** by vpc analysis, and from which 78% vpc-pure **2** was isolated by preparative tlc as a light yellow oil which darkened on exposure to light and air. This **2** showed the following: uv max (95% EtOH) 245 mμ (ε 6900); ir (film) 5.94 and 6.19 μ; nmr ($CDCl_3$) δ 1.73 (d of t, 3, *J* = 7, 1.5 Hz, H_3CCH=), 1.5–2.00 (m, 4), 2.20–2.65 (m, 2), and 6.73 ppm [m, 1, HC(CH_3)=]. These nmr data indicate that **2** was essentially pure *trans*-2-ethylidenecyclohexanone by comparison with literature[20] values for the *trans* olefinic proton of δ 6.62 and the *cis* olefinic proton of δ 5.60 ppm. The 2,4-DNP derived from **2** had mp 222–223°, uv max ($CHCl_3$) 385 mμ (ε 22,100) [lit.[21] mp 222°, uv max ($CHCl_3$) 388 mμ (ε 24,000)].

Reaction of **4** with CH_3MgI afforded **2** as the major product in 45% yield (by vpc analysis), 2,4-DNP mp 221–222°. Reaction of **3** with CH_3Li afforded 44% **2** by vpc analysis and 30% **2** isolated by column chromatography and preparative tlc, 2,4-DNP mp 220–221°. Reaction of **3** with CH_3MgI afforded 85% **2** by vpc analysis, 2,4-DNP mp 219–220°.

2-Pentylidenecyclohexanone (**11**).—Reaction of **4** with *n*-BuLi produced 85% of **11** (by vpc analysis). Pure **11** was obtained by preparative tlc (using 1:3 ether–hexane) and showed uv max (95% EtOH) 247 mμ (ε 4500) and ir (film) 5.95 and 6.20 μ; the 2,4-DNP had mp 102–104°.

Anal. Calcd for $C_{17}H_{22}N_4O_4$: C, 58.95; H, 6.40; N, 16.17. Found: C, 58.95; H, 6.26; N, 16.24.

Reaction of **3** with *n*-BuLi afforded 49% **11** (2,4-DNP mp 101–102°) by vpc analysis which also indicated the presence of at least nine minor products.

(17) We wish to thank Mr. James G. Magyar who isolated and characterized this compound.

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2-Ethylidenecyclododecanone (12).—Reaction of the BF_2 complex of **5** with CH_3Li afforded, after preparative tlc, 61% **12** as an oil: uv max (95% EtOH) 235 mμ (ε 10,000); ir (film) 6.01 and 6.11 μ; nmr ($CDCl_3$) δ 1.24 (s, broad, 16), 1.84 [d, 3, J = 7 Hz, $H_3CC(H)$=], 2.2–2.8 (m, 4), and 6.65 ppm [q, 1, J = 7 Hz, $HC(CH_3)$=]; 2,4-DNP mp 156–157° (lit.[3a] mp 153.5–154°).

Reaction of the BF_2 complex of **5** with CH_3MgI gave a brown oil which was adsorbed from hexane onto alumina. Elution with hexane gave a mixture (12%), whose ir displayed neither hydroxyl nor carbonyl absorption, and elution with 1:19 ether–hexane gave **12** (35%). Elution with ether gave a complex mixture (40–50%) which showed strong hydroxyl and carbonyl absorption in the infrared. Reaction of **5** with CH_3Li yielded 33% **12**, similarly isolated, which solidified, mp 28–29° (lit.[3a] mp 29–30°), 2,4-DNP mp 155–156°. Reaction of **5** with CH_3MgI yielded 58% **12**, similarly isolated, with mp 31–32°.

2-Pentylidenecyclododecanone (13).—Reaction of the BF_2 complex of **5** with n-BuLi afforded, after preparative tlc, 53% **13**: uv max (95% EtOH) 237 mμ (ε 10,000); ir (film) 6.0 and 6.1 μ; 2,4-DNP mp 110–111° (lit.[3a] mp 108–110°). Reaction of **5** with n-BuLi afforded a yellow-brown oil which was adsorbed from hexane onto alumina. Elution with hexane gave a nonpolar mixture (17%), whose ir spectrum displayed neither hydroxyl nor carbonyl absorption, and elution with 1:19 ether–hexane gave impure **13** (43%). Elution with ether gave a complex mixture (25–35%). Purification by preparative tlc gave pure **13** in 35% yield, 2,4-DNP mp 110–111°.

2-Ethylidenecholestan-3-one (14).—Reaction of the BF_2 complex of **6** with CH_3Li afforded, after preparative tlc, 37% **14**, which had mp 86–88° after several recrystallizations from ethanol; uv max (95% EtOH) 246 mμ (ε 6900); ir (KBr) 5.95 and 6.22 μ (lit.[3b] mp 93–94°; uv max (95% EtOH) 246 mμ (ε 7110). Reaction of **6** with CH_3Li afforded, after preparative tlc, 25% **14**, mp 87–89°. Reaction of **6** with CH_3MgI afforded, after preparative tlc, 41% **14**, mp 88–90°.

2-Pentylidenecholestan-3-one (15).—Reaction of the BF_2 complex of **6** with n-BuLi afforded a yellow oil which was adsorbed from benzene onto alumina. Elution with benzene and 1:19 ether–benzene afforded impure **15** (42%) while elution with ether afforded a complex mixture (35–40%) whose ir showed strong hydroxyl and carbonyl absorption. Purification by preparative tlc gave pure **15** in 32% yield as a light yellow oil: uv max (95% EtOH) 249 mμ (ε 7000); ir (film) 5.94 and 6.20 μ. The derived 2,4-DNP had mp 168–170°. Reaction of **6** with n-BuLi afforded, after similar purification, 17% **15**, 2,4-DNP mp 167–170°.

Anal. Calcd for $C_{38}H_{58}N_4O_4$: C, 71.89; H, 9.21; N, 8.82. Found: 71.95; H, 9.25; N, 8.79.

2-Ethylidene-5-methoxy-1-tetralone (16).—Reaction of the BF_2 complex of **7** with CH_3Li afforded, after preparative tlc, 87% **16** as a yellow oil which nmr indicated was a 2:5 mixture of *cis* and *trans* isomers: uv max (95% EtOH) 329 mμ (ε 3600), 275 (14,600) and 232 (11,400); ir (film) 5.94, 6.13, 6.27 (sh), and 6.30 μ; nmr ($CDCl_3$) δ 1.83 [d of t, 2.1, J = 7, 1 Hz, H_3C—C(H)=], 2.08 [d of t, 0.9, J = 7, 1.3 Hz, $H_3CC(H)$=], 2.5–3.1 (m, 4), 3.82 (s, 3, H_3CO–), 6.07 [m, 0.3, $HC(CH_3)$=], 7.07 [m, 0.7, $HC(CH_3)$=], and 6.8–7.8 ppm (AMX system, 3, H_A 7.71, H_M 7.24, H_X 6.94, J_{AX} = 1.5 Hz, J_{AM} = J_{MX} = 7.5 Hz, aromatic protons); 2,4-DNP mp 201–203°. A sample worked up prior to the acid dehydration step gave 2-(1-hydroxyethyl)-5-methoxy-1-tetralone which had a lower tlc R_f than **16**: ir (film) 2.95 (br), 5.97 and 6.31 μ; nmr ($CDCl_3$) δ 1.25 [d' 3, J = 7.5 Hz, $H_3CC(H)OH$–], 1.6–3.5 (m, 5), 3.81 (s, 3, H_3CO–), 4.25 [m, 1, $HC(OH)CH_3$–], and 6.82–7.7 (AMX system, 3, H_A 7.60, H_M 7.23, H_X 6.95, J_{AX} = 2.0 Hz, J_{AM} = J_{MX} = 7.5 Hz, aromatic protons). Treatment of this compound with p-toluenesulfonic acid in benzene as outlined in the general method A gave **16** in 89% yield, 2,4-DNP mp 200–201°. Reaction of **7** with CH_3Li afforded, after elution from a Florisil column with benzene, 89% **16**, 2,4-DNP mp 200–202°. Reaction of **7** with CH_3MgI afforded, after similar purification, 81% **16**, 2,4-DNP mp 201–202°.

Anal. Calcd for $C_{19}H_{18}N_4O_5$: C, 59.68; H, 4.74; N, 14.65. Found: C, 59.71; H, 4.81; N, 14.79.

2-Pentylidene-5-methoxy-1-tetralone (17).—Reaction of the BF_2 complex of **7** with n-BuLi afforded, after elution from a Florisil column with benzene, 38% **17** as a yellow oil: uv max (95% EtOH) 278 mμ (ε 12,500) and 233 (10,500); ir (film) 5.97, 6.17, 6.29 (sh), and 6.31 μ; 2,4-DNP mp 213–214°. Reaction of **7** with n-BuLi afforded, after preparative tlc, 20% **17**, 2,4-DNP mp 208–210°.

Anal. Calcd for $C_{22}H_{24}N_4O_5$: C, 62.25; H, 5.70; N, 13.20. Found: C, 62.12; H, 5.75; N, 13.07.

2-Ethylidenecyclcopentanone (18).—Reaction of the BF_2 complex of **8** with CH_3Li afforded, after filtration in benzene through a grade II alumina column, 62% vpc-pure **18**: ir (film) 5.88 and 6.05 μ; 2,4-DNP mp 211–213° (lit.[21] mp 216°). Reaction of **8** with CH_3Li afforded 56% **18** by vpc analysis, 2,4-DNP mp 213–215°. Reaction of **8** with CH_3MgI afforded 75% **18** by vpc analysis, 2,4-DNP mp 212–214°.

2-Pentylidenecyclopentanone (19).—Reaction of the BF_2 complex of **8** with n-BuLi afforded 60% by vpc analysis of what was assumed to be **19** on the basis of the spectral properties of the crude reaction mixture: ir (film) 5.85 and 6.05 μ. The 2,4-DNP formed from the crude product had mp 115–117° (lit.[22] mp 120.7–121.4°). Reaction of **8** with n-BuLi afforded 48% **19** by vpc analysis, 2,4-DNP mp 117–118°.

Registry No.—**2**, 1122-25-4; **4**, 25726-01-6; **7**, 25677-39-8; **11**, 25677-40-1; **11** (2,4-dinitrophenylhydrazone, 25677-41-2; **12**, 1138-01-8; **13** (2,4-dinitrophenylhydrazone), 1178-47-8; **14**, 14026-01-8; **15**, 25677-44-5; **15** (2,4-dinitrophenylhydrazone), 25677-45-6; **16**, 25677-46-7; **16** (2,4-dinitrophenylhydrazone), 25677-47-8; **17**, 25677-48-9; **17** (2,4-dinitrophenylhydrazone), 25677-49-0; **18**, 14845-53-5; **19**, 16424-35-4; BF_2 complex of 2-formylcyclododecanone, 25677-00-3; BF_2 complex of 2-formylcholestan-3-one, 25677-01-4; BF_2 complex of 2-formyl-5-methoxy-1-tetralone, 25677-02-5.

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Quaternary-Substituted Hydrocarbons. I. A General Method of Synthesis of Hydrocarbons Interspersed with Four *gem*-Dimethyl Units

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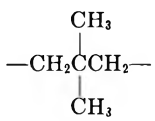
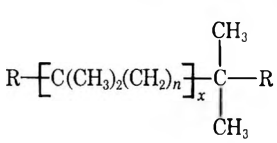
Preparation of seven high-molecular-weight (C_{30}–C_{40}) hydrocarbons containing two and four *gem*-dimethyl units interspersed in the aliphatic chain are described. Addition of mono- and difunctional Grignard reagents to ethyl isopropylidenemalonate was employed to incorporate *gem*-dimethyl units into key intermediates. The use of difunctional Grignard reagents in this reaction has not been previously reported. The acid chloride–organocadmium reaction was better for the preparation of diketone intermediates than the Grignard–nitrile reaction. A three-step procedure of reduction, dehydration, and hydrogenation to convert the diketone intermediates to the desired hydrocarbons was found to be superior to direct Wolff–Kishner reduction.

The data available to assess the effect on such properties as viscosity and thermal and oxidative stability of interspersing quaternary carbon atoms in the structure of compounds in the lubricant molecular-weight range are limited to hydrocarbons[1] with



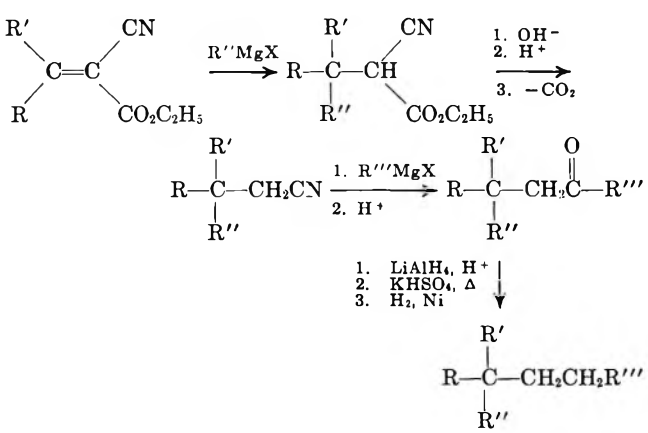
recurring units and esters[2,3] with one or two quaternary carbons.

Of the approximately 150 reported hydrocarbons with quaternary carbons, only eight have more than 28 carbon atoms and none of these have more than two quaternary carbons. The 16 reported hydrocarbons containing two or more quaternary carbons all fall in the C_{18} to C_{24} range, and, except for 2,2,4,4,13,13,15,15-octamethylhexadecane and 6-ethyl-2,2,4,4,11,11,18,18-tetradecane,[4] none were prepared by unequivocal routes nor were their purities verified chromatographically.[5–7] To broaden the scope of these data, we prepared a number of hydrocarbons with up to four quaternary carbon atoms interspersed in the chain with the general structure below, where $n = 4$–8 and $x = 1$ and 3.



The synthesis of high-molecular-weight hydrocarbons in high purity even now presents difficulties,[8] and is further complicated in our case because reactions which form quaternary carbons are limited.

Desgrandchamps[9] has shown that of seven routes which he evaluated for the synthesis of C_{17}-tetraalkylmethanes, only one developed by Rabjohn, *et al.*,[10] yielded hydrocarbons of chromatographic purity. Four methods, the Blaise reaction, reactions of tertiary chlorides and alkyl sodium derivatives, reactions of alkylcadmium reagents with acid chlorides, and reactions of Grignard reagents with aldehydes did not lead to acceptable results, and the Grignard condensations of Petrov,[11] and the reaction of Grignard reagents with tertiary acetylenic chlorides according to Campbell and Eby[12] lead to contaminated products. The Rabjohn method,[10,13] in which the quaternary carbon is formed by 1,4 addition of a Grignard reagent to an alkylidenecyanoacetate,[14] was used by Rabjohn[10] and Desgrandchamps[9] to synthesize pure, high-molecular-weight, unsymmetrical tetraalkylmethanes.



Results and Discussion

In applying Rabjohn's method to the synthesis of 6,6,11,11,17,17,22,22-octamethylheptacosane (**22b**) according to Scheme I we found that in the first step the addition of pentamethylenebis(magnesium bromide) (**2**) to ethyl cyanoisopropylideneacetate (**1**) in ether afforded a complex mixture of at least five major reaction products. Hydrolysis and decarboxylation of this mixture gave only an 11% yield of pure 3,3,9,9-tetramethyl-1,11-undecanedinitrile (**4**). An alternate synthetic approach is the addition of Grignard reagents to

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SCHEME I

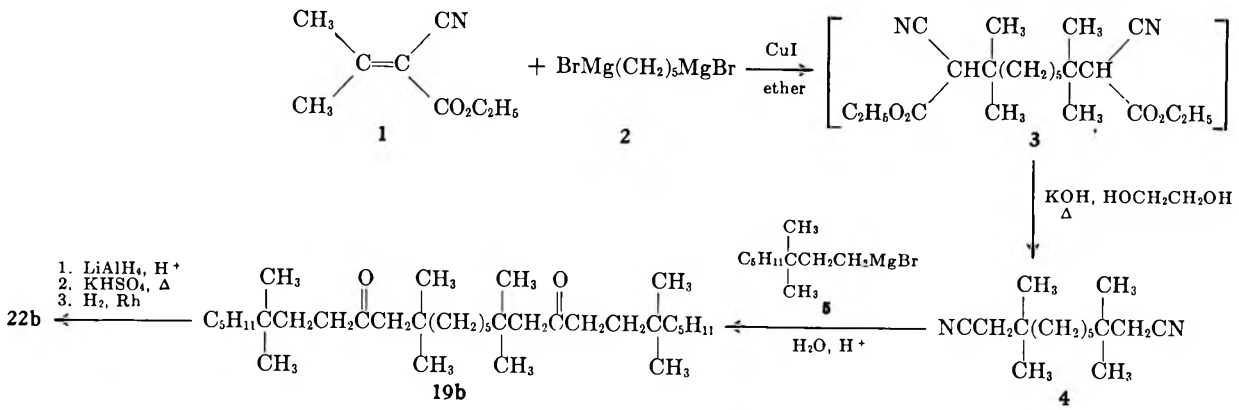
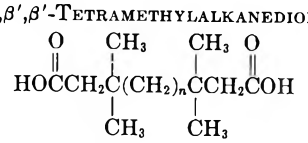


TABLE I.—β,β,β′,β′-TETRAMETHYLALKANEDIOIC ACIDS 17a–d



Compd no.	n	Bp, °C (mm)	Mp, °C	% yield	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
17a	4	180–185 (0.3)	115–116[a]	35	$C_{14}H_{26}O_4$	65.08	10.14	65.58	10.04
17b	5	178–180 (0.1)	96–97[b]	31	$C_{15}H_{28}O_4$	66.14	10.36	66.20	10.23
17c	6	185–190 (0.3)	142–143[a]	49	$C_{16}H_{30}O_4$	67.09	10.55	67.15	10.70
17d	8	210–220 (0.4)	124[a]	46	$C_{18}H_{34}O_4$	68.74	10.89	68.80	10.93

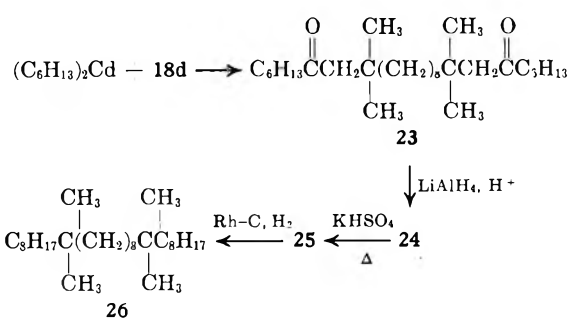
[a] Recrystallized from benzene. [b] Recrystallized from hexane.

alkylidenemalonates.[15] The inverse addition of pentylmagnesium bromide to ethyl isopropylidenemalonate using cuprous iodide catalysis gave yields of ethyl 1,1-dimethylhexylmalonate (**7**) in the range of 65–70%. These yields approach those reported by Hook and Robinson[16] and Rabjohn, *et al.*,[10] for the inverse addition of Grignard reagents to ethyl cyanoisopropylideneacetate using cuprous iodide catalyst. Lower yields, 30–40%, of *t*-alkylmalonic esters were reported by Widequist[16] for the normal addition of methyl- and *n*-butylmagnesium bromide to ethyl isopropylidenemalonate without using cuprous iodide catalysis. The inverse addition of di-Grignard reagents to ethyl isopropylidenemalonate (Table I) gave, after hydrolysis and decarboxylation, the β,β,β′,β′-tetramethylalkanedioic acids (**17a–d**) in yields of 31–49% compared with yields of only 11% for 3,3,9,9-tetramethyl-1,11-undecanedinitrile. Approximately 15% of the malonate is converted to the dihydro dimer during this reaction. Although di-Grignard reagents have been used widely,[17] this is the first report to our knowledge of di-1,4 addition of such a reagent.

In the third step of Scheme I although the reaction of 3,3,9,9-tetramethyl-1,11-undecanedinitrile (**4**) with 3,3-dimethyloctylmagnesium bromide (**5**) gave a good, 61% yield of 6,6,11,11,17,17,22,22-octamethyl-9,19-heptacosanedione (**19b**), this route proved to be inferior to the organocadmium–acid chloride reaction. The addition of di(3,3-dimethyloctyl)cadmium(**16a**) to the chlorides of the β,β,β′,β′-tetramethylalkanedioic acids gave diketones (**19a–d**) with four quaternary carbon atoms in yields of 80% and in high purity (Table II). The acid chlorides (**18a–d**) were used in this reaction without final purification by vacuum distillation because decomposition began at around 125° (pot temperature) when distillation was attempted. Some of the 3,3-dimethyloctyl bromide (**10**), used in excess, coupled in the preparation of the cadmium compounds to yield 15–20% 6,6,11,11-tetramethylhexadecane (**11**).

Similar results were obtained in the reaction of the acid chlorides with di(4,4-dimethylnonyl)cadmium (**15b**) which was obtained as shown in Scheme II from 3,3-dimethyloctyl bromide (**10**) by conventional methods.

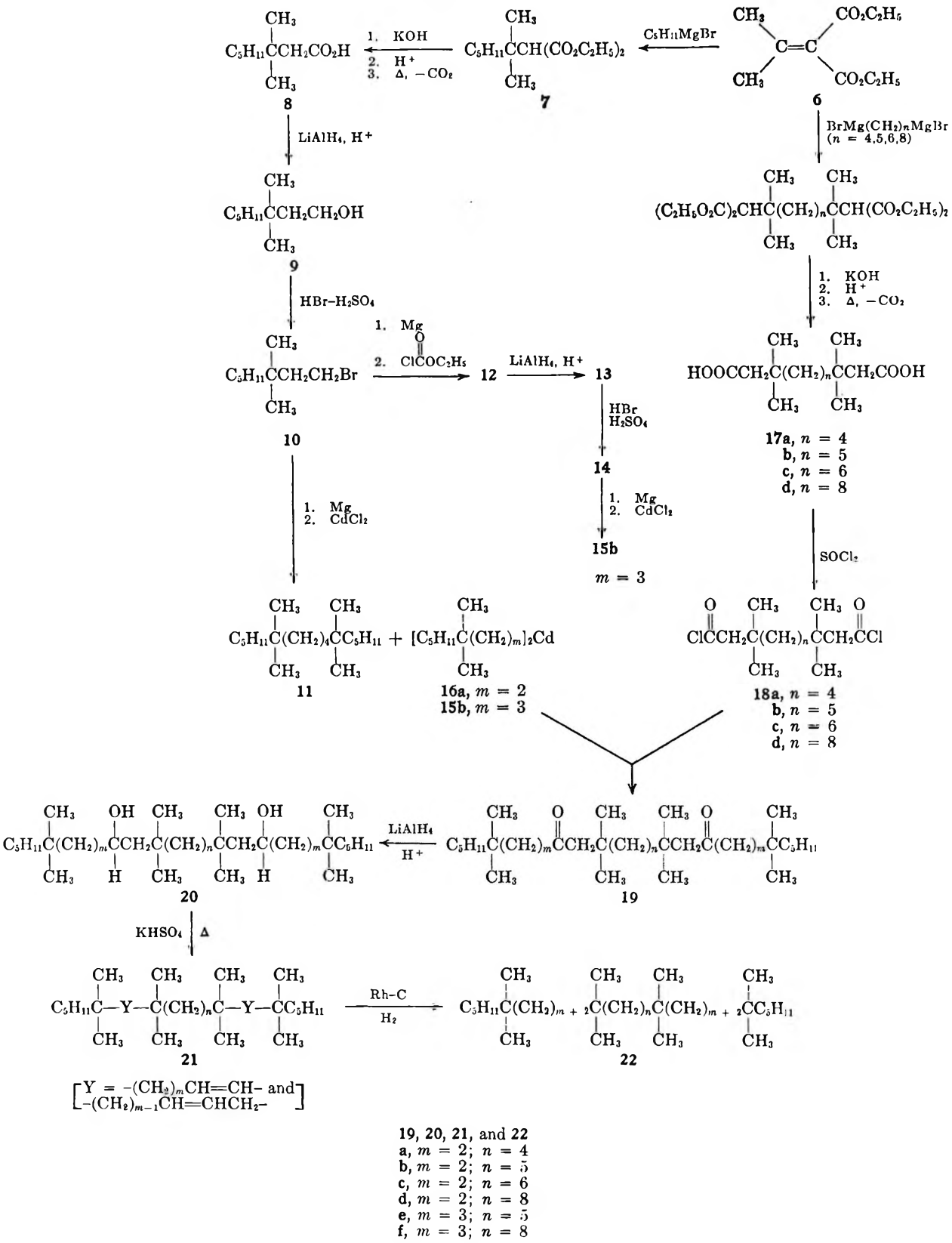
Although our synthetic work was directed primarily toward the synthesis of hydrocarbons containing four *gem*-dimethyl groups, one hydrocarbon with only two, 9,9,18,18-tetramethylhexacosane (**26**), was also prepared. The intermediate diketone, 9,9,18,18-tetramethyl-7-20-hexacosanedione (**23**), was prepared in 88% yield by the reaction of dihexylcadmium with 3,3,-12,12-tetramethyl-1,14-tetradecanedioyl chloride (**18d**).



In an attempt to reduce the diketones directly to the hydrocarbons we selected from the many methods for

(15) S. Widequist, *Ark. Kemi, Mineral. Geol.*, **B23**, No. 4 (1946).
(16) W. H. Hook and R. Robinson, *J. Chem. Soc.*, 1952 (1944).
(17) E. Buchta and E. Weidinger, *Justus Liebigs Chem. Ann.*, **580**, 109 (1953).

SCHEME II

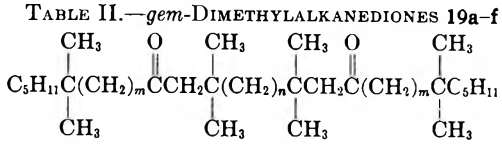


this purpose[18-21] the Wolff–Kishner reduction as the least likely to cause rearrangement.

However, using the Huang-Minlon modification of the Wolff–Kishner reaction[22] we obtained only a 32% yield after chromatography on alumina of the desired hydrocarbon in the reduction of 6,6,11,11,17,17,22,22-octamethyl-9,19-heptacosanedione (**19b**). Reduction of the same diketone by a modification of the Wolff–Kishner reaction, which was developed especially for

(18) E. L. Martin, *Org. React.*, **1**, 155 (1942).
(19) H. Adkins and R. Connor, *J. Amer. Chem. Soc.*, **53**, 1091 (1931).
(20) D. Nightingale and H. D. Radford, *J. Org. Chem.*, **14**, 1089 (1949).
(21) H. Pines, D. R. Strehlau, and V. N. Ipatieff, *J. Amer. Chem. Soc.*, **71**, 3534 (1949); **72**, 1563 (1950).
(22) Huang-Minlon, *ibid.*, **68**, 2487 (1946).

TABLE II.—*gem*-DIMETHYLALKANEDIONES 19a–f

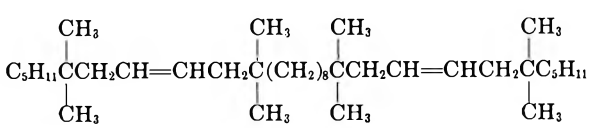


Compd no.	m	n	Bp, °C (mm)	$n^{25}D$	% yield	ν,[a] cm⁻¹ C=O	ν,[a] cm⁻¹ $-C(CH_3)_2-$[b]	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
19a	2	4	198 (0.2)	1.4625	83	1694	1355–1373	$C_{34}H_{66}O_2$	80.56	13.12	80.27	13.04
19b	2	5	210–215 (0.2)	1.4630	86	1692	1355–1373	$C_{35}H_{68}O_2$	80.69	13.15	80.58	13.05
19c	2	6	198–201 (0.05)	1.4630	90	1692	1355–1373	$C_{36}H_{70}O_2$	80.82	13.19	80.59	13.07
19d	2	8	198 (0.15)	1.4636	88	1692	1355–1373	$C_{38}H_{74}O_2$	81.06	13.25	80.69	12.99
19e	3	5	225 (0.15)	1.4630	82	1700	1358–1380	$C_{37}H_{72}O_2$	80.95	13.22	80.94	13.03
19f	3	8	210–218 (0.3)	1.4635	88	1710	1360–1380	$C_{40}H_{78}O_2$	81.28	13.30	81.40	13.75
23[c]			208 (0.3)	1.4631	88	1690	1350–1370	$C_{30}H_{58}O_2$	79.93	12.96	79.60	12.68

[a] Capillary. [b] Range for two bands. [c] 9,9,18,18-Tetramethyl-7,20-hexacosanedione (**23**).

the reduction of hindered or masked carbonyl groups and which uses in the hydrazone formation acid rather than base catalysis and a large (66:1) mole ratio of hydrazine hydrate to carbonyl group,[23] also gave a yield of the desired hydrocarbon after chromatography on alumina of only 35%. This is about the same yield reported for direct reduction of a C_{94} diketone to tetrananonacontane using acid catalysis for hydrazone formation in 1-octanol, followed by decomposition of the hydrazone to hydrocarbon using sodium octylate.[8] These poor yields and the formation of by-products which necessitates tedious purification procedures may result from the conversion of the diketones to azines rather than hydrazones, since these high-molecular-weight diketones have limited solubility in conventional Wolff–Kishner solvents.

Since the Wolff–Kishner reduction proved unsatisfactory, we returned to the three-step method of reduction, dehydration, and hydrogenation reported by Rabjohn, *et al.*[10] This procedure afforded the desired hydrocarbons (**22a–f**) as illustrated in Scheme II, in high yield and purity. The *gem*-dimethylalkanediols (**20a–f**) listed in Table III were obtained in excellent yields (82–99%) *via* lithium aluminum hydride reduction. These diols were dehydrated to diolefin mixtures listed in Table IV in high yields (90–97%) using potassium hydrogen sulfate at 150–160° under reduced pressure. The infrared spectra of these diolefins exhibited no trace of an absorption band for the hydroxyl function and an intense band at 970 cm^{-1} indicative of principally *trans* double bonds. The high ratios of methylene to vinylic protons in the nmr spectra of the diolefins indicate that double bond formation equidistant from the *gem*-dimethyl groups is preferred. In fact, the ratio of methylene protons to vinylic protons of 2.00 in the nmr spectra of the C_{38} diolefin (**21d**) shows that only the less strained olefin is formed.



These results are consistent with the observations of Brown and Berneis[24] that the preferred olefin is the one which has the lowest steric requirements with respect to the *cis*-methyl and *t*-butyl groups in 2,4,4-trimethyl-2-pentene.

(23) W. Nagate and H. Itazoki, *Chem. Ind. (London)*, 1194 (1964).
(24) H. C. Brown and H. L. Berneis, *J. Amer. Chem. Soc.*, **75**, 10 (1953).

The *gem*-dimethylalkanes (**22a–f**) listed in Table V were obtained in excellent yields (82–95%) *via* hydrogenation using 5% rhodium on carbon at elevated temperatures (180°) and pressures of 3200 psi. The infrared spectra of these hydrocarbons exhibited an increase in the intensity of the absorption band due to recurring methylene units and no trace of an absorption band for unsaturation. Their nmr spectra showed no trace of unsaturation and agreed satisfactorily with their proposed structures. The purities of the intermediate diketones, diolefins, and the final quaternary hydrocarbons all exceeded 99% by glc analysis.

Experimental Section[25]

3,3,9,9-Tetramethyl-1,11-undecanedinitrile (4).—A Grignard solution was prepared from 1,5-dibromopentane (114 g, 0.5 mol), magnesium (24.3 g, 1 g-atom) and 1200 ml of ether. This reagent was added to ethyl cyanoisopropylideneacetate (1)[26] (153 g, 1 mol) in a 1200-ml mixture of ether and cuprous iodide (5 g/mol of ester) over 2 hr. The reactants were mixed for 16 hr, refluxed for 1 hr, and decomposed with ice and dilute hydrochloric acid. The aqueous layer was washed several times with ether; the ether solutions were combined and dried ($MgSO_4$). The filtered solutions were concentrated on a steam bath and distilled. The collected forerun was identified as starting material and monoaddition products, bp 105° (1.0 mm) maximum. The pot residue, consisting of crude diaddition reaction product **3** (90 g, 0.238 mol), was refluxed for 3 hr at 135° with potassium hydroxide (56.5 g, 1 mol) and 240 ml of ethylene glycol. This solution was cooled, diluted with 300 ml of water, and extracted with ether. The ether washings were combined, washed with water and a saturated solution of sodium chloride, and dried ($MgSO_4$). The solution was filtered, concentrated on a steam bath, and distilled.

3,3,9,9-Tetramethyl-1,11-undecanedinitrile (**4**) (12.9 g), bp 135–139° (0.2 mm), $n^{25}D$ 1.4569, was obtained in 11% yield in purity greater than 99.5% by glc analysis.

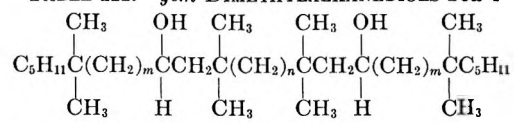
Anal. Calcd for $C_{15}H_{26}N_2$: C, 76.86; H, 11.18; N, 11.95. Found: C, 76.59; H, 11.48; N, 11.73.

Reaction of 3,3-Dimethyloctylmagnesium Bromide (5) and 3,3,9,9-Tetramethyl-1,11-undecanedinitrile (4).—A solution of **4** (11.7 g, 0.048 mol) dissolved in 100 ml of ether was added over a 20-min period to a Grignard reagent prepared from **10** (61 g,

(25) All boiling points and melting points were uncorrected. Microanalysis were performed by Gailbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were determined as a thin film using a Beckman IR-5 spectrometer. All nmr spectra were determined in carbon tetrachloride containing 5% tetramethylsilane as an internal standard using a Varian A-60 nmr spectrometer. Analytical gas–liquid chromatographs were determined using an F & M 720 dual column gas chromatograph. The dual columns were 20 ft, 0.25-in. o.d. packed with 12% Dow Corning high vacuum grease dispersed on 45–50 mesh Chromosorb P. Column temperatures were generally in the range of 250–275° using a helium flow of 70 ml/min. Sample sizes of 0.1 μl were used at maximum attenuation to obtain optimum resolution and detection of any trace impurities for the compounds in the C_{30}–C_{40} molecular-weight range reported herein.

(26) S. Wideqvist, *Acta Chem. Scand.*, **3**, 303 (1949).

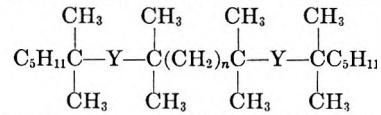
TABLE III.—*gem*-DIMETHYLALKANEDIOLS **20a–f**



Compd no.	m	n	Bp, °C (mm)	$n^{25}D$	% yield	ν,[a] cm⁻¹ O—H	ν,[a] cm⁻¹ −C(CH₃)₂−[b]	ν,[a] cm⁻¹ −C—OH[b]	Formula	Mol wt Calcd	Mol wt Found	Calcd, % C	Calcd, % H	Found, % C	Found, % H
20a	2	4	225–227 (0.02)	1.4692	99	3278	1358–1379	1041–1069	$C_{34}H_{70}O_2$	510	506	79.92	13.81	79.98	13.91
20b	2	5	226 (0.1)	1.4696	97	3246	1355–1373	1041–1069	$C_{35}H_{72}O_2$	522	528	80.07	13.82	80.15	13.56
20c	2	6	225–233 (0.02)	1.4696	97	3246	1355–1373	1036–1069	$C_{36}H_{74}O_2$	539	532	80.22	13.84	80.44	13.72
20d	2	8	240–242 (0.02)	1.4698	99	3246	1355–1373	1036–1052	$C_{38}H_{78}O_2$	567	560	80.48	13.86	80.27	13.75
20e	3	5	245 (0.07)	1.4693	97	3246	1355–1373	1036–1069	$C_{37}H_{76}O_2$	553	551	80.35	13.85	80.45	13.88
20f[c]	3	8	245–255 (0.05)		90	3246	1355–1373	1036–1052	$C_{40}H_{82}O_2$	595	589	80.73	13.89	80.60	14.03
24[d]			210–215 (0.02)	1.4675	82	3246	1352–1373	1035–1060	$C_{30}H_{62}O_2$	454	448	79.22	13.74	79.35	13.65

[a] Capillary. [b] Range for two bands. [c] Semiwaxy diol. [d] 9,9,18,18-Tetramethyl-7,20-hexacosanediol (**24**).

TABLE IV.—*gem*-DIMETHYLALKADIENES **21a–f**

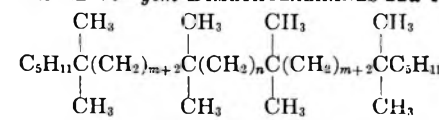


[Y = either $-(CH_2)_mC{=}CH-$, or $-(CH_2)_{m-1}CH{=}CHCH_2-$, both radicals]

Compd no.	m	n	Bp, °C (mm)	$n^{25}D$	% yield	ν,[a] cm⁻¹ −C(CH₃)₂−[b]	ν,[a] cm⁻¹ C=C	Nmr α-CH₂C=C	Formula	Mol wt Calcd	Mol wt Found	Calcd, % C	Calcd, % H	Found, % C	Found, % H
21a	2	4	200–205 (0.02)	1.4658	96	1358–1377	970	1.74	$C_{34}H_{66}$	475	480	85.99	14.00	86.07	13.97
21b	2	5	205–210 (0.1)	1.4662	90	1366–1385	972	1.70	$C_{35}H_{68}$	488	477	85.97	14.02	86.20	13.79
21c	2	6	195–210 (0.02)	1.4660	93	1355–1373	968	1.84	$C_{36}H_{70}$	502	502	85.96	14.03	85.69	13.93
21d	2	8	215–222 (0.04)	1.4662	97	1355–1373	969	2.00	$C_{38}H_{74}$	530	533	85.96	14.04	85.89	13.85
21e	3	5	202–205 (0.02)	1.4660	74	1360–1380	969	1.50	$C_{37}H_{72}$	517	523	85.96	14.04	85.91	14.02
21f	3	8	215–220 (0.08)	1.4662	98	1360–1380	970	1.42	$C_{40}H_{78}$	559	566	85.93	14.07	85.87	14.04
25[c]			178–180 (0.02)	1.4614	93	1355–1373	970	1.68	$C_{30}H_{58}$	418	430	86.03	13.96	85.79	13.84

[a] Capillary. [b] Range for two bands. [c] 9,9,18,18-Tetramethyl-(6)7,19(20)-hexacosadiene (**25**).

TABLE V.—*gem*-DIMETHYLALKANES **22a–f**



Compd no.	m	n	Bp, °C (mm)	$n^{25}D$	d^{25}_4	% yield	ν,[a] cm⁻¹ −C(CH₃)₂−[c]	ν,[a] cm⁻¹ −(CH₂)ₙ−[b]	Formula	Mol wt Calcd	Mol wt Found	CH₃/CH₂ Calcd	CH₃/CH₂ Found (nmr)	Calcd, % C	Calcd, % H	Found, % C	Found, % H
22a	2	4	190–194 (0.02)	1.4570	0.8278	95	1369–1388	725	$C_{34}H_{70}$	479	483	0.500	0.502	85.27	14.73	85.50	14.46
22b	2	5	189–194 (0.03)	1.4568	0.8230	85	1366–1385	724	$C_{35}H_{72}$	493	492	0.476	0.475	85.28	14.72	85.48	14.65
22c	2	6	195–200 (0.02)	1.4575	0.8226	82	1369–1388	726	$C_{36}H_{74}$	507	510	0.454	0.451	85.29	14.71	85.55	14.42
22d	2	8	212–215 (0.02)	1.4580	0.8351	94	1369–1388	725	$C_{38}H_{78}$	535	536			85.30	14.70	85.62	14.33
22e	3	5	202–205 (0.04)	1.4587		79	1355–1372	720	$C_{37}H_{76}$	521	526	0.434	0.436	85.29	14.70	85.27	14.72
22f	3	8	220–225 (0.03)	1.4600		84	1369–1388	720	$C_{40}H_{82}$	563	552	0.384	0.381	85.32	14.68	85.37	14.70
11[d]			136–140 (1.4)	1.4430		15–20[e]	1370–1389	721	$C_{20}H_{42}$	282	286	0.500	0.502	85.01	14.98	84.73	15.00
26[f]			180 (0.03)	1.4528	0.8149	86	1370–1389	721	$C_{30}H_{62}$	422	430	0.273	0.276	85.27	14.72	85.50	14.48

[a] Capillary. [b] Increased methylene absorption. [c] Range for two bands. [d] 6,6,11,11-Tetramethylhexadecane (**11**). [e] Average per cent yield of **11** obtained in preparation of **16a**. [f] 9,9,18,18-Tetramethylhexylcosane (**26**).

0.276 mol), 600 ml of ether and magnesium. The reactants were gently refluxed for 18 hr, cooled, and hydrolyzed with 500 g of ice and 180 ml of concentrated hydrochloric acid. The hydrolyzed reaction mixture was warmed on a steam bath with excess ether (1 l.) for 1 hr with stirring. The aqueous layer was extracted with ether; the ether layers were combined and washed with water, 10% sodium bicarbonate, and finally with water until the washings tested neutral. The dried ether extracts ($MgSO_4$) were filtered and concentrated on a steam bath and the concentrates vacuum distilled. The fraction boiling principally at 199–202° (0.05 mm), 15.2 g (61% yield), $n^{25}D$ 1.4628, had identical glc retention time and infrared spectrum as those observed for 6,6,11,11,17,17,-22,22-octamethyl-9,19-heptacosanedione (**19b**). This diketone (**19b**) was also prepared *via* the organocadmium–acid chloride route. Analysis of equal concentrations of each diketone by glc showed only one peak with no shoulders showing unequivocally that these diketones are identical.

Ethyl 1,1-Dimethylhexylmalonate (7).—A Grignard solution was prepared from 1-bromopentane (151 g, 1 mol), magnesium (24.3 g, 1 g-atom), and 1200 ml of ether. This reagent was added to ethyl isopropylidenemalonate (6)[27] (200 g, 1 mol) dissolved in 1200 ml of ether containing cuprous iodide (5 g/mol of ester) over 2 hr. The reactants were stirred for 16 hr, heated for 1 hr, and decomposed with ice and dilute hydrochloric acid. The aqueous layer was separated and washed several times with ether; the ether solutions were dried ($MgSO_4$). The filtered ether solutions were concentrated on a steam bath and distilled. **7**, bp 128–132° (3.0 mm), $n^{25}D$ 1.4359, was obtained in 65% yield and showed no trace impurities by glc.

Anal. Calcd for $C_{15}H_{28}O_4$: C, 66.63; H, 9.69. Found: C, 66.75; H, 9.86.

3,3-Dimethyloctanoic Acid (8).—**7** (272 g, 1 mol) was added dropwise over 2 hr to a hot solution of potassium hydroxide (200 g, 3.5 mol) and water (200 ml). The mixture was refluxed at 93° for 3 hr, cooled, diluted with 200 ml of water, and distilled to collect 200 ml of ethanol forerun. Cold sulfuric acid (175 ml of concentrated H_2SO_4–450 ml of water) was added cautiously to this mixture (45–50°) before refluxing all these components for 4 hr. The cooled, aqueous layer was separated and washed with benzene; the benzene extracts were combined with the organics. The dried benzene extracts ($MgSO_4$) were filtered, concentrated on a steam bath and distilled with carbon dioxide evolution. Crude **8**, bp 120–125° (3.5 mm), was obtained in 94% yield. The purity of **8** was improved by distillation, bp 104° (1.0 mm), $n^{25}D$ 1.4355.

Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.50; H, 11.80.

3,3-Dimethyl-1-octanol (9).—Addition of an ethereal solution of **8** (75 g, 0.43 mol) to a stirred suspension of 20.3 g of lithium aluminum hydride in 1200 ml of ether, followed by the usual procedures and distillation of the residual oil gave a total of 67.1 g (98%) of **9** boiling principally at 110–111° (2.5 mm). **9** was further purified by distillation, bp 72° (0.7 mm), $n^{25}D$ 1.4378.

Anal. Calcd for $C_{10}H_{22}O$: C, 75.88; H, 14.01. Found: C, 75.81; H, 13.91.

1-Bromo-3,3-dimethyloctane (10).—A mixture of 48% hydrobromic acid (240 g, 1.4 mol), concentrated sulfuric acid (62 g, 0.34 mol), and **9** (87 g, 0.55 mol) was refluxed for 5 hr at 125°. The cooled solution was diluted with water and filtered through Hyflo Super Cel and the bromide layer separated. The crude bromide was washed with 10 ml of cold sulfuric acid, 100 ml of water and 100 ml of 10% sodium carbonate. A light brown oil was dried ($MgSO_4$), filtered and distilled, bp 85–90° (2.5 mm), 85% yield. **10** was further purified by distillation, bp 69° (0.25 mm), $n^{25}D$ 1.4575.

Anal. Calcd for $C_{10}H_{21}Br$: C, 54.29; H, 9.57; Br, 36.13. Found: C, 54.20; H, 9.66; Br, 36.14.

3,3,9,9-Tetramethyl-1,11-undecanedioic Acid (17b).—The ester precursor to this acid (n = 5) was prepared by the same procedure listed for **8**. A Grignard solution prepared from 1,5-dibromopentane (230 g, 1 mol) and magnesium (48.6 g, 2 g-atoms) in 1200 ml of ether was added over a period of 1 hr to **6** (440 g, 2 mol) dissolved in 1200 ml of ether containing 10 g of cuprous iodide. This mixture was stirred for 12 hr at reflux, cooled, and hydrolyzed. After distillation of the low boiling reaction products, bp 55–135° (1.4 mm), the crude ester (~250 g) in the distillation pot was saponified and decarboxylated. Crude **17b**, bp 178–180° (0.1 mm), was obtained in 31% yield. Recrystallization from hexane gave a white crystalline solid, mp 96–97° (*cf.* Table I).

3,3,9,9-Tetramethyl-1,11-undecanedioyl Chloride (18b).—**17b** (41 g, 0.15 mol) was added as a solid to excess thionyl chloride (71.4 g, 0.6 mol) over a period of 40 min with stirring. The mixture was refluxed for 1.5 hr at 55°; excess thionyl chloride was distilled carefully *in vacuo*, after which the crude acid chloride (**18b**, n = 5) was distilled, bp 150–152° (0.2 mm), in 88% yield. Since several of the higher melting acids listed herein had limited solubility in thionyl chloride owing to the endothermic nature of the reaction, it was necessary to heat these mixtures gently at 40–45° during the addition of the acids.

6,6,11,11,17,17,22,22-Octamethyl-9,19-heptacosanedione (19b).—This diketone, and the *gem*-dimethylalkanediones listed in Table II, were prepared using the general procedures described by Cason and Prout.[28] A Grignard solution was prepared from **10** (77.5 g, 0.35 mol) and magnesium (9.7 g, 0.4 g-atom) in 600 ml of ether. Anhydrous cadmium chloride (40 g, 0.22 mol), dried in a vacuum oven at 110°, was added to the decanted Grignard solution in a dry nitrogen atmosphere at ice-bath temperature, and di(3,3-dimethyloctyl)cadmium (**16a**) prepared by conventional techniques.[28] **18b** (27 g, 0.09 mol) dissolved in 50 ml of benzene was added slowly to **16a** at 68° since the reaction was very exothermic. The mixture was refluxed for 2 hr, poured into a 10% solution of sulfuric acid and extracted with ether. The ether solutions were washed with water, 5% sodium carbonate, and a saturated solution of sodium chloride and dried ($MgSO_4$). The reaction products were filtered, concentrated on a steam bath and distilled (*cf.* Table II). A lower boiling component, bp 136° (1.4 mm), $n^{25}D$ 1.4330, was isolated in 18% yield. This was identified as 6,6,11,11-tetramethylhexadecane (**11**).

Anal. Calcd for $C_{20}H_{42}$: C, 85.01; H, 14.98. Found: C, 84.73; H, 15.00.

6,6,11,11,17,17,22,22-Octamethyl-9,19-heptacosanediol (20b).—This procedure is typical of those used to obtain the *gem*-dimethylalkanediols listed in Table III. A mixture of 61 g (0.16 mol) of lithium aluminum hydride in 600 ml of ether was stirred while 20.8 g (0.04 mol) of **19b** in 600 ml of ether was added at a rate sufficient to cause gentle refluxing. After the addition, the mixture was stirred at ambient temperature for 14 hr and refluxed for 5 hr. Excess lithium aluminum hydride was decomposed cautiously by the dropwise addition of cold water at ice-bath temperatures, and the reaction mixture hydrolyzed with 500 ml of 10% sulfuric acid. The ether layer was removed, washed with water, 10% sodium bicarbonate, and again with water and dried ($MgSO_4$). The ether solution was filtered, concentrated on a steam bath and distilled to give 20.5 g (97% yield) of **20b** (*cf.* Table III).

6,6,11,11,17,17,22,22-Octamethyl-(8)9,18(19)-heptacosadiene (21b).—This procedure is typical of those used to obtain the *gem*-dimethylalkadienes listed in Table IV. **20b** (20.5 g, 0.04 mol) was heated with anhydrous potassium bisulfate (6 g, 0.044 mol) at 150–160° for 6 hr at reduced pressure (3–5 mm). The cooled reaction product was decanted, the potassium bisulfate was washed several times with small portions of ether, and the oil and extracts were combined. The concentrate was distilled to give 17.5 g (90% yield) of **21b** (*cf.* Table IV).

6,6,11,11,17,17,22,22-Octamethylheptacosane (22b).—The *gem*-dimethylalkanes listed in Table V were obtained by means of the typical hydrogenation procedure at elevated temperatures and pressures described herein. **21b** (13.8 g, 0.028 mol), methylcyclohexane (75 ml), and 1 g of 5% rhodium-on-carbon catalyst were heated to 180° in a 300-ml bomb and rocked for 8 hr at a final pressure of hydrogen and reactants of 3200 psi. The cooled reaction mixture was filtered free of catalyst and concentrated *in vacuo*, and the concentrate distilled to yield 11.7 g (85% yield) of **22b** (*cf.* Table V).

Ethyl 4,4-Dimethylnonanate (12).—This ester was prepared by a procedure similar to that described by Gaertner.[29] A Grignard reagent prepared from **10** (442 g, 2.0 mol), magnesium (49.5 g, 2.0 g-atoms), and 2 l. of ether was added to ethyl chlorocarbonate (1080 g, 10 mol) in 2 l. of ether at −40° over a 4 hr period. The reactants were allowed to warm to room temperature overnight and washed with a solution of ammonium chloride and the excess ether was removed *in vacuo* with mild heating. Distillation of crude **12**, bp 100–105° (1.2–1.5 mm), gave 245

(27) A. C. Cope and E. M. Hancock, *J. Amer. Chem. Soc.*, **60**, 2644 (1938).

(28) J. Cason and F. S. Prout, *ibid.*, **66**, 47 (1944); *Org. Syn.*, **28**, 75 (1948).

(29) R. Gaertner, *ibid.*, **73**, 3934 (1951).

g (69% yield). Per cent yield is based on the availability of Grignard reagent since 50.5 g of the Grignard dimer 11 was also isolated from this mixture. The purity of 12 was improved by distillation, bp 108° (1.2 mm), $n^{25}D$ 1.4302.

Anal. Calcd for $C_{13}H_{26}O_2$: C, 72.84, H, 12.22. Found: C, 72.50; H, 12.01.

4,4-Dimethyl-1-nonanol (13).—Addition of an ethereal solution of 198 g (0.93 mol) of 12 to a stirred suspension of 33 g of lithium aluminum hydride in 1200 ml of ether, followed by the usual procedures, gave a total of 152 g (95%) of 13, bp 105–109° (1.0 mm). The purity of 13 was improved by distillation, bp 109° (1.0 mm), $n^{25}D$ 4.4400.

Anal. Calcd for $C_{11}H_{24}O$: C, 76.67; H, 14.04. Found: C, 76.67; H, 14.17.

1-Bromo-4,4-dimethylnonane (14).—A mixture of 48% hydrobromic acid (384 g, 2.24 mol), concentrated sulfuric acid (98 g, 1 mol), and 13 (152 g, 0.88 mol) was refluxed for 5 hr at 125°. The cooled solution was diluted with water and filtered through Hyflo Super Cel; the bromide layer separated. The crude bromide was washed with 10 ml of cold sulfuric acid, 100 ml of water, and 100 ml of 10% sodium carbonate. Crude 14 was dried ($MgSO_4$), filtered, and distilled, bp 94° (1.0 mm), $n^{25}D$ 1.4578, yield 75%.

Anal. Calcd for $C_{11}H_{23}Br$: C, 56.16; H, 9.85; Br, 33.97. Found: C, 56.03; H, 10.13; Br, 34.03.

6,6,11,11,17,17,22,22-Octamethylheptacosane (22b). A. Huang-Minlon Modification.—19b (20.0 g, 0.038 mol), 15 ml of 85% hydrazine hydrate, 200 ml of diethylene glycol, and potassium hydroxide (15 g, 0.27 mol) were refluxed for 16 hr at 155° before the heat was increased to 165° to collect 15 ml of low boiling components. The reaction mixture was heated at 195° for 4 hr, cooled, and diluted with ether and water; the ether extracts were collected and washed to neutrality. The dried ether extracts ($MgSO_4$) were concentrated on a steam bath and the residue was distilled under vacuum to yield five fractions. The highest boiling fraction, bp 195–215° (0.2 mm), was shown by glc to be mainly 22b (10.4 g) with minor impurities. Chromatography on alumina using heptane gave 6.0 g (32% yield) of 22b in high purity (>99%), bp 220° (0.2 mm).

B. Nagate and Itazaki Modification.—19b (22.6 g, 0.043 mol), 85% hydrazine hydrate (287 g, 5.57 mol), hydrazine dihydrochloride (73.0 g, 0.7 mol), and triethylene glycol (980 g, 6.5 mol) were heated for 12 hr at 130–150° with a Soxhlet extractor or apparatus containing calcium oxide (50 g) fitted to the reaction flask to remove traces of water. The reaction mixture was heated for an additional 12 hr until the temperature rose to 175° and cooled; after KOH (106 g, 1.9 mol) addition, it was then heated to 175° for 6 hr and finally to 225° for 4 hr. The cooled reaction mixture was worked up by the usual procedure and 13.5 g of a crude reaction product, bp 140–185° (0.07 mm), was obtained. Chromatography on alumina using heptane gave 7.5 g (35% yield) of 22b, bp 208° (0.1 mm), in high purity (>99%) as evidenced by glc analysis.

Registry No.—4, 25570-04-1; 7, 25570-05-2; 8, 14352-59-1; 9, 25570-07-4; 10, 25570-08-5; 11, 19342-94-0; 12, 25570-10-9; 13, 25570-11-0; 14, 25570-12-1; 17a, 20778-76-1; 17b, 22704-13-8; 17c, 25570-15-4; 17d, 25570-16-5; 18b, 25570-17-6; 19a, 25570-18-7; 19b, 25570-19-8; 19c, 25570-20-1; 19d, 25570-21-2; 19e, 25570-22-3; 19f, 25570-23-4; 20a, 25570-24-5; 20b, 25570-25-6; 20c, 25570-26-7; 20d, 25577-25-7; 20e, 25577-26-8; 20f, 25577-27-9; 21a, 25641-47-8; 21b, 25641-48-9; 21c, 25641-49-0; 21d, 25577-28-0; 21e, 25641-50-3; 21f, 25641-51-4; 22a, 25577-29-1; 22b, 25577-30-4; 22c, 25577-31-5; 22d, 25577-32-6; 22e, 25577-33-7; 22f, 25577-34-8; 23, 25577-35-9; 24, 25577-36-0; 25, 25641-52-5; 26, 25577-37-1.

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High Temperature Pyrolysis of C_1 to C_4 Hydrocarbons[1]

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The pyrolysis of nine hydrocarbons at 1200° has been studied. The main products, which were the same for all hydrocarbons studied, were 1,3-cyclopentadiene, benzene, toluene, phenylacetylene, styrene, indene, and naphthalene. Twenty-three minor products were identified. The distribution of products can be accounted for in terms of polymerization of acetylene, produced by the pyrolysis of the hydrocarbon, and the addition of CH_2 or CH_3 to some of the acetylene polymers.

Pyrolyses of simple hydrocarbons have been studied previously by various investigators with the main emphasis on the kinetics and mechanism of decomposition.[2-6] However, these pyrolyses were usually done at relatively low temperatures (500–700°) and only the main end products were analyzed, with a few exceptions.[7-11] We report here pyrolysis reactions that take place at higher temperature (1200°) with particular emphasis on the product analysis. We have attempted to describe the mechanism on the basis of the nature of the end products and their relative yields.

The pyrolysis chamber contained a hot tungsten wire, and the walls of the flask were kept cold so that high-molecular-weight compounds formed by a recombination of the initial fragmentation of the hydrocarbons were condensed on the walls of the chamber and were not subjected to further pyrolysis to a significant degree.[12,13] The major products from these pyrolyses are shown in Table I. The minor components are listed at the bottom of Figure 1 in order of their retention time on the gas chromatograph column.

Results and Discussion

The pyrolysis of each of the hydrocarbons studied at 1200° leads to the same end products, but both the

(1) This work was supported by NSF grant GB-8056.
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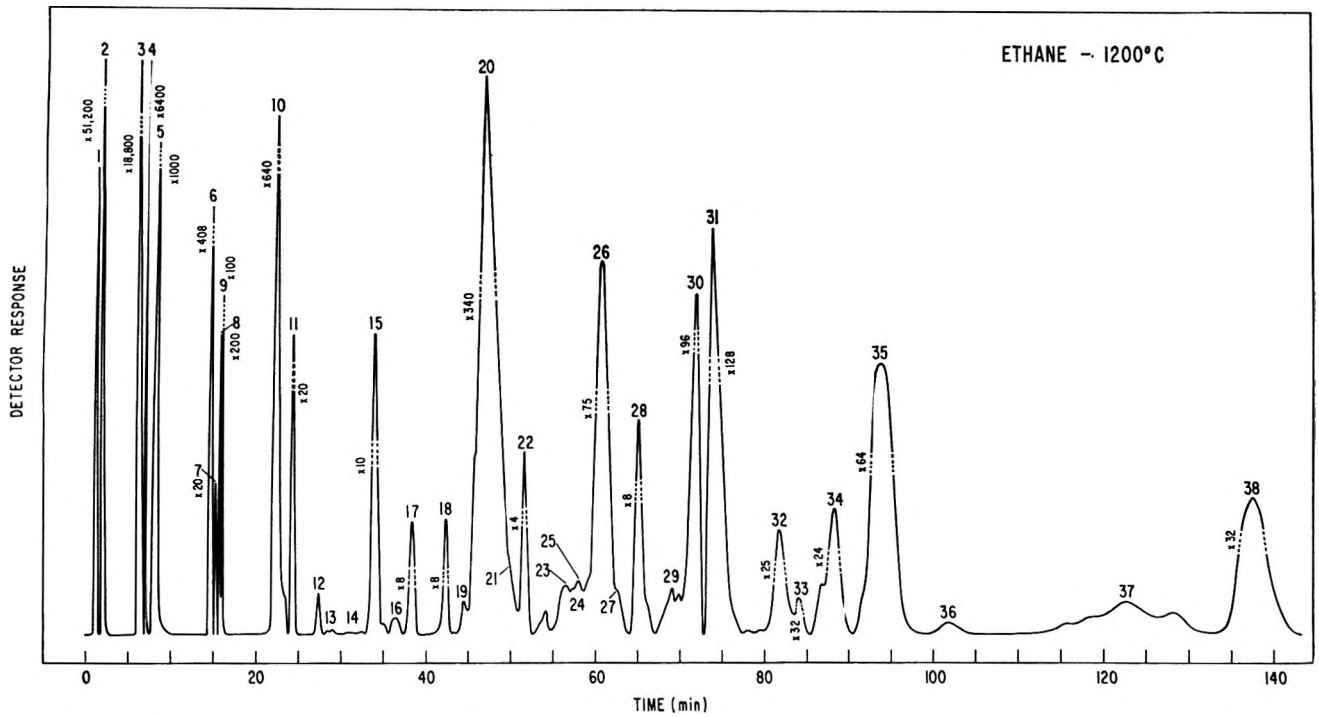


Figure 1.—Gas chromatograph analysis of products from the pyrolysis of ethane at 1200°. Varian Model 1200 was used with 10-ft, 1/8-in. stainless steel Porapak Q. The column temperature was programmed as follows: isothermal at 40° for 5 min, then 8° min^{-1} for 10 min followed by 2° min^{-1} to a temperature of 240° where it remained isothermal to the end of the run. Peaks 1–14 were analyzed with a sample of the gas phase and 15–38 with a sample of the liquid phase: (1) hydrogen; (2) methane; (3) ethylene; (4) acetylene; (5) ethane; (6) propene; (7) propane; (8) propyne; (9) allene; (10) 1,3-butadiene; (11) 1,3-butadiyne; (12) 2-butene; (13) 1-butene; (14) 3-pentene-1-yne; (15) 1,3-cyclopentadiene; (16) 2-pentyne; (17) *trans*-1-pentyne-3-ene; (18) methyldiacetylene; (19) 1,3,5-hexatriene; (20) benzene; (21) 1,3-cyclohexadiene; (22) three hydrocarbons (triacetylene? 1,5-diyne-3-hexene? 2-methylcyclopentadiene?); (23) methyl-1,3-cyclohexadiene; (24) 1-heptyne; (25) C_7H_{10}; (26) toluene; (27) C_7H_{10}; (28) 1,3,5-cycloheptatriene; (29) four hydrocarbons with mol wt 112, 110, 108, 106; (30) phenylacetylene and ethylbenzene; (31) styrene; (32) α- or β-methylstyrene; (33) C_3-benzene (mol wt 120); (34) 2,3-dihydroindene; (35) indene; (36) 4-phenyl-1-butene; (37) 1-methylindene; (38) naphthalene.

TABLE I

MAJOR PRODUCTS FROM THE PYROLYSIS OF HYDROCARBONS AT 1200°

	Benzene[a]	Toluene	Phenyl-acetylene	Styrene	Indene	Naphthalene	Cyclo-pentadiene
Methane	0.1	63	75	96	81	42	375
Ethane	18.4	31	20	35	21	8.1	1.3
Ethylene	22.8	16	5.2	24	18	2.0	4.2
Acetylene	42.3	3.5	15	10	13	8.0	0.1
Propane	15.2	22	3.5	8.2	3.1	1.6	3.6
Cyclopropane	5.3	15	2.0	4.9	0.9	Trace	14
Allene	19	11	2.1	3.1	0.8	0.7	6.9
Butane	12.1	15	5.4	10	7.0	Trace	11
Isobutane	13.2	24	8.7	13	15	6.3	0.5

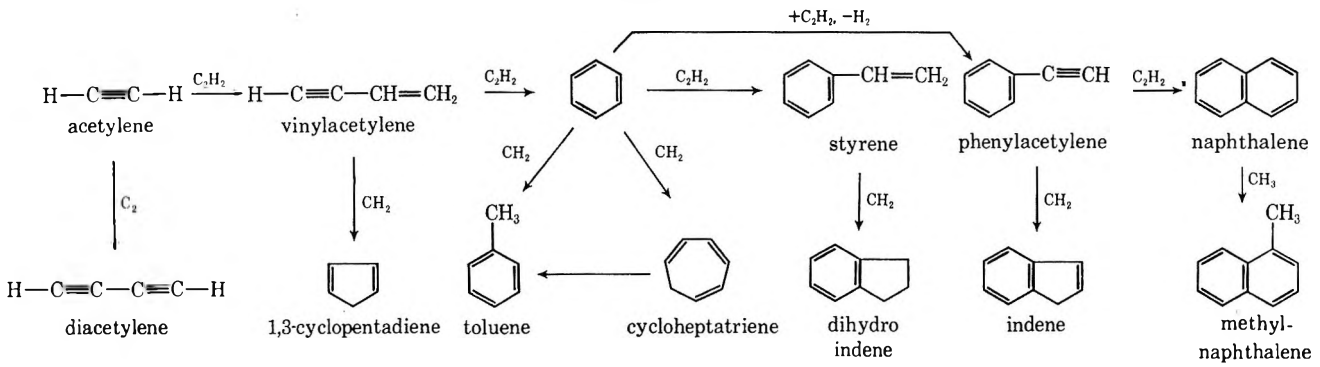
[a] Per cent yield of benzene based on the total carbon initially present. The entries for the other compounds are the yields relative to benzene taken as 100. The pyrolyses lasted for 2 hr.

relative and absolute yields vary markedly (Table I). Benzene is the major end product for all the hydrocarbons pyrolyzed with the exception of methane, and the yield ranges from 5 to 43%. In the case of methane, not only is the absolute yield of benzene 1/50th the yield from any of the other hydrocarbons, but benzene is not the major end product. The yield of 1,3-cyclopentadiene from the pyrolysis of methane is about four times as great as that of benzene.

The effect of changing the wire temperature was studied with the pyrolysis of ethane. Ethane was pyrolyzed for 2 hr at temperatures of 800, 1000, 1200, and 1400°; the yield of benzene based on the initial amount of ethane added was 0.09, 0.12, 18, and 25% respectively. The relative yields of other end products at these different temperatures were nearly the same as the values at 1200° given in Table I.

The similarity of products and yields from the C_2, C_3, and C_4 hydrocarbons, as well as the different results with CH_4, can be explained on the basis that the reactive species in these pyrolyses is acetylene or an activated form of it. A consideration of such an intermediate explains first the relatively low yield of end products from the pyrolysis of methane compared with the yield from the other hydrocarbons. The products from methane, ethane, ethylene, and acetylene account for 0.8, 47, 38, and 63%, respectively, of the initial hydrocarbon added. Secondly, methane yields a ratio of C_{2n} molecules to C_{2n+1} molecules less than unity (0.6), whereas for the other gases this ratio varies from 3.1 for

SCHEME I



ethane to 7.8 for acetylene. Furthermore, since methane cannot undergo initial dehydrogenation to form the reactive C_2 intermediate, a recombination of the initial fragments (methyl radicals or carbene) must take place before any polymerization reaction proceeds. This explains the large yield of cyclopentadiene from the pyrolysis of methane. Once such a two-carbon reactive intermediate has been formed it is more likely to react with a one-carbon radical to form a C_3 molecule than to react with an acetylene. Since the walls of the pyrolyzing chamber are kept only at about $-30°$, a C_3 molecule will not condense on the walls and will be subject to further reactions such as two consecutive additions of a C_1 molecule to form 1,3-cyclopentadiene, which will largely condense on the $-30°$ walls.

The formation of cyclopentadiene, cycloheptatriene, toluene, dihydroindene, and indene can be accounted for by the reaction of CH_2 with even-carbon products of the pyrolysis (Scheme I). The reaction of CH_3 radicals instead of, or in addition to, the CH_2 could also account for the odd-carbon products. Carbene is known to react at lower temperatures with benzene[14,15] to give toluene and cycloheptatriene in a ratio of 1 to 3. The higher temperatures would isomerize most of the cycloheptatriene to toluene. That a one-carbon intermediate is available is also seen from the examination of *n*-butane and isobutane with respect to their yield of 1,3-cyclopentadiene. In the case of butane, once a one-carbon radical is formed it will react with the available parent compound or dehydrogenated products (*e.g.*, diacetylene, vinylacetylene, etc.) to form large quantities of 1,3-cyclopentadiene after further dehydrogenation. In the case of isobutane this is not possible due to the presence of the secondary carbon in the parent compound, and so the yield of 1,3-cyclopentadiene is relatively low.

Pyrolyses at temperatures lower than studied here give more highly hydrogenated products and the reaction mechanism probably involves radical intermediates formed by breaking a single bond. At temperatures above 1000°, acetylene is more stable than ethylene, ethane, or higher hydrocarbons. Rate of bond breaking at 1200° is sufficiently rapid that more than one bond can be broken during the pyrolysis. Therefore, the character of the high temperature pyrolysis is different from those at temperatures between 400 and 700° and appears to be dominated by acetylene polymerizations.

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We have previously shown the role of phenylacetylene in the synthesis of phenylalanine and tyrosine under primitive earth conditions.[13] The other hydrocarbons reported here from pyrolysis reactions may be useful starting materials for other prebiotic synthesis reactions.

Experimental Section

Materials.—Methane, pure grade, was obtained from Phillip's Petroleum Co. Lecture bottles of ethane, ethylene, propane, allene, cyclopropane, butane, and isobutane were obtained from Matheson Co. and were used without further purification. Acetylene was synthesized from calcium carbide and purified on a vacuum line directly before use.

Pyrolysis.—The hydrocarbons were introduced to the pyrolyzing vessel through a vacuum line. The reaction chamber consisted of a 1-l. flask in which a 0.025 × 15 cm tungsten wire was connected between two tungsten electrodes which in turn were connected to an Electro D.C. Power Supply Model NFB. The flask was immersed in an ethanol bath maintained between -35 and $-20°$ by adding Dry Ice. The tungsten wire was heated to temperatures between 800 and 1400° for 2 hr. The temperature of the wire was measured using a Pyrometer Instrument Co. Model 95. When the reaction was completed the flask was cooled to $-78°$, and the products volatile at this temperature were saved for analysis. The vessel was then brought to room temperature and the visible liquid at the bottom was distilled overnight into a tube cooled with Dry Ice. The distillation was completed by heating the reaction vessel to 100°. This distilled material was weighed and then sealed in a tube until used for analysis.

Identification: Benzene, toluene, phenylacetylene, styrene, and indene were identified by their retention time on two gas chromatograph columns, and by their ir and uv spectra. The columns were 5-ft 0.25-in. aluminum tubing containing 20% DEGS on Chromosorb P, and 5-ft $^1/_8$-in. stainless steel tubing containing Porapak Q. The unknown peaks were collected at the column exit. The infrared and ultraviolet spectra were obtained using Perkin-Elmer Infracord and Cary Model 15 spectrophotometers.

The other hydrocarbons were identified by combined gas chromatography and mass spectrometry. The gas chromatograph was a Varian Aerograph Model 1200 and a flame ionization detector. The mass spectrometer was a Hitachi Perkin-Elmer Model RMU-6D single focusing instrument. A 10-ft $^1/_8$-in. stainless steel Porapak Q column was used for the separation. A 4-to-1 splitter divided the column effluent so that 80% of the sample went to the flame ionization detector and 20% went to the mass spectrometer inlet system. A Watson-Biemann helium separator served to enrich the sample and reduce the pressure at the mass spectrometer inlet.[16]

Registry No.—Methane, 74-82-8; ethane, 74-84-0; ethylene, 74-85-1; acetylene, 74-86-2; propane, 74-98-6; cyclopropane, 75-19-4; allene, 463-49-0; butane, 106-97-8; isobutane, 75-28-5.

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Further Observations on the Catalytic Transformation of Benzoic Anhydrides into Fluorenones and Biphenyls

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The catalytic conversion of benzoic anhydrides into fluorenones and biphenyls by several rhodium compounds has been studied. Mixtures of aromatic anhydrides react generally as if they were mixed anhydrides, leading to the formation of asymmetrically substituted products. Equimolar amounts of the isolated phenyl-rhodium complex $PhRhCl(PPh_3)_2$ (**7**) and chlorocarbonylbis(triphenylphosphine)rhodium (**2**) react at 250° to give fluorenone and biphenyl. Both these compounds are assumed to be formed *via* the same rhodium intermediate.

In a previous publication[1] it has been shown that benzoic anhydride and some of its derivatives can be transformed catalytically by chlorotris(triphenylphosphine)rhodium(I), $RhCl(PPh_3)_3$ (**1**), and by chlorocarbonylbis(triphenylphosphine)rhodium(I), $RhCl(CO)(PPh_3)_2$ (**2**), into fluorenones, benzoic acids, carbon monoxide, small quantities of benzophenones, and, according to the experimental conditions, into varying amounts of biphenyls.

We have now extended this study, exploring the scope of the reaction and the possibility of using *mixtures* of anhydrides for the synthesis of fluorenones and biphenyls. In addition to **1** and **2**, several other rhodium complexes, as well as anhydrous rhodium trichloride, proved to be effective catalysts for these reactions (Table I). Palladium dichloride, hydrated ruthenium trichloride, and hydrated iridium trichloride possess low catalytic activity, while rhodium trichloride trihydrate and metallic rhodium have proved to be inactive under our conditions.

TABLE I

CONVERSION OF BENZOIC ANHYDRIDE TO FLUORENONE AND BIPHENYL BY VARIOUS CATALYSTS

	Reaction		Yield	
Catalyst[a]	Temp, °C	Time, hr	Fluorenone, mol %	Biphenyl, mol %
$RhCl(CO)(PPh_3)_2$[b]	240	4.5	35–52	2.2–3
$RhCl(PPh_3)_3$[b]	240	4.5	36–40	6–7
$RhCl_3$, anhydrous	290	6.5	26	3.6
$Rh_2(CO)_4Cl_2$	250	4	22	<1
$RhCl_3(SbPh_3)_3$	250	4	8	1
$RhH(CO)(PPh_3)_3$	250	3	6	<1
$IrCl_3$, $3H_2O$	310	3.5	4.1	Traces
$PdCl_2$	350	4	4.0	Traces
$RuCl_3$, $3H_2O$	290	6	1.3	Traces
$RuCl_2(PPh_3)_3$[c]	340	1	0.8	Traces

[a] Concentration 10^{-2} mol per mol of anhydride. [b] *Cf.* ref 1. [c] 8 mol % of benzophenone was formed in this experiment.

Mixtures of aromatic anhydrides, which often equilibrate with the (unstable) mixed anhydride,[2] could be decarbonylated by **1** to give the fluorenones expected from the *mixed* anhydrides (Table II). Thus a mixture of benzoic and *p*-chlorobenzoic anhydride gives, in addition to the unsubstituted fluorenone and 2,6-dichlorofluorenone,[1] also the "mixed" products, 2- and 3-monochlorofluorenone. A mixture of benzoic and *m*-chlorobenzoic anhydride yielded all four monochlorofluorenones, the 1 and 4 isomers in low yield. Equimolar amounts of *p*-chlorobenzoic and *p*-toluic anhydride give both 2-chloro-6-methyl- and 6-chloro-2-methylfluorenone. The two ketones have been identified by their dipole moments: 4.6 and 2.7 D, respectively. These values are in agreement with the calculated figures of 4.35 and 2.58 D.[3] This decarbonylation seems, however, not to proceed well with some mixtures of benzoic anhydrides, possibly owing to the absence of sufficient quantities of the mixed anhydride in the equilibrium mixture. *E.g.*, a mixture of *p*-fluoro- and *p*-chlorobenzoic anhydride failed to yield significant amounts of the "mixed" chlorofluorofluorenones.

The formation of these "mixed" fluorenones can be explained by the pathway proposed in our previous paper.[1] This mechanism is further confirmed by the formation of 2,6-difluoro-,[4] 2,6-dibromo-,[5] and 1,3,5,7-tetramethylfluorenone from *p*-fluoro-, *p*-bromo-, and 3,5-dimethylbenzoic anhydride, respectively.

Reinvestigation of the decarbonylation of *m*-toluic anhydride by **1** (and also by anhydrous rhodium trichloride) showed that in addition to the previously isolated 1,7- and 2,6-dimethylfluorenone, traces of 1,5- and 3,5-dimethylfluorenone are also formed; these isomers had been predicted by our theory but had not been isolated before. 3,5-Dimethylfluorenone was identified by reduction to the known 3,5-dimethylfluorene[6] and by its nmr spectrum (*vide infra*).

It has been shown that the transformation of substituted benzoic anhydrides to fluorenone is subject to steric effects.[1] Particularly pronounced is the impediment to cyclization of the intermediate **4** (or **6**) caused by the shielding of the hydrogen atom to be extruded. In order to find out whether this steric effect is associated with the large size of the triphenylphosphine ligands, we treated *m*-toluic anhydride with rhodium trichloride at 290°. The results (Table II, footnote *d*) proved, however, that this phosphine-free catalyst behaves in the same manner as **1**. On the other hand it should be borne in mind that, in the rhodium trichloride catalyzed reaction, the ratio of 2,6- plus 3,5-dimethylfluorenone to 1,5- plus 1,7-dimethylfluorenone is close to unity, while, in the reaction catalyzed by **1**, it is 2.6. Though this comparison has only a qualitative meaning (because of the difference in temperature at which the catalyses with **1** and with $RhCl_3$ could be carried out), it may suggest that the step **3** → **4** in Scheme I, in which an acylation takes place at an *ortho* position to the

(1) J. Blum and Z. Lipshes, *J. Org. Chem.*, **34**, 3076 (1969).

(2) *Cf.* J. M. Zeavin and A. M. Fisher, *J. Amer. Chem. Soc.*, **54**, 3738 (1932).

(3) The calculations as based on the structure of fluorenone proposed by E. D. Hughes, C. G. Le Fèvre, and R. J. W. Le Fèvre, *J. Chem. Soc.*, 202 (1937).

(4) J. L. Fletcher, M. J. Namkung, W. H. Wetzel, and H. L. Pan, *J. Org. Chem.*, **25**, 1342 (1960).

(5) N. Campbell, W. Anderson, and J. Gilmore, *J. Chem. Soc.*, 446 (1940).

(6) B. Longo, *Atti. Accad. Sci. Torino, Classe Sci. Fis. Mat. Nat.*, **73**, 440 (1938); *Chem. Abstr.*, **33**, 6286[8] (1939).

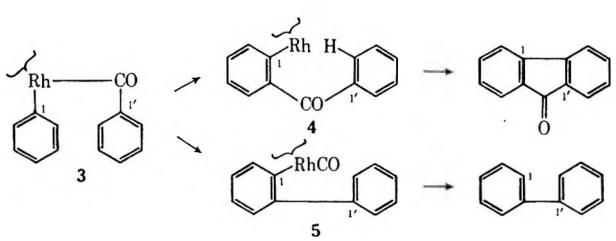
TABLE II

CONVERSION OF SUBSTITUTED BENZOIC ANHYDRIDE BY 1 TO FLUORENONES

Anhydride	Registry no.	Reaction Temp, °C	Reaction Time, hr	Fluorenone formed	Yield, %[a]
Benzoic + *p*-toluic	25569-87-3	250	5	Unsubstituted[b]	18
				2-Methyl-[b]	24
				3-Methyl-[b]	20
				2,6-Dimethyl-[b]	15
Benzoic + *p*-chlorobenzoic	21961-55-7	240	4	Unsubstituted[b]	12
				2-Chloro-[b]	8
				3-Chloro-[b]	12
				2,6-Dichloro-[b]	3
Benzoic + *m*-chlorobenzoic	25569-89-5	240	4	Unsubstituted[b]	8
				1-Chloro-[b]	3
				2-Chloro-[b]	8
				3-Chloro-[b]	10
				4-Chloro-[b]	3
				2,6-Dichloro-[b]	4
				Unidentified dichloro-	<1
p-Chlorobenzoic + *p*-toluic	25569-90-8	250	4	2,6-Dichloro-[b]	24
				2,6-Dimethyl-[b]	16
				2-Chloro-6-methyl-	14
				6-Chloro-2-methyl-	13
p-Fluorobenzoic + *p*-chlorobenzoic	25569-91-9	250	4	2,6-Difluoro-[c]	18
				2,6-Dichloro-[b]	26
				Unidentified chlorofluoro-	<1
m-Toluic[d]		235	3	1,5-Dimethyl-[b]	1
				1,7-Dimethyl-[b]	12
				2,6-Dimethyl-[b]	30
				3,5-Dimethyl-	4
3,5-Dimethylbenzoic		300	1	1,3,5,7-Tetramethyl-	14
p-Fluorobenzoic		250	3	2,6-Difluoro-[c]	40
p-Bromobenzoic		240	4	2,6-Dibromo-[e]	44

[a] Calculations are based on 2 mol of anhydride leading to 1 mol of fluorenone. [b] Compared with authentic sample. [c] Mp 176–178° (*cf.* ref 4). [d] With anhydrous $RhCl_3$ at 290° and 7 hr, the yields of 1,5-, 1,7-, 2,6-, 2,7-, and 3,5-dimethylfluorenone were 2.8, 15.4, 16.5, 0.4, and 2.2%, respectively. [e] Mp 200–201° (*cf.* ref 5).

SCHEME I



rhodium-bearing carbon, is hindered by the voluminous triphenylphosphine ligands. It appears that these factors play a part in determining the details of the reaction paths, but that they are not the only factors involved.

Some further clarification of the reaction mechanism has been made possible by a study of the reaction between chloro(phenyl)bis(triphenylphosphine)rhodium(II), $PhRhCl(PPh_3)_2$ (**7**), and the rhodium–carbonyl complex **2** (both formed in the reaction of benzoic anhydride and **1**[1]) at 250°. In addition to benzene and triphenylphosphine, the formation of 11.1% biphenyl and 15.6% fluorenone has been observed. While at least part of the biphenyl may have been formed by the pyrolysis of **7**, the fluorenone can only result from carbonylation of **7** by **2** (or phenylation of **2** by **7**) to give an aroyl–rhodium complex that would undergo further phenylation to a compound of type **3**. It is clear that the above mechanism accounts also for the observations made in the experiments with mixed anhydrides.

As mentioned before[1] biaryls are formed when benzoic anhydrides are treated with **1** at higher temperatures than those required for the formation of fluorenones. We have now studied this additional reaction, using substituted and "mixed" benzoic anhydrides. *p*-Toluic and *o*-toluic anhydride yield each a single bitolyl, 3,4′- and 2,3′-bitolyl, respectively. *m*-Toluic anhydride is transformed into a mixture of 2,3′- and 3,4′-bitolyl (see Table III). Bitolyls carrying methyl groups at the *ortho* positions are formed in lower yields, probably because of steric interference. A mixture of benzoic and *p*-toluic anhydride gives, in addition to biphenyl and 3,4′-bitolyl, also 3- and 4-methylbiphenyl.

This method of biphenyl formation is obviously different from the known oxidative coupling of aromatic hydrocarbons by palladium complexes[7,8] by which all the possible structural isomers are obtained. The selectivity in our system is rationalized with the aid of a metal–ion promoted mechanism, in which the same intermediate **3** in involved, which is the key intermediate in the formation of the fluorenones. Schemes I and II represent possible pathways (*cf.* footnote 22 of ref 1).

This mechanism can, however, explain only part of the results. Both *p*-bromo- and *p*-chlorobenzoic anhydride give mixtures of halogenated biphenyls, albeit in low yields, in which the 4,4′-dihalo derivatives predominate (see Table III). In these cases either

(7) I. Moritani, Y. Fujiwara, S. Teranishi, H. Itatani, and M. Matsuda, *Amer. Chem. Soc., Div. Petrol. Chem. Prepr.*, **14**, B 172 (1969).

(8) *Cf.* M. O. Unger and R. A. Fouty, *J. Org. Chem.*, **34**, 18 (1969), and references therein.

TABLE III

CONVERSION OF AROMATIC ANHYDRIDES BY 1 INTO BIARYLS

Anhydride	Reaction Temp, °C	Reaction Time, hr	Biaryl formed	Yield, %[a]
o-Toluic	285	3	2,3′-Bitolyl[b]	1.0
m-Toluic	285	2.5	2,3′-Bitolyl[b]	3.7
			3,4′-Bitolyl[b]	9.3
p-Toluic	285	2	3,4′-Bitolyl[b]	17
3,5-Dimethylbenzoic	300	0.75	2,3′,4,5′-Tetramethylbiphenyl	4.0
			3,3′,5,5′-Tetramethylbiphenyl	1.0
p-Fluorobenzoic	290	1.5	3,4′-Difluorobiphenyl[b,c]	3.7
p-Chlorobenzoic	285	2.5	4,4′-Dichlorobiphenyl[b,d]	3.0
p-Bromobenzoic	285	3	4,4′-Dibromobiphenyl[b,d]	0.35
			Other dibromobiphenyls	0.18
2-Thenoic	285	0.25	2,2′-Bithienyl[e]	8.0
			2,3′-Bithienyl[f]	3.9
Benzoic + *p*-toluic	290	3	Biphenyl[b]	0.9
			3-Methylbiphenyl[b]	2.5
			4-Methylbiphenyl[b]	2.5
			3,4′-Bitolyl[b]	2.7

[a] Calculations are based on 1 mol of anhydride leading to 1 mol of biaryl. [b] Compared with an authentic sample. [c] Colorless oil. *Anal.* Calcd for $C_{12}H_8F_2$: C, 75.8; H, 4.2. Found: C, 75.8; H, 4.2 Nmr spectrum showed an unsymmetric multiplet centered at δ 7.3 ppm. [d] When the catalyst was replaced by a mixture of 19.6 mg of 2,5-di-*t*-butylhydroquinone and 327 mg of 1, less than 0.01% of halobiphenyl was obtained. [e] Separated from 2,3′-bithienyl on a 2.6 m × 6.4 mm column, packed with 10% Apiezon L on Chromosorb W at 190°. Analysis and melting point confirm the structure; *cf.* W. Sternkopf and J. Roch, *Justus Liebigs Ann. Chem.*, 482, 260 (1930). [f] The melting point is identical with that reported by J. Teste and N. Lozach, *Bull. Soc. Chim. Fr.*, 492 (1954).

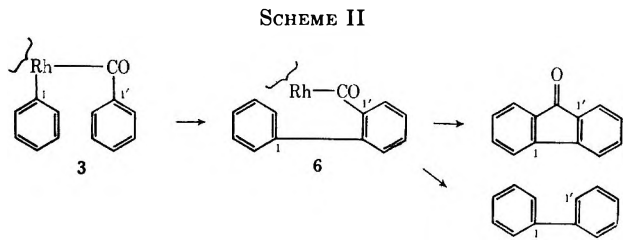
TABLE IV

NMR SPECTRA OF SOME METHYLATED FLUORENONES

Position of methyl groups	Chemical shifts of CH_3 hydrogen atoms, δ (ppm) C-1, C-8	C-2, C-7	C-3, C-6	C-4, C-5	Ref
1,5-Di-Me	2.75			2.48	*a*
1,7-Di-Me	2.56	2.31			*b*
2,6-Di-Me		2.32	2.35		*a*
3,5-Di-Me[c]			2.34	2.47	This work
2,4,5-Tri-Me		2.32		2.44, 2.49	*b*
1,3,5,7-Tetra-Me[c]	2.58	2.32	2.36	2.52	This work

[a] See ref 1. [b] J. Goodfroid, *Bull. Soc. Chim. Fr.*, 2962 (1964). [c] In CCl_4.

SCHEME II



oxidative coupling of the halobenzenes (formed by decarboxylation of the halobenzoic *acids*) or homolytic fission of the anhydrides used, may be invoked. In support of this hypothesis, we have shown that relatively small amounts (19.6 mg per 327 mg of 1) of free-radical scavengers, such as 2,5-di-*t*-butylhydroquinone, interfere strongly with the formation of the halobiphenyls, but are without effect on the transformation of benzoic and *p*-toluic anhydride to the corresponding biaryls.

Some anhydrides are converted to biaryls by both pathways, the metal–ion promoted and the free-radical mechanism. 3,5-Dimethylbenzoic anhydride, *e.g.*, gives, in addition to 4% asymmetric 2,3′,4,5′-tetramethylbiphenyl, 1% 3,3′,5,5′-tetramethylbiphenyl, and 0.1% a third tetramethyl derivative. The yield of these latter compounds could be further reduced by 2,5-di-*t*-butylhydroquinone.

2-Thenoic anhydride gives two biphenyl-type compounds. In this case the symmetric 2,2′-bithienyl is formed in preference to 2,3′-bithienyl. *p*-Phenylbenzoic anhydride is transformed under our standard conditions only into traces of a quaterphenyl, the second product being di-*p*-biphenylyl ketone; none of the expected 2,6-diphenylfluorenone is formed.

The previous study of hydrocinnamic anhydride[1] has been supplemented by an investigation of lauric anhydride. Catalytic amounts of 1 at 275° (for 4.5 hr) give a mixture of 20% 1-undecene, 2% isomeric undecenes, 30% laurone (12-tricosanone), and 41% lauric acid. The low degree of the isomerization of 1-undecene is surprising, as the catalytic decarbonylation of lauroyl chloride by 1 at 250° is coupled with isomerization of the resulting undecene to an extent of 56%.

Some of the decarbonylation products obtained in this study have been identified by nmr spectroscopy. The nmr data for some representative methylated fluorenones and biphenyls are summarized in Tables IV and V. They indicate that distinct chemical shifts may be assigned to the methyl hydrogen atoms at the various positions of the fluorenone and biphenyl molecules. This enabled us to elucidate the structures of the unknown 3,5-dimethyl- and 1,3,5,7-tetramethylfluorenone, as well as those of 2,3′,4,5′- and 3,3′,5,5′-tetramethylbiphenyl.

TABLE V

NMR SPECTRA OF SOME METHYLATED BIPHENYLS

Position of methyl groups	Chemical shifts of CH_3 hydrogen atoms, δ (ppm) o	m	p	Ref
2,4'-Di-Me[a]	2.225		2.375	This work
3,3'-Di-Me[a]		2.36		This work
3,4'-Di-Me[a]		2.35	2.37	This work
4,4'-Di-Me[a]			2.375	This work
2,2',4,4'-Tetra-Me	2.03		2.37	b
2,3',4,5'-Tetra-Me[a]	2.23	2.345	2.36	This work
3,3',5,5'-Tetra-Me[a]		2.34		This work

[a] In CCl_4. [b] High Resolution Nmr Spectra, Varian Associates, Palo Alto, Calif., The National Press, U. S. A., 1963, Spectrum No. 659.

Experimental Section

The catalysts $RhCl(PPh_3)_3$,[9] $RhCl(CO)(PPh_3)_2$,[10] $RhH(CO)(PPh_3)_3$,[11] $RhCl_3(SbPh_3)_3$,[10] and $RuCl_2(PPh_3)_3$[12] have been prepared essentially as described in the literature.

p-Fluorobenzoic anhydride was obtained in 21% yield when a mixture of 10 g of *p*-fluorobenzoic acid and 70 g of acetic anhydride was refluxed for 24 hr. The crude anhydride was flash distilled at 2 mm and recrystallized from hexane: mp 108–110°; ir (KBr) 1720 and 1780 cm^{-1}.

Anal. Calcd for $C_{14}H_8F_2O_3$: C, 64.1; H, 3.1; F, 14.5. Found: C, 64.2; H, 3.4; F, 14.2.

p-Phenylbenzoic anhydride was formed in 82% yield upon refluxing 10 g of *p*-phenylbenzoic acid with 70 g of acetic anhydride for 48 hr: mp 141–142° (from hexane); ir (KBr) 1720 and 1763 cm^{-1}. The analytical sample was further purified from a small contamination by the free acid by heating it at 130° and 2 mm for 5 hr; the free acid sublimed off.

Anal. Calcd for $C_{26}H_{18}O_3$: C, 82.5; H, 4.8. Found: C, 82.5; H, 4.7.

3,5-Dimethylbenzoic Anhydride.—A mixture of 9.5 g of 3,5-dimethylbenzoyl chloride and 26.5 g of dry pyridine was refluxed for 5 min, cooled, and poured onto 60 g of crushed ice and 28 ml of concentrated hydrochloric acid. The crystalline anhydride was washed with 10 ml of cold methanol and 10 ml of dry benzene to yield 8 g (90%) of the colorless anhydrides: mp 127° (from benzene); ir (KBr) 1715 and 1785 cm^{-1}; nmr (CCl_4) 2.35 (s, 12), 7.22 (s, 2), 7.71 (s, 4).

Anal. Calcd for $C_{18}H_{18}O_3$: C, 76.6; H, 6.4. Found: C, 76.7; H, 6.5.

2,3'- and 3,4'-Dichlorobiphenyl.—A solution of *m*-chlorobenzenediazonium chloride (prepared from 80 g of *m*-chloroaniline) was added during 30 min to a stirred mixture of 254 g of chlorobenzene and 140 ml of 5 *N* aqueous sodium hydroxide. The stirring was continued for 12 hr at room temperature, and the organic layer was steam distilled. The distillate was fractionated at 2 mm and the material of bp 150–180° was collected to yield 19 g (13%) of a mixture of the two biaryls. The separation of 2,3'- and 3,4'-dichlorobiphenyl was carried out on a 2 m × 6.4 mm vpc column, packed with 10% diethylene glycol succinate on Chromosorb W, at 170°. The 2,3'-dichlorobiphenyl (retention time, 23 min) was treated with excess butyllithium and carbon dioxide to yield 27% biphenyl-2,3'-dicarboxylic acid of mp 213–214° (lit.[13] 215–216°). The second peak (retention time, 39 min) consisted of 3,4'-dichlorobiphenyl. The ratio of 2,3'-:3,4'-dichlorobiphenyl was 5:8.

Anal. Calcd for $C_{12}H_8Cl_2$: C, 64.6; H, 3.6; Cl, 31.8. Found (2,3' isomer): C, 64.3; H, 3.9; Cl, 32.1. Found (3,4' isomer): C, 64.7; H, 3.6; Cl, 31.8.

The catalytic transformation reactions of the various anhydrides listed in Tables I, II and III are illustrated by the following examples.

Reaction of 3,5-Dimethylbenzoic Anhydride and 1.—A mixture of 3 g of 3,5-dimethylbenzoic anhydride and 150 mg of chlorotris(triphenylphosphine)rhodium (1) was placed in a Claisen flask connected with a receiver and a gas collector, and heated at 300° for 4.5 hr, during which time 0.41 g (18%) of *m*-xylene distilled over. The cooled reaction mixture was digested with 10% aqueous sodium hydroxide, and the neutral material was taken up into warm benzene. The aqueous layer yielded upon acidification 1.6 g (50%) of 3,5-dimethylbenzoic acid. The organic layer was washed with water, dried, and concentrated, and the residue chromatographed on alumina. The first fraction of hydrocarbons was further separated on a 2 m × 6.4 mm vpc column, packed with 10% SE-30 on Chromosorb W at 170°. The first peak (retention time, 19 min) consisted of 2,3',4,5'-tetramethylbiphenyl (4 mol %), which forms a viscous oil (nmr spectrum, see Table V).

Anal. Calcd for $C_{16}H_{18}$: C, 91.4; H, 8.6. Found: C, 91.4; H, 9.0.

The second hydrocarbon (1 mol %), having a retention time of 29 min, corresponded to 3,3',5,5'-tetramethylbiphenyl: mp 44° (lit.[14] 43–45°); nmr spectrum δ 2.34 (s, 12), 6.96 (s, 2), 7.18 (s, 4). A third tetramethylbiphenyl (retention time, 13 min) was formed in a very low yield (0.1 mol %).

The yellow carbonyl-containing fraction obtained from the column chromatography was further purified by preparative vpc on a 2 m × 6.4 mm column, packed with 2% XE-60 on Chromosorb W at 200°, to yield 7 mol % (14% yield) of 1,3,5,7-tetramethylfluorenone: mp 117°; ir (KBr) 1710 cm^{-1} (for nmr spectrum, see Table IV).

Anal. Calcd for $C_{17}H_{16}O$: C, 86.4; H, 6.8. Found: C, 86.1; H, 6.8.

Reaction of *m*-Toluic Anhydride and Anhydrous Rhodium Trichloride.—*m*-Toluic anhydride (4 g) was heated in the presence of 33 mg of anhydrous rhodium trichloride at 290° for 7 hr. The neutral fraction obtained was analyzed on a 5.2 m × 6.4 mm vpc column, packed with 10% stabilized diethylene glycol succinate on Chromosorb W. The biaryls were separated at 170° into 2,3'- (0.5 mol %) and 3,4'-bitolyl (4 mol %). (Authentic samples were prepared from *m*-toluenediazonium chloride and toluene in a similar way as the analogous chlorobiphenyls described above.) The dimethylfluorenones were separated at 235° into five peaks, corresponding to 1,7-, 1,5-, 2,6-, 2,7-, and 3,5-dimethylfluorenone. The yields were 2.8, 15.4, 16.5, 0.4, and 2.2%, respectively. 1,5-, 1,7-, and 2,6-dimethylfluorenone were compared with authentic samples.[1] The structure of 2,7-dimethylfluorenone was proven by its nmr spectrum [(CCl_4) 2.34 (s, 6), Table IV, footnote *b*] and melting point of 156° (lit.[15] 157°). The material corresponding to the last peak on the vpc chromatogram showed an nmr spectrum indicating the structure of 3,5-dimethylfluorenone (see Table IV), mp 102–104°.

Anal. Calcd for $C_{15}H_{12}O$: C, 86.5; H, 5.8. Found: C, 86.8; H, 6.1.

A quantity of 10 mg of this fluorenone was reduced with 28 mg of 55% hydrochloric acid (analytical grade), 14 mg of red phosphorus, and 0.6 ml of acetic acid (reflux for 20 hr), to yield a few crystals of 3,5-dimethylfluorene, mp 81–82° (from ethanol) (lit.[6] 81–82°).

Reaction of a Mixture of *p*-Chlorobenzoic and *p*-Toluic Anhydride with 1.—A mixture of 2.1 g of *p*-chlorobenzoic anhydride, 1.9 g of *p*-toluic anhydride, and 0.2 g of 1 was heated at 250° for 5 hr. The reaction mixture was extracted with chloroform, freed from the carboxylic acids, and separated by preparative tlc on silica gel, using carbon tetrachloride and benzene (3:7) as eluent. The fluorenones formed three yellow bands: the two extreme ones consisted of 2,6-dimethyl-[1] and of 2,6-dichlorofluorenone.[1] The middle broad band proved to be a mixture of two fluorenone derivatives that were separated on a 2.2 m × 6.4 mm vpc column, packed with 10% XE-60 on Chromosorb W at 220°. The first fraction was 6-chloro-2-methylfluorenone according to its dipole moment (2.7 ± 0.1 D), mp 150°, ir (Nujol) 1725 cm^{-1}. The second fraction proved to be 2-chloro-6-methylfluorenone: μ 4.6 ± 0.2 D; mp 208°; ir (Nujol) 1725 cm^{-1}. The yields of 2,6-dimethyl-, 2,6-dichloro-, 2-chloro-6-methyl-, and 6-chloro-2-methylfluorenone were 16, 24, 14, and 13%, respectively.

Anal. Calcd for $C_{14}H_9ClO$: C, 73.5; H, 3.9. Found (2-chloro-6-methylfluorenone): C, 73.5; H, 4.2. Found (6-chloro-2-methylfluorenone): C, 73.5; H, 4.2.

Reaction of Lauric Anhydride with 1.—Lauric anhydride (4 g) and 0.2 g of 1 were heated for 4.5 hr at 275°. Extraction of the

(9) J. A. Osborn, F. H. Jardine, J. F. Young, and G. Wilkinson, *J. Chem. Soc. A*, 1711 (1966).

(10) J. Blum, J. Y. Becker, H. Rosenman, and E. D. Bergmann, *J. Chem. Soc., B*, 1000 (1969).

(11) D. Evans, G. Yagupsky, and G. Wilkinson, *J. Chem. Soc. A*, 2660 (1968).

(12) T. A. Stephenson and G. Wilkinson, *J. Inorg. Nucl. Chem.*, **28**, 945 (1966).

(13) F. Mayer and K. Freitag, *Ber.*, **54**, 347 (1921).

(14) W. Carruthers and A. G. Douglas, *J. Chem. Soc.*, 2813 (1959).

(15) E. D. Bergmann, G. Berthier, Y. Hirshberg, G. Lowenthal, B. Pullman, and A. Pullman, *Bull. Soc. Chim. Fr.*, 669 (1951).

reaction mixture with 10% aqueous sodium hydroxide afforded on acidification 1.7 g (41%) of lauric acid. The neutral residue was analyzed on the following vpc columns: (a) 10% SE-30, (b) 10% diethylene glycol succinate, (c) 5% Apiezon M, and (d) 5% β,β′-oxydipropionitrile on Chromosorb W. There were isolated 20% 1-undecene, 2% other undecenes (mainly *trans*-2-undecene), and 30% 12-tricosanone of mp 68°.[16]

Registry No.—*p*-Fluorobenzoic anhydride, 25569-77-1; *p*-phenylbenzoic anhydride, 25327-57-5; 3,5-dimethylbenzoic anhydride, 25569-79-3; 2,3′-dichlorobiphenyl, 25569-80-6; 3,4′-dichlorobiphenyl, 2974-90-5; 2,3′,4,5′-tetramethylbiphenyl, 25569-82-8; 1,3,5,7-tetramethylfluorenone, 25569-83-9; 3,5-dimethylfluorenone, 25569-84-0; 6-chloro-2-methylfluorenone, 25569-85-1; 2-chloro-6-methylfluorenone, 25569-86-2; *o*-toluic anhydride, 607-86-3; *m*-toluic anhydride, 21436-44-2; *p*-toluic anhydride, 13222-85-0; *p*-chlorobenzoic anhydride, 790-41-0; *p*-bromobenzoic anhydride, 1633-33-6; 2-thenoic anhydride, 25569-97-5; 2,4′-dimethylbiphenyl, 611-61-0; 3,3′-dimethylbiphenyl, 612-75-9; 3,4′-dimethylbiphenyl, 7383-90-6; 4,4′-dimethylbiphenyl, 613-33-2; 3,3′,5,5′-tetramethylbiphenyl, 25570-02-9.

(16) An authentic sample was prepared as described by J. C. Sauer, "Organic Syntheses," Coll. Vol. IV, Wiley, New York, N. Y., 1963, p 560.

Acknowledgment.—The authors wish to thank Professor Ernst D. Bergmann for his advice.

The Mechanism of the Reaction of 2′-Iodo-2-bromomethylbiphenyl with Methyllithium to Yield Fluorene

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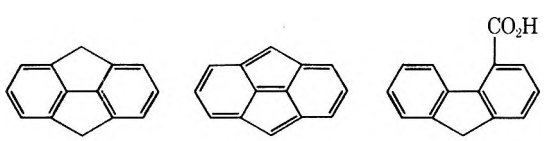
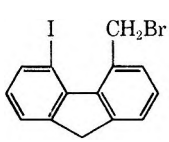
The mechanism of the cyclization of 2′-iodo-2-bromomethylbiphenyl to fluorene using methyllithium was investigated. Evidence that this conversion proceeds by the direct displacement of the benzylic bromine by an aromatic anion is presented.

We have been interested in the synthesis of the strained hydrocarbon **1** as a likely precursor to dibenzo[*cd*,*gh*]pentalene (**2**). Compound **2** can be visualized as a perturbed [12]annulene. The recent synthesis[1] of hydrocarbon **1**, as well as the dianion of **2**, prompts us to report our results at this time.



1 **2** **3**

Friedel–Crafts cyclization of the readily available fluorene-4-carboxylic acid (**3**) cannot be expected to serve as a synthetic method for the preparation of **1**. This acylation would proceed through an acylium ion which must attack the aromatic ring along the π orbital,[2] an impossibility for the rigid, planar acid **3**. We therefore sought a method that would circumvent this difficulty and turned to an investigation of methods potentially capable of converting 5-iodo-4-bromomethylfluorene (**4**) to **1**. We chose to study the cyclization of 2′-iodo-2-bromomethylbiphenyl (**5**) as an easily prepared model for this cyclization. Our investigations were limited to those reactions, such as a back-side displacement of the benzylic bromine by an aromatic anion, which would cyclize **5** in a manner that would not require large changes in geometry. Several reactions were investigated, including those with Zn, Zn–Cu couple, Mg, $Ni(CO)_4$,[3] and methyllithium. Methyllithium proved to be the most satisfactory reagent, affording fluorene in yields of 69–71%. In order to determine whether the cyclization of **5** with methyllithium was indeed proceeding through the desired back-side displacement of the benzylic bromine, a study of the mechanism of this reaction was undertaken and our results are reported below.



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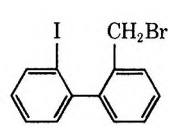


5

A search of the literature provides little information about the relative rates of halogen–lithium exchange for iodobenzene and benzyl bromide, except that the order of reactivity of the halides is I > Br > Cl.[4] We therefore chose to work with methyllithium, the least reactive of the alkyllithiums,[5] in order to enhance any differences in the halogen–lithium exchange rates.

An ethereal solution of **5** at 0° was treated with 2 equiv of methyllithium, allowed to come to room temperature, and worked up with ammonium chloride solution to afford fluorene in isolated yields of 69–71%. The remaining material had no iodine as shown by a lack of absorption at lower field than δ 7.80 (aromatic protons ortho to iodine) in the nmr spectrum.

A priori there are four possible mechanisms for this conversion (Scheme I). Recent work[6,7] indicates that the halogen–lithium exchange reaction proceeds by a one-electron transfer to give a caged radical pair. These radicals may complete the halogen–metal exchange by transferring a second electron or they may

* Author to whom correspondence should be addressed.

(1) B. Trost and P. Kinson, *J. Amer. Chem. Soc.*, **92**, 2591 (1970).

(2) J. von Braun, E. Danziger, and Z. Koehler, *Chem. Ber.*, **50**, 56 (1917); J. von Braun and E. Rath, *ibid.*, **61**, 956 (1928); J. von Braun and E. Anton, *ibid.*, **62**, 145 (1929).

(3) The yields of fluorene obtained from Zn or Zn–Cu couple were 1–6%, those from Mg were 30%, and those from $Ni(CO)_4$ were 2–46%, depending upon the solvent used. A paper on the cyclization of **5** with $Ni(CO)_4$ will appear at a later date.

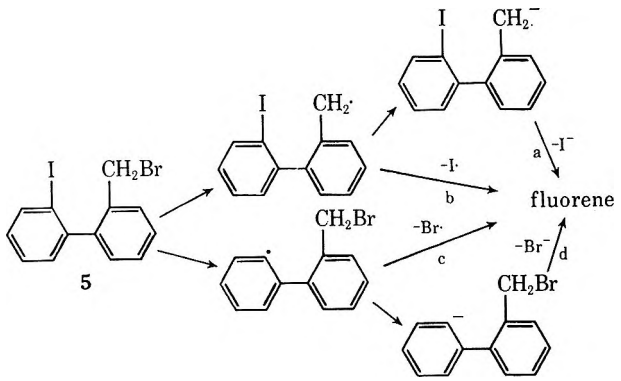
(4) See H. Gilman, *Org. React.*, **6**, 339 (1951), and the references therein.

(5) H. Gilman and F. W. Moore, *J. Amer. Chem. Soc.*, **62**, 1843 (1940).

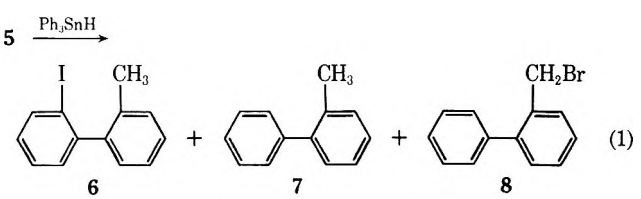
(6) H. R. Ward, R. Lawler, and R. Cooper, *ibid.*, **91**, 746 (1969).

(7) A. R. Lepley and R. Landau, *ibid.*, **91**, 748, 749 (1969).

SCHEME I



undergo further reactions. Reaction of **5** with methyllithium may therefore be proceeding through the formation of either an aromatic or a benzylic radical, depending on which halogen exchanges more rapidly, and this radical might conceivably then displace the second halogen as X· (paths b and c). To test this possibility, the reduction of **5** with triphenyltin hydride, a reduction known to proceed through a radical intermediate,[8] was envisaged. In order to assure ourselves that both the radical intermediates of paths b and c would be produced, a standardized solution of benzyl bromide and iodobenzene was partially reduced with triphenyltin hydride. The ratio of the per cent disappearance of benzyl bromide to iodobenzene, as determined by glpc, was 3, while the ratio of toluene to benzene formed was 2.6. Therefore the reduction of **5** would be expected to produce both the aromatic and the benzylic radicals of paths b and c. When this reduction was carried out in dilute solution to allow the radicals sufficient time to cyclize, a 33% yield of 2′-iodo-2-methylbiphenyl (**6**), a 25% yield of 2-methylbiphenyl (**7**), and an 18% yield of 2-bromomethylbiphenyl (**8**), all based on a 23% recovery of starting material, were

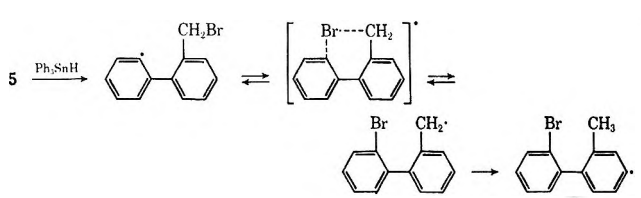


(1)

obtained. Significantly, no fluorene was produced. Since all three possible reduced products were recovered from the reduction, both of the radical intermediates in Scheme I must have been formed, but, because no fluorene was observed, these intermediate radicals do not cyclize and paths b and c are eliminated.[9]

(8) H. G. Kuivila, *Accounts Chem. Res.*, **1**, 299 (1968); H. G. Kuivila, L. W. Menapace, and C. R. Warner, *J. Amer. Chem. Soc.*, **84**, 3584 (1962); L. W. Menapace and H. G. Kuivila, *ibid.*, **86**, 3047 (1964).

(9) Furthermore, no 2′-bromo-2-methylbiphenyl (**9**) was detected from the reduction of **5** (as little as 0.6% could have been detected), thus eliminating the possibility of an intramolecular halogen bridge and transfer.



Since the cyclization does not proceed directly from the radical intermediates, it must go through either of the anionic pathways a or d. To differentiate between paths a and d, the relative rates of exchange of an aromatic iodine and a benzylic bromine with methyllithium had to be determined. As mentioned earlier, nothing conclusive pertaining to this question was found in the literature. Wittig and Witt[10] have observed that when benzyl bromide is treated with phenyllithium the products are bibenzyl and bromobenzene, presumably arising from the reaction

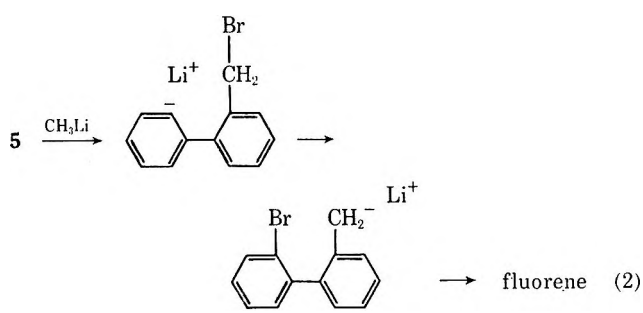
$$PhLi + PhCH_2Br \rightleftharpoons PhBr + PhCH_2Li$$

$$PhCH_2Li + PhCH_2Br \longrightarrow PhCH_2CH_2Ph + LiBr$$

Unfortunately, these results provide no conclusive information regarding the relative rates of halogen–lithium exchange. Therefore a methyllithium competition experiment with benzyl bromide and iodobenzene to determine these relative rates was carried out. When a standardized solution of iodobenzene and benzyl bromide in ether was treated with methyllithium and analyzed by glpc, it was found that less than 1% of the benzyl bromide had disappeared, while nearly 21% of the iodobenzene disappeared; the ratio of benzene to toluene detected was greater than 90:1. Thus the rate of halogen–metal exchange is greater for CH_3Li with PhI than for CH_3Li with $PhCH_2Br$. These results indicate that it is the aromatic anion that is forming more rapidly in the reaction of **5** with methyllithium. This anion then displaces a bromide ion to form fluorene in a rapid reaction as depicted in path d.

That the consequent back-side displacement of bromide is indeed the next step and is rapid is indicated by the following observations. When the cyclization is run at −70° and worked up with acid after 50% reaction, only starting material and fluorene (69% based on reacted **5**) are recovered with no detectable amount of **8**. The absence of **8** indicates that the path d intermediate has a very short lifetime and cannot be trapped by H^+.

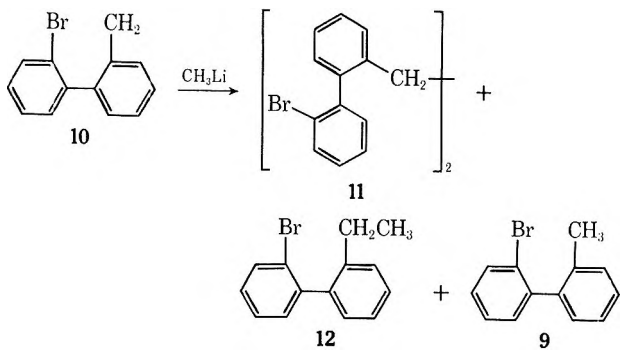
To investigate the possibility that there was actually one more step involved in path d before final closure, namely an internal halogen–lithium exchange and subsequent cyclization as in eq 2, the reaction of 2′-



(2)

bromo-2-bromomethylbiphenyl (**10**) with methyllithium was carried out. The products identified from this reaction were 1,2-bis-2-(2′-bromobiphenyl)ethane (**11**, 44%), 2′-bromo-2-ethylbiphenyl (**12**, 20%), and 2′-bromo-2-methylbiphenyl (**9**, 2%), but no fluorene. In this reaction the benzylic anion is undoubtedly an

(10) G. Wittig and H. Witt, *Chem. Ber.*, **74**, 1474 (1941).



intermediate; however the absence of fluorene indicates that it does not cyclize. Instead, the expected bibenzyl formation[10] and methyl coupling[4] products are obtained. These results therefore eliminate eq 2 as a possible pathway in the reaction of **5** with CH_3Li. Hence, path d of Scheme I is the mechanism by which the cyclization of **5** with methyllithium proceeds.

Experimental Section

Melting points are uncorrected. Nmr spectra were taken in deuteriochloroform with tetramethylsilane (TMS) as internal standard. Silica gel HF_{254} (E. Merck) was used for preparative thin layer chromatography (tlc). Ir spectra of solids were determined as KBr pellets; ir spectra of liquids were determined as thin films.

2′-Amino-2-methylbiphenyl.—A mixture of 4.0 g (18 mmol) of 2′-nitro-2-methylbiphenyl,[11] 5 g of mossy tin, and 12 ml of concentrated HCl were refluxed for 1 hr. The cooled reaction mixture was treated with 50 ml of a 10 *M* NaOH solution and the resulting solution was steam distilled. The distillate was extracted with dichloromethane and the dried extracts were evaporated. The oil that remained was distilled to give 2.4 g of clear oil, bp 94–99° (0.1 mm), which solidified into a white solid, mp 31–34° (lit.[11] 37°).

2′-Iodo-2-methylbiphenyl (6).—To a solution of 1.24 g (7.16 mmol) of 2′-amino-2-methylbiphenyl in 3 ml of concentrated HCl and 9 ml of H_2O at 0° was slowly added a solution of 0.52 g (7.5 mmol) of sodium nitrite in 2 ml of ice water. The resulting yellow solution was poured into a solution of 1.7 g of potassium iodide in 10 ml of H_2O at 0°. Gas was evolved and a dark, red tar formed. The mixture was slowly warmed to room temperature (2 hr) and then extracted with $CHCl_3$. The dried organic extracts were evaporated and the remaining red oil was chromatographed on 100 g of neutral alumina (Woelm, activity I, hexane); 1.30 g of a clear oil was obtained which solidified to a white solid, mp 36–38° (lit.[11] 38–39°).

2′-Iodo-2-bromomethylbiphenyl (5).—A solution of 3.94 g (13.4 mmol) of **6**, 2.48 g (13.9 mmoles) of N-bromosuccinimide, and a few milligrams of benzoyl peroxide in 90 ml of CCl_4 under nitrogen was simultaneously irradiated and refluxed by means of a 500-W incandescent light for 1 hr. The cooled reaction mixture was filtered and the filtrate concentrated to give 5.21 g of orange oil which, upon purification by preparative tlc (hexane as eluent), gave 4.38 g (11.7 mmol, 88%) of **5**: nmr δ 7.94 (d, J = 8 Hz, 1 H), δ 7.5–7.0 (m, 7 H), δ_A 4.13, δ_B 4.37 (AB quartet, J = 10 Hz, 2 H).

Anal. Calcd for $C_{13}H_{10}BrI$: C, 41.85; H, 2.70; I, 34.02. Found: C, 41.53; H, 2.67; I, 33.84.

2′-Bromo-2-bromomethylbiphenyl (10).—A solution of 0.925 g (3.74 mmol) of 2′-bromo-2-methylbiphenyl (**9**),[12] 0.661 g (3.70 mmol) of N-bromosuccinimide, and a few milligrams of benzoyl peroxide in 20 ml of CCl_4 under N_2 was simultaneously irradiated and refluxed with a 500-W incandescent light for 10 min. The cooled mixture was filtered and the filtrate concentrated to give 1.32 g of crude material which, upon purification by preparative tlc, afforded 89 mg of **9** and 1.06 g of 2′-bromo-2-bromomethylbiphenyl (**10**): nmr δ 7.06–7.78 (m, 8 H), δ_A 4.17, δ_B 4.37 (AB quartet, J = 10 Hz, 2 H).

(11) A. M. Sadler and G. Powell, *J. Amer. Chem. Soc.*, **56**, 2650 (1934).
(12) L. Moscarelli and D. Gatti, *Atti Reale Accad. Noz. Lincei*, **15**, 89 (1932).

Anal. Calcd for $C_{13}H_{10}Br_2$: C, 47.89; H, 3.09; Br, 49.02. Found: C, 48.15; H, 3.15; Br, 48.70.

Reaction of Methyllithium with Iodobenzene and Benzyl Bromide.—A standard mixture of 1 g (5 mmol) of iodobenzene, 0.85 g (5 mmol) of benzyl bromide, and 0.51 g (5 mmol) of *p*-xylene in 100 ml of ether was analyzed by vpc (20 ft × 1/8 in. column of 10% SE-30 on Chromosorb W at 130°). The area ratios were PhI/*p*-xylene = 0.729; $PhCH_2Br$/*p*-xylene = 0.654. To one-half of the standardized ether solution at 0° was added 1 ml of a 1.47 *M* methyllithium solution in ether (Foote Mineral Co.). A few pieces of Dry Ice were added to react with any organolithium compounds and the ether layer was analyzed by vpc.: PhI/*p*-xylene = 0.576; $PhCH_2Br$/*p*-xylene = 0.650. To the other half of the standardized ether solution at 0° was added 1 ml of 1.47 *M* methyllithium solution in ether. After 1 min, 2 ml of water was added and the ether layer analyzed by vpc for benzene and toluene: PhH/toluene > 90:1.

Reaction of 5 with Methyllithium.—To a stirred solution of 535 mg (1.43 mmol) of **5** in 50 ml ether at 0° under N_2 were added 2 ml of a 1.47 *M* methyllithium solution in ether. The solution was stirred at 0° for 30 min, then warmed to room temperature before adding 10 ml of a saturated NH_4Cl solution. The ether layer was separated, dried, and concentrated, leaving 231 mg of a slightly yellow solid. Fluorene (165 mg) was separated from the rest of the material by preparative tlc. An nmr of the remaining material (43 mg) had no absorption at lower field than δ 7.80 (protons *ortho* to aromatic I); this material was composed of at least eight components (tlc), the largest of which contained 6 mg. No further attempts at identification were carried out.

Reaction of 10 with Methyllithium.—To a solution of 128 mg (0.392 mmol) of **10** in 25 ml of ether under N_2 at 0° was added 1/2 ml of a 1.47 *M* solution of methyllithium in ether. After 2 hr 2 ml of a saturated NH_4Cl solution was added and the ether layer was separated. The dried ether layer was concentrated and the remaining oil (102 mg) separated by preparative tlc to afford 42 mg of 1,2-bis-2-(2′-bromobiphenyl)ethane (**11**): mp 182–184° (from $CHCl_3$); nmr δ 7.53–7.70 (m, 2 H), 6.78–7.40 (m, 14 H), 2.55 (s, 4 H).

Anal. Calcd for $C_{26}H_{20}Br_2$: C, 63.44; H, 4.09; Br, 32.47. Found: C, 63.64; H, 4.23; Br, 32.47.

A second fraction (20 mg) consisted of two materials (10:1 mol ratio by nmr), the smaller component being identified as **9** (singlet at δ 2.10). The larger component is tentatively identified as 2′-bromo-2-ethylbiphenyl (**12**) on the basis of its nmr spectrum: δ 7.05–7.80 (m, 8 H), δ 4.12 (q, J = 8 Hz, 2 H), δ 1.07 (t, J = 8 Hz, 3 H).

The remaining material (32 mg) consisted of several components (tlc) of 11 mg or less. No further attempts at identification were carried out.

Reaction of 5 with Triphenyltin Hydride.—To a stirred solution of 305 mg (0.818 mmol) of **5** and a few crystals of azobisisobutyronitrile (AIBN) in 20 ml of hexane at 50° under N_2 was added a solution of 304 mg (0.866 mmoles) of triphenyltin hydride in 20 ml of hexane over a period of 80 min. The reaction was refluxed for 26 hr, evaporated to dryness, triturated with CCl_4 to destroy excess triphenyltin hydride, and evaporated to dryness again. The remaining material was purified by preparative tlc to remove triphenyltin halides and two fractions were obtained. Fraction A (98 mg) consisted of a 5:3 mol ratio (nmr) of **5** (AB quartet at δ 4.20) and **8**. Fraction B (86 mg) consisted of a 4:3 mol ratio (nmr) of **6** (singlet at δ 2.07) and **7** (singlet at δ 2.23).

Reaction of Benzyl Bromide and Iodobenzene with Triphenyltin Hydride.—A solution of 1 ml of benzyl bromide, 1 ml of iodobenzene, and 1 ml of *o*-xylene in 10 ml of pentane was analyzed by vpc (area ratios): xylene/PhI/$PhCH_2Br$ = 1:0.76:0.78. To 10 ml of the above solution at reflux under N_2 was added a solution of 2.5 g of triphenyltin hydride in 10 ml of pentane over 15 min. and reflux was continued for an additional 1.25 hr. The reaction mixture was then analyzed by vpc: xylene/PhI/$PhCH_2Br$ = 1:0.67:0.50; xylene/PhH/$PhCH_3$ = 1:0.14:0.37.

Registry No.—**5**, 25860-20-2; **10**, 13379-29-8; **11**, 25860-22-4; methyllithium, 917-54-4.

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

The Autoxidation of 2-Cyano 3,3-Disubstituted Carboxylate Anions. The Synthesis of 3,3-Disubstituted 2-Oxocarboxylates[1]

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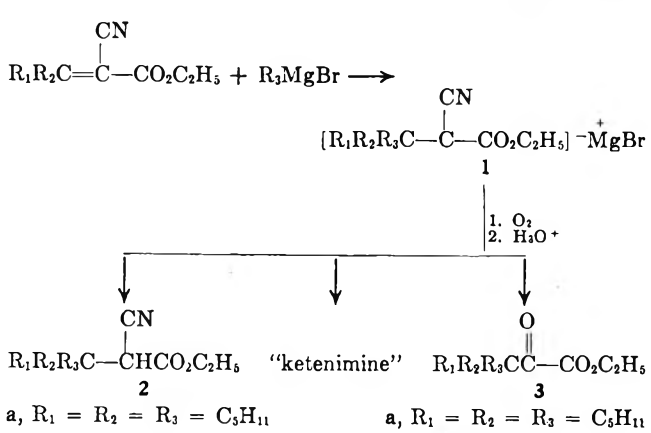
Received February 11, 1970

Ethyl 3,3-dipentyl-2-oxooctanoate, **3a**, was isolated in low yields when oxygen was passed into the Grignard complex, **1**, $R_1 = R_2 = R_3 = C_5H_{11}$, obtained from the conjugate addition of pentylmagnesium bromide to ethyl 2-cyano-3-pentyl-2-octenoate. The extension of this base-catalyzed autoxidation to ethyl 2-cyano 3,3-disubstituted carboxylates, **2**, in polar solvents was found to afford good yields of 2-oxo esters, **3**. It was shown that the nitrile group of **2** is lost during the autoxidation as a mixture of cyanate and cyanide ions in the approximate ratio of 4:1. Suggestions are made with regard to the mechanism by which **2** is converted to **3**.

The conjugate addition of Grignard reagents to alkylidenecyanoacetates offers one of the best approaches to the formation of quaternary carbon atom systems.[3] We have observed more recently[4] that the highest yields of 1,4-addition products result when an excess (30–40%) of the organometallic reagent is employed, and that extended reaction times, in the presence of air, lead to the diminution of the ir nitrile absorption of the reaction product with concomitant production of materials which absorb at 2000–2050 cm^{-1}. It is thought that the latter is due to the presence of the ketenimine grouping (–C=C=N–) which is known[5] to absorb in this range. The present investigation was undertaken to examine in more detail the nature of the products which result from such prolonged reactions.

When an excess (~25%) of a titrated ether solution of pentylmagnesium bromide was added to a mixture of ethyl 2-cyano-3-pentyl-2-octenoate and cuprous iodide catalyst and the resulting complex, **1**, $R_1 = R_2 = R_3 = C_5H_{11}$, stirred at room temperature, the color changed gradually from black to yellow to orange. After several hundred hours, the reaction mixture was hydrolyzed to give a viscous red oil: ir absorptions at 2035 (ketenimine), 1715 and 1750 (carbonyl), and 2255 (nitrile, very weak) cm^{-1}. Vapor phase chromatographic (vpc) analysis indicated the presence of two main components which corresponded to **2a** (35% by area) and an unknown compound (60%) of shorter retention time, as well as six minor constituents. Distillation afforded a small amount of **2a**, considerable tarry residue, and a colorless oil (33%) which was identified as ethyl 3,3-dipentyl-2-oxooctanoate, **3a**. Efforts to isolate and identify the species responsible for the ketenimine absorption were largely futile and will not be described here.



Apparently **3a** was formed by the oxygenation of the Grignard complex, **1**. A similar reaction has been reported by Stork, Herz, and Wendt[6] who oxygenated the conjugate addition complexes of several 16-dehydro-20-oxopregnanes to obtain the corresponding 17α-ols. The isolation of **3a**, rather than a cyanohydrin or a related material, in the present case, indicates that the oxygenated intermediate is unstable and decomposes with the loss of the nitrile group.

In an effort to decrease the reaction time and increase the yield of **3a**, air or oxygen was bubbled into ether solutions of the Grignard complex. The reaction time was lowered to 20 hr, but the yield of **3a** was decreased. Substitution of tetrahydrofuran for ether increased the yield to 41%, whereas the use of anisole led to a complex mixture which was not separated. Also, the solvent combination of benzene–triethylamine[7] was tried, but apparently the 1,4 addition failed in this system. Although the preparation of **3a** by this autoxidative route was novel, the synthetic utility appeared to be limited so attention was turned to an alternative approach.

The base-catalyzed autoxidation of the saturated cyano ester, **2a**, then was investigated since Russell and coworkers[8] have shown that this is an excellent way to oxidize compounds which have active hydrogen atoms. This choice proved to be fortunate since a 71% yield of **3a** was obtained by passing oxygen into a mixture of **2a**, potassium *t*-butoxide, dimethyl sulfoxide, and *t*-butyl alcohol. The use of other solvents was investigated and, since dimethylformamide gave slightly better results, 80% **3a**, it was employed in further autoxidations. *t*-Butyl alcohol was tried without success, and an autoxidation of **2a** in the benzyltrimethylammonium hydroxide–pyridine system[9] afforded the corresponding **3a**, but more volatile by-products were formed also.

The autoxidation was extended to the other **2** in Table I, and the results are recorded in Table II. The yields of **3** were generally good except in the case of ethyl 2-cyano-2-cyclohexylacetate. When the normal

(1) Taken from the Ph.D. Thesis of C. A. Harbert, 1967, and presented in part at the 2nd Midwest Regional American Chemical Society Meeting, Lawrence, Kan., Oct 27–28, 1966.

(2) NDEA Fellow, 1963–1966.

(3) N. Rabjohn, L. V. Phillips, and R. J. DeFeo, *J. Org. Chem.*, **24**, 1964 (1959).

(4) N. Rabjohn and C. L. King, unpublished results.

(5) C. L. Stevens and J. C. French, *J. Amer. Chem. Soc.*, **76**, 657 (1953).

(6) G. Stork, J. E. Herz, and M. W. Wendt, U. S. Patent 3,080,393 (1963); *Chem. Abstr.*, **59**, 8835 (1963).

(7) E. C. Ashby and R. Reed, *J. Org. Chem.*, **31**, 971 (1966).

(8) G. A. Russell, E. G. Janzen, A. G. Bemis, E. J. Geels, A. J. Moye, S. Mak, and E. T. Strom, "Selective Oxidation Processes," Advances in Chemistry Series, No. 51, American Chemical Society, 1965, pp 112–169.

(9) Y. Sprinzak, *J. Amer. Chem. Soc.*, **80**, 5449 (1958).

Table I

Ethyl 2-Cyano 3,3-Disubstituted Carboxylates 2

R_1[a]	R_2[a]	R_3[a]	Bp, °C (mm)	$n^{25}D$	Yield, %	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
C_2H_5	C_2H_5	C_5H_{11}	130–133 (2)	1.4513	72	$C_{15}H_{27}NO_2$ (a)[b]	71.10	10.74	71.33	10.78
$(CH_2)_5$		C_6H_5	118–120 (0.4)	1.5250	76	$C_{17}H_{21}NO_2$ (b)	75.24	7.80	75.34	7.94
C_2H_5	C_7H_{15}	C_4H_9	135–138 (0.4)	1.4530	83	$C_{19}H_{35}NO_2$ (c)	73.73	11.40	73.89	11.25
C_4H_9	C_6H_{13}	C_5H_{11}	117–119 (0.1)	1.4532	77	$C_{21}H_{39}NO_2$ (d)	74.72	11.65	74.64	11.54
C_5H_{11}	C_5H_{11}	C_5H_{11}	119–122 (0.1)	1.4530	85	$C_{21}H_{39}NO_2$[c] (e)	74.72	11.65	74.81	11.75
C_5H_{11}	C_5H_{11}	C_6H_5	123–125 (0.05)	1.4940	89	$C_{22}H_{33}NO_2$ (f)	76.92	9.68	76.69	9.72

[a] All alkyl groups are normal. [b] Identification for registry no. [c] Nmr (CCl_4) δ 4.20 (q, 2, OCH_2CH_3), 3.37 (s, 1, CH), and 0.7–1.7 (m, 36, CH_2, CH_3); ir (film) 2250 (CN) and 1750 cm^{-1} (CO).

Table II

3,3-Dialkyl-2-oxocarboxylates 3

R_1[a]	R_2[a]	R_3[a]	Bp, °C (mm)	$n^{25}D$	Temp, °C	Solvent	Yield, %	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H
$(CH_2)_5$		H	105–107 (6)[b]	1.4514	20	DMF[c]	21	$C_{10}H_{16}O_3$ (g)[d]				
C_2H_5	C_2H_5	C_5H_{11}	112–114 (2)	1.4369	20	DMF	72	$C_{14}H_{26}O_3$ (h)	69.38	10.81	69.58	10.72
$(CH_2)_5$		C_6H_5	120–122 (1)	1.5185	20	DMF	60	$C_{16}H_{20}O_3$ (i)	73.82	7.74	74.04	7.74
C_2H_5	C_4H_9	C_7H_{15}	90–93 (0.05)	1.4428	50	DMF	74	$C_{18}H_{34}O_3$ (j)	72.43	11.48	72.43	11.26
C_2H_5	C_4H_9	C_7H_{15}			20	DMSO–*t*-BuOH[e]	61					
C_4H_9	C_5H_{11}	C_6H_{13}	112–115 (0.35)	1.4442	50	DMF	76	$C_{20}H_{38}O_3$ (k)	73.57	11.73	73.77	11.62
C_5H_{11}	C_5H_{11}	C_5H_{11}	94–96 (0.15)	1.4442	20	DMSO–*t*-BuOH[e]	71	$C_{20}H_{38}O_3$ (l)	73.57	11.73	73.66	11.84
C_6H_{13}	C_5H_{11}	C_5H_{11}			20	DMF	80					
C_5H_{11}	C_5H_{11}	C_6H_5	113–115 (0.05)	1.4860	50	DMF	68	$C_{21}H_{32}O_3$ (m)	75.86	9.70	75.90	9.67

[a] All alkyl groups are normal. [b] R. Fischer and T. Wieland, *Chem. Ber.*, **93**, 1387 (1960): bp 117–120° (15 mm). [c] Dimethylformamide. [d] Identification for registry no. [e] Dimethyl sulfoxide–*t*-butyl alcohol (80:20, v/v).

twofold excess of base was used with the latter, no ethyl cyclohexylglyoxylate was obtained, apparently because of further oxidation at carbon-3 of this initially formed product. This difficulty was alleviated to some extent (21% yield) by employing a stoichiometric amount of potassium *t*-butoxide.

The fate of the cyano group during the autoxidation was of interest since it could leave as cyanide or cyanate ion. Aurich[10] has shown that the base-catalyzed autoxidation of phenylacetonitrile affords cyanide ion, whereas cyanate ion is obtained from diphenylacetonitrile. These results suggest that cyanate ion should be formed on autoxidation of **2**. Accordingly, autoxidation mixtures from **2a** were analyzed by precipitation of the silver salts,[11] and the method was tested against standard solutions of cyanate and cyanide ions. When the method was applied to autoxidation mixtures from diphenylacetonitrile and phenylacetonitrile, the values obtained were 98% cyanate ion from the former and 90% cyanide ion from the latter; these are in good agreement with Aurich's results.[10] The data from the autoxidation of **2a** indicate that cyanate and cyanide ions are produced in the approximate ratio of 4:1.

The mechanism of the autoxidation of **2** has not been established completely, but it obviously must involve peroxy anion, **5** (Chart I). Its formation may be pictured as a direct reaction of **4** with oxygen,[9,12] or as a multistep process through radicals **6** and **7** as suggested by Russell.[8,13] It is not possible to distinguish between these alternative routes on the basis of the present study.[14] The peroxy anion, **5**, might be transformed to products by at least the three routes shown in Chart I. Path "b" is suggested as the predominant one on the basis of the preferential formation of cyanate ion; similar reactions are well documented.[15] Path "a" seems to be the most likely way by which cyanide ion might arise.

The corresponding 2-oxo acids, **9**, were formed as minor products in the autoxidation of the 2-oxo esters, **3**. A plausible route to these compounds might be by a base-catalyzed elimination as shown.[16] Upon heating,

$$\underset{\mathbf{3}}{R_1R_2R_3CCOCO_2CH_2CH_3} \xrightarrow{t\text{-}BuO^-} R_1R_2R_3CCOCO_2H + CH_2{=}CH_2$$
$$\mathbf{9}$$

the 2-oxo acids, **9**, lose carbon dioxide and rearrange to ketones. A study of this reaction will be reported separately.

The autoxidation of 2-cyano-3,3-dipentyloctanenitrile was examined briefly during the course of the present investigation. The expected initial product was an acyl cyanide, **8**. It was hoped that the experiment might help to elucidate the fate of any **8** which arose by path "c" during the autoxidation of **2**; however, the autoxidation of the dinitrile produced a complex mixture which by ir analysis contained **8**, unchanged dinitrile, and acidic materials. No attempt was made to separate the oily product.

(10) H. G. Aurich, *Tetrahedron Lett.*, 657 (1964).

(11) G. Charlot, "Quantitative Inorganic Analysis," R. C. Murray, Translator, Wiley, 1954, pp 310–312.

(12) H. R. Gersmann, H. J. Nieuwenhuis, and A. F. Bickel, *Tetrahedron Lett.*, 1383 (1963).

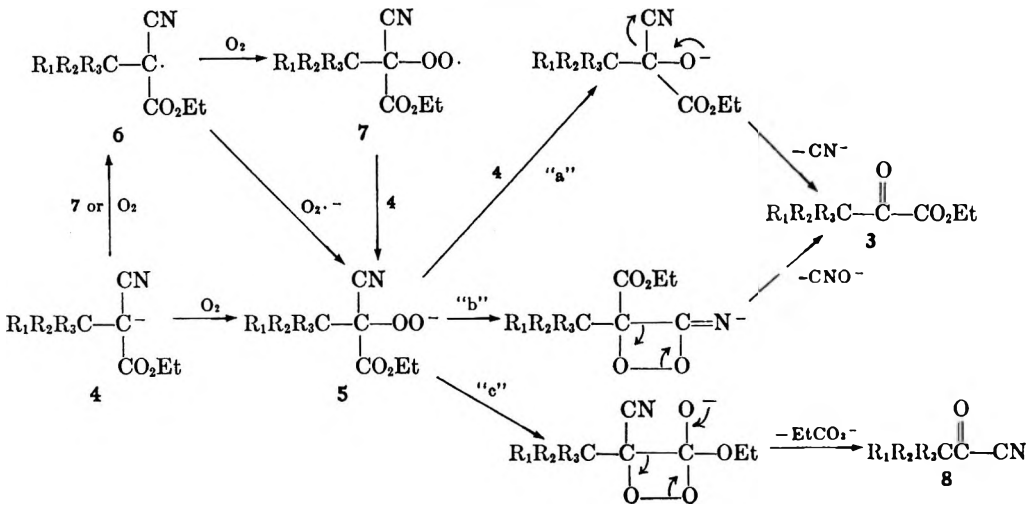
(13) For recent reviews on the relative merits of the one- *vs.* two-electron transfer mechanism, see ref 8 and G. A. Russell, *J. Pure Appl. Chem.*, **15**, 185 (1967).

(14) Russell[8,13] has cited catalysis of the autoxidation of carbanions by nitro aromatics as evidence for the one-electron transfer mechanism. In a single experiment in the present investigation it appeared that the autoxidation of **2a** in DMSO–*t*-BuOH was not catalyzed significantly by nitrobenzene.

(15) C. Walling and S. A. Buckler, *J. Amer. Chem. Soc.*, **77**, 6032 (1955); M. Avramoff and Y. Sprinzak, *ibid.*, **85**, 1655 (1963).

(16) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt, New York, N. Y., 1959, pp 493–494.

CHART I



Experimental Section[17]

Materials.—Unless otherwise stated, reagents were obtained from commercial sources and distilled prior to use. The potassium *t*-butoxide was prepared according to the method of Johnson and Schneider.[18] Magnesium sulfate was employed as the drying agent.

2-Cyano 3,3-Dialkyl Substituted Esters (2).—The compounds listed in Table I were prepared by the addition of Grignard reagents to ethyl alkylidenecyanoacetates in the presence of cuprous iodide according to a previously described procedure.[3] The needed cyanoacetates were synthesized by the method of Cope, *et al.*,[19] and those not described previously in the literature are recorded below.

Ethyl 2-Cyano-3-butyl-2-nonenoate.—This compound was obtained in 88% yield from 5-undecanone and ethyl cyanoacetate: bp 113–115° (0.5 mm); n^{25}D 1.4661.

Anal. Calcd for $C_{16}H_{27}NO_2$: C, 72.41; H, 10.26. Found: C, 72.60; H, 10.41.

Ethyl 2-Cyano-2-cyclohexylacetate.—The method of Marshall and Carroll[20] was adopted. From 50 g (0.26 mol) of ethyl cyclohexylidenecyanoacetate,[19] 3 g (0.08 mol) of sodium borohydride, and 120 ml of ethanol there was obtained 40.7 g (80%) of product: bp 124–125° (3 mm); n^{25}D 1.4580 [lit.[20] bp 112–113° (1.8 mm); n^{26}D 1.4574).

2-Cyano-3-pentyl-2-octenenitrile.—The method of Cope and Hoyle[21] was followed. The condensation of 150 g (0.8 mol) of 6-undecanone with 52.8 g (0.8 mol) of malononitrile afforded 92 g (53%) of material: bp 112–114° (1 mm); n^{25}D 1.4713.

Anal. Calcd for $C_{14}H_{22}N_2$: C, 77.01; H, 10.16. Found: C, 76.87; H, 9.97.

2-Cyano-3,3-dipentyloctanenitrile.—A titrated[22] ether solution of 0.12 mol of pentylmagnesium bromide was added to a mixture of 25 g (0.115 mol) of 2-cyano-3-pentyl-2-octenenitrile and 0.57 g (0.003 mol) of cuprous iodide in 100 ml of anhydrous ether while the temperature was maintained at 24–26°. The mixture was allowed to stir overnight, hydrolyzed with dilute hydrochloric acid, and worked up in the usual manner[3] to give 19.4 g (60%) of product: bp 105–107° (0.1 mm); n^{26}D 1.4550.

Anal. Calcd for $C_{19}H_{34}N_2$: C, 78.56; H, 11.80. Found: C, 78.50; H, 11.65.

Autoxidation of the Grignard Complex, 1, $R_1 = R_2 = R_3 = C_6H_{11}$, from the Reaction of Pentylmagnesium Bromide with Ethyl 2-Cyano-3-pentyl-2-octenoate. A. Prolonged Exposure to Air.—A titrated[22] ether solution of 0.32 mol of pentylmagnesium bromide was added to a mixture of 70 g (0.26 mol) of ethyl 2-cyano-3-pentyl-2-octenoate[19] and 1.32 g (0.007 mol) of cuprous iodide in 250 ml of dry ether while the temperature was maintained at 24–26°. The drying tube was removed from the condenser and the mixture was allowed to stir for 1000 hr at room temperature. The orange reaction mixture was hydrolyzed with dilute hydrochloric acid and worked up to give 89 g of a red oil whose ir spectrum (neat) showed absorptions at 2035 (ketenimine, m),[5] 1655 (C=C, m), and 1750 and 1715 cm^{-1} (C=O, s). The vpc chromatogram (silicone rubber on Chromosorb W, 45–60) had only two major peaks corresponding to cyano ester **2a** (35%) and an unknown (60%) of shorter retention time. A 24-g portion of the crude product was distilled through a spinning-band column to give 7.9 g (33%) of a compound, identified as ethyl 3,3-dipentyl-2-oxooctanoate, **3a**, bp 94–96° (0.15 mm), n^{25}D 1.4442; 4 g of cyano ester **2a**; and 8 g of a tarry residue. An ir spectrum (neat) of the low-boiling ester had peaks at 1745 and 1715 (C=O, s) and 1270 cm^{-1} (CO_2R, s) and the nmr spectrum (neat) had absorptions at δ 4.22 (q, 2, OCH_2CH_3) and 0.7–1.9 (m, 36, CH_2, CH_3).

Anal. Calcd for $C_{20}H_{38}O_3$: C, 73.57; H, 11.73. Found: C, 73.66; H, 11.84.

B. Reaction with Oxygen.—A titrated ether solution of 0.08 mol of pentylmagnesium bromide was added dropwise to a mixture of 17.2 g (0.065 mol) of ethyl 2-cyano-3-pentyl-2-octenoate and 0.33 g (0.002 mol) of cuprous iodide in 65 ml of dry ether. The reaction mixture was allowed to stir at room temperature for 2 hr and the flask was fitted with a Dry Ice condenser and a gas-dispersion tube. Oxygen was admitted for 20 hr and the mixture was hydrolyzed with dilute hydrochloric acid and worked up. The resulting black oil was distilled through a spinning-band column to give 3.8 g (18%) of **3a**, bp 96–98° (0.25 mm), n^{25}D 1.4450, and a tarry residue.

Autoxidation of Ethyl 2-Cyano 3,3-Disubstituted Alkanoates (2).—The following procedure is a modification of the method of Russell and coworkers[8] and is representative of the method used to obtain the 2-keto esters, **3**, recorded in Table II. In a 200-ml three-necked flask equipped with a magnetic stirrer, gas-dispersion tube, and reflux condenser, protected with a drying tube, were placed 16.8 g (0.05 mol) of ethyl 2-cyano-3,3-dipentyloctanoate, **2a**, 11.2 g (0.1 mol) of potassium *t*-butoxide, and 150 ml of anhydrous DMF. Oxygen was passed through the solution for 19 hr at room temperature, and then it was quenched with water (100 ml) and extracted with five 50-ml portions of ether. The combined extracts were washed, dried, and concentrated to give an oil which was distilled through a spinning-band column. There was obtained 13.1 g (80%) of **3a**: bp 103–108° (0.5 mm); n^{25}D 1.4444.

The autoxidation was repeated several times, both at room temperature and 50°; only 7–9 hr was required at the latter temperature. The yields were comparable at both temperatures and varied from 51 to 80%. Similar autoxidations in DMSO–*t*-

(17) The ir spectra were recorded on a Perkin-Elmer Model 237-B spectrophotometer and the nmr spectra were run on a Varian A-60 spectrometer employing tetramethylsilane as an internal standard. Elemental microanalyses were performed by Drs. Weiler and Strauss, Oxford, England, and Galbraith Laboratories, Inc., Knoxville, Tenn. Analytical vpc was done on a Wilkens Aerograph A90-P3 and a Microtek 2000-R gas chromatograph. All boiling points are uncorrected.

(18) W. S. Johnson and W. P. Schneider, "Organic Syntheses," Coll. Vol. IV, N. Rabjohn, Ed., Wiley, New York, N. Y., 1963 p 132.

(19) A. C. Cope, C. M. Hofmann, C. Wyckoff, and E. Hardenbergh, *J. Amer. Chem. Soc.*, **63**, 3452 (1941).

(20) J. A. Marshall and R. D. Carroll, *J. Org. Chem.*, **30**, 2751 (1965).

(21) A. C. Cope and K. E. Hoyle, *J. Amer. Chem. Soc.*, **63**, 733 (1941).

(22) H. Gilman, P. D. Wilkinson, W. P. Fishel, and C. H. Meyers, *ibid.*, **45**, 150 (1923).

BuOH (80:20 v/v) afforded **3a** in 71% yield and in 51–66% yield when carried out at 50 ± 2°, with the balance of the product being a lower boiling ketone.

Autoxidation of Ethyl 2-Cyano-3,3-dipentyloctanoate. Determination of Cyanide and Cyanate Ions.[11]—The determination was carried out several times and the following procedure is representative. Oxygen was passed into a solution of 3.37 g (0.01 mol) of **2a** and 2.24 g (0.02 mol) of potassium *t*-butoxide in 60 ml of DMSO–*t*-BuOH (80:20 v/v) for 7 hr at 50 ± 3°. The mixture was quenched with 50 ml of distilled water and extracted with three small portions of ether and the aqueous portion was adjusted to pH 5–7 with dilute nitric acid. A solution of 2 g (0.012 mol) of silver nitrate in 20 ml of distilled water was added and the white precipitate was collected on a tarred, sintered-glass funnel. It was washed with two small portions of water and treated with five 15-ml portions of dilute (1:5) nitric acid. The remaining silver cyanide was washed with distilled water and dried. The solid weighed 0.33 g (0.0025 mol) which corresponds to 25% cyanide ion; the cyanate ion was taken as the difference from 100%.

The results varied from 25 to 27% cyanide ion in DMSO–*t*-BuOH (80:20 v/v) to 14–18% cyanide ion in DMF. These values represent an approximate product ratio of 80:20 cyanate to cyanide ion on the basis of the determinations with standard solutions. The latter contained 20% cyanide and 80% cyanate ions, in the appropriate solvents, and were subjected to the conditions of the autoxidation and work-up procedure prior to precipitation of the silver salts. The average values for cyanide and cyanate were found to be 23 and 77% in DMSO–*t*-BuOH and 15 and 85% in DMF.

Registry No.—Table I—a, 25593-95-7; b, 25593-96-8; c, 25593-97-9; d, 25593-98-0; e, 25593-99-1; f, 25594-00-7; Table II—g, 13275-31-5; h, 25594-02-9; i, 25565-11-1; j, 25565-12-2; k, 25594-03-0; l, 25594-04-1; m, 25565-13-3; ethyl 2-cyano-3-butyl-2-nonenoate, 25594-05-2; 2-cyano-3-pentyl-2-octenenitrile, 13017-59-9; 2-cyano-3,3-dipentyloctanenitrile, 25594-07-4.

Additions to Bicyclic Olefins. IV. The Facile Reduction of Labile Epoxides of Bicyclic Olefins by Lithium in Ethylenediamine

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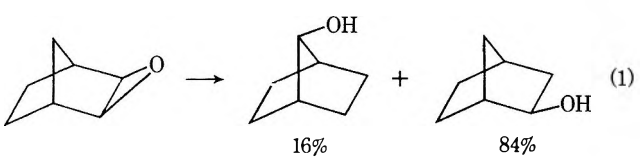
The reduction of many hindered and unstable bicyclic epoxides with lithium aluminum hydride is very slow and is often accompanied by rearrangement. In contrast, the addition of lithium metal to an ethylenediamine solution of such epoxides at 50° reduces such epoxides rapidly, without rearrangement. In this way, norbornene oxide is readily reduced to essentially pure *exo*-norbornanol in 87% yield. Similarly, badly hindered and labile epoxides, such as 2-methylene-7,7-dimethylnorbornane oxide and *exo*- and *endo*-7,7-dimethylnorbornene oxides, were readily reduced to the corresponding tertiary and secondary alcohols, respectively.

We were interested in studying the stereochemistry of the epoxidation of norbornene, 7,7-dimethylnorbornene, and related olefins.[4] If the resulting epoxides could be reduced quantitatively to the corresponding known bicyclic alcohols, the stereochemistry of epoxidation could be conveniently established by vapor phase chromatography.

Unfortunately, the usual reduction of epoxides by lithium aluminum hydride is very slow for many of these bicyclic epoxides. Moreover, such reductions are often accompanied by rearrangements. For example, in order to achieve a reasonable rate, Kwart and Takeshita[5] found it necessary to treat norbornene oxide with lithium aluminum hydride in boiling N-ethylmorpholine. They obtained 16% of the rearranged 7-norbornanol in addition to 84% of the expected 2-norbornanol (eq 1). The 7-norbornanol presumably



(1)

resulted from electrophilic ring opening of the epoxide ring by lithium aluminum hydride.

Data reported by Hallsworth and Henbest[6,7] indicated that some steroidal epoxides, which were quite unreactive to lithium aluminum hydride, were easily reduced with a large excess of lithium in ethylamine. However, they obtained some olefin in the reduction of labile steroidal epoxides.

Consequently, a study was begun to determine whether the various norbornyl epoxides would be reduced quantitatively with lithium–ethylamine to the corresponding alcohols without rearrangements or eliminations occurring to complicate the interpretation of the results.

Results and Discussion

We found ethylenediamine (bp 116°) a more convenient medium to use than the much lower boiling ethylamine (bp 16°) for routine laboratory reduction of hindered epoxides.[8] After some exploratory experiments an exceedingly simple procedure was developed and proved highly satisfactory. This procedure involves dissolving 10 mmol of norbornene oxide in 10 ml of ethylenediamine, adding 30 mg-atoms of lithium wire in 2-mm pieces, and heating at 50° with stirring until a

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(2) Postdoctorate research associate on a grant (GP 6492 X) supported by the National Science Foundation.

(3) Graduate research assistant on grants (G 19878 and GP 6492 X) supported by the National Science Foundation.

(4) H. C. Brown, J. H. Kawakami, and S. Ikegami, *J. Amer. Chem. Soc.*, in press.

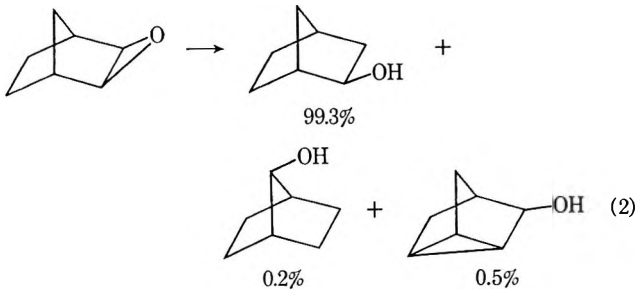
(5) H. Kwart and T. Takeshita, *J. Org. Chem.*, **28**, 670 (1963).

(6) A. S. Hallsworth and H. B. Henbest, *J. Chem. Soc.*, 3571 (1960).

(7) A. S. Hallsworth and H. B. Henbest, *ibid.*, 4604 (1957).

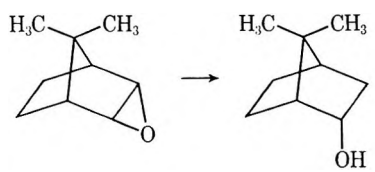
(8) (a) The lithium reduction in ethylenediamine is much less vigorous than in ethylamine. We have encountered side reactions in ethylamine when the reaction conditions were not controlled (see Discussion). (b) Isolation of the alcohol from the epoxide reduction in ethylenediamine is simple because the base is very soluble in water where it exists as the hydrate, and is only slightly soluble in ether, whereas ethylamine is miscible both in water and in ether.

blue color persists. This usually takes approximately 1 hr. The norbornanol was then isolated in 87% yield by the addition of 10 ml of water, followed by extraction with 20 ml of ether or tetrahydrofuran. Analysis by glpc indicated no olefin or epoxide, 99.3% 2-norbornanol, 0.2% 7-norbornanol, and 0.5% nortricyclanol (eq 2). Even the more hindered *endo*-epoxide from



(2)

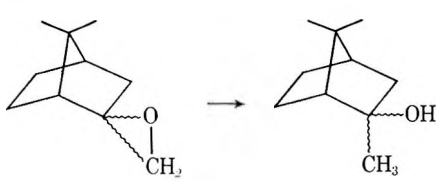
7,7-dimethylnorbornene was readily reduced in 1 hr to 7,7-dimethylnorbornanol in 87% yield (eq 3). In



(3)

contrast, the reduction of this epoxide with lithium aluminum hydride in diglyme at 100° for 24 hr yielded 19% unreacted epoxide, 47% 7,7-dimethylnorbornanol, and 44% rearranged alcohols.[9,10]

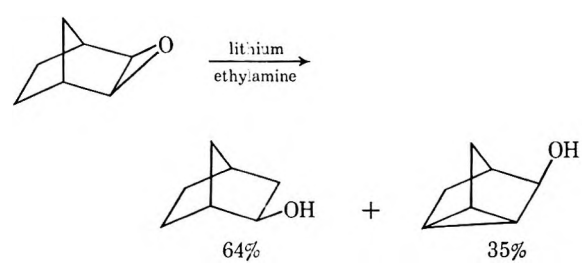
The very labile 2-methylene-7,7-dimethylnorbornane oxide underwent isomerization in all of our attempts at a glpc analysis. Its lability is also indicated by the report that the room temperature reduction with lithium aluminum hydride gives chiefly primary alcohol.[11] Presumably, the labile epoxide undergoes an electrophilic ring opening prior to reduction by hydride. However, this labile oxide readily underwent reduction by lithium–ethylenediamine to give the tertiary alcohol in 89% yield (eq 4).



(4)

This reduction with lithium–ethylenediamine was extended to all of the bicyclic epoxides of interest, as well as to several representative alicyclic and aliphatic epoxides. In all cases the reduction proceeded cleanly and the alcohols were obtained in high yields. The results are summarized in Table I.

Similar results could be obtained using ethylamine, provided that the reaction conditions were rigorously controlled. However, the lithium metal reduction in ethylamine is very vigorous, even at −20°, and is not always easy to control. For instance, a drastic change in reaction products is observed if norbornene oxide is added to a mixture of ethylamine and lithium. If the epoxide was added 5 min after a blue color appeared, there was obtained an 87% yield of recovered epoxide, 10% norbornanol, and 3% tricyclanol. If the epoxide was added 1 min after the appearance of the blue color, there was obtained 1% norbornene oxide, 64% norborneol, and 35% nortricyclanol (eq 5). Nortricyclanol probably results from base attack on norbornene oxide, as reported previously by Crandall.[12]



(5)

Thus, it appears that the use of ethylenediamine in lithium metal reduction of hindered and labile epoxides has a number of significant advantages over that of ethylamine. In addition, this simple and convenient procedure may also find application in the reduction of many simple aliphatic and alicyclic epoxides. Although the lithium–ethylenediamine reduction is not always selective, it appears that it is widely applicable to bicyclic epoxides and may be very helpful in other instances where the reduction by complex hydrides fails.

TABLE I

LITHIUM–ETHYLENEDIAMINE REDUCTION OF EPOXIDES

Epoxides of olefins	Yield of alcohols, %[a]	Alcohols[b]
Norbornene	87	2-Norbornanol
7,7-Dimethylnorbornene	87	7,7-Dimethyl-2-norbornanol
1-Methyl-2-nobornene	88	60% 1-methyl-2-norbornanol 40% 4-methyl-2-norbornanol
2-Methyl-2-norbornene	100	71% 2-methyl-2-norbornanol 29% 3-methyl-2-norbornanol
1,7,7-Trimethylnorbornene	80	51% 1,7,7-trimethyl-2-norbornanol 49% 1,7,7-trimethyl-3-norbornanol
2-Methylenenorbornane	85	2-Methyl-2-norbornanol
2-Methylene-7,7-dimethylnorbornane	88	2,7,7-Trimethyl-2-norbornanol
1-Methylcyclohexene	93	1-Methylcyclohexanol
1-Butene	82	2-Butanol
2-Methyl-2-butene	82	90% 3-methyl-2-butanol 10% 2-methyl-2-butanol

[a] Yield by glpc analysis. [b] Since the epoxides were often mixtures of exo and endo, the corresponding alcohols were also mixtures of stereoisomers. The stereochemistry of the alcohols always conformed to the stereochemistry of the epoxides, as established by pmr and glpc analysis.

Experimental Section

Materials.—Anhydrous ethylenediamine from Fisher Scientific Co. was used without further treatment.

(9) This epoxide is stable to our glpc conditions. However, very labile epoxides, such as 2-methylene-7,7-dimethylnorbornane oxide, rearrange on the glpc column.

(10) The reduction of *exo*-norbornene oxide with lithium aluminum hydride yielded various amounts of *endo*-norbornanol depending upon the reaction conditions (see Experimental Section).

(11) W. Hückel and D. Volkmann, *Justus Liebigs Ann. Chem.*, **664**, 31 (1963).

(12) J. K. Crandall, *J. Org. Chem.*, **29**, 2830 (1964).

Gas Chromatography.—The analyses were carried out on the Perkin-Elmer 226 fitted with a 150 ft × 0.01 in. Golay column. Authentic samples were utilized to identify the products.[13]

Epoxidation of Olefins.—The olefins were epoxidized with *m*-chloroperbenzoic acid in methylene chloride.[4]

Typical Procedure for the Lithium–Ethylenediamine Reduction of Epoxides.—To a 100-ml three-necked flask fitted with a septum outlet, thermometer, and magnetic stirring bar under nitrogen was added 10 mmol of norbornene oxide and 10 ml of anhydrous ethylenediamine. Then 0.21 g (30 mg-atoms) of lithium wire cut into 2-mm pieces and washed with pentane was added at room temperature with vigorous stirring. The reduction is exothermic above room temperature, but a water bath was necessary to keep the temperature at 50° for 1 hr. Many colors are observed during the reduction, but the reduction is complete when a blue-purple color persists. The reaction mixture was cooled and 10 ml of water was added to destroy excess reagent. Extraction with 20 ml of tetrahydrofuran, drying ($MgSO_4$), addition of a calibrated internal standard, and analysis by glpc indicated an 87% yield of 99.3% 2-norbornanol, 0.2% 7-norbornanol, and 0.5% nortricyclanol (Ucon LB 550X at 100°) in order of increasing retention time. No 2-norbornanone, norbornene oxide, or norbornene were detected.

Reduction of Norbornene Oxide with $LiAlH_4$.—To a flame-dried 50-ml round-bottomed flask was added 5 ml of a 1 *M* $LiAlH_4$ solution in diglyme, 15 ml of dry and peroxide-free diglyme, and 0.55 g (5 mmol) of norbornene oxide under nitrogen. After 67 hr at 100° there was obtained a 77% yield of 98.1% *exo*- and 1.9% *endo*-norbornanol, and a trace of 7-norbornanol. If the same reduction was run in the presence of air, the amount of *endo*-norbornanol increased to 7% in 24 hr.[14] Although no 7-norbornanol was detected, there was obtained 9% an unknown with a shorter retention time than *exo*-norbornanol (Ucon LB 550X at 100°).

Reduction of 7,7-Dimethylnorbornene Oxide with $LiAlH_4$.—The crude oxide was reduced at 100° in 24 hr with $LiAlH_4$ in diglyme in the presence of dry air. There was obtained 19% recovered oxide, 18% an unknown (alcohol), 6% 5,5-dimethyl-*exo*-2-norbornanol (?), 2.5% 7,7-dimethyl-2-*exo*-norbornanol, 1% 6,6-dimethyl-2-norbornanol, 47.2% 7,7-dimethyl-2-*endo*-norbornanol, and seven other minor peaks.

Reduction of Norbornene Oxide with Li in Ethylamine.—To a 50-ml flask fitted with a magnetic stirring bar, Dry Ice condenser, and a nitrogen inlet was added 1.1 g (10 mmol) of norbornene oxide and 20 ml of ethylamine *via* a syringe cooled with Dry Ice. The mixture was cooled to −20° and 0.21 g (30 mg-atoms) of Li wire cut in 2-mm pieces was added. The reduction was vigorous. In 5 min a persistent blue color appeared. The Dry Ice condenser was removed and the ethylamine swept out with nitrogen. Water (20 ml) was added; extraction with 20 ml of ether gave on evaporation an 89% yield of 2-norbornanol with only traces of other isomers.

Side Reactions in Reductions with Li in Ethylamine.—After a mixture of 10 ml of ethylamine and 0.21 g (30 mg-atoms) of Li at −20° remained blue for 5 min, a solution of 1.1 g (10 mmol) of norbornene oxide in 30 ml of petroleum ether (35–37°) was added. The blue color dissipated after only 1 mmol of the epoxide solution was added. After stirring the mixture for 15 min at −20°, the work-up indicated an 87% yield of unreacted epoxide, 10% 2-*exo*-norbornanol, and 3% nortricyclanol. In contrast, if the epoxide was added 1 min after the appearance of the blue color, 1% norbornene oxide, 64% 2-norbornanol, and 35% nortricyclanol were obtained.

Reduction of Nonhindered Epoxides.—The lithium–ethylenediamine reductions of nonhindered epoxides such as 1-butene oxide are quite exothermic. The reduction can be controlled with ice cooling.

Registry No.—Norbornene, 498-66-8; 7,7-dimethylnorbornene, 6541-60-2; 1-methyl-2-norbornene, 822-73-1; 2-methyl-2-norbornene, 694-92-8; 1,7,7-trimethylnorbornene, 464-17-5; 2-methylenenorbornene, 497-35-8; 2-methylene-7,7-dimethylnorbornane, 471-84-1; 1-methylcyclohexene, 591-49-1; 1-butene, 106-98-9; 2-methyl-2-butene, 513-35-9.

(13) H. C. Brown and J. H. Kawakami, *J. Amer. Chem. Soc.*, **92**, 1990 (1970).

(14) S. V. Vitt and N. S. Martinkova, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 524 (1964); *Chem. Abstr.*, **60**, 15696 (1964). These authors observed that when benzhydrol-1-*d* and its potassium salt are heated under nitrogen in diglyme and lithium aluminum hydride, benzhydrol loses some deuterium.

Synthesis and Properties of Cobalticinium Salts. I. Synthesis of Monosubstituted Cobalticinium Salts[1]

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Procedures for synthesis of methyl (**2**, **3**), carboxy (**4**, **5**), chlorocarbonyl (**6**), carbalkoxy (**7**), amino (**9**), and nitro (**10**) cobalticinium salts are given. The amino derivative shows extremely low basicity (pK_b = 15.6 ± 0.1) but, in marked contrast to the ferrocene analog, can be diazotized and coupled with phenol to form an azo dye **10**, pK_a = 7.05 ± 0.03. The substituted cobalticinium salts show greater resistance toward oxidation than the corresponding ferrocene analogs and are not degraded by concentrated mineral acids or aqueous base. Hydroxy-2,3,4,5-tetraphenylcobalticinium ion, **15**, exists in proteolytic equilibrium with the stable π-cyclopentadienyltetraphenylcyclopentadienonecobalt complex, **14**, pK_a = 2.3 ± 0.1 in 50% ethanol. Procedure for synthesis of salts of **15** and the acetoxy derivative **16** from **14** are given.

Cobalticinium salts, in contrast to the isoelectronic ferrocene analogs, show strong resistance to oxidation, even by strong oxidizing agents such as fuming nitric acid, potassium permanganate, and ozone.[3] Gill and Mann[4] have found that ferrocene derivatives act as potent haptens, greatly enhancing the ability of synthetic peptides to induce formation of antibodies, but these compounds are degraded by enzymes of the host organism. They proposed the use of the more stable cobalticinium salts as haptens, as tracers in biological systems, as electron dense markers in electron microscopy and X-ray crystallography, and as carriers of Co^{60} in radiotherapy. We have therefore undertaken a systematic study of the synthesis and chemical properties of cobalticinium salts and their rhodium and iridium analogs.

Results and Discussion

Since electrophilic substitution on the cobalticinium nucleus is yet to be accomplished, substituted derivatives must be prepared directly from substituted cy-

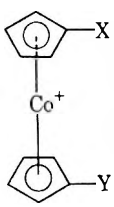
(1) Part II: J. E. Sheats, C. E. Whitten, and W. M. Minihane, paper in preparation.

(2) National Science Foundation Science Faculty Fellow, 1969. Chemistry Department, Rider College, Trenton, N. J. 08602.

(3) E. O. Fischer and G. E. Herberich, *Chem. Ber.*, **94**, 1517 (1961).

(4) T. J. Gill, III, and L. T. Mann, Jr., *J. Immunology*, **96**, 906 (1966).

clopentadienes. Methylcyclopentadiene, readily available commercially, was chosen as the starting material for the syntheses. A mixture of **1**, **2**, and **3** was prepared in 20–30% yield from equimolar amounts of cyclopentadiene, methylcyclopentadiene, and cobalt bromide by a modification of the amine method for preparing metallocenes.[5] Pyrrolidine, which is a stronger base and a better solvent for cobalt bromide, was used instead of diethylamine as the solvent for the reaction. Hexafluorophosphate was employed as the counterion in most of the subsequent syntheses, since the resulting salts crystallized readily, were not hygroscopic, and showed moderate solubility (1–10 g/l.) in both water and polar organic solvents. Elemental analyses of these compounds, however, usually showed a low phosphorus content, possibly because of partial degradation of the hexafluorophosphate ion. When analytical samples were required, the compounds were converted to the tetraphenylborates, which could be purified more readily.

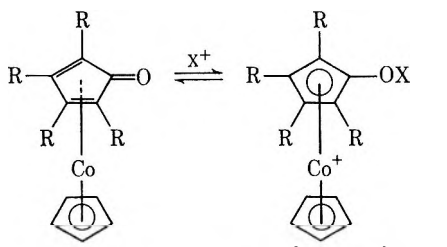


1, X = H; Y = H
2, X = CH_3; Y = H
3, X = CH_3; Y = CH_3
4, X = CO_2H; Y = H
5, X = CO_2H; Y = CO_2H
6, X = COCl; Y = H
7, X = CO_2CH_3; Y = H
8, X = CON_3; Y = H
9, X = NH_2; Y = H
10, X = NO_2; Y = H
11, X = -N=N-*p*-C_6H_4OH; Y = H

Attempts to separate the hexafluorophosphates of **1**, **2**, and **3** by fractional crystallization or column chromatography were unsuccessful. The methyl groups were therefore oxidized to carboxyls by treatment with basic aqueous potassium permanganate.[3] Addition of excess sodium hexafluorophosphate to the basic solution precipitated **1** quantitatively. After acidification, a mixture of the mono- and dicarboxylic acid derivatives, **4** and **5**, precipitated as hexafluorophosphate salts. Compound **4** dissolved readily in acetone, whereas **5** was virtually insoluble. The acyl chloride **6** was prepared from **4** and converted to the methyl ester **7** and the acyl azide **8**. Rearrangement of **8** in concentrated sulfuric acid at 130° produced a 60% yield of the amino derivative **9** and a 20% yield of **4**. No sulfonic acid derivatives of either **4** or **9** were obtained.

Aminocobalticinium ion **9**, $pK_b = 15.6 \pm 0.1$, exhibits the very low basicity expected for a highly deactivated aromatic amine bearing a positive charge. It is less basic than benzene–aminocyclopentadienyl iron(II) fluoroborate,[6] **12**, $pK_b = 14.6$, which also bears a positive charge and the neutral molecules aminocyclopentadienylmanganesetricarbonyl,[7] **13**, $pK_b = 11.79$, and aminoferrocene,[8] $pK_b = 10.35$. In contrast to aminoferrocene, which is destroyed rapidly by atmospheric oxygen, nitrous acid or other oxidizing agents, **9** can be oxidized by hydrogen peroxide to the nitro derivative **10** and can be diazotized in hydrochloric acid. Compounds **12** and **13**, although less stable toward oxidation than **9**, can also be diazotized.[6,7] Coupling of the diazonium salt formed from **9** with phenol in basic solution produced a brilliantly colored azo dye **11**. Compound **11** changes color from yellow in aqueous acid to red in aqueous base, $pK_a = 7.05 \pm 0.03$, and is blue in basic alcohol solutions. The structural changes accompanying the color changes are currently under investigation.

Hydroxycobalticinium salts have been prepared previously,[9] and exist in proteolytic equilibrium with stable π-cyclopentadienyl-π-cyclopentadienone–cobalt(I) complexes.[10,11] Because of the strong electron-withdrawing effect of the tripositive cobalt and the net positive charge, hydroxycobalticinium salts should be much stronger acids than phenol. We wished to determine the acidity constant of a hydroxycobalticinium salt and compare its ir and uv spectra with those of the other substituted cobalticinium salts. The bromide, perchlorate, and fluoroborate salts of **15** were prepared by shaking a chloroform solution of **14** with a concentrated aqueous solution of the appropriate acid.



14, R = C_6H_5
15, R = C_6H_5; X = H
16, R = C_6H_5; X = $COCH_3$

The C=O peak in the ir spectrum shifted from 1585 cm^{-1} in **14** to 1430 cm^{-1} in **15**, indicating a substantial decrease in bond order, and a broad O—H stretch appeared at 3200–3500 cm^{-1}. The π-cyclopentadienyl peak in the nmr spectrum shifted from δ 4.90 in **14** to δ 5.64 in **15** which is comparable to the value δ 5.53 for the unsubstituted ring of the amino derivative **9** (Table I). Thus, spectral evidence indicates that **15** is a hydroxycobalticinium ion, rather than the hydrogen-bonded complex previously postulated for solutions of the tetramethyl analog of **14** (**14**, R = CH_3) in aqueous perchloric acid.[11] The dissociation constant of **15** (chloride salt), $pK_a = 2.28 \pm 0.1$ in 50% ethanol, was determined spectrophotometrically. Thus **15** is approximately 10^7 times as acidic as phenol.

When **14** was heated with acetyl chloride, the acetoxy derivative **16** was obtained, which was isolated as the tetraphenylborate salt. Hydrolysis of **16** to regenerate **14** occurred rapidly in aqueous solution. An attempt to displace the acetoxy group with sodium iodide in acetone also regenerated **14**. Hopefully, with a more powerful leaving group attached to the oxygen, nucleophilic substitution on the ring can be accomplished.

Spectra of Cobalticinium Salts.—Monosubstituted cobalticinium salts show a sharp peak at 3120 cm^{-1} for the C–H stretch and a peak of medium intensity at 1412 cm^{-1} for the unsubstituted ring, but lack the sharp peaks at 1110 and 1000 cm^{-1} commonly observed in monosubstituted ferrocene derivatives. The spectra of

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(6) A. N. Nesmeyanov, N. A. Vol'kenau, and L. S. Isaeva, *Dokl. Akad. Nauk SSSR*, **183**, 606 (1968).
(7) M. Cais and N. Narkis, *J. Organometal. Chem.*, **3**, 188, 269 (1965).
(8) A. N. Nesmeyanov, V. I. Romanenko, and V. A. Sazanova, *Isv. Akad. Nauk SSSR, Ser. Khim.*, 357 (1966).
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(11) G. N. Schrauzer and G. Kratel, *J. Organometal. Chem.*, **2**, 336 (1964).

TABLE I
NMR SPECTRA OF COBALTICINIUM HEXAFLUOROPHOSPHATES AND FERROCENE ANALOGS

	Cobalticinium, δ, ppm				Ferrocene,[c-j] δ, ppm			
Substituent	Unsubstituted ring	H_α	H_β	Other	Unsubstituted ring	H_α	H_β	Other
H	6.25[a]				4.05			
CH_3	6.13[b]	6.10	6.10	2.42[f]	3.99[k]	3.94	3.94	1.96
CO_2H	6.04[a]	6.33	6.09					
COCl	6.00[d]	6.41	6.10					
CO_2CH_3	6.00[b]	6.33	6.07	3.97[f]	4.12	4.27	4.09	
NH_2	5.53[a]	5.50	5.38	5.69[g]	3.95	3.80	3.70	
NO_2	6.23[a]	6.80	6.17		4.26	5.13	4.37	
N=N-*p*-C_6H_4OH	5.60[a]	6.19	5.67	6.96, 7.11[h] 7.80, 7.96				
OH, 2,3,4,5-$(C_6H_5)_4$[l]	5.64[e]			6.9–7.5[i]				
OAc, 2,3,4,5-$(C_6H_5)_4$	5.97[e]			2.25,[f] 6.7–6.9[i] 7.2–7.5				
O^-, 2,3,4,5-$(C_6H_5)_4$[m]	4.90[e]			7.1–7.3, 7.5–7.8[i]				

[a] Spectra in acetone. [b] Spectra in acetone-d_6. [c] Spectra in CCl_4. [d] Spectra in CF_3CO_2H. [e] Spectra in $CDCl_3$. [f] CH_3 group. [g] NH_2 group. [h] Phenol ring AB pattern. [i] C_6H_5 groups. [j] G. G. Dvoryantseva, S. L. Portnova, K. I. Grandberg, S. P. Gubin, and Y. N. Sheinker, *Dokl. Akad. Nauk SSSR.*, **160**, 1075 (1965). [k] Y. Nagai, J. Hooz, R. A. Benkeser, *Bull. Soc. Chem. Jap.*, **37**, 53 (1964). [l] Registry no., 12427-61-1. [m] Registry no., 12427-57-5.

TABLE II
UV SPECTRA OF COBALTICINIUM SALTS

Substituent	λ_{max}, mμ (ε)				
H[a]		264 (33,400)	300 sh (1200)	409 (200)	
1,1′-Di-CH_3[b]		267 (34,000)	308 sh (1200)	416 (255)	
CO_2H[a]	235 (4000)	272 (26,500)	315 (1700)	414 (246)	
1,1′-Di-CO_2H[b]	222 (7300)	271 (23,200)	323 sh (1400)	416 (263)	
NH_2[b]		275 (19,000)	355 (3450)	410 (980)	
NH_3^+[c,h]		268 (28,000)	305 sh (1200)	405 (230)	
N=N-*p*-C_6H_4OH[a]	210 (23,000)	268 (15,000)	358 sh (5800)	416 (7290) 395 (9600)[f]	
N=N-*p*-$C_6H_4O^-$[a,i]	211 (52,500)	265 (13,130)	296 sh (6260)	410 (6720) 395 (4500)	575 (18,700) 530 (13,700)[g]
O^-, 2,3,4,5-$(C_6H_5)_4$[d]	Strong end absorption		334 (15,000)	400 sh (2100)	510 sh (508)
OH, 2,3,4,5-$(C_6H_5)_4$[d]	Strong end absorption		334 (19,000)	400 sh (2000)	510 sh (10)
OAc, 2,3,4,5-$(C_6H_5)_4$[e]		230 (43,500)	335 (13,700)	395 sh (2700)	510 sh (70)

[a] Spectrum in 95% ethanol. [b] Spectrum in H_2O. [c] Spectrum in 10.8 *M* HCl. [d] Spectrum in 50% ethanol. [e] Spectrum in CH_3CN. [f] Spectrum in 0.100 *M* HCl. [g] Spectrum in 0.100 *M* NaOH. [h] Registry no., 12427-44-0. [i] Registry no., 12427-52-0.

the 1,1′ disubstituted derivatives lack the peak at 1412 cm^{-1} but are otherwise very similar to those of the monosubstituted derivatives.

The nmr spectrum of a monosubstituted cobalticinium salt (Table I) consists of a sharp singlet for the unsubstituted ring and an A_2B_2 pattern of two triplets with peak separation of ≃2 Hz for the substituted ring. The triplets are located upfield from the singlet in compounds with electron-releasing substituents and downfield in compounds with electron-withdrawing substituents. A tentative assignment of the downfield triplet to the hydrogens α to the substituent can be made by comparison with the ferrocene analogs.[12,13] Because of the strong electron-withdrawing effect of the tripositive cobalt, the peaks for the cobalticinium salts are shifted 1.5–2.0 ppm downfield from the peaks for the corresponding ferrocene derivatives.

The uv spectra of cobalticinium salts (Table II) show strong end absorption, a peak at 260–275 mμ, a shoulder at 300–325 mμ, and a peak at 400–415 mμ. Both electron-donating and electron-withdrawing substituents diminish the absorbance at 260–275 mμ. The corresponding ferrocene derivatives[14] show similar peaks with weaker absorbance at 20–30-mμ longer wavelengths.

Experimental Section

All chemicals were reagent grade unless otherwise specified. Melting points and boiling points are uncorrected. Ir spectra were measured on a Beckman IR-10 spectrophotometer; uv spectra on a Perkin-Elmer 202 spectrophotometer; nmr spectra on a Varian A-60 spectrometer. The extinction coefficients used for the determination of values of pK_a and pK_b were measured on a Zeiss PMQ-II spectrophotometer. Elemental analyses were performed by C. F. Meade of the Microanalytical Laboratory of the University of Massachusetts.[15]

Synthesis of Cobalticinium (1), Methylcobalticinium (2), and 1,1′-Dimethylcobalticinium (3) Salts.—Methylcyclopentadiene and cyclopentadiene were prepared from the dimers by the procedure of Reynolds and Wilkinson.[16] Pyrrolidine (technical grade) was dried ($CaSO_4$) and distilled, bp 86–87°. Anhydrous cobalt(II) bromide, 83 g (0.4 mol), was added in small portions with continuous stirring to a solution of 80 g (1.0 mol) methylcyclopentadiene and 65 g (1.0 mol) cyclopentadiene in 360 ml of pyrrolidine at 0° in a nitrogen atmosphere. The solution was

(12) D. W. Slocum, T. R. Englemann, R. Lewis, and R. J. Kurland, *J. Chem. Eng. Data*, **13**, 378 (1968).

(13) D. W. Slocum, P. S. Shenkin, and T. R. Engelmann, "Proceedings of the Fourth International Conference on Organometallic Chemistry," Bristol, U. K., July 27–Aug 1, 1969, p G-5.

(14) K. I. Grandberg, S. P. Gubin, and E. G. Perevalova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 549 (1966).

(15) Oxygen analyses were performed by the procedure of C. F. Meade, D. A. Keyworth, V. T. Brand, and J. R. Deering, *Anal. Chem.*, **39**, 512 (1967). The procedure for degradation of cobalticinium salts for cobalt analysis will be described by C. F. Meade in a future publication.

(16) L. T. Reynolds and G. Wilkinson, *J. Inorg. Nucl. Chem.*, **9**, 86 (1959).

allowed to warm to room temperature and the stirring continued for 12 hr. The solvent was evaporated on a rotary evaporator and the purple residue dissolved in 1–2 l. of hot water. A green residue containing cobalt(II) oxide remained. The aqueous solution was extracted with ether to remove unreacted cyclopentadiene and clarified with charcoal. The mixture of **1**, **2**, and **3** was precipitated as the hexafluorophosphate salts by dropwise addition of a solution of 40–50 g of sodium hexafluorophosphate in 150 ml of water: yield 34 g (25%); ir (KBr) 3120, 2920, 2860, 1478, 1465, 1415, 1385, 900–800 (vs) (PF_6^-), 550 and 440 cm^{-1}. The nmr spectrum in trifluoroacetic acid showed sharp singlets for **1** at δ 6.23; **2** at 6.13 (5), 6.10 (4), and 2.42 (3); and **3** at 5.98 (8), and 2.39 (6). The assignments were confirmed by addition of authentic samples of **1** and **3** to the mixture. Integration of the spectrum showed a composition of 5% **1**, 65% **2**, and 30% **3**. Proportions of the three components varied when the synthesis was repeated, but the yield of **2** was usually at least 50%. An attempt to prepare **1**, **2** and **3** from a mixture of sodium cyclopentadienide and sodium methylcyclopentadienide in THF produced a 30% yield of **1** with only traces of **2** and **3** and large amounts of tarry byproducts.

Preparation of Carboxycobalticinium (4) and 1,1′-Dicarboxycobalticinium (5) Salts.—A solution of 26 g (0.17 mol) of potassium permanganate, 3.6 g (0.09 mol) of sodium hydroxide, and 18 g ($\simeq$0.05 mol) of the mixture of **1**, **2**, and **3** in 400 ml of water was heated at 95° for 3 hr. The hot solution was filtered through asbestos to remove the manganese dioxide. Sodium hexafluorophosphate, 10 g, was added and the solution chilled. Approximately 1 g of **1**, identified by its nmr spectrum, was obtained. Dropwise addition of 6 *M* HCl produced a curdy yellow precipitate of the carboxylic acids **4** and **5**, yield 14 g (70%). The nmr spectrum in 96% sulfuric acid gave clearly resolved signals for **4** at δ 6.28 (t, 2, J = 2 Hz), 5.93 (t, 2, J = 2 Hz), 5.86 (s, 5), and **5** at 6.36 (t, 4, J = 2 Hz), 6.10 (t, 4, J = 2 Hz), corresponding to a mixture of 75% **4** and 25% **5**.

The precipitate was washed repeatedly with hot acetone. Compound **4** dissolved readily (solubility 10 g/l.), whereas **5** was virtually insoluble (<0.1 g/l.). The acetone solution was evaporated and 10 g of **4** obtained as yellow flakes: ir (KBr) 3120, 3000–2500 (O–H stretch), 1710 (s), 1490, 1410, 1395, 1295, 1170, 1030 (s), 820 (s), 552, 490 (w), 468 and 440 (w) cm^{-1}.

A 378-mg (1 mmol) sample of **4** was dissolved in 100 ml of water and precipitated by dropwise addition of a solution of 342 mg of sodium tetraphenylborate in 50 ml of water. The precipitate was crystallized twice from acetone–chloroform and dried overnight at 80° *in vacuo*, mp 234–235° dec.

Anal. Calcd for $C_{35}H_{30}BCoO_2$: C, 76.11; H, 5.47; O, 5.79; Co, 10.67. Found: C, 75.90; H, 5.42; O, 5.80; Co, 10.73.

Chlorocarbonylcobalticinium Hexafluorophosphate (6).—A 10-g sample of **4** (hexafluorophosphate salt) was refluxed in 500 ml of thionyl chloride for 24–48 hr. As the reaction progressed, the peaks in the ir (KBr) at 1710, 1490, 1395, and 1295 cm^{-1} disappeared and the carbonyl chloride doublet at 1770 and 1740 cm^{-1} appeared. When the reaction was complete, the solution was concentrated to 150 ml, chilled, and filtered. Approximately 8 g of **6** (probably a mixture of chloride and PF_6^- salts) was obtained as yellow crystals: ir (KBr) 3120, 1770 (s), 1740 (s), 1445, 1420, 1404, 1373, 1240 (s), 1048, 945, 830 (s), 560, and 460 cm^{-1}. Compound **6** hydrolyzed rapidly in a moist atmosphere but could be stored almost indefinitely in a desiccator.

Carbomethoxycobalticinium Salts (7).—A 367-mg sample of **6** was refluxed 30 min in 40 ml of absolute methanol. The ester was precipitated by dropwise addition of 5 ml of a saturated solution of sodium hexafluorophosphate in methanol: yield 192 mg (50%); ir (KBr) 3120, 1725 (s), 1472, 1435, 1418, 1398, 1370, 1285 (s), 1205, 1160 (s), 1030, 965, 830 (s), 560 (s), 510, 475, and 278 cm^{-1}. The tetraphenylborate of **7**, precipitated by the same procedure, was recrystallized twice from acetone–chloroform, mp 215° dec.

Anal. Calcd for $C_{36}H_{32}BCoO_2$: C, 76.34; H, 5.69; O, 5.65; Co, 10.41. Found: C, 76.24; H, 5.80; O, 5.64; Co, 10.40.

Carbonylazidocobalticinium Salts. (8).—An 8.5-g sample of **6** was stirred with 100 ml of 30% aqueous sodium azide at 0° for 30–60 min until the carbonyl chloride peaks in the ir at 1780 and 1745 cm^{-1} disappeared and a carbonyl peak appeared at 1704 cm^{-1}. No hydrolysis to the carboxylic acid, which would also absorb at 1490, 1395, and 1295 cm^{-1} was observed. When the reaction was complete, the yellow precipitate was collected and dried by suction filtration: yield 7 g (probably a mixture of azide and hexafluorophosphate salts); ir (KBr) 3120, 2230, 2190, 2140 (s) (N_3 group), 1690 (s), 1460, 1418, 1400, 1375, 1270 (s), 1180 (s), 1060 (w), 1045 (w), 1000 (w), 950, 830 (s), 560, 500, 450, and 275 cm^{-1}.

Aminocobalticinium Salts (9).—The crude azide **9** (7 g) was dissolved in a solution of 34 ml of 96% sulfuric acid and 7 ml of fuming sulfuric acid. Sodium azide, 1 g, was added and the solution heated on a steam bath for 1 hr, then on a hot plate at 110–130° for an additional 1 hr. Gas evolution was initially rapid but gradually subsided. The solution was poured over 100 g of ice, neutralized by addition of 200 ml of 6 *M* sodium hydroxide in small portions, and diluted with 800 ml of 95% ethanol. A semisolid mass of sodium sulfate precipitated. The alcohol layer was decanted and the solid washed repeatedly with ethanol. The ethanol solutions were combined and concentrated to 50–100 ml on a rotary evaporator. (If the solution were evaporated to dryness, a black residue formed and the yield was reduced.) After treatment with charcoal, the amino derivative **9** was precipitated as the hexafluorophosphate salt, yield 3.6 g (57%). Acidification of the mother liquor produced 1.7 g of **4** (24%). Since the mother liquor was only faintly colored, sulfonation of either **8** or **9** must be only a minor side reaction. The crude amine was recrystallized from acetone–chloroform: mp 324–325° dec; ir (KBr) 3500, 3400, 3240, 3120, 1630 (s), 1530 (s), 1410, 1380, 1050 (w), 1030 (w), 1010 (w), 830 (s), 560 and 440 cm^{-1}. The extinction coefficients of the amine **9** in water [uv max 275 mμ (ϵ 19,000), 355 (3450), 410 (980)]; the protonated amine in 10.8 *M* HCl [uv max 267 mμ (ϵ 28,000), 305 (1200), 405 (230)]; and a mixture of the two in 6.08 *M* HCl were measured over the 300–410-mμ region on a Zeiss PMQ-II spectrophotometer. The amine was calculated to be 77% protonated in 6.08 *M* HCl. Substituting an effective pH of -2.12 for 6.0 *M* HCl given by the Hammett acidity funtion[17] into the Henderson–Hasselbalch equation gave $pK_a = -1.60 \pm 0.1$ for the protonated amine.

The tetraphenylborate of **9** was also prepared and recrystallized from acetone–chloroform, mp 241–243° dec.

Anal. Calcd for $C_{34}H_{31}BCoN$: C, 78.03; H, 5.97; N, 2.68; Co, 11.26. Found: C, 77.80; H, 6.04; N, 2.82; Co. 11.00.

Preparation of Nitrocobalticinium Salts (10).—A 200-mg sample of **9** (0.6 mmol) was added to a solution of 5 ml of 30% hydrogen peroxide and 5 ml of trifluoroacetic acid. The solution was heated at 50–70° for 30 min and allowed to cool, and **10** precipitated as the hexafluorophosphate salt. The crude material was recrystallized from hot water: yield 84 mg (40%); ir (KBr) 3140, 1550 (s), 1420, 1375 (s), 1345, 1020 (w), 830 (s), 720, 555, 495, 472, and 275 cm^{-1}. A portion of **10** was precipitated as the tetraphenylborate, and recrystallized from acetone–chloroform, mp 199–202° dec.

Anal. Calcd for $C_{34}H_{29}BCoNO_2$: C, 73.80; H, 5.28; N, 2.53; O, 5.78. Found: C, 74.00; H, 5.50; N, 2.29; O, 5.48.

Diazotization of Aminocobalticinium Salts.—Aminocobalticinium hexafluorophosphate, 0.700 g (2 mmol), was diazotized in 50 ml of 6 *M* hydrochloric acid at 0° by dropwise addition of 138 mg (2 mmol) of sodium nitrite in 2 ml of water. The solution was stirred for 5 min and then poured into a solution of 1.0 g of phenol (fivefold excess) and 12.5 g of sodium hydroxide (5% excess) in 100 ml of water. A deep purple color formed immediately. After 10 min, the solution was acidified with 3 *M* HCl, extracted repeatedly with ether to remove unreacted phenol, and heated briefly with 1 g of charcoal. The azo dye **11** was precipitated by dropwise addition of 686 mg (2 mmol) of sodium tetraphenylborate in 10 ml of water. After 10% of the solution had been added, the mixture was allowed to stand for 10 min and filtered. The brownish residue was discarded. The rest of the solution was added and the curdy orange precipitate collected, yield 700 mg (40%). A 200-mg portion of the crude material was dissolved in 25 ml of acetone; 10 ml of chloroform and 15 ml of ether were added and the solution chilled at $-20°$ overnight. The dye was obtained as dark orange crystals: mp 175–176°; ir (KBr) 3100 (cyclopentadienyl C–H), 3050 (aromatic C–H), 1585 (s), 1500, 1475, 1412 (s), 1395, 1268, 1220, 1180, 1135 (s), 1060 (w), 1035 (w), 1000 (w), 940, 835, 730 (s), 700 (s), 610, 500, and 450 cm^{-1}.

Anal. Calcd for $C_{40}H_{34}BCoN_2O$: C, 76.45; H, 5.45; N, 4.46; Co, 9.38. Found: 76.01; H, 5.89; N, 4.55; Co, 9.00.

A 1.2×10^{-3} *M* solution of **11** in ethanol was prepared and diluted 1:25 with 0.100 *M* HCl, pH 7 standard buffer (Beckman

(17) A review of the Hammett and other acidity functions for concentrated acid solutions is given in M. A. Paul and F. A. Long, *Chem. Rev.*, **57**, 1 (1957).

Instrument Co.), pH 10 standard buffer (Fisher Chemical Co.), and 0.100 *M* NaOH. From the spectra of the dye in acidic, neutral, and basic solutions [uv max (0.100 *M* HCl) 395 mu (ϵ 9600) and 530 (400); uv max (pH 7 buffer) 530 mμ (ϵ 6850); uv max (0.100 *M* NaOH) 395 mμ (ϵ 4500) and 530 (13,700)], the dye was calculated to be 53% protonated at pH 7.00. The pK_a is therefore 7.05 ± 0.03.

π-Cyclopentadienyltetraphenylcyclopentadienone Cobalt (14).[18]—π-Cyclopentadienylcobaltdicarbonyl (6.0 g, 0.35 mol), tetracyclone (13.6 g, 0.35 mol), and 50 ml of xylene were refluxed overnight in a nitrogen atmosphere. The solution was cooled to room temperature and 15.4 g of purple crystals collected. The solid was chromatographed in 3-g portions on a 10 cm × 30 cm column of alumina. A purple band of tetracyclone was eluted with xylene and an orange band of **14** with chloroform. The crude **14** was recrystallized from chloroform–ligroin: yield 11.0 g (62%); mp 325–326° (lit.[10] 327–329°).

Hydroxy-2,3,4,5-tetraphenylcobalticinium Bromide (15).—A 254-mg sample of **14** (0.5 mmol) was suspended in 30 ml of 48% hydrobromic acid and heated for 30 min at 80–100°, with constant stirring. A gummy oil formed which solidified to a yellow powder. The solution was diluted with 50 ml water and the precipitate collected, yield 244 mg (83%). The crude material was recrystallized from acetone–ether: mp 289–290° dec; ir max (KBr) 3060, 2900–2400 (broad peak possibly due to H–Br bonding), 1600 (w), 1578 (w), 1470, 1430 (C–O stretch), 1410, 1400, 1240, 1170 (s), 1110, 1082, 1030, 1008, 850, 800, 753 (s), 697 (s), 640, 620, 582, 558, 500, 420 cm^{-1}.

Anal. Calcd for $C_{34}H_{26}BrCoO$: C, 69.28; H, 4.45; Br, 13.56; Co, 10.00; O, 2.71. Found: C, 69.00; H, 4.70; Br, 14.00; Co, 9.98; O, 2.70.

Hydroxy-2,3,4,5-tetraphenylcobalticinium Fluoroborate and Perchlorate.—A 508-mg sample of **14** (1 mmol) was dissolved in 25 ml of chloroform and shaken with 10 ml of 37% fluoroboric acid. The chloroform layer was dried over calcium sulfate. Dropwise addition of ligroin precipitated the product as a fine yellow powder, yield 517 mg (87%). The crude product was recrystallized from acetone–ether, mp 245–250° dec. The ir spectrum of the fluoroborate corresponded to the ir of the bromide except that the broad peak at 2900–2400 cm^{-1} was shifted to 3500–3200 cm^{-1}, and a broad peak for the BF_4^- anion appeared at 1130–950 cm^{-1}.

Anal. Calcd for $C_{34}H_{26}BCoF_4O$: C, 68.48; H, 4.40; Co, 9.88; O, 2.68. Found: C, 68.72; H, 4.65; Co, 9.80; O, 2.70.

The perchlorate salt, mp 253–255° dec, was prepared from 60% perchloric acid by the same procedure.

Anal. Calcd for $C_{34}H_{26}ClCoO_5$: C, 67.06; H, 4.30; O, 13.14. Found: C, 67.02; H, 4.45; O, 13.10.

Acetoxy-2,3,4,5-tetraphenylcobalticinium Salts (16).—A 152-mg portion of **14** (0.3 mmol) was dissolved in 10 ml of acetyl chloride. The acetyl chloride was evaporated and the residue was dissolved in 30 ml of water and filtered. The acetoxy derivative **16** was precipitated as the hexafluorophosphate salt: ir (KBr) 3120 (cobalticinium C–H), 3060 (phenyl C–H), 2920, 2860, 1785 (s), 1312 (w), 1275 (w), 1600 (w), 1580 (w), 1500 (w), 1450, 1418 (s), 1400, 1370, 1170 (s), 1100, 1085, 1010, 830 (s), 755 (s), 699 (s), 580 (w), 560 (s), 510, 415, and 278 cm^{-1}. The tetraphenylborate was also prepared and recrystallized twice from acetone–ether, mp 235°.

Anal. Calcd for $C_{60}H_{48}BCoO_2$: C, 82.75; H, 5.56; O, 3.68; Co, 6.77. Found: C, 82.80; H, 5.60; O, 3.68; Co, 6.76.

Registry No.—**1**, 12427-42-8; **2**, 12427-48-4; **3**, 12427-51-9; **4**, 12427-47-3; **5**, 12427-49-5; **6**, 12427-45-1; **7**, 12427-50-8; **8**, 12427-46-2; **9**, 12427-43-9; **9** (tetraphenylborate), 12427-55-3; **9** (diazo derivative), 12427-56-4; **10**, 12427-41-7; **11**, 12427-53-1; **15**, 12427-59-7: **16**, 12427-63-3; **16** (tetraphenylborate), 12427-62-2; **10** (tetraphenylborate), 12427-54-2; hydroxy-2,3,4,5-tetraphenylcobalticinum (BF_4), 12427-58-6; hydroxy-2,3,4,5-tetraphenylcobalticinium (perchlorate), 12427-60-0.

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(18) R. A. Genetti, Ph.D. Thesis, University of Massachusetts, Jan 1969, pp 9–10.

Intermolecular Hydrogen Bonding between Nitriles and Methanol. A Nuclear Magnetic Resonance Study

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The addition of alkyl- and arylnitriles to methanol, with or without CCl_4 dilution, prolongs the residence time for exchange of the –OH proton. The inhibition of –OH exchange is sufficient to allow detection of J_{HCOH}. Studies of binary and ternary (CCl_4) mixtures of acetonitrile and methanol showed a marked variability in the –OH resonance position with increasing CH_3CN concentration. The observed spectral changes support prior postulations of a strong –CN—HO– hydrogen-bonding interaction, and appear to indicate changes in the equilibrium concentration of CH_3OH–CH_3CN associates over a broad range of binary and ternary (CCl_4) solution concentrations.

Studies of intermolecular –CN—HO– hydrogen bonding have been centered primarily on the elucidation of infrared hydroxyl frequency shifts ($\Delta\nu_{OH}$) for binary and ternary (CCl_4) mixtures of nitriles with alcohols and phenols.[1] The $\Delta\nu_{OH}$'s observed for methanol or phenol interacting with a wide variety of nitriles correlated well with Taft σ^* parameters,[2] however, even under carefully controlled experimental conditions it is evident that the magnitude of $\Delta\nu_{OH}$ is not necessarily a measure of hydrogen-bonding acceptor strength.[2,3] Consequently, no definite conclusions could be reached regarding the acceptor strengths of nitriles relative to other known hydrogen-bonding bases.

Recently, we have been concerned with solvent–solute interactions traceable through changes in the –OH and –CH_3 resonances of methanol,[4] *e.g.*, suppression of –OH exchange and the concentration dependence of the –OH resonance for both binary and ternary

(1) (a) S. S. Mitra, *J. Chem. Phys.*, **36**, 3286 (1962). (b) A. Allerhand and P. von R. Schleyer, *J. Amer. Chem. Soc.*, **85**, 371 (1963).

(2) A. Allerhand and P. von R. Schleyer, *ibid.*, **85**, 866 (1963).

(3) A. Allerhand and P. von R. Schleyer, *ibid.*, **85**, 1715 (1963).

(4) N. F. Hepfinger and P. A. Clarke, *J. Org. Chem.*, **34**, 2572 (1969).

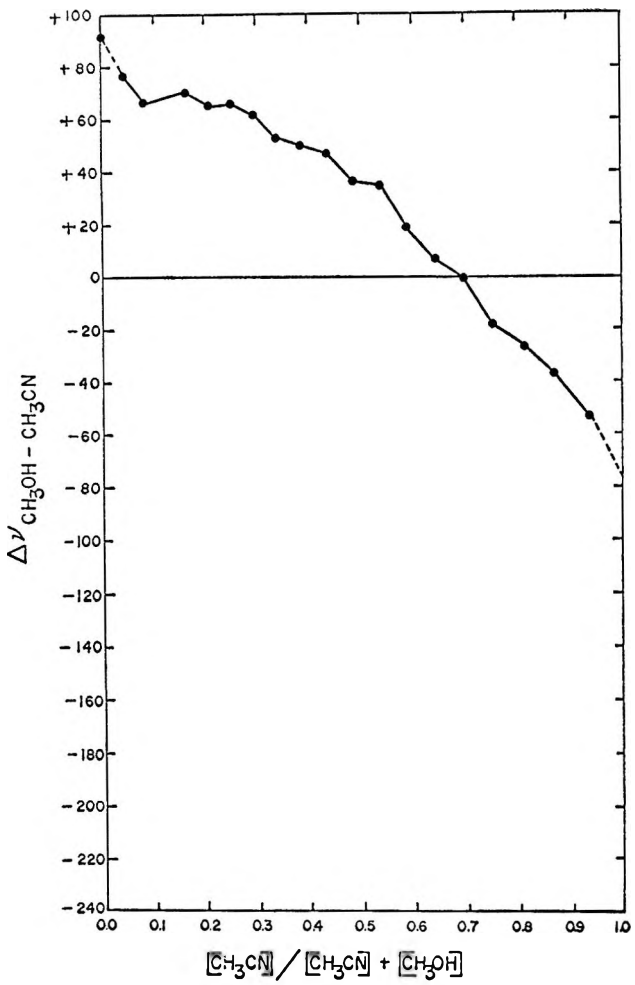

Figure 1.—Effect of CH_3CN on $\Delta\nu_{CH_3OH}$. Negative values correspond to shifts of the –OH proton upfield of the $-CH_3$ resonance of methanol.

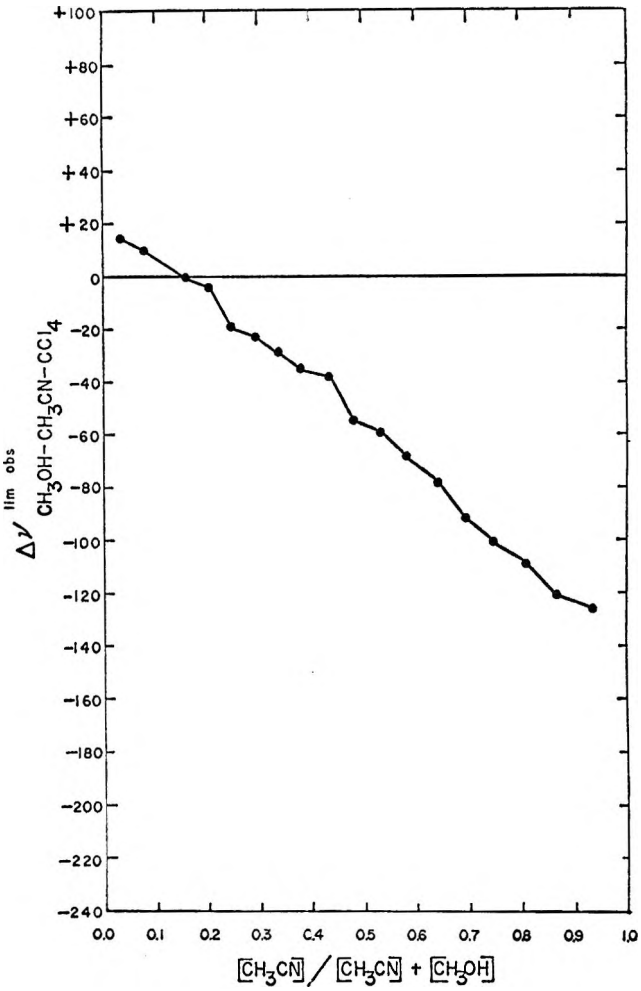

Figure 2.—The relationship between the limiting observed 60-MHz values, $\Delta\nu^{lim\ obs}_{CH_3OH-CH_3CN-CCl_4}$, and the acetonitrile concentration; considering only concentrations of active species in plotting the abscissa.

(CCl_4) mixtures of proton donor and acceptor species. A cursory examination of the CH_3OH–CH_3CN system revealed –OH shift and exchange retardation effects similar to those previously cited in support of hydrogen bonding interactions between alcohols and other proton acceptor species, *e.g.*, acetone,[5,6] DMSO,[5] CH_3NO_2.[4] These preliminary observations prompted the more extensive dilution studies reported here for CH_3OH–CH_3CN mixtures. In broad agreement with prior infrared and nmr investigations,[1,2,7] the present nmr study provides additional support for a strong –CN—HO– hydrogen-bonding interaction.

Experimental Section

Instrumentation.—Nmr spectra were obtained at 32 ± 1° using a Varian A-60 spectrometer equipped with a variable temperature probe. Chemical shifts were measured using the CH_3 resonance of methanol and/or 1–5% tetramethylsilane (TMS) as internal references; side-band techniques were used as a check. Calibration of the instrument was accomplished with an audio signal generator (Hewlett-Packard 205AG) monitored by a frequency counter (Hewlett-Packard 5244L) operated in the period mode. After warm-up, the drift and instability of the instrument were better than one part in 10^6. Spectrometer drift during 1 hr approached ±0.2 cps.

Sample Preparation.—Samples preparation and accuracy are as noted previously.[4] Purification of acetonitrile was according to literature procedures,[8] other nitriles were "shelf variety" dried over $CaSO_4$. Methanol (Fisher) was purified as previously noted;[4] "Spectral Grade" CCl_4 (Fisher) was stored over $CaSO_4$. No detectable impurities were noted in the high gain nmr spectra of the materials used. Temperatures were measured using a sealed sample of purified methanol. Duplicate –OH shift determinations on the same sample, or duplicate determinations on duplicate samples (random selection at ten concentrations for points indicated in Figures 1 and 2 showed a maximum variation of ±0.5 Hz. The filled circles in Figures 1 and 2 represent ±1.0 Hz.

Bulk samples of neat methanol exhibiting splitting in the nmr spectrum sufficient to allow the determination of J_{HCOH} at probe temperature (32°) have been repeatedly prepared in this laboratory. However, methanol exhibiting broadened –OH and $-CH_3$ singlets neat or on dilution to 0.05 *M* with CCl_4 was used for the present study. As a consequence, the observation of induced splitting of the –OH and $-CH_3$ resonances of methanol serves as a diagnostic test for retardation of –OH exchange. Purified methanol exhibiting either type of spectrum showed no significant differences in chemical shifts (*i.e.*, greater than 1.0 Hz at 60 MHz) for the –OH and $-CH_3$ resonances.

Results and Discussion

Minimal concentrations of acetonitrile in methanol produced an nmr spectrum exhibiting three broadened singlets at τ 2.03, 3.38 and 4.67 ppm. The major peaks

(5) W. Drinkard and D. Kivelson, *J. Phys. Chem.*, **62**, 1494 (1958).
(6) P. L. Corio, R. L. Rutledge and J. R. Zimmerman, *J. Mol. Spectrosc.*, **3**, 592 (1959).
(7) A. Loewenstein and Y. Margalit, *J. Phys. Chem.*, **69**, 4152 (1965).
(8) J. F. O'Donnell, J. T. Ayres, and C. K. Mann, *Anal. Chem.*, **7**, 1161 (1965).

(relative intensities 1:3) assignable to the –OH and $-CH_3$ resonances showed no discernable fine structure as the acetonitrile concentration was increased to $[CH_3CN]/[CH_3CN] + [CH_3OH] = 0.7$ (*ca.*). Here, the methanol resonances merged to a singlet due to "accidental" equivalence of the –OH and $-CH_3$ protons. Higher acetonitrile concentrations shifted the –OH resonance upfield of the $-CH_3$ resonance, spin-spin coupling (J_{HCOH} = 5.2 Hz)[9] became apparent and was detected in the spectra of all remaining binary CH_3OH–CH_3CN mixtures studied (Table I). The modifications in the appearance of the nmr spectrum of methanol, observed under conditions of "slow" exchange of the hydroxyl proton, are expected owing to changes in the $J/\Delta\nu$ ratio as the –OH resonance is shifted upfield.[10] Corresponding changes have been noted in the spectra of methanol[5,9] and other alcohols[3] for interactions with strong hydrogen bonding acceptor species, *e.g.*, acetone, DMSO, and, more recently, CH_3NO_2.[4] To our knowledge, this constitutes the first report of nitrile induced suppression of proton exchange in methanol attributable to the –CN—HO– interaction. Other nitriles, *e.g.*, propionitrile, benzylcyanide, β-chloropropionitrile, *o*-tolunitrile and *p*-tolunitrile, were also tested over limited concentrations in methanol. Each nitrile at concentrations approaching a molar excess induced splitting of the methanol $-CH_3$ and –OH resonances;[11] coalescence of the –OH and $-CH_3$ peaks was also observed at higher nitrile concentrations. Thus, the observed phenomenon which is indicative of a strong hydrogen bonding interaction, appears to be general for nitrile–alcohol interactions.

TABLE I

OBSERVED AND EXTRAPOLATED SHIFTS (HERTZ)[a] OF THE –OH RESONANCE FOR CH_3OH–CH_3CN MIXTURES

$[CH_3CN]/[CH_3CN] + [CH_3OH]$	$\Delta\nu$ (CH_3OH–CH_3CN)	$\Delta\nu^{lim\ obs}$ [b] (CH_3OH–CH_3CN–CCl_4)	$\Delta\nu^{\infty}$ [c,d] (CH_3CH–CH_3CN–CCl_4)
0.019			−95.0[e]
0.039	+77.4	+14.9	−15.5
0.079	+67.0	+11.4	−21.0
0.161	+71.0	0.0	−34.3
0.204	+65.6	−3.9	−31.0
0.249	+66.7	−19.4	−58.0
0.293	+62.0	−23.4	−50.0
0.339	+53.5	−29.3	−62.5
0.386	+50.5	−36.1	−74.5
0.436	+47.7	−37.3	−66.0
0.486	+36.8	−53.8	−89.5
0.536	+35.3	−57.7	−95.0
0.588	+19.0	−65.2	−101.5
0.643	+7.8	−78.0	−119.0
0.698	0.0	−90.2	−135.0
0.753	−18.0	−100.8	−142.0
0.814	−26.5	−108.6	−137.5
0.873	−37.0	−121.4	−152.0
0.938	−52.5	−127.2	−150.0
0.968			−193.0[e]

[a] The internal shift of the –OH resonance was measured relative to the methyl resonance of methanol. No appreciable shift (*ca.* >1.0 Hz) of the methanol CH_3 resonance relative to TMS was observed. [b] Limiting observed values are based on the dilution of 0.05 ml of the corresponding binary mixture with 0.95 ml of CCl_4. The $[CH_3CN]/[CH_3CN] + [CH_3OH]$ ratio is maintained although the concentration of CH_3OH varies from 1.2 to 0.06 *M*. [c] Extrapolation values were obtained from a series of six dilutions in CCl_4 for each CH_3OH–CH_3CN mixture indicated. The total variation in the CCl_4 concentration was from 0 to *ca.* 95 mol %. [d] It should be noted that this abbreviation does not signify a constant, but depends upon the relative concentrations of active species. [e] Determined using 100-MHz instrumentation and are included in Figure 3 only.

A preliminary indication of the apparent stability of the –CN—HO– interaction was obtained by diluting the CH_3OH–CH_3CN mixtures exhibiting fine structure in the CH_3OH portion of the spectrum with CCl_4.[12] Additional changes in spectral patterns due to displacement of the –OH resonance were observed, however, J_{HCOH} could still be determined at total methanol concentrations less than 0.06 *M*. Since portions of the purified methanol sample at much lower concentrations in CCl_4 did not exhibit multiplet structure,[13] the observed retardation in –OH exchange for the dilute ternary mixtures is clearly induced by the added nitrile and supports prior evidence for a strong –CN—HO– interaction. Evidence supporting the latter conclusion was also apparent from the general shape of the binary dilution curve (Figure 1).

For the total range of binary CH_3OH–CH_3CN mixtures studied (Figure 1), $\Delta\nu_{CH_3OH\text{-}CH_3CN}$[14] reflected the expected upfield displacement of the –OH resonance to give an extrapolated shift ($\Delta\nu^{\infty}_{CH_3OH\text{-}CH_3CN}$) of 165 Hz, *i.e.*, 72 Hz upfield of the methanol $-CH_3$ resonance. The direction and magnitude of $\Delta\nu^{\infty}_{CH_3OH\text{-}CH_3CN}$ are consistent with variations in the –OH resonance of alcohols previously reported for the addition of hydrogen bonding acceptor species, *e.g.*, DMSO,[5] acetone.[5,6] Some attempts have been made to relate shifts observed for binary systems to the relative strengths of hydrogen bonds formed between various donor–acceptor pairs.[5,15] However, owing to the observed variability in the –OH resonance displacement (Figure 1), any comparison in hydrogen bond strengths for this relative to other reported systems appeared premature. Especially in view of the fact that prior observations of maxima in binary curves for alcohols interacting with proton acceptor species, *e.g.*, acetone,[5,6] DMSO,[5] nitromethane,[4] have been cited as evidence for complex formation. Spectral and freezing point data have also been reported which specifically indicate the complexation of acetonitrile with various proton donors, *e.g.*, phenol,[1b] pyrrole,[1a] $CHCl_3$,[16] and *t*-butyl alcohol.[17] If, as the present data appear to indicate, a consistent (albeit qualitative) explanation for the variability in the

(9) D. Kivelson and M. G. Kivelson, *J. Mol. Spectrosc.*, **2**, 518 (1958) also reported J_{HCOH} = 5.2 Hz and a complete interpretation of the spectral changes encountered in the acetone–methanol system; W. B. Moniz, C. F. Poranski, Jr., and T. N. Hall, *J. Amer. Chem. Soc.*, **88**, 190 (1966) have reported the solvent dependency of this parameter for various alcohols.

(10) For example see P. Laszlo in "Progress in Nuclear Magnetic Resonance Spectroscopy," Vol. III, J. W. Emsley, J. Feeney, and L. H. Sutcliffe, Ed., Pergamon Press, London, 1967.

(11) Observation of fine structure in the ambient temperature spectrum of a specially purified neat sample of methanol has been reported by E. Krakower and L. W. Reeves [*Trans. Faraday Soc.*, **59**, 2528 (1963)]. No significance can be attached to the apparent concentration dependence of the effect observed here.

(12) For a discussion of the major limitations to the use of carbon tetrachloride as an inert diluent see ref 10.

(13) See Experimental Section.

(14) Throughout this communication, $\Delta\nu^{\infty}_{CH_3OH\text{-}CH_3CN}$ and $\Delta\nu^{\infty}_{CH_3OH\text{-}CCl_4}$ signify the extrapolated or infinite dilution shifts (hertz at 60 MHz) for the –OH proton of methanol in the indicated solvent. $\Delta\nu_{CH_3OH\text{-}CH_3CN}$ and $\Delta\nu_{CH_3OH\text{-}CCl_4}$ refer to observed shifts.

(15) C. P. Rader, *J. Amer. Chem. Soc.*, **91**, 3248 (1969).

(16) T. Matsuto and Y. Kudera, *J. Phys. Chem.*, **70**, 4087 (1966).

(17) C. Lussan, *J. Chim. Phys.*, **60**, 1100 (1963).

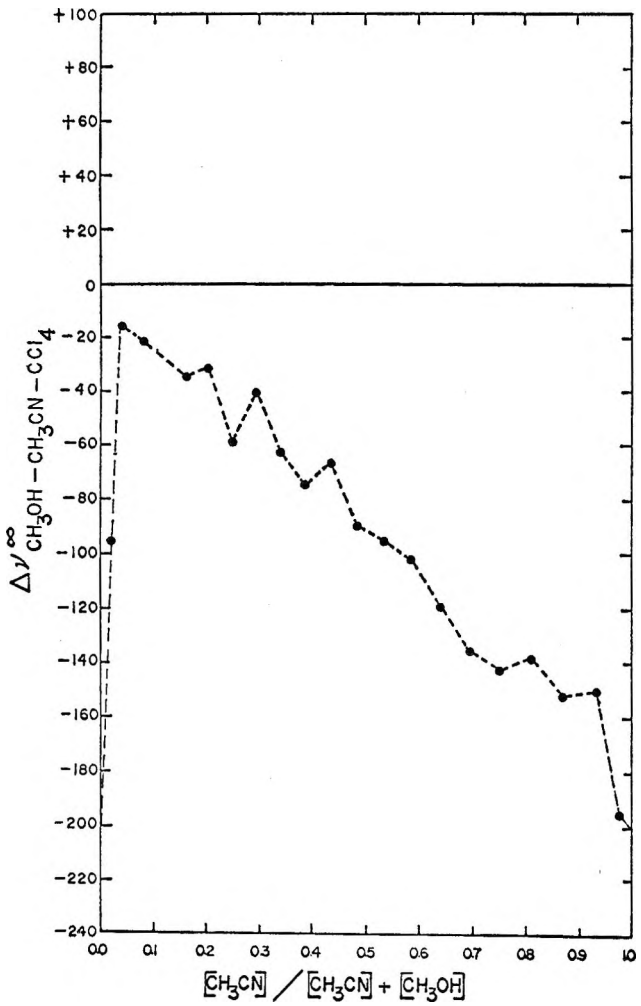

Figure 3.—The relationship between $\Delta\nu^{\infty}_{CH_3OH-CH_3CN-CCl_4}$ and the acetonitrile concentration. The CCl_4 concentration was assumed to be constant; only the concentrations of active species were considered in plotting the abscissa.

concentration dependence of the –OH shifts (Figure 1) can be based on changes in the equilibrium concentration of a series CH_3OH–CH_3CN associates, the complicated nature of binary curves may effectively mask any reliable measure of the bonding interaction. Furthermore, any conclusions regarding relative hydrogen bond strengths based upon data for binary solutions, whether for the interaction of a specific acceptor, *e.g.*, DMSO,[15] with alcohols showing varying degrees of association or to compare various acceptor species with a single alcohol (*e.g.*, methanol)[5] may be untenable.

In an attempt to clarify the mode of complex formation for the present system, more comprehensive dilution studies of the CH_3OH–CH_3CN system were carried out. The limiting observed shifts ($\Delta\nu^{lim\ obs}_{CH_3OH-CH_3CN-CCl_4}$) and $\Delta\nu^{\infty}_{CH_3OH-CH_3CN-CCl_4}$ for each mixture (diluted with CCl_4 as previously noted) plotted *vs.* $[CH_3CN]/[CH_3CN]+[CH_3OH]$ appear as Figures 2 and 3, respectively. Both the low and high acceptor ends of Figure 3 are obtained by extrapolation. Extrapolation of the high acceptor end of this curve using Varian A-60 data was not feasible; however, data obtained from 100-MHz instrumentation allowed an extrapolation at this end of the curve of 200 Hz upfield of the $-CH_3$ resonance of methanol.[18]

The overall upfield displacements of $\Delta\nu^{lim\ obs}_{CH_3OH-CH_3CN-CCl_4}$ and $\Delta\nu^{\infty}_{CH_3OH-CH_3CN-CCl_4}$ relative to $\Delta\nu_{CH_3OH-CH_3CN}$ show the expected disruption of the "residual"–OH—O– bonded structure of the alcohol. However, in that $\Delta\nu^{\infty}_{CH_3OH-CH_3CN-CCl_4}$ for each mixture does not approach $\Delta\nu_{CH_3OH-CCl_4}$ as a limiting value, *i.e.*, 200 Hz upfield of the $-CH_3$ resonance of methanol, one further indication of –CN—HO– hydrogen bonding is obtained.[19]

Perhaps the more interesting and important feature of the ternary curves (Figures 2 and 3) is the repeated occurrence of maxima in the –OH displacement with increasing acceptor concentration, *i.e.*, at average values[20] of $[CH_3CN]/[CH_3CN]+[CH_3OH]$ = 0.05, 0.15, 0.25, 0.4, 0.55, 0.7, and 0.85 (*ca.*).[21] The retention of these maxima in the latter curves under conditions expected to minimize alcohol autoassociation cannot be easily explained without invoking the formation of CH_3OH–CH_3CN aggregates, *i.e.*, consistent with preliminary indications of complexation derived from Figure 1. Accepting the maxima, or for that matter minima, in these curves as indicative of stoichiometric CH_3OH–CH_3CN aggregates having defined geometries presents many intriguing questions. A particular case in point is the initial reversal in $\Delta\nu^{lim\ obs}_{CH_3OH-CH_3CN-CCl_4}$ and $\Delta\nu^{\infty}_{CH_3OH-CH_3CN-CCl_4}$ at $[CH_3CN]/[CH_3CN]+[CH_3OH]$ = 0.05 (*ca.*); the latter cannot be expected to correspond to a specific complex having the corresponding 20:1 molar ratio of CH_3OH–CH_3CN. Consequently, it has been necessary to use a more reasonable working model for hydrogen bonding in this system based, in part, upon suppressed dissociation of methanol aggregates, *i.e.*, that in undergoing a hydrogen-bonded interaction with CH_3CN, the –OH—O– bonded structure of the alcohol is stabilized and does not exhibit the "expected" –OH displacement on dilution with an inert solvent, *e.g.*, CCl_4.[22] Past the initial maximum, the general upfield shift of the –OH resonance with increasing relative concentration of the nitrile can then be ascribed to a decrease in the average number of methanol units possibly associated with an acetonitrile unit.[18] It is also evident, however, that even the simplest explanation for the "sawtooth" curves presented here (Figure 2 or 3) must be modified to include complex formation; otherwise, a gradual diminishment in the CH_3OH/CH_3CN ratio, even if these species are interacting, might not be expected to exhibit any obvious maxima in the –OH displacement.[23] The present data do not allow any firm conclusions as to which of the observed

(18) Preliminary studies using 100-MHz instrumentation for the study of this and other proton donor–acceptor systems, *e.g.*, CH_3NO_2, show that extrapolations of the 60-MHz data reported herein are reliable indications of trends but do not provide limiting values of use for critical comparisons of hydrogen bonding interactions. Additional studies are in progress based on the use of more sensitive 100-MHz instrumentation.

(19) In the absence of hydrogen bonding one would expect $\Delta\nu^{\infty}_{CH_3OH-CH_3CN-CCl_4}$ to approach the extrapolated shift for the CH_3OH–CCl_4 system.

(20) A complete definition of the maxima would require many more points than have been determined in this study.

(21) These maxima appear not only in the binary and ternary curves shown here, but also in the entire family of ternary curves resulting from approximately six incremental dilutions for each binary mixture indicated in Table 1.

(22) We have previously observed the occurrence of similar maxima in ternary curves for the CH_3OH–CH_3NO_2 system. Comparative studies for these two systems are in progress.

(23) The autoassociation curve for methanol shows only a "smooth" displacement of the –OH resonance without any marked deviations; for further discussion see ref 10.

curvature deviations (Figures 1, 2, 3) may be attributed to either acetonitrile induced association of CH_3OH units, or to specific CH_3OH–CH_3CN complexes. More definitive studies of hydrogen bonding in this and other donor–acceptor systems, *e.g.*, CH_3NO_2, DMSO, are in progress in an attempt to resolve this point.

In conclusion, it should be noted that most recent spectral and other studies in this area have been based on the assumed formation of a 1:1 donor–acceptor complex.[24] Our studies reported to date have been limited in scope and cover only the CH_3OH–CH_3CN and CH_3OH–CH_3NO_2 systems; however, it is clearly evident that the above assumption is not consistent with presently available data for these systems.

(24) (a) E. M. Arnett, T. S. S. R. Murty, P. von R. Schleyer, and L. Joris, *J. Amer. Chem. Soc.*, **89**, 5955 (1967). (b) D. Gurka, R. W Taft, L. Joris, and P. von R. Schleyer, *ibid.*, **89**, 5957 (1967). (c) D. Gurka and R. W. Taft, *ibid.*, **91**, 4794 (1969). (d) R. W. Taft, D. Gurka, L. Joris, P. von R. Schleyer, and J. W. Rakshys, *ibid.*, **91**, 4801 (1969).

Registry No.—Methanol, 67-56-1; acetonitrile, 75-05-8.

Acknowledgments.—We are grateful to Dr. R. K. Kullnig of Sterling Winthrop Research Institute for assistance in obtaining 100-MHz nmr data and to the administrators of the Petroleum Research Fund, American Chemical Society (PRF No. 1037-G1), for partial support of this research. We also wish to thank the Materials Branch of NASA for supplying funds to purchase a Varian A-60 nmr spectrometer and Dr. J. Kuder for samples of high purity acetonitrile. One of us, P.A.C., is grateful for an NDEA Fellowship for the period of 1968–1969.

Nitrile Synthesis. The Dehydration of Amides by Silazanes, Chlorosilanes, Alkoxysilanes, and Aminosilanes

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Silazanes, aminosilanes, alkoxysilanes, and chlorosilanes have been found to dehydrate amides to form nitriles at elevated temperatures.

The preparation of nitriles by the dehydration of amides is well known. Reagents used for these dehydrations are either strongly acidic, as, for example, thionyl chloride,[1,2] phosphorus pentoxide,[3] phosphorus oxychloride,[2] zinc chloride–α,α,α-trichlorotoluene,[4] or strongly basic, for example, sodium borohydride[5] and lithium aluminum hydride.[3] The isolation of the products from these reactions is often difficult because of the nature of the by-products.

The reaction of amides with dihalosilanes in the presence of an acid acceptor has been reported to give 2,4-disila-1,3,5-oxadiazine derivatives.[6] Klebe[6] stated that at elevated temperatures nitriles and disiloxanes formed. We wished to determine the utility of this type of dehydration for the preparation of nitriles.

Results and Discussion

The reaction of hexamethylcyclotrisilazane (**1**) with benzamide or acetamide at 180–200° gave benzonitrile or acetonitrile in 95 and 85% yields, respectively.

$$3RC(=O)NH_2 + \underset{\mathbf{1}}{(HNSiMe_2)_3} \longrightarrow 3RC{\equiv}N + 3NH_3 + (OSiMe_2)_x$$

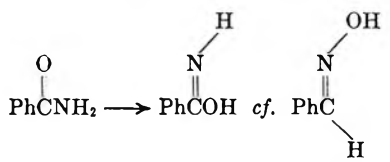
R = Me, Ph

Compound **1** (1 equiv) with benzamide gave a siloxane polymer with a molecular weight $\bar{M}_w$ of 120,000. The number-average molecular weight $\bar{M}_n$ was 6800.

The reaction of **1** with *syn*-benzaldoxime also formed benzonitrile in good yield. An analogy between the

$$3PhCH{=}NOH + (HNSiMe_2)_3 \xrightarrow{\Delta} 3PhC{\equiv}N + 3NH_3 + (OSiMe_2)_x$$

reaction of benzaldoxime and benzamide can be seen if benzamide is written in another tautomeric form.



Octamethylcyclotetrasilazane also dehydrated benzamide to form benzonitrile in good yield. In order to

$$4PhC(=O)NH_2 + (HNSiMe_2)_4 \xrightarrow{\Delta} 4PhC{\equiv}N + 4NH_3 + (OSiMe_2)_x$$

extend the scope and determine the limitations of the dehydration of amides by **1**, some N-substituted amides were examined.

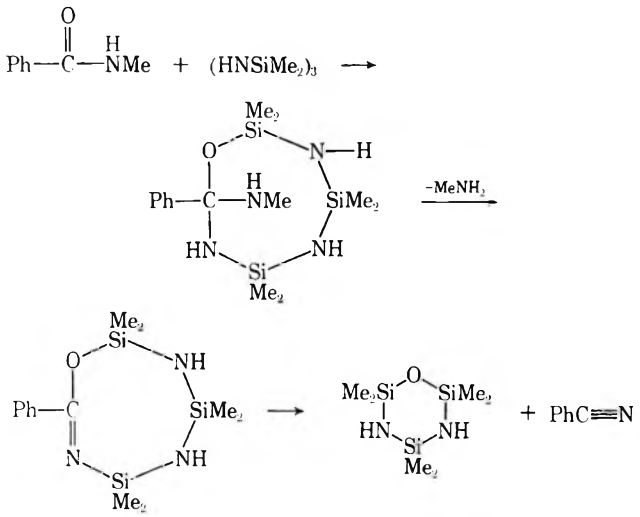
N-Methylbenzamide with **1** gave benzonitrile in 43% yield. *N*-Methylacetanilide gave a 27% yield of acetonitrile. These yields should not be considered the maximum obtainable, because the reactions were not allowed to go to completion. These *N*-methylamides required prolonged heating above 200° for reaction.

$$3PhC(=O)NHMe + (HNSiMe_2)_3 \longrightarrow 3PhC{\equiv}N + (OSiMe_2)_x + 3MeNH_2$$

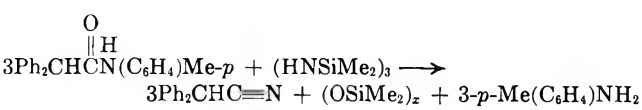
$$3MeC(=O)NPh + (HNSiMe_2)_3 \longrightarrow 3MeC{\equiv}N + (OSiMe_2)_x + 3PhNMeH$$

(1) J. C. Thurman, *Chem. Ind. (London)*, 752 (1964).
(2) B. Rickborn and F. R. Jensen, *J. Org. Chem.*, **27**, 4609 (1962).
(3) L. G. Humber and M. A. Davis, *Can. J. Chem.*, **44**, 2113 (1966).
(4) C. J. Vervanic, U. S. Patent 3,274,229 (1966).
(5) S. E. Ellzey, C. H. Mock, and W. J. Connick, *J. Org. Chem.*, **32**, 946 (1967).
(6) J. F. Klebe, *J. Amer. Chem. Soc.*, **90**, 5246 (1968).

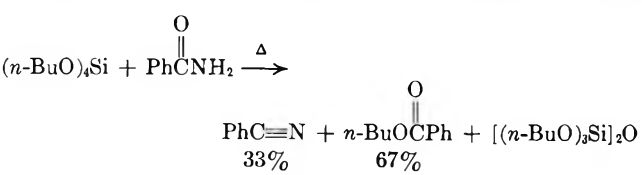
A plausible route for the formation of nitriles from *N*-methylamides is as follows.



The reaction of benzamide with *N*,*N*-dimethylaminohexyldimethylsilane formed benzonitrile and *sym*-dihexyltetramethyldisiloxane after prolonged heating above 200°. *N*-(*p*-Methylphenyl)diphenylacetamide with **1** gave diphenylacetonitrile rapidly and in good yield, 73%.



Benzamide with phenylmethyldichlorosilane or phenyltrichlorosilane gave benzonitrile with the liberation of hydrogen chloride. Phenylmethyldimethoxysilane and benzamide gave benzonitrile, *sym*-diphenyldimethyldimethoxydisiloxane, and a small amount of methyl benzoate. Tetra-*n*-butoxysilane with benzamide gave a 33% yield of benzonitrile and a 67% yield of



n-butyl benzoate. The products obtained in this reaction can be explained as due to the dehydration of 1 mol of benzamide to form 1 mol of water and 1 mol of benzonitrile. Each mole of water then reacted with 2 mol of tetrabutoxysilane to yield 1 mol of hexa-*n*-butoxydisiloxane and 2 mol of *n*-butyl alcohol. Each mol of *n*-butyl alcohol then formed 1 mol of *n*-butyl benzoate.

The use of silicon functionality for the dehydration of amides offers several advantages over conventional dehydrating agents. The choice of silazanes, alkoxysilanes, and chlorosilanes allows the reaction to be run under mildly basic, neutral, or acidic conditions. The nitriles if volatile can be distilled from the siloxane polymer and if solid they can be removed by filtration. If silazanes or chlorosilanes are used the reaction may be followed by the ammonia or hydrogen chloride that is liberated. The use of hexamethylcyclotrisilazane offers an advantage of a low equivalent weight therefore providing good volume efficiency.

Experimental Section

Reagents and Analyses.—*N*-(*p*-Methylphenyl)diphenylacetamide, mp 176–177°, was prepared from *p*-toluidine and diphenylacetyl chloride using a published procedure.[7]

Benzaldehyde, *p*-toluidine, *N*-methylacetanilide, and diphenylacetic acid were obtained from Eastman Organic Chemicals and were used without further purification. Benzoyl chloride and hydroxylamine hydrochloride were Baker Analyzed Reagent grade and were used without purification.

Hexamethylcyclotrisilazane, bp 149° (200 mm), n^{25}D 1.4472 [lit.[8] bp 188° (756 mm), n^{20}D 1.448], and octamethylcyclotrisilazane, bp 174° (60 mm) [lit.[8] bp 225° (756 mm)], were prepared from dimethyldichlorosilane and ammonia. *n*-Butyl silicate, bp 134–136° (5 mm), n^{25}D 1.4106 (lit.[9] n^{20}D 1.4128), was prepared from ethyl silicate. All other silanes were available from Dow Corning Corporation and were >95% pure by glc analysis and were used without further purification. Benzonitrile, *n*-butyl alcohol, *n*-butyl benzoate, benzoic acid, and 1,3,5-triphenyltriazine were identified by comparison of their ir spectra with standards. In addition, their boiling points and melting points gave the correct values.

The ir spectra were obtained on a Perkin-Elmer Model 137 spectrophotometer. The ^{1}H nmr spectra were obtained on a Varian Associates Model A-60 using CCl_4 as a solvent. The glc analyses were obtained on an 8 ft × 0.125 in. stainless steel column packed with 26% Dow Corning SGM-11 on Chromosorb W, 80–100 mesh, using an F & M Scientific Model 5750 research chromatograph.

Acetonitrile from Acetamide and Hexamethylcyclotrisilazane (1).—A mixture of 30 g (0.5 mol) of acetamide (Fisher Scientific Co.) and 100 g (0.46 mol, 1.37 equiv) of **1** was heated to 120–130° for 64 hr and to 170° for an additional 24 hr. Acetonitrile distilled from the mixture: 17.4 g, (85%); bp 80°; n^{25}D 1.3434 (lit.[10] n^{20}D 1.3441). Residue from the distillation, 96 g, had a neutral equivalent of 130. The theoretical value was 110. The difference was probably due to external moisture which caused some loss of NH_3.

Benzonitrile from Benzamide and 1.—A mixture of 60 g (0.5 mol) of benzamide (mp 130–132°) and 100 g (0.46 mol) of **1** was heated at 84–110° for 30 hr and 130° for 18 hr. Distillation then gave 51 g, bp 70–73° (10 mm), which was 85% benzonitrile by glc area per cent. The remainder of the peaks seen by glc analysis corresponded to several siloxane moieties. The yield based on 48.5 g is 94%.

A mixture of 12.1 g (0.1 mol) of benzamide and 7.5 g (0.034 mol, 0.102 equiv) of **1** was heated at 220° for 20 hr. At the end of this time the rate of evolution of ammonia was very slow. The product was distilled to give 9.6 g, 91%, bp 70° (~10 mm), of benzonitrile which was pure by glc analyses. The residue was taken up in hexane and filtered to remove 350 mg, 3.3%, of 1,3,5-triphenyltriazine, mp 234–236°. The siloxane polymer contained no peaks by glc analysis corresponding to cyclic dimethylsiloxanes and the neutral equivalent was 4120. The calculated neutral equivalent for the excess silazane used is 2740. The difference in neutral equivalent corresponds to 17 mg of water.

Benzonitrile from Benzamide and Octamethylcyclotetrasilazane.—A mixture of 12.1 g (0.1 mol) of benzamide and 14.0 g (0.048 mol, 0.19 equiv) of octamethylcyclotetrasilazane was heated at 220° for 4.5 hr. The mixture was distilled to give 9.1 g, bp 87–88° (27 mm), which was 83% benzonitrile by glc area per cent with the remainder of the material appearing as several siloxane peaks, yield 71%.

Benzonitrile from Benzaldoxime and 1.—A mixture of 13.0 g (0.11 mol) of *syn*-benzaldoxime (mp 27–33°) and 10 g (0.046 mol, 0.137 equiv) of **1** was heated at 210° for 6 hr. The mixture was distilled to give 9.4 g of material, bp 59–63° (8 mm), which in addition to siloxanes contained 85% benzonitrile; the yield is 72%.

Benzonitrile from Phenyltrichlorosilane and Benzamide.—A mixture of 10.5 g (0.05 mol) of phenyltrichlorosilane and 6.0 g (0.05 mol) of benzamide was heated to 240–260° for 40 hr. The

(7) C. L. Stevens and J. C. French, *J. Amer. Chem. Soc.*, **75**, 657 (1953).
(8) S. D. Brewer and C. P. Haber, *ibid.*, **70**, 3888 (1948).
(9) B. A. Arbuzon and T. G. Shavsha, *Dokl. Akad. Nauk SSSR*, **68**, 859 (1949).
(10) R. R. Driesbach and R. A. Martin, *Ind. Eng. Chem.*, **41**, 2877 (1949).

mixture was then distilled to give 2.5 g, 47.6%, of pure benzonitrile. A toluene solution of the residue when analyzed by glc contained benzonitrile and nothing else except solvent. Hydrogen chloride was detected during the reaction.

Benzonitrile from *N*,*N*-dimethylaminodimethylhexylsilane and Benzamide.—A mixture of 18.7 g (0.1 mol) of *N*,*N*-dimethylaminodimethylhexylsilane and 6.05 g (0.05 mol) of benzamide was heated to 235°. At the melting point of benzamide, dimethylamine was liberated rapidly. After 4 hr at 235° an ir spectrum of the mixture indicated some benzonitrile by a small absorption at 4.5 μ. There was also a broad absorption at 1060 cm^{-1} corresponding to the SiOSi structure of *sym*-dihexyltetramethyldisiloxane. Ammonium sulfate, 0.5 g, was added and benzonitrile was slowly distilled from the mixture. A total of 5.4 g of distillate was obtained which was 95% benzonitrile by glc area per cent. The yield based on 5.1 g is 96%. Coinjection of this residue with an authentic sample indicated by glc most of the residue was *sym*-dihexyltetramethyldisiloxane.

Reaction of *N*-(*p*-Methylphenyl)diphenylacetamide with Hexamethylcyclotrisilazane.—A mixture of 16 g (0.05 mol) of *N*-(*p*-methylphenyl)diphenylacetamide, mp 176–177°, and 11.0 g (0.05 mol) of **1** was heated at 240° for 4 hr. The evolution of ammonia was noticed at the melting point of the amide and after 4 hr at 240° the rate of ammonia evolution had greatly decreased. The product was triturated with benzene and hexane to give 3.0 g, 18.7%, of starting material, mp 167–174°. Benzene and hexane were removed from the solution *in vacuo* and after filtration 7.1 g of solid, mp 69–70°, corresponding to a 73% yield of diphenylacetonitrile was obtained. A portion of this material was recrystallized (ether–pentane): mp 74–75°; ir (CCl_4) 2250 cm^{-1} (C≡N); nmr 5.10 (s, 1.0, C—**H**), 2.75 (s, 10.0, Ar—**H**). The filtrate did not contain a significant amount of hexamethylcyclotrisilazane or *p*-toluidine by glc analysis but did contain at least 13 broad peaks. The filtrate was taken up in ether and washed with cold dilute hydrochloric acid. The acidic aqueous extract was neutralized with potassium hydroxide and *p*-toluidine was extracted with ether. The ethereal solution was dried over sodium sulfate and after removing the volatiles *in vacuo* 2.75 g, 52%, of *p*-toluidine, mp 37–40°, mixture melting point undepressed, was obtained.

Reaction of *N*-Methylbenzamide with 1.—A mixture of 6.75 g (0.05 mol) of *N*-methylbenzamide and 11.0 g (0.05 mol) of **1** was heated at 220–240° for 48 hr and slowly distilled over 16 hr to give 3.0 g of distillate which was 70% benzonitrile by glc analysis. Other peaks corresponded to several siloxane compounds. The yield based on 2.1 g is 42%.

Reaction of *N*-Methylacetanilide with 1.—A mixture of 14.9 g (0.1 mol) of *N*-methylacetanilide and 7.5 g (0.03 mol) of **1** was heated to 240–260° for 64 hr. The mixture became dark over this period and a basic gas was detected by pH paper. After 64 hr, the product was distilled over a 3-hr period to give 2.2 g of material which was 50% acetonitrile by glc area per cent. The distillate contained several higher boiling components and had an amine odor.

Reaction of *n*-Butyl Silicate with Benzamide.—A stirred mixture of 13.2 g (0.05 mol) of *n*-butyl silicate and 6.05 g (0.05 mol) of benzamide was refluxed at 200° for 44 hr during which time there was no reaction. Three drops of (2-phenylpropyl)methyldichlorosilane was added. The mixture was refluxed an additional 48 hr when glc analysis indicated the presence of *n*-butyl alcohol, benzonitrile, *n*-butyl benzoate, *n*-butyl silicate, and hexa-*n*-butoxydisiloxane. Distillation at 10 mm gave the following fractions: 400 mg, bp 70–73°, benzonitrile; 4.6 g, bp 73–120°, 30% benzonitrile–70% *n*-butyl benzoate; 2.8 g, bp 120–128°, 90% *n*-butyl benzoate–10% *n*-butyl silicate; 1.0 g, bp 128–141°, 50% *n*-butyl benzoate–50% *n*-butyl silicate. The residue, 8.0 g, was 50% *n*-butyl silicate and 50% higher boiling product, presumably hexa-*n*-butoxydisiloxane. The yield of *n*-butyl benzoate based on 6.05 g is 65%, of benzonitrile based on 1.78 g is 34%.

Reaction of Methylphenyldichlorosilane with Benzamide.—A mixture of 1.2 g (10 mmol) of benzamide and 2 ml (12.3 mmol) of methylphenyldichlorosilane was heated at 160–180° for 16 hr. The reaction was two phases and after 16 hr at 160–180° the temperature was increased to 220°. The evolution of hydrogen chloride was observed at this temperature and the mixture was held at this temperature for 28 hr. Analysis by glc contained a peak corresponding to benzonitrile. Estimated conversion based on the ratio of glc area per cents of the peaks corresponding to benzonitrile and starting phenylmethyldichlorosilane was 70%. An ir spectrum of this mixture had an absorption at 4.5 μ indicative of C≡N.

Reaction of Methylphenyldimethoxysilane with Benzamide.—A solution of 1.2 g (10 mmol) of benzamide in 5 ml (27.5 mmol) of methylphenyldimethoxysilane was refluxed for 120 hr. At this time, a glc analysis showed the presence of benzonitrile and a small peak corresponding to methylbenzoate eluting near phenylmethyldimethoxysilane. There was an absorption at 4.4 μ in the ir spectrum for C≡N. In addition there was a small absorption at 5.75 μ (C=O) corresponding to methylbenzoate. The final mixture was neutral. Distillation gave 900 mg of material which was 50% benzonitrile, 40% methylphenyldimethoxysilane, and 10% methyl benzoate by glc area per cent.

Registry No.—**1**, 1009-93-4; acetamide, 60-35-5; benzamide, 55-21-0; octamethylcyclotetrasilazane, 1020-84-4; benzaldoxime, 932-90-1; phenyltrichlorosilane, 98-13-5; *N*,*N*-dimethylaminodimethylhexylsilane, 25913-89-7; *N*-(*p*-methylphenyl)diphenylacetamide, 4107-01-1; *N*-methylbenzamide, 613-93-4; *N*-methylacetanilide, 579-10-2; *n*-butyl silicate, 4766-57-8; methylphenyldichlorosilane, 149-74-6; methylphenyldimethoxysilane, 3027-21-2.

Photodimerization of Thianaphthene 1,1-Dioxide. Structure

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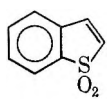
Received September 22, 1969

Thianaphthene 1,1-dioxide (1) forms two isomeric cyclobutane dimers, **2** and **3**, on uv irradiation. Reduction and Raney nickel desulfurization of **2** and **3** afforded products which allowed structural assignment of the dimers as *anti* head to head (**2**) and anti head to tail (**3**). The assignment of dimer **3** was confirmed by Raman and infrared spectroscopy.

The photodimerization of thianaphthene 1,1-dioxide (**1**) has been observed by Davies and James[2a] and



1

Mustafa.[2b] The structure and stereochemistry of the product(s),[3] however, were not elucidated. We would like to report the isolation and structure elucidation of the two isomeric photodimers of thianaphthene 1,1-dioxide (**1**).

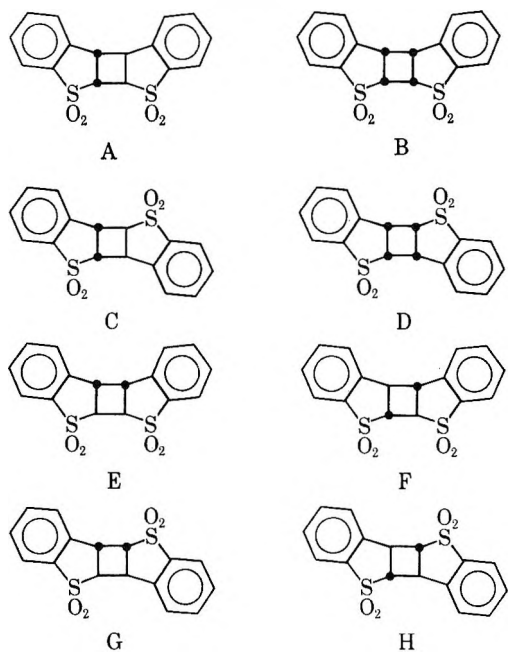
The photodimerization of indene[4] and 1,1-dimethylindene,[5] analogs of **1**, have been studied. In both cases, photodimerization could be effected only in the presence of triplet sensitizers benzophenone (E_T = 69 kcal)[4] and acetophenone (E_T = 73.6 kcal).[5] In contrast, thianaphthene 1,1-dioxide (**1**) does not require the presence of a triplet sensitizer for photodimerization.

In a typical run, a benzene solution of **1** (4.0 g/l.), previously flushed with dry nitrogen, was irradiated with a type L 450-W Hanovia mercury vapor lamp (filtered by Pyrex) for 20 hr at room temperature. A white precipitate crystallized on the walls of the reaction flask. Examination of the solid as well as the residue from the benzene solution by tlc and glpc revealed that two photoproducts had formed, one being a major constituent of the insoluble material (**2**) and the other being a major constituent of the benzene solution (**3**). The total yield of the two photoproducts was 75% (21% of starting material was recovered). The ratio of compound **2** to compound **3** was 2.7 (73:27, glpc).

Elementary analysis and exact mass measurement of the molecular ion of both **2** (332.0192) and **3** (332.0179) agreed with the formula $C_{16}H_{12}S_2O_4$ (*m/e*, M^+ required 332.0177). This indicates the formation of two isomeric dimers. The ir[6] and nmr spectra (AA'BB') for nonaromatic protons are in agreement with any one of the following structures (Chart I).

Structures E, F, G, and H, are highly strained and would be expected to epimerize readily on treatment with base.[7] When **2** and **3** were refluxed with sodium

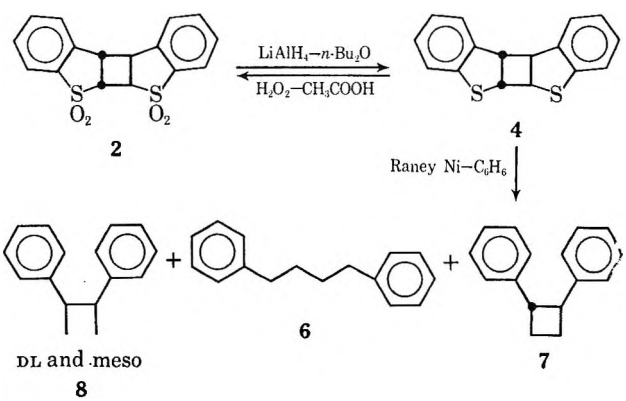
CHART I



methoxide in methanol, no change in the dimers was observed thus ruling out E–H as structures for **2** and **3**.

Evidence for the structures of **2** and **3** has been obtained (Schemes I and II) by converting the sulfone to

SCHEME I



the corresponding sulfide followed by Raney nickel desulfurization to various diphenylcyclobutane derivatives.[8]

Compounds **2** and **3** were reduced by $LiAlH_4$ in *n*-butyl ether to give sulfides **4** and **5** respectively. These compounds (**4** and **5**) were oxidized (35% H_2O_2–HOAc) in over 90% yield to compounds **2** and **3**, respec-

(1) NRCC Bursary holder 1968–1970.

(2) (a) W. Davies and F. C. James, *J. Chem. Soc.*, 314 (1955); (b) A. Mustafa, *Nature*, **175**, 992 (1955); A. Mustafa, *J. Amer. Chem. Soc.*, **78**, 6174 (1956).

(3) Only one product was reported by Davies and James[2a] and Mustafa.[2b]

(4) (a) G. O. Schenck, W. Hartmann, S.-P. Mannsfeld, and C. H. Krauch, *Ber.*, **95**, 1642 (1962). (b) A. G. Anastassiou and G. W. Griffin, *J. Org. Chem.*, **33**, 3441 (1968).

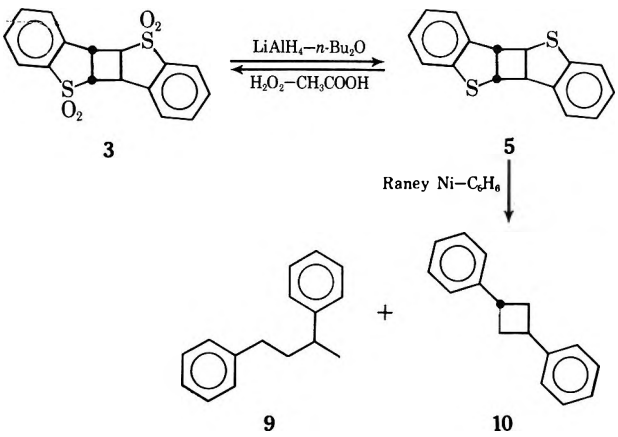
(5) J. J. McCullough, *Can. J. Chem.*, **46**, 43 (1968).

(6) The infrared spectra of **2** and **3** showed marked differences in the 850- and 450-cm^{-1} regions.

(7) E. J. Corey, J. D. Bass, R. LeMahier, and R. B. Mitra, *J. Amer. Chem. Soc.*, **86**, 5570 (1964).

(8) A → *trans*-1,2-diphenylcyclobutane; B → *cis*-1,2-diphenylcyclobutane; C → *trans*-1,3-diphenylcyclobutane; D → *cis*-1,3-diphenylcyclobutane.

SCHEME II



3 5 9 10

tively (ir and mixture melting point were identical with those of the original photodimers). Hence, no rearrangement occurred during reduction of the photodimers with $LiAlH_4$.

Compound **4** was treated with Raney Ni W2 and afforded a mixture of DL- and *meso*-2,3-diphenylbutane[9] (**8**) (27%), 1,4-diphenylbutane (**6**) (11%), and *trans*-1,2-diphenylcyclobutane (**7**) (62%). The identity of this mixture was verified with three different glpc columns (see Experimental Section). In addition, *trans*-1,2-diphenylcyclobutane (**7**) was collected and the nmr spectrum was found to be identical with that of an authentic sample.[14] In order to exclude the possibility of isomerization of *cis*- to *trans*-1,2-diphenylcyclobutane during desulfurization, the *cis* isomer[14] was refluxed in benzene under the same conditions as that of compound **4**. Only a small amount of 1,4-diphenylbutane (**6**) was produced [no DL- or *meso*-2,3-diphenylbutane (**8**)] and no isomerization to *trans*-1,2-diphenylcyclobutane (**7**) was observed. Further, it was shown that no interconversion between DL and *meso* **8** occurred under the conditions of the desulfurization. Based upon the above results, we assign structure A to compound **2** (head to head, *anti*).

Similarly, compound **5** when treated with Raney Ni W2 gave 1,3-diphenylbutane (**9**) (38%) and trans-1,3-diphenylcyclobutane (**10**) (62%). *trans*-1,3-diphenylcyclobutane (**10**) was isolated by preparative glpc. The nmr spectrum[15] of **10** (aromatic, τ 2.82, 10 H, s; methine, τ 6.56, 2 H, p, J = 8.0 Hz; methylene, τ 7.60, 4 H, t, J = 8.0 Hz) in $CDCl_3$ is indicative of *trans* stereochemistry. Changing the solvents to acetone-d_6 or benzene-d_6 did not change the multiplicity or symmetry of the nmr signals. In the *trans* isomer the methylene protons would be symmetrically equivalent hence, a triplet methylene for this *trans*-1,3-disubstituted cyclobutane would be expected. The methylene protons in the *cis* isomer are not equivalent; thus a more complex pattern would likely occur.

Similar arguments have been used in assigning the stereochemistry of *trans*- and *cis*-1,3-dihalocyclobutane,[16] *trans*- and *cis*-1,3-dihalo-1,3-dimethylcyclobutane,[17,18] *trans*- and *cis*-2,4-diphenylthietane,[19] *trans*- and *cis*-2,4-dimethylthietane,[20] and *trans*-1,3-dimethylcyclobutane.[17]

Further evidence as to the structure of **5** was obtained by Raman spectroscopy. It has been established that molecules possessing a symmetry center give fewer coincident vibrational bands (Raman *vs.* infrared spectrum) than do noncentrosymmetric molecules (C_i symmetry).[21] This concept has been utilized to define a number of centrosymmetric photodimers.[21]

Raman and infrared comparisons were made for compounds **4** and **5** scanning from 250 to 3200 cm^{-1} (Tables I and II). Transitions within 10 cm^{-1} for these comparisons were considered coincidences[22] (Table II). The observation of 14 fewer coincident bands (25–39, Table II) for **5** *vs.* **4** strongly indicate that **5** is centrosymmetric.

Based on the above considerations, we assign structure C to compound **2**.

Experimental Section

Materials and apparatus:—Benzene (Fisher Certified reagent) was used as photodimerization solvent. Melting points were taken on a Gallenkamp apparatus and are not corrected. The glpc data were obtained on a Hewlett–Packard F & M series 5670 research chromatograph using three columns (A, B, C). Column A was a 1/8 in. × 6 ft 20% Apiezon L on Chromosorb W, AW, DMCS (acid-washed, dimethyldichlorosilane treated); column B was a 1/8 in. × 6 ft 10% UC-W98 (silicone gum rubber) on Diatoport S; and column C was a 1/8 in. × 6 ft 10% LAC-728 on Chromosorb W, AW, DMCS treated. Infrared spectra were measured on Perkin-Elmer 225 spectrometer, nmr spectra were obtained from Varian Associates A-60 and T-60 spectrometers, mass spectra were recorded on an AEI MS 902 spectrometer, and Raman spectra were recorded as solid samples (several milligrams) on a Jarrel-Ash 25-300 Raman spectrometer.

Thianaphthene 1,1-Dioxide (1).—Sulfone **1** was obtained by the oxidation of thianaphthene with H_2O_2 in glacial acetic acid according to the method of Davies and James.[2] This sulfone was further purified by recrystallization from ethanol–activated charcoal (mp 142.5–143; lit.[2] mp 142°) yield 76%.

The Photodimerization of Thianaphthene 1,1-Dioxide.—Two liters of a benzene solution of **1** (8.0 g, 2.4 × 10^{-2} M), previously

(9) The formation of *meso* **8** was unexpected. If the photodimer **2** has head to head, *syn* stereochemistry (structure B), then not only *meso* **8** but *cis*-1,2-diphenylcyclobutane would be expected from Raney nickel treatment. Since there is ample evidence[10] that racemization or *cis–trans* interconversions of centers α to sulfur are not observed, DL and *meso* **8** must arise from fragmentation processes on the catalyst surface.[11] At least two explanations for DL and *meso* **8** formation are possible and have literature precedent. Simultaneous removal of two sulfur atoms from **4** after α C–C bond reduction would give a 1,4 diradical[12] which would give 2,3-diphenyl-1-butene on disproportionation.[10a,13] Reduction of this molecule would provide DL and *meso* **8**. Also, cleavage of the C–C bond α to each sulfur atom would give a different 1,4 diradical which on disproportionation,[10a,13] desulfurization, and reduction would give DL and *meso* **8**.

(10) (a) S. F. Birch and R. A. Dean, *Ann.*, **585**, 234 (1954); (b) S. F. Birch, R. A. Dean and E. V. Whitehead, *J. Org. Chem.*, **19**, 1449 (1954); (c) A. F. Hussey, H. P. Liao, and R. H. Baker, *J. Amer. Chem. Soc.*, **75**, 4727 (1953); (d) G. Stork, E. E. van Tamelen, L. J. Fredman and A. W. Burgstahler, *ibid.*, **75**, 384 (1953); (e) J. F. Ford, R. C. P. Kethly, and V. O. Young, *Tetrahedron*, **4**, 325 (1958); (f) for an authoritative review on Raney nickel desulfurizations, see W. A. Bonner and R. A. Grimm, in "Organic Sulfur Compounds," Vol. II, N. Kharasch and C. Y. Meyers, Ed., Pergamon Press, N. Y. and London, pp 35–71, 1966, pp 35–71.

(11) H. R. Snyder and G. W. Cannon, *J. Amer. Chem. Soc.*, **66**, 155 (1944).

(12) (a) W. Baker, A. S. El-Nawawy, and W. D. Ollis, *J. Chem. Soc.*, 3163 (1952); (b) C. Djerassi, M. Shamma, and T. Y. Kan, *J. Amer. Chem. Soc.*, **80**, 4723 (1958).

(13) A. W. Weitkamp, *ibid.*, **81**, 3434 (1959).

(14) R. M. Dodson and A. G. Zielske, *J. Org. Chem.*, **32**, 23 (1967).

(15) Chemicals shifts for nmr given in parts per million with tetramethylsilane as τ 10; m = multiplet; s = singlet; t = triplet; p = pentuplet.

(16) K. B. Wiberg and G. M. Lampman, *J. Amer. Chem. Soc.*, **88**, 4429 (1966).

(17) W. von E. Doering and J. F. Coburn, *Tetrahedron Lett.*, 999, (1965).

(18) K. Griesbaum, W. Naegle, and G. G. Wanless, *J. Amer. Chem. Soc.*, **87**, 3151 (1965).

(19) R. M. Dodson and G. Klose, *Chem. Ind. (London)*, 540 (1963).

(20) B. M. Trost, W. L. Schinski, and I. B. Mantz, *J. Amer. Chem. Soc.*, **91**, 4320 (1969).

(21) H. Ziffer and I. W. Levin, *J. Org. Chem.*, **34**, 4056 (1969).

(22) This is 5 cm^{-1} outside the range utilized by previous workers (ref 21) and should easily allow for crystal perturbations.

TABLE I

COMPARISON OF THE RAMAN DISPLACEMENTS AND INFRARED FREQUENCIES FOR THE BENZOTHIOPHENE 1,1-DIOXIDE PHOTODIMERS[a]

5 Head to tail				4 Head to head			
Infrared, cm^{-1}		Raman, cm^{-1}		Infrared, cm^{-1}		Raman, cm^{-1}	
252	1100	252			979	232	
292	1122		1115	252[a]	992	252	992
		330	1130	265	1020		
363	1148			275[a]	1025[a]		1028
	1150	410	1155	282	1055[a]	288	
430[a]	1160				1060	340	1060
432	1181			368	1070	370	1070
445	1190	440	1190	415		415	1035
481	1205	475				430	1048
488			1230	448	1152	450	1155
528		528	1248	470	1188[a]	478	1188
605	1260	605		495	1190	495	1190
692		690	1270	510	1198[a]		1198
711	1282	710	1280	525	1240	520	1240
745		740	1310	535	1248	540	
750	1440			575	1262		1260
768	1458	760	1460	620	1275	621	1282
	1568	785	1565	694	1360	694	
	1580	841	1580	718	1320	720	1320
863		860	2925	728	1400		
871	2950		2950	745	1420[a]	743	
902	2989		2980	753	1460	753	
	3010	928	3010	770[a]	1462[a]	770	
938		942	3020	800	1570		1570
960	3050		3050	833	1579[a]	832	
971	3060	970		855	1582		1582
990		990	3130	862	2932		2930
1022		1020	3160		2960[a]		2955
1055		1055		904	2980	904	2975
				935	3000	930	
				970	3040		3038
					3060		3060

[a] sh denotes shoulder.

TABLE II

COMPARISON OF THE RAMAN AND INFRARED FREQUENCY COINCIDENCES[a]

Head-to-tail photodimer				Head-to-head photodimer			
Compd	ir	R	C[a]	Compd	ir	R	C
	42	39	25[b]		60	42	39[b]
5				4			
	42	39	19[c]		60	42	29[c]

[a] ir, R, and C denote infrared peaks, Raman peaks, and coincidences respectively. [b] Coincidences within 10 cm^{-1}. [c] Coincidences within 5 cm^{-1}.

purged with dry nitrogen for 45 min, was irradiated with a type L 450-W Hanovia mercury vapor lamp in the usual quartz water-cooled immersion apparatus with Pyrex filter for 20 hr at room temperature. A white precipitate (3.0 g) crystallized on the walls of the reaction flask; in addition, 4.7 g of material was recovered from the benzene solution. Examination, by tlc (silica gel eluted with $CHCl_3$:acetone, 85:15) and glpc on column A, of the precipitate and the benzene solution revealed the presence of two compounds, compounds **2** being a major constituent of the insoluble material and compound **3** being a major constituent of the benzene solution. In a typical run the residue from the benzene solution was combined with the precipitate and the total mixture analyzed with glpc on column A. The ratio of **2** to **3** was found to be 73:27. The total yield of the dimers was 6.0 g (75% yield). Recrystallization of the fraction precipitating from benzene with DMSO gave 2.6 g of **2** (mp 329–330° dec): ir 1320 cm^{-1} and 1160 cm^{-1} (SO_2 stretching); nmr τ 1.83–2.15 (8 H m), 5.20–5.80 (4 H AA'BB').

Anal. Calcd for $C_{16}H_8S_2O_4$: C, 57.83; H, 3.62; S, 19.27; exact mass of molecular ion, 332.0177. Found: C, 57.80; H, 3.70; S, 19.18; exact mass of molecular ion, 332.0192.

The residue was obtained by evaporation of the benzene and was extracted with boiling water until **1** no longer crystallized from the water (1.7 g, 21%, of **1** was recovered). The resulting mixture was recrystallized twice from DMSO (crystallizing mixture allowed to stand overnight), resulting in 1.1 g of **3** (mp 334–335° dec): ir 1320 and 1160 cm^{-1} (SO_2 stretching); nmr τ 1.85–2.15 (8 H m), 4.90–5.80 (4 H AA'BB').

Anal. Calcd for $C_{16}H_8S_2O_4$: C, 57.83; H, 3.62; S, 19.27; exact mass measurement of molecular ion, 332.0177. Found: C, 58.22; H, 3.92; S, 19.06; exact mass measurement of molecular ion, 332.0179.

Reduction of Photodimers 2 and 3.—Compound **2** (4.0 g, 0.012 mol) was refluxed with $LiAlH_4$ (2.8 g, 0.073 mol) in 200 ml of *n*-butyl either (previously dried over sodium) for 5 hr. The excess $LiAlH_4$ was decomposed by carefully adding 3 ml of water, 3 ml of 15% NaOH, and 6 ml of water in succession. After filtration and evaporation of the solvent, the crude product was chromatographed over 50 g of neutral alumina with petroleum ether (bp 30–60°) and hexane to give 2.1 g of white crystals of **4**, mp 217–218° (66% yield). Infrared analysis showed the absence of the two SO_2 stretching absorptions.

Anal. Calcd for $C_{16}H_8S_2$: C, 71.64; H, 4.47; S, 23.84. Found: C, 71.55; H, 4.61; S, 23.89.

Compound **3** was treated similarly except that the product **5** was purified by recrystallization from $CHCl_3$–ethanol; 1.8 g (56%) mp 180–180.5° was obtained. Infrared analysis showed the absence of the SO_2 stretching bands.

Anal. Calcd for $C_{16}H_8S_2$: C, 71.64; H, 4.47; S, 23.84. Found: C, 71.69; H, 4.16; S, 23.89.

Oxidation of Bis Sulfides 4 and 5.—After compound **4** (80 mg, 0.03 mmol) was dissolved in 10 ml of glacial acetic acid, 10 ml of 35% H_2O_2 was added and the resulting mixture heated on a steam bath for 1 hr. The solution was cooled and poured into 50 ml of cold water. The suspension was filtered and dried under vacuum. Compound **2** (75 mg, 73%, mp 329–330° dec) resulted. A mixture melting point with photoproduct **2** was not depressed. In addition, the ir spectrum was identical with that of photoproduct **2**.

Similarly, 100 mg of **5** was oxidized to 80 mg (63% yield) of **3** (mp 334–335° dec). A mixture melting point with photoproduct **3** was not depressed and the ir spectrum was identical with that of photoproduct **3**. The mixture melting point of **2** and **3** was 285–290°.

***meso*- and DL-2,3-Diphenylbutane.**—These compounds were prepared from 37 g (0.2 mol) of 1-phenylethyl bromide according to the method of Conant and Blatt.[23] Recrystallization of the mixture in ethanol gave 10 g of *meso*-2,3-diphenylbutane (mp 126–128°; lit.[23] mp 124–126°; 25% yield). The mother liquor was evaporated and the residue distilled under vacuum to give 5 g of DL-2,3-diphenylbutane: bp 100–102° (1 mm); lit.[24] bp 103–104° (1 mm); n^{20} = 1.5552; lit.[24] n^{20}D 1.55516; 13% yield.

1,2-Dibenzoylethane.—1,2-Dibenzoylethane was prepared in 95% yield by the method of Schaefer.[25]

Bis(ethylene dithioketal) of Dibenzoylethane.—This material was prepared by mixing 2.6 g (0.011 mol) of dibenzoylethane with 12 ml of ethylenedithiol and 2 ml of boron trifluoride etherate at room temperature for 1 hr. After recrystallization from dioxane, 3.6 g (85% yield) of white crystals, mp 197–198°, resulted.

Anal. Calcd for $C_{20}H_{22}S_4$: C, 61.28; H, 5.64. Found: C, 61.45; H, 5.65.

1,4-Diphenylbutane (6).—The above bis(ethylene dithioketal) (3 g, 0.0079 mol) was refluxed in ethanol with about 3 g of Raney nickel W2 for 15 hr, affording 1.5 g (89% yield) of 1,4-diphenylbutane (mp 48–49°, lit.[14] mp 50.5–51.5°).

1,2-Diphenylcyclobutene.—This compound was prepared in 40% yield as previously reported.[14]

***cis*-1,2-Diphenylcyclobutane.**—This material was prepared by hydrogenation of 1,2-diphenylcyclobutene over a Pt catalyst in 95% yield:[14] nmr[15] ($CDCl_3$) τ 3.05 (10 H s), 5.88–6.20 (2 H m), and 7.45–7.55 (4 H m).

***trans*-1,2-Diphenylcyclobutane (7).**—The *cis* isomer (0.2 g, 0.96 mmol) was mixed with 0.2 g of potassium *t*-butoxide in anhydrous DMSO at 70° for 22 hr. The solution was added to water, extracted with benzene, and chromatographed over silica gel with petroleum ether. The *trans* isomer (**7**) (0.18 g,

(23) J. B. Conant and A. H. Blatt, *J. Amer. Chem. Soc.*, **50**, 555 (1928).
(24) "Dictionary of Organic Compounds," Vol. III Eyre & Spottiswoode Ltd., London, 1965, p 1274.
(25) J. P. Schaefer, *J. Org. Chem.*, **25**, 2027 (1960).

90% yield) was isolated: nmr[15] ($CDCl_3$) τ 2.81 (10 H s), 6.27–6.61 (2 H m) and 7.52–8.05 (4 H m).

Desulfurization of Compound 4.—Compound 4 (1.7 g, 0.0063 mol) was refluxed with about 4 g of Raney Ni W2 slurry in benzene for 4 hr. After filtration and evaporation of the benzene, 1.1 g of an oil was isolated. Analysis by glpc on columns A, B and C, using internal standards, showed that the mixture contained *trans*-1,2-diphenylcyclobutane (7), DL- and *meso*-2,3-diphenylbutane, and 1,4-diphenylbutane (6) in 62%, 27%, and 11% yield respectively. Using column C, *trans*-1,2-diphenylcyclobutane (7) was collected and the nmr spectrum obtained was identical with that of authentic material.

1,3-Diphenyl-3-butanol.—This compound was prepared by adding 12 g (0.10 mol) of acetophenone to an ether solution of Grignard reagent made from 27.7 g (0.15 mol) of β-phenylylthyl bromide and 5 g of magnesium. The reaction mixture was refluxed for 2 hr and worked up in the usual way. The crude alcohol was distilled at 136° (0.25 mm), giving on cooling an amorphous solid (12 g). The infrared spectrum showed the presence of an OH group and the absence of a carbonyl and bromide groups. This material was used without further purification.

1,3-Diphenylbutane (9).—1,3-Diphenyl-3-butanol (7.6 g, 0.034 mol) in 150 ml of glacial acetic acid was mixed with 0.1 g of 10% Pd–C at 45 psi of hydrogen for 15 hr. After filtration and evaporation of the acetic acid the mixture was chromatographed over silica gel with petroleum ether–CCl_4 (1:1) graduated slowly to CCl_4, affording 1,3-diphenylbutane (9) (3.5 g, 50% yield). The material was found to be glpc pure (column A, B, and C): n^{20} 1.5520; lit.[24] $n^{20}D$ 1.5525); nmr[15] τ 2.80–2.91 (10 H, m), 7.18–7.69 (3 H, m), 7.98–8.40 (2 H, m), and 8.80 (3 H, d).

Desulfurization of Compound 5.—Compound 5 (1.0 g) was refluxed with ~3 g of Raney nickel W2 in benzene for 15 hr. Filtration and evaporation gave 0.5 g (65%) of an oil and 0.3 g of 5. Analysis by glpc showed two compounds were present. The first fraction was identified as 1,3-diphenylbutane by comparing the retention times with an authentic sample on column A, B, and C. About 50 mg of the second fraction was collected from glpc column A and was identified as *trans*-1,3-diphenylcyclobutane: mass spectra (molecular ion) *m/e* 208; nmr τ 2.82 (10 H, s), 6.56 (2 H, p, J = 8.0 Hz), 7.60 (4 H, t, J = 8.0 Hz).

Anal. Calcd for $C_{16}H_{16}$: C, 92.26; H, 7.74; exact mass measurement of molecular ion, 208.1245. Found: C, 92.14; H, 7.55; exact mass measurement of molecular ion, 208.1252.

Attempted Epimimerization of Dimers 2 and 3.—Compounds 2 and 3 (150 mg) were each refluxed 12 hr with 1.2 g of sodium methoxide in 25 ml of methanol. Dimers 2 and 3 were recovered unchanged (glpc, column A; melting point and mixture melting point).

Registry No.—1, 825-44-5; 2, 25558-18-3; 3, 25558-19-4; 4, 25558-20-7; 5, 25558-21-8; 7, 7694-31-7; 9 (*trans*), 25558-23-0; bis(ethylene dithioketal) of dibenzoylethane, 25557-76-0.

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The Chemistry of Small-Ring Sulfur Compounds. Thietanes and 1,2-Dithiolanes[1]

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Received January 19, 1970

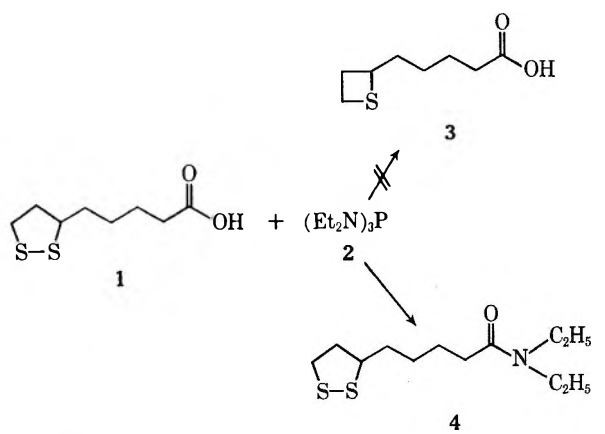
A variety of 1,2-dithiolanes undergo facile desulfurization with tris(diethylamino)phosphine (2) to give thietanes in good yield. By this method, the tetrahydropyranyl ester of α-lipoic acid afforded (after hydrolysis) thietane-2-valeric acid (3). 3H-1,2-Benzodithiole (17) did not give benzo[*b*]thiete (18) on desulfurization, but rather formed the dimeric sulfide (19). The tricyclic steroid 22 underwent rearrangement on desulfurization to afford the steroidal phosphine 25. The use of iodine–triethylamine in a new, modified procedure for the oxidation of propane-1,3-dithiols was found to be an excellent method for the preparation of 1,2-dithiolanes in high yield.

As part of our study on the selective desulfurization[3] of disulfides and related compounds, it occurred to us

$$R{-}S{-}S{-}R' + PR_3 \longrightarrow R{-}S{-}R' + S{=}PR_3$$

that the use of aminophosphines for the desulfurization of 5-membered disulfide rings (dithiolanes) could provide a new synthetic approach to thietanes.[4] Accordingly, the desulfurization of several dithiolanes was attempted and the results are summarized in Table I.

While the dithiolane, α-lipoic acid (1), a coenzyme in the biological oxidation of pyruvic acid, is readily available from natural sources, the corresponding thietane derivative, thietane-2-valeric acid (3), has only recently been prepared *via* a multistep synthesis.[5] However, attempts to obtain this derivative by the desulfurization of α-lipoic acid were unsuccessful. When α-lipoic acid (1) was treated with tris(diethylamino)-phosphine (2), no thietane derivative (3) was obtained. The main product, isolated in 78% yield, was the di-



(1) Organic Sulfur Chemistry. III. For part II, see D. N. Harpp and J. G. Gleason, *Tetrahedron Lett.*, 1447 (1969).

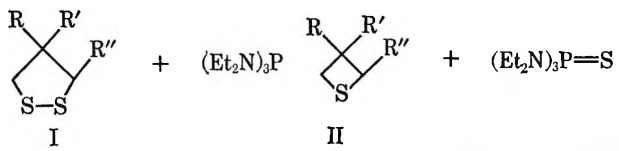
(2) Holder of an NRCC Studentship 1968–1969.

(3) D. N. Harpp, J. G. Gleason, and J. P. Snyder, *J. Amer. Chem. Soc.*, **90**, 4181 (1968).

(4) Although other methods for the synthesis of thietanes are available, the formation of polymer in these reactions is often competitive; see M. Sander, *Chem. Rev.*, **66**, 341 (1966); S. Ogawa, M. Morita, K. Donome, and K. Fujisawa, Japanese Patent 23937 (1967) [*Chem. Abstr.*, **69**, 35919 (1968)].

(5) (a) M. W. Bullock, U. S. Patent 2,788,355 (1957); *Chem. Abstr.*, **51**, 13909 (1957). (b) Sh. Yurugi, H. Yonemoto, and T. Fushimi, *Yakugaku Zasshi*, **80**, 169b (1960); *Chem. Abstr.*, **55**, 12288 (1961). (c) Sh. Yurugi and T. Fushimi, Japanese Patent 6532 (1962); *Chem. Abstr.*, **58**, 13916 (1963).

TABLE I



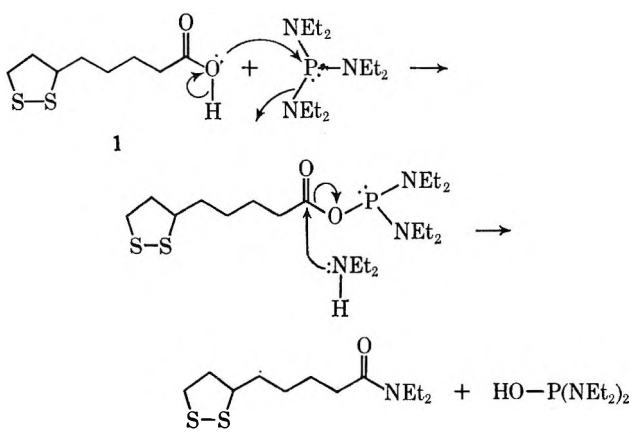
I II

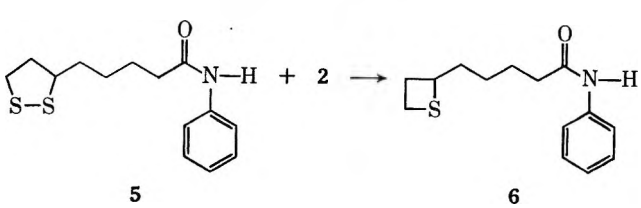
Disulfide	R	R'	R''	Reaction time,[a] hr	Concentration of I, mol. l.$^{-1}$	Yield of II,[b] %
11	H	H	H	432	0.11	82[c]
12	C_6H_5	H	H	4[d]	0.22	87
16	=O		H	0.1	0.2	Polymer
5	H	H	$(CH_2)_4CONHC_6H_5$	1	0.4	64
7	H	H	$(CH_2)_4COOTHP$[e]	24[f,g]	0.8	80

[a] In benzene solvent at room temperature, unless otherwise noted. [b] Yields reported are of crystallized or distilled thietane. [c] Isolated as mercuric chloride adduct. [d] In refluxing benzene. [e] THP = tetrahydropyran. [f] In ethyl acetate. [g] This long reaction time is probably unnecessary.

ethylamide of α-lipoic acid (**4**). The formation of amides from the reaction of carboxylic acids with alkylaminophosphines has been reported.[6] This reaction presumably involves displacement of the dialkylamine moiety by the carboxylic acid; subsequent rearrangement (Scheme I) affords the amide. When the carboxylic acid was masked by suitable protecting groups such as amides or esters, desulfurization proceeded unhindered. The anilide derivative of **1** was prepared; after 1 hr of stirring with the aminophosphine **2**, the yellow color of the disulfide was completely discharged and the absorption maxima at 332 mμ (characteristic of 1,2-dithiolanes)[7] disappeared. A new compound, **6**, mp 56–58°, was obtained in 68% yield (Table I).

SCHEME I



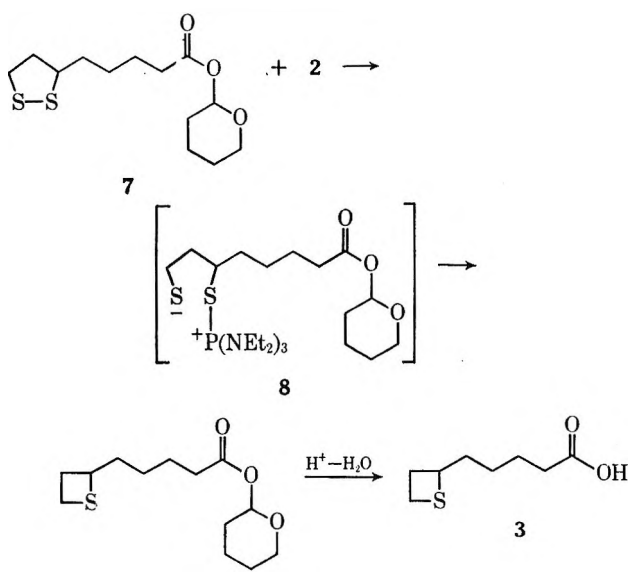


While the nmr and ir spectra of **6** were very similar to those of **5**, the mass spectrum exhibited a parent ion at *m/e* 249.1180 (calcd for $C_{14}H_{19}NOS$: 249.1198) and a fragmentation pattern consistent with the assigned thietane structure.

(6) R. Burgada, *Ann. Chim. (Paris)*, 347 (1963).

(7) G. Bergson, G. Claeson, and L. Schotte, *Acta Chem. Scand.*, **16**, 1159 (1962).

Similarly, the tetrahydropyranyl ester **7** was desulfurized to afford, after hydrolysis, thietane (**3**) in 82% yield. This desulfurization may proceed *via* an internal phosphonium salt of the type **8**, although other intermediates may be present (*vide infra*).



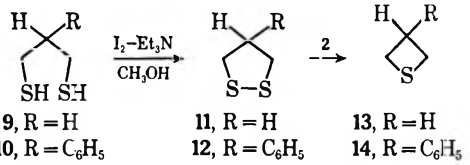
In order to examine the generality of this novel ring contraction, we required a convenient method of preparing 1,2-dithiolanes. Examination of the literature revealed that, except for a few alkyl-substituted dithiolanes, oxidation of bisthiols leads to extensive polymerization.[8] We have found that the use of triethylamine to maintain neutral conditions during iodometric oxidation of bisthiols greatly reduces polymerization. Thus, slow addition of a solution of triethylamine and bisthiol to an iodine solution provides both neutrality and high dilution, the latter being desirable for intramolecular cyclization of bisthiols. This procedure has permitted us to prepare a wide variety of cyclic disulfides in high yield.[9] This method is rapid and appears to be general.

Thus, the oxidation of 1,3-propanedithiol (**9**) with iodine in the presence of triethylamine followed by extraction with benzene afforded a solution of 1,2-dithiolane (**11**), free of polymer. Desulfurization of a 0.1 *M*

(8) For a general review on the preparation of 1,2-dithiolanes, see D. S. Breslow and H. Skolnik, "The Chemistry of Heterocyclic Compounds," Part I, Interscience, New York, N. Y., 1966, pp 313–345.

(9) Using this technique, five- to eight-membered cyclic disulfides, as well as a wide variety of acyclic disulfides, have been prepared in high yields.

solution of **11** provided thietane **13**, isolated as its mercuric chloride adduct, in 82% yield. Similarly, the

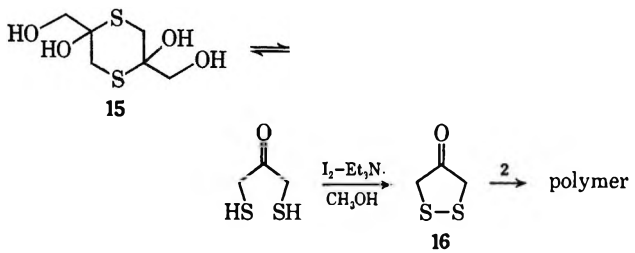


9, R = H
10, R = C_6H_5

11, R = H
12, R = C_6H_5

13, R = H
14, R = C_6H_5

dimer of dimercaptoacetone[10] (**15**) was oxidized to the corresponding disulfide **16**. Addition of phosphine,

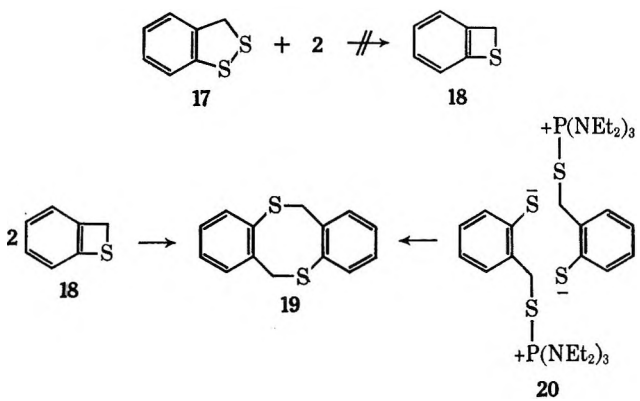


15

16

however, effected immediate polymerization of this material and no characterizable compounds were isolated.

In addition, 4-phenyl-1,2-dithiolane (**12**) and 3H-1,2-benzodithiole (**17**) were readily prepared by the above method. Desulfurization of disulfide **12** gave 3-phenylthietane (**14**) in 85% yield. We had hoped that desulfurization of **17** would provide a simple synthesis of the unknown heterocycle, 2H-benzo[*b*]thiete (**18**). However, the only isolable product was the di-



17

18

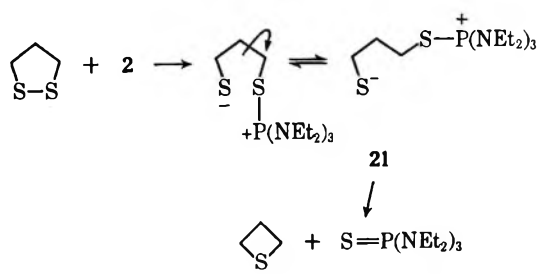
19

20

mer of benzothiete, 6H,12H-dibenzo[*b*,*f*][1,5]dithioocin (**19**). This material could arise from either dimerization of benzothiete **18** or the phosphonium salt **20**.

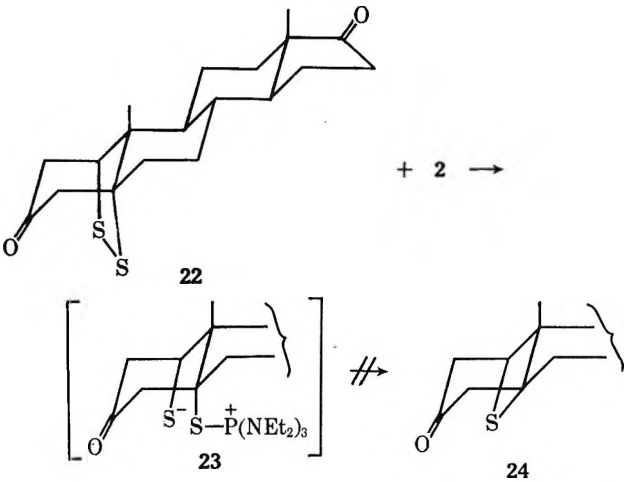
We have suggested[3] (Scheme II) that these desulfurization reactions proceed *via* an internal phospho-

SCHEME II



21

nium salt such as **21**. Of considerable interest is the desulfurization of the novel steroidal disulfide **22**[11,12] as rotation and subsequent S_N2[13] decomposition are not

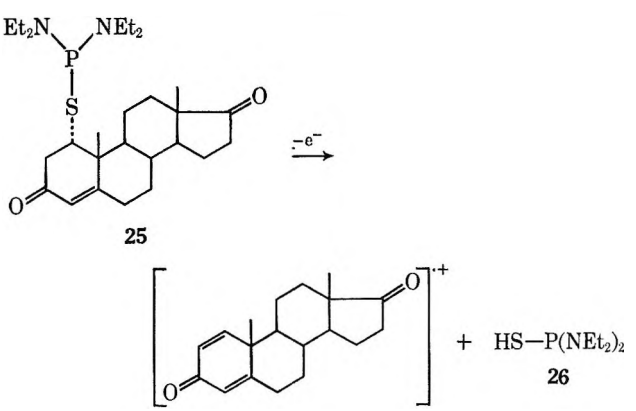


22

23

24

possible. Treatment of this disulfide with aminophosphine **2** did not provide either **23** or **24** but rather a new compound, **25**, $C_{27}H_{45}N_2O_2PS$ (exact mass calcd for $C_{27}H_{45}N_2O_2PS$, 492.2939; found, 492.2960), mp 200–201°. The presence of the Δ(4–5)-androstane-1,17-dione ring system was indicated by the infrared spectrum (1740 and 1670 cm^{-1}) and ultraviolet spectrum (λ_{max}^{MeOH} 228 mμ, ε 650) and the presence of only one olefinic proton at τ 4.2 in the nmr spectrum. The loss of a bis(dimethylamino)phosphine sulfide moiety **26** upon electron impact permitted the assignment of structure **25** for this compound.

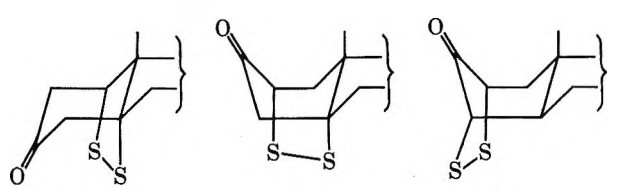


25

26

(10) L. Schotte, *Ark. Kemi*, **5**, 533 (1952).

(11) The synthesis of **22** has been reported;[12] however the presence of a 1,5 disulfide bridge was not rigorously demonstrated. A 100-MHz nmr double resonance experiment was used to show that the methine proton α to the disulfide (a quartet at τ 6.15) is part of an ABX spectrum where the AB portion is centered at τ 7.1. The chemical shift of the methylene (AB) portion of the ABX system rules out the possiblity of a 2,5 disulfide (**22a**) or 2,4 disulfide (**22b**) bridge.



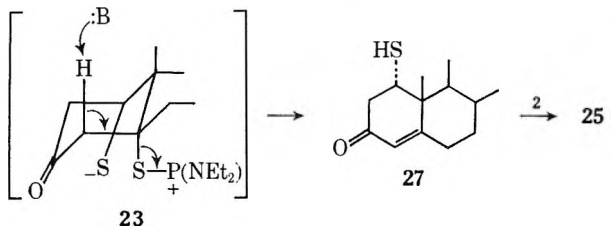
22 **22a** **22b**

(12) R. C. Tweit and R. M. Dodson, *J. Amer. Chem. Soc.*, **81**, 4409 (1959).

(13) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1959, pp 294–296.

A mechanistic rationalization for the formation of **25** is depicted in Scheme III. The phosphonium salt **23**

SCHEME III



initially formed may undergo an elimination reaction to afford the thiol **27**. This thiol would then react[14] with the aminophosphine to provide **25**.

This interesting rearrangement might well be useful in preparing a variety of 1-α-androstane derivatives.

Experimental Section[15]

Tris(diethylamino)phosphine (2).—The procedure used was a modification of the method of Mark.[16] Thus, a solution of 43.0 g (3.4 mmol) of phosphorus trichloride in 3 l. of anhydrous ether was flushed with nitrogen and cooled to 10°; 150 g (2.06 mol) of diethylamine was added dropwise with vigorous stirring over 2 hr. The resulting suspension was stirred overnight, then refluxed for 0.5 hr. After cooling, the mixture was filtered and the filtrate evaporated to dryness. The residue was dissolved in 200 ml of hexane and treated with activated charcoal, and the hexane removed under vacuum. The resulting oil was fractionated in vacuum to afford 50.2 g of **2** (65%), bp 80–84° (0.5 mm), n^{30}D 1.4695 (lit.[17] n^{30}D 1.465).

1,2-Dithiolane-3-valeric Acid Diethylamide (4).—A solution of 0.412 g (2.0 mmol) of **1** and 0.55 g (2.2 mmol) of tris(diethylamino) phosphine (**2**) in 2.5 ml of dry benzene was stirred for 4 hr. An oil which formed immediately upon addition of the phosphine slowly redissolved on stirring and a solid precipitated. The solvent was removed under vacuum and the residue was chromatographed over silica gel. Elution with methylene chloride afforded the diethylamide as a yellow oil, 0.42 g (80%), homogeneous on thin layer and gas chromatography: ir (film) 1640 cm^{-1} (tertiary amide); nmr (CCl_4) τ 6.70 (quartet, J = 7 Hz), 8.90 (triplet, J = 7 Hz), both observable above a broad envelope; mass spectrum parent ion m/e 261, fragments of 58, 115, 72 (Et_2N^+), 100, 128, 189, 228.

dl-**1-2-Dithiolane-3-valeric Acid Anilide (5).**—α-Lipoic acid (**1**) was converted to its anilide (**5**) (aniline dicyclohexylcarbodiimide) in 75% yield: mp 69–71° (lit.[18] mp 72–73°); λ_{max}^{EtOH} 242 mμ (ϵ 30,200), 332 (363); ir (KBr) 3290 (NH), 1660 (amide I), 1540 (amide II), 690 cm^{-1} (aromatic); nmr ($CDCl_3$) τ 1.93 (broad singlet, 1 H, NH), 2.7 (complex multiplet, 5 H, aromatic), 6.48 (multiplet, 1 H, methine), 6.9 (multiplet, 2 H, $-CH_2-S$), broad multiplets centered at τ 7.8 and 8.5 accounting for remaining aliphatic protons; mass spectrum (150°), molecular ion at m/e 281.0919 (calcd for $C_{14}H_{19}NOS_2$: 281.0908), fragments of m/e 93, 135, 41, 55, 56, 148, 155.

Thietane-2-valeric Acid Anilide (6).—A solution of 1.129 g (4 mmol) of the anilide **5** and 1.10 g (4.4 mmol) of tris(diethylamino)phosphine (**2**) in 10 ml of benzene was stirred for 1 hr during which time the yellow color was discharged and the uv maximum at 332 mμ disappeared. The reaction mixture was allowed to stand overnight, the solvent removed under vacuum, and the residue chromatographed over Florisil. The phosphine sulfide was eluted with 1:1 methylene chloride–petroleum ether (bp 60–80°). Elution with methylene chloride afforded 0.634 g (64%) of colorless crystals, mp 51–54°, which after two crystallizations from cyclohexane afforded an analytical sample: mp 55–57°; ir (KBr) 3290 (NH), 1660 (C=O), 1540 (amide II), 760 and 690 cm^{-1} (aromatic); λ_{max}^{MeCH} 242 mμ (ϵ 24,900); nmr (CCl_4) broad multiplet at τ 2.7 (6 H, aromatic + NH) and aliphatic protons from 6.5–9.0; mass spectrum (150°), molecular ion at m/e 249.1180, (Calcd for $C_{14}H_{19}NOS$: 249.1198), fragments of m/e 93, 135, 41, 129.

Anal. Calcd for $C_{14}H_{19}NOS$: C, 67.44; H, 7.68; N, 5.62; S, 12.86. Found: C, 67.47; H, 7.64; N, 5.47; S, 12.85.

Thietane-2-valeric Acid (3).—A solution of 4.04 g (20 mmol) of **1** in 20 ml of dihydropyran was refluxed 3 hr. The solvent was removed under vacuum and the residue dissolved in 25 ml of ethyl acetate containing 5.5 g (22 mmol) of tris(diethylamino)phosphine (**2**). After stirring at room temperature for 24 hr, the solvent was removed under vacuum; 25 ml of dioxane and 25 ml of concentrated HCl were added; the solution was stirred for 18 hr. The solution was diluted with 200 ml of water and extracted with ether; the ethereal layer was extracted with 100 ml of a 5% sodium bicarbonate solution; the bicarbonate solution was carefully acidified and extracted with ether. After drying over anhydrous sodium sulfate, the ethereal solution was evaporated to dryness under vacuum to yield 2.82 g (80%) of **3** as a viscous yellow oil: bp 143° (0.1 mm); n^{27}D 1.5155; ir (film) 3020 (broad, OH), 1708 cm^{-1} (COOH); nmr (CCl_4) τ −1.63 (singlet, 1 H, COOH), multiplet at 6.0–9.2 accounting for 13 protons; mass spectrum (50°), parent ion at m/e 174, fragments of m/e 87, 41, 45, 55, 73, 80. The acid **3** was characterized as its anilide **6** (aniline, dicyclohexylcarbodiimide), mp 55–57°. This material was identical in all respects with the sample prepared by direct desulfurization of **5**.

1,2-Dithiolan-4-one (16).—A solution of 1.22 g (10 mmol) of dimercaptoacetone[10] (as its dimer) and 2.10 g (20 mmol) of triethylamine in 25 ml of methanol was added dropwise to a solution of 2.66 g (10.5 mmol) of iodine in 50 ml of methanol. The reaction mixture was filtered to remove 200 mg of polymer and the filtrate was diluted with 200 ml of benzene. After decolorization with a 10% solution of sodium thiosulfate and several washings with water, the solution was dried over magnesium sulfate and concentrated under vacuum to 50 ml to afford a golden yellow solution[19] of 1,2-dithiolan-4-one in benzene: nmr (benzene) τ 7.15 (singlet); $\lambda_{max}^{benzene}$ 340 mμ (sh) (ϵ 50), 325 (65), 312 (74), 300 (80).

Desulfurization of 1,2-Dithiolan-4-one (16).—To 50 ml of the above solution of **16** was added 2.50 g (10 mmol) of tris(diethylamino)phosphine (**2**). Immediately upon addition of the phosphine, the color changed from yellow to dark brown and a dark brown tar separated out of the solution. This tar was insoluble in all organic solvents tried.

1,2-Dithiolane (11).—A solution of 1.06 g (10 mmol) of 1,3-propanedithiol and 2.10 g (20 mmol) of triethylamine in 10 ml of methanol was added dropwise over 15 min to a solution of 2.66 g (10.5 mmol) of iodine in 25 ml of methanol. The resulting solution was diluted with 250 ml of benzene, decolorized with a 10% solution of sodium thiosulfate, washed with water, dried over magnesium sulfate, and concentrated under vacuum at 30–35° to less than a 50-ml volume, and the solution was transferred to a 50-ml volumetric flask and filled to volume with dry benzene. From the absorption at 330 mμ in the uv spectrum [lit.[20] λ_{max}^{MeOH} 330 mμ (ϵ 147)] the concentration of this solution was found to be 0.112 M corresponding to a yield of 56%: nmr (benzene) τ 7.70 (triplet, 2 H, J = 6 Hz), 8.65 (multiplet, 4 H).

Thiethane (13).—To 50 ml of a 0.112 M solution of **11** in benzene was added 2.50 g (10 mmol) of tris(diethylamino)phosphine (**2**). After standing in the dark for 18 days, the clear solution was added to 25 ml of a 20% solution of mercuric chloride in ethanol. After standing overnight, 1.6 g (82%) of a crystalline solid was obtained, mp 94–99° dec (lit.[21] mp 93–95° dec).

Desulfurization of 3H-1,2-Benzodithiole (17).—To a solution of 0.9 g (6.35 mmol) of 3H-1,2-benzodithiole[22] in 15 ml

(14) C. Stuebe and H. P. Lankelma, *J. Amer. Chem. Soc.*, **78**, 976 (1956).

(15) Melting points were determined on a Gallenkamp block and are corrected. Mass spectra were obtained on an AEI-MS-901B mass spectrometer at 70 eV and are reported in order of decreasing intensity.

(16) V. Mark, *Org. Syn.*, **46**, 42 (1966).

(17) D. Houalli, M. Sanchez, and R. Wolf, *Bull. Soc. Chim. Fr.*, 2368 (1965).

(18) L. J. Reed, M. Koike, M. E. Levitch, and F. R. Leach, *J. Biol. Chem.*, **232**, 143 (1958).

(19) Complete removal of solvent causes polymerization of the disulfide. For this reason, no further attempts were made to characterize this compound.

(20) J. A. Barltrop, P. M. Hayes, and M. Calvin, *J. Amer. Chem. Soc.*, **76**, 4348 (1954).

(21) H. S. Gutowsky, R. L. Ritedge, M. Tamnes, and S. Searles, *ibid.*, **76**, 4242 (1954).

(22) The disulfide was prepared by the oxidation of 2,α-toluenedithiol[23] by iodine–triethylamine–methanol or $FeCl_3$–methanol.

(23) A. Lüttringhaus and K. Hägele, *Angew. Chem.*, **67**, 304 (1955).

of benzene was added slowly 1.88 g (7.6 mmol) of tris(diethylamino)phosphine (2). After 10 min, the benzene was removed under vacuum and the residue chromatographed over silica gel. Elution with 10% chloroform in hexane afforded 50 mg (7%) of 6H,12H-dibenzo[*b,f*][1,5]dithioocin as colorless crystals, mp 172–178°, which after crystallization from ethanol afforded colorless needles, mp 173–175° (lit.[24] mp 174–176°).

2-Phenyl-1,3-propanedithiol (10).—A solution of 4.6 g (10 mmol) of 2-phenyl-1,3-propanediol ditosylate[25] and 10 g (130 mmol) of thiourea in 50 ml of ethanol was refluxed for 4 hr; the ethanol was removed under vacuum and the residue refluxed under nitrogen with 10 g of sodium hydroxide in 50 ml of water for 12 hr. After careful acidification, the mixture was extracted with chloroform and the extract washed well with water, dried, and evaporated to dryness. The crude oil was fractionally distilled under vacuum to afford 1.0 g (55%) of a pale yellow oil: bp 76–78° (0.005 mm); nmr ($CDCl_3$) τ 2.70 (mulitplet, 5 H, aromatic), 6.0–7.4 (multiplet, 5 H), 8.7 (multiplet, 3 H, S–H). This crude dithiol was used without further purification.

4-Phenyl-1,2-dithiolane (12).—A solution of 1.4 g (7.6 mmol) of the dithiol 10 and 1.8 g (1.8 mmol) of triethylamine in 20 ml of methanol was added dropwise with stirring in a nitrogen atmosphere to a solution of 1.95 g (8 mmol) of iodine in 50 ml of methanol. The resulting solution was rapidly filtered and the filtrate cooled in dry ice until crystals formed. The crystals were filtered and washed well with cold methanol to afford 1.0 g (73%) of yellow crystals, mp 77–83°. Sublimation at 75° and 25-μ pressure afforded 488 mg of yellow crystals: mp 82–84°; ir (KBr) 1600, 1490, 1460, 775, and 705 cm^{-1} (aromatic); $\lambda_{max}^{benzene}$ 335 mμ (ϵ 143); nmr ($CDCl_3$) τ 2.66 (multiplet, 5 H, aromatic), 6.5 (multiplet, 5 H).

Anal. Calcd for $C_9H_{10}S_2$: C, 59.29; H, 5.53; S, 35.18. Found: C, 59.09; H, 5.50; S, 34.83.

3-Phenylthietane (14).—A solution of 400 mg (2.2 mmol) of 12 and 600 mg (2.4 mmol) of tris(diethylamino)phosphine (2) in 10 ml of benzene was refluxed 4 hr during which time the yellow color was discharged. The reaction mixture was evaporated to dryness and the residue chromatographed over silica gel. Elution with 1:1 hexane–chloroform afforded 280 mg (87%) of a colorless oil, homogeneous on thin layer and gas chromatography (LAC column at 190°): $n^{25}D$ 1.5895; ir (film) 1610, 1500, 1465, 760, 705 cm^{-1} (aromatic); nmr (CCl_4) τ 2.78 (5 H), 5.50 (multiplet, 1 H), 6.62 (multiplet, 4 H).

This material was characterized as its sulfone (H_2O_2, AcOH): mp 101–101.5°; ir (KBr) 1320, 1140 cm^{-1} (SO_2).

Anal. Calcd for $C_9H_{10}SO_2$: C, 59.29; H, 5.53; S, 17.59. Found: C, 59.67; H, 5.60; S, 17.84.

1α,5α-Epidithicandrostane-3,17-dione (22).—The method used was a modification of the procedure of Tweit and Dodson[12] in that triphenylphosphine was used to remove occluded sulfur from the crude product. This material was crystallized from acetone (33% yield): mp 210–214° (lit.[12] mp 210–214°); ir (KBr) 1730 (C_{17} C=O), 1710 cm^{-1} (C_3 C=O); λ_{max}^{MeOH} 364 mμ (ϵ 51), 280 sh (650), 262 (730); nmr[11] ($CDCl_3$) (100 MHz) τ 6.15 (quartet, 1 H, $J_{AX} + J_{BX} = 7$ Hz, $J_{AX} - J_{BX} = 1$ Hz), 9.10 (singlet, 3 H), 8.59 (singlet, 3 H), and a multiplet centered at about τ 7.5–6.9.

S-Bis(diethylamino)phosphino-1α-thioandrostan-4-ene-3,17-dione (25).—A suspension of 348 mg (1 mmol) of 1α,5α-epidithioandrostan-3,17-dione (22) in 5 ml of dry benzene containing 1.0 g (4 mmol) of tris(diethylamino)phosphine (2) was stirred overnight. The solvent was removed under vacuum and the residue chromatographed over silica gel. After elution of tris(diethylamino)phosphine sulfide with 95:5 dichloroethane–acetone, the product was eluted with 85:15 dichloroethane–acetone. Crystallization from hexane afforded 100 mg (20%) colorless crystals: mp 201–202°; ir (KBr) 1740 (C_{17} C=O), 1670 cm^{-1} (C=C—C=O); λ_{max}^{MeOH} 228 mμ (ϵ 6450), 280 (1470); mass spectrum, parent ion at *m/e* 492.2960 (Calcd for $C_{27}H_{45}N_2O_2PS$: 492.2939) with a fragment ion at *m/e* 284.1785 [$P^+ - (Et_2N)_2PSH$] (calcd for $C_{19}H_{24}O_2$: 284.1776).

Anal. Calcd for $C_{27}H_{45}N_2O_2PS$: C, 65.81; H, 9.21; N, 5.69. Found: C, 65.75; H, 9.02; N, 5.61.

Registry No.—**3,** 25636-58-2; **4,** 25636-59-3; **5,** 1027-31-2; **6,** 25636-60-6; **10,** 25636-61-7; **12,** 6133-92-2; **14,** 25636-63-9; **14** (sulfone), 25636-64-0; **16,** 25636-65-1; **22,** 25632-08-0; **25,** 25631-60-1.

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Aralkyl Hydrodisulfides.[1] XI. The Reaction with Amines

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Aralkyl hydrodisulfides were allowed to react with several amines at room temperature. The amines (morpholine, mono-, di-, and tri-*n*-butylamine, and piperidine) having pK_a values greater than 8.36 behave as bases. The products from 10 mmol of hydrodisulfide consisted of nearly 5 mmol of each hydrogen sulfide and diaralkyl disulfide, and 5 mg-atoms of sulfur, or, alternatively, nearly 5 mmol of hydrogen sulfide and fluctuating amounts of sulfur, diaralkyl disulfide, and polysulfides, the last of which were formed at the expense of the disulfide and sulfur. These results are satisfactorily explained by the basic mechanism reported previously and modified here. The amines (aniline, N,N-dimethylaniline, and pyridine) having pK_a values less than 5.17 behave as nucleophiles and gave hydrogen sulfide, arylalkanethiol, diaralkyl polysulfides, and disulfide, the last of which was formed at the expense of the thiol. These results are explained by the nucleophilic mechanism. 2,4-Lutidine having pK_a value of 6.79 seems to behave as a nucleophile.

It has been well known that amines behave as nucleophiles[4] toward octatomic sulfur or organic sulfur compounds. However, amines could behave as bases rather than nucleophiles in the presence of aralkyl hydrodisulfides which are weakly acidic. Our previous works have shown that nucleophiles such as phosphines,[5,6] phosphites[7] and arsines[8] attack aralkyl hydro-

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TABLE I

PRODUCTS (mmol) OF ARALKYL HYDRODISULFIDES (10 mmol) WITH AMINES UNDER NITROGEN ATMOSPHERE AT ROOM TEMPERATURE

						Products (mmol or mg-atoms)					
								RS_xR			
Run	R in RSSH	Amine	pK_a	Molar ratio of amine/RSSH	Procedure[a]	H_2S	RSH	$x = 2$	$x = 3,4,5$	Mean value of x	S
1	$C_6H_5CH_2$	Aniline	4.58	10	A	4.4	0	1.3	3.6	3.1	0
2	$C_6H_5CH_2$	N,N-Dimethylaniline	5.06	10	A	2.4	4.7	0.2	2.5	3.4	0
3	$C_6H_5CH_2$	Pyridine	5.17	10	A	4.1	0	1.1	3.9	3.0	0
4	$C_6H_5CH_2$	*n*-Butylamine	10.43	10	B	4.6	0	3.7	1.1	2.4	3.0
5	$C_6H_5CH_2$	Di-*n*-butylamine	11.25	10	A	4.7	0	3.0	2.3	2.8	1.0
6	$C_6H_5CH_2$	Piperidine	11.25	10	B	4.8	0	3.4	1.6	2.6	2.0
7	$(C_6H_5)_2CH$	Aniline	4.58	10	A	3.4	2.6	0	3.5	3.8	0
8	$(C_6H_5)_2CH$	N,N-Dimethylaniline	5.06	10	A	2.3	3.3	0.1	2.9	3.9	0
9	$(C_6H_5)_2CH$	Pyridine	5.17	3	C	3.6	1.5	0	4.4	3.2	0
10	$(C_6H_5)_2CH$	2,4-Lutidine	6.79	10	A	4.2	0	1.1	3.7	3.1	0
11	$(C_6H_5)_2CH$	Morphorine	8.36	10	A	4.0	0	5.0	0		4.8
12	$(C_6H_5)_2CH$	*n*-Butylamine	10.43	10	B	4.8	0	4.6	0		5.0
13	$(C_6H_5)_2CH$	Tri-*n*-butylamine	10.89	10	A	3.0	0	3.9	1.0	2.4	3.0
14	$(C_6H_5)_2CH$	Di-*n*-butylamine	11.25	10	A	4.0	0	5.0	0		5.1
15	$(C_6H_5)_2CH$	Piperidine	11.25	6	B	4.3	0	5.0	0		5.6
16	$(C_6H_5)_3C$	Aniline	4.58	10	A	2.8	4.1	...[b]	...[b]	...[b]	...[b]

[a] See the Experimental Section. [b] Not determined.

disulfides both on sulfhydryl and sulfenyl sulfur atoms, and that hydroxide ion[9] abstracts proton from hydrodisulfides, allowing the resulted aralkyl disulfide ions (RSS^-) to react further with hydrodisulfides. Now it seems interesting to examine whether amines behave as bases or as nucleophiles toward hydrodisulfides.

Results and Discussion

The pK_a values of amines used in this work range from 4.58 to 11.25 including primary, secondary, and tertiary amines and both aromatic and aliphatic ones. The aralkyl hydrodisulfide (benzyl, benzhydryl, or triphenylmethyl hydrodisulfide) in benzene was added dropwise to an excess amine in a stream of nitrogen at room temperature. The results are shown in Table I. Comparatively good material balance is observed for each run, in spite of the different molar ratios of amine/hydrodisulfide and different procedures. Product distributions in Table I indicate distinctive feature depending on pK_a values of amines used. Our results show that amines of stronger basicity (pK_a values > 8.36) give a different product distribution from that of amines of weaker basicity (pK_a values < 5.17).

Basic Attack of Amines.—Table I indicates that the reaction products of 10 mmol of benzhydryl hydrodisulfide with amines of stronger basicity are nearly 5 mmol of each hydrogen sulfide and benzhydryl disulfide, and 5 mg-atoms of elemental sulfur for runs 11, 12, 14, and 15. This product distribution reminds us of our previous work[9] on the reaction of hydrodisulfides with concentrated potassium hydroxide. The reaction sequence is cited again here in eq 1–3. Eq 3 shows that

$$RSSH + OH^- \longrightarrow RSS^- + H_2O \quad (1)$$

$$RSSH + RSS^- \longrightarrow RSSR + HS_2^- \quad (2)$$

$$HS_2^- \xrightarrow{H^+} H_2S + \frac{1}{8}S_8 \quad (3)$$

hydrogen sulfide evolves and sulfur precipitates after the neutralization. In the present work, sulfur precipitated after addition of hydrochloric acid. Hydrogen sulfide evolved during the reaction at room temperature in the case of runs 11 (with morpholine), 13 (with tri-*n*-butylamine) and 14 (with di-*n*-butylamine). In the case of runs 12 (with *n*-butylamine) and 15 (with piperidine) hydrogen sulfide evolved only after addition of hydrochloric acid. This difference may come from different stabilities of amine–hydrogen sulfide salts, which depend on basicity and steric hindrance of amines.

A supplementary nmr experiment indicated that dibenzhydryl trisulfide was formed besides the disulfide at an earlier stage of the reaction with piperidine. The trisulfide was found by nmr analysis to be desulfurated with piperidine during the reaction. As shown in run 15, Table I, it disappeared at the end of the reaction. Therefore, eq 5 may be considered to compete with eq

$$RSSH + R'_3N \longrightarrow RSS^- + [R'_3NH]^+ \quad (4)$$

$$RSS^- + RSSH \longrightarrow RSSSR + SH^- \quad (5)$$

2. As to the reaction sequence[9] with concentrated alkali, the similar situation (competition of eq 5 with 2) is conceivable. A nmr reexamination revealed that benzhydryl hydrodisulfide in dioxane-d_8 reacted with a concentrated sodium deuteroxide in deuterated water, giving a 4:1 ratio of disulfide–trisulfide. After neutralization followed by extraction, the disulfide alone was detected. This suggests that the reaction sequence with alkali is not so simple as indicated in eq 1–3.

Regarding the basic attack of amines, we propose that anion RSS^- formed in eq 4 reacts with hydrodisulfide by eq 2 or 5. The cation $[R'_3NH]^+$ from eq 4 combines with anion HS^- from eq 5 or HS_2^- from eq 2, as indicated in eq 6, where x is 1 or 2. The

$$[R'_3NH]^+ + HS_x^- \longrightarrow [R'_3NH]^+HS_x^- \quad (6)$$

(9) S. Kawamura, T. Kitao, T. Nakabayashi, T. Horii, and J. Tsurugi, *J. Org. Chem.*, **33**, 1179 (1968).

succeeding steps, eq 7–8, may explain the results of runs 11, 12, 14, and 15. Eq 8, desulfuration step with

$$\left.\begin{array}{l}[R'_3NH]^+HS_x^- + HCl \longrightarrow [R'_3NH]^+Cl^- + HS_xH \\ [R'_3NH]^+HS_x^- \longrightarrow R'_3N + HS_xH \\ HS_xH \longrightarrow H_2S + \frac{x-1}{8} S_8\end{array}\right\} \quad (7)$$

$$RS_xR + R'_3N \longrightarrow RSSR + R'_3N^+S_{x-2}^- \quad (8)$$

amines, is quite analogous to the desulfuration with trivalent phosphorus compounds.[8,10] The resulted amine sulfide $R'_3N^+S_x^-$ is quite analogous to the product from the reaction of amine with octatomic sulfur.[4b] The constitution of this product and recovery of octatomic sulfur from the product have been discussed[4b] in detail. The amine sulfide resulted from eq 8 must be less stable than phosphine sulfide which can make use of d orbitals of both sulfur and phosphorus atoms to form a strong bond.[11] The amine sulfide may decompose in contact with acid as shown in eq 9. The

$$R'_3N^+S_x^- + HCl \longrightarrow [R'_3NH]^+Cl^- + \frac{x}{8} S_8 \quad (9)$$

formation of dibenzhydryl polysulfides in run 13 (with tri-*n*-butylamine) can be explained by assuming that desulfuration (eq 8) is not complete under the reaction conditions, because of steric hindrance of tri-*n*-butylamine. The product distribution of the reaction of benzyl hydrodisulfide (runs 4, 5, and 6) resembles that of run 13. This result may be explained by the incomplete desulfuration of benzyl polysulfides. Supplementary nmr experiments under similar conditions indicated that dibenzyl tetrasulfide and trisulfide were desulfurated with piperidine more slowly than the corresponding dibenzhydryl compounds.

Nucleophilic Attack of Amines.—The products of runs 7, 8, and 9 are hydrogen sulfide, diphenylmethanethiol and dibenzhydryl polysulfides, and resemble those with nucleophiles (phosphines,[5,6] phosphites,[7] and arsines[8]). If we apply the mechanisms of both the sulfenyl and sulfhydryl sulfur attacks by nucleophiles[8] to the present study, we can explain the product formation for runs 7–9. From the analogy to the mechanism of sulfhydryl sulfur attack, we may write the following equation. The amine sulfides produced in eq 10 are

$$RSSH + R'_3N \longrightarrow RS^-\left[\begin{array}{c}SH\\|\\NR'_3\end{array}\right]^+ \longrightarrow RSH + R'_3N^+S^- \quad (10)$$

considered less stable than the ones from amines of stronger basicity and to react further as indicated in eq 11, in contrast to eq 9. The mechanism of hydrogen

$$R'_3N^+S^- + 2\,RSSH \longrightarrow RSSSSR + R'_3N + H_2S \quad (11)$$
$$\downarrow\uparrow$$
$$[R'_3NH]^+SH^-$$

sulfide formation could be different depending on the basicity of amines (*cf.* eq 7).

For sulfenyl sulfur attack, we propose the following steps by analogy with other nucleophiles. The for-

$$RSSH + R'_3N \longrightarrow \left[\begin{array}{c}RS\\|\\NR'_3\end{array}\right]^+ + SH^- \quad (12)$$

$$SH^- + RSSH \longrightarrow RSS^- + H_2S \quad (13)$$

$$\left[\begin{array}{c}RS\\|\\NR'_3\end{array}\right]^+ + RSS^- \longrightarrow RSSSR + R'_3N \quad (14)$$

mation of polysulfides in runs 7–9 was satisfactorily explained by eq 11 and 14, if the desulfuration of polysulfides does not proceed under these conditions by amines of weaker basicity.

The results from benzyl hydrodisulfide with amines of weaker basicity (runs 1 and 3) make a clear contrast in the point that dibenzyl disulfide is formed at the expense of thiol as compared with the corresponding results from benzhydryl hydrodisulfide. Benzyl hydrodisulfide, which suffers less steric hindrance than benzhydryl compound,[5–8] is considered to be attacked predominantly on sulfenyl sulfur, and hence reacts predominantly *via* eq 12, 13, and 14. The thiol produced as a minor product *via* eq 10 must have reacted with SH^- produced in eq 12, just as the hydrodisulfide reacts with SH^- as indicated in eq 13. The resulted RS^- anion also must have reacted with $[RSNR'_3]^+$ quite similarly to eq 14. Thus the formation of dibenzyl disulfide for runs 1 and 3 are explained by eq 15 and 16. On the other hand, the almost quantitative

$$RSH + SH^- \longrightarrow RS^- + H_2S \quad (15)$$

$$\left[\begin{array}{c}RS\\|\\NR'_3\end{array}\right]^+ + RS^- \longrightarrow RSSR + NR'_3 \quad (16)$$

yield of the thiol and the negligible amount of the disulfide for run 2 with N,N-dimethylaniline can be interpreted by overwhelming sulfhydryl sulfur attack, because of the steric hindrance of the nucleophile, N,N-dimethylaniline. The persistence of the thiol cited in runs 7–9 may be explained also by the same reason; that is, benzhydryl hydrodisulfide is sterically more hindered than benzyl hydrodisulfide.

The product distribution of run 10 (the reaction of benzhydryl hydrodisulfide with 2,4-lutidine) quite resembles that of run 3 (benzyl hydrodisulfide with pyridine). If the disulfide would arise from the desulfuration of the polysulfides, elemental sulfur would be found among the products as indicated in eq 8 and 9. The absence of sulfur for 2,4-lutidine ($pK_a = 6.79$) can be attributed to the nucleophilic mechanism.

Predominance of sulfhydryl sulfur attack by steric hindrance is visualized in run 16, where aniline was allowed to react with triphenylmethyl hydrodisulfide. Owing to the absence of H atom, by which a mixture of polysulfides was conveniently analyzed by nmr, the result of run 16 shows only the amounts of hydrogen sulfide and the thiol. The amount of the latter clearly indicates the predominance of sulfhydryl sulfur attack.

Consideration from Equilibrium Viewpoint.—From the viewpoint of acid–base theory, eq 4 should be written as a reversible step. The equilibrium constant

$$RSSH + R'_3N \rightleftharpoons RSS^- + R'_3NH^+$$

(10) C. G. Moore, and B. R. Treggo, *J. Appl. Polymer Sci.*, **5**, 299 (1961); **8**, 1957 (1964).

(11) R. F. Hudson, "Structure and Mechanism in Organophosphorus Chemistry," Academic Press, London, 1965, p 67.

K is calculated from definition of pK_a as follows. Eq 17 suggests that amines having far less pK_a than

$$\log K = pK_{a_{amine}} - pK_{a_{RSSH}} \quad (17)$$

$pK_{a_{RSSH}}$ cannot be expected to behave as bases toward aralkyl hydrodisulfides which are weak acids. In such cases amines will behave as nucleophiles rather than bases as our results indicate.

Experimental Section

Benzyl hydrodisulfide, benzhydryl hydrodisulfide, and triphenylmethyl hydrodisulfide were prepared and purified by the method reported elsewhere.[12,13] Amines (CP grade) were dehydrated over sodium hydroxide and distilled before use. Benzene (CP grade) was used without further purification. General features of the apparatus have been described previously.[9] Nmr spectra were taken on a JNM 3H-60 spectrometer, with tetramethylsilane as an internal standard. Dibenzhydryl disulfide, when isolated from other products (in runs 11 and 15), was weighed and identified by mixture melting points. Amount of alkanethiol and each amount of diaralkyl disulfide, trisulfide, and tetrasulfide in mixture were determined by nmr spectra.[1,8,9] τ value of –SH in authentic triphenylmethanethiol $(C_6H_5)_3CSH$ was 7.10 (7% in CCl_4). The amount of hydrogen sulfide was estimated by iodometric method,[5] and that of elemental sulfur was determined iodometrically using triphenylphosphine in the same manner as described elsewhere,[5] after identification by mixture melting points. In runs 4, 5, and 6, amounts of elemental sulfur were calculated by substracting those of nmr data (polysulfidic sulfur S_{x-2} in RS_xR) from titrating values ($S_{x-2} + S_8$). We adopted procedures A, B, and C, taking account of behavior of hydrogen sulfide evolution.

Reactions of Aralkyl Hydrodisulfides with Amines. Procedure A (Run 1, 2, 3, 5, 7, 8, 10, 11, 13, 14, and 16).—A solution of 10 mmol of aralkyl hydrodisulfide in 20 ml of benzene and 100 mmol of amine were separately deaerated by bubbling with nitrogen gas for 30 min. The output of nitrogen stream was introduced into a trap (acetone–Dry Ice) for removal of benzene and amine, and then into the absorbing bottles of hydrogen sulfide. The solution of aralkyl hydrodisulfide was added, with stirring, to amine at room temperature. After 2 days, the amount of hydrogen sulfide evolved was estimated. For analysis of the other products, the reaction mixture was chilled on an ice–salt bath. To this mixture was added with stirring 30 ml of 5 N hydrochloric acid for neutralization of the amine. Then the mixture was extracted with benzene, and each component in the dried extract was estimated by nmr spectra (CCl_4) using 1,1,2,2-tetrachloroethane as an internal standard for determination of each amount.

Procedure B (Run 4, 6, 12, and 15).—This procedure was adopted in such a case that hydrogen sulfide was not released before neutralizing the reaction solution which involved amines of large pK_a value. Thus, it was ambiguous to know from the evolution of hydrogen sulfide only whether hydrodisulfides disappeared completely. Therefore, the reaction mixture was acidified after 3 days (1 day longer than in procedure A). Hydrogen sulfide was evolved immediately after the addition of acid. The succeeding treatment of the acidified mixture was identical with that described for procedure A.

Procedure C (Run 9).—To a solution of 10 mmol of benzhydryl hydrodisulfide in 15–20 ml of benzene was added, with stirring, 30 mmol of pyridine under nitrogen atmosphere at room temperature. When hydrogen sulfide almost escaped out, the reaction vessel was heated to 50° in order to sweep out hydrogen sulfide which remained in the reaction mixture. Neutralization was not carried out in this case. The products were extracted with benzene, and diphenylmethanethiol was estimated iodometrically using an aliquot of the dried extract. After the thiol in the remaining extract was oxidized with an excess of alcoholic iodine solution to the corresponding disulfide, dibenzhydryl polysulfides were analyzed by desulfuration with potassium cyanide.[14]

Nmr Spectroscopic Studies. A.—The reaction mixture of benzhydryl hydrodisulfide (5.2 mmol) with piperidine (5.6 mmol), in benzene (20 ml), was analyzed by nmr spectra, which showed the ratio of dibenzhydryl disulfide/trisulfide to be *ca.* 2. Extraction of the mixture changed the ratio to *ca.* 8. Finally, according to procedure A, no dibenzhydryl trisulfide was found.

B.—The reaction of benzhydryl hydrodisulfide (0.7 mmol) in dioxane-d_8 (1 ml) with sodium deuterioxide (5 mmol) in deuterated water (0.5 ml) was traced for 45 min, starting from the time when the reactants were mixed, under the same condition as described previously.[9] In this case the ratio of disulfide/trisulfide was 4 and was almost unchanged as time proceeded.

C.—Preliminary experiments showed that piperidine clearly converts dibenzhydryl trisulfide or tetrasulfide to dibenzhydryl disulfide, since from a mixture of the former and the amine white needles of dibenzhydryl disulfide precipitated (mp 151–152°). Similar treatments of benzyl derivatives, however, did not afford clean dibenzyl disulfide. To a solution of dibenzyl trisulfide, dibenzyl tetrasulfide, dibenzhydryl trisulfide, or dibenzhydryl tetrasulfide (252 μmol) in benzene-d_6 containing dichloromethane or 1,2-dibromoethane (588 or 266 μmol, as internal standard) was added piperidine (1260 μmol). The amount of benzene-d_6 was adjusted so that the total weight was 1 g. Desulfuration of the trisulfide or tetrasulfide in the above solution was traced by nmr spectroscopy. Such experiments showed that the desulfuration is not a simple reaction and that disproportionation occurs, *viz.*, the tetrasulfides, for example, once gave mixtures of polysulfides which gradually change to the disulfides. Therefore, the time required for the absorption of a starting material to diminish to one-half of its original value was determined. For dibenzyl trisulfide and tetrasulfide, and dibenzhydryl trisulfide and tetrasulfide, $t_{1/2}$ values were about 40, 10, 20, and <10 min, respectively. In the case of measurements of benzhydryl compounds, rapid formation of crystalline disulfide made the experiments difficult; hence the half times were roughly estimated.

Registry No.—Benzyl hydrodisulfide, 3492-66-8; benzhydryl hydrodisulfide, 3492-67-9; triphenylmethyl hydrodisulfide, 3492-71-5; aniline, 62-53-3; N,N-dimethylaniline, 121-69-7; pyridine, 110-86-1; 2,4-lutidine, 108-47-4; morpholine, 110-91-8; *n*-butylamine, 109-73-9; tri-*n*-butylamine, 102-82-9; di-*n*-butylamine, 111-92-2; piperidine, 110-89-4.

(12) J. Tsurugi and T. Nakabayashi, *J. Org. Chem.*, **24**, 807 (1959).
(13) T. Nakabayashi, J. Tsurugi, and T. Yabuta, *ibid.*, **29**, 1236 (1964).
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Biologically Oriented Organic Sulfur Chemistry. V. Alkanesulfenyl Iodides[1]

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To provide a better basis for understanding biochemically important sulfenyl iodides (RSI), syntheses and properties of 2-methyl-2-propanesulfenyl iodide (**3**) were studied. Five syntheses gave **3** in yields of 51–92% with uv ϵ_{max} values in reasonable agreement, *viz.*: addition of silver 2-methyl-2-propanethiolate (**2**) to I_2, and of I_2 to **2**; treatment of a sulfenamide with hydriodic acid; and treatment of 2-methyl-2-propanethiol with iodine chloride or with I_2. Average values for **3** were ϵ_{444} 64 and ϵ_{280} 356 in methylcyclohexane (determined by estimating excess I_2 titrimetrically or spectrophotometrically) and ϵ_{444} 75 in carbon tetrachloride (determined through nmr measurement of **3**); charge transfer complexes did not seem to be involved, *e.g.*, of **3** with I_2 or iodide ion. The values of ϵ_{max} in methylcyclohexane were approximately confirmed by photolysis of **3** to *t*-butyl disulfide and I_2, during which **3** disappeared as I_2 formed. This reaction was zero order; it confirmed the structure of **3**. The structure of **3** was further confirmed by nmr (δ 1.45) and by converting it to a known unsymmetrical disulfide and sulfenamide (during which time the spectrum of **3** disappeared as that of the sulfenamide appeared). Nearly all of **3** survived at −12° in the dark for more than 11 days, but at ambient conditions only about half survived for 3 days. Survival of **3** was enhanced by dilution, was little effected by water or iodide ions, and was decreased by thiosulfate or triiodide ions. Apparently, silver 1-butane- or 2-butanethiolate with I_2 gave no sulfenyl iodide, but triphenylmethanethiol with I_2 did.

Sulfenyl iodides (RSI), often postulated as intermediates without having been characterized,[2] seem to be biochemically important. Tobacco mosaic virus forms a stable sulfenyl iodide,[3] and other proteins later were found to do so as well;[4,5] sulfenyl iodides may mediate protein iodination.[6]

Since β-lactoglobulin sulfenyl iodide reacts much more rapidly with antithyroid agents such as thiouracil than with more typical thiols such as 2-hydroxyethanethiol, Cunningham suggested that antithyroid activity might depend upon the reaction between the sulfenyl iodide and the antithyroid agent and therefore that a protein sulfenyl iodide may be a reactive key intermediate in thyroidal iodine metabolism.[7] Others also have speculated on this possibility,[6,8] and evidence now is beginning to appear that iodination of tyrosine moieties in the thyroid gland may indeed involve sulfenyl iodides.[9,10]

The possibility that thyroidal iodination involves a protein sulfenyl iodide points to the desirability of more information regarding simple well defined sulfenyl iodides. This paper contributes such information.

Rheinboldt and Motzkus reported 31 years ago on a simple model, 2-methyl-2-propanesulfenyl iodide (**3**). They prepared **3** by converting the thiol **1** to the silver thiolate (**2**), or (usually) to the mercuric thiolate, and adding the thiolate to I_2 in dry ether at 0–20° (eq 1).[11]

$$\underset{\mathbf{1}}{(CH_3)_3CSH} \xrightarrow{Ag^+} \underset{\mathbf{2}}{(CH_3)_3CSAg} \xrightarrow{I_2} \underset{\mathbf{3}}{(CH_3)_3CSI} + AgI \quad (1)$$

The reactivity of **3** precluded its isolation in a pure state. Oxidation of **1** with I_2 also has been reported to give **3**, but only incidentally and with only the substantiation that the solution turned yellow, then brown, and that the "unforgettable and unmistakable smell of sulfenyl iodides developed."[12] An as yet unpublished preparation of triphenylmethanesulfenyl iodide by Ciuffarin and Tentori also has been mentioned.[13]

Preparation of 3.—Since **3** is best handled in solution, knowledge of its uv extinction coefficients would be helpful in following it. Determination of ϵ_{max} is complicated by such features as the absorption of *t*-butyl disulfide (**4**) and the possibility of extraneous species such as charge transfer complexes. In obtaining values of ϵ_{max} therefore, we ensured reliability by using a variety of syntheses, *viz.*, two variations of the Rheinboldt–Motzkus procedure (procedures A and B, each with four subsidiary analytical determinations), as well as three other syntheses (procedures C–E). The results are summarized in Table I. (Beforehand, as related later, the identity of **3** was confirmed and the spectra were studied extensively.)

Procedure A was like that of Rheinboldt and Motzkus, except that an inert solvent was used to minimize charge transfer complexes. The thiolate **2** was added to I_2, and the unconsumed I_2 then was determined in two ways: titrimetrically, by adding thiosulfate and back-titrating the excess with I_2, and spectrophotometrically, from the absorbance of I_2 before the thiosulfate wash (both our experience and that of Rheinboldt and Motzkus show **3** to be stable to thiosulfate under these conditions).

(1) (a) Paper IV: L. Field and C. H. Foster, *J. Org. Chem.*, **35**, 749 (1970). (b) This investigation was supported by Public Health Service Research Grant No. AM11685 from the National Institute of Arthritis and Metabolic Diseases. (c) Taken from part of the M.S. thesis of J. L. V., Vanderbilt University, Jan 1970; the thesis may be consulted for greater detail. (d) Department of Chemistry, Vanderbilt University, Nashville, Tenn. (e) Department of Biochemistry, Vanderbilt University, Nashville, Tenn.

(2) (a) N. Kharasch, "Organic Sulfur Compounds," Vol. I, Pergamon Press, New York, N. Y., 1961, p 387. (b) I. M. Kolthoff and W. E. Harris, *Anal. Chem.*, **21**, 963 (1949). (c) J. P. Danehy, *Quart. Rep. Sulfur Chem.*, **2**, 325 (1967). (d) G. K. Helmkamp, H. N. Cassey, B. A. Olsen, and D. J. Pettitt, *J. Org. Chem.*, **30**, 933 (1965). (e) S. N. Nabi, S. Ahmad, and S. Ahmad, Jr., *J. Chem. Soc.*, 2636 (1963). (f) R. N. Haszeldine and J. M. Kidd, *ibid.*, 3219 (1953). (g) B. Milligan and J. M. Swan, *ibid.*, 2172 (1962).

(3) H. Fraenkel-Conrat, *J. Biol. Chem.*, **217**, 373 (1955).

(4) L. W. Cunningham and B. J. Nuenke, *ibid.*, **234**, 1447 (1959).

(5) B. T. Kaufman, *Proc. Nat. Acad. Sci. U. S.*, **56**, 695 (1966).

(6) D. M. Fawcett, *Can. J. Biochem.*, **44**, 1669 (1966).

(7) L. W. Cunningham, *Biochemistry*, **3**, 1629 (1964).

(8) (a) N. Kharasch, *J. Chem. Educ.*, **32**, 192 (1955). (b) F. Maloof and M. Soodak, *Pharmacol. Rev.*, **15**, 43 (1963).

(9) D. M. Fawcett, *Can. J. Biochem.*, **46**, 1433 (1968).

(10) L. Jirousek and L. W. Cunningham, *Biochim. Biophys. Acta*, **170**, 160 (1968).

(11) H. Rheinboldt and E. Motzkus, *Ber.*, **72B**, 657 (1939).

(12) J. A. Barltrop, P. M. Hayes, and M. Calvin, *J. Amer. Chem. Soc.*, **76**, 4348 1954).

(13) A. Fava, B. Reichenbach, and U. Peron, *ibid.*, **89**, 6696 (1967).

TABLE I

MOLAR EXTINCTION COEFFICIENTS (ϵ) OF $(CH_3)_3CSI$ (**3**) AT 444 AND 280 nm[a]

Procedure for synthesis of 3	No. of expts	Analytical technique (for substance determined)	Solvent[b]	ϵ_{444}	ϵ_{280}	Range[c] ϵ_{444}	Range[c] ϵ_{280}	Yield, %[d]
A (2 added to I_2)	4	Uv (I_2)	M	64 ± 2	353 ± 8	4	18	53
		Titration (I_2)	M	68 ± 1	376 ± 9	4	22	51
		Photolysis,[e] then uv (I_2)	M	53 ± 0.3	...[f]	1.7		
		Photolysis,[e] then titration (I_2)	M	70 ± 13	...[f]	28		
B (I_2 added to 2)	4	Uv (I_2)	M	61 ± 9	345 ± 45	17	105	62
		Titration (I_2)	M	62 ± 2	350 ± 26	5	61	61
		Photolysis,[e] then uv (I_2)	M	41 ± 10	...[f]	27		
		Photolysis,[e] then titration (I_2)	M	58 ± 14	...[f]	33		
Average value for ϵ_{max} in M[g]				64	356			
C (eq 3, 5 + HI)	5	Nmr (**3**)	C	74 ± 8	...[b]	19		92
D (eq 4, 1 + ICl)	4	Nmr (**3**)	C	72 ± 6	...[b]	15		66
E (eq 5, 1 + I_2)	4	Nmr (**3**)	C	80 ± 5	...[b]	11		90
Average value for ϵ_{max} in C[g]				75				

[a] The ± values are standard deviations calculated as usual, $s = \sqrt{\Sigma d^2/(n-1)}$ (*cf.*, for example, D. A. Skoog and D. M. West, "Fundamentals of Analytical Chemistry," Holt, Rinehart, and Winston, New York, N. Y., 1963, p 47). "Titration" refers to the washing of an I_2 solution with excess $Na_2S_2O_3$ and back titration of the excess with aqueous I_2. [b] M, methylcyclohexane; C, carbon tetrachloride (chosen for its utility in nmr determinations; lack of uv transparency precluded determination of ϵ at 280 nm). [c] The range separating high and low values of the set. [d] Calculated as 100 (moles of **3** determined in the measurement of ϵ)/(theoretical moles of **3** possible); the highest yield observed by each method is reported. [e] Photolysis (eq 2) was followed by determination of I_2 from uv absorbance at 520 nm and by titration. [f] The λ_{max} at 280 nm disappeared upon photolysis, but **4** interfered too greatly for a reliable determination of ϵ. [g] A simple average of the values reported, disregarding standard deviations. Since photolyses were complex (see text), these values from procedures A and B were not included.

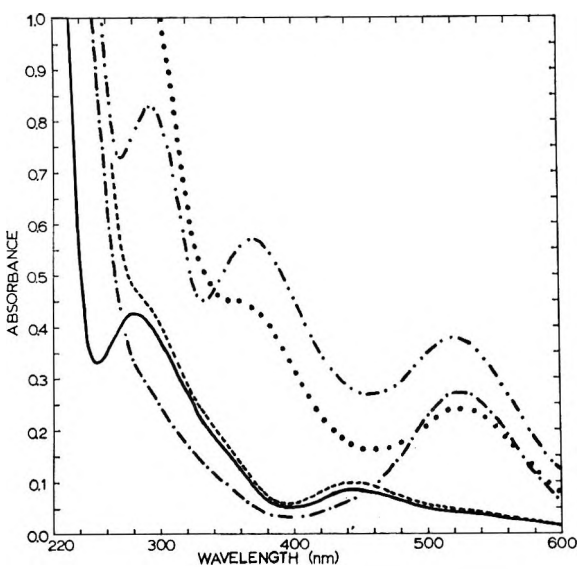

Figure 1.—Uv absorption spectra of **3**: in CCl_4 (0.0013 *M*), ------; in methylcyclohexane (0.0014 *M*), ——; in methylcyclohexane (0.0014 *M*) irradiated 5 min, -·-·-· (this curve is essentially the summation of those for I_2 and **4**); irradiated 2 hr, —·—·—; and irradiated 12 hr, ·····.

Numerous preliminary experiments had established λ_{max} of **3** in methylcyclohexane at 444 nm (relatively little interference from **4** but a little from I_2) and at 280 nm (considerable interference from **4**). These features are reflected in Figure 1, prepared late in the study after such features became clear (it may help interpretation to add that one curve of Figure 1 closely resembles summation of those for I_2 and **4**; *cf.* legend). The absorbance of **3** at 444 nm and 280 nm after the wash, divided by the consumption of I_2 (assuming the amount of **3** equaled this consumption and remained unchanged), gave ϵ_{444} and ϵ_{280}; ϵ_{444} and ϵ_{280} thus could be calculated both from ϵ_{520} for I_2 ("Uv," Table I) and from the titrimetric analyses ("Titration," Table I).

Brief photolysis of **3** gave I_2, as shown by eq 2.

$$\underset{\mathbf{3}}{2(CH_3)_3CSI} \xrightarrow{h\nu} \underset{\mathbf{4}}{[(CH_3)_3CS]_2} + I_2 \qquad (2)$$

Analysis for I_2 both by uv and titration after photolysis of a solution of **3** of known absorbance permitted calculation of the third and fourth values shown for **3** under procedure A of Table I ("Photolysis"). These values were reassuring but (for reasons given later) were not included in the averages taken for ϵ.

In procedure B, the order of addition was reversed. There was no obvious difference in the reaction. Although the averages for ϵ_{444} and ϵ_{280} were slightly lower than by procedure A, they are considered reliable enough for inclusion in the average of all of the values, *i.e.*, ϵ_{444} 64 and ϵ_{280} 356 (Table I), which we suggest be used for solutions of **3** in methylcyclohexane. The lower values probably result from a favoring of the reaction of the salt **2** with **3** to form the disulfide **4** because of addition to excess **2**.

Procedure C was based on the reaction shown by eq 3a. Since eq 3 *in toto* provides a basis for iodometric determination of sulfenamides,[14] it seemed likely that the greater stability of **3** than of most sulfenyl iodides might permit the reaction of **5** to be stopped in its first phase, eq 3a. The realization of this possibility led to

$$\underset{\mathbf{5}}{(CH_3)_3CSN(CH_2)_5} + HI \longrightarrow \underset{\mathbf{3}}{(CH_3)_3CSI} + NH(CH_2)_5 \qquad (3a)$$

$$\downarrow \qquad\qquad \downarrow HI$$

$$^1/_2I_2 + {}^1/_2\underset{\mathbf{4}}{[(CH_3)_3CS]_2} \quad I^-{}^+H_2N(CH_2)_5 \qquad (3b)$$

procedure C. As can be seen from Figure 1, use of carbon tetrachloride as a solvent precludes observation of ϵ_{max} at 280 nm. The most convenient determination of ϵ_{444} proved to be by washing out of piperidinium and iodide ions and evaluation of the concentration of **3** by nmr with an internal standard (**3** shows a sharp singlet

(14) W. Groebel, *Chem. Ber.*, **92**, 2887 (1959).

at δ 1.45, well separated from that of either the sulfenamide **5** at δ 1.18 or the disulfide **4** at δ 1.30). Concentrations were varied in procedure C over a sevenfold range in the evaluation of ϵ_{444} shown in Table I (similar variations in concentration were made in the other procedures to broaden the basis for ε). Photolysis of **3** in procedure C unfortunately could not be used to check ϵ_{444} presumably because of interfering reactions of trace contaminants. Rheinboldt and Mott used a variation of procedure C to prepare 2-methyl-2-propanesulfenyl bromide and chloride but not **3**.[15] By procedure C, **3** was prepared in high yield but seldom was the nmr spectrum of the **3** virtually free of the disulfide **4**. At first, procedure C seemed to be an attractive path to **3** but a study as **3** decomposed indicated otherwise. In the presence of ~10% of the unconverted **5**, and possibly of other trace impurities, the washed solution soon showed a variety of products, and the final yield of *t*-butyl trisulfide was as great as that of the disulfide **4**.

Procedure D was based on eq 4. A slight excess of iodine monochloride was used to assure complete conversion of **1** and then was destroyed with thiosulfate. Procedure D was more difficult to control than the others. The quantities of initial reactants and the time of mixing were critical. Too long a reaction time or too great an excess of ICl carried the final products well beyond **3**. The nmr spectrum of the solution

$$\underset{\mathbf{1}}{(CH_3)_3CSH} + ICl \longrightarrow \underset{\mathbf{3}}{(CH_3)_3CSI} + HCl \qquad (4)$$

ordinarily obtained gave five sharp singlets; these are attributed to **1**, **3**, **4**, *t*-butyl trisulfide, and an unknown.

Procedure E perhaps is the most satisfying preparative route for **3**. It was based on eq 5, which it will be recalled was mentioned earlier without elaboration.[12] Thiol **1** in carbon tetrachloride was added to excess I_2

$$\underset{\mathbf{1}}{(CH_3)_3CSH} + I_2 \longrightarrow \underset{\mathbf{3}}{(CH_3)_3CSI} + HI \qquad (5)$$

in the presence of water. The solution was washed with aqueous thiosulfate and water, operations which proved to be the key to the success of procedure E. The thiol was converted completely to a solution of sulfenyl iodide **3** containing some disulfide **4** (a minimum of ~16% by nmr). Since little reaction reportedly occurs between many thiols and iodine in nonpolar solvents even upon heating,[13,16] the presence of water presumably explains the success of procedure E. The extinction coefficient of **3** was evaluated using nmr as in procedures C and D (Table I; see Experimental Section). The average of all values from procedures C, D, and E gave ϵ_{444} 75, the value suggested for use with **3** in CCl_4.

In procedures A–E, one must be wary of charge transfer complexes involving combinations of **1**, **3**, **4**, and I_2. For example, I_2 and **4** show an absorption peak at 328 nm in methylcyclohexane and a shoulder at ~333 nm in CCl_4 (neither are seen in the spectra of I_2 or **4**), and λ_{max} for I_2 is shifted slightly low from ~520 nm; a charge transfer band has not been reported for I_2 with **4** but has been for I_2 with other disulfides,[17] as well as with thiols.[17a] Species such as triiodide ion,[18] especially in procedure E (eq 5), probably also are involved in the *initial* reaction mixture. The **3** evidently does not form complexes with iodide or iodine, however; thus its solution was not changed when stirred with aqueous potassium iodide (poor distribution of the potassium iodide into CCl_4 presumably is not responsible, since $Na_2S_2O_3$ reacted readily under similar conditions; *vide infra*); similarly, when I_2 was added to **3**, the spectrum simply was the sum of the two and a sodium thiosulfate wash left only **3**. The wash of aqueous thiosulfate and then water in procedures A–E *before* determination of ε for **3** presumably removed any charge transfer species, so that the ε values reported for **3** should be those of **3** and not of other species; reasonable agreement of the ε values obtained by the numerous methods of Table I support this conclusion, as does other evidence for the presence of **3** (*vide infra*).

Reactions.—As mentioned, photolysis of **3** provided a reassuring check on the presence of **3**. Beforehand, however, we had encountered a report that trifluoromethanesulfenyl chloride forms from the disulfide and chlorine upon uv irradiation;[2f] furthermore, Barltrop, Hayes, and Calvin felt that the disulfide **4** was cleaved to **3** by I_2.[12] It therefore seemed wise to check the possibility that light might effect for I_2 the type of cleavage of disulfides which is well known to give sulfenyl chlorides under ordinary conditions with chlorine. Uv irradiation of a solution of I_2 and **4** produced no absorption at 280 or 444 nm which would indicate formation of **3**; I_2 appeared to be consumed and triiodide ion to be formed (appearance of two new absorptions at 288 and 362 nm; *cf.* ref 18). Indeed, as Figure 1 shows and more in accord with expectation, when **3** was irradiated for 5 min, its two characteristic absorbances disappeared and I_2 was released (new absorption at 520 nm; eq 2). After *ca.* 2 hr more, this absorption increased by ~30%, and two new peaks appeared consistent with triiodide formation. These changes are shown in Figure 1. The photolytic decomposition of **3** (eq 2) was zero order (*cf.* Figure 2), with the rate of decomposition of **3** (−0.0019 mequiv/min by loss of absorbance at 280 or 444 nm) being virtually the same as the rate of formation of I_2 (+0.0011 mequiv/min by titration with thiosulfate; +0.0019 mequiv/min by cumulative absorption at 520 nm). After ~50–60% of **3** had decomposed, the complexity of the reaction increased, as reflected by the change in slope of two of the curves in Figure 2, perhaps because accumulating byproducts began to consume I_2 or because accumulated **4** reduced uv absorption by the solution.

Rheinboldt and Motzkus demonstrated the identity of **3** by converting it to sulfenamides with amines.[11] Since we had had experience with N-(*t*-butylthio)-piperidine (**5**),[19] early in our work we confirmed the identity of **3** (from procedure B) by converting it to **5** (90% yield; eq 6); uv and nmr spectra showed that the appearance of **5** corresponded to the disappearance of **3**.

$$\underset{\mathbf{3}}{(CH_3)_3CSI} + 2HN(CH_2)_5 \longrightarrow \underset{\mathbf{5}}{(CH_3)_3CSN(CH_2)_5} + I^{-+}H_2N(CH_2)_5 \qquad (6)$$

(15) H. Rheinboldt and F. Mott, *Ber.*, **72**, 668 (1939).

(16) E. C. Kooyman, "Organosulfur Chemistry," M. J. Janssen, Ed., Interscience, New York, N. Y., 1967, p 6.

(17) (a) M. Good, A. Major, J. Nag-Chaudhuri, and S. P. McGlynn, *J. Amer. Chem. Soc.*, **83**, 4329 (1961). (b) H. Tsubomura and R. P. Lang, *ibid.*, **83**, 2085 (1961). (c) B. Nelander, *Acta Chem. Scand.*, **20**, 2289 (1966).

(18) (a) A. D. Awtrey and R. E. Connick, *J. Amer. Chem. Soc.*, **73**, 1842 (1951). (b) L. I. Katzin, *J. Chem. Phys.*, **21**, 490 (1953).

(19) (a) N. E. Heimer and L. Field, *J. Org. Chem.*, **35**, 3012 (1970). (b) We thank Dr. Heimer for several helpful suggestions.

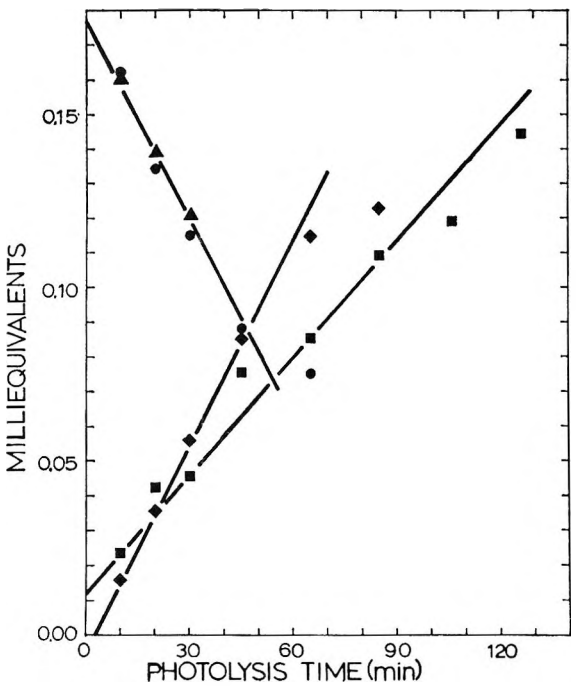

Figure 2.—Photolysis study of **3** (0.17 mequiv): ●, mequiv of **3** remaining as determined by A_{444} (slope, −0.0019 mequiv/min); ▲, mequiv of **3** remaining as determined by A_{280} (slope, −0.0019 mequiv/min); ■, cumulative mequiv of I_2 released as determined by titration (slope, +0.0011 mequiv/min); ◆, cumulative mequiv of I_2 released as determined by A_{520} (slope, +0.0019 mequiv/min).

Further confirmation was obtained by converting **3** to the known unsymmetrical disulfide **6** of eq 7 (27% yield).

$$\underset{\mathbf{3}}{Me_2NC(S)SNa} + (CH_3)_3CSI \longrightarrow \underset{\mathbf{6}}{Me_2NC(S)SSC(CH_3)_3} + NaI \quad (7)$$

Some reactions failed or were unpromising. In testing for the possible use with sulfenyl iodides of a method used to determine sulfenyl chlorides,[20] **3** in methylcyclohexane was added to potassium iodide in acetic acid. Addition of thiosulfate (to measure I_2) and back-titration with I_2 showed that the **3** did not decompose immediately to I_2. Longer contact times still were inconclusive; indeed, back-titration of the thiosulfate required more standard I_2 than had the thiosulfate initially.

Evidence for the identity of **3** now can be summarized. (a) Procedures A–E gave **3** with essentially the same features in the uv spectrum and with ϵ values in reasonable agreement, including values based on photolysis of **3** to I_2 and the disulfide **4**, a reaction which itself supports the structure. (b) Nmr spectra of solutions of **3** (procedure A) showed only two peaks, one being from **3** and the other from **4**; as the spectrum of **3** disappeared, that of **4** increased. Nmr spectra of solutions obtained by the other procedures all were understandable in these terms, although other substances were present. (c) Two known derivatives were prepared from **3**; with one (**5**, 90% yield), the uv and nmr absorptions of **3** disappeared as those of **5** appeared.

Reactivity and Stability.—Rheinboldt and Motzkus made a few qualitative observations on the behavior of **3** in ether.[11] We have extended these more quantitatively. Portions of a solution of **3** in CCl_4 first were subjected to varying conditions of light and temperature. The results are shown in Figure 3. The survival time for 50% of the 0.019 *M* **3** stored under ambient conditions was nearly 3 days. In the dark, 67% survived after 11 days, however, and when a dark sample also was kept cold (−12°) nearly all survived.

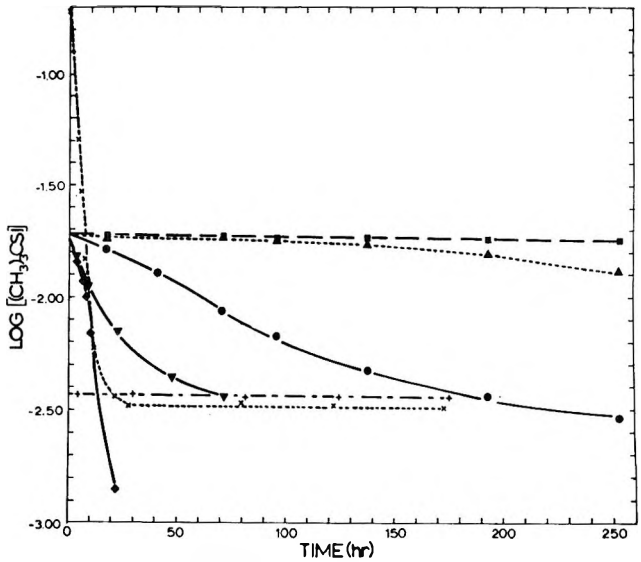

Figure 3.—Reactivity and stability of **3** (original molarity indicated on the vertical axis): ●, ambient conditions; ▲, dark, ~ 25°; ■, dark ~ −12°; ◆, stirred with 0.1 *N* $Na_2S_2O_3$; ▼, stirred with 0.1 *N* KI_3; x, concentrated solution (0.19 *M*); +, diluted solution (0.004 *M*) (the latter two at 25° in the dark).

In an assessment of effects of reagents, when water or aqueous 0.1 *N* potassium iodide was stirred in contact with portions of a 0.018 *M* solution in carbon tetrachloride (dark, ~25%), the survival of **3** was essentially the same as above. However, stirring with 0.1 *N* sodium thiosulfate and 0.1 *N* potassium triiodide resulted in 50% survival times of 9 and 15 hr, respectively (Figure 3). The results with sodium thiosulfate should have negligible relevance to those in determining ϵ_{max}, where only 0.05 *N* sodium thiosulfate was used and where contact was for only 1 min, although they suggest the inapplicability of the sodium thiosulfate-wash technique for determining ϵ_{max} of sulfenyl iodides much more reactive than **3**. The reaction of **3** with potassium triiodide suggests that procedure E might be improved for preparative use by minimizing the excess of I_2, although not for determination of ϵ_{max} where the singlet of **1**(δ 1.42) might complicate use of that of **3** (δ 1.45).

Figure 3 also illustrates the effect of the concentration of **3** on its stability. The 50% survival time of a 0.2 *M* solution of **3** (among the most concentrated used) in the dark at 25° was only 3.5 hr. In marked contrast, a 0.004 *M* solution was largely unchanged after 7 days, suggesting that sulfenyl iodide moieties on proteins may exist, at least in part, because of very low effective concentration, amounting almost to isolation.

Structural effects on reactivity were considered also (although only in a preliminary way), since the relatively low reactivity of **3** has been attributed to a neopentyl-type steric hindrance on the sulfur atom of **3**, which opposes back-side attack by nucleophiles.[16] The tertiary structure of **3** did indeed prove to be a

(20) N. Kharasch and M. M. Wald, *Anal. Chem.*, **27**, 996 (1955).

special case, since the silver thiolates of 1-butane- or 2-butanethiol showed no tendency to form stable sulfenyl iodides (procedure A); thus no product resulted which showed uv absorption near 440 nm or which liberated I_2 on photolysis. On the other hand, triphenylmethanethiol in procedure E showed in the 320–600-nm range a λ_{max} at 440 nm (only); photolysis and titration of I_2 formed indicated a yield of sulfenyl iodide of at least 70%.

Experimental Section[21]

Materials.—Methylcyclohexane, CCl_4, and 1,4-dioxane were Matheson Coleman and Bell Spectroquality reagents. "Baker Analyzed" ACS-grade I_2 was used. The 1 was a practical grade (97%); its nmr spectrum in CCl_4 showed it to be free of 4. Practical grade 4 was redistilled in a 0.5 × 60 cm Nester–Faust annular column, $n^{25}D$ 1.4863 (lit.[23] $n^{20}D$ 1.4899); glpc showed the distillate to be pure; it was stored in the dark under N_2. Silver 2-methyl-2-propanethiolate (2) was prepared fresh for each experiment as reported;[24] it was dried at 0.1 mm overnight. Iodine monochloride[25] was distilled, bp 97–105°.[26]

Preparations and Molar Extinction Coefficients (ϵ) of 2-Methyl-2-propanesulfenyl Iodide (3). A. By Addition of 2 to I_2.—A typical experiment on which the values of Table I are based was as follows. A solution 0.00956 *M* in I_2 in methylcyclohexane was prepared (ϵ_{520} 935). The thiolate 2 (0.990 mmol) was added to 75.00 ml (0.717 mmol) of this solution at ~0° in a glass-stoppered flask. The mixture was shaken for 1 min; then AgI was removed using a sintered-glass funnel.

For the determination of ϵ by "Titration (I_2)" (Table I), the temperature of the filtrate was allowed to rise to ~25°, and a 20.00-ml aliquot was shaken with 0.0612 *N* $Na_2S_2O_3$ (10.00 ml), then twice with water; the washings were combined and titrated with 0.0507 *N* KI_3 (8.09 ml); on the assumption that all I_2 used gave 3, from the absorbances (A_{444} 0.310, A_{280} 1.707) ϵ_{444} and ϵ_{280}, respectively, then were calculated: (0.310)(75.00)/[0.717 − (0.612 − 0.410)(0.5)(75/20)] = 68.7 and (1.707)(75.00)/[0.717 − (0.612 − 0.410)(0.5)(75/20)] = 378.5. The average of four such experiments gave the values of 68 ± 1 (ϵ_{444}) and 376 ± 9 (ϵ_{280}) in Table I. Such solutions of 3 were orange-red with sharp, lachrymatory odors. The highest yield of the four samples, 51%, is reported in Table I. The yield for the foregoing typical sample, for example, was calculated as follows: [0.717 − (0.612 − 0.410)(0.5)(75/20)](100)/(0.717) = 47%.

For the determination of ϵ by "Uv (I_2)" (Table I), uv spectra of the same aliquot before the wash showed the absorbance (*A*) at 520 nm to be 4.647 (0.641 corrected for dilution of 0.40 to 2.90 ml) and after the wash to be 0.151 (slight tailing from A_{444} of 3). The amount of residual I_2 after its reaction with 2 therefore was (4.647 − 0.151)/935 = 0.00481 *M*, and ϵ_{444} thus was 65.3 [0.310/(0.717/75 − 0.00481 = 0.00475)]; similarly, ϵ_{280} was 359.3. The average for four such experiments gave the values 64 ± 2 (ϵ_{444}) and 353 ± 8 (ϵ_{280}) in Table I. The highest yield of the four samples, 53%, is reported in Table I. The yield for the foregoing typical sample was calculated as (0.00475)(100)/(0.717/75) = 50%.

In the analysis by "Photolysis" (Table I), the preferred alternative of determining ϵ_{444} for 3 simply by dividing A_{444} for a solution by twice the moles of I_2 produced on photolysis was precluded by side reactions after about 50–60% completion. Hence ϵ, "Photolysis, then titration (I_2)" (Table I), was determined by dividing *A* for a solution of 3 *after* photolysis by the calculated concentration of 3 remaining *after* photolysis, as follows: The remaining 55 ml of the solution of 3 was washed like the first portion and combined with it. The 75 ml then was photolyzed (the temperature rose to ~100°) for 5.0 min (optimum time established beforehand) in a quartz flask fitted with a reflux condenser. A 20.00-ml aliquot, at ~25°, was washed with 10.00 ml of 0.0612 *N* $Na_2S_2O_3$ (0.612 mequiv) and H_2O; the combined washings were titrated with 11.03 ml of 0.0507 *N* KI_3 (0.559 mequiv); the amount of I_2 formed, hence of 3 decomposed, was (0.612 − 0.559)(75/20) = 0.198 mequiv (59% decomposed). Residual 3 in the 75.00 ml thus was [0.717 − (0.612 − 0.410)(0.5)(75/20)] − 0.198 = 0.140 mmol, *i.e.*, corresponding to a solution 0.00187 *M* in 3. The A_{444} of this remaining 3 was 0.120; hence ϵ_{444} = 64.2. The value of ϵ_{444} 70 ± 13 (Table I) was an average of four such experiments.

Uv spectra of the 75 ml were taken before and after the wash which followed photolysis to determine ["Photolysis, then uv (I_2)"; Table I] the amount of I_2 liberated and, from this, of undecomposed 3. *A*'s of the solution at 520 nm before and after washing were 1.233 and 0.060, respectively; hence the amount of 3 which survived left a 0.00225 *M* solution [0.00475 − 2(1.233 − 0.060)/935 = 0.00250]; therefore ϵ_{444} was 0.120/0.00225 = 53.3. The value of 53 ± 0.3 (ϵ_{444}) in Table I was an average of photolysis results on the four samples used in the other techniques.

A control containing 0.358 mmol of I_2 in 25 ml of methylcyclohexane was photolyzed for 10 min. Titration of a photolyzed aliquot as above showed essentially no change (0.364 mmol) in the concentration of I_2. Uv spectra at 520 nm after this photolysis indicated the amount of I_2 was 0.357 mmol.

B. Addition of I_2 to 2.—A solution 0.01434 *M* in I_2 in methylcyclohexane was prepared. The procedure was essentially that of A except that a known quantity of the I_2 solution at 0° was added in one portion to the thiolate in the proportions used in A. The same procedure was followed as in A for analysis of ϵ_{444} and ϵ_{280}. The average values for procedure B listed in Table I also represent four experiments.

C. Cleavage of N-(*t*-Butylthio)piperidine (5).—As was outlined for 5,[27] disulfide 4 (0.1 mol) was chlorinated in petroleum ether with 0.1 mol of Cl_2 at approximately 25°. This solution was added to 0.4 mol of piperidine in petroleum ether and 0.4 mol of NaOH in H_2O during 30 min. The organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated. Distillation (200-mm Vigreux column) gave colorless 5: 21.0 g (61%); $n^{24}D$ 1.4750, lit.[27b] $n^{20}D$ 1.4765; nmr (CCl_4) δ 1.18 (s). No 4 was observed (δ 1.30, s).

A typical cleavage was as follows: 15.0 ml of 0.2 *M* aqueous HI (3 mmol) was added to 224 mg (1.3 mmol) of 5 in 15 ml of CCl_4 (0.09 *M* solution), and the mixture was shaken vigorously for 2 min (concentrations of the 5 were varied in five experiments from 0.03–0.2 *M*, with proportional changes in the amount of HI used).

The organic layer was washed twice with H_2O, twice with 0.05 *N* $Na_2S_2O_3$, then twice again with H_2O; the uv spectrum was typical of 3 with A_{444} 5.643 (calculated from the observed *A* of 0.513, after dilution of 0.25 to 2.75 ml). The concentration of 3 was determined immediately by placing 10.0 μl of dioxane (0.117 mmol) in an nmr tube with 1.00 ml of the washed solution. The peak areas of the resulting singlets of 4.73 for the 8 protons of dioxane (δ 3.57) and of 3.60 for the 9 protons of 3 (δ 1.45) indicated, since an equimolar amount (*i.e.*, 0.117 mmol) of 3 should have an area of 5.32, that 0.0792 mmol [*i.e.*, (3.60/5.32)(0.117)] of 3 was present in the volume of 1.01 ml of solution. The molar concentration of 3 thus was 0.0784 *M* and ϵ_{444} was 71.9 (*i.e.*, 5.643/0.0784). The value of 74 ± 8 (Table I) is the average of

(21) Uv spectra were obtained using matched 10-mm standard silica cells with a Beckman Model DB recording spectrophotometer; photometric accuracy was checked weekly with a K_2CrO_4 solution;[22] we are much indebted to Professor T. M. Harris for the use of this instrument. Nmr spectra were obtained with a Varian Model A-60 (TMS as internal standard). Mass spectra were kindly determined by C. T. Wetter using an LKB Model 9000 instrument (70 eV, gc inlet), obtained through NSF Science Development Program Grant GU-2057; only parent peaks and those exceeding 5% in relative intensity at m/e >40 are reported. Unless otherwise stated, reactions were done at ~25°, and irradiations were done in a quartz vessel 5 cm from a Hanovia 100-W uv lamp. Glpc measurements were done on a Varian Aerograph instrument using an SE-30 column (3%, 0.6 × 150 cm, 100–120 mesh Chromosorb P). Standard solutions were checked weekly; aqueous KI_3 was standardized against As_2O_3 (99.99% assay, G. Frederick Smith Chemical Co.) and $Na_2S_2O_3$ against the KI_3; solutions of I_2 were standardized by washing aliquots with $Na_2S_2O_3$, then H_2O, combining the washes, and using KI_3; "Vitex" (a modified amylose; G. Frederick Smith Co.) was the indicator. Melting points are corrected.

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(24) *Cf.* ref 18 in T. F. Parsons, J. D. Buckman, D. E. Pearson, and L. Field, *J. Org. Chem.*, **30**, 1923 (1965).

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five such experiments. The chemical shift of the methyl groups of **3** (δ 1.45, s), made this determination possible, since it differed from those of **5** (δ 1.18, s), **4** (δ 1.30, s), or **1** (δ 1.42, s).

Photolysis as a check of the value of ϵ_{444} was inconclusive; no I_2 was liberated, the solution became dark brown (unchanged by $Na_2S_2O_3$), and solid precipitated; trace contaminants (*e.g.*, piperidine or HI) probably led to further reactions of I_2.

D. Addition of ICl to 1.—A solution of 0.728 g (4.49 mmol) of ICl in 7 ml of CCl_4 was added to one of 0.320 g (3.55 mmol) of **1** in 16 ml of CCl_4 in a separatory funnel. The mixture was shaken for 1 min and then was washed immediately three times with H_2O, with 0.05 *N* $Na_2S_2O_3$ until the color remained constant, and then again three times with H_2O. The discernible part of the uv spectrum was identical with that of **3** prepared as in A. The ϵ_{444} of **3** was determined by uv and nmr (dioxane as an internal standard) as in C. Nmr chemical shifts, assignment, and per cent of total peak area, respectively, for the five singlets observed with a typical product were δ 1.30, **4**, 5;[28] δ 1.37, *t*-bu-S_3-*t*-bu, 13;[28] δ 1.42, **1**, 4; δ 1.45, **3**, 69; and δ 1.60, unknown, 10. After 2 days in the nmr tube under ambient conditions only sharp singlets at δ 1.30, 1.37, and 1.60 remained; the relative intensity of δ 1.30 increased tremendously, and I_2 was released.

E. Addition of 1 to Excess I_2.—A 0.095 *M* solution of **1** (30.00 ml, 2.85 mmol) in CCl_4 was poured into a glass-stoppered flask containing 10 g (39.4 mmol) of solid I_2. Water (20 ml) was quickly added, and the mixture was shaken vigorously for 5 min. The organic layer was filtered (sintered glass), washed with H_2O twice, with 0.05 *N* $Na_2S_2O_3$ until the color was constant, then three times more with H_2O; ϵ_{444} was determined by uv-nmr as in C.

Reactions of 3. A. Photolysis.—In the preliminary study (see Discussion), a solution 0.0003 *M* in both **4** and I_2 in methylcyclohexane was irradiated. The uv spectrum was compared periodically with spectra of separate control solutions of I_2 and **4**. No indication of the characteristic absorption of **3** (280, 444 nm) could be seen. It was soon found that **3** from procedure B (~0.002 *N*) when thus irradiated decomposed immediately (*cf.* Figure 1 and Discussion).

The results plotted in Figure 2 were obtained as follows. A suspension of **2** (101.7 mg, 0.516 mmol) in 16 ml of methylcyclohexane was chilled with Dry Ice in a foil-covered centrifuge tube capped with a rubber septum, and a solution of I_2 (25 ml, 0.0208 *N*, 0.520 mequiv) at 5° was introduced with a syringe. The contents were shaken vigorously for 1.5–2.0 min and centrifuged. The supernatant liquid was immediately removed, the uv spectrum was taken, and the liquid was washed with 0.0606 *N* $Na_2S_2O_3$ (10.00 ml, 0.606 mequiv) and water. The combined washings were titrated against 0.0505 *N* KI_3 (8.70 ml, 0.439 mequiv); hence the amount of **3** in the 41.00 ml of solution was 0.176 mmol [(0.520 − 0.167)/2], and the molarity of **3** was 0.0043. The washed solution then was irradiated (*15 cm from the lamp instead of the usual 5*). Periodically, the entire solution (to minimize I_2 absorption) was removed and washed free of I_2 with 10.00-ml aliquots of 0.0606 *N* $Na_2S_2O_3$, which were titrated against 0.0505 *N* KI_3 to determine the amount of I_2 released. Uv spectra were taken before and after each wash to determine both the quantity of I_2 released and *A* at 444 and 280 nm for calculation of **3** surviving. Figure 2 shows the results from both the spectrophotometric and titrimetic analyses of I_2 released, and the remaining concentration of **3** as followed by decrease in *A* at 444 and 280 nm.

B. With Piperidine.—A solution of **3** prepared (procedure B) by adding 0.027 mol of I_2 in CCl_4 (5°) to 0.076 mol of pulverized **2** in CCl_4 (5°), shaking for 1 min, filtering, and washing with $Na_2S_2O_3$ solution and then with water was added over 1 hr to piperidine (0.1 mol) in CCl_4 and 160 ml of aqueous 0.1 *N* buffer (pH 7). Nmr spectra of the CCl_4 solution taken initially, when one-half of the **3** had been added, and at the end of the addition showed the sharp singlet of **3** (δ 1.45) disappearing as the sharp singlet of **5** (δ 1.18) appeared. Uv spectra of the initial solution showed the characteristic absorption of **3** (λ_{max} 444 nm), but uv spectra of the final solution showed no λ_{max}, only end absorption. The organic layer was washed twice with H_2O and dried (Na_2SO_4). Evaporation of solvent left 4.2 g of yellow-orange liquid (90%, calcd as **5**). Glpc indicated the liquid to be virtually pure by comparison with retention times and areas of **4** and authentic N-(*t*-butylthio) piperidine (**5**),[19a,29] $n^{28}D$ 1.4759 (lit.[27b] $n^{20}D$ 1.4765); only the boiling point of **5** was reported by Rheinboldt and Motzkus.[11] The mass spectrum was essentially identical with that of authentic **5**.[19a,29]

C. With Sodium N,N-Dimethyldithiocarbamate.—According to procedure B, 475 ml of 0.142 *M* I_2 (67.4 mmol) in methylcyclohexane was added in one portion to 21 g (106.6 mmol) of **2** with vigorous stirring below −20°. Solid was removed, and the filtrate was added at ~25° (1 hr) to 20 g (140 mmol) of sodium N,N-dimethyldithiocarbamate in 150 ml of H_2O. The mixture was stirred overnight, and the organic layer was washed with H_2O and evaporated. Recrystallization of the residue from MeOH (Dry-Ice cooling) gave 3.75 g (27%) of *t*-butyl N,N-dimethyltrithiopercarbamate (**6**), mp and mmp 70–71°, lit.[30] mp 70–71°; the ir and nmr spectra were identical with those of authentic **6**.[30]

Stability and Reactivity of 3. A. Effect of Ambient Light and Temperature.—A solution of 1.0 ml (~0.01 mol) of **1** in CCl_4 (500 ml) was added (procedure E) to I_2 (10 g, 0.04 mol) and H_2O (100 ml). The mixture was stirred (5 min), filtered, and washed free of I_2 as usual. The concentration of **3** (from A_{444} 1.41, assuming ϵ_{444} 75) was 0.0188 *M*. The solution was placed in three glass-stoppered Pyrex flasks. One (foil-wrapped) flask was stored at −12°; another (foil-wrapped) was stored at ~25°; the third was stored at ~25° in ambient light. Periodically, samples from each were washed with 0.05 *N* $Na_2S_2O_3$ and water; A_{444} was obtained to determine the concentration of **3**. Figure 3 records the results.

B. Effect of Reagents.—A solution like that in part A (but 0.0180 *M* in **3**) was divided into four 100-ml portions, stored in the dark, and vigorously stirred respectively with 100 ml of H_2O, 100 ml of 0.1 *N* KI, 100 ml of 0.1 *N* KI_3, and 100 ml of 0.1 *N* $Na_2S_2O_3$. Samples taken periodically from each were washed with 0.05 *N* $Na_2S_2O_3$ and H_2O (H_2O alone for the solution with the $Na_2S_2O_3$); the concentration of **3** then was determined from A_{444}, with the results shown in Figure 3 for $Na_2S_2O_3$ and KI_3. The H_2O and KI effected no significant change during the period of study.

C. Effect of Concentration.—Part of a solution like that in part A (but 0.192 *M* in **3**) was diluted to 0.0036 *M* (~53-fold, necessitating the use of "Log [$(CH_3)_3CSI$]" for Figure 3). The original and diluted solutions were stored in the dark at ~25° in glass-stoppered flasks. The concentration of **3** was followed by washing samples periodically with 0.05 *N* $Na_2S_2O_3$ and H_2O and observing A_{444}, with the results shown in Figure 3.

D. Structural Considerations. 1. Attempted Synthesis of 1-Butanesulfenyl Iodide and 2-Butanesulfenyl Iodide.—Silver 1-butanethiolate and 2-butanethiolate were prepared fresh by adding NaOAc·$3H_2O$ (6.7 g, 0.05 mol) and the thiol (4.9 g, 0.05 mol) in H_2O (25 ml) to $AgNO_3$ (8.5 g, 0.05 mol) in H_2O (25 ml); the precipitates were washed with H_2O, EtOH, and Et_2O and then were dried at 0.1 mm overnight. To 10.00 ml of 0.0298 *N* I_2 (0.298 mequiv) in methylcyclohexane in a foil-covered centrifuge tube, capped with a rubber septum, and cooled in Dry Ice there was added 0.1122 g (0.569 mmol; the excess was used to minimize residual I_2, which would interfere with later measurements) of silver 1-butanethiolate (procedure A). The contents were shaken 1 min and centrifuged. The supernatant liquid was withdrawn immediately (purple, presumably indicating some unreacted I_2). Without the usual contact with $Na_2S_2O_3$ or H_2O, the solution was quickly diluted and analyzed by uv. Only λ_{max} 520 nm (for I_2) was observed (*A* 1.620). The cuvette then was irradiated for 5 min; the uv spectrum then still showed only a λ_{max} for I_2 (A_{520} 1.332). Since the absorbance of I_2 did not increase upon irradiation, as is characteristic of **3**, 1-butanesulfenyl iodide seems unlikely to have been present. Furthermore, when some of the initial solution was washed with $Na_2S_2O_3$, color was completely removed (similar solutions of **3** were orange-red). When the time of reaction was extended to allow all I_2 just to be consumed (~2 min), the supernatant solution was completely colorless and irradiation had no effect. Identical results were obtained with 0.1012 g (0.514 mmol) of silver 2-butanethiolate.

2. Triphenylmethanesulfenyl Iodide.—Triphenylmethanethiol (2.00 g, 7.25 mmol) in 125 ml of CCl_4 was added (~25°) to 10 g (40 mmol) of I_2 and 75 ml of H_2O. The mixture was shaken for 3 min, washed twice with 0.1 *N* $Na_2S_2O_3$, and twice with H_2O.

(28) L. Field and W. B. Lacefield, *J. Org. Chem.*, **31**, 3555 (1966): **4**, τ 8.65 (s); $(CH_3)_3CSSSC(CH_3)_3$, τ 8.55 (s); solvent not stated.

(29) We thank Dr. N. E. Heimer for a sample of **5**.

(30) L. Field and J. D. Buckman, *ibid.*, **33**, 3865 (1968).

The uv spectrum showed a λ_{max} of 440 nm (only, except for the typical end absorption of **3** in CCl_4, Figure 1) with A_{440} being 6.78≙ (0.424, corrected for dilution of 0.20 to 3.20 ml). The entire 125-ml solution was photolyzed in a quartz flask attached to a reflux condenser for 20 min. Appearance of a new λ_{max} at 520 nm indicated formation of I_2. A 10.00-ml aliquot of the resulting solution was washed with 15.00 ml of 0.0559 *N* $Na_2S_2O_3$, which then consumed 8.52 ml of 0.0508 *N* KI_3, indicating the formation of 5 mequiv of I_2 presumably from 5 mequiv of sulfenyl iodide (yield, at least ~70%).

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Coupling, Carbonylation, and Vinylation Reactions of Aromatic Sulfinic Acids *via* Organopalladium Intermediates

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The expulsion of sulfur dioxide from arenesulfinic acids and their salts by palladous salts in a variety of solvents is reported. The aryl groups couple to form a biaryl in 35% yield, and Pd^{2+} is reduced to metallic palladium. Mercuric chloride acts as a catalyst and doubles the yield of the biaryl. The reaction presumably proceeds by formation of an arylpalladium complex. In the presence of carbon monoxide, olefins, or nitriles insertion reactions take place leading to carbonylation, vinylation, or acylation of arenesulfinate anions in low to medium yields.

Recently the formation of arylpalladium complexes from arylmercuric chloride and palladium chloride was postulated.[1] Owing to the low stability of the organometallic intermediate only the products of subsequent reactions, biaryls and palladium metal or insertion products in the presence of CO or olefins, were isolated. Likewise, benzeneboronic acid and palladium acetate yielded biphenyl and palladium metal,[2] presumably *via* a phenylpalladium complex obtained by electrophilic displacement of boron. Substitution of aromatic hydrogen by palladium salts to give similar intermediates was considered as a first step in coupling reactions of benzene and toluene.[2-4] The present work was undertaken in order to explore whether arylpalladium complexes could be prepared by desulfination of aromatic sulfinic acids. Sulfur dioxide eliminations of arenesulfinate complexes of transition metals have been reported,[5,6] and the preparation of arylmercuric chlorides from aromatic sulfinic acids and mercuric chloride (eq 1) has been known since 1905.[7]

$$ArSO_2H + HgCl_2 \xrightarrow[78°]{H_2O\text{-}EtOH} ArHgCl + SO_2 + HCl \quad (1)$$

Attempts to replace $HgCl_2$ by thallic chloride in reaction 1 were unsuccessful.[8] Crystalline palladium arenesulfinate complexes have been prepared,[9,10] but their chemistry was not explored.

The present work shows that the addition of palladium salts to aromatic sulfinic acids in heated solution leads to evolution of sulfur dioxide, most likely by an electrophilic substitution process. The expected decomposition products of the presumed arylpalladium intermediates, namely biaryls and palladium metal, were isolated. In Table I the experimental conditions and results of this new coupling reaction of sulfinic acids are summarized. The biaryls formed (biphenyl or *p,p'*-bitolyl) were identified by melting point, mixture melting point, ir, and glpc. Accordingly, the main reaction can be expressed as in eq 2. The yields

$$2ArSO_2Na + Na_2PdCl_4 \longrightarrow ArAr + 2SO_2 + Pd + 4NaCl \quad (2)$$

of the by-products, aromatic hydrocarbon, arylchloride, and various sulfur products, depend strongly upon solvent and anion. Benzylacetate formed in entry 7 is a secondary product, derived from oxidation of toluene.

Mercuric chloride catalyzed the coupling reaction of aromatic sulfinic acids in aqueous solution, as reflected in the higher conversions to biaryls in Table II. The production of *p*-bromotoluene in entry 7, apparently derived by a ligand transfer reaction, prompted attempts to synthesize other *para*-substituted toluenes from *p*-toluenesulfinic acid, palladium chloride, and certain anions. However, experiments involving the anions $X^- = F^-$, CN^-, OCN^-, N_3^-, or NO_2^- did not yield any $p\text{-}CH_3C_6H_4X$. Entry 8 shows that a catalytic amount of palladium salt is sufficient in the presence of a reoxidizing agent like cupric chloride.

The intermediate formation of arylpalladium complexes in the desulfination of arenesulfinic acids with $PdCl_2$ was further substantiated by isolating the expected[1b] insertion products with carbon monoxide and olefins. The conversions in Table III again reflect strong solvent effects. Only the double insertion products (two *p*-tolyl groups per olefin) were formed with 1 atm of ethylene (entries 3 and 4). Occasionally the solvent added to the initial olefin or the olefinic product (entries 3, 5, and 8). The last two reactions represent additions of the *p*-tolylpalladium complex into CN triple bonds, a new type of insertion reaction of transition metal aryl complexes. The ketones isolated are

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TABLE I
REACTIONS OF ARENESULFINIC ACIDS WITH PALLADIUM(II) SALTS[a]

Entry	Sulfinate	Pd Salt	Solvent	Temp., °C	Conversion to biaryl, %	Conversion to other products
1	$C_6H_5SO_2Na$[b]	Na_2PdCl_4	H_2O	100	35	3.5% $ArSO_2SAr$, 1% ArCl
2	p-$CH_3C_6H_4SO_2H$	Na_2PdCl_4[c]	H_2O-EtOH	81	27	0.7% Ar_2S
3	p-$CH_3C_6H_4SO_2Na$[d]	Na_2PdCl_4	H_2O	100	19	Trace of Ar_2S
4	p-$CH_3C_6H_4SO_2Na$[d]	Na_2PdCl_4	EtOH	79	27	Traces of Ar_2S, ArCl
5	p-$CH_3C_6H_4SO_2Na$[d]	Na_2PdCl_4	HOAc	116	36	
6	p-$CH_3C_6H_4SO_2Na$[d]	Na_2PdCl_4	CF_3COOH	71	1.7	15% Ar_2S, toluene
7	p-$CH_3C_6H_4SO_2Na$[d]	$Pd(OAc)_2$	HOAc	116	9.5	22% $C_6H_5CH_2OAc$, sulfur products

[a] 0.01 mol of Pd salt and 0.02 mol of sulfinate in 40 ml of solvent. [b] All ingredients heated together. [c] Pd salt solution (20 ml) added dropwise to the boiling sulfinate solution (20 ml). [d] Sulfinate solution (20 ml) added dropwise to the boiling solution of the Pd salt.

TABLE II
REACTIONS OF ARENESULFINIC ACIDS WITH PALLADIUM(II) SALTS AND MERCURIC CHLORIDE[a]

Entry	Sulfinate	Pd Salt	Solvent	Temp, °C	Conversion to biaryl, %	Conversion to other products
1	$C_6H_5SO_2Na$[b]	Na_2PdCl_4	H_2O	100	71	2% $ArSO_2SAr$, trace of ArCl
2	p-$CH_3C_6H_4SO_2Na$	Na_2PdCl_4[c]	H_2O	100	61	1% Ar_2SO_2
3	p-$CH_3C_6H_4SO_2Na$[d]	Na_2PdCl_4	H_2O	100	63	Traces
4	p-$CH_3C_6H_4SO_2Na$[d]	Na_2PdCl_4	CH_3OH	66	23	
5	p-$CH_3C_6H_4SO_2Na$[d]	Na_2PdCl_4	HOAc	116	28	
6	p-$CH_3C_6H_4SO_2Na$[d]	$Pd(OAc)_2$	H_2O	100	26	9% Ar_2S, 2% Ar_2SO_2
7	p-$CH_3C_6H_4SO_2Na$[d]	$Na_2(PdBr_2Cl_2)$	H_2O	100	51	9% ArBr, traces
8	p-$CH_3C_6H_4SO_2Na$[d]	Na_2PdCl + $CuCl_2$[e]	H_2O	100	380	

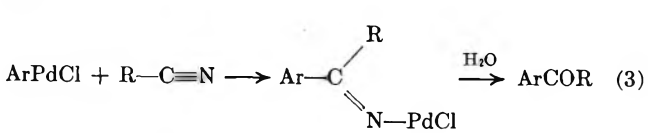
[a] 0.01 mol of Pd salt, 0.02 mol of sulfinate, and 0.001 mol of $HgCl_2$ in 40 ml of solvent. [b] All ingredients heated together. [c] Pd salt solution (20 ml) added dropwise to the boiling sulfinate solution (20 ml). [d] Sulfinate solution (20 ml) added dropwise to the boiling solution of the other ingredients (20 ml). [e] 0.001 mol of Pd salt and 0.01 mol of $CuCl_2$.

TABLE III
REACTIONS OF p-TOLUENESULFINATE ANION AND PALLADIUM(II) SALTS WITH DOUBLE AND TRIPLE BONDS[a]

Entry	Pd Salt	Compound with multiple bond	Solvent	Temp, °C	Conversion to p,p'-bitolyl, %	Conversion to insertion product	Conversion to other products
1	Na_2PdCl_4[b]	CO	CH_3OH	66	Trace	29% $ArCOOCH_3$, 5% Ar_2CO	1.4% ArCl, 1.8% Ar_2S
2	Na_2PdCl_4[b]	CO	H_2O	100	27	2% ArCOOH, 10% Ar_2CO	Traces
3	Na_2PdCl_4[b]	C_2H_4	CH_3OH	63	Trace	11% ArCH=CHAr (*trans*), 30% $ArCH(CH_3)OCH_3$	12% $ArCH(OCH_3)CH_2Ar$, traces
4	Na_2PdCl_4	C_2H_4	CH_3CN-H_2O	76	Trace	48% ArCH=CHAr (*trans*)	Traces
5	Li_2PdCl_4	i-C_4H_8	$(CH_3)_2CO$-H_2O	63	4	25% $ArCH=C(CH_3)_2$, 20% $ArCH(OH)CH(CH_3)_2$	Traces
6	Na_2PdCl_4[b]	c-C_5H_8	EtOH	58	Trace	28% Ar-  + isomers	Traces
7	Na_2PdCl_4[b]	c-C_6H_{10}	EtOH	71	Trace	22% Ar-  + isomers	Traces
8	Na_2PdCl_4[b]	$PhCH=CH_2$	CH_3OH	66		47% ArCH=CHPh (*trans*)	17% $PhCH(CH_3)OCH_3$, 44% $PhCH_2CH(OCH_3)_2$
9	Li_2PdCl_4[b]	$Ph_2C=CH_2$	Dioxane-H_2O	91		33% $ArCH=CPh_2$	1.7% Ph_2CO, traces
10	Na_2PdCl_4	$CH_3C\equiv N$	CH_3CN-H_2O	80	18	14% $ArCOCH_3$	Traces
11	Li_2PdCl	$PhC\equiv N$	PhCN-H_2O	100	Trace	4% ArCOPh	68% $PhCONH_2$

[a] 0.01 mol of Pd salt and 0.05 mol of olefin in 20 ml of solvent were added dropwise to the boiling solution of 0.01 mol of the sulfinate (20 ml). Gaseous olefins and CO were introduced continuously at 1 atm. [b] In the presence of 0.001 mol of $HgCl_2$.

subsequently formed during the aqueous–acidic work-up (eq 3).



Experimental Section

All chemicals were of reagent grade quality and used without further purification. The sulfinates were obtained from K & K Laboratories. Experimental procedures are given in the Tables. Additions of one reagent to another took 1–6 hr and were followed by a reflux period of 1–16 hr. Conversions were not affected by the duration of the reactions. Work-up consisted

of removal of the solution from the palladium metal precipitate, extraction of organic products into ether, washing, drying, and evaporation of the ether. The products were analyzed by glpc on a 2-ft column of 20% SE-60 (silicon rubber) on Chromosorb W, at 100° + 15°/min to 290° with 30 cc of He/min. Samples of pure products (of Table III) were obtained by recrystallization, distillation, and/or preparative glpc and identified by melting point, ir and nmr spectra, and mass determination. The identity of chromatographically pure biaryls was confirmed by melting point, mixture melting point, ir and nmr spectra. In addition, the purity of *p,p'*-bitolyl was proved by glpc on a 15-ft column of 5% Apiezon N on Chromosorb W, operated at 225° with 60 cc of He/min, which separated all $C_{14}H_{14}$ isomers. Conversions were based on palladium salt and obtained from glpc peak areas.

Registry No.—$C_6H_5SO_2Na$, 873-55-2; *p*-$CH_3C_6H_4SO_2Na$, 824-79-3; Na_2PdCl_4, 13820-53-6; $Pd(OAc)_2$, 3375-31-3; $Na_2(PdBr_2Cl_2)$, 25637-01-8; Li_2PdCl_4, 15525-45-8.

Stereochemistry of Amine Additions to Acetylenic and Allenic Sulfones and Sulfoxides

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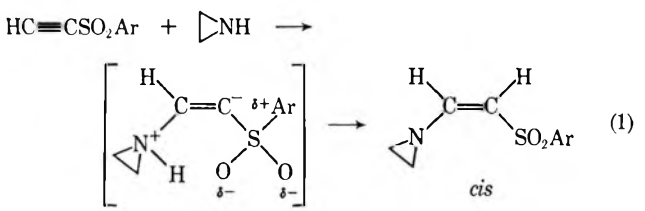
Additions of ethylenimine to *nonterminal* acetylenic sulfones and sulfoxides ($RC{\equiv}CSO_2R'$ and $RC{\equiv}CSOR'$) proceed nonstereoselectively to give mixtures of conjugated adducts. Allenic sulfones and sulfoxides react with ethylenimine to give the nonconjugated adducts, which do not isomerize under the reaction conditions to the conjugated adducts. A solvent effect and a temperature effect show the *trans* addition process to be kinetically favored and the *cis* process to give the more stable *trans* adduct. Both the R and R' groups in $RC{\equiv}CSO_2R'$ affect the *cis–trans* ratio of adducts in the ethylenimine additions. Theories to explain these results are given.

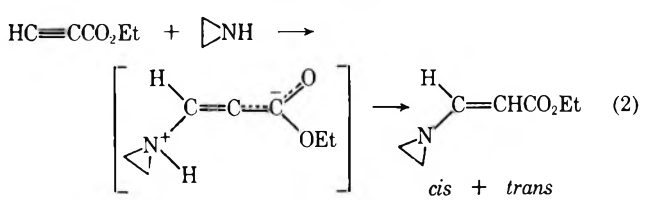
Several years ago, a study in this laboratory of the stereochemistry of additions of amines to acetylenic sulfones and carboxylic esters was reported.[1] This and other work in the area of amine additions to activated acetylenes registered over the last few years, was facilitated by the utility of nmr analysis for configurational determinations[1-3] and the unique advantage of ethylenimine as a nucleophile in producing adducts which resist *cis–trans* isomerization under the reaction conditions.[1,3,4] For example, ethylenimine adds to *p*-tolylsulfonylacetylene giving ≥95% *cis*-1-ethylenimino-2-(*p*-tolylsulfonyl)ethene (eq 1) while simple



(1)

secondary amines as well as primary amines give the *trans* adduct *via* isomerization of the initially produced *cis* isomer.

Ethyl and methyl propiolate undergo nonstereoselective addition with ethylenimine giving both *cis* and *trans* adducts.[1,3,4] It was suggested[1] that the ethyl propiolate–ethylenimine addition involves the formation of a dipolar intermediate which has a linear resonance stabilized carbanion center (eq 2). Protonation from

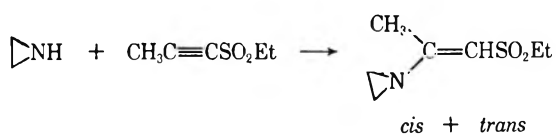


(2)

either side accounts for the nonstereoselectivity of the addition. It was proposed that the *p*-tolylsulfonyl-acetylene–ethylenimine intermediate has an angular carbanion center with the *cis* configuration being stabilized by electrostatic and/or hydrogen-bonding forces (eq 1), thereby accounting for predominant *trans* addition.

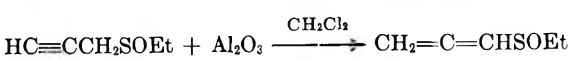
Results and Discussion

Amine additions to *nonterminal* acetylenes of the form $RC{\equiv}CZ$ (where R = CH_3 and CH_2CH_3 and Z = SO_2Et, $SO_2C_6H_4CH_3$-*p*, and SOEt) needed careful examination and constitute part of the basis for this report. In the nonstereoselective reaction, there was the possibility that isomerization and subsequent addition to the allene, $CH_2{=}C{=}CHSO_2Et$, was competing



with addition to the conjugated acetylene.[1,2] Hence the nature of additions of ethylenimine to two allenic sulfones and an allenic sulfoxide as well as two propargyl sulfones and one propargyl sulfoxide was studied and is described herein.

Allenic sulfones have been prepared by isomerization of the propargyl sulfones with either triethylamine or basic alumina.[2,5] Allenic sulfoxides have not been reported, but we have found them to be accessible also in this manner (eq 3). The propargyl and 1-propynyl



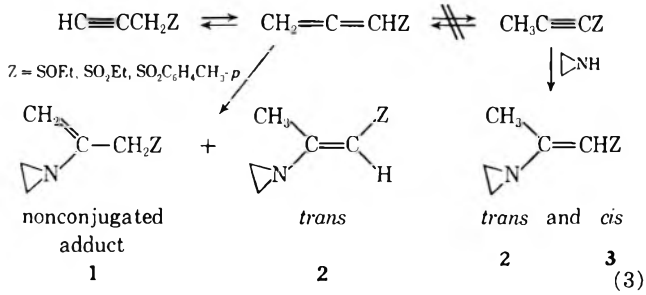
(3)

sulfoxides were prepared by oxidation of the corresponding sulfide with 1 equiv of sodium metaperiodate or 1 equiv of *m*-chloroperbenzoic acid.

Addition of ethylenimine to the allenic and propargylic sulfones and sulfoxides led to the formation of the nonconjugated adduct, by 1,2 addition to the allene directly or through initial isomerization of the

(1) W. E. Truce and D. G. Brady, *J. Org. Chem.*, **31**, 3543 (1966).
(2) C. J. M. Stirling, *J. Chem. Soc., Suppl. I*, 5863 (1964).
(3) J. E. Dolfini, *J. Org. Chem.*, **30**, 1298 (1965).
(4) R. Huisgen, B. Giese, and H. Huber, *Tetrahedron Lett.*, 1883 (1967).
(5) S. T. McDowell and C. J. M. Stirling, *J. Chem. Soc. B*, 351 (1967).

propargyl system to allene. In some systems small amounts of the *trans* conjugated adduct formed by 2,3 addition to the allene (eq 4) were obtained (allenic



(3)

nitriles have also been shown to add amines in both 1,2 and 2,3 fashion[6]). As shown in Table I, the ratio of

TABLE I

ADDITION OF ETHYLENIMINE TO $CH_2{=}C{=}CHZ$ AND/OR $HC{\equiv}CCH_2Z$

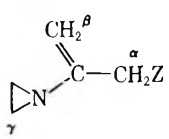
Z	Solvent	Reaction time, hr — Allene	Acetylene	% of 1	Mp or bp (mm) of 1, °C	% of 2
SOEt	C_6H_6	6	...[a]	77	81–84	23
	EtOH	24	24	100	(0.20)	
SO_2Et	C_6H_6	4[b]	4	100	64–65.5	
	EtOH	4[b]	4	100		
$SO_2C_6H_4CH_3$-*p*	C_6H_6	4	4	94	69.5–70.5	6
	EtOH	4	4	93		7

[a] The reaction was very slow. After 72 hr, there was only 6% of the product present. [b] A mixture of 78% ethylsulfonylpropadiene and 22% 3-ethylsulfonylpropyne was used.

nonconjugated to conjugated adducts is solvent dependent. The nmr spectra of the nonconjugated adducts given in Table II support the structural

TABLE II

NMR DATA FOR



Z	α[a]	β[a]	γ[a]
SOEt	3.55	4.57 and 4.63	1.92
SO_2Et	3.73	4.58 and 4.68	1.88
$SO_2C_6H_4CH_3$-*p*	3.87	4.38 and 4.45	1.75

[a] Positions given in parts per million (δ) in $CDCl_3$ relative to TMS. The α, β, and γ peaks all appeared as singlets.

assignments. In comparing the ir spectra of the conjugated and nonconjugated adducts, one finds as expected the olefinic stretching vibration shifted about 50 cm^{-1} lower in the conjugated isomers from that in the nonconjugated.

That the 2,3 adduct (2) does not arise by isomerization of the 1,2 adduct (1) was shown by treating the pure nonconjugated ethylenimine adducts with ethylenimine in both ethanol and benzene; the starting adducts 1 were recovered unchanged. Resistance of adducts 1 to isomerization under reaction conditions rules out an allenic intermediate in the addition of ethylenimine to *nonterminal* acetylenic sulfones and sulfoxides, which yield only conjugated adducts 2 and 3. Also, this change in product composition indicates that, although ethylenimine can isomerize the propargyl systems to the allenes, further isomerization to the *nonterminal* 1-propynyl compounds does not compete with the addition process (eq 4).

Having ruled out an allene intermediate in the nonstereoselective addition of ethylenimine to 1-ethylsulfonylpropyne, it was of interest to study additions to other 1-propynyl sulfones and sulfoxides to gain more knowledge about the addition process. A temperature effect was found to be operative in the ethylenimine additions to *nonterminal* sulfones and sulfoxides and examples of such may be found in Tables III and IV.

TABLE III

TEMPERATURE EFFECT IN THE ADDITION OF ETHYLENIMINE TO $CH_3C{\equiv}CSOEt$ IN BENZENE

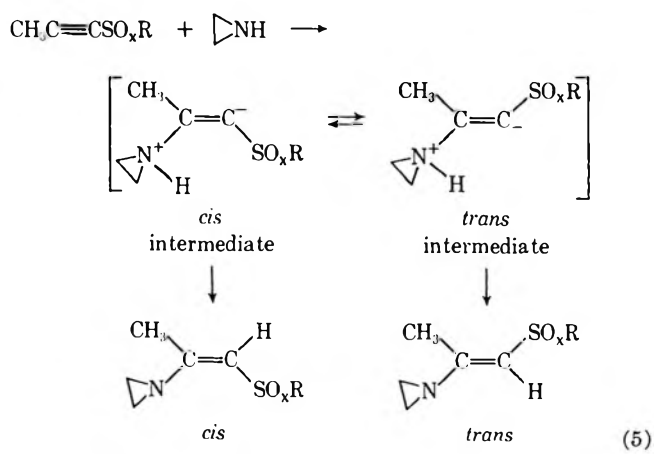
Temp, °C	Reaction time, hr	Configuration, % — *cis*	*trans*
53–54	6	22	78
26–27	6	40	60
3–5	96	66	34

TABLE IV

TEMPERATURE EFFECT IN THE ADDITION OF ETHYLENIMINE TO $CH_3C{\equiv}CSO_2C_6H_4CH_3$-*p* IN BENZENE

Temp, °C	Reaction time, hr	Configuration, % — *cis*	*trans*
53–54	4	31	69
24–25	4	80	20
2–5	96	83	17

Postisomerization does not account for the differences in product compositions, since treating the product mixture, obtained under one set of conditions, with ethylenimine in benzene at a different set of time and temperature conditions resulted in no change in the ratio of *cis–trans* isomers. These results suggest that the *trans* addition process giving *cis* adduct is the kinetically controlled process while *cis* addition yielding *trans* product is thermodynamically more favored. A mechanism incorporating these results involves formation of angular dipolar intermediates, one with a *cis* arrangement of amino and sulfonyl or sulfinyl groups and a second with a *trans* arrangement (eq 5). Protonation



(5)

of the *cis* intermediate gives the *cis* adduct and kinetic control. The *cis* intermediate may alternatively isomerize to the *trans* intermediate; subsequent protonation affords the *trans* adduct, which as will be shown later is the more stable of the two adducts.

(6) P. M. Greaves and S. R. Lander, *Chem. Commun.*, 322 (1966).

The formation of the *trans* intermediate occurs by one of two pathways, direct isomerization of the *cis* intermediate or equilibration of the *cis* intermediate with the starting acetylene and readdition to the acetylene.

Temperature and solvent dependent isomerization of vinyl carbanions has been found to occur in systems such as 1,2-diphenylvinyllithium where the *cis* isomer isomerizes to the more stable *trans* isomer. However, in other systems such as the *cis*- and *trans*-propenyllithiums, both isomers were shown to be quite stable.[7] Montanari and coworkers[8] have reported exchanging *cis*- and *trans*-β-arylsulfinyl- and β-arylsulfonylacrylic acid with sodium deuterioxide in deuterium oxide with complete retention of configuration, suggesting the arylsulfinyl- and arylsulfonylvinyl carbanions do not isomerize under the conditions employed. However, the conditions employed by Montanari would favor retention of configuration owing to facile deuteration of the vinyl carbanion formed and therefore it is not possible to favor one mode of isomerization over the other in the ethylenimine–acetylene additions with the data at hand.

The mechanism (eq 5) accounts not only for the temperature effect but also for an observed solvent effect. As shown in Tables V and VI, solvent effects

TABLE V

REACTION OF ETHYLENIMINE WITH $CH_3C{\equiv}CSO_2C_6H_4CH_3$-*p*

Solvent	Reaction time, hr	Temp, °C	Configuration, %[a] *cis*	*trans*
DMSO	4	24–25	68	32
Et_2O	4	24–25	74	26
C_6H_6	4	24–25	80	20
CCl_4	4	24–25	81	19
EtOH	4	24–25	58	42

[a] The ratios of *cis*–*trans* isomers were determined by nmr analysis on the crude reaction mixtures. The reactions were complete after 4 hr with quantitative yields of the adducts as shown by nmr.

TABLE VI

REACTION OF ETHYLENIMINE WITH $CH_3C{\equiv}CSOEt$

Solvent	Reaction time, hr	Temp, °C	Configuration, %[a] *cis*	*trans*
DMSO	6	26–27	16	84
Et_2O	6	26–27	31	69
C_6H_6	6	26–27	40	60
CCl_4	6	26–27	48	52
EtOH	24	24–26	86	14

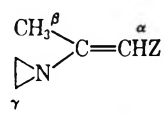
[a] The ratios of *cis*–*trans* isomers were determined by nmr analysis on both the crude reaction mixture and the purified liquid. There was no difference between the crude ratio and the purified. As shown by nmr, the reaction yields were quantitative.

were observed in the nonstereoselective additions of ethylenimine to 1-*p*-tolylsulfonylpropyne and 1-ethylsulfinylpropyne. Solvent effects were also observed in the additions of ethylenimine to 1-ethylsulfonylpropyne,[1] ethyl propiolate,[1,3] and methyl propiolate.[4] The mixture of adducts obtained in one solvent was treated with 1 equiv of ethylenimine in another solvent but there was no change in the ratio of *cis*–*trans* isomers showing there to be no postisomerization of the ethylenimine adducts as was observed with other secondary and primary amines.[1] In the aprotic solvents studied, the greatest amount of *trans* product (*cis* addition) was formed in dimethyl sulfoxide. This may be explained on the basis that dimethyl sulfoxide (having a high dielectric constant) can stabilize the zwitterionic intermediates best, and there is less stabilization of the ammonium moiety by the sulfonyl or sulfinyl groups in the *cis* intermediate shifting the equilibrium to the right in favor of the *trans* intermediate. In a protic solvent, ethanol, rapid proton abstraction from solvent giving kinetic control competes with the stabilization of the intermediates by this polar solvent.

The *cis* and *trans* configurations in the conjugated adducts were assigned on the basis of nmr analysis. The pertinent nmr data are given in Table VII and the

TABLE VII

NMR DATA FOR



Z	α[a] *cis*	*trans*	β[a] *cis*	*trans*	γ[a] *cis*	*trans*
SOEt	5.40	5.55	2.00	2.20	2.05	1.90
SO_2Et	5.37	5.53	1.90	2.25	2.29	2.05
$SO_2C_6H_4CH_3$-*p*	5.51	5.68	1.85	2.20	2.24	1.95
$SO_2CH_2C_6H_5$	5.19	5.38	1.80	1.73	2.15	1.85
$SO_2CH_2CH_2C_6H_5$	5.35	5.47	1.85	2.22	2.25	1.91

[a] Positions given in parts per million (δ) in $COCl_3$ relative to TMS. The α, β, and γ peaks were all singlets.

chemical shifts are similar to those previously published.[1,2] With the 1-benzylsulfonyl-2-(ethylenimino)-propene isomers, the methyl propenyl protons are shifted upfield in the *trans* isomer from those in the *cis*. This may be due to shielding of these protons by the aromatic ring in the *trans* isomer shifting them upfield relative to the *cis*.[9]

Two isomeric intermediates are suggested for the ethylenimine additions to acetylenic sulfones and sulfoxides while a single intermediate has been proposed for the reactions of ethylenimine with methyl and ethyl propiolate (eq 2). If indeed such differences do exist, one would not expect to find a temperature effect on the ratio of *cis*–*trans* isomers in the addition of ethylenimine to methyl propiolate. As shown in Table VIII, there was no temperature effect observed.

TABLE VIII

REACTION OF ETHYLENIMINE WITH $HC{\equiv}CCO_2Me$ IN BENZENE

Temp, °C	Reaction time, hr	Configuration, % *cis*	*trans*
54–55	5	7	93
25–26	5	9	91
3–6	72	9	91

The temperature effect in the ethylenimine additions to *nonterminal* acetylenic sulfones and sulfoxides suggests that the *trans* adduct (*cis* addition) is the more stable isomer. It has been shown that other secondary

(7) (a) A. N. Nesmeyanov, A. E. Borisov, and N. A. Vol'kenau, *Izv. Akad. Nauk SSR, Otd. Khim. Nauk*, 992 (1954); (b) A. N. Nesmeyanov and A. E. Borisov, *Tetrahedron*, **1**, 158 (1957); (c) D. Y. Curtin, H. W. Johnson, Jr., and E. C. Steiner, *J. Amer. Chem. Soc.*, **77**, 4566 (1955); (d) D. Y. Curtin and J. W. Crump, *ibid.*, **80**, 1922 (1958).

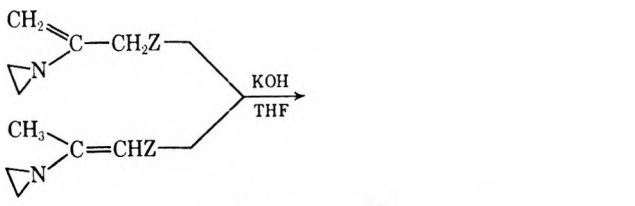
(8) H. Hogeveen, G. Maccagnani, F. Montanari, and F. Taddei, *Boll. Sci. Fac. Chem. Ind. Bologna*, **21**, 259 (1963).

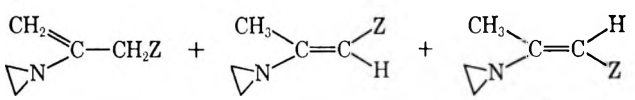
(9) R. C. Pink, R. Spratt, and C. J. M. Stirling, *J. Chem. Soc.*, 5714 (1965).

amines give only the *trans* adduct upon addition to acetylenic sulfones *via* initial *trans* addition giving the *cis* adduct which undergoes isomerization to the final product.[1] The ethylenimine adducts of the acetylenic sulfones and sulfoxides may be isomerized with potassium hydroxide in THF at room temperature giving the mixture shown in Table IX. Both the nonconjugated

TABLE IX

ISOMERIZATION OF NONCONJUGATED AND CONJUGATED ADDUCTS





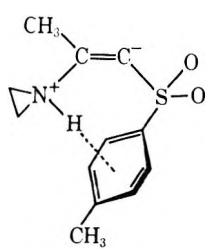
nonconjugated adduct 1 | *trans* 2 | *cis* 3

Z	Reaction time, hr	% yield[a]	% 1 in (1 + 2 + 3)	% 2 in (2 + 3)	% 3 in (2 + 3)
SOEt	48	69	12	88	15
SO_2Et	12	67	9	91	9
$SO_2C_6H_4CH_3$-*p*	30	80	7	95	5
$SO_2CH_2C_6H_5$	12	93	0	93	7
$SO_2CH_2CH_2C_6H_5$	12	91	6	87	13

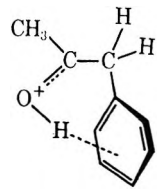
[a] The yields given were those obtained in the isomerization of the conjugated adducts. Similar results were obtained with the nonconjugated adducts.

and conjugated adducts give the same equilibrium mixture, with the *trans* conjugated adducts being the predominate isomer.

In comparing the ratios of *cis*–*trans* isomers obtained in the additions of ethylenimine to 1-*p*-tolylsulfonylpropyne and 1-ethylsulfonylpropyne, one finds quite a difference with the *p*-tolyl system giving more *cis* adduct in aprotic solvents while the ethyl system yields mostly *trans* product. The R′ group in $CH_3C{\equiv}CSO_2R'$ must therefore play a part in the determination of the overall stereochemistry. Models of the *cis* intermediate formed in the ethylenimine addition to 1-*p*-tolylsulfonylpropyne show the aromatic ring within π-hydrogen-bonding distance of the ammonium center, as shown.



This interaction may be similar to the participation depicted by Winstein and Levy in their study of protonated β-phenyl ketones. The greater population of the *syn* isomer, than predicted on the basis of steric effects, was accounted for on the basis of π-hydrogen bonding in the *syn* isomer.[10]



Models of the *cis* intermediate formed in the addition of the ethylenimine to 1-benzylsulfonylpropyne indicate that a similar neighboring-group effect is possible. If participation by the neighboring aromatic ring occurs, one would expect to find decreasing amounts of *cis* adduct as the aromatic ring is moved farther away from the sulfonyl grouping. As shown in Table X,

TABLE X

REACTION OF ETHYLENIMINE WITH $CH_3C{\equiv}CSO_2R'$ IN BENZENE

R′	Temp, °C	Reaction time, hr	Configuration, % *cis*	Configuration, % *trans*
$C_6H_4CH_3$-*p*	24–25	4	80	20
$CH_2C_6H_5$	28–29	4	72	28
$CH_2CH_2C_6H_5$	28–29	4	36	64
CH_2CH_3	25–26	4	16	84

such an effect is observed. The largest amount of *trans* adduct was obtained with 1-ethylsulfonylpropyne where stabilization of the *cis* intermediate as suggested is of course not possible. Neighboring-group stabilization of the initial dipolar intermediate may also be the basis for the fact that 1-ethylsulfinylpropyne gives greater amounts of *cis* adduct with ethylenimine than does 1-ethylsulfonylpropyne. This may be due to greater interaction of the sulfoxide oxygen *vs.* sulfonyl oxygens with the ammonium center.[11]

It was shown previously that the R group in the $RC{\equiv}CSO_2Et$ series affected the equilibrium mixtures obtained in the addition of *n*-propylamine.[1] As the steric bulk of the R group was increased, the amount of *cis* adduct increased owing to greater steric effects in the *trans* isomer. Such a phenomenon was observed in the additions of ethylenimine to 1-ethylsulfonylpropyne and 1-ethylsulfonyl-1-butyne in an aprotic solvent like benzene; however in ethanol this was not apparent as shown in Table XI. The trend observed in benzene

TABLE XI

REACTION OF ETHYLENIMINE WITH $RC{\equiv}CSO_2Et$

R	Solvent	Temp, °C	Reaction time, hr	Configuration, % *cis*	Configuration, % *trans*
CH_3	C_6H_6	24–25	4	16	84
	EtOH	25–26	4	62	38
CH_3CH_2	C_6H_6	25–26	4	37	63
	EtOH	25–26	4	62	38

may also be explained on the basis of steric interactions, the steric effect being observed in the *trans* intermediate giving more *cis* adduct *via* proton abstraction by the *cis* intermediate. Such an effect is not found in ethanol

(10) G. S. Levy and S. Winstein, *J. Amer. Chem. Soc.*, **90**, 3574 (1968).

(11) (a) C. H. McMullen and C. J. M. Stirling, *J. Chem. Soc., B*, 1217 (1966); (b) H. Hogeveen, G. Maccagnani, and F. Montanari, *J. Chem. Soc., C*, 1585 (1966); (c) M. Cinquini, S. Colonna, and F. Montanari, *Tetrahedron Lett.*, 3181 (1966).

where ready proton abstraction from solvent (*trans* addition) washes out any steric effect by the R group.

In summary, it can be concluded that ethylenimine additions to acetylenic sulfones and sulfoxides involve the formation of two equilibrating and isomeric zwitterionic intermediates while addition to propiolic esters occurs with the formation of a single resonance-stabilized (linear) zwitterionic intermediate. Consistent with these hypotheses are the following facts: (a) the *cis–trans* ratio of adducts formed with *nonterminal* acetylenes is temperature dependent while the *cis–trans* ratio of adducts from methyl propiolate is unaffected by temperature; (b) a solvent effect was operative; (c) the R and R′ groups in $RC{\equiv}CSO_2R'$ affect the *cis–trans* ratio of products. Consistent with these facts is the elimination of a possible isomerization of the 1-propynyl sulfones and sulfoxides to the allene with subsequent addition of ethylenimine.

Work is continuing in this laboratory on further elucidating the factors which control the stereochemistry of amine additions to acetylenes.

Experimental Section[12]

Starting Materials.—Ethylenimine was generously supplied by The Dow Chemical Co. and was stored over caustic soda pellets.

General Procedure for the Preparation of 3-Propynyl Sulfides.—All of the 3-propynyl sulfides were prepared by adding a solution of 1 equiv of the corresponding sodium thiolate in methanol to 1 equiv of propargyl bromide in methanol. After stirring for 2 hr, the reaction mixture was dissolved in water and the aqueous mixture was extracted with methylene chloride. The methylene chloride layers were dried ($MgSO_4$) and concentrated, and distillation gave the 3-propynyl sulfides listed in Table XII.

TABLE XII

PREPARATION OF $HC{\equiv}CCH_2SR$

R	% yield	Bp (mm), °C	Ref
$C_6H_4CH_3$-*p*	77	84–85 (0.45)	*a*
$CH_2C_6H_5$	84	103–108 (7.0)	*b*
$CH_2CH_2C_6H_5$	82	84–87 (0.25)	
CH_2CH_3	65	72–75 (103)	*c*

[a] K. Sato and O. Mujamotto, *Nippon Kagaku Zasshi*, **77**, 1409 (1956). [b] Reference 9. [c] G. Pourcelot and P. Cadiot, *Bull. Soc. Chim. Fr.*, 3016 (1966).

General Procedure for the Preparation of 1-Propynyl Sulfides.—Three of the 1-propynyl sulfides were prepared by isomerization of the 3-propynyl sulfides with potassium hydroxide in THF.[2] After stirring, the potassium hydroxide was filtered off and the solvent was removed *in vacuo*. Distillation afforded the 1-propynyl sulfides given in Table XIII in good yield.

TABLE XIII

PREPARATION OF $CH_3C{\equiv}CSR$

R	% yield	Mp or bp (mm), °C	Ref
$C_3H_4CH_3$-*p*	79	26–28	*a*
$CH_2C_6H_5$	78	116–118 (6.0)	
$CH_2CH_2C_6H_5$	79	77–78 (0.17)	

[a] L. Maioli, G. Modena, and P. E. Todesco, *Boll. Sci. Fac. Chim. Ind. Bologna*, **18**, 66 (1960).

(12) All microanalytical analyses were carried out by Dr. C. S. Yeh and the staff of the Purdue Chemistry Microanalytical Laboratory. Elemental analyses were obtained only in representative cases. All nmr spectra were run on either a Varian A-60 or A-60a spectrometer operating at 60 Mc/sec using TMS as an internal standard. All melting points and boiling points are uncorrected. All infrared spectra were run on a Perkin-Elmer Model 137 B Infracord spectrophotometer. The nmr spectra of the adducts were taken on crude as well as on the purified products to preclude isomerization during purification steps.

1-Ethylthiopropyne.—This compound was prepared according to known procedures[13] by treating *cis*-1,2-bis(ethylthio)ethene with 2 equiv of sodium amide in liquid ammonia followed by addition of 2 equiv of methyl iodide. The colorless product had bp 122–128° (lit.[13] bp 134–144°) and was isolated in 56% yield.

1-Ethylthio-1-butyne.—Treatment of *cis*-1,2-bis(ethylthio)-ethene with 2 equiv of sodium amide in liquid ammonia followed by addition of 2 equiv of ethyl bromide afforded the desired product, bp 60–62° (26 mm) [lit.[1] bp 60–61° (25 mm)].

Preparation of Acetylenic Sulfones.—Oxidation of the acetylenic sulfides to the corresponding sulfones was generally effected in two ways. The first involved adding a solution of 2 equiv of *m*-chloroperbenzoic acid in $CHCl_3$ to 1 equiv of the sulfide in $CHCl_3$ at 0° and then allowing the mixture to stand for 1 day at room temperature. The reaction mixture was washed with a saturated solution of $NaHCO_3$ containing a small amount of Na_2SO_3. The $CHCl_3$ layers were dried ($MgSO_4$) and concentrated, and purification was effected by either recrystallization or by vacuum distillation. The second method used was oxidation of 1 equiv of sulfide with 4 equiv of 30% H_2O_2 in glacial acetic acid. The reaction mixture was gently refluxed for 1.5–2 hr after which time the mixture was added to ice-water. If the product was a solid, it precipitated out and was recrystallized. The liquid sulfones were purified by extracting the aqueous mixture with $CHCl_3$, drying the $CHCl_3$ layers ($MgSO_4$), concentration, and distillation.

3-Ethylsulfonylpropyne.—To 20 g (0.20 mol) of 3-ethylthiopropyne in 250 ml of glacial AcOH was added 83 ml (0.80 mol of peroxide) of 30% H_2O_2 dropwise. After gentle reflux, 500 ml of H_2O was added. The aqueous solution was extracted with $CHCl_3$. Work-up and distillation gave 14 g (53%) of product, bp 74° (0.20 mm) [lit.[14] 90–93° (0.001 mm)].

Anal. Calcd for $C_5H_8SO_2$: C, 45.42; H, 6.11; S, 24.26. Found: C, 45.18; H, 5.88; S, 24.19.

3-*p*-Tolylsulfonylpropyne.—To a solution of 30 g (0.19 mol) of 3-*p*-tolylthiopropyne in 250 ml of glacial AcOH was added slowly 77 ml (0.74 mol of peroxide) of 30% H_2O_2. After reflux, the mixture was poured into 1 l. of ice–water. Recrystallization (EtOH–isopropyl ether) gave 26 g (72%) of product, mp 103–105 [lit.[5] mp 99–100.5].

1-Ethylsulfonylpropyne.—Oxidation of 19.2 g (0.17 mol) of 1-ethylsulfinylpropyne in 100 ml of $CHCl_3$ at 0° with 30 g (0.17 mol) of 85% *m*-chloroperbenzoic acid dissolved in 500 ml of $CHCl_3$ yielded 18.6 g (84%) of product after distillation, bp 92–94° (1.35 mm) [lit.[1] bp 82–83° (0.4 mm)].

1-*p*-Tolylsulfonylpropyne.—To a solution of 27.6 g (0.17 mol) of 1-*p*-tolylthiopropyne in 200 ml of $CHCl_3$ cooled to 0° was added slowly 71 g (0.35 mol of peroxide) of 85% *m*-chloroperbenzoic acid dissolved in 800 ml of $CHCl_3$. After recrystallization (benzene–hexane) there was obtained 26.8 g (81%) of product, mp 98–99° (lit.[5] mp 98–99°).

1-Benzylsulfonylpropyne.—This acetylene was prepared by treating 9.3 g (0.057 mol) of 1-benzylthiopropyne with 24 ml (0.23 mol of peroxide) of 30% H_2O_2 in 200 ml of glacial AcOH. After reflux, work-up, and recrystallization (ethanol), 6.0 g (54%) of product was obtained, mp 75–76.5°.

Anal. Calcd for $C_{10}H_{10}SO_2$: C, 61.82; H, 5.20; S, 16.51. Found: C, 61.84; H, 5.19; S, 16.40.

1-(2-Phenylethylsulfonyl)propyne.—Oxidation of 11.6 g (0.066 mol) of 1-(2-phenylethylthio)propyne in 250 ml of glacial AcOH with 27 ml (0.26 mol of peroxide) of 30% H_2O_2 afforded 7.0 g (51%) of product after distillation, bp 145–147° (0.15 mm). Upon standing the product crystallized, mp 43–45°.

Anal. Calcd for $C_{11}H_{12}SO_2$: C, 63.42; H, 5.82; S, 15.40. Found: C, 63.53; H, 6.03; S, 15.26.

1-Ethylsulfonyl-1-butyne.—As previously prepared,[1] 1-ethylthio-1-butyne (1.8 g, 0.16 mol) in 100 ml of $CHCl_3$ at 0° was treated with 87% *m*-chloroperbenzoic acid (6.4 g, 0.032 mol of peroxide) in 100 ml of $CHCl_3$. Distillation gave 1.6 g (69%) of product, bp 78–80° (0.25 mm) [lit.[1] 87–88° (0.4 mm)].

Preparation of Acetylenic Sulfoxides.—The acetylenic sulfoxides were prepared by oxidation of 1 equiv of sulfide with either 1 equiv of sodium metaperiodate at 0° as previously shown[11a] or 1 equiv of *m*-chloroperbenzoic acid in $CHCl_3$ at 0°.

3-Ethylsulfinylpropyne.—Oxidation was effected by treating 15.7 g (0.157 mol) of 3-ethylthiopropyne in 500 ml of CH_3OH

(13) H. J. Boonstra and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, **79**, 866 (1960).

(14) G. Pourcelot and P. Cadiot, *Bull Soc. Chim. Fr.*, 3024 (1966).

at 0° with 33.6 g (0.157 mol) of sodium metaperiodate. After standing at 0° for 12 hr, the precipitated sodium iodate was filtered off and the filtrate was extracted with CH_2Cl_2. Drying ($MgSO_4$), concentration, and distillation gave 18 g (99%) of product, bp 80–82° (0.25 mm), $n^{26.5}D$ 1.513.

Anal. Calcd for C_5H_8SO: C, 51.69; H, 6.94; S, 27.60. Found: C, 51.87; H, 7.12; S, 27.53.

1-Ethylsulfinylpropyne.—This compound was prepared by treating 12.3 g (0.123 mol) of 1-ethylthiopropyne in 100 ml of $CHCl_3$ at 0° with 25 g (0.123 mol of peroxide) of 85% *m*-chloroperbenzoic acid in 300 ml of $CHCl_3$. The reaction mixture was allowed to stand 24 hr at 0°. The *m*-chlorobenzoic acid was filtered off and the filtrate was washed with a solution of $NaHCO_3$ containing Na_2SO_3. Drying the $CHCl_3$ layers ($MgSO_4$), concentration, and distillation gave 8.8 g (62%) of product, bp 58–61° (0.45 mm), $n^{20}D$ 1.5110.

Anal. Calcd for C_5H_8SO: C, 51.69; H, 6.94; S, 27.60. Found: C, 51.67; H, 7.13; S, 27.59.

Preparation of Allenic Sulfones and Sulfoxides.—The allenic sulfones and sulfoxides were prepared by isomerizing the 3-propynyl sulfones or sulfoxides with either triethylamine or activated alumina as previously published.[5,15]

Ethylsulfonylpropadiene.—This compound was prepared by stirring 4.9 g (0.037 mol) of 3-ethylsulfonylpropyne with 5.8 g (0.057 mol) of triethylamine in 100 ml of C_6H_6 for 1 hr. After concentration and distillation, there was obtained 4.1 g (84%) of product, bp 79–81° (0.15 mm), which consisted of 78% the allenic sulfone and 22% starting material. All attempts to remove the starting material with silver nitrate as in the preparation of ethylsulfinylpropadiene caused formation of 1-ethylsulfonylacetone as shown by nmr and ir.

***p*-Tolylsulfonylpropadiene.**—This compound was prepared by pouring 5.0 g (0.26 mol) of 3-*p*-tolylsulfonylpropyne dissolved in 15 ml of CH_2Cl_2 onto an activated alumina column according to known procedures.[5] Elution gave the allene which was recrystallized (EtOH), mp 89–90° (lit.[5] mp 85–87°).

Ethylsulfinylpropadiene.—This compound was synthesized by stirring 7.0 g (0.06 mol) of 3-ethylsulfinylpropyne with 20 g of activated alumina in 75 ml of CH_2Cl_2 for 4 hr. The alumina was removed by filtration and the solvent was removed *in vacuo*. The residue containing some starting material was poured into 150 ml of 5% $AgNO_3$–95% EtOH and to the milky solution was added 250 ml of H_2O. The clear aqueous mixture was extracted with CH_2Cl_2. The CH_2Cl_2 layers were dried ($MgSO_4$) and concentrated, and distillation gave 3.5 g (50%) of product, bp 68° (1.0 mm).

Anal. Calcd for C_5H_8SO: C, 61.69; H, 6.94; S, 27.60. Found: C, 61.81; H, 6.97; S, 27.20.

General Procedure for Ethylenimine Additions to 1-Propynyl-Sulfones and Sulfoxides.—Most of the reactions were run by dissolving 0.0043 mol of the acetylene in 20 ml of the appropriate solvent and placing the mixture in a previously flamed out 125-ml erlenmeyer flask. To the magnetically stirred mixture at the desired temperature was added 0.0043 mol of ethylenimine by means of a syringe. After stirring for the prescribed length of time, the solvent was removed *in vacuo* at room temperature. Purification was accomplished by recrystallization or distillation. The nmr data given for any crystalline product is that of the crude reaction mixture since recrystallization caused fractionation. Distillation of the liquid adducts did not change the *cis–trans* ratio. All of the reactions gave quantitative yields of aminovinylsulfones or sulfoxides as shown by nmr of the crude reaction mixtures.

1-Ethylsulfonyl-2-(ethylenimino)propene.—To 0.57 g (0.004 3 mol) of 1-ethylsulfonylpropyne in 20 ml of benzene was added 0.19 g (0.0043 mol) of ethylenimine. The reaction afforded 0.46 g (70%) of 16% *cis* and 84% *trans* adducts upon distillation, bp 118–120° (0.30 mm) [lit.[1] 115–118° (0.3 mm)].

1-*p*-Tolylsulfonyl-2-(ethylenimino)propene.—To 0.83 g (0.0043 mol) of 1-*p*-tolylsulfonylpropyne in 20 ml of benzene at 24–25° was added 0.19 g (0.0043 mol) of ethylenimine. There was obtained 0.90 g (88%) of product after recrystallization (benzene–hexane), mp 96–97°.

Anal. Calcd for $C_{12}H_{15}NSO_2$: C, 60.72; H, 6.38; N, 5.90; S, 13.51. Found: C, 60.76; H, 6.37; N, 5.94; S, 13.33.

1-Benzylsulfonyl-2-(ethylenimino)propene.—To 0.83 g (0.0043 mol) of 1-benzylsulfonylpropyne in 20 ml of benzene at 28–29° was added 0.19 g (0.0043 mol) of ethylenimine. The reaction gave 0.85 g (83%) of product after recrystallization (EtOH–hexane), mp 54–56°.

Anal. Calcd for $C_{12}H_{15}NSO_2$: C, 60.72; H, 6.38; N, 5.90; S, 13.51. Found: C, 60.75; H, 6.41; N, 5.88; S, 13.50.

1-(2-Phenylethylsulfonyl)-2-(ethylenimino)propene.—To 0.90 g (0.0043 mol) of 1-(2-phenylethylsulfonyl)propyne in 20 ml of benzene was added 0.19 g (0.0043 mol) of ethylenimine. There was obtained 0.81 g (75%) of product after recrystallization (EtOH–hexane), mp 62–64°.

1-Ethylsulfonyl-2-(ethylenimino)-1-butene.—To 0.80 g (0.0055 mol) of 1-ethylsulfonyl-1-butyne dissolved in 26 ml of ethanol was added 0.24 g (0.0055 mol) of ethylenimine. The reaction afforded 0.60 g (60%) of 62% *cis* and 38% *trans* adducts after distillation, bp 122° (0.20 mm).

1-Ethylsulfinyl-2-(ethylenimino)propene.—To 0.50 g (0.0043 mol) of 1-ethylsulfinylpropyne in 20 ml of benzene was added 0.19 g (0.0043 mol) of ethylenimine and there was formed at 26–27° 40% *cis* and 60% *trans* adducts. Distillation gave a 58% yield of pure product, bp 93–95° (0.20 mm).

Anal. Calcd for $C_7H_{13}NSO$: C, 52.79; H, 8.22; N, 8.80; S, 20.14. Found: C, 52.99; H, 8.04; N, 8.51; S, 20.16.

Preparation of the Nonconjugated Adducts.—The nonconjugated adducts were prepared by addition of ethylenimine to both the allenic sulfones and sulfoxides and the propargyl sulfones and sulfoxides. The larger quantities of nonconjugated adducts were prepared from the propargyl acetylenes and these preparations will be given. However the same adducts were obtained using the allenes or mixtures of allene and propargyl acetylene as shown in Table II.

3-Ethylsulfonyl-2-(ethylenimino)propene.—To 2.0 g (0.015 mol) of 3-ethylsulfonylpropyne in 80 ml of EtOH was added 0.64 g (0.015 mol) of ethylenimine. After stirring 4 hr, recrystallization (benzene–pentane) there was obtained 2.1 g (80%) of product, mp (sublimed) 64–65.5°.

Anal. Calcd for $C_7H_{13}NSO_2$: C, 47.96; H, 7.49; N, 7.99; S, 18.30. Found: C, 47.73; H, 7.54; N, 7.93; S, 18.02.

3-*p*-Tolylsulfonyl-2-(ethylenimino)propene.—To 2.0 g (0.010 mol) of 3-*p*-tolylsulfonylpropyne in 80 ml of ethanol was added 0.44 g (0.010 mol) of ethylenimine. After stirring 4 hr, the mixture given in Table II was obtained. Several recrystallizations (benzene–hexane) afforded 1.5 g (63%) pure nonconjugated adduct, mp 69.5–70.5°.

Anal. Calcd for $C_{12}H_{15}NSO_2$: C, 60.72; H, 6.38; N, 5.90; S, 13.51. Found: C, 60.92; H, 6.48; N, 5.78; S, 13.68.

3-Ethylsulfonyl-2-(ethylenimino)propene.—To 3.0 g (0.026 mol) of 3-ethylsulfinylpropyne in 80 ml of ethanol was added 1.11 g (0.026 mol) of ethylenimine. After stirring 2 days and distillation, 2.75 g (78%) of product was obtained, bp 87–91° (0.25 mm).

Anal. Calcd for $C_7H_{13}NSO$: C, 52.79; H, 8.22; N, 8.80; S, 20.14. Found: C, 52.76; H, 8.27; N, 8.78; S, 19.97.

Isomerization of Nonconjugated and Conjugated Adducts to the Thermodynamic Equilibrium Mixture.—As shown in Table IX, either the nonconjugated or conjugated ethylenimine adducts could be isomerized to the thermodynamic equilibrium mixture with KOH in THF at room temperature. The KOH was removed by filtration and the solvent was then removed *in vacuo*. An nmr was taken of the crude mixture before purification.

1-Ethylsulfinyl-2-(ethylenimino)propene.—To 0.58 g (0.0037 mol) of 87% *cis*- and 13% *trans*-1-ethylsulfinyl-2-(ethylenimino)-propene in 40 ml of THF was added 5.5 g (0.098 mol) of KOH. After stirring, filtration, concentration, and distillation, there was obtained 0.40 g (69%) of the mixture, bp 96–98° (0.20 mm) given in Table IX.

1-Ethylsulfonyl-2-(ethylenimino)propene.—To 1.2 g (0.069 mol) of a mixture of 16% *cis*- and 84% *trans*-1-ethylsulfonyl-2-(ethylenimino)propene in 50 ml of THF was added 6.2 g (0.11 mol) of KOH. After stirring, filtration, concentration, and distillation, the mixture, bp 110–112° (0.30 mm), given in Table IX was obtained.

1-*p*-Tolylsulfonyl-2-(ethylenimino)propene.—To 1.0 g (0.0042 mol) of a mixture of 79% *cis*- and 21% *trans*-1-*p*-tolylsulfonyl-2-(ethylenimino)-propene in 50 ml of THF was added 5 g (0.089 mol) of KOH. After stirring, filtration, and concentration, an nmr of the remaining white crystalline solid 0.80 g (80%) showed it to be the mixture given in Table IX.

1-Benzylsulfonyl-2-(ethylenimino)propene.—To 1.5 g (0.0063 mol) of a mixture of 72% *cis*- and 28% *trans*-1-benzylsulfonyl-2-(ethylenimino)propene in 50 ml of THF was added 6.1 g (0.11 mol) of KOH. After stirring, filtration, and concentration,

(15) C. J. M. Stirling, *J. Chem. Soc., Suppl. I*, 5856 (1964).

1.4 g (93%) of the remaining crystalline product was shown to be the mixture given in Table IX. Recrystallization (EtOH–hexane) gave 1.3 g (87%) of the product, mp 52–54°.

1-(2-Phenylethylsulfonyl)-2-(ethylenimino)propene.—To 1.1 g (0.0043 mol) of a mixture of 36% *cis*- and 64% *trans*-1-(2-phenylethylsulfonyl)-2-(ethylenimino)propene in 50 ml of THF was added 6.0 g (0.11 mol) of KOH. After stirring, filtration, and concentration, the mixture (1.0 g, 91%) given in Table IX was present. Recrystallization (EtOH–hexane) gave 0.80 g (73%) of product, mp 60–61°.

Infrared Data.[16]—The 3-propynyl sulfides exhibit the characteristic strong carbonh–ydrogen stretch at 3300 cm^{-1} and a very weak carbon–carbon triple bond stretch in the 2100–2200-cm^{-1} region. The corresponding 3-propynyl sulfones and sulfoxides show in addition to the acetylenes carbon–hydrogen stretch and the carbon–carbon triple bond stretch, the characteristic strong sulfone absorption in the 1300–1350- and 1120–1150-cm^{-1} regions and the strong sulfoxide absorption in the 1020–1060-cm^{-1} region, respectively. The 1-propynyl sulfides exhibit a weak carbon–carbon triple bond stretch at 2180 cm^{-1}. The corresponding sulfones and sulfoxides, however, show a very strong band at 2180–2200 cm^{-1}. The ethylsulfonylpropadiene and ethylsulfinylpropadiene exhibit a strong carbon–carbon double-bond stretch in the 1940–1980-cm^{-1} region which appears as a singlet. As previously published[6] the *p*-tolylsulfonylpropadiene shows a strong doublet at 1960 and 1920 cm^{-1}. The conjugated ethylenimine adducts exhibit strong olefinic absorption in the 1560–1640-cm^{-1} region in addition to the characteristic sulfone and sulfoxide bands which are shifted slightly lower. The nonconjugated ethylenimine adducts exhibit similar absorptions as the conjugated adducts with the olefinic band shifted ~50 cm^{-1} higher in the nonconjugated adduct from that in the conjugated.

(16) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1962.

Registry No.—**1**, Z = SOEt, 25557-97-5; **1**, Z = SO_2Et, 25557-98-6; **1**, Z = $SO_2C_6H_4CH_3$-*p*, 25557-99-7; **2**, Z = SOEt, 25558-40-1; **2**, Z = SO_2Et, 13894-33-2; **2**, Z = $SO_2C_6H_4CH_3$-*p*, 25558-42-3; **2**, Z = $SO_2CH_2C_6H_5$, 25558-43-4; **2**, Z = $SO_2CH_2CH_2C_6H_5$, 25558-44-5; **3**, Z = SOEt, 25558-45-6; **3**, Z = SO_2Et, 13894-50-3; **3**, Z = $SO_2C_6H_4CH_3$-*p*, 25558-47-8; **3**, Z = $SO_2CH_2C_6H_5$, 25558-48-9; **3**, Z = $SO_2CH_2CH_2C_6H_5$, 25558-49-0; $HC{\equiv}CCH_2SR$, R = $CH_2CH_2C_6H_5$, 25558-00-3; $CH_3C{\equiv}CSR$, R = $CH_2C_6H_5$, 22582-35-0; $CH_3C{\equiv}CSR$, R = $CH_2CH_2C_6H_5$, 25558-02-5; 1-benzylsulfonylpropyne. 25558-03-6; 1-(2-phenylethylsulfonyl)propyne, 25558-04-7; 3-ethylsulfinylpropyne, 25558-05-8; 1-ethylsulfinylpropyne, 25558-06-9; ethylsulfinylpropadiene, 25558-07-0; *cis*-1-ethylsulfonyl-2-(ethylenimino)-1-butene, 25558-50-3; *trans*-1-ethylsulfonyl-2-(ethylenimino)-1-butene, 25558-51-4.

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Reductive Dimerization of Difunctional Aryl Imines on Photolysis

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Irradiations of aryl imines which have a nitrile, amide, double bond, or hydroxyl group suitably positioned for interaction with the imine give the *meso*- and *dl*-1,2-diamines resulting from reductive dimerization. Nonconjugated diimines give polymeric products. In the case of 2-cyanoethylamine-N-benzylidene, the mechanism involves initial formation of α-hydroxy radicals by transfer of a hydrogen atom from the alcoholic solvent to the benzaldehyde sensitizer, sequentially followed by production of α-amino radicals by hydrogen transfer from the α-hydroxy radical to the imine and dimerization of the α-amino radicals. One anil and three imidates were found to be unreactive under the specified photolysis conditions.

Recent studies of the photochemistry of imines suggest that many of the reported reactions actually do not involve a photoexcited state of the imine. Aryl imines have been shown to undergo reduction[1,2] and reductive dimerization[3] on photolysis *via* an α-amino radical formed by hydrogen atom transfer to the imine from an α-hydroxy radical initially formed by abstraction of a hydrogen atom from the solvent by the sensitizer. Padwa, Bergmark, and Pashayan have noted the potential generality of this type of reaction for imines in the presence of added or adventitious sensitizers.[3] However, intramolecular reactions not usually explicable in terms of an α-amino radical are observed in some imine photolyses.[4,5]

We have investigated the photochemistry of some acyclic imines which have a second functional group suitably situated for intramolecular reaction with the imine. Although the photochemistry of analogous olefins and ketones suggests that intramolecular reaction might be expected,[6] only reductive dimerization involving conversion of the imine to a substituted 1,2-diamine is observed.

(1) W. F. Smith and B. W. Rossiter, *J. Amer. Chem. Soc.*, **89**, 717 (1967).

(2) M. Fischer, *Chem. Ber.*, **100**, 3599 (1967).

(3) A. Padwa, W. Bergmark, and D. Pashayan, *J. Amer. Chem. Soc.*, **91**, 2653 (1969), and references cited therein.

(4) (a) P. Beak and J. L. Miesel, *ibid.*, **89**, 2375 (1967); (b) B. Singh and E. F. Ullman, *ibid.*, **90**, 6911 (1969); (c) J. L. Derocque, W. T. Theuer, and J. A. Moore, *J. Org. Chem.*, **33**, 4381 (1968); (d) G. M. Badger, C. P. Joshua, and G. E. Lewis, *Tetrahedron Lett.*, 3711 (1964); (e) F. B. Mallory and C. S. Wood, *ibid.*, 2643 (1965); (f) A. Padwa, S. Clough, and E. Glazer, *J. Amer. Chem. Soc.*, **92**, 1778 (1970); (g) W. M. Moore and C. Baylor, Jr., *ibid.*, **91**, 7170 (1969); (h) M. Green and G. Tollin, *Photochem. Photobiol.*, **7**, 129, 145 (1968), and references cited therein; (i) K. H. Grellmann and E. Tauer, *Tetrahedron Lett.*, 1901 (1967); (j) R. W. Binkley, *J. Org. Chem.*, **34**, 2072 (1969); (k) J. Rennert and J. Wiesenfeld, *Photochem. Photobiol.*, **5**, 337 (1966); (l) E. C. Taylor, B. Furth, and M. Pfau, *J. Amer. Chem. Soc.*, **87**, 1400 (1965); (m) W. F. Richey and R. S. Becker, *J. Chem. Phys.*, **49**, 2092 (1968), and references cited therein; (n) M. P. Cava and R. H. Schlessinger, *Tetrahedron Lett.*, 2109 (1964).

(5) Exceptions to intramolecularity include photochemical cycloadditions [F. P. Woerner, H. Reimlinger, and D. R. Arnold, *Angew. Chem., Int. Ed. Engl.*, **7**, 130 (1968); L. A. Singer and P. D. Bartlett, *Tetrahedron Lett.*, 1887 (1964), and subsequent work; S. Searles, Jr., and R. A. Clasen, *ibid.*, 1627 (1965); J. C. Sheehan and I. Lengyel, *J. Org. Chem.*, **28**, 3252 (1963)] and possibly reactions which involved the direct formation of radicals [R. W. Binkley, *ibid.*, **34**, 931 (1969); J. H. Boyer and P. A. J. Frints, *Tetrahedron Lett.*, 3211 (1968)].

(6) (a) R. Srinivasan, *J. Amer. Chem. Soc.*, **82**, 775 (1960); (b) N. C. Yang, M. Nussim, and D. R. Coulson, *Tetrahedron Lett.*, 1525 (1965); (c) J. Meinwald and R. A. Chapman, *J. Amer. Chem. Soc.*, **90**, 3218 (1968); (d) R. R. Sauers and J. A. Whittle, *J. Org. Chem.*, **34**, 3579 (1969).

On photolysis with light from a high-pressure mercury lamp passed through a Pyrex filter, degassed ethanol solutions of the imines **1a–f** give a 50–70% yield of the 1,2-diamines **2a–f** expected for reductive dimerization. For **2a** and **2d**, only *meso*-diamines are

$$\underset{\mathbf{1}}{C_6H_5CR{=}N{-}R'} \xrightarrow{h\nu} \underset{\mathbf{2}}{\begin{matrix} C_6H_5CR{-}NHR' \\ | \\ C_6H_5CR{-}NHR' \end{matrix}}$$

a, R = H, R′ = $(CH_2)_2CN$
b, R = H, R′ = $(CH_2)_2CH{=}CH_2$
c, R = H, R′ = $(CH_2)_3NHCOCH_3$
d, R = H, R′ = $(CH_2)_2NHCOC_6H_5$
e, R = H, R′ = $(CH_2)CH(OH)C_6H_5$
f, R = CH_3, R′ = $(CH_2)_2CN$

isolated but comparable amounts of *dl* and *meso* compounds are obtained for **2b** and **2c**. For **2e** and **2f**, stereochemistry is not assigned; the instability of **2e** precluded preparation of an analytical sample.

The products are identified by a combination of spectral and chemical methods. In addition to the ir, nmr, and uv spectra expected for **2a–f**, mass spectrometry establishes the molecular weight and shows the major fragmentation to be the expected α cleavage.[7] Authentic *meso*-diamine **2a** was synthesized by reaction of *meso*-1,2-diamino-1,2-diphenylethane with acrylonitrile and is identical with the photoproduct. Lithium aluminum hydride reduction of **2a** gives the same tetraamine as does hydrolysis of *meso* **2c** and, establishing the stereochemistry of the latter, aluminum amalgam reduction of **1a** and **1d** also gives the *meso*-diamines **2a** and **2d**.[3,8]

On the basis of previous work,[1-3] the pathway for conversion of **1** to **2** could be anticipated to involve hydrogen transfer from an α-hydroxy radical, formed by abstraction of hydrogen from the solvent by a sensitizer, to the imine followed by dimerization of the relatively stable α-amino radicals. The sensitizer in the photolyses of **2a–e** would be benzaldehyde, either present in trace amounts as in the imine or formed during the irradiation. The contrast of the high sensitizer efficiency of *m*-methoxyacetophenone, which does not abstract hydrogen readily, has been used as a test for "chemical sensitization" by Monroe and Wiener.[9] Consistent with the expected mechanism, the conversion of **1a** to **2a** is efficiently sensitized by benzaldehyde but not by *m*-methoxyacetophenone (Table I). An attempt to intercept the α-hydroxy radicals with 2-mercaptomesitylene[10] and thus increase the probability of observing photoreactions of the imine **1a** was unsuccessful. In fact, retardation of the reductive dimerization, as expected if α-hydroxy radicals are involved in the reaction, was observed (Table I).

Photolyses of ethanol solutions of ethylenediamine-N,N′-dibenzylidene [**1**, R = $(CH_2)_2N{=}CHC_6H_5$] and propylenediamine-N,N′-dibenzylidene [**1**, R = $(CH_2)_3N{=}CHC_6H_5$] gave polymeric products,[11] thus providing further support for the formation of 1,2-diamines by dimerization of α-amino radicals[3] rather than by combination of α-amino radicals with an imine group.

Solutions of **1a–d**, **1f**, and the 1,2-diimines in alkane or benzene solvents do not show reactions upon irradiation. Presumably because the alcohol function served to provide a hydrogen atom for a trace of sensitizer, the alcohol imine **1e** gives a low yield of **2e** under these conditions.

TABLE I

EFFECTS OF ADDED SENSITIZERS AND INHIBITORS ON THE PHOTOLYSES OF 2-CYANOETHYLAMINE-N-BENZYLIDENE (**1a**)

Time, $h\nu$, hr	% 2-cyanoethylamine-N-benzylidene remaining in the presence of			
	Blank	PhCHO[a]	MAP[b]	MMS[c]
0.5		56		
1	96	3	89	100
2	74		73	
3	54	0	65	94
4	38		30	92
9				81
15				59

[a] 1:1 *M* benzaldehyde; benzaldehyde absorbs 50% of incident light. [b] *m*-Methoxyacetophenone absorbs 95% of incident light. [c] 0.1 *M* 2-mercaptomesitylene relative to imine; 2-mercaptomesitylene absorbs 5% of incident light.

Experimental Section[12]

2-Cyanoethylamine-N-benzylidene (**1a**).—A benzene solution of 15 g (0.21 mol) of 3-aminopropionitrile[13] and 22.2 g (0.21 mol) of benzaldehyde was heated at reflux for 6 hr. The benzene was evaporated and the residue was distilled to give 27.9 g (84%) of **1a**: bp 128° (2.0 mm); uv max (95% ethanol) 248 mμ (ϵ 1.68 × 10^4); uv shoulder 280 mμ (ϵ 1.70 × 10^3), 288 (1.11 × 10^3); ir (neat) 2210 (C≡N) and 1620 cm^{-1} (C=N); nmr ($CDCl_3$) δ 8.17 (s, 1, CH=N), 7.79–7.15 (m, 5, ArH), 3.64 (t, 2, J = 6.8 Hz, CH_2); mass spectrum (70 eV) *m/e* (rel intensity) 158 (38, molecular ion), 118 (100), 104 (20), 91 (74), 77 (20). A series of molecular distillations gave analytically pure **1a**.

Anal. Calcd for $C_{13}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 76.07; H, 6.57; N, 17.65.

Acetophenone-N-(2-Cyano)ethylimine (**1f**).—A xylene solution (40 ml) of 2.65 g (0.02 mol) of acetophenone, 1.57 g (0.02 mol) of aminopropionitrile,[13] and 0.5 ml of 48% HBr was heated at reflux for 34 hr. Vacuum distillation gave 1.5 g (40%) of **1f**: bp 135° (0.4 mm); uv max (95% ethanol) 242 mμ (ϵ 1.07 × 10^4); ir (neat) 2220 (C≡N); nmr ($CDCl_3$) δ 8.0–7.2 (m, 5, ArH), 3.65 (t, 2, J = 6.5 Hz, CH_2), 2.77 (t, 2, J = 6.5 Hz, CH_2), and 2.24 ppm (s, 3, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 172 (15, molecular ion), 132 (19), 91 (51), 77 (100). A series of molecular distillations gave a colorless liquid.

Anal. Calcd for $C_{11}H_{12}N_2$: C, 75.71; H, 7.02; N, 16.27. Found: C, 75.17; H, 7.02; N, 16.57.

3-Butenylamine-N-benzylidene (**1b**).—Benzaldehyde, 4.5 g (0.043 mol), 3-butenylamine,[14] 3.0 g (0.043 mol), obtained from 4.5 g of 3-butenylamine hydrochloride, and sodium sulfate, 2 g, were shaken in ether (150 ml) for 11 hr at 25°. After the sodium

(7) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, San Francisco, Calif., 1964, p 63.

(8) R. Jaunin, *Helv. Chim. Acta*, **39**, 111 (1956).

(9) B. Monroe and S. Weiner, *J. Amer. Chem. Soc.*, **91**, 450 (1969).

(10) S. G. Cohen, D. A. Laufer, and W. V. Sherman, *ibid.*, 86, 3060 (1964).

(11) Polymer formation on photolyses of a number of diimines has previously been reported by M. P. Cava, "Report by The Ohio State University Research Foundation," cited in *Sci-Tech Aerosp. Rep.*, **4**, 1614 (1966). In the present case, attempts to detect the reduced amine or products of [3.3] rearrangements were not successful.

(12) All melting points (corrected) were taken on a Büchi capillary melting point apparatus. Ir spectra were run on Perkin-Elmer Model 521 and 137B ir spectrometers, and uv spectra were obtained on a Cary 14 uv–visible spectrometer. Varian Associates T-60, A-60A, A-56/60A, and HA-100 spectrometers were used to determine the nmr spectra, and chemical shifts are reported in δ (parts per million) relative to the internal standard TMS (TMS). The mass spectra were measured on an Atlas CH4 mass spectrometer and relative intensities are reported as per cent of the base peak of the mass spectrum. Preparative tlc plates (2000 mμ) were made of Merck silica gel (PF_{254}). Elemental analyses were provided by Mr. J. Nemeth and associates.

A Hanovia Type L, 450-W, high-pressure quartz mercury-vapor immersion lamp fitted with a Pyrex filter was used for most photolyses. A Hanovia 23-W, Type SC-2537, low-pressure Vycor mercury immersion lamp was employed for irradiations with <300-mμ light.

(13) S. R. Buc, J. H. Ford, and E. C. Wise, *J. Amer. Chem. Soc.*, **67**, 92 (1945).

(14) J. D. Roberts and R. H. Mazur, *ibid.*, **73**, 2509 (1951).

sulfate had been removed, fresh sodium sulfate was added and the mixture was heated at reflux for 40 hr. Low-boiling components were removed by distillation at atmospheric pressure and the residue was vacuum distilled three times to give 3.6 g (54%) of **1b**: bp 75–80° (0.18 mm); uv max (95% ethanol) 248 mμ (ε 2.05 × 10⁴); uv shoulder 270 mμ (ε 1.71 × 10³), and 279 (1.09 × 10³); ir (neat) 1656 (C=C) and 1647 cm⁻¹ (C=N); nmr ($CDCl_3$) δ 8.21 (t, 1, J = 1 Hz, CH=N), 7.52 (m, 5, ArH), 5.83 (m, 1, C=CH–), 5.07 (m, 2, CH_2=), 3.65 (t, d, 2, J = 7.5, 1 Hz, $-CH_2$—N=), and 2.46 ppm (m, 2, J = 7.5 Hz, =CCH_2–); mass spectrum (70 eV) m/e (rel intensity) 159 (18 molecular ion), 118 (65), 104 (10), 91 (100), 77 (15).

Anal. Calcd for $C_{11}H_{13}N$: C, 82.97; H, 8.23; N, 8.80. Found: C, 83.22; H, 8.08; N, 8.62.

N-Acetyl-N′-benzylidene-1,3-propanediamine (1c).—Benzaldehyde, 6.7 g (0.064 mol), and N-(3-aminopropyl)acetamide,[15] 7.3 g (0.064 mol), were heated at reflux in benzene (50 ml) for 26 hr. The benzene and unreacted benzaldehyde were removed by vacuum distillation, and the residue was purified by a series of molecular distillations to give a clear oil. Cooling gave a white solid which was recrystallized from ether to give 2.3 g (17%) of **1c**: mp 61.5–62.5°; uv max (95% ethanol) 248 mμ (ε 1.62 × 10⁴); uv shoulder 279 mμ (ε 1.41 × 10³) and 288 (9.0 × 10²); ir ($CHCl_3$) 3450, 3320 (NH) and 1650 cm⁻¹ (C=O and C=N); nmr ($CDCl_3$) δ 8.24 (t, 1, J = 1 Hz, CH=N), 7.80–7.25 (m, 5, ArH), 6.80 (broad, 1, CONH), 3.66 (t, d, 2, J = 6, 1 Hz, CH_2–N), 3.33 (m, 2, N–CH_2–), 1.95 (s, 3, CH_3), and 1.94 ppm (quintet, 2, J = 6 Hz, C–CH_2–C); mass spectrum (70 eV) m/e (rel intensity) 204 (13, molecular ion), 145 (32), 132 (100), 118 (43), 91 (34), 43 (48).

Anal. Calcd for $C_{12}H_{16}N_2O$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.71; H, 7.81; N, 13.95.

N-Benzylidene-N′-benzoyl-1,2-ethanediamine (1d).—N-(2-Aminoethyl)benzamide,[16] 2.85 g (0.018 mol), and benzaldehyde, 1.84 g (0.018 mol), were heated at reflux in benzene (40 ml) for 12 hr. The benzene was evaporated to give a brown-white solid which was recrystallized from benzene to give 3.17 g (70%) of **1d**: mp 128–130°; uv max (95% ethanol) 244 mμ (ε 2.55 × 10⁴); uv shoulder 215 mμ (ε 1.60 × 10⁴), 280 (2.64 × 10³), and 290 (1.12 × 10³); ir (neat) 3440 (NH), 1650 (C=O), and 1640 cm⁻¹ (C=N); nmr ($CDCl_3$) δ 8.34 (s, 1, CH=N), 7.86–7.15 (m, 10, ArH), 6.80 (broad, 1, CONH), and 3.80 ppm (m, 4, CH_2–CH_2); mass spectrum (70 eV) m/e (rel intensity) 252 (41, molecular ion), 131 (43), 118 (58), 105 (83), 91 (49), 78 (100), 77 (66).

Anal. Calcd for $C_{16}H_{16}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 76.04; H, 6.46; N, 10.96.

2-Hydroxy-2-phenylethylamine-N-benzylidene (1e).—Benzaldehyde, 3.1 g (0.029 mol), and 2-hydroxy-2-phenylethylamine, 4.0 g (0.029 mol), were heated at reflux in benzene (40 ml) for 3 hr. The solution was cooled to give a white precipitate which was recrystallized from benzene to give 5.7 g (86%) of **1e**: mp 115.0–115.5°; uv max (95% ethanol) 248 mμ (ε 1.95 × 10⁴); uv shoulder 280 mμ (ε 1.87 × 10³) and 290 (1.46 × 10³); ir ($CHCl_3$) 3500 (OH) and 1643 cm⁻¹ (C=N); nmr ($CDCl_3$) δ 8.24 (t, 1, J = 1 Hz, CH=N), 7.85–7.14 (m, 10, ArH), 4.97 (m, 1, CH–O), 3.76 (m, 2, CH_2–N), and 3.22 ppm (broad, 1, OH); mass spectrum (70 eV) m/e (rel intensity) 225 (1, molecular ion), 208 (1), 148 (2), 118 (100), 91 (41), 77 (15).

Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.97; H, 6.85; N, 6.35.

5-Hexen-2-one Anil (3).—A benzene solution (40 ml) of 5-hexen-2-one, 10.0 g (0.01 mol), aniline, 9.5 g (0.01 mol), and 48% HBr, 0.1 ml, was heated at reflux for 10 hr. The solvent was removed, and the residue was vacuum distilled three times to give 6.3 g (36%) of pale yellow **3**: bp 71–72° (0.2 mm); uv max (95% ethanol) 221 mμ (ε 1.28 × 10⁴) and 281 (3.58 × 10³); ir (neat) 1670 (C=C) and 1650 cm⁻¹ (C=N); nmr ($CDCl_3$) δ 7.4–6.5 (m, 5, ArH), 5.7 (m, 1, =CH–), 5.0 (m, 2, CH_2), 2.6–2.1 (m, 4, CH_2–CH_2), and 1.73 ppm (s, 3, CH_3); mass spectrum (70 eV) m/e (rel intensity) 173 (35, molecular ion), 158 (28), 118 (100), 77 (84), 55 (43). The anil was stored under vacuum.

Because the anil was too unstable to be characterized by analysis, it was reduced to 5-(N-phenyl)amino-1-hexene. An ether suspension (30 ml) of 5-hexen-2-one anil, 1.6 g (0.0094 mol), and lithium aluminum hydride, 3.5 g (0.094 mol), was heated at reflux for 12 hr. Quenching with moist sodium sulfate and filtration, concentration, and two vacuum distillations gave 1.33 g (80%) of 5-(N-phenyl)amino-1-hexene: bp 79–80° (0.2 mm); uv max (95% ethanol) 252 mμ (ε 1.4 × 10⁴) and 300 (1.8 × 10³); ir (neat) 3350 (NH) and 1640 cm⁻¹ (C=C); nmr ($CDCl_3$) δ 7.3–6.4 (m, 5, ArH), 5.8 (m, 1, =CH–), 5.0 (m, 2, CH_2=C–), 3.40 (m, 1, CH–N), 3.18 (broad, 1, NH), 2.14 (m, 2, CH_2), 1.56 (m, 2, CH_2), and 1.15 ppm (d, 3, J = 6 Hz, CH_3); mass spectrum (70 eV) m/e (rel intensity) 175 (6, molecular ion), 160 (30), 120 (100), 77 (51).

Anal. Calcd for $C_{12}H_{17}N$: C, 82.23; H, 9.78; N, 7.99. Found: C, 82.22; H, 9.90; N, 8.07.

Ethylenediamine-N,N′-dibenzylidene,[17] N-methylbenziminomethyl ether,[18] N-methylbenziminomethyl ether,[19] N-phenylacetiminomethyl ether,[20] and N-phenylbenziliminomethyl ether[21] were prepared by standard procedures.

meso-1,2-Diamino-1,2-diphenylethane was synthesized by the method of Staab and Vogtle:[22] mp 117–118° (lit.[22] mp 118°); uv max (ethanol) 259 mμ (ε 428); ir ($CHCl_3$) 3330 cm⁻¹ (NH); nmr ($CDCl_3$) δ 7.27 (s, 10, ArH), 3.94 (s, 2, CH), and 1.23 ppm (s, 4, NH_2).

***meso*-N,N′-Bis(2-cyanoethyl)-1,2-diamino-1,2-diphenylethane (2a).**—Acrylonitrile, 8.1 g (0.15 mol), and *meso*-1,2-diamino-1,2-diphenylethane, 1.5 g (0.007 mol), plus 40% potassium hydroxide, 0.5 ml, were heated at reflux for 60 hr. The mixture was made strongly basic with 40% sodium hydroxide (20 ml) and was extracted with chloroform. The extract was dried ($MgSO_4$) and concentrated to give a viscous oil which was crystallized from 95% ethanol to give 0.2 g (10%) of **2a**: mp 106–107°; mmp (with **2a** from photolysis) 106–107°; ir (Nujol) 3310 (NH) and 2250 cm⁻¹ (C≡N); nmr ($CDCl_3$) δ 7.52–7.15 (m, ArH), 3.85 (s, Ph–CH), 2.65 (t, J = 6 Hz, CH_2), 2.28 (t, J = 6 Hz, CH_2), and 1.65 ppm (s, NH, exchanges in D_2O); mass spectrum (70 eV) m/e (rel intensity) 318 (0.03, molecular ion), 159 (100), 118 (17), 91 (1), 77 (4).

Anal. Calcd for $C_{20}H_{22}N_4$: C, 75.45; H, 6.96; N, 17.59. Found: C, 75.74; H, 7.01; N, 17.52.

***meso*-N,N′-Bis(3-aminopropyl)-1,2-diamino-1,2-diphenylethane.**—An ether suspension (40 ml) of lithium aluminum hydride, 3 g (0.08 mol), and *meso*-N,N′-bis(2-cyanoethyl)-1,2-diamino-1,2-diphenylethane, 0.279 g (0.0018 mol), was heated at reflux for 16 hr. The reaction was quenched with moist sodium sulfate to give, after evaporation of solvent, 0.116 g (41%) of a pale yellow oil: uv max (95% ethanol) 249 mμ (ε 8.4 × 10²); ir ($CHCl_3$) 3450, 3380, 3300 cm⁻¹ (NH); nmr ($CDCl_3$) δ 7.35 (s, 10, ArH), 3.72 (s, 2, benzyl), 2.4 (m, 8, N–CH_2), 1.36 (broad, 6, NH; exchanges in D_2O), and 1.41 ppm (m, 4, C–CH_2–C); mass spectrum (70 eV) m/e (rel intensity) 327 (3, $M^+ + 1$), 163 (54), 120 (67), 105 (7), 91 (52), 77 (11), 58 (35), 43 (100).

A picrate was made in 95% ethanol and recrystallized from methanol: mp 228–230°; mmp (with picrate of the tetraamine from hydrolysis of **2c**) 228–230°; the ir spectrum was identical with that of tetraamine, obtained from hydrolysis of the photodimer **2c**.

The tetrabenzamide was made by the Schotten–Baumann[23] method and was recrystallized from methanol to give pure material: mp 262–263;° mmp (with tetraamide derived from the photodimer **2c**) 262–263°; ir (KBr) 3350, 3260 (NH) and 1635, 1620 (sh) cm⁻¹ (C=O); mass spectrum (70 eV) m/e (rel intensity) 742 (0.05, molecular ion), 637 (0.1), 460 (5), 371 (16), 267 (2), 249 (24), 146 (37), 105 (100), 91 (5), 77 (31).

Anal. Calcd for $C_{48}H_{46}N_4O_4$: C, 77.60; H, 6.24; N, 7.54. Found: C, 77.32; H, 6.20; N, 7.75.

Aluminum Amalgam Reduction of 2-Cyanoethylamine-N-benzylidene.—An ether suspension (80 ml) of the cyanoimine, 2.5 g (0.016 mol), and aluminum amalgam,[24] 3 g (0.01 mol),

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was allowed to stand for 16 hr. The amalgam residue was removed and triturated with boiling methanol, which was combined with the original solution and condensed to give 2.12 g of yellow oil. The nmr spectrum ($CDCl_3$) of the crude product showed some impurities (δ 7.1 and 3.1 ppm) and possibly 5% *dl* isomer. Part of the product was crystallized to give 0.5 g (20%) of *meso*-N,N′-bis(2-cyanoethyl)-1,2-diamino-1,2-diphenylethane **2a**: mp 106–107°; mmp (with **2a** from photolysis) 106–107°; the ir and nmr spectra were identical with those of **2a** from photolysis.

Aluminum Amalgam Reduction of B-Benzoyl-N′-benzylidene-1,2-ethanediamine (1d).—An ether–tetrahydrofuran suspension (250 ml, 2:1, v:v) of N-benzoyl-N′-benzylidene-1,2-ethanediamine, 0.54 g (0.002 mol), and aluminum amalgam,[24] 5.0 g (0.017 mol), was allowed to stand for 8 hr. The amalgam residue was collected by vacuum filtration and triturated three times with boiling methanol. The filtrates were combined, refiltered, and condensed to give 0.52 g (96%) pale yellow solid which was recrystallized from methanol to give 0.38 g (70%) of **2d**: mp 207–208°; mmp (with **2d** isolated from the photolysis) 207–208°; uv max (95% ethanol) 220 mμ (ϵ 2.06 × 10^4); ir (KBr) 3420 (NH) and 1635 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.7–7.2 (m, 20, ArH), 6.36 (broad, 2, CONH), 3.83 (s, 2, benzyl), 3.36 (m, 4, N–CH_2), 2.60 (m, 4, N–CH_2), and 1.7 ppm (broad, 2, NH); mass spectrum (70 eV) *m/e* (rel intensity) 507 (1, $M^+ + 1$), 253 (51), 148 (76), 118 (52), 105 (71), 91 (51), 77 (100).

General Photolysis Procedure.—Most irradiations were done in a Pyrex vessel containing a water-cooled, quartz immersion well into which were placed the high-pressure lamp and the filter. Before irradiation the solution was degassed with dry, oxygen-free nitrogen for a minimum of 30 min. Nitrogen was also bubbled through the reaction solution during the irradiation. All photolyses in hexane and alcoholic solvents were monitored by the disappearance of the ultraviolet absorption of the imine chromophore.

Photolyses of 2-Cyanoethylamine-N-benzylidene.—A 95% ethanol solution (425 ml) of the benzylidene **1a**, 0.131 g (0.00083 mol), was irradiated for 6 hr. The solution was concentrated to a volume of 5 ml and cooled to give 63% white solid which was recrystallized from methanol and was shown to be *meso*-N,N′-bis(2-cyanoethyl)-1,2-diamino-1,2-diphenylethane (**2d**): mp 106–106.5°; uv max (ethanol) 259 mμ (ϵ 470); ir (Nujol) 3310 (NH) and 2250 cm^{-1} (C≡N); nmr ($CDCl_3$) δ 7.50–7.10 (m, 10, ArH), 3.82 (s, 2, benzyl), 2.64 (t, 4, J = 6 Hz, CH_2), 2.28 (t, 4, J = 6 Hz, CH_2), and 1.65 ppm (s, 2, NH; exchanges in D_2O); mass spectrum (70 eV) *m/e* (rel intensity) 318 (0.4, molecular ion), 159 (100), 118 (16), 91 (9), 77 (2); metastables *m/e* (fragmentation) 87.6 (159–118) and 69.6 (118–91).

Anal. Calcd for $C_{20}H_{22}N_4$: C, 75.45; H, 6.96; N, 17.59. Found: C, 75.60; H, 6.89; N, 17.36.

To determine the yield of **2a**, 0.130 g of crude photoproduct was developed ($CHCl_3$) on a preparative tlc plate. Elution of the bands with methanol–chloroform gave 0.098 g (76%) of a viscous oil whose ir spectrum ($CHCl_3$) was identical with that ($CHCl_3$) of **2a**. Addition of ethanol gave a solid (mp 102–105°).

Experiments were run to determine the effect of sensitizing and inhibiting agents on the irradiation of 2-cyanoethylamine-N-benzylidene (**1a**); the data obtained are summarized in Table I. A 95% ethanol solution (625 ml) of benzylidene **1a** and the appropriate compound was stirred and degassed for 30 min before irradiation. A 100-ml portion was then removed, and the remaining 525 ml was irradiated for the indicated time. The solutions were concentrated and their nmr spectra were recorded. The amount of **1a** remaining was determined from the relative areas of the benzylidene proton (δ 8.17 ppm) and the aromatic protons (δ 7.79–7.15 ppm) in the nmr spectrum.

In one experiment a 95% ethanol solution (525 ml) of 2-cyanoethylamine-N-benzylidene (**1a**) 0.541 g (0.00342 mol), and 2-mercaptomesitylene, 0.568 g (0.00376 mol), was irradiated for 36 hr; the nmr spectrum showed that 46% of the imine **1a** remained. Tlc and the nmr spectrum of the product indicated that the imine **1a**, the mercaptan, hydrobenzoin, 1-phenyl-1,2-propanediol, and the photodimer **2a** were present. The product was then extracted with 8% hydrochloric acid and water. The extract was 0.075 g yellow oil whose nmr spectrum ($CDCl_3$) indicated the presence of the photodimer **2a** (50%) and a mixture of hydrobenzoin (25%) and 1-phenyl-1,2-propanediol (25%). The nonbasic material was then extracted with 40% potassium hydroxide and water to remove as much 2-mercaptomesitylene as possible. The remaining chloroform solution yielded 0.376 g of brown tar whose nmr spectrum ($CDCl_3$) indicated the presence of hydrobenzoin (25%) and 2-mercaptomesitylene (75%). A control extraction showed that the imine hydrolyzed under the extraction conditions. No new photoproducts were found.

Photolyses of **1a** in benzene and hexane led only to recovered **1a**. Photolyses with a low-pressure mercury lamp gave only unidentified products.

Photolysis of Acetophenone-N-(2-Cyano)ethylimine (1f).—A 95% ethanol solution (525 ml) of the azomethine, 0.530 g (0.0032 mol), was irradiated for 35 hr. The ethanol was concentrated to give 0.318 g (60%) of a white solid which was recrystallized from methanol to give pure **2f**: mp 131–133°; uv max (95% ethanol) 259 mμ (ϵ 457); ir (Nujol) 3280 (NH) and 2210 cm^{-1} (C≡N); nmr ($CDCl_3$) δ 7.45–7.95 (m, 10, ArH), 2.80–2.35 (m, 8, CH_2–CH_2), 2.10 (s, 2, NH; exchanges in D_2O), 1.58 (s, 3, CH_3), and 1.49 ppm (s, 3, CH_3); nmr (DMSO-d_6, 90°) no change in position or relative intensity of δ 1.58 and 1.49 ppm signals; mass spectrum (70 eV) *m/e* (rel intensity) 346 (0.2, molecular ion), 173 (100), 132 (16), 91 (17), 77 (8); metastables *m/e* (fragmentation) 100.7 (173–132) and 62.7 (132–91).

Anal. Calcd for $C_{22}H_{26}N_4$: C, 76.27; H, 7.56; N, 16.17. Found: C, 76.36; H, 7.56; N, 16.39.

Photolyses of 3-Butenylamine-N-benzylidene.—The imine **1b**, 0.51 g (0.0032 mol), was irradiated in 95% ethanol (425 ml) for 10 hr. The ethanol was removed, leaving 0.50 g (98%) yellow oil whose nmr spectrum ($CDCl_3$) showed two benzyl peaks at δ 3.76 and 3.68 ppm (area ratio, 1:1). The crude product was chromatographed on a silica gel column.

From a benzene–2% ether elutant was isolated 0.21 g (42%) pale yellow oil which was crystallized from pentane to give 0.14 g (28%) of *meso*-N,N′-bis(3-butenyl)-1,2-diamino-1,2-diphenylethane (**2b**): mp 40–41°; uv max (95% ethanol) 259 mμ (ϵ 5.1 × 10^2); ir (CCl_4) 3420 (NH) and 1640 cm^{-1} (C=C); nmr ($CDCl_3$) δ 7.36 (s, 10, ArH), 5.50 (m, 2, =C–CH), 4.80 (m, 4, CH_2=), 3.78 (s, 2, benzyl), 2.34 (m, 4, CH_2), 2.17 (m, 4, CH_2), and 1.49 ppm (broad, 2, NH, exchanges in D_2O); mass spectrum (70 eV) *m/e* (rel intensity) 320 (1, molecular ion), 160 (100), 131 (175), 118 (74), 104 (22), 91 (85), 77 (30).

Anal. Calcd for $C_{22}H_{28}N_2$: C, 82.45; H, 8.81; N, 8.74. Found: C, 82.55; H, 8.89; N, 8.82.

Eluted from benzene–2% ether was 0.17 g (34%) of pale yellow oil which could not be crystallized. It was assigned the structure of *dl*-N,N′-bis-(3-butenyl)-1,2-diamino-1,2-diphenylethane (**2b**) on the basis of the following evidence: uv max (95% EtOH) 249 mμ (ϵ 7.5 × 10^2); ir (CCl_4) 3300 (NH) and 1640 cm^{-1} (C=C); nmr ($CDCl_3$) δ 7.14 (s, 10, ArH), 5.8 (m, 2, =CH–), 5.1 (m, 4, CH_2=C–), 3.66 (s, 2, benzyl), and 2.7–2.0 ppm (m, 10, CH_2 and NH); mass spectrum (70 eV) *m/e* (rel intensity) 320 (0.4, molecular ion), 160 (100), 131 (35), 118 (9), 104 (5), 91 (16), 77 (5). A bis benzamide was made of this photodimer: mp 248–249°; ir (KBr) 1640 (C=C) and 1630 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 528 (0.3, molecular ion), 264 (69), 105 (100), 91 (10), 77 (41).

Photolyses of N-Acetyl-N′-benzylidene-1,3-propanediamine (1c).—A 95% ethanol solution (525 ml) of the imine **2c**, 2.0 g (0.0098 mol), was irradiated for 12 hr. The ethanol was removed and the residue was dissolved in chloroform, dried (Na_2SO_4), and concentrated to give 2 g (100%) of a pale yellow oil whose nmr spectrum ($CDCl_3$) contained 2 singlets at δ 3.82 and 3.68 ppm (relative area 1:1, benzyl) and 2 singlets at δ 1.92 and 1.88 ppm (relative area 1:1, CH_3). The crude product was chromatographed on a silica gel column.

From the chloroform–5% methanol elutant was isolated 0.76 g (33%) of a yellow oil which was assigned the structure of *meso*-N,N′-bis[3-(N-acetyl)aminopropyl]1,2-diamino-1,2-diphenylethane **2c**: uv max (95% ethanol) 253 mμ (ϵ 9.1 × 10^2); ir ($CHCl_3$) 3420, 3300 (NH) and 1653 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.25 (s, 10, ArH), 6.55 (broad, 2, CONH), 3.86 (s, 2, benzyl), 3.19 (m, 4, N–CH_2), 2.69 (broad, 2, NH, exchanges in D_2O), 2.44 (t, 4, J = 6 Hz, N–CH_2), 1.89 (s, 6, CH_3), and 1.52 ppm (m, 4, C–CH_2–C); mass spectrum (70 eV), *m/e* (rel intensity) 410 (0.2, molecular ion), 205 (48), 146 (3), 105 (8), 100 (30), 83 (22), 91 (16), 77 (6), 58 (21), 43 (100). This viscous oil appeared to be sensitive to heat and air.

A picrate of the photodimer **2c** was made in 95% ethanol and recrystallized from methanol: mp 226–227°; ir (KBr) 3400 (NH) and 1630 cm^{-1} (C=O).

Anal. Calcd for $C_{36}H_{40}N_{10}O_{16}$: C, 49.77; H, 4.64; N, 16.12. Found: C, 49.72; H, 4.59; N, 15.94.

From the chloroform–10% methanol elutant was isolated 0.41 g (21%) pale yellow oil which was assigned the structure of *dl*-N,N′-bis[3-(N-acetyl)aminopropyl]-1,2-diamino-1,2-diphenylethane (**2c**): uv max 253 mμ (ε 8.1 × 10²); ir ($CHCl_3$) 3420, 3295 (NH) and 1653 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.16 (s, 10, ArH), 7.00 (broad, 2, CONH), 3.69 (s, 2, benzyl), 3.34 (m, 4, $N-CH_2$), 2.98 (s, 2, NH, exchanges in D_2O), 2.50 (m, 4, $N-CH_2$), 1.93 (s, 6, CH_3), and 1.64 ppm (m, 4, $C-CH_2-C$); mass spectrum (70 eV) *m/e* (rel intensity) 410 (0.4, molecular ion), 205 (85), 146 (2), 105 (2), 100 (30), 91 (8), 83 (100), 77 (1), 43 (23). Attempts to make a picrate of **2c** were unsuccessful.

From the chloroform–5% methanol elutant was also isolated 0.27 g of a yellow oil whose nmr spectrum ($CDCl_3$) was compatible with a mixture of the *meso* and *dl* photodimers: nmr δ 1.93 and 1.89 ppm (relative area 61.6%:38.4%). From these data total spectroscopic yields of 42% *meso* and 29% *dl* **2c**, respectively, were calculated.

To obtain the *meso*-tetraamine, the 1,2-diamine **2c** (0.106 g, 0.00026 mol) was heated at reflux in 8% hydrochloric acid (25 ml) for 8 hr. The solution was extracted with chloroform, made basic, and again extracted with chloroform, dried (Na_2SO_4), and concentrated to give 0.057 g (68%) of *meso*-N,N′-bis-(3-aminopropyl)-1,2-diamino-1,2-diphenylethane: uv max (95% ethanol) 249 mμ (ε 6.9 × 10²); ir ($CHCl_3$) 3450, 3380, and 3300 cm^{-1} (NH); nmr ($CDCl_3$) δ 7.30 (s, 10, ArH), 3.83 (s, 2, benzyl), 2.4 (m, 8, $N-CH_2$), 1.44 (m, 4, $C-CH_2-C$), and 1.21 ppm (broad, 6, NH, exchanges in D_2O); mass spectrum (70 eV) *m/e* (rel intensity) 326 (0.2, molecular ion), 163 (13), 120 (10), 91 (6), 77 (2), 43 (100).

A picrate was made in 95% ethanol and recrystallized from methanol: mp 228–229°; mmp (with picrate of authentic **2c**) 228–230°. A tetrabenzamide was made by the Schotten-Baumann[23] method: mp 261–263°; mmp (with benzamide from authentic tetraamine) 261–263°; ir (KBr) 3350, 3260 (NH) and 1635, 1620 cm^{-1} (C=O); mass spectrum (70 eV) *m/e* (rel intensity) 742 (0.01, molecular ion), 460 (5), 371 (5), 276 (1), 249 (5), 146 (9), 105 (100), 91 (9), 77 (42).

Anal. Calcd for $C_{48}H_{46}N_4O_4$: C, 77.60; H, 6.24; N, 7.54. Found: C, 77.32; H, 6.20; N, 7.75.

Photolysis of N-Benzoyl-N′-benzylidene-1,2-ethanediamine (1d).—A 95% ethanol solution (525 ml) of the imine **1a**, 1.1 g (0.0044 mol), was irradiated for 26 hr. The ethanol was removed to give an off-white solid whose nmr spectrum ($CDCl_3$) exhibited only one benzyl peak (δ 3.83 ppm). The crude product was chromatographed on silica gel.

From chloroform–2% methanol was eluted 0.55 g (50%) of off-white solid whose nmr spectrum ($CDCl_3$) was identical with that of the *meso*-1,2-diamine (**2d**) produced by aluminum amalgam reduction. This photoproduct was recrystallized from methanol to give 0.48 g (44%) of pure *meso*-N,N′-bis[2-(N-benzoyl)aminoethyl]-1,2-diamino-1,2-diphenylethane (**2d**): mp 201–203°; uv max (95% ethanol) 220 mμ (ε 3.36 × 10⁴); ir (Nujol) 3390 (NH) and 1630 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.8–7.2 (m, 20, ArH), 6.7 (broad, 2, CONH), 3.87 (s, 2, benzyl), 3.44 (m, 4, CH_2), and 2.67 ppm (m, 6, CH_2 and NH); mass spectrum (70 eV) *m/e* (rel intensity) 506 (0.005, molecular ion), 253 (100), 180 (14), 179 (15), 178 (12), 148 (53), 133 (6), 132 (3), 119 (3), 118 (8), 106 (10), 105 (42), 91 (8), 77 (17); metastables (fragmentation) 86.57 (253–148), 74.49 (148–105), 44.41 (253–106), 56.46 (105–77).

Anal. Calcd for $C_{32}H_{34}N_4O_2$: C, 75.86; H, 6.76; N, 11.06. Found: C, 75.69; H, 6.63; N, 11.11.

Photolyses of 2-Hydroxy-2-phenylethylamine-N-benzylidene (1e).—A 95% ethanol solution (525 ml) of the imine (**1e**), 1.5 g (0.0067 mol), was irradiated for 10 hr. The ethanol was removed to give a pale yellow solid which was chromatographed on silica gel.

From chloroform–2% methanol was eluted 0.86 g (58%) of an off-white solid **2e**: mp 138–155° dec; ir (KBr) 3400 cm^{-1} (NHOH). The solid was recrystallized from chloroform to give 0.08 g (6%) of **2e**: mp 199–201° dec; uv max (95% ethanol) 259 mμ (ε 2.4 × 10²); ir (KBr) 3400 cm^{-1} (NH); nmr ($CDCl_3$) δ 7.3 (m, 20, ArH), 4.5 (m, 2, Ph-CH-OH), 3.9 (m, 2, PhCH-NH), 3.6 (m, 8, CH_2, OH, NH); mass spectrum (70 eV) *m/e* (rel intensity) 452 (1, molecular ion), 345 (11), 226 (100), 209 (17), 208 (80), 121 (2), 120 (19), 119 (3), 118 (16), 117 (30), 106 (8), 105 (11), 104 (4), 103 (10), 91 (45), 77 (10). The following metastables (fragmentation) were found: 193.28 (226–209), 191.43 (226–208); 70.39 (208–121), 65.81 (208–117), 54.02 (208–106), 39.81 (208–91).

Attempts to purify or derivatize **2e** failed.

Photolyses of ethylene-N,N′-dibenzylidene, propylene-N,N′-dibenzylidene, N-methyl-O-methyl benzimidate, N-phenyl-O-methyl acetimidate, and N-phenyl-O-methyl benzimidate gave starting materials or polymers which were not characterized. Attempted sensitization of reactions of the imidates with benzaldehyde in ethanol solutions gave recovery of starting materials, hydrobenzoin, and 1-phenyl-1,2-propanediol.

Results and Discussion

The apparently diverse photoreactions of a variety of imines may be rationalized by the intermediacy of an α-amino radical formed by hydrogen atom transfer from an α-hydroxy radical to the imine.[2,3,25,26] Such a rationale is applicable to many of the photoreactions of nitrogen hetero aromatics[27] as well as to simple and substituted imines. Although mechanistic work clearly needs to be done, it is interesting that almost all of the presently known imine photochemistry may be rationalized either by the ground-state process of an imine forming an α-amino radical or by excited-state processes which find formal analogy in systems having carbon–carbon double bonds.[25e]

The nature of the excited species which could be formed on irradiation of the imines **1a–f** is not entirely clear. Although strict analogy with the carbonyl group would suggest n,π* excitation[28] under our conditions, we do not observe the expected solvent shift of the shoulders of the absorption bands at 280–290 mμ for **1a** on changing the solvent from 95% ethanol to hexane.[4a] Detailed curve analysis of the uv spectrum of the anil of benzaldehyde has been taken to indicate[29] that the n,π* absorption appears at 360 mμ and the corresponding absorption in benzophenone imine is reported at 345 mμ.[25d] We were unable to detect any absorption maxima with ε >25 in the 300–400-mμ region for compounds **1a–f**. By analogy with benzaldehyde anil[29] it appears possible that the maxima observed as shoulders for imines in the region 280–290 mμ include absorptions which do not have appreciable contributions from the lone pair on nitrogen. If this is the case,

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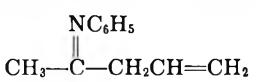
(28) W. Meister, R. D. Guthrie, J. L. Maxwell, D. A. Jaeger, and D. J. Cram, *ibid.*, **91**, 4452 (1969).

(29) H. H. Jaffe, S. Yeh, and R. W. Gardner, *J. Mol. Spectrosc.*, **2**, 120 (1958).

the limited and formal analogy between imine and carbon–carbon double-bond photochemistry, for those cases which involve a chromophore which contains the excited imine, is not so unreasonable as it might appear.

The *meso* isomers of **2a** and **2c** are unambiguously assigned on the basis of the above chemical conversions. Assignments of *meso* and *dl* stereochemistries for **2b** rest on the assumption that the resonances of the benzyl proton in the *meso* isomer will appear downfield from those of the *dl* isomer. Such a difference is observed in the mixture from **2c** and in analogous glycols.[30] The *meso* structure of **2d** is provisional and follows from its preparation by aluminum reduction of the imine, a reaction which appears to give *meso* products.[3,8] Small energy differences due to steric effects and hydrogen bonding in the transition states for radical coupling leading to the *meso* and *dl* products could account for the different sterochemistries,[31] but a contribution from photochemical equilibration has not been ruled out.

Intramolecular photocyclization between a carbonyl group and a carbon–carbon double bond has been observed with 5-hexen-2-ones.[6b] The corresponding



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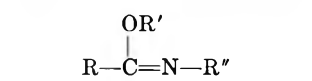

4

R = R′ = CH_3; R″ = C_6H_5
R = C_6H_5; R′ = R″ = CH_3
R = R″ = C_6H_5; R′ = CH_3

anil **3** was prepared and irradiated in hexane, benzene, and alcohol. In each case starting anil or polymeric products were observed. Imidates also appear to be stable to some photolyses.[32] Photolyses of the imidates **4** in hexane, benzene, or ethanol give polymeric products or starting material. Attempts to sensitize the photoreaction with benzaldehyde in ethanol give only hydrobenzoin[33] and 1-phenyl-1,2-propanediol.[34]

Registry No.—**1a**, 25630-14-2; **1b**, 25558-09-2; **1c**, 25558-10-5; **1d**, 25558-11-6; **1e**, 25558-12-7; **1f**, 25558-13-8; **2a** (*meso*), 25558-54-7; **2b** (*dl*), 25558-39-8; **2b** (*meso*), 25558-55-8; **2c** (*dl*), 25558-57-0; **2c** (*meso*), 25558-56-9; **2c** (*meso*) (picrate), 25630-15-3; **2d** (*meso*), 25558-58-1; **2e**, 25558-14-9; **2f**, 25558-15-0; **3**, 25558-16-1; 5-(N-phenyl)amino-1-hexene, 25558-17-2; *meso*-1,2-diamino-1,2-diphenylethane, 951-87-1; *meso*-N,N′-bis(3-aminopropyl)-1,2-diamino-1,2-diphenylethane, 2558-60-5; *meso*-N,N′-bis(3-aminopropyl)-1,2-diamino-1,2-diphenylethane (tetrabenzamide), 25557-86-2.

Acknowledgment.—We are grateful to the Public Health Service (GM-12595) and the Alfred P. Sloan Foundation for support and to the National Science Foundation for an NDEA fellowship to Charles Robert Payet.

(30) J. Wiemann, G. Dana, S. Thuan, and M. Brami, *C. R. Acad. Sci., Ser. C*, **258**, 3724 (1964).
(31) J. H. Stocker and R. M. Jenevein, *J. Org. Chem.*, **34**, 2807 (1969).
(32) L. A. Paquette and G. R. Krow, *J. Amer. Chem. Soc.*, **90**, 7149 (1968); L. A. Paquette and J. R. Malpass, *ibid.*, **90**, 7151 (1968).
(33) G. Ciamician and P. Silber, *Chem. Ber.*, **34**, 1530 (1911).
(34) H. Göth, P. Cerutti, and H. Schmid, *Helv. Chim. Acta*, **48**, 1395 (1965).

Photocyclizations of 5-Vinylnorbornenes

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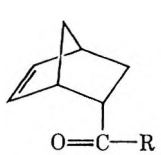
Acetone-sensitized photocyclization of 5-vinylnorbornene (**2**) has been shown to produce tetracyclo[4.2.1.$0^{2,5}$.$0^{3,7}$]nonane (**3**). Ketone **12** has been prepared by an intramolecular thermal cycloaddition of ketene **11**. The chlorides **18c** and **18t** undergo rapid *cis–trans* interconversion in competition with cyclization to form **20**.

Concurrently with our recent studies of photocyclizations of 5-acylnorbornenes (**1**)[1] we initiated a similar investigation of the isoelectronic system 5-vinylnorbornene (**2**).[2] Our interest in this molecule was de-



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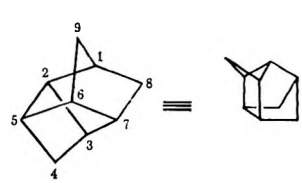
rived from the synthetic potential of the cyclization and from certain photochemical aspects in the realm of 1,5-diene systems.

The first major question we sought to answer concerned the regiospecificity of the cyclization, *i.e* "crossed *vs.* parallel" addition.[3] By analogy with 5-acylnorbornene cyclization, the expected product should be tetracyclo[4.2.1.$0^{2,5}$.$0^{3,7}$]nonane (**3**); however, sim-

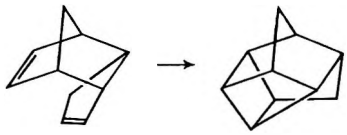


3

ple examples of this type of behavior are absent from the literature.[4] Furthermore, the double bonds of the constrained analog dicyclopentadiene undergo parallel cycloaddition.[5] Although crossed addition is probably

(1) R. R. Sauers, W. Schinski, and M. M. Mason, *Tetrahedron Lett.*, 79 (1969).
(2) R. R. Sauers and W. L. Schinski, Abstracts, 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968, p 112.
(3) R. Srinivasan and K. H. Carlough, *J. Amer. Chem. Soc.*, **89**, 4932 (1967).
(4) Simple γ,δ-unsaturated ketones usually give mixtures of the two product types on irradiation. For a recent summary see W. L. Dilling, *Chem. Rev.*, **66**, 373 (1966). Comparable examples of simple 1,5-diene cyclizations are available only in the gas phase.[3]
(5) G. O. Schenck and R. Steinmetz, *Chem. Ber.*, **96**, 520 (1963).

structurally impossible in this system, it is clear that the parallel mode of addition between the double bonds



of 2 should be feasible. In any event, novel tetracyclic ring systems could be anticipated from cyclization of 2.

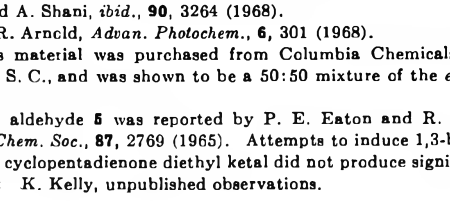
The notable absence of solution-phase photocyclizations of simple 1,5-dienes in the literature undoubtedly is a consequence of the expected inefficiency of vertical energy transfer to simple olefins.[6] In this context, the 5-vinylnorbornene system appeared to be a useful substrate for the study of the behavior of simple 1,5-dienes since triplet energy transfer to norbornene double bonds is well-documented for a variety of sensitizers.[7] Additionally, the ready availability of a variety of substituents on the vinyl group would allow for further elaboration of the details of these cyclizations.

In these initial studies we wish to report on some of the more chemical aspects of sensitized cyclizations of 2 and some of its derivatives.

Results

Irradiation of dilute solutions of commercially available 5-vinylnorbornene (2)[8] in benzene–acetone with Corex-filtered light led to the production of one major and several minor photoproducts. The infrared and nmr spectra of the major product revealed no evidence of unsaturation in agreement with the presumed tetracyclic structure of this material. Owing to the simplicity of the nmr spectrum we were biased toward structure 3 for the major photoproduct. The next experiments were designed with the objective of introducing a substituent into the tetracyclic system which could serve as a site for future manipulations. In this way, it was hoped to provide suitable degradation products to establish the structures of the photoproducts and also to provide intermediates for the synthesis of other molecules of interest.

For these purposes, it was decided to attempt to introduce a carbonyl function at C_9. For convenience, we chose to utilize the ketal 4 in the cyclization step since it appeared readily available from the known[9] aldehyde 5. Thus, reaction of 5 with methylenetriphenylphosphorane gave 4 in 78% yield. Photocyclization of the latter produced a tetracyclic ketal whose structure was correlated with that of 3 *via* hydrolysis to a ketone ($\lambda_{C=O}$ 5.67 μ) which gave 3 on Wolff–Kishner reduction The structures assigned to the ketal and ketone were those of 6 and 7, respectively, on



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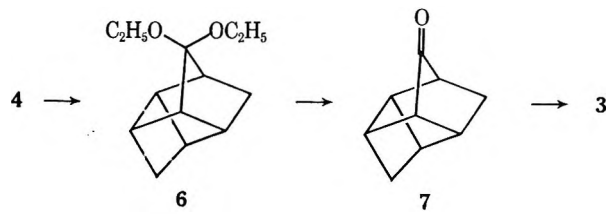
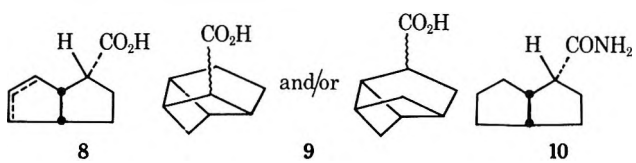


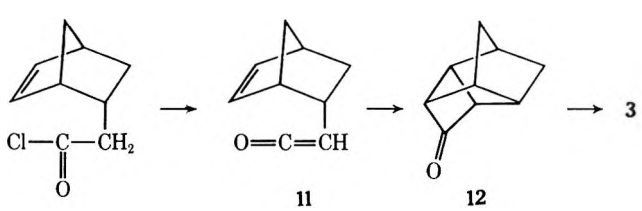
6 7

the basis of the outcome of base-catalyzed cleavage experiments. Thus, under the very mild conditions developed by Gassman and Zalar[10] ketone 7 was transformed into a mixture of unsaturated bicyclic and tricyclic acids. The major component of this mixture was shown to be a *cis*-bicyclo[3.3.0]octene-*endo*-2-carboxylic acid (8) by its conversion to the known[11] *cis*-bicyclo[3.3.0]octane-2-*endo*-carboxamide (10). No attempts were made to define the structure of the tricyclic components (presumably 9 and isomers) owing to the low yields of these.



8 9 10

Although this experiment would appear to establish satisfactorily the basic structures of the tetracyclic systems in question, a more direct correlation was sought.[12] Ketone 12 appeared to be better suited to this type of degradation procedure owing to the expected stability of the product and the presence of the symmetry plane. A viable synthesis of 12 was developed which utilized *in situ* generation and cycloaddition of ketene 11.[13] Not only could 12 be converted into hydrocarbon 3 (*via* the thioketal and Raney nickel desulfurization), but also the base-catalyzed



11 12

cleavage reaction[10] proceeded cleanly with the formation of a new tricyclic acid in good yield. The latter was shown to be tricyclo[3.3.0.$0^{3,7}$]octane-2-carboxylic acid (13) by thermal decarboxylation of the *t*-butyl

(6) For a recent discussion, see J. Saltiel, K. R. Neuberger, and M. Wrighton, *J. Amer. Chem. Soc.*, **91**, 3658 (1969), and N. C. Yang, J. I. Cohen, and A. Shani, *ibid.*, **90**, 3264 (1968).

(7) D. R. Arnold, *Advan. Photochem.*, **6**, 301 (1968).

(8) This material was purchased from Columbia Chemicals Co., Inc., Columbia, S. C., and was shown to be a 50:50 mixture of the *exo* and *endo* isomers.

(9) The aldehyde 5 was reported by P. E. Eaton and R. A. Hudson, *J. Amer. Chem. Soc.*, **87**, 2769 (1965). Attempts to induce 1,3-butadiene to react with cyclopentadienone diethyl ketal did not produce significant yields of adduct: K. Kelly, unpublished observations.

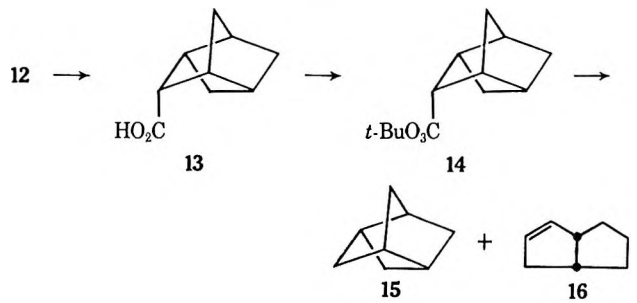
(10) P. G. Gassman and F. V. Zalar, *ibid.*, **88**, 2252 (1966).

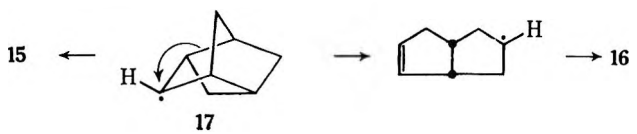
(11) A. C. Cope and M. Brown, *ibid.*, **80**, 2859 (1958). We are indebted to Professor A. Nickon for a sample of this material.

(12) The mechanism by which 8 is formed from 7 must involve addition of hydroxide ion to the carbonyl group followed by two ring openings. The second cleavage presumably involves ring opening of a cyclobutylcarbinyl anion. Precedent for this general type of reaction has been furnished with Grignard reagents. For a discussion and references, see E. A. Hill, R. J. Theissen, and K. Taucher, *J. Org. Chem.*, **34**, 3061 (1969).

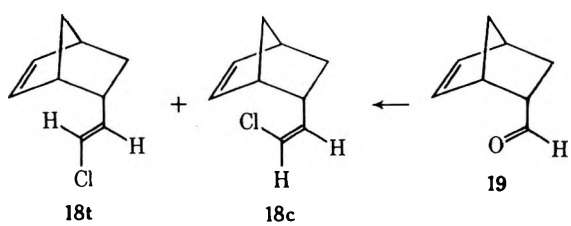
(13) P. Yates and A. G. Fallis, *Tetrahedron Lett.*, 2493 (1968).

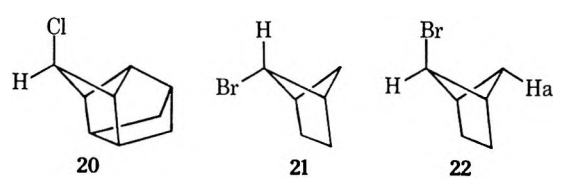
perester (**14**). This sequence produced the known[14] hydrocarbon tricyclo[3.3.0.0^{3,7}]octane (**15**) and, surprisingly, an almost equal amount of bicyclo[3.3.0]-octene-2 (**16**). Apparently, the intermediate free radical in this reaction (**17**) undergoes cleavage in competition with chain transfer.[15]





The final phase of the experimental work dealt with the synthesis and photocyclizations of 1-chloro-2-(5-norbornenyl)ethylenes **18c** and **18t**. The initial experiments utilized the *cis–trans* mixture obtained on treatment of aldehyde **19** with chloromethylenetriphenylphosphorane. The major product obtained on acetone-sensitized photocyclization was assigned structure **20** on the basis of spectral data and the fact that reductive dechlorination produced **3**. The configuration of the chlorine substituent is supported by the nmr spectrum owing to the appearance of a sharp singlet at δ 3.76. The 5-bromobicyclo[2.1.1]hexanes **21** and **22** serve as models for this analysis.[16] Thus, the downfield proton in **21** appears as a multiplet owing to coupling by the two vicinal protons. The geometrical relationships in **22** are such that the only observable coupling is to H_a. The similar geometry about C_4 in **20** coupled with the absence of a proton in the W configuration leads to the prediction of a singlet for the proton in question in agreement with the observed spectrum.





(14) P. K. Freeman, V. N. M. Rao, and G. E. Bigam, *Chem. Commun.*, 511 (1965).

(15) Free-radical chlorination of **18** reportedly leads only to the tricyclic chloride; chain transfer would be expected to be relatively more rapid in this case (private communication from P. K. Freeman).

(16) For a detailed discussion, see K. B. Wiberg, B. R. Lowry, and B. J. Nist, *J. Amer. Chem. Soc.*, **84**, 1594 (1962).

Lastly, samples of the *cis* and *trans* isomers were isolated by preparative gas chromatography and subjected to irradiation in the presence of acetone. Samples were removed at 4 and 21 hr and analyzed (Table I) for total disappearance of starting material, percentage of geometrical isomerization, and percentage of product **20** formed.

TABLE I

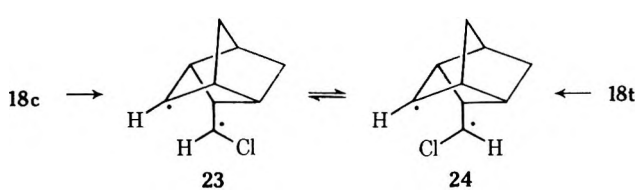
SENSITIZED IRRADIATIONS OF 18t AND 18c

Conversion, %	% yield 18c	18t	20	Time, hr
0	0	100	0	0
19	9	81	3	4
60	18	40	7.5	21
0	100	0	0	0
9	91	7.5	0	4
47	53	19	1	21

Discussion

The formation of tetracyclo[4.2.1.0^{2,5}.0^{3,7}]nonane systems on sensitized irradiation of 5-vinylnorbornenes has been demonstrated for several derivatives. These results reinforce the empirical rules developed for cyclizations of simple 1,5-dienes in the gas phase[3] and for more complex systems in solution.[17] In addition, the results found on photocyclization of the *cis* and *trans* chlorides provide data of mechanistic significance. This data may be summarized as follows: (a) both chlorides produced the same tetracyclic product, *i.e.*, **20**; (b) the *trans* isomer **18t** cyclized considerably faster than the *cis* isomer **18c**; (c) both chlorides underwent geometrical isomerization at about the same rates which in turn were considerably faster than cyclization.

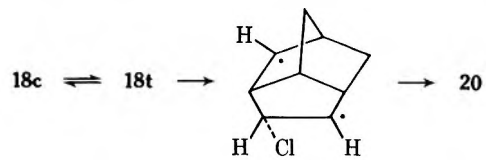
The formation of similar products from geometrically isomeric starting materials has been noted previously and has been attributed to rotational equilibration of intermediate diradicals.[17] In the present context, this argument requires the intermediacy of species **23** and **24** which must equilibrate faster than they cyclize.



It is difficult to rationalize the difference in rates of formation of **20** from **18t** and **18c** if **23** and **24** are necessary intermediates since the rates of formation of the latter would not be expected to be very different. Also, severe distortion of the norbornyl ring must accompany formation of **23** or **24**, an energetically costly process.

(17) R. S. H. Liu and G. S. Hammond, *ibid.*, **89**, 4936 (1967); R. C. Cookson, J. Hudec, S. A. Knight, and B. R. D. Whitear, *Tetrahedron*, **19**, 1995 (1963); R. C. Cookson, *Pure Appl. Chem.*, **9**, 575 (1964); J. D. White and D. N. Gupta, *Tetrahedron*, **25**, 3331 (1969); G. Büchi and I. M. Goldman, *J. Amer. Chem. Soc.*, **79**, 4741 (1957); F. T. Bond, H. L. Jones, and L. Scerbo, *Tetrahedron Lett.*, 4685 (1965); J. L. Charlton, P. DeMayo, and L. Skattebøl, *ibid.*, 4679 (1965); J. L. Courtney and S. McDonald, *Aust. J. Chem.*, **22**, 2411 (1969); J. K. Crandall and C. F. Meyer, Abstracts, 159th National Meeting of the American Chemical Society, Houston, Texas, Feb 1970, ORGN 99.

We believe that the data is better rationalized in terms of the intermediacy of diradical **25**. Clearly, the



25

formation of **25** requires relatively little distortion of the ring system. In addition, the incursion of a large steric effect on the relative ease of formation of a new bond between the ends of the diene systems now seems eminently reasonable provided that the geometrical integrity of the isomers is maintained at the onset of cyclization. In other words, it is the partitioning of the planar triplets between addition and relaxation to twisted states which governs the relative importance of isomerization and cyclization.[18] The fact that 5-vinylnorbornene could be induced to cyclize on sensitization with acetophenone (E_T = 73.6 kcal/mol[19]) is best rationalized in terms of initial energy transfer to the norbornene double bond ($E_T \sim$ 72 kcal/mol)[7] as opposed to the vinyl group ($E_T \sim$ 82 kcal/mol[20]).

The alternate possibility suggested by White and Gupta[17] that initial exiplex formation precedes cyclization would not be inconsistent with our results. Since a close association between the two olefinic centers would be expected, it would not be unlikely that the *trans* chloride would be considerably more reactive than the *cis* isomer.

In any event, it would appear that the nonplanar chloroethylene triplets are not the immediate precursors of the cyclized product.[21,22]

Experimental Section

Elemental analyses were determined by Micro-Tech Laboratories, Skokie, Ill. Infrared spectral data was obtained from a Perkin-Elmer Model 137 spectrometer on thin films or as noted. Nuclear magnetic resonance spectra were obtained from a Varian Model A-60 spectrometer in carbon tetrachloride with tetramethylsilane as internal standard. Gas chromatograms were determined on an Aerograph A90P (analytical and preparative) and a Barber–Coleman Model 5000 chromatograph (capillary) on the following columns: (A) 15-ft 5% Carbowax 20M, (B) 12-ft 2% Carbowax 20M, (C) 12-ft 10% Apiezon L, (D) 150-ft Apiezon L, and (E) 150-ft Castorwax. Melting points were determined on a Mel-Temp apparatus and were uncorrected.

Photocyclization of 2. A. Acetone Sensitization.—A deoxygenated solution of 2.00 g of **2** in a mixture of 2 ml of acetone and 300 ml of benzene was irradiated with the light from a 450-W medium pressure immersion lamp equipped with a Corex filter. Only traces of **2** remained after 22 hr. Analysis by gc (D, 80°) indicated one major component and ~8% minor constituents. The solvents were removed by slow distillation at atmospheric pressure to yield a residue which was distilled at 65–69° (28.5 mm), yield 0.70 g. A pure sample of tetracyclo[4.2.1.$0^{2,5}$.$0^{3,7}$]-nonane (**3**), mp 63.5–64.5°, was obtained by preparative gc (C, 140°): nmr δ 2.30 (m, 5), 1.96 (s, 1), 1.44 (m, 5), 1.09 (d, J = 8 cps, 1).

Anal. Calcd for C_9H_{12}: C, 89.92; H, 10.07. Found: C, 89.78; H, 10.21.

B. Acetophenone Sensitization.—A solution of 10 g of **2** and 10 g of acetophenone in 1200 ml of benzene was irradiated by the above procedure for 33 hr. The benzene was evaporated and the residue was distilled. A 4.0-g fraction was collected which had bp 40–83° (18 mm). Analysis by gc revealed two components in nearly equal amounts and two minor components (<2%). The two major components were collected by gc and shown to be starting material and **3**.

5-Vinylnorbornen-7-one Diethyl Ketal (4).—A slurry of 1.93 g (0.080 mol) of sodium hydride in 35 ml of dimethyl sulfoxide (DMSO) was stirred and heated at 70–75° until the mixture became homogeneous. A solution of 28.67 g (0.083 mol) of methyltriphenylphosphonium bromide in 70 ml of DMSO was added to the above solution. After 10 min. a solution of 13.8 g (0.066 mol) aldehyde **5**[9] in 25 ml of DMSO was added slowly. The temperature of the reaction mixture was kept between 35 and 40° by means of an ice bath. The resulting mixture was allowed to cool to 25° over 1 hr at which time it was poured into 1 l. of an ice–water mixture. The reaction product was extracted into a total of 300 ml of pentane in several stages. After drying and evaporative removal of the solvent, an oil was obtained which on distillation at 58.3 ° (0.3 mm) yielded 10.64 g (78%) of **4**: nmr δ 5.95–5.00 (m, 5), 3.37 (m, 4), 2.08 (m, 1), and 1.10 (m, 7); ir 7.67 (s), 7.82 (s) 8.09 (s), 8.92 (s), 9.30 (s), 10.98 (s), 11.48, 12.05, 12.80, 13.45, 13.62, 13.90, and 14.30 μ.

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.64; H, 9.82.

Tetracyclo[4.2.1.$0^{2,5}$.$0^{3,7}$]nonan-8-one Diethyl Ketal (6).—A solution of 1.5 g of **4** in 600 ml of benzene which contained 1.5 ml of acetone was irradiated for 20 hr under the above conditions. Only a trace of starting material could be detected by gc (A, 150°); one major and one minor peak were seen. Evaporation of the solvent and distillation of the residue gave 1.0 g (66%) of **6**: bp 74–75° (0.3 mm); nmr δ 3.50 (m, 4), 2.48 (s, 4), 2.80–1.30 (m, 4), 1.15 (m, 6); ir 8.80 (s), 8.91 (s), 9.24 (s), 9.44 (s), 10.14, and 11.38 μ.

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.18; H, 9.79.

Tetracyclo[4.2.1.$0^{2,5}$.$0^{3,7}$]nonan-8-one (7).—A solution of 3.34 g (0.016 mol) of **6** in 33 ml of ether was stirred vigorously with 33 ml of 1 *N* hydrochloric acid for 3.5 hr. The ether layer was separated, dried and distilled to yield 1.72 g (80%) of **7**: bp 42° (0.5 mm); nmr δ 2.95-2.35 (m, 4), 2.30–1.97 (m, 2), 1.97–1.66 (m, 3), 1.50–1.05 (m, 1); ir 5.67, 8.84, 11.90, 12.62, 13.21, and 13.61 μ.

Anal. Calcd for $C_9H_{10}O$: C, 80.56; H, 7.51. Found: C, 80.76; H, 7.80.

Wolff–Kishner Reduction of 7.—A solution of 0.30 g (2.29 mmol) of **7** and 0.30 g (6.0 mmol) of hydrazine hydrate in 3 ml of abs ethanol was heated at reflux for 6 hr. After standing overnight at 25° the reaction mixture was diluted with water and the product was extracted into chloroform. The crude hydrazone was dissolved in 2 ml of DMSO and added over 2 hr to a solution of excess potassium *t*-butoxide in 2 ml of DMSO. After standing for 0.5 hr, the mixture was poured into ice–water and the product was extracted into pentane. Evaporation of the solvent followed by sublimation of the residue gave 0.147 g (58%) of **3**: ir identical with that of above material.

Cleavage of 7 with Base.[10]—A slurry of 10.65 g (0.095 mol) of potassium *t*-butoxide and 30 ml of dry ether was cooled in an ice bath in a nitrogen atmosphere. With vigorous stirring, 0.51 g of water was added from a syringe through a rubber septum. The ice bath was removed and 1.65 g (0.012 mol) of ketone **7** was added. After stirring for 2 hr at 25°, the reaction mixture was poured onto ice. The aqueous phase was extracted with ether followed by acidification with hydrochloric acid. On extraction with ether there was obtained 1.42 g (75%) of crude acidic product. A small amount (0.37 g) of crystalline material was separated from the oily acids by trituration with pentane. The two acid fractions were separatedly converted to methyl esters by conversion to acid chlorides (thionyl chloride in benzene) followed by reaction with methanol in benzene–triethylamine. The esters prepared from the noncrystalline fraction were resolved into four components on gc (A, 175°) in the relative proportions 15:30:51:4. On preparative gc the major component and the first two peaks could be collected. The major component proved to be identical with the ester prepared from the crystalline acid: nmr δ 5.45 (m, 2), 3.59 (s, 3), 3.4–1.1 (m, 9); ir 3.27, 5.75

(18) The $S_0 \rightarrow T_1$ transition energy for a vinyl chloride group is unknown. For *trans*-dichloroethylene, estimates range from 72 to 60 kcal/mol; *cf.* G. N. Lewis and M. Kasha, *J. Amer. Chem. Soc.*, **66**, 2100 (1944), and Z. R. Grabowski and A. Bylina, *Trans. Faraday Soc.*, **60**, 1131 (1964).

(19) W. G. Herkstroeter, A. A. Lamola, and G. S. Hammond, *J. Amer. Chem. Soc.*, **86**, 4537 (1964).

(20) D. F. Evans, *J. Chem. Soc.*, 1735 (1960).

(21) It is necessary to assume that energy transfer to the isomeric chloroethylenes does not produce noninterconverting diastereomeric twisted triplet states.

(22) For a relevant discussion with diene triplet states, see P. A. Leermakers, J-P. Montillier, and R. D. Rauh, *Mol. Photochem.*, **1**, 57 (1969).

(s), 8.50 (s), 9.58, 9.72, 10.75, and 14.00 (s) μ. The structure assigned to this ester is that of methyl *endo,cis*-bicyclo[3.3.0]oct-2-ene-6-carboxylate or its isomer **8**.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.94. Found: C, 72.44; H, 8.52.

The nmr of the mixture of the first two components showed no olefinic protons, two methyl peaks at δ 3.63 and 3.56 and complex absorption from δ 2.70 to 1.0. This data is consistent with what would be expected for a mixture of tricyclic esters **9**.

Anal. Calcd for $C_{10}H_{14}O_2$: C, 72.26; H, 8.94. Found: C, 72.59; H, 8.61.

***endo*-cis-Bicyclo[3.3.0]octane-2-carboxamide (10).**—A solution of 0.35 g the above crystalline acid in 20 ml of methanol was reduced at 40 psi of hydrogen in the presence of 5% palladium on carbon. After removal of the catalyst by filtration and evaporation of the methanol, the saturated acid was converted to the acid chloride (thionyl chloride) and the amide (ammonium hydroxide): mp 162–163.8° (lit. mp 162.4–163.3°) after crystallization from benzene; yield, 0.155 g (45%). The infrared spectrum ($CHCl_3$) was virtually identical with that of an authentic sample of **10**[11] and was quite different from that of a sample of *exo-cis* isomer.[23]

Tetracyclo[4.2.1.$0^{2,5}$.$0^{3,7}$]nonan-4-one (12).—A solution of 22.21 g (0.146 mol) of 5-norbornene-2-acetic acid[24] in 250 ml of dry benzene was allowed to react with 23.2 g (0.196 mol) of thionyl chloride for 48 hr at 25°. Evaporation of the solvent followed by distillation of the residue yielded 17.34 g (70%) of acid chloride, bp 55–62° (0.1 mm). A solution of the latter in 50 ml of dry benzene was added over 2 hr to a solution of 10.35 g (0.10 mol) of triethylamine in 1 l. of refluxing benzene. The cooled mixture was poured onto ice–water and the benzene layer was washed successively with dilute aqueous hydrochloric acid and sodium bicarbonate solutions. The dried extracts were concentrated to yield a brown oil which gave 8.37 g (61%) of a white sublimate at 75° (10 mm): nmr δ 2.69 (d, J = 1.3 cps, 3), 2.50 (s, 3), and 1.58 (s, 4); ir (CCl_4) 5.57 (sh), 5.61 (s), 7.72, 7.93, 9.00, and 9.68 μ.

Anal. Calcd for $C_9H_{10}O$: C, 80.56; H, 7.51. Found: C, 80.36; H, 7.42.

Conversion of 12 to 3.—A solution of 0.10 g of ketone **12** in 2 ml of ether was treated with 0.20 g of ethanedithiol and *ca.* 1 mg of boron trifluoride etherate. After 4 hr at 25° the solution was washed with aqueous sodium bicarbonate, dried and evaporated. The crude thioketal was dissolved in 5 ml of ethanol and treated with a small quantity of Raney nickel suspended in ethanol. The resulting mixture was heated at reflux for 4 hr after which time the nickel was removed by filtration. The filtrate was diluted with water and the product was extracted into pentane. Preparative gas chromatography of the concentracted extracts revealed one component whose ir spectrum was identical with that of **3**.

Tricyclo[3.3.0.$0^{3,7}$]octane-2-carboxylic Acid (13).—The ketone (7.24 g, 0.054 mol) was cleaved as before with 47.2 g (0.42 mol) of potassium *t*-butoxide and 2.26 g of water. The acidic fraction obtained (6.37 g, 78%) had mp 99–100.5° after crystallization from hexane: nmr δ 11.98 (s, 1), 2.52–2.38 (s, 5), and 1.42 (s, 6); ir (Nujol) 5.86 (s), 7.76 (s) 10.44 (s), and 13.38 μ.

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 71.08; H, 7.91.

Decarboxylation of 13.[25]—The *t*-butyl perester of **13** was prepared by addition of 0.75 g (4.4 mmol) of the acid chloride (thionyl chloride, triethylamine) to 0.901 g (10.0 mmol) of *t*-butyl hydroperoxide in 5 ml of *p*-cymene. After 2 hr at 0°, the reaction was quenched by addition of ice water. The organic layer was washed with water, hydrochloric acid and aqueous sodium bicarbonate. The dried organic phase was placed in a 15-ml flask equipped with a short-path distillation head. On heating to 125–130° carbon dioxide evolution was observed. After 1 hr the temperature was raised and three fractions were collected: (a) bp <110°; (b) 110–174°; (c) 174–176°. Gc analysis (C, 168°) of these fractions revealed two volatile components in fraction b in the ratio of 57:43. The major component had an infrared spectrum which was identical with that of *cis*-bicyclo [3.3.0]oct-2-ene (**16**).[26] The second component and infrared and nmr spectra congruent with those of tricyclo[3.3.0.$0^{3,7}$]octane (**15**).

cis,trans-**1-Chloro-2-(bicyclo[2.2.1]hept-2-en-5-yl)ethene (18c, 18t).**—A solution of 70 g (0.57 mol) of aldehyde **19**[27] (88% *endo*) in 200 ml of ether was added over 30 min to a suspension prepared from 1.0 mol of *n*-butyllithium, 262 g (1.0 mol) of triphenylphosphine and 99 g (1.0 mol) of methylene chloride in 400 ml of ether.[28] The temperature was maintained at −30° during the addition after which the reaction mixture was allowed to warm to 25° overnight. The resulting mixture was poured onto ice and filtered. The aqueous layer was extracted with ether and the combined extracts were washed with water and dried. The crude product obtained on evaporation of the extracts was triturated with pentane to remove triphenylphosphine oxide. Evaporation of the filtered pentane solution gave 42.14 g (48%) of an oil, bp 74–76° (6 mm). Gc analysis (A, 147°) revealed two main components in nearly equal amounts. Each peak had a small shoulder attributable to the corresponding *exo* isomer. The nmr spectra of the separated materials in both cases revealed clean quartets attributable to the protons on C_2 of the ethylenic moiety. In the spectrum of the component believed to consist of *exo* and *endo trans* isomers this quartet appeared at ~δ 5.25 and showed two couplings, 13 cps (*trans*-HC=CH) and 9 cps (*vic*-CH-CH). In the mixture of *cis* isomers the quartet (δ 5.23) showed couplings of 9 cps (*cis*-HC=CH) and 7 cps (*vic*-HC-CH).

Anal. Calcd for $C_9H_{11}Cl$: C, 69.90; H, 7.17; Cl, 22.93. Found (*trans*): C, 69.74; H, 7.31; Cl, 22.85. Found (*cis*): C, 70.15; H, 7.37; Cl, 23.08.

4-Chlorotetracyclo[4.2.1.$0^{2,5}$.$0^{3,7}$]nonane (20).—A solution of 20.4 g of the mixture of *cis* and *trans* chlorides (**18c, 18t**) in 5 l. of benzene and 25 ml of acetone was irradiated as before for 5 days. The solvents were removed *in vacuo* and the residue was distilled, bp 78–86° (8 mm), to yield 13.24 g of distillate. Gc analysis (E, 100°) showed two new materials in the amounts 11% and 27% (**20**) and considerable amounts of starting materials (~62%). Unsaturated materials were removed by addition of excess bromine in carbon tetrachloride followed by distillation. The only component to survive this treatment was **20**: yield 1.33 g; bp 85–86° (8 mm); nmr δ 3.76 (s, 1), 3.22 (s, 1), 2.6–2.0 (m, 5), and 1.50 (s, 4); ir 7.70, 7.79, 7.90, 8.14, 12.22, 13.00 (s), and 13.58 μ.

Anal. Calcd for $C_9H_{11}Cl$: C, 69.90; H, 7.17; Cl, 22.93. Found: C, 70.12; H, 7.11; Cl, 22.75.

Irradiations of 18c and 18t.—In separate test tubes were placed 65 μl of the *cis* (*exo, endo*) and *trans* (*exo, endo*) chlorides, 100 μl of acetone, and 4 ml of benzene. The tubes were suspended in the center of a Rayonet photochemical reactor and irradiated with the 3000-Å source. Five-microliter aliquots were removed at 4 and 21 hr and analyzed by gc (A, 147°). Since the conditions used did not resolve the *exo* and *endo* components, the percentages reported in Table I refer to the total changes in *cis* and *trans* chlorides normalized to the unirradiated solutions. The qualitative conclusions reached are not affected by the presence of the *exo* isomers.

Conversion of 20 to 3.—To a suspension of 0.60 g (0.263 mg-atoms) of lithium dispersion (1% sodium) in 5 ml of ether was added 0.474 g (3.1 mmol) of **20**. The reaction mixture was stirred and heated at reflux for 2.5 hr. The reaction mixture was quenched with excess methanol and then washed with water. The ether layer was dried and concentrated. Preparative gc (C, 140°) gave 0.105 g (28%) of a single product whose nmr and ir spectra were identical with those of **3**.

Registry No.—**3**, 25557-71-5; **4**, 25554-54-5; **6**, 25557-72-6; **7**, 25557-73-7; **8** (2-ene methyl ester), 25554-55-6; **8** (1-ene methyl ester), 25554-56-7; **12**, 25557-74-8; **13**, 25679-33-8; **18c**, 25554-57-8; **18t**, 25554-58-9; **20**, 25630-08-4.

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New Methods of Introducing the Carbo-t-butoxy Amino-Protecting Group. Investigation of t-Alkyl Chloroformates Substituted with Electron-Withdrawing Substituents

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α-Bromo- and α,α-dibromo-t-butyl chloroformate have been synthesized and found to be significantly more stable than t-butyl chloroformate. On treatment with aniline and other amines the corresponding urethans were obtained although the acylation reaction was generally unsuccessful with amino acid derivatives. Catalytic reduction of the carbanilates over a palladium–carbon catalyst gave the corresponding carbo-t-butoxy derivatives although in low yields only. The α-bromo-t-butyl carbamates were found to undergo a unique "self-cleavage" reaction upon warming in ethanol, being converted to the corresponding ammonium bromide. The chloroformate of 2-methyl-3-butyn-2-ol was also synthesized and shown to be more stable than t-amyl chloroformate.

In addition to its use in peptide chemistry, the carbo-t-butoxy (BOC) group is of considerable importance to the nonpeptide synthetic organic chemist.[1,2] Although for the most part the problem of introducing this group onto an amino function has been solved, a wide variety of acylating agents[3] currently being available, there is still no reagent which is completely satisfactory with the more weakly basic amino compounds. We have therefore sought to develop reagents of this type which would approach acid chlorides in their reactivity. Although t-butyl chloroformate was first synthesized many years ago[4] and has in fact been used occasionally[5,6] to introduce the BOC group, it seems too unstable for general use under ordinary conditions.

In view of the well-known stability of formyl fluoride[7] relative to the corresponding chloride, it was assumed that the same relationship might hold for the related pair of haloformates. With this in mind, numerous methods were investigated for the conversion, at low temperatures, of the unstable chloroformate to the corresponding fluoride. Exchange reactions utilizing hydrogen fluoride[8] and various salts such as sodium[9,10] thallous,[11] and silver fluoride were examined without success. Eventually the fluoroformate (I) was obtained by direct reaction between t-butyl alcohol and carbonyl chlorofluoride[12,13] in methylene dichloride solution in the presence of pyridine. As expected, the fluoroformate proved to be sufficiently stable to be distilled at atmospheric pressure, bp 78–79°, and could be stored without difficulty under ordinary conditions. It showed typical haloformate reactivity toward a variety of amino compounds. Reaction with glycine and alanine in aqueous solution gave the BOC derivatives in a few minutes in 75–80% yield. During the course of our studies Schnabel and Ugi[14] and their associates described a similar method for the preparation of t-butyl fluoroformate and recommended it as a general-purpose carbo-t-butoxylating agent. Unfortunately, however, since carbonyl chlorofluoride is not generally available this would not seem to represent an ideal solution to the problem at hand. On the other hand, if more satisfactory routes to this compound could be devised or if carbonyl chlorofluoride became more readily accessible, I could eventually prove to be one of the carbo-t-butoxylating agents of choice.

A different approach to the problem posed by the instability of t-butyl chloroformate involved the idea of developing stable reagents which would allow introduction of an acyl group which, in a subsequent step, could

(1) For general reviews of amino-protecting groups, see (a) Y. Wolman in "The Chemistry of the Amino Group," S. Patai, Ed., Interscience, New York, N. Y., 1968, Chapter 11. (b) J. F. W. McOmie in "Advances in Organic Chemistry, Methods and Results," Vol. 3, R. A. Raphael, Ed., Interscience, New York, N. Y., 1963, Chapter 4.

(2) For recent applications of the use of the BOC group in the synthesis of nonpeptide nitrogen compounds, see a–n. (a) Y. Inubushi, Y. Masaki, S. Matsumoto, and F. Takami, *J. Chem. Soc. C*, 1547 (1969); (b) G. Zinner and M. Hitze, *Arch. Pharm. (Weinheim)*, **302**, 788 (1969). (c) H. O. House and F. A. Richey, Jr., *J. Org. Chem.*, **34**, 1430 (1969). (d) K. A. Jensen, U. Anthoni and A. Holm, *Acta Chem. Scand.*, **23**, 1916 (1969). (e) K. A. Jensen, G. Felbert, C. T. Pedersen, and V. Svanholm, *ibid.*, **20**, 278 (1966). (f) K. A. Jensen, U. Anthoni, B. Kägi, C. Larsen, and C. T. Pedersen, *ibid.*, **22**, 1 (1968). (g) K. L. Kirk and L. A. Cohen, *J. Org. Chem.*, **34**, 395 (1969). (h) A. M. Felix and R. I. Fryer, *J. Heterocycl. Chem.*, **5**, 291 (1968). (i) T. Sheradsky, *ibid.*, **4**, 413 (1967). (j) C. G. Overberger and W. H. Daly, *J. Amer. Chem. Soc.*, **86**, 3402 (1964). (k) L. A. Carpino and D. E. Barr, *J. Org. Chem.*, **31**, 764 (1966). (l) L. A. Carpino, *ibid.*, **30**, 736 (1965). (m) L. A. Carpino, *J. Amer. Chem. Soc.*, **82**, 3133 (1960). (n) J. R. Bartels-Keith, *J. Chem. Soc. C*, 617 (1966).

(3) In spite of some disadvantages the most widely used reagent is still t-butyl azidoformate. Synthetic routes to this and other, more recently recommended reagents are listed. (a) t-Butyl azidoformate: L. A. Carpino, B. A. Carpino, P. J. Crowley, C. A. Giza and P. H. Terry, *Org. Syn.*, **44**, 15 (1964); K. P. Polzhofer, *Chimia (Aarau)*, **23**, 298 (1969); H. Yajima and H. Kawatani, *Chem. Pharm. Bull. (Tokyo)*, **16**, 182 (1968); M. Itoh and D. Morino, *Experientia*, **24**, 101 (1968); Y. A. Kiryushkin and A. I. Miroshnikov, *ibid.*, **21**, 418 (1965). K. Inouye, M. Kanayama, and H. Otsuka, *Nippon Kagaku Zasshi*, **85**, 599 (1964); D. S. Tarbell, *Accounts Chem. Res.*, **2**, 296 (1969), footnote 27; E. Schnabel, *Justus Liebigs Ann. Chem.*, **702**, 188 (1967). (b) t-Butyl p-nitrophenyl carbonate: G. W. Anderson and A. C. McGregor, *J. Amer. Chem. Soc.*, **79**, 6180 (1957). (c) t-Butyl cyanoformate: L. A. Carpino, *ibid.*, **82**, 2725 (1960); L. A. Carpino, *J. Org. Chem.*, **29**, 2820 (1964); M. Leplawy and W. Stec., *Bull. Acad. Pol. Sci., Ser. Sci. Chim.*, (6) **12**, 21 (1964). (d) N-(t-Butyloxycarbonyloxy)-succinimide: M. Frankel, D. Ladkany, C. Gilon and Y. Wolman, *Tetrahedron Lett.*, 4765 (1966); H. Gross and L. Bilk, *Justus Liebigs Ann. Chem.*, **725**, 212 (1969). (e) t-Butyl 8-quinolyl carbonate: B. Rzeszotarska and S. Wiejak, *ibid.*, **716**, 216 (1968). (f) t-Butylcarbonic diethylphosphoric anhydride: D. S. Tarbell and M. A. Insalaco, *Proc. Natl. Acad. Sci. U. S.*, **57**, 235 (1967); (g) t-Butyl 2,4,5-trichlorophenyl carbonate: W. Broadbent, J. S. Morley, and B. E. Stone, *J. Chem. Soc. C*, 2632 (1967); (h) t-Butyl pentachlorophenyl carbonate: M. Fujino and C. Hatanaka, *Chem. Pharm. Bull. (Tokyo)*, **15**, 2015 (1967).

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be converted to the BOC derivative. The instability of most carbo-*t*-butoxylating agents is a direct consequence of the same factors which promote the rapid acid-catalyzed cleavage of the BOC group, *i.e.*, the ease of formation of the *t*-butyl cation. The stability of alkyl cations can be decreased dramatically by the introduction of electron-withdrawing groups near the cationic center. The effect of α-halogen substitution can be judged from studies on the reactivity of appropriately substituted *t*-butyl chlorides in solvolytic reactions.[15] The effect is also evident in comparisons of the ease of cleavage of appropriate halo-substituted urethans (Table I). The differences are clearly substantial in the case of the bromo- and chlorourethans.

TABLE I

EASE OF CLEAVAGE OF $C_6H_5NHCOOCMe_2CH_2X$ BY HCl-$MeNO_2$ (*ca.* 0.2 *M*)

X	Time[a]
H	1
I	2
Br	240
Cl	600

[a] Time in minutes required for initial appearance of the precipitate of aniline hydrochloride.

In order to make practical use of this stabilizing effect a clean method of reducing the α-halocarbo-*t*-butoxy group to the parent function was required. While it has been possible to effect this conversion the yields have not been high and this and other unforeseen complications have limited the usefulness of this technique. In spite of these other difficulties both α-chloro- and α-bromo-*t*-butyl chloroformates were prepared in fair yields and found to be distillable without difficulty at water aspirator pressure. Reaction with aniline gave the model carbamate derivatives. Although no method could be found by which the α-chlorourethans could be reduced to the BOC derivatives, hydrogenation of the α-bromo analogs proceeded in methanol solution over a palladium–carbon catalyst in the presence of ammonium acetate (eq 1). In the

$$RNHCOC(CH_3)_2CH_2Br \xrightarrow[CH_3OH,\ NH_4OAc]{H_2,\ Pd\text{-}C} RNHCOC(CH_3)_3 \qquad (1)$$

case of model compounds, yields in the reduction never exceeded about 40%. In addition two further difficulties were encountered in the use of α-bromo-*t*-butyl chloroformate. In the first place, although ammonia, aniline, and benzyl amine gave high yields of the corresponding urethans, amino acids, or esters failed to react normally with the chloroformate. Instead of the desired urethan there was isolated the amine hydrobromide (III) and/or the urea derivative (II) (eq 2).

$$ROCOCH_2NH_3^+Cl^- \xrightarrow[Et_3N]{ClCOOCMe_2CH_2Br} \underset{\text{II}}{(ROCOCH_2NH)_2CO} + \underset{\text{III}}{ROCOCH_2NH_3^+Br^-} \qquad (2)$$

R = C_2H_5 or $C_6H_5CH_2$

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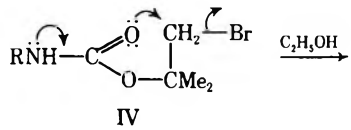
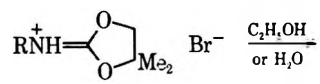
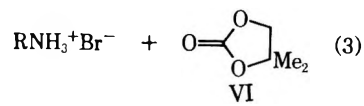
Urea formation in a related reaction involving *t*-amyl chloroformate has been described recently by Sakakibara and coworkers.[16] The amine hydrobromide III may have been derived from the initially formed bromourethan since subsequent experiments showed that the α-bromo-*t*-butyloxycarbonyl derivatives of simple amines such as aniline, while stable in solvents such as benzene and methylene dichloride, underwent conversion to the corresponding amine hydrobromide during attempted recrystallization from polar solvents such as ethanol. This unique reaction represents the "self cleavage" of a protective group and may be visualized as originating in the neighboring-group process pictured in eq 3.[17] Further hydrolysis or



IV

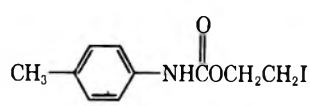


V



VI (3)

solvolysis of intermediate V would lead to the formation of the amine hydrobromide and the cyclic carbonate VI which, in fact, could be isolated from the reaction mixture following filtration of the amine salt. The ease with which this self-cleavage reaction occurs is remarkable, particularly in view of the low solvolytic reactivity reported by Winstein[18,19] for β-bromoethyl carbanilates and the demonstrated stability[21] of the β-iodoethyl derivative VII toward refluxing ethanol.



VII

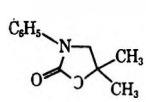
The enhanced solvolytic reactivity of carbanilates such as IV is a notable example of the "*gem*-dimethyl effect."[22] Pertinent data from a limited study of structural effects on this reaction are presented in Table II. The monomethyl derivative (VIII) oc-

(16) S. Sakakibara and M. Itoh, *Bull. Chem. Soc. Jap.*, **40**, 646 (1967).

(17) This represents the first example of a new type of protective group which is of considerable potential utility, namely one which is stable under a variety of conditions but subject to rapid cleavage simply by dissolving in an appropriate solvent. Further studies will deal with the development and possible practical applications of such novel protective groups.

(18) (a) F. L. Scott, R. E. Glick, and S. Winstein, *Experientia*, **13**, 183 (1957). (b) B. Capon, *Quart. Rev. (London)*, **18**, 45 (1964).

(19) If the solvolysis is carried out in ethanolic alkali no carbonate (VI) or aniline is formed. Instead the 2-oxazolidinone (i) is obtained as expected on the basis of preferred N rather than O participation in alkaline solution.



Formation of i was first observed during attempted reduction of IV (R = C_6H_5) to *t*-butyl carbanilate by means of sodium borohydride.[20]

(20) H. C. Brown and H. M. Bell, *J. Org. Chem.*, **27**, 1928 (1962).

(21) J. Grimshaw, *J. Chem. Soc.*, 7136 (1965).

(22) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, pp 196–202.

TABLE II

YIELD OF ANILINE HYDROHALIDE BY REFLUXING IN ETHANOL FOR VARIOUS PERIODS

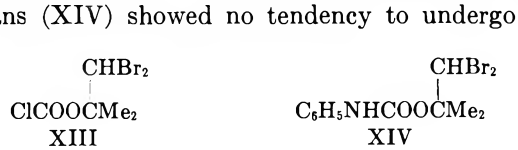
Compd	Yield, % 15 min	1 hr	4 hr
$C_6H_5NHCOOCHCH_2Br$ (VIII)[a] (CH₃)	12	27	
$C_6H_5NHCOOCMe_2CH_2Br$ (IX)[b]	63	92	
$C_6H_5NHCOOCMe_2CH_2Cl$ (X)[c]		16	27
$C_6H_5NHCOOCH_2CMe_2Cl$ (XI)[d]		0	
$C_6H_5NH(CH_2)_3Br$ (XII)[e]		0	

[a] T. Mukaiyama, T. Fujisawa, H. Nohira, and T. Hyugasi, *J. Org. Chem.*, **27**, 3337 (1962). [b] Reference 32. [c] Obtained from the corresponding alcohol and phenylisocyanate, mp 79–81° (benzene–ligroin). *Anal.* Calcd for $C_{11}H_{14}ClNO_2$: C, 58.02; H, 6.20; N, 6.15. Found: C, 58.09; H, 6.32; N, 6.02. [d] E. L. Eliel, C. Herrmann, and J. T. Traxler, *J. Amer. Chem. Soc.*, **78**, 1193 (1956). [e] Obtained as in *c*, mp 44–45.5° (benzene–ligroin, bp 30–50°). *Anal.* Calcd for $C_{10}H_{12}BrNO_2$: C, 46.53; H, 4.69; N, 5.43. Found: C, 46.70; H, 4.82; N, 5.48.

cupies an intermediate position. As expected the α-chloro-*t*-butyloxycarbonyl derivative (X) is considerably less reactive than the corresponding α-bromo derivative (IX). The position of the *gem*-dimethyl groups in IX appears to be optimum as shown by a comparison of the two chloro derivatives, X and XI. The tertiary chloride (XI) is completely unreactive under the conditions used presumably because of hindrance to internal attack at the tertiary center. Although prior ionization of the tertiary chloride might also be expected to result in self-cleavage of XI such an ionization would be inhibited by the inductive effect of the carbamoyloxy group.

Although interesting in themselves these self-cleavage reactions made it impractical to use the α-bromo-BOC group for the present purposes. In view of the relative stability of the corresponding α-chloro derivatives (*e.g.*, X) toward self-cleavage it is unfortunate that no method could be found for the reduction of the α-chloro-BOC to the BOC group.

An attempt was made to avoid the self-cleavage reaction in the case of the α-bromo-*t*-butyl derivatives by introduction of a second α-bromo substituent. As expected,[23] the presence of the second bromine atom markedly increased the stability of the corresponding chloroformate (XIII) and, in addition, the derived urethans (XIV) showed no tendency to undergo the

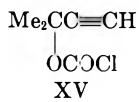


XIII

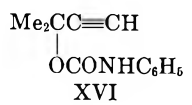
XIV

self-cleavage process. However, in spite of an expectation to the contrary,[24] reduction of the α,α-dibromo-BOC group by catalytic means was no more satisfactory than in the case of the monobromo derivative. Furthermore, the increased bulk around the carbonyl group in chloroformate XIII led to somewhat diminished reactivity toward amino compounds. In view of these difficulties and the various other problems associated with the use of both the α-bromo- and α,α-dibromo-*t*-butyl chloroformates neither of these reagents can be considered to be generally useful in connection with the problem at hand although in certain special circumstances they may prove to be of value, particularly the dibromo derivative.

A final method examined in order to provide appropriate stabilization of a chloroformate precursor to a BOC-like protective group involved replacement of the electronegative halogen atoms in the above series of compounds by a highly electronegative carbon atom. Again judging from solvolysis studies[25] it is clear that the 1,1-dimethyl-2-propynyl cation is considerably less stable than the *t*-amyl cation. In line with this difference the chloroformate (XV) derived from 2-methyl-3-butyn-2-ol proved to be easy to obtain and handle under ordinary conditions. The chloroformate could be distilled without difficulty under water aspirator pressure although the pure material darkened on storage. Reaction with various amino compounds gave the corresponding urethans. It has already been shown that the carbanilate (XVI) may be reduced catalytically over a palladium–carbon catalyst in excellent yield to the *t*-amyloxycarbonyl (AOC) derivative.[26] As is well known that the AOC derivatives are cleaved by trifluoroacetic acid and related reagents as easily as the BOC analogs but heretofore have not offered any significant advantages over the latter, although Sakakibara and coworkers[27] have found that, in direct acylation reactions, *t*-amyl chloroformate is more conveniently handled than *t*-butyl chloroformate. Since the present method gives rather low yields of the chloroformate and requires an extra step its use can be justified only in special cases.



XV



XVI

Experimental Section[28]

α,α-Dibromo-*t*-butyl Alcohol.[29]—To a slurry of 178 g of N-bromosuccinimide in 400 ml of water was added 131.1 g of 1-bromo-2-methylpropene;[30] the mixture was stirred vigorously for 75 min at room temperature. After treatment with $Na_2S_2O_3$ to destroy excess N-bromosuccinimide the mixture was extracted with ether, the ether extracts were dried over $MgSO_4$, and the solution was distilled to give 169 g (75%) of the alcohol: bp 76–78° (12 mm); nmr δ ($CDCl_3$) 1.50 (s, 6 H, CH_3), 2.74 (s, 1 H, OH), 5.72 (s, 1 H, CH).

Anal. Calcd for $C_4H_8Br_2O$: C, 20.71; H, 3.48; O, 6.90. Found: C, 21.00; H, 3.14; O, 6.95.

α,α-Dibromo-*t*-butyl Chloroformate.—Phosgene was passed into 850 ml of methylene dichloride cooled by means of an ice–salt bath until 138 g had been absorbed. To the phosgene solution was added dropwise with stirring 186 g of α,α-dibromo-*t*-butyl alcohol while maintaining the temperature between −15 and −10°. A solution of 70 g of pyridine in 480 ml of methylene dichloride was then dropped in at the same temperature and the mixture then stirred at −10° to 0° for 2 hr. After the mixture

(23) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962, pp 25–26.

(24) *Cf.* L. Horner, L. Schläfer, and H. Kämmerer, *Ber.*, **92**, 1700 (1959).

(25) G. F. Hennion and D. E. Maloney, *J. Amer. Chem. Soc.*, **73**, 4735 (1951).

(26) N. Shachat and J. J. Bagnell, Jr., *J. Org. Chem.*, **28**, 991 (1963).

(27) S. Sakakibara, M. Fujino, Y. Shimonishi, S. Inouye, and N. Inukai, *Bull. Chem. Soc. Jap.*, **38**, 1522 (1965). However, see ref 6.

(28) Elemental analyses are by A. Bernhardt, Mülheim (Ruhr), Germany and C. Meade and associates, University of Massachusetts Microanalytical Laboratory. All melting and boiling points are uncorrected. Infrared spectra were recorded on Beckman IR-5 and IR-10 and Perkin-Elmer 237B instruments. Nmr spectra were obtained on a Varian A-60 instrument using TMS as internal standard.

(29) The method was adapted from that of C. O. Guss and R. Rosenthal, *J. Amer. Chem. Soc.*, **77**, 2549 (1955).

(30) (a) J. K. Farrell and G. B. Bachman, *ibid.*, **57**, 1281 (1935); (b) S. Hünig and M. Kiessel, *Ber.*, **91**, 380 (1958).

had stood overnight at room temperature the salt was separated by filtration and excess phosgene removed by passing nitrogen through the solution for 0.5 hr. The liquid was washed with ice water, 4% $NaHCO_3$ solution, and again with ice water, dried ($MgSO_4$), and distilled to give 173.1 g (74.5%) of the chloroformate: bp 64–67° (1 mm); ir ($CHCl_3$) 5.63 μ; nmr ($CHCl_3$) δ 1.81 (s, 6 H, CH_3), 6.26 (s, 1 H, CH).

Anal. Calcd for $C_5H_7Br_2ClO_2$: C, 20.40; H, 2.40. Found: C, 20.12; H, 2.52.

Treatment of the chloroformate with aniline in methylene dichloride gave the **carbanilate**, mp 58–59.5° (recrystallized from ligroin, bp 60–70°). A polymorphic modification, mp 75–77°, was sometimes obtained.

Anal. Calcd for $C_{11}H_{13}Br_2NO_2$: C, 37.63; H, 3.73; N, 3.99. Found: C, 37.55; H, 3.82; N, 4.16.

α-Bromo-*t*-butyl Chloroformate.—A solution of 79 g of phosgene in 300 ml of methylene dichloride was cooled to −10° and a solution of 68.9 g of α-bromo-*t*-butyl alcohol[31] in 100 ml of CH_2Cl_2 added dropwise over 0.5 hr. There was then added over 2 hr a solution of 35.7 g of pyridine in 250 ml of CH_2Cl_2 while maintaining the temperature between −15 and −10°. The mixture was stirred for an additional 1.5 hr at −10 to 0° and then at 0 to 20° for 12 hr (overnight). The salt was filtered, nitrogen passed through the filtrate for 0.5 hr, and the solution washed once with ice-cold water, once with ice-cold 4% $NaHCO_3$ solution, and again with water. Drying over $MgSO_4$ followed by removal of solvent gave 75.5 g (78%) of the crude chloroformate which was distilled to give 53.7 g (67%), bp 56–64° (6–7 mm). Redistillation gave an analytical sample: bp 54° (5.5 mm); ir ($CHCl_3$) 5.63 μ; nmr ($CDCl_3$) δ 1.62 (s, 6 H, CH_3), 3.63 (s, 2 H, CH_2).

Anal. Calcd for $C_5H_8BrClO_2$: C, 27.87; H, 3.74; Br, 37.09; Cl, 16.45. Found: C, 27.99; H, 3.64; Br, 37.08; Cl, 16.25.

With ammonia the chloroformate gave in 76% yield the **carbamate**, mp 108–110° (recrystallized from C_6H_6). Attempted recrystallization from ethanol gave ammonium bromide.

Anal. Calcd for $C_5H_{10}BrNO_2$: C, 30.62; H, 5.14; N, 7.14; Br, 40.75. Found: C, 30.84; H, 5.19; N, 7.23; Br, 40.65.

With aniline in benzene or methylene dichloride the chloroformate gave in 86% yield the **carbanilate**, mp 77–78° (C_6H_6–ligroin), lit.[32] mp 75.5–76.5°. Attempted recrystallization from ethanol gave aniline hydrobromide. With benzyl amine in methylene dichloride in the presence of triethylamine the chloroformate gave in 60% yield **α-bromo-*t*-butyl N-benzylcarbamate**, mp 75–77° ($CHCl_3$–petroleum ether).

Anal. Calcd for $C_{12}H_{16}BrNO_2$: C, 50.35; H, 5.64; N, 4.90; Br, 27.92. Found: C, 50.42; H, 5.91; N, 5.06; Br, 28.05.

Treatment of Benzyl Glycinate with α-Bromo-*t*-butyl Chloroformate.—To a suspension of 2.0 g of the hydrochloride of benzyl glycinate in 25 ml of methylene dichloride there was added 2.1 g of triethylamine and the solution was cooled in an ice bath and treated during 40 min with a solution of 2.37 g of α-bromo-*t*-butyl chloroformate in 50 ml of methylene dichloride. After the mixture had stood for 20 hr at room temperature it was washed in a separatory funnel with cold water, 0.5 *N* HCl, 2.5% $NaHCO_3$ solution, and finally with water and saturated NaCl solution. Removal of solvent from the dried ($MgSO_4$) solution followed by addition of petroleum ether gave an oil which solidified on cooling to give 0.085 g (6.7%) of the **urea**, $(C_6H_5CH_2OCOCH_2NH)_2CO$, mp 105–106° ($C_6H_6$–petroleum ether).

Anal. Calcd for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86. Found: C, 63.85; H, 5.95; N, 8.22.

From the original petroleum ether filtrate, after removal of solvent, there was obtained 0.158 g (6.5%) of benzyl glycinate hydrobromide, mp 145–148°. With ethyl glycinate the results were similar; the corresponding urea, mp 150–152° (lit.[33] mp 148–150°) was isolated in 23% yield along with varying amounts of ethyl glycinate hydrobromide depending on the conditions.

Reduction of α-Bromo-*t*-butyl Carbanilate.—A solution of 1 g of the carbanilate and 0.5 g of dry NH_4OAc (dried in a desiccator over P_2O_5) in 20 ml of dry methanol [distilled over $Mg(OCH_3)_2$] was treated with 0.1 g of 10% palladium–carbon catalyst and the mixture hydrogenated in a Parr apparatus at 45–55 lb/in² for 8–24 hr. After filtration of the catalyst the filtrate was diluted with 100 ml of water and extracted five times with 15-ml portions of ether. The extracts were washed once with 10 ml of water and 10 ml of $NaHCO_3$ solution (1 *M*), dried ($MgSO_4$), and evaporated to give 0.25–0.31 g (36–44%) of *t*-butyl carbanilate, mp 135–137°, lit.[34] mp 135–137°, identified by comparison of its infrared spectrum with that of an authentic sample. Attempts to carry out the reduction in benzene or ethyl acetate in the presence of NH_4OAc, MgO, or triethylamine were unsuccessful. Similarly Raney nickel in MeOH–NH_4OAc was ineffective. Reduction of the corresponding dibromo urethan by the same method gave a comparable yield of *t*-butyl carbanilate. α-Chloro-*t*-butyl carbanilate was recovered unchanged.

2-Methyl-3-butyn-2-yl Chloroformate.—A solution of 39 g of phosgene in 180 ml of CH_2Cl_2 was stirred and cooled in an ice bath while a solution of 33.2 g of 2-methyl-3-butyn-2-ol and 31.2 g of pyridine in 55 ml of CH_2Cl_2 was dropped in over a period of 1.5 hr. The mixture was allowed to stir in the ice bath for an additional 2 hr and washed twice with 75-ml portions of ice-cold water. After drying ($MgSO_4$), most of the solvent was removed from an ice bath with the aid of a water aspirator. The residue was transferred to a water bath preheated to 50–55° and the chloroformate distilled at 41–44° (20 mm). The distillation was carried out in a large flask because of frothing. The colorless liquid, 19 g (33%), darkened on standing in a refrigerator for a few days: ir ($CHCl_3$) 4.72, 5.62 μ; nmr ($CDCl_3$) δ 1.77 (s, 6 H, CH_3), 2.66 (s, 1 H, ≡CH).

Anal. Calcd for $C_6H_7ClO_2$: C, 49.16; H, 4.81; Cl, 24.19. Found: C, 48.85; H, 4.76; Cl, 24.02.

Treatment of the chloroformate with aniline gave the **carbanilate**, mp 101.5–102.5° [C_6H_6–ligroin (40–70°), 1:10], lit.[26] mp 102–103°.

Self-Cleavage of α-Chloro-*t*-butyl Carbanilate.—A solution of 0.68 g of the urethan in 10 ml of commercial absolute ethanol was refluxed for 1 hr. The solution was allowed to evaporate and the residue triturated with ether, the remaining solid being filtered and washed with ether. There was obtained 0.06 g (15.5%) of aniline hydrochloride, mp 192–196°. The ether filtrates on evaporation gave 0.47 g (69% recovery) of the starting urethan, mp 76.5–77.5°. Related reactions were carried out with other urethans for various periods of time. The results are compared in Table II. The aniline hydrohalides and recovered urethans were identified by spectral comparison (ir, nmr) with authentic samples.

1,1-Dimethylethylene Carbonate.—A solution of 8.47 g of α-bromo-*t*-butyl carbanilate in 180 ml of freshly distilled commercial absolute ethanol was refluxed for 4 hr. Evaporation of the solution gave a semisolid material which was triturated with two 100-ml portions of ether. The filtered ether solutions and washings were combined, dried over $MgSO_4$, and evaporated from a water bath at 40° with the aid of a water aspirator. There was obtained 1.84 g (51%) of a dark oily residue which on distillation gave 0.44 g (12%) of the carbonate, bp 92–94° (10 mm). Repitition of this reaction followed by repeated distillation gave a center cut for analysis: bp 95° (11 mm); ir[35] ($CHCl_3$) 5.52 μ; nmr ($CDCl_3$) δ 1.43 (s, 6 H, CH_3), 4.10 (s, 2 H, CH_2).

Anal. Calcd for $C_5H_8O_3$: C, 51.72; H, 6.94. Found: C, 51.36; H, 7.03.

5,5-Dimethyl-3-phenyl-2-oxazolidinone.—To a solution of 1 g of KOH in 20 ml of methanol was added 1 g of α-chloro-*t*-butyl carbanilate. The solid dissolved and in a few minutes a dense white solid separated. After 5 hr the mixture was diluted with water to 50 ml and the white solid filtered and recrystallized from benzene–ligroin (bp 60–70°) (1:4) to give 0.7 g (83%) of tiny white needles: mp 98–99.5°; ir (Nujol mull) 5.76 μ; nmr ($CDCl_3$) δ 1.55 (s, 6 H, CH_3), 3.78 (s, 2 H, CH_2), 7.45 (m, 5 H, phenyl).

Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.23; H, 7.01; N, 7.45.

***t*-Butyl Chloroformate.**—The original procedure of Choppin and Rogers[4] was followed except that the tedious purification procedure involving thionyl chloride and bromine was omitted. In essence the method was the same as that developed independently by Michejda and Tarbell[36] except that *n*-butane was used as solvent, as in the Choppin–Rogers procedure, rather than ether, as recommended by Michejda and Tarbell. The yield was generally 50–60% after one distillation. The stability of the distilled material was tested by storage at various temperatures.

(31) C. M. Suter and H. D. Zook, *J. Amer. Chem. Soc.*, **66**, 738 (1944).

(32) H. O. House, *ibid.*, **77**, 5083 (1955).

(33) T. C. Frazier, E. D. Little, and B. E. Lloyd, *J. Org. Chem.*, **25**, 1944 (1960).

(34) L. A. Carpino, *J. Amer. Chem. Soc.*, **79**, 4427 (1957).

(35) Ethylene carbonate is reported to show an absorption near 5.5 μ in nonpolar solvents. See C. N. R. Rao, "Chemical Applications of Infrared Spectroscopy," Academic Press, New York, N. Y. 1963, p 234.

(36) C. J. Michejda and D. S. Tarbell, *J. Org. Chem.*, **29**, 1168 (1964).

At −13° there was no decomposition after 1 week although slight decomposition was noted after 5 weeks. In a refrigerator at 6° no change was noted after 1 week. At room temperature complete decomposition occurred in a few days.

The method of Choppin and Rogers was also used to obtain a crude solution of *t*-butyl bromoformate from carbonyl bromide.[37] Upon storage of the bromoformate solution overnight at 6° complete decomposition occurred.

Treatment of *t*-Butyl Chloroformate with Thallous Fluoride.—A mixture of 27.3 g of *t*-butyl chloroformate and 48 g of thallous fluoride was stirred at 0° for 5 days. Distillation gave 16.4 g (89%) of *t*-butyl chloride, bp 52°. After only 10 hr the chloroformate could be recovered unchanged. Similar results were obtained in methylene dichloride and tetramethylene sulfone[38] as solvent or by substitution of alkali or silver fluorides for the thallous salt. In no case could *t*-butyl fluoroformate be obtained in this way.

***t*-Butyl Fluoroformate.**—Carbonyl chlorofluoride was passed into 50 ml of methylene dichloride while cooling in a Dry Ice–ethanol bath until 11 g had been absorbed. There was then dropped in with continued cooling in the same bath over a period of 15 min a solution of 7.4 g of *t*-butyl alcohol in 7.9 g of pyridine. The mixture was stirred in the Dry Ice–ethanol bath for 1 hr, at 0° for 3 hr, and at room temperature for 24 hr. The mixture was shaken in a separatory funnel twice with 25-ml portions of ice water (ice chips present), dried over $MgSO_4$, filtered, and distilled. After removal of the solvent there was obtained 4.6 g (38%) of the fluoroformate: bp[39] 78–79° [lit.[14] bp 4° (15 mm)]; ir (neat) 5.48 μ; nmr ($CDCl_3$) δ 1.27 (s, CH_3).

(37) H. J. Schumacher and S. Lehner, *Ber.*, **61**, 1671 (1928).
(38) C. W. Tullock and D. D. Coffman, *J. Org. Chem.*, **25**, 2016 (1960).

Registry No.—α,α-Dibromo-*t*-butyl alcohol, 24482-83-5; α,α-dibromo-*t*-butyl chloroformate, 25557-88-4; α,α-dibromo-*t*-butyl carbanilate, 25557-89-5; α-bromo-*t*-butyl chloroformate, 25557-90-8; α-bromo-*t*-butyl carbamate, 25557-91-9; α-bromo-*t*-butyl N-benzylcarbamate, 25557-92-0; $(C_6H_5CH_2OCOCH_2NH)_2CO$, 25557-93-1; 2-methyl-3-butyn-2-yl chloroformate, 25557-94-2; 1,1-dimethylethylene carbonate, 4437-69-8; 5,5-dimethyl-3-phenyl-2-oxazolidinone, 25557-96-4.

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(39) Distillation at atmospheric pressure is not recommended since some decomposition must have occurred at this point. Prior to distillation reaction of an aliquot of the crude solution with glycine gave BOC-glycine in 80% yield, mp 88–90°. Further examination of *t*-butyl fluoroformate was discontinued because of the timely appearance of the paper of Schnabel and Ugi and their collaborators[14] who provide detailed descriptions of a similar method for the large-scale synthesis of this compound

The Synthesis and Nuclear Magnetic Resonance Spectra of Some Disubstituted Derivatives of 2-Methyl-6-thiatricyclo[3.2.1.1^{3,8}]nonane[1]

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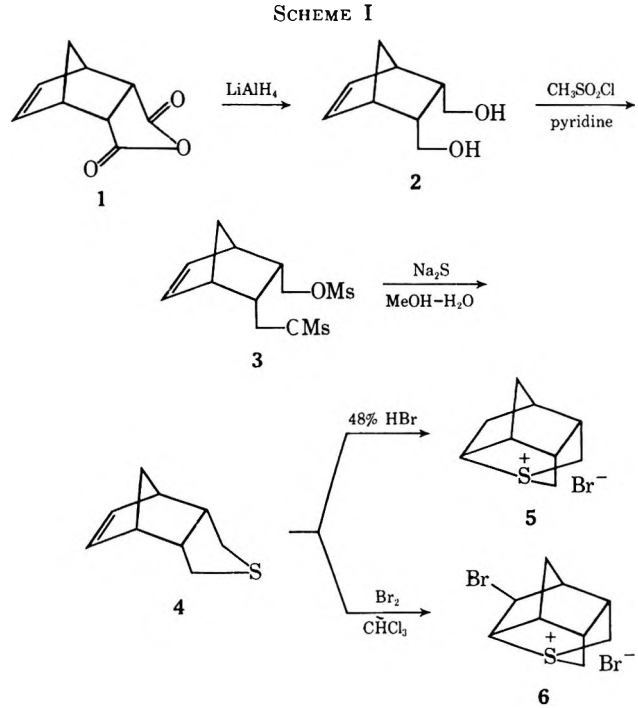
2-Methyl-6-thiatricyclo[3.2.1.1^{3,8}]nonane (**8**) has been prepared by reduction of sulfonium salt **5** with lithium aluminum hydride. A series of 4,10-disubstituted derivatives (**10a–e**) of **8** has been prepared by the reaction of several nucleophiles with bromosulfonium salt **6**. Nmr chemical shifts are presented for the tricyclic compounds, for sulfonium salts **5** and **6**, and for some symmetrical norbornene(ane) derivatives. Spin-decoupling techniques have been used on two of the compounds (**2** and **10a**) to confirm the assignment of chemical shifts. A mechanism for the formation of **10** *via* thiiranium ion **12** has been proposed.

The synthesis of 2-thia-1,2-dihydro-*endo*-dicyclopentadiene (**4**) from *endo-cis*-5-norbornene-2,3-dicarboxylic anhydride (**1**) *via* diol **2** and dimesylate **3** has previously been described.[2] The facile cyclization of **4** to the sulfonium salts **5** and **6** with 48% hydrobromic acid and bromine in chloroform, respectively, has also been reported from this laboratory.[2,3] These reactions are summarized in Scheme I.

The sulfonium salt **5** has been found to react with various nucleophilic reagents to yield monosubstituted products,[4] and the bromosulfonium salt **6** has been reported to react with aqueous lithium carbonate to yield *exo-cis*-2-thiatetrahydro-*endo*-dicyclopentadiene-9,10-diol (**7a**).[3]

At this time we wish to report the preparation and nmr spectrum of 2-methyl-6-thiatricyclo[3.2.1.1^{3,8}]-

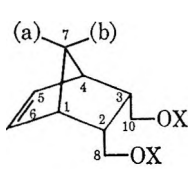
SCHEME I



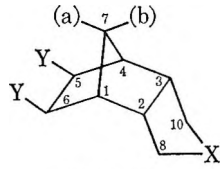
(1) (a) The support of this research by Research Grant CA-4298 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service, is gratefully acknowledged. (b) This work represents part of the research of R. F. G., partially fulfilling the requirements for the degree of Doctor of Philosophy at Duke University.
(2) P. Wilder, Jr., and L. A. Feliu-Otero, *J. Org. Chem.*, **30**, 2560 (1965).
(3) P. Wilder, Jr., and L. A. Feliu-Otero, *ibid.*, **31**, 4264 (1966).
(4) L. A. Feliu-Otero, Ph.D. Thesis, Duke University, Durham, N. C., 1965.

TABLE I

CHEMICAL SHIFTS FOR SOME NORBORNENE(ANE) DERIVATIVES[a]



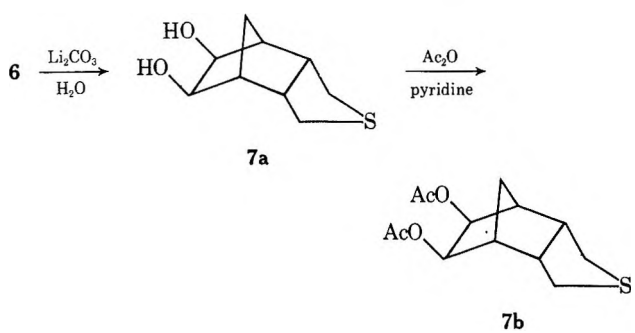
2,3



1,4,7a-b,9

			Chemical shift, δ[b]						
Compd	X	Y	1,4	$2,3_{exo}$	5,6olef	$5,6_{endo}$	7(a)	7(b)	8,10
1	O	C=C	3.50	3.60	6.31		1.82	1.57	*c*
2	H[d]	C=C	2.80	2.52	6.05		1.40[e]	1.40[e]	~3.47
3	SO_2CH_3[f]	C=C	3.00	2.74	6.24		1.65	1.42	~4.01
4	S	C=C	~3.21	~2.44	6.18		1.77[g]	1.77[g]	~2.76
7a	S	OH[h]	2.84	2.21		4.36	1.98	1.32	2.84
7b	S	OAc[i]	2.88	2.33		5.44	2.02	1.45	2.88
9	S	H	2.70	2.17		~1.45[j]	1.48[k]	1.48[k]	2.70

[a] The numbering shown above for compounds 1, 4, 7a–b, and 9, is not correct as far as nomenclature is concerned; *i.e.*, these compounds are derivatives of 2-oxa- or 2-thiadicyclopentadiene. However, the incorrect numbering system is used in order to focus on the relationship of these compounds to their norbornyl analogs. [b] δ values are measured relative to TMS = δ 0.00. Solvent is $CDCl_3$ except for 9 for which it is CCl_4. [c] Compound 1 is an anhydride. [d] OH protons at δ 4.52 (2 H). [e] Center of a triplet, $S \approx 4$ Hz. [f] SO_2CH_3 protons at δ 3.00 (6 H). [g] Center of a triplet, $S \approx 4$ Hz. [h] OH protons at δ 3.77 (2 H). [i] $COCH_3$ protons at δ 2.02 (6 H). [j] Two resonances appear at ~δ 1.78 and ~δ 1.45 for the $5,6_{exo}$ and $5,6_{endo}$ protons. Assignment is indefinite, but the upfield protons are assumed to be *endo*. See ref 8. [k] Center of a quartet, $S \approx 5$ Hz.



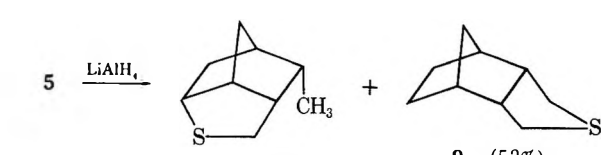
7a

7b

nonane (**8**) and also to report the preparation and nmr spectra of several 4,10-disubstituted derivatives, **10a–e**, of **8**.

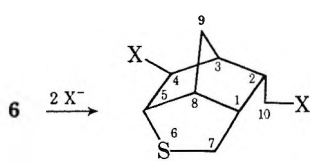
Results

The parent compound **8** was prepared by the reaction of lithium aluminum hydride with **5**. The mixture of compound **8** and 2-thiatetrahydro-*endo*-dicyclopentadiene (**9**)[2,5] which resulted was separated by preparative glpc.



8 (47%) **9** (53%)

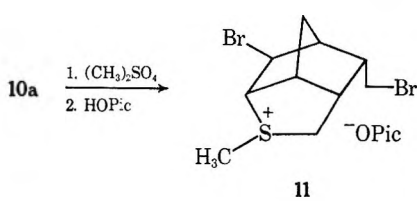
The disubstituted derivatives of **8** were prepared from the bromosulfonium bromide **6**. 4-Bromo-2-bromomethyl-6-thiatricyclo[3.2.1.$1^{3,8}$]nonane (**10a**), a yellow oil, appeared after **6**, a white crystalline solid, was kept for several days at room temperature. The remaining derivatives, **10b–e**, were prepared by the reaction of the sodium or potassium salt of the anion with **6** in an aqueous medium (glacial acetic acid for **10e**).



10a, X = Br
b, X = OPh
c, X = SPh
d, X = 2-SPyr
e, X = OAc

The assignment of structures to compounds **8** and **10a–e** was based primarily upon interpretation of their nmr spectra, which were in no way similar to the spectra of the symmetrical compounds **1–4**, **7a–b**, and **9**, but which were much more closely related to the spectra of the sulfonium salts **5** and **6**. The chemical shift data for the symmetrical compounds are summarized in Table I and for compounds **5**, **6**, **8**, and **10a–e** in Table II.

As a final proof of structure, the methyl picrate salt **11** was prepared from the dibromide **10a** and was subjected to X-ray analysis.[6] This evidence confirmed the structure as written for **11** and eliminated the possibility of sulfur being present in a six-membered sulfide ring.



11

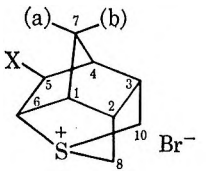
Nmr Spectra.—The assignment of chemical shifts to the protons of the symmetrical norbornene deriva-

(5) S. F. Birch, N. J. Hunter, and D. T. McAllan, *J. Org. Chem.*, **21**, 970 (1956).

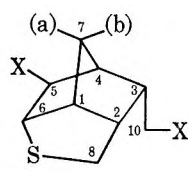
(6) The details of this analysis will be published separately.

TABLE II

CHEMICAL SHIFTS FOR SOME 2-METHYL-6-THIATRICYCLO[3.2.1.1^{3,8}]NONANE DERIVATIVES[a]



5,6



8, 10a–e

		Chemical shift, δ[b]								
Compd	X	1,4	2,3$_{exo}$	5$_{exo}$	5$_{endo}$	6$_{exo}$	7(a)	7(b)	8	10
5	H	3.04	2.75	1.40	1.90	4.13	2.17	1.63	3.69	3.35
6	Br	3.17	3.00		5.05	4.40	2.40	2.10	3.94	3.50
8	H	2.74	1.97	~1.73[c]	~1.73[c]	3.17	~1.52[d]	~1.52[d]	2.62	1.00
10a	Br	2.92	2.68		4.08	3.74	2.27	1.76	2.84	3.58
10b	OPh[e]	2.97	2.62		4.30	3.24	2.20	1.63	2.80	4.20
10c	SPh[f]	2.95	2.38		3.47	3.27	1.97	1.55	2.74	3.12
10d	2-SPyr[g]	2.98	2.48		4.00	3.32	2.05	1.58	2.74	3.52
10e	OAc[h]	2.83	2.32		4.53	3.10	1.93	1.57	2.72	4.18

[a] See footnote *a* to Table I; the salts are dimethanocyclopenta[*c*]thiolium derivatives, and the other compounds are 6-thiatricyclo[3.2.1.1^{3,8}]nonane derivatives. [b] δ values are measured relative to TMS = δ 0.00. Solvent is $CDCl_3$ except for **5** and **6** for which it is D_2O and **8** and **10e** for which it is CCl_4. [c] Center of a multiplet, W_h = 7 Hz. [d] Center of a multiplet, W_h = 8 Hz. [e] Ph protons centered at δ 7.07 (10 H). [f] Ph protons centered at δ 7.24 (10 H). [g] Pyr protons centered at δ 8.44 (2 H) and 7.24 (6 H). [h] $COCH_3$ protons at δ 1.98 (3 H) and 1.95 (3 H).

tives (Table I) is relatively straightforward since different magnetic environments influence each type of proton and give rise to resonances at five or six separate frequencies. The spectrum of compound **1**[7] shows the C_2- and C_3-*exo* protons as a multiplet somewhat downfield from the more complex multiplet of the C_1 and C_4 protons. The deshielding of the C_2- and C_3-*exo* protons is due to the adjacent *endo*-carboxyl functions.[8] In the remaining examples, the C_2- and C_3-*exo* protons occur upfield from the C_1 and C_4 protons with the most shielding in the fully saturated compounds **7a–b** and **9**. The C_5 and C_6 olefinic protons appear in all cases as an "irregular" triplet with a separation (S) between the outer lines of ~4 Hz in agreement with previously reported examples.[8] The C_5- and C_6-*endo* protons in the diol **7a** appear as a doublet (J = 3 Hz) at δ 4.36, and upon acylation the doublet is shifted downfield 1.08 ppm as would be expected.[9] 2-Thiatetrahydro-*endo*-dicyclopentadiene (**9**) exhibits multiplets at ~δ 1.78 and ~1.45 which also overlap with the sharper resonances due to the C_7 protons. These multiplets were assigned to the C_5- and C_6-*exo* and C_5- and C_6-*endo* protons, respectively.[8] The nature of the resonances due to the $C_{7(a)}$ and $C_{7(b)}$ protons varies considerably from compound to compound. Diol **2** and unsaturated sulfide **4** exhibit two-proton triplets with $S \approx 5$ Hz. The remaining compounds have separate resonances for the $C_{7(a)}$ and $C_{7(b)}$ protons with coupling constants J_{ab} = 8–10 Hz. In two of these cases, assignment of chemical shifts to the $C_{7(a)}$ and $C_{7(b)}$ protons is relatively unambiguous. For diol **7a**, the doublet at δ 1.32 may be assigned to the $C_{7(b)}$ proton on the basis of additional small coupling (absent for the doublet at δ 1.98) with the C_5- and C_6-*endo* protons.[8] The diacetate **7b** should be analogous; however, the downfield doublet is hidden under the methyl resonances of the acetate groups and cannot be compared directly with the doublet at δ 1.45.

In the case of anhydride **1** and dimesylate **3**, the upfield doublet is also assigned to the $C_{7(b)}$ proton. Here each line of the downfield doublet shows additional coupling in the form of a triplet ($S \approx 4$ Hz) indicating $J_{C_{7(a)}-C_1} = J_{C_{7(a)}-C_4} \approx 2$ Hz. These results are in agreement with those reported by Laszlo and Schleyer for *cis-endo*-2,3-dichloro-5-norbornene.[8] The interpretation of the resonances due to the C_1, C_4, C_8, and C_{10} protons is difficult. In anhydride **1**, the C_1 and C_4 protons appear as a broad multiplet coupled with C_2- and C_3-*exo* protons, the olefinic protons, and the C_7 proton. In diol **2** the C_1 and C_4 protons appear as a broad singlet at δ 2.80 (W_h = 8 Hz); the C_8 and C_{10} protons exhibit a complex group of lines centered about δ 3.47. Dimesylate **3** has a similar complex multiplet at about δ 4.01. Its bridgehead protons, however, are obscured under the methyl resonances of the methanesulfonate groups. 2-Thia-1,2-dihydro-*endo*-dicyclopentadiene (**4**) has two very complex multiplets at δ 3.21 and 2.76 for the bridgehead and C_8, C_{10} protons, respectively. In the remaining compounds **7a–b** and **9**, a six-proton singlet (W_h = 3–5 Hz) appears for these protons. The simplicity of the signal for the C_8, C_{10}, and bridgehead protons in these latter cases must be due to a fortuitous overlap of the various signals and perhaps to a reduction in the magnitude of the geminal coupling at C_8 and C_{10} caused by the adjacent sulfur atom.[10] So, although there are complications in some of the individual cases, the assignment of chemical shifts to the protons of the symmetrical compounds is feasible.

The nmr spectra of the derivatives of 2-methyl-6-thiatricyclo[3.2.1.1^{3,8}]nonane (**8**, **10a-e**) and of the two salts (**5** and **6**) have certain similarities which led to the postulation of the tricyclic structure for **8** and **10a–e** Bromosulfonium salt **6** has a singlet ($W_h \approx 4$ Hz) at δ 5.05 for the C_5-*endo* proton; all of the other C_5-*exo* substituted compounds have an appropriately positioned singlet (W_h = 3–4 Hz) representing this proton. The C_6-*exo* proton of the salt **6** appears as a doublet (J =

(7) M. Green and E. A. C. Lucken, *Helv. Chim. Acta*, **45**, 1870 (1962).

(8) P. Laszlo and P. von R. Schleyer, *J. Amer. Chem. Soc.*, **86**, 1171 (1964), and references therein.

(9) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, p 55.

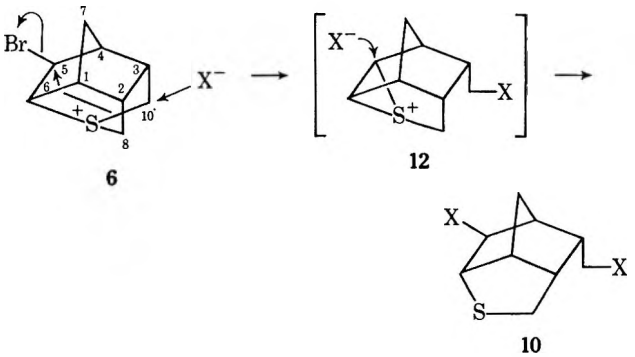
(10) Y. Allingham, R. C. Cookson, and T. A. Crabb, *Tetrahedron*, **24**, 1989 (1968).

5 Hz) at 4.40 coupled to the C_1 proton; in the dibromide **10a**, it is a doublet (J = 5 Hz) at δ 3.74; and, in the remaining compounds, it is also a doublet (J = 4–5 Hz) at δ 3.10 to 3.32 (except for the parent compound **8** where the lack of a C_5-*exo* substituent allows additional coupling). These results are in agreement with those obtained for the 6-oxatricyclo[3.2.1.1^{3,8}]nonane derivatives studied by Ramey, *et al.*[11] In all but one of these unsymmetrical compounds, the $C_{7(a)}$ and $C_{7(b)}$ protons appear as a pair of doublets (J = 11 Hz) near δ 2.00, the exception being the parent compound **8** where overlapping resonances obscure the details. The downfield resonance is assigned to the $C_{7(a)}$ proton in each case.[11] Also, the upfield doublet is generally less sharp owing to long range coupling with the C_5-*endo* proton. The other main diagnostic feature present in all of the 6-thiatricyclo[3.2.1.1^{3,8}]nonane derivatives is a doublet ($J \approx 7$ Hz) for the C_{10} protons. In the parent compound **8** this appears upfield at δ 1.00. In the other compounds, it appears at an appropriate position downfield owing to the variation in substituents at C_{10}. The remaining protons appear between δ 2 and 3, frequently as two broad singlets (W_h = 8–10 Hz) and one sharper singlet (W_h = 3–4 Hz) near δ 3. Decoupling experiments (see below) have helped somewhat to unravel these resonances, but no unequivocal interpretation can be given. In particular the ABX splitting observed for the C_8 protons in the 6-oxa analog[11,12] is not seen because of overlapping resonances.

In order to gain more confidence in the assignment of chemical shifts to the C_1, C_4, C_2- and C_3-*exo*, and the $C_{8(10)}$ protons, decoupling experiments were run on several samples. For diol **2** irradiation of the broad multiplet at δ 2.52 simplifies considerably the complex pattern of the $C_{8(10)}$ protons at $\sim\delta$ 3.47, which indicates that this multiplet represents the C_2- and C_3-*exo* protons. Irradiation of the sharper multiplet at δ 2.80 sharpens both the olefinic resonance and the C_7 proton resonances which indicates that this multiplet represents the C_1 and C_4 protons. In the case of dibromide **10a** the spectrum was run in benzene solution to provide better separation of the various resonances, an exception being part of the doublet for the $C_{7(a)}$ proton which is lost under the broad resonance due to the C_2- and C_3-*exo* protons at δ 2.10 The pertinent experiments here are (1) irradiation of the $C_{7(b)}$ proton at δ 1.22 with observed sharpening of the signal for the C_5-*endo* proton at δ 3.87, (2) irradiation of the resonance due to the C_1 and C_4 protons at δ 2.47 with the observation of the collapse of the doublet for the C_6-*exo* proton at δ 3.53 into a singlet, and (3) irradiation of the resonance due to the C_2- and C_3-*exo* protons at δ 2.10 with the observation of the collapse of the doublet for the C_{10} protons at δ 3.05 into a singlet. Thus, these decoupling experiments have been helpful in assigning the resonances found between δ 2 and 3.

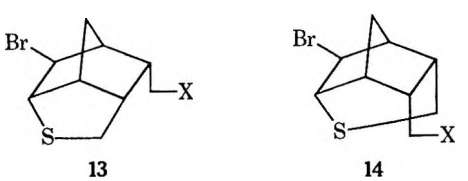
Mechanism.—Several possible mechanisms may be proposed for the reaction of the bromosulfonium salt **6** with the various nucleophiles reported above. It is apparent that the reaction of **6** with aqueous lithium carbonate which produces the symmetrical diol **7a**[3] proceeds by a different route, probably one in which the lithium cation coordinates with the unshared electrons of the bromine at C_5 leading to loss of bromide ion and nucleophilic attack in a concerted process.

In the present example, the following sequence is proposed.



Nucleophilic attack at C_8 or C_{10} predominates since these positions are less sterically hindered than C_6. Concerted loss of bromide ion leads to the formation of a thiiranium ion (episulfonium ion)[13] intermediate, **12**. The subsequent addition of a second mole of X^- at C_5 yields the product containing the five-membered sulfide ring.[14]

Since these reactions are run in refluxing aqueous solution, generally for 12 hr or more, it is probable that the thermodynamically favored products are formed. Additional intermediates such as **13** and **14** may be



involved although **14** does appear to suffer from excessive nonbonded interactions and no products analogous to it are observed. Concerted loss of bromide ion in the formation of **12** is not necessary. Initial attack of X^- at C_6 is not likely because of steric hindrance to its approach by the C_5 bromine and the $C_{7(a)}$ hydrogen and also no symmetrical products analogous to **7a** are observed.

Experimental Section[15]

2-Thia-1,2-dihydro-*endo*-dicyclopentadiene (4) was prepared by the method previously described:[2] bp 55–57° (0.3 mm) [lit.[2] bp 57° (0.45 mm)]; nmr ($CDCl_3$) δ 6.18 (2 H), ~3.21 (2 H), ~2.76 (4 H), ~2.44 (2 H), and 1.77 (2 H).

Hexahydro-1H-1,5:2,4-dimethanocyclopenta[*c*]thiolium bromide (5)[2] was prepared from **4** and 48% hydrobromic acid: mp 243–245° dec (lit.[2] mp 245–247° dec); nmr (D_2O) δ 4.13 (1 H), 3.69 (2 H), 3.35 (2 H), 3.04 (2 H), 2.75 (2 H), 2.17 (1 H), 1.90 (1 H), 1.63 (1 H), and 1.40 (1 H).

(11) K. C. Ramey, D. C. Lini, R. M. Moriarty, H. Gopal, and H. G. Welsh, *J. Amer. Chem. Soc.*, **89**, 2401 (1967).

(12) D. J. Goldsmith, B. C. Clark, Jr., and R. C. Joines, *Tetrahedron Lett.*, **11**, 1149 (1966).

(13) W. H. Mueller, *Angew. Chem., Int. Ed. Engl.*, **8**, 482 (1969), and references therein.

(14) F. Lautenschlaeger, *J. Org. Chem.*, **33**, 2620 (1968).

(15) Melting points and boiling points are uncorrected. Analyses are by Galbraith Laboratories, Knoxville, Tenn., or M-H-W Laboratories, Garden City, Mich. Analytical glpc analyses were performed on a Varian-Aerograph Series 1200 instrument; preparative glpc analyses were performed on an Aerograph Model A-700 Autoprep. Nmr spectra were recorded on a Varian A-60 or Varian T-60 spectrometer; decoupling experiments were done on the T-60. Mass spectra were recorded on a Bendix time-of-flight spectrometer.

endo-**7-Bromohexahydro-1H-1,5:2,4-dimethanocyclopenta[c]-thiolium bromide** (**6**)[3] was prepared from **4** and bromine in $CHCl_3$: mp 117–118° (lit.[3] mp 117–118°); nmr (D_2O) δ 5.05 (1 H), 4.40 (1 H), 3.94 (2 H), 3.50 (2 H), 3.17 (2 H), 3.00 (2 H), 2.40 (1 H), and 2.10 (1 H).

exo-cis-**2-Thiatetrahydro-*endo*-dicyclopentadiene-9,10-diol** (**7a**)[3] was prepared from **6** and aqueous lithium carbonate: mp 106–108° (lit.[3] mp 102–106); nmr ($CDCl_3$) δ 4.36 (2 H), 3.77 (2 H), 2.84 (6 H), 2.21 (2 H), 1.98 (1 H), and 1.32 (1 H).

exo-cis-**2-Thiatetrahydro-*endo*-dicyclopentadiene-9,10-diacetate** (**7b**).—To a solution of 3 ml of acetic anhydride in 15 ml of dry pyridine (distilled from BaO) was added a solution of 100 mg (0.00054 mol) of diol **7a** in 15 ml of dry pyridine. The mixture was stirred and refluxed overnight. The reaction mixture was poured into 100 ml of ice water and the aqueous solution extracted with three 25-ml portions of ether. The ethereal extract was washed with dilute HCl, dried over $MgSO_4$, and concentrated. Final purification was accomplished by preparative glpc on a 5 ft × $^3/_8$ in. 20% SE-30 column at 175° (200-ml/min He flow): nmr ($CDCl_3$) δ 5.44 (2 H), 2.88 (6 H), 2.33 (2 H), 2.02 (7 H), and 1.45 (1 H).

Anal. Calcd for $C_{13}H_{18}O_4S$: C, 57.75; H, 6.71. Found: C, 57.99; H, 6.73.

Lithium Aluminum Hydride Reduction of 5.[4] Preparation of 2-Methyl-6-thiatricyclo[3.2.1.1^{3,8}]nonane (**8**) **and 2-Thiatetrahydro-*endo*-dicyclopentadiene** (**9**).—A suspension of 0.25 g (0.066 mol) of lithium aluminum hydride and 1.5 g (0.065 mol) of sulfonium salt **5** in 50 ml of anhydrous ether (dried over Na) was refluxed overnight. Water (25 ml) was carefully added to the reaction mixture to destroy excess lithium aluminum hydride, and 10% HCl was added to solubilize the aluminum salts. The aqueous layer was extracted with two 50-ml portions of ether. The extracts were combined with the original ether layer, dried over $MgSO_4$, and concentrated. Analytical glpc on a 5 ft × $^1/_8$ in. 3% SE-30 column at 100° indicated two components to be present in the ratio 47:53. Preparative glpc on a 10 ft × $^3/_8$ in. 20% SE-30 column at 165° (200-ml/min He flow) was used to separate the mixture.

The 53% component (longer glpc retention time) was identified as 2-thiatetrahydro-*endo*-dicyclopentadiene (**9**) by comparison with an authentic sample: mp 123.5–124.5° (lit.[5] mp 123.5–125); nmr (CCl_4) δ 2.70 (6 H), 2.17 (2 H), ~1.78 (2 H), 1.48 (2 H), and ~1.45 (2 H).

The 47% component (shorter glpc retention time) was identified as 2-methyl-6-thiatricyclo[3.2.1.1^{3,8}]nonane (**8**): mp 143–144°; nmr (CCl_4) δ 3.17 (1 H), 2.74 (2 H), 2.62 (2 H), 1.97 (2 H), ~1.73 (2 H), ~1.52 (2 H), and 1.00 (3 H).

Anal. Calcd for $C_9H_{14}S$: C, 70.06; H, 9.14. Found: C, 69.72; H, 8.97.

A methiodide derivative was prepared by dissolving the sulfide in dry ether and adding a large excess of methyl iodide: mp 158° on recrystallization from EtOH–Et_2O.

Anal. Calcd for $C_{10}H_{17}IS$: C, 40.54; H, 5.79. Found: C, 40.28; H, 5.91.

4-Bromo-2-bromomethyl-6-thiatricyclo[3.2.1.1^{3,8}]nonane (**10a**) was formed when bromosulfonium salt **6** was allowed to stand at room temperature for about 1 week. The yellow oil which appeared was distilled: bp 137–142° (0.4 mm); nmr ($CDCl_3$) δ 4.08 (1 H), 3.74 (1 H), 3.58 (2 H), 2.92 (2 H), 2.84 (2 H), 2.68 (2 H), 2.27 (1 H), and 1.76 (1 H); mass spectrum *m/e* (rel intensity) 310 (42), 312 (73), 314 (58), 233 (100), 231 (92), 201 (38), 199 (38), and 152 (88).

Anal. Calcd for $C_9H_{12}Br_2S$: C, 34.63; H, 3.88; Br, 51.21; S, 10.27. Found: C, 34.72; H, 3.79; Br, 51.22; S, 10.10.

A methylsulfonium picrate **11** was prepared by treating **10a** with excess dimethyl sulfate in anhydrous ether, dissolving the resulting precipitate in absolute ethanol, and adding an ethanolic solution of picric acid. This derivative, mp 172–173° (from MeOH), was used in the X-ray analysis.

Anal. Calcd for $C_{16}H_{17}Br_2N_3O_7S$: C, 34.61; H, 3.09. Found: C, 34.45; H, 2.96.

4-Phenoxy-2-phenoxymethyl-6-thiatricyclo[3.2.1.1^{3,8}]nonane (**10b**).—To a solution of 3.36 g (0.06 mol) of potassium hydroxide and 5.64 g (0.06 mol) of phenol in 40 ml of water was added 1.6 g (0.0051 mol) of sulfonium salt **6**. The mixture was stirred and refluxed overnight. The oily material which separated from the aqueous solution was recrystallized from 95% EtOH four times: mp 69.5–71°; nmr ($CDCl_3$) δ 7.07 (10 H), 4.30 (1 H), 4.20 (2 H), 3.24 (1 H), 2.97 (2 H), 2.80 (2 H), 2.62 (2 H), 2.20 (1 H), and 1.63 (1 H); mass spectrum *m/e* (rel intensity) 338 (16), 261 (10), 245 (100), 184 (63), 168 (73), and 152 (96).

Anal. Calcd for $C_{21}H_{22}O_2S$: C, 74.53; H, 6.55; S, 9.46. Found: C, 74.84; H, 6.76; S, 9.68.

4-Thiophenoxy-2-thiophenoxymethyl-6-thiatricyclo[3.2.1.1^{3,8}]-nonane (**10c**).[16]—To a solution of 3.36 g (0.06 mol) of potassium hydroxide and 6.61 g (0.06 mol) of thiophenol in 40 ml of water was added 2.18 g (0.007 mol) of sulfonium salt **6**. The mixture was stirred and refluxed overnight. The oily material which separated from the aqueous solution was recrystallized from absolute EtOH: mp 80–80.5°; nmr ($CDCl_3$) δ 7.24 (10 H), 3.47 (1 H), 3.27 (1 H), 3.12 (2 H), 2.95 (2 H), 2.74 (2 H), 2.38 (2 H), 1.97 (1 H), and 1.55 (1 H); mass spectrum *m/e* (rel intensity) 370 (37), 261 (100), and 152 (76).

Anal. Calcd for $C_{21}H_{22}S_3$: C, 68.06; H, 5.98; S, 25.96. Found: C, 67.88; H, 5.97; S, 25.93.

4-(2-Thiopyridyl)-2-(2-thiopyridylmethyl)-6-thiatricyclo[3.2.-1.1^{3,8}]nonane (**10d**).—To a solution of 5.39 g (0.096 mol) of potassium hydroxide and 10.68 g (0.096 mol) of 2-mercaptopyridine in 50 ml of water was added 1.5 g (0.0048 mol) of sulfonium salt **6**. The mixture was stirred and refluxed overnight. The black oily material which separated from the aqueous solution was taken up in ether and decolorized with Norit. The ether solution was evaporated, and the white solid which remained was recrystallized from absolute EtOH: mp 86.5–88°; nmr ($CDCl_3$) δ 8.44 (2 H), 7.24 (6 H), 4.00 (1 H), 3.52 (2 H), 3.32 (1 H), 2.98 (2 H), 2.74 (2 H), 2.48 (2 H), 2.05 (1 H), and 1.58 (1 H); mass spectrum *m/e* (rel intensity) 372 (10), 264 (64), and 152 (100).

Anal. Calcd for $C_{19}H_{20}N_2S_3$: C, 61.28; H, 5.41; N, 7.52; S, 25.78. Found: C, 61.32; H, 5.46; N, 7.52; S, 25.97.

A dipicrate was prepared by dissolving the sulfide in 95% ethanol and adding a saturated solution of picric acid: mp 173.5–175° on recrystallization from 95% EtOH.

Anal. Calcd for $C_{31}H_{26}N_8O_{14}S_3$: C, 44.81; H, 3.15. Found: C, 45.28; H, 3.21.

4-Acetoxy-2-acetoxymethyl-6-thiatricyclo[3.2.1.1^{3,8}]nonane (**10e**).—To a solution of 1.50 g (0.018 mol) of anhydrous sodium acetate in 25 ml of glacial acetic acid was added 0.5 g (0.0016 mol) of sulfonium salt **6**. The mixture was stirred and refluxed overnight. The reaction mixture was poured into 100 ml of water, neutralized with sodium carbonate, and the aqueous solution extracted with three 25-ml portions of ether. The extracts were dried over $MgSO_4$ and concentrated. Final purification was accomplished by preparative glpc on a 5 ft × $^3/_8$ in. 20% SE-30 column at 175° (200-ml/min He flow): nmr (CCl_4) δ 4.53 (1 H), 4.18 (2 H), 3.10 (1 H), 2.83 (2 H), 2.72 (2 H), 2.32 (2 H), 1.98 (3 H), 1.95 (3 H), 1.93 (1 H), and 1.57 (1 H); mass spectrum *m/e* (rel intensity) 270 (49), 211 (70), 184 (44), and 152 (100).

Anal. Calcd for $C_{13}H_{18}O_4S$: C, 57.75; H, 6.71. Found: C, 57.90; H, 6.55.

Registry No.—**1**, 129-64-6; **2**, 699-97-8; **3**, 2590-37-6; **4**, 2434-67-5; **5**, 2433-70-7; **6**, 25630-10-8; **7a**, 14751-18-9; **7b**, 25558-28-5; **8**, 25558-29-6; **8** methyl iodide, 25558-30-9; **9**, 2590-39-8; **10a**, 25558-32-1; **10a** methylsulfonium picrate, 25558-33-2; **10b**, 25558-34-3; **10c**, 25558-35-4; **10d**, 25558-36-5; **10d** dipicrate, 25558-37-6; **10e**, 25558-38-7.

Acknowledgment.—We wish to express our appreciation to Professor Andrew T. McPhail and Dr. Philip Coggon of this department for the X-ray structure determination.

(16) This compound was prepared by J. Raper, NSF Undergraduate Research Participant, 1966–1967.

Fluoroketenes. III. Reactions of Bis(trifluoromethyl)ketene with Unsaturated Compounds[1]

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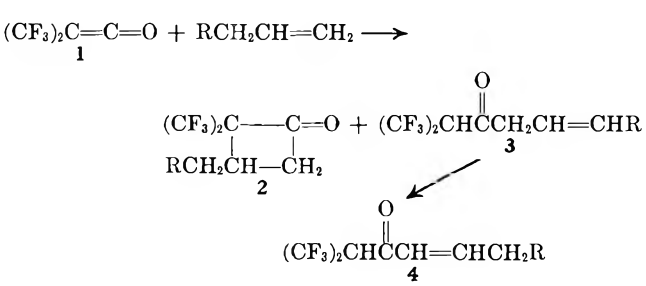
Bis(trifluoromethyl)ketene reacts with simple olefins to give cyclobutanones by cycloaddition to its carbon–carbon double bond and linear ketones by an ene reaction. Dienes react at the carbonyl group of bis(trifluoromethyl)ketene in Diels–Alder fashion to give dihydropyrans and related adducts. Implications of these findings on the mechanism of cycloadditions to ketenes are discussed.

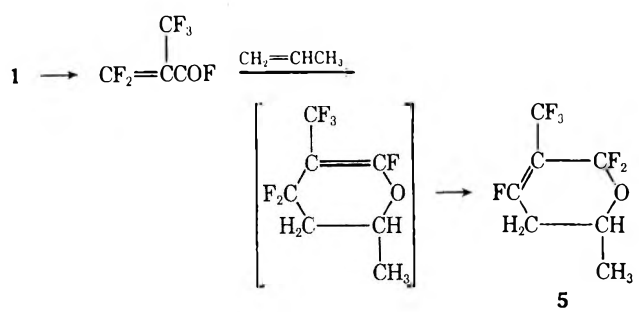
The first authenticated perfluoroketene, bis(trifluoromethyl)ketene (**1**), has become readily available from a simple process[2] and its chemistry is being studied.[2,3] The purpose of this paper is to report in detail on some previously communicated[2a] reactions of ketene **1** with olefins and dienes.

The electrophilic nature of the ketene group is greatly enhanced by the electron-withdrawing effect of the trifluoromethyl groups in **1**, and most of its reactions can be interpreted through polar intermediates. Previous work[2b] demonstrated the reactivity of **1** toward nucleophiles and the tendency of **1** to form an anion $[(CF_3)_2\overline{C}-C(O)B]$ with bases such as fluoride ion. The same type of stabilized anion has been shown to form by removal of a proton from the conjugate acid, $(CF_3)_2CHCOF$.[4] As will be discussed below and in subsequent publications, neutral unsaturated compounds also tend to react with ketene **1** to give polarized transition states or dipolar intermediates in which negative charge resides on the fluorinated segment of the intermediate. The products isolated are cycloadducts obtained by ring closure and/or linear adducts by proton transfer, depending on the reaction conditions and on the nature of the unsaturated coreactant.

Olefins.—Terminal olefins add to the carbon–carbon double bond of ketene **1** to form cyclobutanones (**2**) and acyclic β,γ-unsaturated ketones (**3**). Conjugated acyclic ketones (**4**) are formed from **3** in a slower secondary reaction.

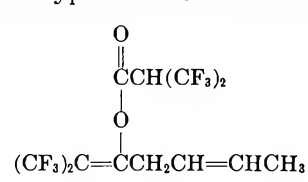


Several attempted reactions of **1** with propylene in sealed glass tubes above the critical temperature of propylene (92°) gave no product under conditions where no liquid phase was present (100–200° and modest pressures). At 60–80° with the same loading density, however, products were slowly formed over a period of weeks. Higher pressure (~850 atm) at 150° gave higher yields in less time. A similar response was observed with butene-1. The products isolated from the reaction at 150° with excess propylene were cyclobutanone **2** (R = H, 13%), β,γ-unsaturated ketone **3** (R = H, 6%), and compound **5** (35%). Compound **5** resulted from the side reaction of isomerization of ketene **1** to perfluoromethacryloyl fluoride,[2] since it can be prepared under milder conditions directly from perfluoromethacryloyl fluoride.[5] The β,γ-unsaturated ketone **3** (R = H) isomerized to α,β-unsaturated ketone **4** (R = H) on long standing, but **4** was at best a very minor product in the original reaction.



Ethylene (critical temperature 9°) did not react appreciably with **1** at 130–200° under moderate pressure. Since these conditions were successful for propylene, a much lower reactivity for ethylene is indicated.

Butene-1 (critical temperature 146°) gave no significant reaction with **1** in sealed tubes at 175° for 8 hr, but at the same loading density reacted to a moderate extent in 3 days at 100°. Products from a reaction with excess ketene at 100° for 37 days were the cyclic ketone **2** (R = CH_3, 16%), the β,γ-unsaturated ketone **3** (R = CH_3, 11%), and 34% product characterized as the vinyl ester **6**. Ester **6** is not formed in a secondary reaction of **1** with the enol of **3** (R = CH_3) since this reaction was shown separately not to occur. Several enol esters of this type were isolated from reactions of **1**.



Hexene-1 (critical temperature 243°) reacted appreciably with the ketene in a sealed tube at 150° for 8

(1) Part II: D. C. England and C. G. Krespan, *J. Org. Chem.*, **33**, 816 (1968).

(2) (a) D. C. England and C. G. Krespan, *J. Amer. Chem. Soc.*, **87**, 4019 (1965); (b) *ibid.*, **88**, 5582 (1966).

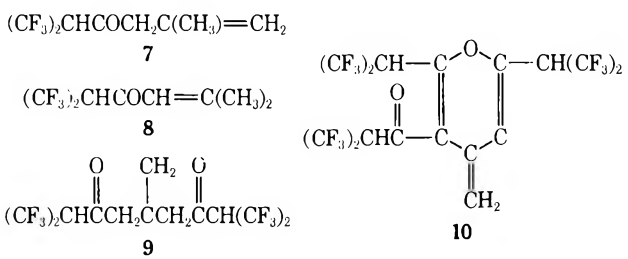
(3) Y. A. Cheburkov and I. L. Knunyants, *Fluorine Chem. Rev.*, **1**, 107 (1967).

(4) Y. A. Cheburkov, M. D. Bargamova, and I. L. Knunyants, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 339 (1964).

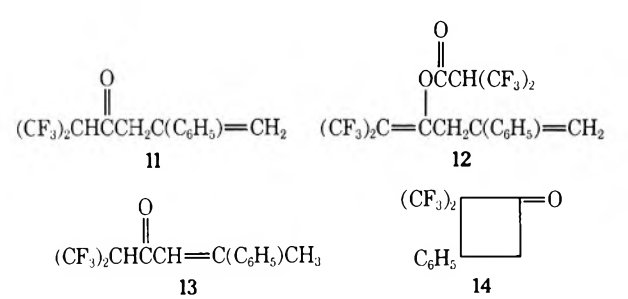
(5) Reactions of perfluoromethacryloyl fluoride will be published separately.

hr giving the cyclic ketone **2** (R = C_3H_7, 12%) and the β,γ-unsaturated ketone **3** (R = C_3H_7, 8%), along with a small amount of higher boiling product, apparently an enol ester analogous to the above product from butene-1.

Isobutylene reacted more readily at 100° with **1** than the previously considered terminal olefins such as propylene, in keeping with an increased nucleophilicity because of the additional methyl group. Although conditions were milder (isobutylene reacts with **1** even at room temperature[3]), no cyclobutanone was formed. When isobutylene was used in 2:1 excess, the β,γ-unsaturated ketone **7** was obtained in 86% yield after 20 hr at 100°. When the reaction mixture was heated for 60 hr, the product was a mixture of **7** and the isomeric α,β-unsaturated ketone, **8**. From a reaction of **1** with **7**, a low yield of the 2:1 product **9** was isolated, the main product being a compound believed to have the structure **10**. **9** may arise from attack of a second molecule of **1** at the terminal olefinic bond of **7** in an "ene" reaction analogous to the formation of **7** from isobutylene. Attack of a third molecule of **1** on **9** or on the internal double-bond isomer of **9** followed by dehydration of an enol form would give **10**.

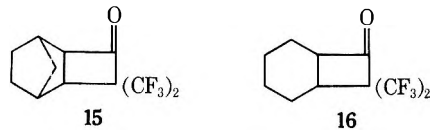


α-Methylstyrene, similar to isobutylene in being a disubstituted terminal olefin containing allylic hydrogen, reacts with **1** in 2 hr at 100° to give a 96% yield of products. Some enol ester **12** was formed along with linear adduct **11**, but here also it was not possible to react **11** with **1** to give **12**. However, **12** did decompose thermally to form **1** and **11** and could also be hydrolyzed under mild conditions to give the α,β-unsaturated ketone, **13**.



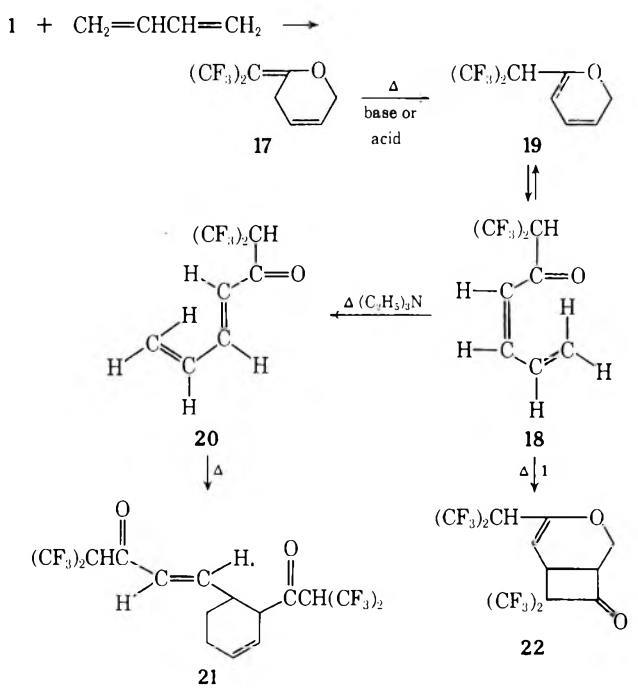
Styrene, with an activating substituent capable of stabilizing a positive charge but no allylic hydrogens, reacts readily with **1** at 100° to give cyclobutanone **14** in 87% yield.[6]

Norbornene did not react appreciably with **1** at 100°; at 175° norbornene added to the carbon–carbon double bond of **1** nearly quantitatively to give a cyclic ketone of structure **15**, but with unknown configuration. The rate of reaction of **1** with norbornene was much higher in nitroethane than in hexane, but formation of byproducts was a serious complication in both solvents.



Although the strained double bond in norbornene is sufficiently reactive to undergo cycloaddition to ketene **1**, more normal internal olefins have resisted attempts to force reaction. No reaction was detected with *trans*-butene-2 at 100° overnight or with tetramethylethylene at 100° for 45 days. Cyclopentene gave little or no adduct in 8 hr at 175° and formed decomposition products at 250°. Cyclohexene reacted slowly at 100° over 2 months giving a low yield of cyclobutanone **16** and mixed acyclic ketones.

1,3-Dienes and Related Compounds.—Unlike ketenes in general, **1** reacts with conjugated dienes in the Diels–Alder manner and the addition occurs at the carbonyl group of ketene **1**. Reaction of **1** with butadiene has been studied most intensively and is at the same time one of the most sensitive to the precise conditions employed.[7] Reactions at 100° gave products which were easily decomposed. The use of acid-washed equipment helped stabilize the products, and even better yields of the initial adduct **17** were achieved by running the reaction with excess **1**. The conversion of **17** to acyclic *cis*-diene **18** is base catalyzed and apparently proceeds through a tautomerization to pyran **19** followed by an electrocyclic transformation of **19** to **18**. **17** is also sensitive to protic acids and will undergo isomerization to **18** on distillation from acid-washed equipment. With excess butadiene, **18** was obtained directly from the reaction, but in low yield, along with



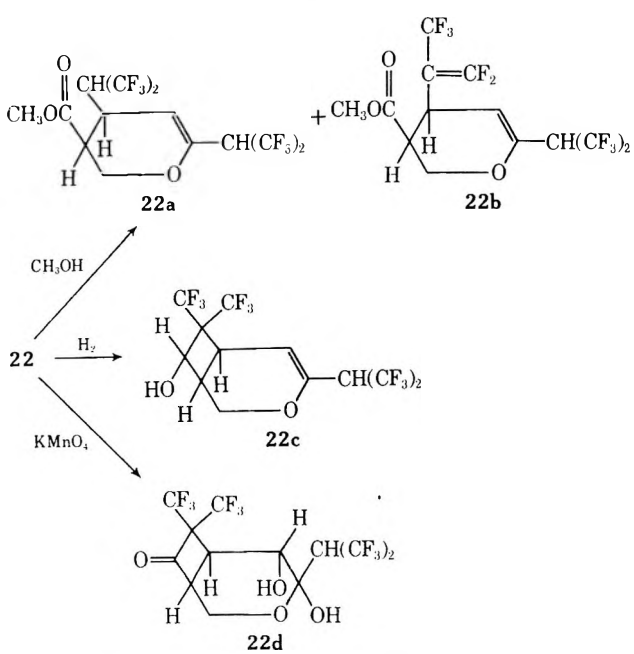
(6) Y. A. Cheburkov, N. Mukhamadaliev, and I. L. Knunyants, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 384 (1966), also report this cycloadduct from styrene.

(7) Y. A. Cheburkov, N. Mukhamadaliev, and I. L. Knunyants, *Tetrahedron*, **24**, 1341 (1968), also discuss 1,4 addition of butadiene to **1**. We present here additional data and a partial reinterpretation of these authors' work.

its polymer. When the reaction of butadiene and **1** was conducted in hexane with phenothiazine present as inhibitor, it was possible to isolate 58% **18** containing an isomer, apparently the ring-closed form, **19**.[8] Although **18** polymerized easily, the *trans* isomer **20** preferentially formed an isomeric mixture of dimers (proposed to have general structure **21**) even at room temperature. **18** was converted to **20** by treatment with catalytic amounts of triethylamine. The behavior of **18** and **20** is analogous to that of *cis*-piperlyene, which polymerizes rather than form a Diels–Alder dimer, and *trans*-piperylene, which readily dimerizes. With the *cis*-dienes, the substituents presumably prevent the cisoid configuration of the diene necessary for a concerted Diels–Alder addition to give dimer.

Preparations of **17**, preferably carried out with excess **1**, gave varying amounts of a 2:1 **1**–butadiene adduct, especially in reactions at longer times or higher temperatures. The evidence best fits structure **22** for the 2:1 adduct, a product which would arise by cycloaddition of **1** to the unhindered but activated double bond of **19**. It was not possible to define conditions giving exclusively **17** or **22**, because results were not reproducible. Nevertheless, overall yields of **17** and/or **22** were consistently very good when excess **1** was used.

Chemical evidence for the structure of **22** was obtained as follows. Evidence for the cyclobutanone structure was provided by its reaction with alcohols which is analogous to the reaction of **14** with nucleophiles.[7] Reaction with methanol gave a mixture of saturated (**22a**) and unsaturated (**22b**) esters. The small-ring carbonyl group indicated by the ir spectrum was easily reduced to an alcohol (**22c**) by hydrogenation. Oxidation with permanganate occurred at the double bond, apparently to give the *cis*-glycol **22d**. Both the ^{19}F and ^{1}H spectra of the 2:1 product are in agreement with structure **22**. A cyclic 8-membered ring lactone structure which has been proposed[7] is unlikely in view of the above evidence. In addition the ^{1}H spectrum should have three instead of the one vinyl hydrogen observed, and the ^{19}F spectrum should be a doublet and singlet of equal areas instead of the doublet and pair of quartets observed.



(8) Cyclization of such dienones to 2H-pyrans is generally a preferred reaction, so that compound **18** is a member of a class rarely isolated; *cf.*, P. Schiess, H. L. Chia, and C. Suter, *Tetrahedron Lett.*, 5747 (1968).

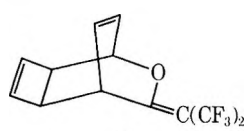
The reaction of **1** and butadiene was examined by nmr in hexane and in nitroethane. The results show the rate of reaction of **1** to increase with solvent polarity. Similarly, conversion of **17** to **18** and to polymeric products is favored in the polar solvent (Table I).

TABLE I
REACTION OF **1** WITH BUTADIENE[a]

Solvent	Temp, °C	Time, hr	Per cent of total **1**	**17**	**18** + others
Hexane	100	1.25	100	0	0
	140	3.5	62	34	4
	140	13	18	73	9
	140	19	10	74	16
Nitroethane	50	0.25	84	2	14
	100	0.25	42	43	15
	100	1.25	7	76	17
	140	3.5	0	0	100

[a] Carried out in sealed tubes as described in part V: ref. 11.

Cyclooctatetraene, reacting in the bicyclic form at 100°, added slowly to the carbonyl group of **1** in Diels–Alder fashion to form **23**. Cycloheptatriene also added 1,4 to the carbonyl of **1**, the product of which contained a reactive double bond similar to that in norbornene; another mole of **1** appeared in the final product as a result of a cycloaddition to the carbon–carbon double bond of **1**. The 2:1 adduct actually obtained is formulated as structure **24** on the basis of minimized steric hindrance.



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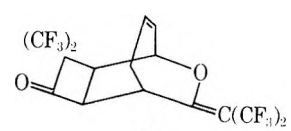
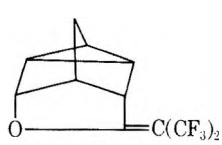


24

Bicycloheptadiene is known to react with dienophiles such as hexafluoro-2-butyne to give a homo-Diels–Alder addition.[9] Bicycloheptadiene added readily to the carbonyl of **1** at 100° to give adduct **25** in 81% yield.



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Discussion

A monoalkylethylene containing allylic hydrogen will add to **1** with formation of two products, a cyclobutanone by cycloaddition and a β,γ-unsaturated ketone by an "ene" reaction.[10] The alkyl-substituted cyclobutanones are stable to the reaction conditions (80–175° and only moderately polar media); so the

(9) C. G. Krespan, B. C. McKusick, and T. L. Cairns, *J. Amer. Chem. Soc.*, **83**, 3428 (1961).

(10) J. A. Berson, R. G. Wall, and H. D. Perlmutter, *ibid.*, **88**, 187, (1966), use this convenient name for K. Alder's "indirect substitutive addition" in which acyclic products are obtained from thermal addition of olefins to dienophiles.

acyclic ketones or the corresponding enols are considered to be primary products. A preliminary cycloaddition to the ketene carbonyl group to give unstable oxetanes may in principle also occur, but we find no evidence that this possibility bears on formation of the ene products. No oxetanes have been detected in the reaction of 1 with simple alkenes, even though the oxetanes from 1 and more reactive olefins such as vinyl esters[11] have been isolated and can be stable at 100° and above in nonpolar media, but form α,β-unsaturated ketones in polar media.

Although oxetane formation may not be involved in reactions of 1 with simple olefins, an intermediate of some sort is indicated by the formation of enol esters as by-products. These enol esters are not obtainable from 1 and the related β,γ-unsaturated ketones under the reaction conditions. One interpretation in accord with the known facts is that the ene products from simple olefins arise at least in part *via* a cyclic transition state in which the enol of ketone 3 is formed as an intermediate with sufficient lifetime to react with another molecule of 1.

The preference for a liquid phase in these reactions suggests a polarized transition state or perhaps even a dipolar intermediate stabilized by solvation. Orbital symmetries in ketenes are such that an analysis according to Woodward–Hoffmann methods has only recently been made.[12] Our results fit the idea that the less nucleophilic olefins cycloadd to the carbon–carbon double bond of 1 by way of an unsymmetrical, polarized transition state or perhaps a dipolar intermediate of very low stability. The reactions are accelerated in polar solvents and by substituents in the olefin capable of stabilizing a positive charge, but tend to be relatively slow even at elevated temperatures. On the other hand, extremely nucleophilic olefins have been shown to cycloadd thermally to both the C=C and C=C of 1 by a nonconcerted process involving dipolar intermediates.[11] Since cyclobutanone formation, in particular, seems to present an unusual instance in which the mechanism can vary all the way from nonconcerted to concerted, it appears that ketene 1 can act normally in cycloaddition to the C=C unless the stabilization of positive charge by substituents in the olefinic segment and by solvation is sufficient to favor a dipolar intermediate.

Wide variations in mechanism have also been reported for cycloadditions to dimethylketene and diphenylketene. At one extreme there is good evidence that enamines add to dimethylketene *via* an ionic intermediate.[13,14] On the other hand, strong support is available for a nearconcerted mechanism with relatively little charge separation in the transition state for cycloadditions of diphenylketene to vinyl ethers.[15,16] Therefore, there seems to be no single mechanism for cycloadditions to the C=C of ketenes. Rather, there exists a continuum of slightly to highly charge-separated intermediates or transition states, and bond formation can be stepwise or not symmetrical in the transition state.[17]

The ease of reaction of 1 with isobutylene and the absence of cyclobutanone as a product can be attributed to the presence of an additional methyl group. Reactivity is enhanced by increased nucleophilicity due to the added methyl, but steric hindrance prevents formation of a cyclobutanone containing adjacemt *gem*-substituted carbon atoms. Oxetane formation, which would imply capability of forming a dipolar intermediate with 1, is not observed either. The presence of a methyl group with its reactive allylic hydrogen atoms in the ene product 7 promotes a second ene reaction to give 9. We observed no enol ester formation with isobutylene, but low yields of this product were reported at 0°.[7]

Reactivity similar to that of isobutylene is observed with α-methylstyrene in formation of acyclic ketone 11 as the primary product. Lack of reactive allylic hydrogens in 11, however, precludes formation of a 2:1 ene product, and enol ester 12 is formed in a manner similar to that with the monoalkylethylenes and 1.

Conjugated dienes generally add to ketene, dialkylketenes, and diphenylketene in a 1,2 manner to give cyclobutanones.[18] Even the negatively substituted ketene, dichloroketene, cycloadds 1,2 to cyclopentadiene to form a cyclobutanone ring.[19] One example of a 1,4 addition is known with these various ketenes, that of 2-methoxybutadiene to the carbonyl bond of diphenylketene.[16] In contrast to the behavior of other ketenes, 1 adds dienes 1,4 in general to its carbonyl group.

Butadiene and 1 show pronounced acceleration of reaction rate in a polar solvent, unusual in a Diels–Alder reaction and presumably indicating a significant charge separation in the transition state. The fact that neither oxetane nor, in a nonpolar solvent, cyclobutanone was observed is an indication that a more or less concerted 4 + 2 addition has taken precedence. This interpretation and the results of other work[11] lead us to postulate that cycloadditions to the ketene carbonyl group, when they occur, are to the isolated π system and follow Woodward–Hoffmann rules.

Experimental Section[20]

Bis(trifluoromethyl)ketene and Ethylene.—No monomeric product could be isolated from attempted reactions of the ketene with ethylene at 950-atm pressure and 150–175° with or without 1,1,2-trichlorotrifluoroethane as solvent.

Bis(trifluoromethyl)ketene and Propylene.—No product could be isolated from attempted reactions in sealed glass tubes at 100–200°. However, a mixture of 34 g of the ketene and 14 g of propylene heated for 3 weeks in a water bath at 60–80° gave 5 g of a mixture of products. A similar mixture was obtained in higher yield at elevated pressure and temperature. A metal tube charged with 35 g (0.20 mol) of the ketene and 100 g of propylene was heated at 150° for 6 hr. The top pressure of 855 atm dropped to 730 atm. There was recovered 34 g of liquid boiling above room temperature. Distillation gave 8 g (19% yield on ketene

(11) Part V, *J. Org. Chem.*, **35**, 3312 (1970), describes the formation of such oxetanes from 1 and very nucleophilic olefins. Such adducts are formed under comparatively mild conditions *via* a dipolar intermediate, a mechanism which also allows proton transfer to occur with formation of α,β- rather than β,γ-unsaturated acyclic ketones.

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(18) See J. C. Martin, P. G. Gott, V. W. Goodlett, and R. H. Hasek, *J. Org. Chem.*, **30**, 4175 (1965), for recent extensive work in this area and for leading references.

(19) H. C. Stevens, D. A. Reich, D. R. Brandt, K. R. Fountain, and E. J. Gaughan, *J. Amer. Chem. Soc.*, **87**, 5257 (1965).

(20) Melting points and boiling points are uncorrected. ^{19}F nmr spectra are reported in parts per million upfield from external trichlorofluoromethane. ^{1}H nmr resonances are relative to external tetramethylsilane and were run at 60 MHz unless otherwise noted.

charged) of a mixture, bp 63–70° (100 mm); separation by glpc gave 30% 1,1,1-trifluoro-2-(trifluoromethyl)-5-hexen-3-one (**3**, R = H) and 70% 2,2-bis(trifluoromethyl)-3-methylcyclobutanone (**2**, R = H). In addition there was obtained 15 g (35%) of 2,2,4-trifluoro-5,6-dihydro-6-methyl-3-(trifluoromethyl)-2H-pyran (**5**), bp 102° (100 mm).

For the linear ketone **3**: ir 5.77 (C=O), 6.15 μ (C=C); nmr ^{1}H at about τ 5.00 (multiplet, 3, CH=CH$_2$), 5.98 [septet, $J_{H/F}$ = 8.0 Hz, 1, (CF$_3$)$_2$CH], 6.95 (doublet, $J_{H/H}$ = 8.0 Hz, 2, CH$_2$); ^{19}F at 64.8 ppm [doublet, $J_{H/F}$ = 8.0 Hz, (CF$_3$)$_2$CH].

Anal. Calcd for $C_7H_6F_6O$: C, 38.21; H, 2.75; F, 51.82. Found: C, 38.44; H, 2.73; F, 51.93.

Reexamination of the above sample after storage in glass for about 4 years showed that it had been converted to the isomeric α,β-unsaturated ketone, 1,1,1-trifluoro-2-(trifluoromethyl)-4-hexen-3-one (**4**, R = H): ir 5.91 μ (C=O); nmr ^{1}H at τ 3.18 (doublet, $J_{H/H}$ = 16.0 Hz, to quartets, $J_{H/H}$ = 7.0 Hz, 1, COCH=CH–), 4.01 (doublet, $J_{H/H}$ = 16.0 Hz, to quartets, $J_{H/H}$ = 1.5 Hz, 1, COCH=CH–), 5.80 [septet, $J_{H/F}$ = 8.0 Hz, 1, (CF$_3$)$_2$CH], 8.49 (doublet, $J_{H/H}$ = 7.0 Hz, to doublets, $J_{H/H}$ = 1.5 Hz, 3, CH$_3$); ^{19}F at 65.1 ppm [doublet, $J_{H/F}$ = 8.0 Hz, (CF$_3$)$_2$CH].

For the cyclic ketone **2** (R = H): ir 5.50 μ (C=O); nmr ^{1}H at τ 6.80 to 7.43 (multiplet, 3, ring CH), 8.88 (multiplet, 3, CH$_3$); ^{19}F at 64.9 (quartet, $J_{F/F}$ = 9.2 Hz, with fine structure, 3, CF$_3$), 70.2 ppm (quartet, $J_{F/F}$ = 9.2 Hz, C, CF$_3$).

Anal. Calcd for $C_7H_6F_6O$: C, 38.21; H, 2.75; F, 51.82. Found: C, 38.34; H, 2.74; F, 51.71.

For the perfluoromethacryloyl fluoride derivative **5**: ir 5.85 μ (C=C); nmr ^{1}H at τ 5.85 (quartet, $J_{H/H}$ = 7.0 Hz, 1, –CH—CH$_3$), 7.70 (multiplet, 2, CH$_2$), 8.80 (doublet, $J_{H/H}$ = 7.0 Hz, 3, CH$_3$); ^{19}F at 84.5 (quartet, $J_{F/F}$ = 17.0 Hz with fine structure, 1, =CF), 59.5 (doublet, $J_{F/F}$ = 17.0 Hz, 3, CF$_3$), 56.4, 59.5, 71.0, and 74.1 ppm (AB, 2, CF$_2$).

Anal. Calcd for $C_7H_6F_6O$: C, 38.21; H, 2.75; F, 51.82. Found: C, 37.70; H, 2.61; F, 51.90.

The above compound is also the major product of the reaction of propylene with perfluoromethacryloyl fluoride.

Bis(trifluoromethyl)ketene and Butene-1.—There was no appreciable reaction in a sealed tube at 175° but appreciable reaction at 100°. A mixture of 9.5 g of **1** and 8.5 g of butene-1 sealed in a Carius tube was heated on a steam bath for 3 days. There was obtained 4.2 g of distilled product. The reaction was repeated on 9 g (0.05 mol) of **1** and 5 g (0.09 mol) of butene-1 for 37 days to give 7 g of distilled product, consisting of 3.5 g (27%) of 1:1 products, and 3.5 g (34%) of a 2:1 ketene–butene-1 product. The 1:1 mixture, bp 52–55° (20 mm), was separated by glpc into 36% 1,1,1-trifluoro-2-(trifluoromethyl)-5-hepten-3-one (**3**, R = CH$_3$) and 64% 2,2-bis(trifluoromethyl)-3-ethylcyclobutanone (**2**, R = CH$_3$).

For the linear ketone **3** (R = CH$_3$): n^{23}D 1.3553; ir 5.75 (C=O) and 6.16 μ (C=C); nmr ^{1}H at τ 4.75 (multiplet, 2, CH=CH), 5.85 [septet, $J_{H/F}$ = 7.5 Hz, 1, (CF$_3$)$_2$CH], 6.90 (doublet, $J_{H/H}$ = 6.0 Hz, CH$_2$), 8.67 (doublet, $J_{H/H}$ = 5.0 Hz, 3, CH$_3$); ^{19}F at 63.1 ppm [doublet, $J_{H/F}$ = 7.5 Hz, (CF$_3$)$_2$CH].

Anal. Calcd for $C_8H_8F_6O$: C, 41.06; H, 3.45; F, 48.72. Found: C, 41.41; H, 3.64; F, 48.54.

After standing for 4 years the sample was about 40% converted to the α,β isomer **4** (R = CH$_3$): ir 5.90 (C=O) and 6.16 μ (C=C); mmr ^{1}H at τ 3.17 (doublet, $J_{H/H}$ = 16.0 Hz, to triplets, $J_{H/H}$ = 6.0 Hz, COCH=CH), 4.04 (doublet, $J_{H/H}$ = 16.0 Hz with fine structure, COCH=CH–), 5.85 [septet, $J_{H/F}$ = 7.5 Hz, 1, (CF$_3$)$_2$CH], 8.11 (fine peaks, overlapping quartets, $J_{H/H}$ = 7.0 Hz, and doublets, $J_{H/H}$ = 6.0 Hz, 2, CH$_2$), 9.34 (triplet $J_{H/H}$ = 7.0 Hz, 3, CH$_3$); ^{19}F at 62.9 [doublet, $J_{H/F}$ = 7.5 Hz, (CF$_3$)$_2$CH], 63.2 ppm (a similar doublet of one-fourth the intensity, possibly due to *cis–trans* isomers).

For the cyclic ketone **2** (R = CH$_3$): n^{25}D 1.3545; ir 5.52 μ (C=O); nmr ^{1}H at τ 6.7–7.4 (multiplet, 3, ring CH), 8.40 (broad, 2, CH$_2$), 9.23 (triplet, $J_{H/H}$ = 7.0 Hz, 3, CH$_3$); ^{19}F at 64.1 (broad quartet $J_{F/F}$ = 9.4 Hz, 3, CF$_3$), 69.75 ppm (sharp quartet, $J_{F/F}$ = 9.4 Hz, 3, CF$_3$).

Anal. Calcd for $C_8H_8F_6O$: C, 41.06; H, 3.45; F, 48.72. Found: C, 40.84; H, 3.44; F, 48.94.

The 2:1 ketene–butene-1 product, bp 82° (20 mm), n^{24}D 1.3492, was characterized as the enol ester **6**, 1,1,1-trifluoro-2-(trifluoromethyl)-2,5-heptadien-3-ol 3,3,3-trifluoro-2-(trifluoromethyl)propionate, based on analysis, ir, and nmr: ir 5.58 (C=O), 5.96 μ (C=C); the proton nmr was essentially the same as for the linear ketone **3** (R=CH$_3$) above—^{1}H at τ 4.4 to 5.3 (multiplet, 2, CH=CH), 6.18 [septet, $J_{H/F}$ = 7.0 Hz, 1, (CF$_3$)$_2$CH], 6.96 (doublet, $J_{H/H}$ = 6.0 Hz with fine structure, 2, CH$_2$), 8.65 (doublet, $J_{H/H}$ = 5.5 Hz, 3, CH$_3$); ^{19}F at 58.9 (quartet, $J_{F/F}$ = 9.5 Hz, 1, CF$_3$), 61.3 (broad quartet, $J_{F/F}$ = 9.5 Hz, 1, CF$_3$), 66.0 ppm [doublet, $J_{H/F}$ = 7.0 Hz to quartets, J = 2.0 Hz, 2, (CF$_3$)$_2$CH].

A 5-g sample of a mixture of cyclic and linear ketones, **2** and **3** (R = CH$_3$) (about 3:1 ratio), containing none of the enol ester **6** was sealed in a glass tube with 5.2 g of **1** and heated for 100 hr in a steam bath. Examination by glpc showed no change, and none of the enol ester **6** was detected. The materials were recharged with a trace of BF$_3$ and heated for 62 hr. There was recovered most of the ketene (4.5 g) and a viscous liquid. Glpc showed the presence of the cyclic ketone **2** (R = CH$_3$) and the absence of both the linear ketone **3** (R = CH$_3$) and the enol ester **6**.

1,1,1-Trifluoro-2-(trifluoromethyl)-5-nonen-3-one (3, R = C$_3$H$_7$) and 2,2-Bis(trifluoromethyl)-3-butylcyclobutanone (2, R = C$_4$H$_9$).—A mixture of 17 g (0.20 mol) of hexene-1 and 36 g (0.20 mol) of **1** was heated in a sealed glass tube at 150° for 8 hr. On distillation there was obtained 11 g (20%) of material boiling mostly at 70° (14 mm) which was separated by glpc into about 40% linear ketone **3** (R = C$_3$H$_7$) and 60% cyclic ketone **2** (R = C$_3$H$_7$). In addition, the distillation gave 1 g of material boiling at 94° (14 mm).

For the linear ketone **3** (R = C$_3$H$_7$): ir 5.73 (C=O), 6.15 μ (C=C); nmr ^{1}H at τ 4.3–5.2 (multiplet, 2, CH=CH), 5.90 [septet, $J_{H/F}$ = 7.5 Hz, 1, (CF$_3$)$_2$CH], 6.92 (doublet, $J_{H/H}$ = 5 Hz, 2, CH$_2$), 8.10–8.50 (multiplet, 2, CH$_2$), 8.60–9.30 (multiplet, 2, CH$_2$), 9.47 (triplet, $J_{H/H}$ = 6.0 Hz, 3, CH$_3$); ^{19}F at 64.6 ppm [doublet, $J_{H/F}$ = 7.5 Hz, (CF$_3$)$_2$CH].

Anal. Calcd for $C_{10}H_{12}F_6O$: C, 45.84; H, 4.62; F, 43.51. Found: C, 45.39; H, 4.59; F, 43.20.

After 4 years of storage, the vinyl protons of the α,β isomer were easily identified, one as a doublet (J = 16 Hz) to triplets (J = 6.5 Hz) centered at τ 2.93 and one as a doublet (J = 16.0 Hz) at 3.77: ^{19}F nmr at 64.7 ppm [doublet, J = 7.5 Hz, (CF$_3$)$_2$CH].

For the cyclic ketone **2** (R = C$_3$H$_7$): ir 5.50 μ (C=O); nmr ^{1}H at τ 7.10 (multiplet, 3, ring CH), 8.40 (broad peak, 2, CH$_2$), 8.88 (multiplet, 4, CH$_2$CH$_2$), 9.34 (multiplet, 3, CH$_3$); ^{19}F nmr consisted of a pair of quartets.

Anal. Calcd for $C_{10}H_{12}F_6O$: C, 45.84; H, 4.62; F, 43.51. Found: C, 46.58; H, 4.57; F, 41.78.

The higher boiling product was characterized only by ir data [5.50 (C=O) and 5.88 μ (C=C)], which were consistent with an enol ester analogous to that obtained with the ketene and butene-1 (**6**).

1,1,1-Trifluoro-2-(trifluoromethyl)-5-methyl-5-hexen-3-one (7).—A mixture of 16 g (0.09 mol) of **1** and excess isobutylene (10 g, 0.18 mol) in a Carius tube was heated overnight in a steam bath. There was obtained 18 g (86%) of the β,γ-unsaturated ketone **7**: bp 76° (100 mm); n^{25}D 1.3505; ir 5.75 (C=O), 6.05 μ (C=C); nmr ^{1}H at τ 5.38 and 5.50 (multiplets, 2, CH=CH), 5.93 [septet, $J_{H/F}$ = 8.0 Hz, 1, (CF$_3$)$_2$CH], 7.00 (singlet, 2, CH$_2$), 8.70 (doublet, $J_{H/H}$ = 1.8 Hz, to doublets, $J_{H/H}$ = 1.0 Hz, 3, CH$_3$); ^{19}F at 65.2 ppm [doublet, $J_{H/F}$ = 8.0 Hz, (CF$_3$)$_2$CH].

Anal. Calcd for $C_8H_8F_6O$: C, 41.06; H, 3.45; F, 48.72. Found: C, 41.67; H, 3.89; F, 47.87.

1,1,1-Trifluoro-2-(trifluoromethyl)-5-methyl-4-hexen-3-one, (8).—The above reaction was repeated, doubling the quantities and heating on the steam bath for a longer time (60 hr). There was obtained 21 g (50%) of the above β,γ-unsaturated ketone (**7**) and 15.5 g (37%) of the higher boiling α,β-unsaturated ketone (**8**): bp 90° (100 mm); n^{25}D 1.3760; ir 5.91 (C=O), 6.20 μ (C=C); nmr ^{1}H at τ 3.83 (broad, 1, CH=), 5.87 [septet, $J_{H/F}$ = 8.0 Hz, 1, (CF$_3$)$_2$CH], 8.07 (doublet, $J_{H/H}$ = 1.3 Hz, 3, CH$_3$), 8.30 (doublet, $J_{H/H}$ = 1.4 Hz, 3, CH$_3$); ^{19}F at 65.1 ppm [doublet, $J_{H/F}$ = 8.0 Hz, (CF$_3$)$_2$CH].

Anal. Calcd for $C_8H_8F_6O$: C, 41.06; H, 3.45; F, 48.72. Found: C, 40.89; H, 3.64; F, 48.00.

2,8-Bis(trifluoromethyl)-1,1,1,9,9,9-hexafluoro-5-methylenenonane-3,7-dione (9) and 4-Methylene-2,6-bis[2,2,2-trifluoro-1-(trifluoromethyl)ethyl]-3-[3,3,3-trifluoro-2-(trifluoromethyl)propionyl]-4H-pyran (10).—In another experiment designed to prepared products containing more of the ketene, a mixture of the β,γ-unsaturated ketone **7** (18 g, 0.077 mol) and 16 g (0.09 mol) of **1** was heated in a Carius tube in a steam bath for 60 hr.

There was obtained by distillation 8 g (50%) of recovered β,γ-ketone mixed with its α,β-unsaturated isomer (**8**). In addition 1 g (3%) of white solid was collected which was recrystallized from carbon tetrachloride, mp 81–83°, as well as 7.9 g (46%) of higher boiling material which solidified, mp 114–142°. After two recrystallizations of the latter from carbon tetrachloride there remained 5.5 g, mp 142–143°.

The material melting at 81–83° was characterized as **9**: ir 5.74 (C=O), 6.07 μ (C=C); nmr ^{1}H at τ 5.07 (singlet, 1, =CH$_2$), 5.28 [septet, $J_{H/F}$ = 8.0 Hz, 1, (CF$_3$)$_2$CH], 6.58 (singlet, 2, CH$_2$); ^{19}F at 64.8 ppm [doublet, $J_{H/F}$ = 8.0 Hz, (CF$_3$)$_2$CH].

Anal. Calcd for $C_{12}H_8F_{12}O_2$: C, 34.98; H, 1.95; F, 55.34. Found: C, 35.00; H, 1.89; F, 55.56.

The material melting at 142–143° was characterized as **10**: ir 5.88 (C=O) and 6.07, 6.16, 6.44 μ (C=C); nmr ^{1}H at τ 2.05 (doublet, $J_{H/H}$ = 2.0 Hz, 1, =CHH), 3.48 (doublet, $J_{H/H}$ = 2.0 Hz, 1, =CHH), 4.19 (singlet, 1, =CH), 5.40 [3 overlapping septets, $J_{H/F}$ = 8.0 Hz, 3, (CF$_3$)$_2$CH]; ^{19}F at 65.1 [doublet, $J_{H/F}$ = 8.0 Hz, 1, (CF$_3$)$_2$CH], 66.2 ppm [triplet of overlapping doublets, $J_{H/F}$ = 8.0 Hz, 2, (CF$_3$)$_2$CH].

Anal. Calcd for $C_{16}H_6F_{18}O_2$: C, 33.59; H, 1.40; F, 59.79. Found: C, 33.39; H, 1.29; F, 59.28.

2,2-Bis(trifluoromethyl)-3-phenylcyclobutanone (14).—A mixture of 10 g (0.056 mol) of **1** and 6.0 g (0.058 mol) of styrene containing phenothiazine as polymerization inhibitor sealed in a Carius tube was immiscible at room temperature. After being heated 4 hr in a steam bath, the homogeneous reaction mixture distilled to give 12.6 g (80%) of **14**: bp 72° (1 mm); n^{25}D 1.4420; ir 5.48 μ (C=O); nmr ^{1}H at τ 3.03 (singlet, 5, C$_6$H$_5$), 5.90–7.41 (multiplet, 3 CH); ^{19}F at 54.9 (quartet, $J_{F/F}$ = 8.6 Hz, 1, CF$_3$), 59.7 ppm (quartet, $J_{F/F}$ = 8.6 Hz, 1, CF$_3$).

Anal. Calcd for $C_{12}H_8F_6O$: C, 51.11; H, 2.86; F, 40.43. Found: C, 50.73; H, 2.85; F, 40.14.

1,1,1-Trifluoro-5-phenyl-2-(trifluoromethyl)-5-hexen-3-one (11) and 1,1,1-Trifluoro-5-phenyl-2-(trifluoromethyl)-2,5-hexadien-3-ol 3,3,3-Trifluoro-2-(trifluoromethyl)propionate (12).—A mixture of 6.5 g (0.055 mol) of α-methylstyrene, 0.5 g of phenothiazine, and 8.0 g (0.045 mol) of **1** sealed in a Carius tube formed two layers at room temperature. After being warmed 15 min on a steam bath, the mixture was homogeneous and crystallized at room temperature. After 2-hr heating, the product was distilled at ~82° (1 mm) (12.8 g, 96%). In spite of a nearly constant boiling point, it was a mixture of the β,γ-unsaturated ketone **11** and its enol ester **12**. Recrystallization from petroleum ether (bp 30–60°) gave 4.6 g (35%) of purified **11**: mp 68–70°; ir 5.78 μ (C=O); nmr ^{1}H at τ 3.1 (multiplet, 5, C$_6$H$_5$), 4.75 (singlet, 1, =CHH), 5.12 (singlet, 1, =CHH), 5.23 [septet, $J_{H/F}$ = 8.0 Hz, 1, (CF$_3$)$_2$CH–], 6.33 (singlet, 2, CH$_2$); ^{19}F at 64.5 ppm [doublet, $J_{H/F}$ = 8.0 Hz, (CF$_3$)$_2$CH–].

Anal. Calcd for $C_{13}H_{10}F_6O$: C, 52.75; H, 3.41; F, 38.51. Found: C, 52.68; H, 3.54; F, 38.45.

A pure sample of the enol ester **12** was prepared as follows. A mixture of 11.8 g (0.10 mol) of α-methylstyrene, 36 g (0.2 mol) of **1**, and 0.1 g of phenothiazine (polymerization inhibitor) was heated in a sealed tube in a steam bath for 46 hr. Recovered was 8 g of ketene and 33.5 g (70%) of enol ester boiling mostly at 65° (0.1 mm): n^{25}D 1.4150; ir 5.58 (C=O), 5.96 μ (C=C); nmr ^{1}H at τ 6.54 [septet, $J_{H/F}$ = 7.4 Hz, (CF$_3$)$_2$CH], 6.47 (multiplet, 2, CH$_2$), 5.17 (singlet, 1, =CH), 4.84 (singlet, 1, =CH), 2.99 (singlet, 5, C$_6$H$_5$); ^{19}F at 58.8 (quartet, $J_{F/F}$ = 9.2 Hz, 1, CF$_3$), 60.6 (broad quartet, $J_{F/F}$ = 9.2 Hz, 1, CF$_3$), 65.0 ppm [doublet, $J_{F/H}$ = 7.4 Hz, to quartets, $J_{F/F}$ = 2.5 Hz, 2, (CF$_3$)$_2$CH].

Anal. Calcd for $C_{17}H_{10}F_{12}O_2$: C, 43.07; H, 2.12; F, 48.10. Found: C, 44.19; H, 2.27; F, 47.13.

A sample of the above enol ester **12** (4.5 g) was heated in a sealed tube with water (5 ml) in a steam bath for 20 hr. It was immiscible and remained unchanged; so 15 ml of tetrahydrofuran was added and the heating continued for 1 week. Removal of the solvents gave a gelatinous polymer and an oil which was characterized by ir as being largely the α,β-unsaturated ketone **13** (see below).

A sample of the enol ester **12** when added to 10% sodium hydroxide solution became warm and gave a tar. A similar result was obtained with the β,γ-unsaturated ketone **11** and dilute alkali.

Passage of a sample of the enol ester **12** through a preparative gas chromatography column at 147° gave **1**, which was collected and characterized by ir, as well as the β,γ-unsaturated ketone **11**, characterized by ir and mixture melting point.

1,1,1-Trifluoro-5-phenyl-2-(trifluoromethyl)-4-hexen-3-one (13).—In a reaction of excess α-methylstyrene with **1** heated for only a short time it was possible to isolate the α,β-unsaturated ketone **13**. The α-methylstyrene (23.6 g, 0.2 mol), 20 g (0.11 mol) of **1**, and 0.1 g of phenothiazine were charged into a Carius tube and heated in a steam bath for 20 min. Distillation of the product gave 17.5 g of material, bp 65° (0.3 mm). By crystallization of these fractions from petroleum ether it was possible to isolate 3 g of the α,β-unsaturated ester **13**: mp 42–42.5°; ir 5.92 (C=O) and 6.25, 6.35, 6.69 (conjd linear and aromatic C=C); nmr ^{1}H (CDCl$_3$) at τ 7.37 (doublet, $J_{H/H}$ = 1.3 Hz, 3, CH$_3$), 5.90 [septet, $J_{H/F}$ = 8.0 Hz, 1, (CF$_3$)$_2$CH], 3.38 (broad singlet, 1, =CH), 2.53 (singlet, 5, C$_6$H$_5$); ^{19}F at 64.0 ppm [doublet, $J_{H/F}$ = 8.0 Hz, (CF$_3$)$_2$CH].

Anal. Calcd for $C_{13}H_{10}F_6O$: C, 52.75; H, 3.41; F, 38.51. Found: C, 53.14; H, 3.48; F, 39.00.

Samples of the above α,β-unsaturated ketone, **13**, mp 42°, and the β,γ-unsaturated isomer, **11**, mp 70°, were each sealed in nmr tubes with equimolar amounts of bis(trifluoromethyl)-ketene and heated in a steam bath for 18 hr. No reaction occurred as evidenced by crystallization and separation of the ketene on cooling. Addition of BF_3 to the tube containing the β,γ-unsaturated isomer and continued heating caused darkening and some tar formation but only starting ketone and no enol ester **12** could be detected by infrared absorption.

8,8-Bis(trifluoromethyl)bicyclo[4.2.0]octan-7-one (16).—A mixture of cyclohexene (8 g, 0.1 mol), **1** (18 g, 0.1 mol), and 0.1 g of phenothiazine was sealed in a Carius tube and heated in a steam bath for 7 weeks. There was recovered 15 g of crude product. From about 5 g boiling around 45° (0.25 mm) there was collected by glpc 0.6 g of **16** and two less pure fractions (0.7 and 0.5 g) which appeared to be hexafluoroisobutyryl cyclohexenyl ketones. From another run using double quantities of cyclohexene and ketene at 175° for 8 hr, there was obtained only 1.6 g of a mixture similar to the above and a higher boiling mixture.

For the cyclobutanone **16**: ir 5.54 μ (C=O); nmr ^{1}H at τ 6.51 (multiplet, 1), 7.19 (multiplet, 1), 8.55 (multiplet, 8); ^{19}F at 62.7 (quartet, $J_{F/F}$ = 9.7 Hz, 1, CF$_3$), 69.4 ppm (quartet, $J_{F/F}$ = 9.7 Hz, 1, CF$_3$).

Anal. Calcd for $C_{10}H_{10}F_6O$: C, 46.19; H, 3.88; F, 43.85. Found: C, 45.61; H, 3.90; F, 43.23.

4,4-Bis(trifluoromethyl)tricyclo[4.2.1.0^{2,5}]nonan-3-one (15).—An equimolar (0.05 mol) mixture of **1** (9.5 g) and norbornene (5 g) sealed in a Carius tube remained immiscible at room temperature after being heated overnight in a steam bath. However, heating at 175° for 8 hr gave 13.3 g (97%) of **15**: bp 79° (10 mm); n^{25}D 1.4086; ir 5.53 μ (small-ring ketone C=O); nmr ^{1}H at τ 6.30 (multiplet, 1) 7.30 (multiplet, 3), 8.53 (multiplet, 6); ^{19}F at 63.2 (quartet, 1, $J_{F/F}$ = 10.2 Hz, CF$_3$), 68.7 ppm (quartet, to doublets, 1, $J_{F/F}$ = 10.2 Hz, $J_{F/H}$ = 2.0 Hz, CF$_3$).

Anal. Calcd for $C_{11}H_{10}F_6O$: C, 48.57; H, 3.71; F, 41.91. Found: C, 48.53; H, 3.64; F, 42.15.

Hexahydro-6-(hexafluoroisopropylidene)-1,2,4-methenopentalen-5(6H)-one (25).—A mixture of 9.0 g (0.05 mol) of **1** and 5.0 g (0.054 mol) of bicycloheptadiene in a Carius tube was miscible at room temperature but immiscible on cooling. After being heated for 1 hr in a steam bath, the mixture no longer separated on cooling. After 2 hr, there was obtained 11 g (81%) of **25**, bp 62° (1 mm), n^{25}D 1.4297. Recrystallization from cold petroleum ether gave 7.6 g: mp 32–33°; ir 6.04 μ (C=C); nmr ^{1}H at τ 5.20 (1), 6.64 (quartet, 1, $J_{H/F}$ = 2.0 Hz), 7.77 (1), 8.28 (2), 8.48 (3) (all of the peaks had some fine structure); ^{19}F at 55.8 (quartet to doublets, 1, $J_{F/F}$ = 8.8 Hz, $J_{F/H}$ = 2.0 Hz, CF$_3$), 57.7 ppm (quartet, 1, $J_{F/F}$ = 8.8 Hz, CF$_3$).

Anal. Calcd for $C_{11}H_8F_6O$: C, 48.93; H, 2.99; F, 42.22. Found: C, 49.18; H, 3.11; F, 41.87.

10-Hexafluoroisopropylidene-9-oxatricyclo[4.2.2.0^{2,5}]deca-3,7-diene (23).—Cyclooctatetraene (7.0 g, 0.067 mol) with 0.5 g of phenothiazine added and **1** (9.5 g, 0.053 mol) in a Carius tube were immiscible at room temperature. After the mixture was heated overnight in a steam bath, strong cooling was necessary to separate two layers. Heating for 3 days in a steam bath gave 4 g of the ketene, 3.3 g of cyclooctatetraene, and 5.4 g (36%) of product, bp 70° (1 mm), which solidified: mp 78–79° (petroleum ether); ir 6.08 and 6.15 μ (C=C); nmr ^{1}H at τ 4.00 (multiplet, 4), 5.83 (multiplet, 1), 5.84 (multiplet, 1), 6.82 (multiplet, 1), 7.17 (multiplet, 1); ^{19}F at 53.1 (quartet, 1, $J_{F/F}$ = 9.8 Hz, CF$_3$), 56.7 ppm (quartet, 1, $J_{F/F}$ = 9.8 Hz, CF$_3$).

Anal. Calcd for $C_{12}H_8F_6O$: C, 51.11; H, 2.86; F, 40.43. Found: C, 50.97; H, 2.79; F, 39.83.

3,3-Bis(trifluoromethyl)-11-hexafluoroisopropylidene-10-oxatricyclo[4.3.2.0^{2,5}]undec-8-en-4-one (24).—A mixture of 20 g (0.2 mol) of cycloheptatriene (91% pure), 0.1 g of phenothiazine, and 37 g (0.2 mol) of **1** sealed in a Carius tube was immiscible at room temperature, but homogeneous after being heated overnight in a steam bath. Distillation gave 30 g (68%) of a 2:1 ketene–cycloheptatriene product: bp 90° (9 mm); ir 5.55 (C=O), 5.90 μ with 6.00 μ sh (C=C); nmr ^{1}H at τ 2.15 (singlet, 1), 3.55 (multiplet, 2), 4.05 (multiplet, 2), 4.80 (multiplet, 2), 7.80 (triplet, 1, $J_{H/H}$ = 6.0 Hz); ^{19}F at 61.3 (quartet, 1, $J_{F/F}$ = 6.4 Hz, CF_3), 63.5 [singlet, 2, $C(CF_3)_2$], 64.6 ppm (quartet to doublets, 1, $J_{F/F}$ = 6.4 Hz, $J_{F/H}$ = 1.5 Hz, CF_3).

Anal. Calcd for $C_{15}H_8F_{12}O_2$: C, 40.21; H, 1.80; F, 50.89. Found: C, 40.84; H, 2.05; F, 51.07.

6-Hexafluoroisopropylidene-5,6-dihydro-2H-pyran (17).—A Carius tube was charged with 41 g (0.23 mol) of **1**, 5.0 g (0.09 mol) of butadiene, and 0.1 g of phenothiazine and heated 60 hr in a steam bath. There was recovered 25 g of the ketene and 21 g (98%) of crude **17** which was 94% pure by glpc. Distillation gave 16.7 g (78%): bp 65° (9 mm); n^{25}D 1.3957; ir 6.10 μ (C=C); nmr (220 MHz, 20% in $CDCl_3$, internal TMS) ^{1}H at τ 3.98 (multiplet, 1, =C**H**), 4.12 (multiplet, 1, =C**H**), 5.38 (multiplet, 2, CH_2), 6.80 (multiplet, 2, CH_2); ^{19}F at 57.2 (quartet, $J_{F/F}$ = 9.8 Hz, to triplet, $J_{H/F}$ = 2.2 Hz, 1, CF_3), 58.7 ppm (quartet, $J_{F/F}$ = 9.8 Hz, to triplet, $J_{H/F}$ = 1.8 Hz, 1, CF_3).

Anal. Calcd for $C_8H_6F_6O$: C, 41.41; H, 2.61; F, 49.14. Found: C, 40.82; H, 2.74; F, 48.82.

***cis*-1,1,1-Trifluoro-2-trifluoromethyl-4,6-heptadien-3-one (18) and 6-[2,2,2-Trifluoro-1-(trifluoromethyl)ethyl]-2H-pyran (19).**—By contrast to the above experiment, when excess ketene was not used, usually only polymeric oils were obtained from such long heating periods. By using hexane as solvent and less heating the open chain *cis* isomer **18** was obtained and the possible presence of the cyclic isomer **19** was indicated by ^{1}H nmr.

A mixture of 21 g (0.39 mol) of butadiene, 35 g (0.20 mol) of **1**, 25 ml of hexane, and 0.1 g of phenothiazine was heated in a Carius tube 16 hr at 70°. Recovered was 27 g (58%) of 1:1 products, bp 41–46° (20 mm), n^{25}D 1.3910, and 6 g of higher boiling mixture. The material boiling at 42–46° appeared pure by glpc, but ^{1}H nmr of different fractions showed it to be a mixture. There were varying amounts of peaks not present in either the pure *cis* (**18**) or *trans* (**20**) isomer. These peaks included a well-separated septet which was at about 0.8-ppm higher field with a slightly larger (0.4 Hz) J value and may have been due to the presence of cyclic isomer **19**. Its presence diminished in the higher boiling cuts and in all cuts on standing.

The *cis* isomer **18** was distinguished from *trans* **20** (see below): ^{1}H nmr (220 MHz, 20% in $CDCl_3$, internal TMS) τ 5.82 [septet, $J_{H/F}$ = 7.9 Hz, 1, $(CF_3)_2CH$], 4.30 (doublet, $J_{H/H}$ = 10.0 Hz, 1, $-C{=}C\langle^{H}_{H}$), 4.27 (doublet, $J_{H/H}$ = 18.0 Hz, 1, $-C{=}C\langle^{H}_{H}$), 3.89 [doublet, $J_{H/H}$ = 10.0 Hz, 1, $(CF_3)_2CHCO-CH{=}$], 3.34 [doublet $J_{H/H}$ = 10.0 Hz to doublet, $J_{H/H}$ = 10.0 Hz as apparent triplet, 1, $(CF_3)_2CHCO-CH{=}CH-$], 2.39 (doublet, $J_{H/H}$ = 18.0 Hz to doublet, $J_{H/H}$ = 10.0 Hz to doublet, $J_{H/H}$ = 10.0 Hz as overlapping pattern, 1, $-CH{=}CH_2$); ir 5.89 (C=O) and 6.18, 6.37 μ (C=C).

Anal. Calcd for $C_8H_6F_6O$: C, 41.41; H, 2.61; F, 49.14. Found: C, 41.46; H, 2.40; F, 48.70.

***trans*-1,1,1-Trifluoro-2-trifluoromethyl-4,6-heptadien-3-one (20).**—A sample (10.6 g) of the above material, bp 43–45° (20 mm), which by ^{1}H nmr was largely *cis* isomer **18** containing some **19** was mixed with three drops of triethylamine and slowly fractionated. The first fraction had about the same boiling point [43–50° (20 mm)] as the starting material, but glpc now showed a definite shoulder on the starting material peak and a small, well-separated peak which eluted later (*trans* isomer **20**). Later fractions (3.4 g, 32%) were nearly pure *trans* isomer **20**, bp 61° (20 mm), n^{25}D 1.4088. These fractions became crystalline because of dimer formation (see below) after standing at room temperature for 60 hr. The first fraction remained liquid even after 2 months, but became viscous because of polymer formation. The *trans* isomer **20** was further characterized as follows: ir 5.90 doublet (C=O) and 6.15, 6.30 μ (C=C); nmr (220 MHz, 20% in $CDCl_3$, internal TMS) τ 5.73 [septet, $J_{H/F}$ = 7.9 Hz, 1, $(CF_3)_2CH$], 4.30 (doublet, $J_{H/H}$ = 10.0 Hz, 1, $_{H}{>}C{=}C\langle^{H}_{H}$), 4.23 (doublet, $J_{H/H}$ = 17.0 Hz, 1, $_{H}{>}C{=}C\langle^{H}_{H}$), 3.64 [doublet, $J_{H/H}$ = 15.0 Hz, 1, $(CF_3)_2CHCO-CH{=}$], 3.40 (doublet, $J_{H/H}$ = 17.0 Hz to doublet, $J_{H/H}$ = 11.0 Hz to doublet, $J_{H/H}$ = 10.0 Hz, 1, $-CH{=}CH_2$), 2.64 [doublet, $J_{H/H}$ = 15.0 Hz to doublet, $J_{H/H}$ = 11.0 Hz, 1, $(CF_3)_2CHCOCH{=}CH-$].

Dimer 21.—A sample (1.8 g) of the *trans* isomer **20** mixed with excess **1** (6.8 g) and 0.1 g of hydroquinone was heated in a sealed tube in a steam bath 16 hr. Removal of the unreacted ketene gave an oily solid which crystallized from hexane gave 0.9 g (50%) of dimeric **20**, mp 95–99°. Repeated recrystallizations raised the melting point to 107–108°, giving a relatively pure isomer of unknown structure represented by formula **21**: ir 5.75 (C=O), 5.90 (conjugated C=O), 6.13 μ (C=C); nmr ^{1}H at about τ 5.10 [two overlapping septets, $J_{H/F}$ = 8.0 Hz, 2, $(CF_3)_2CH$], 2.9 to 4.5 (complex pattern, 4, vinyl **H**), 6.4 to 8.6 (complex patterns, 6, C**H**); ^{19}F at 64.5 [doublet, $J_{H/F}$ = 8.0 Hz, 1, $(CF_3)_2CH$], 64.8 ppm [doublet, $J_{H/F}$ = 8.0 Hz, 1, $(CF_3)_2$-CH]. Each of these doublets was overlapped slightly by a smaller doublet (J = 8.0 Hz), probably due to an isomer.

Anal. Calcd for $C_{16}H_{12}F_{12}O_2$: C, 41.41; H, 2.61; F, 49.14; mol wt, 464. Found: C, 41.81; H, 2.63; F, 48.67; mol wt, 482 (cryoscopic in benzene).

8,8-Bis(trifluoromethyl)-3-[2,2,2-trifluoro-1-(trifluoromethyl)-ethyl]-4-oxabicyclo[4.2.0]oct-2-en-7-one (22).—A sample (1.7 g) of the *cis* isomer **18** mixed with 0.1 g of hydroquinone was treated with excess **1** (6.8 g) in a sealed tube in a steam bath for 16 hr exactly as described above for the *trans* isomer **20**. In this case no solid was isolated but removal of unreacted ketene gave an oil which was shown by glpc to be **22**, containing 2 mol of **1** per mol of butadiene. Product **22** could be prepared in high yield by long heating of butadiene with excess **1**. The use of excess **1** gave excellent overall yields of cyclic products **17** and **22**, but conditions for obtaining one to the exclusion of the other were not well defined. The following conditions are essentially those described above for preparation of **17**, but in this case a high yield of **22** was obtained.

A mixture of 28 ml (47 g, 0.26 mol) of **1**, 7.1 g (0.13 mol) of butadiene, and 0.1 g of phenothiazine was heated for 60 hr in a sealed tube in a steam bath. There was distilled 41.4 g (77%) of the product **22**: bp 64° (0.4 mm); n^{25}D 1.3687; ir 5.50 (small ring, C=O), 5.95 μ (C=C); nmr ^{1}H (220 MHz, 20% in $CDCl_3$, internal TMS) at τ 6.40 [doublet, $J_{H/H}$ = 12 Hz to doublet, $J_{H/H}$ = 5 Hz, 1, $(CF_3)_2C-CH$], 6.43 [septet, $J_{H/F}$ = 8.0 Hz, 1, $(CF_3)_2CH$], 6.18 (doublet, $J_{H/H}$ = 12.0 Hz, to doublets, $J_{H/H}$ = 5.0 Hz, 1, $-OCHH$), 5.98 (unresolved broad peak, 1, $O{=}C-CH$), 5.55 (doublet, J = 12.0 Hz, to doublets, J = 2.0 Hz, 1, $-COHH$), 4.55 (doublet, J = 5.0 Hz, 1, $C{=}CH$); ^{19}F at 62.2 (quartet with fine structure, $J_{F/F}$ = 9.0 Hz, 1, ring CF_3), 64.2 [doublet, $J_{H/F}$ = 8.0 Hz to quartets, $J_{H/?}$ = 2.0 Hz, 2, $(CF_3)_2CH$], 66.9 ppm (quartet, $J_{F/F}$ = 9.0 Hz, 1, ring CF_3).

Anal. Calcd for $C_{12}H_6F_{12}O_2$: C, 35.15; H, 1.48; F, 55.61. Found: C, 35.33; H, 1.64; F, 55.53.

8,8-Bis(trifluoromethyl)-3-[2,2,2-trifluoro-1-(trifluoromethyl)-ethyl]-4-oxabicyclo[4.2.0]oct-2-en-7-ol (22c).—Product **22** (20 g, 0.05 mol) in 100 ml of ethanol with 5 g of Raney nickel catalyst was shaken 4 hr at 125° under 2000 psi of hydrogen. There was isolated 13.9 g of material boiling mainly at 82° (0.9 mm). It was shown by glpc to be a 7:3 mixture of solid hydrogenation product (49% yield) and liquid products of reaction with ethanol (analogous to methanol reaction below). The first distillation cut (1.5 g) solidified and after four recrystallizations from petroleum ether there was obtained 0.7 g of **22c**: mp 63–65° [both mass spectrum (parent peak 412) and ^{1}H nmr indicated additions of two hydrogen atoms to **22**, and ir and ^{1}H nmr (one exchangeable proton) indicated formation of an alcohol; ir also showed hydroxyl and loss of the small-ring carbonyl group]; ir broad 2.82 (OH), 5.95 μ (C=C); nmr ^{1}H (220 MHz, 20% in $CDCl_3$, internal TMS) τ 7.29 (broad, exchangeable with D_2O, 1, $-OH$), 6.77 (multiplet, 2, CH_2), 6.41 [septet, $J_{H/F}$ = 8.1 Hz, 1, $(CF_3)_2$-CH], 5.99 (multiplet, 1, CH), 5.53 (multiplet, 1, CH), 5.14 (broad, 1, CHOH), 4.66 (multiplet, 1, $C{=}CH$); ^{19}F at 60.9 (quartet, $J_{F/F}$ = 10.1 Hz, 1, CF_3), 65.5 [doublet, $J_{H/F}$ = 8.1 Hz, 2, $(CF_3)_2CH$], 72.5 ppm (quartet, $J_{F/F}$ = 10.1 Hz, 1, CF_3).

Anal. Calcd for $C_{12}H_8F_{12}O_2$: C, 34.98; H, 1.96; F, 55.34. Found: C, 35.61; H, 2.40; F, 55.13.

Methyl 4,6-Bis[2,2,2-trifluoro-1-(trifluoromethyl)ethyl]-3,4-dihydro-2H-pyran-3-carboxylate (22a) and Methyl 4-[2,2-Difluoro-1-(trifluoromethyl)vinyl]-6-[2,2,2-trifluoro-1-(trifluoromethyl)ethyl]-3,4-dihydro-2H-pyran-3-carboxylate (22b).—Compound **22** (42 g) in 50 ml of methanol containing a trace of sodium methoxide (probably unnecessary) was heated in a sealed tube in a steam bath 16 hr. After removal of methanol there was distilled in ten fractions 35 g of oil boiling mostly at 58–60° (0.05 mm). This product was shown by glpc to consist of two compounds, and when separated by preparative glpc, one of them crystallized. Early fractions were richer in the liquid product, which proved to be a methanol adduct assigned structure **22a**. Later fractions were richer in the solid product and could be recrystallized (petroleum ether) to mp 46–48°. The solid product, a methanol adduct minus HF, was assigned structure **22b**. Attempts to convert **22a** to **22b** were unsuccessful under the reaction conditions (methanol containing $NaOCH_3$ at 100°), in methanol saturated with hydrogen chloride at 100°, in glyme saturated with cesium fluoride at 100°, or in aqueous sodium hydroxide at 100°. Therefore it appears that nucleophilic attack of **22** with methanol or methoxide ion gives a carbanionic center which either loses fluoride ion to give **22b** or adds a proton to give **22a**, and **22b** is not formed from **22a**.

Compound **22a** was characterized as follows: ir 5.72 (C=O), 5.91 μ (C=C); nmr ^1H (220 MHz, 20% in $CDCl_3$, internal TMS) τ 6.84 (multiplet, 1, CH_3O_2C–C**H**), 6.75 [multiplet, 1, $(CF_3)_2$-CH–C**H**], 6.48 [septet, $J_{H/F}$ = 8.0 Hz, $[CF_3)_2CHC$=C], 6.35 [multiplet, 1, $(CF_3)_2CHCH$], 6.26 (singlet, 3, OCH_3), 5.70 (doublet, $J_{H/H}$ = 6.0 Hz, 2, CH_2), 4.84 (broad, 1, C=C**H**); ^{19}F at 61.2 (broad quintet, presumably quartet, $J_{F/F}$ = 10.0 Hz, to doublet, $J_{H/F}$ = ~8 Hz, 1, CF_3), 65.2 (broad quintet, presumably quartet, $J_{F/F}$ = 10.0 Hz, to doublet, $J_{H/F}$ = ~8 Hz, 1, CF_3), 65.7 ppm [doublet, $J_{F/F}$ = 8.0 Hz, $(CF_3)_2CHC$=C].

Anal. Calcd for $C_{13}H_{10}F_{12}O_3$: C, 35.32; H, 2.28; F, 51.58; mol wt, 442.0437 (high resolution mass spectrum). Found: C, 35.48; H, 2.23; F, 51.54; mol wt, 442.0432.

Compound **22b** was characterized as follows: ir 5.78 (C=O), 5.95 μ (C=C); nmr ^1H (220 MHz, 20% in $CDCl_3$, internal TMS) τ 6.84 (multiplet, 1, C**H**), 6.44 [septet, $J_{H/F}$ = 8.0 Hz, 1, $(CF_3)_2$-C**H**], 6.39 (multiplet, 1, C**H**), 6.30 (singlet, 3, OCH_3), 5.85 (multiplet, 1, C**H**), 5.70 (multiplet, 1, C**H**), 4.91 (doublet, $J_{H/H}$ = 4.5 Hz, 1, C=C**H**); ^{19}F at 58.7 (doublet, J_{F/CH_3} = 22.0 Hz to doublet, $J_{F/F}$ = 10.8 Hz, 3, CF_3), 69.7 (quartet, J_{F/CF_3} = 22.0 Hz, to doublet, $J_{F/F}$ = 10.8 Hz, to doublet, $J_{H/F}$ = 2.5 Hz, 1, C=C**F**), 72.1 (overlapping quartet, J_{F/CF_3} = 10.8 Hz, to doublet, $J_{F/F}$ = 10.8 Hz, 1, C=C**F**), 66.0 ppm [doublet, $J_{H/F}$ = 8.0 Hz, to doublet, $J_{H/F}$ = 2.0 Hz, 6, $(CF_3)_2CH$].

Anal. Calcd for $C_{13}H_9F_{11}O_3$: C, 37.00; H, 2.15; mol wt, 422.0376 (high resolution mass spectrum). Found: C, 37.38; H, 2.47; mol wt, 422.0381.

Compound **22** was treated with ethanol and with water (in equal amount of tetrahydrofuran) at 100° to give in each case a mixture of two products (adduct and adduct minus HF) analogous to the above methanol reaction. The mixtures were characterized only by nmr and not separated.

7,7-Bis(trifluoromethyl)-4,5-dihydroxy-4-[2,2,2-trifluoro-1-(trifluoromethyl)ethyl]-3-oxabicyclo[4.2.0]octan-8-one (22d).—Starting material was recovered in an attempt to oxidize **22** (15 g, 0.037 mol) with acid permanganate at room temperature. It was redissolved in 50 ml of acetone, 50 ml of water, and 10 ml of concentrated sulfuric acid. While this solution was refluxed, a total of 36 g of potassium permanganate was added in small portions giving a vigorous reaction. After cooling, the mixture was decolorized with SO_2 and water added to dissolve inorganic salt. A heavy oil (12 g) separated and partly crystallized. Filtration gave 3.4 g (21%) of white crystals, mp 167–168°, and 6 g of oil. Recrystallization from xylene gave 3.0 g white needles, mp 167–168°. Structure **22d** is proposed for this product [mass spectrum (parent peak 444) indicated the addition of two hydroxyls to **22**, and ir showed loss of double bond, gain of hydroxyl and retention of the small ring carbonyl]: ir 2.78 (OH), 5.60 μ (C=O); nmr ^1H (220 MHz, 20% in acetone-d_6, internal TMS) τ 7.17 (broad multiplet, 1, C**H**), 6.93 (singlet, exchangeable with D_2O, 1, O**H**), 6.77 (broad multiplet, 1, C**H**), 5.86 [multiplet, 1, $(CF_3)_2CH$], 5.76 (multiplet, 1, C**H**), 5.63 (multiplet, 1, C**H**), 5.48 (multiplet, 1, C**H**), 4.09 (multiplet, exchangeable with D_2O, <1, O**H**); ^{19}F at 61.0 (quartet, $J_{F/F}$ = 9.0 Hz, 1, CF_3), 61.5 (quartet, $J_{F/F}$ = 9.0 Hz, 1 CF_3), 62.8 (quintet, presumably quartet, $J_{F/F}$ = 10.0 Hz, to doublet, $J_{H/F}$ = ~10 Hz, CF_3), 65.7 ppm (quintet, presumably quartet, $J_{F/F}$ = 10.0 Hz, to doublet, $J_{H/F}$ = ~10 Hz, 1, CF_3).

Anal. Calcd for $C_{12}H_8F_{12}O_4$: C, 32.46; H, 1.81; F, 51.35. Found: C, 32.97; H, 1.95; F, 51.19.

Registry No.—**1**, 684-22-0; **2** (R = H), 25636-67-3; **2** (R = CH_3), 25679-30-5; **2** (R = C_3H_7), 25636-68-4; **3** (R = H), 4141-85-9; **3** (R = CH_3), 25636-70-8; **3** (R = C_3H_7), 25636-71-9; **4** (R = H), 25636-72-0; **4** (R = CH_3), 25636-73-1; **4** (R = C_3H_7), 25636-74-2; **5**, 25636-75-3; **6**, 25636-76-4; **7**, 5548-89-0; **8**, 5548-91-4; **9**, 25636-79-7; **10**, 25636-80-0; **11**, 25636-81-1; **12**, 25636-82-2; **13**, 25636-83-3; **14**, 5604-68-2; **15**, 25636-85-5; **16**, 25636-86-6; **17**, 17698-59-8; **18**, 7108-74-9; **19**, 25636-87-7; **20**, 10253-48-2; **21**, 25631-63-4; **22**, 25636-88-8; **22a**, 25636-89-9; **22b**, 25636-90-2; **22c**, 25636-91-3; **22d**, 25631-64-5; **23**, 25636-92-4; **24**, 25636-93-5; **25**, 25636-94-6.

Fluoroketenes. IV. Cycloadducts of Bis(trifluoromethyl)ketene with Acetylenes[1]

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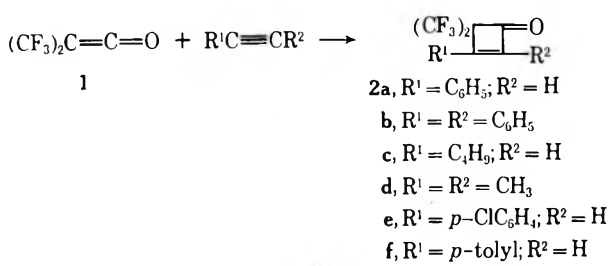
Cyclobutenones have been obtained from the reaction of bis(trifluoromethyl)ketene with hexyne-1, butyne-2, phenylacetylene, and diphenylacetylene. Evidence is given for possible mechanisms of these reactions and some unusual chemistry of the products is described. For example, pyrolysis of the cyclobutenone obtained with phenylacetylene has given five products, **10**, **11**, **12**, **13**, or **14**, depending on conditions.

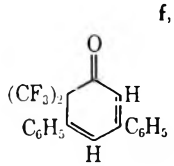
Cycloaddition of bis(trifluoromethyl)ketene (**1**) to phenylacetylene was previously shown to give a cyclobutenone directly.[2] This reaction has now been found to have some generality for aryl- and alkyl-substituted acetylenes. Ketene **1** does not react readily with acetylene or ethyl propiolate, probably because of low nucleophilicity of these acetylenes, nor with methylacetylene because of difficulty in obtaining a condensed phase. However, cycloadducts to the carbon–carbon double bond of **1** have been obtained from hexyne-1, butyne-2, phenylacetylene, and diphenylacetylene. Ethoxyacetylene, an exceptionally nucleophilic acetylene, reacts at the carbonyl group of **1** to give a different type of product.[3]

As reported earlier,[2] phenylacetylene with ketene **1** gave 80% cyclobutenone **2a** in a slow reaction at 100°. A by-product of this reaction, apparently of structure **3**, is formed in good yield by reaction of **2a** with phenylacetylene. Characterization of **3** is discussed below.



1

2a, $R^1 = C_6H_5$; $R^2 = H$
b, $R^1 = R^2 = C_6H_5$
c, $R^1 = C_4H_9$; $R^2 = H$
d, $R^1 = R^2 = CH_3$
e, $R^1 = p$-ClC_6H_4; $R^2 = H$
f, $R^1 = p$-tolyl; $R^2 = H$

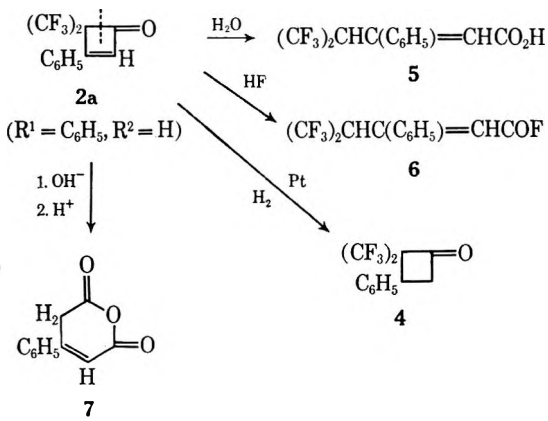


3

Diphenylacetylene at 200° gave a 95% yield of **2b**. Hexyne-1 reacted with **1** at 150° for 8 hr to give a low yield of cyclobutenone **2c**. Butyne-2 gave with **1** in 60 hr at 100° a 65% yield of **2d** along with a 2:2 adduct of unknown structure.

These cycloadditions with direct formation of cyclobutenones are, with few exceptions, the only such examples known. Previous reactions with other ketenes and various acetylenes have resulted in products of rearrangements.[4] One exception is the additions of ethoxyacetylene which, unlike its reaction with **1**, gave cyclobutenones with diphenylketene[5] and dimethylketene.[6] Also, reactions of a number of diethylaminoacetylenes with arylketenes have recently been shown to give cyclobutenones.[7]

Ring-opening reactions of the new cyclobutenones in every case proceeded by initial scission of the carbon–carbon bond between the carbonyl group and the carbon bearing *gem*-trifluoromethyl groups. Cyclobutenone **2a** hydrolyzed readily with warm water to give acid **5** and reacted with fluoride in a liquid phase to form acid fluoride **6**. Aqueous alkali followed by acidification resulted in hydrolysis of all fluorine from **2a** and formation of the stable acid anhydride **7**. Hydrogenation of **2a** gave a cyclobutanone **4**, identical with that obtained from **1** and styrene.



2a ($R^1 = C_6H_5$, $R^2 = H$)

5

6

4

7

Pyrolysis of **2a** might be expected to give an α,β-unsaturated ketene **8** in a reversible isomerization.[8] Ketene **8**, a vinylog of ketene **1**, could reversibly isomerize to acid fluoride **9** in the same manner as **1** equilibrates with perfluoromethacryloyl fluoride.[9] Products isolated from pyrolyses of **2a** in a flow system

(1) Part III: D. C. England and C. G. Krespan, *J. Org. Chem.*, **35**, 3300 (1970).

(2) D. C. England and C. G. Krespan, *J. Amer. Chem. Soc.*, **87**, 4019 (1965).

(3) For details, see part V. *J. Org. Chem.*, **35**, 3312 (1970).

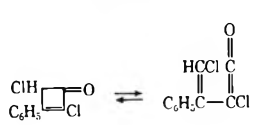
(4) R. N. Lacey in "The Chemistry of Alkenes," S. Patai, Ed., Interscience, New York, N. Y., 1964, p 1161.

(5) J. Druey, E. F. Jenny, K. Schenker, and R. B. Woodward, *Helv. Chim. Acta*, **45**, 600 (1962).

(6) R. H. Hasek and J. C. Martin, *J. Org. Chem.*, **27**, 3743 (1962).

(7) W. E. Truce, R. H. Baury, and P. S. Bailey, Jr., *Tetrahedron Lett.*, 5651 (1968).

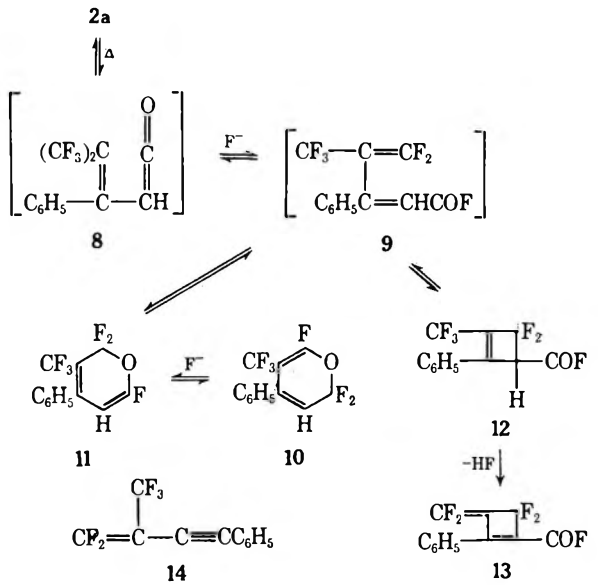
(8) (a) E. F. Jenny and J. D. Roberts, *J. Amer. Chem. Soc.*, **78**, 2005 (1956), report evidence for the equilibrium



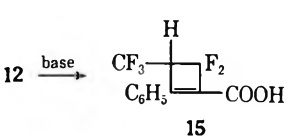
(b) J. E. Baldwin and M. C. McDaniel, *ibid.*, **90**, 6118 (1968); (c) Y. A. Cheburkov, N. Mukhamadaliev, and I. L. Knunyants, *Tetrahedron*, **24**, 1341 (1968), report reaction of **2a** with methanol to give 1,2 and 1,4 adducts of methanol to **8** plus a third, uncharacterized product.

(9) D. C. England and C. G. Krespan, *J. Amer. Chem. Soc.*, **88**, 5582 (1966).

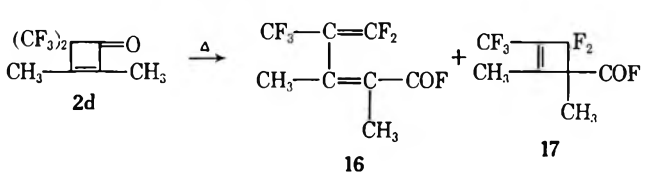
corresponded to the two possible modes of ring closure of the proposed common intermediate, **9**. At 350–500°, isomeric ethers **10** and **11** were formed by closure of the six-membered ring,[10] and cyclobutenecarbonyl fluoride **12** is also formed by cyclization of **9** as a diene to give a cyclobutene ring. In these experiments, lower pyrolysis temperatures favored ethers **10** and **11** and higher temperatures favored the cyclobutenecarbonyl fluoride **12**.



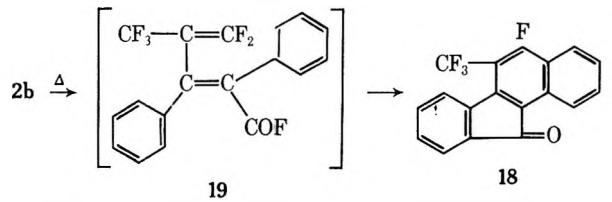
The interrelationship between **10** and **11** on the one hand and **12** on the other through common intermediate **9** was demonstrated by separate pyrolyses of these products. Starting with either a mixture of **10** and **11** or with purified **12**, pyrolysis gave the expected mixture of all three compounds. Higher pyrolysis temperatures (600–650°) with **2a** caused loss of hydrogen fluoride to give **13** and further of carbon monoxide to give rearranged enyne **14**. Loss of hydrogen fluoride may have occurred from **12**, since the proton was shown to be labile on treatment with base, giving a proton shift to form **15**. Simple hydrolysis or methanolysis of **12** gave the unrearranged acid and methyl ester, respectively.



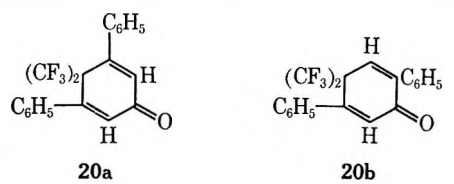
More direct evidence for the presence of **9** was obtained by isolation of the related butadienyl acid fluoride **16** from the pyrolysis of **2d**. Approximately equal amounts of **16** and the corresponding cyclobutene **17** were formed at 500°.

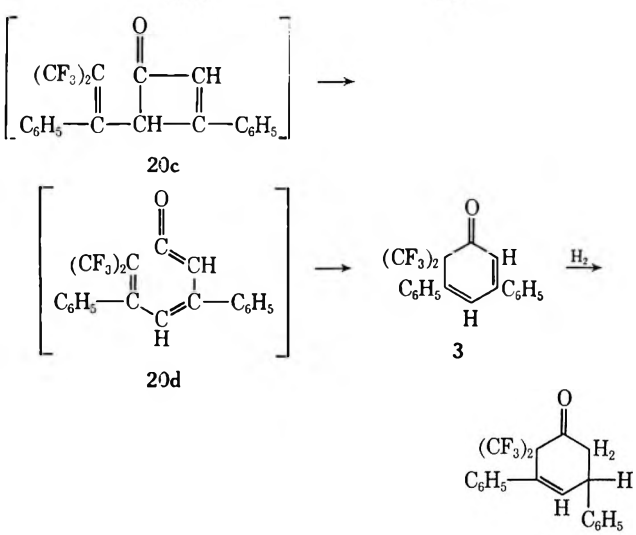


Pyrolysis of **2b** at 515° gave a product (60%) believed to be the aromatic ketone **18**, which could be derived from the expected intermediate **19** by two Friedel–Crafts condensations.



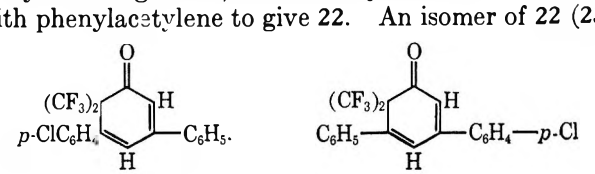
The 2:1 product formed by reaction of **2a** with phenylacetylene is, according to spectral data, a conjugated ketone containing two different vinyl protons having a coupling constant of 1.4 Hz. Almost certainly the reaction proceeds by initial scission of the carbon–carbon bond between the carbonyl groups and the carbon bearing *gem*-trifluoromethyl groups. Products of addition of another mole of phenylacetylene can then be postulated through intermediate **8**. 1,4 Addition could give **20a** or **20b**, but **20a** can be ruled out





because it contains only one kind of vinyl proton. 1,2 addition of phenylacetylene to **8** in the same manner as addition to **1** would give **20c** which could easily cleave to **20d** and cyclize to **3**. Structure **3** is selected over **20b** because addition of 1 mol of hydrogen gave an unconjugated ketone **21**, whereas addition of 1 mol of hydrogen to **20b** would give a conjugated ketone. By forcing the hydrogenation it was possible to add 1 and 2 more mol, giving saturated ketone and alcohol, respectively (detected by mass spectrometry and infrared).

It was also possible to react **1** with *p*-chlorophenylacetylene to give **2e**, and this cyclobutenone reacted with phenylacetylene to give **22**. An isomer of **22** (**23**)



(10) See P. Schiess, H. L. Chia, and C. Suter, *Tetrahedron Lett.*, 5747 (1968), for a discussion of the tendency for dienones such as **9** to exist in the isomeric 2H-pyran form. Although the isomerization **9** → **11** may be uncatalyzed, the formation of **9** from **8** and the interconversion of cyclic ethers **10** and **11** are probably catalyzed by fluoride ion, just as are some analogous reactions starting from ketene **1**.

was prepared by reacting 2a with *p*-chlorophenylacetylene.

Experimental Section[11]

1 and Acetylene.—A bomb charged with 36 g of 1 and 26 g of acetylene was heated at 150° for 12 hr. The pressure reached was 725 atm. Recovered material boiling above room temperature consisted of 4 g of perfluoromethacryloyl fluoride and 4 g of a higher boiling mixture. Ir did not indicate the presence of cyclobutenone.

1 and Methylacetylene.—A mixture of 8.5 g of 1 and 3.5 g of methylacetylene heated in a Carius tube at 175° for 8 hr gave no product.

1 and Ethyl Propiolate.—A mixture of 20 g of 1 and 10 g of ethyl propiolate heated in a Carius tube in a steam bath 13 days at 150° for 12 hr gave no product. Decomposition occurred at 200°.

4,4-Bis(trifluoromethyl)-3-butyl-2-cyclobuten-1-one (2c).—A mixture of 16.5 g (0.20 mol) of hexyne-1 and 37 g (0.21 mol) of 1 was heated in a Carius tube at 150° for 8 hr. There was obtained 6.2 g (11.5%) of the above cyclobutenone: bp 58–59° (5 mm); $n^{25}D$ 1.3778; ir 5.53 (C=O), 6.26 μ (C=C); nmr ^1H at τ 3.77 (singlet, 1 =CH), 7.68 (triplet, 2, $J_{H/H}$ = 7.0 Hz, CH_2), 8.75 (multiplet, 4, CH_2CH_2), 9.35 (triplet, 3, $J_{H/H}$ = 6.2 Hz, CH_3); ^{19}F at 67.5 ppm (singlet, CF_3).

Anal. Calcd for $C_{10}H_{10}F_6O$: C, 46.19; H, 3.88; F, 43.85. Found: C, 46.53; H, 4.17; F, 44.04.

4,4-Bis(trifluoromethyl)-2,3-dimethyl-2-cyclobuten-1-one (2d).—A mixture of 36 g (0.20 mol) of 1 and 11 g (0.20 mol) of butyne-2 in a Carius tube was heated 60 hr at 100°. Distillation gave 29 g (65%) of the above cyclobutenone, bp 58° (20 mm), $n^{25}D$ 1.3638, and 8 g (17%) of an unknown compound, bp 97° (1.25 mm), which solidified and was recrystallized twice from carbon tetrachloride to give 5.9 g, mp 67°.

For the cyclobutenone: ir 5.57 (C=O), 6.02 with a 6.09 μ shoulder (C=C); nmr ^1H at τ 8.11 (singlet, 1, CH_3), 8.54 (singlet, 1, CH_3); ^{19}F at 68.1 ppm (singlet, CF_3).

Anal. Calcd for $C_8H_6F_6O$: C, 41.41; H, 2.61; F, 49.14. Found: C, 41.38; H, 2.40; F, 49.07.

Pyrolysis of 2d. 5,5-Difluoro-2,3-dimethyl-4-(trifluoromethyl)-2,4-pentadienoyl Fluoride (16) and 4,4-Difluoro-1,2-dimethyl-3-(trifluoromethyl)-2-cyclobutene-1-carbonyl Fluoride (17).—The above cyclobutenone (17.9 g, 0.077 mol, $n^{25}D$ 1.3540) was slowly passed through a quartz-packed tube at 500° (1 mm). There was recovered in a liquid nitrogen trap 17 g, $n^{25}D$ 1.3658, indicating little change. The material was repyrolyzed at 660° (1 mm), and the recovered material ($n^{25}D$ 1.3800) distilled to give 4.2 g, bp 58–72° (60 mm), and 9.3 g boiling mostly at 72–90° (60 mm). The first fraction was separated by vpc into about equal amounts of 16 and 17. They were characterized by analyses, ir, and nmr.

For the diene 16: ir 5.49 (conjd COF), 5.74 [CF_2=C(CF_3)–], 6.11 μ (conjd C=C); nmr ^1H at τ 8.10 (multiplet, 1, weak splitting, CH_3), 8.35 (multiplet, 1, weak splitting, CH_3); ^{19}F at −38.3 (singlet, 1, COF), 60.5 ppm (doublet, 3, $J_{F/F}$ = 18.5 Hz, into doublets, $J_{F/F}$ = 11.5 Hz, CF_3), 78.5 ppm (multiplet, 2, CF_2).

Anal. Calcd for $C_8H_6F_6O$: C, 41.41; H, 2.61; F, 49.14. Found: C, 41.89; H, 2.78; F, 49.05.

For the cyclobutene 17: ir 5.42 (COF), 5.86 μ (C=C); nmr ^1H at τ 8.2 (multiplet, 1, CH_3), 8.8 (multiplet, 1, CH_3); ^{19}F at −36.1 (doublet, 1, $J_{F/F}$ = 6.2 Hz, COF), 64.8 (singlet, 3, CF_3), 109.8 and 114.5 ppm (quartet with fine structure, 2, AB, $J_{F/F}$ = 200 Hz, CF_2).

Anal. Calcd for $C_8H_6F_6O$: C, 41.41; H, 2.61; F, 49.14. Found: C, 41.90; H, 2.66; F, 49.14.

4,4-Bis(trifluoromethyl)-3-phenyl-2-cyclobuten-1-one (2a).—Phenylacetylene (5.5 g, 0.054 mol) and the ketene (9.0 g, 0.05 mol) were heated 60 hr in a steam bath to give 11.1 g (79%) of the above cyclobutenone: bp 75° (1 mm); ir 6.40 and 6.69 (aromatic and conjugated C=C), 5.55 μ (C=O); nmr ^1H at τ 2.75 (multiplet, 2, aromatic CH), 3.10 (multiplet, 3, aromatic CH), 3.55 (singlet, 1, =CH); ^{19}F at 65.7 ppm (singlet, CF_3).

Anal. Calcd for $C_{12}H_6F_6O$: C, 51.47; H, 2.16; F, 40.71. Found: C, 52.15; H, 2.12; F, 40.37.

(11) Melting points and boiling points are uncorrected. Nmr peak center positions for ^1H are reported τ = 10 − δ_H ppm. ^{19}F nmr spectra are reported in parts per million upfield from external trichlorofluoromethane.

3,5-Diphenyl-6,6-bis(trifluoromethyl)-2,4-cyclohexadienone (3). A.—In addition to cyclobutenone 2a in the above reaction there was distilled 2 g of material, bp 165–180° (1 mm), which partly crystallized. Recrystallization from petroleum ether gave 9 g (9.5%) of yellow crystalline 3: mp 120–121°; ir 6.01 (conjugated C=O), 6.12, 6.27, 6.34, 6.38, and 6.72 μ (aromatic and conjugated C=C); nmr ^1H at τ 2.70 (multiplet 10, aromatic CH), 3.18 (doublet, 1, $J_{H/H}$ = 1.4 Hz, =CH), 3.69 (doublet, 1, $J_{H/H}$ = 1.4 Hz, =CH); ^{19}F at 61.4 ppm [singlet, $(CF_3)_2$]; uv $\lambda_{max}^{isooctane}$ 232 mμ (ϵ 14,100), 299 (8300), 329 (8200).

Anal. Calcd for $C_{20}H_{12}F_6O$: C, 62.88; H, 3.17; F, 29.84. Found: C, 62.84; H, 3.02; F, 29.34.

B.—Compound 3 could be prepared in good yield from phenylacetylene and cyclobutenone 2a. A mixture of 7.0 g of 2a and 5.0 g of phenylacetylene in a sealed tube was heated 185 hr in a steam bath. The resulting solid was recrystallized from petroleum ether to give 7.0 g (73%) of 3, identical with the above by melting point and mixture melting point. The long heating period was subsequently found to be unnecessary.

3,5-Diphenyl-2,2-bis(trifluoromethyl)-3-cyclohexenone (21) from Hydrogenation of 3.—Using a Parr hydrogenator 4.8 g of the conjugated ketone 3, 50 ml tetrahydrofuran, and 0.1 g PtO_2 were shaken for 3 hr at room temperature and 40-psi hydrogen pressure. After removal of tetrahydrofuran by distillation, the residue was recrystallized from petroleum ether to give 2.7 g of colorless crystals and 2 g of oil. After one more recrystallization there was obtained 2.0 g of 21: mp 101–105°; ir 5.74 μ C=O); nmr ^1H (220 MHz) at τ 2.85 (singlet and surrounding multiplet, 10, aromatic CH), 3.83 (doublet, 1, $J_{H/H}$ = 3.0 Hz, =CH), 6.13 [doublet to doublets to doublets, 1, $J_{H/H}$ = 9.0, 6.8 and 3.0 Hz, C(C_6H_5)H], an AB quartet further split to doublets at 7.05 (1, $J_{H/H}$ = 13.5 and 6.8 Hz, CHH), 7.19 (1, $J_{H/H}$ = 13.5 and 9.0 Hz, CHH); ^{19}F at 60.5 (quartet, 1, $F_{F/F}$ = 9.5 Hz, CF_3), 61.5 ppm (quartet, 1, $J_{F/F}$ = 9.5 Hz, CF_3); uv $\lambda_{max}^{isooctane}$ 258 mμ (ϵ 620), 264 (470), 288 (70).

Anal. Calcd for $C_{20}H_{14}F_6O$: C, 62.55; H, 3.68; F, 29.69; mol wt, 384.0948. Found: C, 62.53; H, 3.86; F, 29.81; mol wt, 384.0943 (mass spectrum).

In another hydrogenation carried out in alcohol using Raney nickel catalyst at 100° and 2175 psi, the same product (21) was isolated along with a viscous oil which contained hydroxyl by infrared. By mass spectrometry it was possible to determine that the starting material had absorbed 1, 2, and 3 mol of hydrogen. Use of ruthenium-on-carbon catalyst in ethanol–water at 40° and 500 psi gave a syrup which by mass spectrometry appeared to be largely the alcohol resulting from addition of 3 mol of hydrogen.

Neutral Hydrolysis of 2a. 5,5,5-Trifluoro-3-phenyl-4-(trifluoromethyl)-2-pentenoic Acid (5).—An immiscible mixture of the cyclobutenone (25 g, 0.089 mol) and water (13 ml) was warmed on a steam bath for 30 min. Acid 5 crystallized and was recrystallized from chloroform to give 15.5 g of first crop, mp 125–128°, and 5.5 g of second crop: mp 123–125° (total yield 79%); ir 3–4 (carboxylic OH), 5.87 (C=O), 6.15 (conj C=C), 13.45 and 14.43 μ (monosubst aromatic); nmr [$(CD_3)_2CO$] ^1H at τ 0.00 (broad, 1, COOH), 3.08 (singlet, 5, aromatic CH), 3.86 [septet, 1, $J_{H/F}$ = 9.3 Hz, CH($CF_3)_2$], 4.24 (singlet, 1, =CH); ^{19}F at 62.8 ppm [doublet, $J_{H/F}$ = 9.3 Hz, CH($CF_3)_2$]. Both nmr spectra indicated the presence of a small amount of a second isomer (probably a *cis–trans* mixture).

Anal. Calcd for $C_{12}H_8F_6O_2$: C, 48.36; H, 2.70; F, 38.36. Found: C, 48.66; H, 2.97; F, 38.18.

Basic Hydrolysis of 2a. 3-Phenylglutaconic Anhydride (7).—The cyclobutenone (5.0 g, 0.018 mol) was added dropwise to 10 ml of 10% sodium hydroxide solution and then more alkali was added to make the solution basic. Acidification with aqueous hydrochloric acid gave 1.0 g (30%) of the cyclic anhydride which was recrystallized from chloroform: mp 193–195°; ir 5.59, 5.46 (C=O), 6.12 μ (C=C); nmr ^1H at τ 2.70 (multiplet, 5, aromatic CH), 3.65 (triplet, 1, $J_{H/H}$ = 1.5 Hz, =CH), 6.31 (doublet, 2, $J_{H/H}$ = 1.5 Hz, CH_2).

Anal. Calcd for $C_{11}H_8O_3$: C, 70.27; H, 4.29. Found: C, 70.09; H, 4.47.

5,5,5-Trifluoro-3-phenyl-4-(trifluoromethyl)-2-pentenoyl Fluoride (6).—A mixture of 25 g (0.089 mol) of 2a, 25 ml of glyme, and 1 g of cesium fluoride was refluxed overnight and then poured into cold water, and the heavy layer was washed with cold water and distilled to give 5 g (19% of crude acid fluoride 6, bp 66° (1.5 mm).

It was purified by preparative glpc to give 3.3 g redistilled at 50° (0.5 mm) to give 2.6 g: $n^{25}D$ 1.4370; ir 5.46 (COF), 610 μ (C=C); nmr indicated a mixture of *cis* and *trans* isomers; nmr for one isomer ^1H at τ 3.14 (singlet, 5, C_6H_5), 4.40 (doublet, 1, $J_{H/F}$ = 4.0 Hz, CHCOF), 4.42 [septet, 1, $J_{H/F}$ = 8.0 Hz, $CH(CF_3)_2$]; ^{19}F at −46.0 (doublet, 1, $J_{H/F}$ = 4.0 Hz, CHCOF), 62.9 ppm [doublet, 6, J = 8.0 Hz, $CH(CF_3)_2$]; nmr for the other isomer ^1H at τ 3.17 (singlet, 5, C_6H_5), 3.99 (broad, 1, CHCOF), 6.40 [septet, 1, $J_{H/F}$ = 7.5 Hz, $CH(CF_3)_2$]; ^{19}F at −43.5 (doublet, 1, $J_{H/F}$ = 1.0 Hz, CHCOF), 56.1 ppm [doublet, 6, $J_{H/F}$ = 7.5 Hz, $CH(CF_3)_2$].

Anal. Calcd for $C_{12}H_7F_7O$: C, 48.00; H, 2.33; F, 44.33. Found: C, 48.39; H, 2.47; F, 44.04.

Pyrolysis of 2a. 4,4-Difluoro-2-phenyl-3-(trifluoromethyl)-2-cyclobutene-1-carbonyl Fluoride (12).—The cyclobutenone (100 g, 0.36 mol) was metered dropwise under vacuum (1–5 mm) over 1/4-in. sections of 8-mm quartz tubing packed in a 1-in.-diameter quartz tube heated by a 12 in. wrap-around electric heater to a maximum of 400° inside temperature. The product was condensed in a trap cooled by liquid nitrogen and then distilled. There was obtained 43 g of starting cyclobutenone, 37 g boiling at 48–52° (0.6 mm) described further below, and 10.5 g (10.5% conversion) of **12**, bp 63–64° (0.6 mm), which crystallized and after recrystallization from petroleum ether melted at 38.5°: ir 5.41 (COF), 5.97 μ (C=C); nmr (CCl_4) ^1H at τ 2.55 (singlet, 5, aromatic CH), 5.60 (broad, 1, CH); ^{19}F at −45.5 (doublet, 1, $J_{F/F}$ = 5.6 Hz, COF), 61.7 ppm (multiplet, 3, CF_3), 5553, 5754, 5977, and 6177 Hz (AB, 2, $J_{F/F}$ = 5.6 Hz, doublets for last two, CF_2).

Anal. Calcd for $C_{12}H_6F_6O$: C, 51.47; H, 2.16; F, 40.71. Found: C, 51.55; H, 2.18; F, 41.08.

4,4-Difluoro-2-phenyl-3-(trifluoromethyl)-2-cyclobutene-1-carboxylic Acid.—The above acid fluoride **12** (1 g) was warmed on the steam bath in 10 ml of water. It melted and was immiscible, but was soon converted to the white, crystalline acid (1 g, mp 124–125°): ir 3–4 (broad), 5.87 (CO_2H), 6.02 μ (C=C); nmr [$(CD_3)_2$] ^1H at τ −0.60 (singlet, 1, COOH), 2.83 (multiplet, 5, aromatic CH), and 5.65 (multiplet, 1, CH); ^{19}F at 62.4 ppm (multiplet, 3, CF_3), 5695, 5893, 6163, and 6361 Hz (AB with fine structure, 2, ring CF_2).

Anal. Calcd for $C_{12}H_7F_5O_2$: C, 51.84; H, 2.54; F, 34.17. Found: C, 51.64; H, 2.49; F, 34.28.

Methyl 4,4-Difluoro-2-phenyl-3-(trifluoromethyl)-2-cyclobutene-1-carboxylate.—The acid fluoride **12** (2 g) was mixed with methanol giving an exothermic reaction. Evaporation of excess methanol gave 2 g (96%) of crystalline ester which could be recrystallized from petroleum ether: mp 48–50°; ir 5.73 (C=O), 6.00 μ (C=C); nmr (CCl_4) ^1H at τ 2.44 (singlet, 5, aromatic CH), 5.64 (multiplet, 1, ring CH), 6.27 (singlet, 3, CH_3); ^{19}F at 61.4 ppm (fine structure, 3, CF_3), 5604, 5804, 6089, and 6290 Hz (AB with fine structure, 2, ring CF_2).

Anal. Calcd for $C_{13}H_9F_5O_2$: C, 53.47; H, 3.11; F, 32.53. Found: C, 53.23; H, 3.15; F, 33.06.

4,4-Difluoro-2-phenyl-3-(trifluoromethyl)-1-cyclobutene-1-carboxylic Acid (15), 2,2,6-Trifluoro-4-phenyl-5-(trifluoromethyl)-2H-pyran (10), and 2,2,6-Trifluoro-4-phenyl-3-(trifluoromethyl)-2H-pyran (11).—The lowest boiling fractions from the above pyrolysis [37 g, bp 48–52° (0.6 mm)] were combined with another 20 g of similar fractions obtained by repyrolyzing the above recovered starting material (43 g) at 400°. This composite was washed twice with 10% sodium hydroxide rapidly. Reaction with acid fluoride **12** was immediate, leaving a base-insoluble (reacting only slowly) oil boiling mostly at 50–54° (0.6 mm) (41.5 g, 41.5% of original). It could be further separated into about equal amounts of the cyclic ethers **10** and **11** by vpc. Compound **10**, $n^{25}D$ 1.4545, was obtained quite pure, but **11**, $n^{25}D$ 1.4640, was contaminated appreciably with **10**. Acidification of the sodium hydroxide solution gave 4.8 g of **15**, mp 181–182°. This acid could be prepared quantitatively by dissolving **12** in 10% sodium hydroxide followed by acidification. It could be recrystallized from chloroform.

For **15**: ir 3–4 (acidic OH), 5.87 (C=O), 6.17 μ (conjd C=C); nmr [$(CD_3)_2CO$] ^1H at τ −0.4 (singlet, 1, CO_2H), 2.25 (multiplet, 2, aromatic CH), 2.80 (multiplet, 3, aromatic C–H), 5.50 (multiplet, 1, CH); ^{19}F at 66.3 (doublet, 3, $J_{F/F}$ = 12.4 Hz, into doublets, $J_{H/F}$ = 7.9 Hz, into doublets, $J_{F/F}$ = 3.4 Hz, CF_3), 5752 and 5963 Hz (doublets, A branch of AB, $J_{H/F}$ = 4.0 Hz, into overlapping quartets, $J_{H/F}$ = 3.4 Hz, CF), 6341 and 6552 Hz (quartets, B branch of AB, $J_{F/F}$ = 12.4 Hz, CF).

Anal. Calcd for $C_{12}H_7F_5O_2$: C, 51.84; H, 2.54; F, 34.17. Found: C, 51.79; H, 2.59; F, 34.13.

For **10**: ir 5.91 μ (C=C); nmr ^1H at τ 3.1 (singlet, 5, aromatic CH), 4.93 (multiplet, 1, =CH); ^{19}F at 54.3 (doublet with fine structure, 3, $J_{F/F}$ = 26.0 Hz, CF_3), 78.6 (quartet with fine structure, 1, $J_{F/F}$ = 26.0 Hz, =CF), 42.3 ppm (multiplet, 2, CF_2).

Anal. Calcd for $C_{12}H_6F_6O$: C, 51.47; H, 2.16; F, 40.71. Found: C, 51.31; H, 2.41; F, 41.11.

For **11**: ir 5.88 μ (C=C); nmr ^1H at τ 3.10 (singlet, 5, aromatic CH), 5.21 (multiplet, 1, =CH); ^{19}F at 54.2 (triplet, 3, $J_{F/F}$ = 10.0 Hz, into doublets, $J_{F/F}$ = 1.6 Hz, CF_3), 41.5 (quartet, 2, $J_{F/F}$ = 10.0 Hz, into doublets, $J_{H/F}$ = 1.8 Hz, CF_2), 85.1 ppm (doublet, 1, $J_{H/F}$ = 1.6 Hz into quartets, $J_{F/F}$ = 1.6 Hz, CF).

Anal. Calcd for $C_{12}H_6F_6O$: C, 51.47; H, 2.16; F, 40.71. Found: C, 51.82; H, 2.29; F, 40.30.

Equilibrium between Pyrolysis Products.—A mixture of **10** and **11** which had been washed with alkali to remove **12** and distilled [14 g, bp 50° (0.6 mm), $n^{25}D$ 1.4565] was pyrolyzed as described above at 400°. Distillation of the product gave 10 g which was largely the same as the starting material by boiling point and refractive index. In addition there was 2 g of higher boiling material. A fraction (1.1 g), bp ~65° (0.5 mm), $n^{25}D$ 1.4602, crystallized on standing and was largely **12**.

Similarly a 10-g sample of pure crystalline **12** was pyrolyzed at 400°. The 9 g recovered on distillation of the product was largely unchanged, but infrared and partial insolublity in alkali indicated the presence of **10** and **11** in the first fraction. Recovered **12** (7 g) was repyrolyzed at 500°. Again the 6 g recovered on distillation was largely **12** but the first fraction, 0.7 g, bp 50–54° (0.7 mm), $n^{25}D$ 1.4581, was largely a mixture of **10** and **11**, insoluble in alkali.

Pyrolysis of 2a at 500°.—When the pyrolysis of the above cyclobutenone was carried out at 500° instead of 400°, there was less recovered starting material and a higher ratio of cyclobutenyl acid fluoride **12** (47% conversion) to lower boiling cyclic ether **10** and **11** (35% conversion).

Pyrolysis at 650°. 1,1-Difluoro-4-phenyl-2-(trifluoromethyl)-1-buten-3-yne (14) and 4,4-Difluoro-3-(difluoromethylene)-2-phenyl-1-cyclobutene-1-carbonyl Fluoride (13).—Material obtained by pyrolyzing **2a** at lower temperatures (66 g) was repyrolyzed at 650° using the apparatus described above. Distilled product amounted to only 31 g. There was obtained 13 g of the vinylacetylene **14**, bp 34° (0.75 mm), $n^{25}D$ 1.4749. It redistilled essentially unchanged after washing with concentrated H_2SO_4, dilute sodium hydroxide, and dilute hydrochloric acid and was 97% pure by vpc on a silicone column: ir 3.27 (=CH), 4.50 (C≡C), 5.83 μ (C=C); nmr ^1H at τ 3.2 ppm (multiplet, aromatic CH); ^{19}F at 62.1 (doublet, 3, $J_{F/F}$ = 21.6 Hz, to doublets, $J_{F/F}$ = 10.6 Hz, CF_3), 69.4 ppm (complex multiplet, 2, CF_2).

Anal. Calcd for $C_{11}H_5F_5$: C, 56.94; H, 2.17; F, 40.95. Found: C, 57.18; H, 2.77; F, 41.40.

A higher boiling product [5 g, bp 74° (0.75 mm)] solidified and was recrystallized from hexane, mp 84–85°. It appeared to be the acid fluoride **13**: ir 3.24 (=CH), 5.66 (conjd COF), 5.72 (exocyclic C=CF_2), 6.10 μ (conjd ring C=C); nmr ^1H at τ 2.2 (multiplet, aromatic CH); ^{19}F at −35.1 (triplet, 1, $J_{H/F}$ = 2.8 Hz, COF), 78.7 (multiplet, 2, =CF_2), 109.4 ppm (multiplet, 2, CF_2).

Anal. Calcd for $C_{12}H_5F_5O$: C, 55.43; H, 1.94; F, 36.54. Found: C, 55.58; H, 1.95; F, 36.15.

4,4-Bis(trifluoromethyl)-2,3-diphenyl-2-cyclobuten-1-one (2b).—A mixture of 9.0 g (0.051 mol) of diphenylacetylene and 18 g (0.10 mol) of 1 in a Carius tube remained immiscible after heating 2 hr at 100°. After 8 hr at 200° there was recovered 9 g of low-boiler and 17.0 g (95%) of the above light yellow cyclobutenone, which after two recrystallizations from petroleum ether melted at 52–53° (10.2 g): ir 5.57 (shoulder), 5.65 (C=O), 6.18, 6.27, 6.38, 6.67, and 6.75 μ (C=C and aromatic rings); nmr ^1H at τ 2.2–2.8 (multiplet, aromatic C–H); ^{19}F at 64.5 ppm (singlet, CF_3).

Anal. Calcd for $C_{18}H_{10}F_6O$: C, 60.72; H, 2.83; F, 32.02. Found: C, 60.77; H, 2.72; F, 32.15.

5-Fluoro-6-(trifluoromethyl)-11H-benzo[a]fluoren-11-one (18).—**2b** (20.0 g, 0.056 mol) was recovered unchanged when passed over quartz under vacuum (1 mm) at 400°. However, at 515°, 10.6 g (60%) of crude **18** was recovered in two crops by recrystallization from nitromethane. A second recrystallization of the first crop (6.5 g) from nitromethane gave 5.2 g: mp 195–

196° (further recrystallization from chloroform did not raise the melting point); ir 5.8 μ (C=O); nmr (THF) ^1H at τ 2.4 (broad multiplet, aromatic CH); ^{19}F at 55.4 (doublet, 3, $J_{F/F}$ = 37.0 Hz, CF_3), 111.2 ppm (quartet, 1, $J_{F/F}$ = 37.0 Hz, CF).

Anal. Calcd for $C_{18}H_8F_4O$: C, 68.41; H, 2.55; F, 24.05. Found: C, 68.56; H, 2.77; F, 24.36.

An attempt to repeat the reaction over new quartz chips gave a much lower yield, but the yield was improved by pyrolysis over sodium fluoride pellets.

4,4-Bis(trifluoromethyl)-3-(*p*-tolyl)-2-cyclobutenone (2b).—*p*-Tolylacetylene (3.0 g, 0.026 mol) and **1** (8.7 g, 0.049 mol) were heated 16 hr in a steam bath to give, after three crystallizations from petroleum ether, 3.0 g (39.5%) of the cyclobutenone: mp 44.5–45.5°; ir 5.58 (C=O), 6.20, 6.30, 6.42, and 6.64 μ (aromatic and conjugated C=C); nmr ($CDCl_3$) ^1H at τ 2.27, 2.41, 2.61, and 2.75 (AB quartet, 4, *para*-aromatic C_6H_4), 3.19 (singlet, 1, =CH), 7.60 (singlet, 3, CH_3); ^{19}F at 64.6 ppm [singlet, $(CF_3)_2$].

Anal. Calcd for $C_{13}H_8F_6O$: C, 53.11; H, 2.74; F, 38.78. Found: C, 52.66; H, 2.79; F, 39.11.

4,4-Bis(trifluoromethyl)-3-(*p*-chlorophenyl)-2-cyclobutenone (2e).—*p*-Chlorophenylacetylene (3.5 g, 0.026 mol) and **1** (8.7 g, 0.047 mol) were heated 16 hr in a steam bath to give, after two recrystallizations from petroleum ether, 5.0 g (62%) of **2e**: mp 55–60°; ir 5.57 (C=O), 6.25, 6.31, 6.43 and 6.71 μ (aromatic and conjugated C=C); nmr ($CDCl_3$) ^1H at τ 2.38 (multiplet, 4, aromatic C_6H_4), 3.08 (singlet, 1, =CH); ^{19}F at 64.5 ppm [singlet, $(CF_3)_2$].

Anal. Calcd for $C_{12}H_5F_6ClO$: C, 45.82; H, 1.60; F, 36.25; Cl, 11.28. Found: C, 46.63; H, 1.52; F, 35.10, Cl, 11.49.

3-Phenyl-5-(*p*-chlorophenyl)-6,6-bis(trifluoromethyl)-2,4-cyclohexadienone (22).—Cyclobutenone **2e** (2.0 g, 0.0064 mol) and excess phenylacetylene were heated in a steam bath for 60 hr. Distillation up to 160° (45 μ) gave 1.3 g of oil which crystallized in petroleum ether and on recrystallization gave 1.0 g (38%) of **22**: mp 105–107°; ir 5.97 (conjd C=O), 6.09, 6.26, 6.36, 6.71, and 6.91 μ (aromatic and conjd C=C); nmr ($CDCl_3$) ^1H at τ 2.53 (multiplet, 5, C_6H_5), 2.75 (multiplet, 4, C_6H_4), 3.12 (doublet, 1, $J_{H/H}$ = 1.4 Hz, =CH), 3.60 (doublet, 1, $J_{H/H}$ = 1.4 Hz, =CH); ^{19}F at 61.5 ppm [singlet, $(CF_3)_2$].

Anal. Calcd for $C_{20}H_{11}F_6ClO$: C, 57.67; H, 2.66; F, 27.37; Cl, 8.51. Found: C, 57.04; H, 2.72; F, 27.14; Cl, 8.85.

3-(*p*-Chlorophenyl)-5-phenyl-6,6-bis(trifluoromethyl)-2,4-cyclohexadienone (23).—A 7.0-g (0.025 mol) sample of **2a** and 3.5 g (0.025 mol) of *p*-chlorophenylacetylene were heated in a steam bath for 50 hr. Rapid distillation gave an oil, bp ~120° (0.4 mm), which solidified. Recrystallization from petroleum ether gave 2.0 g (20%) of crystals, Further crystallization gave 0.6 g of **23**, mp 90–94°; ir 5.96 (conjd C=O), 6.09, 6.25, 6.31, 6.40, and 6.66 μ (aromatic and conjd C=C); nmr ($CDCl_3$) ^1H at τ 2.45 (multiplet, 4, C_6H_4), 2.57 (singlet, 5, C_6H_5), 3.03 (doublet, 1, $J_{H/H}$ = 1.4 Hz, =CH), 3.48 (doublet, 1, $J_{H/H}$ = 1.4 Hz, =CH); ^{19}F at 61.4 ppm [singlet, $(CF_3)_2$].

Anal. Calcd for $C_{20}H_{11}F_6ClO$: C, 57.67; H, 2.66; F, 27.37; Cl, 8.51. Found: C, 57.83; H, 2.73; F, 27.43; Cl, 8.33.

Registry No.—**2a**, 4141-87-1; **2b**, 25631-73-6; **2c**, 25631-74-7; **2d**, 25631-75-8; **2e**, 25631-76-9; **2f**, 25631-77-0; **3**, 25631-78-1; **5**, 14203-12-4; **6**, *cis*, 25631-80-5; **6**, *trans*, 25798-19-0; **7**, 25631-82-7; **10**, 25631-83-8; **11**, 25631-84-9; **12**, 25631-85-0; **13**, 25631-86-1; **14**, 25631-87-2; **15**, 25631-88-3; **16**, 25631-89-4; **17**, 25631-90-7; **18**, 25631-91-8; **21**, 25631-92-9; **22**, 25631-93-0; **23**, 25631-94-1; 4,4-difluoro-2-phenyl-3-(trifluoromethyl)-2-cyclobutene-1-carboxylic acid, 25679-32-7; 4,4-difluoro-2-phenyl-3-(trifluoromethyl)-2-cyclobutene-1-carboxylic acid Me ester, 25631-95-2.

Fluoroketenes. V. Cycloadditions to the Bis(trifluoromethyl)ketene Carbonyl Group[1]

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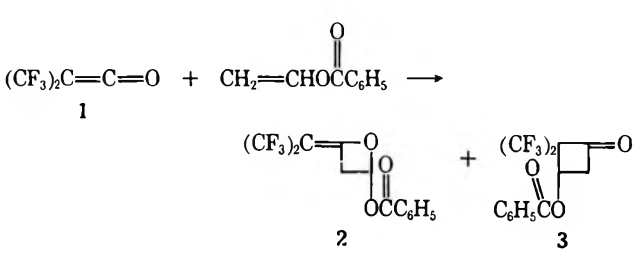
Cycloadditions of very nucleophilic olefins to bis(trifluoromethyl)ketene tend to occur at the carbonyl group to form oxetanes. The mechanism for this reversible cycloaddition involves a dipolar intermediate, as shown by isomerizations with *cis*- and *trans*-propenyl propyl ethers. Supporting evidence is the increase in rate and in products of proton transfer with increase in solvent polarity, an increasing reactivity with increasing nucleophilicity of olefinic coreactant, the orientation of substituents in product, and a cationic polymerization of vinyl ethers and styrenes as a side reaction. A second mode of cycloaddition to the ketene carbon–carbon double bond also occurs to give thermodynamically more stable cyclobutanones. The latter cycloaddition is also reversible in the vinyl ether case, and evidence that it proceeds through a second type of dipolar intermediate is presented.

Vinyl Esters.—Ketenes normally form cyclobutanones with very reactive olefins as well as with simple alkenes.[2] Aside from the special case of ketene dimerizations to give β-lactones, the only example of a 1,2 cycloaddition to a ketene carbonyl group to form an oxetane seems to be with bis(trifluoromethyl)ketene (**1**).[3] Reaction of **1** with vinyl benzoate neat at 100° was reported to form 2-benzoyloxy-4-hexafluoroisopropylidenoxetane (**2**) and 2,2-bis(trifluoromethyl)-3-benzoyloxycyclobutanone (**3**) in 34 and 42% yields, respectively.



More extensive work with this system has shown that the ratios of products vary erratically and that the presence of solvent encourages by-product formation. Table I summarizes the results obtained by ^{19}F nmr for

(1) For parts III and IV on reactions at the double bond of bis(trifluoromethyl)ketene, see D. C. England and C. G. Krespan, *J. Org. Chem.*, **35**, 3300, 3308 (1970).

(2) For a review of the chemistry of ketenes, see R. N. Lacey in "The Chemistry of Alkenes," S. Patai, Ed., Interscience, New York, N. Y., 1964, p 1161.

(3) D. C. England and C. G. Krespan, *J. Amer. Chem. Soc.*, **87**, 4019 (1965).

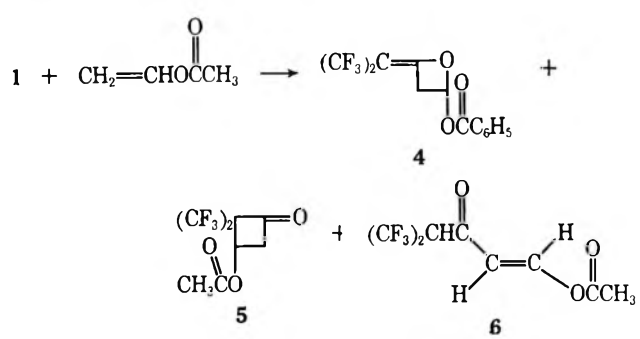
TABLE I
REACTION OF $(CF_3)_2C{=}C{=}O$ WITH VINYL BENZOATE[a]

Solvent	Time, hr	1	2	3	2/3
CH_3NO_2	0.5	25	32	10	3.2
$CH_3CO_2C_2H_5$	3.0	26	32	14	2.3
CH_2Cl_2	6.0	24	24	20	1.2
C_6H_{14}	56.0	23	12	25	0.5

[a] Solutions 0.5 *M* in 1 and 1.0 *M* in vinyl benzoate were heated at 100° in sealed glass tubes.

a series of runs at 100° in solvents of differing polarity. From the series in each solvent, one run was picked in which about 25% of the ketene remained unreacted. The combined yield of **2** and **3** was about 40% in each case, the remaining 35% being by-products. Although the reaction is not a good one for quantitative study because of difficult reproducibility and the presence of numerous by-products, the results in Table I are felt to be significant and can be used to illustrate two important points. First, the overall cycloaddition reaction proceeds much faster in polar solvents than in nonpolar solvents. A possible anomaly is the order observed for ethyl acetate and methylene chloride, the reverse of that to be expected by most measures of solvent polarity.[4a] A second trend is the increase in ratio of oxetane **2** to cyclobutanone **3** with increasing polarity of solvent, although again ethyl acetate and methylene chloride are in unexpected order.

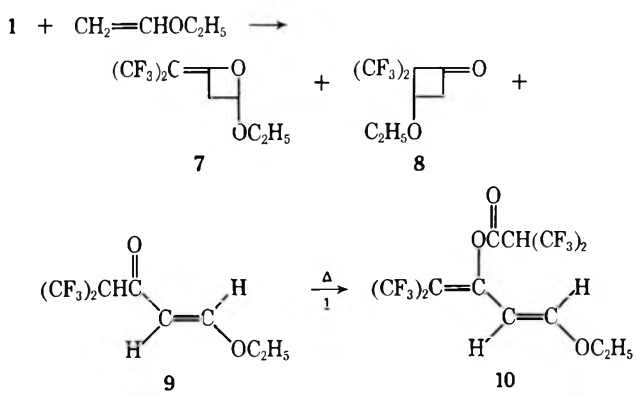
Vinyl acetate reacted readily with **1**, going to completion in 4 hr at 100° without solvent to form mainly linear product **6**, along with oxetane **4** and cyclobutanone **5**. In hexane at 100°, a much longer time was required, and oxetane **4** was the major product while only a trace of **6** was isolated. The study was complicated by formation of unidentified by-products in various solvents, in addition to a pronounced tendency to form linear adduct **6** in polar media.



The structures of these adducts were assigned on the basis of elemental and spectral analyses. Ir bands for cyclobutanone carbonyl characteristically appear around 5.5 μ, while those of the exocyclic double bond in the oxetanes are near 5.8 μ, both at shorter wavelength than normal because of the small ring. Compound **6** exhibits the expected band at relatively short wavelength (5.58 μ) for vinyl ester carbonyl.[4b] Nmr bands for ^{19}F in the cyclobutanones are widely separated (*ca.* 3 ppm) quartets for nonequivalent trifluoromethyl groups on the unsymmetrically substituted ring. In the oxetanes they are less well-separated quartets and appear at lower field because of attachment to vinylic carbon. Compound **6** shows the expected ^1H septet for a hexafluoroisopropyl group ($J_{H/F}$ = 8 Hz) and two vinylic protons apparently in a *trans* arrangement ($J_{H/H}$ = 13 Hz). Similar evidence coupled in some cases with chemical conversions is used to support the structural assignments below.

Qualitatively, the over-all reaction rate of **1** with both vinyl esters is slower and formation of cyclobutanone is favored by nonpolar solvents, whereas formation of oxetanes and linear products is favored in a much faster reaction in polar solvents. The precise extent of these effects is obscured by secondary reactions of the cycloadducts and accumulation of by-products. However, reactions of ketene **1** with vinyl ethers proceed much more rapidly than those with vinyl esters and can be studied at temperatures where the primary products are stable.

Vinyl Ethers.—Nmr showed a high yield of oxetane **7** as the primary product from **1** and ethyl vinyl ether in hexane at about 0°. When warmed in hexane to 50°, **7** reacted readily to form cyclobutanone **8** along with lesser amounts if linear ketone **9**. Actual isolated yields of a similar reaction in hexane heated for 15 min at 100° were 67% **8** and 13% **9**. With nitromethane as solvent, the isolated yields were 43 and 40% **8** and **9**, respectively, indicating that a polar solvent facilitates the proton transfer particularly well. The use of **1** containing POF_3 as impurity in a reaction without solvent resulted in a high (92%) yield of **9**. Cyclobutanone **8** is converted to the linear ketone **9** when heated at 100°, more rapidly in nitromethane or neat than in hexane. Compound **9** has been reported previously alone with speculation as to its source.[5]



Excess ketene **1** and ethyl vinyl ether can give a 2:1 adduct, vinyl ester **10**, when the reaction is conducted at elevated temperatures. The reaction path probably involves **9** as an intermediate, since **9** will combine with **1** at 100° to give 93% **10**.

In one case the oxetane from **1** and a vinyl ether has been sufficiently stable to be isolated. Methyl trifluorovinyl ether and **1** reacted at 100° to give oxetane **11** (55%) and cyclobutanone **12** (20%) as distillable products. Heating is required since methyl trifluorovinyl ether is less nucleophilic than unfluorinated vinyl ethers. Although no ring-opened products were obtained from the thermal reaction, fluoride ion catalysis readily converted the cyclobutanone **12** to the acid fluoride **13**. This ring opening, which provides support for structure **12**, is analogous to that observed with

(4) (a) *Cf.* R. Huisgen, L. A. Feiler, and P. Otto, *Tetrahedron Lett.*, 4485 (1968); (b) D. C. England and C. G. Krespan, *J. Org. Chem.*, **33**, 816 (1968).

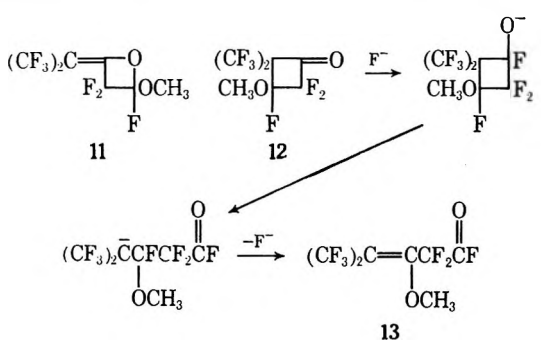
(5) Y. A. Cheburkov, N. Mukhamadaliev, and I. L. Knunyants, *Tetrahedron*, **24**, 1341 (1968).

TABLE II
REACTIONS OF *cis*-PROPENYL PROPYL ETHER WITH BIS(TRIFLUOROMETHYL)KETENE[a]

			Products, per cent of total[b]						
			Oxetane			Cyclobutanone		Linear	Other
Solvent	Temp, °C	Time	*cis* 16	*trans* 19	Mix	*cis* 17	*trans* 20	products[c]	products[d]
n-Hexane	−50	10 min	79	0		20	0	1	
	0	2 hr	79	0		19	0	2	
	25	30 min	78	0		20	0	2	
	25	1 hr	77	0		20	0	3	
	25	8 hr	75	0		22	0	3	
	25	20 hr	64	0		30	0	6	
	100	1 hr	5	0		88	0	7	
CH_2Cl_2	−50	2–3 weeks	90	0		5	0	5	
	0	1 hr	90	0		5	0	5	
	25	30 min			78	13	0	9	
	25	1 hr			71	18	0	11	
	25	8 hr			33	45	7	15	
	25	20 hr			17	56	9	18	
$CH_3CO_2C_2H_5$	−50	2–3 weeks	92	0		0	0	8	
	0	1 hr			67	5	0	16	12
	0	2 hr			64	5	0	18	13
	25	30 min			51	9	0	20	20
	25	1 hr			43	9	2	27	19
	25	8 hr			13	13	5	59	10
	25	20 hr			10	14	6	64	6
$C_2H_5NO_2$	−50	10 min	100	0		0	0	0	0
	0	1 hr			83	13	0	4	0
	0	2 hr			80	15	0	5	0
	25	30 min			42	32	10	16	0
	25	1 hr			25	40	15	20	0
	25	4 hr			0	60	25	15	0
	25	20 hr			0	62	26	12	0

[a] Solutions were 1.0 *M* in *cis*-propenyl propyl ether, 0.50 *M* in bis(trifluoromethyl)ketene, and 0.50 *M* in reference compound, *o*-bis(trifluoromethyl)benzene. The reference compound was occasionally omitted since its presence as solid prevented complete mixing at temperatures below −50°. Reactions duplicate in each solvent were carried through the entire temperature range. [b] Ketene 1 completely reacted in all cases. [c] Largely or entirely linear ketone 18, varying amounts of unidentified products containing CF_3 groups attached to saturated carbon being present. [d] Unidentified products characterized by low-field CF_3 groups.

related cyclobutanones[5,6] and proceeds by addition of fluoride ion to the carbonyl carbon, ring opening to a stable carbanion, and elimination of fluoride ion. Under the same conditions, **11** did not react.



A proof of position of methoxy group in both **11** and **12** was obtained by hydrolysis with concentrated sulfuric acid. In both cases the product obtained after ring cleavage and decarboxylation was the expected difluoromethyl hexafluoroisopropyl ketone.

To provide further insight into the course of cycloadditions to ketene **1**, a detailed study was made of reactions between *cis*- and *trans*-propenyl propyl ethers and **1**. *cis*-Propenyl propyl ether (**14**) and *trans*-propenyl propyl ether (**15**) were prepared by a modified literature[7] procedure. The mixture of ethers from this preparation was about 70% **14** and 30% **15**; fractionation gave samples of **14** containing 3.5% **15** and of **15** containing 5.8% **14** by glpc. The ethers showed no tendency to interconvert during 8 days at 100° in sealed, alkali-washed glass tubes. Even in the presence of hexafluoroisobutyric acid, the acidic impurity generated in reactions of **1**, equilibration was slow at 100°. The 96.5:3.5 mixture of **14** and **15** was converted to a 70.5:29.5 mixture after 8 days. The 94.2:5.8 mixture of **15** and **14** was slowly converted to a 44.5:55.5 mixture in 21 days. After 1 month, some polymerization had occurred; so the equilibrium point was not determined. However, the equilibrium mixture must contain between 55 and 70% *cis* ether **14**. The rate of interconversion is sufficiently slow that acid catalysis did not influence the stereochemical results of reactions carried out in the temperature range −50 to 100°. Since light also effects interconversion between **14** and **15**, reactions with **1** were carried out in the dark.

Reactions of **1** with ethers **14** and **15** followed the same general pattern as that with ethyl vinyl ether. Examination of the cycloaddition of **14** to **1** by ^{19}F nmr showed that **1** was consumed very rapidly, even at −50°, and that the major product area (79%) appearing at low temperature could be ascribed to *cis*-oxetane **16**, while *cis*-cyclobutanone **17** was a minor product (20%). No change was observed after 2 hr at 0°, showing the absence of secondary reactions in hexane at low temperatures. At 25° a slow increase in proportion of **17** and linear ketone **18** at the expense of **16** was observed. This secondary reaction also proceeded

(6) D. C. England and C. G. Krespan, *J. Amer. Chem. Soc.*, **88**, 5582 (1966).

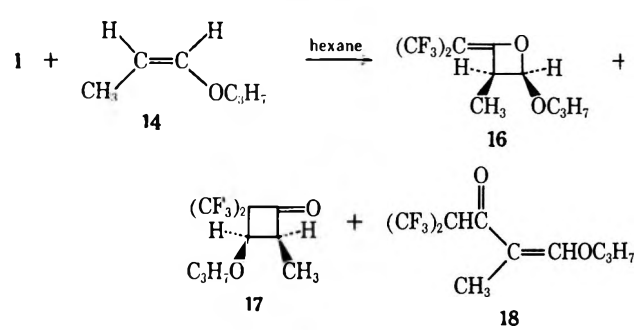
(7) W. Rottig and O. Liethen, German Patent 1,019,090 (1957); *Chem. Abstr.*, **54**, 10403 (1960).

TABLE III
REACTIONS OF *trans*-PROPENYL PROPYL ETHER WITH BIS(TRIFLUOROMETHYL)KETENE[a]

Solvent	Temp, °C	Time	Unreacted ketene 1	Products, per cent of total: Oxetane *cis* 16	Oxetane *trans* 19	Oxetane Mix	Cyclobutanone *cis* 17	Cyclobutanone *trans* 20	Linear product	Other products
Hexane	−50	10 min	100							
	0	15 min	21	0	26		0	51	2	
	0	1 hr	4	0	32		0	62	2	
	0	2 hr	0	0	34		0	63	3	
	25	30 min	0	0	31		0	67	2	
	25	24 hr	0	0	33		0	66	1	
	100	1 hr	0	0	15		4	78	3	
CH_2Cl_2	−50	2–3 weeks	0			37	15	33	15	
	0	15 min	0			36	12	34	18	
	0	2 hr	0			36	17	30	17	
	25	30 min	0			36	15	39	10	
	25	1 hr	0			34	12	41	13	
	25	8 hr	0			22	23	44	11	
	25	20 hr	0			11	31	46	12	
$CH_3CO_2C_2H_5$	−50	2–3 weeks	0			37	7	26	30	
	0	15 min	0			37	7	26	30	
	0	2 hr	0			30	9	28	33	
	25	30 min	0			37	6	30	27	
	25	1 hr	0			33	8	32	27	
	25	8 hr	0			12	18	34	27	9
	25	20 hr	0			9	22	39	27	3
$C_2H_5NO_2$	−50	10 min	60			16	5	8	11	
	0	15 min	0			44	19	26	11	
	0	1 hr	0			41	17	27	15	
	0	2 hr	0			38	19	28	15	
	25	30 min	0			31	24	34	11	
	25	1 hr	0			13	32	36	19	
	25	4 hr	0			0	40	43	17	
	25	24 hr	0			0	43	43	14	

[a] Solutions 1.0 *M* *trans*-propenyl propyl ether, 0.50 *M* in 1, and occasionally 0.50 *M* in reference [*o*-bis(trifluoromethyl)benzene].

stereospecifically, and even at 100°, formation of **17** as the major product (88%) was stereospecific. These results are summarized in Table II. In accord with the spectral results, a reaction between **1** and **14** in hexane at 100° gave 89% isolated yield of **17** containing an amount of *trans*-cyclobutanone **20** corresponding to the *trans* isomer in the starting ether **14**.



A check on the material balance in these reactions was obtained by incorporation of *o*-bis(trifluoromethyl)-benzene, which provided a known, constant ^{19}F nmr absorption for reference. By this method a reasonable correspondence was shown between total amount of products observed from ketene **1** at various stages of reaction and the expected amount. The values obtained, however, are not very accurate, since the lower limit of detection by the nmr method in these systems represents a yield greater than 5%. That this is so can be seen, for example, from the lack of observed peaks for *cis* products in reactions in hexane of *trans* ether **15** (Table III), when starting **15** contained 6% of the much more reactive *cis* ether **14** as impurity. Vpc analysis was frequently not satisfactory because of the mobile equilibria involved (see below).

Although the reaction of **1** and **14** is stereospecific in hexane even up to 100°, more polar solvents induce isomerization (Table II). Stereospecificity is preserved at 0° in methylene chloride, but lost rapidly from the oxetane **16** and slowly from cyclobutanone **17** at 25°. In both ethyl acetate and nitroethane, stereospecificity is lost from **16** but preserved with **17** at 0° and lost from **17** at 25° (more slowly in ethyl acetate). The trend is clearly one of increased isomerization with increased solvent polarity, although again ethyl acetate (ϵ 6.0) is anomalous in being more effective than methylene chloride (ϵ 9.1). Since the reactions are complicated and, in the case of ethyl acetate, lead to unusually large amounts of by-products, deviations from a simple ranking by polarity are not unexpected.[8]

Another striking feature of Table II is the increasing amount of oxetane **16** and decreasing amount of cyclobutanone **17** formed with increasing solvent polarity at −50°, *i.e.*, under conditions which give kinetically determined products. With increasing temperature and/or increasingly polar solvents the labile oxetane **16** is easily scrambled and, at 25° or over, also easily converted to cyclobutanones, the latter being the first isolable products. Cyclobutanone **17** is converted at still higher temperature and especially in the more polar

(8) S. Proskow, H. E. Simmons, and T. L. Cairns, *J. Amer. Chem. Soc.*, **88**, 5254 (1966), observed a similar order in olefin cycloadditions involving dipolar intermediates.

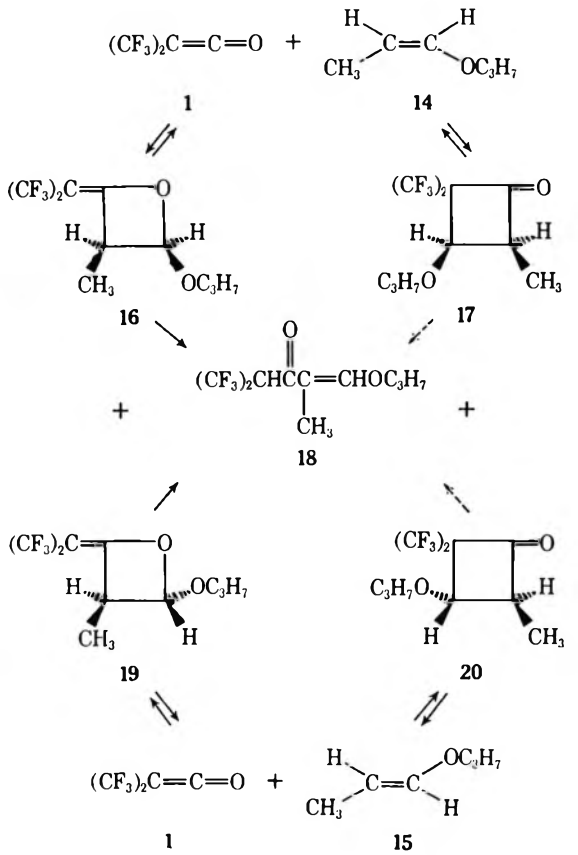


Figure 1.—Reaction scheme for *cis*- and *trans*-propenyl propyl ether.

solvents to isomeric cyclobutanone **20** and ring opened to linear ketone **18**. The slow isomerization **17** → **20** + **18** has been carried out separately; a neat sample of **17** was converted in 60 hr at 100° to a mixture containing 80% **17** and **20** (13:87) and 20% **18**. Under the same conditions, pure **20** was converted to essentially the same mixture.

Equilibration of **17** ⇄ **20** is quickly established with a trace of cesium fluoride in a small amount of glyme. Mixtures containing varying amounts of **17** and **20** equilibrated exothermically when shaken with the fluoride catalyst to give 10:90 mixtures of **17** and **20** with substantially no **18** present. Heating of the mixture at 100° for several hours in the presence of fluoride ion catalyst converted it entirely to linear ketone **18**. The activity of the catalyst is apparently due to its ability to abstract a proton α to the carbonyl group, causing loss of stereochemistry at that position. At elevated temperatues the resulting anion undergoes irreversible ring opening to give **18** after protonation.

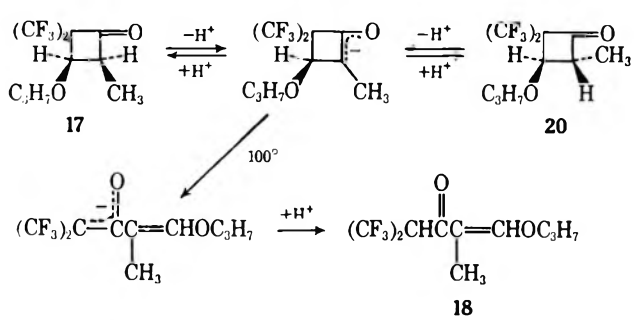


Table III summarizes the results with *trans* ether **15** and **1**. Trends similar to those observed with ether **14** can also be seen to obtain with **15**. Stereospecificity is preserved with **15** in hexane up to 25°, but slowly lost at 100°. With increasingly polar solvents, stereospecificity is more easily lost and mixed oxetanes and cyclobutanones are obtained in nitroethane even at −50°. With *trans* ether **15**, the scrambling of oxetanes under milder conditions than for cyclobutanones was not observed (as it was with **14**), perhaps because of the ease with which both were scrambled. The ratio of oxetanes to cyclobutanones in the primary reaction increased with solvent polarity, as did the rate of conversion of oxetanes to cyclobutanones and the formation of ring-opened products.

Additional points emerge from comparison of the results in Tables II and III. Ether **15** reacts much less rapidly than **14**, even though the *trans*-substituted cyclic products are thermodynamically the more stable, so that at low temperatures unreacted **1** can be detected.[9] Since with **15** the reaction can be slowed sufficiently for observation while **1** is still present, a much slower rate of reaction of **1** with **15** in hexane than in nitromethane can be observed at −50°. The solvent dependence of rate of ketene **1** reaction is the same as that of the secondary reactions, increasing with increasing solvent polarity. Product from **15** are more easily scrambled, to the extent that in nitroethane, at −50°, mixed cyclobutanones and oxetanes are obtained. With **14** in nitroethane, on the other hand, stereochemistry is retained at −50°, and lost from oxetane but not cyclobutanone at 0°.

The ratios of oxetane:cyclobutanone mixtures formed at low temperatures can be used to indicate the dependence of product types formed in the primary reaction on solvent. These ratios of oxetane to cyclobutanone increased steadily for both **14** at −50° and **15** at 0°, but was larger for **14** (Table IV).

TABLE IV
SOLVENT DEPENDENCE OF
OXETANE–CYCLOBUTANONE RATIOS

ϵ (°C)	Solvent	Oxetane–cyclobutanone from *cis* **14**	Oxetane–cyclobutanone from *trans* **15**
1.89 (20)	Hexane	4.0	0.53
9.08 (20)	CH_2Cl_2	18	0.77
6.02 (25)	$CH_3CO_2C_2H_5$	Very large	1.1
28.0 (30)	$C_2H_5NO_2$	Very large	1.0

The evidence indicates that the system **1**:**14**:**15** at 25° in a polar solvent can be a complicated pseudo-equilibrium in which first oxetanes and then cyclobutanones predominate, and from which components can go irreversibly to acyclic ketones and other unidentified products. The generalized scheme, parts of which can be isolated by the use of nonpolar solvents, is shown in Figure 1 with racemic partners omitted for simplication.

Styrenes.—Olefins with insufficient nucleophilicity to cycloadd to the carbonyl group of **1** give only cyclobutanones as cycloadducts.[1] One such olefin, styrene, showed no indication of oxetane formation with **1**, even when the reaction was examined by nmr in the same manner as described above for the propenyl propyl ethers. The product, 2,2-bis(trifluoromethyl)-3-

(9) The same difference in reactivity has been reported in ref 4, wherein cyclobutanone formation with diphenylketene was found to be *ca.* 200 times faster with **14** than with **15**.

TABLE V
REACTION OF 1 WITH STYRENE[a]

Solvent	Unreacted ketene 80°, 14 hr	Unreacted ketene 180°, 30 min	Cyclobutanone 80°, 14 hr	Cyclobutanone 180°, 30 min	Linear products 80°, 14 hr	Linear products 180°, 30 min
Hexane	100	80	0	20	0	0
CH_2Cl_2	31	13	51	67	18	20
$CH_3CO_2C_2H_5$	27	5	41	60	32	35
CH_3NO_2	0	0	36	36	64	64

[a] Solutions were 1.0 *M* in styrene, 0.50 *M* in **1**, and 0.50 *M* reference [*o*-bis(trifluoromethyl)benzene]. Sealed tubes were heated at 80° for 14 hr, examined by nmr, and then heated at 180 ° for 30 min and reexamined. Values given are per cent of total products + ketene **1**.

phenylcyclobutanone, is apparently the first and only cycloadduct formed in a reaction which requires elevated temperatures. Both reaction rate and amount of linear products increased markedly with increasing polarity of solvent. At 80° for 14 hr, no reaction was detected in hexane, whereas complete reaction had occurred in nitromethane. At 180° for 30 min, only cyclobutanone was found as product in hexane, in contrast to the 2:1 ratio of linear products to cyclobutanone formed at 80° in nitromethane and remaining unchanged at 180° (Table V).

Activation by a *p*-methoxy group is sufficient to allow reaction at 25° and below. Isolation of the product afforded a good yield of cyclobutanone **22**, but an unstable oxetane, **21**, was detected by nmr. The oxetane was the major product in the polar solvent, nitroethane, at low temperature and the minor product in hexane. The reaction was also much faster in nitroethane (Table VI).

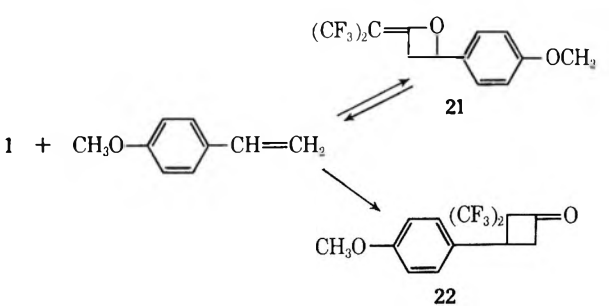
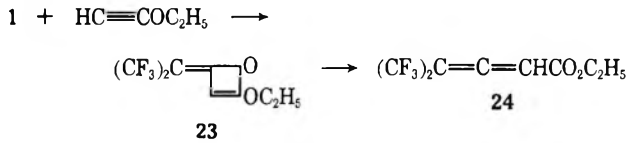


TABLE VI
REACTION OF 1 WITH *p*-METHOXYSTYRENE[a]

Solvent	Temp, °C	Time	Per cent of total 1	21	22	Linear products
Hexane	25	15 min	73	4	15	8
	25	18 hr	1	23	68	8
	100	30 min	1	2	89	8
$C_2H_5NO_2$	−50	15 min	27	56	2	17
	50	5 min	1	25	57	17
	25	18 hr	0	0	80	20

[a] Tubes loaded as described for the propenyl propyl ether runs, 1.0 *M* in *p*-methoxystyrene and 0.50 *M* in **1**.

Ethoxyacetylene.—Acetylenes cycloadd to **1** with direct formation of cyclobutenones,[1] while other ketenes give cyclobutenones only with activated acetylenes such as with ethoxyacetylene[10] and various diethylaminoacetylenes.[11] Reaction of **1** with ethoxyacetylene at −80° follows an entirely different course; just as with the more nucleophilic olefins and **1**, this very reactive acetylene appears to add to the carbon–oxygen bond of **1**. Evidence for the oxete **23** so formed was obtained by low temperature nmr. This unstable oxete did not isomerize to a cyclobutanone, but rather underwent an electrocyclic transformation to allenic ester **24**.[12]



Discussion

Two modes of cycloaddition to compound **1** are available, across the carbon–oxygen and the carbon–carbon double bonds. The previously described[1,5] Diels–Alder addition of butadiene to the carbonyl group of **1** accords with the Woodward–Hoffmann selection rules[13] for concerted cycloadditions in carbon systems. The pronounced solvent effect[1] may be interpreted as resulting from a polarized transition state in which the oxygen atom and trifluoromethyl groups stabilize a partial negative charge. Evidence against a stepwise 4 + 2 cycloaddition, aside from possible violation of the selection rules, is the absence of 2 + 2 cycloadducts and the relatively stringent conditions required for the reaction, both indicative of a highly ordered transition state leading to product.

Concordant with the view that cycloadditions to the ketene carbonyl follow Woodward–Hoffmann rules, the present work demonstrates that 2 + 2 cycloadditions to carbonyl of **1** proceed through dipolar intermediates of finite lifetime. The isomerization reactions observed with propenyl ethers, **14** and **15**, are direct evidence for such intermediates, **25a** and **25b**, formed as tight ion pairs in nonpolar solvents and as essentially a single solvent-separated dipolar species in polar solvents (Figure 2). However, intermediate **25** (from **1** and either **14** or **15**) is not necessarily in equilibrium with the possible cyclobutanone precursor, **26**, since mixtures of the isomeric oxetanes can be obtained with little or no indication of formation of mixtures of the isomeric cyclobutanones.[14] Another distinguishing characteristic is the increase in ratio of oxetane to cyclobutanone formed at low temperatures as solvent polarity increases, indicating an intermediate or transition state on the way to cyclobutanone of lower polarity than **25** (Table IV). These observations contrast with the assumption of Binsch, Feiler, and Huisgen that dipolar intermediates from dimethylketene and **14** or **15** would necessarily be identical and capable of closing to a cyclobutanone.[15]

We take our results as an indication that a significant barrier exists between **25** and **26**. Formation of **25a** or

(10) (a) J. Druey, E. F. Jenny, K. Schenker, and R. B. Woodward, *Helv. Chim. Acta*, **45**, 600 (1962); (b) R. H. Hasek and J. C. Martin, *J. Org. Chem.*, **27**, 3743 (1962).

(11) W. E. Truce, R. H. Bavry, and P. S. Bailey, Jr., *Tetrahedron Lett.* 5651 (1968).

(12) W. J. Middleton, *J. Org. Chem.*, **30**, 1307 (1965), reports a similar series of reactions with ethoxyacetylene and hexafluoroacetone.

(13) R. B. Woodward and R. Hoffmann, *J. Amer. Chem. Soc.*, **87**, 2046 (1965).

(14) As examples see the results in Table II for reactions of **14** in methylene chloride at 25° and in nitroethane at 0°. Cyclobutanone isomerization seems to require a somewhat higher temperature than that for oxetane.

(15) G. Binsch, L. A. Feiler, and R. Huisgen, *Tetrahedron Lett.*, 4497 (1968).

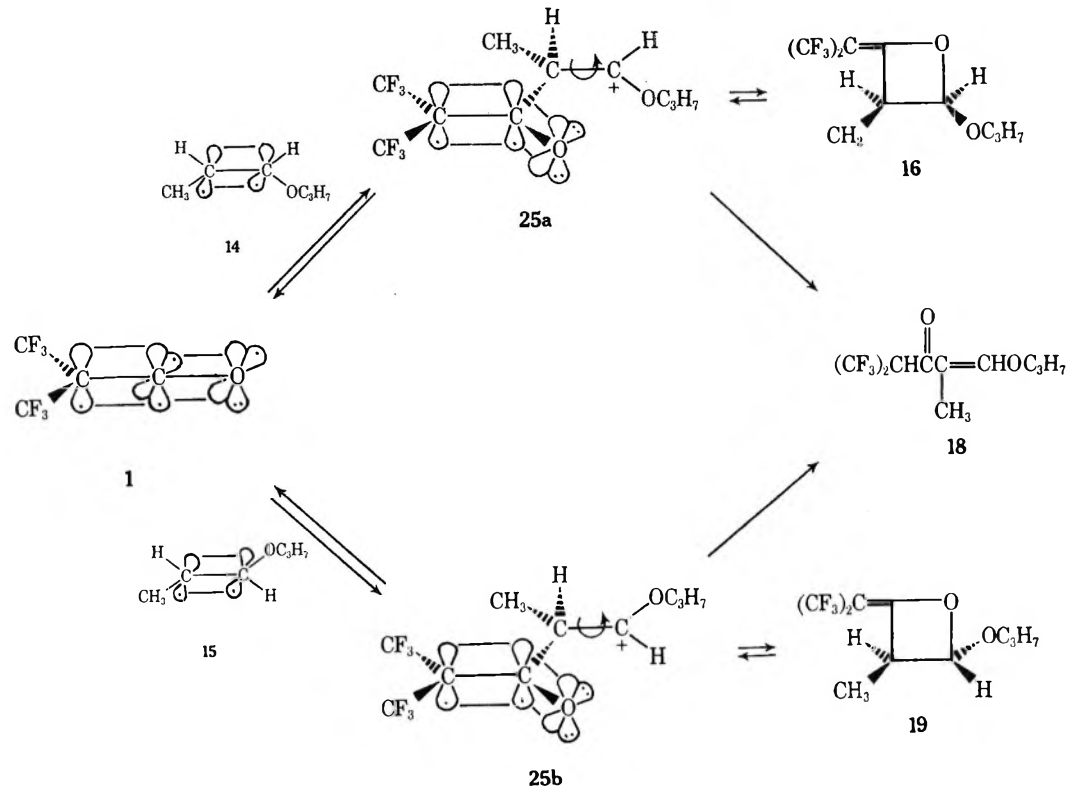


Figure 2.—Intermediates in a cycloaddition to the carbonyl of bis(trifluoromethyl)ketene.

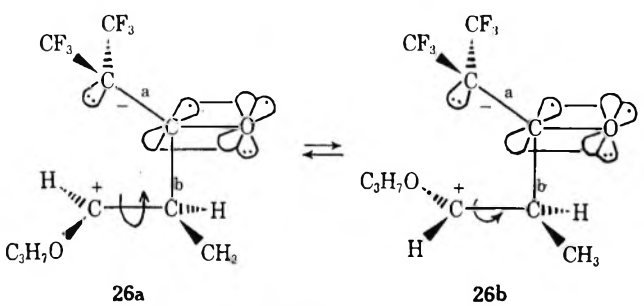


Figure 3.—Proposed intermediates in cycloaddition of propyl propenyl ether to the C=C of bis(trifluoromethyl)ketene.

25b as depicted in Figure 2 involves attack at the isolated carbonyl π system to give directly the delocalized, well-stabilized anionic portion of a dipolar intermediate which can ring close with minimum movement of nuclei. Attack on the olefinic bond to form **26** would involve approaching the other π orbital on the central carbon atom, leading to a presumably higher energy dipole with a stabilized (but not delocalized) negative charge in an sp^3 orbital. Closure of **26** to cyclobutanones could occur directly, but equilibration with **25** would require not only solvation to reduce Coulombic attraction but also synchronous rotation about bonds a and b (Figure 3).

Although conditions have been found where **25** is not readily transformed to **26**, facile interconversion in other cases can by no means be ruled out, particularly at temperatures above 25°.

Because all the cycloadducts seem to dissociate to starting materials in the 25–100° temperature range (see below), the observed equilibration between cyclobutanones **17** and **20** can occur indirectly. The dissociated ethers can isomerize *via* oxetane intermediate **25** and then re-form the mixed cyclobutanones without having to pass through intermediate **26**. However, the results with *trans* ether **15** at −50°, where the reverse reaction is not seen even on long standing, provide evidence for the existence of **26a** and **26b** as rotational conformers. Stable mixtures (at low temperatures) of cyclobutanones as well as oxetanes are formed in all solvents but hexane (Table III).

The effect of solvent polarity on rate of cyclobutanone formation appears to be large and can also be attributed to the intermediacy of **26**, in which the negative charge is stabilized by trifluoromethyl groups.[16] Where positive charge is well stabilized, as by an alkoxy oxygen, the dipolar intermediate is favored.[17] With less nucleophilic coreactants, **1** appears to form cyclobutanones by a less polar mechanism, perhaps involving an unsymmetrical polarized transition state.[1] Similar concerted, though unsymmetrical, cycloadditions have been proposed or implied for other ketenes.[15,18–22]

In addition to *cis–trans* isomerization reactions, intermediates from **1** and **14** or **15** were found to initiate polymerization of the vinyl ethers. In these cationic polymerizations, ketene **1** is acting as a Friedel–Crafts catalyst to generate a dipolar species (presumably **25**,

(16) *Cf.* S. Andreades, *J. Amer. Chem. Soc.*, **86**, 2003 (1964).

(17) R. H. Hasek and J. C. Martin, *J. Org. Chem.*, **28**, 1468 (1963); J. C. Martin, P. G. Gott, and H. U. Hostettler, *ibid.*, **32**, 1654 (1967). Indications that cycloaddition of very nucleophilic olefins to nonfluorinated ketenes can also be stepwise were obtained from reactions of enamines with dimethylketene.

(18) R. Huisgen, L. Feiler, and G. Binsch, *Angew. Chem., Int. Ed. Engl.*, **3**, 753 (1964).

(19) W. T. Brady and H. R. O'Neal, *J. Org. Chem.*, **32**, 612 (1967).

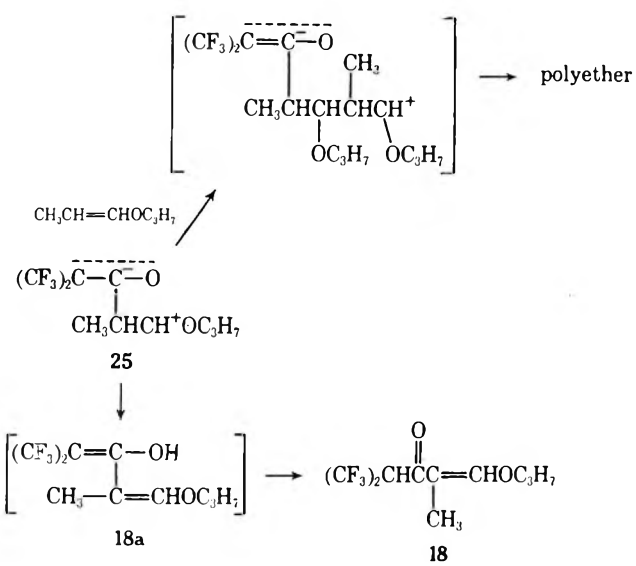
(20) T. J. Katz and R. Dessau, *J. Amer. Chem. Soc.*, **85**, 2172 (1963).

(21) R. Montaigne and L. Ghosez, *Angew. Chem., Int. Ed. Engl.*, **7**, 221 (1968).

(22) J. C. Martin, V. W. Goodlett, and R. D. Burpitt, *J. Org. Chem.*, **30**, 4309 (1965).

since its charge separation is greater than that of **26**), which is trapped by another molecule of vinyl ether in a propagation reaction which leads ultimately to polymer. The cycloaddition studies were carried out with excess **14** and **15** to ensure complete reaction of **1**. Polymerization was most troublesome with *trans* ether **15**. The unusual by-products formed in ethyl acetate as solvent may have originated in a similar attack of dipolar intermediate on ethyl acetate.

Acyclic products of proton transfer, such as **18**, are easily explained through the dipolar intermediates. The generally increasing amounts of **18** with decreasing amounts of oxetanes, particularly in polar solvents (Tables II and III), indicate that **25** is capable of stabilizing itself by migration of a proton. The enol **18a** is not necessarily an intermediate, since proton migration could give **18** directly.



According to Figure 1, the cycloadditions of **14** and **15** to **1** are reversible reactions from which acyclic products such as **18** may be withdrawn by essentially irreversible processes. Evidence for the reversibility of oxetane formation was obtained by reacting **1** and a twofold excess of **14** in hexane at 0° to convert **1** to oxetane **16** (65%) and cyclobutanone **17** (35%), then adding a sixfold excess of ethyl vinyl ether and warming to 25°. Reaction was slow, since no change in the ^{19}F nmr spectrum was observed after 2 and 6 hr. After 24 hr at 25°, the nmr spectrum of the mixture showed the presence of ethyl vinyl ether cycloadducts to **1**. Integration of ^{19}F nmr peaks and comparison with a synthetic mixture of the two cyclobutanones (which had been isolated) indicated a mixture of 38% **16**, 19% **7**, 38% **17**, and 5% **8**. The conditions for generation and capture of **1** in this experiment correspond to the mildest conditions for conversion of oxetane **16** to cyclobutanone **17**, further evidence that intermediates **25** and **26** are not easily interconverted.

Repetition of the above experiment in nitroethane resulted in conversion of all oxetane to cyclobutanones in 4 hr at 25° with peaks attributable to **8** present. Since both **17** and **20** were present, the amount of **8** could not be determined by integration, but was found to be greater than 20% by comparison with a synthetic mixture of known amounts.

Complete reversibility of cyclobutanone formation was also demonstrated by capture of dissociated **1** with ethyl vinyl ether. Pure samples of **17** and **20** were heated at 100° with a twofold excess of ethyl vinyl ether, conditions shown before to lead to slow isomerization of both **17** and **20**. Increased viscosity showed polymerization of vinyl ethers had occurred. Examination by vpc at low temperature showed that **17** gave product composed of 11.5% **17**, 13.5% **20**, 29% **8**, and 46% **9**. Similarly, **20** was shown to give **9** as the major product.

A related series of experiments involving isomerization of **17** and **20** at 100° for 9 hr in the presence of **14** or **15** with and without solvents gave unexpected results. In all cases **17** or **20** was converted to mixtures of **17**, **20**, and **18**. With *cis* ether **14** present, regardless of whether the cyclobutanone was **17** or **20** and regardless of the solvent, only the *cis* ether **14** (no **15**) could be detected after heating. However, if *trans* ether **15** was used, mixtures of **14** and **15** were detected after heating. Our explanation of these results is that **26a** and **26b**, although rotamers which can be interconverted at 25–100°, have appreciable differences in energy and in stability. Rotamer **26a**, derived from **14**, is least stable and dissociates preferentially to form **1** and **14**. This rationalization would, of course, not be available if the concerted mechanism for cycloaddition of vinyl ethers to **1** were assumed.

Experimental Section[23]

2-Benzoyloxy-4-hexafluoroisopropylidenoxetane (**2**) **and 2,2-Bis(trifluoromethyl)-3-benzoyloxycyclobutanone** (**3**).—Vinyl benzoate (8.0 g, 0.054 mol) containing 0.5 g of phenothiazine and **1** (9.0 g, 0.05 mol) were sealed in an evaculated Carius tube and heated on a steam bath overnight. The low boiler (1 g) was evaporated and the solid residue was recrystallized from hexane to give 5.6 g (34%) of **2**, mp 99–100°. Another recrystallization from hexane gave 5.35 g: mp 100–101°; ir 5.72 (ester C=O), 5.82 μ (exocyclic C=C); nmr ^1H at τ 2.17 (multiplet, area 2, phenyl **H**), 2.68 (multiplet, area 3, phenyl **H**), 3.09 (triplet, area 1, $J_{H/H}$ = 3.7 Hz, ring C-**H**), 6.32 (complex multiplet, area 2, ring CH_2); ^{19}F at 58.7 (multiplet, area 1, CF_3), 59.3 ppm (multiplet, area 1, CF_3).

The filtrates from recrystallization of **2** were distilled to give 1.7 g of recovered vinyl benzoate and 6.9 g (42%) of **3**, bp 86° (1 mm), $n^{25}D$ 1.4464. The product solidified on standing; recrystallization from hexane gave 3.5 g: mp 45–46°; ir 5.50 (ring C=O), 5.74 μ (ester C=O); nmr ^1H at τ 1.85 (multiplet, 2, phenyl **H**), 2.40 (multiplet, 3, phenyl **H**), 3.93 (triplet, 1, $J_{H/H}$ = 8.0 Hz, with further fine structure, ring C**H**), 6.23 (doublet, 2, $J_{H/H}$ = 8.0 Hz, with further fine structure, ring CH_2); ^{19}F at 64.8 (quartet, 1, $J_{F/F}$ = 9.0 Hz, CF_3), 68.6 ppm (quartet, 1, $J_{F/F}$ = 9.0 Hz, CF_3).

Anal. Calcd for $C_{13}H_8F_6O_3$: C, 47.89; H, 2.47; F, 34.97. Found for **2**: C, 48.09; H, 2.67; F, 35.23. Found for **3**: C, 47.91; H, 2.70; F, 34.79.

2-Acetoxyvinyl Hexafluoroisopropyl Ketone (**6**).—A mixture of 9.0 g (0.05 mol) of **1** and 6.0 g (0.07 mol) of vinyl acetate was heated overnight in a sealed tube at 100°. Near the end of the heating cycle, rapid darkening occurred; so the reaction mixture was distilled to give 13.3 g (99%) of mixed products, bp 30–90° (1 mm). (A similar complete reaction was obtained in only 4 hr at 100° in a separate experiment.) Fractions totaling 5.3 g (40%), bp 55–57° (1 mm), solidified and two recrystallizations from CCl_4 gave 1.1 g of pure **6**, mp 49–50°. Lower boiling cuts

(23) Melting and boiling points are uncorrected. Proton nmr spectra were obtained with a Varian A-60 spectrometer. Peak center positions for ^1H are reported τ = 10 − δ_H ppm. Fluorine nmr spectra were obtained with a Varian A56-60 spectrometer using $CFCl_3$ as an external standard. Peak center positions for ^{19}F are reported in parts per million upfield from $CFCl_3$. Solid samples were dissolved in acetone-d_6 (20% solutions) for nmr determinations.

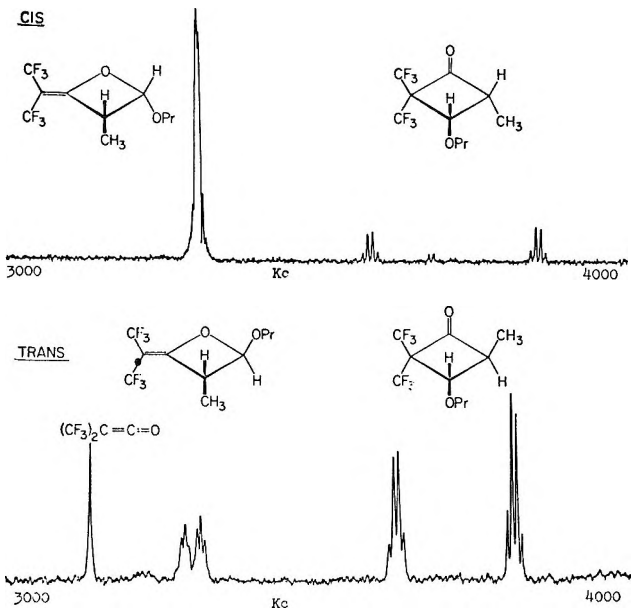


Figure 4.—^{19}F spectra observed for $(CF_3)_2C{=}C{=}O$ plus *cis*- and *trans*-propenyl propyl ethers in hexane at −50°.

were shown to contain **5** and higher boiling cuts 4 along with more **6**. For **6**: ir 5.58 (ester C=O), 5.86 (ketone C=O), 6.09 μ (C=C); nmr ^1H at 486, 473, 359, and 346 Hz (AB, 2, $J_{H/H}$ = 13 Hz, *trans* CH=CH), τ 5.20 [septet, 1, $J_{H/F}$ = 8.0 Hz, $(CF_3)_2CH$–], 8.23 (singlet, 3, CH_3); ^{19}F at 64.7 ppm [doublet, $J_{H/F}$ = 8.0 Hz, $(CF_3)_2CH$–].

Anal. Calcd for $C_8H_6F_6O_3$: C, 36.39; H, 2.29; F, 43.18. Found: C, 36.49; H, 2.68; F, 43.00.

2-Acetoxy-4-hexafluoroisopropylidenoxetane (4) and 2,2-Bis(trifluoromethyl)-3-acetoxycyclobutanone (5).—The reaction above of vinyl acetate and 1 without solvent gave largely the linear product **6** and was complete in 4 hr at 100°. The same reactants in hexane gave very little reaction after 5 hr at 100°. Long reaction times are required in a nonpolar solvent such as hexane, but the stablizing influence of hexane allows retention of the products with cyclic structures.

A mixture of vinyl acetate (17.0 g, 0.20 mol), **1** (36.0 g, 0.20 mol), 0.5 g of phenothiazine, and 25 ml of hexane in a sealed tube was heated for 63 hr in a steam bath. By distillation there was isolated 21.8 g (41%) of a mixture, bp 60–80° (14 mm), and 23.2 g (44%) of **4**, bp 98° (14 mm). The lower boiling material could be separated by vpc into nearly equal amounts of **5** and an unknown compound plus a trace of **6**. The unknown product gave a single broad ^{19}F nmr peak and on standing was converted to **6**; the unknown and **6** may therefore be *cis* and *trans* isomers, respectively. For **4**: ir 5.61 (ester C=O), 5.83 μ (exocyclic C=C); nmr ^1H at τ 3.48 (triplet, 1, $J_{H/H}$ = 3.6 Hz, CH), 6.62 (broad, 2, CH_2), 8.18 (singlet, 3, CH_3); ^{19}F at 59.1 (quartet, 1, $J_{F/F}$ = 6.5 Hz, CF_3), 59.9 ppm (quartet, 1, $J_{F/F}$ = 6.5 Hz, plus fine structure, CF_3). For **5**: ir 5.49 (ring C=O), 5.65 μ (ester C=O); nmr ^1H at τ 4.45 (broad triplet, 1, $J_{H/H}$ = 7.6 Hz, CH), 6.61 (doublet, 2, $J_{H/H}$ = 7.6 Hz, CH_2), 8.22 (singlet, 3, CH_3); ^{19}F at 65.5 (quartet, 1, $J_{F/F}$ = 8.5 Hz, CF_3), 68.6 ppm (quartet, 1, $J_{F/F}$ = 8.5 Hz, CF_3).

Anal. Calcd for $C_5H_6F_6O_3$: C, 36.39; H, 2.29; F, 43.18. Found for **4**: C, 36.38; H, 2.19; F, 43.67. Found for **5**: C, 36.63; H, 2.48; F, 43.07.

2-Ethoxyvinyl Hexafluoroisopropyl Ketone (9).—A mixture of 9.0 g (0.05 mol) of **1** and 4.0 g (0.055 mol) of ethyl vinyl ether in a sealed tube was allowed to warm from a liquid nitrogen temperature. Reaction occurred immediately on melting, and direct distillation gave 0.6 g (5%) of **8** (characterization below), bp 38° (5 mm), and 11.6 g (92%) of **9**, bp 77° (5 mm), $n^{25}D$ 1.3912. The latter solidified on cooling and could be recrystallized from hexane: mp 27°; ir 5.92 (conjd C=O), 6.30 μ (conjd C=C); nmr ^1H at 463.8, 451.2, 345.0, and 332.4 Hz (AB, 2, $J_{H/H}$ = 12.6 Hz, *trans* CH=CH), τ 5.85 [septet, 1, $J_{H/F}$ = 8.1 Hz, $(CF_3)_2CH$–], 6.22 (quartet, 2, $J_{H/H}$ = 7.4 Hz, CH_2CH_3), 9.00 (triplet, 3, $J_{H/H}$ = 7.4 Hz, CH_2CH_3); ^{19}F at 65.1 ppm [doublet, $J_{H/F}$ = 8.1 Hz, $(CF_3)_2CH$–].

Anal. Calcd for $C_8H_8F_6O_2$: C, 38.43; H, 3.23; F, 45.60. Found: C, 38.61; H, 3.38; F, 45.52.

2,2-Bis(trifluoromethyl)-3-ethoxycyclobutanone (8).—Ethyl vinyl ether (20.0 g, 0.28 mol), **1** (40.0 g, 0.22 mol), and 25 ml of hexane in a sealed, evacuated tube were allowed to warm to 25° and stand overnight. Distillation of the reaction mixture gave 33.7 g (67%) of **8**, bp 47° (10 mm), and 6.7 g (13%) of **9**, bp 77° (5 mm). For **8**: ir 5.50 μ (ring C=O); nmr ^1H at τ 5.57 (triplet, 1, $J_{H/H}$ = 8.0 Hz with fine structure, CH), 6.76 (doublet, 2, $J_{H/H}$ = 8.0 Hz, ring CH_2), 6.59 (quartet, 2, $J_{H/H}$ = 7.0 Hz, CH_2CH_3), 9.05 (triplet, 3, $J_{H/H}$ = 7.0 Hz, CH_2CH_3); ^{19}F at 64.8 (quartet, 1, $J_{F/F}$ = 8.6 Hz, CF_3), 68.5 ppm (quartet, 1, $J_{F/F}$ = 8.6 Hz, CF_3).

Anal. Calcd for $C_8H_8F_6O_2$: C, 38.43; H, 3.23; F, 45.60. Found: C, 38.57; H, 3.15; F, 45.05.

Essentially the same experiment using nitromethane in place of hexane gave 21.3 g (43%) of **8** and 20.2 g (40%) of **9**. Examination of the reaction products in hexane and in nitromethane at −50° by fluorine nmr showed low-field ^{19}F resonances as multiplets at 58.8 and 59.4 ppm, respectively, for oxetane **7**, which disappeared on warming while resonances for **8** and **9** appeared.

1,1-Bis(trifluoromethyl)-4-ethoxybuta-1,3-dien-2-yl Hexafluoroisobutyrate (10).—Products from **1** and ethyl vinyl ether depend on conditions. Uncontrolled neat reactions tend to form **9** and reactions in nonpolar solvents give **8** as the main product isolated, but numerous by-products may also appear. One such product is the 2:1 adduct **10** formed with excess **1** and heat.

A mixture of 15.7 g (0.063 mol) of **9** and 21.0 g (0.12 mol) of **1** was heated in a sealed tube at 100° overnight. Distillation afforded 25 g (93%) of **10**: bp 73° (1 mm); $n^{25}D$ 1.3575; ir 5.53 (vinyl ester C=O), 5.82 (vinyl ester C=C), 6.07 μ (C=C); nmr ^1H at 357, 352, 265, and 260 Hz (AB, 2, $J_{H/H}$ = 5.0 Hz, CH=CH), τ 6.48 [septet, 1, $J_{H/F}$ = 8.0 Hz, $(CF_3)_2CH$ overlapping with quartet, 2, $J_{H/H}$ = 7.0 Hz, CH_2CH_3], 9.02 (triplet, 3, $J_{H/H}$ = 7.0 Hz, CH_2CH_3); ^{19}F at 63.5 (quartet, 3, $J_{F/F}$ = 11.1 Hz, $=CCF_3$), 67.2 (quartet, 3, $J_{F/F}$ = 11.1 Hz, $=CCF_3$), 66.9 ppm [doublet, 6, $J_{H/F}$ = 8.0 Hz, $(CF_3)_2CH$].

Anal. Calcd for $C_{12}H_8F_{12}O_3$: C, 33.67; H, 1.89; F, 53.27. Found: C, 34.32; H, 2.04; F, 52.88.

2-Methoxy-2,3,3-trifluoro-3-hexafluoroisopropylidenoxetane (11) and 2,2-Bis(trifluoromethyl)-3-methoxy-3,4,4-trifluorocyclobutanone (12).—A mixture of 36 g (0.20 mol) of **1** and 11.2 g (0.10 mol) of methyl trifluorovinyl ether containing some phenothiazine as inhibitor was heated in a sealed tube for 60 hr at 100°. Distillation gave 6.0 g (20%) of **12**, bp 94–96°, and 15.1 g (55%) of **11**, bp 110–112°. A sample of **12**, bp 95°, was purified by vpc: ir 5.42 μ (ring C=O); nmr ^1H at τ 6.52 (multiplet, CH_3); ^{19}F at 64.1 ppm [unresolved structure, 6, $(CF_3)_2C$], 6473, 6733, 6948, and 7208 Hz (AB with fine structure, 2, $J_{F/F}$ = 260 Hz, ring CF_2), 134.1 ppm (multiplet, 1, CF).

A sample of **11**, bp 112°, was analyzed: ir 5.72 μ (exocyclic C=C); nmr ^1H at τ 6.58 (doublet, $J_{H/F}$ = 0.7 Hz, CH_3); ^{19}F at 61.5 (multiplet, 3, CF_3), 62.5 (multiplet, 3, CF_3), 117.5 (multiplet, 2, CF_2), 90.1 ppm (multiplet, 1, CF).

Anal. Calcd for $C_7H_3F_9O_2$: C, 28.99; H, 1.04; F, 58.97. Found for **12**: C, 29.25; H, 0.85; F, 59.34. Found for **11**: C, 30.15; H, 1.80; F, 58.68.

As proof of structure, both **11** and **12** were hydrolyzed with sulfuric acid.

An immiscible mixture of 15.0 g of **12** and 30 ml concentrated H_2SO_4 was heated in a sealed tube at 175° for 8 hr. When the tube was opened, carbon dioxide (characterized by ir) was evolved. Distillation of the clear top layer afforded 4.9 g (41%) of difluoromethyl hexafluoroisopropyl ketone: bp 67°; ir 5.62 μ (C=O); nmr ^1H at τ 4.49 (triplet, 1, $J_{H/F}$ = 53.5 Hz, CF_2H), 5.67 [septet, 1, $J_{H/F}$ = 7.3 Hz, $(CF_3)_2CH$]; ^{19}F at 130.3 (doublet, 1, $J_{H/F}$ = 53.5 Hz into septets, $J_{F/F}$ = 2.6 Hz, CF_2H), 65.6 ppm [doublet, 3, $J_{H/F}$ = 7.3 Hz into triplets, $J_{F/F}$ = 2.6 Hz, $(CF_3)_2CH$].

Anal. Calcd for $C_5H_2F_8O$: C, 26.11; H, 0.88; F, 66.09. Found: C, 26.56; H, 1.30; F, 65.81.

In like manner, a mixture of 16.7 g of **11** and 30 ml of concentrated H_2SO_4 was heated at 175° for 8 hr. Similarly, carbon dioxide was evolved and a clear layer obtained, which gave on distillation 1.9 g (14%) of difluoromethyl hexafluoroisopropyl ketone.

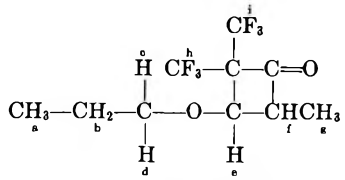
3-Methoxy-2,2,5,5,5-pentafluoro-4-(trifluoromethyl)-pent-3-enoyl Fluoride (13).—Compound **12** (4.4 g) was mixed in a sealed tube with 0.1 g of CsF, 0.1 g of tetraethylammonium chloride,

TABLE VII
NMR DATA FOR *cis*- AND *trans*-PROPENYL PROPYL ETHERS

$CH_3(a)—CH_2(b)—CH_2(c)—O—CH(d)=CH(e)—CH_3(f)$

Ether	Chemical shifts, τ a	b	c	d	e	f	Coupling constants, Hz a/b	b/c	d/e	d/f	e/f
14	9.22	8.49	6.56	4.32	5.92	8.63	6.4	6.3	6.2	1.7	6.8
15	9.26	8.51	6.68	4.04	5.51	8.68	6.5	6.2	12.4	1.5	6.4

TABLE VIII
NMR DATA FOR *cis*- AND *trans*-CYCLOBUTANONES 17 AND 20[a]



	Chemical shifts, τ a	b	c	d	e	f	g	Ppm h	i
17	8.82	8.12	6.11	6.25	5.15	5 97	8.49	68.7	63.6
20	8.95	8.25	6.26	6.40	5.68	5 95	8.61	68.0	64.3

	Coupling constants, Hz a/b	b/c + b/d	c/d	e/f	e/h	f/g	h/i
17	7.5	6.4	8.9	9.4	1.0	7.8	8.8
20	7.5	6.4	8.7	7.2	<1.0	7.3	8.6

[a] Proton spectra taken on a Varian 220-MHz instrument, using 10% solutions in $CDCl_3$ with TMS as internal standard.

and 5 ml of methylene chloride. After the mixture was heated overnight at 100°, **13** was essentially the only product present. The crude product was purified by vpc to give 2.6 g (59%) of **13**: ir 5.30 and 5.34 (COF), 6.04 μ (C=C); nmr ^1H at τ 6.24 (singlet, CH_3); ^{19}F at −16.0 (triplet, 1, $J_{F/F}$ = 10.9 Hz, COF), 59.1 (triplet, 3, $J_{F/F}$ = 13.6 Hz into quartets, $J_{F/F}$ = 9.0 Hz, CF_2), 61.2 (quartet, 3, $J_{F/F}$ = 9.0 Hz, CF_3), 105 ppm (5 lines, 2, overlapping quartet, $J_{F/F}$ = 13.6 Hz, into doublet $J_{F/F}$ = 10.9 Hz, CF_2).

Anal. Calcd for $C_7H_3F_9O_2$: C, 28.99; H, 1.04; F, 58.97. Found: C, 29.31; H, 1.38; F, 58.53.

***cis*- and *trans*-Propenyl Propyl Ethers (14 and 15).**—An adaptation of the literature procedure[7] was used. A mixture of 574 g of hexane, 386 g of propionaldehyde, 976 g of *n*-propyl alcohol, and 4 g of *p*-toluenesulfonic acid was refluxed with a water separator and 125 ml of water was removed in 1 day. Slow distillation gave the desired ethers, bp 88–90°. Too rapid distillation gave the high boiler (*ca.* 140°), apparently the acetal, while slow distillation allowed propanol to split out. The distillate was washed with 2% potassium hydroxide to remove propanol, and the remaining *cis*- and *trans*-propenyl ethers were fractionated. From two such runs and fractionation through a Podbielniak column there was obtained 265 ml of **14**, bp 94° (96.5% *cis*, 3.5% *trans* by glpc), and 101 ml of **15**, bp 101° (94.2% *trans*, 5.8% *cis* by glpc). Nmr data are given in Table VII.

***cis*- and *trans*-2,2-Bis(trifluoromethyl)-3-propoxy-4-methylcyclobutanones (17 and 20).**—Examination of the reaction between **1** and **14** or **15** by ^{19}F nmr (see Tables II and III) showed that ketene was consumed very rapidly even at −50° and that initially large amounts of oxetane were formed along with cyclobutanone (Figure 4). When warmed to room temperature, oxetane was converted to cyclobutanone. It was, therefore, not possible to isolate oxetane, but cyclobutanone could be isolated in good yield. Further heating caused isomerization and opening of the cyclobutanone ring to give a linear ketone (see below).

In a typical experiment, 10 g (0.10 mol) of **14**, 25 ml of hexane, and 18.0 g (0.10 mol) of **1** were sealed in a Carius tube, warmed to room temperature, and then heated 1 hr in a steam bath. After the tube was opened and solvent removed, the crude product examined by analytical vpc indicated that the reaction was essentially stereospecific. During a slow fractionation, the isomers apparently equilibrated somewhat. One initial fraction, bp 63–64° (13 mm), was 89% **20** and 11% **17** while a final cut, bp 69–70° (13 mm), was 99% **17** and 1% **20** (Table VIII). Total recovery of distilled fractions was 25 g (89%). An attempt to separate the isomers by preparative vpc resulted in some equilibration and ring opening on the column. A similar experiment starting with **15** and **1** gave predominantly **20**. For **17**, ir 5.51 μ (ring C=O). For **20**, ir 5.50 μ (ring C=O).

Anal. Calcd for $C_{10}H_{12}F_6O_2$: C, 43.20; H, 4.35; F, 41.01. Found for **17**: C, 43.39; H, 4.22; F, 41.39. Found for **20**: C, 43.08; H, 4.35; F, 41.41.

1-Methyl-2-propoxyvinyl Hexafluoroisopropyl Ketone (18).—A 5-g mixture of **17** and **20** (over 80% **17**), when shaken with a source of fluoride ion (trace of cesium fluoride in 1 ml of glyme), became warm. Examination by vpc showed that the isomer mixture had changed to 90% **20** and 10% **17**. Similarly a 5-g mixture which was 80% **20** changed to 90.7% **20** and 9.3% **17**. Warming of the mixture in the presence of fluoride ion catalyst on a steam bath for several hours converted it entirely to **18**: bp 60° (0.1 mm); mp 45–46° (from petroleum ether); ir 5.72 and 5.79 (C=O doublet), 6.01 and 6.11 μ (C=C); nmr ^1H at τ 2.38 (singlet, 1, =CH), 5.38 [septet, 1, $J_{H/F}$ = 7.5 Hz, $(CF_3)_2CH$], 5.78 (triplet, 2, $J_{H/H}$ = 6.4 Hz, OCH_2), 8.09 (quartet, 2, $J_{H/H}$ = 7.2 Hz, into triplets, $J_{H/H}$ = 6.4 Hz, CH_2CH_3), 8.10 (singlet, 3, $=CCH_3$), 8.93 (triplet, 3, $J_{H/H}$ = 7.2 Hz, CH_2CH_3); ^{19}F at 63.6 ppm [doublet, $J_{H/F}$ = 7.5 Hz, $(CF_3)_2CH$].

Anal. Calcd for $C_{10}H_{12}F_6O_2$: C, 43.20; H, 4.35; F, 41.01. Found: C, 43.46; H, 4.71; F, 39.46.

Method for the ^{19}F Nmr Study of the Reaction of 1 with 14 and 15 in Solvents of Different Polarity.—The nmr tubes were first necked down with a neck large enough to permit insertion of a hypodermic needle, but small enough to allow easy sealing with a flame under vacuum. By means of a hypodermic syringe, the tubes were charged with 64 μl (0.05 g, 0.0005 mol) of the propenyl propyl ether, 370 μl of solvent, and 37 μl (0.0535 g, 0.00025 mol) of *o*-bis(trifluoromethyl)benzene. The latter was used as a standard for integration of fluorine peaks since it gave a single peak which did not interfere with product peaks. However, its melting point prevented mixing at low temperature, and it was sometimes omitted. The tube was then placed on a manifold system to which was also attached a vacuum pump, manometer, and supply of **1**. The tube was cooled in liquid nitrogen, evacuated, and cut off from the system by a stopcock. The system was then pressured with **1** so that a calibrated amount (measured by pressure drop to an accuracy of ±1.5%) was delivered when the stopcock to the liquid nitrogen cooled tube was opened. The tube, now containing 0.5 *M* ketene, 0.5 *M* reference, and 1.0 *M* propenyl ether (excess to allow for some polymerization), was sealed and mixed while completely submerged in a Dry Ice–acetone bath at −80°. For tubes containing the *o*-bis(trifluoromethyl)benzene reference, it was necessary to warm to about −50°. After mixing, the tubes were stored in a Dry Ice–acetone bath. They were examined by ^{19}F nmr with the

probe cooled to −50°. The nmr spectra were taken after heating at different temperatures for varying times followed by quenching in Dry Ice–acetone. The heating schedules were 0.25, 0.5, 1, and 2 hr at 0° (wet ice bath) and 0.25, 0.5, 1, 2, 4, 8, 16, 20, and 24 hr at 25° (refluxing $CFCl_3$ bath).

2,2-Bis(trifluoromethyl)-3-(*p*-methoxyphenyl)cyclobutanone (22).—*p*-Methoxystyrene (27.0 g, 0.20 mol), **1** (43.0 g, 0.24 mol), 25 ml of benzene, and 0.1 g of phenothiazine were heated overnight at 100° in a sealed tube. After removal of volatiles, the resulting solid was recrystallized from CCl_4 to give 49 g (79%) of **22**, mp 84–86°. Another recrystallization gave an analytical sample, mp 85–87°. In other experiments, it was found that the reaction goes at 25° and the product can be distilled: bp 96° (1 mm); ir 5.53 μ (ring C=O); nmr [$(CD_3)_2CO$] ^1H at τ 3.2 (AA'BB', 4, aromatic CH), 6.3 (overlapping multiplets, 3, $CHCH_2$), 6.7 (singlet, 3, CH_3); ^{19}F at 64.3 (quartet, 1, $J_{F/F}$ = 8.6 Hz, CF_3), 68.6 ppm (quartet, 1, $J_{F/F}$ = 8.6 Hz, CF_3).

Anal. Calcd for $C_{13}H_{10}F_6O_2$: C, 50.04; H, 3.23; F, 36.54. Found: C, 49.82; H, 3.16; F, 36.49.

In hexane at 25°, oxetane **21** was also formed, causing an nmr signal for ^{19}F at 58.9 ppm (multiplet).

Ethyl 5,5,5-Trifluoro-4-(trifluoromethyl)penta-2,3-dienoate (24).—A sealed tube containing 14 g (0.20 mol) of ethoxyacetylene and 39 g (0.22 mol) of **1** was held at −80° overnight in an attempt to control the exothermic reaction. Distillation gave 19.5 g (39%) of **24**: bp 68° (50 mm); $n^{25}D$ 1.3580; ir 5.03 (C=C=C), 5.77 μ (ester C=O); nmr ^1H at τ 3.77 (septet, 1, $J_{H/F}$ = 2.5 Hz, =CH), 6.12 (quartet, 2, $J_{H/H}$ = 7.2 Hz, CH_2), 9.10 (triplet, 3, $J_{H/H}$ = 7.2 Hz, CH_3); ^{19}F at 62.6 ppm (doublet, $J_{H/F}$ = 2.5 Hz).

Anal. Calcd for $C_8H_6F_6O_2$: C, 38.74; H, 2.44; F, 45.97. Found: C, 39.10; H, 2.72; F, 46.31.

Evidence for oxete **23** was ^{19}F nmr signals obtained at *ca.* 57.0 (quartet, 1, $J_{F/F}$ = 7.0 Hz, CF_3), 59.8 ppm (quartet, 1, $J_{F/F}$ = 7.0 Hz, CF_3), along with the doublet at 62.6 ppm when rapidly scanned while warming from −80° in the probe at 30°. These quartets rapidly disappeared as the doublet signal became stronger.

Registry No.—**1**, 684-22-0; **2**, 4233-20-9; **3**, 4141-80-4; **4**, 25636-21-9; **5**, 25636-22-0; **6**, 25631-65-6; **8**, 25636-23:1; **9**, 25631-66-7; **10**, 25631-67-8; **11**, 25636-24-2; **12**, 25636-25-3; **13**, 25636-95-7; **14**, 143360-78-2; **15**, 21087-24-1; **17**, 25631-70-3; **18**, 25679-31-6; **20**, 25631-71-4; **22**, 25636-96-8; **24**, 25636-97-9; difluoromethyl hexafluoroisopropyl ketone, 25636-98-0.

Fluoroketenes. VI. Cycloadditions of Cumulenes to Bis(trifluoromethyl)ketene[1]

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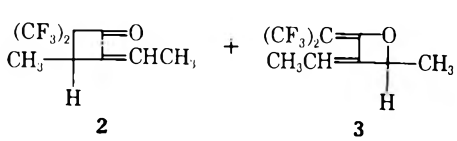
Dimethylallene cycloadds to bis(trifluoromethyl)ketene to form both oxetane and cyclobutanone, but tetramethylallene forms only products of an ene reaction because of steric hindrance to ring closure. Cycloadditions of ketene and methylketene to bis(trifluoromethyl)ketene proceed easily and in good yield to form β lactones derived only from addition across the C=C of the nonfluorinated ketene. A dipolar intermediate is proposed for this reaction. Dimethylketene cycloadds to bis(trifluoromethyl)ketene to form both cyclobutanedione and β lactone, a change presumably induced by increased steric hindrance. The direction of this latter reaction is strikingly dependent on solvent polarity.

Allenes.—The reactions of bis(trifluoromethyl)ketene (**1**) with allenes and with simple olefins are somewhat analogous, indicating that some factors governing the reaction courses are similar. As with ethylene, allene itself has not been made to react with **1** up to 165°. 1,3-Dimethylallene showed reactivity like that of a vinyl ester[1] in that it gave an unusual cycloaddition to **1** (apparently unique for an allene–ketene combination) at 100° to form both cyclic ketone **2** and oxetane **3**. The orientation of substituents in the adducts is that expected from bond formation at the central allene carbon atom to form stabilized dipolar intermediates and/or polar transition states.

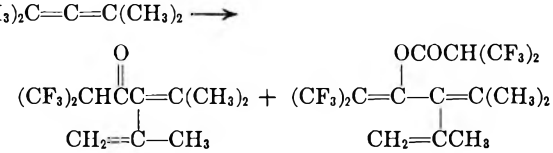
$(CF_3)_2C{=}C{=}O$ (**1**) + $CH_3CH{=}C{=}CHCH_3$ →



2 **3**

Tetramethylallene resembled isobutylene in its slow reaction with **1** at 25° to form only open-chain products of an ene reaction. Steric hindrance to closure of either the normally stable cyclobutanone ring or the oxetane ring resulted in preferential formation of products of hydrogen migration. Even when equimolar amounts of reactants were used, the enol ester **5** was the major product (79%). The ketodiene **4** was isolated in only 9% yield and could not be reacted in a separate step with **1** to give **5**. This is analogous to the formation of enol esters through intermediates not isolated in the reactions of **1** with butene-1 and with α-methylstyrene.[2]

1 + $(CH_3)_2C{=}C{=}C(CH_3)_2$ →



4 **5**

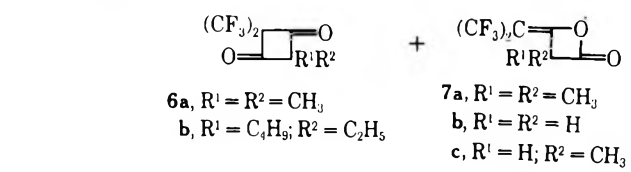
Ketenes.—Mixed ketene dimers have seldom been studied, presumably because of a tendency to form in low yield along with simple dimers.[3] Since ketene **1** does not dimerize thermally but is extremely reactive toward unsaturated nucleophiles, mixed dimers of **1** with various other ketenes form easily and in high yield. Dimers of both the 1,3-dione type **6** and β-lac-

(1) Part V: D. C. England and C. G. Krespan, *J. Org. Chem.*, **35**, 3312 (1970).

(2) D. C. England and C. G. Krespan, *ibid.*, **35**, 3300 (1970).

(3) *Cf.* W. E. Hanford and J. C. Sauer, *Org. React.*, **3**, 129 (1946).

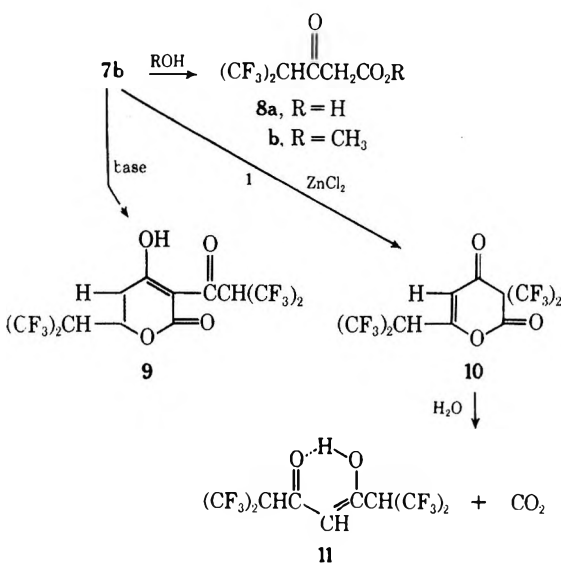
tone type **7** have been observed, but these dimers were derived *only* from cycloaddition to the carbon–carbon double bond and not to the carbon–oxygen double bond of the nonfluorinated ketene.



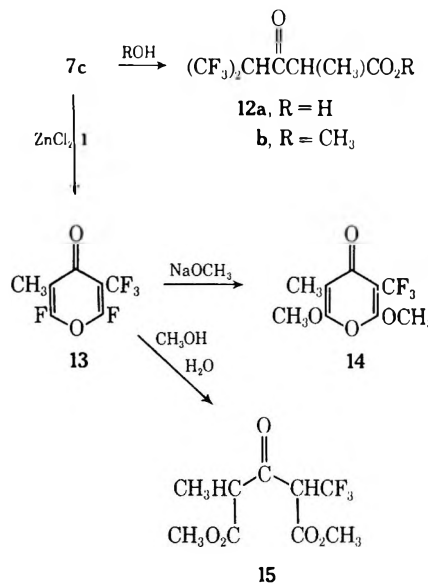
6a, $R^1 = R^2 = CH_3$
b, $R^1 = C_4H_9$; $R^2 = C_2H_5$

7a, $R^1 = R^2 = CH_3$
b, $R^1 = R^2 = H$
c, $R^1 = H$; $R^2 = CH_3$

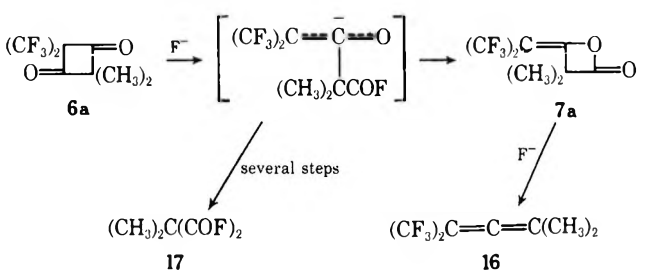
Ketene reacted exothermically with ketene **1** at very low temperature to give lactone **7b** in 89% yield. On pyrolysis this lactone reverted to starting materials in preference to loss of carbon dioxide with allene formation. This behavior is similar to that of ketene alone, which dimerizes solely to the β lactone[4] which in turn pyrolyzes mainly to regenerate ketene.[5] Reaction of **7b** with water gave the keto acid **8a** and with methanol the corresponding ester **8b**. The β lactone was readily dimerized by base to give **9**, a reaction analogous to the formation of dehydroacetic acid from diketene. Lactone **7b** also reacted with another equivalent of ketene **1** in the presence of zinc chloride as catalyst to give the insertion product, **10**. δ-Lactone **10** hydrolyzed in high yield with loss of carbon dioxide to the 1,3-dione **11**, an excellent chelating agent which exists mainly in the enol form. Compound **9** has also been isolated from the reaction of **1** with acetic anhydride, and both **9** and **10** were isolated from a reaction of **1** with acetyl chloride in the presence of zinc chloride. These reactions apparently proceed through the formation of ketene, perhaps with mixed anhydride as a coproduct.



Methylketene, like ketene, reacted with **1** to give a mixed lactone, **7c**, in good yield. Even under conditions found to favor 1,3-dione formation with dimethylketene (see below), no dione or related product derived from cycloaddition of methylketene to the carbon–carbon double bond of **1** was detected. This behavior is unlike that of methylketene alone, which affords both cyclobutane and oxetane rings on dimerization.[6] Pyrolysis of dimer **7c** proceeded normally, however, giving starting materials in preference to allene formation with loss of carbon dioxide. The mixed dimer which could be hydrolyzed to keto acid **12a**, gave the corresponding methyl ester **12b** with methanol, and polymerized readily with basic catalysts. Attempted reaction of **7c** with another mole of **1** in the presence of zinc chloride did not give a homolog of **10**, but a hydrogen fluoride elimination product believed to be pyranone **13** was isolated. This ring structure is the same as that present in some aldoketene trimers[4,7] and in a derivative prepared from diketene and water.[8] Reaction of pyranone **13** with sodium methoxide replaced two fluorine atoms to give the dimethoxypyranone **14** and with methanol gave the keto diester **15**.



Dimethylketene gave with **1** both dione (**6a**) and lactone (**7a**) as cycloadducts in a reaction which was strikingly solvent dependent. In cyclohexane a high yield of dione was formed, but in a more polar solvent (ethyl acetate) a mixture of the dione and the lactone was produced. Dione **6a** was shown to be stable in polar solvents once formed, but was easily isomerized to lactone **7a** by fluoride ion at room temperature. The isomerization proceeded to completion, indicating the lactone to be the more stable isomer, a reverse order of stability to that observed for the oxetane–cyclobutanone systems.[1] At 200° fluoride ion in glyme promoted formation of allene **16** from the dione **6a** presumably through the lactone **7a** and of dimethylmalonyl fluoride



(4) D. G. Farnum, J. R. Johnson, R. E. Hess, T. B. Marshall, and B. Webster, *J. Amer. Chem. Soc.*, **87**, 5191 (1965).

(5) R. N. Lacy, "The Chemistry of Alkenes," S. Patai, Ed., Interscience, New York, N. Y., 1964, p 1171.

(6) Reference 5, p 1183.

(7) E. Wedekind, J. Haussermann, W. Weisswange, and M. Miller, *Justus Liebigs Ann. Chem.*, **378**, 261 (1911).

(8) E. Marcus, J. K. Chan, and C. B. Strow, *J. Org. Chem.*, **31**, 1369 (1966), report 2,6-dimethyl-4H-pyran-4-one as a product of base-catalyzed hydrolysis of diketene.

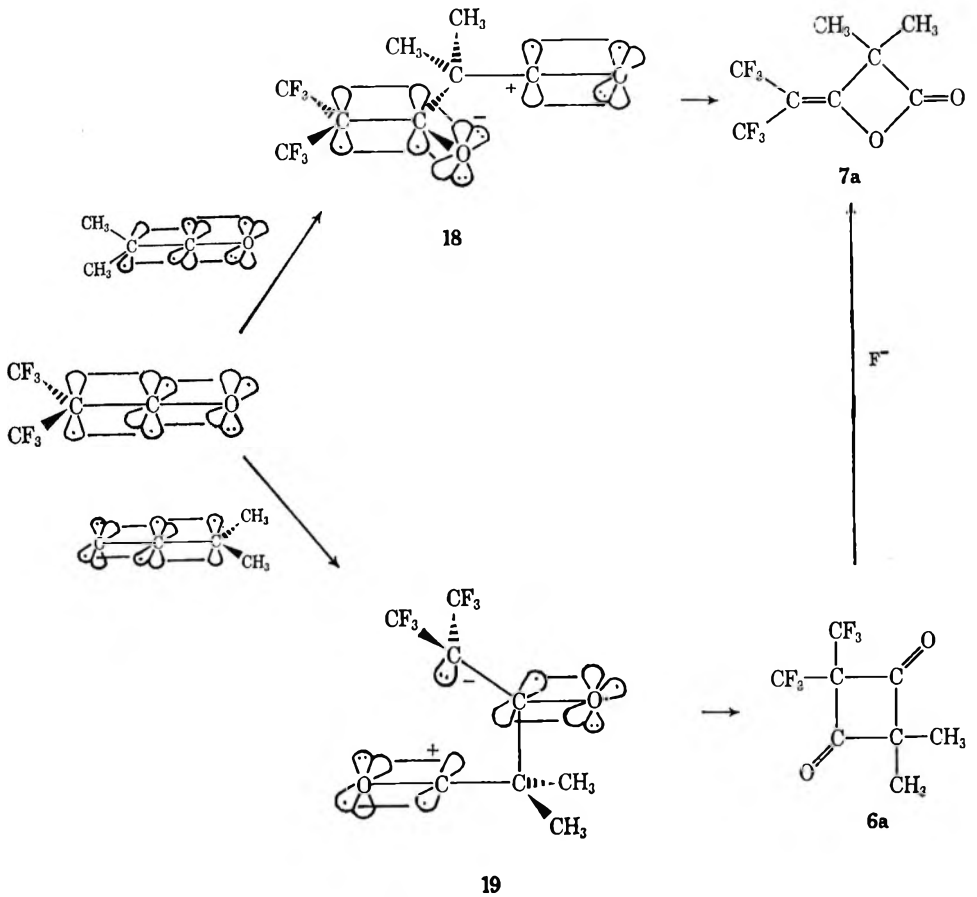


Figure 1.—Proposed intermediates in the cycloaddition of dimethylketene to bis(trifluoromethyl)ketene.

17, the latter probably from a side reaction involving the anionic intermediate. Hydrolysis of **7a** and methanolysis of **6a** gave the expected ring-opened products.

Butylethylketene reacted with **1** in hexane similarly to dimethylketene to give dione **6b** in 87% yield. However, diphenylketene did not react with **1** at 100° over a period of a week.

Discussion

The evidence suggests that cycloadditions of ketenes to the carbonyl group of **1** to form β lactones go through a dipolar intermediate similar to that from **1** and nucleophilic olefins.[1] Reactions are rapid, even at low temperature. They are highly selective, in that only the β lactone derived from the most highly stabilized dipolar intermediate is formed. The second mode of cycloaddition, to the carbon–carbon double bond of **1** with cyclobutanedione formation, is less favored and is not seen except with dialkylketenes. We propose that the results with dimethylketene are explicable on the basis that steric hindrance to the formation of intermediate **18** (Figure 1) allows formation of an intermediate (or unsymmetrical transition state) such as **19** to compete. That **18** has the greater charge separation is indicated by the fact that formation of **7a** is favored by polar solvents. There is no indication of a readily accessible pathway from **18** to possible intermediate **19**; indeed the observed dramatic product shifts with solvent polarity may stem from large differences most likely to be associated with separate reaction paths. Formation of cyclobutanedione **6a** may, of course, proceed by an essentially concerted mechanism rather than a discrete intermediate, insofar as our evidence can show.

Both types of product (**6** and **7**) are stable under reaction conditions once formed, but dissociate to starting materials at higher temperatures. The preferred path of lactone decomposition is probably by way of the stable polarized species represented by **18**, in a reversal of the original reaction. Loss of CO_2 from the β lactones to form allenes was negligible. Thus, the equilibria seen with **1** and reactive olefins[1] were not observed with **1** and other ketenes, and the reason seems to be the greater stability of the β lactones as compared with the oxetanes.

Allenes are generally considered to cycloadd as 2π systems which follow Woodward–Hoffmann rules.[9] In a stepwise 2 + 2 case, allenes are presumed to be able to stabilize an unpaired electron or positive charge by generating an allyl system. Combined with the negatively charged 3-atom system from **1**, the allylic cation may provide an intermediate uniquely capable of closing to either an oxetane such as **3** or cyclobutanone such as **2**. This system merits detailed study.

Experimental Section[10]

2-Ethylidene-3-methyl-4,4-bis(trifluoromethyl)cyclobutanone (2) and 2-Methyl-3-ethylidene-4-hexafluoroisopropylidenoxetane

(9) *E.g.*, see W. R. Dolbier, Jr., and S.-H. Dai, *J. Amer. Chem. Soc.*, **90** 5028 (1968).

(10) Melting and boiling points are uncorrected. Proton nmr spectra were obtained with a Varian A-60 spectrometer. Peak center positions for ^1H are reported $\tau = 10 - \delta_H$ ppm. Fluorine nmr spectra were obtained with a Varian A56–60 spectrometer using $CFCl_3$ as an external standard. Peak center positions for ^{19}F are reported in parts per million upfield from $CFCl_3$.

(3).—2,3-Dimethylallene, bp 48°, was prepared by pyrolysis of the β-lactone dimer of methylketene under vacuum at 600°. A sample of the allene (4 g, 0.06 mol) was sealed in a Carius tube with 31 g (0.16 mol) of 1. The mixture separated into two layers on cooling to −80°. After being heated 0.5 hr at 100°, the mixture no longer separated on cooling, indicating reaction. After 60 hr at 100° there was recovered 20 g of 1 and 14 g of crude product. The crude material was partially separated by distillation into fractions, bp 56–70° (10 mm) and bp 70–80° (10 mm). Further separation was accomplished by preparative vpc and the purified products were characterized. The lower boiling material was largely a mixture of *cis* and *trans* isomers having the conjugated cyclobutanone structure 2. The conjugated structure is preferred on the basis of uv absorption. The yields were 27 and 38% in the order of increasing boiling point, but *cis* was not distinguished from *trans*. The higher boiling material is largely compound 3, formed in 17% yield. Other higher and lower boiling products isolated amounted to about 8% and were not characterized.

For the more volatile vpc isomer of 2: ir 5.62 (C=O), 5.97 μ (C=C); uv $\lambda_{max}^{isooctane}$ 241 mμ (ε 13,100); nmr ^1H at τ 4.25 (quartet, 1, $J_{H/H}$ = 7.5 Hz into doublets, $J_{H/H}$ = 2.5 Hz, =CH), 6.85 (broad, 1, ring CH), 8.27 (doublet, 3, $J_{H/H}$ = 7.5 Hz, into doublets, $J_{H/H}$ = 3.0 Hz, =CCH$_3$), 8.88 (doublet, 3, $J_{H/H}$ = 7.5 Hz, into doublets, $J_{H/H}$ = 1.6 Hz, CH$_3$); ^{19}F at 64.1 (quartet into multiplet, 1, $J_{F/F}$ = 9.0 Hz, CF$_3$), 69.2 ppm (quartet,1, $J_{F/F}$ = 9.0 Hz, CF$_3$).

For the second vpc isomer of 2: ir 5.62 (C=O), 5.79 μ (C=C); uv $\lambda_{max}^{isooctane}$ 245 mμ (ε 12,300); nmr ^1H at τ 3.50 (quartet, 1, $J_{H/H}$ = 7.6 Hz, into doublets, $J_{H/H}$ = 3.2 Hz, =CH), 6.47 (broad, 1, ring CH), 8.32 (doublet, 3, $J_{H/H}$ = 7.6 Hz, into doublets, $J_{H/H}$ = 2.2 Hz, =CCH$_3$), 8.63 (doublet, 3, $J_{H/H}$ = 7.6 Hz, into doublets, $J_{H/H}$ = 1.6 Hz, CH$_3$); ^{19}F at 64.0 (quartet into multiplets, 1, $J_{F/F}$ = 9.1 Hz, CF$_3$), 69.5 ppm (quartet, 1, $J_{F/F}$ = 9.1 Hz, CF$_3$).

For 3: ir 5.86 and 6.01 μ (C=C); uv $\lambda_{max}^{isooctane}$ 256 mμ (ε 9850); nmr ^1H at τ 3.88 (quartet, 1, $J_{H/H}$ = 7.2 Hz, =CH), 4.65 (quartet, 1, $J_{H/H}$ = 6.6 Hz, ring CH), 8.55 (doublet, 3, $J_{H/H}$ 7.2 Hz, =CCH$_3$), 8.68 (doublet, 3, $J_{H/H}$ = 6.6 Hz, CH$_3$); ^{19}F at 57.8 ppm [complex multiplet, =C(CF$_3$)$_2$].

Anal. Calcd for $C_9H_8F_6O$: C, 43.94; H, 3.28; F, 46.34. Found for first isomer of 2: C, 44.25; H, 3.47; F, 45.64. Found for second isomer of 2: C, 43.77; H, 3.46; F, 46.47. Found for 3: C, 43.69; H, 2.99; F, 46.50.

Hexafluoroisopropyl 1-Isopropenyl-2-methylpropenyl Ketone (4) and 1,1,1-Trifluoro-2-trifluoromethyl-4-isopropenyl-5-methyl-2,4-hexadien-3-yl Hexafluoroisobutyrate (5).—A mixture of 8.0 g (0.045 mol) of 1 and 25 ml of ether was frozen in a Carius tube at liquid nitrogen temperature and 4.5 g (0.047 mol) of tetramethyallene was added. The tube was sealed, warmed to room temperature with mixing, and allowed to stand overnight. Distillation gave a fraction, bp 83–98° (25 mm), containing 4 and 5. A sample of 4 was purified by vpc. The product with bp 98° (25 mm) was 5 with a minor impurity which could be removed by vpc. Yields based on vpc data were 9% 4 and 79% 5. Purified 4 (50 mg) was sealed in a glass tube with 1.0 g of 1 and heated overnight in a steam bath. Removal of 1 under vacuum gave recovered 4, and no 5 could be detected by ir or glpc.

For 4: ir 3.27 (vinyl CH), 3.39, 3.45 and 3.52 (satd CH), 5.90 (C=O), 6.10 μ (C=C); uv λ_{max}^{hexane} 326 mμ (ε 74), 258 (7100); nmr ^1H at τ 4.95 (5 lines, 1, $J_{H/H}$ = 1.6 Hz, =CH), 5.35 (broad, 1, =CH), 5.63 [septet, 1, $J_{H/F}$ = 8.0 Hz, (CF$_3$)$_2$CH], 8.35 (singlet, 3, CH$_3$), 8.47 (unresolved structure, 6, CH$_3$); ^{19}F at 64.7 ppm [doublet, $J_{H/F}$ = 8.0 Hz, (CF$_3$)$_2$CH].

Anal. Calcd for $C_{11}H_{12}F_6O$: C, 48.22; H, 4.41; F, 41.61. Found: C, 48.51; H, 4.63; F, 40.29.

For 5: ir 3.21 (vinyl CH), 3.33, 3.39 and 3.47 (satd CH), 5.55 (vinyl ester C=O), 5.99 (conjd C=O), 6.09 μ (C=C); uv λ_{max}^{hexane} 269 mμ (ε 3070); nmr ^1H at τ 5.06 (multiplet, 1, =CH), 5.45 (broad, 1, =CH), 6.32 [septet, 1, $J_{H/F}$ = 7.3 Hz, (CF$_3$)$_2$CH], 8.35 (broad, 3, CH$_3$), 8.45 (broad, 3, CH$_3$), 8.53 (broad, 3, CH$_3$); ^{19}F at 61.0 (quartet, 3, $J_{F/F}$ = 8.2 Hz with fine structure, =CCF$_3$), 62.2 (quartet, 3, $J_{F/F}$ = 8.2 Hz, =CCF$_3$), 65.8 ppm [doublet, 6, $J_{H/F}$ = 7.3 Hz with fine structure, (CF$_3$)$_2$CH].

Anal. Calcd for $C_{15}H_{12}F_{12}O_2$: C, 39.86; H, 2.68; F, 50.44. Found: C, 40.42; H, 3.12; F, 49.15.

β-Hexafluoroisopropylidene-β-propiolactone (7b).—Freshly prepared ketene (8.0 g, 0.19 mol, from cracking of the dimer) was vacuum distilled into a Carius tube cooled in liquid nitrogen. Compound 1 (34 g, 0.19 mol) was then condensed into the tube, and the tube was sealed and placed in a fiber glass sleeve on its side on a mechanical shaker. Reaction was immediate and exothermic on thawing. After the tube had reached room temperature, it was opened and the contents distilled to give 37 g (89%) of 7b: bp 43° (6 mm); $n^{25}D$ 1.3603; ir 5.12 (C=O), 5.74 μ (C=C); nmr ^1H at τ 5.63 (multiplet, CH$_2$); ^{19}F at 59.2 (quartet, 1, $J_{F/F}$ = 6.6 Hz with fine structure, CF$_3$), 60.3 ppm (quartet, 1, $J_{F/F}$ = 6.6 Hz with fine structure, CF$_3$).

Anal. Calcd for $C_6H_2F_6O_2$: C, 32.75; H, 0.92; F, 51.82. Found: C, 33.06; H, 1.14; F, 51.35.

The above product (15 g) was pyrolyzed by passing it through a hot tube under vacuum at 558°. Tar was formed and the only distillable material was 3.0 g, bp 38–48°. Infrared showed it to be a mixture of perfluoromethacrylyl fluoride and bis(trifluoromethyl)ketene, which are known to equilibrate under similar conditions. Pyrrolysis apparently reverses the cycloaddition.

Hexafluoroisobutyrylacetic Acid (8a).—Lactone 7b (6 g, 0.027 mol) was placed in a crystallizing dish with 1 ml of water and allowed to stand overnight. The resulting crystals were recrystallized from hexane (2.50 g, 38.5%) and after a second recrystallization melted at 77–78° (2.2 g): ir broad 3–4 (OH), 5.95 (C=O) typical of a carboxylic acid, 6.02 and 6.12 μ (conjd C=O and/or C=C); nmr (CDCl$_3$) ^1H at τ 4.55 (singlet, 1, CH), 6.30 [septet, 1, $J_{H/F}$ = 7.7 Hz, (CF$_3$)$_2$CH], two exchangeable (D$_2$O) singlets of equal area (1) at τ −0.9 (enol OH) and −1.8 (COOH); ^{19}F at 64.6 ppm [doublet, $J_{H/F}$ = 7.7 Hz, (CF$_3$)$_2$CH]. The presence of another tautomer in about 0.25 this amount was indicated by a doublet (7.7 Hz) at 63.0 ppm and still another doublet (7.7 Hz) in 1/20 this amount at 63.5 ppm. One of the corresponding septets (7.7 Hz) was also visible for ^1H at τ 5.55.

Anal. Calcd for $C_6H_4F_6O_3$: C, 30.28; H, 1.69; F, 47.90. Found: C, 30.46; H, 1.95; F, 47.74.

Methyl Hexafluoroisobutyrylacetate (8b).—Methanol (25 ml) was stirred while 19.0 g (0.086 mol) of 7b was added dropwise, keeping the temperature below 10°. The product was distilled directly to give 16.8 g (77.5%) of 8b: bp 47° (8 mm); $n^{25}D$ 1.3626; ir 5.75 and 5.98 (keto and ester C=O), 6.09 μ (enol C=C); nmr (CDCl$_3$) ^1H at τ 4.72 (singlet, CH), overlapping peaks for 6.28 (singlet, CH$_3$), 6.40 [septet, $J_{H/F}$ = 7.9 Hz, (CF$_3$)$_2$CH], an exchangeable (D$_2$O) peak at −2.1, a small septet ($J_{H/F}$ = 7.7 Hz) at 5.50 for an isomer; ^{19}F at 65.2 [doublet, $J_{H/F}$ = 7.9 Hz, (CF$_3$)$_2$CH], a second isomer in 40% this amount at 63.6 (doublet, $J_{H/F}$ = 7.7 Hz), a third isomer (6%) at 64.0 ppm (doublet, $J_{H/F}$ = 7.9 Hz).

Anal. Calcd for $C_7H_6F_6O_3$: C, 33.36; H, 2.40; F, 45.24 Found: C, 33.69; H, 2.53; F, 45.32.

3-Hexafluoroisobutyryl-3,4-dihydro-4-keto-6-hexafluoroisopropyl-2H-pyran-2-one (9).—A sample (8.9 g, 0.040 mol) of 7b was sealed in a glass tube and heated overnight on a steam bath. The resulting solid was recrystallized from carbon tetrachloride to give 8.3 g (93%) of 9, mp 76–83°. Three sublimations and another recrystallization from carbon tetrachloride gave 6.5 g of white crystals, mp 84–85°. The following data are in agreement with structure 9: ir 3.23 (vinyl CH), 5.78, 6.01, 6.10 (sh), and 6.40 μ (C=O and C=C); nmr (CDCl$_3$) ^1H at τ −5.1 [singlet, 1, exchangable (D$_2$O)OH], 3.50 (singlet, 1, =CH), 3.80 [septet, 1, $J_{H/F}$ = 7.5 Hz, (CF$_3$)$_2$CH], 5.91 [septet, 1, $J_{H/F}$ = 7.5 Hz, (CF$_3$)$_2$CH]; ^{19}F at 62.9 [doublet, 1, $J_{H/F}$ = 7.5 Hz, (CF$_3$)$_2$CH], 64.5 ppm [doublet, 1, $J_{H/F}$ = 7.5 Hz, (CF$_3$)$_2$CH].

Anal. Calcd for $C_{12}H_4F_{12}O_4$: C, 32.75; H, 0.92; F, 51.82. Found: C, 32.75; H, 0.88; F, 51.47.

The reaction of 1 with acetic ahydride gives a mixture of products. The only one characterized is the same dimer (mp 85°) obtained above from dimerization of the lactone obtained from the reaction of 1 with ketene.

A mixture of 20.4 g (0.20 mol) acetic anhydride and 38 g (0.21 mol) of 1 was sealed in a Carius tube and heated 2 hr on a steam bath. After this time refluxing had ceased, the tube was cooled and opened, and the contents were distilled to give 31.5 g of liquid, bp 49–55° (20 mm), shown by vpc to contain three major components, 4.3 g of forerun mixture, and 10.6 g, bp 82–86° (75 mm). This latter material solidified and was recrystallized from carbon tetrachloride three times to yield 6.2 g, mp 85°. It was identical by mixture melting point and nmr with the material described above for 9.

3,3-Bis(trifluoromethyl)-3,4-dihydro-4-keto-6-hexafluoroisopropyl-2H-pyran-2-one (10) and 1,1,1,7,7,7-Hexafluoro-2,6-bis(trifluoromethyl)heptane-3,5-dione (11).—In the presence of zinc

chloride as catalyst, lactone **7b** reacted slowly with **1** at steam-bath temperature giving a product with structure **10**. This structure is based on analyses, ir, nmr, and reaction with water to give carbon dioxide and 1,3 diketone **11**.

A mixture of **7b** (25.0 g, 0.11 mol), **1** (35.0 g, 0.20 mol), and 1 g of zinc chloride was sealed in a Carius tube and heated 10 days on a steam bath. There was recovered 18 g of **1** and 26.5 g (58.5%) of crystalline product **10**: bp 90° (18 mm); mp 79–80° (from carbon tetrachloride); ir 3.22 (=CH), 3.35 (satd CH), 5.50 and 5.82 (C=O), 5.99 μ (C=C); nmr ($CDCl_3$) ^1H at τ 3.72 (singlet, 1, =C**H**), 6.00 [septet, 1, $J_{H/F}$ = 7.2 Hz, $(CF_3)_2CH$]; ^{19}F at 64.4 [doublet, 1, $J_{H/F}$ = 7.2 Hz, $(CF_3)_2CH$], 63.4 ppm [singlet, 1, $(CF_3)_2C$].

Anal. Calcd for $C_{10}H_2F_{12}O_3$: C, 30.18; H, 0.50; F, 57.29. Found: C, 29.86; H, 0.66; F, 57.47.

An immiscible mixture of crystalline **10** (10 g, 0.025 mol) and water (10 ml) was sealed in a Carius tube and heated overnight on a steam bath. The tube was cooled, carbon dioxide vented, and the crystalline residue filtered and sublimed to give 7.3 g (82%) of the 1,3 diketone **11** which could be recrystallized from petroleum ether: mp 60–60.5°; ir 6.05 and 6.25 μ (C=O and C=C); nmr ($CDCl_3$) ^1H at τ 3.95 (singlet, 1, =C**H**), −3.75 (singlet, 1, acidic **H**), 6.12 [septet, 2, $J_{H/F}$ = 7.7 Hz, $(CF_3)_2CH$]; ^{19}F at 64.1 ppm [doublet, $J_{H/F}$ = 7.7 Hz, $(CF_3)_2CH$]. The peak at τ −3.75 exchanged with D_2O.

Anal. Calcd for $C_9H_4F_{12}O_2$: C, 29.06; H, 1.09; F, 61.29. Found: C, 29.04; H, 1.36; F, 61.17.

A number of chelates of **11** were prepared by conventional means. The zinc chelate was prepared from a solution of 4.5 g of zinc acetate dihydrate in 25 ml of water and 5.0 g (0.013 mol) of **11** in 5 ml of methanol. A white oil separated which crystallized to give 6.1 g of crude product. Recrystallization from toluene gave 4.7 g (80%) of white crystals: mp 145–150° dec; ir 6.12 6.51 and 6.79 μ; nmr [$(CD_3)_2CO$] ^1H at τ 4.84 (singlet, 1, =C**H**), 6.19 [septet, 2, $J_{H/F}$ = 8.5 Hz, $(CF_3)_2CH$] [additional singlets at τ 6.56 (area 0.5) and 7.22 (area 1.5) along with analytical data indicated the presence of methanol of crystallization]; ^{19}F nmr at 65.1 ppm [doublet, $J_{H/F}$ = 8.5 Hz, $(CF_3)_2CH$].

Anal. Calcd for $C_{18}H_6F_{24}O_4Zn \cdot CH_3OH$: C, 27.17; H, 1.20; F, 54.30; Zn, 7.78. Found: C, 27.46; H, 1.38; F, 54.46; Zn, 7.65.

α-Methyl-β-hexafluoroisopropylidene-β-propiolactone (7c).—Methylketene was best prepared by pyrolysis of propionic anhydride under vacuum (*ca.* 1 mm) in a vertically mounted quartz tube (1-in. diameter and 22 in. long) packed with quartz chips and heated in the center section to 600° with an electric furnace. The anhydride was added at the top of the tube and the pyrolysis products were passed through two traps connected in series to the bottom of the tube. The first trap was cooled with Dry Ice–acetone and the second with liquid nitrogen. Propionic acid and any unreacted propionic anhydride were collected in the first trap and only methylketene (yellow) passed into the second trap and was condensed there. From 40 g (0.31 mol) of propionic anhydride 10.5 g (60%) of the yellow ketene was collected. Methylketene could be transferred as a gas under vacuum in small amounts. However, even at −80° the liquid ketene dimerized quite rapidly. If the dimerization proceeded at a moderate rate, the product was the solid dione (enol form), mp 138°. However, if the dimerization became very exothermic, the product was the liquid β lactone, bp 61° (25 mm). This β lactone was also the dimer obtained by reaction of propionyl chloride with triethylamine.[4]

The mixed dimer **7c** of methylketene and **1** was best prepared as follows. The fluoroketene (72 g, 0.40 mol) was condensed into the liquid nitrogen trap prior to connecting it to the system described above for generation of methylketene. Methylketene from 50 g (0.38 mol) of propionic anhydride was then condensed on top of the fluoroketene, and the trap was warmed to −80°. After a vigorous reaction there was recovered 27 g (38%) of fluoroketene, indicating that 45 g had reacted (equivalent to 14 g of methylketene). Distillation gave 36 g (61%) of **7c**, bp 43° (10 mm), and 13 g of syrupy polymer: ir 5.20 (C=O), 5.85 μ (C=C); nmr ^1H at τ 5.78 (quartet, 1, $J_{H/H}$ = 7.6 Hz with fine structure, CH), 8.75 (doublet, 3, $J_{H/H}$ = 7.6 Hz, CH_3); ^{19}F at 59.1 ppm (multiplet, CF_3).

Anal. Calcd for $C_7H_4F_6O_2$: C, 35.93; H, 1.72; F, 48.72. Found: C, 36.08; H, 2.00; F, 47.37.

7c was rapidly polymerized by base. Samples stored in glass at room temperature usually polymerized within a few days.

Lactone **7c**, like the corresponding β-lactone mixed dimer of ketene and **1**, did not lose carbon dioxide and give the corresponding allene in any appreciable amounts as do nonfluorinated ketene β-lactone dimers. Pyrolysis of **7c** (29 g) in a quartz-packed tube at *ca.* 1 mm pressure and 600° and condensation of the products in a liquid nitrogen trap gave 20 g of liquid. Distillation gave a fraction, 5.3 g, bp <48°, that was mostly perfluoromethacrylyl fluoride (the rearrangement product of **1**), identified by ir. A fraction (6.3 g) boiling about 66° (32 mm) was the β-lactone dimer of methylketene identified by ir; a fraction (7.4 g) boiling about 73° (32 mm) was largely the starting mixed dimer and about 1.1 g of higher boiling oil.

α-(Hexafluoroisobutyryl)propionic Acid (12a).—Lactone **7c** (25 g, 0.11 mol) was dissolved slowly in 25 ml of concentrated sulfuric acid with cooling to keep the temperature near 50°. The resulting solution was poured onto 100 g of ice. The resulting crystals were filtered and recrystallized from hexane to give 19 g (70%) of **12a**. A little color was removed from this material by recrystallizing again from hexane using charcoal to give 16.5 g. This product melted over a wide range (59–80°), and the melting point rose some (*ca.* 65–95°) on standing and was lowered again on sublimation (*ca.* 67–82°), indicating an isomer mixture. Proton and ^{19}F nmr spectra were in agreement with a keto–enol mixture: ir 3 (broad, H bond), 6.01 and 6.23 μ (C=O, C=C); nmr [$(CD_3)_2CO$] ^1H at τ 1.79 (broad, 1.45, O**H**), 5.02 [septet, 0.45, $J_{H/F}$ = 8.4 Hz, $(CF_3)_2CH$], 5.48 [septet, 0.55 $J_{H/F}$ = 8.4 Hz, $(CF_3)_2CH$], 6.40 (quartet, 0.55, $J_{H/H}$ = 7.0 Hz, CH_3CH), 8.52 (singlet, 1.35, =CCH_3), 9.10 (doublet, 1.65, $J_{H/H}$ = 7.0 Hz, CH_3CH) [this corresponds to a 55:45 keto–enol mixture]; ^{19}F nmr at 63.6 [doublet, $J_{H/F}$ = 8.4 Hz, $(CF_3)_2CH$], 65.1 ppm [doublet, $J_{H/F}$ = 8.4 Hz, $(CF_3)_2CH$].

Anal. Calcd for $C_7H_6F_6O_3$: C, 33.36; H, 2.40; F, 45.24. Found: C, 33.71; H, 2.49; F, 45.25.

Methyl α-(Hexafluoroisobutyryl)propionate (12b).—Compound **7c** (22 g, 0.094 mol) was added dropwise to 25 ml of methanol with cooling to maintain 40°. The resulting solution was poured into cold water, extracted with methylene chloride, washed with water, dried, and distilled to give 19.8 g (80%) of **12b**, bp 68° (13 mm), $n^{25}D$ 1.3650. Proton and ^{19}F nmr data were in agreement with a 65:35 keto–enol mixture: ir 5.68, 5.75, and 5.98 (C=O), 6.10 μ (C=C).

Anal. Calcd for $C_8H_8F_6O_3$: C, 36.12; H, 3.03; F, 42.86. Found: C, 36.85; H, 3.36; F, 41.78.

2,6-Difluoro-3-(trifluoromethyl)-5-methyl-4H-pyran-4-one (13).—A mixture of 28.5 g (0.12 mol) of **7c**, 1 g of zinc chloride, 25 ml of ether, and 38 g of **1** was sealed in a Carius tube and heated for 12 days on a steam bath. There was recovered 42 g of the low boiler (including ether and ketene) and 41 g of liquid. Distillation gave 1.4 g boiling up to 82° (30 mm), 15.2 g with bp 82–91° (30 mm) which partially solidified, and 7 g boiling higher. The fraction containing solid was recrystallized from carbon tetrachloride to yield 6.6 g (25%) of **13**, mp 81–82°. A second recrystallization gave 5.5 g, mp 81–83°. The crystals were large white plates which changed to needles on standing overnight at room temperature without change in melting point: ir 5.80 (C=O), 5.96 μ (C=C); nmr ($CDCl_3$) ^1H at τ 8.05 (doublet, $J_{H/F}$ = 2.4 Hz, CH_3); ^{19}F at 60.8 (doublet, 3, $J_{F/F}$ = 24.4 Hz, CF_3), 72.7 (quartet, 1, $J_{F/F}$ = 24.4 Hz, into doublets, $J_{F/F}$ = 7.4 Hz, C**F**), 85.4 ppm (doublet, 1, $J_{F/F}$ = 7.4 Hz, into quartets, $J_{H/F}$ = 2.4 Hz, C**F**).

Anal. Calcd for $C_7H_3F_5O_2$: C, 39.29; H, 1.41; F, 44.39; mol wt, 214. Found: C, 39.09; H, 1.47; F, 44.40; mol wt, 214 (mass spectrum).

2,6-Dimethoxy-3-(trifluoromethyl)-5-methyl-4H-pyran-4-one (14).—Compound **13** (2.0 g, 0.01 mol) was dissolved in 10 ml of methanol and 0.1 g of sodium methoxide was added, which caused the solution to become warm. The mixture was refluxed 5 hr and poured into cold water. Filtration gave 0.6 g of oily crystals which were recrystallized from methanol, 0.35 g (16%), mp 173–175°, yielding **14**: ir 5.95 (C=O), 6.15 μ (C=C); nmr ^1H at τ 6.20 (singlet, 1, CH_3O), 6.28 (singlet, 1, CH_3O), 8.60 (singlet, 1, CH_3); ^{19}F at 58.5 ppm (singlet, CF_3).

Anal. Calcd for $C_9H_9F_3O_4$: C, 45.42; H, 3.81; F, 23.95. Found: C, 45.41; H, 3.86; F, 24.31

Dimethyl 2-Methyl-3-keto-4-(trifluoromethyl)glutarate (15).—Compound **13** (7.0 g, 0.033 mol) was refluxed in 20 ml of methanol for 3 hr to give 7.9 g (95%) of crude compound **15** on dilution with water. Distillation gave 7.2 g (86%): bp 78° (0.5 mm); $n^{25}D$ 1.4050; ir 5.69 and shoulder at 5.76 μ (two C=O); nmr ^1H at τ 5.30 (quartet, 1, $J_{H/F}$ = 8.3 Hz, $CHCF_3$), 6.34 (quartet,

1, $J_{H/H}$ = 7.0 Hz, into quartets, $J_{H/F}$ = 6.4 Hz, $CHCH_3$), 6.47 (singlet, 3, CH_3O), 6.57 (singlet, 3, CH_3O), 8.93 (doublet, 3, $J_{H/H}$ = 7.0 Hz, $CHCH_3$); ^{19}F at 65.4 ppm (doublet, $J_{H/F}$ = 8.3 Hz, into doublets, $J_{H/F}$ = 6.4 Hz, $CHCF_3$).

Anal. Calcd for $C_9H_{11}F_3O_5$: C, 42.22; H, 4.33; F, 22.27. Found: C, 42.30; H, 4.38; F, 22.39.

2,2-Dimethyl-4,4-bis(trifluoromethyl)cyclobutane-1,3-dione (6a) and α,α-Dimethyl-β-hexafluoroisopropylidene-β-propiolactone (7a). **A.**—Ethyl acetate (50 ml) containing 11 g (0.16 mol) of yellow dimethylketene was frozen in liquid nitrogen and 33 g (0.19 mol) of 1 condensed on it. The mixture was allowed to liquify in a Dry Ice–acetone bath, which resulted in a mildly exothermic reaction to give a white solution. On distillation two major fractions were recovered after removal of ethyl acetate: **6a**, 7.3 g (19%), bp 52–58° (53 mm), and **7a**, 9.5 g (24%), bp mostly at 70° (53 mm).

The β-lactone **7a** was essentially pure as obtained from the above distillation, but was further purified by vpc: $n^{25}D$ 1.3633; ir 5.25 (C=O), 5.90 μ (C=C); nmr ^1H at τ 8.75 (unresolved fine structure, CH_3); ^{19}F at 60.1 ppm (complex multiplet, CF_3).

Anal. Calcd for $C_8H_6F_6O_2$: C, 38.74; H, 2.44; F, 45.97. Found: C, 38.83; H, 2.49; F, 45.83.

A sample of **7a** (2.0 g) was dissolved in 5 ml of concentrated sulfuric acid and the solution poured onto ice causing crystals to separate. These were filtered, air-dried (1.2 g), and recrystallized from carbon tetrachloride to give 1.05 g of α-hexafluoroisobutyrylisobutyric acid: mp 97–98°; it showed broad absorption in the infrared at 2.8–4 μ characteristic of a carboxylic acid and carbonyl absorption at 5.8 μ; nmr [$(CD_3)_2CO$] ^1H at τ 0.52 (singlet, 1, CO_2H), 5.08 [septet, 1, $J_{H/F}$ = 7.5 Hz, $CH(CF_3)_2$], 9.03 (singlet, 6, CH_3); ^{19}F at 64.0 ppm [doublet, $J_{H/F}$ = 7.5 Hz, $CH(CF_3)_2$].

Anal. Calcd for $C_8H_8F_6O_3$: C, 36.12; H, 3.03; F, 42.86. Found: C, 36.35; H, 3.10; F, 43.34.

B.—Another reaction run as described above but using a cyclohexane solution of dimethylketene gave only the dione **6a** in 81% yield: bp 48° (50 mm); $n^{25}D$ 1.3453; ir 5.62 μ (C=O); nmr ^1H at τ 8.90 (singlet, CH_3); ^{19}F at 64.4 ppm (singlet, CF_3).

Anal. Calcd for $C_8H_6F_6O_2$: C, 38.74; H, 2.44; F, 45.97. Found: C, 38.92; H, 2.57; F, 45.44.

In contrast to the behavior of **7a**, the dione **6a** was not soluble in concentrated sulfuric acid even when heated. However, the ring was cleaved by methanol using base catalysis to give the methyl ester of α-hexafluoroisobutyrylisobutyric acid.

Dione **6a** (15 g) in 10 ml of methanol containing 0.5 g of sodium methoxide was refluxed on a steam bath for 15 min, poured into cold, dilute HCl, extracted with methylene chloride, washed with water, dried, and distilled. There was obtained 12 g (70%) of the keto ester: bp 100° (60 mm); $n^{25}D$ 1.3650; ir 5.78 μ (C=O); nmr ^1H at τ 4.92 [septet, 1, $J_{H/F}$ = 7.4 Hz, $CH(CF_3)_2$], 6.23 (singlet, 3, CH_3O), 8.49 (singlet, 6, CH_3); ^{19}F at 63.3 ppm (doublet, $J_{H/F}$ = 7.4 Hz, CF_3).

Anal. Calcd for $C_9H_{10}F_6O_3$: C, 38.60; H, 3.60; F, 40.71. Found: C, 38.66; H, 3.71; F, 40.67.

Reaction of 6a with Fluoride Ion. A. Isomerization of 6a to 7a.—A mixture of 5 g of **6a**, 1 ml of glyme, and 0.1 g of cesium fluoride was allowed to stand overnight at room temperature. It was shown by vpc and by ir that **6a** had been completely converted to **7a**.

An unsuccessful attempt was made to convert **6a** to **7a** by aluminum chloride catalysis. The dione (15 g) was added dropwise to 25 ml of benzene containing 1 g of $AlCl_3$. There seemed to be an exothermic reaction at first and the mixture became dark, but later in the addition no heat was evolved and on distillation only starting material was recovered. Similarly, refluxing overnight an ether solution of **6a** containing zinc chloride catalyst gave no **7a**.

An unsuccessful attempt was also made to isomerize **7a** to **6a** in refluxing ethyl acetate with zinc chloride. Addition of aluminum chloride was also without effect.

B. 1,1-Dimethyl-3,3-bis(trifluoromethyl)allene (16) and Dimethylmalonyl Fluoride (17).—The reaction with fluoride was carried out using 15 g of **6a**, 1 ml of glyme, and 0.1 g of cesium fluoride with heating at 200° for 4 hr to give 7.5 g of impure **7a** boiling at *ca.* 100° (195 mm), and 5.2 g of lower boiling [45–50° (195 mm)] material from which there was obtained by vpc 2.9 g of **16** and 0.6 g of **17**. For **16**: ir 5.02 μ (C=C=C); nmr ^1H at τ 8.59 (singlet, CH_3); ^{19}F at 63.2 ppm (singlet, CF_3).

Anal. Calcd for $C_7H_6F_6$: C, 41.21; H, 2.96; F, 55.88. Found: C, 41.10; H, 2.71; F, 55.85.

For **17**: ir 5.40 μ (COF); nmr ^1H at τ 8.73 (triplet, $J_{H/F}$ = 0.8 Hz, CH_3); ^{19}F at −30.3 ppm (septet, $J_{H/F}$ = 0.8 Hz, CF_3).

Anal. Calcd for $C_5H_6F_2O_2$: C, 44.15; H, 4.45; F, 27.94. Found: C, 44.25; H, 4.64; F, 28.01.

2-Ethyl-2-butyl-4,4-bis(trifluoromethyl)cyclobutane-1,3-dione (6b).—A mixture of 65 g of 20% hexane solution of butylethylketene (*ca.* 0.1 mol) and 21 g (0.12 mol) of 1 was sealed in a Carius tube and gave a yellow solution at room temperature. After about 15-min warming on a steam bath it became colorless and on distillation there was obtained 26.6 g (87%) of **6b**: bp 32° (0.25 mm); ir 5.66 μ (C=O); nmr ^1H was a complex set of peaks at τ 8.1 − 9.6; ^{19}F at 65.0 ppm (singlet, CF_3).

Anal. Calcd for $C_{12}H_{14}F_6O_2$: C, 47.41; H, 4.64; F, 37.50. Found: C, 47.50; H, 4.57; F, 37.32.

Registry No.—**1**, 684-22-0; **2**, *cis*, 25631-96-3; **2**, *trans*, 25798-20-3; **3**, 25636-29-7; **4**, 25636-30-0; **5**, 25636-31-1; **6a**, 25636-32-2; **6b**, 25636-33-3; **7a**, 25636-34-4; **7b**, 19311-56-9; **7c**, 19311-57-0; **8a**, 25636-37-7; **8b**, 25636-38-8; **9**, 25636-39-9; **10**, 20262-24-2; **11**, 19475-86-6; **11** zinc chelate, 25636-99-1; **12a**, 25636-42-4; **12b**, 25636-43-5; **13**, 25636-44-6; **14**, 25636-45-7; **15**, 25636-46-8; **16**, 25636-47-9; **17**, 25636-48-0; α-hexafluoroisobutyrylisobutyric acid, 25636-26-4; α-hexafluoroisobutyrylisobutyric acid Me ester, 25636-27-5.

Thermal Decomposition Reactions of Carboxybenzenediazonium Salts. I. 1,4-Dehydro Aromatic Compounds from *p*-Carboxybenzenediazonium Salts[1]

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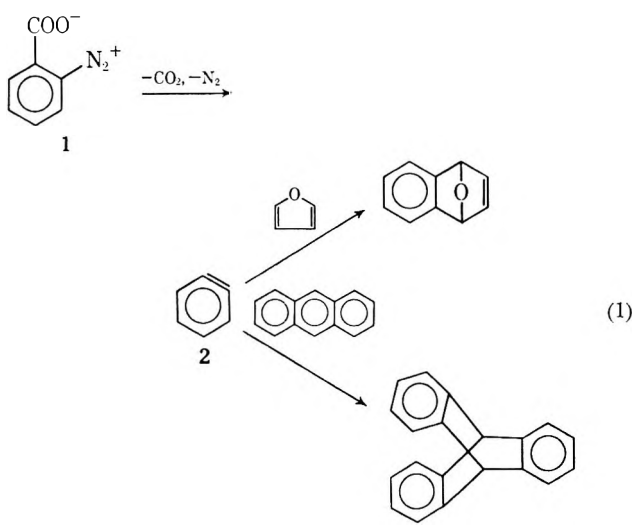
The thermal decomposition reaction of *p*-carboxybenzenediazonium chloride (**5**) and 4-carboxy-3-nitrobenzenediazonium chloride (**6**) was studied and the mixture of gases evolved (HCl, N_2, and CO_2) and the solid products obtained were identified and determinated for each experiment. The solid products were separated into substances with one phenyl ring and polymeric products. A heterolytic mechanism is proposed for this decomposition reaction. Evolution of nitrogen is postulated to lead to a carbonium ion followed by loss of carbon dioxide which produces a 1,4-dehydro aromatic compound. This latter intermediate yields a chloro derivative (HCl trapping) and polymeric products (autocondensation).

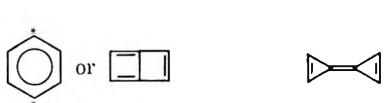
The thermal decomposition of benzenediazonium-2-carboxylate salt (**1**) has resulted in the evolution of both nitrogen and carbon dioxide. The decomposition product was a complex mixture, largely polymeric, which has not been resolved. Stiles and Miller[3] proposed the formation of 1,2-dehydrobenzene (**2**) after considering addition reactions with furan and anthracene (eq 1). Similar results were obtained in the



(1)

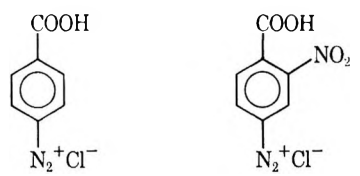
thermal decomposition of 2-carboxybenzenediazonium chloride.[4,5]

Berry, Clardy, and Schafer[6] studied the photoinitiated decomposition of benzenediazonium-4-carboxylate salt. Masses 28 (N_2), 44 (CO_2), and 76 ($-C_6H_4-$) were the strongest peaks in the mass spectrum. Some of the suggested structures for the $-C_6H_4-$ species were **3** and **4**.



3 **4**

In the present study, we investigated the thermal decomposition of solid *p*-carboxybenzenediazonium chloride (**5**) and 4-carboxy-3-nitrobenzenediazonium chloride (**6**).



5 **6**

Results

The thermal decompositions of diazonium compounds **5** and **6** were carried out in an appropriate apparatus, which is illustrated in Figure 1, where the evolved gases, nitrogen, carbon dioxide, and hydrogen chloride, were measured (Table I).

The *p*-carboxybenzenediazonium chloride (**5**) exploded at 110° and a white smoke deposited as a microcrystalline solid on the walls of the reaction flask. From the mixture of obtained products we separated, after chromatography, *p*-chlorobenzoic acid (35.0%), 4,4′-dicarboxyazobenzene (31.0%), and a polymeric fraction that we named P_1 (24.0%).

P_1 was separated in two fractions: P_{1a} (19.0%) had an average equivalent weight of 151 and a phenyl/carboxylic group ratio of 1.14; P_{1b} (5.0%) had an average equivalent weight of 171 and a phenyl/carboxylic group ratio of 1.65. Elemental analysis of this fraction revealed the presence of one azo group ($-N_2-$) per three phenyl groups ($-C_6H_4-$).

The 4-carboxy-3-nitrobenzenediazonium chloride (**6**) exploded at 146°, with light emission. The residue was a black powder, which was resolved by successive extractions into *m*-chloronitrobenzene (5.4%), 4-chloro-2-nitrobenzoic acid (13.2%), and two polymeric fractions that we named P_1 and P_2. Polymeric fraction P_1 (38.8%) had an average equivalent weight of 286, and a phenylnitro/carboxylic group ratio of 2.0. Polymeric fraction P_2 (44.0%) resulted in a polynitrophenyllic compound. Evidence for the *p*-polynitrophenyllic structure is based upon the C:N atomic ratio obtained from elemental analysis, TGA, ir spectrum, insolubility, color, and thermal stability (Table II).

The polymer P_2 contained 59.0% carbon and 12.0% nitrogen (calcd for $C_6H_4NO_2$: C, 59.02; N, 11.47). The C:N atomic ratio is 5.70. *p*-Polynitrophenyllic polymers possess a limiting theoretical C:N atomic ratio of 6.00.

(1) Abstracted in part from the Ph.D. Thesis of R. H. de Rossi, Universidad Nacional de Córdoba, Córdoba, Argentina, 1968.

(2) Fellow of the the Consejo Nacional de Investigactiones Científicas y Técnicas, Buenos Aires, Argentina, 1966–1969.

(3) M. Stiles and R. G. Miller, *J. Amer. Chem. Soc.*, **82**, 3802 (1960).

(4) R. W. Hoffmann, "Dehydrobenzene and Cycloalkynes," Academic Press, New York, N. Y., 1967, p 74.

(5) G. R. Ziegler, *J. Amer. Chem. Soc.*, **91**, 446 (1969).

(6) R. S. Berry, J. Clardy, and M. E. Schafer, *Tetrahedron Lett.*, No. 15 1003 (1965).

TABLE I

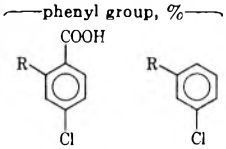
GASES EVOLVED IN THE THERMAL DECOMPOSITION REACTIONS OF *p*-CARBOXYBENZENEDIAZONIUM SALTS

Diazonium salts No.	Diazonium salts mmol	CO_2, mmol	Yield, %[a]	HCl, mmol	Yield, %[a]	N_2 mmol	Yield, %[a]	Temp, °C
5	0.50	0.03	6.0	0.10	20	0.19	38	110
	0.63	0.04	6.3	0.16	25	0.26	41	112
	0.78	0.04	5.1	0.19	24	0.31	40	109
	1.10	0.07	6.3	0.26	24	0.46	41	112
	1.57	0.09	5.7	0.37	24	0.52	33	108
	1.80	0.10	5.6	0.37	21	0.60	33	111
	2.00	0.12	6.0	0.48	24	0.72	36	108
	2.68	0.15	5.6	0.60	23	0.92	34	110
		Average[b]	5.8 ± 0.4		23 ± 2		37 ± 3	110
6	0.30	0.20	66	0.24	80	0.30	100	146
	0.87	0.52	61	0.62	71	0.85	97	145
	0.91	0.61	67	0.69	76	0.90	99	148
		Average[b]	65 ± 3		76 ± 4		99 ± 1	146

[a] Yields are calculated on the basis of the diazonium salts. [b] The deviations represent the reproducibility of all determinations for each diazonium salt.

TABLE II

SOME OF THE PRODUCTS OBTAINED IN THE THERMAL DECOMPOSITION REACTIONS OF *p*-CARBOXYBENZENEDIAZONIUM SALTS

Diazonium salt	Products with one phenyl group, % 		Polymeric fractions, % P_1[a]	P_2[b]
5	35.0[c]	0.0[c]	24.0	0.0
6	13.2[d]	5.4[d]	38.8	44.0

[a] Relation of phenyl:carboxylic group higher than one and lower than three. [b] Relation of phenyl:carboxylic group higher than three. [c] R = H. [d] R = $-NO_2$.

In nitrogen, TGA[7] showed a slow loss of weight with 60% of original weight remaining even up to 900°. The weight loss (40.0%) could be attributed to (1) residual solvent (not likely considering the drying conditions), (2) fractions of low molecular weight. But, we believe that it is principally caused by elimination of the nitro group (the nitro group represented 37.67% of the polymer weight). Elhers, *et al.*,[8] synthesized polyxylidenes with nitro groups and they observed that after 4 hr at 300° the nitro group was completely removed. Our results agree with this observation. In air, the TGA curve showed an initial break at approximately 300° with recovery at 507° and only 4% of the original weight remaining at 900°. The softening under load curve[9] shows hardly any softening and the penetration above 325° probably can be attributed to loss of material from decomposition. It can be seen that the penetration begins at about the temperature where the rate of weight loss in air begins to increase.

In the ir spectrum, the principal absorption band occurred at 1360 cm^{-1} characteristic of aromatic nitro group. The less intense absorption band at 1220 cm^{-1} can be attributed to 1,2,4-trisubstituted benzene rings.

(7) TGA and softening under load analysis were carried out through the courtesy of Dr. G. F. L. Elhers, Air Force Materials Laboratory, Wright-Patterson Air Force Base.

(8) G. F. L. Elhers and coworkers, personnel communication.

(9) G. F. L. Elhers and W. M. Powers, *Mater. Res. Stand.*, **4**, 298 (1964).

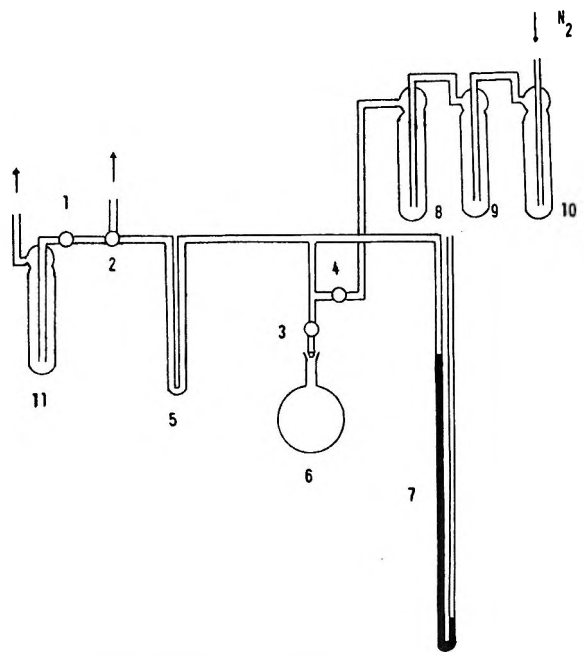


Figure 1.—Scheme of the apparatus used in the study of thermal decomposition reactions of *p*-carboxybenzenediazonium salts: 1, 2, 3, and 4, stopcocks; 5, trap, cooled in liquid air; 6, decomposition flask; 7, manometer; 8, 9, and 10, gas washing bottles; 11, wash bottle containing standard sodium hydroxide solution to trap hydrogen chloride and carbon dioxide.

Additional bands of secondary intensity were situated at 1520 and 1540 cm^{-1}. The absence of fine structure in the spectrum may possibly result from a high degree of orientation involving the polymer chains. A comparison of the spectra of the lower *p*-polyphenyls reveals a decrease in intensity of the fine structure as one moves up the homologous series.[10]

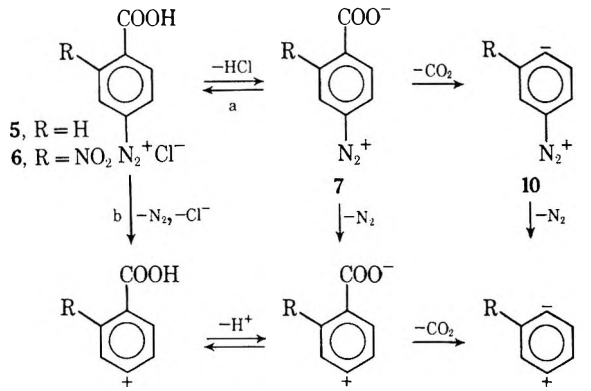
Discussion

The thermal decomposition reactions of the diazonium salts **5** and **6** could take place according to one of the paths written in Scheme I.

Some aromatic carboxylic acids were found to de-

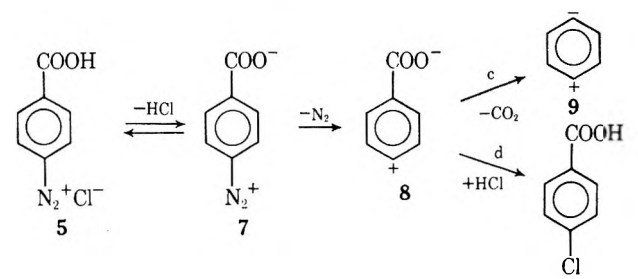
(10) (a) P. Kovacic and A. Kyriakys, *J. Amer. Chem. Soc.*, **85**, 454 (1963); (b) J. Dale, *Acta Chem. Scand.*, **11**, 640 (1957).

SCHEME I



compose as carboxylates by heterolytic paths.[11,12] It is supposed that the thermal decomposition of compounds **5** and **6** could take place through the intermediates **7** and/or **8**. The low proportion of carbon dioxide evolved from the diazonium salt **5** (Table I) can be explained by a competition reaction similar to that proposed for the *ortho* isomer[13] (Scheme II).

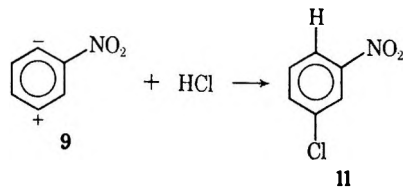
SCHEME II



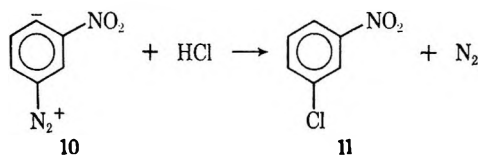
Once the intermediate **8** is formed, the reaction can follow two different ways: path c with carbon dioxide evolution and formation of the dehydro aromatic compound **9**, or path d, the reaction of **8** with hydrogen chloride, or with another nucleophilic reagent present in the reaction mixture. The low proportion of carbon dioxide eliminated (5.8%) compared with the *p*-chlorobenzoic acid formed (35.0%) would indicate the preference of the reaction for path d.

In order to prove the existence of this competitive reaction, the thermal decomposition of the *p*-carboxybenzenediazonium hydrogen sulfate was studied.[14] There was a 7.8% yield of carbon dioxide and a 56.0% yield of nitrogen. The 34% greater yield of carbon dioxide can be attributed to the low nucleophilicity of the hydrogen sulfate anion. Similar results were observed in *o*-carboxybenzenediazonium salts, where more nucleophilic anions lowered the proportion of 1,2-dehydrobenzene.[15]

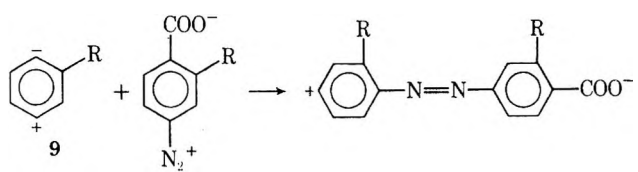
In the thermal decomposition reaction of the diazonium salt **6**, inductive and mesomeric effects of the nitro substituent accelerate the decarboxylation process and increase the proportion of carbon dioxide evolved. Furthermore, the influence of the nitro substituent stabilizing the dehydro aromatic compound acts as driving force in its formation. The higher proportion of **9** and its greater stability made possible the addition of hydrogen chloride, with formation of *m*-chloronitrobenzene (**11**). This compound probably was not formed by decarboxylation of the 4-chloro-2-nitrobenzoic acid, since temperatures greater than 160° are required for decarboxylation of this acid.



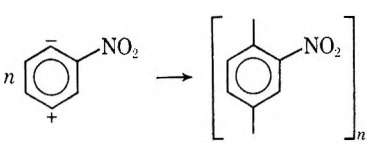
The possibility for the formation of an intermediate **10** and addition of hydrogen chloride to give *m*-chloronitrobenzene (**11**) was excluded after considering the absence of other products from this intermediate **10**.



The fraction P_1 could result from a reaction between a dehydro aromatic compound **9** and a diazonium salt. We could consider other addition reactions of **9** with other molecules present in the system. Reactions of this type between benzenediazonium-*o*-carboxylate salts and 1,2-dehydrobenzene have been published.[16]



The formation of the macromolecules P_2, observed in the thermal decomposition of the diazonium salt **6** and not in **5**, agrees with the following reaction and with the evolved gases (Table I).



The polynitrophenyllic structure was postulated after considering elemental and thermogravimetric analysis of the product. This structure could be taken as a strong evidence of the intermediary 2-nitro-1,4-dehydrobenzene (**9**).

Structure for the Proposed Intermediate 2-Nitro-1,4-dehydrobenzene.—In order to find if **9** was formed as a biradical, the presence of compounds like *o*-chloronitrobenzene (**12**), 2,5-dichloronitrobenzene (**13**), and nitrobenzene (**14**) was investigated by glpc. Those com-

(11) B. R. Brown, *Quart. Rev., Chem. Soc.*, **5** 131 (1951).

(12) A. S. Sultanor, *J. Gen. Chem. USSR*, **16**, 1835 (1946); *Chem. Abstr.*, **41**, 6223*h* (1947).

(13) V. R. Gompper, G. Seybold, and B. Schmolke, *Angew. Chem.*, **80**, 404 (1968).

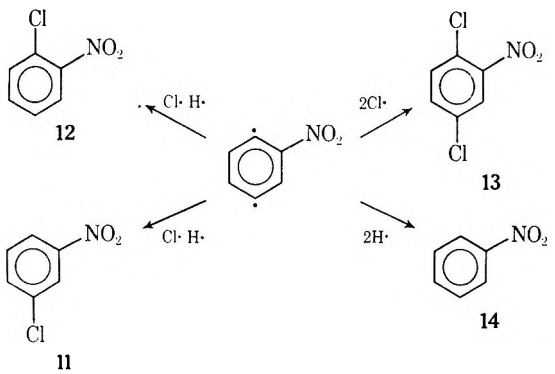
(14) R. H. de Rossi, Ph.D. Thesis, Universidad Nacional de Córdoba, Córdoba, Argentina, 1968.

(15) Reference 4, p 75.

(16) T. Miwa, M. Kato, and T. Tamano, *Tetrahedron Lett.*, No. 23, 2743 (1968).

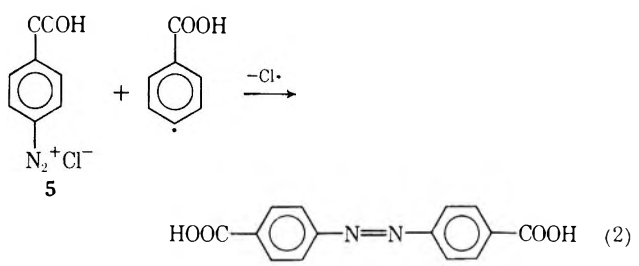
pounds could be formed according to Scheme III, but they were not obtained [excepting *m*-chloronitrobenzene (**11**), as has been explained above].

SCHEME III



An ionic structure for the intermediate 2-nitro-1,4-dehydrobenzene agrees better with the obtained results and with the mechanisms observed in the thermal decompositions of arylcarboxylic acids[11,12] and benzenediazonium salts.[17]

The formation of compounds like 4,4′-dicarboxyazobenzene (31.0%) in the thermal decomposition of compound **5** could take place also through a homolytic mechanism (eq 2). Homolytic and heterolytic processes may be present in the same reaction.[18]



Experimental Section

Reagent grade chemical products were used without further purifications unless so specified. Melting points are uncorrected and they were taked with a Büchi, model by Dr. Tottoli, capillary apparatus. Gas–liquid partition chromatography was carried out with a F & M Model 400 flame ionization instrument using a 4 ft × 0.25 in. 3.8% silicon rubber SE 30 on 80–100 mesh diatoports column (F & M Scientific Corp.) using N_2 as gas carrier. For analytical determinations, correction factors for weight ratio area ratio data were determined with standards. Thin layer chromatography was performed on silica gel G (Merck) plates, and were developed with mixtures of solvents. Ir data were determined from potassium bromide pellets using a Beckman IR 8 spectrophotometer. Uv spectra were determined with a Cary recording spectrophotometer, Model 14. The microanalyses were carried out with an F & M carbon–hydrogen–nitrogen analyzer, Model 185. In all cases, the criteria for the identity of known compounds were based on mixture melting point, uv and ir spectra, and glpc and tlc. Potentiometric titrations were carried out with a Beckman pH meter, Model 72, with combined glass–calomel electrode (Beckman) and silver–calomel electrode. Assessment of error in equivalent weight determinations was obtained by titration of standard solutions of carboxylic acids. The error was found to be ±2.3%.

***p*-Aminobenzoic acid** was the commercially available highest purity reagent (Productos Químicos Purest).

4-Amino-2-nitrobenzoic acid was prepared by selective reduction of 2,4-dinitrobenzoic acid according to Rossi and Bertorello,[19] mp 230–231° (lit.[19] mp 230–231°, 232°[20]), yield 84%.

***m*-Chloronitrobenzene** was prepared from *m*-nitroaniline according to Hartman and Brethen,[21] mp 43.5–44.5° (lit.[21] mp 44–45°), yield 54%.

***p*-Chlorobenzoic acid** was prepared from *p*-aminobenzoic acid by the same procedure used for *m*-chloronitrobenzene, mp 236–237° (lit.[22] 238–239°), yield 79%.

4-Chloro-2-nitrobenzoic acid was prepared from 4-amino-2-nitrobenzoic acid by the same procedure used for the two preceding products, mp 138–139° (lit.[23] 138–140°), yield 70%.

4,4′-Dicarboxyazobenzene.—*p*-Aminobenzoic acid (0.010 mol) was diazotized in the usual form[24] with sodium nitrite (0.829 g, 0.012 mol) and hydrochloric acid (3 ml, *d* 1.19). Besides, we prepared a mixture of copper sulfate (2.85 g) dissolved in 10 ml of water and 20 ml of concentrated ammonium hydroxide (27%) and added to it hydroxylamine sulfate $(H_2NOH)_2 \cdot SO_4H_2$ (8.5 g). To this mixture heated to 60–70° we added the solution of the diazonium salt, then boiled for 30 min, cooled, and acidified with hydrogen chloride. After 10–20 min the brown insoluble product obtained was filtered, washed with water, ethanol, and ether, and dried, yielding 0.20 g (7.4%) of a product with mp 390° dec (lit.[25] 398° dec); uv max (0.010 *N* NaOH) 230 mμ (log ε 4.072), 330 (4.413) [lit.[26] uv max (0.010 *N* NaOH) 225 mμ (log ε 4.075), 331 (4.408)].

4-Carboxybenzenediazonium Chloride.—*p*-Aminobenzoic acid (1.37 g, 0.010 mol) was diazotized in the usual way,[24] dissolved in methanol (2 ml) and HCl (3 ml, *d* 1.19, 0.030 mol), by addition of an aqueous sodium nitrite solution (2.3 ml, 30%), in 20 min. The diazonium salt was precipitated by addition of a mixture of methanol–ether (4:40). The white insoluble product obtained was filtered, washed with absolute ethyl ether, and dried at room temperature. This solid was purified of inorganic salts by dissolving the diazonium salt in absolute methanol and precipitating by adding absolute ethyl ether. The process was repeated until total purification of the product was achieved: yield 1.29 g (70%); uv max (MeOH) 227 mμ (log ε 2.941), 262 (3.940), 317 (2.169). *Anal.* Calcd for $C_7H_5N_2O_2Cl$: Cl, 19.20. Found: Cl, 19.32.

4-Carboxy-3-nitrobenzenediazonium chloride was prepared from 4-amino-2-nitrobenzoic acid by the same procedure as that used for the former diazonium salt: yield 50%; uv max (MeOH) 223 mμ (log ε 3.091), 233 (3.090), 318 (2.711). *Anal.* Calcd for $C_7H_4N_3O_4Cl$: Cl, 15.44. Found: Cl, 15.60.

Thermal Decomposition Reactions.—The apparatus used is illustrated in Figure 1. Once the reactant was placed in flask 6, the system was evacuated until meter 7 reached 0 (30 μ of residual pressure) and then it was slowly heated until the decomposition temperature of the diazonium salt was reached. When the system was back again at room temperature, the pressure increase, produced by release of gases (N_2, CO_2, and HCl), was determined. Carbon dioxide and hydrogen chloride were trapped using liquid air in the trap (5) and nitrogen was eliminated by aspiration. The observed increment in pressure, after removing liquid air from the trap (5) and reading at room temperature, gave the pressure of the mixture carbon dioxide and hydrogen chloride. The difference gave the proportion of nitrogen evolved. The proportion of carbon dioxide and hydrogen chloride was known after introducing nitrogen (free of CO_2) into the system and bubbling the gas mixture through standard sodium hydroxide solution contained in trap 11. Potentiometric titration gave the proportion of carbon dioxide and hydrogen chloride evolved in the decomposition reactions.

Thermal Decomposition Reaction of *p*-Carboxybenzenediazonium Chloride.—In Table I, percentage of gases evolved and decomposition temperatures are specified. The fractions obtained after chromatography on Whatman CF 11 cellulose were the following.

(17) R. L. Damley and M. Eseyian, *J. Polym. Sci.*, **46**, 105 (1960).

(18) (a) E. S. Gould, "Mecanismos y Estructura en Química Orgánica," Kapeluz, Buenos Aires, Argentina, 1967, p 557; (b) K. A. Bilevitch, N. N. Bubnov, and O. Yu Okhlobystin, *Tetrahedron Lett.*, No. 31, 3465 (1968).

(19) R. A. Rossi and H. E. Bertorello, *An. Asoc. Quím. Argent.*, **55**, 227 (1967).

(20) J. Wheeler, *Beilstein*, XIV, 583.

(21) W. W. Hartman and M. R. Brethen, "Organic Syntheses," Coll. Vol. I, Wiley, New York, N. Y., 1963, p 162.

(22) A. I. Vogel, "A Textbook of Practical Organic Chemistry," Longmans, London, 3rd ed, 1959, p 760.

(23) N. J. Leonard and S. N. Boyd, Jr., *J. Org. Chem.*, **11**, 405 (1946).

(24) Reference 22, p 597.

(25) E. B. Reid and E. G. Pritchett, *J. Org. Chem.*, **18**, 715 (1953).

Fraction 1 consisted of 0.416 g (35.0% yield) of a product identified as *p*-chlorobenzoic acid. It was eluted by petroleum–ether:benzene (20:80). Ir spectra and melting point are identical with those of a pure sample of *p*-chlorobenzoic acid; mixture melting point was also identical with that of an authentic sample.

Fraction 2 was eluted with chloroform–ethyl ether (50:50). Uv spectra and melting point were identical with those of a pure sample of 4,4′-dicarboxyazobenzene. The equivalent weight was found to be 138 (calcd for $C_{14}H_{10}N_2O_4$: 135). The yield was 0.360 g (31.0%).

Fraction 3 consisted of 0.220 g (19.0% yield). This fraction was obtained using acetone–ethyl ether (70:30) as eluent and was a mixture of various substances according to analysis by tlc. The average equivalent weight for this fraction was 151.

Fraction 4 consisted of 0.058 g (5.0% yield). This fraction eluted with ethanol and was a dark-brown powder, infusible up to temperatures of 500°. The equivalent weight was 171. *Anal.* Found: C, 58.2; N, 8.0; H, 4.7.

Thermal Decomposition Reaction of 4-Carboxy-3-nitrobenzenediazonium Chloride.—The reaction was carried out in the way indicated above. The evolved gases in the different experiments are specified in Table I. The residue, a mixture of products, was resolved by extraction with fractions of 20 ml of boiling solvents until the evaporate did not leave residue. The solvents were petroleum ether (bp 60–80°), carbon tetrachloride, benzene, chloroform, ethyl ether, acetone, ethanol, methanol, and water. The residue (1 g) gave the following fractions.

Fraction 1 consisted of 0.054 g (5.4% yield). This fraction was extracted with petroleum ether. It was *m*-chloronitrobenzene identified by comparison with a pure sample by the following tests: tlc, eluent (R_f), acetone (0.94), ethanol (0.87), ethanol–water (9:1) (R_f 0.80); (b) glpc (115°, retention time 3.25 min); (c) identical ir spectra were observed for both products.

Fraction 2 consisted of 0.132 g (13.2% yield) of 4-chloro-2-nitrobenzoic acid. It was removed by benzene. Ir, melting point, and mixture melting point are all identical with the synthetic sample data.

Fraction 3 was obtained from acetone. Tlc showed a mixture of substances with an average equivalent weight of 286. The yield was 0.388 g (38.8%).

Fraction 4 consisted of 0.440 g (44.0% yield). This fraction was an insoluble black product. Washed with fractions of 100 ml of boiling solvents, the resulting solutions did not leave residue after evaporation. The solvents used were petroleum ether (bp 60–80°), cyclohexane, carbon tetrachloride, benzene, chloroform, ether, ethyl acetate, pyridine, acetone, ethanol, methanol, water, DMS, and DMF. Cold sulfuric acid does not change the product after 30 min of contact. The substance was infusible up to temperatures of 500°. *Anal.* Calcd for ($-C_6H_4NO_2-$): C, 59.02; N, 11.47; H, 3.30. Found: C, 59.0; N, 12.0; H, 2.4.

Registry No.—**5**, 17405-00-4; **6**, 25859-42-1.

Acknowledgment.—This research was supported by Grant AFOSR-68-1425 from Air Force Office of Scientific Research, Office of Aerospace Research, U. S. Air Force.

Thermal Decomposition Reactions of Carboxybenzenediazonium Salts. II. 1,3-Dehydro Aromatic Compounds from *m*-Carboxybenzenediazonium Salts[1]

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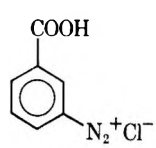
We studied the thermal decomposition reaction of 3-carboxybenzenediazonium chloride (**5**), 3-carboxy-5-nitrobenzenediazonium chloride (**6**), and 3-carboxy-4-nitrobenzenediazonium chloride (**7**). Each of the three decomposes with evolution of carbon dioxide, nitrogen, and hydrogen chloride (Table I), and a solid mixture of products is obtained. They were identified and determined for each experiment and resolved into substances with one phenyl ring and into polymeric products (Table II). The formation of the different products is in agreement with the intermediacy of 1,3-dehydro aromatic compounds. The results are compared with those of the *p*-carboxybenzenediazonium salt and an asynchronic mechanism is proposed with elimination of nitrogen prior to elimination of carbon dioxide. The influence of nitro group and positive charge in the carbon dioxide elimination is discussed, and it was found that the log yield (%) of CO_2 is in straight relation with $\Sigma\sigma$ of substituents.

Berry, Clardy, and Schafer[3] studied the flash-initiated decomposition of the benzenediazonium-3-carboxylate salt and they reported the evidence for a transient $-C_6H_4-$ species which appears to be 1,3-dehydrobenzene. They identified this substance principally by its mass spectrum, and they inferred that the most likely structures for those species are **1** or **2**.

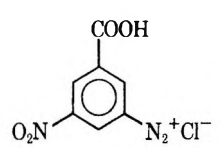
1

2

The thermal decomposition of *p*-carboxybenzenediazonium chloride (**3**) and 4-carboxy-3-nitrobenzenediazonium chloride (**4**)[1] lead to intermediates similar to that found in the photoinitiated decomposition of the benzenediazonium-*p*-carboxylate salt.[4] We now studied the thermal decomposition of *m*-carboxybenzenediazonium chloride (**5**), 3-carboxy-5-nitrobenzenediazonium chloride (**6**), and 3-carboxy-4-nitrobenzenediazonium chloride (**7**) in order to learn about the intermediacy of 1,3-dehydro aromatic compounds.



5



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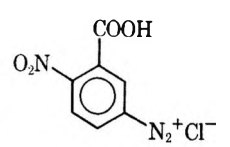


7

Results and Discussion

The thermal decomposition, *in vacuo*, of the solid diazonium salts **5**, **6**, and **7** was explosive with gas evolution (Table I). The solid products obtained were separated and studied by different methods, and they were classified in each reaction as (a) compounds with

(1) Part I: R. H. de Rossi, H. E. Bertorello, and R. A. Rossi, *J. Org. Chem.*, **35**, 3328 (1970).

(2) Fellow of the Consejo Nacional de Investigaciones Científicas y Técnicas, Buenos Aires, Argentina, 1966–1969.

(3) R. S. Berry, J. Clardy, and M. E. Schafer, *Tetrahedron Lett.*, No. 15, 1011 (1965).

(4) R. S. Berry, J. Clardy, and M. E. Schafer, *ibid.*, No. 15, 1003 (1965).

TABLE I

GASES EVOLVED IN THE THERMAL DECOMPOSITION REACTIONS OF *m*-CARBOXYBENZENEDIAZONIUM SALTS

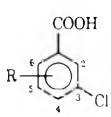
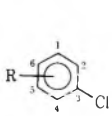
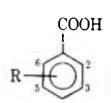
Diazonium salts Compd no.	mmol	CO_2, mmol	Yield of CO_2, %[a]	HCl, mmol	Yield of HCl, %[a]	N_2, mmol	Yield of N_2, %[a]	Temp, °C
5	0.457	0.054	11.8	0.177	38.7	0.386	84.5	96
	0.550	0.096	17.4	0.192	34.9	0.443	80.6	94
	0.742	0.141	19.0	0.251	33.8	0.665	89.6	95
	0.872	0.165	18.9	0.287	32.9	0.771	88.4	98
	0.891	0.169	19.0	0.338	37.9	0.776	87.1	93
	1.34	0.179	13.4	0.487	36.3	1.20	89.5	98
	1.50	0.251	16.7	0.554	36.9	1.28	85.3	99
	1.54	0.226	14.7	0.517	33.6	1.34	87.0	96
	1.68	0.313	18.6	0.633	37.7	1.46	86.9	97
	1.90	0.236	12.4	0.622	32.7	1.53	80.5	95
	2.22	0.295	13.3	0.752	33.9	1.80	81.1	95
		Average[b]	15.9 ± 2.7		35.4 ± 2.1		85.5 ± 3.3	96
6	0.239	0.091	38.1	0.070	29.3	0.201	84.1	105
	0.418	0.169	40.4	0.120	28.7	0.338	80.9	110
	0.584	0.242	41.4	0.167	28.6	0.457	78.3	107
	0.696	0.266	38.2	0.199	28.6	0.540	77.6	108
	0.804	0.315	39.2	0.265	33.0	0.635	79.0	110
	0.871	0.378	43.4	0.305	35.0	0.702	80.6	106
	1.00	0.413	41.3	0.323	32.3	0.794	79.4	108
	1.13	0.466	41.2	0.441	39.0	0.878	77.7	110
	1.19	0.496	41.7	0.457	38.4	0.953	80.1	108
	1.35	0.616	45.6	0.467	34.6	1.06	78.5	107
		Average[b]	41.1 ± 2.2		32.8 ± 3.8		79.6 ± 1.8	108
7	0.409	0.361	88.3	0.222	54.3	0.391	95.6	118
	0.519	0.455	87.7	0.270	52.0	0.509	98.1	114
	0.647	0.543	83.9	0.329	50.8	0.598	92.4	120
	0.876	0.733	83.7	0.422	48.2	0.857	97.8	119
	1.63	1.36	83.5	0.839	51.4	1.65	100.8	113
	1.81	1.59	88.0	0.940	52.0	1.83	101.0	116
	2.09	1.77	84.4	1.12	53.3	2.01	95.9	112
		Average[b]	85.6 ± 2.1		51.7 ± 1.8		97.4 ± 2.8	116

[a] Yields are calculated on the basis of the diazonium salts. [b] The deviations represent the reproducibility of all determinations for each diazonium salt.

one phenyl ring, and (b) compounds with more than one phenyl ring: P_1 compounds with a ratio of phenyl/carboxylic group higher than 1 and lower than 3, P_2 compounds with a ratio of phenyl/carboxylic group higher than 3 (Table II).

TABLE II

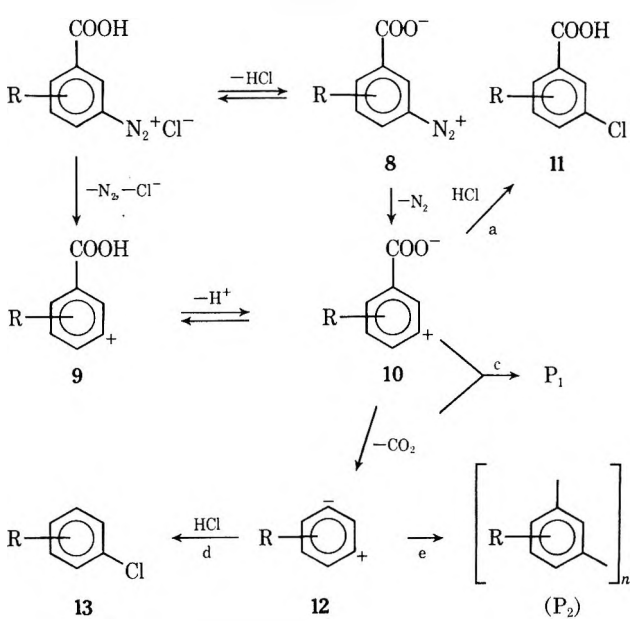
SOME OF THE PRODUCTS OBTAINED IN THE THERMAL DECOMPOSITION REACTIONS OF *m*-CARBOXYBENZENEDIAZONIUM SALTS

Diazonium salt	—Products with one phenyl ring,[a] %—			Polymeric —fractions, %—	
				P_1[b]	P_2[c]
5	36.3[d]	0.22[d]	0.33[d]	60.7	0.0
6	27.9[e]	1.7[e]	2.0[e]	62.1	4.9
7	1.7[f]	0.55[f]	1.15[f]	36.5	55.9

[a] Analytical determination was carried out by glpc of methyl esters. [b] Ratio of phenyl/carboxylic group higher than 1 and lower than 3. [c] Ratio of phenyl/carboxylic group higher than 3. [d] R = H. [e] R = 5-NO_2. [f] R = 6-NO_2.

The solid products obtained from the thermal decomposition reaction of **5**, **6**, and **7** (Table II) and the study of gases evolved (Table I) allow the writing of a general scheme (Scheme I) that is comparable with those proposed for the thermal decomposition of the benzenediazonium-2-carboxylate salt[5] and *p*-carboxybenzenediazonium salts.[1]

SCHEME I



R = H (**5**) ; R = 5-NO_2 (**6**); R = 6-NO_2 (**7**)

After formation of the ion **10**, the reaction could follow path b, with loss of carbon dioxide and an inter-

(5) (a) R. W. Hoffmann, "Dehydrobenzene and Cycloalkynes," Academic Press, New York, N. Y., 1967, p 75; (b) V. R. Gompper, G. Seybold, and B. Schmolke, *Angew. Chem.*, **80**, 404 (1968).

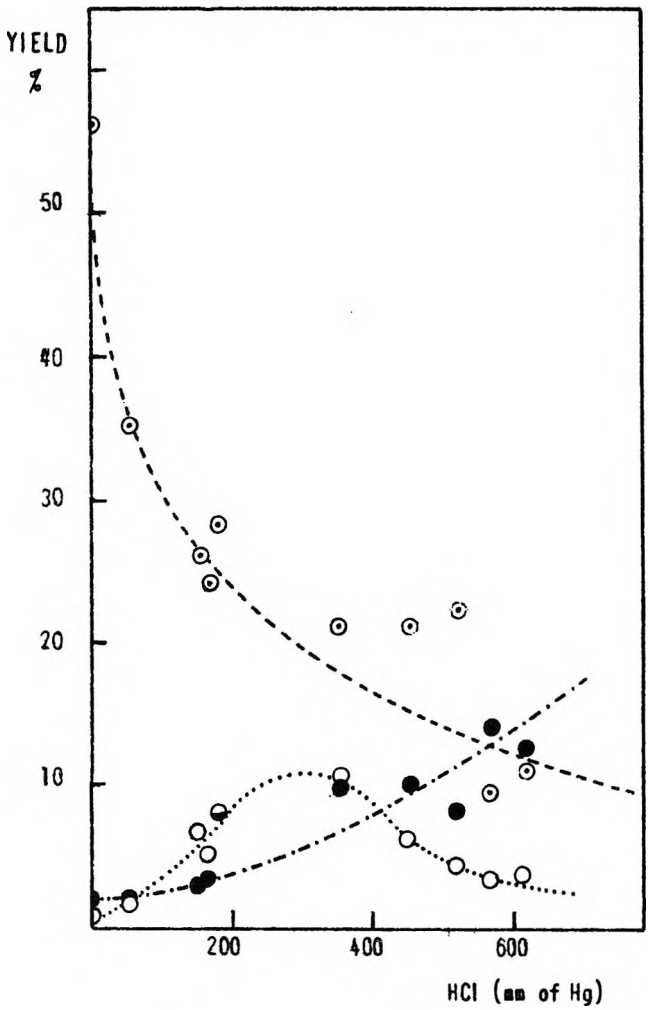


Figure 1.—Plot of percentage of P_2, **11**, and **13** against added HCl (mm): ⊙- - -, P_2; ●-·-·, **11**; and ○· · · ·, **13**.

mediate 1,3-dehydro aromatic compound, or a path a, the reaction of **10** with hydrogen chloride or with other nucleophilic reagents present in the medium. In order to confirm the existence of this competitive reaction (paths a and b), the thermal decomposition reaction of **7** was studied under different pressures of hydrogen chloride. We have determined **13** and P_2 from path b, and **11** from path a (Table III). The intermediate **12** in competitive reactions could follow path d with addition of hydrogen chloride and formation of **13**, or path e, autocondensation reactions leading to P_2.

When the pressure of hydrogen chloride was increased, path a was followed principally as could be inferred from the increment of product **11**. Since product **13** also increased when reactions were carried out under pressures of hydrogen chloride lower than 358 mm, and decreased using higher pressures of hydrogen chloride, it agrees with the postulated reactions of Scheme I, because the *p*-chloronitrobenzene (**13**) formed depends on hydrogen chloride as much as the intermediate **12** (eq 1).

$$d(\mathbf{13})/dt = k_d(HCl)(\mathbf{12}) \quad (1)$$

Moreover, the diminution of P_2 and the increment of **11** proportionally with the added hydrogen chloride (Figure 1) account for the existence of competitive reactions such as that quoted above (Scheme I).

TABLE III

PRODUCTS OBTAINED IN THE THERMAL DECOMPOSITION REACTION OF THE DIAZONIUM SALT **7** IN THE PRESENCE OF HYDROGEN CHLORIDE

HCl, mm	Yield of **11**, %[a,b]	Yield of **13**, %[a,c]	Yield of P_2, %[a,d]	Ratio **11**/**13**	Temp, °C
0	1.8	0.60	57	3.0	114
0	1.5	0.50	55	3.1	118
58	2.1	1.5	35	1.4	114
160	2.6	6.5	26	0.4	118
173	3.2	5.0	24	0.6	123
183	8.0	8.0	28	1.0	126
358	9.6	10.4	21	0.9	138
458	10.0	6.0	21	1.6	130
528	8.1	4.5	22	1.8	129
579	14.0	3.2	9.4	4.3	130
618	12.5	3.6	11	3.5	135

[a] Yields are calculated on the basis of the diazonium salts. [b] Analytical determination was carried out by glpc of methyl ester. [c] Analytical determination was carried out by glpc. [d] Insoluble in all common solvents.

The comparison of products obtained in the decomposition reaction of diazonium salts **3**–**7** is also in accord with the results shown above. Therefore it has been found that the products in the formation of compounds like **11**, formed by addition of hydrogen chloride in the initially formed carbonium ion **10**,[6] are in reverse proportion to the carbon dioxide evolved (Table IV, Figure 2).

TABLE IV

THERMAL DECOMPOSITION OF CARBOXYBENZENEDIAZONIUM SALTS. PRODUCTS OBTAINED

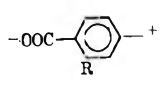
Diazonium salt	Yield of CO_2, %[a]	Yield of **13**, %[a]	Yield of **11**, %[a]	Yield of P_1, %[a,b]	Yield of P_2, %[a,c]	S[d]
3[e]	5.8	0.0	35.0	24.0	0.0	12.0
4[e]	65	5.4	13.2	38.8	44.0	67.8
5	15.9	0.22	36.3	60.7	0.0	30.5
6	41.1	1.7	27.9	62.1	4.9	37.7
7	85.6	0.55	1.7	36.5	55.9	74.8

[a] Yields are calculated on the basis of the diazonium salts. [b] Ratio of phenyl/carboxylic group higher than 1 and lower than 3. [c] Ratio of phenyl/carboxylic group higher than 3. [d] $S = (P_1)/2 + (P_2) + (\mathbf{13})$. [e] See ref 1.

Once the intermediacy of dehydro aromatic compounds **12** is accepted, three types of reaction can follow.

(1) The first is path c, reaction with a molecule of diazonium salt, or with any molecule of its partial decomposition, leading to products with an equivalent weight which agrees with a ratio of phenyl/carboxylic group higher than 1 and lower than 3. To the formation of this product that we named P_1, the intermediate **12** contributes almost 50% by weight. In this group of compounds we found 3-carboxy-3′-chloroazobenzene (**14**) (7.5% yield) in the decomposition reaction of *m*-carboxybenzenediazonium chloride (**5**), and it could be

(6) **10** is the compound



in the preceding paper; see ref 1.

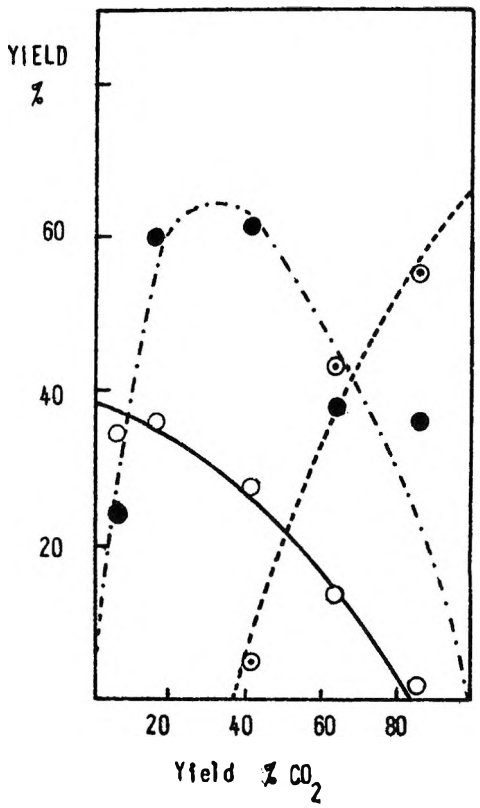
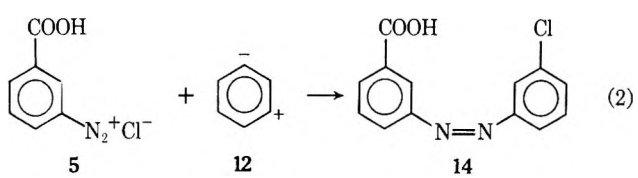


Figure 2.—Plot of percentage of P_1, P_2, and **11** against % carbon dioxide evolved in the thermal decomposition of *p*- and *m*-carboxybenzenediazonium salts: ●-·-·, P_1; ⊙---, P_2; and O—, **11**.

formed by eq 2. This type of reaction resembles one between the benzenediazonium-*o*-carboxylate salt and 1,2-dehydrobenzene.[7]



(2) Path e is autocondensation reaction between dehydro aromatic intermediates, leading to polynitrophenyllic macromolecules, with a ratio of phenyl/carboxylic group higher than 3 (P_2). The amount of P_2 obtained from diazonium salts **3**–**7** is directly proportional to the carbon dioxide evolved (Figure 2).

(3) Path d is reaction with hydrogen chloride, leading to product **13**.

Then, if the mechanism presented in Scheme I is correct, the sum of all products proceeding from dehydro aromatic intermediates [$(P_1)/2 + (P_2) + (13) = S$] must be directly proportional to the evolved carbon dioxide. Experimental results show a linearity of S (Table IV) with the carbon dioxide evolved (Figure 3).

All these relations allow us to infer that 1,4- and 1,3-dehydro aromatic intermediates are formed by an asynchronic elimination mechanism, and that the nitrogen is eliminated prior to carbon dioxide. However, the existence of other two elimination mechanisms is possible. Those are (a) synchronic elimination, and (b) asynchronic elimination with carbon dioxide eliminated prior to nitrogen (Scheme II). It has not been

(7) T. Miwa, M. Kato, and T. Tamano, *Tetrahedron Lett.*, **23**, 2743 (1968).

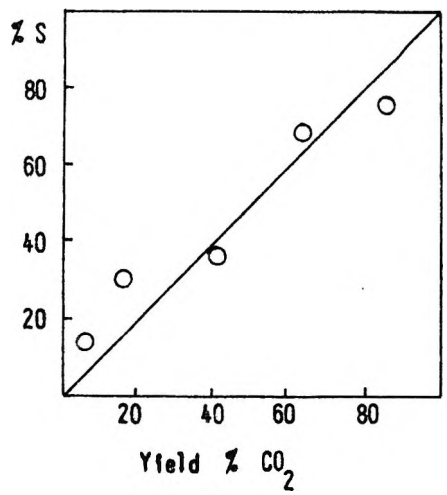
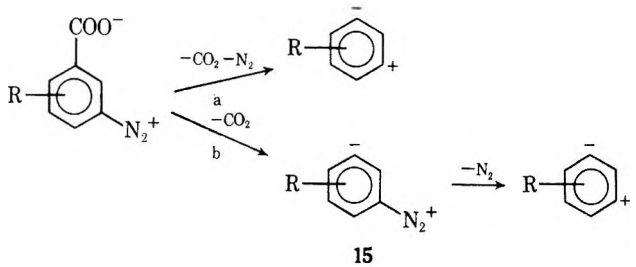


Figure 3.—Plot of $S = (P_1)/2 + (P_2) + (11)$ against % carbon dioxide evolved in the thermal decomposition reaction of *p*- and *m*-carboxybenzenediazonium salts: —, theoretical curve; O, experimental points.

SCHEME II



possible to isolate products that could be formed from a intermediary such as **15**, and the elimination of nitrogen turns out to be independent from the diazonium salt used; furthermore, no relation was found with the obtained products.

Influence of Substituent.—The nitro group, by inductive and mesomeric effects, labilizes the bond between the ring and the carboxylate group, decreasing the bond energy. This effect would be expected to be more important for the diazonium salt **7** where the nitro group is *ortho* to the carboxylate group. Furthermore, the nitro group would act as driving force in the formation of **12**, stabilizing the intermediate. The obtained results agree with this. The evolved nitrogen for the three diazonium salts with values of 85.4 (**5**), 79.6 (**6**), and 97.4% (**7**) is similar; nevertheless, the evolved carbon dioxide for **7** (85.6%) is appreciably higher than the value observed for **6** (41.1%) and **5** (15.9%).

Sultanov[8] studied the thermal decomposition of *o*-, *m*-, and *p*-nitrobenzoic acids and determined that the decarboxylation, which is preceded by ionic dissociation, depends on the effect of the substituent group; *o*-nitrobenzoic acid needed 4 hr at 180° to loose 90% carbon dioxide. Similarly, the *meta* isomer gave 92% nitrobenzene at 238° and the *para* isomer 62% nitrobenzene at 240°. The thermal decomposition reactions carried out by us using solid benzenediazonium salts happened explosively and at lower temperatures. Evidently, there must be another fact accelerating the reaction, and this could be attributed to the intermediacy of

(8) A. S. Sultanov, *J. Gen. Chem.* USSR, **16**, 1835 (1946), *Chem. Abstr.*, **41**, 6223*h* (1947).

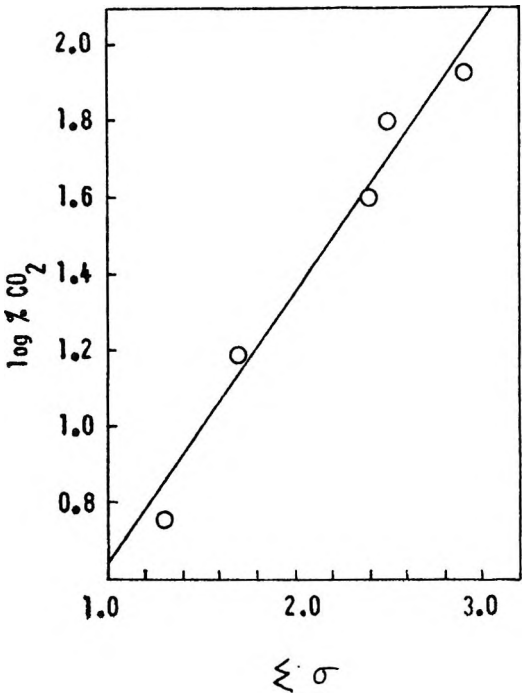
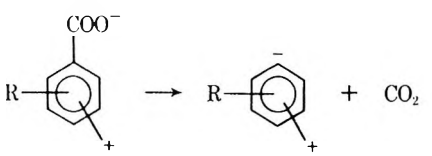


Figure 4.—Plot of log (% CO_2) obtained in the thermal decomposition reactions of *p*- and *m*-carboxybenzenediazonium salts against $\Sigma\sigma$ of substituents (nitro group and positive charge).

a carbonium ion **10**, affecting the process of decarboxylation (eq 3).



(3)

10 **12**

10a, R = H; position 4
b, R = H; position 5
c, R = 3-NO_2; position 5
d, R = 2-NO_2; position 4
e, R = 2-NO_2; position 5

The rate of elimination of carbon dioxide, in the carbonium ion **10**, is proportional to the quantity of the carbon dioxide evolved and depends principally on the ability of **10** to lose carbon dioxide. This could be measured using a similar equation to that proposed by Hammett (eq 4).[9]

$$\log (\%\ CO_2) = \rho\Sigma\sigma \qquad (4)$$

The elimination of carbon dioxide in the intermediate **10** would be affected by the group R and the positive charge. The value $\Sigma\sigma$ is then the sum of the both substituents,[10] considering the positive charge as a substituent different from hydrogen.

The nitro group has the following values: $\sigma_{o\text{-}NO_2} = 1.22$[11] and $\sigma_{m\text{-}NO_2} = 0.71$.[9] The values for the positive charge, in the *meta* or *para* position, were calculated by successive approximations and according to Jaffé, who proposed the redefining of the substituent constant ideally "as the value of σ which best fits the entire body of experimental data."[10] The obtained values were $\sigma_{+m} = 1.69$ and $\sigma_{+p} = 1.29$, for the positive charge situated on the positions *meta* and *para*. Comparing those values with one of the major known values, $\sigma_{m\text{-}N_2^+} = 1.7$ and $\sigma_{p\text{-}N_2^+} = 1.8$.[12] We can appreciate the importance of the carbonium ion in the decarboxylation reaction. A plot of log (% CO_2) against $\Sigma\sigma$ (Table V) gives us a straight line coinciding with the Hammett equation (Figure 4).

TABLE V
INFLUENCE OF SUBSTITUENTS IN THERMAL DECOMPOSITION REACTIONS OF *m*- AND *p*-CARBOXYBENZENEDIAZONIUM COMPOUNDS

Diazonium salt	Yield of CO_2, %[a]	Log (% CO_2)	$\Sigma\sigma$
3[b]	5.8	0.7634	1.29
4[b]	65	1.8129	2.51
5	15.9	1.2014	1.69
6	41.1	1.6138	2.40
7	85.6	1.9324	2.91

[a] Yields are calculated on the basis of the diazonium salts. [b] See ref 1

The results obtained in the present study add weight to the mechanism proposed for the decomposition reactions of *m*- and *p*-carboxybenzenediazonium salts. The fit of the experimental data to a Hammett linear free-energy relation suggests that electron distribution in the benzene ring largely determines the relative stabilities and reactivities of the compounds studied. The positive value of the reaction constant (+0.672 ± 0.045) further permits the conclusion that the aromatic group is formed as a carbanion when carbon dioxide is eliminated because electron-attracting substituents facilitate the formation of an anion. The formation of the carbanion portion of the dehydrobenzene intermediate happens after loss of nitrogen, which agrees with the mechanism proposed for the thermal decomposition reactions of *m*- and *p*-carboxybenzenediazonium salts.

Experimental Section

All melting points were obtained on a Büchi melting point apparatus, model by Dr. Tottoli, and are uncorrected. Gas chromatographic analysis were performed on a F & M Model 776 or 400 flame ionization instruments. The following columns were used: column A, a 4 ft × 0.25 in. stainless steel column 20% UC-W 98 (60–80 mesh) (F & M Scientific Corp.), and column B, a 4 ft × 0.25 in. aluminum column packed with 3% silicon rubber SE 30 on firebrick (60–80 mesh). For analytical determinations correction factors for weight ratio/area ratio data were determinated with standards containing the same compounds as were in the known mixture. Carboxylic acids were treated with diazomethane and the obtained esters were analyzed by glpc. The microanalyses were carried out with a F & M carbon–hydrogen–nitrogen analyzer, Model 185. Ir spectra were determined in potassium bromide pellets using a Beckman IR-8 spectrophotometer. Uv spectra were determined with a Cary recording spectrophotometer, Model 14. Mass spectral analyses were performed on an AEI-MS 902 spectrophotometer, at The Ohio State University. Tlc plates were prepared from silica gel G (Merck). Potentiometric titrations were carried out with a Beckman pH meter, Model 72, using a combined glass–calomel electrode (Beckman) and a combined silver–calomel electrode. The assessment of error in equivalent weight determinations was ob-

(9) (a) L. P. Hammett, *Chem. Rev.*, **17**, 125 (1935). (b) For equations similar to Hammett, see W. E. McEwen and N. B. Mehta, *J. Amer. Chem. Soc.*, **74**, 526 (1952).

(10) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

(11) R. W. Taft, Jr., "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, 1956, p 619.

(12) E. S. Lewis and M. D. Johnson, *J. Amer. Chem. Soc.*, **81**, 2070 (1959).

TABLE VI
RETENTION TIME AND MELTING POINT DATA

Compd	Retention time, sec[a] Column A[b] 105°	130°	145°	200°[c]	Column B,[c] 130°	Melting points, °C Found	Lit.[d]
Chlorobenzene	46						
Benzoic acid[e]	192	71	50	21	20	121–122	122
m-Chloronitrobenzene		136	92	36		44–45	46
p-Chloronitrobenzene		149	100	44		80–82	83
m-Chlorobenzoic acid[e]	525	163	121	61	51	158–158.5	158
o-Nitrobenzoic acid[e]		341	213		78	147–148	146–148
m-Nitrobenzoic acid[e]			271	85	140	140–141	140–141
5-Chloro-2-nitrobenzoic acid[e]		674	365		146	135–136	139
5-Chloro-3-nitrobenzoic acid[e]		805	429	124	220	147–148	147

[a] Retention times are given in seconds, using nitrogen as carrier gas (75 ml/min). [b] Stainless steel column 20% UC-W 98. [c] 3% silicon rubber SE 30. [d] Melting points were taken from the "Dictionary of Organic Compounds," I. Heilbron and H. M. Bunbury, Ed., Oxford University Press, New York, N. Y., 1953, and ref 13. [e] Glpc of methyl ester.

tained by titration of standard solutions of carboxylic acids. The error was found to be ±2.3%. The criteria for the identity of known compounds were established by mixture melting point, ir, glpc, and tlc.

Materials.—Reagent grade chemical products were used without further purifications unless so specified: *m*-aminobenzoic acid (Fluka), 3,5-dinitrobenzoic acid (Aldrich Chemical Co.), *o*-nitrobenzoic acid (BDH), *m*-nitrobenzoic acid (BDH), benzoic acid (Productos Químicos Purest), nitrobenzene (Carlo Erba), and chlorobenzene (Carlo Erba). *m*-Chlorobenzoic acid, *m*-chloronitrobenzene, *p*-chloronitrobenzene, and 3-chloro-5-nitrobenzoic acid were obtained from suitables amines by the Sandmeyer reaction,[13] and their purity was determined by melting point, ir, and glpc.

5-Amino-2-nitrobenzoic acid (Aldrich Chemical Co.) was recrystallized from acetic acid, mp 232° dec (lit.[14] 235° dec).

5-Amino-3-nitrobenzoic acid was prepared by selective reduction of 3,5-dinitrobenzoic acid with sodium polysulfide in the same form as was reported for 2,4-dinitrobenzoic acid:[15] yield 74%; mp 206–208° (lit.[16] 208°); equiv wt 184.5 (calcd for $C_7H_6N_2O_4$: 182.1).

3-Carboxybenzenediazonium Chloride.—*m*-Aminobenzoic acid (4.11 g, 0.030 mol) was dissolved in 23 ml of methanol and saturated with dry HCl. To the cooled solution (−5°) was added 6.45 ml of fresh distilled amyl nitrite, with stirring for 40 min. Addition of ether caused precipitation of the diazonium salt, which was purified by dissolution in methanol and precipitation with ether. This procedure was repeated until total purification of the diazonium salt resulted: yield 62%; tlc (water as eluent) R_f 0.68 (the spot was detected with a spray containing 5% N-(1-naphthyl)ethylenediamine dihydrochloride); ir (KBr) 2227 cm^{-1} ($-N_2^+$); 1724 (−C=O); uv max (MeOH) 237.5 mμ (log ε 3.759), 257 (3.663), 296 (3.000). *Anal.* Calcd for $C_7H_5N_2O_2Cl$: Cl, 19.20. Found: Cl, 18.82.

3-Carboxy-4-nitrobenzenediazonium Chloride.—5-Amino-2-nitrobenzoic acid was diazotized in the same way as was described for the preceding diazonium salt: yield 71%; tlc (water as eluent) R_f 0.47 (the spot was detected with a spray containing 5% N-(1-naphthyl)ethylenediamine dihydrochloride); ir (KBr) 2272 cm^{-1} ($-N_2^+$), 1724 (−C=O), 1557, and 1370 ($-NO_2$); uv max (MeOH) 242 mμ (log ε 4.941), 312 (4.983). *Anal.* Calcd for $C_7H_4N_3O_4Cl$: Cl, 15.44. Found: Cl, 15.80.

3-Carboxy-5-nitrobenzenediazonium Chloride. 5-Amino-3-nitrobenzoic acid was diazotized in a similar way to that described for the preceding diazonium salts: yield 51%; tlc (water as eluent) R_f 0.15 (the spot was detected with a spray containing 5% N-(1-naphthyl)ethylenediamine dihydrochloride; ir (KBr) 2227 cm^{-1} ($-N_2^+$); 1725 (−C=O), 1550 and 1350 ($-NO_2$); uv max (MeOH) 223 mμ (log ε 4.299), 302 (3.130). *Anal.* Calcd for $C_7H_4N_3O_4Cl$: Cl, 15.44. Found: Cl, 15.59.

Thermal Decomposition Reactions.—The thermal decomposition reactions of the diazonium salts **5**, **6**, and **7** were carried out in the previously described apparatus,[1] where the evolved gases were trapped and measured (Table I).

(1) **3-Carboxybenzenediazonium chloride** (**5**) exploded at 96°. The residue was a brown powder; 2.50 g of this powder was chromatographed on 200 g of cellulose, Whatman CF 11, and afforded the following products in order of elution.

Fraction a was a mixture of chlorobenzene (0.022%), *m*-chlorobenzoic acid (36.3%), benzoic acid (0.33%), and 3-carboxy-3′-chloroazobenzene (7.5%). This mixture was dissolved in 20 ml of benzene; 1 ml of this solution was treated with diazomethane (prepared from N-nitroso-N-methylurethan and alcoholic potassium hydroxide[17]), resolved, and identified by glpc (Table VI). The chromatographic behavior of all substances was identical with that of synthetic sample (except for 3-carboxy-3′-chloroazobenzene). The remaining 19 ml of benzene solution was extracted with three 10-ml portions of NaOH (10%). From the combined aqueous extracts, carboxylic acids were precipitated by concentrated HCl, filtered, and dried to give 1.10 g. The solid was sublimed at 80° (400 μ) to give 0.90 g of *m*-chlorobenzoic acid, whose melting point, mixture melting point, ir, and tlc behavior (R_f 0.67 with benzene–methanol–AcOH 49:8:4 as mixture eluent) are all identical with that of an authentic sample. 3-Carboxy-3′-chloroazobenzene was the remainder of the sublimation. An analytical sample, mp 181–182°, was prepared by repeated recrystallization from petroleum ether–benzene (60:40): tlc (benzene–methanol–AcOH 48:8:4) R_f 0.79; equiv wt, 259 (calcd 260.7); ir (KBr) 1680 (−C=O), 1580 (−N=N−), 730 (−C−Cl) cm^{-1}; mass spectrum (70 eV) *m/e* (rel intensity) 260 (4), 139 (100), 111 (34), 75 (15). *Anal.* Calcd for $C_{13}H_9N_2O_2Cl$: C, 59.89; N, 10.74; H, 3.47. Found C, 59.77; N, 10.58; H, 3.49.

Fraction b was obtained from chloroform as eluent. It was a complex mixture of unidentified substances, totaling 31.4%: average equiv wt 215; ir (KBr) 1700 (−C=O), 750 cm^{-1} (1,3 disubstituted).

Fraction c was obtained from ether–acetone (9:1). It was a complex mixture of substances totaling 7.1% whose ir was identical with that of fraction b: average equiv wt 238.

Fraction d was obtained from acetone as eluent: yield 10.3%; equiv wt 240; ir spectra identical with that of the former fractions.

Fraction e was obtained from NH_4OH–water (4:6). The solid was precipitated by concentrated HCl affording 0.11 g (4.4% yield): average equiv wt 240; the ir spectrum of this substance does not show fine structure and only one band at 1700 cm^{-1} (−C=O) is well defined.

Fractions b to e and 3-carboxy-3′-chloroazobenzene have been denoted P_I (see text).

(2) **3-Carboxy-5-nitrobenzenediazonium chloride** (**6**) exploded at 108° with light emission. The dark residue was extracted successively with 20 ml of the following boiling solvents: petroleum ether (bp 60–80°), benzene, chloroform, ether, acetone, ethanol, methanol, and water. Extractions were carried out until no more residue was obtained by elimination of the solvent. The following fractions were collected.

(a) This fraction was extracted with benzene, and the products were determined and identified by glpc (Table VI). The retention times were identical with those of authentic samples.

(13) (a) M. S. Newman and N. S. Fones, *J. Amer. Chem. Soc.*, **69**, 1221 (1947); (b) W. W. Hartman and M. R. Brethen, "Organic Synthesis," Coll. Vol. I, Wiley, New York, N. Y., 1963, p 162; (c) A. I. Vogel, "A Text book of Practical Organic Chemistry," 3rd ed, Longmans, London, 1959, p 760.

(14) L. Kalk and O. Gross, *Chem. Ber.*, **59**, 736 (1926).

(15) R. A. Rossi and H. E. Bertorello, *An. Asoc. Quim. Argent.*, **55**, 227 (1967).

(16) H. C. Huenink, *Beilstein*, XIV, 415.

(17) V. Pechmann, *Chem. Ber.*, **27**, 1888 (1894); **28**, 855 (1895).

The identified compounds were benzoic acid (0.16%), *m*-chloronitrobenzene (1.7%), *m*-chlorobenzoic acid (0.85%), *m*-nitrobenzoic acid (2.0%), and 3-chloro-5-nitrobenzoic acid (27.9%).

(b) This fraction was extracted by acetone, and it was a mixture of unidentified substances, whose average equivalent weight was 225: yield 62.1%; ir (KBr) 1690 (-C=O), 1515 and 1351 cm^{-1} ($-NO_2$).

(c) This fraction resulted in a black powder insoluble in all the above-mentioned solvents. It does not melt up to 500° and has an equivalent weight of 530. The equivalent weight of this material was obtained by boiling it for 30 min with a standard solution of NaOH (in N_2 atmosphere) and then determining the NaOH consumed with a standard solution of HCl: ir (KBr) 1690 (-C=O), 1515 and 1351 cm^{-1} ($-NO_2$).

(3) **3-Carboxy-4-nitrobenzenediazonium chloride (7)** exploded at 116° with light emission. The residue, a microcrystalline black powder, was worked up in the same form of diazonium salt (6). Three fractions were obtained.

Fraction a was extracted by benzene, and glpc (Table VI) indicated the presence of *p*-chloronitrobenzene (0.55%), benzoic acid (0.07%), *o*-nitrobenzoic acid (0.15%), 5-chloro-2-nitrobenzoic acid (1.7%), and *m*-chlorobenzoic acid (0.05%).

Fraction b was extracted by acetone and methanol, affording a complex mixture of unidentified substances with an average equivalent weight of 230: ir (KBr) 1695 (-C=O), 1515 and 1333 cm^{-1} ($-NO_2$).

Fraction c, the remaining residue after the successive extractions with the indicated solvents, was a black powder infusible up to 500° with an equivalent weight of 1840. In the ir spectrum the principal absorption band occurred at 1575 cm^{-1}, characteristic of aromatic nitro group. The absence of fine structure in the spectrum may possibly result from a high degree of orientation involving the polymer chains as has been reported.[1,18]

Thermal Decomposition Reaction of 7 in the Presence of Hydrogen Chloride.—The diazonium salt **7** was placed in the reaction flask as indicated in ref 1. To the evacuated apparatus was added pure, dry hydrogen chloride, until the pressure indicated in Table III was reached. Once the desired pressure was obtained, the diazonium salt in the flask (6) was heated until the product exploded. The temperature of the bath at the moment of the explosion was taken and the residue was washed with different boiling solvents (benzene, acetone, and methanol) until the extraction was complete. The following products were determined: *p*-chloronitrobenzene and 5-chloro-2-nitrobenzoic acid (glpc) and P_2 (insoluble in all above-mentioned solvents) (Table III).

Registry No.—**5**, 25116-40-9; **6**, 25116-41-0; **7**, 25116-42-1; **14**, 25116-43-2.

Acknowledgment.—This research was supported by the Air Force Office of Scientific Research, Office of Aerospace Research, U. S. Air Force, under Grant No. AFOSR-68-1425.

(18) (a) P. Kovacic and A. Kyriakys, *J. Amer. Chem. Soc.*, **85**, 454 (1963); (b) J. Dale, *Acta Chem. Scand.*, **11**, 640 (1957).

Resin Acids. XX. The Structure of Levopimaric Acid Dioxide[1,2]

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The reaction of levopimaric acid transannular peroxide (**1a**) with triphenylphosphine affords a monoxide whose structure has been shown to be 8α,14α-oxidoabiet-12-en-18-oic acid (**8a**). Since epoxidation of **8a** affords levopimaric acid dioxide, the structure of the latter is revised to 8α(14α),12α,13α-dioxidoabietan-18-oic acid (**2a**). Other transformations of **1a** are described.

The transannular peroxide **1a** of levopimaric acid can be isomerized[5,6] to a dioxide for which structures **2a** or **3a** may be written. Expression **3a** has been given preference on the basis of limited chemical studies,[6] but this interpretation has been questioned,[7] largely because a similar ambiguity of long standing concerning the structure of isoascaridole or pseudoascaridole,[8] the thermal rearrangement product of ascaridole (**4**), has now been settled in favor of **5**.[9,10] In the present paper we present conclusive proof that levopimaric acid dioxide possesses structure **2a** and that its formation presents no departure from other thermal transannular peroxide rearrangements.

Doubts about the structure previously[6] assigned to the dioxide arose when attempts to correlate it with the potassium permanganate oxidation product **7**[11] of levopimaric acid ended in failure.

In an effort to prepare the dioxide by an unambiguous route, the transannular peroxide **1b** was refluxed with triphenylphosphine in hexane, a treatment which resulted in formation of a new monoxide. This reaction when originally applied to ascaridole was reported[12] to yield a 1,4-oxide. However, recent reinvestigation while our work was in progress has shown that the product from ascaridole is 3,4-epoxy-1-menthene (**6**).[10]

The monoxide from **1b** was eventually shown to have the analogous structure **8**. The nmr spectrum exhibited a one-proton multiplet (H-12) at 5.47 and a narrow one-proton doublet (H-14) at 3.02 ppm whose splitting (2 Hz) was reasonable for allylic coupling. These observations seemed to rule out a structure based on **3b**. However, efforts to confirm the location of the oxide ring by chemical methods failed. Attempts to rearrange the epoxide by treatment with

(1) From Florida State University. Previous paper: W. Herz and M. G. Nair, *J. Org. Chem.*, **34**, 4016 (1969).

(2) Work at Florida State University supported in part by a grant from the National Science Foundation (GP-12582).

(3) National Research Council–Agricultural Research Service Postdoctoral Research Associate, 1968.

(4) One of the laboratories of the Southern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(5) W. H. Schuller, J. C. Minor, and R. V. Lawrence, *Ind. Eng. Chem., Prod. Res. Develop.*, **3**, 97 (1964).

(6) H. Kanno, W. H. Schuller, and R. V. Lawrence, *J. Org. Chem.*, **31**, 4138 (1966).

(7) J. Hudec and R. S. A. Kelly, *Tetrahedron Lett.*, 3175 (1967).

(8) For literature citations, see ref 6.

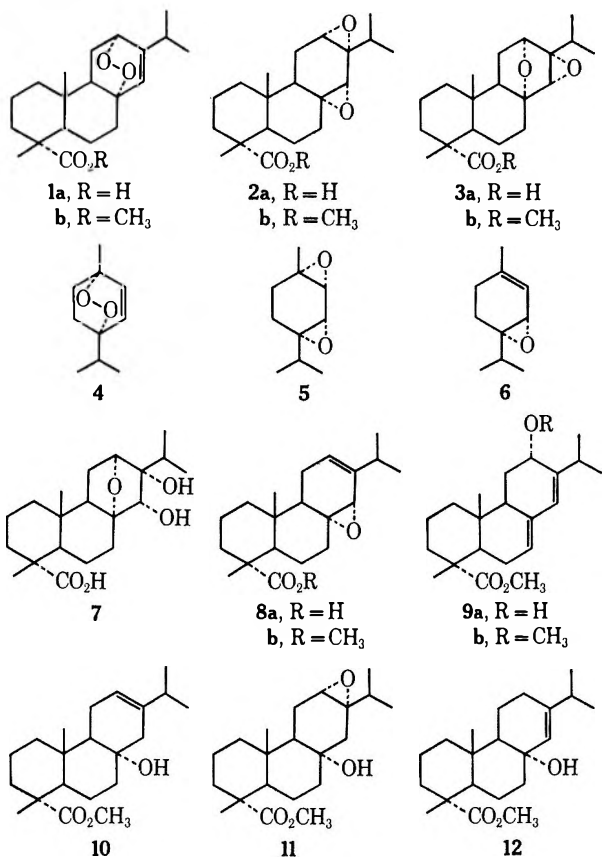
(9) J. Boche and O. Runquist, *J. Org. Chem.*, **33**, 4285 (1968).

(10) G. O. Pierson and O. Runquist, *ibid.*, **34**, 3654 (1969).

(11) W. Herz and R. Ligon, unpublished results.

(12) L. Horner and W. Jurgeleit, *Justus Liebigs Ann. Chem.*, **591**, 138 (1955).

Lewis acids led to complex mixtures. Perchloric acid catalyzed epoxide ring opening in methanol led to methyl 12-methoxyabietate (**9b**), identified by comparison of its nmr spectrum with that of **9a**,[13] and oxidation with BF_3–DMSO[14] gave a quantitative yield of methyl dehydroabietate.



Attempted hydrogenation of the monoxide (platinum oxide catalyst, ethanol) resulted quite unexpectedly in hydrogenolysis of the allylic carbon–oxygen bond and formation of an unsaturated alcohol which had to be formulated as **10**.[15] In the nmr spectrum of this substance the signal of the vinylic proton appeared as a multiplet at 5.52 ppm; its locus therefore was not likely to be C-14 and must be C-12. That the BC ring fusion was cis was indicated by the relatively high-field position (0.83 ppm) of the C-10 methyl signal.[16]

Further evidence for the structure assigned to **10** was its conversion by epoxidation to **11**. The infrared spectrum of this compound indicated the presence of a weak intramolecular hydrogen bond (narrowly split hydroxyl band, $\Delta\nu = 12$ cm^{-1}, which did not change on dilution) between the α-oriented hydroxyl and epoxide groups as suggested by the model. The nmr spectrum of **11** displayed the epoxidic proton as a multiplet, not as a singlet, at 3.18 ppm. Now the H-14 signal of $\Delta^{13(14)}$- or $\Delta^{8(14)}$-abietanes is broadened by long-range coupling; hence the multiplet character of the vinylic proton signal of **10** could not be used to dismiss quite unequivocally formulas such as **12** and **13**, the latter of which should also exhibit somewhat shielded C-10 methyl signals. On the other hand, it was difficult to see how an epoxy alcohol derived from **12** or **13** could give rise to a complex H-14 multiplet of the type observed, even if some W-type coupling were present.[17]

Convincing evidence for the formulation of the monoxide as **8b** was finally obtained from spin-decoupling experiments at 90 MHz.[18] Irradiation of **8b** at a frequency corresponding to the vinyl proton resonance collapsed the signal assigned to H-14 to a singlet still slightly broadened by allylic coupling to H-15.[19] Conversely, irradiation of the H-14 signal converted the signal at 5.47 ppm to a triplet ($J_{11\alpha,12} = J_{11\beta,12} = 3$ Hz) slightly broadened by allylic coupling to H-15 also.[19] These results which confirm that the only significant coupling experienced by the epoxidic proton is allylic coupling to the vinyl proton are consistent only with fromula **8b** and not with **14** or **15**.

Epoxidation of **8b** led to a substance identical in all respects with the dioxide obtained by rearrangement of methyl levopimarate transannular peroxide **1b**. Hence the structure of the dioxide is **2b** The glycol produced[6] from **2b** by the action of sulfuric acid (formula **8b** of ref 6) can now be assigned formula **16** because of the nmr spectrum which displays a somewhat deshielded C-10 methyl signal at 1.10 ppm. The α orientation of the C-14 hydroxyl group then follows from the usual trans-diaxial mode of epoxide ring opening. By analogy the chlorohydrin obtained from **2b** by action of hydrogen chloride (formula **7b** of ref 6) which can be reconverted to **2b** by treatment with base[6] is **17**.

In the following we report briefly the results of other transformations of **1b** and related experiments undertaken in the course of this work. Epoxidation of **1b** gave **18** whose nmr spectrum (multiplet at 4.30, H-12, singlet at 3.31 ppm, H-14) was in accord with the postulated formula. Treatment of **18** with base resulted in the isolation of two compounds **20** and **21** whose formation can be understood as proceeding through a Favorskii rearrangement of the intermediate not isolable, hydroxyepoxy ketone **19**.[20] The more soluble product **20** was transformed into **21** by lengthening the reaction time.

Structures were assigned to these substances on the basis of the following evidence. The dihydroxy diester **20** (strongly bonded hydroxyl band, two carbonyls at 1727 and 1690 cm^{-1} identified as carbomethoxy functions by the nmr spectrum) contained one secondary hydroxyl group (nmr doublet at 3.38 ppm which collapsed to a singlet on deuterium exchange) and the usual two methyl singlets and isopropyl doublets. The other hydroxyl group was apparently tertiary and, because of the convertibility to **21**, necessarily γ to the newly introduced ester function. That the two hy-

(13) W. Herz, H. J. Wahlborg, W. D. Lloyd, W. H. Schuller, and G. W. Hedrick, *J. Org. Chem.*, **30**, 3190 (1965).

(14) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 304.

(15) Inspection of the models of **8** and **10** does not afford an obvious explanation for our failure to effect reduction of the C-12, C-13 double bond under these and other (low pressure) conditions.

(16) J. W. Huffman, T. Kamiya, L. H. Wright, J. J. Schmid, and W. Herz, *J. Org. Chem.*, **31**, 4128 (1966).

(17) *Cf.* the nmr spectrum of **25b** (*vide infra*) where H-14 appears as a sharp singlet.

(18) The Bruker 90-MHz nmr spectrometer use in this study was purchased with the aid of an NSF grant to Florida State University. We wish to thank Mr A. L. Hall for performing the decoupling experiments.

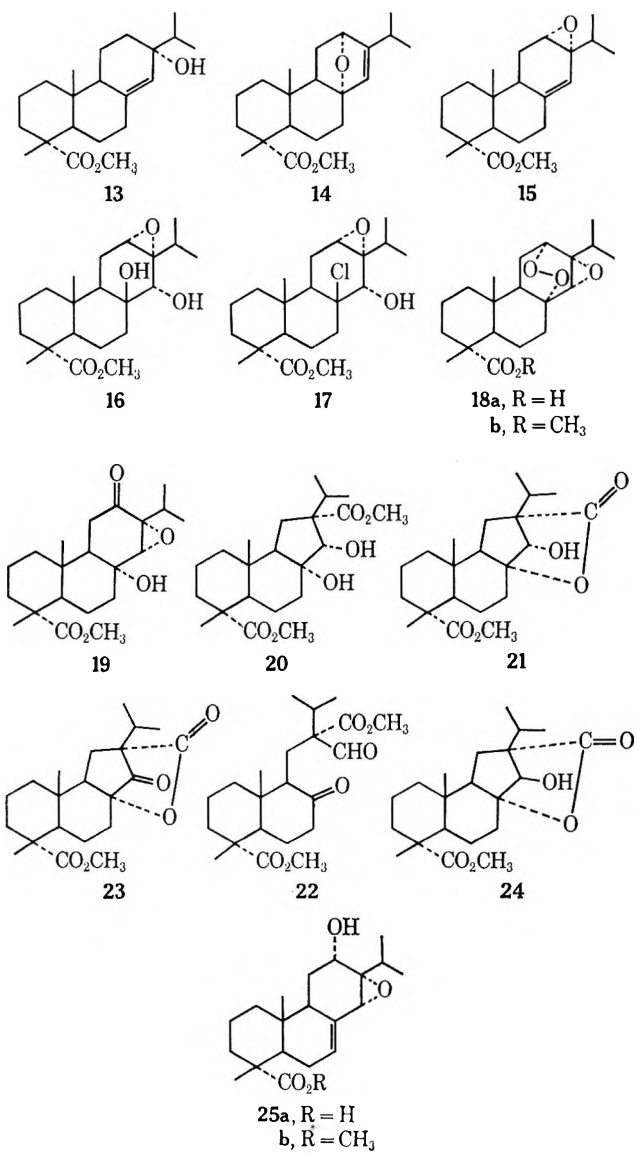
(19) The H-15 signal could be located at 2.29 ppm by irradiating at the frequency of the isopropyl methyl doublet.

(20) The formation of **19** from **18** is characteristic of peroxides containing at least one hydrogen α to the peroxidic linkage.[21] For other examples of Favorskii rearrangements involving α-epoxy ketones, see W. Herz and M. G. Nair, *J. Org. Chem.*, **34**, 4016 (1969).

(21) N. Kornblum and P. De La Mare, *J. Amer. Chem. Soc.*, **73**, 880 (1951).

droxyl groups of **20** were vicinal was shown by lead tetraacetate oxidation which gave a noncrystalline ketoaldehyde **22** characterized as a dinitrophenylhydrazone.

Analysis and physical properties of **21** (ir bands at 3438, 1734, and 1718 cm^{-1}, one methoxyl signal in the nmr) indicated that it was the lactone of **20** and contained a secondary hydroxyl group flanked by quaternary carbon atoms (singlet at 4.07 ppm after D_2O exchange). Oxidation of **21** with Jones reagent afforded a ketolactone ester **23** whose ir spectrum indicated the presence of a γ-lactone function (band at 1818 cm^{-1}, high frequency shift due to strain imposed by ketone group), strained cyclopentanone (band at 1764 cm^{-1}), and one ester function (band at 1720 cm^{-1}, nmr signal at 3.71 ppm). The absence of other low-field protons confirmed that the second hydroxyl group of the precursor **20** was tertiary.



Sodium borohydride reduction of **23** furnished a monohydroxy compound **24** (new nmr singlet at 3.81 ppm), presumably by attack from the less hindered α side (model). Consequently the secondary hydroxyl group of **20** and **21** was deduced to be α. This is in accord with the ease of lead tetraacetate oxidation of **20**.

Reaction of **18a** with triphenylphosphine resulted in formation of an unsaturated epoxy alcohol. This was formulated as **25a** on the basis of the nmr spectrum which exhibited a multiplet at 5.9 whose shape and chemical shift was characteristic of vinylic H-7,[22] a multiplet at 4.0 obviously associated with hydrogen on carbon carrying the hydroxyl because it underwent simplification on D_2O exchange and which, because of its complexity, had to be attached to C-12, and a singlet due to epoxidic hydrogen at C-14. The formation of **25a** which implies attack by triphenylphosphine on **18a** in a sense opposite to that favored by the same reagent in the case of **1a** or **1b** is difficult to understand. Models suggest that the oxygen atom removed from **1a** as triphenylphosphine oxide, *i.e.*, the one attached to C-12, is somewhat less encumbered than the oxygen atom attached to C-8 which is not removed. This situation is exacerbated rather than relieved in the case of **18a**, yet the considerably more hindered oxygen atom attached to C-8 of **18a** is removed preferentially. It is possible that the polar effect of the epoxidic oxygen atom, which from the model appears to be somewhat closer to the peroxydic oxygen at C-8 than to the one at C-12, is responsible for directing the attack of triphenylphosphine.

Experimental Section[23]

8α(14α),12α,13α-Dioxidoabietan-18-oic Acid and Methyl Ester (2a and 2b).—The preparation of **2a** was generally carried out as described earlier using ferrous sulfate.[7] The methyl ester **2b** was prepared from **1b** in the same manner.

Methyl 8α,14α-Oxidoabiet-12-en-18-oate (8b). A.—A solution of 2.84 g of **1a** in 980 ml of *n*-heptane was allowed to stand with 6.7 g of triphenylphosphine for 8 days until the optical rotation had leveled off at $[\alpha]^{25}D$ −27°. The mixture was filtered and evaporated *in vacuo*. The residue was mixed with 0.9 g of cyclohexylamine. The salt which precipitated weighed 1.6 g (45%). When recrystallized to constant rotation $[\alpha]^{25}D$ −60° (c 0.6), it had mp 187–188° dec; no uv absorption in the range 220–320 nm.

Anal. Calcd for $C_{26}H_{43}NO_3$: C, 74.78; H, 10.38; N, 3.35; O, 11.49. Found: C, 74.67; H, 10.21; N, 3.48; O, 11.28.

The acid **8a** was formed by suspending 11.3 g of the salt in ether and washing with a slight excess of dilute phosphoric acid. The crude acid, wt 8.65 g (100%), was converted to the methyl ester **8b** by treatment with diazomethane. The product was recrystallized from methanol–water to constant rotation, $[\alpha]^{25}D$ −77.0° (*c* 0.87), and had mp 104–106°; ir bands at 1727, 1387, 1362, and 990 cm^{-1}; nmr signals at 5.47 m (H-12), 3.71 (methoxyl), 3.02 d (J = 2 Hz, H-14), 1.20 (C-4 methyl), 1.09 d (J = 7 Hz, isopropyl methyls), and 0.81 ppm (C-10 methyl); mass spectrum (70 eV) 332 (molecular ion, intensity 17.8 compared with base peak at 239).

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70; O, 14.44. Found: C, 75.65; H, 9.71; O, 14.47.

B.—The following procedure for preparing **8b** was more convient and gave better yields. A solution of 1.0 g of **1b** and 0.8 g of triphenylphosphine in 150 ml of *n*-hepane was refluxed for 3 hr, cooled, filtered, and evaporated. The residue (**8b**) was recrystallized from methanol–water, yield 0.7 g (70%), mp 104–106°.

Epoxidation of 2.25 g of **8b** in 165 ml of ethylene dichloride with 1.6 g of *m*-chloroperbenzoic acid at reflux temperature for 2.5 hr, cooling, washing, and drying followed by evaporation at reduced pressure afforded 2.59 g of crude **2b**. After recrystallization from aqueous methanol there was obtained 1.9 g (81%) of **2b**: mp 120–121°; $[\alpha]^{25}D$ −72° (*c* 0.7), mmp (with **2b** from rearrangement of **1b**) 120–121°; nmr and ir spectra superimposable.

(22) H. J. Wahlborg, Ph.D. Dissertation, Florida State University, 1965.

(23) Melting points are uncorrected. Nmr spectra were run on a Varian A-60 nmr spectrometer in deuteriochloroform solution, unless otherwise specified, using tetramethylsilane as internal standards. Ultraviolet spectra and rotations were determined in 95% ethanol solution. Infrared spectra were run as KBr pellets unless otherwise specified.

Treatment of 8b with Acid. A.—A solution of 1.0 g of **8b** and 0.5 ml of BF_3-etherate in 25 ml of dimethyl sulfoxide was stirred mechanically. The process of the reaction was followed by tlc and nmr analysis. After 20 hr, quantitative conversion to methyl dehydroabietate had occurred.

B.—A solution of 1.0 g of **8b** in tetrahydrofuran-methanol was cooled in an ice bath and stirred for 1 hr with 0.5 ml of 60% perchloric acid solution. The mixture was poured into brine and extracted with ether. The washed and dried ether extract was evaporated and the residue was recrystallized from methanol-water. Pure **9b**, yield 0.46 g (50%), had mp 110–112°; $[\alpha]^{25}D$ −4.9°; ir bands at 1714 cm^{-1}; nmr signals at 6.01 (H-14), 5.75 m (H-7), 3.88 m (H-12), 3.73 (methoxyl), 3.46 (methoxyl), 1.19 (C-4 methyl), 1.10 d, 1.08 d (J = 7 Hz, isopropyl methyls), and 0.84 ppm (C-10 methyl).

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89; O, 13.85. Found: C, 76.14; H, 9.78; O, 13.97.

Methyl 8α-Hydroxyabiet-12-en-18-oate (10).—A solution of 2.0 g of **8b** was hydrogenated in ethanol solution with platinum oxide at 15 psi for 20 hr. The solution was filtered and evaporated at reduced pressure. The crude **10** was recrystallized from hexane, yield 1.3 g (65%), and had mp 132–133°; $[\alpha]^{25}D$ −49.4° (c 0.79); ir bands at 3560 and 1720 cm^{-1}; nmr signals at 5.52 m (H-12), 3.70 (methoxyl), 2.05 (-OH, disappears on D_2O exchange), 1.17 (C-4 methyl), 1.00 d (J = 6 Hz, isopropyl methyls), and 0.83 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25; O, 14.35. Found: C, 74.92; H, 10.03; O, 14.65.

Methyl 8α-Hydroxy-12α,13α-oxidoabietan-18-oate (11).—A solution of 1.3 g of **10** and 0.9 g of *m*-chloroperbenzoic acid in 50 ml of chloroform was allowed to stand at room temperature for 2 hr and then extracted thoroughly with saturated sodium bicarbonate solution. The washed and dried organic layer was evaporated. The residue was recrystallized from hexane: yield of **11**, 1.1 g (79%); mp 142.5–143.5°; $[\alpha]^{25}D$ +4.9° (c 0.82); ir bands at 3460–3440 and 1718 cm^{-1}; nmr signals at 4.50 (-OH, disappears on D_2O exchange), 3.67 (methoxyl), 3.18 m (H-12), 1.15 (C-4 methyl), 0.99 d and 0.96 d (J = 7 Hz, isopropyl methyls), and 0.87 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78; O, 18.26. Found: C, 72.06; H, 9.84; O, 17.82.

Methyl 8β,14α-Dihydroxy-12α,13α-oxidoabietan-18-oate (16).—This substance, prepared by the literature method,[6] had nmr signals at 3.68 (methoxyl), 3.41 t (J = 2 Hz, H-12), 3.22 d (J = 9.5 Hz, H-14, collapses to singlet on D_2O exchange), 2.52 d (J = 5 Hz, -OH, disappears on D_2O exchange), 1.21 (C-4 methyl), 1.10 (C-10 methyl), and 1.03 d and 0.96 d (J = 6 Hz, isopropyl methyls).

Epoxidation of 1a. Formation of 18.—A solution of 20 g of **1a** and 16 g of *m*-chloroperbenzoic acid in ethylene dichloride was refluxed on the steam bath for 4 hr, allowed to stand overnight, washed thoroughly with saturated sodium bicarbonate solution, water, and brine, and dried. Removal of solvent furnished crude **18a**, wt 19.8 g (95%), which was purified to constant rotation, $[\alpha]^{25}D$ +121° (c 1.1), by recrystallization from *n*-heptane: yield of pure **18a** 6.22 g (78%); mp 165–167° dec; nmr signals at 4.40 m (H-12), 3.36 (H-14), 1.20 (C-4 methyl), 1.14 d and 0.84 d (J = 7 Hz, isopropyl methyls), and 0.87 ppm (C-10 methyl).

Anal. Calcd for $C_{20}H_{30}O_5$: C, 68.54; H, 8.63; O, 22.83. Found: C, 68.70; H, 8.70; O, 23.01.

Methylation of **18a** with diazomethane afforded **18b** in quantitative yield. It melted unsharply in the range 175–188° dec, presumably due to thermal decomposition, but tlc and spectrometric analysis indicated homogeneity: $[\alpha]^{25}D$ +98.5° (c 0.79), ir bands 1724, 1391, and 1251 cm^{-1}; nmr signals at 4.30 m (H-12), 3.66 (methoxyl), 3.31 (H-14), 1.15 (C-4 methyl), 1.10 and 0.80 d (J = 7 Hz, isopropyl methyls), and 0.81 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85; O, 21.95. Found: C, 69.08; H, 8.77; O, 22.22.

Base Treatment of 18b. Formation of 20 and 21.—A solution of 5 g of **18b** in 700 ml of 95% ethanol and 75 ml of 1 M sodium hydroxide in ethanol was refluxed for 20 min, cooled, filtered, and acidified with dilute phosphoric acid. The acid fraction was isolated in the usual manner and methylated with ethereal diazomethane. The solution was concentrated to ~50 ml and chilled in the refrigerator for 2 hr. This resulted in separation of **21** (2.8 g). Concentration to 30 ml and chilling produced an additional 0.3 g of **21**. The mother liquor was evaporated to dryness *in vacuo* and the residue was recrystallized from aqueous methanol. This resulted in separation of 1.6 g of **20**. When the hydrolysis mixture was refluxed for 40 min or longer, only **21** was isolated in ~90% yield.

Ester **20** was recrystallized from aqueous methanol and had mp 106–107°; $[\alpha]^{25}D$ −16.6° (c 0.75); ir bands at 3480–3280 (broad, hydrogen bonded), 1727, and 1690 cm^{-1}; nmr signals at 4.56 d (J = 9 Hz, C-13, -OH, disappears on D_2O exchange), 3.74 and 3.68 (two methoxyls), 3.38 d (J = 9 Hz, H-13, collapses to singlet on D_2O exchange), 1.25 (C-4 methyl), 1.00 d and 0.93 d (J = 6 Hz, isopropyl methyls), and 0.83 ppm (C-10 methyl).

Anal. Calcd for $C_{22}H_{36}O_6$: C, 66.74; H, 9.15; O, 24.21. Found: C, 66.75; H, 9.03; O, 24.19.

Ester **21** was recrystallized from ether and had mp 242–244°; $[\alpha]^{25}D$ +61.7° (c 0.78); ir bands at 3438, 1734, and 1718 cm^{-1}; nmr signals at 4.07 d (J = 7 Hz, H-13, collapses to singlet on D_2O exchange), 3.70 (methoxyl), 2.22 d (J = 7 Hz, -OH, disappears on D_2O exchange), 1.18 (C-4 methyl), 1.12 d (J = 7 Hz, isopropyl methyls), and 0.91 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85; O, 21.95. Found: C, 69.31; H, 8.81; O, 21.97.

Lead Tetraacetate Oxidation of 20.—A solution of 0.45 g of **20** and 0.5 g of lead tetraacetate was stirred overnight, filtered, and evaporated. The residue (**22**) was taken up in hexane, but could not be induced to crystallize. The nmr spectrum had signals at 11.33 (-CHO), 3.69 (two methoxyls), 1.17 (C-4 methyl), 1.08 d and 0.91 d (J = 7 Hz, isopropyl methyls), and 0.70 ppm (C-10 methyl). The material was converted to a crystalline bis-2,4-dinitrophenylhydrazone which was recrystallized from ethanol and then decomposed at 135°.

Anal. Calcd for $C_{34}H_{42}N_8O_{12}$: C, 55.15; H, 5.88. Found: C, 55.36; H, 5.60.

Oxidation of 21.—Oxidation of 1.0 g of **21** with Jones reagent in acetone solution by stirring overnight, pouring into water, extracting with ether, washing and drying the ether extract, and removal of solvent afforded crude **23** which was recrystallized from methanol-water. The product, wt 0.95 g (95%), had mp 94–95.5°; $[\alpha]^{25}D$ +77.8° (c 0.76); ir bands at 1818, 1763, and 1720 cm^{-1}; nmr signals at 3.71 (methoxyl), 1.20 (C-4 methyl), 1.12 d (J = 7 Hz, isopropyl methyls), and 0.78 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{30}O_5$: C, 69.59; H, 8.34; O, 22.07. Found: C, 69.63; H, 8.39; O, 22.08.

Reduction of 23 to 24.—A solution of 0.3 g of **23** in 4:1 methanol–water containing sufficient ether to dissolve the substrate was stirred overnight with 23 mg of $NaBH_4$, poured into 15% phosphoric acid solution, and extracted with ether. The washed and dried extract was evaporated and the residue (**24**) recrystallized from methanol–water: yield 240 mg (80%); mp 225–227°; $[\alpha]^{25}D$ +120° (c 0.23); ir bands at 3465, 1743, and 1724 cm^{-1}; nmr signals at 3.8 br (H-13, sharpens to singlet on D_2O exchange), 3.71 (methoxyl), 2.92 br (-OH, disappears on D_2O exchange), 1.20 (C-4 methyl), 1.11 d and 1.08 d (J = 7 Hz, isopropyl methyls), and 1.09 ppm (C-10 methyl).

Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85; O, 21.95. Found: C, 69.51; H, 8.80; O, 21.62.

12α-Hydroxy-13α,14α-oxidoabiet-7-en-18-oic Acid and Methyl Ester (25a and 25b).—A solution of 9.5 g of **18a** and 7.08 g of triphenylphosphine in 380 ml of benzene was allowed to stand at room temperature until the optical rotation became constant (45 hr). The solution was evaporated at reduced pressure; the residue was dissolved in 23 ml of acetone and mixed with 3.23 g of cyclohexylamine. The salt, wt 10 g, was recrystallized from acetone: yield 8.5 g (73%); $[\alpha]^{25}D$ +15.7° (c 0.8), mp 208° dec; ir bands at (Nujol mull) 3580, 1625, 1240, 1048, 885, and 765 cm^{-1}.

Anal. Calcd for $C_{26}H_{43}NO_4$: C, 72.01; H, 10.00; N, 3.23; O, 14.75. Found: C, 71.96; H, 9.88; N, 3.55; O, 14.83.

The free acid was regenerated from the salt by shaking an ether suspension with an excess of 1 M phosphoric acid. Recrystallization from acetonitrile afforded **25a** in 84% yield: mp 142–144° dec; $[\alpha]^{25}D$ +25.7° (c 0.8); no characteristic uv absorption in the range 220–320 nm; ir bands ($CHCl_3$) at 3510, 1690, and 885 cm^{-1}.

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.05; O, 19.14; neut equiv, 334. Found: C, 71.86; H, 9.07; O, 19.15; neut equiv, 335.

Treatment of **25a** with ethereal diazomethane and recrystallization from aqueous acetonitrile afforded a 94% yield of **25b**:

mp 128–130°; $[\alpha]^{26}D$ +23.8° (*c* 1.0); ir bands ($CHCl_3$) at 3510 and 1715 cm^{-1}; nmr signals (CCl_4) at 5.9 m (H-7), 4.0 m (H-12, simplifies on D_2O exchange), 3.51 (methoxyl), 3.25 (H-14), 2.25 d (J = 10 Hz, -OH, disappears on D_2O exchange), 1.21 (C-4 methyl), 1.01 d and 0.94 d (J = 7 Hz, isopropyl methyls), and 0.74 ppm (C-10 methyl); mass spectrum 348 (molecular ion).

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26; O, 18.37. Found: C, 72.13; H, 9.18; O, 18.43.

Registry No.—**2a**, 23160-61-4; **8a** cyclohexylamine salt, 25859-58-9; **8b**, 25859-59-0; **9b**, 25236-84-4; **10**, 25859-61-4; **11**, 25859-62-5; **16**, 25859-63-6; **18a**, 25859-64-7; **18b**, 25859-65-8; **20**, 25859-66-9; **21**, 25859-67-0; **22** bis-2,4-DNP, 25907-93-1; **23**, 25859-68-1; **24**, 25907-94-2; **25a**, 25859-69-2; **25a** cyclohexylamine salt, 25859-70-5; **25b**, 25859-71-6.

Electrophilic Substitution in Highly Substituted Diphenyl Ethers[1]

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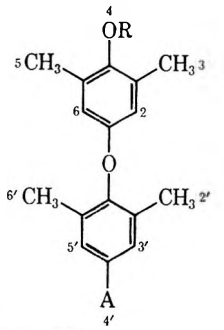
Derivatives of 4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether (**1**) have been of interest for some time as analogs of thyroxine in which the iodo groups have been replaced with methyls. These products have been obtained by electrophilic substitution on **1** or its methyl ether (**2**), which, in each case, is reported to occur in the 4′ position. For example, **1** is reported to give 4′-bromo-4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether (**8**) on bromination in acetic acid. We have repeated all of the reported substitution reactions and obtained products identical with those prepared earlier. However, we have shown by pmr and ir spectral analyses that each of these products is substituted in the 2 position. Thus **1** is brominated to give 2-bromo-4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether (**10**). We have explained this result on the basis of the steric effect of the two methyl groups *ortho* to the aryl ether linkage which interfere with resonance forms that activate the 4′ position for substitution, but which do not interfere with resonance forms that activate the 2 position. This hypothesis is supported by additional substitution data and ultraviolet spectra, which show that there is little or no electronic interaction between the aryl ether oxygen "p" electrons and the hindered aryl ring. These results show that no authentic tetramethyl analogs of thyroxine have been prepared, and that conclusions regarding bioactivity based on compounds prepared by electrophilic substitution of **1** and **2** are in error.

Electrophilic substitution products of 4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether (**1**) and its methyl ether (**2**) have been used as intermediates for the preparation of tetramethyl analogs of thyroxine. In this connection, Bruice, Kharasch, and Winzler in 1954 reported that nitration of **2** in acetic anhydride resulted in 4′-nitro-4-methoxy-3,5,2′,6′-tetramethyldiphenyl ether (**3**).[3] This product was subsequently converted to the amino derivative of **1**, reported to have structure **4**, which was tested for biological activity.[4] Later, Bielig and Lützel reported that bromination and chloromethylation experiments with **2** resulted in the derivatives **5** and **6** which are substituted in the 4′ position of the phenoxy ring.[5] The product obtained by chloromethylation was converted to an amino acid derivative of **1** which was reported to be **7**, the structural analog of thyroxine in which all of the iodines have been replaced with methyl groups. This product has since been used in several biological studies designed to determine the effect of methyl relative to that of other substituents on the thyroxine nucleus.[6] More recently, Van Heyningen has brominated **1** in acetic acid and reported the 4′-bromo derivative **8**.[7] This product was converted by metal exchange and carbonation to a carboxylic acid. This product, reported to have structure **9**, has also been used in biological studies.[8] In none of the above cases did the authors offer structural proofs for their products, nor did they discuss the possibility of alternative structures.



1, R = A = H
2, R = CH_3; A = H
3, R = CH_3; A = NO_2
4, R = H; A = NH_2
5, R = CH_3; A = Br
6, R = CH_3; A = CH_2Cl
7, R = H; A = CH_2CHNH_2COOH
8, R = H; A = Br
9, R = H; A = COOH

Because of our interest in obtaining **8** for use in another connection, we have repeated the bromination reactions of Van Heyningen[7] and Bielig and Lützel[5] and obtained products which are identical with those reported. However, we have determined by proton magnetic resonance (pmr) spectral data that the products are substituted in the 2 position of the phenolic ring rather than the 4′ position of the phenoxy ring as previously reported. These results have led us to repeat other electrophilic substitution reactions of **1** and **2** and to determine the structures of the products. This paper describes the results of these experiments and the structural identifications and includes a discussion of the unexpected substitution pattern.

(1) This work was presented in part at the 142nd National Meeting of the American Chemical Society in Atlantic City, N. J., Sept 1962.
(2) General Electric Space Sciences Laboratory, Valley Forge, Pa.
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(4) T. Bruice, N. Kharasch, and R. Winzler, *J. Biol. Chem.*, **210**, 1 (1954).
(5) H. Bielig and G. Lützel, *Justus Liebigs Ann. Chem.*, **608**, 140 (1957).
(6) (a) E. Jorgensen and R. Wiley, *J. Med. Pharm. Chem.*, **5**, 1307 (1962); (b) C. Pittman, H. Shida, and S. Barker, *Endocrinology*, **68**, 248 (1961); (c) S. Barber, *Fed. Proc., Fed. Amer. Soc. Exp. Biol.*, **21**, 635 (1962).
(7) E. Van Heyningen, *J. Org. Chem.*, **26**, 3850 (1961).
(8) R. G. Herrmann, C. C. Lee, and R. Parker, *Arch. Int. Pharmacodyn. Ther.*, **133**, 284 (1961).

Results

The bromination of compound **1** in acetic acid was carried out according to the directions of Van Heyningen[7] to give an excellent yield of a solid that melted at 101–103°, which is identical with the reported melting point, and that provided an elemental analysis consistent with $C_{16}H_{17}BrO_2$.

The pmr spectra of **1** and its derivatives were obtained in deuteriochloroform solutions. The positions of the peaks in τ units and the number of protons obtained from area measurements are shown in Table I. The number of protons is determined by dividing the total area under each of the peaks by the area corresponding to a single proton.

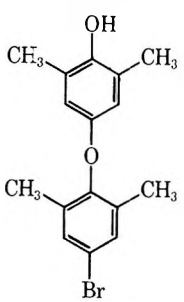
TABLE I

PMR SPECTRA OF DERIVATIVES OF 4-HYDROXY-3,5,2′,6′-TETRAMETHYLDIPHENYL ETHER (1) AND ITS METHYL ETHER (2)

	Pmr spectra[a]			
Derivative	ArH	$ArCH_3$	-OH	$-OCH_3$
1 (parent phenol)	3.05 (3)	7.94 (6)	5.95 (1)	
	3.75 (2)	7.97 (6)		
2 (parent anisole)	3.03 (3)	7.84 (6)		6.46 (3)
	3.74 (2)	7.93 (6)		
10 (2-bromophenol)	3.05 (3)	7.70 (3)	5.60 (1)	
	4.10 (1)	7.97 (6)		
		8.05 (3)		
12 (2-nitroanisole)	3.05 (3)	7.80 (3)		6.55 (3)
	4.05 (1)	7.93 (9)		
13 (2-bromoanisole)	3.05 (3)	7.70 (3)		6.48 (3)
	3.95 (1)	7.95 (9)		
14 (2-chloromethyl-anisole	3.04 (3)	5.18 (2)		6.43 (3)
	4.13 (1)	7.66 (3)		
		7.95 (9)		
15 (2-aminoanisole)	2.96 (3)	7.81 (3)		6.43 (3)
	4.06 (1)	7.86 (6)		
		7.97 (3)		
16 (2-aminophenol)	2.98 (3)	7.89 (9)	5.8–6.2 (3)	
	4.14 (1)	8.03 (3)		
17 (2-nitrophenol)	2.98 (3)	7.85 (3)	4.86 (1)	
	3.96 (1)	7.88 (9)		

[a] The positions of the peaks are given in τ units. The number of protons, accurate to within ±5% of the whole numbers, are in parentheses. The spectra were taken in $DCCl_3$ solution on a Varian A-60 spectrometer with the exception of those for **2**, **13**, and **14**, which were taken at 40 Mc.

The structural formulas of the three possible monobromo compounds are



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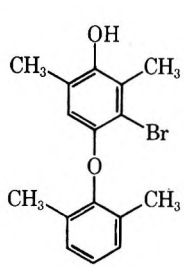

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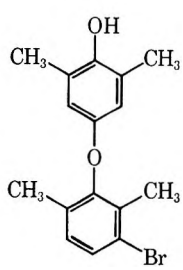
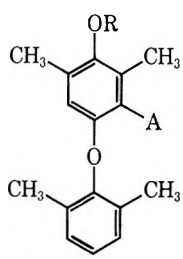


11

The pmr spectrum of **1** shows two peaks for the aliphatic protons at τ 7.95 and 7.97 corresponding to two pairs of magnetically equivalent methyl groups. In the brominated compound, the methyl groups appear as three peaks shifted to τ values of 7.70, 7.97, and 8.05, corresponding to areas 3, 6, and 3, respectively. This shows that there are four methyl groups, two of which are magnetically nonequivalent to any of the others. This spectrum is reasonable for structures **10** or **11**, but not for **8**. Because of the position of the bromine and its equal influence on the magnetic environment of the two nearest methyl groups, **8** would be expected to show two peaks in the region τ 7.0–8.5, characteristic of two pairs of magnetically equivalent methyl groups. This evidence alone rules out the possibility that the brominated product is **8**.

In the spectrum of **1**, the peaks at τ 3.05 and 3.75 are due to the three aromatic protons of the phenoxy ring and the two aromatic protons of the phenolic ring, respectively. The fact that the peak at τ 3.05 in the spectrum of **1** remains unchanged as to area and position in the spectrum of the brominated compound shows that the three aromatic protons of the phenoxy moiety of the starting material have not been affected by bromination. The fact that the peak at τ 3.75 has been reduced to one-half of its former area and has been shifted to τ 4.10 shows that one of the two aromatic protons of the phenol moiety has been removed by bromination and that the remaining aromatic proton is in a substantially different magnetic environment from that in the starting material. Such a pmr spectrum requires that the bromine substitution occurred at the 2 position of the diphenyl ether to produce compound **10**.



10, R = H; A = Br
12, R = CH_3; A = NO_2
13, R = CH_3; A = Br
14, R = CH_3; A = CH_2Cl
15, R = CH_3; A = NH_2
16, R = H; A = NH_2
17, R = H; A = NO_2

Further evidence for the selection of **10** as the structure of the monobromo compound is found in the fact that when the brominated compound was polymerized to a polyphenylene ether, in a reaction in which the mechanism of growth of the polymer chain removes halogen from the *para* position if it were present in the 4′ position as it is in structure **8**,[9] it was found that the polymer had been formed without loss of bromine.

When the bromination reaction was repeated using carbon tetrachloride and carbon disulfide as solvents in place of acetic acid, the product in each case was identical with that obtained above. Both products had the same melting points and infrared spectra as obtained for the product described above. Thus, within the scope of these experiments, the particular solvent used does not influence the position that is brominated.

In another attempt to obtain **8**, we prepared the acetyl derivative of **1**, in the hope that the phenolic ring

(9) A. S. Hay, H. S. Blanchard, G. F. Endres, and J. W. Eustance, *J. Amer. Chem. Soc.*, **81**, 6335 (1959); H. S. Blanchard, H. Finkbeiner, and G. F. Endres, Polymer Division Preprints, 140th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1961.

TABLE II

ELEMENTAL ANALYSES OF DERIVATIVES OF 4-HYDROXY-3,5,2′,6′-TETRAMETHYLDIPHENYL ETHER (1) AND ITS METHYL ETHER (2)

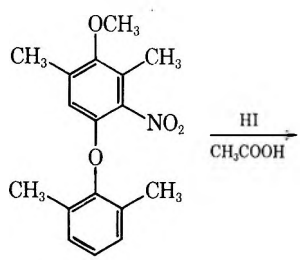
Derivative	Formula	Mp, °C Found	Mp, °C Lit.	Calcd, % C	Calcd, % H	Calcd, % N	Calcd, % Br	Calcd, % Cl	Found, % C	Found, % H	Found, % N	Found, % Br	Found, % Cl
1	$C_{16}H_{18}O_2$	109–110	105–108[a]	79.2	7.5				79.5	7.6			
2	$C_{17}H_{20}O_2$	58–59	57.5–58.5[a]	79.7	7.9				79.9	8.0			
10	$C_{16}H_{17}BrO_2$	101–103	101–103[b]	59.8	5.3		24.9		59.5	5.5		24.5	
12	$C_{17}H_{19}NO_4$	111–112	111–112[a]	67.8	6.3	4.7			67.9	6.3	4.8		
13	$C_{17}H_{19}BrO_2$	76–77	78–79[c]	60.9	5.7		23.8		61.2	5.5		23.4	
14	$C_{18}H_{21}ClO_2$	68–69	71[c]	70.9	6.9			11.9	70.5	7.0			11.9
15	$C_{17}H_{21}NO_2$	92–94	89–90[a]	75.3	7.8	5.2			75.2	7.7	5.1		
16	$C_{16}H_{19}NO_2$	154–155	150–151[a]	74.8	7.5	5.5			74.9	7.3	5.5		
17	$C_{16}H_{17}NO_4$	159–161		67.0	6.0	4.9			66.7	6.1	5.0		

[a] Reference 3. [b] Reference 7. [c] Reference 5.

would become less active toward electrophilic reagents. Bromination of the acetyl derivative in acetic acid at room temperature led to a 90% yield of a monobromo derivative, which upon hydrolysis gave a quantitative yield of the bromophenol **10**, as shown by melting point and infrared comparisons. Thus, acetylation of the phenolic hydroxyl of **1** does not significantly alter the reactivity of the respective rings toward electrophilic reagents.

Nitration, bromination, and chloromethylation experiments with the anisole **2** were carried out according to the directions of Bruice, Kharasch, and Winzler[3] and Bielig and Lützel,[5] respectively. As shown in Table II, the elemental analyses and melting points confirmed the identity of these products with those previously obtained. The identification of the structures of these products was obtained by pmr data which are summarized in Table I along with the data for compound **2**. In each case, the methyl groups of the substituted product appeared as three peaks, with areas corresponding to 3, 6, and 3 protons, indicating unsymmetrical substitution with respect to the methyl groups. In addition, the peak corresponding to the 3′, 4′, and 5′ aromatic protons of **2** appeared unchanged as to area and position in the spectrum in the substituted products, while the peak corresponding to the 2 and 6 protons of **2** was reduced to an area corresponding to one proton and shifted upfield. These facts establish the structures of the nitro-, bromo-, and chloromethyl derivatives of **2** as **12**, **13** and **14**, respectively, rather than **3**, **5**, and **6**, as previously reported.

The nitroanisole **12** was converted into an aminophenol by two different routes. Following the directions of Bruice, *et al.*, the nitroanisole was catalytically reduced to the aminoanisole, which was converted to the aminophenol by methoxyl group cleavage with hydriodic acid in acetic acid. The amino derivatives of **1** and **2** were shown to be identical with those reported by Bruice, *et al.*,[3] by melting point and elemental analyses (Table II). Pmr spectral analyses confirmed that these derivatives possessed the structures **15** and **16**, rather than those previously reported. The conversion of the nitroanisole to the nitrophenol by treatment with hydriodic acid in refluxing acetic acid was also attempted. We were surprised to observe the generation of iodine in copious amounts during this reaction. When the product was precipitated in water, a low yield of the nitrophenol was obtained. This product was identified as **17** by elemental and pmr analyses. When the acidic filtrate was neutralized by ammonium carbonate, a product, identified as the aminophenol **19**, precipitated. Thus the hydriodic acid had served the dual functions of cleaving the methyl ether and reducing the nitro group (eq 1).



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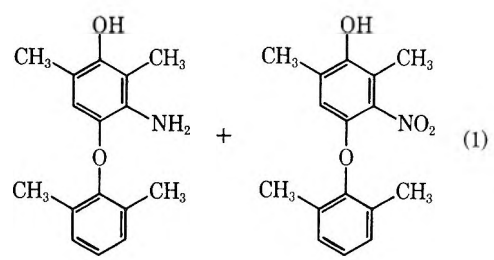


(1)

16 **17**

The infrared spectra of compounds **1** and **2** and their monosubstituted derivatives show absorption bands at 9.1 to 9.2 μ characteristic of three adjacent hydrogens in an aromatic ring. Both 2,6-dimethylphenol and 2,6-dimethylanisole, likewise, show this absorption band. However, this band is missing in the spectra of compounds such as 2,4,6-trimethylphenol, 2,4,6-trimethylanisole, and 4′-substituted derivatives of **1** and **2**.[10] Thus, within this series of compounds, the absorption band at 9.2 μ is of diagnostic value for determining the position of substitution in compounds such as **1** and **2**.

Discussion

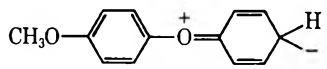
It is well documented that a substituent in one ring of a diphenyl ether has a profound effect on the reactivity of both rings.[11] Brewster and Slocombe have shown that 4-methoxydiphenyl ether is brominated exclusively in the 4′ position (phenoxy ring) more rapidly than diphenyl ether itself[12] (eq 2). These data constitute part of the evidence that the tautomeric or inductive effects of a substituent may be transmitted across the

(10) S. B. Hamilton, Jr., and H. S. Blanchard, U. S. Patent 3,351,667 (1967).

(11) H. A. Scarborough, *J. Chem. Soc.*, **132**, 2361 (1952); H. A. Scarborough and J. L. Sweeten, *ibid.*, 52 (1934); R. Brewster and F. Strain, *J. Amer. Chem. Soc.*, **56**, 117 (1934); R. Brewster and H. S. Choguill, *ibid.*, **61**, 2702 (1939).

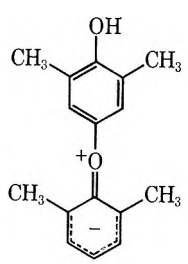
(12) R. Brewster and R. Slocombe, *ibid.*, **67**, 562 (1945).

ether linkage from one ring to another. The enhanced reactivity in the 4′ position can be attributed to the increased electron density provided by the resonance form **18** which is stabilized by the electron-releasing methoxyl group at the 4 position. This fact plus the



18

apparently unfavorable steric hindrance to substitution in the 2 position represent the principal reasons for expecting substitution in the 4′ positions of **1** and **2**. The contribution of such a resonance structure will be at a maximum when the phenoxy ring is coplanar with the oxygen valence angle. Steric factors which oppose such a configuration will decrease the activating influence of the ether group toward electrophilic substitution. In this connection we examined molecular models of **1** and **2**. The two methyl groups *ortho* to the phenyl ether linkage prohibit the coplanarity of the phenoxy ring and the oxygen valence angle. In fact, the degree of hindrance is so great that the oxygen nonbonding orbitals must be practically perpendicular to the electrons of the phenoxy ring. Thus, a resonance structure such as **19** which would activate the 4′ position for electrophilic substitution is sterically prohibited. In contrast to this situation, resonance



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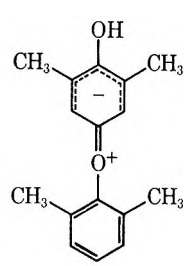

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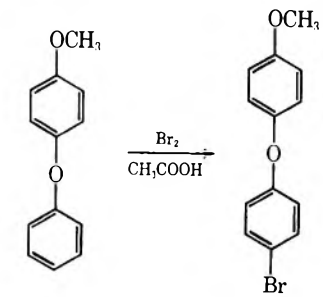
structure **20**, in which the ether oxygen is conjugated with the phenolic ring, is entirely compatible with the stereochemistry of **1** and **2**. It is also apparent that to the extent that **20** contributes, the phenoxy ring will be deactivated by the electron-withdrawing inductive effect of the electropositive oxygen. Thus the selectivity for electrophilic substitution in the 2 positions of **1** and **2** can be accounted for by the sterically enforced predominance of resonance form **20**, which both activates the phenolic ring and deactivates the phenoxy ring, and by the 3,5-methyl groups which also activate the 2 position through conjugative effects.

In hopes of determining the importance of the conjugative effects of the 3,5-methyl groups relative to the steric effect of the 2′,6′-methyl groups, we studied the bromination of 4-methoxy-2′,6′-dimethyldiphenyl ether (**21**) and 4-methoxy-3,5-dimethyldiphenyl ether (**22**). In the case of **21**, a single product was obtained in over 95% yield. Infrared and pmr spectra provided proof that bromination had occurred in the ring bearing the methoxyl. Based on our interpretation of the pmr data, we have identified the product as 2-bromo-4-methoxy-2′,6′-dimethyldiphenyl ether (eq 3). Thus the steric effect of the 2′,6′-methyls alone is sufficient to change the position of the electrophilic substitution.



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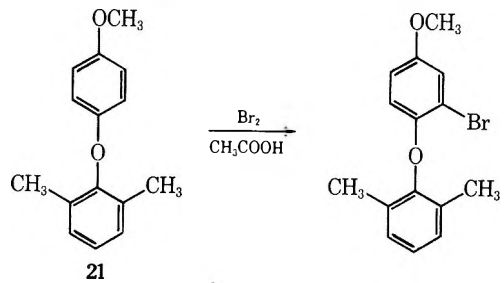

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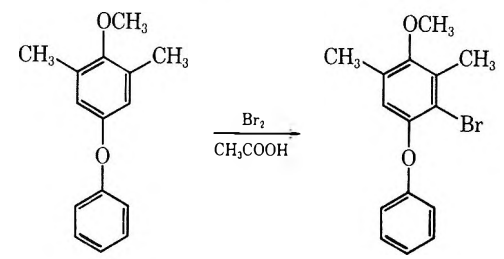

(4)

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Similarly, monobromination of **22** occurred exclusively in the 2 position (eq 4). Thus it appears that the conjugative effects of the 3,5-methyls are also great enough to direct substitution into the 2 position. However, this interpretation is not unambiguous since these methyl groups also prevent coplanarity of the 4-methoxyl with the ring and, therefore, would be expected to reduce contributions of a resonance form analogous to **18**.

Ultraviolet Spectra.—In order to test our interpretation of the substitution data, we have examined the electronic spectra of a number of substituted phenyl ethers in the 250–300 mμ region. This band is associated with electronic contributions from the quinonoid structure. Due to resonance forms such as **18**, the bonds connecting the aryl rings *via* the ether oxygen in unhindered diphenyl ethers will have some double bond character. The effect of twisting such a single bond in a conjugated system away from coplanarity by steric forces may affect the spectrum in any of three ways: (1) no change in wavelength of the maximum but a decrease in the absorption intensity, caused by relatively small twists, (2) absorption maximum shifts to shorter wavelengths in addition to decreased absorption intensity, caused by larger twists than the first effect, (3) spectrum is similar to the sum of the spectra of the component parts of the molecule on either side of the twisted bond; this effect occurs when the twist is large enough to almost completely eliminate interaction between the two portions of the molecule.[13] Studies reported by Burawoy and Chamberlain,[14] Dahlgard

(13) L. L. Ingraham, "Steric Effects in Organic Chemistry," M. Newman, Ed., Wiley, New York, N. Y., 1956, p 484.

(14) A. Burawoy and J. Chamberlain, *J. Chem. Soc.*, 2310 (1952).

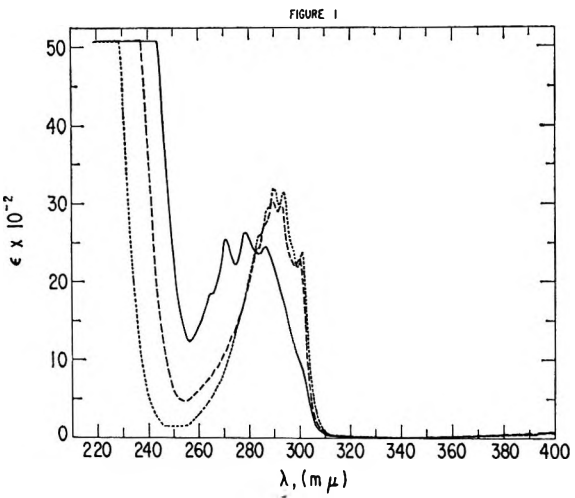


Figure 1.—Ultraviolet spectra of the diaryl ethers, 4-hydroxydiphenyl ether (——), 4-hydroxy-2′,6′-dimethyldiphenyl ether (---), and 4-methoxyphenol (· · ·), in cyclohexane.

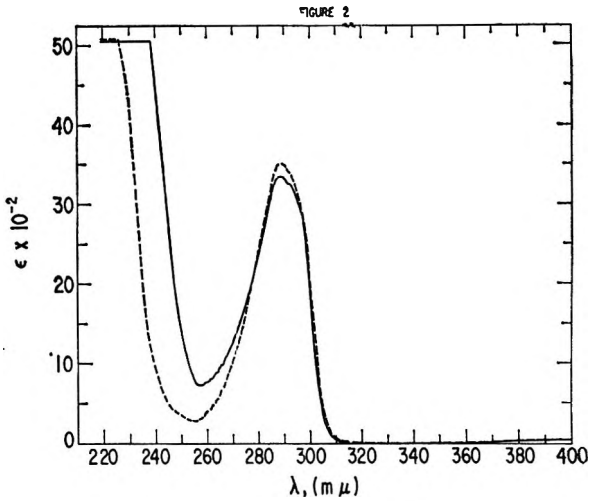


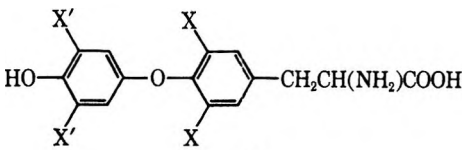
Figure 2.—Ultraviolet spectra of 4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether (——) and 4-methoxy-2,6-dimethylphenol (---) in cyclohexane.

and Brewster,[15] and Baddeley, *et al.*,[16] have shown that steric factors that result in twists of the oxygen aryl bonds in aralkyl ethers result in absorption maximum shifts to shorter wavelengths and decreased absorption intensity. Similar behavior might be expected in the case of **1** and **2** except for the fact that steric effects, while interfering with resonance structure **19**, strongly favor structure **20**, which would be expected to absorb strongly in the ultraviolet. In confirmation of this hypothesis, it was found that the spectrum of 4-hydroxy-2′,6′-dimethyldiphenyl ether (**23**) compared to 4-hydroxydiphenyl ether is shifted to longer wavelength and is increased in intensity as shown in Figure 1. In order to demonstrate that this spectral behavior was due to steric effect of the methyls and not to the conjugative or inductive effects, we compared these spectra with that of 4-methoxyphenol, which we chose as the closest facsimile, from an electronic standpoint, of the resonance form of **23** corresponding to **20**. This spectrum is almost superimposable with that of **23** as shown in Figure 1.

We also examined the spectra of a number of other di-*ortho*-substituted diaryl ethers and their electronic models, *i.e.*, the methoxy-substituted analogs of the unhindered ring moiety. The extremely similar spectra of **1** and 4-methoxy-2,6-dimethylphenol (Figure 2) are typical of these results. Thus it can be generalized that the spectra of diaryl ethers with bulky di-*ortho* groups on one of the rings are similar to spectra of the methoxy analogs of the unhindered rings.

These results demonstrate that in the case of *o*-dimethyl-substituted phenylene ethers such as **1**, **2**, and **23**, conjugation of the ether oxygen with the hindered ring is not significant; consequently, substituent effects are not transmitted from one ring to another as in the case of unhindered diaryl ethers.

Biological Significance.—The study of ring substituted analogs of thyroxine (**24**, X = X′ = I) has led to the following correlation of structure and thyroxine-like activity. When the hydrogens of thyronine (**24**, X = X′ = H) are substituted, activity decreases in the order: for X′, $CH_3 > I > Br > Cl > NO_2$; for X, $I > Br > Cl > CH_3 > NO_2$. The placement of methyl in the former sequence is based on results with 3,5-diiodo-3′,5′-dimethylthyronine (**24**, X = I; X′ = CH_3) in tadpole metamorphosis studies. However, methyl placement in the latter sequence is based upon studies of a compound presumed to be **4**, which proved to be almost inactive.



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More recently, Jorgensen studied the effect of nuclear substituents in rat antigoiter tests and reported the order I > Br > Me > Cl > H for X′ substituents.[6a] In this study, methyl placement was based on a compound presumed to be 3,5,3′,5′-tetramethylthyronine (**24**, X = X′ = CH_3) which had been prepared by Bielig and Lützel[5] from a chloromethyl intermediate which we have shown to be **14**. Pittman and coworkers tested this same material and found that it displayed no detectable metabolic activity in thyroidectomized rats.[6b] Likewise, the compounds presumed to be **9** and its methyl ether prepared by Van Heyningen have been tested by Herrmann, *et al.*, and found to be inactive in lowering tissue cholesterol levels in the rat.[8]

Our results show that all of the compounds used in these studies have structures analogous to **10** and that no authentic tetramethyl structural analogs of thyroxine have been tested. Thus, the conclusions regarding tetramethyl analogs must be withheld until authentic analogs can be synthesized and tested. As an extension of our work in this area, we have undertaken the synthesis of certain analogs and will report the results in future publications.

Experimental Section

The pmr spectral data and elemental analyses for compounds **1**, **2**, **10**, and **12–17** are given in Tables I and II. The infrared spectra were determined in KBr pellets with a Perkin-Elmer instrument. Melting points are not corrected.

Bromination of 4-Hydroxy-3,5,2′,6′-tetramethyldiphenyl Ether (1).—Bromine (0.25 ml, 6.1 mmol) was added in one portion to a

(15) M. Dahlgard and R. Brewster, *J. Amer. Chem. Soc.*, **80**, 5861 (1958).
(16) G. Baddeley and N. Smith, *J. Chem. Soc.*, 2516 (1961), and earlier papers.

solution of 1 g (4.1 mmol) of 1 in 30–40 ml of carbon tetrachloride. Within 0.5 min, evolution of hydrogen bromide commenced and appeared complete after 1 hr with stirring at room temperature. The excess bromine was removed by two washings with aqueous sodium bisulfite followed by water. The solution was dried over anhydrous sodium sulfate, filtered, and film-stripped to a red-brown residue, which crystallized on standing overnight. The crude product melted at 98–101°. On recrystallization from *n*-hexane the melting point was 101–103°, yield 1.19 g (91%). The product was identified as 2-bromo-4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether (**10**) on the basis of the pmr spectrum and the elemental analysis reported in Tables I and II.

The reaction was also carried out in acetic acid by adding dropwise a solution of 6.4 g (0.04 mol) of bromine in 20 ml of glacial acetic acid to a solution of 9.7 g (0.04 mol) of 1 in 80 ml of glacial acetic acid at room temperature. The solution was stirred until hydrogen bromide evolution appeared complete and was then poured into water containing a few grams of sodium bisulfite. The solid which precipitated was filtered and dried, mp 101–103°, 12.5 g (95%). The spectrum of the product was identical with that obtained in the experiment above, thereby establishing the product as **10**.

Bromination of 4-Methoxy-3,5,2′,6′-tetramethyldiphenyl Ether (2).—A solution of 3.2 g (0.02 mol) of bromine in 10 ml of glacial acetic acid was added dropwise to a solution of 5.0 g (0.0196 mol) of **2** in 20 ml of acetic acid at 15°. After addition was complete, the mixture was allowed to stand at room temperature for 12 hr. During this period, a solid precipitated that melted at 76–77° after drying, yield 0.8 g (11.4%). Pouring the filtrate into water led to a further crop which melted at 71–75°, 5.5 g (79%). The compound prepared by Bielig and Lützel[5] in a similar manner and reported to be 4′-bromo-4-methoxy-3,5,2′,6′-tetramethyldiphenyl ether (**3**) melts at 78–79°. By pmr spectra, the product was identified as 2-bromo-4-methoxy-3,5,2′-6′-tetramethyldiphenyl ether.

Acetylation of 4-Hydroxy-3,5,2′,6′-tetramethyldiphenyl Ether (1).—A suspension of 2 g (8.3 mmol) of **1** in 2 ml of acetic anhydride was stirred with a glass rod whose tip had been moistened with concentrated sulfuric acid. Within 0.5 min, the mixture became homogeneous, and the temperature increased slightly. Within several minutes, a white solid separated. The mixture was poured into water and the solid was collected by filtration, yield 2.2 g (85%), and had mp 123–123.5°. The infrared spectrum showed no hydroxyl and a strong carbonyl at 5.85 μ consistent with acetate derivative.

Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.1; H, 7.1. Found: C, 76.0; H, 7.2.

The acetate derivative (0.5 g, 1.76 mmol) was dissolved in 10 ml of acetic acid and 0.09 ml (1.71 mmol) of bromine was added. The resulting homogeneous, red-brown mixture was heated at 50–60° for 30 min, and at 60–70° for 10 min. During this time hydrogen bromide was steadily evolved and the red-brown color disappeared. The solution was poured into water containing sodium bisulfite yielding a sticky, white solid which was collected by filtration, dried, and recrystallized from *n*-hexane. This gave 0.5 g (78%) of a white, crystalline solid, melting at 87–89°. The infrared spectrum showed no hydroxyl and a strong carbonyl at 5.85 μ.

A portion of this product (0.4 g) was dissolved in 10 ml of methanol containing 0.5 g of potassium hydroxide and refluxed for several minutes. The solution was then poured into water containing excess hydrochloric acid and extracted with ether. Evaporation of the ether led to a solid whose melting point (94–96°) and infrared spectrum confirmed it as 2-bromo-4-hydroxy-3,5,2′-6′-tetramethyldiphenyl ether (**10**).

Polymerization of 2-Bromo-4-hydroxy-3,5,2′,6′-tetramethyldiphenyl Ether. (10).—A mixture of 27 ml of nitrobenzene, 9 ml of pyridine, and 25 mg of the bispyridine–chloride methoxide copper(II) complex was placed in an oxygen absorption apparatus maintained at 30°. After equilibrium had been attained, a solution of **10** (1.93 g, 6.0 mmol) in 4 ml of nitrobenzene was injected by means of a hypodermic syringe. The solution was stirred for 7 hr, during which 54.5 ml (2.8 mmol) of oxygen was absorbed. The reaction mixture was poured into 150 ml of methanol containing 1 ml of concentrated hydrochloric acid, yielding a coarse, white solid. The solid was collected and dried, weighing 1.80 g (94%). The infrared spectrum showed marked similarities to the spectrum of poly-2,6-dimethylphenylene ether and was consistent with a polyaryl ether. The intrinsic viscosity measured in chloroform at 25° was 0.27 dl/g.

Anal. Calcd for $C_{16}H_{15}O_2Br$: Br, 25.1. Found: Br, 25.0.

Nitration of 4-Methoxy-3,5-2′,6′-tetramethyldiphenyl Ether (2).—**2** (12.8 g, 0.05 mol) was converted to its nitro derivative by nitration in acetic anhydride according to the method of Bruice, Kharasch, and Winzler.[3] After recrystallization from methanol, the product melted at 111–112°, yield 13.0 g (89%). This product was identified as 2-nitro-4-methoxy-3,5,2′,6′-tetramethyldiphenyl ether (**12**) on the basis of the elemental analysis and pmr spectra reported in Tables I and II.

Hydriodic Acid Cleavage of 2-Nitro-4-methoxy-3,5,2′,6′-tetramethyldiphenyl Ether (12).—A mixture of **12** (8.6 g, 0.023 mol), 40 ml of glacial acetic acid, and 40 ml of 57% hydriodic acid was refluxed for 16 hr under a nitrogen atmosphere. A copious amount of iodine was liberated during this period. Addition of water led to 1.1 g (16.7%) of a yellow crystalline product, mp 159–161°, after recrystallization from ethanol–water. The infrared spectrum of this product showed strong absorption bands at 2.84 (–OH) and 6.58 μ ($-NO_2$). On the basis of the infrared and pmr spectra, and the elemental analysis, this product has been identified as 2-nitro-4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether (**17**).

By neutralizing the acidic mother liquor from the cleavage reaction, a white crystalline product was obtained. After recrystallization from ethanol–water the product melted at 154–155°, yield 3.41 g (58%). This product was identical with that obtained by catalytic reduction of **12**, followed by hydriodic acid cleavage of the methyl ether linkage, *i.e.*, 2-amino-4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether (**16**).

2-Amino-4-methoxy-3,5,2′,6′-tetramethyldiphenyl Ether (15).—2-Nitro-4-methoxy-3,5,2′,6′-tetramethyldiphenyl ether (**12**) (1.74 g, 0.006 mol) was dissolved in 60 ml of 95% ethanol and shaken at 30 psi hydrogen pressure with a Raney nickel catalyst. When hydrogen uptake was complete, the catalyst was removed and the filtrate concentrated *in vacuo* to a small volume. A crystalline product was obtained on cooling, which after recrystallization from 95% ethanol weighed 1.53 g (94%) and melted at 92–94°. The product was identified as **15** on the basis of the elemental analysis, and the ir and pmr spectra. Bruice, *et al.*,[3] reported a melting point of 89–90° for their product.

The amino anisole **15** (1.40 g, 0.005 mol) prepared just above, was refluxed in 20 ml of glacial acetic acid and 20 ml of 57% hydriodic acid for 15 hr under a nitrogen atmosphere. By neutralizing the acidic solution, a white crystalline product was obtained which weighed 1.1 g (83%) and melted at 154–155° after recrystallization from ethanol–water. On the basis of the elemental analysis and the ir and pmr spectra, this product was identified as 2-amino-4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether (**16**). Bruice, *et al.*,[3] report a melting point of 150–151° for this product, to which they assigned structure **4**.

2-Chloromethyl-4-methoxy-3,5,2′,6′-tetramethyldiphenyl Ether (14).—Following the directions of Bielig and Lützel,[5] 12.8 g (0.5 mol) of 4-methoxy-3,5,2′,6′-tetramethyldiphenyl ether (**2**), 2 g (0.67 mol) of paraformaldehyde in 50 ml of glacial acetic acid, and 6 ml of concentrated hydrochloric acid were stirred at room temperature with hydrogen chloride bubbling through the solution. After 16 hr, the product was poured into water and formed a rubbery solid which partially crystallized after being washed with more water. The product was taken up in pentane, washed with more water, dried over anhydrous magnesium sulfate, and concentrated on a steam bath. The product crystallized on cooling and melted sharply at 68–69° after several recrystallizations (Bielig and Lützel[5] reported mp 71°), yield 12.3 g (81%).

The infrared spectrum of the product in CS_2 solution showed a strong peak at 1090 cm^{-1}, which is indicative of three adjacent aromatic protons. The elemental analysis and the pmr spectrum confirm the identification of this product as **14**.

Bromination of 4-Methoxy-2′,6′-dimethyldiphenyl Ether (21).—The bromination of **21** was performed by stirring 1.14 g (1.0 mmol) of **21** with 1.60 g (1.0 mmol) of bromine in 15 ml of acetic acid for 24 hr. The product was poured into water and taken up into hexane solution which was washed with water and sodium bisulfite. The hexane solution was dried over anhydrous magnesium sulfate and concentrated *in vacuo*, yield 1.85 g (95%). Despite repeated attempts to attain a crystalline product, the product remained an oil. Vpc analysis showed that the oil consisted of a single product and a trace of unreacted **21**.

Anal. Calcd for $C_{15}H_{15}O_2Br$: C, 58.7; H, 4.9; Br, 26.0. Found: C, 58.6; H, 5.1; Br, 25.6.

The infrared spectra of both **21** and the brominated product show a peak at 9.2 μ. We have found that this band is associated with the 3′, 4′, and 5′ protons in compounds of this type. This evidence represents a strong indication that the brominated compound is substituted in the ring bearing the methoxyl group.

The pmr spectrum of **21** showed peaks at τ 7.90 (two methyl groups), 6.36 (OCH_3), 3.32 (four aromatic protons of the methoxyl bearing ring), and 3.02 (three aromatic protons of the ring bearing the methyls). After bromination, the spectrum has a single peak for the two methyl groups at τ 7.90, 6.24 (OCH_3), and 2.99 (three nuclear protons). The peak at τ 3.32 representing the four nuclear protons in the methoxyl-bearing ring of the starting material was split into an unsymmetrical array of peaks between τ 2.9 and 3.37. The pattern was observed to be typical of the aromatic protons in 1,2,4-trisubstituted compounds such as 2-chloro-1,4-dihydroxybenzene. Thus, the pmr spectrum is consistent only with a product brominated in the ring bearing the methoxyl group. It is not possible to determine whether the product has bromine in the 2 or 3 position on the basis of present evidence.

Bromination of 4-Methoxy-3,5-dimethyldiphenyl Ether (22).—The bromination of **22** was carried out by the same procedure used for **21**. A solution of 1.14 g (1.0 mmol) of **22** and 1.62 g (1.0 mmol) of bromine dissolved in 15 ml of acetic acid was stirred for 24 hr. The product was poured into water, taken up in hexane, and washed with aqueous solutions of sodium bisulfite and sodium bicarbonate. The hexane solution was dried over magnesium sulfate and evaporated to dryness leaving an oil which did not crystallize, yield 1.75 g (90%). Vpc analysis of the oil showed a single product in over 90% yield along with a trace of unreacted **22** and a small peak at higher retention time, possibly a dibromo derivative of **22**.

Anal. Calcd for $C_{15}H_{15}O_2Br$: C, 58.7; H, 4.9; Br, 26.0. Found: C, 58.2; H, 4.5; Br, 26.5.

The infrared spectra of both **22** and the brominated product showed strong bands at 693 and 740 cm^{-1}, indicative of monosubstituted phenyl groups. This represents strong evidence that the product is substituted in the 2 position.

The pmr spectrum of **22** showed absorption bands at τ 7.92 (6 protons), 6.40 (3 protons), 3.47 (2 protons), and a group of bands ranging from τ 2.7 to 3.3 typical of monosubstituted phenyl. The spectrum of the brominated product showed two peaks of equal intensity at τ 7.82 and 7.51 corresponding to 3 protons each representing two nonequivalent methyl groups, τ 6.34 (OCH_3), 3.29 (single aromatic proton), and the group of peaks in the range τ 2.7 to 3.3 corresponding to monosubstituted phenyl. These data are consistent with the conclusion that bromination of **22** has occurred in the 2 position and that the product is 2-bromo-3,5-dimethyl-4-methoxydiphenyl ether.

Registry No.—**1**, 3698-40-6; **1** (acetate), 15770-84-0; **2**, 10181-98-3; **10**, 18133-80-7; **12**, 25528-27-2; **13**, 18133-81-8; **14**, 25528-29-4; **15**, 25528-30-7; **16**, 25528-31-8; **17**, 25528-32-9; 2- or 3-bromo-4-methoxy-2′,6′-dimethyldiphenyl ether, 25641-46-7; 2-bromo-3,5-dimethyl-4-methoxydiphenyl ether, 25528-33-0.

Synthesis of 4′-Bromo-4-hydroxy-3,5,2′,6′-tetramethyldiphenyl Ether *via* Selective Debromination

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4′-Bromo-4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether (**1**) has been sought as a precursor to tetramethyl analogs of thyroxine and as a model compound for use in polymerization mechanism studies. Conventional aryl ether syntheses, such as the Ullmann condensation and the reactions of diaryliodonium salts with phenoxides, were successful in preparing **1**. Electrophilic substitution reactions of 4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether (**2**) and its methyl ether (**3**) invariably yielded the 2-monosubstituted products. The successful synthesis of **1** was based on the observation that the 2-bromo derivatives of **2** or **3** undergo debromination when treated with hydriodic acid in acetic acid at reflux. The dehalogenation reaction proved to be general for chloro or bromo groups in highly electron-rich ring positions, *e.g.*, *ortho* or *para* to a phenyl ether or phenolic group. The 2,4′-dibromo derivative of **3** was prepared by prolonged treatment of **3** with 2 equiv of bromine and debrominated exclusively in the 2 position by treatment with hydriodic acid giving a high yield of **1**. Compound **1** was converted into the 4′-carboxy and hydroxymethyl derivatives, which represent the first authentic tetramethyl thyroxine analogs.

4′-Bromo-4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether (**1**) has been sought as a precursor to tetramethyl-substituted thyroxine analogs and was reported to be the product of the monobromination of 4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether (**2**). Similarly, bromination of 4-methoxy 3,5,2′,6′-tetramethyldiphenyl ether (**3**) has been reported to result in 4′-bromo-4-methoxy-3,5,2′,6′-tetramethyldiphenyl ether (**4**).[1] Other electrophilic substitution reactions, such as nitration[2] or chloromethylation,[1] with **3** were also reported to yield the 4′ derivatives.

We have desired **1** as a model compound in order to study the mechanism of the oxidative polymerization of 4-bromo-2,6-dimethylphenol under basic conditions and attempted its synthesis by bromination of **2** and **3** according to the directions of Van Heyningen.[3] As we have already reported, these reactions resulted in 2-bromo-4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether (**5**) and its methyl ether (**6**), respectively.[4] Furthermore, we repeated all of the electrophilic substitution reactions that have been reported for **1** or **3** and found that the 2-monosubstituted products were obtained exclusively in each case.

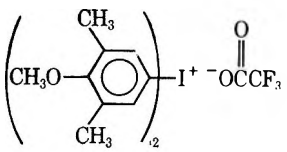
Because of the difficulties encountered in electrophilic reactions with **1** and **3**, we attempted the synthesis of 4′-substituted derivatives of **1** and **3** by other methods that are of general utility for the synthesis of diaryl ethers. The first of these involved the copper-catalyzed condensation of phenoxides and aryl halides first discovered by Ullmann and Stein.[5]

The copper-catalyzed reaction of 4-iodo-2,6-dimethylanisole with the potassium salts of 4-substituted 2,6-dimethylphenols proved to be unsuccessful where the

(1) H. Bielig and G. Lützel, *Justus Liebigs Ann. Chem.*, **608**, 140 (1957).
(2) T. Bruice, N. Kharasch, and R. Winzler, *J. Org. Chem.*, **18**, 83 (1953).
(3) E. Van Heyningen, *ibid.*, **26**, 3850 (1961).
(4) S. B. Hamilton, Jr., and H. S. Blanchard, *ibid.*, **35**, 3342 (1970). See also S. B. Hamilton, Jr., and H. S. Blanchard, U. S. Patent 3,351,667 (Nov 7, 1967).
(5) F. Ullmann and A. Stein, *Ber.*, **39**, 623 (1906).

4 substituent was Br, Cl, NO_2, or $COCH_3$. In the first two examples, the reaction produced nondistillable polyphenylene oxide resins and the unchanged iodoanisole.[6] In the latter two cases, both starting materials were recovered in high return, further substantiating earlier reports[1,3] that the combined steric and electronic effects associated with the phenolic reactant render such a reaction impossible with conventional procedures.

The diaryl ether synthesis developed by Beringer, *et al.*,[7] involving the reaction of alkali phenoxides and diarylicdonium salts was next investigated as a means of preparing the desired derivatives of **2** and **3**. In this connection we prepared 4,4′-dimethoxy-3,3′,5′5′-tetramethyldiphenyliodonium trifluoroacetate (**7**) and in-



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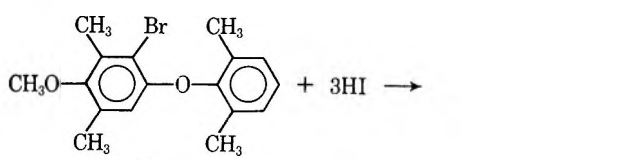
vestigated its reactions with the sodium salts of 4-chloro- and 4-bromo-2,6-dimethylphenol in a variety of solvents, methanol, acetone, and dimethyl sulfoxide. During the course of these reactions a white solid, whose infrared spectrum was identical with that of poly-2,6-dimethylphenylene ether, separated from solution.[8] No simple diphenyl ethers could be isolated from these reactions.

The successful preparation of **1** was based on the discovery that demethylation of the bromoanisole **6** with hydriodic acid in refluxing acetic acid proceeds with concomitant debromination, resulting in 2 rather than the expected bromophenol **5**.[9]



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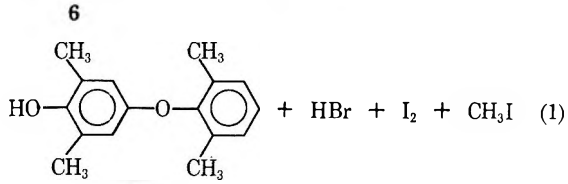

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The dehalogenation of aryl halides has been reported in several isolated cases as a side reaction that takes place during the dealkylation of a halophenylalkyl ether.[3,10,11] Only in the case of iodo aromatics has dehalogenation been studied in depth and found to be general for iodo groups *ortho* and *para* to hydroxy or amino groups.[12,13] The potential use of this kind of reaction in synthesis has not been generally recognized or applied.

We examined the scope of the debromination reaction by treating a variety of aryl bromides and aryl chlorides with hydriodic acid in acetic acid at reflux. The reactions were followed in several cases by titration of the liberated iodine with sodium thiosulfate solution and by vapor chromatography of the organic product. The results show that bromo or chloro substituents *ortho* or *para* to phenolic or phenyl ether groups are susceptible to reductive dehalogenation by hydriodic acid. *m*-Bromophenol was not affected by this treatment. Halogenated hydrocarbons, such as the bromo derivatives of benzene, toluene, *p*-xylene, and napthalene, are likewise not affected by this treatment. Bromo groups are removed significantly faster than chloro groups as evidenced by the fact that 4-bromo-2,6-dimethylphenol was quantitatively debrominated after 2 hr, while 4-chloro-2,6-dimethylphenol was 81% dechlorinated after 24 hr. In addition, it was possible to demethylate 4-methoxy-2′,6′-dichlorodiphenyl ether by refluxing 4 hr in the acid mixture without loss of chlorine from the product. These results suggested that it should be possible to selectively debrominate 4-bromo-2,6-dichlorophenol by this treatment. This was confirmed by the finding that when this reaction was carried out to the point that 70% of the theoretical amount of iodine was liberated, two products, namely 2,6-dichlorophenol and 2-chlorophenol, were formed in 85 and 15% yields, respectively. When halo anisoles were subjected to this treatment, the product was always the dehalogenated phenol, indicating that demethylation is at least as fast as dehalogenation under these conditions. These results suggested that demethylation might be required before dehalogenation could occur and that the dehalogenation reaction is specific for phenols. However, the observation that 4-bromodiphenyl ether is debrominated yielding diphenyl ether indicates that this is not the case.

The mechanism postulated for dehalogenation is essentially the reverse of that for halogenation of aromatics. In the first step, the nucleus is reversibly protonated in the most electron-rich positions, *i.e.*, *ortho* and *para* to the phenolic group, resulting in the resonance stabilized proton–arene σ complex, **8**. The protonated species also reversibly dissociates to the debrominated phenol and a bromonium ion that, in the presence of iodide ion, is irreversibly reduced to bromide ion, thereby shifting the equilibrium to provide the debrominated phenol.[13] At the same time, iodine, which is not capable of iodinating the phenol under these conditions, is generated.

(6) These results are not surprising since G. Staffin and C. C. Price [*J. Amer. Chem. Soc.*, **82**, 3622 (1960)], have shown that the potassium salts of 4-bromo- and 4-chloro-2,6-dimethylphenol are polymerized under a variety of oxidizing conditions.

(7) F. Beringer, R. Falk, M. Karniol, J. Lillien, G. Masullo, M. Mausner, and E. Sommer, *ibid.*, **81**, 342 (1959).

(8) Iodine, a common impurity in diaryliodonium salts, catalyzes the polymerization of potassium-4-bromo-2,6-dimethylphenoxide (see ref 6).

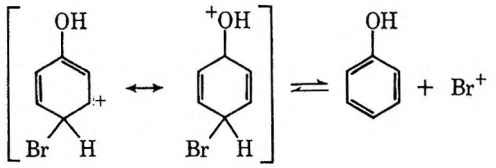
(9) The debromination reaction was also observed by Van Heyningen (ref 1), although it was reported incorrectly because of the erroneous assignment of the structure of the bromoanisole **6**.

(10) V. Kryuchkova and S. Zangordnii, *J. Gen. Chem. USSR*, **30**, 3827 (1960).

(11) H. Rappoport, T. P. King, and J. B. Lavigne, *J. Amer. Chem. Soc.*, **73**, 2718 (1951).

(12) (a) B. H. Nicclet and J. R. Sampey, *ibid.*, **49**, 1796 (1921); (b) B. H. Nicolet and W. L. Ray, *ibid.*, **49** 1301 (1921); (c) B. H. Nicolet and R. B. Sandin, *ibid.*, **49** 1806 (1921); (d) B. H. Nicolet, *ibid.*, **49** 1810 (1921).

(13) Following the completion of this work, the reversible nature of bromination reactions in the presence of hydrogen bromide has been disclosed by E. J. O'Bara, R. B. Balsey, and I. Stare, *J. Org. Chem.*, **35**, 16 (1970). The mechanism postulated is essentially the same as that postulated in the present case with the exception that reaction with hydrogen bromide results in the formation of bromine, which is capable of bromination, leading to a mixture of products.



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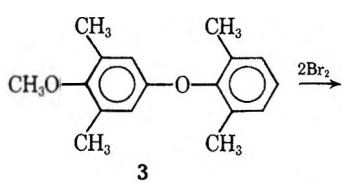
$$Br^+ + 2I^- \longrightarrow I_2 + Br^-$$

The capability of removing bromo groups selectively from positions of high electron density gave hopes of obtaining **1** if the 4′,2-dibromo derivative of **2** or **3** could be prepared. Because of the high degree of reactivity in the 2 position, monobromination of **2** and **3** occurs rapidly and exclusively in the 2 position when 1 equiv of bromine is used.[4] A study of molecular models indicated that if dibromination could be accomplished, the second bromo group would substitute in the unbrominated ring because of steric hindrance to substitution in the brominated ring. The methyl ether **3** was treated with 2 equiv of bromine added in two equal quantities at room temperature in acetic acid and the reaction was followed by vapor chromatography. The first equivalent was consumed completely within several hours, and analysis showed exclusive formation of the monobromo derivative **6**. The addition of the second equivalent of bromine resulted in a gradual disappearance of the red color and a slow development of a new product detectable by vapor chromatography. After 24 hr at room temperature, a crystalline product separated from solution. This product, obtained in 88% yield, was identified as 2,4′-dibromo-4-methoxy-3,5,2′,6′-tetramethyldiphenyl ether (**9**, eq 2).



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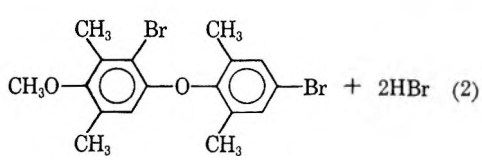

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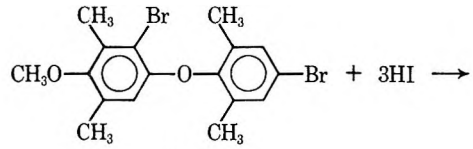
. When the dibromo derivative **9** was treated with hydriodic acid in acetic acid at reflux for several hours, bromine was removed rapidly and exclusively from the 2 position resulting in the desired bromophenol **1** in over 80% yield (eq 3).

The selective monodebromination of **9** in the 2 position is another example of the unusual positional differences in reactivity of highly substituted diphenyl ethers. As we have already reported, the difference in the reactivity of the two rings can be largely attributed to the bulk of the 2′,6′-dimethyl groups, which prevent the interaction of the nonbonding electrons of the phenyl ether oxygen with the ring to which they are



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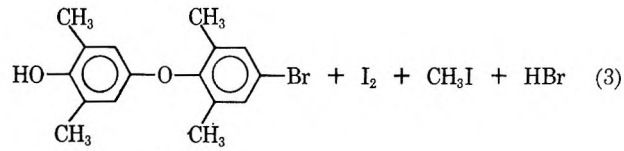

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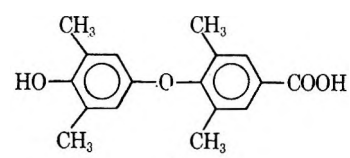
attached. On the other hand, they do not hinder the electronic interaction of the ether oxygen with the other ring. This hypothesis is fully supported by ultraviolet spectral studies which show that the contribution to the ultraviolet spectrum of **1** of the phenoxy ring bearing the 2′,6′-dimethyl groups is little different from that of a methoxy group. Thus, the spectrum of **1** is almost superimposable with that of 4-methoxy-2,6-dimethylphenol.[4]

The successful synthesis of **1** has made possible the study of the mechanism of the oxidative polymerization of 4-bromo-2,6-dimethylphenol and these results are being reported separately. In addition, **1** has been converted to 4′-carboxy-4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether (**10**) and 4′-hydroxymethyl-4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether (**11**) by lithiation, followed by reactions with carbon dioxide



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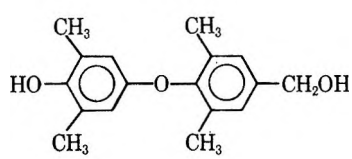

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and formaldehyde, respectively. These products represent the first authentic tetramethyl thyroxine analogs synthesized to date.

Experimental Section

Attempted Syntheses of 4′-Substituted Derivatives of 4-Methoxy-3,5,2′,6′-tetramethyldiphenyl Ether *via* Ullmann Condensation.[5]—The condensation of 4-iodo-2,6-dimethylanisole with potassium salts of 4-bromo-, 4-chloro-, 4-nitro-, and 4-aceto-2,6-dimethylphenols were attempted by mixing 0.55 mol of the iodoanisole, 0.50 mol of the substituted phenol, 0.50 mol of KOH, and 0.5 g each of activated copper powder and cupric acetate under nitrogen in a round-bottom flask fitted with a stirrer and Dean–Stark trap. The reactant mixture was heated slowly to 150° to remove water and finally to 260° for 3.5 hr. After cooling, the reaction product was worked up by extraction into benzene solution, which was washed with dilute alkali to remove the unreacted phenol. In the reactions with the 4-bromo- and 4-chloro-2,6-dimethylphenols, a solid was precipitated from the benzene solution by addition of methanol. The ir spectra of the solid products were identical with that of poly-2,6-dimethyl-

phenylene ether.[14] Vpc analysis of the benzene filtrates showed a large quantity of unreacted 4-iodo-2,6-dimethylanisole and small peaks at higher retention times that presumably represented the desired products in very low yield. The reactions involving 4-nitro- and 4-aceto-2,6-dimethylphenols resulted in the formation of low yields of unidentified resins. Both the phenolic and anisole reactants were recovered in 60–80% recovery. If the desired diphenyl ethers were formed, their yields were too low for them to be detected or isolated during the work-up procedures.

4,4′-Dimethoxy-3,3′,6,6′-tetramethyldiphenyliodonium Trifluoroacetate (7).—Iodine trifluoroacetate was prepared from 25.0 g (0.1 mol) of iodine, 25 ml of fuming HNO_3 (sp gr 1.51), and 47 ml of CF_3COOH (0.612 mol) in 70 ml of acetic anhydride, according to the directions of Beringer, *et al.*[7] The white solid salt was next dissolved in 150 ml of acetic anhydride and cooled to −10°. Then a solution of 109 g (0.8 mol) of 2,6-dimethylanisole, 350 ml of acetic anhydride, and 50 ml of CF_3COOH was added over a 2-hr period while the temperature was maintained at −10°. The solution was refrigerated overnight. Removal of the solvent at reduced pressure afforded an oil to which was added 600 ml of cool anhydrous ether, giving 20.7 g (19.7%) of the iodonium salt **7**, mp 203–205° dec.

Anal. Calcd for $C_{20}H_{22}O_4F_3I$: C, 47.1; H, 4.34. Found: C, 47.5; H, 4.1.

Reactions of the Iodonium Salt 7 with Sodium Salts of 4-Bromo- and 4-Chloro-2,6-dimethylphenol.—The iodonium salt **7** (5.1 g, 0.01 mol) was added to a solution of 0.05 mol of sodium 2,6-dimethyl-4-bromophenate in 100 ml of CH_3OH and the solution was heated to reflux. After several minutes of reflux, a solid material began to separate from solution. After 24 hr at reflux, the reaction mixture was cooled and the solid was collected by filtration. The infrared spectrum of this product proved to be identical with that of poly-2,6-dimethylphenylene ether prepared by other methods.[14] The CH_3OH filtrate was evaporated and redissolved in benzene. The benzene solution was washed with NaOH solution, followed by a washing with water, and dried ($MgSO_4$). Vpc analysis of this solution showed the principal component to be 2,6-dimethyl-4-iodoanisole with several peaks at higher retention time, too small to be of preparative significance.

Under otherwise similar conditions, the reactions of **7** with the sodium salts of 2,6-dimethyl-4-bromophenol and 2,6-dimethyl-4-chlorophenol were investigated using both acetone and anhydrous dimethyl sulfoxide as solvents. Again the only isolable products were 2,6-dimethyl-4-iodoanisole and poly-2,6-dimethylphenylene ether.

Dehalogenation of Aryl Halides with Hydriodic Acid.—The dehalogenation experiments were performed by adding 0.01 mol of the respective aryl halide to a solution of 12.5 ml of hydriodic acid (57%) and 12.5 ml of glacial acetic acid under N_2 atmosphere. The mixtures were refluxed for 24 hr and the product was worked up by pouring the reaction mixture into water and extracting with benzene. The benzene solutions were treated with solutions of $NaHCO_3$ and $NaHSO_3$ to remove acid and iodine impurities. The products were analyzed by vpc indicating both the extent of the reaction and the product distribution when the retention times were compared with known samples. Titration of iodine liberated in the reaction with 0.1 *N* $Na_2S_2O_3$ correlated well with the extent of reaction indicated by vpc data. The results obtained with a variety of aryl halides are summarized in Table I.

2,4′-Dibromo-4-methoxy-3,5,2′,6′-tetramethyldiphenyl Ether (9).—The dibromo compound **9** was prepared by adding a solution of 6.4 g (0.04 mol) of Br_2 in 20 ml of glacial acetic acid in two equal portions to a solution of 5.12 g (0.02 mol) of 4-methoxy-3,5,2′,6′-tetramethyldiphenyl ether (**3**) in 20 ml of acetic acid at room temperature. After the addition of the first portion of the Br_2 solution, the red color disappeared within several hours and vpc analysis showed a single peak, which had a retention time identical with that of 2-bromo-4-methoxy-3,5,2′,6′-tetramethyldiphenyl ether (**6**). After the addition of the second portion of Br_2 solution, the red color persisted and vpc analysis indicated the formation of a new product at higher retention time than either **3** or **6**. The reaction mixture was allowed to stand with stirring for an additional 24 hr. The solid product was precipitated by addition of water, filtered, and recrystallized from acetic acid giving 6.7 g (81%) of the dibromo compound **9**: mp 134–135°; nmr ($CDCl_3$) τ 2.95 (s, 2, ArH), 4.13 (s, 1, ArH), 6.44 (s, 3, OCH_3), 7.65 (s, 3, $ArCH_3$), 7.93 (s, 9, $ArCH_3$).

(14) A. S. Hay, *J. Polym. Sci.*, **58**, 581 (1962).

Table I

Dehalogenation Results

Aryl halide	Product	Conversion, %
4-Bromo-2,6-dimethylphenol	2,6-Dimethylphenol	100 (2 hr)
4-Bromo-3,5-dimethylphenol	3,5-Dimethylphenol	100 (2 hr)
2-Bromoanisole	Phenol	100
4-Bromoanisole	Phenol	100
4-Bromophenol	Phenol	100
4-Bromodiphenyl ether	Diphenyl ether	66
3-Bromophenol		0
4-Chloroanisole	Phenol	90
4-Chloro-2,6-dimethylphenol	2,6-Dimethylphenol	81
4-Bromo-2,6-dichlorophenol	2,6-Dichlorophenol (85%) 2-Chlorophenol (15%)	70
4-Bromotoluene		0
α-Bromonaphthalene		0
1,3,5-Tribromobenzene		0
Bromo-*p*-xylene		0
Bromobenzene		0

Anal. Calcd for $C_{17}H_{18}O_2Br_2$: C, 49.3; H, 4.4; Br, 38.6. Found: C, 49.5; H, 4.5; Br, 38.1.

2,4′-Dibromo-4-hydroxy-3,5,2′,6′-tetramethyldiphenyl Ether—The dibromophenol was prepared by dibromination of 4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether in the same manner as the dibromoanisole (**9**) above in 57% yield: mp 131–133°; nmr ($CDCl_3$) τ 2.95 (s, 2, ArH), 4.17 (s, 1, ArH), 5.74 (s, 1, OH), 7.65 (s, 3, $ArCH_3$), 7.99 (s, 9, $ArCH_3$).

Anal. Calcd for $C_{16}H_{16}O_2Br_2$: C, 48.1; H, 4.0; Br, 39.8. Found: C, 48.6; H, 4.1; Br, 39.3.

4′-Bromo-4-hydroxy-3,5,2′,6′-tetramethyldiphenyl Ether (**1**).—A solution of 4.14 g (0.01 mol) of 2,4′-dibromo-4-methoxy-3,5,2′,6′-tetramethyldiphenyl ether (**9**) was dissolved in a solution of 12.5 ml of HI (57%) and 12.5 ml of glacial acetic acid and refluxed for 2 hr. The reaction mixture was poured into water containing $NaHSO_3$ to precipitate the product and remove the iodine. The solid product was recrystallized from hexane giving 2.7 g (80%) of the bromo derivative **1**: mp 132–134°; pmr ($CDCl_3$) τ 2.89 (s, 2, ArH), 3.73 (s, 2, ArH), 5.80 (s, 1, OH), 7.85 (s, 6, $ArCH_3$), 7.93 (s, 6, $ArCH_3$).

Anal. Calcd for $C_{16}H_{17}O_2Br$: C, 59.8; H, 5.3; Br, 24.9. Found: C, 60.0; H, 5.5; Br, 24.7.

4′-Carboxy-4-hydroxy-3,5,2′,6′-tetramethyldiphenyl Ether (**10**).—A solution of 0.015 mol of butyllithium in 10 ml of anhydrous ether was added with stirring to a solution of 1.6 g (0.005 mol) of 4′-bromo-4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether (**1**) in 50 ml of anhydrous ether at −30°. The mixture was stirred at −30° for 2 hr, allowed to warm to 25°, and stirred an additional 30 min. The solution was poured onto crushed Dry Ice, allowed to warm to room temperature, neutralized with dilute acid, and extracted into ether solution. The ether extract was extracted with dilute NaOH several times, and the basic solution was neutralized with dilute HCl. The resulting solid was recrystallized (ethanol–water) giving 1.2 g (84%) of the carboxy derivative **10**: mp 215–216°; ir 5.9–6.0 (C=O), 2.9–3.0 μ (OH); pmr (perdeuteriopyridine) τ −2.15 (s, 2, -OH), 1.74 (s, 2, ArH), 3.27 (s, 2, ArH), 7.58 (s, 6, $ArCH_3$), 7.71 (s, 6, $ArCH_3$). A potentiometric titration run in triplicate using tetra-*t*-butylammonium hydroxide in pyridine solution showed two inflections indicating two ionizable acidic groups of different basicity. The values obtained showed 285.3, 281.1, and 283.7 ml/mequiv of carboxyl and 282.4, 292.2, and 288.0 ml/mequiv of hydroxyl compared to 286.3 ml/mequiv for each in $C_{17}H_{18}O_4$.

Anal. Calcd for $C_{17}H_{18}O_4$: C, 71.3; H, 6.32. Found: C, 70.9; H, 6.45.

4′-Hydroxymethyl-4-hydroxy-3,5,2′,6′-tetramethyldiphenyl Ether (**11**).—The dilithio salt of 4′-bromo-4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether (**1**) was prepared by reacting 1.6 g (0.005 mol) of **1** with 0.015 mol of butyllithium in ether at −30° under nitrogen. The solution was allowed to warm to room temperature after 2 hr of stirring, and 1.5 g of paraformaldehyde, decomposed by heating in a nitrogen stream, was introduced. The reaction product was stirred an additional hour and neu-

tralized with dilute H_2SO_4. The ether layer was washed with water, dried ($MgSO_4$), and evaporated to give 1.0 g (65%) of the hydroxymethyl derivative 11, mp 175–176°.

Anal. Calcd for $C_{17}H_{20}O_3$: C, 74.9; H, 7.4. Found: C, 75.2; H, 7.2.

Registry No.—**1**, 18133-84-1; **7**, 25517-40-2; **9**, 18133-83-0; **10**, 25517-93-5; **11**, 25517-94-6; 2,4′-dibromo-4-hydroxy-3,5,2′,6′-tetramethyldiphenyl ether, 18133-82-9.

Double-Bond Isomerizations in Unsaturated Esters and Enol Ethers. I. Equilibrium Studies in Cyclic and Acyclic Systems[1,2]

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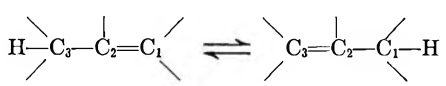
Equilibrium data are presented for tautomeric equilibria in three carbon olefinic systems incorporating methyl, methoxy, and methoxycarbonyl substituents on five- and six-membered rings and acyclic chains. Geometric equilbria have been studied for combinations of these same groups as substituents on a double bond. Equilibrations were achieved thermally, with base catalysis in protic and aprotic solvents, with iron pentacarbonyl in hydrocarbon solvent, and, in those cases in which an enol ether structure is maintained in the isomerization, by trace amounts of iodine in an inert solvent. The iodine-catalyzed isomerization has been demonstrated to be intermolecular by a deuterium exchange experiment.

Since the pioneering studies of Kon, Linstead, and coworkers, the effect of structure on the position of olefin equilibrium in three-carbon systems has continued to receive attention.[3] In general, the relative stabilities of the 1,2 and 2,3 isomers of acyclic systems have been successfully correlated with the conjugative and induc-



tive contributions of substituents located on the three-carbon allylic chain.[4] Notable failures of the predictive power of this approach can be expected when unfavorable steric[5] or polar[6] interactions are superimposed on normal conjugative and inductive effects. Such departures from predicted behavior appear to be especially prevalent in cyclic systems in which conversion to a more favorably disposed geometric arrangement is precluded.[6,7] For example, the fact that equilibration of 2-alkoxy-1-alkoxycarbonylcyclohexenes strongly favors the 2,3 isomer[8] would not have been expected on the basis of earlier analyses.[4] In an effort to sort out and evaluate the contributions of these various factors in cyclic systems of particular interest to us, we have studied positional and configurational equilibria in unsaturated cyclic and acyclic systems incorporating methyl, methoxy, and carbomethoxy groups in various combinations. This paper reports the results of the equilibrium studies. A quantitative assessment of the electronic, steric, and polar contributions of these substituents is made in the accompanying paper.[9]

(1) Taken in part from the Ph.D. dissertations of J. K. Chattopadhyay, University of Wyoming, 1967, and E. E. Waali, University of Wyoming, 1970.

(2) This research was supported by National Science Foundation Grants GP-1517 and GP-6375. E. E. W. expresses his gratitude for a National Science Foundation Summer Traineeship in 1967.

(3) See D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, p 200, for a summary and leading references to recent work.

(4) (a) C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, p 562; (b) P. B. de la Mare, *J. Chem. Soc.*, 1602 (1952).

(5) K. L. Rinehart, Jr., and L. J. Dolby, *J. Org. Chem.*, **22**, 13 (1957)

(6) R. C. Fuson and J. A. Haefner, *ibid.*, **27**, 1957 (1962).

(7) N. Heap and G. H. Whitman, *J. Chem. Soc. B*, 164 (1966).

(8) S. J. Rhoads and R. W. Hasbrouck, *Tetrahedron*, **22**, 3557 (1966), and this paper.

(9) S. J. Rhoads and E. E. Waali, *J. Org. Chem.*, **35**, 3358 (1970).

Results

The systems examined are displayed in Tables I and II. The cyclic compounds in Table I are subject to tautomeric equilibration but not to geometric; the acyclic systems in Table I are subject to both. The olefinic systems in Table II were included in the study in order to assess the magnitude of steric and polar interactions of the three variable groups when any two of them are held in a *cis* relationship.

The required compounds were prepared in a variety of standard ways, detailed in the Experimental Section. In each system, the individual isomeric species involved were isolated and characterized by their spectral properties and, when possible, by comparison with authentic samples prepared by independent routes. In this connection, the synthetic utility of photochemical *trans* to *cis* isomerizations of the unsaturated esters **9a**, **10a**, **11**, and **14** and of the photoconversion of α,β, to β,γ isomerides in the ester systems **9** and **10** deserves notice. Others[10] have called attention to the fact that irradiation of α,β-unsaturated esters provides a general synthetic method for the preparation of the often less accessible β,γ isomer. In the case of the ester system **10**, the photoisomerization may be exploited to permit the preparation of the two geometric isomers of each positional isomer. As may be seen in Figure 1, the photochemical behavior of *E*-**10a**[11] is characterized by a rapid buildup of *Z*-**10a**,[11] the geometric species required for the α,β–β,γ isomerization.[10] A decay in the concentration of *Z*-**10a** is accompanied by the formation of *Z*- and *E*-**10b**. The desired isomer(s) may be isolated from the photoreaction mixture after the appropriate irradiation time by glpc trapping.

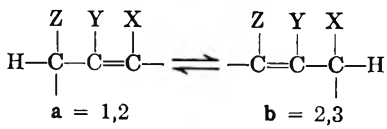
The method required for equilibration depends strongly on the structural features of the isomeric system. In the unsaturated ester systems **1**, **2**, **5**, **6**, **9**, **10**, and **11**, equilibrium is achieved only after rather extended heating at temperatures of 100–120° in the presence of strong base or iron pentacarbonyl.[12] Purely

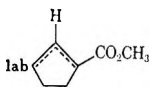
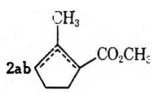
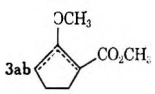
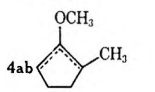
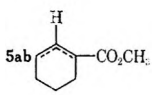
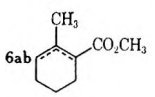
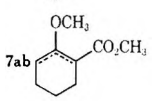
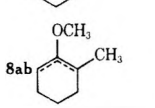
(10) P. J. Kropp and H. J. Krauss, *ibid.*, **32**, 3222 (1967); R. R. Rando and W. von E. Doering, *ibid.*, **33**, 1671 (1968).

(11) See J. E. Blackwood, C. L. Gladys, K. L. Loening, A. E. Petrarca, and J. E. Rush, *J. Amer. Chem. Soc.*, **90**, 509 (1968), for the designation of geometric isomers as *E* and *Z*.

(12) R. Damico, *J. Org. Chem.*, **33**, 1550 (1968).

TABLE I
TAUTOMERIC EQUILIBRIA IN
CYCLIC AND ACYCLIC ALLYLIC SYSTEMS



System	K_{eq} (2,3/1,2)	$\Delta G^{\circ a}$ (kcal/mol)	Equilibration method[b] and temp, °C
 1ab	0.06	+2.1 ± 0.2	A, 100
 2ab	0.06	+2.1 ± 0.2	A, 100
 3ab	0.47 0.53	+0.64 ± 0.04 +0.37 ± 0.03	B, 150 C, 25
 4ab	2.0	−0.41 ± 0.03	C, 25
 5ab	0.05	+2.2 ± 0.2	A, 100
 6ab	0.32	+0.85 ± 0.04	A, 100
 7ab	5.0 7.5	−1.35 ± 0.05 −1.2 ± 0.05	B, 150 C, 25
 8ab	1.5	−0.26 ± 0.02	C, 25
$CH_3CH{=}CH{-}$	0.45	+0.63 ± 0.04	A, 117
$CHCO_2CH_3$	0.51	+0.53 ± 0.04	D, 117
9ab (*Z* and *E*)	0.36	+0.79 ± 0.05	E, 117
$CH_3OCH{=}CH{-}$	12.7	−2.9 ± 0.3	B, 300
$CHCO_2CH_3$	31.3	−2.5 ± 0.3	E, 92
10ab (*Z* and *E*)			

[a] Uncertainties are based on reproducibility of equilibrium composition of ±1% on duplicate runs. [b] Methods: A, sodium methoxide–methanol; B, thermal, neat; C, iodine–cyclohexane; D, sodium methoxide–HMPT; E, iron pentacarbonyl–octane.

thermal isomerizations[13] of these systems require prolonged heating at 250–300° and show extensive material losses. On the other hand, those systems in which an enol ether function is maintained in the isomerization, *i.e.*, **3**, **4**, **7**, **8**, **12**, **13**, and **14**, are quite labile. Trace amounts of acidic impurities often suffice to bring about rapid equilibration at ordinary temperatures. Although various protic acids have been employed as catalysts to isomerize enol ethers of this type,[14,15] we have found iodine, used in low concentration in an inert solvent, to be much superior for equilibrium studies. In most cases, equilibrium is established within minutes at room temperature without detectable diversion of material by side reactions.

Analyses of the equilibrated systems were made by glpc methods, standardized against synthetic mixtures of known composition. Whenever possible, the achievement of equilibrium was accomplished from both directions. Results of such experiments generally agreed with ±1%. The conditions used for the equilibrations, the equilibrium constants, and the corresponding free energy changes are shown in the tabulations.[16]

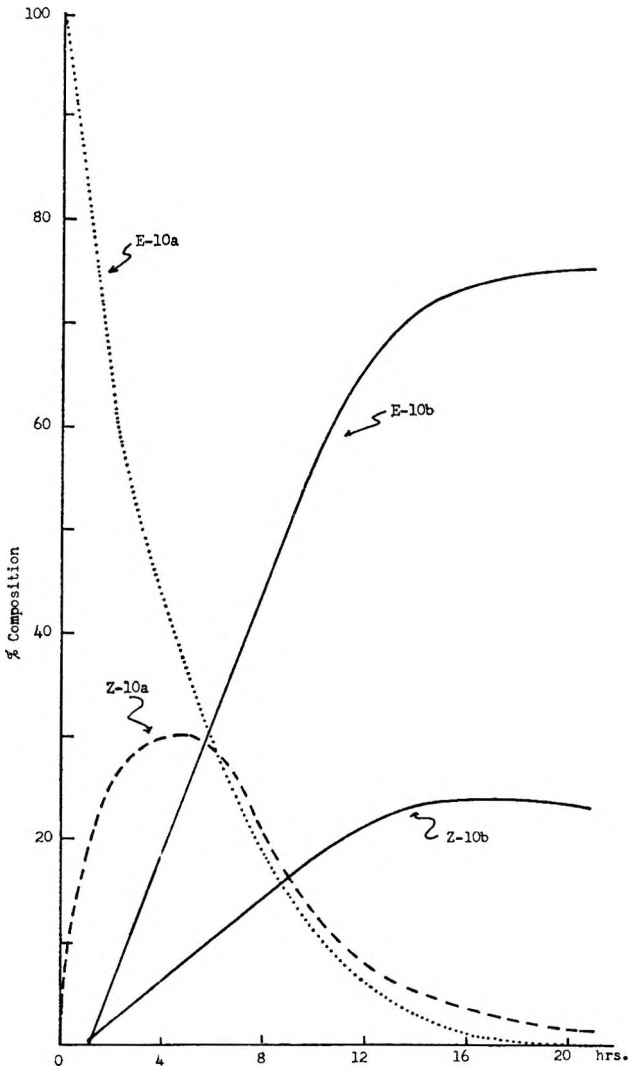


Figure 1.—Photoisomerization of methyl 4-methoxy-2-butenoate, *E*-**10a**, and *Z*-**10a**.

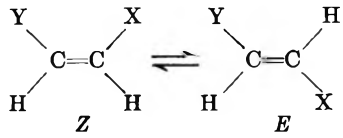
Discussion

Several of the systems, or close relatives of them, have been studied by other workers. Linstead's early work included the carboxylate anions of the pentenoic[17] and cyclohexene carboxylic acids,[18] corresponding to the ester systems **9** and **5**. Equilibrium values of K = 0.47 (ΔG° = +0.6 kcal/mol) and K = 0.05 (ΔG° = +2.2 kcal/mol) for the acyclic and cyclic systems, respectively, were found when the equilibrations were carried out in aqueous sodium hydroxide at 100°. The

(13) D. E. McGreer and N. W. K. Chiu, *Can. J. Chem.*, **46**, 2225 (1968), and earlier papers quoted therein.
(14) H. O. House and V. Kramer, *J. Org. Chem.*, **28**, 3362 (1963).
(15) P. Salomaa and P. Nissi, *Acta Chem. Scand.*, **21**, 1386 (1967).
(16) It is noteworthy that the differences in solvent and temperature which were utilized for equilibration of the various isomeric systems appear to have only small effects on the equilibrium composition and/or the corresponding free energy change for a given system. See, for example, the data for systems **3ab**, **7ab**, **9ab**, and **10b**. In the free energy terms, these changes reflect, at most, a difference of only a few tenths of a kilocalorie.
(17) Quoted in ref 4b.
(18) E. Boorman and R. P. Linstead, *J. Chem. Soc.*, 258 (1935).

TABLE II

GEOMETRIC EQUILIBRIA IN OLEFINIC SYSTEMS



Z E

No.	System Y	System X	K_{eq} (E/Z)	$\Delta G°$, kcal/mol	Equilibration method[a] and temp, °C
11	CH_3	CO_2CH_3	6.25	-1.4 ± 0.05	D, 117
12	CH_3	OCH_3	1.21	-0.12 ± 0.03	C, 25
13	C_2H_5	OCH_3	1.82	-0.36 ± 0.03	C, 25
14	CH_3O	CO_2CH_3	124	-3.6 ± 0.5	C, 100
9a	C_2H_5	CO_2CH_3	~11–23[b]	~−2	A, D, E, 117
10a	CH_3OCH_2	CO_2CH_3	~4–5[b]	~−1	E, 92
10b	CH_3O	$CH_2CO_2CH_3$	~1[b]	~0	E, 92
			1.15	-0.08 ± 0.02	C, 25

[a] See footnote *b*, Table I. [b] Estimates based on analyses of tautomeric equilibria under conditions cited in Table I.

agreement with the results for the corresponding methyl esters recorded in Table I is remarkably good, and confirms the idea that the stabilizing effects of $-CO_2^-$ and $-CO_2R$ are approximately equal.[4] Owen and Sultanbawa[19] examined the base catalyzed isomerization of the anion of γ-methoxycrotonic acid (corresponding to the ester system **10**) in aqueous and alcoholic media, and concluded that the equilibrium favored the β,γ isomer with $K = 2.3$ ($\Delta G° = -0.6$ kcal/mol). This result contrasts with our findings for the methyl esters, wherein we find a much stronger preference for the β,γ isomer, **10b**. Hine and coworkers[20] also examined this system as the methyl ester equilibrated with potassium methoxide in *t*-butyl alcohol at 35° and could detect none of the α,β isomer, **10a**, after 60 half-lives. As Hine has pointed out, it seems highly unlikely that such a difference could be accounted for by the mere replacement of carboxylate by carbomethoxy. One may speculate that the experiments of Owen and Sultanbawa were complicated by a concurrent addition of solvent to the olefinic bond; that such addition occurs readily has been demonstrated by Hine[20] and also has been observed in our investigation.

The methyl crotonate–methyl isocrotonate system, **11**, has been studied by three other groups. Thermal equilibrations at 195° in the liquid phase[21] and at 200–500° in the gas phase[22] provided values of $K = 7$ and $K = 4.5$, whereas an N-bromosuccinimide (NBS) catalyzed equilibration in carbon tetrachloride at 77°[23] led to a value of $K = 10$. Our value for this system, measured in hexamethylphosphortriamide (HMPT) at 117° ($K = 6.25$), is in fair agreement with these reports.

House and Kramer[14] have reported equilibrium values for the ethyl ether analogs of the methyl enol ethers, **4** and **8**. Their method of equilibration consisted of heating the ethers at 100° with *p*-toluenesulfonic acid for 60–100 hr. Under these conditions, they found equal amounts of the 1,2 and 2,3 isomers in both ring systems, *i.e.*, $K = 1$. These results differ somewhat from our findings for the methyl ethers; using the iodine catalysis method, we observe a preponderance of the 2,3 isomer in both cases ($K = 1.2$ and 2.0).

Finally, attention is called to the *E*/*Z* equilibrium values for methyl propenyl ether, **12**, and methyl 1-butenyl ether, **13**. In both cases, the equilibrium values reflect a slight bias in favor of the *E* isomer. These results are at variance with other reports on acyclic enol ethers which claim that the *Z* isomer is the more stable. Thus, Price and Snyder[24] report that in the phenyl propenyl ether system, the *Z* isomer is the more stable, accounting for 65% of the equilibrium mixture. Salomaa and Nissi[15] have reported $K_{E/Z} = 0.5$ for the methyl propenyl ether system, **12**, and $K_{E/Z} = 0.24$ for the methyl butenyl ether system, **13**. The equilibration method used by Price and Snyder was not reported, but Salomaa and Nissi stated that they followed the isomerizations in dilute dioxane solution at 25° in the presence of benzoic acid (ether–catalyst ~3:1). We have been unable to duplicate these experiments. Our experience with protic acid catalysts such as benzoic and *p*-toluenesulfonic acid is that consumption of the catalyst occurs before equilibration is complete. If larger amounts of acid are used, polymerization ensues. Quite recently, Okuyama, Fueno, and Furukawa[25] have presented a careful study of *cis*–*trans* equilibria in a series of enol ethers, including the system **12**. Equilibrations were carried out in the liquid phase with mercuric acetate as a catalyst. For methyl propenyl ether, **12**, they report $K_{E/Z} = 1.03$ at 25°, *i.e.*, a slight preponderance of the *trans* isomer, in qualitative agreement with our results in a hydrocarbon solvent. Attention is also directed to the relative stabilities of the *cis*/*trans* pair, *Z*-**10b** and *E*-**10b**. As in the case of the simple enol ether, **12**, the geometric isomers show almost equal stabilities at 25°. From such examples, one may conclude either that the steric requirement of the methoxy group is very small or that there are other, unappreciated, factors which stabilize enol ethers in the *cis* geometry.[25] It also follows, from a comparison of the systems **12** and **10b**, that, sterically, the groups $-CH_3$ and $-CH_2CO_2CH_3$ are about equivalent. In the same way, comparison of the geometric equilibria of the systems **11** and **10a** reveals similar steric requirements for $-CH_3$ and $-CH_2OCH_3$.

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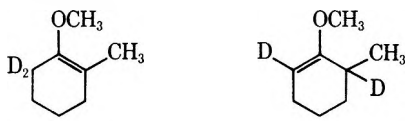
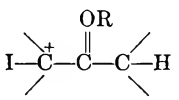
(24) C. C. Price and W. H. Snyder, *J. Amer. Chem. Soc.*, **83**, 1773 (1961).
(25) T. Okuyama, T. Fueno, and J. Furukawa, *Tetrahedron*, **25**, 5409 (1969).

The facility and cleanness of the iodine-induced 1,3-hydrogen migrations in the enol ether systems **3**, **4**, **7**, and **8** prompted an investigation of the inter- *vs.* intramolecular nature of the rearrangement. Conceivably, the hydrogen transfer could occur intramolecularly within an iodine–enol ether complex. Accordingly, an exchange experiment using a mixture of the deuterated ethers, **8a**-d_2 and **8b**-d_2, and nondeuterated ethers was carried out under the isomerization conditions. Mass spectral analysis of the d_2, d_1, and d_0 composition before and after equilibration showed that a distribution of the deuterium labels close to statistical had been achieved during the equilibration. We conclude that the isomerization is intermolecular and visualize an ionic process initiated by the electrophilic species[26]



8a-d_2 **8b**-d_2



Experimental Section

Infrared spectra were recorded as thin films with a Perkin-Elmer Model 621 or Beckman IR-10 instrument. Ultraviolet spectra were measured in methanol in matched 1-cm silica cells at 25° with a Beckman DB spectrophotometer. Nmr spectra were obtained on solutions in carbon tetrachloride with TMS internal standard with either a Varian A-60 or HA-100 instrument. Mass spectral analyses were performed with a Consolidated Engineering Corporation 21-103-C mass spectrometer. Photoisomerizations were carried out at ambient temperature in dilute solutions in quartz tubes placed within a circular bank of 16 General Electric G8T5 Germicidal Lamps (rich in 2537 Å). Carefully purified solvents were employed in all the equilibration experiments and spectral measurements.

Methyl 1-Cyclopentene-1-carboxylate (1a) and Methyl 2-Cyclopentene-1-carboxylate (1b).—Cyclopentene-1-carboxylic acid, mp 120–121° (lit.[27] 121°), prepared by the method of Wheeler and Lerner,[27] was esterified with diazomethane to give the corresponding methyl ester, **1a**: bp 63–65° (10 mm); ir 1724, 1636 cm^{-1}; uv max 222 nm (ϵ 8300); nmr δ 6.70 (m, 1, HC=C) (lit.[28] δ 6.9), 3.67 (s, 3, OCH_3), ~2.5 (m, 4, allylic CH_2), 1.92 (m, 2, CH_2); purity by glpc, >99%. Reduction of 2-carbomethoxycyclopentanone with $NaBH_4$ in methanol and dehydration of the resulting hydroxy ester with P_2O_5 in benzene, according to the procedure of Bokil and Nargund,[29] produced a 1:3 mixture of **1a** and **1b**, bp 60–65° (15 mm). **1b** was isolated by glpc trapping: ir 1741, 1620 cm^{-1}; uv no max >210 nm; nmr δ 5.7 (m, 2, HC=CH) (lit.[28] δ 5.8), 3.65 (s, 3, OCH_3), ~3.3 (m, 1, allylic H α to ester), 2.8–2.0 (br m, 4, CH_2CH_2).

Methyl 2-Methyl-1-cyclopentene-1-carboxylate (2a) and Methyl 2-Methyl-2-cyclopentene-1-carboxylate (2b).—Dehydration of the cyanohydrin of 2-methylcyclopentanone according to the procedure of King and Robinson[30] gave a mixture of unsaturated nitriles, bp 70–75° (16 mm). Hydrolysis and esterification of the crude acids with diazomethane yielded a mixture of methyl esters, bp 73–75° (15 mm). Glpc analysis showed the presence of three components which were isolated by glpc trapping and purified by recycling. The major component was identified as **2a** by its spectral properties; ir 1720, 1650 cm^{-1}; uv max 231 (ϵ 10,900); nmr δ 3.67 (s, 3, OCH_3), ~2.5 (m, 4, allylic CH_2), 2.08 (m, 3, allylic CH_3), 1.75 (m, 2, CH_2). The component with the shortest retention time was identified as **2b**: ir 1742, 1660 cm^{-1}; uv no max >210 nm; nmr δ 5.47 (m, 1, HC=C), 3.65 (s, 3, OCH_3), ~3.25 (br m, 1, allylic H α to ester), ~2.5–1.9 (br m, 4, CH_2CH_2), 1.72 (m, 3, allylic CH_3). The minor component with intermediate retention time was identified as methyl 5-methyl-1-cyclopentene-1-carboxylate: ir 1728, 1630 cm^{-1}; uv max 222 nm (ϵ 9300); nmr δ 6.60 (m, 1, HC=C), 3.50 (s, 3, OCH_3), ~2.9 (m, 1, tertiary allylic H), ~2.3 (br m, 4, CH_2CH_2), 1.13 (d, 3, CH_3).

Methyl 2-Methoxy-1-cyclopentene-1-carboxylate (3a) and Methyl 2-Methoxy-2-cyclopentene-1-carboxylate (3b).—Treatment of 2-carbomethoxycyclopentanone with an ethereal solution of diazomethane according to the procedure of Lacasa, *et al.*,[31] yielded **3a**, white platelets from pentane, mp 39.5–40.0° (cor) in 85% yield; S. E. 159 (calcd for $C_8H_{12}O_5$ 156); ir 1717, 1695, 1636 cm^{-1}, str bands characteristic of β-alkoxy-α,β-unsaturated esters[32]; uv max 254 nm (ϵ 13,600); nmr δ 3.78 (s, 3, OCH_3 of ether), 3.57 (s, 3, OCH_3 of ester), 2.5 (m, 4, allylic CH_2), 1.83 (m, 2, CH_2). Distillation of **3a** through a Podbielniak column at 40 mm pressure at a rate which allowed equilibration produced the β,γ isomer, **3b**: bp 120–125° (40 mm); ir 1743, 1655 cm^{-1} (C=O and C=CO of unconjugated ester and enol ether[32]); uv no max >210 nm; nmr δ 4.57 (m, 1, HC=C), 3.60 (s, 3, OCH_3), 3.52 (s, 3, OCH_3), ~3.4 (m, 1, tertiary allylic H α to ester), ~2.5–1.8 (br m, 4, CH_2CH_2).

1-Methoxy-2-methyl-1-cyclopentene (4a) and 2-Methoxy-3-methyl-1-cyclopentene (4b).—The dimethyl ketal of 2-methylcyclopentanone was prepared with methyl orthoformate in methanol with *p*-toluenesulfonic acid catalyst according to the general procedure of House and Kramer,[14] bp 80–84° (40 mm), in 65% yield. Dealcoholation with $NH_4H_2PO_4$[14] produced a mixture of **4a** and **4b**, bp 120° (590 mm), in 86% yield. The enol ethers were separated and purified by glpc trapping (15% Carbowax 20M on Gas-Chrom P, 115°). **4a**: ir 1692 cm^{-1}, str (C=CO); uv no max >210 nm; nmr δ 3.51 (s, 3, OCH_3), 2.5–2.0 (br, m, 4, allylic CH_2), 1.8 (m, 2, CH_2), 1.50 (m, 3, CH_3). **4b**: ir 3072, w (HC=C), 1643 cm^{-1}, str (C=CO); uv no max >210 nm; nmr δ 4.29 (m, 1, HC=C), 3.51 (s, 3, OCH_3), 2.7–1.2 (br complex, 5, CH_2CH_2CH), 1.03 (d, 3, CH_3).

Methyl 1-Cyclohexene-1-carboxylate (5a) and Methyl 2-Cyclohexene-1-carboxylate (5b).—Diazomethane esterification of 1-carboxycyclohexene, mp 37–38°,[27] produced **5a**, bp 100° (30 mm): ir 1719, 1657 cm^{-1}; uv max 217 nm (ϵ 10,300); nmr[12] δ 6.90 (m, 1, HC=C), 3.66 (s, 3, OCH_3), 2.2 (m, 4, allylic CH_2), 1.6 (m, 4, CH_2CH_2). The β,γ isomer, **5b**, was isolated from equilibrated mixtures of **5a** and **5b** by glpc trapping: ir 1734, 1645 cm^{-1}; nmr[12] δ 5.68 (m, 2, H-C=C-H), 3.56 (s, 3, OCH_3), 2.94 (m, 1, tertiary), 2.5–2.1 (br, complex, 6, $CH_2CH_2CH_2$).

Methyl 2-Methyl-1-cyclohexene-1-carboxylate (6a) and Methyl 2-Methyl-2-cyclohexene 1-carboxylate (6b).—The method of Jones, *et al.*,[33] was followed for the preparation of 2-methyl-1-cyclohexane-1-carboxylic acid, mp 86–87° (lit.[33] 87°). Diazomethane esterification afforded **6a**, isolated and purified by glpc: ir 1722, 1654 cm^{-1}; uv max 225 nm (ϵ 9600); nmr δ 3.61 (s, 3, OCH_3), ~2.2 (m, 4, allylic CH_2), 1.96 (m, 3, CH_3), ~1.6 (m, 4, CH_2CH_2). The unconjugated isomer, **6b**, was isolated from equilibrated mixtures by glpc trapping: ir 1735, 1666 cm^{-1}; nmr δ 5.45 (m, 1, HC=C), 3.54 (s, 3, OCH_3), 2.84 (m, 1, tertiary), 2.1–1.2 (br complex, 6, $CH_2CH_2CH_2$), 1.59 (narrow m, 3, allylic CH_3).

Methyl 2-Methoxy-1-cyclohexene-1-carboxylate (7a) and Methyl 2-Methoxy-2-cyclohexene-1-carboxylate (7b).—Treatment of 2-carbomethoxycyclohexanone with methyl orthoformate and sulfuric acid according to the procedure of Michael[34] furnished the dimethyl ketal. Slow distillation of the latter through a Podbielniak column at 40 mm promoted dealcoholation and the more volatile isomer, **7b**, was collected as a colorless liquid. Recrystallization of the solid pot residue from pentane yielded **7a**, colorless plates; mp 45.5–46.0° (cor); S.E. 172 (calcd for $C_9H_{14}O_3$, 170); ir 1716, 1690, 1628 cm^{-1};[32] uv max

(26) This species is implicated by the kinetic studies of Eley and coworkers on the iodine-promoted polymerization of vinyl ethers: D. D. Eley and A. W. Richards, *Trans. Faraday Soc.*, **45**, 425, 436 (1949); D. D. Eley and J. Saunders, *J. Chem. Soc.*, 4167 (1952).

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(32) See ref 8 and S. J. Rhoads and R. W. Holder, *Tetrahedron*, **25**, 5443 (1969), for characteristic spectral properties of enol ethers of β-keto esters.

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(34) A. Michael, *J. Amer. Chem. Soc.*, **57**, 161 (1935).

254 (ε 10,300); nmr δ 3.60 (s, 6, OCH_3), ~2.2 (m, 4, allylic CH_2), ~1.6 (m, 4, CH_2CH_2). The β,γ isomer, **7b**, showed bp 123–128° (40 mm); ir 1746, 1671 cm^{-1}; uv no max >210 nm; nmr δ 4.68 (t, 1, HC=C), 3.60 (s, 3, OCH_3), 3.45 (s, 3, OCH_3), ~3.1 (m, 1, allylic H α to ester); 2.3–1.4 (br complex, 6, CH_2-CH_2CH_2).

1-Methoxy-2-methyl-1-cyclohexene (8a) and 2-Methoxy-3-methyl-1-cyclohexene (8b).—The dimethyl ketal of 2-methylcyclohexanone, prepared in the manner described for the corresponding cyclopentanone derivative, underwent dealcoholation when heated with anhydrous ferric chloride[34] to yield a mixture of **8a** and **8b**, bp 58–60° (22 mm), which was separated by preparative glpc. The component with the shorter retention time proved to be **8b**: ir 1671 cm^{-1} (str, C=CO); nmr δ 4.45 (t, 1, HC=C), 3.41 (s, 3, OCH_3), ~2.4–1.2 (br complex, 7, $CH_2CH_2CH_2$ and tertiary allylic H), 1.03 (d, 3, CH_3). The second component, **8a**, showed the spectral properties: ir 1685 cm^{-1} (str, C=CO); nmr δ 3.38 (s, 3, OCH_3), ~2.2–1.4 [br complex, 8, $(CH_2)_4$], 1.54 (m, 3, CH_3).

Methyl 2-Pentenoate (9a) and Methyl 3-Pentenoate (9b).—Esterification of a mixture of 2- and 3-pentenoic acids produced by dehydrobromination[35] of 2-bromopentanoic acid yielded a mixture consisting of 85% **9a** and 15% **9b**, bp 58–60° (35 mm). Pure samples of *E*-**9a**, *Z*-**9a**, and *E*-**9b** were trapped by preparative glpc (15% Carbowax 20M on Gas-Chrom P at 110°) for spectral analysis. *E*-**9a**: ir 1725, 1657, 970 cm^{-1}; nmr δ 6.87 (d of t, 1, *J* = 15 and 6 Hz, HC_3=C), 5.67 (d of t, 1, *J* = 15 and 1.7 Hz, HC_2=C), 3.55 (s, 3, OCH_3), 2.16 (m, 2, CH_2), 1.02 (t, 3, CH_3). *Z*-**9a**: ir 1721, 1629 cm^{-1}; nmr δ 6.10 (d of t, *J* = 11.2 and 7.2 Hz, 1, HC_3=C), 5.62 (d of t, *J* = 11.2 and 1.6 Hz, 1, HC_2=C), 3.60 (s, 3, OCH_3), 2.62 (m, 2, CH_2), 1.04 (t, 3, CH_3). *E*-**9b**: ir 1740, 1657, 961 cm^{-1}; nmr δ 5.47 (m, 2, HC=CH), 3.57 (s, 3, OCH_3), 2.89 (m, 2, CH_2), 1.68 (m, 3, CH_3).

Samples of **9b** were also prepared by irradiation of the mixture of *E*-**9a** and *Z*-**9a** as a dilute solution in pentane (5%) containing 6% benzene.[10] The presence of a small amount of *Z*-**9b** in the photoproduct was indicated by the appearance of two methoxy signals in the nmr spectrum of the β,γ isomer but the geometric isomers were not separable by the glpc conditions employed.

Methyl 4-Methoxy-2-butenoate (10a) and Methyl 4-Methoxy-3-butenoate (10b).—The conjugated isomer, **10a**, prepared by the method of Sultanbawa, *et al.*,[36] was largely *E*-**10a**, accompanied by a small amount of *Z*-**10a**. Preparative glpc (15% Carbowax 20M on Gas-Chrom-P at 130°) furnished a pure sample of *E*-**10a**: ir 1724, 1664, 965 cm^{-1}; nmr[20] δ 6.86 (d of t, *J* = 15.6 and 4.0 Hz, 1, HC_3=C), 5.97 (d of t, *J* = 15.6 and 2.0 Hz, 1, HC_2=C), 3.66 (s, 3, OCH_3), 3.32 (s, 3, OCH_3), 4.02 (d of d, *J* = 2.0 and 4.0 Hz, 2, CH_2). Irradiation of a 5% solution of *E*-**10a** in pentane containing 2% benzene was continued 4 hr at which time *Z*-**10a** had reached its maximum concentration (Figure 1). Glpc trapping afforded pure *Z*-**10a**: ir 1711, 1651 cm^{-1}; nmr δ 6.28 (d of t, *J* = 11.7 and 4.9 Hz, 1, HC_3=C), 5.71 (d of t, *J* = 11.7 and 3.2 Hz, 1, HC_2=C), 4.40 (d of d, *J* = 4.9 and 3.2 Hz, 2, CH_2), 3.64 (s, 3, OCH_3), 3.32 (s, 3, OCH_3). Samples of *E*-**10b** and *Z*-**10b** could be isolated from the photoreaction mixture allowed to proceed to completion (rich in *E*-**10b**), or from the thermal (~1:1 in *trans* and *cis* isomers) or base-catalyzed (almost exclusively *Z*-**10b**) equilibration mixtures. Glpc trapping afforded pure samples. *E*-**10b**: ir 1739, 1659 cm^{-1}; nmr[20] δ 6.32 (d of t, *J* = 12.8 and 1.4 Hz, 1, HC_4=C), 4.72 (d of t, *J* = 12.8 and 7.5 Hz, 1, HC_3=C), 3.56 (s, 3, OCH_3), 3.46 (s, 3, OCH_3), 2.84 (d of d, 2, CH_2). *Z*-**10b**: ir 1737, 1668 cm^{-1}; nmr[20] δ 5.91 (d of t, *J* = 6.1 and 1.7 Hz, 1, HC_4=C), 4.48 (d of t, *J* = 6.1 and 7.0 Hz, 1, HC_3=C), 3.68 (s, 3, OCH_3), 3.62 (s, 3, OCH_3), 2.99 (d of d, 2, CH_2).

Methyl 2-Butenoate (11).—Fischer esterification of crotonic acid produced **11**, bp 110–112° (590 mm). Preparative glpc (15% Reoplex-400 on Gas-Chrom P at 110°) permitted isolation of pure *E*-**11**: ir 1722, 1658, 965 cm^{-1}; nmr[37] δ 6.89 (d of q, *J* = 15.4 and 6.9 Hz, 1, HC_3=C), 5.76 (d of q, *J* = 15.4 and 1.65 Hz, 1, HC_2=C), 3.62 (s, 3, OCH_3), 1.86 (d of d, *J* = 6.9 and 1.65 Hz, 3, CH_3). The *cis* isomer, *Z*-**11**, was prepared by photoisomerization of *E*-**11** in a pentane–benzene solution by the method described earlier. After 25 hr of irradiation the concentration of *Z*-**11** had reached a maximum and only minor amounts of the β,γ isomer, methyl 3-butenoate, had formed. Preparative glpc gave pure *Z*-**11**: ir 1720, 1648 cm^{-1}; nmr[37] δ 6.28 (d of q, *J* = 11.4 and 7.0 Hz, 1, HC_3=C), 5.72 (d of q, *J* = 11.4 and 1.6 Hz, 1, HC_2=C), 3.64 (s, 3, OCH_3), 2.14 (d of d, *J* = 7.0 and 1.6 Hz, 3, CH_3).

Methyl Propenyl Ether (12).—Base-catalyzed isomerization of methyl allyl ether (bp 35–39° at 590 mm, ir 1646 cm^{-1}) was accomplished by a 17-hr reflux period in 0.15 *M* sodium methoxide solution in DMSO. The major component of the reaction mixture (96%) was the *cis* isomer, *Z*-**12**, which was purified by glpc trapping: ir 1667, 720 cm^{-1}; nmr[38] δ 5.72 (d of q, *J* = 6.4 and 1.8 Hz, 1, HC(O)=C), 4.21 (d of q, *J* = 6.4 and 7.0 Hz, 1, HC(O)=C), 3.42 (s, 3, OCH_3), 1.47 (d of d, *J* = 7.0 and 1.8 Hz, 3, CH_3). Isomerization of *Z*-**12** with iodine in *n*-decane produced a *cis–trans* mixture from which the pure *trans* isomer, *E*-**12**, was isolated by glpc trapping: nmr[38] δ 6.15 (d of q, *J* = 12.6 and 1.5 Hz, 1, HC(O)=C), 4.52 (d of q, *J* = 12.6 and 6.5 Hz, 1, HC(O)=C), 3.34 (s, 3, OCH_3), 1.49 (d of d, *J* = 6.5 and 1.5 Hz, 3, CH_3).

Methyl 1-Butenyl Ether (13).—The mixture of *E*-**13** and *Z*-**13** obtained by dealcoholation of *n*-butyraldehyde dimethyl acetal with $NH_4H_2PO_4$, by the procedure of House and Kramer,[14] was separated by preparative glpc (25% Reoplex-400 on Chromosorb W at 65°). *E*-**13**: ir 1674, 1657 cm^{-1}; nmr[39] δ 6.21 (d of t, *J* = 12.5 and 1.3 Hz, 1, HC(O)=C), 4.62 (d of t, *J* = 12.5 and 5.6 Hz, 1, HC(C)=C), 3.38 (s, 3, OCH_3), 1.92 (m, 2, CH_2), 0.96 (t, *J* = 7.6 Hz, 3, CH_3). *Z*-**13**: ir 1664 cm^{-1}; nmr[39] δ 5.71 (d of t, *J* = 6.3 and 1.5 Hz, 1, HC(O)=C), 4.23 (d of t, *J* = 6.3 and 7.0 Hz, 1, HC(C)=C), 3.47 (s, 3, OCH_3) 2.02 (m, 2, CH_2), 0.92 (t, *J* = 7.7 Hz, 3, CH_3).

Methyl 3-Methoxy-2-propenoate (14).—The dimethyl acetal of methyl α-formylacetate, prepared by the general method described by Deno[40] from methyl α-bromoacetate and methyl orthoformate, was examined without purification by nmr: δ 4.67 [t, *J* = 6 Hz, 1, $HC(OCH_3)_2$], 3.56 (s, 3, CO_2CH_3), 3.19 [s, 6, $(CH_3O)_2C$], 2.26 (d, *J* = 6 Hz, 2, CH_2). Dealcoholation of the acetal was accomplished in the following way: 5.2 g of the acetal and 0.1 g *p*-toluenesulfonic acid were placed in a flask equipped with a short path distillation head and heated to 120°. Methanol was slowly removed as the pot temperature rose to 150°. Additional quantities of catalyst were added; the procedure was repeated until the formation of methanol ceased. Distillation of the residue produced *E*-**14**: bp 159–164° (594 mm), in 61% yield; ir 1710, 1646, 1626 cm^{-1}; nmr[41] δ 7.47 (d, *J* = 12.2 Hz, 1, HC(O)=C), 5.06 (d, *J* = 12.2 Hz, 1, HC(C)=C) 3.61 (s, 3, OCH_3), 3.55 (s, 3, OCH_3). The *cis* isomer, *Z*-**14**, could be prepared by short term photoisomerization of *E*-**14** in carbon tetrachloride solution. Under these conditions, the maximum concentration of *Z*-**14** attained in the mixture was 6%. Nmr analysis of this enriched mixture showed the presence of signals attributed to *Z*-**14**:[41] δ 6.35 (d, *J* = 6.7 Hz, 1, HC(O)=C), 4.69 (d, *J* = 6.7 Hz, 1, HC(C)=C), 3.80 (s, 3, OCH_3), 3.57 (s, 3, OCH_3).

Equilibration Methods.—In all the equilibrations except the iron pentacarbonyl catalyzed cases, samples of the substrate, neat or in solution, with the appropriate catalyst and internal standard, were degassed and sealed under nitrogen in thoroughly

(35) C. F. Allen and M. J. Kalm, "Organic Syntheses," Coll. Vol. IV, Wiley, New York, N. Y., 1963, p 398.

(36) M. U. S. Sultanbawa, P. Veeravagu, and T. Padmanathan, *J. Chem. Soc.*, 1262 (1960).

(37) R. R. Fraser and D. E. McGreer, *Can. J. Chem.*, **39**, 505 (1961).

(38) T. Higashimura, S. Kusudo, Y. Obsumi, A. Mizote, and S. Okamara, *J. Polym. Sci., Part A-1*, 2511 (1968).

(39) N. J. Turro and P. A. Wriede, *J. Org. Chem.*, **34**, 3562 (1969), report nmr data for the isomeric methyl butenyl ethers in which some of the *J* values appear to be transposed.

(40) N. C. Deno, *J. Amer. Chem. Soc.*, **69**, 2233 (1947).

(41) E. Winterfeldt and H. Preuss, *Chem. Ber.*, **99**, 450 (1966).

cleaned Pyrex tubes. The progress of the isomerizations was monitored by glpc analysis. Whenever possible, equilibrium was achieved starting with each isomer. In the iron pentacarbonyl catalyzed systems, the substrate and catalyst were dissolved in octane or "isooctane" and the mixture held at reflux temperature under a nitrogen atmosphere. Isomerizations induced by iron pentacarbonyl were followed by ir analysis. After equilibrium had been established, heating was continued to destroy the remaining iron catalyst before glpc analysis of the equilibrated sample was carried out. The methods and results are summarized in Tables III and IV. In the cases of catalysis by iodine

TABLE III

TAUTOMERIC EQUILIBRATIONS

Starting material	Equilibrium composition[a] % 1,2 isomer	% 2,3 isomer	Equilibration conditions[b]
1a	94.3	5.7	A: 0.5 *M* in substrate
1b	95.2	4.8	and catalyst; 4–10 hr, 100 ± 5°
2a	94.3	5.7	A: 0.5 *M* in substrate
2b	94.2	5.8	and catalyst; 4–10 hr, 100 ± 5°
3a	69.6	30.4	B: neat, 240 hr, 150
3b	67.0	33.0	± 5°
3a	64.5	35.5	C: 2.0 *M* in substrate,
3b	65.4	34.6	0.05 *M* in catalyst, 0.5–1 hr, 25 ± 1°
4a	34.5	65.5	C: 0.15 *M* in sub-
4b	33.2	66.8	strate, 0.003 *M* in catalyst, 10–20 min, 25 ± 1°
5a	95.5	4.5	A: 0.5 *M* in substrate and catalyst, 4–10 hr, 100 ± 5°
6a	75.6	24.4	A: 0.5 *M* in substrate and catalyst, 4–10 hr, 100 ± 5°
7a	11.7	88.3	C: 2.0 *M* in substrate,
7b	11.8	88.2	0.05 *M* in catalyst, 0.5–1 hr, 25 ± 1°
8a	39.4	60.6	C: 2.0 *M* in substrate,
8b	39.6	60.4	0.05 *M* in catalyst, 0.5–1 hr, 25 ± 1°
9a	73.5	26.5	E: 0.2 *M* in substrate, 0.04 *M* in catalyst, 46 hr, 117 ± 5°
9a	66.3	33.7	D: 1.4 *M* in substrate, 0.02 *M* in catalyst, 4 hr, 117 ± 5°
80% **9a** + 20% **9b**	69.1	30.9	A: 0.5 *M* in substrate and catalyst, 9 hr, 117 ± 5°
E-**10a**	8.6	91.4	B: neat, 500 hr, 220 ± 5°
Z-**10a**	7.2	92.8	B: neat, 15 hr,
22% **10a** + 78% **10b**	7.5	92.5	300 ± 5°
22% **10a** + 78% **10b**	3.1	96.9	E: 0.2 *M* in substrate, 0.04 *M* in catalyst, 50 hr, 92 ± 5°

[a] Values are averages of at least three determinations on a given equilibrium mixture. [b] See footnote *a*, Table I.

(method C) and by iron pentacarbonyl (method E) the material balance was excellent as judged by internal standards or by comparison of glpc analyses of an equilibrated mixture against a synthetic mixture which had not been subjected to equilibration conditions. Thermal isomerizations (method B) often were accompanied by appreciable material loss and were extremely slow; only the more labile systems **3**, **7**, and **10** could be brought to near equilibrium by this method. Method A showed good reproducibility and material balance for the cyclic esters **1**, **2**, **5**, and **6** but extensive material loss was observed for the acyclic

TABLE IV

GEOMETRIC EQUILIBRATIONS

Starting material	Equilibrium composition[a] % *Z* isomer	% *E* isomer	Equilibration conditions[a]
Z-**11**	13.8	86.2	D: 1.4 *M* in substrate, 0.02 *M* in catalyst, 3 hr, 117 ± 5°
Z-**12**	44.8	55.2	C: 0.15 *M* in substrate, 0.003 *M* in catalyst, 2–5 hr, 25 ± 1°
Z-**13**	36.0	64.0	C: 0.15 *M* in sub-
21% *Z*-**13** + 79% *E*-**13**	34.5	65.5	strate, 0.003 *M* in catalyst, 2.5 hr, 25 ± 1°
E-**14**	0.8	99.2	C: CCl_4 solution,
6% *Z*-**14** + 94% *E*-**14**	0.8	99.2	0.15 *M* in substrate, 0.003 *M* in catalyst, 8 hr, 100 ± 5°
19% *Z*-**10b** + 81% *E*-**10b**	46.5	53.5	C: 0.12 *M* in substrate, 0.003 *M* in catalyst, 10 hr, 25 ± 1°

[a] See footnotes, Table III.

systems 9 and 10, presumably by addition of solvent to the olefinic bond. Substitution of the aprotic solvent, HMPT, and a lower catalyst concentration corrected this problem and also shortened the time required for the achievement of equilibrium (method D).

Glpc Analysis.—The equilibrated samples were analyzed by glpc methods standardized against synthetic mixtures of known composition. In all cases, the integrated areas of the peaks corresponded to the composition of the mixture within the reproducibility of duplicate runs (±1%). Analysis conditions were carefully checked for each isomeric system to assure that isomerization did not occur during analysis. Analyses were performed with either a Perkin-Elmer 154-C vapor fractometer or a Varian Aerograph A-90-P instrument. Helium was the carrier gas in all cases. The columns and conditions for each system are shown in Table V.

TABLE V

GLPC ANALYSIS CONDITIONS

System	Column[a]	Temp, °C	Elution order
1ab	I	140	**1b**, **1a**
2ab	I	150	**2b**, **2a**
3ab	II	124	**3b**, **3a**
4ab	III	72	**4b**, **4a**
5ab	I	150	**5b**, **5a**
6ab	I	150	**6b**, **6a**
7ab	II	124	**7b**, **7a**
8ab	III	114	**8b**, **8a**
9ab	IV	75	*Z*-**9a**, *Z*- + *E*-**9b**, *E*-**9a**
10ab	V	82	*Z*-**10a**, *Z*-**10b**, *E*-**10b**, *E*-**10a**
11	IV	72	*Z*-**11**, *E*-**11**
12	IV	20	*Z*-**12**, *E*-**12**
13	IV	50	*Z*-**13**, *E*-**13**
14	VI	117	*E*-**14**, *Z*-**14**

[a] I: Perkin-Elmer "K" packing, 2.6 m. II: 2.5% Reoplex-400 on Gas-Chrom P, 3 m. III: 10% UCON Polar, on Gas-Chrom P, 3 m. IV: 15% diisodecyl phthalate on Gas-Chrom P, 3 m. V: 15% diphenyl phthalate on Gas-Chrom P, 3 m. VI: 15% Reoplex 400 on Chromosorb W, 4 m.

2,6,6-d_3-2-Methylcyclohexanone.—The trideuterated ketone was prepared by the general procedure described by Seibl and

Gauman[42] by three successive treatments of 2-methylcyclohexanone with a 10% solution of $DCl-D_3PO_4$ in D_2O. Nmr analysis of the exchanged ketone indicated the deuterium content to be about 95% of that calculated for the d_3 compound.

6,6-d_2-1-Methoxy-2-methylcyclohexene (8a-d_2) and 1,3-d_2-2-Methoxy-3-methylcyclohexene (8b-d_2).—The enol ethers of the deuterated 2-methylcyclohexanone, prepared in the presence of methanol-d_1 by the method described earlier, were isolated by glpc trapping and identified by their spectral properties. Mass spectral analysis of 8b-d_2 at low ionization voltage showed the deuterium distribution to be 78.8% d_2 species, 18.4% d_1 species, and 2.8% d_0 species after correction for natural isotopic contributions.[43] Moreover, analysis of a sample of 8b-d_2 before and after glpc trapping showed that negligible amounts of exchange or fractionation occurred on the column.

Deuterium Exchange Experiment.—An equilibrium mixture of 8a-d_2 and 8b-d_2 was diluted with nonlabeled equilibrated ethers to give a sample with the deuterium distribution: d_2, 41.1%, d_1, 20.3%, and d_0, 38.6%. The mixture was then subjected to the conditions of the iodine catalyzed equilibrations. After 24 hr the mixture of isomers was isolated by glpc trapping and the deuterium distribution redetermined. The final distribution was d_2, 23.5%, d_1, 49.1%, and d_0, 27.4%, in close agreement with the statistical distribution of d_2, 26.8%, d_1, 48.8%, and d_0, 24.4%.

Registry No.—**1a**, 25662-28-6; **1b**, 2258-56-2; **2a**, 25662-30-0; **2b**, 25662-31-1; **3a**, 25662-32-2; **3b**, 25662-33-3; **4a**, 25662-34-4; **4b**, 25662-35-5; **5a**, 18448-47-0; **5b**, 25662-37-7; **6a**, 25662-38-8; **6b**, 25662-39-9; **7a**, 25662-40-2; **7b**, 25662-41-3; **8a**, 1728-38-7; **8b**, 1728-37-6; **9a** (*E*), 15790-88-2; **9a** (*Z*), 15790-87-1; **9b** (*E*), 20515-19-9; **10a** (*E*), 13168-99-5; **10a** (*Z*), 25665-54-7; **10b** (*E*) 13168-97-3; **10b** (*Z*), 13214-13-6; **11** (*E*), 623-43-8; **11** (*Z*), 4358-59-2; **12**(*E*), 4188-69-6; **12** (*Z*), 4188-68-5; **13** (*E*), 10034-13-6; **13** (*Z*), 10034-12-5; **14** (*E*), 5788-17-0; **14** (*Z*), 5739-81-1; methyl 5-methyl-1-cyclopentene-1-carboxylate, 25662-44-6.

(42) J. Seibl and T. Gauman, *Helv. Chim. Acta*, **46**, 2857 (1963).

(43) K. Biemann, "Mass Spectrometry, Organic Chemical Application," McGraw-Hill, New York, N. Y., 1962, Chapter 5.

Double-Bond Isomerizations in Unsaturated Esters and Enol Ethers. II. Evaluation of Conjugative, Steric, and Polar Effects of Alkyl, Alkoxy, and Alkoxycarbonyl Substituents on Positional and Configurational Equilibria[1]

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Three carbon tautomeric equilibrium data for five- and six-membered cyclic olefinic systems bearing methyl, methoxy, and methoxycarbonyl substituents are analyzed in terms of stabilizing and destabilizing contributions to the observed free-energy changes. Stabilizing energies of 2.3, 6.8, and 2.6 kcal/mol are assigned to alkyl, OCH_3, and CO_2CH_3, respectively. Destabilizing *cis* interactions found for the six-membered ring and acyclic systems are CH_3 *vs.* CO_2CH_3, 1.4 kcal/mol; OCH_3 *vs.* CO_2CH_3, 3.5 kcal/mol; CH_3 *vs.* OCH_3, 0.1 kcal/mol. In the five-membered ring, the destabilizing *cis* interaction of OCH_3 *vs.* CO_2CH_3 amounts to 1.8 kcal/mol. A destabilizing interaction resulting from opposed alkyl–methoxy conjugation is assigned a value of 1.7 kcal/mol.

In 1952, in an analysis of the factors affecting the position of prototropic equilibrium in a number of open-chain unsaturated systems, de la Mare presented an empirical method for correlation of experimentally observed free-energy changes with the individual free-energy contributions of various substituent groups.[3] The group contributions were assessed from available heat of hydrogenation and equilibrium data. Pertinent to the present discussion are the values assigned to alkyl and ester groups, alone and in combination. Thus, a stabilizing value of 2.3 kcal/mol was assigned to each alkyl or substituted alkyl group in an ethylenic system and a stabilizing value of only 1.0 kcal/mol for each α- or β-alkyl substituent in an α,β-unsaturated acid derivative. It was further postulated that the effectiveness of any alkyl group is reduced by 0.5 kcal/mol for each cross- or opposed-hyperconjugation involving another alkyl group. A stabilizing, conjugative interaction of 3.8 kcal/mol was assigned to a carboxylate, ester, or nitrile function. de la Mare's calculated values for the free energy differences in a series of α,β–β,γ-unsaturated acid, ester, and nitrile systems were in reasonably good agreement with the experimental values. It may be noted, however, that the systems tested involved only open chain acid derivatives, most of them capable of configurational as well as positional isomerization, and that the substituent variation in these systems was limited to alkyl groups.

In the present paper, a similar analysis of five- and six-membered cyclic systems bearing methyl, methoxy, and methoxycarbonyl substituents is offered. In these cases, however, the introduction of a geometry-constraining ring and an additional polar group invalidates the simple treatment derived for alkylated acyclic acid derivatives. In order to restore the predictive power of the analysis, it has been necessary to evaluate the magnitude of such steric and polar effects and to include their contributions to the net free energy changes.

Results

The equilibrium data employed in this analysis are presented in the accompanying paper.[4] The free energy changes involved in the equilibrations of these systems will be interpreted according to the following postulates. (1) That the conjugative (or hyperconjugative) interaction of a double bond with an alkyl or substituted alkyl, methoxy, or methoxycarbonyl group stabilizes an ethylenic system. (2) That *cis* interactions

(1) Abstracted in part from the Ph.D. dissertation of E. E. Waali, University of Wyoming, 1970. Financial support of this investigation under National Science Foundation Grants GP-1517 and GP-6375 is gratefully acknowledged.

(2) National Science Foundation Summer Research Fellow, 1967.

(3) P. B. D. de la Mare, *J. Chem. Soc.*, 1602 (1952).

(4) S. J. Rhoads, J. K. Chattopadhyay, and E. E. Waali, *J. Org. Chem.*, **35**, 3352 (1970).

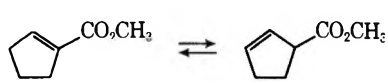
(steric and polar) between two substituents on a double bond and opposing, conjugative interactions involving two alkyl groups or an alkyl group and a methoxy group contribute to the destabilization of an ethylenic system. (3) That these effects are additive.

The values adopted for the free-energy contributions of these various interactions are summarized in Table I.

TABLE I
FREE-ENERGY CONTRIBUTIONS TO DOUBLE-BOND STABILIZATION

Stabilizing interactions (X)	$\Delta G°_X$, kcal/mol
Alkyl and substituted alkyl	−2.3
CO_2CH_3	−2.6
OCH_3	−6.8
Destabilizing interactions	**$\Delta G°_X$, kcal/mol**
cis Effects in Six-Membered Cyclic and Acyclic Systems	
CH_3, CO_2CH_3	+1.4
OCH_3, CO_2CH_3	+3.5
OCH_3, CH_3	+0.1
cis Effects in Five-Membered Cyclic System	
CH_3, CO_2CH_3	0.0
OCH_3, CO_2CH_3	+1.8
OCH_3, CH_3	0.0
Opposed Conjugation	
Alkyl, alkyl	+0.5
Alkyl, OCH_3	+1.7

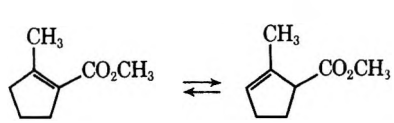
A stabilizing value of 2.3 kcal/mol for alkyl and substituted alkyl groups reflects a representative value deduced from heats of hydrogenation of olefins,[3] calculated values of free energies of olefin isomerization,[5] and experimental values of the free energies of isomerization of methylpentenes reported by Schriesheim and Rowe.[6] Further refinement of this value in terms of primary, secondary, or tertiary structure,[7] or of substituted alkyl groups of the type $CH_2CO_2CH_3$ and CH_2OCH_3,[8] was not attempted. This value of 2.3 kcal/mol for each alkyl or substituted alkyl group is retained even when the group is a substituent in the α,β isomer. In this aspect of our treatment, we depart from the procedure of de la Mare outlined above. Our reason for this change is apparent from consideration of the following equilibria. The identity of the



1ab

$\Delta G°_{100} = +2.1$ kcal/mol

and



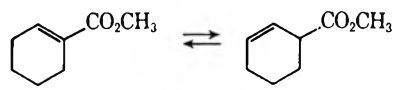
2ab

$\Delta G°_{100} = +2.1$ kcal/mol

free energy changes for the systems **1ab** and **2ab** implies that alkyl substituents have the same power to stabilize a double bond whether it be isolated or conjugated with the ester function. Thus the α,β and β,γ isomers of system **2ab** are receiving an identical contribution from the β-methyl group so that the net change from the unsubstituted system, **1ab**, is zero.

Viewed in this way, the observed free energy change of 2.1 kcal/mol in the systems **1ab** and **2ab** must be attributed entirely to the conjugative interaction of the double bond with the ester function since in both systems the α,β and β,γ isomers are receiving identical net contributions from the alkyl substituents (two in the system **1ab**, three in the system **2ab**). In these cyclic systems, one additional factor is involved in that an asymmetric center is present in the β,γ isomer. This isomer, then, is further favored by an entropy of mixing term (R ln 2)[9] which makes an additional free energy contribution of 0.5 kcal/mol at 100° (RT ln 2). Corrected for the latter, the conjugative stabilization energy of the ester function amounts to −2.6 kcal/mol, the value shown in Table I.

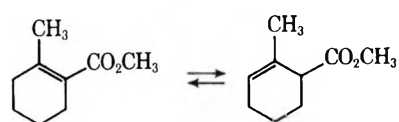
The system **5ab** is completely analogous to **1ab** and,



5ab

$\Delta G°_{100} = +2.2$ kcal/mol

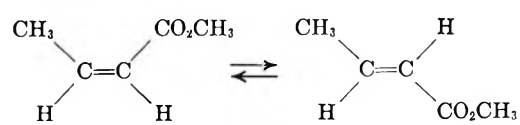
again, is interpreted to reflect only the conjugative interaction of the double bond with the ester function, diminished by the mixing factor RT ln 2. On the other hand, the introduction of a methyl group at the β-carbon atom of the six-membered cyclic system does reduce the free energy change in **6ab** by 1.35 kcal/mol



6ab

$\Delta G°_{100} = +0.85$ kcal/mol

in comparison with its parent, **5ab**. This decrease in free energy is attributed to a *cis* steric destabilization energy of the coplanar methyl and ester groups in the α,β isomer. An independent check of the magnitude of this *cis* interaction is provided by the *cis–trans* equilibrium value for the acyclic methyl 2-butenoate system, **11ab**.



11ab

$\Delta G°_{117°} = -1.4$ kcal/mol

Comparison of the equilibrium values for the cyclopentene systems, **1ab** and **2ab**, with those of the cyclohexene derivatives, **5ab** and **6ab**, further reveals that the *cis* disposed groups in **2ab** are producing no detectable destabilizing interaction; *i.e.*, the free energy contribution of the *cis* effect of methyl and methoxycarbonyl is virtually zero in the five-membered ring. The absence

(5) J. E. Kilpatrick, E. J. Prosen, K. S. Pitzer, and F. D. Rossini, *J. Res. Nat. Bur. Stand.*, **36**, 559 (1946).

(6) A. Schriesheim and C. A. Rowe, Jr., *J. Amer. Chem. Soc.*, **84**, 3160 (1962).

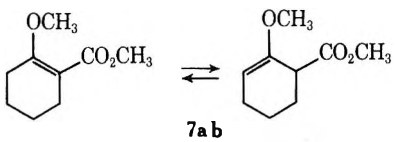
(7) L. Bateman and J. I. Cunneen, *J. Chem. Soc.*, 2283 (1951).

(8) R. Damico, *J. Org. Chem.*, **33**, 1550 (1968), has presented evidence that $CH_2CO_2CH_3$ and CH_2OCH_3 groups are somewhat less stabilizing than alkyl groups, presumably because the inductive effect of the oxygenated function is transmitted through the methylene group. The magnitude of the free energy correction for this effect would be small, however, and less than the uncertainty involved in the value assumed here for the alkyl group stabilization.

(9) E. L. Eliel, "Stereochemistry of Carbon Compounds," McGraw-Hill, New York, N. Y., 1962, p 215.

of a *cis* steric interaction in the cyclopentene derivative may reasonably be accommodated by the concept of increased external bond angles (>120°) about the double bond in the cyclopentene ring resulting from the enhanced "s" character of these bonds.[10]

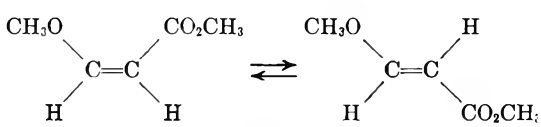
The destabilizing *cis* interaction of the two polar functions, methoxy and methoxycarbonyl, in the six-membered ring is quite large as demonstrated by the strong displacement of the tautomeric equilibrium in **7ab** in favor of the β,γ isomer, in which the interaction



7ab

$\Delta G^\circ_{25^\circ} = -1.2$ kcal/mol

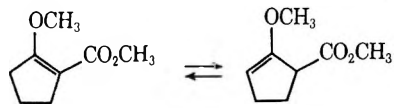
is relieved.[11] A value of +3.4 kcal/mol for this interaction may be assessed directly from the observed free energy change by means of the free energy contributions already derived for the alkyl and ester groups. Since both **7a** and **7b** have two alkyl and one methoxy substituent on the olefinic bond, the effects of these substituents cancel one another. The observed free energy change (−1.2 kcal/mol), then, simply reflects the balance of the stabilization afforded by the ester function (−2.6 kcal/mol) and the destabilization due to the *cis* interaction in **7a**, corrected by 0.4 kcal/mol for the mixing contribution to the formation of **7b**. The magnitude of this value of the *cis* interaction of methoxy and methoxycarbonyl is confirmed by the geometric equilibrium value measured for the methyl 3-methoxypropenoates, **14ab**.



14ab

$\Delta G^\circ_{100} = -3.6$ kcal/mol

Not unexpectedly, the magnitude of the destabilizing *cis* interaction of methoxy and methoxycarbonyl groups in the cyclopentene system is smaller than that found for the cyclohexene and open chain cases.[12] In the

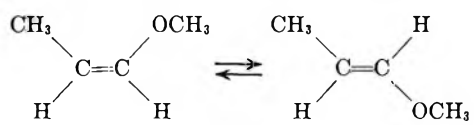


3ab

$\Delta G^\circ_{25^\circ} = +0.4$ kcal/mol

system, **3ab**, the α,β isomer is still dominant, but a marked shift toward the β,γ isomer is apparent when the system is compared with its parent, **1ab**, and its methyl analog, **2ab**. A destabilizing *cis* effect of 1.8 kcal/mol for the two oxygenated functions in the cyclopentene system may be derived in the manner described above for the cyclohexene system.

A measure of the *cis* effect of methyl and methoxy groups in the cyclohexene system is provided by the acyclic methyl propenyl ether equilibrium. From this

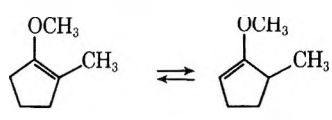


12ab

$\Delta G^\circ_{25} = -0.1$ kcal/mol

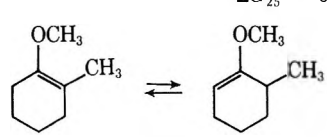
value, and other literature data,[13] it is evident that the *cis* effect of methyl *vs.* methoxy is quite small, even about normal olefinic bonds of ~120°. It may safely be assumed that the *cis* interaction of these same groups in the cyclopentene system is zero.

Examination of the enol ether systems, **4ab** and **8ab**, reveals that the favored isomer in both ring systems is the one with the *less* heavily substituted double bond, a result which can only mean that some effect is more



4ab

$\Delta G^\circ_{25} = -0.4$ kcal/mol



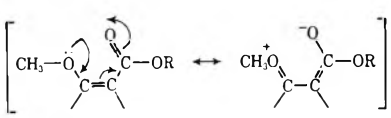
8ab

$\Delta G^\circ_{25} = -0.3$ kcal/mol

than offsetting the 2.3 kcal/mol stabilization anticipated from the methyl group in **4a** and **8a**. While a part of this effect can be attributed to the diminution of the alkyl stabilizing effect by the extra opposed hyperconjugative effect in the "a" isomer (netting 0.5 kcal/mol in favor of "b"), and an additional 0.4 kcal/mol can be attributed to the mixing contribution in favor of the "b" isomer, there remains a residual of 1.8 kcal/mol in the system **4ab** to be accounted for. In the six-membered cycle, correction for a minor *cis* interaction of 0.1 kcal/mol still leaves an energy term of 1.6 kcal/mol destabilizing **8a** relative to **8b**. We assign this destabilizing contribution of 1.6–1.8 kcal/mol[14] to an opposed conjugative interaction between alkyl and

(10) (a) S. J. Rhoads, J. C. Gilbert, A. W. Decora, T. R. Garland, R. J. Spangler, and M. J. Urbigkit, *Tetrahedron*, **19**, 1625 (1963); (b) S. J. Rhoads and A. W. Decora, *ibid.*, **19**, 1645 (1963); (c) S. J. Rhoads, *J. Org. Chem.*, **31**, 171 (1966).

(11) While it might have been expected that extended conjugation between the ether and ester functions



would stabilize the α,β isomer relative to the β,γ, this clearly is not the case. Nor is there any infrared spectral evidence for such an interaction; both esters, **3a** and **7a**, exhibit carbonyl stretching bands of a frequency considered normal for simple α,β-unsaturated esters (ref 4). If extended conjugation with the ether function were important in these systems, a detectable decrease in the carbonyl frequency might be anticipated.

(12) The "*cis*" interaction is considered to be a composite of steric and dipole–dipole interactions of the methoxy and methoxycarbonyl groups in the six-membered ring and open chain systems but to reflect only a polar interaction in the cyclopentene system. This view follows from the absence of a *cis* effect between methyl and methoxycarbonyl in **2ab** and the relative sizes of methyl and methoxy as judged by conformational free energy differences. See ref 9, p 236.

(13) T. Okuyama, T. Fueno, and J. Furukawa, *Tetrahedron*, **25**, 5409 (1969).

(14) The difference in the residuals in **4ab** and **8ab** may have its origin in conformational effects as discussed by F. Johnson, *Chem. Rev.*, **68**, 375 (1968). We believe these effects to be minor ones, however, and for the present have chosen to neglect them.

alkoxy groups, similar in nature to that which diminishes the stabilizing power of alkyl groups when opposed on double bonds.[15] Since the "a" isomer in the enol ether systems, **4ab** and **8ab**, has two such oppositions and the "b" isomer has only one, the net effect will be to shift the equilibrium to the less heavily substituted isomer.

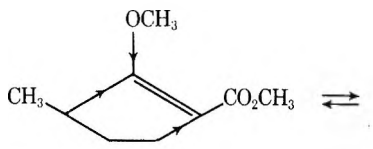
The very powerful conjugative interaction of the methoxy group with the double bond has been remarked by others[8,16] and is illustrated by the equilibrium value for the methyl 4-methoxybutenoate system, **10ab**, in which the conjugative power of methoxy is pitted against that of methoxycarbonyl. Application of the

$$\underset{\textbf{10ab}}{CH_3OCH_2CH{=}CHCO_2CH_3} \longrightarrow CH_3OCH{=}CHCH_2CO_2CH_3$$

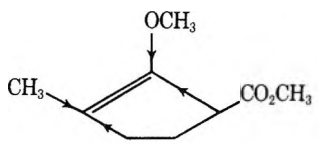
$$\Delta G^\circ_{92} = -2.5 \text{ kcal/mol}$$

values for the free energy contributions of methoxycarbonyl (−2.6 kcal/mol), alkyl (−2.3 kcal/mol), and the opposed alkyl methoxy effect (+1.7 kcal/mol) to the observed free energy change (−2.5 kcal/mol) permits the evaluation of the free energy of stabilization of the methoxy group as −6.8 kcal/mol,[17] the value given in Table I.

As a system suitable for testing the validity of the approach used in this study and the reliability of the values of the free energy contributions deduced, we have examined the system **15ab**, which brings together the three variable groups as substituents on the three carbon allylic system of a cyclopentene ring.



15a



15b

The free energy change for this system, calculated by considering the free energy contributions of the stabilizing groups and destabilizing effects to each of the isomers, is +0.7 kcal/mol corresponding to an equilibrium composition, 76% **15a** and 24% **15b**. Equilibrated by the iodine–cyclohexane method[4] at 25°, the system showed an actual composition of 67% **15a** and 33% **15b** for ΔG° = +0.4 kcal/mol. We consider the agreement between the calculated and experimental values sufficiently good to warrant further investigation of substituted cyclic systems.

Experimental Section

Infrared spectra were recorded as thin films with a Perkin-Elmer Model 621 spectrophotometer. Nmr spectra were run in carbon tetrachloride solution with TMS internal standard with a Varian HA-100 instrument. A Varian-Mat CH-5 mass spectrometer was used to obtain the mass spectra. Glpc analyses employed 2-m columns of 10% SE-30 on Gas-Chrom P at 120°.

Methyl 3-Methyl-2-methoxy-1-cyclopentenecarboxylate (15a).—Prepared by a Dieckmann cyclization of dimethyl α-methyladipate,[18] 5-methyl-2-methoxycarbonylcyclopentanone (bp 106–108° at 14 mm, ir 1752 s, 1725 s, 1655 w, 1614 w cm^{-1})[19] was treated with diazomethane in the manner described earlier[4] for the preparation of its unmethylated parent. Purified by preparative glpc, **15a** showed ir 1706, 1687, 1624 cm^{-1}; nmr δ 3.81 (s, 3, OCH_3), 3.52 (s, 3, CO_2CH_3) 2.7 (m, 1, allylic tertiary), 2.44 (m, 2, allylic CH_2), 1.97 and 1.35 (m, 2, CH_2), 1.04 (d, 3, CH_3, J = 6.7 Hz); mass spectrum (70 eV) m/e 170 (M^+), 155, 138, 123, 111.

Methyl 3-Methyl-2-methoxy-2-cyclopentenecarboxylate (15b).—Isolated by glpc trapping from isomerization mixtures, **15b** showed the spectral properties: ir 1735, 1690 cm^{-1}; nmr δ 3.58 (s, 3, OCH_3), 3.49 (s, 3, OCH_3), 3.6–3.3 (br m, tertiary allylic H α to ester), 2.5–1.9 (br complex, 4, CH_2CH_2), 1.57 (m, 3, CH_3); mass spectrum (70 eV) m/e 170 (M^+), 155, 139, 123, 111.

Equilibration of 15a and 15b.—Equilibrium was established using the iodine–cyclohexane system described earlier[4] (0.7 M in ester, 0.003 M in iodine). Approached from both sides, the equilibrium composition was found to be 67 ± 1% **15a** and 33 ± 1% **15b** by glpc analysis.

Calculations.—The free-energy calculations follow from the relationships

$$\Delta G^\circ_{a\rightarrow b} = -RT \ln K$$

$$\Delta G^\circ_{a\rightarrow b} = \Sigma\Delta G^\circ x(\text{isomer b}) - \Sigma\Delta G^\circ x(\text{isomer a})$$

Registry No.—15a, 25662-45-7; **15b,** 25662-46-8.

(15) H. O. House and V. Kramer, *J. Org. Chem.*, **28**, 3362 (1963), have proposed the same explanation for the greater stability of the less heavily substituted isomer in tautomeric equilibria involving enolate anions and enol ethers. It is noteworthy that corresponding enol acetates exhibit the opposite relative stabilities; *i.e.*, the more heavily substituted isomer is the more stable. Presumably, these contrasting results reflect the diminished conjugative power of the acetoxy group in opposing the alkyl contribution.

(16) (a) J. Hine, L. G. Mahone, and C. L. Liotta, *ibid.*, **32**, 2600 (1967); (b) C. D. Broaddus, *J. Amer. Chem. Soc.*, **87**, 3706 (1965).

(17) This value may be compared with a value of 5.8 kcal/mol estimated in unpublished work of Doering and Vollrath, quoted in ref 16b. The difference in this value and ours stems mainly from our method of evaluation which takes into account the effect of opposed alkyl and alkoxy conjugation.

(18) J. P. Schaefer and J. J. Bloomfield, *Org. React.*, **15**, 43 (1967).

(19) See ref 10a for characteristics of the infrared spectra of enolizable β-keto esters.

Kinetics and Mechanism of *vic*-Diol Dehydration. II. The *p*-Anisyl Group in Pinacolic Rearrangements[1,2]

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Received December 16, 1969

The kinetics of the sulfuric acid catalyzed rearrangements of 1,2-di-*p*-anisyl-1,2-diphenylethylene glycol (1) and epoxide (3) and tetra-*p*-anisylethylene glycol (2) and epoxide (4) were studied in anhydrous acetic acid. The spectrophotometric rate of rearrangement and the titrimetric rate of dehydration of 1 under the same conditions are identical within experimental error. That no epoxide intermediate does accumulate above a small steady-state concentration was further substantiated by independent spectrokinetic studies of the corresponding epoxide 3 which rearranged about seven times faster than the glycol 1. Activation parameters for 1 and 3 are compared with those from benzopinacol and tetraphenylethylene oxide. Similar studies were carried out for glycol 2 and the corresponding epoxide 4, where the same situation prevails as for 1 and 3. Plots of the rate coefficients for rearrangement, k_r, *vs.* $[H_2SO_4]$ are linear with 2 and 4 showing a stronger dependence than 1 and 3. Added water serves only to reduce the proton-donating capacity of the medium and does not, within the limits of thin layer chromatographic detection, divert the carbonium ion derived from epoxide ring opening to the corresponding glycol. From spectrokinetic, titrikinetic, and product analysis, the order of neighboring-group reactivity is *p*-anisyl > –OH ≥ *p*-tolyl > phenyl. The factors determining this order are discussed.

In our previous paper in this series[1] the kinetic and mechanistic aspects of the pinacolic rearrangement associated with benzopinacol, tetraphenylethylene oxide, and the symmetrical di- and tetra-*p*-methyl substituted derivatives of these were explored. We noted that the acid-catalyzed dehydration of the various glycols was characterized by the concurrent and rather substantial accumulation of an intermediate, which decomposed in a subsequent process to the carbonyl function diagnostic of these molecular reorganizations. Identification of this intermediate as the corresponding epoxide was accomplished through the application of titrimetric and spectrokinetic measurements in conjunction with thin layer chromatography. Furthermore, these complementary techniques made it possible to construct time concentration curves for all the components found in these rearrangement processes. Further insight into these pinacolic transformations was gained by analyzing the stereochemical and energetic features pertaining to acid-catalyzed epoxide ring opening. Thus we concluded that a benzhydryl-like carbonium ion was a common intermediate in both the epoxide ring opening and glycol dehydration reactions. The kinetic scheme shown below was proposed, where

$$G \xrightarrow{k_1} R^+ \underset{k_4}{\overset{k_3}{\rightleftharpoons}} E, \quad R^+ \xrightarrow{k_2} K$$

G represents glycol, E, epoxide and K, ketone, and where

$$\left(\frac{-d[G]}{dt}\right)_{init} = \left(\frac{d[E]}{dt}\right)_{init} + \left(\frac{d[K]}{dt}\right)_{init}$$

From the above formulation of the dynamics of *vic*-diol dehydration it would be anticipated that the glycols would be distinguished by their kinetic behavior into three categories: (a) those following explicitly the above scheme where

$$\left(\frac{-d[G]}{dt}\right) > \left(\frac{d[K]}{dt}\right)$$

and thus

$$\left(\frac{d[E]}{dt}\right)_{init} > 0$$

(b) those for which

$$\left(\frac{-d[G]}{dt}\right) = \left(\frac{d[K]}{dt}\right)$$

and

$$\left(\frac{d[E]}{dt}\right) = 0$$

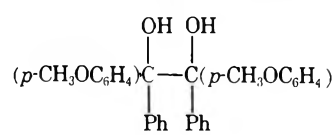
and (c) those for which

$$\left(\frac{-d[G]}{dt}\right) = \left(\frac{d[E]}{dt}\right)$$

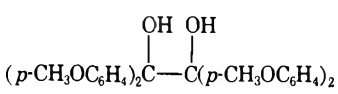
and thus

$$\left(\frac{d[K]}{dt}\right) = 0$$

The present paper reports on a kinetic and mechanistic study of the dehydration of 1 and 2 which belong to the



1



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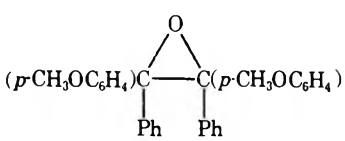

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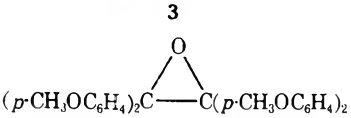


4

(1) Part I: Y. Pocker and B. P. Ronald *J. Amer. Chem. Soc.*, **92**, 3385 (1970), and references cited therein.

(2) Supported in part by the National Science Foundation Grant GP-5103 and in part by the National Institutes of Health Public Health Service Grants AM 09221 and GM-10181. We gratefully acknowledge the donors of these funds.

(3) To whom inquiries should be directed.

(4) Taken in part from the Ph.D. thesis of B. P. Ronald, University of Washington, 1968.

b category and compares these with the rearrangement of the corresponding epoxides **3** and **4**.

Experimental Section

Materials.—The glycols, **1** and **2**, were synthesized from their respective *para*-substituted benzophenones by photochemical bimolecular reduction in isopropyl alcohol.[5] Purity after repeated recrystallization from benzene–petroleum ether (bp 30–60°) (1:1) was verified by tlc, uv spectral analysis, and melting point. Each glycol was converted to the corresponding ketone or ketones by acid-catalyzed dehydration with sulfuric acid in acetic acid solvent.[6] Ketone mixtures were analyzed by cleaving in *t*-BuO$^-$K$^+$–DMSO, isolating the resultant benzoic acids,[7] and then esterifying them using a tenfold excess of MeOH. The resultant esters were then submitted to vpc analysis. Examination of standard ester mixtures confirmed that the ratio of the peak areas was proportional to the mole ratio.

The epoxides, **3** and **4**, corresponding to the above glycols were synthesized by the controlled[8] perbenzoic acid oxidation of the appropriate tetraarylethylenes in chloroform solution. The purity of each epoxide was assayed by thin layer chromatography, uv spectral analysis, as well as melting point. Further substantiation came from analyzing by the above methods the product(s) derived from acid-catalyzed rearrangement. These tetraarylethylenes in turn were synthesized from the appropriate ketonic product derived from glycol dehydration. The ketone was reduced with $LiAlH_4$ in ether–benzene solvent (1:1) to the corresponding alcohol,[9] which without purification was dehydrated to the olefin with a catalytic amount of sulfuric acid or acetyl chloride in acetic acid solvent.[10] The purity of these tetraarylethylenes was established by melting point and uv, nmr, and thin layer chromatographic analyses.

Solvent acetic acid for kinetics has been discussed, as has anhydrous 100% sulfuric acid.[1] Other solutions such as 0.100 or 0.05 *N* potassium acid phthalate, KHP, in acetic acid, 0.100 *N* potassium dichromate in water, 0.1 *N* sodium thiosulfate, starch indicator, 0.1 *N* lead tetraacetate in acetic acid, 0.1 *M* potassium iodide in water, and 1.0 *M* sodium acetate in water were all made in accordance with currently accepted procedures.

Since the acidity required to cause the rearrangement of the substrates at a convenient rate was very low, 10^{-2} to 10^{-5} *M* sulfuric acid in acetic acid, H_2SO_4–HOAc, it was not possible to assay independently the amount of acid catalyst in each rate measurement. Rather, a stock solution of 0.1 *M* H_2SO_4–HOAc whose acid content was accurately determined by titration against 0.100 *N* KHP tot he α-naphtholbenzein end point was sequentially diluted to give a series of secondary stock solutions. Where possible these secondary stock solutions were restandardized and then used as catalysts for the rate measurements.

Kinetic Measurements.—The rate of glycol dehydration was followed by lead tetraacetate oxidation and iodometric titrimetry of aliquots withdrawn from the reaction solutions at various times.[11-13] To *ca.* 10^{-2} *M* solution of the glycol in acetic acid the appropriate amount of acid catalyst was added at time zero. At recorded time intervals aliquots were quenched in acetic acid containing enough sodium acetate to neutralize all the acid catalyst. A measured amount of lead tetraacetate was added to oxidize the glycol completely and the solution set aside for 2 hr.[14] The excess lead tetraacetate remaining after complete glycol oxidation was determined by iodometric titrimetry. Rate coefficients were determined graphically.

Spectrophotometric rate measurements were made with a Beckman Model D.U. fitted with a specially designed cell compartment containing a liquid bath (water). This bath was thermostated by bucking a Sargent Thermonitor and coil heater against a cold water stream circulating through a copper pipe traversing the bottom of the cell compartment. Later a Forma Temp Jr. circulated a liquid (antifreeze) thermostated to 25.0 ± 0.02° through the copper pipe and eliminated the need for the Thermonitor unit. Stirring the bath precluded any but the minutest temperature fluctuations.

Depending upon the specific compound and the wavelength to be used, enough substrate was weighed into a 50-ml volumetric flask in order to make a 10^{-3} to 10^{-4} *M* solution in acetic acid. After prior thermostating, the rate measurement was begun by adding a predetermined amount of stock H_2SO_4–HOAc at time zero. Infinity values of the absorbance taken well after 10 half-lives were stable for a period of several days to several weeks depending upon the acid concentration. Rate coefficients were determined graphically.

Thin layer chromatography was performed on lantern slides coated with a uniform layer of silica gel G. The samples were dissolved in benzene. The developing solvent was a mixture of benzene–pet ether or heptane–ethyl acetate in varying proportions as found expedient for good separation. The chromatograms were visualized with $SnCl_4$–$SOCl_2$ vapor, I_2 vapor, and uv light. The limit of detection by these methods is about 1%. When thin layer chromatographic analysis was performed on reacting solutions, the procedure was as follows. Aliquots were taken at various times and quenched in aqueous NaOH–NaCl. Enough base was present to render the pH of the quenched solution *ca.* 4 or higher. The organic material usually precipitated immediately and was filtered, washed with water, dried, and chromatographed as described above.

Uv spectra were measured on a Cary Model 14 recording ultraviolet spectrophotometer. Nmr spectra were measured on either a Varian Model HA-60 or Model A-60 nuclear magnetic resonance spectrometer. The solvent was carbon tetrachloride and the internal standard was TMS. Vapor phase chromatograms were measured on an Aerograph 1520 equipped with a flame ionization detector whose output was connected to a Leeds and Northrup Speedomax H strip chart recorder.

Results

In pure anhydrous acetic acid solvent the rate of dehydration of 1,2-di-*p*-anisyl-1,2-diphenylethylene glycol,[15] **1**, as followed by lead tetraacetate oxidation and iodometric titrimetry shows good linear pseudo-first-order kinetics for 1 to 2 half-lives, Figure 1. The convenient rate range falls in the concentration region of 10^{-5} up to 10^{-3} *M* H_2SO_4–HOAc. Under precisely the same conditions (temperature, catalyst concentration, and solvent) the rate of product formation was observed at its λ_{max}, 330 mμ, in the Beckman D. U. spectrophotometer. These spectrophotometric rate measurements showed good linear pseudo-first-order kinetics for 2 to 3 half-lives, Figure 1. Furthermore, the rate coefficients from the titrimetric and spectrophotometric rate measurements were identical within experimental error. Thus the rate of glycol dehydra-

(5) W. E. Bachman, "Organic Syntheses," Coll. Vol. II, A. H. Blatt, Ed., Wiley, New York, N. Y., 1943, p 71.

(6) See ref 5, p 73. Although acetyl chloride was occasionally used to effect these rearrangements, whenever a product mixture could result, kinetic conditions (solvent, temperature, catalyst concentration and type) were employed.

(7) P. G. Gassman, and F. V. Zaler, *Tetrahedron Lett.*, No. 40, 3031 (1964).

(8) L. S. Silbert, E. Siegel, and D. Swern, *J. Org. Chem.*, **27**, 1336 (1962). Since the epoxides **3** and **4** are very sensitive to acids only small amounts of the peracid were added when necessary. The epoxidation reaction was monitored by thin layer chromatography, uv spectra, and crude iodometric titration. When no olefin could be detected by uv spectra, any excess peracid was destroyed by reaction with cyclohexene and the desired epoxide was quickly removed, washed, and dried.

(9) J. Levy, and R. Lagrave, *Bull. Soc. Chim. Fr.*, **43** [4], 437 (1928).

(10) J. Levy, *ibid.*, **29** [4], 897 (1921). The dehydration of 2,2-di-p-anisyl-1,2-diphenylethanol results in the formation of 1,2-di-*p*-anisyl-1,2-diphenylethylene.

(11) R. Criegee, L. Kraft, and B. Rank, *Justus Liebigs Ann. Chem.*, **507**, 157 (1933).

(12) R. Criegee, E. Buchner, and W. Walther, *Ber.*, **73**, 571 (1940).

(13) R. Criegee, E. Hoger, G. Huber, P. Kruck, F. Markscheffel, and H. Schellenberger, *Justus Liebigs Ann. Chem.*, **599**, 81 (1956).

(14) J. P. Cordner, and K. H. Pausacher, *J. Chem. Soc.*, 104 (1953). Two hours was found to be adequate for at least 98% oxidation of the glycol.

(15) This glycol consists of a mixture of DL and *meso* forms which were indistinguishable by thin layer chromatography. Although two crystalline forms of dianisyldiphenylethylene glycol were isolated from acetic acid solutions, no stereochemical assignment could be made. A small difference in rate was observed between these two forms (*ca.* 7%), but neither form appears to give detectable amounts of epoxide. If these crystalline forms correspond to the two diastereomers existing in this system, then they appear to rearrange faster than they equilibrate. Further studies pertaining to this point and other aspects of stereochemistry are in progress.

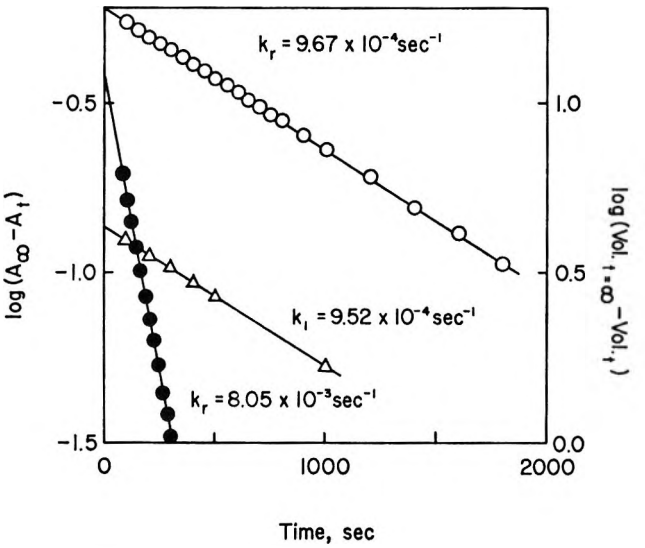
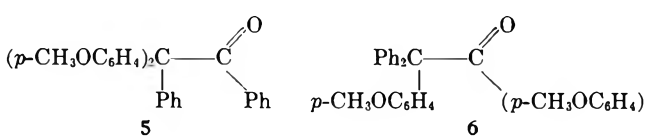


Figure 1.—First-order plots of the spectrophotometric rates of rearrangement of **1** (○) and **3** (●), and the titrimetric rate of dehydration of **1** (△). Data given for 2×10^{-3} *M* H_2SO_4–HOAc at 25.0°.

tion is equal to the rate of ketone formation, and any intermediate, if present, may accumulate only to the extent of its small steady-state concentration. In fact, thin layer chromatographic analysis of samples removed from the reacting solution confirmed that only two components were present, the reacting glycol and its ketonic product; *i.e.*, no epoxide was detected. The ketonic product is actually a mixture of the two ketones, **5**, and **6**, the composition of which reflects the relative



tendency of the aromatic rings to undergo migration. Analysis of this mixture of ketones by vapor phase chromatography established that the *p*-anisyl group migrates in preference to the phenyl group by a factor of 1000:1.

Since no epoxide could be detected in glycol solutions undergoing dehydration an independent study was undertaken to ascertain the rate of rearrangement of the epoxide, 1,2-di-*p*-anisyl-1,2-diphenylethylene oxide,[16] **3**. The spectrophotometric rates of epoxide rearrangement were determined under conditions identical to those prevailing for its corresponding glycol and obeyed good linear pseudo-first-order kinetics for 2 to 3 half-lives, Figure 1. The observed rate coefficient was about 10 times as great as that found for glycol dehydration. It appears that even in these weakly acidic media, epoxide **3** is much more reactive than glycol **1** and furthermore displays a slightly stronger dependence upon the concentration of the acid catalyst. Analysis of solutions resulting from either glycol dehydration or epoxide rearrangement indicated the ketonic products to be formed in quantitative yield. Also, the melting points, uv spectra, and thin layer chromatographic behavior of the products from the glycol dehydration were identical with those obtained from the epoxide rearrangement.

Tetra-*p*-anisylethylene glycol, **2**, was found to be even more sensitive than **1** to acid catalysis. The spectrophotometric rate of glycol rearrangement showed good linear pseudo-first-order kinetics from 2 to 3 half-lives, Figure 2. Thin layer chromatographic analysis of reacting solutions indicated that only two components were present, the unreacted glycol and its corresponding ketone; no epoxide was observed here either. Furthermore, the conversion of the glycol to ketone was shown to be quanitative through uv spectral and thin layer chromatographic analysis. Because glycol **2** possesses limited solubility in the reaction medium, it was not possible to perform titrimetric rate measurements similar to those carried out for glycol **1**. However, the totality of the data presented herein established that for glycol **2**

$$\frac{-d[G]}{dt} = \frac{d[K]}{dt}$$

The epoxide, tetra-*p*-anisylethylene oxide, **4**, corresponding to glycol **2**, was independently studied to determine whether it behaved as its dianisyl analog. When **4** was subjected to the identical conditions (temperature and solvent and catalyst concentration) prevailing for glycol rearrangement, good linear pseudo-first-order kinetics were observed from 2 to 3 half-lives, Figure 2. The rate coefficient for epoxide rearrangement was about 3 times larger than that for glycol rearrangement. Thin layer chromatographic and uv spectrophotometric analysis indicated that the conversion to one and the same ketone was quantitative. Furthermore, since no epoxide was detected by tlc methods in solutions of glycol undergoing dehydration these substrates **2** and **4** mirror the behavior of their dianisyl analogs **1** and **3**. The gross kinetic and thin layer chromatographic characteristics exhibited by these systems implies that during glycol dehydration epoxide intermediates do not accumulate to any detectable extent.[17a] This is to be contrasted with the kinetic and thin layer chromatographic behavior for benzopinacol and its corresponding epoxide.[1]

(16) This epoxide is believed to be a mixture of DL and *meso* forms which were indistinguishable by thin layer chromatography.

(17) (a) According to our kinetic scheme, the amount of epoxide formed on partitioning R^+ is given by $k_3[R^+]/(k_2 + k_3)$. However, the neighboring-group reactivities of *p*-anisyl *vs.* –OH are such that k_2 is at least 100-fold larger than k_3 so that actually more than 99% of the R^+'s get converted directly to ketone while epoxide formation must amount to less than 1%. Actually, epoxide accumulation should be further reduced by the operation of the rearrangement term, $k_4k_2[E]/(k_2 + k_3) \simeq k_4[E]$. Thus when $k_2 \gg k_3$, the partitioning of R^+ becomes the dominant factor while the relative rate at which epoxide rearranges is no longer of primary importance in determining the amount of epoxide buildup from its conjugate glycol. (b) It is interesting to note that the free energies of activation for benzopinacol as determined by us and by Gebhard and Adams [*J. Amer. Chem. Soc.*, **76**, 3925 (1954)] are very similar: $\Delta F^{\ddagger}_{25}°$ (Pocker and Ronald) = 20.8 kcal/mol; $\Delta F^{\ddagger}_{35}°$ (Gebhard and Adams) = 20.4 kcal/mol. Yet, our medium and that of Gebhard and Adams is quite different. They used low concentrations of $HClO_4$ (2×10^{-4} to 5.5×10^{-3} *M*) in acetic acid which contained as much as 1.7×10^{-1} *M* H_2O. Since water is more basic than HOAc the major protonating species in their media was probably H_3O^+ ClO_4^-. We have employed H_2SO_4 (10^{-2} to 1.1 *M*) in anhydrous acetic acid. The major protonating species in our studies is $AcOH_2^+$ HSO_4^-. Since the protonation equilibria of benzopinacol and of tetraphenylethylene oxide are included in the experimental rate coefficients, it is perhaps not surprising that the corresponding Arrhenius activation parameters differ in the two studies. (c) L. L. Schaleger and F. A. Long, *Advan. Phys. Org. Chem.*, **1**, 1 (1963). (d) Stereochemical and energetic considerations pertaining to epoxide ring opening force us to discard the concerted participation by a neighboring aromatic group as a possible pathway for these reactions. See ref 1.

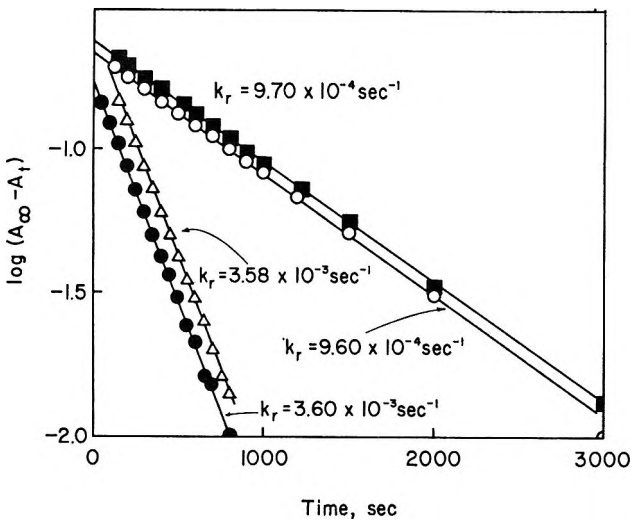
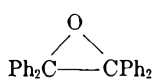


Figure 2.—Duplicate first-order spectrophotometric rate plots for the rearrangement of 2 (■ and ○) and 4 (△ and ●). Values pertaining to 4 (●) plotted as (t − 100) sec for clarity. Data given for 6 × 10⁻⁵ M H_2SO_4–HOAc at 25.0°.

It is conceivable that solvent attack in a ring opening process may occur upon these reactive epoxides, especially 4. One must conclude, however, that the epoxide does not suffer solvent attack to any detectable extent, since thin layer chromatographic analysis of solutions of 4 undergoing rearrangement reveals the presence of only two components, the original epoxide and its corresponding ketone. Even under conditions conducive to attack by added water, the epoxide did not form any glycol. When 5.55 M water was added to the medium and the rates of rearrangement of both the glycol, 2, and the epoxide, 4, were measured under identical conditions, good linear pseudo-first-order kinetics were observed. Both rates were depressed from their normal values in anhydrous solvents, and the epoxide rate coefficient was almost an order of magnitude larger than that of the glycol. It seems unlikely therefore that any significant fraction of the epoxide would be undergoing solvent attack under our kinetic conditions, Table I.

TABLE I

THE EFFECT OF ADDED WATER ON THE RATE OF REARRANGEMENT AT 25°

Substrate	H_2SO_4–HOAc, M	Added H_2O, M	k_r[a] × 10⁴, sec⁻¹	% reaction[b]
2	6 × 10⁻⁵	0.0	9.65	81
		5.55	1.54	89
	5 × 10⁻¹	0.0	17.2	84
		1.0	2.9	93
		2.0	0.93	89
4	6 × 10⁻⁵	0.0	35.9	75
		5.55	10.7	86

[a] Rate coefficients derived from first-order plots of spectrophotometric measurements. Good linearity was observed for the percentage of reaction indicated. [b] Percentage reaction over which spectrophotometric rate data was accumulated.

The rates of rearrangement of all these *p*-methoxyl substituted compounds are very strongly dependent upon the acidity of the medium. For both systems, plots of k_r *vs.* acid concentration, H_2SO_4–HOAc, show

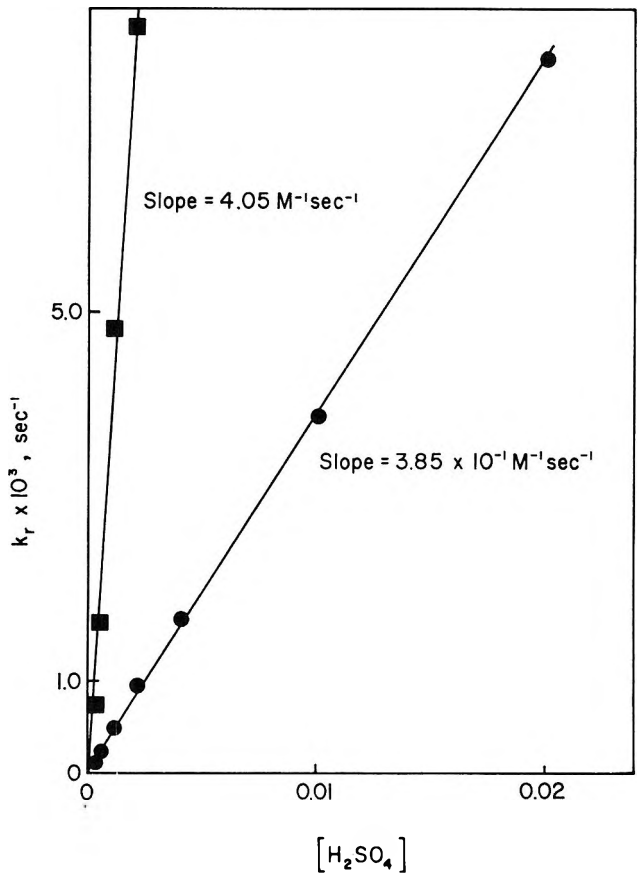


Figure 3.—Acidity plot of k_r *vs.* [H_2SO_4] at 25.0° for the rearrangement of 1 (●) and 3 (■).

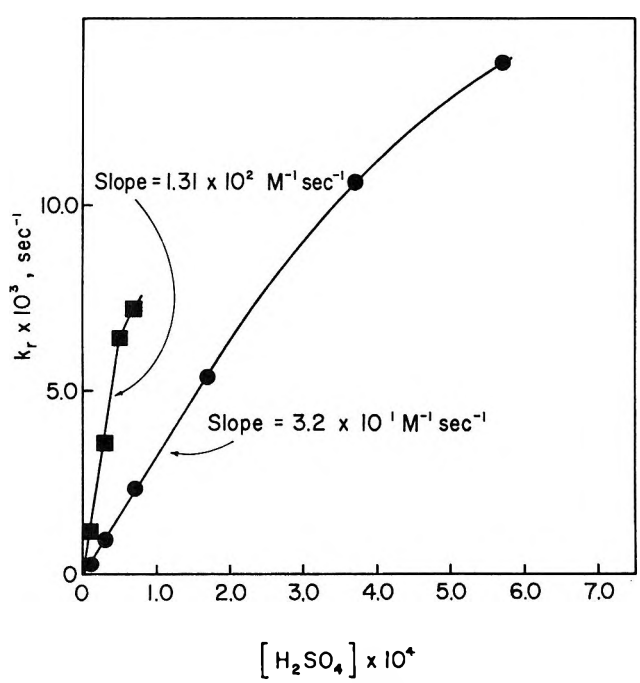


Figure 4.—Acidity plot of k_r *vs.* [H_2SO_4] at 25.0° for the rearrangement of 2 (●) and 4 (■).

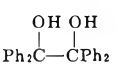
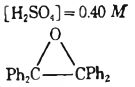
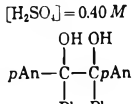
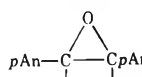
linearity with the epoxides being more sensitive to the amount of the acid catalyst than the glycols, Figures 3 and 4. The rate depression observed with added water is due to a reduction in the proton donating capacity of this medium, Table I.

Preliminary Arrhenius activation parameters measured for 1,2-di-*p*-anisyl-1,2-diphenylethylene glycol

and oxide were in accord with expectations, E_a^{glycol} = 20.0 kcal mol^{-1}, $E_a^{epoxide}$ = 18.8 kcal mol^{-1}. For comparison these parameters for benzopinacol and tetraphenylethylene oxide are E_a^{glycol} = 23.5 kcal mol^{-1}, $E_a^{epoxide}$ = 20.7 kcal mol^{-1}.[17b] The entropies of activation for these compounds are also in accord with what is known about these processes.[17c] The values for both the glycols and the epoxides are near zero, Table II. For further comparison, entropies of activation have been calculated for these reactions after the two systems were brought to the same free energy of activation.

TABLE II

ARRHENIUS ACTIVATION PARAMETERS

Substrate	t, °C	$k_r \times 10^4$, sec^{-1}	E_a, kcal mol^{-1}	$\Delta S^{\ddagger}$,[a] eu
 $[H_2SO_4] = 0.40\ M$	25	2.78[b]		+4[c]
	35	9.82[b]	23.5	+7[d]
	45	32.7[b]		+5[e]
 $[H_2SO_4] = 0.40\ M$	25	9.75		
	33	23.5	20.7	−3
	42	63.2		−5[f]
 $[H_2SO_4] = 2 \times 10^{-4}\ M$	25	1.0		
	35	3.0	20.0	+5
	45	8.2		−3[g]
 $[H_2SO_4] = 2 \times 10^{-4}\ M$	25	7.7		
	34	19.9	18.8	+9
	42	42.7		+5[h]

[a] Calculated from $\Delta F^{\ddagger}_{25°} = \Delta H^{\ddagger}_{25°} - T\Delta S^{\ddagger}_{25°}$ where $\Delta F^{\ddagger}_{25°} = 2.303\,RT\,(\log kT/h - \log k_r/[H_2SO_4])$ and $\Delta H^{\ddagger}_{25°} = E_a - RT$. [b] Initial spectrophotometric rates of ketone formation. [c] Calculated from glycol rearrangement using $k_r^i = 2.78 \times 10^{-4}$ sec^{-1} at 25.0° and $[H_2SO_4] = 0.40\ M$. [d] Calculated from glycol dehydration using $k_1 = 1.71 \times 10^{-3}$ sec^{-1} at 25.0° and $[H_2SO_4] = 0.40\ M$. [e] Calculated for glycol dehydration using first-order rate coefficient. [f] Calculated for epoxide rearrangement using first-order rate coefficient. [g] Calculated for glycol dehydration using the first-order rate coefficient, $k_r = 1.71 \times 10^{-3}$ sec^{-1} at 25° and $[H_2SO_4] = 4.45 \times 10^{-3}\ M$. This k_r value was extrapolated from a plot of k_r *vs.* $[H_2SO_4]$ whose slope was $3.85 \times 10^{-1}\ M^{-1}$ sec^{-1}. [h] Calculated for epoxide rearrangement using the first-order rate coefficient, $k_r = 18.0 \times 10^{-3}$ sec^{-1} at 25° and $[H_2SO_4] = 4.45 \times 10^{-3}\ M$. This k_r value was extrapolated from a plot of k_r *vs.* $[H_2SO_4]$ whose slope was $4.0\ M^{-1}$ sec^{-1}.

Discussion

A unique feature characterizing the acid-catalyzed pinacolic rearrangement and dehydration of certain glycols is the accumulation and eventual destruction of an intermediate whose identity was established as the corresponding epoxide. Those glycols then are representatives of category a where initially

$$\frac{-d[G]}{dt} > \frac{d[K]}{dt}$$

and

$$\frac{d[E]}{dt} > 0$$

Another kinetic feature pertaining to this category was curved rate plots for the spectrophotometric rates of glycol rearrangement.[1] These distinctive characteristics are notably absent from the acid-catalyzed dehydration of the *p*-methoxyl bearing substrates **1** and **3**.

Careful scrutiny of the experimental data suggests that the proper category for substrates **1** and **3** is b where

$$\frac{-d[G]}{dt} = \frac{d[K]}{dt}$$

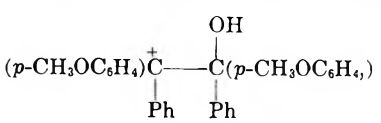
and

$$\frac{d[E]}{dt} = 0$$

Our inability to detect any epoxide intermediates in the dehydration reactions of **1** and **3** after applying titrikinetic, spectrokinetic and thin layer chromatographic methods of analysis supports the contention that only steady-state concentrations of intermediates can be present. The previously proposed mechanism[1] uniquely accommodates the experimental observations related to *p*-methoxyl bearing substrates with the single stricture that $k_4K_{eq}[E][acid] \gg k_3[R^+]$.

The carbonium ion, R^+, is itself interesting because it possesses certain outstanding properties. If R^+ undergoes ring closure with the neighboring hydroxyl group to form the conjugate acid of the epoxide it must by the principle of microscopic reversibility ring open to form the same R^+.[17d] It is eminently reasonable to suppose that this same carbonium ion is generated from glycol dehydration. Furthermore this process should in principle be reversible. However, energetically more favorable routes for carbonium ion destruction appear to exist, since conditions conducive to collapse with solvent fail to produce solvent adduct products.

The preferred pathway for carbonium ion destruction is through attack on the neigboring aromatic rings. These reactions then resemble electrophilic aromatic substitution processes and electrophilic aromatic dealkylations. Little is known about the latter process where one alkyl group displaces another from the aromatic ring.[18] Electrophilic aromatic substitution processes have been studied in some detail and have a definite bearing upon aryl migration reactions.[18] The attack of R^+ upon the neighboring aromatic ring leads to a transition state similar to that suggested for electrophilic aromatic substitution reactions. The aromatic ring undergoing attack possesses a certain characteristic susceptibility which reflects its capacity to support and stabilize a positive charge. Those aromatic rings possessing substituents capable of accepting some of the positive charge through resonance interaction have an enhanced probability of undergoing reaction. The susceptibility of aromatic rings to attack by electrophiles is further influenced by their propinquity to the positive center and the stability of this positive center. When both the aromatic rings and the carbonium ion are contained within the same carbon skeleton as in ion **7**, then entropic considerations favor collapse with the



7

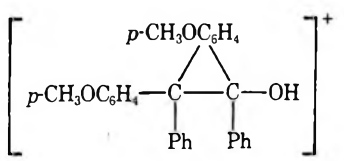
rings as opposed to collapse with the solvent.[19,20] The reaction with solvent is a bimolecular process,

(18) L. M. Stock, and H. C. Brown, *Advan. Phys. Org. Chem.*, **1**, 35 (1963).

(19) T. C. Bruice, and S. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, New York, N. Y. 1965, pp 119–125.

(20) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N. Y. 1969, pp 7–30.

whereas the reaction with the neighboring aromatic ring is a unimolecular process. In the former not only is there a considerable loss in translational entropy accompanying the bringing together of the reactants, but R^+ and the nucleophile in all probability are desolvated as the activated complex is formed. On the other hand, no such translational entropic restriction applies to the unimolecular process, and furthermore only a slight, if any, reorganization of the solvent may be required to attain the transition state configuration. At the same time these effects together with the compensating resonance delocalization must counterbalance any strain energy accumulated in the attack of the carbonium ion on its neighboring groups. Thus a phenonium ion may have transient existence in the migration step involving the aromatic ring.



The stability of R^+ strongly governs its selectivity.[21] When the carbonium ion is very stable, *i.e.*, it has a long life time, it tends to be very discriminating towards approaching nucleophiles. On the other hand only a small or negligible discriminatory capacity is displayed by those carbonium ions possessing a short life time. The carbonium ion generated in these studies either from glycol dehydration or epoxide ring opening is a tertiary ion possessing two aromatic rings which aid in delocalizing the positive charge and thus in enhancing its stability. An adverse inductive effect due to the β-hydroxyl group and the β-aromatic rings reduces the stability somewhat.[22,23] Perhaps the best description of the ion is that it is benzhydryl-like.

The observation that ion **7** prefers to attack the neighboring *p*-anisyl group to the phenyl group in the ratio of 1000:1 suggests some discriminatory ability. That this discriminatory capacity is not large is shown by comparison with the data of Bethel and Gold on the attack of substituted benzhydryl cations on various aromatic rings.[24] Anisole reacts 10^6 times as fast as benzene with 4-methoxybenzhydryl cation generated by the sulfuric acid catalyzed dehydration of 4-methoxybenzhydrol in acetic acid solvent. The reactivity of anisole to benzene in other electrophilic aromatic substitution reactions[18] ranges from 10^3 to 10^5. Thus ion **7** and those analogous to it do not seem to possess the discriminatory capacity exhibited by the benzhydryl cations in the above bimolecular electrophilic substitutions. However they do effectively discriminate against the solvent. Admittedly though, acetic acid containing sulfuric acid is a solvent possessing a very low order of nucleophilic character. Perhaps the structural feature possessing the dominant influence on the reactions of ion **7** and its analogs is the neighboring group whose observed order of reactivity is

p-anisyl	>	–OH	≳	*p*-tolyl	>	phenyl
>1000		37–10		11		1

The position of the hydroxyl group in this series is unique, for in most other nucleophilic series it is better than most aromatic groups. This new order and the position of the –OH group results from the following factors: (1) the collapse of these carbonium ions is a unimolecular process; (2) all neighboring groups have the same relative concentration within the solvation shell; and (3) strain energy is accumulated when either the –OH group or the aromatic rings react with the positive center but resonance stabilization compensates for this strain energy only in the latter case. Further studies concerning the various kinetic categories (a, b, and c), the effect of solvent composition, and the energetics of neighboring-group migration are being actively pursued in these laboratories and will be communicated presently.

Registry No.—DL-**1**, 19235-02-0; *meso*-**1**, 19235-01-9; **2**, 19920-00-4; DL-**3**, 25124-98-5; *meso*-**3**, 25124-99-6; **4**, 25125-00-2.

(21) M. Stiles, and R. P. Mayer, *J. Amer. Chem. Soc.*, **81** 1497 (1959).

(22) C. A. Bunton, T. Hadwick, D. R. Llewellyn, and Y. Pocker, *J. Chem. Soc.*, 403 (1958).

(23) J. Hine, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1962, p 327.

(24) D. Bethel, and V. Gold, *J. Chem. Soc.*, 1905, 1930 (1958).

Relative Migratory Aptitudes of the Methyl and Ethyl Groups in a σ Complex Intermediate[1]

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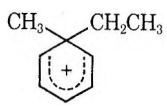
4-Ethyl-4-methyl-1-keto-1,4-dihydronaphthalene (2) was synthesized and subjected to the dienone–phenol rearrangement. The sole identifiable product was that formed by rearrangement of the ethyl group, namely, 3-ethyl-4-methyl-1-naphthyl acetate (4). No trace of the isomeric 3-methyl-4-ethyl-1-naphthyl acetate (5) could be detected by vpc or nmr. The structure of 4 was strongly suggested by its nmr spectrum and proved by converting it to 1-methyl-2-ethylnaphthalene (10), identified by comparison of its vpc and nmr characteristics with those of an independently synthesized specimen and shown by the same means to differ from 1-ethyl-2-methylnaphthalene (11) and to contain no detectable amounts of the latter. The investigation accords with previously published observations that ethyl migrates in preference to methyl in structures in which the two groups compete for access to an adjacent electron-pair-deficient carbon atom but contrasts with one report of a preferential methyl migration in another dienone–phenol rearrangement.

Interpretation of observations made in the course of another investigation required information about the relative migratory aptitudes of methyl and ethyl groups in σ complex intermediates of general structure **1**.



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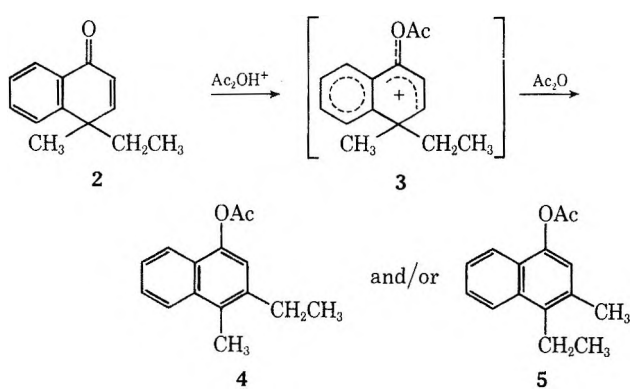
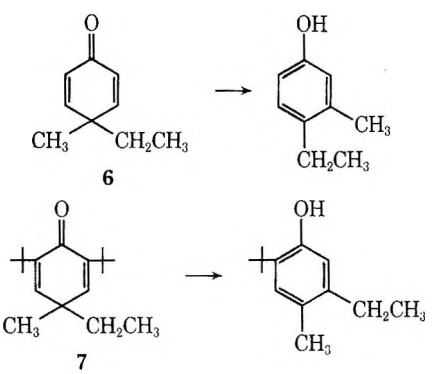
The literature contains a substantial weight of evidence suggesting that the relative rates of alkyl migration in the rearrangement of alkylaromatics follows the order *t*-butyl > *i*-propyl > ethyl > methyl, but a precise interpretation of the data is obstructed by the intervention of intermolecular processes involving all alkyl groups but methyl.[2] Furthermore, although σ complexes seem to be generally accepted as intermediates in the rearrangement of alkylaromatics, no case clearly involving one containing a quaternary carbon atom of type **1** can be identified. The work of Stiles and Meyer[3] showed a strong preference for 1,2 rearrangements of ethyl over methyl in pinacol systems, but steric factors not present in sigma complexes render uncertain the relationship between alkyl migration behavior in pinacol-derived ions and in σ complexes.

The dienone–phenol rearrangement seemed to offer a satisfactory reaction matrix from which to derive the required information, since σ complexes (*e.g.*, **3**) are considered to be intermediates in this process,[2] starting materials such as **2** are accessible synthetically, and the potential products **4** and **5** should be separable and subject to structure proof. If the relative alkyl migratory aptitudes in **3** are those observed in the pinacol rearrangement, as Arnold suggested,[4] then **4** should be the major product. In fact the extensive literature on the dienone–phenol rearrangement contains but two examples of structural systems such as **2**, in which methyl and ethyl groups are in migratory competition, and these are contradictory. Burnell[5] reported only methyl migration in **6**, whereas Miller and Marguiles[6] reported only ethyl migration in **7**. The



2 **3** **4** **5**



6 **7**

work hereinafter reported was undertaken in an effort to help resolve the contradiction, as well as to provide data for use in our other investigation.

A satisfactory synthesis of **2** followed the pathway formulated in Scheme I. All products were characterized by analysis and ir and nmr spectroscopy, and the uv spectra of the final three products also were measured. The Experimental Section gives the pertinent data, all of which accord with the structures assigned.

An effort to synthesize **2** by a simpler scheme, patterned after that employed by Arnold[7] for the preparation of the 4,4-dimethyl-1-keto-1,4-dihydronaphthalene (**9**), lower homolog of **2**, failed when γ-ethyl-γ-methyl-butyrolactone reacted with benzene in the presence of aluminum chloride to produce in less

(1) (a) From the doctoral thesis by K. P. Sivaramakrishnan, Carnegie-Mellon University. (b) This work was supported by Grant GP-1948 from the National Science Foundation.

(2) *Cf.* H. J. Shine, "Aromatic Rearrangements," Elsevier, New York, N. Y., 1967, Chapter 1.

(3) M. Stiles and R. P. Meyer, *J. Amer. Chem. Soc.*, **81**, 1497 (1959).

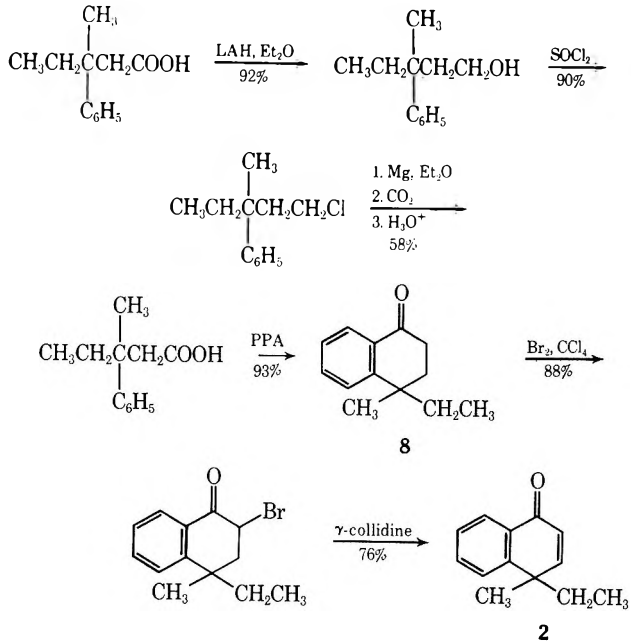
(4) R. T. Arnold and J. S. Buckley, Jr., *ibid.*, **69**, 2322 (1947).

(5) R. H. Burnell, *J. Chem. Soc.*, 1307 (1958).

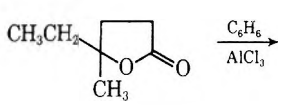
(6) B. Miller and H. Marguiles, *J. Amer. Chem. Soc.*, **87**, 5706 (1965).

(7) R. T. Arnold, J. S. Buckley, Jr., and J. Richter, *ibid.*, **69**, 2322 (1947).

SCHEME I



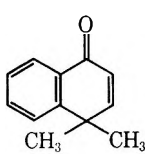
than 40% yield a ketone mixture that contained only about 30% 4-methyl-4-ethyl-1-tetralone (**8**), the intended product. The separation from and identifica-



8 (<12%) + unidentified ketonic material (<30%)

tion of **8** in the product mixture were accomplished by vpc, but its clean separation on a preparative scale could not be effected by convenient means, including fractional crystallization of the semicarbazone mixture. No effort was made to identify the remaining 70% of the isolated product, which appeared as a single peak on the vpc trace, with a shorter retention time than that from **8**. By contrast, the reaction of γ,γ-dimethyl-γ-butyrolactone with benzene afforded, in our hands as in those of Arnold,[7] an essentially homogeneous 4,4-dimethyl-1-tetralone in nearly 60% yield.

The latter was converted to 4,4-dimethyl-1-keto-1,4-dihydronaphthalene (**9**), by procedures reported by Arnold,[7] which employed the same reactions formulated



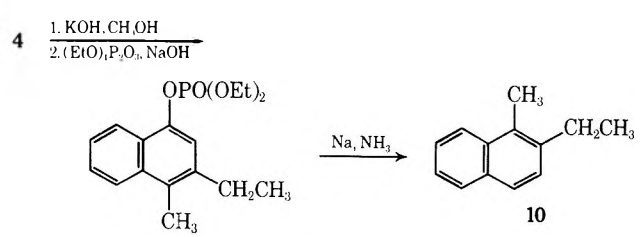
9

in Scheme I for the conversion of **8** to **2**. This known substance, and its previously reported[7] dienone–phenol rearrangement products, were prepared for comparison of their spectra, especially nmr, with those of **2** and its rearrangement product(s).

Treatment of **2** at room temperature with acetic anhydride containing a little sulfuric acid gave a crystalline product in 92% yield which afforded but one vpc peak. Analysis and spectroscopic properties showed it to be an ethylmethylnaphthyl acetate. The nmr spectrum provided strong evidence for (1) assignment of the ethyl and methyl groups to the 3 and 4 positions, respectively; and (2) establishing the substantial absence of the isomer with the alkyl groups reversed in position. Part of the supporting evidence is based on the observations of Yew, Kurland, and Mair,[8] who showed that nmr signals from methyl groups in the α position of naphthalene in polymethylnaphthalenes usually appear in the τ 7.40–7.50 region, whereas β-methyl signals are normally located in the τ 7.52–7.65 region. The sharp singlet assigned to aromatic methyl in the nmr spectrum of the rearrangement product appeared at τ 7.47 characteristic of α-methyl, and no singlet signal could be detected in the β-methyl region. The remaining nmr evidence was adduced by comparing the spectrum of the rearrangement product from **2** with that of the known 3,4-dimethyl-1-naphthyl acetate, which yielded singlet aromatic methyl signals at τ 7.50 and 7.58, and a singlet assigned to acetate methyl at τ 7.66. The acetate methyl signal from the rearrangement product of **2** appeared at τ 7.65.

Had the crude rearrangement product from **2** contained an appreciable amount of the isomer **5**, the nmr spectrum should have included a sharp singlet signal in the τ 7.55–7.58 region. In fact the spectrum showed only a scarcely discernible shoulder at the base of the τ 7.65 acetate methyl signal which is probably an artifact. However, even if this shoulder is assumed to be a singlet signal owing to a 3-methyl from traces of **5**, this isomer could not comprise more than 3–4% of the crude mixture. The failure of the vpc trace to show more than one sharp peak also suggests that any **5** actually present probably amounted to much less than 3–4% of the whole. The vpc evidence cannot be considered wholly reliable, however, since **5** was not actually prepared, isolated, and shown to be separated from **4** by vpc. Thus, we are able to conclude with some assurance only that the **4**:**5** ratio in crude product from **2** must be at least 25.

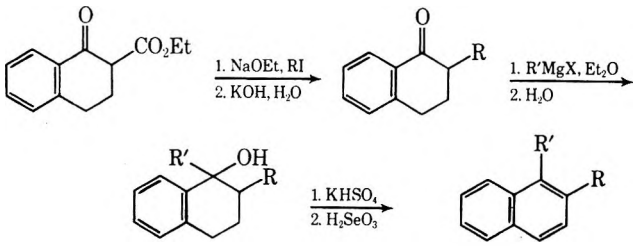
Confirmation of the structure **4** for the sole identifiable product of the dienone–phenol rearrangement of **2** was provided by its conversion through the corresponding naphthol to the diethyl phosphate derivative and then reduction of the latter by sodium and ammonia in tetrahydrofuran[9] to 1-methyl-2-ethylnaphthalene (**10**). The latter was identified with a sample prepared



by independent synthesis and shown to be different from 1-ethyl-2-methylnaphthalene (**11**) by comparison of the nmr spectra and by vpc. The hydrocarbon **10** obtained from the dienone–phenol rearrangement product contained no trace of **11** detectable by nmr or vpc.

Both ethylmethylnaphthalenes **10** and **11** were synthesized from ethyl-1-tetralone-2-carboxylate, as follows.

(8) F. F. Yew, R. J. Kurland, and B. J. Mair, *Anal. Chem.*, **36**, 843 (1964).
(9) G. W. Kenner and N. R. Williams, *J. Chem. Soc.*, 523 (1956).



10, R = C_2H_5; R' = CH_3
11, R = CH_3; R' = C_2H_5

Since nmr data for di- and polyalkylnaphthalenes containing ethyl groups have not hitherto been reported, it may be useful here to observe that the chemical shifts of the alkyl group signals in the nmr spectra of **10** and **11** also accorded with the generalizations of Yew, Kurland and Mair.[8] The 1- (α-) methyl signal from **10** appeared at τ 7.47, whereas that of the 2- (β-) methyl from **11** occurred upfield at τ 7.68. Furthermore, the quartet signal from the ring-bound methylene group of 1- (α-) ethyl in **11** was centered at τ 7.06, while that of the 2- (β-) ethyl in **10** had its center upfield at τ 7.23. The upfield position of the signal from the methylene protons of **10** relative to those of **11** is particularly significant in the light of the observation that the triplet signal from **10** owing to the methyl not joined to the ring is actually centered downfield (τ 8.81) compared with that from **11** (τ 8.89).

This investigation has therefore disclosed only ethyl migration in the postulated σ complex **3** derived from **2**; no methyl migration product could be detected; and nmr data preclude its occurrence to the extent of more than 1 part in 25. This new evidence therefore accords with that of Miller and Marguiles[6] but not with that reported by Burnell;[5] it is also consistent with the results of the quantitative study of the pinacol system reported by Stiles and Meyer.[3] We now consider it reasonable to suppose that the ethyl group will migrate substantially more rapidly than methyl in σ complexes of general structure **1**.

Experimental Section

A Cary automatic recording spectrophotometer was used to measure uv spectra. Some infrared spectra were measured with an Infracord double-beam instrument and some with a Perkin-Elmer 21 spectrophotometer. All nmr spectra were measured with a Varian A-60 spectrometer on samples dissolved in deuteriochloroform with tetramethylsilane as an internal standard. Vapor phase chromatograms were obtained by means of a Wilkens Aerograph Model 328, equipped with a Hy-Fl Model 600D hydrogen flame detector, with nitrogen as the carrier gas. Chemical analyses were carried out by Galbraith Laboratories, Inc., Knoxville, Tenn.

3-Methyl-3-phenyl-1-pentanol.—A solution of 80 g (0.416 mol) of 3-methyl-3-phenylpentanoic acid[10] in 300 ml of anhydrous ether was added to a solution of 18 g (0.515 mol) of lithium aluminum hydride in 300 ml of anhydrous ether at such a rate that the solution refluxed spontaneously. The slurry was stirred for 24 hr and treated with 60 ml of aqueous sodium sulfate; then the ether solution was filtered and dried over anhydrous sodium sulfate. Removal of the ether and distillation of the residue afforded 68.0 g (92%) of 3-methyl-3-phenyl-1-pentanol, a colorless liquid: bp 133° (2 mm); $n^{24.4}$D 1.5195; ir (neat) 2.95 (OH), 6.23 μ (C_6H_5); nmr τ 2.75 (s, 5, C_6H_5), 6.58 (t, 3, CH_2OH), 7.96–8.55 (m, 4, CH_2CCH_2), 8.72 (s, 3, CCH_3), 9.33 (t, 3, CH_2CH_3).

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 81.04; H, 10.18.

1-Chloro-3-methyl-3-phenylpentane.—A mixture of 135 g (0.757 mol) of 3-methyl-3-phenyl-1-pentanol and 180 g (1.514 mol) of thionyl chloride was stirred and heated at reflux for 24 hr. Removal of volatile material and distillation of the residual brown liquid afforded 132 g (90%) of 1-chloro-3-methyl-3-phenylpentane as a colorless liquid: bp 115–116° (3 mm); $n^{24.4}$D 1.5182; nmr τ 2.70 (s, 5, C_6H_5), 6.55–7.0 (m, 2, CH_2Cl), 7.67–8.09 (m, 2, CH_2CH_2Cl), 8.20–8.58 (m, 2, CH_2CH_3), 8.72 (s, 3, CCH_3), 9.33, (t, 3, J = 7 Hz, CH_2CH_3).

Anal. Calcd for $C_{12}H_{17}Cl$: C, 73.26; H, 8.71. Found: C, 73.16; H, 8.76.

4-Methyl-4-phenylhexanoic Acid.—A solution of 66.0 g (0.32 mol) of 1-chloro-3-methyl-3-phenylpentane in 500 ml of anhydrous ether was added gradually to 8.99 g (0.37 g-atom) of magnesium turnings being stirred in 250 ml of anhydrous ether, after the reaction was initiated by an iodine crystal. The mixture was boiled for 2 hr after addition of the halide was complete, then treated with 500 g of powdered Dry Ice and stirred for an hour. The mixture was stirred with 5% aqueous sulfuric acid, the aqueous layer was extracted with ether and the latter combined with the original ether solution. The combined ether solution was washed with water, dried over anhydrous sodium sulfate and concentrated. Distillation afforded 39.8 g (58%) of 4-methyl-4-phenylhexanoic acid as a colorless liquid: bp 136° (2 mm); $n^{24.4}$D 1.5165; ir (neat) 3.6–3.8 (OH), 5.83 (C=O), 6.23 μ (C_6H_5); nmr τ −1.40 (s, 1, COOH), 2.52 (s, 5, C_6H_5), 7.80–8.00 (m, 2, CH_2COOH), 8.10–8.50 (m, 4, CH_2CH_2COOH, CH_2CH_3), 8.71 (s, 3, CH_3), 9.30 (t, 3, J = 7 Hz, CH_2CH_3).

Anal. Calcd for $C_{13}H_{18}O_2$: C, 75.69; H, 8.80. Found: C, 75.90; H, 8.94.

4-Ethyl-4-methyl-1-tetralone (8).—The procedure was adapted from that reported by Cromwell and Bell[11] for the preparation of 4,4-dimethyl-1-tetralone. A 27.8-g (0.135 mol) sample of 4-methyl-4-phenylhexanoic acid was warmed to 65° and added in one portion to 80 g of polyphosphoric acid which had been preheated to 90°. The mixture was stirred for 5 min, warmed on the steam bath, and then treated with an additional 40 g of polyphosphoric acid. The temperature of the mixture was maintained at 90° while it was stirred for 35 min; then it was cooled and stirred into ice water. When the color of the viscous, water-immiscible oil had completed its change from brown to yellow, it was extracted into three 250-ml portions of ether. The combined ether extracts were washed successively with 300 ml of water, 200 ml of 5% aqueous sodium hydroxide, 300 ml of water, 200 ml of 3% aqueous acetic acid, and finally with 200 ml of water. The solution was dried over anhydrous sodium sulfate, the ether was removed, and the residual oil distilled to yield 23.5 g (93%) of 4-ethyl-4-methyl-1-tetralone (**8**) as a colorless oil: bp 112–113° (4 mm); $n^{24.4}$D 1.5487; uv max (95% EtOH) 247 mμ (ϵ 12,760), 290 (2145); ir (neat) 5.93 (C=O), 6.23 μ (C_6H_5); nmr τ 1.91 (complex d, 1, J = 7 Hz, C_8H), 2.4–2.8 (m, 3, C_5H, C_6H, C_7H), 7.29 and 7.96 (A_2X_2 mult, 4, $COCH_2CH_2$, respectively), 8.3–8.48 (m, 2, CH_2CH_3), 8.66 (s, 3, CCH_3), 9.15 (t, 3, J = 7.5 Hz, CH_2CH_3).

The 2,4-dinitrophenylhydrazone crystallized from ethyl acetate as reddish needles, mp 183–184°.

Anal. Calcd for $C_{19}H_{20}N_4O_4$: C, 61.94; H, 5.47; N, 15.21. Found: C, 61.75; H, 5.61; N, 15.00.

2-Bromo-4-ethyl-4-methyl-1-tetralone.—A solution of 16 g (0.1 mol) of bromine in 80 ml of carbon tetrachloride was added with stirring over a period of 45 min to a solution of 18.8 g (0.1 mol) of 4-ethyl-4-methyl-1-tetralone in 200 ml of carbon tetrachloride; then the solution was stirred for an additional 30 min. Removal of solvent left 26 g of a viscous oil which afforded 23.41 g (88%) of crystalline 2-bromo-4-ethyl-4-methyl-1-tetralone, mp 73–75°, when triturated with petroleum ether (bp 65–110°). Recrystallization from the same solvent afforded white crystals: mp 74–75°; uv max (95% EtOH), 251 mμ (ϵ 11,200), 294 (1747); ir 5.91 μ (C=O), 6.23 (C_6H_5).

The nmr spectrum revealed the presence of two stereoisomers: τ 2.0 (complex d, 1, J_{78} = 7 Hz, C_8H), 2.4–2.8 (m, 3, C_5H, C_6H, C_7H), 4.90 and 4.99 (two overlapping "X" quartets of ABX systems, 1, $COCHBrCH_2$), 7.08–7.91 (two overlapping "AB" multiplets of ABX systems, 2, $COCHBrCH_2$), 8.20 and 8.31 (two overlapping quartets, 2, J = 7 Hz, CH_2CH_3), 8.61 and 8.63 (both s, 3, CCH_3), 9.07 and 9.19 (two overlapping triplets, 3,

(10) N. Rabjohn, Ed., "Organic Syntheses," Coll. Vol. IV, Wiley, New York, N. Y., 1963, p 97.

(11) N. H. Cromwell and V. Bell, *J. Org. Chem.*, **23**, 789 (1953).

J = 7 Hz, CH_2CH_3). The τ values for CHBr suggested axial bromine for both isomers.[12]

Anal. Calcd for $C_{13}H_{15}BrO$: C, 58.44; H, 5.66; Br, 29.90. Found: C, 58.69; H, 5.87; Br, 29.71.

4-Ethyl-4-methyl-1-keto-1,4-dihydronaphthalene (2).—A solution of 20.037 g (0.075 mol) of 2-bromo-4-ethyl-4-methyl-1-tetralone in 65 ml of γ-collidine was boiled for 75 min, cooled to 0°, and diluted with 300 ml of ether. The solution was filtered free of 12 g of precipitated γ-collidine hydrobromide and washed successively with 5% aqueous hydrochloric acid, 5% aqueous sodium hydroxide, and finally water. The liquid remaining after removal of the ether solvent was distilled to afford 10.54 g (76%) of 2 as a colorless liquid: bp 150° (4 mm); $n^{24.4}$D 1.5649; uv max (95% EtOH) 242 mμ (ε 10,820); ir (neat) 6.04 (C=C—C=O), 6.24 μ (C_6H_5); nmr τ 1.82 (doublet of quartets, 1, J_{78} = 8 Hz, C_8**H**), 2.42–2.83 (m, 3, C_5**H**, C_6**H**, C_7**H**), 3.24 (d, 1, J = 10 Hz, COCH=CH), 3.56 (d, 1, J = 10 Hz, COCH=C**H**), 8.04 and 8.13 (minor and major overlapping quartets, 2, J = 7 Hz, CH_2CH_3), 8.57 and 8.67 (major and minor singlets, 3, CCH_3), 9.51 (t, 3, J = 7 Hz, CH_2CH_3).

The 2,4-dinitrophenylhydrazone was obtained as scarlet needles from ethyl acetate: mp 195–196°; uv max (95% EtOH) 391 mμ (ε 39,270).

Anal. Calcd for $C_{19}H_{18}N_4O_4$: C, 62.98; H, 4.95; N, 15.29. Found: C, 62.51; H, 5.19; N, 15.10.

3-Ethyl-4-methyl-1-naphthyl Acetate (4) by Rearrangement of 2.—After standing for 6 hr at room temperature, a solution of 0.93 g (0.005 mol) of 2 in 17.5 ml of acetic anhydride containing 0.25 g of sulfuric acid was poured, with vigorous stirring, into 150 ml of cold water. Continued stirring converted the original water-insoluble oil into 1.05 g (92%) of a white powder, mp 42–43°. Recrystallization from petroleum ether (bp 30–60°) afforded tiny white crystals: mp 43.5–44.5°; uv max (95% EtOH) 227 mμ (ε 74,470), 287 (6460), 322 (1188); ir (Nujol) 5.65 μ (ester C=O); nmr τ 1.8–2.65 (complex, 4, C_5**H**, C_6**H**, C_7**H**, C_8**H**); 2.86 (s, 1, C_2**H**), 7.17 (q, 2, J = 7 Hz, CH_2CH_3), 7.47 (s, 3, $ArCH_3$), 7.65 [s, 3, $OCOCH_3$ (compare with $OCOCH_3$ signal from 3,4-dimethyl-1-naphthyl acetate, τ 7.66)], 8.76 (t, 3, J = 7 Hz, CH_2CH_3).

The vpc analysis using a Dow-11 column at 150° with N_2 (48 ml/min) as carrier gas and H_2 flow of 33 ml/min afforded a trace showing but one peak, retention time 16.4 min.

Anal. Calcd for $C_{15}H_{16}O_2$: C, 78.92; H, 7.06. Found: C, 79.07; H, 7.25.

3-Ethyl-4-methyl-1-naphthol.—A solution of 0.52 g (0.00238 mol) of 4 in 15 ml of 5% methanolic potassium hydroxide was boiled for 2 hr, and the methanol was removed. Dilution with water and acidification with aqueous hydrochloric acid yielded 0.412 g (99%) of 3-ethyl-4-methyl-1-naphthol, mp 81–82°. Recrystallization from carbon tetrachloride and petroleum ether (bp 65–110°) gave colorless crystals: mp 83–84°; uv max (95% EtOH) 239 mμ (ε 40,700), 302 (5327); ir (Nujol) 2.95 μ (OH); nmr τ 1.85–2.25 and 2.6–2.85 (m, 4, ring C_5**H**, C_6**H**, C_7**H**, C_8**H**), 3.70 (s, 1, ring C_2**H**), 4.55 (broad, 1, OH), 7.38 (q, 4, J = 7 Hz, CH_2CH_3), 7.55 (s, 3, $ArCH_3$), 8.88 (t, 3, J = 7 Hz, CH_2CH_3).

Anal. Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.63; H, 7.66.

1-Methyl-2-ethylnaphthalene (10) by Reduction of (3-Ethyl-4-methyl-1-naphthyl)diethyl Phosphate.—A solution of 0.372 g (0.002 mol) of 3-ethyl-4-methyl-1-naphthol in 2 ml of 1 *N* sodium hydroxide was shaken vigorously with 0.508 ml (0.002 mol) of tetraethyl pyrophosphate. The brown oil that separated was extracted into 25 ml of ethyl acetate, and the solution was washed first with 0.01 *N* sodium hydroxide and then with water. Evaporation of solvent from the dried (K_2CO_3) solution afforded 0.512 g (81%) of the naphthyldiethyl phosphate as a brown oil, which was dissolved in 1.5 ml of dry tetrahydrofuran. The solution, cooled in Dry Ice–acetone, was diluted with 10 ml of anhydrous ammonia, and the new solution maintained just below the boiling point while 75 mg of clean sodium was added in small pieces. After 3 hr, about 1 ml of ethanol was added, and the ammonia was permitted to evaporate. The residue was shaken with chloroform and water, the chloroform solution was washed successively with aqueous sodium bicarbonate, sodium hydroxide, and then water, the solution was dried ($CaCl_2$), the chloroform was removed under reduced pressure, and the residual brown oil was (0.310 g) subjected to vpc analysis. A sample introduced into a Dow-11 column at 150° with N_2 as the carrier gas (33 ml/min) and hydrogen flowing at 33 ml/min gave a trace with a single peak, retention time 7.1 min. A mixture of this oil with an authentic sample of 1-methyl-2-ethylnaphthalene (10) (see below), introduced into the same column under the same conditions, again showed a single peak with the same retention time. A mixture of the oil and an authentic sample of 1-ethyl-2-methylnaphthalene (11) (see below), on the other hand, afforded 2 peaks with retention times 7.1 and 7.4 min, the latter being the retention time of pure 1-ethyl-2-methylnaphthalene in the same column, under the same conditions.

2-Methyl-1-tetralone was prepared by the method of Bailey and Stavely[13] from ethyl 1-tetralone-2-glyoxalate, which was obtained by the procedure of Huisgen and Rauenbush.[14] The colorless liquid, bp 112° (13 mm), $n^{24.4}$D 1.5558 (lit.[13] n^{26}D 1.5538), gave a 2,4-dinitrophenylhydrazone, scarlet needles from benzene, mp 236°, as reported.[12]

2-Ethyl-1-tetralone, similarly prepared from ethyl 1-tetralone-2-glyoxalate was a colorless liquid, bp 140–141° (13 mm), $n^{24.4}$D 1.5454 (lit.[13] n^{25}D 1.5460).

1-Ethyl-2-methyl-1-tetralol was prepared by the procedure of Adkins and Davis.[15] It formed white crystals, mp 66–67° (lit.[15] mp 65–67°), from acetone at about −70°.

1-Ethyl-2-methylnaphthalene (11) was prepared in two steps from 1-ethyl-2-methyl-1-tetralol by the procedure of Christol,[16] colorless liquid: bp 133–134° (15 mm) [lit.[15] bp 153° (30 mm)]; uv max (95% EtOH) 225 mμ (ε 81,890), 273 (5505), 282 (5937), 306 (958), 321 (718); nmr τ 1.96–2.91 (complex, 6, Ar**H**), 7.06 (q, 2, J = 7.5 Hz, CH_2CH_3), 7.68 (s, 3, $ArCH_3$), 8.89 (t, 3, J = 7.5 Hz, CH_2CH_3); vpc retention time (conditions as described above) 7.4 min, single peak.

1-Methyl-2-ethylnaphthalene (10), prepared from 2-ethyl-1-tetralone as its isomer was from 2-methyl-1-tetralone, was a colorless liquid: bp 150° (30 mm) [lit.[14] bp 155° (30 mm)]; uv max (95% EtOH) 226 mμ (ε 91,520), 273 (5334), 282 (5701), 306 (889), 321 (600); nmr τ 1.96–2.91 (complex, 6, Ar**H**), 7.23 (q, 2, J = 7.5 Hz, CH_2CH_3), 7.47 (s, 3, $ArCH_3$, partially obscuring upfield lobe of CH_2 quartet), 8.81 (t, 3, J = 7.5 Hz, CH_2CH_3); vpc retention time (conditions as described above) 7.1 min, single peak. All spectroscopic data, including ir, matched those of the sample obtained by reduction of the rearrangement product (above).

4,4-Dimethyl-1-tetralone, prepared by the method of Arnold,[7] afforded a far simpler nmr spectrum than did its 4-methyl-4-ethyl homolog. Although the aromatic protons gave entirely similar signals, τ 1.95 (doublet of quartets, J_{78} = 7 Hz, 1, C_8H), 2.43–2.81 (complex 3, C_5**H**, C_6**H**, C_7**H**). The methylene groups afforded relatively simple signals, centered at τ 7.28 ($COCH_2$) and τ 8.02 ($COCH_2CH_2$), only slightly more complex than an A_2X_2 triplet pair in which $J_{AX} = J'_{AX}$ = 7 Hz. The geminal methyl groups yielded a lone singlet at τ 8.65.

2-Bromo-4,4-dimethyl-1-tetralone[7] also afforded a much simpler nmr spectrum than did its homolog with an ethyl displacing one of the methyl groups. The aromatic proton signals comprised a doublet of quartets at τ 1.92 (1, J_{78} = 7 Hz, C_8**H**) and a complex pattern at 2.35–2.83 (3, C_5**H**, C_6**H**, C_7**H**). With methyl groups at both 4 positions, the signals for the protons of the $COCHBrCH_2$ grouping appeared as a triplet and a doublet at 4.88 and 7.43, respectively (J = 9 Hz), an uncomplicated A_2X pattern. By contrast, the ethyl analog gave two overlapping ABX patterns, characteristic of stereoisomers. In both cases the chemical shift associated with the COCHBr signal suggested axial bromine.[12] Finally, the two methyl groups yielded separate signals at τ 8.52 and 8.58, respectively.

4,4-Dimethyl-1-keto-1,4-dihydronaphthalene[7] showed nmr spectral features in common with those of the 4-ethyl homolog (2). The aromatic proton signals, τ 1.80 (complex d, 1, J_{78} = 7 Hz, C_8**H**), and 2.4–2.7 (m, 3, C_5**H**, C_6**H**, C_7**H**), were quite similar to those from 2, as was the AB quartet with the 1-proton doublets located at τ 3.08 and 3.66 (J = 10 Hz) arising from COCH=CH. Strikingly, major and minor singlets from the methyls appeared in this spectrum (τ 8.56 and 8.64) as they did in that of 2.

(12) *Cf.* D. Chapman and P. D. Magnus, "Introduction to Practical High Resolution Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York, N. Y., 1966, p 76.

(13) A. S. Bailey and C. M. Stavely, *J. Inst. Petroleum*, **42**, 97 (1956).

(14) R. Huisgen and E. Rauenbush, *Justus Liebigs Ann. Chem.*, **641**, 51 (1961).

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3,4-Dimethyl-1-naphthyl acetate[7] gave an nmr spectrum whose aromatic portion was substantially superimposable over those of the two methyl ethyl homologs. The three methyl singlets appeared at τ 7.50, 7.58, and 7.66 (4-CH_3, 3-CH_3, and $OCOCH_3$, respectively).

Registry No.—3-Methyl-3-phenyl-1-pentanol, 25594-39-2; 1-chloro-3-methyl-3-phenylpentane, 13556-52-0; 4-methyl-4-phenylhexenoic acid, 25607-04-9; 2-bromo-4-ethyl-4-methyl-1-tetralone, 25607-05-0; 3-ethyl-4-methyl-1-napthol, 25607-06-1; 4,4-dimethyl-1-tetralone, 2979-69-3; 2-bromo-4,4-dimethyl-1-tetralone, 17426-90-3; 4,4-dimethyl-1-keto-1,4-dihydronapthalene, 16020-16-9; 3,4-dimethyl-1-napthyl acetate, 25607-10-7; **2**, 25607-11-8; **2** (2,4-dinitrophenylhydrazone), 25607-12-9; **4**, 25607-13-0; **8**, 25607-14-1; **8** (2,4-dinitrophenylhydrazone), 25607-15-2; **10**, 25607-16-3; **11**, 17057-93-1.

Boron Fluoride Catalyzed Ethylation of Benzene with Radioactive Ethyl Fluoride

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Boron fluoride catalyzed ethylation of benzene was carried out with ethyl-2-^{14}C fluoride in homogeneous solution of nonpolar organic or basic organic solvent. The ethylbenzenes obtained were oxidized with nitric acid. Radioactivity of *p*-nitrobenzoic acid which was found in the *n*-hexane, cyclohexane, or nitromethane system was 47.9, 34.1, or 3.5% of radioactivity of ethyl-2-^{14}C fluoride, respectively. It was confirmed that an electrophile in boron fluoride catalyzed ethylation is either an ethyl carbonium ion in the nonpolar organic solvent or a nonionized complex in the basic organic solvent.

In basic solvent the catalytic activity of Friedel–Crafts catalyst decreases in terms of a competing donor effect of the solvent. Solvated Friedel–Crafts catalyst forms with ethyl fluoride the nonionized complex which is an electrophile of Friedel–Crafts ethylation in basic solvents.[1] In nonpolar solvents a Friedel–Crafts catalyst which does not form a complex with the solvent ruptures a C–X bond of ethyl halide, and an incipient ethyl carbonium ion is an ethylating agent. This was proved by a finding that, when aluminum bromide catalyzed ethylation of benzene with ethyl-2-^{14}C iodide was carried out in the *n*-hexane solution, oxidation of the ethylbenzene with nitric acid gave radioactive *p*-nitrobenzoic acid, indicating the migration of radioactivity from β to α carbon atom of the ethyl group.[2] When the ethyl carbonium ion is an ethylating agent, an anomalous substrate selectivity (a relative rate of toluene to benzene lower than 1) was found.[2]

In this work boron fluoride catalyzed ethylation of benzene with ethyl-2-^{14}C fluoride in the nonpolar solvent has been carried out to obtain an additional evidence for the formation of the incipient ethyl carbonium ion as an ethylating agent.

Results and Discussion

Ethyl fluoride forms a yellow polarized complex with boron fluoride at low temperatures.[3–5] The complex completely dissociates into gaseous components at room temperature. When the gaseous mixture was left for many hours, a yellow-brown oily polymer was formed. The gaseous mixture is soluble in the nonpolar solvent like *n*-hexane or cyclohexane, although the solubility of boron fluoride is low. The colorless solution is thus formed. Also, when the colorless solution was left for many hours, the yellow-brown oily polymer was formed and deposited on the bottom of the vessel. These results suggest that the ethyl carbonium ion is formed as an intermediate.[6] When the gaseous mixture was introduced in the nonpolar solvent with a trace of water, the polymer was immediately formed, and the solution showed a Tyndall effect. The gaseous mixture is very soluble in a basic solvent like nitromethane. Even if the solution was left for many hours, the oily polymer was not formed, indicating the impossibility of formation of the ethyl carbonium ion in the solution.

The gaseous mixture of ethyl fluoride and boron fluoride was dissolved in the nonpolar solvents, in which the aromatics were dissolved. When the homogeneous colorless solution thus formed was left for many hours, the oily polymer was not formed, but the ethylation of aromatics proceeded gradually.[2] However, the materials should be the purest, for when a trace of water exists in the solution, the oily polymer is immediately formed, and the solution shows the Tyndall effect.

Ethylation with Radioactive Ethyl Fluoride.—Boron fluoride catalyzed ethylation of benzene was carried out at room temperature with ethyl-2-^{14}C fluoride in the homogeneous solution of *n*-hexane, cyclohexane, or nitromethane. The ethylbenzenes obtained were oxidized with nitric acid. The *p*-nitrobenzoic acid thus obtained was dissolved in a liquid scintillator, and the radioactivity of the solution was counted.[2,7] The results are summarized in Table I. When the ethylation was carried out in *n*-hexane solution, 47.9% of radioactivity of ethyl-2-^{14}C fluoride was found in the *p*-nitrobenzoic acid obtained, indicating the formation of ethyl-1-^{14}C-benzene and hence the migration of radioactivity from β to α carbon position of the ethyl

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(6) D. C. Pepper, in "Friedel-Crafts and Related Reactions," Vol. II, Part 2, G. A. Olah, Ed., Interscience, New York, N. Y., 1964, p 1293.
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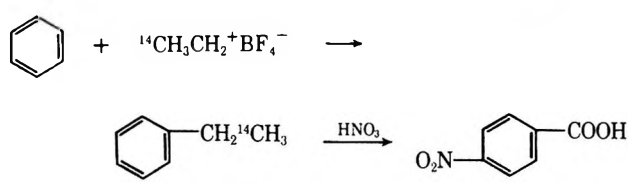
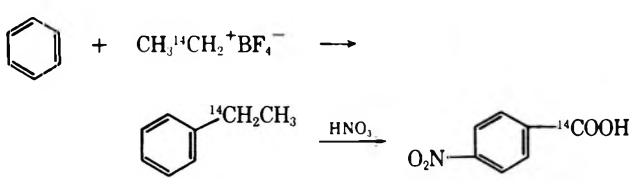
TABLE I
BORON FLUORIDE CATALYZED ETHYLATION OF BENZENE WITH ETHYL-2-^{14}C FLUORIDE (206.5 mμCi/mmol)

Solvent	Radioactivity of *p*-nitrobenzoic acid, mμCi/mmol
n-Hexane	98.9
Cyclohexane	70.4
Nitromethane	7.3

group. If the ethyl carbonium ion is formed as an intermediate and an internal hydride shift occurs completely in the ethyl group before the ethyl carbonium ion combines with the benzene ring, a maximum of 50% isotope position rearrangement, corresponding to a complete equilibration of the α and β carbons of the ethyl group, should be reached. The ethylbenzene obtained, therefore, exhibits almost complete rearrangement, indicating that the ethyl carbonium ion is an electrophile in the ethylation carried out in the *n*-hexane solution. When the ethylation was carried out in the

$$^{14}CH_3CH_2F + BF_3 \rightleftharpoons {}^{14}CH_3CH_2^+BF_4^- \rightleftharpoons CH_3{}^{14}CH_2^+BF_4^-$$



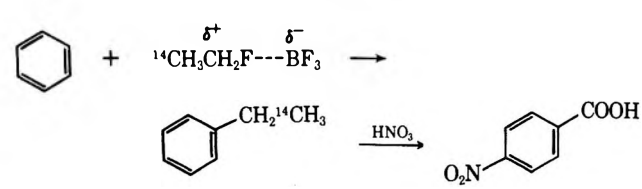


cyclohexane solution, 34.1% of radioactivity of ethyl-2-^{14}C fluoride was found in the *p*-nitrobenzoic acid obtained. This result also suggests that the ethyl carbonium ion is an electrophile. However, when the ethylation was carried out in the nitromethane solution, only 3.5% of radioactivity of ethyl-2-^{14}C fluoride was found in the *p*-nitrobenzoic acid obtained. The ethylation of benzene in the basic solution gave the ethylbenzene, in which only a little isotope position rearrangement in the ethyl group was taken place. This suggests that the ethylation in the basic solution proceeds almost in terms of a displacement mechanism involving no free ethyl fragments. The electrophile in the basic solvents is the nonionized complex, $C_2{}^{\delta+}H_5F\cdots{}^{\delta-}BF_3$.

$$BF_3 + CH_3NO_2 \rightleftharpoons \overset{\delta-}{BF_3}\text{---}\overset{\delta+}{O_2NCH_3}$$

$$^{14}CH_3CH_2F + \overset{\delta-}{BF_3}\text{---}\overset{\delta+}{O_2NCH_3} \rightleftharpoons$$

$$^{14}\overset{\delta+}{CH_3CH_2F}\text{----}\overset{\delta-}{BF_3} + CH_3NO_2$$



Reaction Mechanism of Boron Fluoride Catalyzed Ethylation.—When the competitive boron fluoride catalyzed ethylations of benzene and toluene were carried out with ethyl fluoride at 25° in the homogeneous solutions, the relative rates of toluene to benzene, k_T/k_B, were 0.56 in the *n*-hexane solution and 0.57 in the cyclohexane solution, respectively, but 2.66 in the nitromethane solution, as observed in the previous work.[2] That benzene is more reactive than toluene in the nonpolar solvents was also observed in the ethylations carried out in the separate runs, but there was a question whether the competitive ethylation in the nonpolar solvents proceeded in kinetically controlled electrophilic substitutions or not. Therefore, we carried out the following control experiments in a glass flask. Boron fluoride and isopropyl fluoride were introduced in the *n*-hexane solution of *o*-ethyltoluene in presence of benzene. When a part of *o*-ethyltoluene and benzene were isopropylated, the solution was quenched in water. Unchanged *o*-ethyltoluene and benzene were found, but ethylbenzene was not formed. Next, boron fluoride and ethyl fluoride were introduced in the *n*-hexane solution of *p*-cymene in presence of benzene. Ethylation proceeded, but even a trace of cumene could not be found in presence of unchanged benzene. These results show that the transalkylations between *o*-ethyltoluene and benzene and between *p*-cymene and benzene do not take place in the *n*-hexane solution. The transalkylations between isopropylmesitylene and benzene[8] and between *p*-t-butyltoluene and benzene[9] with aluminum chloride catalyst were observed to take place under the conditions employed in the alkylations. However, since the experiments were carried out in the glass flask, hydrogen fluoride produced could be immediately captured by the wall of the flask and a protonated alkylbenzene tetrafluoroborate complex could not be formed. Consequently, the thermodynamically controlled consecutive transalkylations do not take place.[10] The competitive boron fluoride catalyzed ethylations of benzene and toluene with ethyl fluoride were carried out under the similar conditions. Thus, when boron fluoride catalyzed ethylation with ethyl fluoride is carried out in the nonpolar solvent contained in the glass or stainless steel flask, the ethylation proceeds in kinetically controlled substitutions, for the hydrogen fluoride as a product is captured by the wall of the flask, and the protonated alkylbenzene tetrafluoroborate complex is not formed and then the thermodynamically controlled consecutive transethylations do not take place.

The results obtained in this work support our previous conclusions[2] that the electrophile of Friedel–Crafts ethylation is either the ethyl carbonium ion in the nonpolar solvents or the nonionized complex in the basic solvents, and that the substrate and positional selectivities in all Friedel–Crafts alkylations are determined by the activation energy of formation of the σ complex.

Experimental Section

Material.—Benzene, toluene, ethyl fluoride, isopropyl fluoride, boron fluoride, *n*-hexane, cyclohexane, and nitromethane were

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prepared and purified by the previously described methods.[2,11] Ethyl-2-^{14}C fluoride was prepared from ethyl-2-^{14}C iodide (The Radiochemical Centre, Amersham, England) by reaction with mercuric fluoride[12] and purified by distillation at low temperatures; 330 mg of the ethyl-2-^{14}C fluoride obtained was dissolved in a liquid scintillator (10 ml); and the radioactivity of the solution was counted. The solution had a radioactivity of 206.5 mμCi/mmol. Mercuric fluoride was prepared from mercuric chloride (Junsei Pure Chemical Co., Tokyo, Japan) by the reaction with elemental fluorine[12] (Daikin Kogyo Co., Osaka, Japan). *o*-Ethyltoluene and *p*-cymene were obtained from Tokyo Kagaku Seiki Co. (Tokyo, Japan). Their purities were more than 99% by gas chromatographic analyses. They were used without further purification.

Ethylation with Ethyl-2-^{14}C Fluoride.—When the boron fluoride catalyzed ethylation of benzene was carried out with ethyl-2-^{14}C fluoride in the *n*-hexane solution, benzene (0.15 mol), and *n*-hexane (1.5 mol) were first charged in the glass flask. From gas reservoirs gaseous ethyl-2-^{14}C fluoride (0.09 mol) and gaseous boron fluoride (0.01 mol) were introduced in the flask and dissolved in the solution. Then a magnetic stirrer was started. After the reaction which continued for 120 hr, the solution was quenched in water. When the ethylation was carried out in the cyclohexane solution, benzene (0.1 mol), cyclohexane (1 mol), ethyl-2-^{14}C fluoride (0.026 mol), and boron fluoride (0.014 mol) were charged in the flask and the solution was quenched in water after the reaction which continued for 17 hr. When the ethylation was carried out in the nitromethane solution, benzene (0.15 mol), nitromethane (0.45 mol), ethyl-2-^{14}C fluoride (0.015 mol), and boron fluoride (0.03 mol) were charged in the flask, and the solution was quenched in water after the reaction which continued for 1 hr. In the preliminary experiments with nonradioactive ethyl fluoride by the similar procedure it was confirmed that about 5% of benzene was ethylated in each case. The organic layer was washed with 4% NaOH solution and then five times with water. The organic solution was dried over calcium chloride and subjected to fractional distillation. A large amount of solvents was removed. Oxidation of the remaining solution was carried out by the previously described methods.[2,7] The *p*-nitrobenzoic acid obtained (5 mg) was dissolved in a liquid scintillator (10 ml), and the radioactivity of the solution was counted.

Radiochemical purity of the ethyl-2-^{14}C iodide obtained from the Radiochemical Centre was 99%. Radiochemical purity of the ethyl-2-^{14}C fluoride prepared was not measured. When the ethylation was carried out in the nitromethane solution, 3.5% of radioactivity of ethyl-2-^{14}C fluoride was found in the *p*-nitrobenzoic acid. This result suggests the following two possibilities: the one is that the radiochemical purity of ethyl-2-^{14}C fluoride was 96.5%, because a little isotope position rearrangement in the ethyl group was taken place when ethyl-2-^{14}C fluoride was prepared from ethyl-2-^{14}C iodide by the reaction with mercuric fluoride; the other is that the radiochemical purity of ethyl-2-^{14}C fluoride was 99%, but a little rearrangement proceeded in the ethylation. At any rate, the radiochemical purity of ethyl-2-^{14}C fluoride was equal to or higher than 96.5%.

Isopropylation of Benzene and *o*-Ethyltoluene with Isopropyl Fluoride in *n*-Hexane Solution.—Isopropyl fluoride (0.0025 mol) and boron fluoride (0.0015 mol) were introduced in the glass flask, in which benzene (0.0125), *o*-ethyltoluene (0.0125 mol), and *n*-hexane (0.25 mol) were charged. After the reaction which continued for 20 min, the solution was quenched in water, extracted with ether, dried over calcium chloride, and analyzed by gas chromatography.

Ethylation of Benzene and *p*-Cymene with Ethyl Fluoride in *n*-Hexane solution.—Ethyl fluoride (0.0025 mol) and boron fluoride (0.0025 mol) were introduced in the glass flask, in which benzene (0.0125 mol), *p*-cymene (0.0125 mol), and *n*-hexane (0.25 mol) were charged. After the reaction, which continued from 24 hr, the solution was quenched in water, extracted with ether, dried over calcium chloride, and analyzed by gas chromatography.

Radioactivity Measurements.—Radioactivity measurements were carried out with a Beckman LS-150 liquid scintillation system at room temperatures by an external channel ratio method. Dioxane containing the usual scintillators was used as a solvent. A counting efficiency of about 85% with a background of about 50 cpm was obtained.

Gas Chromatographic Analyses.—Analyses were carried out with a Hitachi Perkin-Elmer gas chromatograph Model F6D using a hydrogen flame ionization detector. Golay column HB-2000 (1, 45 m, i.d. 0.25 mm) coated with polypropylene glycol (Ucon oil 50-HB-2000 Poly) was used. The column temperature was 120° with dry nitrogen gas flow rate at approximately 1.1 at ml/min atmospheric pressure.

Registry No.—Boron fluoride, 7637-07-2; benzene, 71-43-2; ethyl-2-^{14}C fluoride, 25636-50-4.

Acknowledgment.—The authors wish to thank Dr. Osamu Kurihara for his valuable advice on many of the experimental details.

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Relative Reactivities of Cycloalkanone Dimethyl Ketals to Hydrogenolysis by Dichloroaluminum Hydride

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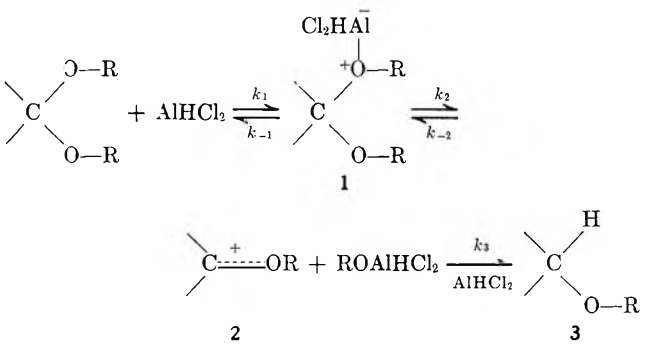
The relative rates of hydrogenolysis of a series of cycloalkanone dimethyl ketals by $AlCl_2H$ to the corresponding cycloalkyl methyl ethers have been determined. The order of reactivity varies with ring size in the following manner: $C_7 > C_8 > C_9 \approx C_5 > C_{11} \approx$ 3-pentanone $> C_{10} > C_6 > C_{12} > C_4$. These results are consistent with the concept of I (internal) strain, and it is suggested that formation of the oxocarbonium ion is the rate-controlling step in the hydrogenolysis reaction.

Following the discovery of lithium aluminum hydride (LAH) and its many applications to the reduction of organic compounds, it had been found that LAH in combination with other reagents gave compounds with reducing properties[2] different from those of LAH itself. LAH and aluminum halides give hydridoaluminum halides, "mixed hydrides," which unlike LAH have the ability to hydrogenolyze acetals and ketals to ethers. The "mixed hydrides" which exist in ether as an etherate, complex with an oxygen of the acetal or ketal. This complex **1** decomposes to give the oxocarbonium ion **2** which in turn is attacked by hydride to yield the ether **3**. Brown and Leggetter have studied[3] the ease



and direction of ring opening hydrogenolysis of a large number of substituted 1,3-dioxolanes. They concluded that the results were consistent with the formation of the oxocarbonium ion being the rate-controlling step because the predominant product is the one resulting from the more inductively stabilized oxocarbonium ion. Eliel, *et al.*,[4] later pointed out that evidence available from the hydrogenolysis of substituted 1,3-dioxolanes, 2-tetrahydropyranyl ethers and 2-tetrahydrofuranyl ethers did not necessarily indicate which step was rate controlling. With such unsymmetrical acetals and ketals, that reduction product which passes through the more stable carbonium ion normally predominates.[3,5,6] Eliel argued that since the oxocarbonium ion **2** was a relatively unstable intermediate, the energies of both the transition state leading to the oxocarbonium ion **2** and the transition state leading to the product **3** reflect the stability of the intermediate oxocarbonium ion **2**. Thus, no information was obtained as to whether the formation of the oxocarbonium ion, *i.e.*, $k_3 \gg k_{-2}$, or whether the acquisition of hydride, *i.e.*, $k_3 \ll k_{-2}$, was rate determining.

The formation of an oxocarbonium ion **2** from a ketal **1** involves a change in the coordination number of the reacting carbon from four to three, and the formation of an ether **3** from an oxocarbonium ion **2** involves a change in the coordination number from three to four. In the reaction of any cyclic series of compounds such as the reduction of cycloalkanone dimethyl ketals, the relative reactivities of the members will vary in a unique way depending on the change in coordination number (4 to 3 or 3 to 4). The changes of reaction rates and equilibria as a function of ring size in homologous series have been extensively researched[7-17] and the explanation for such changes can be found in the steric strains inherent in ring compounds. These steric strains and their effects on the reactivity of cyclic compounds are qualitatively understood.[11,17-19]

Results

Direct determination of the rate constants for the hydrogenolysis of the cycloalkanone dimethyl ketals is experimentally difficult because of the rapidity with which the reaction proceeds. Competitive reductions among the cycloalkanone dimethyl ketals, however, would give the desired trend in reactivity. Each ketal was competitively reduced at least twice, either both times against a second ketal or against two different ketals which had been reduced against each other.

The most convenient and accurate method of measuring the ratio of products is by gas chromatography. Unfortunately, the ketals are unstable on the gas chromatograph owing to fragmentation to enol ethers. However, under the experimental work-up conditions the

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(19) J. Sicher, "Progress in Stereochemistry," Vol. III, P. B. D. de la Mare and W. Klyne, Ed., Butterworths, Washington, D. C., 1962, p 202.

ketals were quantitatively converted to ketones. The gas chromatograms of the reaction mixtures of the competitive reductions then showed methyl ethers produced by reduction and ketones which corresponded to unreacted ketal. The exception is cyclobutanone dimethyl ketal which does not hydrolyze readily and, since it is reasonably stable on the gas chromatograph, it was examined as the ketal.

It had been the original plan to obtain corrections for detector responses for all ketones and methyl ethers and to express the results as percent ketal reduced. However, it became apparent that there was a material loss for ketones of some ring sizes. Cyclopentanone had the largest shortage in material balance. A possibility is that the ketones produced in the work-up of the unreacted ketals undergo condensation reactions. Eliel[20] has reported that, for the reduction of ketones by hydride transfer from alkoxyaluminum dichloride, some condensation of the ketones especially cyclopentanone had occurred. Another possibility is that the ketal could lose methanol to form an enol ether which under acidic conditions polymerizes. This loss of some of the unreacted ketal does not interfere with the results here because it occurs after the competitive reduction.

When competitive reactions are controlled such that only small percentages of products are formed, the molar ratio of products approximates the ratio of rate constants for the formation of these products. Detector responses (see Experimental Section) were used to correct the measured ratio of cycloalkyl methyl ethers to a molar ratio. The relative reactivities thus obtained are in Table I.

TABLE I

RELATIVE REACTIVITIES OF DIMETHYL KETALS TO HYDROGENOLYSIS BY DICHLOROALUMINUM HYDRIDE

Dimethyl ketal of	Relative reactivity	Dimethyl ketal of	Relative reactivity
Cyclobutanone	0.06	Cyclononanone[a]	1.6
Cyclopentanone	1.3	Cyclodecanone[a]	0.7
Cyclohexanone	0.5	Cycloundecanone[a]	1.0
Cycloheptanone	7.0	Cyclododecanone	0.3
Cyclooctanone	1.7	3-Pentanone	1.0

[a] Reduced on one-tenth the scale of the other reductions.

Discussion

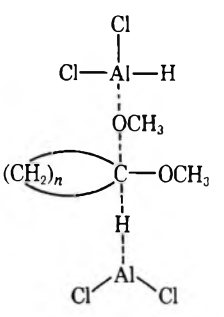
The relative reactivities of the cycloalkanone dimethyl ketals should increase when there is a decrease in strain in the rate-controlling step and decrease when there is an increase in strain in the rate-controlling step. The change in the strain present in the cycloalkanone dimethyl ketal rings will be in the opposite direction in the two steps of the hydrogenolysis because the change in coordination number is four to three in the first step (1 → 2) and three to four in the second step (2 → 3). That k_{-2} is unimportant (dissociation is irreversible) has been demonstrated by Leggetter and Brown[21] in the hydrogenolysis of the *cis*- and *trans*-2,4-dimethyl-1,3-dioxolanes. No isomerization is detectable in the hydrogenolysis reaction of these compounds. If one then assumes that k_1/k_{-1} is the same for all ketals then the observed rate will reflect oxocarbonium ion 2 formation.

The results of the competitive reduction of cyclobutanone, cyclopentanone, cyclohexanone, and cycloheptanone dimethyl ketals suggest that the formation of the oxocarbonium ion intermediate 2 is the rate-controlling step of these "mixed hydride" reductions. Cyclobutanes possess considerable angle strain. The formation of an oxocarbonium ion would increase this angle strain. Cyclobutanone dimethyl ketal is 17 times less reactive than 3-pentanone dimethyl ketal. Cyclohexanes are able to stagger all their bonds and formation of an oxocarbonium ion would introduce some eclipsing. Cyclohexanone dimethyl ketal is only half as reactive as 3-pentanone dimethyl ketal. The slowness of these reductions show that the strain increasing step (formation of the oxocarbonium ion) is rate controlling. Cyclopentanone dimethyl ketal is reduced 1.3 times as fast as 3-pentanone dimethyl ketal. Cycloheptanone dimethyl ketal is reduced seven times as fast as 3-pentanone dimethyl ketal. There is a decrease in eclipsing strain in the five- and seven-membered-ring dimethyl ketals with the formation of the oxocarbonium ion intermediate. This decrease in strain in the rate-controlling step causes these ketals to be more reactive than an open-chain ketal.

Because cycloalkanone dimethyl ketals of medium rings would greatly reduce their transannular strain in forming the oxocarbonium ion intermediate, their reductions were expected to be very rapid. This is not the case. Cyclooctanone and cyclononanone dimethyl ketals are reduced only slightly faster than 3-pentanone dimethyl ketal, and cyclodecanone, cycloundecanone and cyclododecanone dimethyl ketals are reduced at the same rate or slightly slower than 3-pentanone dimethyl ketal (Table I). The hydrogenolysis of cycloalkanone dimethyl ketals does not show the large release of strain found for other ring reactions such as SN1 displacements.

One explanation might be that the transannular strain in the medium rings has other effects besides being a driving force for the formation of the oxocarbonium ion. It can hinder the complexing of a ketal by dichloroaluminum hydride which has ether and ketal as ligands in rapid equilibrium. The transannular strain in cycloalkanone dimethyl ketals of medium rings could decrease their association with dichloroaluminum hydride (k_1/k_{-1} is not the same for these ketals). Thus, the relative reactivities of cycloalkanone dimethyl ketals of ring sizes eight to twelve might more accurately reflect the degree of association of the ketal and dichloroaluminum hydride than the rate (k_2) of oxocarbonium ion formation.

A second explanation might be that the hydrogenolysis of ketals may resemble an SN2 displacement. This mechanism involves a change of coordination number of four to five to four. While a pentacoordinated intermediate 4 is not usually considered as an intermediate



4

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(21) B. E. Leggetter and R. K. Brown, *Can. J. Chem.*, **43**, 1030 (1965).

in ketal hydrogenolysis, the results do not exclude the possibility. This type of intermediate has been postulated to account for the stereochemistry of similar hydrogenolysis reactions.[22,23] For this the methoxide complexed with a dichloroaluminum hydride would be the leaving group and a second dichloroaluminum hydride would approach from the other side. The introduction of a fifth coordinating group in the rate-controlling step would not change the interpretation of results for the smaller cycloalkanone dimethyl ketals, but would be expected to slow the hydrogenolysis of the ketals of medium ring size because the rate-controlling step would increase the transannular strain.

Experimental Section

Preparation of Compounds.—Cyclobutanone was prepared by the procedure described by Roberts and Sauer.[24] The remaining ketones were obtained from Aldrich Chemical Co., Inc. Cyclobutanone, cyclopentanone, and cyclohexanone dimethyl ketals were prepared by the method of Lorette and Howard.[25] A modification of the method of Helferich and Hausen[26] was employed for the synthesis of the ketals of seven- to twelve-membered rings.

A ketone, tetramethoxylsilane and methanol were mixed in a molar ratio of 1:3.1:4.0. A catalytic amount of dry hydrogen chloride was added and the mixture was allowed to stir at room temperature for 3 days. The mixture was then made basic with sodium methoxide, distilled to separate it from the silicon polymer which causes bumping and distilled again to purify the ketal.

The boiling points, °C (mm), for dimethyl ketals[27] are as follows: cyclobutanone, bp 112–113; cycloheptanone, 73 (10); cyclooctanone, 88 (7.7); cyclononanone, 58–61 (0.5); cyclodecanone, 63–64 (0.2); cycloundecanone, 87–88 (0.7); Methyl ethers[27] obtained by preparative glc are cyclononyl, cyclodecyl, and cycloundecyl.

The methyl ethers expected from the competitive reductions of the cycloalkanone dimethyl ketals were synthesized either by the "mixed hydride" reduction of individual ketals or by the sodium borohydride reductions of the corresponding ketones and methylation of the resulting alcohols by the procedure of Diner, Sweet, and Brown.[28]

Competitive Reductions.—Into a 500-ml three-neck flask equipped with a mechanical stirrer, rubber septum, and drying tube was placed 400 ml of anhydrous ether. To the ether was added 0.300 g (0.00750 mol) of 95% LAH and 3.00 g (0.0225 mol) of aluminum chloride. The mixture was allowed to stir for 0.5 hr. The reaction flask was cooled using a Dry Ice–acetone bath and a mixture of 0.025 mol of two ketals was syringed into reaction flask and allowed to warm for another 0.5 hr. Then 20% sodium hydroxide (about 4.5 ml) was added dropwise until a granular precipitate formed leaving a clear ether layer. The ether was filtered and evaporated to concentrate the products. Suitable precautions were taken depending upon the volatilities of the products. The hydrolysis of the aluminum salts initially produces a large amount of hydrochloric acid. Ketals are not stable under acidic conditions and they were always found to be partially hydrolyzed to the ketones. The hydrolysis was completed by adding two drops of dilute hydrochloric acid to the ether solution. The ether solution was examined by gas chromatography; peaks corresponding to the cycloalkylmethyl ethers were measured under conditions identical with those used to measure the competitive reductions. The gas chromatograms were obtained on a F & M Model 720 thermal conductivity gas chromatograph equipped with a 0.25 in. × 6 in. 10% Carbowax column. The helium gas flow was adjusted to 10 cc/sec. The injection port and detector were 250 and 360°, respectively. The column was set at 65° and programmed 10°/min.

The detector response corrections for the cycloalkyl methyl ethers are as follows: cyclobutyl, 0.82; cyclopentyl, 0.93; cyclohexyl, 1.00; cycloheptyl, 1.07; cyclooctyl, 1.12; cyclononyl, 1.21; cyclodecyl, 1.29; cycloundecyl, 1.36; cyclododecyl, 1.44; and 3-pentyl, 0.76.

Registry No.—Dichloroaluminum hydride, 13497-97-7; cyclobutanone dimethyl ketal, 4415-90-1; cyclopentanone dimethyl ketal, 931-94-2; cyclohexanone dimethyl ketal, 933-40-4; cycloheptanone dimethyl ketal, 25632-02-4; cyclooctanone dimethyl ketal, 25632-03-5; cyclononanone dimethyl ketal, 25632-04-6; cyclodecanone dimethyl ketal, 25632-05-7; cycloundecanone dimethyl ketal, 25632-06-8; cyclododecanone dimethyl ketal, 950-33-4; 3-pentanone dimethyl ketal, 25636-49-1.

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Intermediates in Nucleophilic Aromatic Substitution. VIII.[1,2] Kinetic and Proton Magnetic Resonance Investigations of the Interaction of Methoxide Ions with 1-Methoxy-2,4,5-trinitronaphthalene

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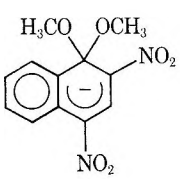
The rate constants (k_1) for the formation of the methoxyl complex of 1-methoxy-2,4,5-trinitronaphthalene (**3**) in methanol at 13.45, 25.00, and 35.00° have been determined spectroscopically by following the increase in absorbance at 495 nm as a function of time in 3.35×10^{-5} *M* solutions of 1-methoxy-2,4,5-trinitronaphthalene (**5**) in the presence of methoxide ions [$(3.3 - 82.7)10^{-4}$ *M*]. The rate constants (k_2) for the decomposition of **3** have been determined directly at the same three temperatures by following the decrease in the absorbances of dilute methanolic solutions of the isolated complex **3**. From these values the equilibrium constant for the formation of **3** ($K_{25.00°} = 2.93 \times 10^4$ l. mol^{-1}) and the enthalpies and entropies of activation both for the formation and decomposition of **3** have been obtained. These data indicate **3** to be more stable than 1,1-dimethoxy-2,4,6-trinitrocyclohexadienylide ion ($K_{25.00°} = 1.7 \times 10^4$ l. mol^{-1}) or the methoxyl complex of 1-methoxy-2,4-dinitronaphthalene ($K_{25.00°} = 230$ l. mol^{-1}). The stabilities of these complexes are discussed. The rate of decomposition of crystalline **3** has also been examined in aqueous buffers in the pH range of 5.63–10.96; the decomposition is acid catalyzed. The structure of **3** has been established from pmr spectra of both the isolated and the *in situ* generated complex. A comparative discussion of the pmr parameters is offered.

In a previous part of this series we have reported that the equilibrium constant for the formation of the methoxyl complex of 1-methoxy-2,4-dinitronapthalene (**1**)[4] is several orders of magnitude greater than that obtained for the corresponding complex of 2,4-dinitroanisole[5] (**2**). This result is a reflection of the greater



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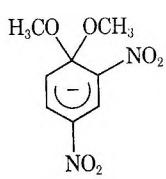

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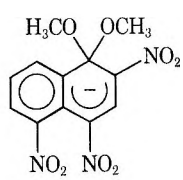

3

resonance energy required for the stabilization of structure **2** than that for **1**.[6]

Although studies of nucleophilic aromatic substitution in polyaromatic systems are potentially important, there have been relatively few mechanistic investigations concerning the transmission of electronic effects from one ring to the other in substituted naphthalenes and other polyaromatic systems. Ellias and Parker have found that the rate constant for the reaction of aniline with 1-chloro-2,4,5-trinitronaphthalene is only greater than that with 1-chloro-2,4-dinitrobenzene by a factor of 14 in ethanol at 25.0°, whereas the corresponding difference in reactivity between 2,4-dinitro- and 2,4,6-trinitrochlorobenzene is 16,100.[7] The effects of nitro groups in the 2,4,5[8] and in the 2,4,7[9] positions of 1-methoxy-substituted naphthalenes on the rates of symmetrical methoxyl exchange reactions have been investigated. The nature of these experiments did not allow, however, quantitative information to be obtained for all of the processes involved.[8,9] As a part of our systematic studies on the structures and reactivities of Meisenheimer complexes we have determined kinetic and thermodynamic parameters for the formation and decomposition of the methoxyl complex of 1-methoxy-2,4,5-trinitronaphthalene (**3**) in methanol and have obtained protons magnetic resonance parameters both for the isolated and for the *in situ* generated complex **3**.

Experimental Section

The solvents and reagents were prepared, purified, and standardized as previously described.[10] N,N-Dimethylacetamide, DMA (Baker analyzed reagent grade) was stored over Linde Type 5A molecular sieve and its purity was verified by its pmr spectrum.

1-Chloro-2,4,5-trinitronaphthalene (**4**) was prepared by the method of Rindl.[11] After recrystallization from benzene–acetic acid (50:50, v/v) using decolorizing charcoal, **4** melted at 143–144° (lit.[11] mp 143–144°).

1-Methoxy-2,4,5-trinitronaphthalene (**5**) was prepared by the dropwise addition of 1.30 ml of 5.05 *M* (6.54 mmol) potassium methoxide in methanol to a hot solution of **4** in 75 ml of anhydrous methanol. The reaction mixture was refluxed for 30 min, allowed to cool slowly to room temperature, cooled to ~0° with an ice bath, and filtered. The yellow crystals were recrystallized from acetic acid, mp 151.5–152° (lit.[11] mp 150.5–151.5°).

The methoxy complex (**3**) of 1-methoxy-2,4,5-trinitronaphthalene was prepared by the addition of 0.421 ml of 5.05 *M* (2.125 mmol) potassium methoxide in methanol to a solution of 0.6325 g (2.16 mmol) of **5** in 1.5 ml of dry dioxane. After evaporation of some solvent with dry nitrogen and cooling, the red crystals were filtered under nitrogen and washed with dry benzene (three times) and anhydrous ether (twice). Pulverization of the crystals in a dry nitrogen atmosphere and drying *in vacuo* over P_2O_5 gave a red solid, mp 180° dec.

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Anal.[12] Calcd for $C_{12}H_{10}KN_3O_8$: C, 39.7; H, 2.76; K, 10.8; N, 11.6. Found: C, 38.3; H, 2.7; K, 10.8; N, 11.0.[13]

The attainment of the equilibrium for the formation of complex **3** from **5** in methanol was followed at 500 nm in the thermostated cell compartment of a Beckman DU-2 spectrophotometer. The temperature was measured inside the cells and was maintained within ±0.02°. The mixing techniques for fast reactions have been described previously.[15]

The rate constants for the decomposition of the solid complex **3** in methanol and in aqueous buffers were obtained by following the rates of decrease in absorbance at 500 nm in appropriate solutions of **3** in the thermostated cell compartment of the spectrophotometer. The pH of the buffer solutions was measured at 25.00° with an Orion-801 digital pH meter. Since the concentration of **5** was kept at least tenfold smaller than that of the sodium methoxide and since the concentration of the complexes were in the order of 5×10^{-5} *M*, pseudo-first-order kinetics were observed for both the attainment of the equilibrium for **3** and for the decomposition of complex **3**. Such first-order plots for typical runs are given in Figure 1.

Pmr spectra (60 MHz) were obtained with a Varian Associates A-60 spectrometer at ambient probe temperature (31°) or at 25° (probe temperature maintained with a V6040 variable temperature controller). All spectra were determined on solutions in DMSO-d_6 or in DMA using tetramethysilane (TMS) as an internal standard; chemical shifts are given on the τ scale in ppm relative to TMS (τ = 10.00 ppm) and are accurate to ±0.03 ppm. Chemical shift data were taken from spectra determined at sweep widths of 500 Hz or were calculated from the average resonance frequencies observed at 50-Hz sweep widths (at least three determinations) using the computer program LAOCOON III.[16] The reported coupling constants were calculated simultaneously with LAOCOON III and are accurate to ±0.2 Hz.

Results

Upon the addition of sodium methoxide to dilute methanolic solutions of **5** the development of a red color is observed. The intensity of this color above 10^{-1} *M* $NaOCH_3$ remains constant over a large range of alkoxide ion concentration indicating that the equilibrium (eq 1)

$$5 + NaOCH_3 \underset{k_2}{\overset{k_1}{\rightleftharpoons}} 3 \qquad (1)$$

is complete. In the concentration range of 3.3–82.7 × 10^{-4} *M* methanolic sodium methoxide and 3.34×10^{-5} *M* **5**, it was possible to follow the attainment of the equilibrium by measuring the increase in absorbance at 495 nm [ϵ_{495} of **3** = $(1.9 \pm 0.1)10^4$ cm^{-1} l. mol^{-1}]. Under the experimental conditions, the observed first-order rate constant for equilibrium attainment, k_{obsd}, is given by[1]

$$k_{obsd} = k_1[NaOCH_3] + k_2 \qquad (2)$$

where k_1 is the second-order rate constant for the formation of the complex and k_2 is the first-order rate constant for its decomposition. Table I contains the data for the attainment of equilibrium 1 for complex **3** at 13.45, 25.00, and 35.00° as a function of sodium methoxide concentration. From the slopes of plots of k_{obsd} *vs.* [$NaOCH_3$], *M*, values for k_1 have been obtained and are given in Table I. The value for k_2 is very small and interpolation from the intercepts of the plots is impossible. We have obtained k_2 values, however, directly from decomposition of solid **3** in methanol at the appropriate temperatures. The obtained k_2, and hence *K*, values are also given in Table I.

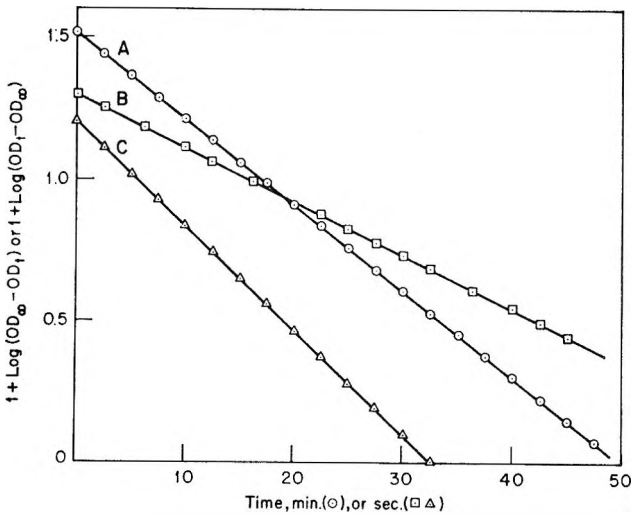

Figure 1.—(A) Plot of log ($OD_t - OD_\infty$) against time for the decomposition of **3** in methanol at 25.00°. (B and C) Plots of log ($OD_\infty - OD_t$) against time for the attainment of equilibrium for **3** in methanol at 25.00°, [**3**] = 3.34×10^{-5} *M*, for (B) [$NaOCH_3$] = 1.32×10^{-3}*M* and for (C) [$NaOCH_3$] = 2.64×10^{-3}*M*.

TABLE I

INTERACTION OF 1-METHOXY-2,4,5-TRINITRONAPHTHALENE (3.34×10^{-5} *M*) WITH METHANOLIC SODIUM METHOXIDE

Temp, °C	10^4[$NaOCH_3$], *M*	10^2k_{obsd}, sec^{-1}	k_1, M^{-1} sec^{-1} [a]	10^4k_2, sec^{-1} [b]	$10^{-4}K$, l. mol^{-1} [c]
13.45	0.00		13.75	2.88	4.77
	16.5	2.24			
	33.0	5.11			
	41.3	5.19			
	57.9	7.59			
	66.0	8.74			
	74.4	10.1			
	82.7	11.1			
25.00	0.00		32.8	11.2	2.93
	3.31	0.805			
	4.13	1.27			
	4.96	1.72			
	6.62	2.02			
	8.27	2.42			
	9.91	2.87			
	13.2	4.30			
	16.5	5.52			
	19.8	6.80			
	26.4	8.51			
	33.1	10.8			
	41.3	13.9			
35.00	0.00		59.7	27.2	2.19
	3.31	1.40			
	4.14	2.44			
	6.61	3.90			
	8.27	4.37			
	9.93	5.89			
	13.2	7.80			
	19.8	11.5			
	26.4	15.9			

E_1 = 12.2 ± 0.8 kcal mol^{-1}, E_2 = 18.6 ± 0.8 kcal mol^{-1}, $\Delta S_1^{\ddagger}$ = −12.5 ± 2.0 eu,[d] $\Delta S_2^{\ddagger}$ = −11.7 ± 2.0 eu[d]

[a] Obtained from the slope of k_{obsd} *vs.* [$NaOCH_3$], *M*. [b] Mean of six runs (each within ±3%) obtained by following the decomposition of the solid complex **3** in methanol. [c] $K = k_1/k_2$. [d] At 25.00°.

(12) The analysis was performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

(13) The carbon content of Meisenheimer complexes has been found to be low in several other cases.[1,14] Since complex **3** is spectroscopically pure, the low carbon analyses may be due to the loss of methanol or the presence of carbonate in the ash.

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Data for the decomposition of **3** in aqueous solutions at different pH values are given in Table II.

TABLE II
DECOMPOSITION OF THE METHOXYL COMPLEX OF 1-METHOXY-2,4,5-TRINITRONAPHTHALENE (**3**) IN WATER AT 25.00°

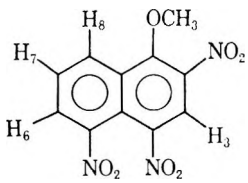
pH[a]	10^3k_1, sec^{-1}	$10^{-3}k_2^{H^+}$, M^{-1} sec^{-1}[b]
5.38	5.63	1.32
5.44	5.06	1.35
5.46	4.68	1.32
5.49	4.54	1.36
5.58	4.21	1.54
5.64	3.28	1.36
5.75	2.49	1.31
6.07	1.32	1.37
6.30	0.90	1.48
8.07[c]	0.22	
10.44[d]	0.157	
10.55[d]	0.163	
10.96[d]	0.157	

[a] 0.01 M KH_2PO_4 buffer, except where stated otherwise. [b] $k_2^{H^+} = k_2^{obsd} - k_2^{\circ}/[H^+]$, where $k_2^{\circ} = 1.59 \times 10^{-4}$ sec^{-1}. [c] 0.01 M Na_2HPO_4 buffer. [d] 0.005 M Na_2HPO_4 buffer.

In methanol **5** undergoes solvolysis to give the corresponding naphthol; the half-life for this "solvolysis" is, however, several orders of magnitude less than the time scale used in the present work.[8] The slow decomposition of **3** also produces naphthol, but its extinction coefficient at 500 nm is negligible compared to that of **3** and therefore does not interfere with the rate measurements.

The pmr parameters for 1-methoxy-2,4,5-trinitronaphthalene (**5**) and for the 1,1 complex of **3** in DMSO-d_6 and DMA solutions are given in Table III.

TABLE III
PMR PARAMETERS FOR 1-METHOXY-2,4,5-TRINITRONAPHTHALENE AND ITS METHOXYL MEISENHEIMER COMPLEX[a]



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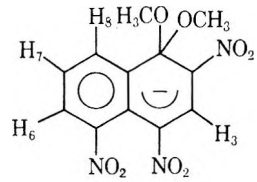

3[b]

Solvent	DMSO-d_6	DMA	DMSO-d_6	DMA
τ_3	1.08[c]	0.93[c]	0.92[c]	0.73[c]
			(0.92)[c]	(0.74)[c]
τ_6	1.18	1.02	2.07	1.96
			(2.05)	(1.95)
τ_7	1.92	1.81	2.62	2.58
			(2.63)	(2.57)
τ_8	1.36	1.24	2.14	2.09
			(2.15)	(2.10)
$\tau_{1\text{-}OCH_3}$	5.81[c]	5.63[c]	7.20[c]	7.12[c]
			(7.17)[c]	(7.10)[c]
J_{67}	8.7	8.6	8.1	8.0
			(8.1)	(8.0)
J_{68}	1.2	1.1	1.4	1.4
			(1.4)	(1.5)
J_{78}	7.8	7.8	7.9	7.7
			(7.7)	(7.7)

[a] Calculated from the resonance frequencies observed at 50-Hz sweep widths using LAOCOON III (see Experimental Section) unless specified otherwise. [b] Values in parentheses have been obtained in the *in situ* formation of **3** by the dropwise addition of 5.05 M potassium methoxide in methanol to a solution of **5** in the indicated solvent. [c] Taken from spectra determined at 500-Hz sweep widths.

Discussion

The order of stability of Meisenheimer complexes parallels the extent of electron delocalization caused by substituents. It is instructive to compare the kinetic and thermodynamic parameters for the formation and decomposition of the 2,4-dinitro- (**2**)[5,17] and 2,4,6-trinitro- (**7**)[17] substituted 1,1-dimethoxycyclohexadienylide ions with those of their 2,4-dinitronaphthalene (**1**) and 2,4,5-trinitronaphthalene (**3**) analogs. The equilibrium constants for the formation of the complexes increase in the order **3** > **7** ≫ **1** ≫ **2**[18] (at 25.00°, $K_2 \approx 10^{-4}$; K_1 = 230; K_7 = 17,000; and K_3 = 29,300 l. mol^{-1}). More significantly, however, the introduction of a third nitro group in the 6 position of 2,4-dinitroanisole enhances the complex stability by a factor of 10^8 (K_7/K_2) whereas the corresponding increase in the equilibrium constant resulting from an additional nitro group in the 5 position of 1-methoxy-2,4-dinitronaphthalene is only 127 (K_3/K_1). These results are not unexpected[7] and can be rationalized in terms of the differences between the position of the nitro groups in the parent ethers of **3** and **1**. The 5-nitro group in 1-methoxy-2,4,5-trinitronaphthalene (**5**) is further removed from the seat of substitution than the 6-nitro group in 2,4,6-trinitroanisole and hence its inductive effect results in a substantially smaller decrease in the electron density at C-1. Additionally, the proximity of the 4- and 5-nitro groups in **5** most probably decreases the extent of conjugation by steric hindrance,[19] and thus the activating power of both groups, as well as resulting in lesser resonance stabilization of complex **3**.[20] In the case of 2,4,6-trinitroanisole and its complex **7**, on the other hand, the nitro group in the 6 position activates C-1 inductively, and all three nitro groups delocalize the negative charge of the cyclohexadienylide ion by resonance effects. The significant electron delocalizing influence of the second aromatic ring in **3** results, however, in an overall increase in the equilibrium constant for the formation of **3** compared to that for **7**. The full extent of this effect can easily be appreciated by comparison of the stabilities of **1** and **2** ($K_1/K_2 \simeq 2 \times 10^6$).

The higher equilibrium constant for **3** compared to that for **1** is a consequence of a significant increase in the rate constant for the formation of **3** (k_1 for **3**/k_1 for **1** = 35.6) which is paralleled by a smaller decrease in the rate constant for its decomposition (k_2 for **1**/k_2 for **3** = 3.5). Changes in the equilibrium constants for the complexes derived from the isomeric 2,4,6-cyanodinitro and dicyanonitroanisoles, on the other hand, are dependent to a greater extent on changes in k_2 than those in k_1.[1] Although the available data are not

(17) J. H. Fendler, *J. Amer. Chem. Soc.*, **88**, 1237 (1966).

(18) The value reported by Katsanos for K_3 (1.76 × 10^3 l. mol^{-1} at 34.9°) is clearly too low and probably in error due to the experimental uncertainties involved in its estimation.[8]

(19) V. Balasubramaniyan, *Chem. Rev.*, **66**, 567 (1966).

(20) We are currently studying the rates and equilibrium constants for the formation of tri- and tetranitro-substituted naphthalene Meisenheimer complexes to substantiate quantitatively this postulate.[21]

(21) E. J. Fendler and J. H. Fendler, unpublished work.

sufficiently extensive to justify generalizations, it appears that substituents with different electron-withdrawing ability exert a greater effect on k_2 than on k_1, whereas the reverse is the case if the extent of electron-delocalization is altered by the introduction of the same functional group.

The greater stability of **3** compared to **1** is a consequence of a decrease in the energy and an increase in the entropy of activation for the formation of the complex. Similarly, decomposition of **3** requires somewhat more energy and has a higher entropy of activation than **1**.[4] In many instances it has been found that the driving force for the formation and decomposition of complexes is both enthalpy and entropy dependent.[1]

The greater stability of **3** relative to **1** is further demonstrated by the rate constant for its decomposition in water ($k_2°$ in Table II) which is a factor of 11-fold smaller than that for **1** ($k_2°$ for **1** at 25.0° = 1.76×10^{-3} sec^{-1} [4]). This reaction like the analogous decomposition of **1**[4] and **7**[22] is catalyzed by hydronium ions, although this catalysis is smaller ($k_2^{H^+} = 1.38 \times 10^3\ M^{-1}$ sec^{-1} for **3**) than that observed for **1**[4] ($k_2^{H^+} = 1.73 \times 10^4\ M^{-1}$ sec^{-1}) or for **7**[21] ($k_2^{H^+} = 4.0 \times 10^3\ M^{-1}$ sec^{-1}).

We continue to use proton magnetic resonance spectroscopic techniques to confirm the postulated structure of the intermediate **3** and to observe its formation *in situ* by the addition of methoxide ions to solutions of **5** in DMSO-d_6 and in DMA. The only previous reports of pmr data for naphthalene Meisenheimer complexes are those on **1**[4,23] and other 1-alkoxy-2,4-dinitronaphthalenes.[4,24] No pmr data has previously been reported, however, for Meisenheimer complexes of trinitronaphthalenes.

The pmr parameters for the complex **3** and its parent ether **5** as well as those observed previously[3] for complex **1** and the parent are given in Table III. The spectra of **3** are completely consistent with the postulated structure (*i.e.*, the 1,1 complex) and eliminate the possibility of alternative complexes such as those resulting from attack of methoxide ion at C-3, C-6, or C-8. Pmr criteria for the structure of Meisenheimer complexes have been discussed previously[1,2,4,10,15,24] and therefore are not reiterated here in detail. Rehybridization of C-1 from sp^2 in the parent ethers to sp^3 in the 1,1 complexes has been found to result in an upfield shift of the methoxy proton resonances in dinitro-, trinitro-, and cyanonitroanisoles ($\Delta\delta$ 1.00–1.50 ppm)[1,2,10,15] and in 1-methoxy-2,4-dinitronaphthalene ($\Delta\delta$ 1.33–1.35 ppm).[4] A comparable upfield shift of the methoxyl resonance ($\Delta\delta$ 1.39 ppm in DMSO-d_6 and 1.49 ppm in DMA) is observed for **5**. It has also been observed previously that the aromatic proton resonances of Meisenheimer complexes are relatively strongly shielded as compared to the parent ethers[1,2,4,10,15,24] and that the magnitude of the upfield shift ($\Delta\delta$) for 1,1-dialkoxy-2,4-dinitrocyclohexadienylides[10] reflects the relative charge densities at the various positions, *i.e.*, H-3, 0.04–0.07; H-5, 1.26–1.40; H-6, 2.50–2.57 ppm. The aromatic proton resonances of the second ring of **3** and **5** comprise an ABX system whereas those of the dinitronaphthalenes **1** and **6** compose a less readily interpretable ABCD system.[4] The aromatic proton resonances of the ether **5** consist of a one-proton singlet (H-3) at τ 1.08 and three one-proton doublets of doublets centered at τ 1.16 (H-6), 1.36 (H-8), and 1.95 (H-7) in DMSO-d_6 solution (see Table III for the calculated chemical shifts of H-6, H-7, and H-8). The aromatic resonances of complex **3** resemble those of **5** in terms of multiplicity but the chemical shifts are altered markedly. The H-6, H-7, and H-8 resonances show the expected upfield shifts: H-6, τ 2.07 ($\Delta\delta$ 0.89); H-7, 2.62 ($\Delta\delta$ 0.70); and H-8, 2.14 ppm ($\Delta\delta$ 0.78); but the magnitude of the upfield shifts are considerably smaller than those cited previously for the three ring protons of benzene complexes. These smaller shifts are explicable in terms of delocalization of the negative charge over more atoms in **3** than in the benzene complexes. The H-3 resonance, however, is shifted downfield to τ 0.92 ppm ($\Delta\delta$ −0.16 ppm). The shifts of the aromatic protons of **3** indicate a significant increase in electron density at the 6, 7, and 8 positions of the complex relative to the parent ether **5** but a decrease in electron density at the 3 position. The increase in electron density is expected but the similarity in the increase at H-6, H-7, and H-8 is not readily explicable in terms of canonical contributions and anisotropic deshielding of H-8 by the methoxyl groups of the complex. HMO calculations of π-electron densities of **6** and its methoxyl complex **1** indicate that there is a slight increase in electron density in the second ring, and that the negative charge is primarily localized in the nitro groups.[25] The electron density in the first ring, therefore, should be markedly decreased, *i.e.*, at H-3, in the complex relative to the parent ether. Our observed $\Delta\delta$ values are in qualitative agreement with the results of these HMO calculations.

The proton chemical shifts of **3** and **5** show only a slight dependence on the dipolar aprotic solvent used, *i.e.*, DMSO-d_6 and DMA (Table III). In general, the proton resonances are observed at lower fields in DMA than in DMSO-d_6 for both the parent ether **5** and its complex **3**; consequently the magnitude of the chemical shift differences ($\Delta\delta$) between **5** and **3** are quite similar in these two solvents.

In several activated aromatic systems, *i.e.*, 2,4,6-trinitroanisole,[15,26,27] isomeric cyanodinitroanisoles,[15] 2,4-dicyano-6-nitroanisole,[1] and 3,5-dinitro-2-methoxypyridine,[28] initial attack of the nucleophile has been observed by pmr[1,15,26–28] and calorimetric[29] techniques to occur at C-3 resulting in the formation of a transient 1,3 complex. However, on a considerably shorter time scale, the presence of other transient species and the formation of the 1,3-methoxyl complex of 1-methoxy-2,4-dinitronaphthalene (**6**) has been inferred from kinetic data obtained by the use of stopped-flow techniques.[30] In order to observe any fairly stable transient species in the interaction of methoxide ions with **5**, we examined the generation of **3** *in situ* in

(22) J. Murto and J. Vainioupaa, *Suomen. Kemistilehti*, **B39**, 133 (1966).
(23) R. Foster and C. A. Fyfe, *Tetrahedron*, **21**, 3363 (1965).
(24) E. J. Fendler, J. H. Fendler, W. E. Byrne, and C. E. Griffin, *J. Org. Chem.*, **33**, 4141 (1968).
(25) P. Caveng, P. B. Fischer, E. Heilbronner, A. L. Miller, and H. Zollinger, *Helv. Chim. Acta*, **50**, 848 (1967).
(26) K. L. Servis, *J. Amer. Chem. Soc.*, **87**, 5495 (1965); K. L. Servis, *ibid.*, **89**, 1508 (1967).
(27) M. R. Crampton and V. Gold, *J. Chem. Soc. B*, 893 (1966).
(28) C. A. Fyfe, *Tetrahedron Lett.*, 659 (1968); G. Illuminati and F. Stegel, *ibid.*, 4169 (1968); C. Abbolito, C. Iavarone, G. Illuminati, F. Stegel, and A. Vazzoler, *J. Amer. Chem. Soc.*, **91**, 6746 (1969).
(29) J. W. Larsen, J. H. Fendler, and E. J. Fendler, *ibid.*, **91**, 5903 (1969).
(30) F. Millot and F. Terrier, *Bull. Soc. Chim. Fr.*, 2692 (1969).

DMSO-d_6 and in DMA.[31] In these experiments, no additional resonances could be observed and, hence, on the time scale necessitated by pmr techniques at 25° (~2.5 min),[1,15] the 1,3 complex of **5** is either not formed or is not detectable.

(31) DMA has been found to considerably enhance the stability of the 1,3-dimethoxy-2,4,6-trinitrocyclohexadienylide ion as compared to that in DMSO.[32] However, no 1,3-complex formation could be detected in the *in situ* formation of complex **1** from **6** either in DMSO-d_6[4] or in DMA.

Registry No.—**3**, 25734-07-0; **5**, 25599-63-7.

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(32) Unpublished work: J. W. Larsen, E. J. Fendler, and J. H. Fendler.

Electron Spin Resonance Studies of Radical Formation in Nucleophilic Addition Reactions. III. On the Mechanism of Radical Formation and Chemiluminescence in the Cyanide Addition and Oxygenation of *N*-Methylacridinium Chloride[1]

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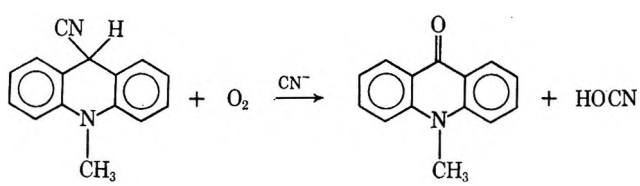
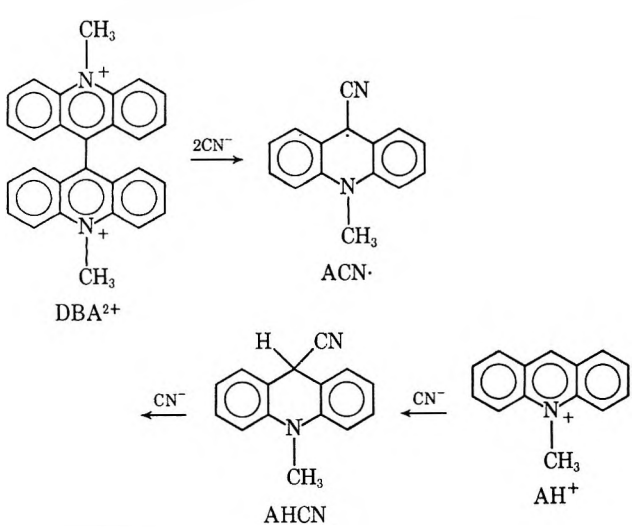
The reaction of KCN with *N*-methylacridinium chloride in 90% dimethyl sulfoxide–10% water produces *N*-methyl-9-cyanoacridan. With excess cyanide the red *N*-methyl-9-cyanoacridanide anion is produced. In the presence of oxygen *N*-methylacridone and potassium cyanate are produced with light emission. The reaction stoichiometry is shown to be



The initial rate of oxygen uptake shows the same dependence on the potassium cyanide concentration as the maximum light emission intensity on this variable and the time required to reach the light emission maximum is about the same as the time required for the major portion of the oxygen to be absorbed in the same experiment. The significance of these observations is discussed. In these experiments *N*-methyl-9-cyanoacridanyl is detected. A carbanion electron transfer oxidation mechanism involving this radical as an intermediate is suggested.

In a previous report[2] we described the detection of *N*-methyl-9-cyanoacridanyl radical in the cyanide ion addition to oxygen free solutions of lucigenin (*N*,*N*′-dimethyl-9,9′-biacridinium dinitrate) or to air-saturated solutions of *N*-methylacridinium chloride. The structure of the radical was verified by electrolytic reduction of *N*-methyl-9-cyanoacridinium chloride. The esr spectrum was analyzed and coupling constants assigned on the basis of molecular orbital calculations and by analogy to radicals of similar structure.



The unusual reaction between cyanide ion and *N*-methylacridinium chloride to produce *N*-methyl-9-cyanoacridanyl radicals (ACN·)[3] in air-saturated solutions has been investigated in more detail. Reactions of *N*-methyl-9-cyanoacridan (AHCN) and the chemiluminescent production of *N*-methylacridone have also been studied.

Experimental Section

Equipment.—The esr and light detection equipment was the same as used for a previous study.[4] Relative chemiluminescence light emission was monitored using a Firefly photometer with a IP21 photomultiplier tube. Solutions of *N*-methylacridinium chloride were placed in the sample compartment of the photometer and an appropriate amount of potassium cyanide in the same solvent was injected by syringe into the solution so that the final volume of the reaction mixture was 5 ml. Oxygen was continuously bubbled through the reaction mixture and the intensity of chemiluminescence was recorded. Chemiluminescence spectra were obtained with an Aminco spectrophotofluorometer equipped with a xenon arc light and a IP28 photomultiplier tube. A typical solution contained 0.04 *M* *N*-methylacridinium chloride and 0.06 *M* potassium cyanide in 90% dimethyl sulfoxide –10% water (by volume) saturated with oxygen.

* Author to whom correspondence should be addressed.

(1) This work was supported by the Atomic Energy Commission Contract No. AT-(40-L)-2851.

(2) Part II: J. W. Happ and E. G. Janzen, *J. Org. Chem.*, **35**, 96 (1970).

(3) For abbreviation, "A" is used as the symbol for the *N*-methylacridanyl moeity. "A" is followed by symbols representing the substituent(s) in the 9 position of the acridine ring.

(4) E. G. Janzen, J. B. Pickett, J. W. Happ, and W. DeAngelis, *J. Org. Chem.*, **35**, 88 (1970).

TABLE I

STOICHIOMETRY OF THE KCN ADDITION TO *N*-METHYLACRIDINIUM CHLORIDE[a]

AH^+Cl^-,[b] mmol	KCN, mmol	O_2,[c] mmol	Time, hr	Product[b]	Crude yield, mmol	Mp,[d] °C	CN^-,[e] mmol
1.01	0.50	0.02	27	AHCN	0.50	136–138	Negative test
1.01	0.72		5.0	AHCN	0.68	115 (141–142[f])	Negative test
1.00	1.00	0.79	6.6	NMA	0.82	204.0–204.5	
1.00	1.51	0.74	2.1	NMA	0.80	199–200	0.63
1.00	1.52	0.93	40.1	NMA	0.88	203–204	Positive test
1.00	1.72	0.73	2.8	NMA	0.77	203.5–204.0	0.73
1.01	1.86		27	NMA	0.77	202–203	0.90

[a] Reaction run in 25 ml of 90% DMSO–10% water by volume and agitated by magnetic stirrer. [b] AH^+Cl^- = *N*-methylacridinium chloride, AHCN = *N*-methyl-9-cyanoacridan; NMA = *N*-methylacridone. [c] Corrected to STP conditions. [d] Lit. mp of AHCN 143°, NMA 204–205° uncorr. [e] Determined by titration or by qualitative test described in text. [f] After one recrystallization from absolute ethanol.

The rate and amount of oxygen absorption was monitored at constant (atmospheric) pressure and at room temperature using a volumetric gas absorption apparatus. The solution was vigorously shaken in a creased 200-ml flask by means of a wrist-action shaker constructed from a Waco stirrer. A typical flask is photographed, and the shaker diagrammed and the technique described in ref 5 and 6.

Chemicals.—The source of the chemicals needed in this study was reported previously.[2,4]

Isolation of Products.—The *N*-methyl-9-cyanoacridan produced in the reaction of potassium cyanide with *N*-methyl-9-cyanoacridinium chloride in 90% DMSO–10% H_2O was isolated by diluting the solution with water tenfold. The precipitate was filtered, washed with water, and dried under vacuum. Identification was by melting point (see Table I), nmr spectrum, color, and solubility in chloroform.

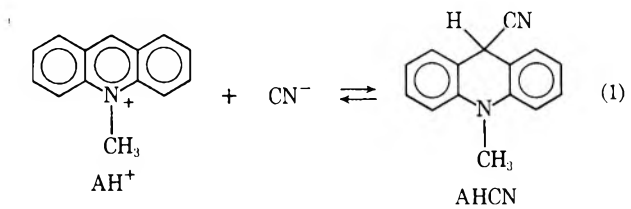
N-Methylacridone isolated from oxidation experiments with excess cyanide was obtained by diluting the solutions with tenfold excess of water and filtering. Identification was by melting point, mixture melting point with an authentic sample, nmr spectrum, color, and solubility.

Cyanide and Cyanate Determinations.—The solutions obtained from the oxidations were diluted with water and the *N*-methylacridone was filtered. Cyanide ion was determined in the filtrate with a standard solution of silver nitrate according to the Liebig–Deniges method.[7] No correction was made for the presence of 10% DMSO in the aqueous solution. Titration of standard aqueous KCN solutions indicated a 6% error at 0.002 *M* cyanide, 12% error at 0.001 *M* cyanide, and 31% error at 0.0005 *M* cyanide concentration due to the presence of the DMSO. Therefore, titrimetric analysis of cyanide ion was performed only on solutions of more than 0.002 *M* cyanide ion containing 10% DMSO.

The same filtrates were tested for cyanate ion by the addition of cobalt(II) chloride which forms a blue color in the presence of cyanate ion.[8] The test was negative for solutions of commonly used concentrations. Further experiments indicated that the limit of detection of KOCN in 10% DMSO–90% water by this method was 0.018 *M* KOCN. When *N*-methylacridinium chloride initially 0.5 *M* was oxidized in the presence of 0.7 *M* KCN, the filtrate at the end of the reaction after dilution to 90% water produced a blue color with $CoCl_2$. Appropriate control tests with and without KOCN verified that cyanide ion, methylacridone, and methylacridinium chloride did not interfere with the appropriate color formation.

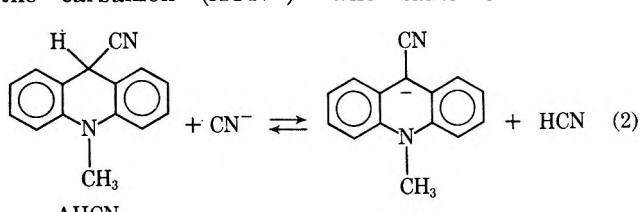
Results and Discussion

KCN Addition to *N*-Methylacridinium Chloride–*N*-Methyl-9-cyanoacridan.—It is well known that the addition of cyanide ion to *N*-methylacridinium salts (AH^+) yields AHCN.[9] In 90% dimethyl sulfoxide (DMSO) and 10% water (by volume), nearly quantitative yields of AHCN could be isolated when potassium cyanide was added to excess *N*-methylacridinium chloride (see runs 1 and 2, Table I). Under such conditions in air-saturated solutions of AHCN in DMSO, dimethylformamide, benzene, or dimethoxyethane small concentrations of the ACN· radical could be detected, the polar solvents providing the highest concentration of radicals. In the crystalline solid state, AHCN was found to give an esr signal which in solution was due to ACN· radicals. The radical impurity was estimated to be approximately 1% and was enhanced by recrystallization in boiling absolute ethanol and removed by dissolving in chloroform. (The latter is probably the result of a reaction with solvent which produces *N*-methyl-9-cyanoacridinium chloride). Although the presence of small amounts of ACN· radicals in polar solvents appeared to be the result of air oxidation of AHCN, negligible amounts of oxygen were absorbed by AHCN solutions over long periods of time in experiments where oxygen uptake was monitored with a volumetric gas absorption apparatus.



AH⁺ AHCN (1)

Oxygenation of *N*-Methyl-9-cyanoacridanide Anion.—In the presence of potassium cyanide or potassium *tert*-butoxide, solutions of AHCN in DMSO acquire a cherry red color. These solutions give a broad absorption at 530–600 mμ (Figure 1). Since diphenylacetonitrile and 9-phenylfluorene also give colored solutions with KCN in DMSO which are typical of the carbanions (red and yellow-orange respectively), the cherry red color in the case of AHCN is attributed to formation of the carbanion (ACN^-). The same coloration is observed when *excess* cyanide is added to AH^+ solutions. The conclusion is that the *in situ* formation of AHCN (eq 1) is rapidly followed by carbanion formation (eq 2).



AHCN ACN⁻ (2)

(5) E. G. Janzen, Ph.D. Thesis, Iowa State University, Ames, Iowa, 1963.
(6) G. A. Russell, E. G. Janzen, A. G. Bemis, E. J. Geels, A. J. Moye, S. Mak, and E. T. Strom, *Advan. Chem. Ser.*, **51**, 112 (1965); see p 164–165.
(7) G. H. Ayres, "Quantitative Chemical Analysis," Harper and Bros., New York, N. Y., 1958, p 308.
(8) A. Scattergood, *Inorg. Syn.*, **2**, 86 (1946).
(9) C. Kaufmann and A. Albertini, *Chem. Ber.*, **42**, 1999 (1909).

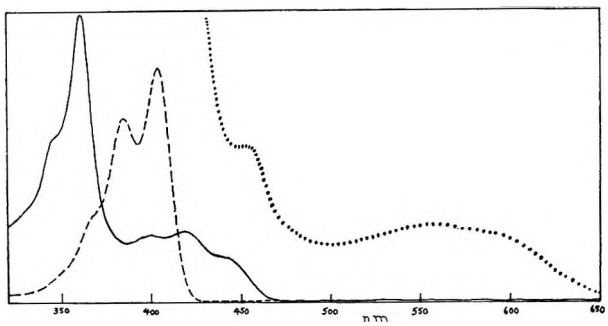


Figure 1.—Absorption spectra of *N*-methylacridinium chloride (——), *N*-methylacridone (-----), and *N*-methylacridinium chloride in the presence of excess KCN (·····) in 90% DMSO–10% water. The *N*-methylacridinium chloride concentration in the latter was *ca.* three times the concentration in the former.

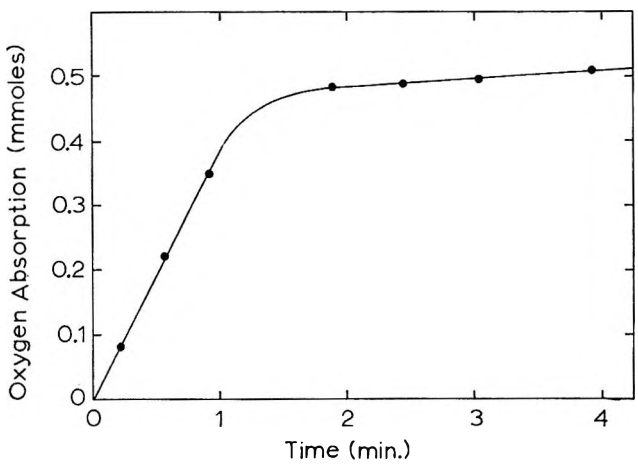


Figure 2.—Oxygen absorption as a function of time for 1.00 mmol of *N*-methylacridinium chloride and 1.52 mmol of potassium cyanide in 25 ml of 90% DMSO–10% water at 25.0°.

Solutions of ACN^- produced by the addition of excess cyanide to AH^+ rapidly absorb oxygen. The plot of oxygen absorption *vs.* time is nonautocatalytic, *i.e.*, not S-shaped (Figure 2) and is typical of carbanionic oxidations.[5,6,10] The major portion (>50%) of the oxidation is over in 1–2 min. This portion of the plot is practically linear. Further absorption of oxygen gives a stoichiometry of 0.7–0.8 by 2–3 hr. The highest stoichiometry obtained was 0.93 after 40 hr (see Table I). These observations suggest a 1 to 1 stoichiometry between the moles of oxygen absorbed to the moles AH^+ converted to NMA.

The *initial* slope of the oxygen absorption *vs.* time plot should depend on the initial concentrations of the reactants involved in the slow step. If the initial

$$[dO_2/dt]_{t=0} \propto [O_2]_0^m[AH^+]_0^n[CN^-]_0^p$$

concentration of AH^+ is held constant and the exposure to oxygen is arranged to be the same in a series of runs where the concentration of cyanide ion is varied one might expect to obtain the order in cyanide ion for the oxygen absorption reaction. Such data has been obtained (Table II). A plot of the initial rate in mol/l. min *vs.* cyanide ion concentration is shown in Figure 3. The very slow *initial* rate of oxygen absorption in deficient cyanide concentration has already been discussed. Thus at KCN/AH^+ ratios of up to 0.75 a

(10) G. A. Russell, A. J. Moye, E. G. Janzen, S. Mak, and E. R. Talaty, *J. Org. Chem.*, **32**, 137 (1967).

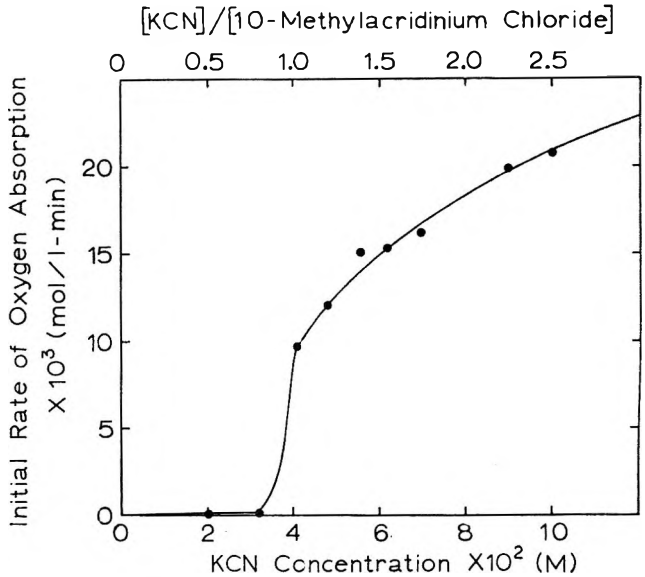


Figure 3.—Dependence of the initial rate of oxygen absorption on potassium cyanide concentration from solutions initially containing 0.0400 *M* *N*-methylacridinium chloride in 90% DMSO–10% water.

TABLE II
INITIAL RATE OF OXYGEN ABSORPTION[a]

$[AH^+Cl^-]$,[b] *M*	[KCN], *M*	Initial rate, (mol/l. min)
0.0400	0.0202	0.00[c]
0.0400	0.0319	0.00[c]
0.0400	0.0410	0.0097
0.0400	0.0484	0.0121
0.0400	0.0558	0.0151
0.0400	0.0616	0.0153
0.0400	0.0696	0.0162
0.0400	0.0900	0.0199
0.0400	0.0998	0.0208

[a] Reactions run in 25 ml of 90:10 DMSO–water by volume and agitated by shaker. [b] AH^+Cl^- = *N*-methylacridinium chloride. [c] Reaction mixture agitated by magnetic stirrer.

negligible amount of oxygen is absorbed compared to experiments where cyanide is in excess. This indicates that the rate of addition of cyanide to AH^+ to produce AHCN is faster than the ionization of AHCN to ACN^- (if the assumption is made that the species reacting with oxygen is mainly ACN^-). Since the first equivalent of cyanide produces AHCN rapidly the initial rate of oxygen uptake should depend on the remaining cyanide concentration. A first-order dependence on excess cyanide ($KCN/AH^+ > 1.00$) would point to a rate-limiting formation of ACN^-. The observed dependence on excess cyanide concentration shown in Figure 3 is not very encouraging. Although increasing the cyanide concentration does increase the initial rate of oxidation, the effect diminishes at higher KCN/AH^+ ratios. This result is not understood at this time but may be a function of the activity and/or "basicity" of cyanide ion at these concentrations in 90% DMSO–10% water. Ion pairing effects may be operative and influential. Another possibility is that the rate of oxygen uptake has reached the rate of availability (*i.e.*, dissolution and diffusion) of oxygen but this appears unlikely from previous experience with this type of oxidation.[5,6,10]

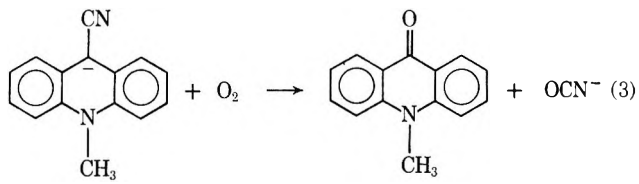
The most logical oxidation mechanism appears to involve rapid addition of cyanide to give AHCN and a

slower rate-limiting ionization of AHCN to ACN^-. This mechanism is not inconsistent with the data in Figure 3 and has precedence in the literature.[11,12]

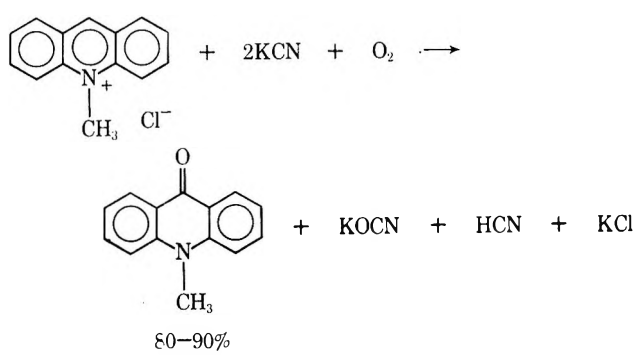
The discussion up to this point has implied that the equilibrium constant for eq 1 is large, *i.e.*, AHCN is produced rapidly essentially quantitatively. That this is not entirely correct can be deduced from the rate of initial oxygen uptake at ratios of KCN/AH^+ from 0.75 to 1.25. At a ratio of 1.0, a rapid rate of oxygen absorption is observed. It is apparent that a significant amount of cyanide ion is present in solution at these concentrations to effect ionization to ACN^-. Morecver since a relatively high oxygen stoichiometry and yield of oxidized product (*N*-methylacridone) is realized (Table I) the cyanide ion appears to act in a catalytic capacity. This means that a base at least as effective as cyanide ion is produced in the oxidation. A likely candidate is the hydroperoxide anion probably produced in the oxidation of the carbanion. Since the pK_a's of alkyl hydroperoxides are somewhat smaller than the pK_a's of alcohols ($\sim$19) the hydroperoxide and cyanide anions are probably of comparable basicity in this solvent system (the K_a of HCN in water is 7.2×10^{-10}).

In this study only one solvent system was used (90% DMSO–10% water) because of solubility difficulties. The appreciable amount of water present will of course hydrolyze the cyanide ion and protonate the hydroperoxide anion. The expected leveling effect of water probably precludes detecting a difference in rates of oxygen uptake with bases of differing basicity. Although the hydroxide ion produced may be ionizing AHCN to ACN^-[9,13] the almost quantitative isolation of AHCN from the addition of cyanide to AH^+ in solutions deficient in cyanide (Table I) proves that hydroxide does not compete with cyanide in the addition to AH^+ under such conditions.[14] Although product studies do not necessarily rule out the intermediacy of AHOH produced by hydroxide addition in the presence of excess cyanide, since *N*-methylacridone (NMA) is also the expected oxidation product in this case, the very clean 1:1 oxygen to product stoichiometry found (Table I) indicates that the secondary alcohol is probably not the major species oxidized.[15] However, the inability to obtain quantitative yields of NMA based on starting AH^+ concentrations might be due to the production of a small amount of the alcohol. AHOH would be expected to oxidize very slowly by a chain mechanism (by analogy to benzhydrol[12]). A comparison of runs in Table I shows that an additional amount of oxygen is absorbed after 2 hr and the yield of NMA is increased by 8% after 40 hr. The slight decrease in NMA yield with increase in cyanide concentration may also be significant since higher concentrations of cyanide ion would also produce higher concentrations of the hydroxide ion.

The results of Table I clearly show that 1 mol of oxygen produces 1 mol of NMA in the oxidation of AHCN. Since cyanate ion has been detected in the



basic oxidation of diphenylactonitrile to benzophenone,[16] a search was made for this species in these oxidations. Solutions were diluted tenfold with water to precipitate NMA and tested for the presence of cyanate. The test was positive only for experiments run with highly concentrated solutions (see Experimental Section). Quantitative results were not obtained. The cyanide ion concentration remaining in the same filtrates was determined quantitatively however. These results support the postulated formation of cyanate ion since the sums of the cyanide ion and NMA concentrations (the concentration of cyanate should be equal to the concentration of NMA according to eq 3) are within 10% of the total amount of cyanide added to the solution: 1.43, 1.50, and 1.67 mmol/25 ml, respectively (Table I). Our data thus supports the cyanate stoichiometry in eq 3. The overall reaction is



80–90%

***N*-Methyl-9-cyanoacridanyl Radical.**—Solutions of AH^+ containing excess cyanide ion exposed to oxygen produce the highest concentrations of ACN· observed. Thus, the addition of excess KCN to 2.00×10^{-2} *M* AH^+ in 90% DMSO–10% water gave 2.96×10^{-4} *M* ACN· (1.5%). However, the lifetime of the radical under such conditions is less than 2 min. In fact the time period wherein ACN· is most readily detectable in solutions through which oxygen is continuously bubbled correlates well with the time period for maximum oxygen absorption (Figure 2). For studies of the radical over more extended periods of time (*e.g.*, for obtaining esr spectra at high resolution), a solution originally saturated with air closed to further oxygen exposure provides a reasonable concentration of radicals stable over a period of many hours.

(11) G. A. Russell and A. G. Bemis, *J. Amer. Chem. Soc.*, **88**, 5491 (1966).

(12) G. A. Russell, A. G. Bemis, E. J. Geels, E. G. Janzen, and A. J. Moye, *Advan. Chem. Ser.*, **75**, 174 (1968).

(13) AHCN is known to be oxidized in alkaline ethanol to *N*-methylacridone: (a) F. McCapra, D. G. Richardson, and Y. C. Chang, *Photochem. Photobiol.* **4**, 111 (1965); (b) F. McCapra and D. G. Richardson, *Tetrahedron Lett.*, **43**, 3167 (1964).

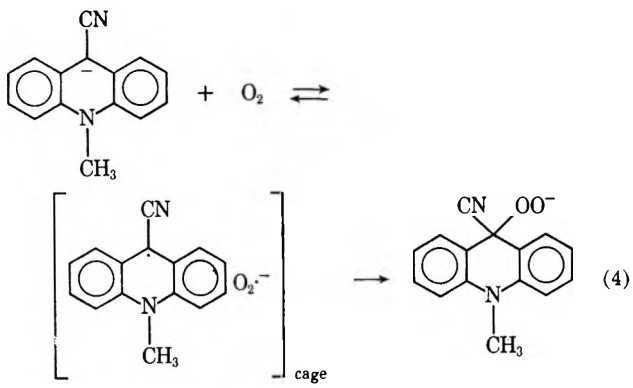
(14) The formation of *N*-methyl-9-hydroxyacridan from the nucleophilic addition of hydroxide ion to *N*-methylacridinium bromide is known to be slow in polar solvents as determined by uv studies and the equilibrium appears to favor *N*-methylacridinium hydroxide: R. M. Acheson and L. E. Orgel, "Acridines," Interscience, New York, N. Y., 1956, p 281; A. Albert, "The Acridines," St. Martin's Press, New York, N. Y., 1966, p 540.

$$AH^+ Br^- + OH^- \rightleftharpoons AH^+ OH^- \rightleftharpoons AHOH$$

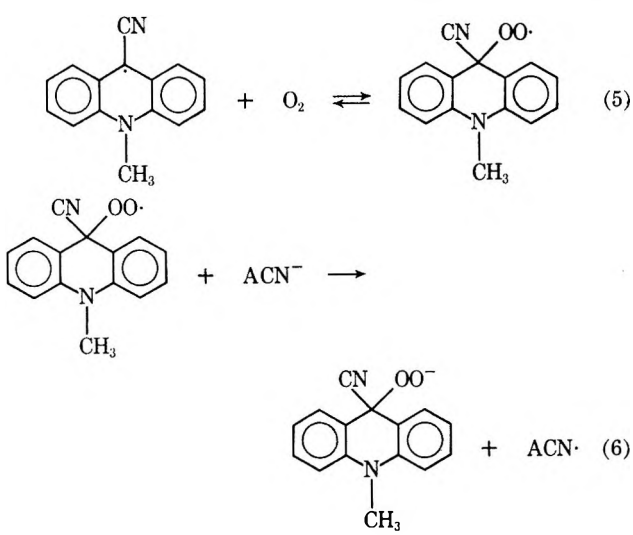
(15) Weak carbon-acid alcohols (*e.g.*, benzhydrol) oxidize to ketones with relatively high oxygen stoichiometries ($\sim$1.5).[12] The oxidation of AHOH–aqueous DMSO would be expected to behave similarly.

(16) H. G. Aurich, *Tetrahedron Lett.*, **12**, 657 (1964); B. R. Garrett, Ph.D. Thesis, University of Delaware, Newark, Del., 1959, in A. J. Moye, Ph.D. Thesis, Iowa State University, Ames, Iowa, 1961.

The most reasonable oxygenation mechanism consistent with the stoichiometry of eq 3 and the relatively low yield of radical detected is an electron transfer oxidation of ACN^- by O_2 to give a radical superoxide pair. Most of the product probably arises from collapse of this radical pair after spin relaxation to produce the peroxy anion. The formation of detectable concentrations of ACN· radicals could be the result of dissociation of the caged radical pair. The reaction of



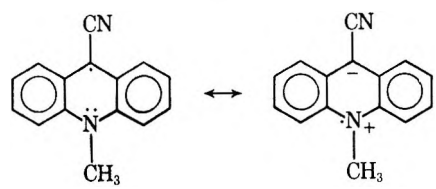
ACN· with oxygen should produce the peroxy anion *via* the peroxy radical by a chain electron transfer oxidation.



Numerous experiments with varying amounts of oxygen failed to detect the intermediate peroxy radicals. Only on one occasion a low-field signal was obtained in addition to the spectrum of ACN· which might have been due to the peroxy radical but this result could not be reproduced.

Neutral radicals presumably produced in the oxygen electron transfer oxidation of carbanions are usually not detected by esr. This is probably due to a very rapid rate of reaction of oxygen with the radicals and a large equilibrium constant favoring the peroxy radical (eq 5). The existence of a temperature dependent equilibrium between a peroxy radical and the corresponding radical plus oxygen was suspected for some time[17] and has been demonstrated for triphenylmethyl radical in the solid state.[18] Other examples of the detection of neutral stable free radicals in the oxygenation of stable carbanions are Koelsch's radical (I),[19] phenalenyl (II),[20] and tris-*p*-nitrophenylmethyl (III).[5,21] In these cases and in the case of ACN· the rate of eq 5 must be relatively slow and the equilibrium must favor the carbon radical. Rapid carbon radical producing reactions (4 and 6, particularly 6) are obviously necessary for radical detection. The reversibility of reactions 4 or 6 for ACN· has not been demonstrated although this possibility for reaction 4 seems reasonable.

In comparing the esr detectability of neutral radical intermediates in the oxygenation of carbanions of weak carbon acids ($pK_a \simeq 20$–25) the reaction most likely to be crucial in determining the "stability" of the radical to oxygen is reaction 5 since the rates of reaction 4 and 6 probably do not vary markedly with change in structure within this pK_a range. The equilibrium constant for reaction 5 must depend solely on the delocalization stability of the radical since the intrinsic thermodynamic stability of the peroxy radical will be almost the same regardless of the structure of the radical. The unusual stability of ACN· may be due to sizable delocalization of the unpaired electron onto the nitrogen



atom. The spin density on nitrogen is 0.127 (estimated from MO calculations and nitrogen hyperfine coupling) whereas the spin density on C-9 is only approximately 0.3. The only good system available for comparison is the 9-xanthyl radical system.[22] Unfortunately, analogous derivatives have not been studied. Vincow and coworkers have not made 9-cyanoxanthyl radical and we have not studied the *N*-methyl-9-phenylacridanyl. A study of the comparitive stability of these radicals to oxygen would appear to be worth while.

Chemiluminescence.—Oxygenation of the cyanide ion addition product of AH^+ is a chemiluminescent reaction. When excess KCN is added to a solution of AH^+ the color of the solution turns from yellow to red. The oxygen uptake is rapid at this time and a blue glow is visible in the dark. Finally the color of the solution is yellow with a green fluorescence. The chemiluminescence spectrum shows a maximum at 442 mμ. Since the fluorescence spectrum of *N*-methylacridone has a maximum at 440–442 mμ in a variety of solvents,[13,23,24] this compound is implicated as the light emitter. This conclusion has been reached by others[13] in the NH_4OH/H_2O_2 or OH^-/O_2 aqueous ethanol–*N*-methyl-9-cyanoacridinium nitrate systems for the same reasons.

A typical plot of the relative light intensity as a function of time is given in Figure 4. The initial slope

(17) (a) G. A. Russell in "Peroxide Reaction Mechanisms," J. O. Edwards, Ed., Interscience, New York, N. Y., 1962, p 110; (b) D. G. Hendry and G. A. Russell, *J. Amer. Chem. Soc.*, **86**, 2371 (1964).

(18) C. L. Ayers, E. G. Janzen, and F. J. Johnston, *ibid.*, **88**, 2610 (1966); E. G. Janzen, F. J. Johnston, and C. L. Ayers, *ibid.*, **89**, 1176 (1967).

(19) J. G. Pacifici, J. F. Garst, and E. G. Janzen, *ibid.*, **87**, 3014 (1965).

(20) D. H. Reid, *Chem. Ind. (London)*, 1504 (1956); *Tetrahedron*, **3**, 339 (1958).

(21) M. F. Hawthorne and G. S. Hammond, *J. Amer. Chem. Soc.*, **77**, 2549 (1955).

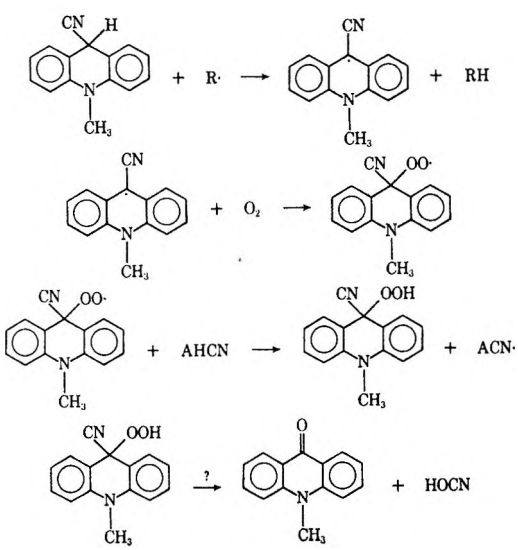
(22) M. D. Sevilla and G. Vincow, *J. Phys. Chem.*, **72**, 3641, 3647 (1968).

(23) J. R. Totter, *Photochem. Photobiol.*, **3**, 231 (1964); A. S. Van der Burg, *Recl. Trav. Chim. Pays-Bas*, **69**, 1525 (1950).

(24) M. M. Raubut, D. Sheehan, R. A. Clarke, B. G. Roberts, and A. M. Semsel, *J. Org. Chem.*, **30**, 3587 (1965); K. D. Legg and D. M. Hercules, *J. Amer. Chem. Soc.*, **91**, 1902 (1969).

of light emission *vs.* time and the time for the emission to reach its maximum varies with exposure to oxygen, *i.e.*, agitation of the solution. However, it is clear that the major portion of the oxygen is absorbed in the initial stages of the reaction during the time when the rate of increase of light emission is greatest (compare Figures 2 and 4). It was thus of interest to compare the relative light intensity and uptake of oxygen profiles. Both the uptake of oxygen and the relative light intensity were monitored simultaneously for a stirred 0.04 *M* AH^+ solution containing 0.062 *M* KCN initially. The time profiles are identical for the first minute of the reaction (Figure 5) and the maximum relative light intensity occurs at the same time as the break in the oxygen absorption time curve (Figure 5). This result shows that the steps between the oxygen absorption reaction and the NMA* precursor are either very fast or the same one; *i.e.*, the reaction with oxygen may produce the precursor to NMA* directly. Moreover, it appears that the NMA* precursor has a reasonable lifetime since light emission continues although at a diminishing level for a relatively long period after the maximum intensity point is reached (Figure 5).

A plot of the maximum relative intensity of light emission during oxidation as a function of added cyanide ion is shown in Figure 6. Very low light intensities are detected in the oxidation of AHCN in the absence of excess cyanide (KCN/AH^+ ratios of <0.75, indicated as A on plot) which is consistent with the negligible oxygen uptake observed under such conditions (Figure 3).[25]



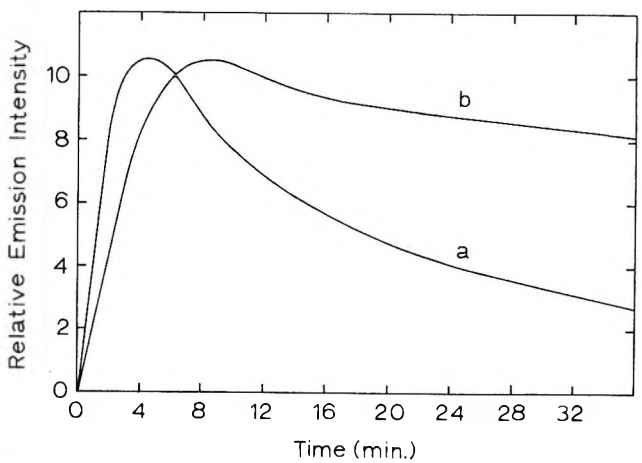


Figure 4.—Relative emission intensity as a function of time for (a) 0.017 *M* *N*-methylacridinium chloride and 0.021 *M* potassium cyanide, and (b) 0.012 *M* lucigenin (DBA^{2+}) and 0.021 *M* potassium cyanide in 90% DMSO–10% water through which oxygen was continuously bubbled.

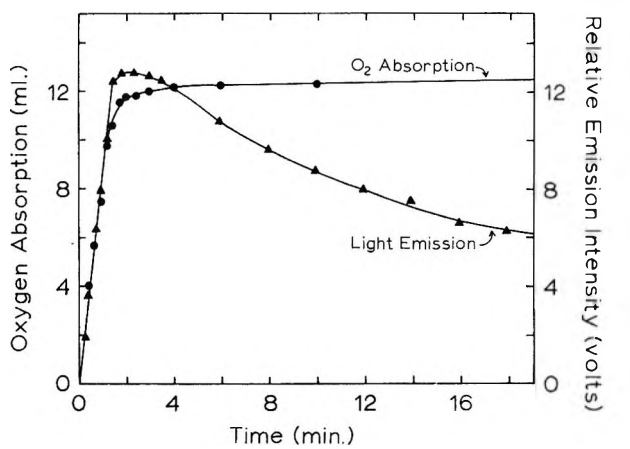


Figure 5.—Oxygen absorption (left scale) and relative light emission (right scale) as a function of time measured simultaneously from a stirred solution initially containing 0.04 *M* *N*-methylacridinium chloride and 0.062 *M* potassium cyanide.

Chemiluminescence becomes appreciable after the ratio of KCN to AH^+ exceeds 0.75. The maximum relative intensity increases thereafter as a function of cyanide ion concentration. The shape of this plot is remarkably similar to the plot of the initial rate of oxygen uptake as a function of cyanide ion (Figure 3). The plots are almost superimposable using the same KCN/AH^+ ratios up to a ratio of 1.50 (indicated as B on plot). Thereafter the maximum emission intensity continues to increase with increase in cyanide ion concentration (indicated as C on plot) although the initial rate of oxygen uptake levels off.

The fact that the initial rates of oxygen uptake show the same dependence on excess cyanide ion concentration as the relative maximum light intensities (Figures 3 and 6) provides further support for the conclusion that the concentration of the NMA* precursor depends directly on the concentration of the species reacting with oxygen.

(25) Further experiments show that a chain autoxidation of AHCN to produce chemiluminescence cannot be initiated with free-radical initiators. Thus azobisisobutyronitrile or phenylazotriphenylmethane, sources for 2-cyanopropyl or phenyl radicals, produce only low levels of light in solutions of AHCN in DMSO, toluene, or ethanol at 30, 55, or 70° exposed to various amounts of oxygen. This observation is not unprecedented. Tris-*p*-nitrophenylmethane is totally inert to radical-initiated autoxidation[21] and triphenylmethane is itself rather inert to autoxidation reactions.[17b] The inability of these compounds to sustain an autoxidation reaction is attributed to the slow reaction of the carbon radical with oxygen [G. A. Russell, *J. Amer. Chem. Soc.*, **78**, 1047 (1956)]. This observation is of interest for another reason. It has been suggested that certain compounds might serve as radical detectors by emitting light when in the presence of free radicals [J. R. Totter, V. J. Medina, and J. L. Scoseria, *J. Biol. Chem.*, **235**, 238 (1960); J. R. Totter, E. C. de DuGros, and C. Riveiro, *ibid.*, **235**, 1839 (1960); J. R. Totter, W. Stevenson, and G. E. Philbrook, *J. Phys. Chem.*, **68**, 752 (1964)]. Since sensitive equipment for the detection of small amounts of light is readily available, this technique might provide greater sensitivity than, for example, esr spectrometry. The autoxidation of AHCN might have served as such a system if the detection of radicals could be reliably based on the initiation of an efficient chemiluminescent chain reaction.

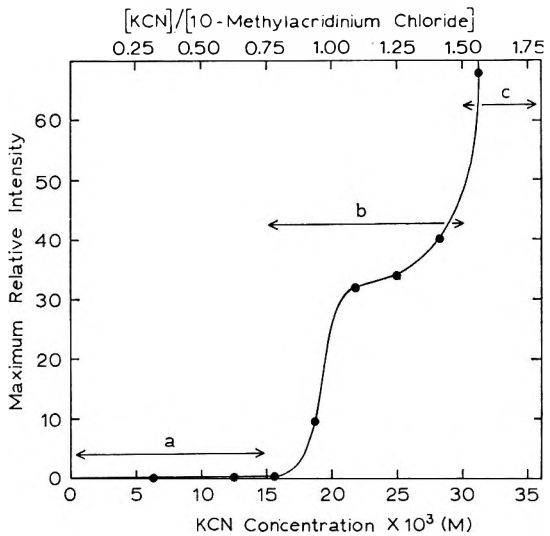
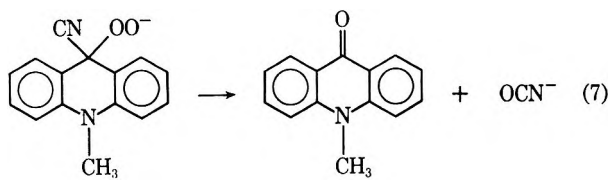
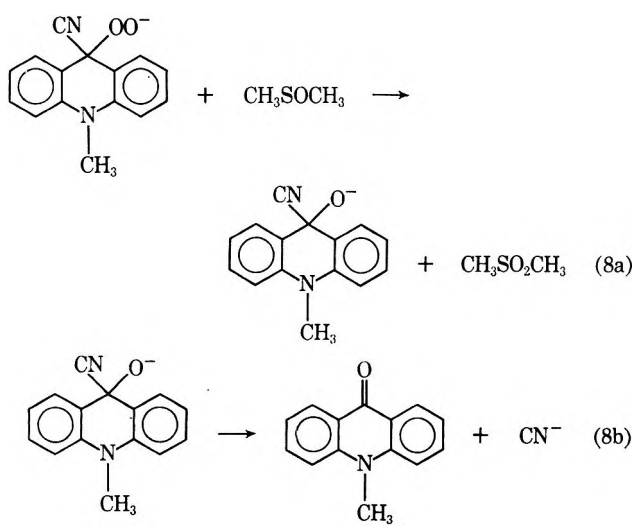


Figure 6.—Dependence of the maximum chemiluminescence emission intensity on potassium cyanide concentration from solutions initially containing 0.020 *M* *N*-methylacridinium chloride in 90% DMSO–10% water.

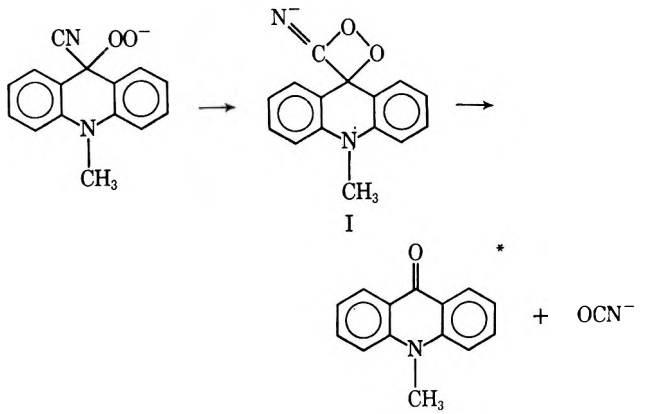
The major and only isolated product in these oxidations is *N*-methylacridone. It is probably produced from the hydroperoxide or hydroperoxide anion. The



detection of cyanate and the quantitative determination of cyanide remaining after the reaction, rule out the following product-forming route.

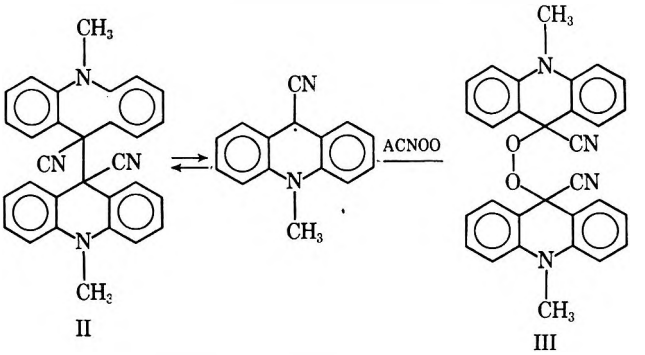


There is precedence for the involvement of DMSO in the basic oxygenation of triphenylmethane.[11] Thus triphenylmethyl hydroperoxide is converted to the carbinol in 94% yield with production of dimethyl sulfone in the presence of base in DMSO. If this reaction is fast it can be concluded that eq 7 must proceed considerably faster than eq 8 or a stable intermediate peroxide ion exists which is inert to DMSO. A mechanism previously proposed for product and excited-state formation in these and similar chemiluminescent reactions involves a four-membered peroxide ring.[13,26]

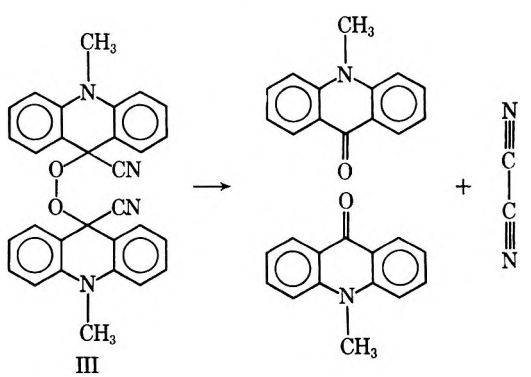


The lifetime of I, if an intermediate, is not known since evidence for the existence of this molecule has not been reported by those who proposed its structure. It would appear to fill the requirements necessary as a final intermediate in the oxygenation of AHCN in our system, since it might be more stable to DMSO than a free peroxide anion. If I is in fact the precursor to NMA* it must be reasonably long lived since light emission is seen for quite a long period after most of the oxygen is absorbed (Figure 4).

However, the chemiluminescence results could be rationalized in terms of another scheme. Two probable products in reactions producing stable radicals in the presence of oxygen are dimers and peroxides. The formation of these side products is certainly possible in this system particularly because of the relatively high concentrations of ACN· radicals produced during the oxygen uptake. If the decomposition of the peroxide



III is chemiluminescent the maximum light intensity observed would be a function of the concentration of III



(26) See, however, M. M. Rauhut, *Accounts Chem. Res.*, **2**, 80 (1969).

which in turn would depend on the steady-state concentrations of ACN· and A(CN)OO·. Since an increase in cyanide concentration increases the rate of oxygen uptake and thus the steady-state concentrations of ACN· and A(CN)OO· the concentration of III should increase with increase in cyanide concentration as observed.

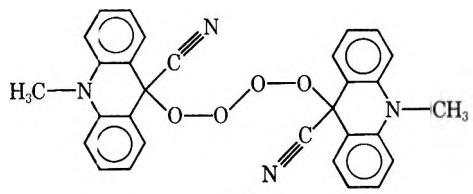
An additional possibility is the storage of ACN· radicals as the dimer, II. The dimer might be expected to dissociate relatively slowly to ACN· radicals and in the presence of oxygen more of the peroxide III would be produced. The concentration of II would depend on the concentration of ACN· present during the oxygenation which itself would be dependent on the cyanide ion concentration.

A test for the possible involvement of the dimer in the chemiluminescence step was attempted. Previous experiments have shown that the addition of cyanide ion to lucigenin produces esr detectable amounts of ACN· radicals.[2] The addition of cyanide to lucigenin in the presence of oxygen *does* produce chemiluminescence which has a time profile not too different from that observed with cyanide and AH^+ (Figure 4). Thus mechanisms which incorporate A(CN)OO· radicals in the chemiluminescence scheme have some support. In addition to the reaction of A(CN)OO· and ACN· to produce the peroxide III, one might expect the reaction of two peroxy radicals to be possible. The formation of

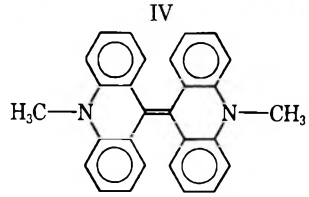
$$2A(CN)OO\cdot \longrightarrow A(CN)OOOO(CN)A$$

short-lived tetroxides and their decomposition to give oxygen and the corresponding oxy radicals has been extensively studied recently.[27] In this case the decomposition should be chemiluminescent and should produce cyano radicals and oxygen (or cyanato radicals) in addition to excited *N*-methylacridone.

The possibility of using this reaction (*i.e.*, lucigenin plus cyanide ion in oxygen) to study this aspect of the reaction quantitatively is unfortunately limited by the apparent tendency of cyanide to reduce this highly electrophilic compound by electron transfer giving presumably cyano radicals and the radical cation of lucigenin by analogy to observations made on similar compounds.[28] A product study of a cyanide addition–oxygenation experiment gave 60% *N*,*N*′-dimethyl-9,9′-biacridylidene (V), the product of a two-electron reduction of lucigenin.



IV



V

No comment has been made on the fact that increasing the cyanide ion concentration past a ratio of 1.50 (indicated as portion C on Figure 6) serves to increase further the maximum intensity of light emission although the initial rate of oxygen increases very little with increase in cyanide concentration after this point. No explanation for this observation is obvious although a cyanide ion induced decomposition of the peroxide III is suggested. The chloride ion reduction of benzoyl peroxide has recently been studied[29] and could be considered analogous to the proposed possible reaction.

Registry No.—*N*-Methylacridinium chloride, 5776-39-6; KCN, 151-50-8; AHCN, 837-43-4; NMA, 719-54-0.

(27) P. D. Bartlett and G. Guaraldi, *J. Amer. Chem. Soc.*, **89**, 4799 (1967); P. D. Bartlett and P. Gunther, *ibid.*, **88**, 3288 (1966); N. A. Miles and G. G. Arzoumanidis, *Chem. Ind.* (*London*), 67 (1966).

(28) L. Papouchado, R. N. Adams, and S. W. Feldberg, *J. Electroanal. Chem.*, **21**, 410 (1969).

(29) N. J. Bunce and D. D. Tanner, *J. Amer. Chem. Soc.*, **91**, 6096 (1969).

Stereochemical Aspects of R_2O-3 Participation. Lithium Aluminum Hydride Reduction of 9-Oxabicyclononan-2-yl Iodides

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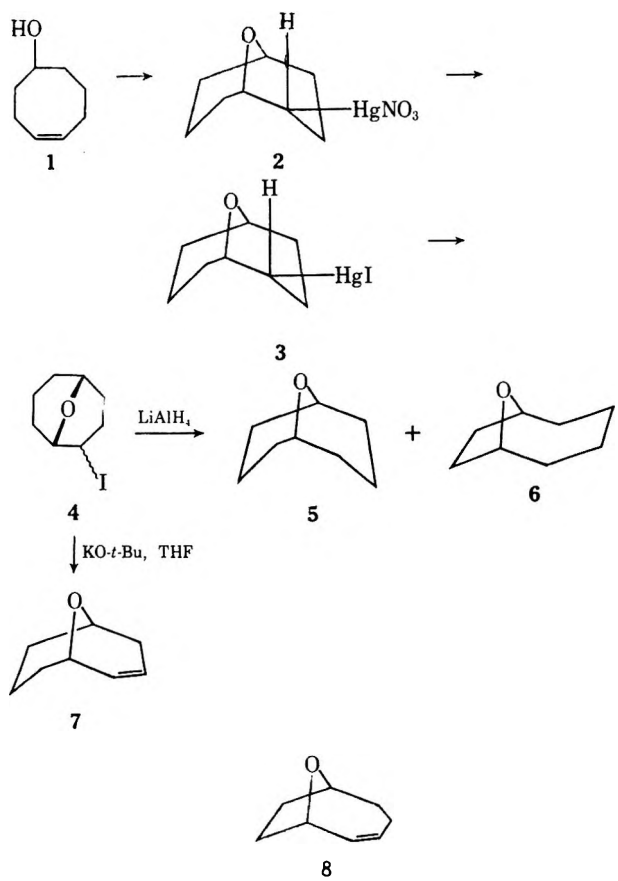
Iododemercuration of *endo*-2,6-epoxycyclooctylmercuric iodide with iodine in carbon tetrachloride solution affords chiefly 2-iodo-9-oxabicyclo[3.3.1]nonane, probably as a statistical mixture of the two possible isomers. Lithium aluminum hydride reduction of this mixture in ether solution results in the formation of equal parts of 9-oxabicyclo[3.3.1]nonane and 9-oxabicyclo[4.2.1]nonane. In contrast, 2-iodo-9-oxabicyclo[4.2.1]nonane, similarly obtained as a mixture of isomers from *endo*-2,5-epoxycyclooctylmercuric iodide, affords exclusively 9-oxabicyclo[4.2.1]nonane upon hydride reduction. The mechanistic implications of these transformations are discussed.

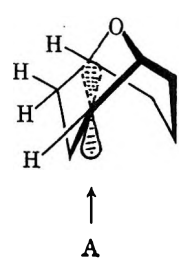
In an earlier paper from this laboratory,[1] it was shown that acetolysis of *endo*-9-oxabicyclo[4.2.1]nonan-2-yl brosylate proceeds with anchimeric assistance involving R_2O-3 participation by the oxygen bridge. Also, although the geometry of the related *exo* isomer prohibits such direct neighboring-group participation, a similar oxonium ion does intervene later in the mechanistic scheme. In neither case was carbon–carbon bond migration noted. In the present work, the solvolytic behavior of 9-oxabicyclononan-2-yl iodides under conditions of lithium aluminum hydride reduction was examined to obtain further information on the stereochemical aspects of R_2O-3 participation. This study was prompted by a number of isolated earlier reports which indicated that metal hydride reductions of certain aralkyl and alkyl arenesulfonate and halide systems result in the formation of appreciable quantities of rearranged hydrocarbons as a consequence of anchimerically assisted ionization.[2] The oxygen-bridged molecules **4** and **11** represent interesting substrates with which to probe further into the structural requirements of such transformations; an assessment of their reactivity is herein presented together with the mechanistic implications.

SCHEME I



Results

Oxymercuration of 4-cycloocten-1-ol (**1**) with mercuric nitrate in aqueous potassium nitrate solution according to the procedure of Bordwell and Douglass[3] led rapidly to the precipitation of *endo*-2,6-epoxycyclooctylmercuric nitrate (**2**). Conversion of **2** to the corresponding mercuric iodide (**3**) was achieved by means of potassium iodide in dilute sodium hydroxide solution (Scheme I). Iododemercuration of **3** with iodine in carbon tetrachloride solution afforded in good yield a colorless liquid. Considerable evidence attests to the fact that the cleavage of mercurials with halogens involve free-radical intermediates.[4] In the particular case of free radical A, considerations of product control and accessibility to the reactive site both favor preferred attack from the "equatorial" direction to give the thermodynamically favored *endo* isomer of **4**. Analogous factors appear to control the preferred *exo* bonding of various halogen donors to the 2-norbornyl free radical; in particular, the dominant *exo* selectivity is significantly overwhelming as the steric demands of the



(1) L. A. Paquette and P. C. Storm, *J. Amer. Chem. Soc.*, **92**, 4295 (1970).

(2) (a) H. Schmid and P. Karrer, *Helv. Chim. Acta*, **32**, 1371 (1949); (b) D. J. Cram, *J. Amer. Chem. Soc.*, **74**, 2149, 2152 (1952); (c) E. J. Corey; M. G. Howell, A. Boston, R. L. Young, and R. A. Sneen, *ibid.*, **78**, 5036 (1956); (d) P. R. Story, *ibid.*, **83**, 3347 (1961); (d) P. R. Story and M. Saunders, *ibid.*, **84**, 4876 (1962); (f) H. C. Brown and H. M. Bell, *ibid.*, **85**, 2324 (1963); (g) S. Winstein, A. H. Lewin, and K. C. Pande, *ibid.*, **85**, 2324 (1963); (h) E. L. Allred and S. Winstein, *ibid.*, **89**, 4008 (1967).

(3) F. G. Bordwell and M. L. Douglass, *ibid.*, **88**, 993 (1966).

(4) For a review of this subject, consult F. R. Jensen and B. Rickborn, "Electrophilic Substitution of Organomercurials," McGraw-Hill, New York, N. Y., 1968, Chapter 4.

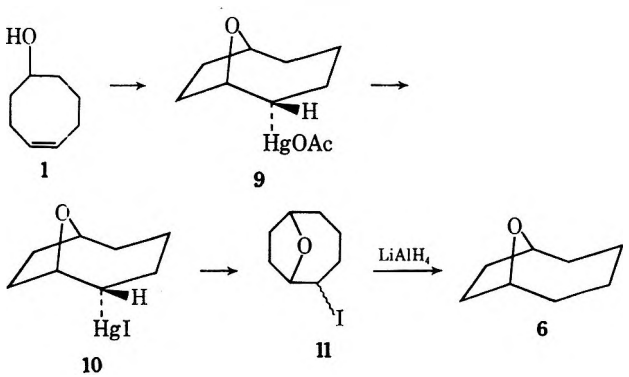
halogen source are increased.[5] Notwithstanding, Jensen[6] has shown that bromodemercuration of *cis*- and *trans*-4-alkylcyclohexylmercuric bromides in carbon tetrachloride proceeds *via* a free-radical pathway to give approximately 1:1 mixtures of *cis*- and *trans*-4-alkylcyclohexylbromides. On this basis, the reaction of **3** with iodine would not be expected to be stereospecific.

The nmr spectrum of **4** (see Experimental Section) was too complex for quantitative purposes. However, thin layer and vapor phase chromatographic techniques indicated the substance to be inhomogeneous. Preparative vpc and column chromatographic separation of the components was not possible because of partial decomposition and/or rearrangement under the conditions employed. In order to establish whether any skeletal rearrangement had transpired during the iododemercuration, distilled **4** was dehydrohalogenated with potassium *t*-butoxide in tetrahydrofuran under mild conditions. Since the product distribution from this reaction (after 8 hr) consisted of a maximum amount of 6% **8** (vpc and nmr analyses), **4** is composed chiefly of 9-oxabicyclo[3.3.1]nonan-2-yl iodides. Further comment on the probable configurational composition of this mixture is deferred to the Discussion section.

After being heated at reflux for 2 hr, a diethyl ether solution of **4** and lithium aluminum hydride was allowed to stand at room temperature overnight and worked up by addition of water and 25% aqueous sodium hydroxide solution. After filtration and careful evaporation of the ether, the concentrate was analyzed by vpc prior to, and after, distillation [crystalline distillate, bp 70–76° (20 mm)]. Two products were formed in *equal* amounts and these were identified as 9-oxabicyclo[3.3.1]nonane (**5**) and 9-oxabicyclo[4.2.1]-nonane (**6**) by comparison with authentic samples.

Oxymercuration of **1** in buffered aqueous mercuric acetate solution under conditions of kinetic control[3] led to the formation of mercurial acetate **9** (Scheme II).

Scheme II

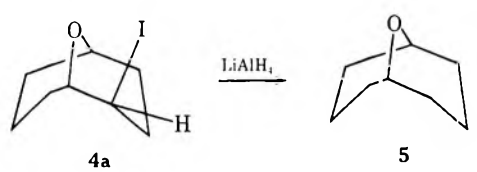


Exposure of **9** to potassium iodide solution gave **10** which was converted in 91% yield to a mixture of iodides when treated with iodine in carbon tetrachloride solution. As in the case of **4**, **11** was a nonseparable mixture of epimeric iodides; demonstration of the fact that the unpurified iodide was not purely of the 9-oxabicyclo[4.2.1]nonanyl series was gained by dehydrohalogenation to a mixture of **7** (15%) and **8** (85%). Nevertheless, lithium aluminum hydride reduction of unpurified **11** results exclusively in the formation of 9-oxabicyclo[4.2.1]nonane (**6**). No 9-oxabicyclo[3.3.1]-nonane (**5**) was detected by vpc or nmr methods.

Discussion

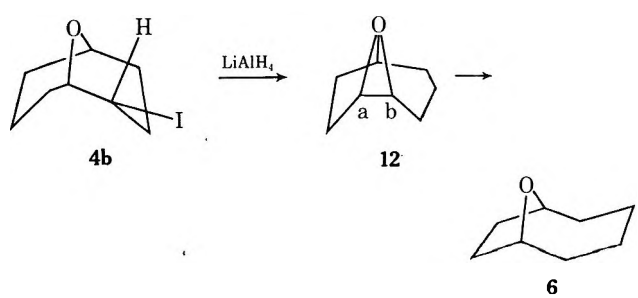
Although complex metal hydride reductions of arenesulfonates and halides are generally considered to proceed by the SN2 displacement pathway,[7] it is clear that certain systems do undergo reduction by processes which involve prior ionization. Perhaps the three most well-studied examples of this phenomenon are cholesteryl tosylate ($LiAlH_4$),[2a,c] 7-norbornadienyl chloride ($LiAlH_4$[2d,e] and $NaBH_4$[2f,g]), and 4-methoxy-1-pentyl brosylate ($LiAlH_4$).[2h] Each of these molecules is capable of ionization to a particularly stable cationic species. Apparently, the salt effect produced upon dissolution of a metal hydride in a solvent such as ether is quite capable of promoting anchimerically assisted ionization[8] when this is energetically feasible.

With such considerations in mind, it follows logically that the *exo* epimer of **4** (*i.e.*, **4a**) should undergo hydride reduction by direct SN2 displacement of iodide ion, due to geometric constraints which deter anchimeri-



4a 5

cally assisted ionization.[1] The reduction of **4a** therefore would not eventuate in skeletal rearrangement. In contrast, the *trans*-disposed iodine substituent in *endo* isomer **4b** is ideally positioned for facile initial salt-promoted R_2O-3 participation to give oxonium ion **12**. Although no definitive information is available as to the number of intermediate ion and ion-pair species which may be involved, it is entirely plausible that lithium aluminum hydride reduction of this isomer does not result in direct hydride displacement of iodide ion. Rather,



4b 12 6

a slow ionization step to afford **12** is logically involved, this oxonium ion then suffering rapid kinetically controlled reduction to **6**. The high degree of selectivity formulated for the reduction of **12** is founded on earlier

(5) See, for example, (a) E. C. Kooyman and G. C. Vegter, *Tetrahedron*, **4**, 382 (1958); (b) S. J. Cristol, J. R. Douglass, W. C. Firth, Jr., and R. E. Kral, *J. Org. Chem.*, **27**, 2711 (1962); (c) S. J. Cristol, L. K. Gaston, and T. Tiedeman, *ibid.*, **29**, 1279 (1964).

(6) (a) F. R. Jensen and L. H. Gale, *J. Amer. Chem. Soc.*, **82**, 148 (1960); (b) F. R. Jensen, L. H. Gale, and J. E. Rodgers, *ibid.*, **90**, 5793 (1968).

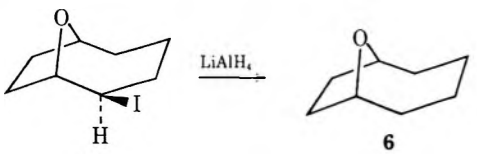
(7) L. W. Trevoy and W. G. Brown, *ibid.*, **71**, 1675 (1949). However, see also M. S. Newman, J. R. Le Blanc, H. A. Karnes, and G. Axelrod, *ibid.*, **86**, 868 (1964).

(8) A close analogy is seen in the fact that ether solutions which are at least 0.036 *M* in lithium perchlorate become better ionizing media than acetic acid [S. Winstein, E. C. Friedrich, and S. Smith, *ibid.*, **86**, 305 (1964); S. Winstein, S. Smith, and D. Darwish, *ibid.*, **81**, 5511 (1959)].

observations that the 9-oxabicyclo[4.2.1]nonyl system is strongly favored under conditions of kinetic control.[3]

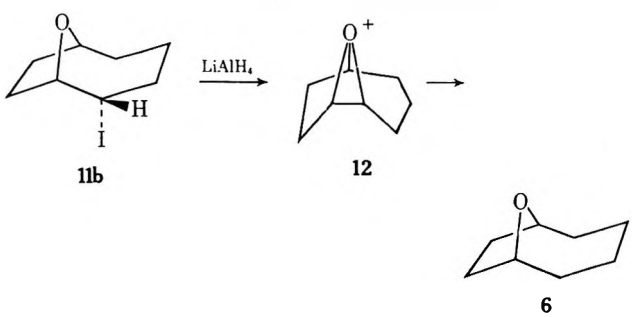
A most salient feature of this interpretation resides in the requirement that an approximate 1:1 distribution of **4a** and **4b** be realized in the iododemercuration step.[9] In agreement with this conclusion of a statistical product distribution are the results derived from several related halogen atom transfer reactions which tend to have only small structure development in their transition states because of their low heats of reaction.[6,10] There exists little doubt that iodine will function like bromine and chlorine in having less bonding in the transition state and as a result be unselective (in the stereochemical sense) in its reactions.[6,11]

Similar arguments can be advanced in the case of **11**. Clearly, *exo* isomer **11a** is not subject to reductive rearrangement and therefore this isomer can be expected



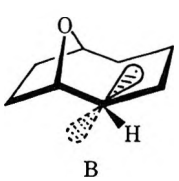
11a

to lead cleanly to **6**. The *endo* isomer **11b** would, however, again involve **12** which, as discussed above, is likewise a precursor of **6**. In actual fact, therefore, either isomer of **11** is predicted to afford only **6** and this



11b **12**

is observed. As in the case of intermediate A, free radical B is not expected to exert torsional effects which



B

would cause deviation from a statistical distribution of epimers.

Finally, some comment should be made on the intervention of crossover products during the iododemercuration reaction. Since leakage from free radical A to free radical B and *vice versa* are highly unlikely transpositions, the source of the rearrangements was considered to be mercuric iodide catalyzed skeletal rearrangement of the resulting iodides. Because **4b** and **11b** are expected to be the more reactive isomers of each structural pair,[1] HgI_2-induced interconversion of these products was implicated. In a limited number of control experiments, it was demonstrated that an increase in crossover product resulted[12] as the duration of the iododemercuration was extended from 4 to 12 hr. Since oxonium ion **12** is the very likely intermediate in these rearrangements, the crossover products must accordingly be *trans* disposed to the oxygen bridge and therefore ultimately give rise exclusively to 9-oxabicyclo[4.2.1]nonane upon lithium aluminum hydride reduction. As a result, the proportion of **6** in the final product should not be dependent on the extent of isomerization since all structural elements involved lead to **6** upon reduction. This conclusion was supported by several reduction experiments.

(9) Refer to the ensuing discussion for comments on the fate of the small amount of 9-oxabicyclo[4.2.1]nonyl impurity present in the various samples of **4**.

(10) Reactions which have more bond formation in their transition states (*e.g.*, *exo*-norbornyl) would naturally tend to give chiefly those products which arise from pathways involving less torsional strain complications.

(11) F. D. Greene, M. L. Savitz, F. D. Osterholtz, H. H. Lau, W. N. Smith, and P. M. Zanet, *J. Org. Chem.*, **28**, 55 (1963).

Experimental Section

2,6-Epoxycyclooctylmercuric Iodide (3).—A solution of 66.0 g (0.4 mol) of potassium iodide dissolved in 100 ml of 10% sodium hydroxide solution was added dropwise to a solution of 17.5 g (0.045 mol) of **2**[3] in 175 ml of 10% sodium hydroxide. The precipitated product was collected on a filter and washed with 75 ml of cold 95% ethanol. Recrystallization of this solid from methanol afforded 20.0 g (98%) of **3** as white crystals, mp 143–144°.

Anal. Calcd for $C_8H_{13}HgIO$: C, 21.22; H, 2.89. Found: C, 21.66; H, 2.97.

2-Iodo-9-oxabicyclo[3.3.1]nonane (4).—To a solution of 4.5 g (0.01 mol) of **3** in 300 ml of carbon tetrachloride cooled to 0° under a nitrogen atmosphere was added 2.5 g (0.01 g-atom) of iodine. After the mixture had been stirred for 8 hr at room temperature, the salts were removed by filtration. The filtrate was decolorized with aqueous sodium thiosulfate, dried, and evaporated to afford 2.2 g of **4**. The nmr spectrum of **4** was characterized by a one-proton multiplet at δ 4.45–4.70, a two-proton multiplet at 3.75–4.15, and a ten-proton multiplet at 1.1–2.8.

Hydride Reduction of 4.—To a slurry of 0.4 g (0.01 mol) of lithium aluminum hydride in 25 ml of ether was added dropwise a solution of 2.5 g (0.01 mol) of **4** in 10 ml of anhydrous ether. The mixture was heated at reflux for 2 hr. After being stirred at ambient temperature overnight, the solution was cooled and treated successively with 0.4 ml of water, 0.4 ml of 25% sodium hydroxide solution, and 1.2 ml of water. After the addition of some anhydrous magnesium sulfate, the solids were separated by filtration and rinsed well with ether. The combined filtrates were evaporated and distilled to give 0.7 g (55%) of a crystalline distillate, bp 70–76° (20 mm). Vpc and nmr analysis demonstrated the presence in this solid of equal parts of **5** and **6**.

Authentic samples of **5** and **6** were prepared by the method of Bordwell and Douglass[3] and shown to be identical with the hydride reduction products.

Dehydrohalogenation of 4.—A solution of 2.1 g (8.33 mmol) of **4** in 25 ml of anhydrous tetrahydrofuran was cooled in ice while 1.03 g (9.2 mmol) of powdered potassium *t*-butoxide was added. The ice bath was removed after 30 min, and the mixture was stirred at room temperature for an additional 3.5 hr. The contents were poured into 300 ml of ice cold water and extracted with ether. Distillation of the dried ether solution gave 0.76 g (74%) of colorless oil. Vpc analysis (12 ft × 0.25 in. Al column packed with 15% FFAP on Chromosorb W at 130°) of this liquid indicated the presence of 6% **8** and 94% **7**. This was confirmed by nmr analysis.

Preparative scale vpc separation on the above column gave pure **7**: $\delta_{TMS}^{CDCl_3}$ 5.47–6.11 (m, 2, vinyl), 3.92–4.30 (br m, 2, CHO–), 2.30–2.88 (m, 1, allyl), 1.15–2.17 (m, 7, one allyl and methylene).

Anal. Calcd for $C_8H_{12}O$: C, 77.37; H, 9.74. Found: C, 77.21; H, 9.97.

The collected sample of **8** was identical in all respects with an authentic sample.[1,13]

(12) Determined by potassium *t*-butoxide induced dehydrohalogenation and vpc analysis of the mixture of **7** and **8**.

(13) A. C. Cope, M. A. McKervey, and N. M. Weinshenker, *ibid.*, **34**, 2229 (1969).

Hydrogenation of 7.—A solution of 50 mg of **7** in ~20 ml of ether was catalytically hydrogenated over Adams catalyst at room temperature. The catalyst was filtered and the product was isolated by preparative scale gas chromatography (32 mg). The substance was identical with 9-oxabicyclo[3.3.1]nonane (**5**).

Iododemercuration of 3 for Various Time Periods.—To determine the extent of isomerization of **4** as a function of time, **3** was treated as above with iodine for varying periods. The reaction mixture was divided in half; one half was dehydrohalogenated in the predescribed manner, and the second half was reduced with lithium aluminum hydride as outlined above. The product distribution results are tabulated in Table I.

Table I

Time, hr	Per cent composition[a] Dehydrohalogenation 7	8	Reduction 5	6
4	96	4	50	50
8	92	8	50	50
10	86	14	50	50
12	82	18	50	50

[a] Vpc analyses.

2-Iodo-9-oxabicyclo[4.2.1]nonane (11).—A solution of 4.5 g (0.01 mol) of mercurial iodide **10** and 2.5 g (0.01 g-atom) of iodine in 300 ml of carbon tetrachloride at 0° under a nitrogen atmosphere was stirred for 8 hr while slowly being allowed to come to room temperature. The salts were removed by filtration, and the filtrate was decolorized with aqueous sodium thiosulfate, dried, and concentrated to give 2.3 g (91%) of **11**. The nmr spectrum of **11** was characterized by a one-proton multiplet at δ 4.6–4.85, a two-proton multiplet at 3.95–4.55, and a ten-proton multiplet at 1.0–2.5.

Hydride Reduction of 11.—A solution containing 2.5 g (0.01 mol) of **11** in 10 ml of anhydrous ether was reduced with lithium aluminum hydride as described above to give 0.9 g (72%) of a single product, bp 74–76° (24 mm), mp 31°, which was identical in all respects with authentic 1,4-epoxycyclooctane.[3]

Dehydrohalogenation of 1.—A 2.0-g (7.95 mmol) sample of **11** was dehydrohalogenated as above with 1.02 g (9.0 mmol) of potassium *t*-butoxide in 25 ml of anhydrous tetrahydrofuran. There was obtained 750 mg (76%) of a colorless liquid, vpc analysis of which indicated the presence of **7** (15%) and **8** (85%).

Registry No.—**3**, 25662-59-3; **4a**, 25662-60-6; **4b**, 25662-61-7; **5**, 281-05-0; **6**, 284-20-8; **7**, 25665-25-2; **11a**, 25716-05-6; **11b**, 25662-62-8; lithium aluminum hydride, 16853-85-3.

Acknowledgment.—Support of this research by the donors of the Petroleum Research Fund, administered by the American Chemical Society, is acknowledged with gratitude.

Synthesis and Kinetics of Decomposition of Di-*t*-butyl Tricarbonate, Di-*t*-butyl Dithioltricarbonate, and the Related Dicarbonates[1]

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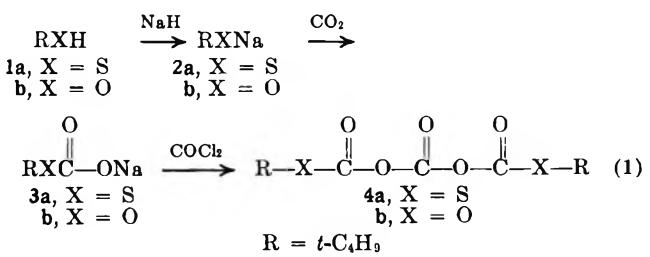
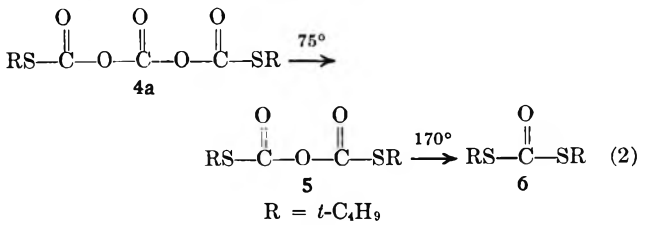
Received April 10, 1970

Details of the preparation of di-*t*-butyl dithioltricarbonate, $[(CH_3)_3C\text{–}S\text{–}CO_2\text{–}]_2CO$, and di-*t*-butyl tricarbonate by the action of phosgene on sodium *t*-butyl thiolcarbonate and potassium *t*-butyl carbonate are given. Both tricarbonates decompose when heated above their melting points, the former producing di-*t*-butyl dithioldicarbonate and carbon dioxide, and the latter fragmenting into isobutene, *t*-butyl alcohol, and three molecules of carbon dioxide. The decomposition of the di-*t*-butyl tricarbonate can be arrested at the dicarbonate stage by refluxing the tricarbonate in carbon tetrachloride in the presence of a trace of triethylamine. When heated di-*t*-butyl dicarbonate fragments into isobutene, *t*-butyl alcohol, and two molecules of carbon dioxide, whereas di-*t*-butyl dithioldicarbonate gives the corresponding monocarbonate. Kinetic studies on all of these decompositions in both decalin and chlorobenzene, following the reactions by infrared spectroscopy, have shown them all to be strictly first order, and activation parameters have been determined. The mechanisms of the processes have been discussed.

The action of phosgene on sodium *t*-butyl thiolcarbonate **3a** has been found to give di-*t*-butyl dithioltricarbonate[2] (eq 1) **4a** and by a similar procedure[3] di-*t*-butyl tricarbonate **4b** has been made from potassium *t*-butyl carbonate **3b**; both are crystalline compounds.



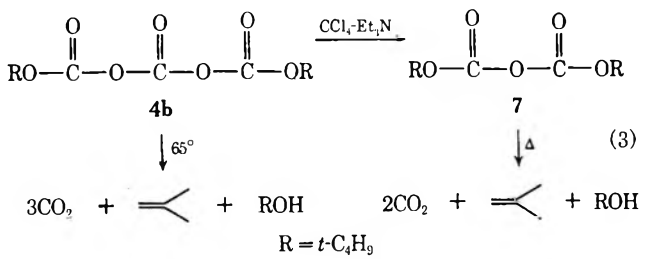
Several other oxygen tricarbonates **4b**, where R is isopropyl or other, were prepared but could not be obtained pure.[3] When heated above its melting point (71–72°) di-*t*-butyl dithioltricarbonate **4a** decomposes very rapidly with the loss of one molecule of carbon dioxide to give di-*t*-butyl dithioldicarbonate **5** which, if heated at 170° for 45 min, similarly loses carbon dioxide to yield di-*t*-butyl dithiolmonocarbonate[4] **6** (eq 2). The same results were observed when the decomposition was effected in decalin and chlorobenzene as solvents.



In contrast to the behavior of the dithiol tricarbonate **4a**, di-*t*-butyl tricarbonate **4b** when heated above its melting point (64.5–65°), fragments into three molecules of carbon dioxide, one molecule of isobutene, and

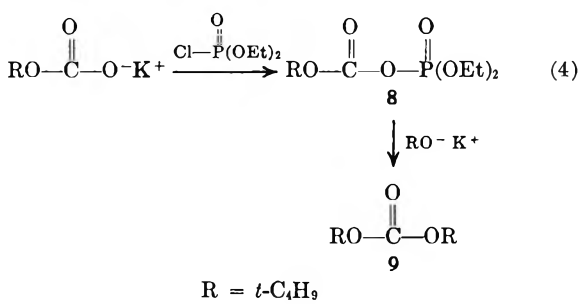
(1) Aided by Grant GP-7874 from the National Science Foundation.
(2) A. W. Friederang and D. S. Tarbell, *Tetrahedron Lett.*, 5535 (1968).
(3) C. S. Dean and D. S. Tarbell, *Chem. Commun.*, 728 (1969).
(4) D. S. Tarbell and L. Wei, *J. Org. Chem.*, **33**, 1884 (1968).

one molecule of *t*-butyl alcohol.[3,5] The same results were observed in both decalin and chlorobenzene as solvents. However, in refluxing carbon tetrachloride in the presence of a trace of triethylamine, the decomposition is arrested at the di-*t*-butyl dicarbonate[6,7] **7** stage. All attempts to convert the oxygen dicarbonate into the monocarbonate **9** were unsuccessful, the products being two molecules of carbon dioxide, one molecule of *t*-butyl alcohol, and one molecule of isobutene (eq 3). Further it appears that the di-*t*-



(3)

butyl monocarbonate[8] **9** does not function as an intermediate, because, when the dicarbonate is decomposed in the presence of the monocarbonate, the monocarbonate remains unchanged in all respects. An authentic sample of di-*t*-butyl monocarbonate **9** was obtained from *t*-butyl carbonic diethylphosphoric anhydride[9] **8**, by reaction with potassium *t*-butoxide (eq 4). *t*-Amyl *t*-butyl carbonate was prepared by the same procedure.



(4)

The present paper gives experimental details for the results previously reported[2,3] in preliminary form. It further reports kinetic studies of the transformation of di-*t*-butyl dithioltricarbonate **4a** to dicarbonate **5** and **5** to the monocarbonate **6**, and also the decomposition of di-*t*-butyl tricarbonate **4b** and of di-*t*-butyl dicarbonate **7** into their fragmentation products.

The reactions were readily followed by measuring the decrease in the infrared absorption of the selected carbonyl band. The results are tabulated in Table I. All the reactions gave good first-order constants up to 70–85% completion, and the first-order rate constants were essentially unchanged by a twofold increase in concentration. The rates of the reactions were not affected by the presence of the decomposition products. A typical rate run is shown in Table II.

Discussion of Kinetic Results.—As can be seen from Table I, the rates of decomposition of the dithiol tricarbonate **4a** (reaction A, Table I) and of the oxygen tricarbonate **4b** (reaction B, Table I) are considerably increased in changing from the nonpolar solvent, decalin, to the more polar chlorobenzene. This indicates that the transition states of the reactions have considerable ionic character. The data is given in Table III; all values but the last in this table were obtained by extrapolation from rate runs made at other temperatures using the temperature coefficients determined. It may

TABLE I

KINETICS OF DECOMPOSITION OF TRI- AND DICARBONATES

Temp, °C	Concn, *M*	First order $k \times 10^5$ sec^{-1}	$\Delta H^{\ddagger}$, kcal mol^{-1}	$\Delta S^{\ddagger}$, eu
A. RS—C(=O)—O—C(=O)—O—C(=O)—SR ⟶ RS—C(=O)—O—C(=O)—SR + CO_2				
In Decalin				
98.10	0.02716	2.66		
105.50	0.02520	6.20	28.14	−4.05
114.75	0.05200	14.4		
In Chlorobenzene				
62.80	0.02020	3.46		
72.25	0.02035	10.4	24.43	−5.96
82.35	0.02500	28.5		
82.35	0.05000	28.2		
B. RO—C(=O)—O—C(=O)—O—C(=O)—OR ⟶ $3CO_2$ + ROH + =<				
In Decalin				
101.77	0.02495	2.69		
110.35	0.02495	6.50		
114.35	0.02473	8.58	27.17	−7.22
114.35	0.05015	9.08		
116.60	0.02595	10.37		
120.95	0.02140	17.65		
In Chlorobenzene				
68.55	0.02534	5.67		
C. RS—C(=O)—O—C(=O)—SR ⟶ RS—C(=O)—SR + CO_2				
In Decalin				
144.15	0.02775	3.17	29.77	−8.60
151.75	0.02775	5.42		
159.95	0.02315	12.05		
D. RO—C(=O)—O—C(=O)—OR ⟶ $2CO_2$ + ROH + =<				
In Decalin				
143.30	0.02825	2.97		
149.35	0.02763	4.92		
157.81	0.02763	10.71	30.57	−6.53

TABLE II[a]

RS—C(=O)—O—C(=O)—O—C(=O)—SR ⟶ RS—C(=O)—O—C(=O)—SR + CO_2

Time × 10^{-2} sec	OD_t	Log $\frac{OD_t}{OD_0}$	% reaction	First order $k \times 10^5$ sec^{-1}
0	0.4366	0	0	
7.2	0.4013	−0.0367	8.085	11.74
18.0	0.3636	−0.0795	16.72	10.17
36.0	0.3034	−0.1581	30.51	10.11
72.0	0.2068	−0.3245	52.63	10.38
159.6	0.0810	−0.7316	81.45	10.57

[a] Temp, 72.25°; solvent, chlorobenzene; ir band, 1840 cm^{-1}.

(5) For cleavage of *t*-butyl esters, see R. Altschul, *J. Amer. Chem. Soc.*, **68**, 2605 (1946), and references therein. For synthetic application, see G. S. Fonken and W. S. Johnson, *ibid.*, **74**, 831 (1952).

(6) J. W. Howe and L. R. Morris, *J. Org. Chem.*, **27**, 1901 (1962).

(7) W. Thoma and H. Rinke, *Justus Liebigs Ann. Chem.*, **624**, 31 (1959).

(8) A. R. Choppin and J. W. Rogers, *J. Amer. Chem. Soc.*, **70**, 2967 (1948).

(9) M. A. Insalaco and D. S. Tarbell, *Proc. Nat. Acad. Sci. U. S.*, **57**, 233 (1967).

TABLE III
COMPARISON OF REACTION RATES IN DECALIN AND CHLOROBENZENE AT 68.55°

Reaction	Solvent	First order $k \times 10^7$ sec^{-1}
A[a]	Decalin	9.34
A	Chlorobenzene	671
B	Decalin	6.98
B	Chlorobenzene	567

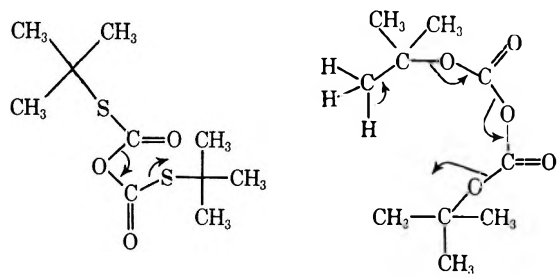
[a] Table I.

also be noted that the rates of decomposition for both tricarbonates are essentially similar in decalin and also in chlorobenzene as are their activation parameters in decalin. This would suggest that the slow step in both decomposition reactions, as well as being first order, is the same mechanistically.

The reaction of aninile with both di-*t*-butyl dithioltricarbonate **4a** and di-*t*-butyl tricarbonate **4b** yields diphenylurea. Further work on the reaction of several aromatic amines (to be reported later) has shown that attack of the amines on the tricarbonates is at the central carbonyl group.[10] Nucleophilic attack at either of the other two equivalent carbonyls would be expected to produce the corresponding carbamates, N-phenyl-*t*-butyl thiolcarbamate[11] or N-phenyl-*t*-butyl carbamate[8], as primary products, both of which are stable compounds. Since no such compounds were isolated it may be inferred that the effect of the triethylamine in arresting the decomposition of di-*t*-butyl tricarbonate at the dicarbonate stage is brought about by an association of the tertiary amine moiety at the central carbonyl group, which in some way stabilizes the reactive intermediate long enough for the dicarbonate to form. Hence we may conclude that the slow step involves the loss of the middle carbonyl group in both cases. Further, since the rate of decomposition of di-*t*-butyl dicarbonate into its fragmentation products is much slower than the rate of decomposition of the tricarbonate, the dicarbonate does not function as an intermediate in the latter process.

The formation of isobutene in the decomposition of di-*t*-butyl tricarbonate and di-*t*-butyl dicarbonate illustrates the ready ability of *t*-butyl oxygen compounds to form *t*-butyl carbonium ions and emphasizes the well-known failure of *t*-butyl thiol compounds to reciprocate this behavior[4,5,12,13] and it may well be this behavior which causes the di-*t*-butyl tricarbonate and dicarbonate to fragment, rather than lose one molecule of carbon dioxide, as is the case with the sulfur analogs.

From the activation parameters for the decomposition of di-*t*-butyl dithioldicarbonate and di-*t*-butyl dicarbonate ($\Delta H^{\ddagger}$ 29.77 and 30.57 kcal mol^{-1}, and $\Delta S^{\ddagger}$ −8.60 and −6.53 eu), coupled with the fact that their rate constants are almost the same, it would seem that the slow step is mechanistically the same. Whereas the decomposition of the dithiol dicarbonate **5** produces the corresponding monocarbonate, in the case of the oxygen di-*t*-butyl dicarbonate **7** none of the corresponding monocarbonate is produced, nor does it function as an intermediate. This would indicate that the first and slow step in both decompositions is the breaking of a C–O bond, the di-*t*-butyl dicarbonate then going on to form its fragmentation products on account of the ready ability of *t*-butyl oxygen compounds to generate *t*-butyl carbonium ions, and the di-*t*-butyl dithioldicarbonate stopping at the monocarbonate stage. Whereas this process is probably an ionic dissociation process, a cyclic transition state as depicted below cannot be ruled out.



The tricarbonates are a new class of compounds, and there are no close mechanistic analogies. The dicarbonates **5** and **7** are related to the *t*-butylcarbonic[12] and thiolcarbonic anhydrides[4,13] previously studied in these laboratories. Many cases of carbon dioxide evolution which have received detailed kinetic study have involved peroxide derivatives decomposing by a free-radical path.[14] The large solvent effect in the present case indicates a considerable polar character in the transition state.[15] The intensively studied decarboxylation reactions of malonate and β-keto esters[16] do not present many points of similarity to the reactions described in the present paper.

Experimental Section[17]

Di-*t*-butyl Tricarbonate (4b).—Dry carbon dioxide was passed through an ice-cold solution of potassium *t*-butoxide (11.2 g, 0.1 mol) in THF (200 ml, distilled from aluminohydride) with vigorous stirring for 1 hr. Phosgene was then passed into the resulting white gel for 1–1.5 hr with vigorous stirring while the temperature was maintained below 0° (acetone–Dry Ice). The resulting solution was stirred for 1 hr more, again below 0°, and then dry nitrogen was passed through for 1 hr to remove excess phosgene. The bulk of the solvent was removed on a rotary evaporator, at 0° and water pump pressure, and the residue taken up in ice-cold pentane. The precipitated potassium chloride was filtered off and the filtrate evaporated under vacuum at 0° to give a pale yellow oil which crystallized on standing. Recrystallization from pentane gave 6.6 g (50%) of white needles, mp 64.5–65°. The ir spectrum (CCl_4) showed carbonyl absorptions at 1845, 1810, and 1780 cm^{-1} and the nmr spectrum showed a singlet at 1.66 ppm.

(10) Diphenyl triketone [J. D. Roberts, D. R. Smith, and C. C. Lee, *J. Amer. Chem. Soc.*, **73**, 618, 5927 (1951)] loses its central carbonyl group, under a variety of conditions, as CO or CO_2, with formation of benzoin or benzil.

(11) E. Dyer and J. F. Glenn, *ibid.*, **79**, 366 (1957).

(12) C. J. Michejda and D. S. Tarbell, *J. Org. Chem.*, **29**, 1168 (1964).

(13) T. Parasaran and D. S. Tarbell, *ibid.*, **29**, 2471 (1964).

(14) P. D. Bartlett and R. E. Pincock, *J. Amer. Chem. Soc.*, **82**, 1769 (1960), and earlier papers; T. Koenig and R. Cruthoff, *ibid.*, **91**, 2562 (1969); J. W. Taylor and J. C. Martin, *ibid.*, **89**, 6904 (1967), and earlier papers.

(15) *Cf.* S. J. Rhoads and R. E. Michel, *ibid.*, **85**, 585 (1963).

(16) For leading references, see B. R. Brown, *Quart. Rev. (London)*, **5**, 131 (1951); E. J. Corey, *J. Amer. Chem. Soc.*, **75**, 1163 (1953); R. Steinberger and F. H. Westheimer, *ibid.*, **73**, 429 (1951).

(17) Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. All melting points and boiling points are uncorrected unless otherwise specified. Infrared spectra were recorded on a Beckman IR-10 or a Perkin-Elmer 621 spectrometer. The nmr spectra were recorded on a Varian A-60 spectrometer using TMS as an internal standard. Temperature control in the kinetic experiments was achieved by the use of an E. H. Sargent Co. mercury capillary thermoregulator. The temperatures at which the kinetic runs were performed are corrected by calibration against a Dymec Model DY-2801 A quartz thermometer (Hewlett-Packard, Dymec Division, Palo Alto, Calif.).

Anal. Calcd for $C_{11}H_{18}O_7$: C, 50.39; H, 6.92; mol wt, 262. Found: C, 50.71; H, 7.04; mol wt, 270.

Di-*t*-butyl Dicarbonate (7).—Di-*t*-butyl tricarbonate (0.9 g) and triethylamine (5 drops) in 50 ml of dry carbon tetrachloride were refluxed until the ir spectrum of an aliquot indicated that no tricarbonate remained (~30 min). Removal of the solvent at reduced pressure gave 600 mg (81%) of colorless mobile dicarbonate: bp 64° (1.0 mm), mp 23°; lit.[6] bp 56–57° (0.5 mm), mp 21–22°. The ir spectrum showed carbonyl absorptions at 1820 and 1765 cm^{-1} and the nmr spectrum showed a singlet at 1.61 ppm.

A second run was made in order to determine the quantity of carbon dioxide evolved. The apparatus consisted of a side-arm round bottomed flask equipped with a condenser attached to the top of which were two tubes, connected in series, containing ascarite. The tricarbonate (0.897 g) and 5 drops of triethylamine in 50 ml of dry carbon tetrachloride were placed in the flask and a stream of pure dry nitrogen passed through the apparatus slowly *via* the side arm. (The nitrogen was passed through a third tube of ascarite prior to entry into the apparatus.) The passage of nitrogen was continued for 2 hr and then for further 0.5-hr periods until the weight of the two ascarite tubes attached to the top of the condenser remained constant. The decomposition flask was immersed in an oil bath and heated at approximately 70° for 2 hr. After this initial period the ascarite tubes were weighed at 30-min intervals until their weights remained constant. The weight of carbon dioxide evolved was 120 mg (94% of 1 mol). Work-up of the carbon tetrachloride solution gave 600 mg (81%) of the colorless dicarbonate, mp 23°, bp 64° (1.0 mm).

Thermal Decomposition of Di-*t*-butyl Tricarbonate in the Absence of Solvent.—The tricarbonate (0.572 g, 0.00214 mol) was decomposed at 90–100° exactly as described above. The apparatus also incorporated a Dry Ice–acetone trap containing a solution of bromine in dry chloroform to estimate the isobutene. At the end of the experiment the contents of the trap were evaporated to yield 245 mg (90%) of a pale yellow liquid, bp 149°. Its nmr spectrum was identical with that of 1,2-dibromo-2-methylpropane. The residue in the decomposition flask, 125 mg (76%), bp 82°, had an ir spectrum identical with that of *t*-butyl alcohol. The weight of carbon dioxide evolved was 265 mg (93% of 3 mol).

Thermal Decomposition of Di-*t*-butyl Dicarbonate. A. In the Absence of Solvent.—In the apparatus described above 240 mg (0.001 mol) of di-*t*-butyl dicarbonate was decomposed at 130–140° to give isobutene, *t*-butyl alcohol (not estimated), and carbon dioxide (107 mg, 110% of 2 mol).

B. In Solvent.—In an attempt to isolate di-*t*-butyl monocarbonate, a number of runs were made using various solvents (decalin, chlorobenzene, *o*-dichlorobenzene) and catalysts (N-methylpiperidine, benzoyl peroxide) at various temperatures. In all cases, the dicarbonate decomposed to carbon dioxide, isobutene, and *t*-butyl alcohol. The dicarbonate (282 mg) plus 3 drops of N-methylpiperidine in 10 ml of o-dichlorobenzene was heated at 140° in the usual apparatus. Carbon dioxide (114 mg, 104% of 2 mol) was evolved.

C. In the Presence of Di-*t*-butyl Monocarbonate.—Di-*t*-butyl monocarbonate 9 (100 mg) and di-*t*-butyl dicarbonate (100 mg) in 6 ml of pure chlorobenzene were heated at 130–150°. After 1 hr, the dicarbonate absorption in the ir had partially disappeared (40%). After 2 hr the dicarbonate had almost disappeared but the monocarbonate absorptions remained. Removal of the solvent gave unchanged monocarbonate.

Di-*t*-butyl Monocarbonate (9).—A solution of 5.6 g (0.05 mol) of potassium *t*-butoxide in 150 ml of THF was carbonated as described previously. A solution of diethyl chlorophosphate, 8.6 g (0.05 mol) in 30 ml of THF, was added dropwise with stirring over a period of 60 min to the resulting ice cooled gel. The resulting gelatinous, turbid solution was stirred at 0° for a further hour. A solution of 5.6 g of potassium *t*-butoxide in 50 ml of THF was added dropwise with stirring at 0° over a period of 1 hr and the resulting slurry allowed to stir at room temperature overnight. Filtration followed by removal of the solvent at reduced pressure and ambient temperature gave a pale yellow oil. Distillation gave 3.5 g (40%) of colorless mobile di-*t*-butyl monocarbonate, bp 46–50° (1.0 mm), which crystallized on standing. Recrystallization from EtOH–H_2O gave white prisms, mp 40–41° [reported[8] bp 158° (767 mm), mp 39.5–40.5°]. The ir spectrum showed absorption at 1760 cm^{-1} and the nmr showed a singlet at 1.42 ppm. A second fraction, diethyl *t*-butyl phosphate, bp 72° (1 mm), was also collected. A stream of dry nitrogen was passed through the apparatus for the duration of the experiment.

t-Amyl *t*-butyl monocarbonate has been prepared using this method in 60% yield as a colorless mobile liquid, bp 106–109° (6.3–6.5 mm). The nmr spectrum is in agreement with the assigned structure.

Di-*t*-butyl Dithioltricarbonate[2] (4a).—A 50% suspension of sodium hydride in mineral oil (2.5 g, 0.0543 mol) was washed with three 30-ml portions of pure THF to remove the mineral oil. The washed sodium hydride was placed in 250 ml of pure THF and a solution of *t*-butyl mercaptan (4.5 g, 0.05 mol) was added dropwise over a period of 15 min to the stirred suspension under nitrogen. The mixture was then refluxed for 1 hr resulting in the formation of a thick white slurry. This was cooled in a Dry Ice–acetone bath and dry carbon dioxide passed through with vigorous stirring for 3 hr. Phosgene was passed through the resulting colorless gel for 1 hr. A turbid solution formed which was stirred for a further hour and then the excess phosgene was removed by passing dry nitrogen through the solution. The temperature was allowed to warm to 0° and the bulk of the solvent was removed under reduced pressure at this temperature. The addition of ice-cold pentane caused the precipitation of sodium chloride, which was filtered off. Evaporation of the filtrate at 0° gave a pale yellow oil, which crystallized on standing. Recrystallization from pentane yielded 3.7 g (50%) of colorless needles, mp 71–72°. The nmr spectrum showed a singlet at 1.55 ppm. The elemental analysis has been reported previously.[2] Di-*t*-butyl dithioldicarbonate 5 and di-*t*-butyl dithiolmonocarbonate 6 were obtained as previously described.[2]

Reaction of Di-*t*-butyl Dithioltricarbonate with Aniline.—A solution of 150 mg (0.0016 mol) of freshly distilled aniline in 3 ml of carbon tetrachloride was added to a solution of 150 mg (0.00051 mol) of di-*t*-butyl dithioltricarbonate in 3 ml of carbon tetrachloride at 0°. The reactants were allowed to warm to room temperature and stand for 1 hr. A white precipitate formed shortly after the addition was complete. Filtration gave 100 mg (theoretical yield, 92 mg) of amide product, mp 241–242°, whose ir spectrum was identical with that of diphenylurea. Recrystallization from EtOH–H_2O gave white needles, mp 241–242°. Nothing was isolated from the filtrate.

Reaction of Di-*t*-butyl Tricarbonate with Aniline.—Aniline (50 mg, 0.0054 mol) was added to a solution of 34 mg (0.00013 mol) of the tricarbonate in 4.5 ml of decalin at room temperature. A crystalline white solid appeared after several minutes. Filtration gave 20 mg (82%) of white needles, mp 241–242°, which were identical with diphenylurea.

Kinetic Studies. Purification of Solvents. A. Decalin.—The Eastman Kodak Practical sample was stirred with concentrated H_2SO_4 for 12 hr. The organic phase was separated, washed with water, with saturated Na_2CO_3, again with water, dried with CaH_2, filtered, and fractionally distilled through a 30-cm Vigreux column. The fraction boiling at 191–192° was collected, $n^{20}D$ 1.4774 (lit.[18] *cis* isomer, $n^{20}D$ 1.48113; *trans* isomer, $n^{20}D$ 1.46968).

B. Chlorobenzene.—The "Baker Analyzed" reagent was washed several times with concentrated H_2SO_4, then with aqueous Na_2CO_3 and water, and dried with $CaCl_2$ and then P_2O_5. The sample was fractionally distilled twice through a 30-cm Vigreux column and the fraction boiling at 128–129° was collected, $n^{20}D$ 1.5244 (lit.[19] $n^{20}D$ 1.5248).

The kinetic runs were done in a constant temperature bath controlled to within ±0.1°.

Pyrex tubes of 8-mm i.d. were cleaned thoroughly by soaking in concentrated H_2SO_4 for 24 hr and then rinsing with water, dilute NH_4OH, water, and then several times with distilled water. Tubes of 20-cm length were drawn out and pulled thin at 16-cm length for convenient sealing. The tubes were dried in an oven at *ca.* 100° for at least 12 hr.

Stock solutions of di-*t*-butyltricarbonate and di-*t*-butyl dithioltricarbonate, which had been recrystallized prior to the kinetic runs and always had a melting range of less than 1°, and di-*t*-butyldicarbonate and di-*t*-butyl dithioldicarbonate which had been purified by distillation, were prepared from weighed samples.

Into each tube, 1 ml of stock solution was transferred with a syringe. The solution was degassed, the tubes were flushed with nitrogen and sealed and stored in Dry Ice until the kinetic runs

(18) W. F. Seyer and R. D. Walker, *J. Amer. Chem. Soc.*, **60**, 2125 (1938).

(19) D. D. Perrin, W. L. F. Amerigo, and D. R. Perrin "Purification of Laboratory Chemicals," Pergamon Press, 1966, p 108.

were done. Generally, eight to ten tubes were prepared for each run. The tubes were placed in a metal rack which was then immersed in the thermostated Ucon oil bath (each tube was immersed up to 13 cm). It usually took 1.5–2.5 min for the temperature of the solution to reach equilibrium with the bath temperature. This was taken as the zero time of the reaction; one tube was withdrawn and immersed immediately in a Dry Ice–acetone bath as the zero time. The other tubes were withdrawn at suitable time intervals in the same way. The last tube was usually removed after about three half-lives of the reaction. The tubes were stored in Dry Ice until the ir analyses could be effected.

Analyses of the Kinetic Runs by Infrared Spectroscopy and Treatment of the Data.—The rate of thermal decomposition was followed by measuring the decrease in absorbance of the selected carbonyl band, Table IV, using a Perkin-Elmer Model 621

TABLE IV

Compd	Solvent	Band used, cm^{-1}
Di-*t*-butyl dithioltricarbonate	Chlorobenzene	1840
Di-*t*-butyl dithioltricarbonate	Decalin	1837
Di-*t*-butyl dithioldicarbonate	Decalin	1773
Di-*t*-butyl tricarbonate	Chlorobenzene	1870
Di-*t*-butyl tricarbonate	Decalin	1805
Di-*t*-butyl dicarbonate	Decalin	1775

infrared spectrometer[20] and KBr cells of 0.5-mm thickness. Beer's law was shown to be followed in all cases where the initial concentration of the tricarbonate or dicarbonate was less than 4×10^{-2} mol.

The spectrum was scanned two to three times in the region of 1950–1650 cm^{-1}. The same procedure was used for all the kinetic runs. Transmittance (T_0 and T_{100}) were adjusted at the carbonyl maximum of the band measured when both cells were filled with pure solvent. To avoid the possibility of setting the pen against the mechanical stop, zero transmittance was set at 0–5% and 100% was set at 95–100%. The true per cent transmittance, T_X, of a sample was thus calculated from the observed transmittance, T_{obsd}, $T_X = (T_{obsd} - T_0)/(T - T_0)$. Each time the sample cell was cleaned with spectroscopic grade carbon tetrachloride and dried under a stream of air, and rinsed two or three times with the sample solution which was warmed to room temperature before analysis.

Generally in the region of 20–80% transmittance, the transmittance could be determined with an accuracy of ±0.3%. Therefore the tricarbonate and dicarbonate solutions were made up at (or uniformly diluted to) such a concentration that the zero time would be around 20–30% and thus two to three half-lives transmittance would be around 80%. From the per cent transmittance, the optical density at time t was obtained, and first-order rate constants were determined from the slope of the first-order plots of log OD_t/OD_0 against time. The activation parameters were calculated from the Eyring equation in the usual way.[21]

The enthalpy of activation, $\Delta H^{\ddagger}$, was obtained at 100° from the Arrhenius energy of activation which was determined from the slope through the points on a plot of log k against $1/T$. The entropy of activation, $\Delta S^{\ddagger}$, was calculated at 100° by substituting the known value of $\Delta H^{\ddagger}$ into the equation.

Registry No.—**4a**, 22085-39-8; **4b**, 24424-95-1.

(20) *Cf.* P. D. Bartlett and R. R. Hiatt, *J. Amer. Chem. Soc.*, **80**, 1398 (1958).

(21) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," Wiley, New York, N. Y., 1961, p 98.

Phenyl Migration in Pseudohalogen Additions to 3,3,3-Triphenylpropene[1]

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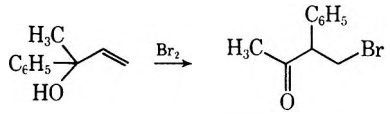
Addition of iodine azide (IN_3) to tritylethylene (1), unlike to *t*-butylethylene, leads to complete rearrangement producing 3-azido-2,3,3-triphenyl-1-propyl iodide (2) in 99% yield. Treatment of 2 with potassium *t*-butoxide gave triphenylacrolein. Under milder conditions it was possible to isolate an intermediate allylic azide. A rearranged product was also noted on iodine isocyanate addition to 1. Similarly, benzonorbornadiene gave a 1,3 adduct resulting from a Wagner–Meerwein phenyl migration and methylenenorbornene produced a rearranged IN_3 adduct.

Though electrophilic addition of halogens to terpene olefins often leads to rearrangement of the carbon skeleton,[2] there are reported only few instances of alkyl migration occurring during halogen additions to acyclic olefins. A favorable case such as *t*-butylethylene, for example, which gives 60% methyl migration in HCl addition, renders no rearranged products when Cl_2, Br_2, or IN_3 is added to it under ionic conditions.[3] The first example of rearrangement in an acyclic system appears to be the Cl_2 addition to *trans*-di-*t*-butylethylene.[4]

Many more examples exist for phenyl migration. Although addition of HBr in acetic acid to allylbenzene gives only the normal adduct in 92% yield,[5] the presence of two of three allylic phenyl groups or of a hydroxy group augments rearrangement by stabilizing the carbonium ion resulting from phenyl migration.[6,7] Such an example is shown below for bromine addition to 2-phenyl-3-buten-2-ol.



Recent studies on the reaction of olefins with iodine azide (IN_3) revealed that such additions occur with a remarkably high degree of stereo- and regioselectivity,[8] suggesting a three-membered ring iodonium ion intermediate. Thus *n*-butylethylene adds IN_3 to yield 2-

(1) Stereochemistry. LIV. For the previous paper in this series, see A. Hassner, F. P. Boerwinkle, and A. B. Levy, *J. Amer. Chem. Soc.*, **92**, 4879 (1970).

(2) See, for instance, H. Kwart, *ibid.*, **75**, 5942 (1953); L. Kaplan, H. Kwart, and P. von R. Schleyer, *ibid.*, **82**, 2341 (1960).

(3) (a) G. C Ecke, N. E. Cook, and F. C. Whitmore, *ibid.*, **72**, 1511 (1950); (b) W. H. Puterbaugh and M. S. Newman, *ibid.*, **79**, 3469 (1957); (c) A. Hassner and F. W. Fowler, *J. Org. Chem.*, **32**, 2686 (1968).

(4) W. H. Puterbaugh and M. S. Newman, *ibid.*, **81**, 1611 (1959).

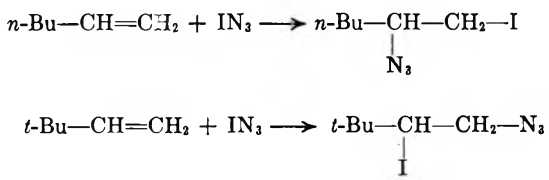
(5) H. E. Carter, *J. Biol. Chem.*, **108**, 619 (1935).

(6) I. V. Bodrikov, V. R. Karwashov, and T. I. Temikova, *Russ. J. Org. Chem.*, **3**, 1640 (1967).

(7) While this work was in progress the addition of bromine to 1 was reported by R. O. C. Norman and C. B. Thomas, *J. Chem. Soc. B*, 598 (1967).

(8) *Regio* is used to describe directional effects in bond making and breaking: A. Hassner, *J. Org. Chem.*, **33**, 2684 (1968).

azidohexyl iodide, whereas *t*-butylethylene gives a non-rearranged product of opposite regiochemistry.[3c]



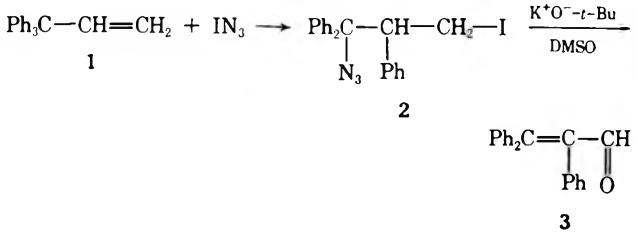
The greater stability of a three-membered-ring iodonium *vs.* bromonium ion was suggested by the stereospecific anti addition of IN_3 to *cis*-β-deuteriostyrene as contrasted to the stereorandom addition of BrN_3 to this olefin.[9a]

It was therefore of interest to determine whether phenyl migration will occur with opening of an iodonium ion. The foregoing considerations prompted us to investigate the behavior of tritylethylene (3,3,3-triphenylpropene, **1**) toward IN_3 and INCO.

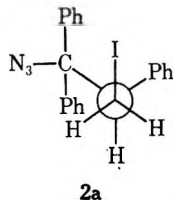
Results and Discussion

When 3,3,3-triphenylpropene (**1**) was added to a solution of IN_3 in acetonitrile, the 1,3 adduct, 3-azido-2,3,3-triphenyl-1-propyl iodide (**2**), was obtained in 99% yield. The evidence for this structure is as follows. The mass spectrum of **2** shows a base peak at *m/e* 180 ($Ph_2C{=}N^+$) and a smaller peak at 208 ($Ph_2C^+{-}N_3$), whereas the 1,2-dibromide of **1** has its base peak at 243 (Ph_3C^+). Though phenyl migrations can occur in the mass spectrometer, such rearrangements should not account for the base peak. The nmr spectrum of adduct **2** shows aromatic peak areas in a ratio of 13:2, the two low field protons presumably belonging to the migrated phenyl group. This phenomenon also has been noted by Norman, *et al.*,[7] for the rearranged 1,3-bromomethoxide formed by the addition of Br_2 to **1** in methanol.

Finally, treatment of **2** with potassium *t*-butoxide in ether or with tertiary amines in acetone, a general reaction for 1,2-iodoalkyl azides,[3c] failed to cause HI elimination. When the solvent was dimethyl sulfoxide, however, an immediate color change was observed and nitrogen gas was evolved. The product formed in 82% yield, proved to be triphenylacrolein (**3**), identified by

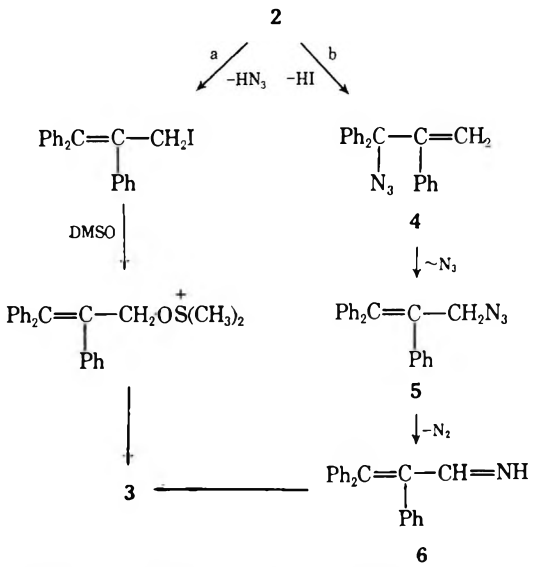


its nmr spectrum, melting point, and 2,4-dinitrophenylhydrazone derivative. The low reactivity of alkyl iodide **2** toward base can be attributed either to the high degree of steric interaction in the conformer **2a** leading to anti elimination of HI or to steric hindrance in the approach of *t*-butoxide to **2**.



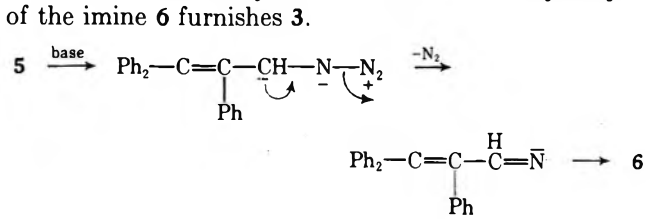
2a

Two plausible pathways are suggested below for the transformation of **2** to **3**.

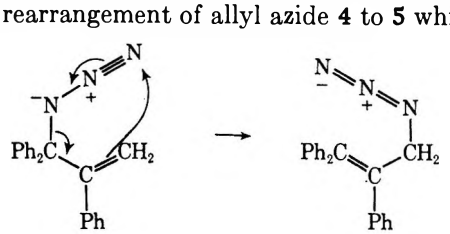


Differentiation between these paths became possible by carrying out the reaction in ether–DMSO (82:18) at 0°, in which case intermediate **5** was isolated.[9b] This azide, a stable white solid, was identified by nmr which shows three singlets in the aromatic region (5:5:5 protons) and one at τ 5.88 (two protons). Its uv spectrum indicated extensive conjugation at 276 nm (ε 16,700). By comparison, α-methyl-β-phenylstilbene has a maximum at 275 nm (ε 10,000). Further proof for structure **5** was furnished by its synthesis from allyl bromide **10** with NaN_3.

Treatment of **5** with potassium *t*-butoxide in DMSO gave **3** and 1 equiv of N_2 was collected during the reaction. This transformation which requires the presence of base, apparently involves proton abstraction from **5** and loss of N_2 to yield the anion of **6**. Hydrolysis of the imine **6** furnishes **3**.



The other interesting feature in the conversion of **2** to **3** is the rearrangement of allyl azide **4** to **5** which prob-

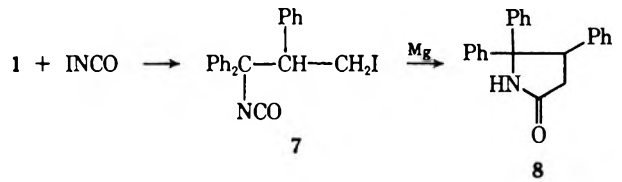


4 **5**

(9) (a) See Hassner, *et al.*,[1] and references cited. (b) The well-known conversion of alkyl halides to aldehydes by means of DMSO (path a) [N. Kornblum, W. J. Jones, and G. J. Anderson, *J. Amer. Chem. Soc.*, **81**, 4113 (1959)], is not followed in this case and instead dehydroiodination in being facilitated by the polar solvent.

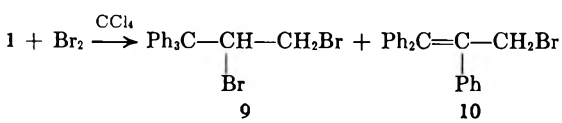
ably involves a concerted migration of the azide function leading to the more substituted olefin.[10]

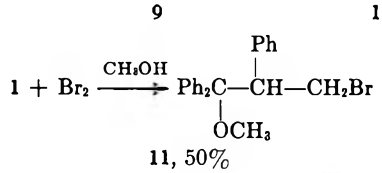
Addition of iodine isocyanate to triphenylpropene **1** in ether led to an adduct in 60–75% yield, to which structure **7** is assigned by analogy with **2** and on the basis that, as a hindered tertiary isocyanate, **7** showed a low reactivity toward methanol in the presence of $LiOCH_3$.[11]



Treatment of **7** with magnesium in ether, after initiation of the Grignard reaction with methyl iodide, furnished lactam **8**. The γ-lactam structure, rather than a β-lactam which could have arisen from intramolecular cyclization of a 1,2-INCO adduct, was apparent from the characteristic carbonyl stretching frequency at 1695 cm^{-1}.

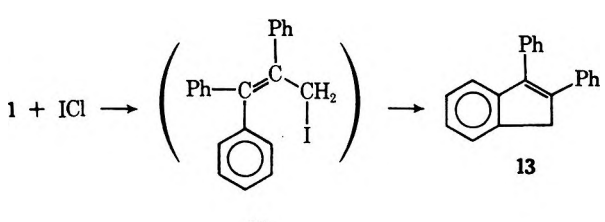
It is useful to contrast the addition of the nitrogen containing pseudohalogens IN_3 and INCO to that of Br_2. In an extensive investigation of **1** and related systems, Norman and coworkers[7] found that bromine addition to **1** in CCl_4 led to the 1,2 adduct **9** and the allylic bromide **10** in a ratio of 4:6. The allylic bromide presumably arose from dehydrobromination of a





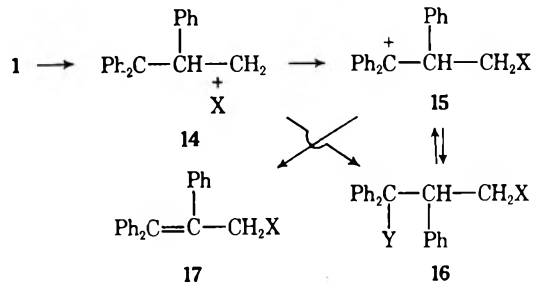
primarily formed 1,3-dibromo adduct. In the presence of methanol a rearranged 1,3 adduct **11** was obtained in 50% yield.

It was therefore of interest to determine which course the addition of ICl to triphenylpropene **1** would take. The reaction proceeded readily in either acetonitrile or ether to produce 2,3-diphenylindene (**13**), which most likely resulted from the allyl iodide **12** by solvolytic



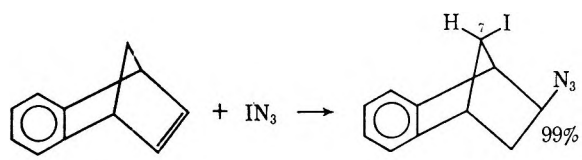
ring closure. Indene **13** was also formed in the attempted Prevost reaction (I_2–AgOAc) on **1**.[12]

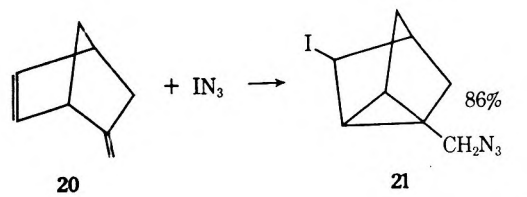
It is clear that in the various additions to triphenylpropene **1**, phenyl migration leads to opening of the halonium ion **14**. This can occur either with formation of a carbonium ion **15** or of a bridged phenonium ion, or in a concerted manner with the nucleophile Y^- forming a bond as the phenyl group migrates. When Y^- is azide or isocyanate ion the adduct **16** is formed irreversibly whereas in most other cases olefin **17** is formed



either directly from **15** or after an equilibrium between **15** and **16** has been established. Opening of the three-membered-ring iodonium ion by phenyl migration is enhanced by the relief of steric crowding of the three phenyl groups and stabilization of a full or incipient positive charge in the transition state by two phenyl groups.

Further examples of rearrangements during IN_3 addition are provided by benzonorbornadiene (**18**) and methylenenorbornene (**20**). The 1,3 adduct **19**, formed in quantitative yield, shows a quintet at τ 5.96 (*syn* H at C-7) diagnostic of an *exo*-5,*anti*-7-dihalobenzonorbornene system.[13] The formation of the *exo* isomer **19** suggests a concerted opening of an initially formed





three-membered-ring iodonium ion or involvement of a stabilized nonclassical carbonium ion. The product of IN_3 addition to **20** was an oil that readily decomposed at room temperature. It showed an $(M - 127)^+$ instead of an M^+ peak in its mass spectrum and in the nmr singlets at τ 6.1 (CH-I) and 6.53 (CH_2–N_3) and a multiplet at 7.8–9.1 (integrating for 7 H), consistent with structure **21** or with a regioisomeric nortricyclene. Structure **21** is favored by analogy with the INCO adduct of **20**.[14]

(10) A. Gagneux, S. Winstein, and W. G. Yound, *J. Amer. Chem. Soc.*, **82**, 5956 (1960).

(11) A. Hassner, M. E. Lorber, and C. Heathcock, *J. Org. Chem.*, **32**, 540 (1967).

(12) R. O. C. Norman and C. B. Thomas, *J. Chem. Soc. B*, 604 (1967).

(13) S. J. Cristol and G. W. Nachtigall, *J. Org. Chem.*, **32**, 3738 (1967).

(14) A. Hassner, R. P. Hoblitt, C. Heathcock, J. E. Kropp, and M. E. Lorber, *J. Amer. Chem. Soc.*, **92**, 1326 (1970).

Experimental Section[15]

3,3,3-Triphenylpropene (1).—This compound was prepared from β,β,β-triphenylpropionic acid by modification of reported procedures.[16] A mixture of 160 ml of *t*-butyl alcohol and 16.5 g (0.422 mol, 4.6 equiv of 2 *N* base) of potassium was heated cautiously under reflux and 35.5 g (0.092 mol) of finely ground 3,3,3-triphenyl-1-propyl iodide (mp 174–177°) was added. The heterogeneous mixture was stirred at reflux for 4.5 days (until the melting point of the solid obtained from work-up of aliquots was 74–78°), and quenched in 300 ml of ice water. Three benzene extracts were combined and washed with water until neutral. After drying ($MgSO_4$), evaporation gave 24.0 g (93%) of the crude solid, mp 74–80°. Recrystallized from methanol it furnished 21.5 g (90%) of pure 3,3,3-triphenylpropene (1), mp 80–81° (lit.[16a] 78–78.8°). The nmr and ir spectra were consistent with those reported.[7]

General Procedure for Iodine Azide Additions.—Using a modification of the reported procedure,[17] a 100-ml three-necked round-bottom flask fitted with a reflux condenser, drying tube, and a mechanical stirrer was predried and charged with 2.60 g (40 mmol) of sodium azide and 30 ml of acetonitrile. The flask was covered with foil and stirred in an ice bath during the slow addition of 4.88 g (30 mmol) iodine monochloride using a weighed 2-ml syringe with a Luer–Lok fitting. The mixture was stirred 10–15 min, 20 mmol of the olefin was added, and the ice bath was removed. After stirring for 18–26 hr, the solution was forced with air through Celite 545 in a coarse sintered glass funnel into 50-ml of saturated (50% w/v) sodium bisulfite solution in a 125-ml separatory funnel. Addition of 25 ml of ether and shaking gave a clear ethereal layer which was forced through magnesium sulfate into a tared flask and the solvent removed by rotary evaporation. The adduct was usually obtained as a slightly orange oil.

3-Azido-2,3,3-triphenyl-1-propyl Iodide (2).—Using the general procedure the adduct of 1 was obtained in 99% yield (8.44 g). The oily pale orange adduct solidified on exposure to a stream of air overnight, mp 91–100°. Recrystallization from methanol gave pale yellow crystals: mp 104–106°; ir (neat oil) 2105 (N_3, s), 580 cm^{-1} (C–I, m); nmr τ 6.69 (dd, 1, J = 10 and 11.5 Hz), 6.16 (dd, 1, J = 2 and 10 Hz), 5.81 (dd, 1, J = 2 and 11.5 Hz), 3–3.4 (m, 2), 2.5–3 (m, 13) (the crude adduct and the analytical sample gave identical nmr spectra); mass spectrum *m/e* (rel intensity) 51 (13), 77 (44, Ph^+), 78 (12), 104 (35, $Ph-C^+H-CH_2$), 180 (100, $Ph_2C{=}N^+$), 181 (15), 208 (20, $Ph_2C-N_3^+$).

Anal. Calcd for $C_{21}H_{18}IN_3$: C, 57.41; H, 4.13. Found: C, 57.53; H, 4.15.

Triphenylacrolein (3) from Iodo Azide (2).—To a solution of 0.80 g (1.8 mmol) of the adduct 2 in 12 ml of DMSO was added 13.3 ml of 0.5 *N* potassium *t*-butoxide in DMSO[18] (6.6 mmol, 3.7 equiv of base) with magnetic stirring. An immediate red-black color and nitrogen evolution were observed. After 23 hr the mixture was quenched by pouring into 80 ml of ice water and the resulting emulsion was extracted with three 30-ml portions of benzene. The combined extracts were washed, dried ($MgSO_4$), and chromatographed on alumina to give 0.38 g (82%) of crude **3**, mp 167–182°. Two recrystallizations from methanol furnished a pure sample of triphenylacrolein, mp 180–183° (lit.[19] 177°), which gave a red 2,4-dinitrophenylhydrazone: mp 232–240° (lit.[18] 223–224°); ir (neat oil) 2857, 2755 (-CHO), 1667 (C=O, s), and 1636 cm^{-1} (C=C, s); nmr τ 0.26 (s, 1, CHO), 2.64 (m, 5), 2.86 (m, 10).

Anal. Calcd for $C_{21}H_{16}O$: C, 88.70; H, 5.67. Found: C, 88.58; H, 5.80.

2,3,3-Triphenylallyl Azide (5).—Iodo azide 2 (0.33 g, 0.75 mmol) was taken up in 7 ml of dry ether and cooled in an ice bath with magnetic stirring. To the cold solution was added dropwise 1.50 ml of 0.5 *N* *t*-BuOK in DMSO (0.75 mmol). A color change to rust red was observed but no gas evolution was detected. After stirring for 1.5 hr, the reaction mixture was poured into 50 ml of ice water and extracted with ether. The dried ether extract was diluted with 10 ml of CCl_4 and evaporated to a volume of ~5 ml to remove the ether. Two more 10-ml portions of CCl_4 were added and the process was repeated. Nmr integration of the singlet at τ 5.88 versus aromatic peaks indicated the allylic azide in 84% purity but no triphenylacrolein was detectable. The product was inert to DMSO at 25° for 10 hr. Crystallization of the allylic azide from ethanol provided an analytical sample: mp 69–71°; ir 2095 cm^{-1} (N_3); nmr (CCl_4) τ 2.71 (s, 5), 2.75 (s, 5), 3.04 (s, 5), 5.88 (s, 2); uv max (95% EtOH) 229 nm (ε 30,000), 276.5 (16,700).

Anal. Calcd for $C_{21}H_{17}N_3$: C, 81.00; H, 5.50. Found: C, 81.16; H, 5.69.

Treatment of allyl azide 5 with potassium *t*-butoxide in DMSO under conditions of formation of 3 from 2 led to isolation of triphenylacroein 3 in 80% yield and evolution of N_2 in 95% yield.

Heating of allyl azide 10[7] with NaN_3 in acetone for 4 hr led to formation of 5 in 80% yield.

3-Isocyanato-2,3,3-triphenyl-1-propyl Iodide (7).—Addition of iodine isocyanate to 5.24 g of 1 (4 hr at −25°) followed by treatment with methanol–lithium methoxide[11] gave, after quenching in water and ether extraction, a mixture of white solid and liquid. Filtration gave 1.45 g (17%) of the 1,3 adduct, mp 145–150°. The liquid filtrate still showed a strong isocyanate peak at 2275 cm^{-1} and only a weak carbonyl absorption at 1700 cm^{-1}. When the methanol treatment was omitted the isocyanate 7 was recovered in up to 70% yield. Recrystallization from 40% ether in pentane at 0° gave an analytical sample: mp 152–155°; ir 2275 (NCO) and 578 cm^{-1} (C–I, s); nmr τ 6.46 (dd, 1, J = 10 and 11 Hz), 6.0 (dd, 1, J = 2.5 and 10 Hz), 5.8 (dd, 1, J = 2.5 and 11 Hz); *m/e* (rel intensity), 104 (25), 165 (10), 180 (10, $Ph_2C{=}N^+$), 208 (100, Ph_2C^+-NCO).

Anal. Calcd for $C_{22}H_{18}NOI$: C, 60.14; H, 4.13. Found: C, 60.26; H, 4.25.

3,4,4-Triphenyl-δ-lactam (8).—Magnesium turnings (0.115 g, 4.73 g-atoms) and 0.344 g (0.78 mmol) of the 1,3 adduct 7 were added to a predried flask under N_2 and 30 ml of ether (distilled directly from $LiAlH_4$) was added. Attempts to initiate Grignard reagent formation failed until 3 drops (~0.4 mmol) of methyl iodide was added resulting in a color change and formation of a pasty precipitate. After stirring for 3 hr, the mixture was quenched with 0.75 ml of saturated NH_4Cl, and then with 50 ml of H_2O and extracted with ether. The ethereal layer furnished 0.244 g (100%) of a yellow solid, mp 158–174°. Two recrystallizations from CCl_4 gave an analytical sample, mp 183–184°. This compound analyzed as a monocarbon tetrachloride solvate: mass spectrum *m/e* (rel intensity) 82 (24, CCl_2^+), 84 (17, CCl_2^+), 117 (100, CCl_3^+), 119 (93, CCl_3^+) 121 (32, CCl_3^+), 196 (44), 197 (63), 198 (98, $M^+ - NH$), 199 (17), 313 (3, M^+); ir 1694 cm^{-1} (C=O) and 3435 cm^{-1} (N–H); nmr (CCl_4) τ 2.2–3.4 (m, 15), 5.46 (t, 1, J = 8 Hz), 7.25 (d, 2, J = 8).

Anal. Calcd for $C_{22}H_{19}NO \cdot CCl_4$: C, 59.13; H, 4.10; N, 3.00. Found: C, 59.43; H, 4.09; N, 3.02.

ICl Addition to 1.—Iodine monochloride (2.44 g, 15 mmol) was added slowly to 10 ml of ether with stirring at 0° followed by 2.44 g (15 mmol) of 3,3,3-triphenylpropene and 3 ml of ether. After 24 hr of stirring at 25°, the solution was worked up as in the case of IN_3 additions to give 2.81 g (105%) of crude yellow 2,3-diphenylindene, mp 94–101°. This compound became red-brown at ambient temperatures and gave a positive Beilstein test. The nmr spectrum of the crude products showed singlets at τ 5.62, 5.77, and 6.20 integrating to 7, 14, and 68% of the total aromatic peak (14 H), respectively. One of the singlets (probably τ 5.77) may correspond to the unstable 2,3,3-triphenylallyl iodide. Recrystallization from 15% ether in pentane gave 262 mg (10%) of 2,3-diphenylindene, mp 110–112° (needles, lit.[12] 108–109°). The nmr[12] and uv[20] spectra were consistent with those previously reported: τ 6.15 (5.2); ir 1660 cm^{-1} (C=C, weak); uv (95% EtOH) 233 nm (ε 34,200), 304 (31,000); mass spectrum *m/e* (rel intensity) 165 (10), 189 (13), 191 (15), 265 (15), 267 (25), 268 (100, M^+), 269 (25).

Anal. Calcd for $C_{21}H_{16}$: C, 93.99; H, 6.01. Found: C, 93.02; H, 6.04.

(15) All solvents used were distilled. Melting points were determined on a Fisher block and are uncorrected. Infrared spectra were obtained using ~3% w/v solution in CCl_4 with 0.5-mm KBr solution cells unless otherwise noted on a Perkin-Elmer 457 instrument. Nmr spectra were obtained on a Varian A-60 or A-60A spectrometer with TMS as an internal standard, using approximately a 20% w/v solution in $CDCl_3$ unless otherwise noted. Uv spectra were recorded on a Cary 14 spectrometer. Mass spectra were obtained at 70 eV on a Varian MAT CH5 mass spectrograph. Elemental analyses were performed by Chemalytics, Inc., Tempe, Ariz., or Galbraith Laboratories, Knoxville, Tenn. Thin layer chromatographs were carried out on silica gel F_{254} precoated plates or silica gel PF_{254} 2-mm coated plates for preparative layers.

(16) (a) F. J. Piehl and W. G. Brown, *J. Amer. Chem. Soc.*, **75**, 5026 (1953); (b) W. D. McPhee and E. G. Linstrom, *ibid.*, **65**, 2177 (1943).

(17) F. W. Fowler, A. Hassner, and L. A. Levy, *J. Amer. Chem. Soc.*, **89**, 2077 (1967).

(18) F. C. Chang and N. F. Wood, *Steroids*, **4**, 55 (1964).

(19) G. E. Moussa, *J. Appl. Chem.*, **12**, 385 (1962).

Addition of ICl (0.498 g, 3.06 mmol) to 3,3,3-diphenylpropene (0.537 g, 1.98 mmol) in 12 ml of acetonitrile gave a product the nmr spectrum of which was nearly identical with that of pure 2,3-diphenylindene. Integration of the singlet at τ 6.15 (2 H) *vs.* the aromatic multiplet (14 H) indicates a yield of 92% for 2,3-diphenylindene (**13**).

exo-**5-Azido-*anti*-7-iodobenzonorbornene** (**19**).—In a modification of general procedure 1.1 equiv. of IN_3 was allowed to react with 0.861 g of benzonorbornadiene for 94 hr to furnish 1.85 g (99%) of the adduct, mp 58–67°. Prisms were obtained from ethanol: mp 77.5–78°; ir 2125 cm^{-1} ($C-N_3$); nmr τ 2.9 (s, 4), 5.96 (qui, 1), 6.37 (m, 3), 7.55 (2t, 1), 8.11 (d, 1); mass spectrum *m/e* (rel intensity) 63 (11), 115 (45, indenyl cation) 116 (10), 127 (23), 128 (49), 129 (100, dihydronaphthalene cation), 130 (15), 141 (4), 156 (19).

Anal. Calcd for $C_{11}H_{10}IN_3$: C, 42.46; H, 3.24. Found: C, 42.33; H, 3.30.

1-Iodomethyl-3-azidonortricyclane (**21**).—Adduct **21** (5.4 g 100%) was obtained from 2.12 g of methylene norbornene. The oil showed no vinylic protons in the nmr, turned dark at room temperature and could not be purified by distillation: ir 2105 cm^{-1} (N_3); nmr τ 6.1 (s, 1), 6.53 (s, 2), 7.8–9.1 (m, 7); mass spectrum *m/e* (rel intensity) 39 (49), 41 (30), 51 (25), 53 (21), 54 (48), 65 (45), 66 (43), 67 (21), 77 (94), 78 (25), 79 (39), 91 (98), 93 (100), 120 (37), 141 (10, $CH_2{=}I^+$?), 148 (24, $M^+ - I$).

Anal. Calcd for $C_8H_{16}IN_3$: C, 34.93; H, 3.66; I, 46.13; N, 15.28. Found: C, 33.92; H, 3.76; I, 44.80; N, 17.64.

Registry No.—**1**, 3282-07-3; **2**, 25683-82-3; **3**, 25683-83-4; **3** 2,4-DNP, 25683-84-5; **5**, 25683-85-6; **7**, 25683-86-7; **8**, 25683-87-8; **13**, 5324-00-5; **19**, 25683-89-0; **21**, 25683-90-3.

Acknowledgment.—Support of this investigation by Petroleum Research Fund Grant 2004A from the American Chemical Society and by the U. S. Public Health Service Grant CA-4474 from the National Cancer Institute is gratefully acknowledged.

Coupling and Disproportionation Reactions of Cumyl Radical–Cyclohexyl Radical Pairs from α-Cumylazocyclohexane[1]

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The new unsymmetrical azo compound, α-cumylazocyclohexane (A), has been synthesized and the products resulting from its thermal decomposition in cumene (110°) have been quantitatively determined. Products formed and their observed yields given in mol % based on the starting azo compound were cyclohexene (5%), cyclohexane (78%), α-cumylcyclohexane (21%), bicumyl (51%), and α-methylstyrene (4%). All of the cyclohexene, α-cumyleyclohexane, and *ca.* one-third of the cyclohexane are cage products giving a cage effect of *ca.* 0.50. The remaining cyclohexane arises *via* hydrogen abstraction from cumene by diffused cyclohexyl radicals. A comparison of these data with those for decomposition of carbo-*t*-butylperoxycyclohexane (*t*-butyl perester of cyclohexane carboxylic acid) in cumene permitted a detailed analysis of the origins of the products in both systems. The data from A give the relative rates of the coupling and the two available disproportionation reactions for a cyclohexyl radical–cumyl radical pair. These data for a mixed alkyl radical–aralkyl radical pair are compared with similar data for symmetrical alkyl radical pairs and aralkyl radical pairs and indicate that the high combination–disproportionation ratios observed for the latter are the result of a special property of a *pair* of aralkyl radicals.

As part of a continuing study of the effects of pressure on free radical reactions we have determined the pressure dependence of the cage effect associated with decomposition of various radical initiators.[2] One such initiator was the *t*-butyl perester of cyclohexanecarboxylic acid (carbo-*t*-butylperoxycyclohexane) (P) which decomposes by the two-bond scission mechanism shown in Scheme I.[2b,d] In this system, the cage effect

SCHEME I

$$C_6H_{11}\text{–}CO_3C(Me)_3\ (P) \xrightarrow{k_1} \overline{C_6H_{11}CO_2OC(Me)_3} \xrightarrow{k_e} C_6H_{11}OC(Me)_3 \qquad \overline{C_6H_{11}CO_2OC(Me)_3} \xrightarrow{k_a} C_6H_{10} + (Me)_3COH \quad (1)$$

$$\overline{C_6H_{11}CO_2OC(Me)_3} \xrightarrow{k_d} C_6H_{11}\cdot + \cdot OC(Me)_3 \xrightarrow{\text{cumene}} Me_3COH + PhC(Me)_2$$

was calculated using the relative amounts of *t*-butyl cyclohexyl ether, cyclohexene, and *t*-butyl alcohol. While the results obtained were reasonable by comparison with other systems, we were unable to provide concrete evidence that cyclohexene arose only from the cage reaction shown in Scheme I. It also seemed possible that it could have been formed by disproportionation of a pair of cyclohexyl radicals, and/or a cyclohexyl and cumyl radical pair, subsequent to separative diffusion of the primary geminate cyclohexyl and *t*-butoxy radicals.

In order to provide data relating to the possible origin of cyclohexene from these latter reactions, we have synthesized the new compound α-cumylazocyclohexane (A) and have quantitatively determined the products arising from its thermal decomposition in cumene. The anticipated decomposition mechanism is outlined in Scheme II and it can be seen that this system should

SCHEME II

$$C_6H_{11}N{=}N\text{–}C(Me)_2Ph\ (A) \rightarrow \overline{C_6H_{11}N_2C(Me)_2Ph} \xrightarrow{k_d} C_6H_{11}\cdot + PhC(Me)_2 \quad \text{cage products}$$

(1) Support by the National Science Foundation (GP-7349 and 8670) is gratefully acknowledged.

(2) (a) R. C. Neuman, Jr., and R. J. Bussey, *J. Amer. Chem. Soc.*, **92**, 2440 (1970); (b) R. C. Neuman, Jr., and J. V. Behar, *ibid.*, **91**, 6024 (1969); (c) R. C. Neuman, Jr., and R. J. Bussey, *Tetrahedron Lett.*, 5859 (1968); (d) R. C. Neuman, Jr., and J. V. Behar, *ibid.*, 3281 (1968); (e) R. C. Neuman, Jr., and J. V. Behar, *J. Amer. Chem. Soc.*, **89**, 4549 (1967).

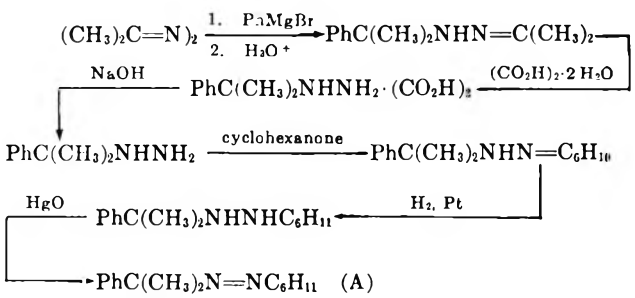
provide within the initial cage the cyclohexyl–cumyl encounter proposed as a potential alternate route to cyclohexene formation from P. Additionally, separative diffusion of the initially formed geminate radicals leads to a system of solvent separated radicals, formally equivalent to that obtained from decomposition of P, in which extra-cage cyclohexyl–cumyl and cyclohexyl–cyclohexyl encounters are both conceivable.

The results which we have obtained support our earlier contention[2b] that P decomposition in cumene gives cyclohexene only *via* the cage reaction shown in Scheme I. The data also provide information about the relative importance of disproportionation and combination reactions for cumyl radical–cyclohexyl radical pairs.

Results and Discussion

Synthesis and Decomposition Mechanism.—The azo compound α-cumylazocyclohexane (A) was synthesized from acetone azine according to the route[3a] outlined in Scheme III and its structure was verified by

SCHEME III



infrared, ultraviolet, and nmr spectral data, and microanalytical results. No attempt was made to obtain extensive kinetic data for decomposition of A; however, a single kinetic run at 90.0° (cumene solvent), carried out by monitoring N_2 evolution (>94% theoretical N_2 evolved), gave a value of 2×10^{-6} sec^{-1} for the first order decomposition rate constant. This corresponds to a value of ~31 kcal/mol for ΔF^* (90°) which is the same as the corresponding value for solution phase decomposition of the similar compound α-cumylazo-2-propane.[3b] This similarity suggests that the decomposition mechanisms of these two compounds are the same, but the data do not distinguish between one-bond or concerted two-bond scission processes.[4] Seltzer, however, has demonstrated that α-phenylethylazo-2-propane [ΔF^* (90°) = 33 kcal/mol] decomposes by a two-bond scission route.[5] Thus it seems reasonable that such a mechanism characterizes the decomposition of α-cumylazocyclohexane as well.

Products and Their Origins.—Product yields expressed in mol % based on starting azo compound from thermal decomposition of 0.1 *M* cumene solutions of A are reported in Table I. New product data for P decomposition (79.6 and 110°) in cumene (0.1 *M*) are also given. The products were analyzed using glpc and their yields were determined by comparisons with standard solutions containing authentic samples of the products.

TABLE I

PRODUCTS FROM DECOMPOSITION OF COMPOUNDS A AND P IN CUMENE[a,b]

Product	Mol %, A (110°)	P (79.6°)	P (110°)
Cyclohexene	5	16	20
Cyclohexane	78	64	77
α-Cumylcyclohexane	21	0	0
Cyclohexyl *t*-butyl ether		20	15
Total cyclohexyl	104	100	112
Bicumyl	51	59	52
α-Methylstyrene	4	0	0

[a] Solutions about 0.1 *M* and degassed. [b] Values are absolute mol % based on A or P [(mol of product/mol of initiator) × 100]. Products identified and quantitatively determined by glpc.

These products account for all of the significant peaks (except that for *t*-BuOH) observed in the glpc traces. Since cumene was the solvent its possible formation from P and A could not be verified. An apparent multiplet of at least two peaks (<1%) was visible in traces of the decomposition reaction mixtures of both P and A at a slightly longer retention time than that for α-cumylcyclohexane. We suggest that this corresponds to products arising from ring substitution of cyclohexyl radicals on cumene. We have no explanation for the yield values which are greater than 100% (Table I) and assume that these are the result of experimental error. While the absolute percentage yields for the products from P (79.6°) are higher than those previously reported,[2b,d] their ratios are essentially identical.[6]

Reactions which could have occurred subsequent to separative diffusion of the initially formed geminate radicals from either P or A are outlined in equations 2–5. These are divided into four groups representing the three possible bimolecular encounters for a system of solvent separated cyclohexyl and cumyl radicals (reactions 3, 4, and 5) and the hydrogen abstraction reaction from solvent available to cyclohexyl radicals (eq 2). Reactions 3a–c, arising from an encounter between a cyclohexyl and cumyl radical, also represent the possible cage processes available to the initial geminate pair from the azo compound A (see Scheme II). The possible cage reactions associated with decomposition of P are shown in Scheme I.

$$C_6H_{11}\cdot + PhCH(Me)_2 \longrightarrow C_6H_{12} + PhC\dot{(}Me)_2 \quad (2)$$

$$C_6H_{11}\cdot + PhC\dot{(}Me)_2 \longrightarrow \begin{cases} C_3H_{12} + PhC(Me)=CH_2 & (3a) \\ C_6H_{10} + PhCH(Me)_2 & (3b) \\ C_6H_{11}-C(Me)_2Ph & (3c) \end{cases}$$

$$C_6H_{11}\cdot + C_6H_{11}\cdot \longrightarrow \begin{cases} C_6H_{10} + C_6H_{12} & (4a) \\ C_6H_{11}-C_6H_{11} & (4b) \end{cases}$$

$$PhC(Me)_2 + PhC\dot{(}Me)_2 \longrightarrow \begin{cases} PhC(CH_3)_2C(CH_3)_2Ph & (5a) \\ PhCH(Me)_2 + PhC(Me)=CH_2 & (5b) \end{cases}$$

The absence of α-cumylcyclohexane from among the products resulting from decomposition of the perester P clearly rules out the presence of the coupling reaction

(3) (a) C. G. Overberger and A. V. DiGiulio, *J. Amer. Chem. Soc.*, **80**, 6562 (1958); (b) C. G. Overberger and A. V. DiGiulio, *ibid.*, **81**, 2154 (1959).

(4) The activation parameters for a one-bond scission mechanism would reflect the formation of the cumyl and $RN_2\cdot$ radicals. The probable similarity in the stability of the isopropyl and cyclohexyl radicals would be consistent with the comparative values of ΔF^* if the mechanism involved two-bond scission.

(5) S. Seltzer, *J. Amer. Chem. Soc.*, **85**, 14 (1963).

(6) The absence of any significant peaks in the glpc traces other than those identified suggests that the products given in Table I should add up to 100% for P and A.

3c in this system. Additionally, this observation together with the comparative yield data for cyclohexene, cyclohexane, and α-cumylcyclohexane from A, also require that reactions 3a and 3b did not contribute significantly during decomposition of P. Analysis of Scheme II and reactions 2–5 leads to the material balance shown in eq 6 for decomposition of A.[7] Substitution of the data from Table I into this equation leads to the result that the unknown quantity % cyclohexane_{3a} is approximately 24%. This cor-

$$\%\ \text{A} = \%\ \text{cyclohexene}_{\text{total}} + \%\ \text{cyclohexane}_{3a} + \%\ \text{cumylcyclohexane}_{\text{total}} + \%\ \text{bicumyl}_{\text{total}} + \%\ \alpha\text{-methylstyrene}_{5b} \quad (6)$$

responds to about one-third of the total yield of cyclohexane (Table I). Assuming that all cyclohexene from A was formed by reaction 3b, it can be calculated from these data that the relative rates of reactions 3a:3b:3c were on the order of 5:1:4. Since no cumylcyclohexane (reaction 3c) was detected from P under any conditions, it may be reasonably concluded that virtually none of the cyclohexane or cyclohexene formed from P arose from reactions 3a and 3b.

The absence of cyclohexyl radical–cumyl radical encounters during decomposition of P suggests that cyclohexyl–cyclohexyl encounters would have been highly improbable since cyclohexyl radicals can additionally abstract hydrogen from the solvent (reaction 2). Thus, it must be concluded that decomposition of the perester P yielded cyclohexene only *via* disproportionation of the primary cyclohexyl-*t*-butoxy radical pair (Scheme I). This requires that all cyclohexane from P was formed by hydrogen abstraction from cumene and that the reaction sequence subsequent to the chemistry shown in Scheme I includes only reactions 2, 5a, and 5b.

Based on this analysis the cage effect associated with decomposition of P (79.6°) was ~36% (ether + cyclohexene), or, conversely, solvent-separated cyclohexyl and cumyl radicals were produced to the extent of ~64% of the starting concentration of P. Since cyclohexyl–cumyl and cyclohexyl–cyclohexyl encounters did not occur under these conditions, products derived from reactions 3a–c during decomposition of A must have been formed only from the primary cages containing the cyclohexyl and cumyl radical pair and not from such encounters subsequent to separative diffusion. This supports the assumption that cyclohexene from A arose only from reaction 3b and confirms the predicted relative rate ratio for reactions 3a:3b:3c of ~5:1:4. The data thus give a cage effect of ~50% for A decomposition. As in the case of P, reactions 2, 5a, and 5b represent the sole processes which occurred subsequent to separative diffusion of the geminate radicals produced from A.[8]

(7) (a) These quantities represent the mole-percentage yields of each product based on starting azo compound. The value of % A used in the calculation was 104 (see Table I). The subscript "total" signifies the value reported in Table I. The numerical subscript refers to a particular reaction origin among the several possible sources. The value of % α-methylstyrene$_{5b}$ used was 3% and this was calculated from the yield of bicumyl on the basis that the relative rates of reactions 5a:5b were 94:6 and that reaction 5a was the only source of bicumyl.[7b] The true α-methylstyrene yield must have been significantly larger than actually observed (*vide infra*) and we assume that it underwent polymerization. (b) S. F. Nelsen and P. D. Bartlett, *ibid.*, **88**, 137 (1966).

(8) These schemes predict that the α-methylstyrene yields from decomposition of P should have been on the order of 3–4%, while that from A should have been ~25%. The former value is obtained using the reasoning outlined in footnote 7 and the conclusion that reaction 5b is the only source of this compound. The large value for decomposition of A arises from the conclusion that reaction 3a, in which equimolar amounts of cyclohexane and α-methylstyrene were formed, accounts for about 20–25% of the starting azo compound.

Radical Disproportionation and Combination.—The competition between disproportionation (reactions 3a and 3b) and combination (reactions 3c) for the cyclohexyl radical–cumyl radical pair is compared with analogous data for pairs of cyclohexyl radicals[9] and pairs of cumyl radicals[7b] in Table II. The entry desig-

TABLE II
DISPROPORTIONATION–COMBINATION RATIOS FOR SYMMETRICAL AND MIXED PAIRS OF CYCLOHEXYL AND CUMYL RADICALS

Radical pair	k_{dis}/k_{com}[a]	β H[b]	k'_{dis}/k_{com}[c]
Cumyl[d]	0.054	12	0.005
Cumyl–cyclohexyl[e]	0.24	4	0.06
Cyclohexyl–cumyl[f]	1.1	6	0.18
Cyclohexyl[g]	1.1	8	0.14

[a] Ratio of rate constants for disproportionation and combination. [b] Number of abstractable β hydrogens. [c] Equal to $(k_{dis}/k_{com})/(\beta\ \text{H})$. [d] See ref 7b. [e] k_{3b}/k_{3c}. [f] k_{3a}/k_{3c}. [g] See ref 9.

nated "cumyl/cyclohexyl" corresponds to the competition between coupling and the formation of cumene and cyclohexene (k_{3b}/k_{3c}) while that designated "cyclohexyl/cumyl" corresponds to the competition between coupling and the formation of cyclohexane and α-methylstyrene (k_{3a}/k_{3c}). After statistical correction of the data based on the number of β hydrogens it can be seen that the disproportionation pathway leading to the more stable olefin (α-methylstyrene) is about three times as favorable as the alternative pathway (cyclohexene) formation.

It is also apparent from these data that the statistically corrected ratio k'_{dis}/k_{com} for a cumyl radical pair is significantly lower than the other values in the table. The abnormally low value for this ratio in comparison with those for a variety of other alkyl radical pairs was previously noted by Bartlett.[7b] However, the comparison in Table II is unique in that it seems to demonstrate that the origin of this effect could reside in some special property of a *pair* of cumyl radicals rather than in a combination of properties of the individual radicals.

Shelton has shown that this seemingly abnormal behavior is also characteristic of a variety of *para*-substituted cumyl radicals.[10] From the data collected together in Table III[7b,9–14] it seems, in fact, that low values of k'_{dis}/k_{com} are predominantly associated with symmetrical radical pairs in which the odd electron can be delocalized.

Such electron delocalization and subsequent radical stabilization was considered by Bartlett[7b] as a potential explanation for the low percentage of disproportionation from a cumyl radical pair. However, he also noted that it was not clear why such stabilization should

(9) W. A. Cramer, *J. Phys. Chem.*, **71**, 1171 (1967).

(10) J. R. Shelton, C. K. Liang, and P. Kovacic, *J. Amer. Chem. Soc.*, **90**, 354 (1968).

(11) See W. A. Pryor, "Free Radicals," McGraw-Hill, New York, N. Y., 1966, p 317.

(12) P. D. Bartlett and J. M. McBride, *Pure Appl. Chem.*, **15**, 89 (1967).

(13) F. D. Greene, M. A. Berwick, and J. C. Stowell, *J. Amer. Chem. Soc.*, **92**, 867 (1970).

(14) A. F. Bickel and W. A. Waters, *Recl. Trav. Chim. Pays-Bas*, **69**, 1490 (1950).

TABLE III

DISPROPORTIONATION–COMBINATION RATIOS FOR RADICAL PAIRS[a]

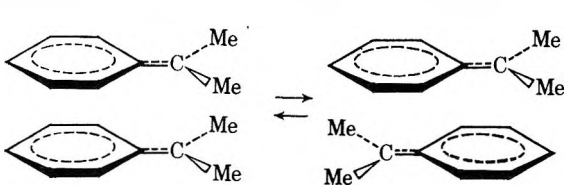
Radical pair	k_{dis}/k_{com}	β-H	k'_{dis}/k_{com}	Ref
2-Propyl	0.5	12	0.02	*b*
2-Butyl	2.3	10	0.23	*b*
t-Butyl	4.6	18	0.26	*c*
Cyclohexyl	1.1	8	0.14	*d*
Cumyl	0.054	12	0.005	*e*
p-Me-cumyl	0.06	12	0.005	*f*
p-*i*-Pr-cumyl	0.07	12	0.006	*f*
p-*t*-Bu-cumyl	0.11	12	0.009	*f*
p-Br-cumyl	0.20	12	0.016	*f*
2-Phenyl-3-methyl-2-butyl	0.3	8	0.04	*c*
α-Phenylethyl	0.14	6	0.023	*g*
2-Cyano-2-propyl	0.1	12	0.008	*h*
Cyclohexyl–cumyl	1.1	6	0.18	
Cumyl–cyclohexyl	0.24	4	0.06	
t-Butoxy–cyclohexyl	0.8	4	0.20	

[a] See footnotes in Table II. [b] See ref 11. [c] See ref 12. [d] See ref 9. [e] See ref 7b. [f] See ref 10. [g] See ref 13. [h] See ref 14.

not comparably retard both combination and disproportionation. In fact, Hammond[15] has presented results which suggest that the absolute rate constant k_{dis} is essentially the same for both cumyl and cyclohexyl radicals, and that the absolute value of k_{com} is much larger for the former than the latter.

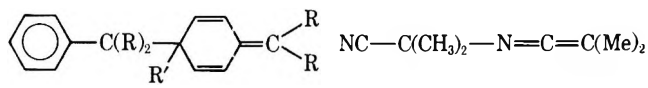
It seems clear that additional studies will be required before these variations in the ratios k'_{dis}/k_{com} will yield to a general correlation. However, we wish to summarize some features of these systems which may enter into such an explanation. Radical delocalization, as suggested by Bartlett,[7b] does provide a crude correlation. However, the data for 2-phenyl-3-methyl-2-butyl, α-phenylethyl and for the mixed pair, cyclohexyl-cumyl, seem to deviate. Hammond[15] has indicated that radical solvation may be important in determining the termination rate constants for radicals in solution and such effects might also enter into the disproportionation–combination ratios.

Additionally, however, those radicals exhibiting low values of k'_{dis}/k_{com} might be expected to form dimeric association complexes as shown below for a pair of cumyl radicals. Such complexes might be expected to



easily collapse to the coupling product, but be rather geometrically unfavorable for disproportionation. In this regard it should be noted that increasing steric bulk either on the ring or side chain, features expected to destabilize such a complex, lead to increasing relative amounts of disproportionation (*p*-*t*-butylcumyl, 2-phenyl-3-methyl-2-butyl, and *p*-bromocumyl). While the relatively high value of k_{dis}/k_{com} for α-phenylethyl cannot be explained on this basis, it could reflect a reduction in steric interactions in the disproportionation step due to the absence of one of the benzylic methyl groups.

Finally, all radicals in which delocalization can occur may potentially undergo abnormal coupling to form unstable coupling products such as, for example, the quinoid type structure for aralkyl radicals[7b,16] and the well-documented ketenimine from 2-cyano-2-propyl radicals.[17] It is not at all obvious how such interme-



diates could be related to the disproportionation–combination ratios and further it is *presumed* that the quinoid type structures are only minor contributors to the primary product distribution.[7b,18] However, it again should be noted that for those radical pairs which might be expected to yield particularly strained quinoid type structures, the ratios k_{dis}/k_{com} increase.

Experimental Section

α-Cumylhydrazine.—The synthetic scheme used by Overberger and DiGiulio[3a] was followed: yield 17.2 g (0.115 mol, 66%), bp 80–82° (1.5–1.6 mm); lit.[3a] yield 17.0 g (65%), bp 72–73° (0.6 mm). The infrared spectrum showed an absorption peak for NH at 3350 cm^{-1} (lit.[3a] 3310 cm^{-1}).

Cyclohexanone α-Cumylhydrazone.—A 17-g (0.11 mol) sample of α-cumylhydrazine was added over a 2-min period to a suspension of 6.0 g of anhydrous magnesium sulfate in 130 ml of freshly distilled cyclohexanone under an atmosphere of nitrogen. The mixture, under nitrogen, was stirred and heated at 45–50° for 14 hr and then stirred at room temperature for an additional 14 hr. The magnesium sulfate was removed and the solvent was evaporated under nitrogen. The yellow fraction boiling at 139–140° (2.5 mm) was collected: yield 19.0 g (0.083 mol, 72%); infrared 3300 (NH) and 1640 cm^{-1} (C=N); nmr (CCl_4) multiplet (aromatic), τ 2.5–3.0 (5 H), singlet (NH), 5.3 (0.97 H), broad absorption (α-cyclohexyl), 7.8 (4.04 H), broad multiplet (β,γ-cyclohexyl), 8.2–8.6, and singlet (methyl), 8.5 (combined, 12.3 H).

Cyclohexane α-Cumylhydrazine.—A solution containing 18.9 g (0.083 mol) of cyclohexanone α-cumylhydrazone and 0.83 g of platinum oxide (Adams catalyst) in 500 ml of absolute ethanol was shaken under 60-psi hydrogen pressure at room temperature for 46 hr using a Parr apparatus. The resulting yellowish-green solution was filtered and the solvent was evaporated *in vacuo*. The light yellowish-green fraction boiling at 134–138° (2.2–2.3 mm) was collected, yielding 15.5 g (0.067 mol, 82%) of product: ir 3250 cm^{-1} (NH); nmr (CCl_4) multiplet (aromatic), τ 2.5–3.0 (5 H), singlet (NH), 6.6 (0.64 H), broad absorption (α-cyclohexyl), ~7.5 (<1 H), broad multiplet (β,γ,δ-cyclohexyl), 8.0–8.7, and singlet (methyl), 8.5 (combined, 15.6 H). The low NH integration probably indicates substantial conversion *via* air oxidation to the azo compound. At the time that these studies were done we were unaware of the ease of such a process. In retrospect, the following procedure could have probably been totally eliminated.

α-Cumylazocyclohexane.—A 3-g (0.012 mol) sample of cyclohexane α-cumylhydrazine in 20 ml of absolute ethanol was cooled in an ice bath and stirred while 8.0 g (0.37 mol) of red mercuric oxide was slowly added. Stirring was continued for 6 hr at ice temperature and for 18 hr at room temperature, and the solution was then left undisturbed for 3 days at room temperature in the dark. The resulting dark gray precipitate was separated by filtration from the light yellowish-green solution and the solvent was evaporated *in vacuo*. The slightly turbid liquid was centrifuged for 1 hr and the clear supernatant was drawn off and

(15) S. A. Weiner and G. S. Hammond, *J. Amer. Chem. Soc.*, **91**, 986 (1969).

(16) H. Lankamp, W. Th. Nauta, and C. MacLean, *Tetrahedron Lett.*, 249 (1968).

(17) (a) M. Talat-Erben and S. Bywater, *J. Amer. Chem. Soc.*, **77**, 3710, 3712 (1955). (b) G. S. Hammond, *et al.*, *ibid.*, **82**, 5386, 5394 (1960).

(18) Unpublished results of M. Amrich in our laboratory indicate that quinoid dicumyls may be formed in higher yields than previously suggested.[7b]

chromatographed on Florisil (100–200 mesh) using purified pentane: yield 2.6 g (0.011 mol); ir *no* peak at 3250–3300 cm^{-1} (N–H); nmr (CCl_4) multiplet (aromatic), τ 2.6–3.0 (5 H), broad absorption (α-cyclohexyl), 6.5 (0.97 H), broad multiplet (β,γ,δ-cyclohexyl), 8.0–9.0, and singlet (methyl), 8.5 (combined, 16.0 H); uv λ_{max} 365 mμ (ε 30–35).

Anal. Calcd for $C_{15}H_{22}N_2$: C, 78.21; H, 9.63; N, 12.16. Found: C, 78.53; H, 9.83; N, 12.06. Greater than 94% theoretical nitrogen evolution on thermal decomposition (see text).

α-Cumylcyclohexane (2-Cyclohexyl-2-phenylpropane).—A sample of α-cumylazocyclohexane was dissolved in cumene and heated for 4 days under nitrogen at 110–115°. The compound corresponding to the single unidentified peak on an analytical glpc trace of the reaction mixture was collected by pseudo-preparative glpc methods and shown to be pure by glpc analysis on the analytical column (see next section). Nmr, mass spectral, and infrared data were obtained: nmr (neat) multiplet (aromatic), τ 2.8–3.2 (5 H), multiplet (cyclohexyl), 8.2–9.1, and singlet (methyl), 8.8, (combined, 17.7 H); mass spectrum parent peak 202 ($C_{15}H_{22}$, 202), base peak 119 (cumyl ion radical). Glpc retention time was consistent with a molecular weight of 202. These data and the infrared spectrum were consistent with the structural assignment of α-cumylcyclohexane.

Product Analyses.—Degassed ampoules containing a 0.1 *M* solution of α-cumylazocyclohexane in cumene were heated at 110° for 6 days and degassed ampoules containing a 0.1 *M* solution of carbo-*t*-butylperoxycyclohexane in cumene were heated at 110° for 6 days or at 79.6° for 4 days. The low boiling products (cyclohexane, cyclohexene, and α-methylstyrene) were resolved at 75° on a 10-ft $AgNO_3$–Carbowax column at a flow rate of about 30 ml/min. The high boiling products (*t*-butyl cyclohexyl ether, α-cumylcyclohexane and bicumyl) were resolved on a 6-ft 10% UC-W98 column using temperature programming from 65° up to 230° at a 10/min rate. Benzene was used as an internal standard, and standard solutions containing known amounts of the products were used to obtain relative and absolute yields.

Registry No.—A, 25683-93-6; P, 20396-49-0; cyclohexanone α-cumylhydrazone, 25683-95-8; cyclohexane-α-cumylhydrazine, 25683-96-9; α-cumylcyclohexane, 25683-97-0.

A Method for the Extension of Carbon Chains by γ-Alkylation of Metalated α,β-Ynamines

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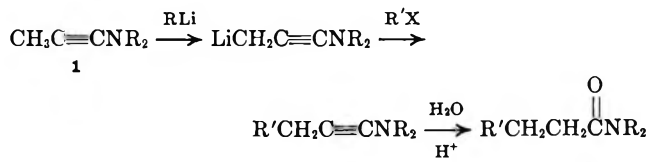
α,β-Ynamines of type **1** can be metalated by alkyllithium–tetramethylethylenediamine complexes to form lithium derivatives which undergo alkylation upon treatment with a variety of halides. The resulting ynamines can be converted to amides and carboxylic acids, thus affording the overall transformation of a halide RX to a carboxylic acid derivative RCH_2CH_2COX.

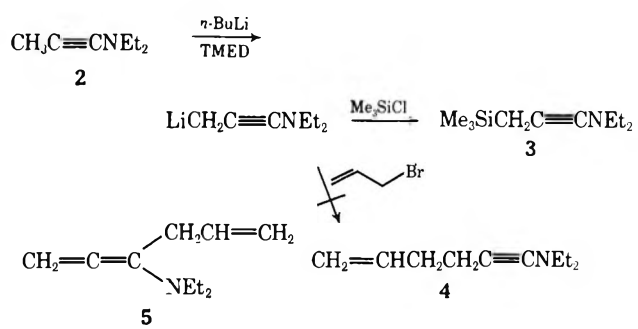
The introduction of a three-carbon chain terminating in a carboxyl function is often accomplished by the attachment of electrophilic reagents of type >C=CCOX to nucleophilic carbon by the Michael reaction[1] or by the addition of organoboranes to α,β-unsaturated aldehydes.[2] These methods are not applicable, however, when neither the metalloalkyl nor the organoborane derived from the unit to be elaborated, for example, the geranyl group, can be utilized satisfactorily.

A nucleophilic reagent, capable of performing the desired chain extension, would thus be a useful tool for the synthetic chemist. The lithium acetylide of propargyl tetrahydropyranyl ether[3] and the Grignard derived from the ethylene acetal of 3-bromopropionaldehyde[4] are two such reagents which have already been used in organic synthesis.

In principle the metalation of an ynamine of type **1** followed by reaction with a suitable electrophile,



coupled with the ready conversion of ynamines to amides or esters,[5] could provide a convenient and versatile method for the desired chain extension. We have studied such a procedure and report our results below.



Results

The first ynamine we chose to study was 1-diethylaminopropyne (**2**). This substance underwent metalation with *n*-butyllithium–tetramethylethylenediamine complex as evidenced by subsequent reaction with trimethylchlorosilane, which gave the acetylenic silane **3** in 85% yield (vpc analysis). Using identical conditions, however, reaction of this metalation product of **2** with either methyl iodide or allyl bromide gave neither of the expected acetylenic products nor any other material detectable by vpc analysis. The infrared spectra of the crude reaction mixtures contained allenic absorption at 5.2 μ, suggesting that the propargylic carbanion

(1) (a) E. D. Bergmann, D. Ginsburg, and R. Pappo, *Org. React.*, **10**, 179 (1959); (b) H. A. Bruson, *ibid.*, **5**, 79 (1949); (c) H. O. House in "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, pp 204–215.

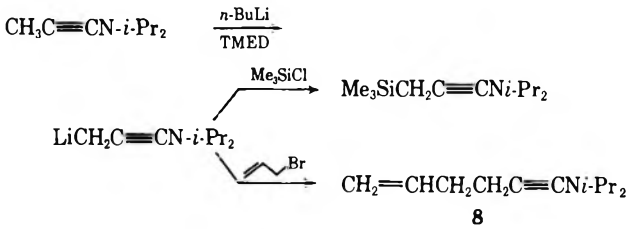
(2) (a) A. Suzuki, A. Arase, H. Matsumoto, M. Itoh, H. C. Brown, M. M. Rogić, and M. W Rathke, *J. Amer. Chem. Soc.*, **89**, 5708 (1967); (b) H. C. Brown, M. M. Rogić, M. W. Rathke, and G. W. Kabalka, *ibid.*, **89**, 5709 (1967); (c) H. C. Brown and G. W. Kabalka, *ibid.*, **92**, 712, 714 (1970).

(3) (a) E. J. Corey, K. Achiwa, and J. A. Katzenellenbogen, *ibid.*, **91**, 4318 (1969); (b) E. J. Corey and K. Achiwa, *Tetrahedron Lett.*, 1839 (1969).

(4) G. Buchi and H. Wuest, *J. Org. Chem.*, **34**, 1122 (1969).

(5) For a review of ynamines and their reactions, see H. G. Viehe, *Angew. Chem., Int. Ed. Engl.*, **6**, 767 (1967), and references cited therein.

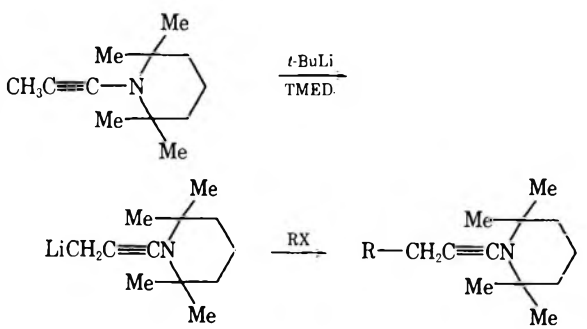
had been attacked exclusively at the carbon adjacent to the nitrogen, forming thereby an allenyl amine, **5**,[6] which is evidently thermally unstable. Attention was turned at this point to an ynamine containing bulkier groups on nitrogen. 1-Diisopropylaminopropyne (**6**), synthesized from the isomeric propargylamine[7] by the



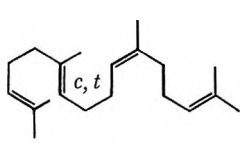
8

method of Viehe,[6a] could be metalated and then alkylated with trimethylchlorosilane in 80% (vpc) yield. Alkylation of the reagent from **6** with allyl bromide did afford the desired acetylenic product (**8**) but only in 40% yield even under optimum experimental conditions. The optimization experiments are summarized briefly in the Experimental Section.

A more effective reagent was found to be that derived from 1-propynyl-2,2,6,6-tetramethylpiperidine (**9**). *t*-Butyllithium–tetramethylethylenediamine rapidly and quantitatively metalated **9**, and reaction of the resultant carbanion with allyl iodide gave **10b** in 62% (vpc) yield.



10a, R = $(CH_3)_3Si$
b, R = CH_2=$CHCH_2$
c, R = CH_3
d, R = $CH_3(CH_2)_3$
e, R = geranyl



11

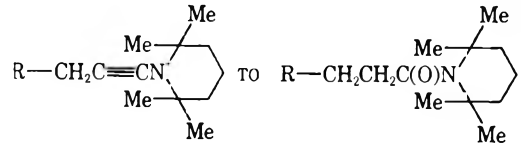
The reactions of the carbanion from **9** with a series of alkyl halides were examined; the results are recorded in Table I. As can be seen, fair yields of alkylated ynamines could be obtained. For the series allyl iodide, bromide, and chloride, the yield of **10b** decreased in that order. No unusual difficulties were encountered in reactions with simple *n*-alkyl iodides. However,

(6) (a) Allenyl amines are intermediates in the base-catalyzed rearrangement of propargyl amines to ynamines and may sometimes be isolated. See A. J. Hubert and H. G. Viehe, *J. Chem. Soc. C*, 228 (1968); A. J. Hubert and H. Reimlinger, *ibid.*, 606 (1968). (b) A stable allenyl amine is reported by J. L. Dumont, *C. R. Acad. Sci.*, **261**, 1710 (1965).

(7) Hindered propargyl amines were prepared by a two-step procedure: (1) reaction of 2,3-dibromopropene with the amine and (2) dehydrobromination with sodium amide. See R. F. Parcell and C. B. Pollard, *J. Amer. Chem. Soc.*, **72**, 2385, 3312 (1950). Reaction of the hindered amine directly with propargyl bromide gave only low (5–10%) yields of the desired product accompanied by large quantities of nondistillable resins.

TABLE I

CONVERSION OF R—X *via*

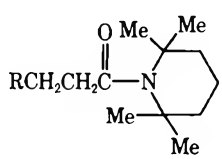


Alkyl halide	—Yield of ynamine, %— Vpc	Isolated	Yield of amide, %[a]
Allyl iodide	62	45	28
Allyl bromide	50		
Allyl chloride	0		
Trimethylchlorosilane	85	60	50
Methyl iodide	50	35	22
n-Butyl iodide		50	22
Geranyl bromide		40[b]	20

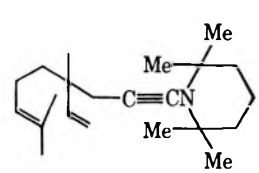
[a] Based on alkyl halide; two-step reaction. [b] Plus 20% **11**.

lithium–halogen exchange was a serious side reaction in alkylations with geranyl bromide. The ynamine **10e** was always accompanied by the hydrocarbon **11**. The chromatographic separation of **10e** and **11** resulted in concomitant hydrolysis of **10e** to the amide **12e** (see below). The nmr spectrum of the distilled ynamine–dimer mixture was consistent with the proposed structure **10e**, as was the mass spectrum which contained a parent ion of *m/e* 315.2926 (calcd for $C_{22}H_{37}N$: 315.2926). None of the product which would result from allylic transposition (**13**) was detected by nmr analysis.

Hydrolysis.—Whereas ynamines **2** and **6** and their derivatives could be smoothly and quantitatively converted to the corresponding amides under very mildly acidic conditions (magnesium sulfate and water), **9** proved resistant to the same hydrolytic procedures. Attempted hydrolysis with 0.1, 1.0, or 3.0 *N* hydrochloric acid or with magnesium sulfate produced varying quantities of amide severely contaminated by several by-products. An 83% yield of the amide **12f** could be obtained, however, upon passage of an ether solution of **9** through a column of activity II acidic alumina (Merck).



12a, R = $(CH_3)_3Si$
b, R = CH_2=$CHCH_2$
c, R = CH_3
d, R = $CH_3(CH_2)_3$
e, R = geranyl
f, R = H



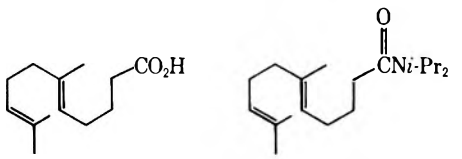
13

In practice, the ynamines could be isolated and then hydrolyzed in a subsequent step or, more conveniently, hydrolyzed directly by passage of the crude alkylation mixture through a column of alumina. Amides were then purified further by chromatography on silica gel.

Hydrolysis of the hindered amides with potassium hydroxide in refluxing ethylene glycol[8] gave the corre-

(8) J. Schmidt-Thomé, *Chem. Ber.*, **88**, 895 (1955).

sponding carboxylic acids. The hydrolysis of **12e** yielded 90% acid **14**, identical (nmr, ir, and tlc) with an authentic sample prepared by an alternate route.[3b]



14 **15**

From the above results it is clear that reactive nucleophiles can be generated by metalation of α,β-ynamines and also that these nucleophiles are susceptible to electrophilic attack at both α and γ carbons[9] with the balance depending to a high degree on steric factors.[10]

Experimental Section

Infrared spectra were taken using a Perkin-Elmer Model 137 infracord, and nmr data were obtained using a Varian Associates Model A-60 spectrometer. Nmr shifts are expressed in parts per million downfield from internal tetramethylsilane. Mass spectra were recorded on an AEI-MS-9 double focusing spectrometer. Vpc analyses were performed on an F & M Model 810 unit using a 9 ft × 0.125 in. column with 5% Carbowax plus 2% KOH on Chromosorb W acid washed, DMCS treated. Microanalyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

Reagents.—The following reagents were used: *n*-butyllithium (Foote Mineral Co.), 1.3 *M* pentane solution; *t*-butyllithium (Foote), 1.8 *M* pentane solution, titrated; diethyl ether (Mallinckrodt A.R.), used from freshly opened can or dried over sodium wire; tetrahydrofuran, distilled from lithium aluminum hydride and stored under argon. All metalations with alkyllithiums were carried out under an argon atmosphere.

2-Bromo-3-(N,N-diisopropylamino)propene.—2,3-Dibromopropene (100 g, 0.5 mol) was added dropwise to a stirred solution of 280 ml (202 g, 2.0 mol) of diisopropylamine and 150 ml of dry benzene. The mixture was refluxed for 12 hr and then allowed to stand overnight. Nmr analysis of small aliquots withdrawn at various intervals served to monitor the course of the reaction. When the reaction was complete, ether was added, the reaction mixture was filtered, and the solvent was evaporated. Distillation of the residue provided 81.5 g of 2-bromo-3-(N,N-diisopropylamino)propene, bp 70–78° (10 mm).

Reaction of 2,2,6,6-Tetramethylpiperidine with 2,3-Dibromopropene.—A mixture of 91.7 g (0.65 mol) of 2,2,6,6-tetramethylpiperidine, 60 g (0.30 mol) of 2,3-dibromopropene, and 90 ml of dry toluene was refluxed for 22 hr and then diluted with 700 ml of ether and filtered. Concentration of the filtrate under reduced pressure and distillation of the residue gave 50.64 g (65%) of 2-bromo-3-(2,2,6,6-tetramethylpiperidyl)propene: bp 45–71° (0.25 mm); nmr (CCl_4) δ 1.01 (s, CH_3, 12 H), 1.50 (s, CH_2, 6 H), 3.24 (t, J = 2 Hz, allyl, 2 H), 5.48 (m, vinyl, 1 H), 6.23 (m, vinyl, 1 H); ir λ_{max}^{neat} 6.08 μ (C=C); mass spectrum *m/e* 261, 259, 246, 244, 190, 188. An exact mass determination gave *m/e* 261.0915 (calcd for $C_{12}H_{22}NBr$: 261.0916).

N,N-Diisopropylpropargylamine.—To a 1-l., three-neck flask, equipped with a Dry Ice–acetone condenser and Hershberg stirrer and containing 400 ml of ammonia was added 1 g of sodium. Addition of 0.5 g of ferric chloride discharged the deep blue color and caused evolution of hydrogen. Additional sodium was added in portions to a total of 20.3 g (0.88 g-atom), and the volume of ammonia was increased to 650 ml. After 1.5 hr of stirring, 81 g (0.37 mol) of 2-bromo-3-(N,N-diisopropylamino)propene was added dropwise and stirring was continued for 5 hr. The ammonia was then allowed to evaporate down to ~200 ml, and 200 ml of ether was added followed by cautious addition of 60 g (1 mol) of solid ammonium chloride. The resulting mixture was stirred overnight; then 200 ml of water was added along with 200 ml of ether. After filtration of the entire reaction mixture through Super-cel, the ether layer was separated, and the aqueous layer was extracted with 100 ml of ether. The combined ether portions were shaken with saturated sodium chloride solution, dried over sodium sulfate, the solvent was evaporated, and the residue was distilled to yield 41.7 g (81%) of N,N-diisopropylpropargylamine: bp 68–72.5° (42–50 mm) [lit.[7] bp 152.5–153° (760 mm)].

1-Propargyl-2,2,6,6-tetramethylpiperidine.—A 1-g piece of sodium was added to a 1-l., three-neck flask equipped with a Dry Ice–acetone condenser and a Hershberg stirrer and containing 500 ml of ammonia. Addition of 0.5 g of ferric chloride discharged the deep blue color and caused evolution of hydrogen. Additional sodium was added in portions to a total of 13.8 g (0.6 g atom). After 1.5 hr, 50 g (0.192 mol) of 2-bromo-3-(2,2,6,6-tetramethylpiperidyl)propene was added dropwise, and stirring was continued for 6 hr. Ether (200 ml) was added prior to cautious addition of 40 g (0.8 mol) of solid ammonium chloride. After 15 min, 250 ml of water was added, and the mixture was stirred an additional hour to evaporate the ammonia. Ether (100 ml) was then added followed by filtration of the entire reaction mixture through Super-cel. The ether layer was separated, and the aqueous phase was extracted with two 200-ml portions of ether. The combined ether solutions were shaken with saturated sodium chloride solution and dried over sodium sulfate, the solvent was evaporated, and the residue was distilled to yield 30.84 g (89%) of 1-propargyl-2,2,6,6-tetramethylpiperidine: bp 80–80.5° (8 mm); nmr (CCl_4) δ 1.10 (s, CH_3, 12 H), 1.47 (s, CH_2, 6 H), 1.90 (t, J = 2.5 Hz, C≡C**H**, 1 H), 3.27 (d, J = 2.5 Hz, CH_2C≡C, 2 H); ir λ_{max}^{neat} 3.1 μ (C≡C—H); mass spectrum *m/e* 179, 164, 108, 69, 42, 41, 39. An exact mass determination gave *m/e* 179.1677 (calcd for $C_{12}H_{21}N$: 179.1674).

N,N-Diisopropylamino-1-propyne[6a] (6).—A catalyst was prepared by dissolving 2.0 g of potassium in 100 ml of ammonia, then adding a crystal (~5 mg) of ferric chloride. The mixture was stirred for 1 hr after which 20 ml of dry basic alumina (Woelm) was added, and the ammonia was allowed to evaporate with stirring. The powder which remained was heated overnight at 65° under argon. The catalyst was poured, under argon, into a burette wrapped in heating tape and equipped with a thermometer. The column was heated to 63–65° and maintained at this temperature for the course of the reaction. A solution of 41 g (0.30 mol) of N,N-diisopropylpropargylamine in 65 ml of hexane was passed through the column at a flow rate of between 15 and 30 ml/hr (av 20 ml/hr). The eluent was collected in 5- to 10-ml portions and the contents analyzed by ir spectroscopy. All fractions showed a strong band at 4.4 μ (C≡C—N) and some absorption at 6.1 μ (C=C, dimers and polymers), and no bands at either 2.9 μ (C≡C—H) or 5.2 μ (C=C=C—N). The hexane was evaporated from the combined fractions, and the residual liquid was distilled from calcium hydride to give 30.75 g (75%) of **6**: bp 42.5–43.5° (12 mm); nmr (CCl_4) δ 1.10 (d, J = 6.5 Hz, $CHCH_3$, 12 H), 1.86 (s, ≡CCH_3, 3 H), 3.0 (sept, J = 6.5 Hz, **C**H, 2 H); ir $\lambda_{max}^{CCl_4}$ 4.48 μ (C≡C).

1-Propynyl-2,2,6,6-tetramethylpiperidine[6a] (9).—The isomerization catalyst, prepared as above, was poured, under argon, into a 60-ml addition funnel wrapped in heating tape and equipped with a thermometer. The column was heated to 63–65° and maintained at this temperature for the duration of the reaction. A solution of 30 g (0.16 mol) of 1-propargyl-2,2,6,6-tetramethylpiperidine in 50 ml of hexane was passed through the column at a flow rate of ~1 drop every 20 to 40 sec. The eluent was collected in 5- to 10-ml portions, and the contents were analyzed by ir spectroscopy. Any fractions containing a band at 3.1 μ (C≡C—H) were recirculated. The hexane was evaporated from the combined fractions, and the residual liquid was distilled from calcium hydride to give 22.6 g (75%) of the ynamine (**9**): bp 86–86.5° (12 mm); nmr (CCl_4) δ 1.18 (s, CH_3, 12 H), 1.45 (s, CH_2, 6 H), 1.88 (s, C≡CCH_3, 3 H); ir $\lambda_{max}^{CCl_4}$ 4.51 μ (C≡C); mass spectrum *m/e* 179, 164, 126, 109, 96, 70, 69, 58, 56, 55. An exact mass determination gave *m/e* 179.1674 (calcd for $C_{12}H_{21}N$: 179.1674).

Hydrolysis of N,N-Diisopropylamino-1-propyne (6).—A solution of 0.25 ml (0.20 g, 1.44 mmol) of N,N-diisopropylamino-1-propyne (**6**), in 1 ml of tetrahydrofuran was added dropwise to 10 ml of a 1:1 mixture of tetrahydrofuran and 1% aqueous magnesium sulfate at 0°. After 20 min of stirring at room temperature, the tetrahydrofuran was evaporated, and the residual solution was extracted with two 30-ml portions of ether. The ether extracts

(9) (a) For a theoretical treatment of one aspect of this problem, see G. Klopman, *J. Amer. Chem. Soc.*, **90**, 223 (1968); (b) R. Gompper, *Angew. Chem., Int. Ed. Engl.*, **3**, 558 (1964); (c) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *J. Amer. Chem. Soc.*, **77**, 6269 (1955).

(10) Compare (a) E. J. Corey and D. E. Cane, *J. Org. Chem.*, **34**, 3053 (1969), and (b) E. J. Corey and H. A. Kirst, *Tetrahedron Lett.*, 5041 (1968).

were then shaken with saturated aqueous sodium chloride and dried over magnesium sulfate. Evaporation of the solvent gave 0.250 g of the expected N,N-diisopropylpropionamide, identical with a sample prepared by reaction of diisopropylamine with propionyl chloride: nmr (CCl_4) δ 1.02 (t, J = 7.5 Hz, CH_3, 3 H), 1.25 (d, J = 7 Hz, $CHCH_3$, 12 H), 2.22 (q, J = 7.5 Hz, CH_2, 2 H), 3.0–4.3 (m, CH, 2 H); ir λ_{max}^{neat} 6.08 μ (C(O)N).

Hydrolysis of 1-Propynyl-2,2,6,6-tetramethylpiperidine (9).—1-Propynyl-2,2,6,6-tetramethylpiperidine (9) (0.186 g, 1.04 mmol) in 2 ml of ether was placed on a column packed with 5.1 g of acid-washed alumina (Merck, activity II). Ether (25 ml) was passed through the column, and evaporation of the solvent gave 0.176 g (83%) of 1-propionyl-2,2,6,6-tetramethylpiperidine (12f): nmr (CCl_4) δ 1.07 (t, J = 7 Hz, CH_2CH_3, 3 H), 1.42 (s, CH_3, 12 H), 1.73 (s, CH_2, 6 H), 2.28 (q, J = 7 Hz, CH_2CH_3, 2 H).

Metalation of N,N-Diethylamino-1-propyne (2).[11] Reaction with Trimethylchlorosilane.—*n*-Butyllithium (1.3 *M*, 21.0 ml, 27.3 mmol) was added to a dry flask, and the pentane was evaporated under vacuum. Ether (28 ml) was then added at 0° followed by 3.17 g (27.3 mmol) of tetramethylethylenediamine and 3.04 g (27.3 mmol) of 2. The solution was stirred for 5.5 hr at 0°, after which 2.96 g (27.3 mmol) of trimethylchlorosilane was added, and stirring was continued for 14 hr. At this point a 1-ml aliquot was withdrawn, diluted with pentane, and filtered. Analysis by vpc (160°) showed three components: tetramethylethylenediamine (0.8 min, area 1); 2 (1.2 min, area 0.15); and 3 (2.4 min, area 0.85). The remainder of the reaction mixture was poured into 30 ml of 1% potassium carbonate solution at 0° and quickly extracted with two 30-ml portions of ether at 0°. The combined ether extracts were shaken with 5 ml of saturated sodium chloride solution containing 1% potassium carbonate, also at 0°, then dried over sodium sulfate containing a small amount of potassium carbonate. Evaporation of the solvent left 4.84 g of oil of which 3.37 g were distilled from calcium hydride in a Holtzmann apparatus to yield 1.92 g (57%) of 3: bp 30° (0.02 mm); nmr (CCl_4) δ 0.08 (s, $SiCH_3$, 9 H), 1.14 (t, J = 7 Hz, CH_3, 6 H), 1.45 (s, $SiCH_2$, 2 H), 2.78 (q, J = 7 Hz, NCH_2, 4 H); ir $\lambda_{max}^{CCl_4}$ 4.50 μ (C≡C).

Metalation of N,N-Diethylamino-1-propyne (2). Reaction with Allyl Bromide.—N,N-Diethylamino-1-propyne (2) (3.90 mmol) was metalated in the manner described above. After 5.5 hr at 0° the solution was cooled to −40°, and 0.472 g (3.90 mmol) of allyl bromide was added. At the end of 0.5 hr, two 0.2-ml aliquots were withdrawn, diluted with pentane, and filtered. The first of these was analyzed by vpc (145°). Besides tetramethylethylenediamine (area 1) and 2 (area 0.15) there were no significant amounts of material with retention times longer than 2. The ir spectrum of the second aliquot showed an allene absorption at 5.2 μ.

Metalation of N,N-Diisopropylamino-1-propyne (6). Reaction with Trimethylchlorosilane.—*n*-Butyllithium (1.3 *M*, 3.00 ml, 3.90 mmol) was added to a dry flask, and the pentane was evaporated under vacuum. Ether (2.0 ml) was added at 0° followed by 0.452 g (3.90 mmol) of tetramethylethylenediamine and 0.552 g (3.90 mmol) of 6. The solution was stirred for 8.5 hr at 0°, after which 0.423 g (3.90 mmol) of trimethylchlorosilane was added. Vpc analysis (140°) of an aliquot showed three components: tetramethylethylenediamine (0.8 min, area 1), 6 (1.4 min, area 0.2), and 7 (3.2 min, area 0.8). Potassium carbonate (10 ml of 1% solution) was added to the remainder of the reaction mixture at 0°, and the resulting mixture was extracted with two 10-ml portions of ether at 0°. After shaking the combined ether extracts at 0° with 2 ml of saturated sodium chloride containing 1% potassium carbonate and drying over sodium sulfate–potassium carbonate, evaporation of the solvent gave 0.690 g of an oil shown by nmr analysis to consist of a mixture of 6 and 7 in a ratio of ~1:4: nmr (7) (CCl_4) δ 0.08 (s, $SiCH_3$, 9 H), 1.11 (d, J = 6.5 Hz, $CHCH_3$, 12 H), 1.53 (s, $SiCH_2$, 2 H), 3.00 (sept, J = 6.5 Hz, CH, 2 H).

Metalation of N,N-Diisopropylamino-1-propyne (6). Reaction with Allyl Bromide.—*n*-Butyllithium (1.3 *M*, 1.00 ml, 1.30 mmol) was added to a dry flask, and the pentane was evaporated under vacuum. Tetrahydrofuran (0.68 ml) was added at −20° followed by 0.15 g (1.27 mmol) of 6. The solution was stirred for 17 hr at −20° after which 0.158 g (1.30 mmol) of allyl bromide was added, and the solution was stirred for 1.25 hr at 0°. At this point 0.112 g (0.65 mmol) of dodecane was added as an internal vpc standard followed by 5 ml of 1% potassium carbonate at 0°. After the extraction procedure described above, vpc analysis (145°) showed two major components: 6 (1.4 min, area 0.14), and 8 (3.8 min, area 0.40). In a separate experiment, distillation of 0.69 g of the crude reaction product gave, after a small forerun, 0.1 g of 8: bp 60–62° (5 mm); greater than 90% pure by nmr (CCl_4), δ 1.10 (d, J = 6.5 Hz, CH_3, 12 H), 2.1–2.35 (m, CH_2, 4 H), 3.00 (sept, J = 6.5 Hz, CH, 2 H), 4.8–5.2 (m), and 5.5–6.2 (m) (vinyl, 3 H). See Table II.

TABLE II

METALATION AND ALLYLATION OF 6

Metalation			Allylation			
Solvent	Temp, °C	Time, hr	Temp, °C	Time, hr	% yield of 8	% yield of 6
Ether	0	16	0	1	25	20
THF	−20	16.5	0	1.25	40	14
THF	−20	19	0[a]	1	23	11
n-Pentane	25	19	25[b]	1	5[b]	10
THF	−20	16	0[c]	0.5	26	26

[a] Hexamethylphosphoramide (15% vol) added prior to reaction with allyl bromide. [b] Reaction with trimethylchlorosilane; yield of 7. [c] Sodium methoxide (1 equiv) added prior to reaction with allyl bromide.

Metalation of N,N-Diisopropylamino-1-propyne (6). Reaction with Geranyl Bromide.—*n*-Butyllithium (1.3 *M*, 3.00 ml, 3.90 mmol) was added to a dry flask, and the pentane was evaporated under vacuum. Tetrahydrofuran (2.00 ml) was added at −20° followed by 0.45 g (3.90 mmol) of tetramethylethylenediamine and 0.544 g (3.90 mmol) of 6. The solution was stirred for 17 hr at −20°. Geranyl bromide (0.846 g, 3.90 mmol), in 1 ml of tetrahydrofuran, was added dropwise at −10°, and the solution was stirred for 1.5 hr at 0°. The reaction mixture was then added dropwise to 30 ml of a 1:1 mixture of tetrahydrofuran and 1% aqueous magnesium sulfate at 0°. The tetrahydrofuran was evaporated, and the residual solution was extracted with three 40-ml portions of ether. Shaking of the ether extracts with saturated aqueous sodium chloride followed by drying over magnesium sulfate and evaporation of the solvent gave 0.886 g of crude oil. Preparative layer chromatography (silica gel, 6:2:1 hexane–methylene chloride–tetrahydrofuran) on 0.297 g of this oil gave two main bands (hot-wire visualization). The slower moving of the two (R_f 0.2–0.3) gave 0.064 g of the desired amide, 15: nmr (15) (CCl_4) δ 1.23 (d, J = 7 Hz, $CHCH_3$, 12 H), 1.5–1.8 (m, $=CCH_3$, CH_2, 11 H), 1.8–2.5 (m, allyl, CH_2CO, 8 H), 2.5–4.2 (m, NCH, 2 H), 5.1 (m, vinyl, 2 H); ir λ_{max}^{neat} 6.08 μ (C(O)N).

Elution of the second band (R_f 0.33) gave 0.060 g of material shown by nmr and tlc analysis to consist of a mixture of 15 and an unidentified substance.

The Metalation–Alkylation of 1-Propynyl-2,2,6,6-tetramethylpiperidine (9). General Procedure.—*t*-Butyllithium (1.8 *M*, 0.72 ml, 1.3 mmol) was added dropwise to a solution of 0.15 g (1.30 mmol) of tetramethylethylenediamine and 0.232 g (1.30 mmol) of 9 in 0.5 ml of ether at −78°. The solution was then briefly warmed to 0° and stirred until homogeneous, then cooled to −50°. After several minutes a solid formed which dissolved upon rewarming to 0° for 0.5 hr. Alkyl halide (1.3 mmol) was added dropwise, and the resultant mixture was stirred overnight at 0°.

A. Isolation of Alkylated Ynamines.—Cold aqueous 1% potassium carbonate (4 ml) was added, and the reaction mixture was extracted at 0° with three 4-ml portions of ether. The ether extracts were shaken with saturated aqueous sodium chloride containing 1% potassium carbonate and then dried over sodium sulfate–potassium carbonate. The extractions were performed at 0° as rapidly as possible to avoid any unwanted hydrolysis. Filtration and evaporation of the solvent gave an oil which was purified by high-vacuum (0.0008 mm) bulb-to-bulb distillation.

B. Direct Hydrolysis to the Amide.—In this case the reaction mixture was diluted with additional ether, then passed through a column of 25 g of activity II acidic alumina (Merck) with 100 ml of ether. Evaporation of the solvent and preparative layer chromatography (plc) on silica gel yielded the pure amide.

1-(3-Trimethylsilylpropynyl)-2,2,6,6-tetramethylpiperidine (10a).—Trimethylchlorosilane (0.138 g, 1.30 mmol) was added at 0° to 1.3 mmol of the lithio anion of 9, generated in the usual manner, and the reaction mixture was stirred overnight. Addi-

(11) Fluka, A. G., Buchs, Switzerland.

tion of 4 ml of 1% aqueous potassium carbonate followed by the usual isolation procedure gave 0.276 g of crude oil which was purified by bulb-to-bulb distillation at 25° (0.0008 mm) to give 0.203 g (62%) of **10a**: nmr (CCl_4) δ 0.08 [s, $(CH_3)_3Si$, 9 H], 1.13 (s, CH_3, 12 H), 1.4 (m, CH_2, 8 H); ir $\lambda_{max}^{CCl_4}$ 4.48 μ (C≡C); mass spectrum *m/e* 251, 236, 168, 126, 84, 83. An exact mass determination gave *m/e* 251.2070 (calcd for $C_{15}H_{29}NSi$: 251.2069).

1-(5-Hexen-1-ynyl)-2,2,6,6-tetramethylpiperidine (10b).—Allyl iodide (0.222 g, 1.30 mmol) was added to 1.3 mmol of the lithio anion of **9**, and the reaction mixture was stirred overnight. The usual isolation procedure gave 0.254 g of crude oil which was purified by bulb-to-bulb distillation at 25° (0.0008 mm) to give 0.126 g (42%) of **10b** as a clear oil: nmr (CCl_4) δ 1.15 (s, CH_3, 12 H), 1.46 (s, CH_2, 6 H), 2.20 (m, allyl, 4 H), 4.75–5.15 (m, vinyl, 2 H), 5.4–6.2 (m, vinyl, 1 H); ir $\lambda_{max}^{CCl_4}$ 4.49 (C≡C), 6.07 (C=C), 10.1 and 10.9 μ (CH=CH_2); mass spectrum *m/e* 219, 204, 178, 126, 122, 109, 94, 70, 69. An exact mass determination gave *m/e* 219.1985 (calcd for $C_{15}H_{25}N$: 219.1987).

1-Butynyl-2,2,6,6-tetramethylpiperidine (10c).—Methyl iodide (0.185 g, 1.30 mmol) was added to 1.3 mmol of the lithio anion of **9**, and the reaction mixture was stirred overnight. The usual isolation procedure gave 0.251 g of crude product which was purified by bulb-to-bulb distillation at 25° (0.0008 mm) to give 0.096 g (38%) of **10c**: nmr (CCl_4) δ 1.12 (t, J = 7 Hz, CH_3) and 1.18 (s, CH_3) (total 15 H), 1.47 (s, CH_2, 6 H), and 2.25 (q, J = 7 Hz, CH_2, 2 H); ir $\lambda_{max}^{CCl_4}$ 4.51 μ (C≡C); mass spectrum *m/e* 193, 178, 168, 126, 109. An exact mass determination gave *m/e* 193.1824 (calcd for $C_{13}H_{23}N$: 193.1830).

1-Heptynyl-2,2,6,6-tetramethylpiperidine (10d).—*n*-Butyl iodide (0.239 g, 1.30 mmol) was added to 1.3 mmol of the anion of **9**, and the reaction mixture was stirred overnight. The usual isolation procedure gave 0.293 g of crude product which was purified by bulb-to-bulb distillation at 30° (0.001 mm) to yield 0.149 g (49%) of **10d**: nmr (CCl_4) δ 1.1 (m, CH_3) and 1.18 (s, CH_3) (total area 15 H), 1.4 (m, CH_2, 12 H), 2.3 (m, CH_2C≡C, 2 H); ir $\lambda_{max}^{CCl_4}$ 4.50 μ (C≡C); mass spectrum *m/e* 235, 220, 180, 178, 168, 164, 126. An exact mass determination gave *m/e* 235.2291 (calcd for $C_{16}H_{29}N$: 235.2300).

Reaction of the Lithio Anion of 1-Propynyl-2,2,6,6-tetramethylpiperidine (9) with Geranyl Bromide.—Geranyl bromide (0.282 g, 1.30 mmol) was added to 1.3 mmol of the lithio anion of **9**, and the reaction mixture was stirred overnight. The usual isolation procedure gave 0.423 g of crude product which was bulb-to-bulb distilled at 50–80° (0.0008 mm) to give 0.270 g of oil: nmr analysis showed this material to consist of a mixture of 0.55 mmol of **10e** and 0.25 mmol of **11**: nmr (**10e**, interpolated) (CCl_4) δ 1.18 (s, CH_3, 12 H), 1.46 (s, CH_2, 6 H), 1.63 (m, C=C-CH_3, 9 H), 2.1 (m, allyl CH_2, 8 H), 5.0 (m, vinyl, 2 H); mass spectrum *m/e* 315,300. An exact mass determination gave *m/e* 315.2926 (calcd for $C_{22}H_{37}N$: 315.2926).

1-(3-Trimethylsilylpropionyl)-2,2,6,6-tetramethylpiperidine (12a).—Trimethylchlorosilane (0.552 g, 5.2 mmol) was added to 5.20 mmol of the lithio anion of **9**, generated in the usual fashion in 2.0 ml of ether. After the reaction mixture had stirred overnight, 25 ml of pentane was added, the solvent was evaporated, and the residue was dissolved in *n*-hexane and placed on a column of 60 g of activity II acidic alumina (Merck). Elution with 100 ml of hexane gave a forerun of 0.069 g of oil after evaporation. Further elution with 100 ml of ether and evaporation of the solvent gave 0.992 g of oil. Preparative layer chromatography (silica gel; 12:4:1 hexane–methylene chloride–tetrahydrofuran) of 0.950 g of this substance and removal of the uv fluorescent band of R_f 0.4 gave 0.633 g (47%) of **12a** as a white solid: nmr (CCl_4) δ 0.05 [s, $(CH_3)_3Si$, 9 H], 0.8 (m, CH_2Si, 2 H), 1.42 (s, CH_3, 12 H), 1.74 (s, CH_2, 6 H), 2.2 (m, CH_2CO, 2 H); ir λ_{max}^{neat} 6.08 μ [C(O)N]; mass spectrum *m/e* 269, 254, 170, 168, 130, 126, 73, 69. An exact mass determination gave *m/e* 269.2185 (calcd for $C_{15}H_{31}NOSi$: 269.2175). An analytical sample (mp 49–50.5°) was prepared by sublimation at 45° (0.01 mm).

Anal. Calcd for $C_{15}H_{31}NOSi$: C, 66.85; H, 11.59; N, 5.20. Found: C, 66.94; H, 11.56; N, 5.44.

1-(5-Hexenoyl)-2,2,6,6-tetramethylpiperidine (12b).—Allyl iodide (0.222 g, 1.30 mmol) was added to 1.30 mmol of the lithio anion of **9**. After the reaction mixture had stirred overnight, ether was added, and the mixture was passed through a column of 25 g of activity II acidic alumina (Merck) with a total of 100 ml of ether as eluent. Evaporation of the solvent yielded 0.235 g of oil which was purified by plc (silica gel; 18:6:1 hexane–methylene chloride–tetrahydrofuran) to give 0.086 g (28%) of **12b** (R_f 0.4): nmr (CCl_4) δ 1.42 (s, CH_3, 12 H), 2.72 (s and m, CH_2, 8 H), 2.2 (m, allyl CH_2, 4 H), 5.0 (m, vinyl, 2 H), 5.8 (m, vinyl, 1 H); ir λ_{max}^{neat} 6.09 (C(O)N), 10.1, and 10.95 μ (vinyl); mass spectrum *m/e* 237, 222, 126, 70, 69. An exact mass determination gave *m/e* 237.2095 (calcd for $C_{15}H_{27}NO$: 237.2093). An analytical sample was prepared by bulb-to-bulb distillation at 80° (0.01 mm).

Anal. Calcd for $C_{15}H_{27}NO$: C, 75.89; H, 11.46; N, 5.90. Found: C, 75.96; H, 11.52; N, 5.84.

1-Butyryl-2,2,6,6-tetramethylpiperidine (12c).—Reaction of 1.30 mmol of the lithio anion of **9** with 0.185 g (1.30 mmol) of methyl iodide gave, after hydrolysis and purification by plc, 0.060 g (22%) of **12c**: nmr (CCl_4) δ 0.92 (t, J = 7 Hz, CH_3, 3 H), 1.42 (s, CH_3, 12 H), 1.6 (m, CH_2) and 1.72 (s, CH_2) (total 8 H), 2.3 (m, CH_2CO, 2 H); ir λ_{max}^{neat} 6.09 μ [C(O)N]; mass spectrum *m/e* 211, 196, 168, 126. An exact mass determination gave *m/e* 211.1926 (calcd for $C_{13}H_{25}NO$: 211.1936). An analytical sample was prepared by bulb-to-bulb distillation at 80° (0.01 mm).

Anal. Calcd for $C_{13}H_{25}NO$: C, 73.88; H, 11.92; N, 6.63. Found: C, 73.50; H, 11.75; N, 6.74.

1-Heptanoyl-2,2,6,6-tetramethylpiperidine (12d).—Reaction of 1.30 mmol of the lithio anion of **9** with 0.239 g (1.30 mmol) of *n*-butyl iodide gave, after hydrolysis and purification by plc, 0.074 g (22%) of **12d**: nmr (CCl_4) δ 0.9 (m, CH_3, 3 H), 1.3 (m, CH_2) and 1.42 (s, CH_3) (total 20 H), 1.72 (s, CH_2, 6 H), 2.2 (m, CH_2CO, 2 H); ir λ_{max}^{neat} 6.09 μ [C(O)N]; mass spectrum *m/e* 253, 238, 170, 126, 70, 69. An exact mass determination gave *m/e* 253.2408 (calcd for $C_{16}H_{31}NO$: 253.2406). An analytical sample was prepared by bulb-to-bulb distillation at 80° (0.01 mm).

Anal. Calcd for $C_{16}H_{31}NO$: C, 75.83; H, 12.34; N, 5.53. Found: C, 75.80; H, 12.23; N, 5.69.

1-(3-Geranylpropionyl)-2,2,6,6-tetramethylpiperidine (12e).—Geranyl bromide (0.282 g, 1.30 mmol) was treated with 1.30 mmol of the lithio anion of **9**. After the reaction mixture had stirred overnight, 10 ml of pentane was added, the solution was filtered, and the solvent was evaporated. The residue was redissolved in hexane and placed on a column of 25 g of activity II acidic alumina (Merck). The column was washed with hexane until all the hydrocarbon material (0.057 g of **11**) had been eluted. Ether (100 ml) eluted the more polar material, giving 0.244 g of oil after solvent evaporation. This oil was purified by plc (silica gel; 6:2:1 hexane–methylene chloride–tetrahydrofuran; two developments) to yield 0.094 g (22%) of **12e**: nmr (CCl_4) δ 1.41 (s, CH_3, 12 H), 1.6 (m, C=CCH_3, 9 H), 1.72 (s, CH_2, 6 H) superimposed on 1.6 (m, CH_2, 2 H), 2.1 (m, C=CCH_2 and CH_2-CO, 8 H), 5.1 (m, vinyl, 2 H); ir λ_{max}^{neat} 6.09 μ [C(O)N]; mass spectrum *m/e* 333, 318, 264, 196, 183, 168, 164, 140, 127, 126, 125, 124, 109. An exact mass determination gave *m/e* 333.3039 (calcd for $C_{22}H_{39}NO$: 333.3031). An analytical sample was prepared by bulb-to-bulb distillation at 150° (0.01 mm).

Anal. Calcd for $C_{22}H_{39}NO$: C, 79.22; H, 11.79; N, 4.20. Found: C, 79.08; H, 11.69; N, 4.39.

Alkaline Hydrolysis of 1-(3-Geranylpropionyl)-2,2,6,6-tetramethylpiperidine (12a).—Ethylene glycol (5 ml) containing 0.043 g (0.13 mmol) of **12e** and 0.75 g (0.013 mol) of potassium hydroxide was refluxed for 15 hr, whereupon the reaction mixture was diluted with 40 ml of water, acidified with hydrochloric acid, and extracted with three 50-ml portions of ether. The combined ether layers were shaken with 15 ml of saturated aqueous sodium chloride and dried over magnesium sulfate. Evaporation of the solvent gave 0.025 g (90%) of **14**, identical by nmr, ir, and tlc with an authentic sample:[3b] nmr (CCl_4) δ 1.6 (m, C=CCH_3, 9 H), 1.6–2.5 (m, CH_2, 10 H), 5.0 (m, vinyl, 2 H), 11.3 (s, CO_2H, 1 H); ir $\lambda_{max}^{CCl_4}$ 2.8–4.2 (O—H), 5.81 μ (C=O).

Registry No.—**3**, 25665-32-1; **6**, 25665-33-2; **7**, 25665-34-3; **8**, 25665-35-4; **9**, 25665-36-5; **10a**, 25716-08-9; **10b**, 25665-37-6; **10c**, 25665-38-7; **10d**, 25665-39-8; **10e**, 25662-77-5; **12a**, 25665-40-1; **12b**, 25665-41-2; **12c**, 25665-42-3; **12d**, 25665-43-4; **12e**, 25662-78-6; **12f**, 25665-44-5; **15**, 25716-09-0; 2-bromo-3-(N,N-diisopropylamino)propene, 14326-36-4; 2-bromo-3-(2,2,6,6-tetramethylpiperidyl)propene, 25665-46-7; 1-propargyl-2,2,6,6-tetramethylpiperidine, 25665-47-8.

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Optical Activity. An Empirical Correlation between Optical Rotation and Bond Refraction[1]

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An empirical correlation between optical rotation and bond refraction has been discovered and it has been used to correlate the rotations of a number of *sec*-butyl, *sec*-pentyl, *sec*-octyl and α-phenethyl compounds, including the organic derivatives of mercury, silicon, germanium, tin, and lead.

During the course of investigations related to the stereochemistry of electrophilic aliphatic substitution[4] the question of the rotations of optically pure 2-haloalkanes has arisen repeatedly. These fundamental physical constants, necessary to the complete elucidation of the mechanisms of many organic reactions,[5] have been particularly elusive.

Classical chemical techniques for the determination of the values of optically pure alkyl halides are limited to interconversion reactions. This method has been applied to 2-bromo-[6b] and 2-chlorobutane[6a] by Letsinger using the following reaction sequence.

$$(+)\text{-}C_2H_5(CH_3)CHBr + PhCH_2Na \longrightarrow (-)\text{-}C_2H_5(CH_3)CHCH_2Ph \quad (1)$$
$$[\alpha]^{25}D\ +6.84° \qquad [\alpha]^{25}D\ -2.25°$$

$$(+)\text{-}C_2H_5(CH_3)CHCH_2Br + PhNa \longrightarrow (+)\text{-}C_2H_5(CH_3)CHCH_2Ph \quad (2)$$
$$[\alpha]^{25}D\ +3.84° \qquad [\alpha]^{25}D\ +10.73°$$

From the accepted value[7] for the rotation of pure 2-methyl-1-bromobutane ($[\alpha]^{25}D \pm 4.04°$), the maximum value for the rotation of 1-phenyl-2-methylbutane is determined to be $[\alpha]^{25}D\ +11.28°$; consequently the product from reaction 1 is 19.94% optically pure. The starting 2-bromobutane must be at least 19.94% optically pure; the maximum value for the rotation of 2-bromobutane is $[\alpha]^{25}D$ 6.84°/0.1994, or $[\alpha]^{25}D \pm 34.3°$. A similar analysis for 2-chlorobutane gives an upper limit of $[\alpha]^{25}D \pm 38°$.

Conversion of the alcohols, whose pure enantiomers are readily obtained by resolution, to alkyl halides is the usual method by which the minimum values for the rotation are obtained. This conversion involves variable amounts of racemization depending upon reagents and conditions. The halogen cleavage of optically active alkylmercuric salts is a superior method of obtaining minimum values.[4b] 2-Bromobutane of the highest observed rotation, $[\alpha]^{25}D\ +33.1°$, was obtained in this manner.

Skell, Allen, and Helmkamp[8] have devised a procedure for the determination of the optical purity of 2-bromobutane which differs from the classical method of interconversion. A study of the base elimination reaction of optically active $CH_3CH(D)CH(Br)CH_3$ led to a value of $[\alpha]^{25}D \pm 39.4°$ for the rotation of optically pure 2-bromobutane. In view of Letsinger's absolute upper limit of $[\alpha]^{25}D \pm 34.3°$, the value of 39.4° is unlikely.

Goodwin and Hudson[9] have also expressed doubt as to the validity of this upper limit of 39.4°. A value of $[\alpha]^{25}D\ -33.4°$ for L-(−)-2-bromobutane was observed and a maximum value of 34.8° was calculated. Whitesides and Fischer, *et al.*,[10] have recently reviewed the available data, including their own, and have expressed the view that the value probably lies between 33.4 and 35.7°. This range is in good agreement with the estimate in the present investigation of 33.1 to 35.3°.

Traynham[11] has summarized the available data for 2-bromooctane. Data for other alkyl halides are, in general, lacking (see Table III).

Theoretical[12] and empirical[13] approaches have had limited success in the precise prediction of optical rotations. The qualitative (sign of rotation) and quantitative success of Brewster's method[13] suggests that a more empirical approach may yield a relationship between an easily measured physical property and optical rotation.

Brewster's hypothesis[13] that "A center of optical activity can usefully be described as an asymmetric screw pattern of polarizability" and that the magnitude of the molecular rotation[14] produced by such a pattern is related to the refractions of the atoms making up the pattern led to the discovery that there is a linear correlation between the bond refractions of the carbon–halogen bonds and the molecular rotations of 2-halobutanes of equal optical purities and identical configurations, Figure 1. The values for the 2-halobutanes were obtained from the products of the halogen cleavage of alkylmercuric salts under conditions of complete retention,[4a,b] Table I. Since these alkyl halides were obtained in one laboratory from the same compound, they are expected to represent a set possessing good internal consistency.

(1) From the Ph.D. Dissertation of D. D. Davis, University of California, Berkeley, Aug 1966.

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(14) The molecular optical rotation (molecular rotation, M) as used here corresponds to the quantity $[M] = [\alpha]\,(\text{mol wt})/100$.

Table I

Rotational Relationships of Alkyl Halides from Alkylmercuric Halides[a]

(S)-(+)-sec-BuHgX			(S)-(+)-sec-BuX		
X	$[\alpha]^{25}D$ (c 4, EtOH)[b]	Conditions	X	$[\alpha]^{25}D$ (neat)	$[M]^{25}D$ (neat)
Br	25.8	Br_2, pyridine-γ-collidine, −65°	Br	33.1	45.3
Cl	26.0	Br_2, pyridine-α-picoline, −75°	Br	32.6	44.7
Cl	26.0	Cl_2, pyridine, −30°	Cl	36.0	33.3
Cl	26.0	ICl, pyridine-DMF, −10°	I	33.4	61.6

[a] References 4a and 4b. [b] Actual conversions carried out with material of lower activity and then recalculated using the maximum reported value for 2-bromomercuributane (25.8°).

With the working hypothesis that the magnitude of the molecular rotation of an asymmetric screw pattern is linearly related to the refractions of the bonds making up the pattern, the bond refraction-optical rotation relationship was investigated in a number of systems.

The common bond refractions[15] used in this study are listed in Table II.[16] The values given are the mean of

Table II

Common Bond Refractions[a]

Bond	Refraction (cm³, 20°, sodium D line)
C–H	1.676
C_{al}–C_{al}	1.296
C_{al}–C_{ar}	1.59
C_{ar}–C_{ar}	2.688
C=C	4.17
C≡C (terminal)	5.87
C–F	1.44
C–Cl	6.51, 6.74 in 2-chlorobutane
C–Br	9.32, 9.80 in 2-bromobutane
C–I	14.61, 14.08 in 2-iodobutane
C–O (ethers)	1.54
O–H (alcohols)	1.66
O–H (acids)	1.80
C=O	3.32
C≡N	4.82
C–N	1.57
N–H	1.76
C–Hg	7.21, 7.51 for secondary compounds
Hg–Cl	10.9[b]
Hg–Br	14.5[b]

[a] Reference 16. [b] B. C. Curran, *J. Amer. Chem. Soc.*, **64**, 830 (1942).

a large number of compounds containing such a bond. In the interest of higher accuracy the experimental value has been used when available. If a specific value is not available, then the bond refraction for the most nearly analogous compound has been used (*i.e.*, for the *sec*-pentyl and *sec*-octyl series the bond refraction of the similarily substituted *sec*-butyl derivative was used).

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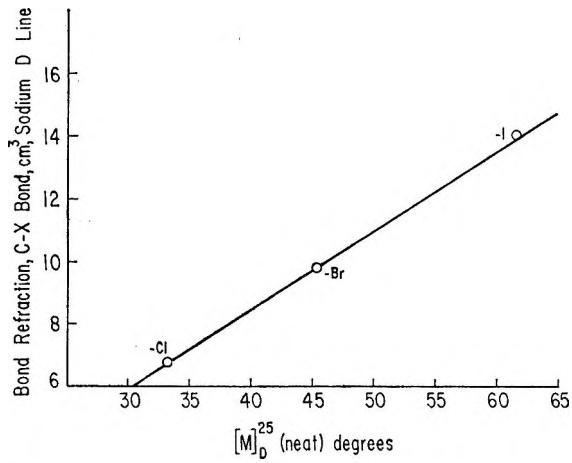


Figure 1.—Relationship between bond refraction and molecular optical rotation, *sec*-butyl halides.

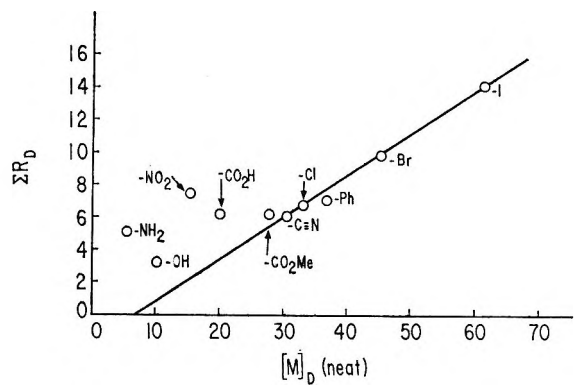


Figure 2.—Bond refraction-optical rotation correlation, *sec*-butyl compounds including nonsymmetrical substituents.

Results

In the *sec*-butyl series the alcohol, acid, and amine are easily resolved to optical purity and when plotted in a similar manner (using ΣR_D for multivalent substituents[17]) the points for these compounds are found to fall to the left of the line determined by the halides (Figure 2) and are not correlated.[18] Since neither carboxy, amino, nor hydroxy substituents are correlated, it appears that there is a symmetry requirement for correlation. Lack of fit was observed for the nitro and phenyl groups but the methyl group does correlate, (*vide infra*) indicating that a threefold axis of rotation (which coincides with the asymmetric carbon-substituent axis) is the minimum symmetry requirement.

It is also expected that a similarity in rotamer populations is also necessary, but there are too few data available to test this aspect. For the majority of the compounds discussed here it is expected that the rotamer with the alkyl groups *trans* is heavily populated.

(17) The rotations of the alkyl–HgX (X = Cl, Br, R) indicate that the Hg–X bond also contributes to the pattern of polarizability. The influence of bonds 2,3 to the asymmetric center is a general phenomenon. The substituent bond refraction, as pertains to optical activity, is then defined to be the sum of the bond refractions surrounding the atom bonded to the asymmetric center, and denoted by ΣR. For example, $\Sigma R_D(-C{\equiv}N) = R_D(C{-}C) + R_D(C{\equiv}N)$; $\Sigma R_D(-HgR) = 2R_D(C{-}Hg)$.

(18) Points falling to the left of the line are either not correlated or not of the same optical purity as those on the line. Since it is generally accepted that Kenyon's value[19] for the rotation of *sec*-butyl alcohol represents optical purity, the points falling to the left of the line are not correlated. A point falling to the right of the line indicates that it is either not correlated or that the line represents a lesser degree of optical purity.

(19) R. H. Pichard and J. Kenyon, *J. Chem. Soc.*, **99**, 45 (1911).

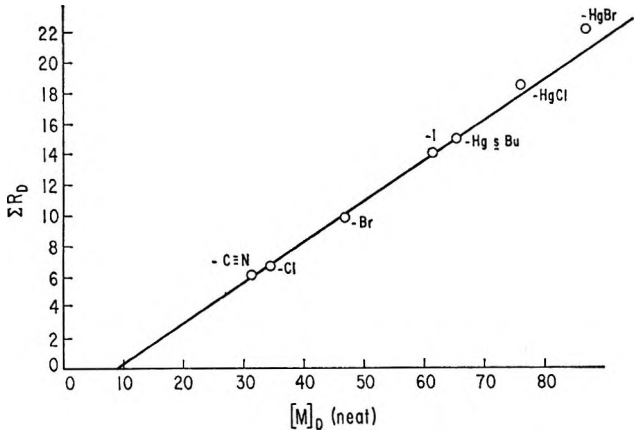


Figure 3.—Bond refraction–optical rotation correlation for *sec*-butyl compounds.

The rotation of optically pure 2-methylbutyronitrile can be determined by its relationship to 2-methylbutyric acid:

$$\underset{(S)\text{-}(+)}{\text{RCOOH}} \xrightarrow[2.\ NH_3\quad 3.\ P_2O_5,\ \text{heat}]{1.\ SOCl_2} \underset{(S)\text{-}(+)}{\text{RC}\equiv\text{N}} \xrightarrow[\Delta]{HCl,\ H_2O} \underset{(S)\text{-}(+)}{\text{RCOOH}}$$

R = *sec*-butyl (3)

The molecular rotation of optically pure 2-methylbutyronitrile lies between 30.1 and 32.5° (see Experimental Section) and is found to correlate with the halogen substituted *sec*-butyl compounds (Figure 2) using the ΣR_D value.

Other substituents which have a cylindrical axis of symmetry, such as –HgCl and –HgBr correlate with slight deviation which may be due to a solvent effect on the rotation. All of the mercury compounds are of the same optical purity as shown by conversion reactions.[20]

It is concluded that the bond refraction correlation is valid for substituents that possess a threefold or greater axis of symmetry which coincides with the bond axis and that the only bonds which contribute significantly to the magnitude of the optical rotation are those in the 1,2 and 2,3 positions.

The upper and lower limits, when available, of optical rotation for (*S*)-*sec*-butyl, *sec*-pentyl, *sec*-octyl, and α-phenethyl compounds are given in Table III. The correlation plots for these systems are shown in Figure 3 and 4. The equations for the lines are

$$\textit{sec}\text{-butyl } [M]_D = 3.78\Sigma R_D + 8.8 \quad (4)$$

$$\textit{sec}\text{-pentyl } [M]_D = 5.3\Sigma R_D + 15.7 \quad (5)$$

$$\textit{sec}\text{-octyl } [M]_D = 9.3\Sigma R_D - 14.3 \quad (6)$$

Because of the inclusion of effects more than one atom removed from the asymmetric center, it is reasonable to expect that the 2-methylbutyl system follows the bond refraction correlation. However, since the $-CH_2X$ group does not have an axis of symmetry the 2-methylbutyl compounds cannot be considered as $-CH_2X$ substituted *sec*-butyl compounds. Brauns[7] has determined both the molecular rotation and molecular refraction for the configurationally related series 2-methylbutyl alcohol, fluoride, chloride, bromide, and iodide shown in Table IV. The chloride, bromide, and iodide correlate as shown in Figure 5, the alcohol fails again, and the fluoride correlates only if the sign of the bond refraction is changed. A discussion of the mean-

(20) F. R. Jensen, *J. Amer. Chem. Soc.*, **82**, 2469 (1960).

TABLE III
ROTATIONS OF *sec*-BUTYL, *sec*-PENTYL, *sec*-OCTYL, AND α-PHENETHYL COMPOUNDS

Compd	Molecular rotation[a], 22 ± 3°, sodium D line, Lower limit	Molecular rotation[a], 22 ± 3°, sodium D line, Upper limit	Specific rotation, 22 ± 3°, sodium D line	Ref
2-Butanol	10.3	10.3	13.8	*b*
2-Aminobutane	5.43	5.43	7.44	*c*
2-Methylbutyric acid	20.2	20.2	19.8	*d*
2-Methylbutyric acid methyl ester	27.8		23.9	*d*
1-Phenyl-2-methylbutane	15.8	17.2	11.2 ± 0.5[e]	*f*
2-Phenylbutane	37		27.6	*g*
2-Nitrobutane	15.6		15.2	*h*
2-Methylbutyronitrile	30.1	32.5	37.7 ± 1.4[e]	*i, j*
2-Chlorobutane	33.3	35.3	37 ± 1[e]	*k, l*
2-Bromobutane	45.4	48.4	34.2 ± 1.1[e]	*k, m*
2-Iodobutane	61.6		33.5	*n*
Bis(2-butyl)-mercury	65.5		20.8[o,p]	*n*
2-Chloromercuributane	76.2		26[p]	*n*
2-Bromomercuributane	87.1		25.8[p]	*n*
2-Pentanol	12.1	12.1	13.7	*b*
2-Chloropentane	46	46.5	42.5	*q, r*
2-Bromopentane	63		41.6	*q*
2-Iodopentane	92		46.7	*q*
2-Phenylpentane	25.8		17.4	*s*
2-Octanol	12.7	12.7	9.76	*t*
2-Nitrooctane	29.4	30.4	18.8 ± 0.3[e]	*u*
2-Chlorooctane	54		36.15	*q*
2-Bromooctane	81.1		42.1	*q*
2-Iodooctane	115		47.9	*q*
1-Phenylethyl alcohol	52.3	52.3	42.9	*t*
1-Phenyl-1-chloroethane	146		103.9	*v*
1-Phenyl-1-bromoethane	178		96.4	*w*
1-Phenyl-1-chloromercuriethane	275		80.6	*x*
1-Phenyl-1-cyanoethane	−16.5		−14.5[y]	*z*

[a] All rotations in the homogenous state unless indicated otherwise. [b] See ref 19. [c] L. G. Thomé, *Ber.*, **36**, 582 (1903). [d] K. Freudenberg and W. Lwowski, *Justus Liebigs Ann. Chem.*, **594**, 76 (1955). [e] The range within which the rotation of the optically pure substance must lie. [f] See ref 6. [g] P. A. Levene and R. E. Marker, *J. Biol. Chem.*, **100**, 685 (1933). [h] N. Kornblum, J. T. Patton, and J. B. Nordmann, *J. Amer. Chem. Soc.*, **70**, 746 (1948). [i] J. Kenyon and W. A. Ross, *J. Chem. Soc.*, 3407 (1951). [j] This work. [k] See ref 4a. [l] See ref 6a. [m] See ref 6b. [n] See ref 4b. [o] One group active. [p] *c* 4 in ethanol. [q] D. H. Brauns, *Recl. Trav. Chim. Pays-Bas*, **65**, 799 (1946). [r] See ref 23. [s] D. J. Cram, *J. Amer. Chem. Soc.*, **74**, 2152 (1952). [t] See ref 14. [u] N. Kornblum and L. Fishbein, *ibid.*, **77**, 6269 (1955). [v] R. L. Burwell, A. D. Shields, and H. Hart, *ibid.*, **76**, 909 (1959). [w] H. Dauben and L. L. McCoy, *ibid.*, **81**, 5404 (1959). [x] D. S. Matteson and R. A. Bowie, *ibid.*, **87**, 2587 (1965). [y] This compound has the opposite sign of rotation for the same configuration as the rest of the series. [z] K. Patterson, *Ark. Chem.*, **10**, 283 (1956).

Table IV[a]

Rotations of (*S*)-2-Methylbutyl Compounds

Compd	$[M]^{20}D$, deg	$[M]^{20}D$, deg	Bond refraction C-X Bond	ΣR_D
2-Methylbutyl alcohol	−5.76	−5.06	−1.54	3.11
2-Methylbutyl fluoride	−8.86	−7.98	−1.49	3.16
2-Methylbutyl chloride	+1.64	+1.75	6.45	11.10
2-Methylbutyl bromide	+4.04	+6.11	10.0	14.65
2-Methylbutyl iodide	+5.68	+11.25	14.53	19.18

[a] Rotations and bond refractions calculated from the data given in ref 7.

ing and validity of this sign change is given in the section on configurational relationships. The equation for the line is eq 7.

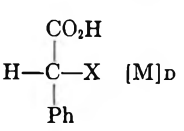
$$[M]_D = 1.2\Sigma R_D - 11.7 \quad (7)$$

The slope of the line is approximately one-third of the *sec*-butyl slope, in accord with Thomson's proposal.[13b] Thomson's method of predicting the rotation of hydrocarbons by means of pairwise interactions considers that the contribution of a particular group is given by $(1/3)^n X$, where X is the basic rotational value of the group and n is the number of carbon atoms between the group and the center of asymmetry.

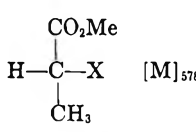
The bond refraction–molecular rotation correlation can also be applied to substituted (*R*)-1-phenethyl compounds. Figure 6 shows the data plotted in the usual manner, with the sign of the cyano group reversed (*vide infra*). The equation for the line is eq 8.

$$[M]^{20}D = 12.3\Sigma R_D + 59.7 \quad (8)$$

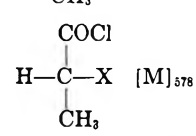
Other systems for which a linear relationship has been shown between three or more derivatives include the substituted phenylacetic acids[21] and the methyl esters and acid chlorides of 1-substituted propionic acids.[22] The equations for the lines and the substituents used to determine the lines are in eq 9–11.



$$[M]_D = -16.7\Sigma R_D - 216 \text{ (X = Me, Cl, Br)} \quad (9)$$



$$[M]_{578} = 24.0\Sigma R_D - 140 \text{ (X = Cl, Br, I)} \quad (10)$$



$$[M]_{578} = 17.7\Sigma R_D - 120 \text{ (X = Cl, Br, I)} \quad (11)$$

A large body of data is available concerning the halogen-substituted acylated sugars (*O*-acylglycosyl halides) owing to the work of Brauns.[23] Using this data for a series of ten *O*-acylglycosyl halides the bond refraction–molecular rotation correlation was applied with excellent results, Table V. The bond refraction values were those of the *sec*-butyl compounds for lack of a better model system. The slope of the lines appear to be independent of the structure of the sugar in accord with Hudson's first Rule of Isorotation.[24] Other halogen-substituted sugars studied by Brauns were *p*-halosalicin and its pentaacetate, and (1-haloacetyl)tetraacetyl-α-D-glucose (Table VI). For these sugars, which have the halogen substituent further removed from the asymmetric center, the slopes of the lines are smaller, in agreement with the general principles of Thomson.[13]

The bond refraction–optical rotation correlation has also been applied to the asymmetric silicon compounds

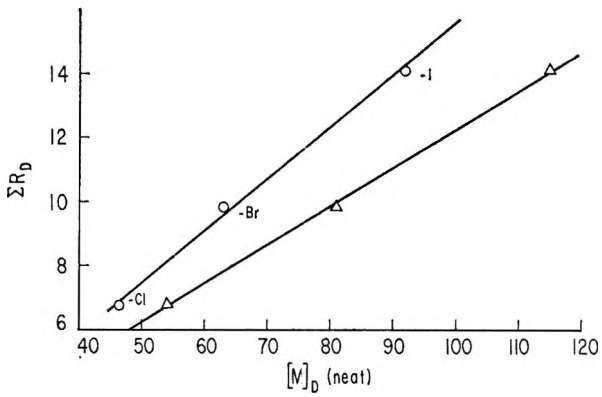


Figure 4.—Bond refraction–optical rotation correlation for *sec*-pentyl (○) and *sec*-octyl (△) compounds.

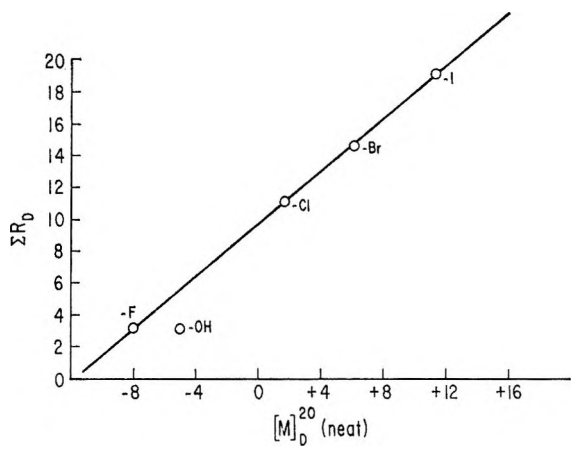


Figure 5.—Bond refraction–optical rotation correlation for (*S*)-2-methylbutyl compounds.

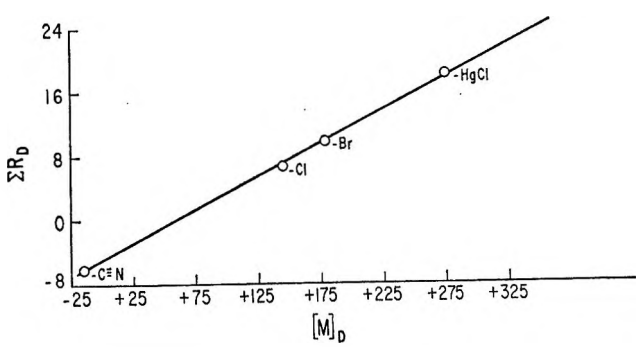


Figure 6.—Bond refraction–optical rotation correlation for (*R*)-1-phenethyl compounds.

(21) W. Klyne, in "Determination of Organic Structures by Physical Methods," E. A. Braude and F. C. Nachod, Ed., Academic Press, New York, N. Y., 1955, p 93.

(22) K. Freudenberg, W. Kuhn, and I. Bumann, *Ber.*, **63**, 2380 (1937).

(23) D. H. Brauns, *Recl. Trav. Chim. Pays-Bas*, **69**, 1175 (1960).

(24) C. S. Hudson, *J. Amer. Chem. Soc.*, **31**, 66 (1909).

TABLE V

BOND REFRACTION–OPTICAL ROTATION CORRELATION APPLIED TO ACYLATED SUGARS[a]

Sugar	Slope	Std devn	Intercept	Std devn	No.[b] pts
1-Halooctaacetyl-maltose	65.5	1.8	611	12	3
1-Haloheptaacetyl-melibiose	60.8	2.6	862	18	3
1-Haloheptaacetyl-cellobiose	59.0	2.3	95.1	21	4
1-Haloheptaacetyl-glucosido-4-mannose	59.1	4.1	−24.5	38	4
1-Haloheptaacetyl-gentiobiose	52.5	1.8	192	17	4
1-Halotetraacetyl-α-D-glucose	61.6	1.8	2.5	17	4
1-Halotriacetyl-β-L-arabinose	73.4	3.2	257	30	4
1-Halotriacetyl-α-D-xylose	63.1	2.6	91.4	18	3
1-Halotetraacetyl-β-D-fructose	−54.8	2.5	−233	17	3
1-Halotetraacetyl-α-D-mannose	63.0	5.5	−50	50	4
mean slope	61.2				

[a] Data taken from ref 23. [b] Equations determined by the method of least squares; all correlation coefficients greater than 0.992.

TABLE VI

BOND REFRACTION–OPTICAL ROTATION CORRELATION APPLIED TO ACYLATED SUGARS (SUBSTITUENT NOT DIRECTLY ON ASYMMETRIC CARBON)[a]

Sugar	Slope	Std devn	Intercept	Std devn	No.[b] pts
p-Halosalicin	−3.88	0.12	−142	1.2	3
p-Halosalicin-pentaacetate	2.21	0.16	103	1.7	3
Haloacetyl-tetra-acetyl-α-D-glucose	8.53	1.0	367	6.9	3

[a] Data taken from ref 23. [b] Equations determined by the method of least squares; all correlation coefficients greater than 0.992.

prepared by Sommer.[25a] The halogen-substituted α-naphthylphenylmethylsilanes conform to the equation

$$[M]_D = 16.6\Sigma R_D + 97 \quad (12)$$

However the unsubstituted silane shows appreciable deviation. No explanation for this result is immediately evident. The pertinent data are shown in Table VII.

TABLE VII

ROTATIONS OF R_3Si^aX COMPOUNDS

X	$[\alpha]_D$, (pentane)[b]	$[M]_D$	ΣR_D[c]
H	+34	+84	−3.17
F	+47	+125	−1.7
Cl	−6.3	−17.8	7.1
Br	−22	−72	10.1

[a] R_3Si = α-naphthylphenylmethylsilicon. [b] All compounds of the same configuration, data taken from ref 25. [c] A. I. Vogel, W. T. Cresswell, and J. Leicester, *J. Phys. Chem.*, **58**, 174 (1954).

(25) (a) L. H. Sommer, "Stereochemistry, Mechanism and Silicon," McGraw-Hill, New York, N. Y., 1965, p 44; (b) H. M. Walborsky and C. G. Pitt. *J. Amer. Chem. Soc.*, **84**, 4831 (1962).

Another series of compounds with atomic asymmetry are the 1-methyl-2,2-diphenylcyclopropyl halides. The rotations[26b] of the (*S*) chloride, bromide, and iodide and the (*R*) hydrocarbon correlate to eq 13.

$$[M]_D = 52.7\Sigma R_D - 184 \quad (13)$$

Discussion

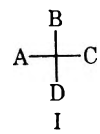
The bond refraction–optical rotation correlation corresponds to the general eq 14 where m is the slope,

$$[M] = m\Sigma R + I \quad (14)$$

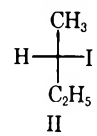
ΣR is the bond refraction parameter as defined earlier, and I is the intercept rotation. A linear equation, in two terms, one substituent dependent and one substituent independent, is a direct consequence of Brewster's model.[13a]

Kirkwood's polarizability theory of optical rotatory power[12a] also results in a two-term equation with substituent dependent and substituent independent terms.[26] The bond refraction–optical rotation correlation is in general agreement with the predictions of the one-electron and many electron models of optical activity.[12b]

Configurational Relationships.—Since a center of optical activity can be considered as an asymmetric screw pattern of refractivities, the sense of the Brewster screw determines the observed sign of rotation. Molecules with a right-handed Brewster screw,[13a] I, with ΣR A > B > C > D, will be dextrorotatory.



I



II

The absolute configuration[27] of (*S*)-(+)-*sec*-butyl iodide, II leads to the conclusion that ΣR I > Me > Et > H, in accordance with the numerical values of ΣR as defined earlier.[28]

For two previously mentioned compounds, 1-fluoro-2-methylbutane and 1-phenylethyl cyanide, the correlation fails unless the formal sign of the bond refraction[29] is reversed. This occurs when the value of the bond refraction is such that two groups have changed their relative order of refraction (ΣR CH_2I > ΣR CH_3 but ΣR CH_2F < ΣR CH_3). These compounds have the same configuration as the others in the series considered but the sense of the Brewster screw is reversed. To account for this, the sign of the substituent dependent term is changed by reversing the formal sign of the bond refraction. When three substituents change their orders of refractivities as in the case of the substituted

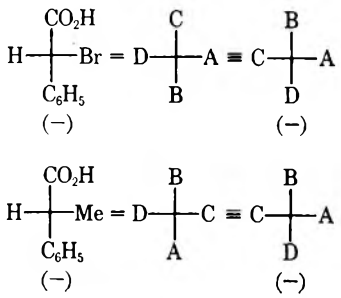
(26) A direct mathematical correspondence between the two-term equations for these three models is not implied.

(27) D. S. Tarbell and M. C. Paulson, *J. Amer. Chem. Soc.*, **64**, 2842 (1942).

(28) Although Brewster ascribes the rotations of *sec*-alkyl compounds to conformational asymmetry, analysis of these compounds by atomic asymmetry considerations gives, perhaps coincidentally, the correct answer when ΣR is used to rank substituents.

(29) Bond refractions can have either positive or negative values; however only one bond, the S–O bond, is known to have a negative value. Consequently, all bond refractions will be considered as having positive *formal* signs.

phenylacetic acids (eq 9) the sense of the Brewster screw remains the same, but the formal sign is still reversed. *In any substitution which causes a change in the order of refractivities, the formal sign of the substituent is reversed.*



The relative order of refractivities, as determined by ΣR, closely parallels the rotational rank of substituents as determined by Brewster.[13] A comparison of ΣR and Brewsters' conformational rotatory powers is shown in Table VIII.

Table VIII
Rotational Ranking of Substituents

Substituent (X)	Bond refractivity parameter, ΣR	Conformational rotatory power, k (C-H) (X-H)[a]
-I	14.1	250
-Br	9.8	192
-Cl	6.74	170
$-C_6H_5$	6.98	140
-C≡N	6.1	160
$-CO_2H$	6.2	90
-Me	6.3	60
-Et	5.95	
$-NH_2$	5.09	55
-OH	3.2	50
-H	1.676	0
-D	1.65	No data
-F	1.44	No data

[a] Reference 13a.

The empirically derived order of ranking (from the sign of rotation for a given configuration, as determined by the sense of the Brewster screw) is I > Br > Cl > C_6H_5 > CO_2H > Me > Et > H > D > F; and C_6H_5 > C≡N > Me. This order is in good agreement with that derived by ΣR values except in the range of values 6 to 7. The deviants are those substituents which fail to meet the symmetry requirement or whose rank is determined by small differences in refraction.

Variation with Wavelength.—The bond refraction–optical rotation relationship has been examined in the range of wavelengths 434–436 nm, a wavelength at which the bond refractions are known[16] and the rotation easily measured.[30] When the rotations of the *sec*-butyl halides and 2-methylbutyronitrile at 436 nm are compared with the bond refractions at 434 nm, Table IX, a linear relationship results; $[M]_{436} = 8.53\Sigma R_{434} + 7.6$.[14] It is concluded that the bond refraction–optical rotation relationship is valid at other wavelengths when both the rotation and the refraction are measured at the same wavelength.

(30) The Zeiss photoelectric polarimeter permits the measurement of optical rotation at 578, 546, 436, 405, and 365 nm. The bond refractions are commonly determined at 656, 589, 486, and 434 nm. The difference between 434 and 436 nm is assumed to be negligible.

Table IX
Rotation Relationships of *sec*-Butyl X Compounds at 589 and 436 nm

(*S*)-(+)-*sec*-Butyl X X	Observed rotations, 436/589 ratio	$[M]_{589}$[a]	$[M]_{436}$	ΣR_{434}[b]
-CN	1.944	31.3	60.8	6.24
-Cl	2.007	33.3	66.4	6.89
-Br	2.036	45.4	92.4	10.12
-I	2.193	61.6	135.2	14.9

[a] *Cf.* Table III. [b] Reference 16.

Toward the *a priori* Prediction of Rotations.—The bond refraction–optical rotation correlation does not allow the complete *a priori* prediction of the optical rotation of a compound RX. It does permit, however, an accurate value of the rotation of RX to be determined if the following criteria are satisfied. (1) The substituent, X, possesses a greater than twofold axis of symmetry (considering the asymmetric atom and two positions beyond) which coincides with the asymmetric atom–substitutent bond. (2) The bond refractions for the substituents are known or can be measured. (3) The correlation equation for the system R– has been determined. By far the most stringent condition is 3, since accurate data for all but a few systems are completely lacking. The theoretical prediction of the slope and intercept for any system R– is not possible at the present. For the closely related series, *sec*-butyl, *sec*-pentyl, *sec*-octyl, the slopes appear to be a constitutive function of the chain length. The slopes (m) of these systems follow the linear relationship in eq 15

$$m = 0.0984(\mathrm{MW}) - 1.84 \qquad (15)$$

where MW is the molecular weight of the chain. Other constitutive functions such as chain "size" are also applicable. This functionality allows the estimation of the slopes of the *sec*-hexyl, *sec*-heptyl, and *sec*-nonyl systems. Unfortunately there are no accurate data available for these systems.

The demonstrated applicability of Thomson's rule of 1/3[13b] permits the prediction of the slopes of the 2-methylpentyl, 2-methylhexyl, 2-methylheptyl, 2-methyloctyl, and 2-methylnonyl systems to be made. Again, no accurate data are available for these systems.

There appears to be no correlation between the intercepts (I) and any obvious function, precluding the complete prediction of the rotations of the 2-substituted hexyl, heptyl, and nonyl compounds.

Predicted Molecular Rotations.—The equations derived previously for the *sec*-butyl, *sec*-pentyl, *sec*-octyl, and 1-phenethyl systems may be used with available bond refraction data to predict the rotations of previously unstudied compounds. The rotations listed in Table X are for compounds of the (*S*) configuration, in the homogeneous state for liquids or as dilute solutions in nonpolar solvents for solids. The estimated accuracy of these predictions is ±5%.

The predicted value for 3-phenylbutyne (1-phenethylacetylene) is subject to some doubt because of uncertainty as to the formal sign of the acetylenic group in this compound. When the ΣR_D for two groups differ by a small amount (-C≡C—H = 7.17, $-C_6H_5$ = 6.97) the sense of the Brewster screw may be determined by factors other than those considered here, such as an

TABLE X

PREDICTED MOLECULAR ROTATIONS OF (S)-RX, [M]D

X	ΣRD[a]	sec-Butyl	sec-Pentyl	sec-Octyl	α-Phenethyl
-C≡C—H	7.17	36	54	52	−148 or 28
-C≡N	6.12	...[c]	48	43	...[c]
-HgR[b]	15.02	...[c]	95	125	−244
-HgCl	18.4	...[c]	113	157	...[c]
-HgBr	22.0	...[c]	132	190	−330
-CPh3	6.07	31.7	48	42	−134
-SiPh3	11.3	51.5	76	91	−199
-SiR'3[d]	10.1	47.0	70	80	−184
-GePh3	11.93	53.9	79	97	−206
-GeR'3	12.2	54.9	80	99	−210
-SnPh3	15.5	67.4	98	130	−250
-SnR'3	16.6	71.5	104	140	−264
-PbPh3	30.9	125.6	180	273	−440
-PbR'3	24.0	99.5	143	209	−355

[a] Bond refractions taken from ref 16. [b] One group active. [c] Known compound, see Table III. [d] R' = an alkyl group.

unusual conformational preference or significant contributions from lower wavelength absorptions.

Experimental Section

Melting points and boiling points are uncorrected. Rotations were measured with a Zeiss photoelectric polarimeter. All solvents and reagents were of the best commercial grades.

(+)-2-**Methylbutyric Acid.**—Using the procedure of Freudenberg and Lwowski,[31] 40 g (0.455 mol) of 2-methylbutanol ($[\alpha]^{22}D$ −4.04°, neat, 1 dm, K & K Laboratories) was oxidized by basic permanganate to (+)-2-methylbutyric acid. The acid exhibited bp 78–80° (16 mm), $[\alpha]^{22}D$ +16.2° (neat); lit. bp 78° (15 mm), d^{25}_4 0.9332. The yield was 20 g (43%). The product was diluted with racemic material for further use.

(+)-2-**Methylbutyronitrile.**—A mixture of 20 g (0.2 mol) of (+)-2-methylbutyric acid, $[\alpha]^{22}D$ +4.90°, neat, and 47 g (0.4 mol) of thionyl chloride was stirred at room temperature for 5 hr. The excess thionyl chloride was removed at room temperature on a rotorary-film evaporator and the remaining acid chloride added slowly to 100 ml of concentrated NH_4OH solution at −45°. The resulting amide was filtered while cold, the solid partially dissolved in chloroform and filtered to remove the insoluble ammonium chloride, and the amide precipitated by addition of petroleum ether (60–90°). The amide was filtered and dried to yield 9.3 g (40%) of (+)-2-methylbutryamide. The product was not crystallized in order to avoid optical fractionation, and was used directly in the next step.

Using the procedure of Jensen and Rickborn[32] 5.9 g (0.0505 mol) of (+)-2-methylbutyramide was treated with 7 g (0.048 mol) of phosphorus pentoxide. The solids were mixed in a simple distillation flask and then placed in a vacuum distillation apparatus, in which the receiver was cooled in liquid nitrogen. A vacuum was applied and the pot immersed in a 140° oil bath. The nitrile distilled as formed and 3.7 g (88.5%) was collected: $[\alpha]^{22}D$ +9.00° (neat); d^{25} 0.806, $n^{23}D$ 1.3955 (lit.[33] $n^{20}D$ 1.3900).

(+)-2-Methylbutyronitrile of +9.0 degrees rotation was prepared in two steps, not involving the asymmetric center, from (+)-2-methylbutyric acid, $[\alpha]^{22}D$ +4.90 (neat). Freudenberg and Lwowski determined the rotation of optically pure acid to be $[\alpha]^{25}D$ 19.8° (neat); thus the starting acid was 24.7% optically pure and an upper limit to the optical purity of the nitrile is 24.7% and a lower limit to the rotation for optically pure 2-methylbutronitrile is 9.00/0.247 or $[\alpha]^{22}D$ 36.3° (neat). Kenyon's[34] reported upper limit for the rotation of optically pure material is $[\alpha]^{25}D$ 39.1°.

Registry No.—(+)-2-Methylbutyronitrile, 25570-03-0.

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(32) F. R. Jensen and B. Rickborn, *J. Org. Chem.*, **27**, 4608 (1962).

(33) L. Friedman and H. Shechter, *ibid.*, **25**, 877 (1960).

(34) J. Kenyon and W. A. Ross, *J. Chem. Soc.*, 3407 (1951).

Debromination of *meso*- and DL-Stilbene Dibromides by Sodium Iodide in Dimethylformamide[1a]

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In the sodium iodide promoted debromination of the stilbene dibromides in DMF, the *meso*-dibromide gives *trans*-stilbene while the *dl*-bromide gives both stilbenes with [*cis*]/[*trans*] ≃ 10. The activation parameters for elimination in the temperature range of 25–60° are, for *meso*, $\Delta H^{\ddagger}$ = 16.3 kcal/mol and $\Delta S^{\ddagger}$ = −15 eu; for *dl*, $\Delta H^{\ddagger}$ = 22.3 kcal/mol and $\Delta S^{\ddagger}$ = −7 eu. At 36°, the relative rates are $k[meso]/k[dl]$ = 323. A detailed estimate of the free-energy terms for solvation in DMF relative to methanol indicates that the iodide term is most important in this elimination. Sodium nitrate and lithium bromide exert a positive salt effect on the iodide reaction. As compared with methanol, the rates in DMF are larger, the spread in the *meso* and *dl* rates is greater, and the *anti* stereoselectivity of the *dl* reaction is higher: this is termed *solvent dispersion* of the rates of isomers into a *selectivity spectrum*. Our observations appear to be more consistent with stepwise ion-pair processes than with one-step dehalogenation mechanisms.

Broadly speaking, this series of papers deals with the conformational responses of a pair of diastereoisomers, the stilbene dibromides (**1**), subjected to a given process, elimination, under widely varying circumstances.[2]

$$\underset{\textit{meso}\text{- or }\textit{dl}\text{-1}}{C_6H_5CHBrCHBrC_6H_5} + 3I^- \longrightarrow I_3^- + 2Br^- + \underset{\textit{trans}\text{- or }\textit{cis}\text{-2}}{C_6H_5CH{=}CHC_6H_5} \quad (1)$$

Kinetic and mechanistic information was obtained for the iodide-promoted debromination of the *dl*- and *meso*-**1** in the standard solvent methanol.[2c] Here, we hoped to uncover any differential conformational medium effects that might be typical of an aprotic solvent,

(1) (a) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research. This paper was presented at the 148th National Meeting, American Chemical Society, Chicago, Ill., Sept 1964, Abstracts p 39V. (b) Author to whom inquiries should be addressed.

(2) (a) W. K. Kwok, I. M. Mathai, and S. I. Miller, *J. Org. Chem.*, **35**, 3420 1970; (b) I. M. Mathai, K. Schug, and S. I. Miller, *ibid.*, **35**, 1733 (1970); (c) C. S. T. Lee, I. M. Mathai, and S. I. Miller, *J. Amer. Chem. Soc.*, **92**, 4602 (1970); (d) W. K. Kwok and S. I. Miller, *ibid.*, **92**, 4599 (1970); (e) W. K. Kwok and S. I. Miller, *J. Org. Chem.*, in press.

e.g., dimethylformamide (DMF). Moreover, some 1,2-dibromides, *e.g.*, *dl*-**1**, are reluctant to undergo elimination and in hydroxylic solvents may choose a solvolytic decomposition route (eq 2).[2c] In DMF, the elimination process would, of course, not be complicated by competing hydrolysis. The advantages of DMF as a medium for 1,2 debrominations as well as for their kinetic study was realized by Roumanian workers.[3]

$$(C_6H_5CHBr)_2 \xrightarrow{CH_3OH} (C_6H_5CHOCH_3)_2 \qquad (2)$$

Kinetic data on the reactions of both **1** with iodide in acetone were available,[4,5a] and more on *meso*-**1** in DMF appeared recently.[5] It turned out that our emphasis on the *dl*-**1** reaction was fortunate, in that this led to an expanded view of the debromination mechanism.

Experimental Section

Materials.—Our solvent was Fisher certified dimethylformamide (DMF). *meso*-**1** had mp 237–238°, from xylene; *dl*-**1** had mp 112–113°, from ethanol.[2b] All of the other substances were reagent grade; the salts, sodium nitrate, sodium iodide, and lithium bromide were dried at 150° for ~3 hr and stored in a desiccator until required.

Analysis.—Triiodide production in eq 1 was followed by titration with standard thiosulfate.[2c] In DMF, the starch indicator is ineffective; undoubtedly the DMF–iodine complex is involved here. However, if a tenfold dilution of the DMF–iodine solution with water is made and 1 ml of acetic acid added, titration to the starch end point is feasible. Near the end point the thiosulfate should be added slowly. In some experiments, the amount of bromide ion was estimated with standard silver nitrate.

The composition of *cis–trans*-**2** mixtures was determined by the absorbance ratio method on a Cary Model 11 spectrophotometer at 280, 290, 300, and 310 mμ.[6] Solutions in absolute ethanol were made up to contain 28.5%, 13.6% *cis* and 71.5%, 86.4% *trans* respectively. Our method of analysis yielded 29%, 15% *cis* and 71%, 85% *trans* respectively. Of course, *cis–trans* mixtures recovered after reaction are not likely to be more accurately determined.

Kinetics in DMF.—Aliquots of stock solutions of **1** and sodium iodide in DMF were placed in separate compartments of a flask (125, 150, or 250 ml) containing an inner well. The flask was stoppered and placed in a constant temperature bath. After reaching bath temperature, the closed flask was inverted and shaken vigorously (~40 sec) and replaced in the bath. Aliquots (5.00 or 10.00 ml) were taken at intervals, run into ice water, and titrated with thiosulfate. Conversions ranged from 50% to 80% and were normally ~60%. Since DMF has bp 152° and our highest temperatures for the kinetic runs was 60–70°, it is unlikely that solvent evaporation from the stoppered flasks was significant.

Since organic halides react with DMF,[2b,e,7] both 1's were checked. By bromide analysis, less than 1% decomposition of stock solutions (0.015 *M*) of *meso* at 46° in 24 hr and *dl* at 70° in 20 hr was observed; these conditions are more severe than those used in the kinetic runs. However, when *meso*-**1** (0.2 g) in DMF was refluxed (~152°) for 10 hr, an 80% yield of *trans*-stilbene, mp 123°, was isolated. Indeed, even at ~25°, stock stilbene dibromide solutions turn yellow on long standing. For this reason, freshly prepared solutions were used in the kinetic studies.

The possibility that iodine might be consumed by DMF was tested; a DMF solution of sodium iodide (0.26 *M*) and iodine (0.017 *M*) showed no loss in titer after 20 hr at 70°.

The stoichiometry of the iodide–stilbene dibromide reaction is substantially that given by eq 1. Weighed samples of the dibromides were treated with excess sodium iodide (6 g) in DMF; the iodine content was determined. After 23 or 48 hr at 70° a total of six trials for *meso* indicated 93.5% reaction; after 48 hr at 70° three trials for *dl* indicated 93.9% reaction. In other experiments, debrominations were carried out at 70° for 48 hr. The iodine was decolorized with aqueous sodium sulfite, the solution was extracted with ether, and the extract was dried with calcium chloride and evaporated. On the basis of their infrared and ultraviolet spectra, the residues appeared to be the stilbenes. Yields from the *meso*- and *dl*-**1** (0.2 g scale) were 85 and 88% respectively. Spectrophotometric analyses indicated that the *meso*-iodide system led to *trans*-**2** and the *dl*-iodide system led to 88% *cis*-**2** and 12% *trans*-**2**. Under the same experimental conditions the conversion of *cis*- to *trans*-**2** by sodium triiodide was less than 5%.[2b]

Rate constants for process 1 were obtained from the standard expression ($a = [1]_0$, $b = [NaI]_0$) or from the slopes of plots of

$$kt = \frac{2.303}{(b - 3a)} \log \frac{a(b - 3x)}{b(a - x)} \qquad (3)$$

the right-hand side of eq 3 *vs.* *t*. Typically, 6–10 points were taken per run for 4–7 runs and the average deviation in *k* was <4%. The applicability of eq 3 depends on several factors: the initially formed IBr is rapidly transformed into I_3^-; there is sufficient iodide ion ($b > 3x$); the triodide is stable ($K_{diss} \simeq 10^{-7}$ at 25° in DMF[8]). The rate constants together with their average deviations are collected in Tables I and II. Because of solvent expansion, correction factors were applied to the mean rate constants to yield mean corrected rate constants given as k_{corr}. The factors were 0.998 at 25°, 1.005 at 36°, 1.011 at 46°, and 1.019 at 60.1°.[7b]

Table I

Debromination of *meso*-Stilbene Dibromide by Sodium Iodide in Dimethylformamide[a,b]

Temp, °C ± 0.05°	*meso*-Dibromide, $M \times 10^3$	NaI, $M \times 10^2$	k, M^{-1} sec$^{-1} \times 10^2$
36.1	17.18	8.09	1.13
	9.71	4.57	1.10
	5.81	3.51	1.12
	4.29	1.62	1.00
	3.99	3.00	1.07
	9.61	5.28	1.09
	9.55	7.04	1.13
			k_{corr} 1.10 ± 0.04
25.0	7.97	7.51	0.390
	5.82	3.51	0.368
	4.19	2.10	0.361
	11.13	7.54	0.384
	9.59	8.12	0.381
	6.56	6.95	0.366
			k_{corr} 0.372 ± 0.01
45.8	8.20	8.41	2.32
	7.56	4.95	2.48
	4.31	2.35	2.33
	4.31	5.88	2.25
			k_{corr} 2.39 ± 0.07

[a] The mean rate constant was corrected for solvent expansion to k_{corr}. The average deviation is indicated. [b] Reference 5 reports rate constants of 2.68×10^{-2} M^{-1} sec^{-1} for KI at 50.3° and 5.2×10^{-3} M^{-1} sec^{-1} for $(n\text{-}C_4H_9)_4NI$ at 25°. The quaternary salt was more reactive than KI by a factor of ~2.

Activation energies were obtained from Arrhenius plots. The other activation parameters given in Table III were calculated in eq 4. Salt effects on the rate constants are given in Table IV.

$$\Delta H^{\pm} = E_{act} - RT \qquad k = (kT/h)e^{\Delta S^{\pm}/R}e^{-\Delta H^{\pm}/RT} \qquad (4)$$

(3) F. Badea, T. Constantinescu, A. Juvara, and C. D. Ninitzescu, *Justus Liebigs Ann. Chem.*, **706**, 20 (1967).

(4) J. Mulders and J. Nasielski, *Bull. Soc. Chim. Belg.*, **72**, 322 (1963).

(5) (a) E. Baciocchi and P. L. Bocca, *Ric. Sci.*, **37**, 1182 (1967); (b) E. Baciocchi and A. Schiroli, *J. Chem. Soc. B*, 554 (1969).

(6) M. Ish-Shalom, J. D. Fitzpatrick, and M. Orchin, *J. Chem. Educ.*, **34**, 496 (1957).

(7) (a) R. S. Kittila, "Dimethylformamide," E. I. du Pont de Nemours and Co., Wilmington, Del., 1967, Chapter 12. (b) "A Review of Catalytic and Synthetic Applications for DMF/DMAC," and Supplement; and "DMF," a product information bulletin, prepared and published by E. I. du Pont de Nemours and Co., Inc., Wilmington, Del.

(8) R. Alexander, E. C. F. Ko, Y. C. Mac, and A. J. Parker, *J. Amer. Chem. Soc.*, **89**, 3703 (1967).

TABLE II
DEBROMINATION OF *dl*-STILBENE DIBROMIDE BY SODIUM IODIDE IN DIMETHYLFORMAMIDE[a]

Temp, °C ± 0.05°	*dl*-Dibromide $M \times 10^3$	NaI $M \times 10^2$	k, M^{-1} sec$^{-1} \times 10^4$
36.1	9.15	5.50	0.338
	11.12	6.73	.341
	13.68	13.25	.352
	13.72	6.60	.341
	17.79	10.77	.318
			k_{corr} 0.340 ± 0.01
45.8	13.68	13.25	1.13
	11.12	6.73	1.04
	21.89	9.05	1.07
	13.72	6.60	1.13
	7.33	6.93	1.07
	9.15	5.50	1.09
			k_{corr} 1.10 ± 0.04
60.1	21.89	9.05	4.81
	13.79	14.48	4.88
	11.21	7.35	4.79
	6.96	5.28	4.94
	7.33	6.95	4.91
	9.38	6.40	5.07
			k_{corr} 4.99 ± 0.07

[a] The mean rate constant was corrected for solvent expansion to k_{corr}. The average deviation is indicated.

Did bromide ion compete with iodide to any significant degree in the kinetic runs? The rate constants for the reactions of lithium bromide with *meso*-**1** was ~40 times lower at 46° and with *dl*-**1** was ~10 times lower at 60° than the corresponding constants for the iodide reactions.[2a] Given the concentrations in our runs (Tables I, II), rate acceleration due to bromide ion would be insignificant in the usual range of our kinetic observations.

Results and Discussion

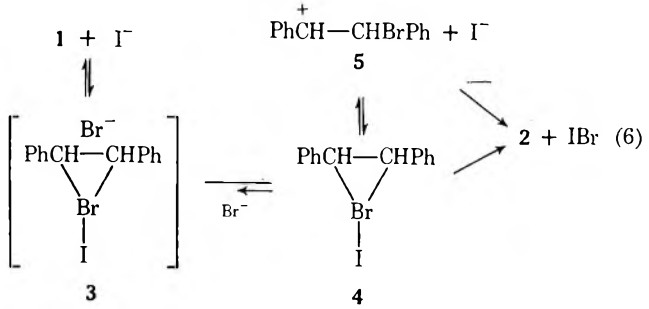
The reaction of iodide with either stilbene dibromide is first order in each reactant. In the concentration range of 0.02–0.14 *M* sodium iodide, salt effects were within the experimental uncertainty. The stoichiometry is essentially that of eq 1: based on iodine production, infinite time reaction is ~93–94% for both dibromides; based on preparative scale work, the yield of stilbenes was ~90%. The products (**2**) were produced under conditions of kinetic control, *i.e.*, little or no isomerization. Processes 5 were not significant

$$\text{DMF or } Br^- + C_6H_5CHBrCHBrC_6H_5 \xrightarrow{\text{DMF}} C_6H_5CH{=}CHC_6H_5 + C_6H_5CH{=}CBrC_6H_5 \quad (5)$$

under the conditions of the kinetic runs, but may interfere at higher temperatures.[2a,b,e] All of the rate data are given in Tables I–IV.

The debromination of *meso*-**1** is stereospecific—only *trans*-**2** is produced.[9] The debromination of *dl*-**1** is stereoselective giving 88% *cis*- and 12% *trans*-**2**. Thus, the *anti* elimination predominates in both cases. Considering that $K = [trans\text{-}2]/[cis\text{-}2] > 300$ in the range of 25–75°,[10] the selectivity of the *dl*-**1** reaction is remarkably high.[9]

The 12% *trans*-stilbene found in the product of *dl*-**1** can be rationalized in several ways.[11] One may suppose that there is an independent path from *dl*-**1** to *trans*-**2**, *e.g.*, by *syn* debromination[12] or by an SN2–E2 sequence *via erythro*-1-bromo-2-iodo-1,2-diphenylethane;[13] our arguments against these alternatives are best characterized as cumulative and indicative rather than as conclusive.[2a–c] Here and in related work, we prefer the single scheme in which both *cis*- and *trans*-**2** can be formed, as in eq 6.[2c]



In the general case (Ph = any group), if there is no great energy difference in the products, the intermediate can fall apart to yield **2**, before isomerization sets in; if there are large energy factors favoring one of the products, this would probably be reflected in **5** and the relative rates from **4** to **5** *vs.* **4** to **2**. Thus, a range of selectivity has been observed:[9] *anti* stereospecificity for *meso*-**1** under all conditions;[2] *anti* selectivity for *dl*-**1** and sodium iodide in methanol[2c] or DMF; *syn* selectivity for *dl*-**1** and lithium bromide or stannous chloride in DMF.[2a,d] Equation 6 also allows for a range in sensitivity of the intermediates to the medium. In eq 6, the open carbonium ion represents several rotomers which can lead to both **2**'s or be captured by another nucleophile, *e.g.*, methanol.[2c] Since stable open carbonium ions are less likely to return to starting dibromide in the presence of bromide salts, aryl and highly substituted alkyl dibromides show less rate retardation with lithium bromide than simpler dibromides.[4] Finally, eq 6 is also consistent with accepted mechanisms for bromine addition to **2**[14] or isomerization of **2** in the presence of halogen and halide ions. Although portions of eq 6 have been examined previously for specific systems,[4] our position is that it is useful to regard *all* of the iodide promoted debrominations in this way.[2] (We exclude, of course, cases which go *via* radicals,[2] carbanions, or the SN2–E2 path[11].)

Following the analytical approach that has been systematized by Parker,[15] one can dissect the relative

$$\log k^M/k^D = \log {}^D\gamma^M_{I^-} + \log {}^D\gamma^M_{RBr_2} - \log {}^D\gamma^M_{\ddagger} \quad (7)$$

(9) S. I. Miller, *Advan. Phys. Org. Chem.*, **6**, 185 (1968).

(10) G. Fischer, K. A. Muszkat, and E. Fischer, *J. Chem. Soc. B*, 1156 (1968).

(11) (a) D. V. Banthorpe, "Elimination Reactions," Elsevier, New York, N. Y., 1963, Chapters 1, 6. (b) J. Hine, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1962, p 116–119.

(12) A concerted *syn* process would lead to IBr_2^- and *trans*-**2**. From the viewpoint of the products, this would be thermodynamically superior to the *anti* process, which gives IBr + *cis*-**2** + Br^-. A *syn* transition state would have serious steric interactions and would violate the orbital *anti* rule.[9]

(13) The displacement–elimination path has been established for terminal dibromides.[11] A crude SN2 estimate follows. Consider stilbene dibromide to be derived from ethyl bromide for which the exchange rate constant with iodide in acetone at 25° is $k = 1.7 \times 10^{-3}$ M^{-1} sec^{-1}. Data for the analogous reaction with substituted chlorides and bromides have been tabulated so that the independent effects of α- and β-phenyl groups, β-bromine, and β branching as in isobutyl bromide can be estimated [C. K. Ingold, *Quart. Rev.*, **11**, 1 (1957); A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill, New York, N. Y., 1962.] If one further assumes that exchange rates in acetone and DMF are the same, $k \cong 8 \times 10^{-5}$ M^{-1} sec^{-1} at 25° for iodide attack at carbon of stilbene dibromide. This figure does establish the possibility of SN2 attack in *dl*-**1** (Table III).

(14) P. S. D. de la Mare and R. Bolton, "Electrophilic Additions to Unsaturated Systems," Elsevier, Amsterdam, 1966, Chapter 6, 7.

(15) (a) A. J. Parker, *Chem. Rev.*, **69**, 1 (1969); (b) C. F. Ko and A. J. Parker, *J. Amer. Chem. Soc.*, **90**, 6447 (1968).

TABLE III

RATE DATA OF THE IODIDE–STILBENE DIBROMIDE REACTION

Stilbene dibromide	Solvent	$\Delta H^{\ddagger}$, kcal/mol	$-\Delta S^{\ddagger}$, eu	Temp., °C	$k \times 10^3$, M^{-1} sec^{-1}	$\frac{k(meso)}{k(dl)}$	$\frac{k(\text{solvent})}{k(CH_3OH)}$
meso	CH_3OH	19.8	14	36	0.14[a]	40	
dl	CH_3OH	23.2	9	36	0.0035[a,b]		
meso	DMF	16.3[c]	15[d]	36	11.0	323	78.5
dl	DMF	22.3[c]	7[d]	36	0.034		9.7
meso[e]	$(CH_3)_2CO$	15.4		23	1.48	22	~100
dl[e]	$(CH_3)_2CO$			23	0.066		~95

[a] Reference 2. [b] Extrapolated value. [c] Estimated uncertainty ±1 kcal/mol. [d] Estimated uncertainty ±3 eu. [e] Reference 4.

TABLE IV

SALT EFFECTS IN THE REACTIONS OF STILBENE DIBROMIDES WITH IODIDE ION IN DIMETHYLFORMAMIDE

System	Added salt	M	$k \times 10^3$, M^{-1} sec^{-1}
meso, 0.002786 *M*	$NaNO_3$	0	3.04
NaI, 0.03156 *M*		0.1544	3.12
Temp, 25.0°		0.2566	3.39
		0.3592	3.45
		0.5132	3.62
		0.6158	3.73
meso, 0.009961 *M*	LiBr	0	10.9
NaI, 0.05231 *M*		0.1187	11.7
Temp, 36.1°		0.2091	12.0
dl, 0.009403 *M*	LiBr	0	0.499
NaI, 0.06464 *M*		0.02869	0.522
Temp, 60.1°		0.05739	0.550
		0.08608	0.55
		0.1148	0.570
		0.1429	0.587
		0.2000	0.63
dl, 0.007116 *M*	$NaNO_3$	0	0.0945
NaI, 0.04318 *M*		0.6158	0.100
Temp, 45.8°			

rate in two solvents. Here ${}^{D}\gamma_{Y}^{M}$ is a "solvent transfer" activity coefficient for Y at infinite dilution in D (*e.g.* DMF) and M (*e.g.* methanol). Taking log ${}^{D}\gamma_{I^-}^{M} \simeq 2.6$,[15] log ${}^{D}\gamma_{RBr_2}^{M} \simeq 0.3$,[15] and k values at 36° from Table III, we obtain log ${}^{D}\gamma_{\ddagger}^{M} \simeq 0.4$ for the *meso*-**1** reaction and log ${}^{D}\gamma_{\ddagger}^{M} \simeq 1.3$ for the *dl*-**1** reaction. In essence this indicates that the transfer term of iodide ion, which favors methanol over DMF, is the dominant solvation factor in these eliminations. Transition state solvation favors methanol over DMF, but this is a much larger contributor in the *dl* reaction as compared with the *meso* reaction. These results are qualitatively consistent with a somewhat larger charge dispersal in the transition state.[15] One cautionary note: the terms in eq 7 do vary with concentration[16] and we did have to guess at the value ${}^{D}\gamma_{RBr_2}^{M}$; therefore, this analysis is semiquantitative.

In a practical sense, the rate discrimination of the diastereoisomers in the protic and aprotic solvents is interesting (Table III). At 36°, $k[meso]/k[dl] \simeq 320$ for DMF and 40 for methanol; at 23° the same ratio is 22 for acetone. It should be obvious that relative reaction rates of any pair of compounds will change with solvent as they do with temperature, coreactant, etc. Although its origin is complex and often obscure, the device of *solvent dispersion* of rates into a *selectivity spectrum* can be applied to any pair of isomers to effect their separation.

(16) (a) R. Fuchs, J. L. Bear, and R. F. Rodewald, *J. Amer. Chem. Soc.*, **91**, 5797 (1969); (b) G. Choux and R. L. Benoit, *ibid.*, **91**, 6221 (1969).

When comparing the rate processes for two isomers, it is useful to break down the energetics. The appropriate relation is eq 8, where the terms refer to free energies of reactants and transition states, and the free energies of activation.[2c,9] It is convenient to extrapo-

$$(G_{dl} - G_{meso}) + (\Delta G^{\ddagger}_{dl} - \Delta G^{\ddagger}_{meso}) = (G^{\ddagger}_{dl} - G^{\ddagger}_{meso}) \quad (8)$$

late our rate data to 80°, at which temperature we have the only available figure for the first term, $(G_{dl} - G_{meso}) \simeq 0.78$ kcal/mol (from benzene).[2a] Since $k_{meso}/k_{dl} \simeq 115$ at 80°, the second term in eq 8 is 3.3 kcal/mol. Therefore, $G^{\ddagger}_{dl} - G^{\ddagger}_{meso} \simeq 4$, a figure similar to that given for the product difference, $(G_{cis} - G_{trans}) \simeq 3.7$ kcal/mol.[10] Since we believe that the time scale and reaction profile of eq 6 vary from *meso* to *dl*, we should not insist that the transition states themselves are literally "productlike."

The Effect of Lithium Bromide.—Observations of salt effects in debrominations have often been scattered and unsystematic.[5,17,18] The data (Table IV) for sodium nitrate on the elimination from *meso*-**1** indicate a small positive effect of ~25% at concentrations of 0–0.6 *M*. These data establish the scale of "ordinary" salt effects whatever their origin.

In contrast to our observations (Table IV), lithium bromide depresses the rate of the reaction of iodide with *meso*-**1** in acetone,[4] and of bromide with fumaric ester dibromide in DMF.[3] As the sodium iodide concentration increases, the rate constant for its reaction with *sym*-tetrabromoethane decreases.[17] It is interesting that the rate constant for *meso*-**2** with tetrabutylammonium iodide is appreciably larger (~2) than that for potassium iodide in methanol or DMF.[5] We take all of this as evidence for the presence of ion pairs which are *less* nucleophilic than free halide.

The addition of 0.2 *M* lithium bromide to iodide–stilbene dibromide reactions leads to a rate enhancement of ~30%. This appears to be a larger than ordinary effect. Separate experiments *without* iodide established that the reaction of bromide ion with the stilbene dibromides was too slow to increase the apparent rate when iodide was present.[2a] Our tentative explanation is that BrI_2^- forms in these solutions[8] and increases the concentration of iodide ion. The rate enhancement by bromide ion also indicates that there must be little or no return to *dl*-**1** from **4** in mechanism 6. Whether bromide ion also assists in the destruction of **3** before it returns to *dl*-**1** is a matter of conjecture at this stage.

Registry No.—*meso*-**1**, 13440-24-9; *dl*-**1**, 13027-48-0; sodium iodide, 7681-82-5.

(17) W. G. Lee and S. I. Miller, *J. Phys. Chem.*, **66**, 655 (1962).

(18) C. F. Van Duin, *Recl. Trav. Chim. Pays-Bas*, **43**, 341 (1924); **45**, 345 (1926).

Debromination of *meso*- and DL-Stilbene Dibromides by Lithium Bromide in Dimethylformamide[1a,b]

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In the title system, *meso*-stilbene dibromide gave *trans*-stilbene, while *dl*-stilbene dibromide gave both stilbenes, [*trans*]/[*cis*] $\simeq$ (83 $\pm$ 2)/(17 $\pm$ 2). The rate data at 59.4° were, for *meso*, $\Delta H^{\pm}$ = 20.6 kcal/mol and $\Delta S^{\pm}$ = −9 eu; for *dl*, $\Delta H^{\pm}$ = 28.9 kcal/mol and $\Delta S^{\pm}$ = 8 eu; $k(meso)/k(dl)$ = 50. Stannous chloride proved to be an efficient scavenger in the *dl* reaction, for which rate data could not otherwise have been obtained. In methanol, lithium bromide is inert; in the aprotic solvent (DMF), it is an effective debrominating agent. A complete conformational analysis has been performed: the reactant free-energy difference in benzene at 80° has been measured, $(G_{dl} - G_{meso})$ = 0.78 kcal/mol; the transition state free-energy difference in DMF at 80° has been estimated, $(G^{\pm}_{dl} - G^{\pm}_{meso}) \simeq$ 4.6 kcal/mol. Our rates show the trend, *anti* debromination of *meso* >> *syn* debromination of *dl* $\simeq$ *anti* debromination of *dl* >>>> *syn* debromination of *meso*, in accordance with the idea that "discrete" stereoelectronic and steric factors may make aligned or opposed contributions to the rates.

This study is concerned with the mechanism and stereoselectivity of the debromination of *meso*- and *dl*-stilbene dibromides (1) by bromide ion in dimethylformamide (DMF). In related work, we have investi-

$$\underset{\textit{meso}\text{- and }\textit{dl}\text{-}\mathbf{1}}{(C_6H_5CHBr)_2} + 3Br^- \xrightarrow[DMF]{} \underset{\textit{trans}\text{- and }\textit{cis}\text{-}\mathbf{2}}{C_6H_5CH{=}CHC_6H_5} + Br_3^- \quad (1)$$

gated several facets of dehalogenation, namely, kinetics, stereoselectivity, mechanism, nature of reductant and dihalide, medium effects, etc.[2-4] At first glance, bromide ion might appear to be an impractical choice as a nucleophile: after all, bromine additions in the presence of bromide ion or the reverse of process 1 are commonplace. Nevertheless, the kinetics of dehalogenation by bromide ion of *meso* and *erythro* forms in aprotic solvents have been published recently.[5,6] The scope of the reaction, as well as the difficulties likely to be encountered for *dl* forms, have also been surveyed.[5] However, we were able to solve the problem of reversibility and associated problems for *dl*-1. Then, we could investigate DMF as a medium for eq 1, the nucleophilicity of bromide ion toward 1, and stereoselection in bromide-promoted debromination in an aprotic solvent.

Experimental Section[1b]

Our DMF, lithium bromide, stannous chloride (95.5%), 1, and 2 have been described.[2e,4a] Bromide ion was estimated with standard silver nitrate, either potentiometrically or by the eosin indicator method. Stannous chloride (~0.1–0.05 *M*) in DMF was diluted with water, acidified with concentrated sulfuric acid, and titrated with standard iodine to the starch end point.

Kinetic studies and some product identifications were made spectrophotometrically in Beckman DK-2 or Cary-11 spectrophotometers. Since the extinction coefficients, ϵ, for *cis*- and *trans*-2 are much greater than those of the reactants, it was possible to monitor them in process 1.[2e] When both stilbenes were produced, the ratio of [*cis*-2]/[*trans*-2] could be obtained by a method of simultaneous equations,[7] or preferably as described below.

Kinetic Procedures.—For process 1, we used lithium bromide and 1 in DMF; the *dl*-1 runs also contained stannous chloride. This removes bromine on mixing in DMF, and does not interfere with product analysis. Incidentally, β-naphthol also appeared to be an excellent trap for bromine, but its ϵ (310 mμ) 750 and ϵ (297 mμ) 428 were high, and it reacted slowly with *dl*-1 at ~25° to produce *trans*-2. Acetone reacted too slowly with bromine to be useful.

In some of our first runs, the eliminations were carried out in a specially designed flask (Figure 1). The thermostated flask, containing lithium bromide in DMF was flushed with nitrogen; in the case of *dl*-1, stannous chloride solution was added at this time. With the stirrer going, an aliquot of 1 in DMF at thermostat temperature was added to the flask against a stream of nitrogen, and the port was then closed. Under these conditions, essentially no air oxidation of the stannous ion was observed. Aliquots were taken at intervals and analyzed as described below.

The ampule technique was used for most of the runs, particularly at the higher temperatures. Typically, solutions were made up at room temperature and distributed among nitrogen-flushed ampules, which were then capped and later sealed. The ampules were immersed in thermostated baths, removed after known periods, then cooled quickly in Dry Ice–acetone slush; later, the contents of the ampules were diluted with DMF and analyzed spectrophotometrically.

The eliminations were carried out under pseudo first order conditions with an excess of lithium bromide over stannous chloride and 1. The pseudo first order rate constants, k_ψ, were obtained from the slope of a plot of log $(A_\infty - A)$ against t, where A_∞ and A are the optical densities at times, t_∞ and t, respectively. The second-order rate constants were obtained from $k = k_\psi/[Br^-]$ and were corrected for solvent expansion.[8]

Activation parameters were determined from Arrhenius plots and the standard relations (eq 4, ref 2a). All of the rate data are given in Tables I–III.

In the case of *dl*-1, both 2's were produced. Under pseudo first order conditions, it is possible to "follow" both products at 310 mμ and yet have a simple rate law. We take [*dl*-1] = a, L as the cell length, and C and T as labels for *cis*- and *trans*-2. If *dl*-1 disappears along one path, (2) applies; for $\epsilon_a \simeq 0$, we derive (3)

$$\ln a/a_0 = -k_\psi t \quad (2)$$

$$\ln (A_\infty - A) = -k_\psi t + \ln La_0(\epsilon_C F + \epsilon_T)/(1 + F) \quad (3)$$

in which $A_\infty = A_C + A_T$ and $F \equiv$ [*cis*-2]/[*trans*-2]. On the other hand, if *dl*-1 decomposes along competitive paths to give both 2's, then we would have $k = k_T + k_C$ and $F = k_C/k_T$. The plots of

(1) (a) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work. This paper was presented in part at the 151st National Meeting, American Chemical Society, Pittsburgh, Pa., March 1966, Abstract 68 N. (b) Taken largely from the Ph.D. Thesis of W. K. K., Illinois Institute of Technology, 1967. (c) Author to whom inquiries should be addressed.

(2) (a) I. M. Mathai and S. I. Miller, *J. Org. Chem.*, **35**, 3416 (1970); (b) I. M. Mathai, K. Schug, and S. I. Miller, *ibid.*, **35**, 1733 (1970); (c) C. S. T. Lee, I. M. Mathai, and S. I. Miller, *J. Amer. Chem. Soc.*, **92**, 4602 (1970); (d) W. K. Kwok and S. I. Miller, *ibid.*, **92**, 4599 (1970); (e) W. K. Kwok and S. I. Miller, *J. Org. Chem.*, in press.

(3) (a) W. G. Lee and S. I. Miller, *J. Phys. Chem.*, **66**, 655 (1962); (b) S. I. Miller and R. M. Noyes, *J. Amer. Chem. Soc.*, **74**, 3403 (1952).

(4) W. K. Kwok and S. I. Miller, *Can. J. Chem.*, **45**, 1161 (1967); (b) W. G. Lee and S. I. Miller, *J. Amer. Chem. Soc.*, **82**, 2463 (1960).

(5) (a) F. Badea, T. Constantinescu, A. Juvara, and C. D. Nenitzescu, *Justus Liebigs Ann. Chem.*, **706**, 20 (1967). (b) F. Badea, S. Rosca, I. G. Dinulescu, M. Avram, and C. D. Ninitzescu, *Rev. Roumaine Chem.* **10**, 1201 (1965).

(6) (a) E. Baciocchi and P. L. Bocca, *Ric. Sci.*, **37**, 1182 (1967); (b) E. Baciocchi and A. Schiroli, *J. Chem. Soc. B*, 554 (1969).

(7) M. Ish-Shalom, J. D. Fitzpatrick, and M. Orchin, *J. Chem. Educ.*, **34**, 496 (1957).

(8) "A Review of Catalytic and Synthetic Applications for DMF/DMAC," and Supplement; and "DMF", a product information bulletin, prepared and published by E. I. du Pont de Nemours and Co., Inc., Wilmington, Del.

TABLE I

DEBROMINATION OF *meso*-STILBENE DIBROMIDE BY BROMIDE IN DIMETHYLFORMAMIDE

Temp, ±0.05°	*meso*-Dibromide, $M \times 10^3$	LiBr, $M \times 10^2$	k,[a] M^{-1} sec$^{-1} \times 10^1$
59.40	11.27	9.31	2.36
	2.88	4.65	2.48[b]
	2.31	8.79	2.27
	2.40	4.81	2.37
	0.51	4.86	2.38
	0.52	1.44	2.40
			k_{av} 2.36 ± 0.03
39.51	2.47	9.95	0.304
	11.74	9.96	0.301
	2.41	5.13	0.310
			k_{av} 0.305 ± 0.003
49.50	2.39	9.35	0.864
	11.55	10.83	0.873
			k_{av} 0.869 ± 0.005
50.20	0.52	5.15	0.892
	2.47	9.79	0.903
	0.52	9.28	0.916
	2.49	4.86	0.939
	0.52	1.44	0.945
			k_{av} 0.919 ± 0.018

[a] Reference 6 gives k values of 0.827×10^{-3} at 50.0° for sodium bromide and 7.35×10^{-5} at 25.0° for tetrabutylammonium bromide. [b] Run contains stannous chloride (5.84×10^{-3} M); k was not included in the average.

TABLE II

DEBROMINATION OF *dl*-STILBENE DIBROMIDE BY BROMIDE IN DIMETHYLFORMAMIDE

Temp, ±0.05°	*dl*-1, $M \times 10^3$	LiBr, $M \times 10^2$	$SnCl_2$, $M \times 10^3$	k, M^{-1} sec$^{-1} \times 10^3$ $(1 + F)^{-1}$[a]	
59.48	0.62	38.97	1.51	0.049	
	2.97	46.85	7.75	0.047	
	0.62	55.25	1.44	0.046	
				k_{av} 0.047 ± 0.001	0.844
74.90	0.62	21.04	1.53	0.338	
	2.92	20.30	5.52	0.306	
	0.68	21.38	2.24	0.355	
	2.86	15.75	5.94	0.367	
				k_{av} 0.342 ± 0.019	0.852
83.90	0.64	8.82	1.94	1.17	
	2.92	12.56	7.31	1.10	
	0.65	8.91	7.37	1.11	
	0.65	6.57	2.11	1.13	
	0.13	3.74	0.53	1.15	
				k_{av} 1.13 ± 0.02	0.837
85.44	0.32	4.63	1.09	1.25	
	0.65	9.06	2.26	1.20[b]	
				k_{av} 1.23 ± 0.03	0.81
100.22	0.63	2.81	2.05	6.18	
	0.67	3.52	1.98	6.03	
	0.33	3.97	1.09	6.14	
				k_{av} 6.12 ± 0.06	0.79

[a] Fraction of *trans* in the stilbene product; F = [*cis*-2]/[*trans*-2]. [b] Water (0.1%) was added in this run.

the left-hand side of eq 3 against t, including 15–25 points, were, in fact, linear and gave the k values of Table II. Note that, if eq 3 is to apply, the partitioning factor F must remain constant and kinetic control of product formation must prevail. We evaluated F (Table II) from the intercept of plots of eq 3; this was far more convenient and reliable than a direct determination of F based on the optical density of the solution at two wavelengths.[2,7]

A number of ancillary experiments are of interest. Rate constants for the reaction of *meso*-1 with lithium bromide (39–60°) are the same in the presence or absence of stannous chloride. At higher temperatures, the debromination of *meso*-1 by stannous

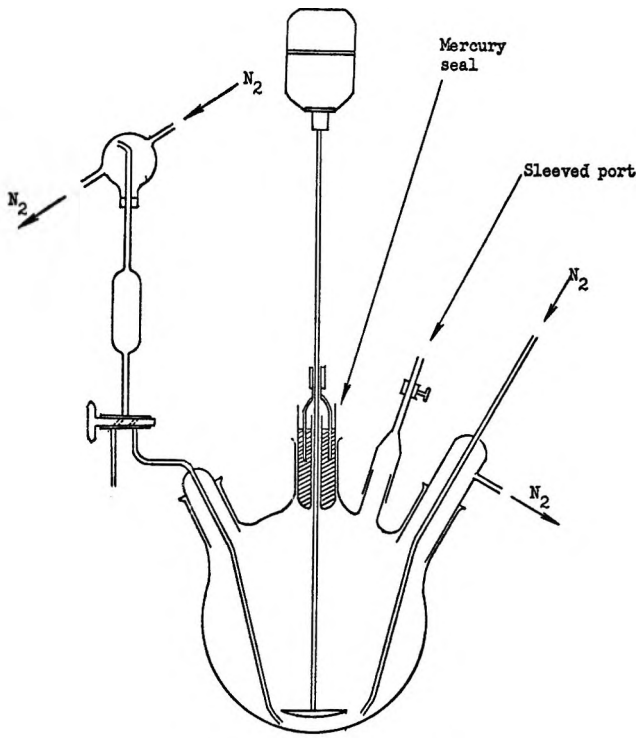


Figure 1.—Reaction vessel.

TABLE III

ACTIVATION PARAMETERS AND RATE CONSTANTS AT 59.4° FOR THE REACTION OF THE STILBENE DIBROMIDES WITH BROMIDE OR IODIDE IONS IN DIMETHYLFORMAMIDE

$(C_6H_5CHBr)_2$	X^-	$\Delta H^{\pm}$,[a] kcal/mol	$\Delta S^{\pm}$,[b] eu	k, M^{-1} sec^{-1} $\times 10^3$	$\frac{k(meso)}{k(dl)}$
meso	Li^+Br^-	20.6	−9.0	2.36	50
dl	Li^+Br^-	28.9	8.4	0.047	
meso[c]	Na^+I^-	16.3	−15.1	74.2	154
dl[c]	Na^+I^-	22.3	−6.9	0.481	

[a] ±1.0 kcal/mol. [b] ±3 eu. [c] Reference 2a.

ion (50–75°) and by DMF (75°) does occur.[2d] Although DMF dehydrobrominates *dl*-1 in our temperature range,[2b,e] this reaction is inhibited (fortunately) by stannous chloride. As for debromination of *dl*-1, adjustment of the ratio, [LiBr]/[$SnCl_2$], makes a kinetic study of either reductant feasible.[2d]

In the absence of stannous chloride, the processes of elimination, addition, isomerization, and bromine consumption, all temperature dependent, may compete in our system

$$cis\text{-}2 \underset{}{\overset{Br_2,\ LiBr}{\rightleftharpoons}} trans\text{-}2 \overset{Br_2,\ LiBr}{\rightleftharpoons} meso\text{-}1 \qquad (4)$$

A fresh solution of *meso*-1 (0.01 M) in DMF or lithium bromide (0.35 M) in DMF gave no color, but a solution of all three produced an immediate color similar to that obtained from solutions of bromine in DMF; after 19 hr at 36°, sodium iodide was added and titration with thiosulfate indicated ~82% reaction. *meso*- or *dl*-1 (0.5 g) and lithium or ammonium bromide (5 g) in DMF (30 ml) at 70° for 48 hr gave *trans*-2 (0.2 g) in ~80% yield.

trans-2 (1 g), lithium bromide (5 g), and bromine (1 ml) were left in DMF (50 ml) at room temperature for 2 days. Work-up of the products gave *meso*-1 (0.6 g), mp 233–236°, from benzene; without lithium bromide, bromine addition appeared to proceed more slowly. Infrared examination of the residues established that *cis*-2 and *dl*-1 were absent. When similar experiments were carried out at 70° with or without lithium bromide, *trans*-2 and little or no *meso* could be isolated.

It was shown that the oxidizing power of DMF solutions of bromine (0.33 M) fell rapidly, ~37% in 14 hr at 60°. Added bromide ion appears to retard the consumption of bromine. In the presence of bromine, the isomerization (eq 4) of *cis*-2 to *trans*-2 in DMF was found to proceed readily at 70–100°. In

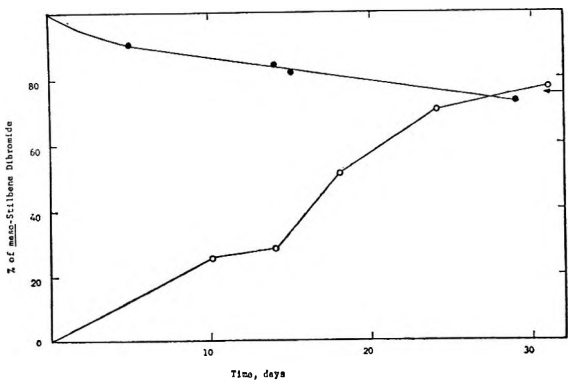


Figure 2.—Progress of the isomerization of *meso*- and *dl*-stilbene dibromide (1) in benzene at 80°. Starting compound (and a trace of I_2): ● *meso*-1; ○ *dl*-1. The arrow indicates 75% *meso*.

DMF alone, or with lithium bromide and/or stannous chloride, no isomerization of *cis*-2 occurred in 140 hr at 60–100°.

Isomerization of the Stilbene Dibromides (1).—Preliminary experiments indicated that a solution of *dl*-1 (0.5 g, 1.5×10^{-3} mol) and iodine (0.01 g, 4×10^{-5} mol) in benzene (10 ml) deposited *meso*-1 after 20 hr at 100° or 20 days at 25°. Equilibration studies were actually made on solutions which did *not* deposit *meso*-1, *i.e.*, *meso*-1 or *dl*-1 (0.35 g, 1.03×10^{-3} mol) and iodine (6×10^{-3} g) in benzene (40 ml) at reflux temperature (80°). After a fixed period, the solution was cooled, evaporated under reduced pressure, and the residue taken up in DMF (100 ml) containing sodium iodide (1.5 g, 0.01 mol). After 20 hr at ~25°, an aliquot (10 ml) of the DMF solution was titrated with standard sodium thiosulfate to the starch end point.[2a] This gave the quantity of *meso*-1 in the mixture. Another portion of the solution was kept at 60° for 24 hr, then analyzed in the same way to give both [1]'s. In order to test the precision of the analysis, a blank was run with a mixture of *meso*-1 (0.1925 g) and *dl*-1 (0.1560 g) or [*meso*-1]/[*dl*-1] = 1.30. Our method gave the ratio 1.36: the accuracy was ~5%. Some results are given in Figure 2.

Results and Discussion

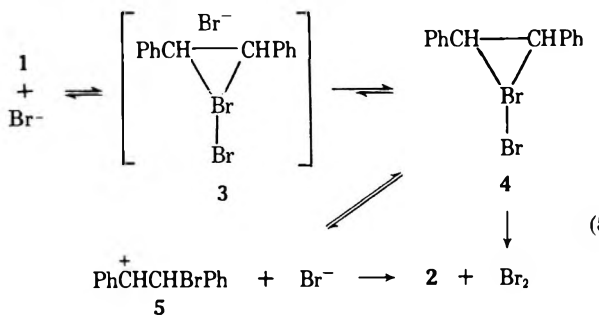
In DMF, process 1 was kinetically second order, first order in 1 and first order in lithium bromide. The stoichiometry of eq 1 was established, since high conversions (>98%) were observed spectrophotometrically. Although DMF debrominates *meso*-1 at 152°, and dehydrobrominates *dl*-1 at ~75°, these reactions did not complicate our kinetic studies.[2e] With *meso*-1 and excess lithium bromide, process 1 is mush faster than the solvent reaction and also appears to be irreversible. As for *dl*-1, we could not follow its kinetics according to eq 1, unless we added a scavenger to destroy the bromine produced. Stannous chloride proved to be efficient both for removing bromine quickly and for rendering the DMF ineffective as a dehydrobrominating agent; although stannous ion also reduces *dl*-1, the rate was relatively low under our conditions.[2d]

A few general remarks about our system can be made. At 59.4°, *meso*-1 reacts ~50 times as fast with bromide ion as does *dl*-1. By taking into account product compositions, we can alter the comparison: $k(meso\text{-}1)/k(dl\text{-}1) \simeq 60$ for the production of *trans*-2 but ≃310 for the *anti* eliminations. Unlike iodide, bromide does not debrominate 1 in methanol;[2c,3] yet their elimination rates are similar in DMF. This striking rate enhancement is presumably due to the large and favorable transfer energy (destabilization) of bromide ion between the two solvents.[9]

(9) A. J. Parker, *Chem. Rev.*, **69**, 1 (1969).

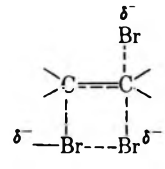
Lithium bromide may be associated. Assuming $K_a \simeq 0.3$, Nenitzescu, *et al.*, were able to remove a trend in the rate constants in the debromination of *meso*-methyl dibromosuccinate by lithium bromide.[5a] We found no such trend, perhaps because our salt concentrations were low. The possibility that both associated and free bromide ion are reacting adds to the complexity of the system.

The debromination by bromide ion converts *meso*-1 into *trans*-2 and *dl*-1 into 83 ± 2% *trans*-2 and 17 ± 2% *cis*-2. In the absence of a scavenger, *dl*-1 gives only *trans*-2. In the other papers of this series,[2] we have argued that a slow halide-promoted ionization, such as the formation of **3** in eq 5, provides a useful mechanistic



framework for such dehalogenations. The virtues of this scheme are that the steps can be telescoped to accommodate a concerted process, that the incursion of onium rearrangements or solvolysis in hydroxylic solvents is possible, that the intermediates **3**–**5** can linger if the energetic barrier they face is unfavorable, and, most important, that polar debromination and bromine addition mechanisms in protic and aprotic solvents are unified.[2] Here we assume that the *dl*-1 reaction is diverted, at least in part, through the open onium ion **5** which can be partioned to give both 2.[2]

Although other mechanistic possibilities cannot be ruled out in specific cases,[10-12] we believe the weight of the evidence favors eq 5.[2] Some of these are recalled. A concerted *anti* elimination from *meso*-1 could account for the stereospecific production of *trans*-2, and various combinations of the following *discrete* processes could conceivably account for the *dl* product, namely *anti* elimination, *syn* elimination, and displacement followed by elimination. Alternatively, the merged transition state **6** could lead either to *anti* elimination or



6

isomerization of *dl*-1 to *meso*-1. Note that in general each one of the many recognized halogen addition mechanisms, *e.g.*, attacks led by halogen or halide in second, third, and complex rate laws, is necessarily the reverse of a dehalogenation. While eq 5 includes a number of these, which involve 1 and halide ion in a rate-determining step, there must, of course, be other

(10) D. V. Banthorpe, "Elimination Reactions," Elsevier, New York, N. Y., 1963, Chapters I, 6.
(11) J. Csapilla, *Chimia*, **18**, 37 (1964).
(12) J. Mulders and J. Nasielski, *Bull. Soc. Chem. Belg.*, **72**, 322 (1963).

dehalogenation paths for some 1,2-dihalides and for other reaction conditions.

In addition to previous rationalizations of eq 5, we now find that the product ratio from *dl*-**1** is essentially constant over the temperature range (Table II). Our interpretation is that there is one rate-determining step and rapid partitioning of unstable intermediates (*e.g.*, **4**, **5**),[2b] rather than two or more competitive slow steps to **2**. Secondly, we find that in the debromination of *dl*-**1** in DMF $k(Br^-)/k(I^-) \simeq 0.1$ (Table III). Since bromide ion is a more powerful nucleophile than iodide toward carbon in SN2 processes in DMF,[9] we believe that observed rate ratio is a strong indication that rate-determining displacement[10] or a merged transition state (**6**)[11] are *not* involved in process 1.[13]

Conformational Analysis.—In systems such as ours, conclusions about conformational effects are best made when all of the necessary energy terms are at hand.[14] The determination of the equilibrium constant for the isomerization of **1** had never been done satisfactorily. Eliel cites the figure $K \simeq 4$, on the basis of work by Buckles.[15] Because their spectra lack strong character-

$$dl\text{-}\mathbf{1} \rightleftharpoons meso\text{-}\mathbf{1} \qquad (6)$$

istic absorptions in the wavelength region accessible to us, ir and uv analysis of **1** could not be used. (During the period of our work, however, Heublein devised a convenient method of analysis for mixtures of **1** based on their ir absorption spectra below 600 cm^{-1}.[16]) We found that the low solubility of *meso*-**1** in several solvents, *e.g.*, carbon tetrachloride, DMF, benzene, acetonitrile, methanol, precluded accurate nmr analysis. Buckles promoted the isomerization of **1** by bromine vapor on the solid, and estimated the product composition, after recrystallization, from its melting point.

Although our analytical procedure for mixtures of **1** was not elegant, it did work (Experimental Section). It is based on selective debromination rates with iodide in DMF: the relative rate of reaction of *meso*-**1** and *dl*-**1** is ~320 at 36°.[2a] DMF cannot be used as the solvent for the isomerization (eq 6) because it debrominates *meso*-**1** and dehydrobrominates *dl*-**1**.[2e] Benzene was suitable for the equilibrium measurements; both **1**'s, at concentrations below the saturation value of *meso*-**1**, could be equilibrated at 80°. As shown in Figure 2, the approach to equilibrium is slow. At 80°, the value $K = [meso\text{-}\mathbf{1}]/[dl\text{-}\mathbf{1}] = 3.0 \pm 0.3$ or $(G_{dl} - G_{meso}) = 0.78 \pm 0.1$ kcal/mol.

It is now possible to look at the conformational terms that contribute to the *dl*-**1** *vs.* *meso*-**1** rates at 80° (eq 8, ref 2a).[2,4,14] A minor assumption is that the ground state free energy difference determined in benzene can be used for DMF.[17] Since $(\Delta G^{\ddagger}_{dl} - \Delta G^{\ddagger}_{meso}) = 3.8$ for the *anti* eliminations, $(G^{\ddagger}_{dl} - G^{\ddagger}_{meso}) = 4.6 \pm 0.2$ kcal/mol. Since the products have $(G_{cis} - G_{trans}) = 3.7 \pm 0.1$ kcal/mol, one might be inclined to say that the transitions states in eq 1 are "product like." Because the transition state difference is *not* bracketed, or $(G_{dl} - G_{meso}) < (G^{\ddagger}_{dl} - G^{\ddagger}_{meso}) < (G_{cis} - G_{trans})$, it is clear that conventional analogies of the type contained in the Hammond postulate, the Brønsted α, etc. are inadequate.[4] Judging from the activation parameters in Table III, the mix of enthalpy and entropy contributions in the transition states of *meso*- and *dl*-**1** are substantially different. If the transition states of the rate determining step of eq 1 do, in fact, resemble **3**, then there are obvious reasons, such as shape, charge distribution, etc., for their properties not to lie between those of reactants and products.

The preceding analysis is consistent with a rather general approach to stereoselection. *anti* elimination is favored *stereoelectronically* or by favorable orbital symmetry and energies of the reacting centers.[14] The total structure, however, is subject to geometric or bulk limitations which we label as the *steric* factor (for lack of a more elegant term).[14] For the *anti* eliminations, both factors are favorable for *meso*-**1** and opposed for *dl*-**1**; for hypothetical *syn* eliminations, both factors are unfavorable for *meso*-**1** and opposed for *dl*-**1**. We can expect, therefore, the kind of rate sequence implicit in Table III: *anti* debromination of *meso* > > *syn* debromination of *dl* ~ *anti* debromination of *dl* > > > > *syn* debromination of *meso*.

Registry No.—*meso*-**1**, 13440-24-9; *dl*-**1**, 13027-48-0; lithium bromide, 7550-35-8.

(13) According to our mechanism, the higher proportion of *trans*-**2** formed from *dl*-**1** with bromide ion as compared with iodide ion would depend on the fate of **4** as compared with its iodo analog (Table III). We find it difficult to rationalize these results convincingly.

(14) S. I. Miller, *Advan. Phys. Org. Chem.*, **6**, 185 (1968).

(15) (a) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, p 25; (b) R. E. Buckles, W. E. Steinmetz, and N. G. Wheeler, *J. Amer. Chem. Soc.*, **72**, 2496 (1950).

(16) (a) G. Heublein, *J. Prakt. Chem.*, **31**, 84 (1966); (b) G. Drefahl and G. Heublein, *ibid.*, **21**, 18 (1963).

(17) (a) R. J. Abraham, L. Cavalli, and K. G. R. Pachler, *Mol. Phys.*, **11**, 471 (1966); (b) L. I. Peterson, *J. Amer. Chem. Soc.*, **89**, 2677 (1967).

Aziridinemethanols

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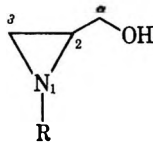
Procedures for the synthesis of substituted aziridinemethanols from aziridine esters have been developed. The stereochemistry of hydride reductions leading to α-phenylaziridinemethanols is highly dependent on the solvent and hydride reagent. Stereochemistry of these hydride reductions is assigned by independent chemical means and discussed in terms of models for asymmetric induction. A number of transformations of aziridine alcohols in which the aziridine ring remains intact are described. The mass spectra of aziridinemethanols are also discussed.

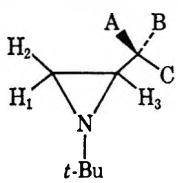
Our interest in the interaction of the aziridine ring with incipient positive charge[2] necessitated the preparation of a series of α-substituted aziridinemethanols and their derivatives. Although there are a number of



known routes to substituted aziridinemethanols,[3] our desire to study a homologous set of compounds and the availability of aziridine esters led to developing the high yield sequence of reactions shown in Scheme I. General structures were assigned to these compounds on the basis of their nmr spectra (Table I) as well as infrared, mass spectral (see below), and elemental analyses.

TABLE I

NMR SPECTRAL PROPERTIES OF *t*-BUTYLAZIRIDINE DERIVATIVES[a]

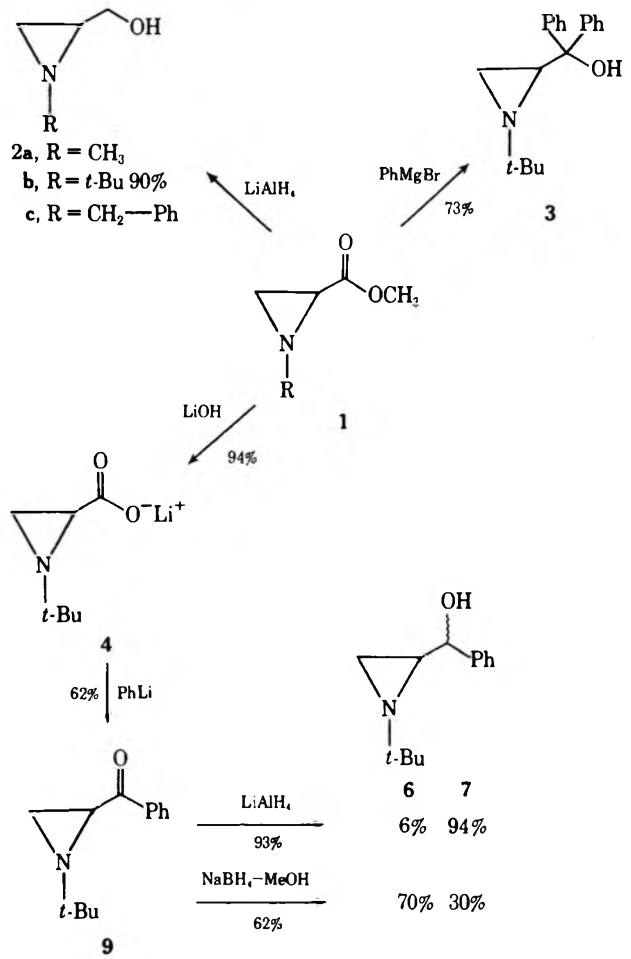


Compd	H_1	H_2	H_3	A	B	*t*-Bu
1b[b]	1.67	1.85	2.12			0.97
2b	1.33–1.50		1.80	3.43		0.97
6	1.37–1.57		1.83	4.25		0.84
7	1.34	1.55	1.97		4.60	0.85
3	1.60–1.75		2.59			0.77
4	1.82	2.04	2.93			1.03

[a] Values are expressed in parts per million (δ) downfield from TMS. [b] R = *t*-Bu.

It will be noted from Scheme I that a change in the hydride donor and solvent resulted in an inversion of stereoselectivity. Although this result allows investigation of the stereochemical consequences of aziridine interactions with a carbinyl center, an unambiguous stereochemical assignment must precede such study.

SCHEME I



Various models have been invoked to explain and predict the stereochemistry of addition to carbonyl groups adjacent to asymmetric carbon atoms.[4] In the absence of interaction between the carbonyl and the asymmetric center, attack apparently occurs on the most stable conformation and from the least hindered side (open chain model). Additions for which this model is valid seldom display high stereoselectivity. Presence of a heteroatom at the asymmetric carbon offers potential coordination of the heteroatom and the carbonyl group with a metal species (cyclic model). Additions to which this model is applicable usually are highly stereoselective. A third model in which the conformational preference is dominated by repulsion between the carbonyl oxygen and heteroatom has been proposed (and criticized[4b]).

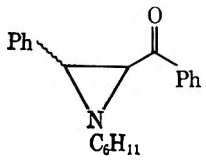
(1) Support of this research by National Science Foundation Grants GP-5531 and GP-8044 is gratefully acknowledged.

(2) J. A. Deyrup and C. L. Moyer, *Tetrahedron Lett.*, 6179 (1968).

(3) (a) R. V. Capeller, R. Griot, M. Haring, and T. Wagner-Jauregg, *Helv. Chim. Acta*, **40**, 1652 (1957); (b) N. H. Cromwell, *J. Amer. Chem. Soc.*, **69**, 258 (1947); (c) N. H. Cromwell, J. H. Anglin, Jr., F. W. Olsen, and N. G. Barker, *ibid.*, **73**, 2803 (1951); (d) D. K. Wall, J. L. Imbach, A. E. Pohland, R. C. Badger, and N. H. Cromwell, *J. Heterocycl. Chem.*, **5**, 77, 1968.

(4) (a) D. J. Cram and D. R. Wilson, *J. Amer. Chem. Soc.*, **85**, 1245 (1963); (b) G. J. Karabatsos, *ibid.*, **89**, 1367 (1967).

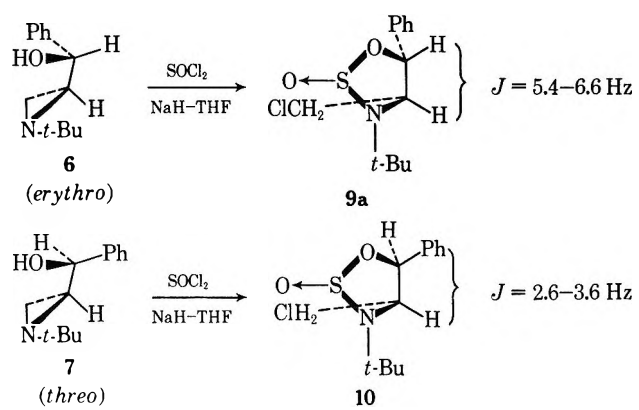
The stereochemistry of reduction of several aziridinyl ketones (**8**) has recently been studied by Cromwell.[3d]



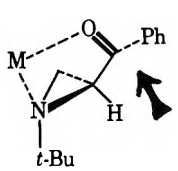
8

In contrast to our results, both $LiAlH_4$ and $NaBH_4$ yielded the same isomer as the major product. The stereochemistry of this major product was assigned the *erythro* configuration on the basis of the open chain model. The high stereoselectivity observed in both studies with $LiAlH_4$ is, however, suggestive of the cyclic model which also predicts preferential formation of the erythro isomer. Reductions with $NaBH_4$ were of diminished stereoselectivity in the case of **8** and of inverted stereoselectivity in the case of **5**. The different selectivity exhibited by $NaBH_4$ toward **8** and **5** clearly indicates the delicate balance between those factors which govern orientation of addition. Attempts to apply current theories concerning asymmetric induction and reagent size failed to explain convincingly the difference between the two ketones. This failure casts a certain amount of doubt on the validity of stereochemical assignments based solely on these models.

Fortunately, it was possible to obtain independent chemical evidence for the stereochemistry of **6** and **7**. Reaction of **6** with $SOCl_2$ gave oxathiazolidine **9a**.[5] Similarly, **7** yielded **10**. The stereochemistry of these



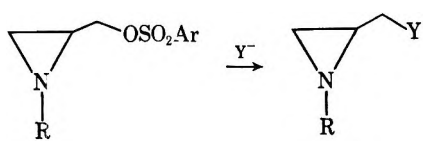
compounds can readily be assigned from the magnitude of the coupling constants in these relatively rigid heterocycles. Since oxathiazolidine formation does not affect the configuration at either asymmetric carbon, the stereochemistry can be assigned as shown. The erythro isomer (**6**) is, therefore, probably formed by attack from the least hindered side of the carbonyl group as shown in the following structure.



(5) J. A. Deyrup, C. L. Moyer, and P. S. Dreifus, *J. Org. Chem.*, **35**, 3428 (1970).

Chemistry of the Aziridinemethanols.—Our study of the properties of the aziridine ring as a neighboring group necessitated the conversion of these alcohols into esters which would serve as suitable leaving groups.[2] The conventional procedure for tosylate preparations from alcohols using tosyl chloride and pyridine was unsuccessful. This failure presumably arises from the greater base strength of the aziridine (relative to pyridine) and results in open chain products *via* chloride ion attack on the protonated aziridine ring. Use of triethylamine or sodium hydride as proton scavengers overcame this problem. In this manner, tosylates of **2a**, **2b**, and **2c** as well as the nosylate of **2b** could be prepared in good yield. The sulfonate esters with R = *t*-Butyl were relatively stable and could be obtained in analytical purity. The other sulfonate esters (R = CH_3 and CH_2Ph) were stable in solution. These solutions could be analyzed spectrally and used for further reactions. Removal of solvent, however, resulted in exothermic polymerization. It appears probable that the *t*-butyl group inhibits intermolecular alkylation. Attempts to prepare esters of **3**, **6**, and **7** have been unsuccessful. In all cases, conditions required for formation of these derivatives proved too drastic or unselective.

The sulfonate esters described above underwent facile displacement in poor ionizing solvents.[2] In each case, the displacement product, **11**, was obtained in



11

good yield and uncontaminated by ring-opened or ring-expanded by-products. Although only halide and alcoxide nucleophiles were investigated, it seems certain that such nucleophilic displacements offer quite general procedures for connecting the aziridine methyl system to various groups.

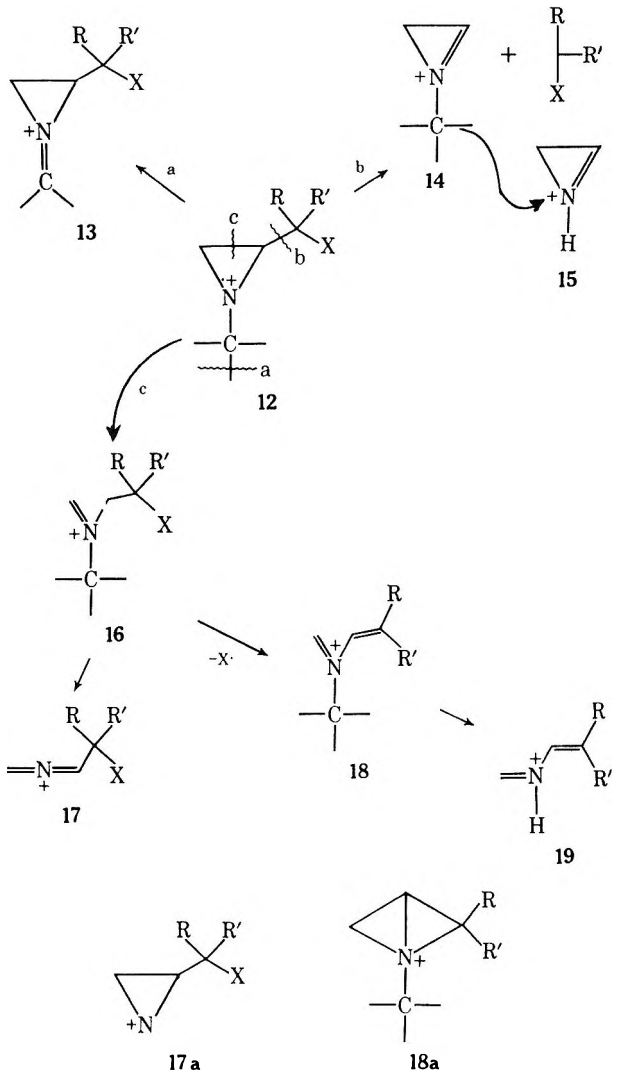
Mass Spectra of Aziridinemethanols.—The closely related series of compounds available from the synthetic work described in this paper prompted us to examine their mass spectral behavior. In addition to providing precedent for future aziridine mass spectral structural assignments, the mass spectra of these compounds offered the potentially interesting features of interplay between the nitrogen atom and the exocyclic heteroatom. The lower ionization potential of nitrogen relative to oxygen generally results in the predominance of molecular ions formed by the removal of an electron from nitrogen when both nitrogen and oxygen are present.[6] In the case of aziridines, the high s character of the unshared electron pair results in a higher ionization potential (relative to larger nitrogen heterocycles)[7] and thus might diminish the effectiveness of nitrogen in directing fragmentation. In spite of this fact, it seems quite clear that the important fragmentation pathways can best be rationalized in terms of initial ionization at the nitrogen atom.

(6) K. Biemann, "Mass Spectrometry," McGraw-Hill, New York, N. Y., 1962, pp 87–90; H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, 1967, pp 9–26.

(7) H. C. Brown and M. Gerstein, *J. Amer. Chem. Soc.*, **72**, 2926 (1950)

Although space does not allow depiction of all the mass spectra and discussion of their detailed interpretation, certain common fragmentation patterns and trends dominate the spectra.[8] These patterns are summarized in Scheme II. It is reasonable to expect

SCHEME II



those aziridine fragmentations which are directed by nitrogen will be similar to the facile fragmentations which are characteristic of other amines. In the case of **12**, three different types (a, b, and c) of α cleavage are possible. Fragments from type a cleavage are present in all *t*-butylaziridines. Type b cleavage is only important when X = OH and/or R = phenyl. Apparently, considerable stabilization of the expelled radical is required to overcome the instability of ion **14**. The third type of α cleavage (c) cannot be directly verified by experiment since the product is isomeric with the molecular ion. Nevertheless, the strain relief of this process and potential resonance stabilization make it an attractive possibility. This possibility is strengthened by the facility with which it allows rationalization of a large number of peaks. In addition, it offers reasonable alternatives to **18a** and the even more improbable **17a**.

(8) The mass spectra of these and related compounds are reproduced in the Ph.D. thesis of C. L. Moyer, Harvard University, Cambridge, Mass., 1968.

Experimental Section

Melting points and boiling points are uncorrected. Liquid samples of less than 5 g were molecularly distilled using a hot air bath and the boiling point reported was the temperature of the air bath. Routine infrared spectra were recorded on a Perkin-Elmer 137 spectrophotometer and the expanded infrared spectra were run on a Perkin-Elmer 337 spectrophotometer. All nmr spectra were recorded on a Varian A-60A spectrometer. Chemical shifts of nmr spectra run in organic solvents are reported in parts per million downfield from internal TMS (δ). Chemical shifts run in D_2O are reported in parts per million downfield from a point 4.99 ppm upfield from the DOH peak. Mass spectra were obtained on a RMU 6E mass spectrometer for all compounds reported in this paper except **4**. In each case molecular weights in agreement with theory were obtained. Fragments are reported as *m/e* (relative intensity). Microanalyses were obtained from Galbraith Laboratories, Inc., Knoxville, Tenn. Reductions with $LiAlH_4$ were worked up according to the procedure of Micovic and Mihailovic.[9] Solvents such as THF, dimethoxyethane, and 1,4-dioxane were distilled from $LiAlH_4$ just prior to use.

Methyl 1-*t*-Butyl-2-aziridinecarboxylate.—Triethylamine (230 g, 2.28 mol) was added to methyl 2,3-dibromopropionate[10] (520 g, 2.11 mol) in 3 l. of benzene over 0.5 hr with stirring in an ice-water bath. The mixture was stirred for 1 hr at room temperature and additional *t*-butylamine (200 g, 2.74 mol) added over 0.25 hr. The mixture was refluxed for 24 hr, *t*-butylamine (73 g, 1.0 mol) added, and reflux continued for 24 hr. The reaction mixture was cooled to room temperature, filtered, and evaporated to a crude oil which was distilled without washing to give the aziridine ester (293 g, 88%): bp 58–59° (4 mm); $n^{25}D$ 1.4379; ir (CCl_4)[11,12] 1735 and 1755 cm^{-1}.

Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62; N, 8.91. Found: C, 60.95; H, 9.70; N, 9.01.

1-*t*-Butyl-2-aziridinemethanol.—A solution of methyl 1-*t*-butyl-2-aziridinecarboxylate (95 g, 0.61 mol) in 100 ml of ether was added over 0.25 hr to lithium aluminum hydride (20 g, 0.52 mol) suspended in 1 l. of ether. The reaction was stirred at room temperature for 3 hr. Excess lithium aluminum hydride was destroyed; the metal salts were removed by filtration and washed with two 100-ml portions of ether. The combined filtrate and washings were evaporated and distilled to give aziridinol (71.5 g, 90%): bp 58–59° (4 mm); mp 36–37°; $n^{25}D$ 1.4516.

Anal. Calcd for $C_7H_{15}NO$: C, 65.07; H, 11.70; N, 10.84. Found: C, 65.04; H, 11.73; N, 10.94.

1-Methyl-2-aziridinemethanol.—Methyl 1-methyl-2-aziridinecarboxylate[13] (30.4 g, 264 mmol) was added in 50 ml of ether to a suspension of lithium aluminum hydride (15 g, 0.40 mol) in 500 ml of ether over 0.25 hr and the reaction mixture stirred for 4 hr at room temperature. Excess lithium aluminum hydride was destroyed; the metal salts were removed by filtration and washed with several 50-ml portions of ether. The combined filtrate and washings were evaporated to a crude oil (36% of the expected aziridinol). Continuous extraction of the metal salts with ether in a Soxhlet extractor for 6 hr yielded an additional 34% of the aziridinol (total yield 15.9 g, 70%). A macro "kugelrohr" distillation gave 14 g of the aziridinol. This material, however, still contained a small amount (~10%) of an impurity. The entire sample was redistilled through an annular Teflon spinning-band column and a center cut obtained of pure (97% by analysis of the nmr spectrum) 1-methyl-2-aziridinemethanol: nmr (CCl_4) δ 1.0–1.7 (m, 3, ring H's), 2.30 (s, 3, CH_3), 3.0–3.8 (m, 2, CH_2–O), 5.15 (6 hr, 1, OH); bp 40° (2.5 mm).

(9) V. M. Micovic and M. L. Mihailovic, *J. Org. Chem.*, **18**, 1190 (1953).

(10) C. S. Marvel, J. Dec, H. G. Cooke, Jr., and J. C. Cowan, *J. Amer. Chem. Soc.*, **62**, 3495 (1940).

(11) Similar spectra have been obtained from other aziridine esters. Two carbonyl frequencies have been reported for some α-halo esters. They have been interpreted in terms of rotational isomers. L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, p 183.

(12) A. Rosowsky in "Heterocyclic Compounds with Three- and Four-Membered Rings," Part 1, A. Weissberger, Ed., Interscience, New York, N. Y., 1964, p 17.

(13) Prepared from methyl 2,3-dibromopropionate and 30% aqueous methylamine in an equal volume of methanol in a reaction similar to that of Antonov and Berlin.[14]

(14) V. K. Antonov and A. Y. Berlin, *Zh. Obshch. Khim.*, **30**, 151 (1960); *J. Gen. Chem. USSR*, **30**, 161 (1960); *Chem. Abstr.*, **54**, 22552*b* (1960).

Anal. Calcd for C_4H_9NO: C, 55.14; H, 10.41; N, 16.08. Found: C, 54.94; H, 10.54; N, 15.91.

1-*t*-Butyl-α,α-diphenyl-2-aziridinemethanol.—Methyl 1-*t*-butyl-2-aziridinecarboxylate (39 g, 0.25 mol) in 100 ml of ether was added over 0.25 hr to a solution of phenylmagnesium bromide prepared from magnesium (12 g, 0.5 g-atom) and bromobenzene (78.5 g, 0.5 mol) in 225 ml of ether. The mixture was stirred at room temperature for 1 hr and then a solution of ammonium chloride (30 g) in 250 ml of ice water was added slowly with stirring. The ether layer was decanted and the aqueous layer stirred with two 200-ml portions of ether which were also decanted. Evaporation of the combined ether layers yielded a crude solid (68 g, 97%) which was recrystallized from aqueous ethanol to give 1-*t*-butyl-α,α-diphenyl-2-aziridinemethanol (51 g, 73% recrystallized): mp 124–125°.

Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 81.01; H, 8.30; N, 5.09.

1-*t*-Butyl-2-aziridinecarboxylic Acid Lithium and Sodium Salts.—Lithium hydroxide monohydrate (13 g, 0.31 mol) was added in four portions over 0.5 hr to a solution of methyl 1-*t*-butyl-2-aziridinecarboxylate (47 g, 0.30 mol) in 150 ml of water and stirred at room temperature overnight. Evaporation gave a viscous syrup which solidified when triturated with ether. The salt was dried at 70° for 2 hr, ground to a fine powder, and redried at 70° (0.01 mm) overnight (42 g, 94%): nmr (D_2O) δ 1.20 [s, 9, $C(CH_3)_3$], 1.9–2.1 (m, 2, AB of ABX, $H_{b,c}$), and 2.47 ppm (m, 1, X of ABX, H_a). The sodium salt has been prepared in the same way from sodium hydroxide.

1-*t*-Butyl-2-aziridinyl Phenyl Ketone.—Phenyllithium (200 ml of an ether solution[15] (~130 g or ~0.30 mol) was added to a solution of lithium 1-*t*-butyl-2-aziridinecarboxylate (45 g, 0.30 mol) in 600 ml of dimethoxyethane. The mixture was stirred for 1 hr at room temperature and evaporated to an oil which was taken up in 500 ml of ether and 500 ml of water. The ether layer was washed with saturated sodium chloride solution, dried (K_2CO_3), and evaporated to a crude oil (47.5 g, 80% aziridinyl ketone by analysis of the nmr spectrum, 62% yield) which contained some biphenyl[16] (8% by analysis of the nmr spectrum). On standing in the ice chest overnight, the ketone crystallized. The crystals were filtered, washed with low boiling (20–40°) petroleum ether, and dried to give 1-*t*-butyl-2-aziridinyl phenyl ketone (22 g, 36%): mp 41–44°; bp 100° (0.2 mm); ir (CCl_4) 1675 cm^{-1}.

Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.66; H, 8.25; N, 7.02.

Reduction of 1-*t*-Butyl-2-aziridinyl Phenyl Ketone to *erythro*- and *threo*-1-*t*-Butyl-α-phenyl-2-aziridinemethanol (6 and 7, Respectively). (1) Sodium Borohydride.—1-*t*-Butyl-2-aziridinyl phenyl ketone (10 g, 95% pure, 47 mmol) was dissolved in 100 ml of methanol and enough water added (~5 ml) to turn the solution cloudy. Sodium borohydride (3.0 g, 70 mmol) was then added in small portions with stirring over 0.5 hr at room temperature. The reaction was refluxed for 0.25 hr, cooled to room temperature, and evaporated to an oil. This oil was extracted with 50 ml of ether, washed with two 25-ml portions of water and 25 ml of saturated sodium chloride solution, dried (K_2CO_3), and evaporated to a solid (6.0 g, 62%). This solid was identified (by analysis of its nmr spectrum) as a mixture of the two diastereomeric α-phenylaziridinemethanols (70%; 6, 30%). This mixture, when recrystallized from hexane (6 g in 10 ml), gave pure 7 (1.7 g, 28%; no 6 was detected in the nmr spectrum). The filtrate was evaporated to a slush (4.0 g) which was fractionally sublimed with no separation of the two diastereomers. An analytical sample of 7 was prepared by recrystallization from low boiling (20–40°) petroleum ether: mp 86–87°; mixture melting point with 6, 65–80°.

Anal. Calcd for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82. Found: C, 76.19; H, 9.23; N, 6.64.

(2) Lithium Aluminum Hydride.—1-*t*-Butyl-2-aziridinyl phenyl ketone (20 g, 80%, 78 mmol) in 60 ml of ether was added over 0.25 hr to lithium aluminum hydride (3.0 g, 79 mmol) suspended in 500 ml of ether and the reaction stirred overnight at room temperature. Excess lithium aluminum hydride was destroyed in the usual way; the metal salts were removed by filtration and washed with two 50-ml portions of ether and the combined filtrate and washings evaporated to a crude solid (15 g, 93%). The solid was identified (by analysis of the nmr spectrum) as a mixture of the two diastereomeric α-phenylaziridinemethanols (7, 6%; 6, 94%). This solid, when recrystallized from low boiling (20–40°) petroleum ether (15 g in 75 ml), yielded the pure 6 (56%; no 7 was detected in the nmr spectrum). A second crop was also obtained (2 g, 12%). An analytical samples of 6 was prepared by recrystallization from low boiling petroleum ether: mp 85–86°.

Anal. Calcd for $C_{13}H_{19}NO$: C, 76.05; H, 9.33; N, 6.82. Found: C, 75.89; H, 9.21; N, 6.82.

1-*t*-Butyl-2-aziridinemethyl Tosylate.—A solution of 1-*t*-butyl-2-aziridinemethanol (7.5 g, 58 mmol) and tosyl chloride (10.6 g, 56 mmol) in 125 ml of triethylamine was kept at 0° for 3 days. Triethylamine hydrochloride was then removed by filtration and washed with two 10-ml portions of triethylamine. The combined filtrate and washings were evaporated to an oil which was dissolved in 100 ml of carbon tetrachloride or methylene chloride, washed with two 50-ml portions of water, dried (K_2CO_3), and evaporated to give an oil (10.2 g, 65%) which would not crystallize. Rotary evaporation under high vacuum (1.0 mm) for 6 hr produced an analytical sample of the tosylate: nmr (CCl_4) δ 0.90 (s, 9, $C(CH_3)_3$), 1.28 (d, 1, H_1) 1.85 (m, 1, H_3), 2.43 (s, 3, CH_3Ar), 3.55–4.05 (m, 2, CH_2–O), 7.1–7.8 (9, 4, Ar).

Anal. Calcd for $C_{14}H_{21}NO_3S$: C, 59.35; H, 7.47; N, 4.94. Found: C, 59.24; H, 7.35; N, 4.99.

1-*t*-Butyl-2-aziridinemethyl Nosylate.—Nosyl chloride (11.0 g, 45 mmol) was stirred at 0° in 250 ml of triethylamine for several minutes until most of it had dissolved. 1-*t*-Butyl-2-aziridinemethanol (7.0 g, 54 mmol) was added in one portion and stirred for 1 hr. The entire reaction mixture was evaporated to a thick paste and extracted with 250 ml of methylene chloride and 250 ml of water. The organic layer was washed with 100 ml of saturated sodium bicarbonate solution and two 150-ml portions of water, dried (K_2CO_3), and evaporated. The resultant solids were dissolved in 100 ml of carbon tetrachloride, filtered, and evaporated twice, then dried at room temperature for 48 hr (0.01 mm) to give the aziridine nosylate:[17] mp 81–81.5°; nmr ($DCCl_3$) δ 0.93 [s, 9, $C(CH_3)_3$], 1.38 (d, 1, H_2), 1.60 (d, 1, H_1), 193 (m, 1, H_2), 3.7–4.3 (m, 2, CH_2–O), 8.0–8.5 (9, 4, Ar).

Anal. Calcd for $C_{13}H_{18}N_2O_5S$: C, 49.68; H, 5.77; N, 8.91. Found: C, 49.45; H, 5.71; N, 8.85.

1-Methyl-2-aziridinemethyl Toylate.—Tosyl chloride (4.0 g, 21 mmol) was added in several portions over a period of 0.5 hr to a mixture of sodium hydride (1.5 g, 50% in mineral oil, 31 mmol, washed with three 20-ml portions of hexane) and 1-methyl-2-aziridinemethanol (2.0 g, 23 mmol) in 75 ml of benzene. The mixture was stirred at 5–10° for 2 hr, washed with two 40-ml portions of water, dried (K_2CO_3), and evaporated to a crude solution with a volume of 25 ml. The nmr spectrum showed only one broad methyl peak at 2.0 ppm. About 30 ml of tetrachloroethylene was added and the mixture evaporated to a volume of ~25 ml: nmr ($Cl_2C{=}CCl_2$) 1.08 (d, 1, H_1), 1.4–1.5 (m, 2, H_2 and H_3), 2.18 (s, 1, N–CH_3), 2.41 (s, 1, $ArCH_3$), 3.8–4.0 (m, 2, CH_2–O), 7.25–7.90 (9, 4, Ar). The nmr spectrum of the crude material showed a considerable amount of benzene present (~45 mol%) and a small amount (~5 mol %) of a material which no longer retained the aziridine ring. Evaporation, even at 0°, gave an oil which quickly polymerized with frothing and could not be extracted with hexane or tetrachloroethylene. The original crude solution in benzene could be kept several days in the ice chest without extensive loss due to polymerization. This crude solution was used directly in the preparation of 1-methyl-2-aziridinemethyl bromide.

1-Benzyl-2-aziridinemethyl Tosylate.—Tosyl chloride (3.8 g, 20 mmol) was added in several portions over a 0.5-hr period with stirring to a solution of sodium hydride (1.5 g, 50% in mineral oil, 31 mmol, washed with three 20-ml portions of hexane) and 1-benzyl-2-aziridinemethanol[18] (3.3 g, 20 mmol) in 100 ml of benzene at room temperature. After stirring for 20 hr, the reaction mixture was washed with two 50-ml portions of water and dried (K_2CO_3) to give a crude solution of the tosylate in benzene: nmr (CCl_4), δ 1.28 (d, 1, H_1), 1.5–1.7 (m, 2, H_2, H_3), 2.31 (s, 1,

(15) A. I. Vogel, "Practical Organic Chemistry," 3rd ed, Wiley, New York, N. Y., 1962, p 931.

(16) Biphenyl could be removed from the ketone by recrystallization with considerable loss (40–50%) of ketone. Since the biphenyl was easily removed from the aziridinemethanols by recrystallization, the ketone–biphenyl mixture was usually analyzed for ketone content and used directly in the carbinol syntheses.

(17) The nosylate could be recrystallized from benzene or cyclohexane, but it was not possible to completely remove these solvents without decomposing some of the nosylate.

(18) Prepared from methyl 1-benzyl-2-aziridinecarboxylate by the method of Capeller and coworkers.[28]

$ArCH_3$), 3.27 (9, 2, CH_2–Ph), 3.88 (m, 2, CH_2–O), 7.1–7.8 (m, 9, Ar). This crude solution could be kept for several days in the ice chest without appreciable polymerization and was used directly in the preparation of 1-benzyl-2-aziridinemethyl bromide. Evaporation of the crude benzene solution gave an oil which would not crystallize and after standing at room temperature overnight, had polymerized.

1-*t*-Butyl-2-aziridinemethyl Bromide.—1-*t*-Butyl-2-aziridinemethyl tosylate (7.0 g, 25 mmol, as a crude oil) and tetrabutylammonium bromide (10.0 g, 31 mmol) were refluxed in 100 ml of benzene for 12 hr. After cooling to room temperature, the reaction mixture was washed with two 100-ml portions of water, dried (K_2CO_3), and evaporated to an oil (4.0 g, 97% pure by analysis of the nmr spectrum, 81% yield) which was distilled to give an analytical sample of the aziridinemethyl bromide: bp 75–80° (0.3–0.5 mm); nmr (CCl_4) δ 0.97 [s, 9, $C(CH_3)_3$], 1.38 (d, 1, H_1), 1.62 (d, 1, H_2), 1.95 (m, 1, H_3), 2.96–3.44 (m, 2, CH_2–Br).

Anal. Calcd for $C_7H_{14}BrN$: C, 43.78; H, 7.34; N, 7.29. Found: C, 43.95; H, 7.47; N, 7.00.

1-Methyl-2-aziridinemethyl Bromide.—Tetrabutylammonium bromide (7.0 g, 22 mmol) was added with stirring to a solution of 1-methyl-2-aziridinemethyl tosylate (85 mg, ~18 mmol, freshly prepared from 1-methyl-2-aziridinemethanol) in 20 ml of benzene. Within 5 min, the nmr spectrum showed that ~50% of tosylate had been converted to the corresponding aziridinemethyl bromide. The reaction mixture was allowed to stand overnight, washed with two 25-ml portions of water, dried (K_2CO_3), and evaporated to an oil which was distilled with some decomposition to yield the 1-methyl-2-aziridinemethyl bromide (100 mg, 36%): bp 80–90° (40–50 mm); nmr (CCl_4) δ 1.24 (δ, 1, H_1), 1.3–1.7 (m, 2, H_2, H_3), 2.31 (s, 3, CH_3), 3.25–3.45 (m, 2, CH_2–Br).

1-Benzyl-2-aziridinemethyl Bromide.—Tetrabutylammonium bromide (7.0 g, 22 mmol) was added to a crude solution of 1-benzyl-2-aziridinemethyl tosylate (~10 mmol) in 35 ml of benzene. This mixture was stirred for 12 hr, then washed with two 25-ml portions of water, dried (K_2CO_3), and evaporated to an oil which was distilled to give 1-benzyl-2-aziridinemethyl bromide (1.2 g, 53%): bp 100° (0.5 mm); nmr (CCl_4) δ 1.3–2.0 (m, 3, H_1, H_2, H_3), 2.9–3.7 (m, 4, CH_2), 7.22 (s, 5, Ar).

1-*t*-Butyl-2-aziridinemethyl Methyl Ether.—1-*t*-Butyl-2-aziridinemethyl tosylate (5.6 g, 20 mmol) in 20 ml of methanolic sodium hydroxide (1 *N*, 20 mmol) was allowed to stand at room temperature and the reaction followed by observation of the *t*-butyl peaks in the nmr spectra. The reaction was approximately 50% completed in 22 hr. After 2 days, in order to complete the reaction, an additional 2 ml of methanolic sodium hydroxide (15% wt/total vol, 7.5 mmol) was added and the reaction allowed to stand for several additional days. The aziridinemethyl ether was the only product observed in the nmr spectrum of the crude reaction mixture which was filtered and evaporated to an oil. This oil was dissolved in 15 ml of ether, washed with 3 ml of water, dried (K_2CO_3), evaporated, and distilled to give an analytical sample of the aziridinyl ether (2.0 g, 65%): bp 85° (water aspirator); $n^{25}D$ 1.425; nmr (CCl_4) δ 0.95 [s, 9, $C(CH_3)_3$], 1.24 (d, 1, J = 3.0 Hz, H_c), 1.42 (d, 1, J = 6.5 Hz, H_b), 1.5–1.9 (m, 1, H_a), 3.20 (d, 2, CH_2), and 3.32 ppm (s, 3, OCH_3).

Anal. Calcd for $C_8H_{17}NO$: C, 67.09; H, 11.69; N, 9.78. Found: C, 67.16; H, 11.91; N, 9.69.

1-*t*-Butyl-2-aziridinemethyl Ethyl Ether from 1-*t*-Butyl-2-aziridinemethyl Tosylate.—Sodium (0.50 g, 22 g-atoms) in 70 ml of absolute ethanol was allowed to stand until all of the sodium had reacted. 1-*t*-Butyl-2-aziridinemethyl tosylate (1.25 g, 4.4 mmol) was added and the reaction mixture refluxed overnight under nitrogen. Flash evaporation gave an oil which was extracted with ether, washed with water, dried (K_2CO_3), flash evaporated, and distilled to give the aziridinemethyl ethyl ether (~0.4 g, ~50%), bp 60° (10 mm).

Anal. Calcd for $C_9H_{19}NO$: C, 68.75; H, 12.15; N, 8.92. Found: C, 69.02; H, 12.39; N, 9.08.

Registry No.—**1a**, 25662-13-9; **1b**, 25662-14-0; **2a**, 25662-15-1; **2a** (tosylate), 25662-16-2; **2b**, 25665-28-5; **2b** (tosylate), 23398-26-7; **2b** (nosylate), 25716-11-4; **2c** (tosylate), 25662-19-5; **3**, 25665-26-3; **4**, 25662-21-9; **6**, 25662-70-8; **7**, 25662-73-1; **9**, 25662-27-5; 1-*t*-butyl-2-aziridinemethyl bromide, 25662-22-0; 1-methyl-2-aziridinemethyl bromide, 25662-23-1; 1-benzyl-2-aziridinemethyl bromide, 25662-24-2; 1-*t*-butyl-2-aziridinemethyl methyl ether, 25662-25-3; 1-*t*-butyl-2-aziridinemethyl ethyl ether, 25662-26-4.

Reaction of Aziridinemethanols with Thionyl Chloride[1]

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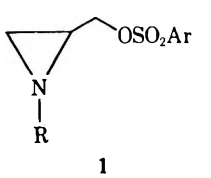
Aziridinemethanols react with thionyl chloride in the presence of base to yield aziridinemethyl chlorides (both rearranged and unrearranged), dihalamines, and 1,2,3-oxathiazolidines. The distribution among these products is a function of structure of the aziridinemethanol and the base used. The mechanisms of these reactions are discussed.

We have recently reported the investigation of the solvolytic behavior of primary aziridinemethyl sulfonates (**1**).[2] Our study of these compounds suggested



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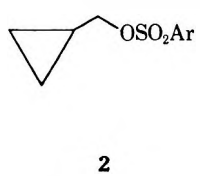
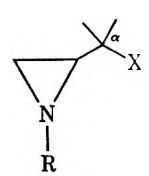


2

that reactivity was probably derived from classical (albeit sluggish) participation by the annular nitrogen, and thus little charge was developed on the primary carbon. These aziridines thus differ markedly from their cyclopropyl carbinyl analogs (**2**) in which participation is characterized by extensive charge delocalization. In hopes of obtaining more information concerning the interaction of the aziridine ring with adjacent cationic centers, we sought to prepare a variety of aziridinemethyl derivatives (**3**) substituted



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at the α position by groups which would facilitate positive charge development. This paper describes various attempts to prepare these derivatives by the

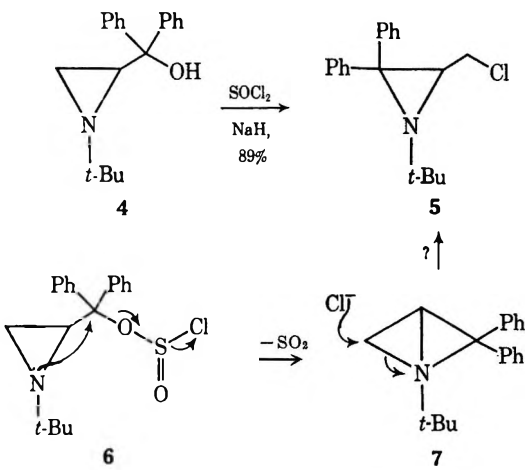
(1) Support of this research by National Science Foundation Grants GP-5531 and GP-8044 and by a Research Corporation Grant is gratefully acknowledged.

(2) J. A. Deyrup and C. L. Moyer, *Tetrahedron Lett.*, 6179 (1968).

reaction of aziridinemethanols[3] with thionyl chloride.

Results

The first such reactions studied were between **4** and $SOCl_2$ in THF with excess NaH. The latter reagent was added to consume the acid liberated during the reaction. Although the product had the proper empirical formula, it was possible to show (*vide infra*)

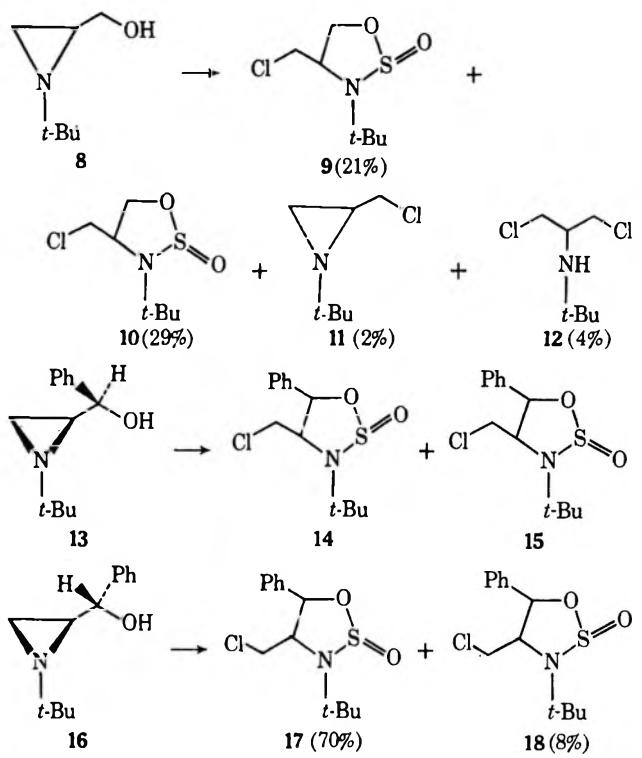


that it actually possesses rearranged structure **5**. A reasonable route to **5** would involve initial formation of chlorosulfite ester **6**. Since chlorosulfite esters apparently decompose by ion pair intermediates,[4] capture of the ion pair by the unshared nitrogen electrons could yield **7**. Nucleophilic atatck on **7** would then yield **5**. Attempted extension of this reaction revealed it to be more complex than expected. In each case, the major products were not aziridines but a mixture of isomeric 2-oxo-1,2,3-oxathiazolidines. The results of these reactions of aziridinemethanols with $SOCl_2$ and NaH in THF are summarized in Scheme I.[5]

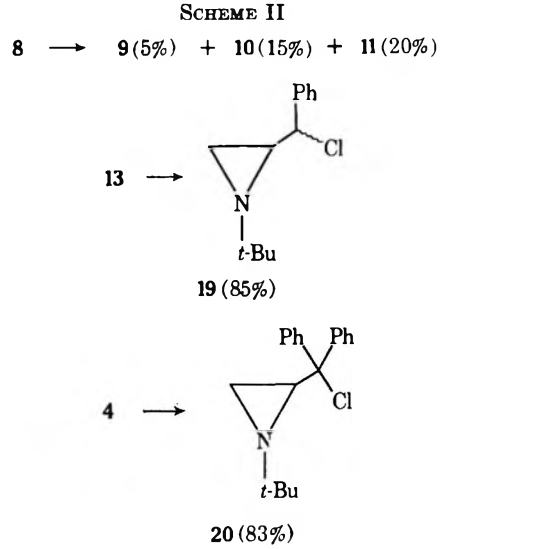
The isolation of identifiable (**11**) and nonidentified (*e.g.*, from **13**) dichloramines indicated that the heterogeneous base NaH might not be totally effective in scavenging protons. For this reason, an alternative reaction procedure was used in which the aziridinemethanols were first converted to their lithium salts with an equivalent amount of BuLi and subsequently reacted with $SOCl_2$. The results of this procedure are summarized in Scheme II for the reaction aziridinemethanols **4**, **8**, and **13** with $SOCl_2$ in THF.

Structural Assignments.—The nmr spectra of the crude $SOCl_2$–NaH reaction mixtures were characterized by the presence of downfield (δ 1.25–1.45) *t*-Bu singlets. Separation of the reaction mixtures showed that these peaks were attributable to neutral substances which contained sulfur. These compounds have been assigned the 2-oxo-1,2,3-oxathiazolidine structure. This assignment is based partially on their elemental analyses and mass spectra. This structure is also supported by the close spectral correlation with oxathiazolidines previously prepared by an alternative route.[6] As would be expected from these earlier

SCHEME I



SCHEME II

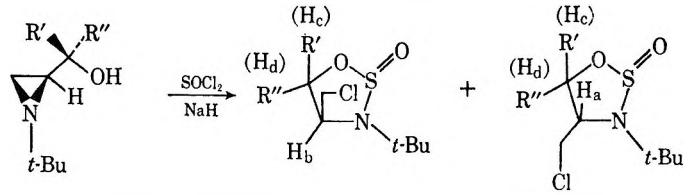


results, asymmetry at sulfur results in the formation of two isomers from each aziridinemethanol. The stereochemistry is assignable on the basis of deshielding by the sulfoxide bond as previously discussed. The spectral properties of these oxathiazolidines are summarized in Table I. Open-chain dichloramine **12** was an unstable liquid which could not be isolated in pure form or fully characterized. It gave an immediate precipitate with silver nitrate and showed mass spectral peaks for the expected molecular weight (see Experimental Section). Reaction of this material with Et_3N converted it to chloroaziridine **11**. Although the nmr specturm was in agreement with the proposed structure, the N-*t*-Butyl-2,3-dichloropropylamine structure could not be excluded.

The mass spectra, elemental analyses, and infrared and nmr spectra of **5** and **20** were consistent with the aziridine structure.[3] Comparison of the nmr spectra

(3) J. A. Deyrup and C. L. Moyer, *J. Org. Chem.*, **35**, 3424 (1970).
(4) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart and Wilson, New York, N. Y., 1959, p 294.
(5) The relative amounts of **9** and **10** varied somewhat from run to run.
(6) J. A. Deyrup and C. L. Moyer, *J. Org. Chem.*, **34**, 175 (1969).

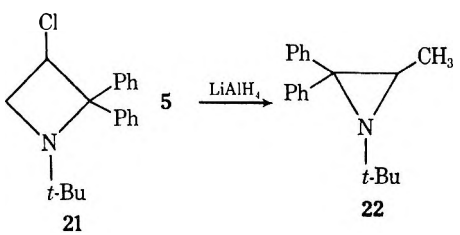
TABLE I
2-OXO-3-*t*-BUTYL-4-CHLOROMETHYL-1,2,3-OXATHIAZOLIDINES FROM AZIRIDINEMETHANOLS. INFRARED AND NMR SPECTRAL PROPERTIES



Compd no.	R	R′	Ir (S=O), cm⁻¹	Nmr, ppm Ha	Hb	Hc	Hd	CH_2Cl	R,R′	$C(CH_3)_3$
9	H	H	1148		3.5–4.1	4.4–4.9[a]		3.5–4.1		1.33
10	H	H	1152	3.6–4.0		4.5–5.0[a]		3.3–3.5		1.40
14	H	Ph	1170		4.04		5.55	3.1–3.8	7.33	1.45
15	H	Ph	1159	3.94		6.16		2.9–3.6	7.3–7.4	1.45
17	Ph	H	1170		3.5–4.1	6.03		3.5–4.1	7.32	1.25
18	Ph	H					5.66			1.33

[a] Two-proton unresolved multiplet.

of **4**, **20**, and **5** showed the first two to be very similar to each other and quite different from **5**. The relationship between **20** and **4** was also demonstrated by the hydrolysis of **20** to **4**. In contrast, **5** was inert under the same hydrolysis conditions. On this basis, **20** was assigned the unrearranged structure. Chemical proof (including exclusion of structure **21**) for the structure of **5** was obtained by its reduction with $LiAlH_4$ to methylaziridine **22**. The aziridinemethyl chloride **11** was

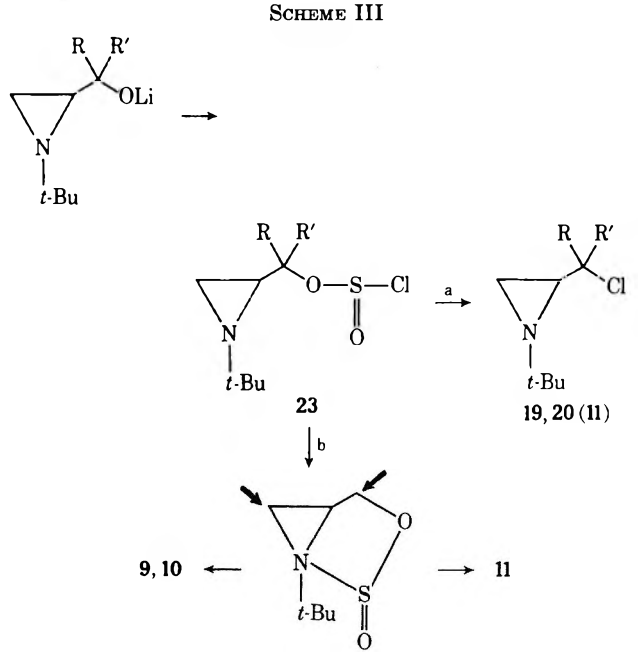


identified by comparison of its mass and nmr spectra with the corresponding bromide prepared by an alternative procedure.[2] The structure assigned to **19** (an apparent epimeric mixture) is tentative owing to our inability to separate or purify this high boiling liquid. This assignment is based on the mass spectrum of the mixture, the presence of the characteristic ring hydrogen shift and pattern of 1,2-disubstituted azirdines as well as the chemical shift of the downfield doublets.

Discussion

A consistent picture of the above observations must account for the striking difference between the behavior of NaH and BuLi as bases. The stability of the aziridine ring toward the attack by acid chlorides has been established in numerous cases.[7] It is probable, therefore, that the initial reaction step is formation of a chlorosulfite ester. It is not possible, however, that the same chlorosulfite ester can give different products as a function of its mode of formation. *A priori*, it is most likely that the homogeneous solutions which resulted from the reaction of aziridinemethanols with BuLi would yield chlorosulfite ester **23**. Decomposition of this chlorosulfite ester to a carbonium ion would be facilitated by the phenyl groups (path a of Scheme III). The apparent lack of stereospecificity in formation of **19** is in agreement with capture of an ion pair intermediate. The increased stability of primary chlorosulfite esters would allow competitive attack at sulfur by nitrogen to produce a bicyclic intermediate (path b of Scheme III). This intermediate could then undergo bimolecular attack at either position to yield the observed products **9–11**.

SCHEME III

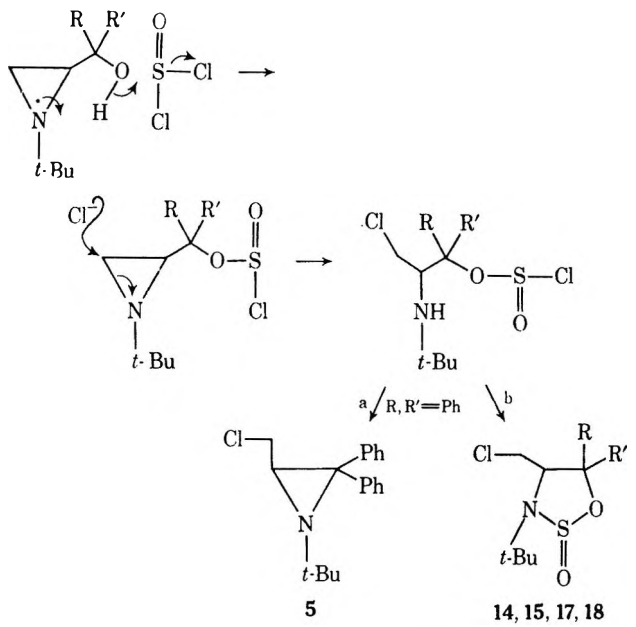


If the above picture is correctly drawn for the BuLi reactions, it is reasonable to postulate that the heterogeneous base, NaH, is a less efficient proton scavenger than the aziridine ring. The protonated chlorosulfite ester is now susceptible to nucleophilic ring opening by chloride (Scheme IV). The fate of this ring-opened intremediate is apparently governed by the substituents. Ionization (path a of Scheme IV) can result in carbonium ion capture by nitrogen to yield aziridine. Diminished ease of ionization allows nitrogen attack at sulfur with concomitant formation of oxathiazolidine

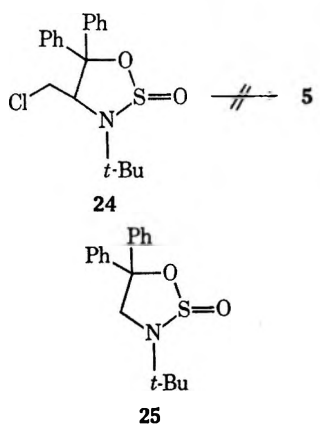
(7) The aziridine ring has been shown to be stable toward a variety of acid chlorides in the presence of base.[2,8] Even in the absence of base, **22** was recovered in 75% yield after 12 hr at room temperature with $SOCl_2$ in THF.

(8) C. L. Moyer, S. C. Clough, unpublished results.

SCHEME IV



(path b of Scheme IV). An alternative route to **5** from **24** was excluded by the finding that model compound **25**[6] was stable under the reaction conditions.



The reactions discussed in this paper open up a new route to substituted aziridines as well as alternative paths to the oxathiazolidine ring system. A search for additional examples of these and similar reactions as well as chemical studies of the compounds described in this paper is now in progress.

Experimental Section

Melting points and boiling points are uncorrected. Liquid samples of less than 5 g were molecularly distilled using a hot air bath and the boiling point reported was the temperature of the air bath. Routine infrared spectra were recorded on a Perkin-Elmer 137 spectrophotometer and the expanded infrared spectra were run on a Perkin-Elmer 337 spectrophotometer. All nmr spectra were recorded on a Varian A-60A spectrometer. Chemical shifts of nmr spectra run in organic solvents are reported in parts per million downfield from internal TMS (δ). Chemical shifts run in D_2O are reported in parts per million downfield from a point 4.99 ppm upfield from the DOH peak. Mass spectra were obtained on a RMU 6E mass spectrometer for all compounds reported in this paper except **4**. In each case molecular weights in agreement with theory were obtained. Fragments are reported as *m/e* (relative intensity). Infrared spectra obtained on the aziridines and oxthiazolidines reported in the Experimental Section were consistent with expected absence of N–H and unsaturation implicit in the assigned structure. Microanalyses were obtained from Galbraith Laboratories, Inc., Knoxville, Tenn.

Reactions of 1-*t*-Butyl-2-aziridinemethanol (8) with Thionyl Chloride. (1) **Sodium Hydride in Tetrahydrofuran.**—Tetrahydrofuran (600 ml) was distilled directly from lithium aluminum hydride into a flask containing sodium hydride (19.2 g, 50% in mineral oil, 400 mmol, washed with three 150-ml portions of hexane). 1-*t*-Butyl-2-aziridinemethanol (**8**, 20 g, 155 mmol) was added in several portions with stirring at room temperature. A solution of thionyl chloride (24.8 g, 15 ml, 208 mmol) in 110 ml of tetrahydrofuran was added at room temperature at a rate which avoided noticeable temperature change (1.5 hr) and the reaction was then stirred overnight. It was evaporated to a paste and taken up in 200–300 ml of hexane. After 100 ml of water had been added with caution, the reaction mixture was washed with 50 ml of saturated sodium bicarbonate solution. The hexane layer was dried (K_2CO_3) and evaporated to an oil (20–25 g) which was fractionally distilled using a 20-cm Vigreux column to give fraction 1 (1.5 g, 5.5%), a mixture of ~25% 1-*t*-butyl-2-aziridinemethyl chloride (**11**) and 75% 1,3-dichloro-2-*t*-butylaminopropane (**12**) (by analysis of the nmr spectrum) [bp 31° (0.5–0.3 mm); mass spectrum (mixture, 70 eV) *m/e* (relative intensity) 187 (0.09), 185 (0.5), 183 (0.85), 172 (8.5), 170 (46), 168 (68), 149 (1.4), 147 (2.8), 134 (28), 132 (63), 112 (26), 57 (97), 56 (100)] and fractions 2–4 (16.5 g, 50%), mixtures of *cis* and *trans*-oxathiazolidines **9** and **10** (*cis/trans* ratios: fraction 2, 0.24; fraction 4, 0.71, by analysis of the nmr spectra). Elemental analysis was obtained on a mixture of the *cis*- and *trans*-oxathiazolidines.

Anal. Calcd for $C_7H_{14}ClNO_2S$: C, 39.77; H, 6.68; N, 6.62. Found: C, 39.94; H, 6.80; N, 6.54.

A sample of fraction 4 (1.0 g) was separated on a column of 5% deactivated alumina (2.5 × 30 cm) packed in hexane and eluted with 200 ml of hexane, 200 ml of 1:1 hexane–benzene, and 250 ml of benzene. Fractions of 50 ml were collected. Fraction 11 was evaporated several times from carbon tetrachloride and rotary evaporated under high vacuum to give a pure sample of the *trans*-oxathiazolidine (**10**). Fraction 13, treated in the same manner, gave a pure sample of *cis*-oxathiazolidine (**9**).

(2) **Butyllithium in Tetrahydrofuran.**—About 75 ml of tetrahydrofuran was distilled directly from lithium aluminum hydride into a flask containing 1-*t*-butyl-aziridinemethanol (**8**, 3.4 g, 13 mmol). Butyllithium (26 ml, 1.4 m, 36 mmol) was added through a syringe over 3 min with stirring in an ice–water bath. A solution of thionyl chloride (1.9 ml, 36 mmol) in 10 ml of tetrahydrofuran was then added over 0.25 hr. The reaction was allowed to warm to room temperature, stirred for an additional 0.5 hr, evaporated to a paste, and taken up in ~100 ml of hexane. The hexane layer was washed with 50 ml of water and 50 ml of aqueous sodium bicarbonate solution, dried (K_2CO_3), and evaporated to an oil (2.0 g, 40%). Analysis of the nmr spectrum of this oil showed that it contained ~50% 1-*t*-butyl-2-aziridinemethyl chloride (**12**), 12% *cis*-2-oxo-3-*t*-butyl-4-chloromethyl-1,2,3-oxathiazolidine (**9**), and 36% *trans*-2-oxo-3-*t*-butyl-4-chloromethyl-1,2,3-oxathiazolidine (**10**).

Ring Closure of 1,3-Dichloro-2-*t*-butylaminopropane (12) to 1-*t*-Butyl-2-aziridinemethyl Chloride (11).—Fraction 1 from the fractional distillation of the product mixture from the reaction of thionyl chloride with 1-*t*-butyl-2-aziridinemethanol (1.5 g, 75% 1,3-dichloro-*t*-butyl-aminopropane; see procedure above) was added to 10 ml of triethylamine and allowed to stand at room temperature for several weeks. The crude reaction mixture was evaporated to a paste and extracted with 15 ml of carbon tetrachloride and 10 ml of water. The organic layer was washed with 10 ml of water, dried (K_2CO_3), and evaporated to an oil which was distilled to give the aziridinemethyl chloride (**11**) (600 mg, 48%): bp 85–100° (water aspirator); nmr (CCl_4) 3.30 (q, 2, CH_2Cl), 1.87 (m, 1, C_2 H), 1.53 (d, 1, C_3 H_{trans}), 1.36 (d, 1, C_3 H_{cis}), 0.96 (s, 9, *t*-Bu).

Reactions of *erythro*-1-*t*-Butyl-α-phenyl-2-aziridinemethanol (13) with Thionyl Chloride. (1) **Sodium Hydride in Tetrahydrofuran.**—Thionyl chloride (0.50 ml, 6.9 mmol) in 20 ml of tetrahydrofuran was added to a solution of sodium hydride (0.75 g, 50% in mineral oil, 15.5 mmol, washed with three 20-ml portions of hexane) and *erythro*-1-*t*-butyl-α-phenyl-2-aziridinemethanol (**12**, 1.00 g, 4.9 mmol) in 60 ml of tetrahydrofuran over 0.75 hr at room temperature. After stirring for 4 hr, the reaction mixture was evaporated to a paste which was taken up in 150 ml of hexane. Water was added with caution and the hexane solution was washed with 50 ml of water and 50 ml of sodium

bicarbonate solution, dried (K_2CO_3), and evaporated to an oil (1.4 g, 100%). The nmr spectrum of this oil showed the presence of ~75% a mixture of the *cis,syn*- (**14**) and *cis,anti*-2-oxo-3-*t*-butyl-4-chloromethyl-5-phenyl-1,2,3-oxathiazolidine (**15**) and 20% unidentified *t*-butyl species. This crude oil was taken up in carbon tetrachloride, washed with dilute hydrochloric acid and water, dried (K_2CO_3), and evaporated to an oil which precipitated solids and contained only the isomeric oxathiazolidines **14** and **15**. About 1–2 ml of hexane was added to the oil and the supernatant solution removed from the solids. Recrystallization of these solids from hexane gave *cis,syn*-oxathiazolidine **14** (~100 mg, 7%), mp 116–117.5°.

Anal. Calcd for $C_{13}H_{18}NO_2SCl$: C, 54.28; H, 6.31; N, 4.87. Found: C, 54.54; H, 6.46; N, 4.94.

The filtrate from the *cis,syn*-oxathiazolidine (**14**) was evaporated to an oil which contained ~15% *cis,syn*- and 85% *cis,anti*-oxathiazolidine (**15**). The oil was rotary evaporated (1.0 mm) for 4 hr to yield an analytical sample of the mixture of oxathiazolidines **14** (15%) and **15** (85%).

Anal. (*cis,trans* mixture). Calcd for $C_{13}H_{18}NO_2SCl$: C, 54.28; H, 6.31; N, 4.87. Found: C, 54.06; H, 6.35; N, 4.75.

(2) **Butyllithium in Tetrahydrofuran.**—Thionyl chloride (0.35 ml 4.9 mmol) in 10 ml of tetrahydrofuran was added to a solution of *erythro*-1-*t*-butyl-α-phenyl-2-aziridine methanol (**13**, 1.00 g, 4.9 mmol) and butyllithium (5 ml, 1.4 g, 7 mmol) in 75 ml of tetrahydrofuran over 0.25 hr at room temperature. The reaction mixture was stirred for 0.5 hr and evaporated to a paste which was taken up in 50 ml of hexane, washed with water, dried (K_2CO_3), and evaporated to an oil (0.85 g, 77%). The nmr spectrum of this oil showed *ca.* a 2:1 mixture of two compounds: δ 0.67 and 0.72 (*t*-Bu), 4.17 and 4.62 (CHCl). Attempts to further purify and assign stereochemistry to these compounds were not successful.

Reactions of *threo*-1-*t*-Butyl-α-phenyl-2-aziridinemethanol (16) with Thionyl Chloride. (1) **Sodium Hydride in Tetrahydrofuran.**—A solution of thionyl chloride (0.25 ml, 3.5 mmol) in ~10 ml of tetrahydrofuran was added to a solution of sodium hydride (0.5 g, 50% in mineral oil, 10 mmol, washed with three 20-ml portions of hexane) and *threo*-1-*t*-butyl-α-phenyl-2-aziridine methanol (**16**, 550 mg, 2.7 mmol) in 50 ml of tetrahydrofuran over 0.5 hr at room temperature. After stirring for 4 hr, the reaction mixture was evaporated to a paste and taken up in ~50 ml of hexane. The excess sodium hydride was destroyed by the careful addition of water and the hexane layer washed with water, dried (K_2CO_3), and evaporated to an oil (0.6 g, 85%). The nmr spectrum of this oil showed it to contain ~85–90% a 1:10 mixture of oxathiazolidines **18** and **17**. The oil was dissolved in 50 ml of carbon tetrachloride and washed with 5% aqueous hydrochloric acid and water, dried (K_2CO_3), and evaporated to an oil which showed only the oxathiazolidines in its nmr spectrum. The two isomers were not separated but the major isomer was identified as the *trans,syn*-2-oxo-3-*t*-butyl-4-chloromethyl-5-phenyl-1,2,3-oxathiazolidine (**17**) and the minor isomer was identified as *trans,anti* isomer **18**. Rotary evaporation under high vacuum (1.0 mm) for 1 hr gave an analytical sample which still contained some hydrocarbon impurities. The mass spectrum of this mixture was virtually identical with that obtained from the *cis,anti* compound **15**.

Reactions of 1-*t*-Butyl-α,α-diphenyl-2-aziridinemethanol (4) with Thionyl Chloride. (1) **Sodium Hydride in Tetrahydrofuran.**—Thionyl chloride (1.5 ml, 21 mmol) in 30 ml of tetrahydrofuran was added to a solution of sodium hydride (1.5 g, 50% in mineral oil, 31 mmol, washed with three 30-ml portions of hexane) and aziridinemethanol (**4**) (5.6 g, 20 mmol) in 125 ml of tetrahydrofuran over 0.5 hr with stirring in an ice–water bath. The reaction mixture was stirred overnight, evaporated to a paste, and extracted with 100 ml of low boiling petroleum ether and 45 ml of sodium bicarbonate solution. The petroleum ether layer was dried (K_2CO_3), stirred overnight with 10 g of 10% deactivated alumina,[9] and then evaporated to give 1-*t*-butyl-3,3-diphenyl-2-aziridinemethyl chloride (**5**) as an oil which would not solidify (5.7 g, 89%): bp 110–120° (0.01 mm); nmr ($CDCl_3$) δ 6.9–7.5 (m, 10, ArH), 2.8–3.3 (m, 3, $-CH_2-$, and C_2 H), 0.93 (s, 9, *t*-Bu).

Anal. Calcd for $C_{19}H_{22}ClN$: C, 76.13; H, 7.40; N, 4.67. Found: C, 76.12; H, 7.31; N, 4.56.

(2) **Triethylamine in Hexane.**—Thionyl chloride (0.72 ml, 10 mmol) in 20 ml of hexane was added to a solution of triethylamine (1.1 g, 11 mmol) and aziridinol (**4**) (2.8 g, 10 mmol) in 200 ml of hexane over 0.5 hr at room temperature, washed with 50 ml of water and 50 ml of sodium bicarbonate solution, dried (K_2CO_3), and evaporated to give 1-*t*-butyl-α,α-diphenyl-2-aziridinemethyl chloride (**20**) as an oil (83%) which would not crystallize. Rotary evaporation for 2 hr (0.2 mm) yielded an analytical sample: nmr (CCl_4) δ 6.9–7.7 (m, 10, ArH), 2.57 (q, 1, C_2 H), 1.56 (q, 1, C_3 H_{trans}) 1.24 (q, 1, C_3 H_{cis}), 0.90 (s, 9, t-Bu).

Anal. Calcd for $C_{19}H_{22}ClN$: C, 76.20; H, 7.40; N, 4.68. Found: C, 76.27; H, 7.56; N, 4.72.

(3) **Butyllithium in Tetrahydrofuran.**—Thionyl chloride (1.15 ml, 16 mmol) in 10 ml of tetrahydrofuran was added to a solution of butyllithium (10 ml, 1.4 m, 14 mmol) and aziridinol **4** (2.81 g, 10 mmol) in 50 ml of tetrahydrofuran over 2 min at 0°. The reaction mixture was stirred for 10 min and evaporated to a paste which was taken up in 50 ml of hexane and washed with 30 ml of water and 30 ml of sodium bicarbonate solution. The hexane layer was dried (K_2CO_3) and evaporated to an oil (2.5 g, 82%). The nmr spectrum of this oil showed only the 1-*t*-butyl-α,α-diphenyl-2-aziridinemethyl chloride (**20**).

1-*t*-Butyl-2,2-diphenyl-3-methylaziridine (22).—A mixture of 3.5 g of 1-*t*-butyl-α,α-diphenyl-2-aziridinemethyl chloride and 5 g of $LiAlH_4$ in 250 ml of THF was refluxed for 30 hr. The reaction mixture was cooled and 2.2 g additional $LiAlH_4$ was added. The mixture was then heated at reflux for 24 more hr and cooled, and the excess $LiAlH_4$ carefully decomposed. After removal of inorganic salts by filtration, the filtrate was concentrated to a crude oil which still contained some starting material. Final purification was affected by thick layer chromatography and molecular distillation [110–120 (0.5 mm)]: nmr (CCl_4) δ 7.0–7.4 (10, m, ArH), 2.82 (1, q, C_3 H), 0.86 (3, d, CH_3) 0.90 (9, s, *t*-Bu).

Anal. Calcd $C_{19}H_{23}N$: C, 85.98; H, 8.74; N, 5.28. Found: C, 86.14; H, 8.95; N, 5.31.

Hydrolysis of 1-*t*-Butyl-α,α-diphenyl-2-aziridinemethyl Chloride (20).—A solution of 1-*t*-butyl-α,α-diphenyl-2-aziridinemethyl chloride (**20**) (3.0 g, 10 mmol) and sodium hydroxide (0.5 g, 12 mmol) in 50 ml of tetrahydrofuran and 30 ml of water was refluxed for 4 days. Evaporation gave an oil which was extracted with 50 ml of ether, washed with 25 ml of water, dried (K_2CO_3), and evaporated to an oil. The only product apparent in the nmr spectrum of this oil was 1-*t*-butyl-α,α-diphenyl-2-aziridinemethanol (**4**).

Attempted Hydrolysis of 1-*t*-Butyl-3,3-diphenyl-2-aziridinemethyl Chloride (5).—A solution of 1-*t*-butyl-3,3-diphenyl-2-aziridinmethyl chloride (**5**) (2.0 g, 6.7 mmol) and sodium hydroxide (0.5 g, 12 mmol) in 50 ml of tetrahydrofuran and 30 ml of water was refluxed for 4 days. The reaction mixture was evaporated to an oil which was extracted with 25 ml of carbon tetrachloride, washed with 15 ml of water, dried (K_2CO_3), and evaporated to an oil (1.6 g, 80%). The only material apparent in the nmr spectrum of this oil was the starting aziridinemethyl chloride (**5**).

Registry No.—**4**, 25665-26-3; **5**, 25665-27-4; **8**, 25665-28-5; **9**, 25662-68-4; **10**, 25662-69-5; **11**, 21452-72-2; **12**, 25665-30-9; **13**, 25662-70-8; **14**, 25662-71-9; **15**, 25662-72-0; **16**, 25662-73-1; **17**, 25662-74-2; **18**, 25662-75-3; **20**, 25665-31-0; **22**, 25716-07-8; thionyl chloride, 7719-09-7.

(9) This treatment was necessary to remove trace amounts of acid and/or acid-forming products which led to the slow decomposition of the product.

Acetyl Nitrate Addition to Cyclic Olefins. The Isomeric 9-Acetoxy-10-nitro-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrenes[1]

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Addition of acetyl nitrate to 1,2,3,4,4a,10a-(*trans*-4a,10a)-hexahydrophenanthrene produced a mixture of nitro acetates and olefinic nitro compounds. The four isomeric 9-acetoxy-10-nitro-octahydrophenanthrene addition products were separated and characterized based on nmr spectral data and X-ray diffraction techniques.

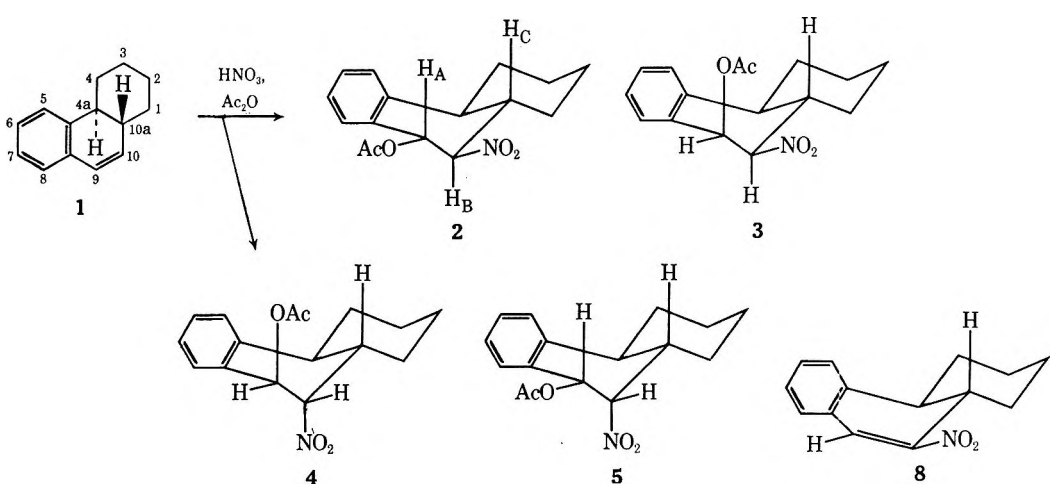
Addition of acetyl nitrate to various olefins has been reported to be a useful method of preparation of β-nitro acetates, the stereochemistry of which is somewhat dependent on the nature of the starting olefin. This fact, coupled with our interests in obtaining some substituted 2-amino-1-phenylethanol derivatives prompted us to explore this addition to a polycyclic styrene, 1,2,3,4,4a,10a-(*trans*-4a,10a)-hexahydrophenanthrene (**1**).[3]

Earlier workers have reported products of cis and trans addition depending on the structure of the olefinic starting material.[4,5] Net cis addition has been reported to *cis*- and *trans*-2-butene,[4a] and in many styryl systems, such as *trans*-1-phenylpropene,[4b,5a] *cis*-2-phenyl-2-butene,[4b] *cis*-3-phenyl-2-pentene,[4b] and in *trans*-stilbene.[4c,5b] However trans addition is preferred to some similar olefins, *e.g.*, *cis*-1-phenylpropene,[4b] *trans*-2-phenyl-2-butene,[4b] and to *trans*-3-phenyl-2-pentene.[4b] Addition to styryl systems which are partially incorporated into a cyclic structure, such as 1-phenylcyclohexene, affords mixtures of products with trans addition predominating.[4d,e] From 1-phenylcyclopentene only the product of trans addition was isolated.[4e]

In view of the variability of the steric course of the addition of this electrophilic reagent, we considered that this process might lead to some or all of the four isomeric 9-acetoxy-10-nitro compounds, **2**, **3**, **4**, and **5**, at the same time offering the opportunity for investigation of conformational aspects of this addition process.

Olefin **1** was prepared by borohydride reduction of 1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydro-9-oxophenanthrene (**6**)[6] followed by acid-catalyzed elimination of water using β-naphthalenesulfonic acid as catalyst.[7]

Addition of acetyl nitrate to the olefin afforded a complex mixture of products. Careful column chromatography afforded, in addition to a small amount of starting material, *ca.* 50% nitration products and nitroalkenes from which was isolated a mixture of nitro acetates and nitrostyrene **8** in about 10% yield. β-Nitrostyrene **8** accounted for about half of this amount.



The four nitro acetates were separated by column chromatography and tedious fractional crystallization.

Structure assignment to the two compounds with equatorial nitro groups, **2** and **3**, proved reasonably facile.[8] The nmr spectra of these compounds show large J_{BC} coupling constants (Table I) since proton H_B is axially disposed adjacent to C-10a leaving axial proton H_C. The nmr spectra showed J_{BC} = 11 Hz in **2** and 10 Hz in **3**, both consistent with an axial proton at C-10. Differences were noted in J_{AB} consistent with

(1) A preliminary account of this work was presented at the 24th Northwest Regional Meeting of the American Chemical Society, Salt Lake City, Utah, June 1969, Abstract 199.

(2) (a) University of Washington. Author to whom correspondence should be addressed. (b) U. S. Public Health Service Predoctoral Fellowship, 1-F1-GM-33,942, 1966–1969. (c) Taken in part from the Ph.D thesis of D. D. Miller submitted to the Graduate School, University of Washington, July 1969. (d) State University of New York at Buffalo.

(3) All materials are racemic although only a single isomer is drawn.

(4) (a) F. G. Bordwell and E. W. Garbisch, Jr., *J. Amer. Chem. Soc.*, **82**, 1388 (1960); (b) F. G. Bordwell and J. B. Biranowski, *J. Org. Chem.*, **32**, 629 (1967); (c) F. G. Bordwell and E. W. Garbisch, Jr., *ibid.*, **27**, 2322 (1962); (d) *ibid.*, **27**, 3049 (1962); (e) *ibid.*, **28**, 1765 (1963).

(5) (a) G. Drefahl, H. Crahmer, and W. Thomas, *Chem. Ber.*, **91**, 282 (1958); (b) G. Drefahl and H. Crahmer, *ibid.*, **91**, 754 (1958).

(6) C. D. Gutsehe and W. S. Johnson, *J. Amer. Chem. Soc.*, **68**, 2239 (1946).

(7) (a) W. L. Nelson and D. D. Miller, *J. Med. Chem.*, **13**, 807 (1970); (b) D. D. Miller, Ph.D. Thesis, University of Washington, July 1969.

(8) (a) The central ring is arbitrarily assigned the half-chair conformation where the equatorial (e) and axial (a) substituents at C-9 are in fact pseudoequatorial and pseudoaxial, respectively. (b) Consistently throughout the nmr discussion of the 9,10-disubstituted compounds, the proton at C-9 is designated A, the proton at C-10, B, and the C-10a axial proton, C.

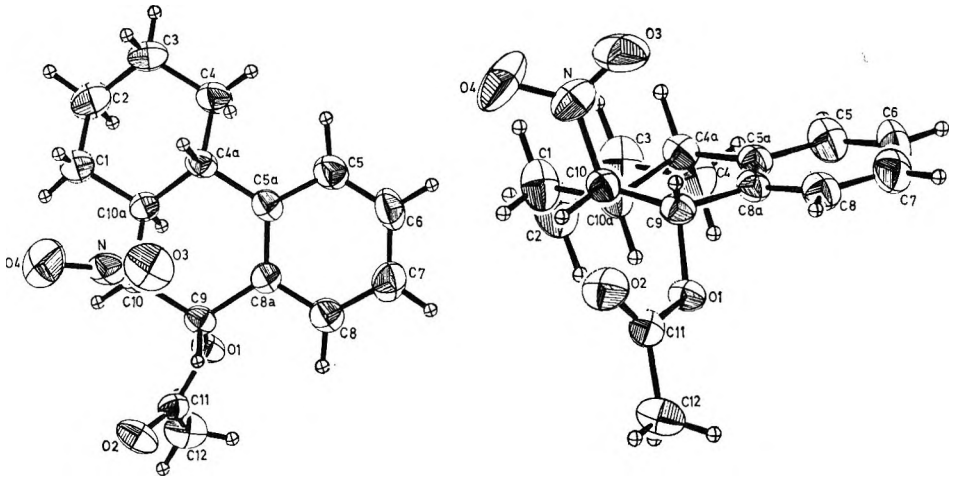


Figure 1.—Top and side views of nitro acetate **4**. The thermal ellipsoids enclose a probability density of 0.50 of the nonhydrogen atoms, plotted according to the program of C. K. Johnson, ORTEP, U. S. Atomic Energy Commission Report, ORNL-3794, 1965. Coincidentally, the absolute configuration of molecules in this figure is the same as used for structural formulas in this paper, but are viewed from the opposite side of the molecule.

assignment of the 9(e)-acetoxyl group to **3** and 9(a)-acetoxyl to **2**. Benzylic proton H_A showed a doublet, $J_{AB} = 9$ Hz in **2**, and $J_{AB} = 4$ Hz in **3**, consistent with an axial–axial coupling in the former compound and an equatorial–apial coupling in the latter.[9]

TABLE I

60-MHz NMR DATA ON THE ISOMERIC NITRO ACETATES[a]

Compd	Isolated yield, %	H_A (δ)	J_{AB} (Hz)	H_B (δ)	J_{BC} (Hz)
2	0.3	6.72	9	4.75	11
3	3.8	6.43	4	4.79	10
4	0.9	6.34	2.5	4.83	4
5	1.1	6.07	2	5.20	$2 \sim 3$

[a] Recorded in $CDCl_3$ solution relative to tetramethylsilane as internal standard.

Assignment of the relative stereochemistry of **4** and **5** proved to be much more difficult. The nmr spectra of these nitro acetates showed only small differences in chemical shifts for protons H_A and H_B, and no great differences in coupling constants.

Attempts to compare and correlate nmr spectral data of these two compounds with analogous amino alcohols and azido alcohols in this system[7] and with 6α,7α- and 6β,7α-dichloroestrone[10] were only partly successful. However, some similarities were noted: *e.g.*, consistent differences of similar magnitude between chemical shifts of benzylic protons when comparing pseudoaxial and pseudoequatorial isomeric pairs. Considering the differences in anisotropy of the azido, acetamido, and chloro substituents, especially when compared with the nitro group, no definitive assignments could be made.

An attempt to analyze the effect of the nitro group, known to be axial in the nitro acetates in question, on adjacent protons was made by comparison with reported nmr spectra of *cis*- and *trans*-4-*t*-butylnitrocyclohexane.[11] The 2,6-equatorial protons are further downfield than the 2,6-axial protons in both of these rigid nitrocyclohexanes, and are further downfield in the cis compound (axial nitro group) than in the trans compound (equatorial nitro group), indicating a large deshielding effect of the axial nitro group on the adjacent equatorial protons. If this model can be validly applied to the nitro acetates, then the compound with the more deshielded H_A proton must have the equatorial H_A and the 9(a)-acetoxy group, and structure **4**. A large difference in chemical shifts of the H_A proton is noted in **4** and **5**, *ca.* δ 0.27, consistent with the nitrocyclohexane model. Also a difference in chemical shifts of protons H_B of δ 0.37 was noted with H_B being upfield in **4**, in agreement with a possible shielding effect of the axial acetoxyl group on the adjacent equatorial proton.[12] However, these analogies suffer from the disadvantage of comparing cyclohexane with cyclohexene systems and cannot take into account effects of the benzene ring, other carbon–carbon or carbon–hydrogen bonds, or combinations of effects of one functional group in the presence of another.

Attempts to generate chemical evidence to differentiate between these structures failed. Base-catalyzed isomerization of the nitro group to the equatorial position, which would have provided compounds of known configuration, **2** and **3**, failed. Insufficient material was available for reduction to amino alcohols of known configuration.[7]

Single-crystal X-ray analysis of one of the compounds allowed structure assignment. Analysis of **4** showed unequivocally that both the acetoxy and nitro substituents are in the axial position, thus allowing for assignment of the 9(e)-acetoxy group to **5**. The structure of **4** is shown in Figure 1 from the top and side of the molecule. The dihedral angle between the nitro and acetoxy groups is 159.5°, and the angle between H_A and H_B is 78.2°. These results are consistent with expected angles, Dreiding models, and the nmr spectral analysis made in terms of the rigid nitrocyclohexane models.

Because of the low total yield of nitro acetates obtained from this olefin, no worthwhile speculation can

(9) (a) M. Karplus, *J. Amer. Chem. Soc.*, **85**, 2870 (1963); (b) K. L. Williamson and W. S. Johnson, *ibid.*, **83**, 4623 (1961); (c) M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).

(10) Y. Osawa and M. Neeman, *J. Amer. Chem. Soc.*, **85**, 2856 (1963).

(11) A. C. Huitric and W. F. Trager, *J. Org. Chem.*, **27**, 1926 (1962).

(12) N. W. Bhacca and D. H. Williams, "Application of NMR Spectroscopy in Organic Chemistry: Illustrations from the Steroid Field," Holden-Day, San Francisco, Calif., 1964, p 185–188.

be made concerning the stereoselectivity of this addition process. It is noteworthy that all four of the possible nitro acetates are produced, in contrast to additions to some noncyclic olefins from which a single addition product is found.[4,5] The nitro acetate obtained in greatest yield is cis adduct **3**, resulting from addition on the same side of the molecule as the axial proton at C-10a, and the sum of products resulting from addition to this side is greater than from the opposite side, which seems slightly less hindered in Dreiding models. This may be only a coincidence because of the propensity of **3** isolated. These results are in contrast to the trans addition of iodine isocyanate and hypobromous acid to this olefin, but similar to the direction of epoxidation with peracid.[7]

Experimental Section[13]

9(ξ)-Hydroxy-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (7).—At room temperature 2.28 g (0.053 mol) of sodium borohydride (Alfa Inorganics, Inc.) in 20 ml of water was added slowly over a 20-min period to 20 g (0.10 mol) of ketone **6**[6] in 1 l. of 95% ethanol. The mixture was stirred 19 hr. After the addition of 10 ml of 1 *N* sodium hydroxide, the ethanol was removed *in vacuo*. The oily residue was dissolved in ether and washed with water, dried (Na_2SO_4), and evaporated *in vacuo* to give 19.5 g (92%) of white solid material, mp 102°. An analytical sample was prepared by recrystallization from petroleum ether (bp 30–60°): mp 102°; ir (KBr) 3.05 (broad peak, O–H stretching), 3.40 and 3.48 (aliphatic C–H stretching), 6.75, 6.93, 9.38, 9.54, 9.95 and 13.3 μ (broad); nmr ($CDCl_3$) δ 7.90–7.55 (m, 1, C-8 aromatic proton), 7.50–7.18 (m, 3, aromatic protons), 5.13–4.65 (m, 1, benzylic proton), and 3.8–0.7 (m, 12, methylene–methine envelope).

Anal. Calcd for $C_{14}H_{18}O$: C, 83.12; H, 8.97. Found: C, 83.08; H, 8.79.

A *p*-nitrobenzoate derivative was prepared, mp 130–131°; the nmr ($CDCl_3$) multiplet of the benzylic proton between δ 5.13 and 4.65 was replaced by a triplet at δ 6.40 (J = 8.5 Hz).

1,2,3,4,4a,10a-(*trans*-4a,10a)-Hexahydrophenanthrene (1). A mixture of 24.0 g (0.12 mol) of alcohol **7** and 500 mg (2.4 mmol) of 2-naphthalenesulfonic acid (Eastman Organic Chemicals) in 1 l. of benzene was refluxed with an attached Dean–Stark trap for 48 hr. The mixture was evaporated *in vacuo* and the remaining residue was dissolved in ether and washed with several portions of an aqueous saturated sodium bicarbonate solution and water. The ether layer was dried (Na_2SO_4) and then evaporated *in vacuo* to give 25 g of a yellow oil. Column chromatography on 900 g of silica gel (Brinkmann), Brockmann activity III, using hexane as eluent afforded 20.6 g of colorless alkene (93%) in first 750 ml of hexane collected: uv max (95% C_2H_5OH) 262 (ε 8200); ir (neat) 3.27 (vinyl C–H stretching), 3.39 and 3.49 (aliphatic C–H stretching), 6.72, 6.90, 12.23, 13.50, 13.70, and 14.4 μ; nmr ($CDCl_3$) δ 7.26 (m, 4, aromatic protons), 6.55 (q, 1, J_{AB} = 10 Hz, J_{AC} = 2 Hz, C-9 proton, H_A), 5.85 (d, 1, J_{BC} = 0–1 Hz, C-10 proton, H_B), 3.0–1.0 (m, 10, broad methylene–methine envelope); mass spectrum (70 eV) m/e 184.

Addition of Acetyl Nitrate to 1,2,3,4,4a,10a-(*trans*-4a,10a)-hexahydrophenanthrene (1).—The nitration reagent was prepared using the method of Bordwell and Biranowski[4b] by adding 7.3 g (81 mmol) of 70% nitric acid to 52 ml of acetic anhydride at 25°, and the resulting mixture was cooled with stirring to −20° and then 5.0 g of the alkene **1** in 16 ml of acetic anhydride was added. The temperature was allowed to warm to 0°, and the solution was then cooled again to −20° and maintained at this temperature for 5 min. The resulting solution was then poured into 200 ml of water and this mixture was stirred until the excess acetic anhydride was hydrolyzed. The mixture was then extracted with several portions of ether, and the ether layers were combined, dried (Na_2SO_4), and then evaporated *in vacuo* to give 7.3 g of light yellow oil. The oil was placed on 360 g of silica gel (Brinkmann), Brockmann activity I, and eluted with 2400 ml of hexane, 1650 ml of 5% ether in hexane, 1050 ml of 10% ether in hexane, 900 ml of 15% ether in hexane, 450 ml of 20% ether in hexane, 750 ml of 50% ether in hexane, 500 ml of chloroform, and 600 ml of methanol. First collected in the hexane eluent was 362 mg of unreacted alkene followed by 2.18 g of a yellow oil that could be aromatic ring substitution products plus some conjugated nitroalkene. Next was collected a 700-mg mixture of nitrostyrene **8** plus *cis*-β-nitro acetate **5**. The solid material was dissolved in a combination of ether–hexane and two types of crystals formed which were separated using magnifying glass and forceps. The clear plate crystals were dissolved in ether–hexane and 74 mg of square crystals were isolated, mp 115–116°, assigned 9(e)-acetoxy-10(a)-nitro-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (**5**): ir (KBr) 3.40 and 3.48 (aliphatic C—H stretching), 5.80 (C=O stretching), 7.15, 7.30 (N=O stretching), 7.38, 8.25, 9.85, 10.30, 10.90, 11.25, 11.78 (broad), 12.75, 13.30, 13.75, 14.50, and 15.75 μ; nmr ($CDCl_3$) δ 7.30 (s, 4, aromatic protons), 6.07 (d, 1, J_{AB} = 2 Hz benzylic proton H_A), 5.20 (m, 1, $J_{BC} \approx$ 3 Hz, C-10 proton H_B), 2.05 (s, 3, methyl protons), and 2.9–0.8 (m, 10, methylene–methine envelope).

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.15; H, 6.98; N, 4.87.

The yellow needles that were separated were recrystallized from ether–hexane to give 111 mg of light yellow needles of the nitrostyrene **8**: mp 102–103°; ir (KBr) 3.25, 3.39, and 3.49 (aliphatic C–H stretching), 6.12, 6.69, 6.92, 7.50, 8.18, 13.11, 13.28, and 14.95 μ; uv max (95% C_2H_5OH) 239 mμ (ε 5400), 331 (5800); nmr ($CDCl_3$) δ 7.45–7.05 (m, 5, aromatic and C-9 proton), 2.8–0.8 (m, 10, methylene–methine envelope).

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59; N, 6.11. Found: C, 73.58; H, 6.62; N, 6.05.

This was followed by another fraction which contained two nitro acetates. Upon crystallization of the solid material from ether–hexane, 267 mg of clear square plate-like crystals of 9(a)-acetoxy-10(e)-nitro-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (**3**) were formed: mp 139°; ir (KBr) 3.38 and 3.48 (aliphatic C—H stretching), 5.80 (C=O stretching), 6.50 (N=O stretching), 6.70, 6.92, 7.32 8.20 (broad), 8.75, 9.78, 10.48, 13.18, 13.31, and 13.85 μ; nmr ($CDCl_3$) δ 7.30 (broadened s, 4, aromatic protons), 6.43 (d, 1, J_{AB} = 4 Hz, benzylic proton, H_A), 4.79 (q, 1, J_{BC} = 10 Hz, C-10 proton, H_B), 2.13 (s, 3, methyl protons), and 2.8–0.7 (m, 0, methylene–methine envelope).

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.58; H, 6.75; N, 5.00.

When the mother liquor from the above fraction was concentrated, two types of crystals formed which were separated using magnifying glass and forceps. The square plate-like crystals had mp 139° and were identical with those of β-nitro acetate **3**. The light yellow needlelike crystals separated from the mixture were recrystallized from hexane ether to give 22 mg of clear needle-like crystals of 9(e)-acetoxy-10(e)-nitro-1,2,3,4,4a,9,10,-10a-(*trans*-4a,10a)-octahydrophenanthrene (**2**): mp 136–137°; ir (KBr) 3.38 and 3.48 (aliphatic C—H stetching), 5.73 (C=O stretching), 6.48 (N=O stretching), 7.32 (N=O stretching), 8.2 (broad), 9.8, 13.23, and 13.52 μ; nmr ($CDCl_3$) δ 7.31 (m, 4, aromatic protons), 6.72 (d, 1, J_{AB} = 9 Hz, benzylic proton, H_A), 4.75 (q, 1, J_{BC} = 11 Hz, C-10 proton, H_B), 2.13 (s, 3, methyl protons), 2.9–0.8 (m, 10, methylene–methine envelope).

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.65; H, 6.67; N, 4.95.

In the next fraction 110 mg of a light yellow solid was isolated. The material was recrystallized from ether–hexane to give 60 mg of clear long needle crystals of 9(a)-acetoxy-10(a)-nitro-1,2,3,4,-4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene (**4**): mp 137°; ir (KBr) 3.40 (broad) and 3.50 (aliphatic C—H stretching), 5.80 (broad, C=O stretching), 6.15, 6.55, 6.95, 8.25, 9.40, 10.35, 11.52, 13.02, 13.35, and 13.80 μ; nmr ($CDCl_3$) δ 7.31 (m, 4, aromatic protons), 6.34 (d, 1, J_{AB} = 2.5 Hz, benzylic proton, H_A), 4.83 (q, 1, J_{BC} = 4 Hz, C-10 proton, H_B), 2.10 (s, 3, methyl protons), 2.9–0.7 (m, 10, methylene–methine envelope).

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.43; H, 6.64; N, 4.74.

X-Ray Analysis of 4.—The following crystallographic data were obtained from a prism of nitro acetate **4**: a = 9.878

(13) Melting points were obtained on a calibrated Thomas–Hoover Unimelt and are corrected. Infrared data were recorded on Beckman IR-5A, IR-8, and IR-20 spectrophotometers. Nmr spectra were determined with Varian A-60 and Varian T-60 spectrometers using tetramethylsilane as internal standard. In nmr descriptions, s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Mass spectra were recorded on AEI MS-9. Microanalyses were conducted by Drs. G. Weiler and F. B. Strauss, Oxford, England.

(±0.002) Å, b = 17.509 (±0.002) Å, c = 8.833 (±0.001) Å, β = 102.78 (±0.03)°, space group, $P2_1/c$, molecules/unit cell, 4, density (calcd) = 1.289 g/cm³, and density (measured by flotation) = 1.32 g/cm³.

Intensity data were collected by the stationary counter–stationary crystal technique using balanced filters for Cu Kα radiation.[14] The intensities (maximum *two* θ = 100°) were converted to structure factor amplitudes by applying appropriate corrections for absorption, α_1–α_2 splitting, and Lorentz-polarization effects. These data were scaled by Wilson statistics[15] and converted to their respective normalized structure factors.

The phases of the 159 largest normalized structure factors were derived by the application of the Sayre relationships.[16] Electron density and least squares calculations using all the data enabled the atomic coordinates of atoms and the thermal parameters (hydrogens isotropically and others anisotropically) to be refined. The final R index for the observed data was 0.038. A table of the positional and thermal parameters for the molecule, as well as the F tables, the bond distances, and angles, can be obtained from the authors.

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Registry No.—**1**, 16804-85-6; **2**, 25662-67-3; **3**, 25716-06-7; **4**, 25662-64-0; **5**, 25743-82-2; **8**, 25662-76-4; 9(ξ)-hydroxy-1,2,3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene, 25662-65-1; 9(ξ)-hydroxy-1,2,-3,4,4a,9,10,10a-(*trans*-4a,10a)-octahydrophenanthrene *p*-nitrobenzoate, 25662-66-2.

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Halogenation with Copper(II) Halides. The Synthesis of Aryl Iodides

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Aryl iodides have been synthesized by a simple, single-step reaction of aromatic compounds with copper salts and an iodide donor. The reaction is capable of application to substituted and unsubstituted aromatic substrates. Iodination fails to occur only with ring systems bearing strongly deactivating substituents or possessing functional groups that deactivate the copper salt through complexation. Iodine may be supplied to the reaction by molecular iodine or by any group I–VIII metallic or nonmetallic iodide. Certain metal iodides exhibit greater reactivity than iodine itself; aluminum and ferrous iodides, in particular, have been found to be potent catalysts for this iodination reaction. The new synthetic method affords several advantages with regard to classical iodination procedures.

Halogenation by molecular halogen is one of the classical reactions of aromatic compounds and has been thoroughly investigated for both its theoretical and synthetic value.[1] The reactions of chlorine, bromine, and iodine with aromatic structures have generated a wealth of physical-organic data that define the structure-reactivity relationships and the steric and electronic factors that control these systems. The general reaction is agreed to involve the electrophilic attack of polarized halogen, or suitable halogen donor, on the aromatic and to proceed through a sequence of π and σ complexes to aryl halide product. The reaction is markedly sensitive to the presence of a catalyst whose principal function is to polarize the halogen source.

In contrast to chlorination and bromination which occur in the absence of catalysts, iodination demands the use of a catalytic agent. The failure of noncatalyzed iodination to occur was originally believed to be indicative of the reduction of aryl iodide product by hydrogen iodide.[2] Rather, the fact is that the role of the catalyst is to convert molecular iodine to a more reactive species, notably the iodonium (I^+) ion. Historically, this has *not* been accomplished through the use of conventional Lewis acid metal salts, for the coordination of iodine with these salts is reportedly weak owing to steric inhibition of orbital overlap.[1] Consequently, the synthesis of aryl iodides has required specialized conditions. These traditional procedures include (1) iodination of active aromatics with iodine in water;[3,4] (2) iodination of benzene and its alkyl homologs in the presence of strong mineral acids,[4–6] oxidizing agents,[4,6] or silver and mercury salts;[4,6,7] (3) decomposition of diazonium salts or arylthallium ditrifluoroacetates[8] with potassium iodide; (4) reaction of iodine with certain arylmercury chlorides.[4]

All of these procedures suffer from one or more deficiencies. The most serious of these are substrate limitations due to reaction conditions and the loss of iodine from the reaction as hydrogen iodide or metallic iodide.

The reaction of olefins with copper halides in various solvent media has been a topic of investigation in these laboratories.[9] During these studies it had been found that olefins react readily with copper(II) chloride and iodine in an inert hydrocarbon diluent to give high yields of chloroiodoalkanes.[10] When this reaction was performed in high-boiling aromatic solvents, the forma-

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(1) For a recent general review of aromatic halogenation, see H. P. Braendlin and E. T. McBee in "Friedel-Crafts and Related Reactions," Vol. III, G. A. Olah, Ed., Wiley, New York, N. Y., 1964, Chapter 46.
(2) J. D. Roberts and M. C. Caserio, "Basic Principles of Organic Chemistry," W. A. Benjamin, New York, N. Y., 1965, p 789.
(3) See ref 1, p 1521.
(4) L. F. Fieser and M. F. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, pp 495–497.
(5) See ref 1, p 790.
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tion of by-product aryl iodides was surprisingly observed. The realization that this system represented a new and potentially general synthesis of aryl iodides prompted a detailed study of the reaction of aromatics with copper salt–iodine donor combinations. The remainder of this paper presents the results of the investigation of this new procedure. The scope of this reaction has been defined in terms of the following variables: the copper salt, the iodine source, the nature of the aromatic substrate, the effect of Lewis acid catalysis.

Results and Discussion

The Nature of the Copper Salt.—The reaction of xylene and iodine with copper(I) and copper(II) salts was studied to determine the ability of various copper compounds to participate in the synthesis of aryl iodides. Table I presents the results of these experiments.

TABLE I
COPPER SALTS FOR ARYL IODIDE SYNTHESIS

Copper salt	Time, at reflux hr	Yield of iodoxylene, %
$CuCl_2$	5	85
CuCl	5.5	22
CuF_2	5	42
$CuF_2 \cdot 2H_2O$	5	26
$CuCl_2 \cdot 2H_2O$	6	12
$Cu(OAc)_2$	5.5	<5
$Cu(OAc)_2 \cdot H_2O$	5.5	<5
CuCN	5.5	0

The observed reactivity order for these various copper(I) and copper(II) salts [$CuCl_2 > CuF_2 > CuCl > Cu(OOCCH_3)_2$] indicates that these compounds play a dual role in the iodination reaction. The primary function is to promote the iodination reaction *via* Lewis acid catalysis; the other, which is valid only for copper(II) compounds, is to recycle by-product hydrogen iodide to the reaction as iodine *via* a redox reaction. While aromatic iodination has been reported to be insensitive to Lewis acid catalysts,[1] the present results are certainly indicative of and best interpreted by such catalysis. Furthermore, subsequent sections of this report will clearly demonstrate that the reported failure of Lewis acid catalysts to promote aromatic iodination is erroneous.

Both copper(I) and copper(II) halides are known to possess Lewis acid characteristics and have shown mild to moderate activity as Friedel–Crafts catalysts.[11] Copper(II) chloride, in particular, has been effective in chlorination and bromination reactions.[1] It is not especially surprising then that this copper salt has demonstrated the greatest activity in aromatic iodination. In line with the previously proposed dual function of copper(II) salts the reaction based on copper(II) chloride may be considered to involve the sequence illustrated by eq 1–2. In the first step iodination of the ring is catalyzed by copper(II) chloride to produce aryl iodide and hydrogen iodide. The latter is subsequently oxidized to iodine or iodine monochloride, a potent iodination reagent,[1] which iodinates a second mole of aromatic under the influence of either copper(I) or copper(II) chloride as a catalyst. The overall stoichiometry of the reaction (eq 3) is in accord with this

$$ArH + I_2 \xrightarrow{(CuCl_2)} ArI + HI \quad (1)$$

$$ArH + HI + 2CuCl_2 \longrightarrow 2HCl + ArI + 2CuCl \quad (2)$$

$$2ArH + I_2 + 2CuCl_2 \longrightarrow 2ArI + 2HCl + 2CuCl \quad (3)$$

interpretation, and the isolated yields of organic and inorganic products are equally consistent with this reaction path. Whether iodine monochloride plays a transient role in the reaction cannot be definitely stated; that hydrogen iodide is oxidized by copper(II) chloride and can serve as an iodide donor for aromatic iodination has been demonstrated as will be seen subsequently.

The diminished reactivity of copper(II) fluoride is derived from two sources. The salt possesses little Lewis acid activity owing to its highly ionic fluoride type lattice,[11] and the oxidation of hydrogen iodide is complicated by the unstable nature of cuprous fluoride[11] which leads to its conversion to cuprous iodide in the presence of iodine.

Copper(I) chloride possesses mild Friedel–Crafts properties, and the reaction with this salt is solely metal halide catalyzed iodination. The chloride is recovered unchanged from the reaction, and by-product hydrogen iodide is lost from the system. The poor activity exhibited by the hydrates of copper(II) chloride and fluoride, copper acetates, and copper(I) cyanide is best rationalized by the diminished Lewis acid character of these salts. Water is a notorious Lewis acid poison, the available coordination sites of the metal ion being preempted by this ligand. In a similar manner the coordinating ability of the copper ion is destroyed by the strongly bridging acetate and cyanide ions, and the ability of these salts to activate iodine through complexation is lost.

Iodide Donors for the Synthesis of Aryl Iodides — Iodine may be supplied to the synthesis of aryl iodides in a variety of forms. While molecular iodine is a convenient source, it has been shown that virtually any group I–VIII metallic or nonmetallic iodide is satisfactory. The reactivity of certain of these iodide salts permits achieving iodination reactions that fail to occur with elemental iodine. Table II lists various iodides

TABLE II
IODIDE DONORS FOR ARYL IODIDE SYNTHESIS

Iodide donor	Time, at reflux hr	Yield of iodoxylene, %
BaI_2	6	49
BiI_3	7	81
CoI_2	1	62
$FeI_2 \cdot 4H_2O$	2	100
$FeI_2 \cdot 4H_2O$	0.5	54
FeI_2	0.5	26
SnI_4	5	85
LiI	5	36
NH_4I	6	17
HI	5	14
AlI_3	6	13[a]

[a] Reaction yielded condensed aromatic products of undetermined structure. *Anal.* Found: C, 88.36; H, 9.25.

(11) G. A. Olah, "Friedel-Crafts and Related Reactions," Vol. I, G. A. Olah, Ed., Wiley, New York, N. Y., 1963, pp 215–216.

that have been tested in this reaction. The reactions occurred with the general overall stoichiometry illustrated by eq 4; at the conclusion of the reaction the

$$MI_n + 2nCuCl_2 + nArH \longrightarrow nArI + nHCl + 2nCuCl + MCl_n \quad (4)$$

metal iodide had been completely transformed to the corresponding metal chloride. All of these reactions proceeded with the release of elemental iodine in the early stages of the reaction period. The generally better performance of the more covalent iodides relative to the ionic iodides is attributed to a more facile generation of iodine in the former reactions and to the Lewis acid properties of the metals involved.

The impact of Lewis acid character is apparent from the data of Table II, for optimum yields of iodoxylene were produced under more moderate conditions in those reactions that generated strong Friedel–Crafts catalysts. The reactions utilizing the iodides of cobalt, bismuth, iron, tin, and aluminum in general required shorter reaction periods, lower temperatures, and gave better yields. The active "catalyst" in these reactions is probably a blend of copper(I) chloride and other metal halide. The two metal salts operating in concert appear to exert a synergistic effect on the reaction although the exact mechanism of this influence is vague.

It is interesting to note that the use of a hydrated metal iodide does not inhibit the reaction as does the use of hydrated copper(II) chloride. One of the most active iodide salts, iron(II) iodide, is supplied to the reaction as the tetrahydrate without deleterious effect. The absence of serious inhibition in the latter case may be ascribed to unusual features of the iron(II) iodide–copper(II) chloride reaction. One of these is the release of water of hydration from the metal ions during the iodide to iodine oxidation. The resultant metal chlorides possess a degree of reactivity that surpasses that encountered in the reaction with anhydrous iron(II) iodide. The reasons for this distinction are not wholly apparent.

The reactivity of the aluminum(III) iodide and iron(II) iodide systems permits the iodination of aromatics that fail to experience reaction with iodine and copper(II) chloride. This technique is most applicable to aromatics bearing deactivating groups and to benzene and its alkyl homologs that either react sluggishly or not at all. While this topic is more completely discussed in the following section, a few comments are relevant at this point. The high activity of the aluminum(III) iodide–copper(II) chloride couple leads to undesirable side reactions when alkyl benzenes serve as the aromatic substrate. This is in large part due to the production of aluminum chloride as the reaction proceeds. Xylenes not only experience nuclear iodination, but are also converted to arylmethanes, biaryls, and disproportionated and polymerized materials.[12] *tert*-Butylbenzene does not undergo iodination with this couple, but is totally disproportionated to benzene and *m*- and *p*-di-*tert*-butylbenzenes. For these reasons the use of aluminum iodide is restricted to the reactions of benzene, toluene, and halobenzenes. Iron(II) iodide, which does not induce the destruction of the aromatic compound by any of the cited side reactions, is consequently a preferred iodide donor.

Synthesis of Aryl Iodides —This section describes the iodination of various aromatic structures by copper(II) chloride–iodine donor combinations. Iodine was selected as the primary iodine donor; other more reactive iodine sources were employed where necessary as noted subsequently. Table III summarizes the aromatic substrates that yielded aryl iodides.

Benzene is not iodinated by copper(II) chloride in combination with iodine or iron(II) iodide but is converted to iodobenzene in the presence of aluminum(III) iodide. The reaction is completely free of the polyphenyls obtained by treatment of benzene with aluminum and copper(II) chlorides.[12] The absence of these benzene polymers is ascribed to the destruction of the requisite copper(II) chloride by the oxidation of aluminum iodide to iodine and aluminum chloride. While the latter may initiate polymerization of the aromatic, the copper(II) salt is required for propagation of the reaction.

Toluene is converted to iodotoluenes in 25% yield by iodine–copper(II) chloride. The ortho/para ratio, 41:59, is reminiscent of that observed during the iron(III) bromide catalyzed bromination of this aromatic (ortho/para = 37:63).[13] An 81% yield of iodotoluenes is realized with iron(II) iodide under milder conditions (3 hr at reflux *vs.* 7 hr); in this case the ortho/para distribution is shifted to 53:47. It is not clear whether this change in substitution pattern is indicative of a smaller steric requirement of the attacking complex in the latter reaction; it is conceivable that the greater degree of reactivity of this iodinating system renders it less selective. The antimony(V) chloride catalyzed chlorination of toluene exhibited a threefold preference for ortho attack while iron(III) chloride catalysis gave an ortho/para distribution of 64:32.[14] This distinction has been attributed to a smaller steric factor in the antimony reaction; it is of interest to note, however, that antimony(V) chloride is a more reactive chlorinating agent than iron(III) chloride. Postisomerization of the iodotoluenes is not likely, for halogenation reactions are not reversible at temperatures below 150° and generally become significant only in the range 200–400°.[1] The presence of strong Lewis acid metal halides seems to have little bearing on this point.

Xylene, mesitylene, and durene are all readily iodinated by copper(II) chloride and iodine. As anticipated, the degree of reactivity increased with increasing alkylation of the ring indicating that the reaction is abetted by high aromatic basicity. The observed order of xylene reactivity (meta > ortho $\cong$ para) is in accord with the basicity of the xylene isomers toward electrophiles.[15]

Chloro- and bromobenzene were inert toward iodine–copper(II) chloride, but aluminum(III) iodide and iron(II) iodide did effect the iodination of these halobenzenes. Bromobenzene experienced exclusively para substitution, a manifestation of steric control rather than electronic. Chlorobenzene yielded chloroiodobenzenes in which the ortho/para distribution was 18:82. The degree of ortho substitution is higher than

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TABLE III

SYNTHESIS OF ARYL IODIDES

Aromatic ml or g (mol)	Solvent[a]	Iodine source g (mol)	Copper salt g (mol)	Reaction conditions Time, hr	Temp, °C	Product	Yield, %	Isomeric distribution
Benzene 75 ml		AlI_3 8.1 (0.02)	$CuCl_2$ 16.1 (0.12)	5	80	Iodobenzene	65	
Toluene 70 ml		I_2 13.0 (0.05)	$CuCl_2$ 13.3 (0.10)	7	110	Iodotoluene	25	2-Iodo 41% 4-Iodo 59%
Toluene 100 ml		$FeI_2 \cdot 4H_2O$ 9.5 (0.025)	$CuCl_2$ 16.1 (0.12)	3	110	Iodotoluene	81	2-Iodo 53% 4-Iodo 47%
m-Xylene 75 ml		I_2 12.7 (0.05)	$CuCl_2$ 13.3 (0.10)	7	145	Iodoxylene	63	1,3-Dimethyl-4-iodo 86% 1,3-Dimethyl-2-iodo 14%
o-Xylene 75 ml		I_2 12.7 (0.05)	$CuCl_2$ 13.4 (0.10)	7	145	Iodoxylene	13	1,2-Dimethyl-4-iodo 75% 1,2-Dimethyl-3-iodo 25%
p-Xylene 75 ml		I_2 12.7 (0.05)	$CuCl_2$ 13.4 (0.10)	7	145	Iodoxylene	34	1,4-Dimethyl-3-iodo
Mesitylene 50 ml		I_2 12.7 (0.05)	$CuCl_2$ 13.4 (0.10)	0.5	150	Iodomesitylene	86	
Durene 26.8 (0.20)	50 ml C_6H_5Cl 10 ml C_6H_6	I_2 12.7 (0.05)	$CuCl_2$ 13.4 (0.10)	20	115	Iododurene	100	
tert-Butylbenzene 50 ml		$FeI_2 \cdot 4H_2O$ 9.6 (0.025)	$CuCl_2$ 16.8 (0.13)	5	150	*p*-Iodo-*tert*-butylbenzene	76	
Chlorobenzene 75 ml		AlI_3 8.1 (0.02)	$CuCl_2$ 16.1 (0.12)	5	80	Chloroiodobenzene	29	1-Chloro-4-iodo 82% 1-Chloro-2-iodo 18%
Bromobenzene 75 ml		$FeI_2 \cdot 4H_2O$ 9.5 (0.025)	$CuCl_2$ 16.8 (0.13)	11	150	*p*-Bromoiodobenzene	33	
Acetanilide 13.5 (0.10)	60 ml C_6H_5Cl 10 ml C_6H_6	I_2 12.7(0.05)	$CuCl_2$ 13.3 (0.10)	28	115	*p*-Iodoacetanilide	76	
Anisole 50 ml		I_2 12.7 (0.05)	$CuCl_2$ 13.3 (0.10)	6	140	*p*-Iodoanisole	80	
Phenol 9.4 (0.10)	50 ml C_6H_5Cl	I_2 12.7 (0.05)	$CuCl_2$ 13.3 (0.10)	29	130	*p*-Iodophenol	69	
N,N-Dimethylaniline 36.0 (0.30)	70 ml C_6H_6	I_2 12.7 (0.05)	$CuCl_2$ 13.3 (0.10)	0.5	60	*p*-Iododimethylaniline	47	
Naphthalene 12.8 (0.10)	50 ml C_6H_5Cl 10 ml C_6H_6	I_2 12.7 (0.05)	$CuCl_2$ 13.3 (0.10)	21	115	1-Iodonaphthalene	44	
Anthracene 17.8 (0.10)	40 ml C_6H_5Cl 10 ml C_6H_6	I_2 12.7 (0.05)	$CuCl_2$ 13.3 (0.10)	20	95	9-Chloroanthracene	92	
Anthracene 8.9 (0.05)	50 ml C_6H_5Cl 10 ml C_6H_6	I_2 12.7 (0.05)	CuCl 5.9 (0.05)	42	120	9-Chloroanthracene	48	
Anthracene 17.8 (0.10)	80 ml C_6H_5Cl	I_2 19.0 (0.076)	CuF_2 5.0 (0.05)	48	132	9-Iodoanthracene	26	
Biphenyl 15.4 (0.10)	20 ml C_6H_5Cl	I_2 12.7 (0.05)	$CuCl_2$ 13.3 (0.10)	48	130	*p*-Iodobiphenyl *p,p'*-Diiodobiphenyl	45 14	
Terphenyl 23.0 (0.10)	45 ml C_6H_5Cl	I_2 12.7 (0.05)	$CuCl_2$ 13.3 (0.10)	52	130	Iodoterphenyl	30	

[a] C_6H_6 = benzene; C_6H_5Cl = chlorobenzene.

expected, for electronegative chlorine is known to deactivate the ortho position more effectively than the para. The result may be rationalized by coordination between the copper–aluminum chloride catalyst and the ring chlorine that facilitates iodination in the ortho position.[16]

The other benzene derivatives listed in Table III were converted to the corresponding *p*-iodo products by reaction with iodine–copper(II) chloride; the iodination of *tert*-butylbenzene was best accomplished by iron(II) iodide. The observed substitution pattern was that anticipated on the basis of steric and electronic control. The reaction of phenol was free of chlorocyclohexenones which are generally produced upon treatment of this aromatic with copper(II) chloride.[17] The absence of this side reaction is indicative of a preferential interaction of copper(II) chloride with iodine. Biphenyl and *p*-terphenyl were also iodinated by these reagents; the exact structure of the iodoterphenyl was not established owing to difficult separation and purification problems. Naphthalene yielded 1-iodonaphthalene, the normal product of Lewis acid catalyzed halogenation of this condensed ring system.[18] No isomerization to the 2 isomer was apparent.

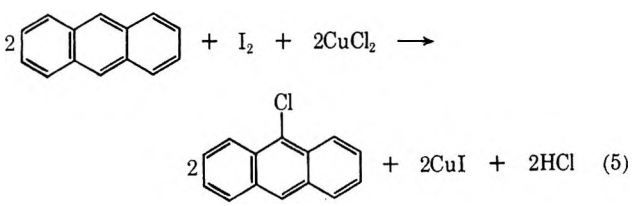
The reaction of anthracene with copper(II) chloride and iodine did not yield any isolable iodoanthracene, but 9-chloroanthracene was recovered from the reaction

(16) Reference 12, pp 113–114.

(17) L. Deniville and R. Fort, *Bull. Soc. Chim. Fr.*, 392 (1959).

(18) Reference 1, p 1552.

in >90% yield. The reaction occurred in accord with the stoichiometry and the products illustrated by eq 5.



(5)

While anthracene is halogenated by copper(II) halides in aromatic and aryl halide solvents,[19] the chemistry of this reaction is inconsistent with that observed in the iodine–copper(II) chloride reaction. A rationale for the observed reaction was suggested by a reaction sequence in which anthracene experienced normal iodination and the 9-iodoanthracene subsequently underwent halogen exchange with copper(I) chloride to form the isolated product. This proposed scheme appeared reasonable in the light of other organic iodide–copper(I) halide exchange reactions.[20]

In order to test this proposal, a sample of 9-iodoanthracene was required. This compound was ultimately synthesized by the iodination of anthracene with iodine–copper(II) fluoride; the success of this reaction lay in the inability of copper(II) and -(I) fluorides to participate in halide exchange reactions,[20b] and any exchange with copper(I) iodide would be inconsequential. Treatment of 9-iodoanthracene with copper(I) chloride in refluxing chlorobenzene failed to produce any 9-chloro compound. Reaction of 9-iodoanthracene with excess (10:1) copper(II) chloride in refluxing chlorobenzene resulted in the destruction of the iodide as evidenced by the appearance of iodine vapor in the reaction. From this reaction was isolated a 74% yield of 9,10-dichloroanthracene. The dichloride is generated by the initially formed monochloro compound being further chlorinated by excess copper(II) chloride; the latter reaction has been previously described.[20b]

The key distinction then between the reaction of anthracene and that of other aromatics is the exchange reaction that occurs between 9-iodoanthracene and copper(II) chloride. The mechanism of this exchange is obscure and open to speculation. It is quite reasonable to presume that the π-complexing affinity of the anthracene nucleus for copper(II) chloride[19] is a critical factor.

Those aromatic compounds that failed to undergo iodination by copper(II) chloride–iodine donor combinations include methyl benzoate, aniline, thiophene, quinoline, pyridine, cumene, and diphenylmethane. Methyl benzoate was too strongly deactivated to experience reaction. The reactions of cumene and diphenylmethane were complicated by two side reactions that rendered the iodination reaction synthetically useless. The first of these was the sensitivity of the methine and methylene carbons toward halogenation in the presence of metal halides;[21] the second was the coupling of these reactive aryl alkyl halides by copper(I) salts.[20b] The remaining compounds failed to react owing to the fact that these materials all formed strong complexes with copper(II) chloride. This coordination destroyed both the Lewis acid properties of the copper salt and its oxidizing power. The latter was depleted by the nature of the bonding between copper(II) and these bases, for the strong σ bonding associated with these ligands stabilizes copper(II) relative to copper(I).[22] An interesting distinction was apparent between the behavior of aniline and its *N,N*-dimethyl derivative. While the former complexed the copper and ultimately underwent condensation and oxidation to aniline dyes, *N,N*-dimethylaniline was converted to its *p*-iodo derivative in 47% yield. This difference is ascribed to the poorer complexing ability of the *N,N*-dimethyl compound toward copper. The adverse steric factors inherent in the formation of the copper complex permit the creation of a dynamic equilibrium, and the iodination of the free amine may proceed in a normal manner.

Lewis Acid Catalysis of Aromatic Iodination — Throughout the preceding discussion reference has frequently been made to Lewis acid catalysis of the addition of iodine to aromatics. Recourse to this interpretation has been predicted on the basis that the experimental observations and results are consistent with this position. The activity of the various copper salts, the poisoning of the reaction by the addition of Lewis bases, and the enhanced reactivity of systems containing known Lewis acid metal ions all support this contention. These facts lead to the conclusion that the historical view that aromatic iodination is insensitive to Lewis acid catalysis is false.[23]

The erroneous nature of this statement is clearly apparent from the successful iodination of aromatics by iodine–copper(II) chloride reactions to which a catalytic quantity of a Lewis acid iodide has been added. The results of such studies are found in Table IV. Iron(II) iodide has been utilized exclusively in these reactions; although aluminum(III) iodide would also undoubtedly serve as a potent catalyst, the disproportionation and coupling reactions induced by this salt limit its utility. From the data of Table IV there can be little doubt that the addition of the iron salt has had a profound catalytic effect on the reaction. While the active form of the iron salt is the chloride derived from the redox reaction with copper(II) chloride, the structure of the actual catalytic species is not known. It is likely that the true catalyst is a composite of both iron and copper salts.

TABLE IV

LEWIS ACID CATALYZED SYNTHESIS OF ARYL IODIDES

Aromatic	Reaction conditions—Time, hr	Reaction conditions—Temp, °C	Catalyst (mol of I_2/mol of Cat)	Aryl iodide, %
Xylene	1.5	145		23
Xylene	1.5	145	$FeI_2 \cdot 4H_2O$ (50:1)	87
tert-Butylbenzene	23	170		8
tert-Butylbenzene	5	150	$FeI_2 \cdot 4H_2O$ (50:1)	74

In conclusion, a few remarks pertaining to the utility and effectiveness of this new iodination reaction are

(19) D. C. Nonhebel, *J. Chem. Soc.*, 1216 (1963).

(20) For a discussion of the coordination of copper salts with aromatic rings and aryl halides, see (a) ref 19; (b) R. G. R. Bacon and H. A. O. Hill, *ibid.*, 1103 (1964).

(21) Reference 12, pp 114–115.

(22) H. J. Emeleus and J. S. Anderson, "Modern Aspects of Inorganic Chemistry," Rutledge and Kegan Paul Ltd., London, England, 1960, Chapter 6.

(23) Reference 1, p 1531.

TABLE V
COMPARISON OF ARYL IODIDE SYNTHESES

Reagent	Yield of aryl iodide, %									
	Benzene	Toluene	*m*-Xylene	Mesitylene	Naphthalene	Phenol	Anisole	Chlorobenzene	*N,N*-Dimethylaniline	Biphenyl
$CuCl_2$	65	81	63	86	44	69	80	29	47	45
HNO_3[a,b]	80	60	56	40	Trace			59		
$AgOOCCF_3$[c,d]	85	88					75	62	41	
$Th(OOCCF_3)_6$–KI[e]	96		100	94			75	80		
$Na_2S_2O_8$[f]	70	78	70	83						68
HIO_3[f]	83	81			40		40	53		68
$AgClO_4$[g]	80	65			85	80		95		
H_2SO_4–HNO_3[h]	80	65						41		64

[a] R. L. Datta and N. R. Chatterjee, *J. Amer. Chem. Soc.*, **39**, 435 (1917). [b] R. L. Datta and N. R. Chatterjee, *ibid.*, **41**, 292 (1919). [c] A. L. Henne and W. F. Zimmer, *ibid.*, **73**, 1362 (1951). [d] R. N. Haszeldine and A. G. Sharpe, *J. Chem. Soc.*, 993 (1952). [e] Reference 8. [f] H. O. Wirth, D. Königstein, and W. Kern, *Justus Liebigs Ann. Chem.*, **634**, 84 (1960). [g] L. Birckenbach and J. Goubeau, *Ber.*, **65**, 395 (1932). [h] B. V. Tronov and A. N. Novikof, *Izv. Vyssh. Ucheb. Zaved., Khim. Khim. Tekhnol.*, **3**, 872 (1960); *Chem. Abstr.*, **55**, 8348 (1961).

appropriate. The data of Table V illustrate that the new method competes quite satisfactorily with previous synthetic routes to aryl iodides on the basis of product yield. In those instances where reliable isomer distributions are available, no significant variations among these procedures have been noted. The copper(II) halide based system affords some advantages relative to these established methods. These include simplicity of operation and isolation–purification of products; absence of by-product formation; ability to convert all iodine charged; nonreactive environment that does not degrade starting material or product; preparation of reactive intermediates, *e.g.*, diazonium salts, organomercury and thallium salts, not required. Like the other preparative methods, the present case does suffer from some substrate limitations, the nature of which have been reviewed above.

Experimental Section

Nmr spectra were determined on a Varian Associates A-60 spectrometer using tetramethylsilane as an internal standard. Infrared spectra were recorded on a Beckman IR-5A spectrophotometer. Vapor phase chromatography (vpc) was performed on a Perkin-Elmer Model 226 chromatograph, a Perkin-Elmer Model 154D fractometer, and a Varian Aerograph Autoprep Model A-700 equipped with analytical columns. Preparative scale vpc was carried out on the latter instrument equipped with preparative columns. Melting points and boiling points are not corrected. All reagents were obtained from commercial sources and used as received.

Copper Salts for Aryl Iodide Synthesis.—In a typical experiment a 500-ml flask was equipped with a Teflon paddle stirrer and a reflux condenser. Into the flask were placed 70 ml of xylene, 13.0 g (0.05 mol) of iodine, and 13.3 g (0.1 mol) of copper(II) chloride. The reaction was stirred at 140° for 5 hr. The reaction mixture was cooled and filtered, and the filtrate was washed with 100 ml of 20% sodium thiosulfate solution to discharge any residual iodine. The filtrate was dried over magnesium sulfate, the solution was filtered, and the excess xylene removed on a rotary evaporator at 60° (13 mm). The crude product (22.8 g) was distilled to give 19.8 g (85%) of iodoxylenes, bp 65–72° (0.2 mm). *Anal.* Calcd for C_8H_9I: C, 41.40; H, 3.91; I, 54.68; mol wt, 232. Found: C, 41.75; H, 3.95; I, 54.3; mol wt, 260. Vpc analysis (2 m × 0.25 in. 20% DC-200 column, 150°, 105 ml/min) showed two product peaks at 16 min (93%) and 19 min (7%) from air. The nmr spectrum (neat) showed a methyl proton/aromatic proton ratio of 2:1 consistent with iodoxylene.

The reactivity of other copper salts was evaluated by an identical procedure; xylene was the aromatic substrate in all cases. The experimental results are summarized by Table I.

Iodide Donors for Aryl Iodide Synthesis.—In a typical experiment 5.7 g (0.03 mol) of copper(I) iodide, 8.0 g (0.06 mol) of copper(II) chloride, and 45 ml of xylene were stirred at reflux for 6 hr. A strong iodine color developed in the reaction as the temperature approached reflux. The reaction mixture was cooled and filtered to give 8.6 g of copper(I) chloride (theory 8.9 g). The filtrate was washed with 10% sodium thiosulfate solution and was dried over magnesium sulfate. The excess xylene was removed on a rotary evaporator at 60° (15 mm) to give 5.8 g of crude product. Analysis by vpc (2 m × 0.25 in. DC-550 column, 150°, 105 ml/min) showed the product to contain 83% iodoxylene, which corresponded to a ~70% yield.

The activity of other iodide donors was evaluated by a similar procedure; xylene was the aromatic substrate in all cases. The results of these experiments are tabulated in Table II. The stoichiometries were balanced according to eq 4.

Synthesis of Aryl Iodides.—The synthesis of aryl iodides from various aromatic substrates was carried out by a procedure identical with that described above for the preparation of iodoxylene. The reagent quantities, reaction conditions, yield, and isomeric distribution are presented in Table III.

Reactions of liquid aromatics were performed with an excess of the aromatic serving as the reaction diluent. Solid aromatic substrates were reacted in chlorobenzene, which is a reasonably inert solvent. A small amount of benzene was added to reactions carried out in chlorobenzene in order to facilitate the return of sublimed iodine from the cooler portions of the reactor to the liquid phase. The use of chlorobenzene as a diluent decreased the reaction rate markedly so that long reaction periods were required; this was frequently the case even when reactive aromatics were being iodinated. This effect is attributed partially to solvent–copper(II) complexation.[19]

The reactions were worked up by removal of the inorganic salts by filtration and the washing of the filtrates with 10–20% sodium thiosulfate solution. The decolorized aryl iodide solutions were dried over magnesium sulfate, and the excess hydrocarbon or the solvent was removed on a rotary evaporator [60–80° (14–20 mm)]. Liquid products were purified by distillation; solid aryl iodides were recrystallized or sublimed. Fractional sublimation was employed in some cases (naphthalene, anthracene) to separate unreacted starting material. Product purification in some cases was extremely difficult owing to the mutual solubility or insolubility of starting material and products. Yield data in these cases were obtained by vpc analysis using internal standards. Highly insoluble aryl iodides were extracted from the filter cake with acetone when necessary.

The aryl iodides were identified by conventional nmr and vpc techniques,[24] comparison of physical properties with those of authentic samples, and elemental analysis.

Reaction of 9-Iodoanthracene with Copper(I) and Copper(II) Chlorides.—A 5 g (0.01 mol) sample of 9-iodoanthracene was stirred with 5 g (0.049 mol) of copper(I) chloride in refluxing chlorobenzene for 9 hr. At the conclusion of this period vpc analysis indicated that no halogen exchange had occurred. A few crystals of iodine were added as a potential catalyst, and the

(24) In addition to the vpc columns previously mentioned, the following were also useful for analysis of aryl iodides: 2 ft × 0.25 in. 10% silanized polypropylene glycol on Haloport F; 300 ft × 0.01 in. silicone (DC-550); 3 ft × 0.25 in. 3% Dowfax on Chromosorb W.

reaction was refluxed for 2 hr. No 9-chloroanthracene was detected by vpc analysis.

A mixture of 2 ml of chlorobenzene, 0.5 g (0.0016 mol) of 9-iodoanthracene, and 2.0 g (0.015 mol) of copper(II) chloride was refluxed and stirred for 2 hr. Within 30 min a strong iodine color developed in the reaction. At the end of the reaction period no 9-iodoanthracene remained; vpc analysis (3 ft × 0.25 in. 3% Dowfax, 215°, 100 ml/min) showed two product peaks at 4.9 min (71%) and 14.8 min (29%). Work-up of the reaction mixture gave 0.3 g of yellow-green crystals (74%). Recrystallization from ethanol and subsequently from acetone gave yellow needles: mp 211–213° (lit. 209–210°);[20b] retention time, 4.9 min. *Anal.* Calcd for $C_{14}H_8Cl_2$: C, 68.04; H, 3.26; Cl, 28.70. Found: C, 66.36; H, 3.38; Cl, 28.20.

Catalysts for the Synthesis of Aryl Iodides.—Into 70 ml of xylene were placed 12.7 g (0.05 mol) of iodine, 14.7 g (0.11 mol) of copper(II) chloride, and 0.38 g (0.001 mol) of iron(II) iodide tetrahydrate. The reaction was stirred and refluxed for 1.5 hr. After the normal work-up, an 87% yield of iodoxylene was isolated. A control experiment containing no iron(II) iodide gave a 23% yield under identical conditions.

Registry No.—Benzene, 71-43-2; toluene, 108-88-3; *m*-xylene, 108-38-3; *o*-xylene, 95-47-6; *p*-xylene, 106-42-3; mesitylene, 108-67-8; durene, 95-93-2; *tert*-butylbenzene, 98-06-6; chlorobenzene, 108-90-7; bromobenzene, 108-86-1.

Synthesis of Two Benzothiacyclanones *via* a Novel Two-Carbon Ring Expansion of Thiolactones with Vinyllithium

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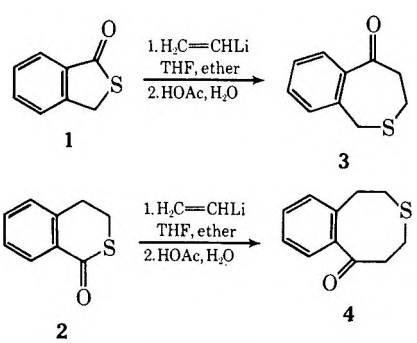
Received March 3, 1970

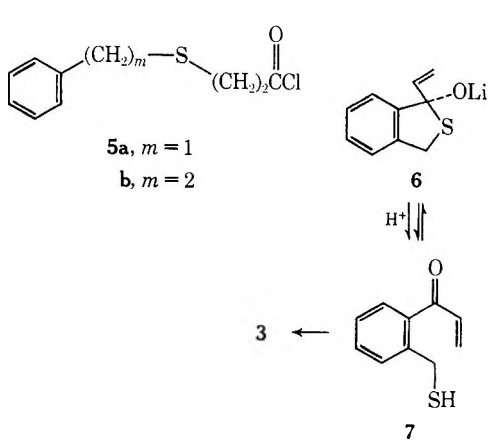
The thiolactones thiophthalide (1) and 2-thiochroman-1-one (2) react with 1 equiv of vinyllithium in ether–tetrahydrofuran followed by acetic acid to form, respectively, seven- and eight-membered ring γ-keto sulfides by a novel two-carbon ring expansion. This method is an improvement on existing, inefficient Friedel–Craft acylation routes to such ketones. Syntheses of 2-thiochroman-1-one and a much improved synthesis of thianapthen-2-one are reported.

In the course of our studies of organic sulfur chemistry, we required pure samples of 4,5,6,7-tetrahydro-2H-benzo[*c*]thiepin-5-one (**3**) and 3,4,7,8-tetrahydro-2H-benzo[*e*]thiocin-4-one (**4**), These ketones had previously been obtained as impure oils in low yield by the $AlCl_3$-catalyzed cyclization of acid chlorides **5a** and **b**, respectively.[1] We decided to attempt the addition of 1 equiv of vinyllithium to the readily available thiophthalide (**1**), in anticipation that the initial tetrahedral adduct **6** might be stable toward vinyllithium, but ring open to the vinyl ketone **7** upon hydrolysis. The latter should then cyclize by conjugate addition of the mercaptan to form **3**. As expected, a 51% yield of crystalline **3** was obtained from treatment of a cold ether solution of **1** with a 2 *M* solution of vinyllithium in tetrahydrofuran, followed by acidification with glacial acetic acid, vacuum distillation, and sublimation. Analogous reaction of thiolactone **2** at −70° gave 19% crystalline **4**.



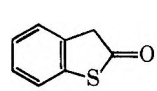
1 3

2 4



The crude ketones **3** and **4** were contaminated with polymeric material, variable amounts of recovered starting material, and a volatile, pungent oil which has not been identified.

Recovery of thiolactones implies that they undergo either enolate formation or competing addition of 2 equiv of vinyllithium to form divinylcarbinols, which may be responsible for polymer formation. Enolate formation was the predominant reaction between vinyllithium and thianaphthen-2-one (**8**), at 25 to



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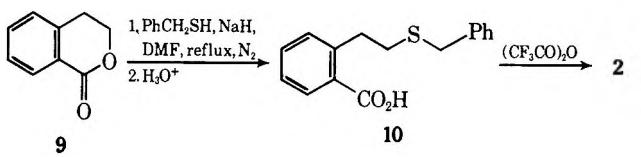
−78°, as evidenced by recovery of 84–95% of this material after treatment with vinyllithium followed by work-up with glacial acetic acid.

Several attempts to synthesize the previously unreported 2-thiochroman-1-one (**2**) by reaction of derivatives of *o*-(2-hydroxyethyl)benzoic acid with sulfur nucleophiles gave only 2-chroman-1-one (**9**). It was found, after considerable experimentation, that lactone **9** reacted with sodium benzylmercaptide in dimethylformamide at reflux to give the carboxylic acid **10** in

* To whom inquiries should be addressed: Merck Sharp & Dohme, Research Laboratories, Rahway, N. J. 07065.

(1) P. Cagniant and D. Cagniant, *Bull. Soc. Chim. Fr.*, 1998 (1959).

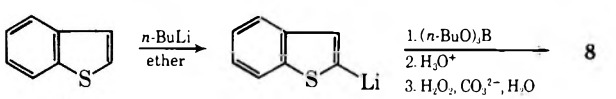
81% yield. The latter was recovered from polyphosphoric acid at 120° but reacted exothermically at room



9 10

temperature with trifluoroacetic anhydride to afford a mixture of recovered starting material and 2 in 48% yield. This transformation presumably involves an acid-catalyzed debenzylation with concomitant or subsequent lactonization, analogous to the transformation of phthalide to thiophthalide.[2]

An attempt to synthesize thianaphthen-2-one (8) from *o*-nitrotoluene[3] was unsuccessful. Thianaphthene (11), however, could be oxidized to 8 in good yield by the sequence 11 to 12 to 8. This procedure was adapted from the method of Hornfeldt and Gronowitz for the oxidation of thiophenes to the tautomers of 2-hydroxythiophenes.[4]



11 12

Experimental Section

Melting points and boiling points are uncorrected and the former were measured in an electrically heated Thiele–Dennis tube. Infrared spectra were recorded on a Perkin-Elmer 457 grating spectrophotometer and nmr spectra on a Varian HA-100 instrument in the frequency sweep mode. Chemical shifts are reported in δ units. Vpc analyses and isolations were performed on a 5 ft × $^3/_8$ in., 10% SE-30 on Anakrom ABS (70–80 mesh) using a Varian Model A-90-P3 instrument with thermal conductivity detector (He carrier at 80 ml min^{-1}). Microanalyses were performed by Galbraith Laboratories, Inc.

Materials.—Commercially available materials were used without purification. A solution of ~2 *M* vinyllithium in tetrahydrofuran, previously available from Alpha Inorganics, Inc., was standardized by double titration and used in this work.[5]

4,5,6,7-Tetrahydro-2H-benzo[*c*]thiepin-5-one (3).—A magnetically stirred solution of thiophthalide (1), 3.00 g, 20.0 mmol, in 100 ml of anhydrous ether in a side-arm flask fitted with serum cap and nitrogen inlet, was cooled under a slight positive pressure of nitrogen in a Dry Ice–acetone bath until crystallization began. The mixture was then warmed until homogeneous and treated during 5 min with 12.0 ml of 1.68 *M* solution of vinyllithium in tetrahydrofuran from a syringe. A copious precipitate formed after a few minutes.

The mixture was warmed to room temperature, treated with glacial acetic acid (1.7 ml) and 25 ml of water, and then stirred until two nearly clear layers had formed. The layers were separated and the water layer was extracted with an equal volume of ether. The combined ether layers were washed with saturated sodium bicarbonate solution (10 ml), dried over $MgSO_4$ (anhydrous), filtered, and evaporated *in vacuo* leaving 3.91 g of a cloudy, two-phase residue. Distillation of this material gave 2.64 g of a partially crystalline oil, bp 100–130° (0.01 mm). Vpc analysis of this fraction (8 ft × $^1/_4$ in. 20% SE-30 on 60–80 mesh Chromosorb P at 210°, He carrier 80 ml min^{-1}) showed one major peak for the desired ketone **3** (>98 area %). Trituration of this material with pentane–ether gave a crude white solid which was sublimed (50°, 0.01 mm) to give 1.81 g (51%) of crystalline **3**: mp 50–51°; $\nu_{max}^{CCl_4}$ 2925, 1680, 1600 cm^{-1}; nmr ($CDCl_3$) 7.65 (1 H, q, J = 7.2 Hz), 7.4 (3 H, complex), 3.85 (2 H, s), 2.94 (4 H, A_2B_2).

Anal. Calcd for $C_{10}H_{10}OS$: C, 67.38; H, 5.66; S, 17.98. Found: C, 67.18; H, 5.70; S, 18.12.

The oxime melted at 168–169° dec (recrystallized from benzene–pentane).

Anal. Calcd for $C_{10}H_{11}NOS$: C, 62.14; H, 5.74; N, 7.25; S, 16.59. Found: C, 62.06; H, 5.83; N, 7.05; S, 16.82.

3,4,7,8-Tetrahydro-2H-benzo[*e*]thiocin-4-one (4).—A stirred solution of 2.69 g (16.4 mmol) of 2-thiochroman-1-one (2) in 350 ml of anhydrous ether was cooled to −70° under N_2 and treated with 11.0 ml of an ~1.6 *M* solution of vinyllithium in tetrahydrofuran. The resulting mixture was warmed, treated with 1.7 ml of glacial acetic acid, and worked up as for **3** to give 0.59 g (19%) of **4**: mp 58–60°; $\nu_{max}^{CCl_4}$ 3070, 3020, 2925, *1708*, *1675*, 1597, 1447, 1418, 1320, 1287, 1035, 915, 848 cm^{-1} (the carbonyl doublet in the ir is not due to ring opening to a vinyl ketone since the nmr is devoid of vinyl absorption; this doublet is either due to the presence of unaveraged conformers of **4** or to Fermi resonance of the true frequency of the C=O stretch, *e.g.*, with the first overtone of the weak 848-cm^{-1} band); nmr ($CDCl_3$) 7.3 (4 H, complex), 3.1 (4 H, A_2B_2), 2.9 (4 H, A_2B_2).

Anal. Calcd for $C_{11}H_{12}OS$: C, 68.71; H, 6.30; S, 16.68. Found: C, 68.68; H, 6.44; S, 16.72.

***o*-(2-Benzylmercaptoethyl) benzoic Acid (10).**—Sodium hydride (12.0 g of a 60% dispersion in Nujol, 0.3 mol) was washed free of Nujol with hexane by decantation under nitrogen. To the residue was added dropwise under nitrogen 37.2 g (0.300 mol) of benzyl mercaptan in 100 ml of dimethylformamide with magnetic stirring. Initial hydrogen evolution was exothermic and cooling was required to prevent foaming. The resulting mixture was treated with a solution of 18.0 g (0.12 mol) of isochroman-1-one (9)[6] in 100 ml of dimethylformamide, and the mixture was stirred and refluxed vigorously for 24 hr under N_2. The resulting dark mixture was poured on ice and 100 ml of 20% hydrochloric acid and extracted with ether. The combined ether extracts were washed with at least five portions of 10% aqueous potassium carbonate. (Extraction of the acid **10** was inefficient with aqueous sodium bicarbonate or carbonate and it was only slowly soluble in aqueous potassium carbonate.) Acidification of the carbonate washings with 20% hydrochloric acid at 0° gave 30 g (81%) of crude, crystalline, desired acid, mp 88–94°. Recrystallization from aqueous methanol and then twice from ether–hexane gave off-white prisms: mp 100–101°; $\nu_{max}^{CHCl_3}$ 3500–2500 (broad), 1680, 1601, 1570, 1485, 1445, 1390, 1295, 1123, 1067 cm^{-1}; nmr ($CDCl_3$) 11.0 (1 H, broad), 7.94 (1 H, q, J = 8, 2 Hz), 7.35–6.95 (8 H, complex), 3.50 (2 H, s), 2.8 (4 H, 8 lines, $\Delta\nu$ = 56 Hz).

Anal. Calcd for $C_{16}H_{16}O_2S$: C, 70.55; H, 5.92; S, 11.78. Found: C, 70.68; H, 5.88; S, 11.82.

2-Thiochroman-1-one (2).—To 25.0 g (0.092 mol) of powdered *o*-(2-benzylmercaptoethyl)benzoic acid (**10**) in round-bottomed flask fitted with a reflux condenser was added 30 ml of trifluoroacetic anhydride dropwise to moderate the very exothermic reaction. After standing 0.5 hr the resulting mixture was refluxed 0.5 hr, cooled, and poured on ice. The mixture was extracted with two equal volumes of ether and the dark ether layers were combined and washed with water and then 5% potassium carbonate solution until the washings were basic.

The ether layer was then dried over $MgSO_4$, filtered, and evaporated *in vacuo* giving 9.0 g of a dark orange oil which was distilled to give 5.0 g of a yellow oil, bp 104–110° (0.02 mm), which crystallized. Sublimation of this material gave yellow crystals, mp 59–61°. The yield of sublimed material, based on recovered acid **10** from the acidified aqueous layer, was 48%. Recrystallization of sublimed **2** from aqueous methanol gave white needles: mp 60–61.5°, after drying *in vacuo*; $\nu_{max}^{CCl_4}$ 3070, 3030, 2938, 2840, 1715 (weak), 1655, 1601, 1485, 1450, 1430, 1280, 1205, 1105, 945 (very strong), 880 (doublet) cm^{-1}; nmr ($CDCl_3$) 7.92 (1 H, q, J = 7, 2 Hz), 7.5–7.1 (3 H, complex), 3.23 (4 H, s, accidental equivalence).

Anal. Calcd for C_9H_8OS: C, 65.82; H, 4.91; S, 19.53. Found: C, 65.57; H, 4.85; S, 19.25.

Thianaphthen-2-one (8).—Benzothiophene (26.8 g, 0.200 mol) in 100 ml of anhydrous ether was metalated with 130 ml of commercial solution of 1.6 *M* *n*-butyllithium in hexane accord-

(2) M. Protiva, M. Rajsner, E. Adlerova, V. Seidlova, and Z. Vejdelek, *Coll. Czech. Chem. Commun.*, **29**, 2161 (1964).

(3) C. Marshalk, *J. Prakt. Chem.*, **88** [2], 237 (1913).

(4) A. B. Hornfeldt and S. Gronowitz, *Ark. Kemi*, **21**, 239 (1963).

(5) For a recent summary of preparations of this reagent and methods for standardization, see J. M. Mallan and R. L. Bebb, *Chem. Rev.*, **69**, 693 (1969).

(6) P. Maite, *Colloq. Int. Cent. Nat. Rech. Sci. (Paris)*, No. 64, 197 (1955); *Chem. Abstr.*, **55**, 10426.

ing to the procedure of Shirley and Cameron.[7] The resulting magnetically stirred solution of 2-lithiobenzothiophene was cooled in a Dry Ice–acetone bath and treated with 64.5 g (0.280 mol) of tributylborate giving a gelatinous precipitate. Hydrochloric acid (1 *N*, 200 ml) was added to the stirred mixture at 0°. After stirring 1 hr at 0–25°, the layers were separated and the aqueous phase extracted with ether. The combined ether layers were extracted with 200 ml of 1 *N* NaOH and the basic aqueous layer was backwashed with ether. Acidification of the aqueous layer with ice cold 3 *N* hydrochloric acid gave a pink-yellow odiferous precipitate of crude boronic acid which was collected and washed with water by suction. The crude boronic acid was dissolved in a small volume of ether and the stirred solution treated with 96 ml of 10% hydrogen peroxide containing 2 ml of saturated aqueous sodium carbonate. The resulting mixture was refluxed and stirred for 1 hr and then stirred overnight at room temperature. The layers were separated; the aqueous layer was extracted with ether. The combined ether extracts were washed with water until free of H_2O_2 by the ferrous ion test. The ether layer was then washed with saturated NaCl solution, dried over $MgSO_4$, filtered, and evaporated *in vacuo* giving 21.7 g (72%) of crystalline thianaphthen-2-one, mp 32–34°. Recrystallization from hot aqueous methanol by cooling to −20° gave pale yellow needles: mp 34–35° (lit. mp 33–34°, 44–45°[3,8]); $\nu_{max}^{CCl_4}$ No–OH absorption, 1723, 1595, 1460 (doublet), 1390, 1130, 1088, 1010 cm^{-1}; nmr ($CDCl_3$) 7.24 (4 H, m), 3.92 (2 H, s).

(7) D. A. Shirley and M. D. Cameron, *J. Amer. Chem. Soc.*, **72**, 2788 (1950).

Registry No.—**1**, 1194-57-6; **2**, 25606-96-6; **3**, 25606-97-7; **3** oxime, 25606-98-8; **4**, 25606-99-9; **8**, 496-31-1; **10**, 25607-01-6; vinyllithium, 917-57-7.

Acknowledgment.—This work was generously supported by the Department of Chemistry, St. Louis University. Support from the National Science Foundation Grant No. GP-8510 for the 100-MHz nmr spectrometer is gratefully acknowledged.

(8) Two crystalline forms "stout prisms," mp 44–45°, and "fine needles," mp 33–34°, of **8** have been isolated.[3] The lower melting form is reported to be the more stable. In our laboratory sublimation of the low melting form at 0.005 mm gave nearly colorless, stout prisms, mp 46–48°. Recrystallization from aqueous methanol gave either form, with the high melting form being the more frequent. Infrared spectra of both materials in CCl_4 were identical and consistent *only* with the ketotautomer **8**.

N,N-Dialkylamino-1,2,3-triazole-α-diazoamidine Tautomers from Substituted Benzenesulfonyl Azides and Ynamines

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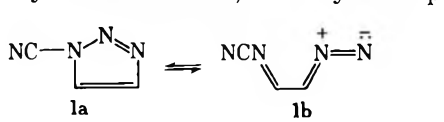
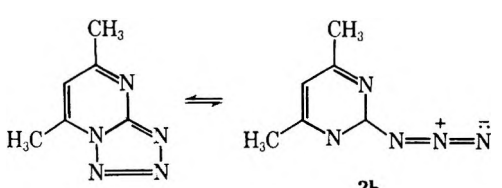
The 1,3 dipolar additions of a number of substituted benzenesulfonyl azides to *N,N*-diethylaminoprop-1-yne yielded 1,2,3-triazoles and α-diazoamidines which, in solution, were shown by nmr and ir spectroscopy to exist in a tautomeric equilibrium. The structure and stereochemistry of one of the products were proved by chemical degradation. The 1,3 dipolar additions of all the substituted benzenesulfonyl azides to *N,N*-dimethylaminophenylacetylene afforded only α-diazoamidines.

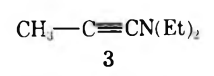
During the last few years, several interesting examples of ring–chain tautomerism involving a variety of functional groups have been reported.[1-3] For instance, in 1967, Hermes and Marsh[4] reported the existence of ring–chain equilibrium between 1-cyano-1,2,3-triazole (**1a**) and α-diazo-*N*-cyanoethylidenimine (**1b**). A similar type of equilibrium between 5,7-dimethyltetrazole[1,5-*a*]pyrimidine (**2a**) and 2-azido-4,6-dimethylpyramidine (**2b**) was also recently reported by Huisgen, *et al.*[5] From the reaction of substituted benzenesulfonyl azides and *N,N*-diethylaminoprop-1-yne (**3**), we have obtained strong evidence for the existence of a ring–chain equilibrium between *N,N*-diethylamino-1,2,3-triazole and α-diazoamidine functions. A number of 1,3 dipolar additions to ynamines have been reported to produce a series of five-membered heterocycles.[6-8] For example, the additions of both aryl and aroyl azides to *N,N*-dimethylaminophenylacetylene (**4**) gave only the corresponding 1,2,3-triazoles **5a** and **5b**, respectively. As an extension of this reaction, we studied the 1,3 dipolar additions of a number of substituted benzenesulfonyl azides (**6**) to ynamines **3** and **4**. The reactions were conducted by adding equimolar solutions of **6** to either **3** or **4** in tetrahydrofuran at 0 to −78°. Removal of the solvent by evaporation under reduced pressure afforded the corresponding crystalline *N,N*-dialkylamino-1,2,3-triazoles **7a–d**, and the diazoamidines **8e–f** and **9a–e**. The infrared (ir) spectra of compounds **8e–f** and **9a–e** in chloroform solutions or as KBr pellets showed strong peaks around 2060 cm^{-1},



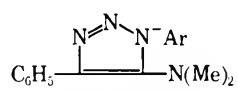
1a **1b**



2a **2b**



3 **4**



5a, Ar = C_6H_5
b, Ar = COC_6H_5

* To whom correspondence should be addressed.

(1) R. E. Harmon, J. L. Parsons, and S. K. Gupta, *J. Org. Chem.*, **34**, 2760 (1969), and other references mentioned in this paper.

(2) C. Temple, Jr., C. L. Kussner, and J. A. Montgomery, *ibid.*, **32**, 2241 (1967).

(3) M. Regitz and H. Schwall, *Justus Liebigs Ann. Chem.*, **728**, 99 (1969).

(4) M. E. Hermes and F. D. Marsh, *J. Amer. Chem. Soc.*, **89**, 4760 (1967).

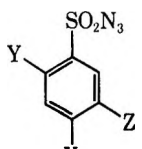
(5) R. Huisgen, K. V. Fraunberg, and H. J. Sturm, *Tetrahedron Lett.*, 2589 (1969).

(6) R. Huisgen, *Angew. Chem.*, **75**, 604 (1963); *Angew. Chem., Int. Ed. Engl.*, **2**, 565 (1963).

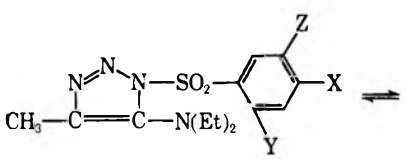
(7) R. Fuks., R. Buijle, and H. G. Viehe, *Angew. Chem.*, **78**, 594 (1966); *Angew. Chem., Int. Ed. Engl.*, **5**, 585 (1966).

(8) H. G. Viehe, "Chemistry of Acetylenes," Marcel Dekker, New York, N. Y., 1969, p 901.

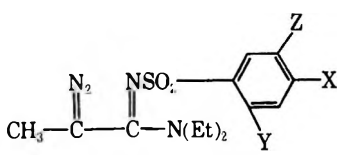
characteristic of the diazo group.[9] This suggested that compounds **8e–f** and **9a–e** existed mainly in one form as represented by the given structures. The ir spectra of compounds **7a–d** as KBr pellets showed the absence of diazoamidine form (no peaks around 2060 cm^{-1}). On the other hand, the ir spectra of chloroform solutions of the same compounds showed absorptions characteristic of the diazoamidine forms **8a–d**. Thus, the ir spectroscopy revealed the possibility of an equilibrium between **7a–d** and **8a–d**. However, this method was not very convenient to determine the equilibrium ratios of these



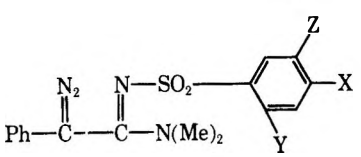
6



7a, X = Y = Z = H
b, X = OCH_3
c, X = CH_3
d, X = $NHCOCH_3$



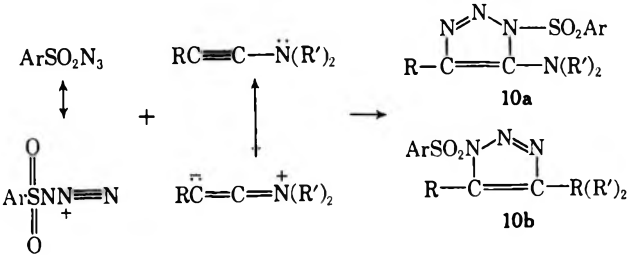
8a, X = Y = Z = H
b, X = OCH_3
c, X = CH_3
d, X = $NHCOCH_3$
e, X = NO_2
f, X = Y = Cl



9a, X = OCH_3
b, X = NO_2
c, X = Br
d, Z = NO_2
e, Y = Z = Cl

two forms. The nuclear magnetic resonance (nmr) spectra of compounds **9a–e** were consistent with the proposed structures and they did not indicate the possibility of ring–chain equilibrium. The nmr spectra of the products obtained by the addition of sulfonyl azides **6** to the ynamine **3** were quite interesting. They revealed the existence of a definite equilibrium between structures **7a–d** and **8a–d**. The nmr data of **7a–d** are given in Table I, **8e–f** and **9a–e** in Table II. The *N*-methylene protons in structures **7a–d** and **8a–d** showed sharp quartets with different chemical shifts. The quartets at δ 3.04–3.09 were attributed to the $N(CH_2CH_3)_2$ protons in structures **7a–d**, whereas the quartets at δ 3.34–3.37 were assigned to the $N(CH_2CH_3)_2$ protons in structures **8a–d**. In each nmr spectrum, the combined integration for these two quartets was, as expected, for four protons. The relative ratios of these two quartets were correlated to the equilibrium ratios of structure **7a–d** and **8a–d** in solution. The results (given in Table III) indicate that in the equilibrium solutions of these compounds, the cyclic form (**7a–d**) predominates. This was also consistent with the ir data for these compounds mentioned earlier.

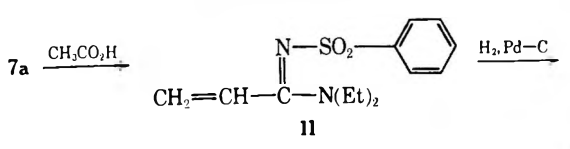
Structure Proof.—Theoretically, the addition of benzenesulfonyl azides to ynamines can occur in two ways, giving compounds of the type of **10a** and **10b**.



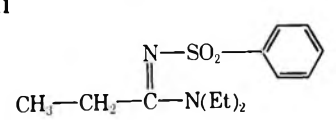
10a

10b

However, considering the most important resonance reference structures of the sulfonyl azides[10] and the ynamines,[8] the structure **10a** should be preferred over **10b**. This preferred mode of addition is also consistent with the known 1,3 cycloadditions to vinyl ethers and enamines.[11–13] In order to further substantiate the above theoretical considerations, a chemical structure proof of one of the reaction products was undertaken. Thus, 1-benzenesulfonyl-4-methyl-5-*N,N*-diethylamino-1,2,3-triazole (**7a**) was treated with glacial acetic acid to yield *N,N*-diethylamino-*N*-benzenesulfonylpropionamidine (**11**) in 70% yield. The structure of the amidine **11** was proved by elemental (C, H, N) analysis and spectroscopic (nmr and ir) data. Catalytic hydrogenation of **11** afforded *N,N*-diethylamino-*N*-benzenesulfonylpropionamidine (**12**) in almost quantitative yield. The structure of compound **12** was proved by elemental analysis, spectroscopic (nmr and ir) data and



11



12

an independent synthesis which was accomplished by the method of Pinner.[14] This involved treating propionitrile with equivalent amounts of absolute ethanol and hydrogen chloride gas at 0°. The resulting ethyl propionimidate hydrochloride **13** was treated with an excess of diethylamine to yield *N,N*-diethylaminopropionamidine hydrochloride (**14**). Treatment of **14**, as free base, with benzenesulfonyl chloride in the presence of sodium hydroxide afforded *N,N*-diethylamino-*N*-

(9) C. N. R. Rao, "Chemical Applications of Infrared Spectroscopy," Academic Press, New York, N. Y. 1963, p 269.

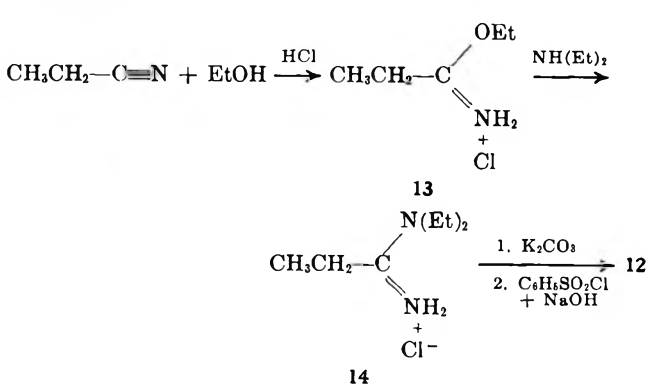
(10) G. L'Abbé, *Chem. Rev.*, **69**, 347 (1969).
(11) D. L. Rector and R. E. Harmon, *J. Org. Chem.*, **31**, 2837 (1966).
(12) G. Caronna and S. Palazzo, *Gazz. Chim. Ital.*, **82**, 292 (1952).
(13) J. E. Franz, M. W. Dietrich, A. Henshall, and C. Osuch, *J. Org. Chem.*, **31** 2847 (1966).
(14) E. G. Pinner, *Chem. Ber.*, **16**, 1654 (1883).

TABLE I

ANALYTICAL AND NMR DATA OF COMPOUNDS 7a–d

Compd	Mp, °C	Yield, %	Empirical formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Nmr data (δ)
7a	84–85	62	$C_{13}H_{18}N_4O_2S$	54.41	6.55	18.17	54.74	6.63	18.07	0.8 and 1.12 [two triplets, 6, J = 7 cps, $N(CH_2CH_3)_2$], 2.18 and 2.24 (two singlets, 3, J = 7 cps, CH_3), 3.09 (quartet, 2.7, J = 7 cps, N-CH_2 structure **7a**), 3.39 (quartet, 1.3, J = 7 cps, NCH_2 structure **8a**), 7.79 (multiplet, 5, ArH)
7b	54–56	58	$C_{14}H_{20}N_4O_3S$	51.85	6.17	17.60	51.91	6.13	17.45	0.87 and 1.17 [two triplets, 6, J = 7 cps, $N(CH_2CH_3)_2$], 2.24 and 2.3 (two singlets, 3, CH_3), 3.05 (quartet, 3.42, J = 7 cps, NCH_2 structure **7b**), 3.39 (quartet, 0.58, J = 7 cps, N-CH_2 structure **8b**), 4.1 (singlet, 3, OCH_3), 8.8 (multiplet 4, ArH)
7c	49–52	65	$C_{14}H_{20}N_4O_2S$	54.51	6.55	18.17	54.74	6.63	18.07	0.83 and 1.13 [two triplets, 6, J = 7 cps, $N(CH_2CH_3)_2$], 2.17 and 2.25 (two singlets, 3, J = 7 cps, CH_3), 3.04 (quartet, 3.2, J = 7 cps, N-CH_2 structure **7c**), 3.37 (quartet, 0.8, J = 7 cps, NCH_2 structure **8c**), 4.06 (singlet, 3, OCH_3), 7.5 (multiplet, 4, ArH)
7d	131–132	78	$C_{15}H_{21}N_5O_3S$	51.26	6.03	19.93	51.32	6.11	19.63	1.0 [mulitplet, 6, $N(CH_2CH_3)_2$], 2.25 (multiplet, 3, CH_3), 3.05 (quartet, 2.72, J = 7 cps, NCH_2 structure **7d**), 3.36 (quartet, 1.28, J = 7 cps, NCH_2 structure **8d**), 7.91 (multiplet, 4, ArH), 8.86–9.34 (multiplet, 1, NH)

benzenesulfonylpropionamidine (12) which was identical in all respects with the degradation product of the triazole **7a**.



Summary and Conclusion

The existence of ring–chain type of equilibrium between *N*,*N*-diethylamino-1,2,3-triazole and α-diazoamidines has been demonstrated. The mode of addition of benzenesulfonyl azides to ynamines has been proved by degradation methods.

Experimental Section

Melting points were taken on a Thomas–Hoover Unimelt apparatus and are uncorrected. A Beckman IR-8 spectrophotometer was used to determine the ir spectra. The nmr spectra were run using a Varian A-60 spectrometer using tetramethylsilane as internal standard. The elemental analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. The substituted benzenesulfonyl azides **6** were prepared by treating the appropriately substituted benzenesulfonyl chlorides with

TABLE II

ANALYTICAL AND NMR DATA OF COMPOUNDS 8e–f AND 9a–e

Compd	Mp,°C	Yield, %	Empirical formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N	Nmr data (δ)
8e	97–98	81	$C_{13}H_{17}N_5O_4S$	46.06	5.01	20.65	46.01	5.11	20.39	1.15 [multiplet, 6, $N(CH_2CH_3)_2$], 2.24 (singlet, 3, CH_3), 3.47 (quartet, 4, J = 7 cps, NCH_2–), 8.5 (multiplet, 4, ArH)
8f	87–88	62	$C_{13}H_{16}Cl_2N_4O_2S$	42.98	4.45	15.4	43.09	4.46	15.16	1.18 [multiplet, 6, $N(CH_2CH_3)_2$], 2.20 (singlet, 3, CH_3), 3.47 (quartet, 4, J = 7 cps, NCH_2–), 7.90 (multiplet, 3, ArH)
9a	95–96	79	$C_{17}H_{18}N_4O_3S$	56.96	5.06	8.95	56.89	5.01	8.63	3.0 [singlet, 6, $N(CH_3)_2$], 3.75 (singlet, 3, OCH_3), 6.6–7.8 (multiplet, 9, ArH)
9b	106–107	70	$C_{16}H_{15}N_5O_4S$	56.48	4.02	18.76	56.20	4.10	18.48	3.1 [singlet, 3, $N(CH_3)_2$], 6.7–8.1 (multiplet, 9 ArH)
9c	102–103	65	$C_{16}H_{15}BrN_4O_2S$	47.19	3.68	13.75	46.93	3.82	13.35	3.0 [singlet, 6, $N(CH_3)_2$], 6.7–7.8 (multiplet, 9, ArH)
9d	104–105	78	$C_{16}H_{15}N_5O_4S$	51.48	4.02	18.76	51.44	4.06	18.51	3.1 [singlet, 6, $N(CH_3)_2$], 6.7–8.2 (multiplet, 9, ArH)
9e	112–113	83	$C_{16}H_{14}Cl_2N_4O_2S$	48.38	3.52	14.10	48.09	3.83	13.98	3.1 [singlet, 6, $N(CH_3)_2$], 6.7–8.1 (multiplet, 8, ArH)

TABLE III

EQUILIBRIUM RATIOS OF COMPOUNDS 7a–d AND 8a–d IN $CDCl_3$ SOLUTION AS CALCULATED FROM THEIR NMR SPECTRA DETERMINED AT 40°[a]

Compd (%)	Compd (%)
7a (67)	**8a** (33)
7b (85)	**8b** (15)
7c (80)	**8c** (20)
7d (68)	**8d** (32)

[a] In crystalline form all these compounds exist only in the 1,2,3-triazole form **7a–d**. These equilibrium ratios were found to be independent of temperature.

sodium azide according to the method of Leffler and Tusno.[15] *N,N*-Diethylaminoprop-1-yne (**3**) was obtained from Fluka AG Chemische Fabrik, Switzerland, whereas *N,N*-dimethylaminophenylacetylene (**4**) was prepared by treating 1-chloro-2-phenylacetylene with trimethylamine according to the procedure of Fuks and Viehe.[16]

General Procedure for the Reaction of Benzenesulfonyl Azides 6 with the Ynamine 3.—A solution of the sulfonyl azide **6** (0.01 mole), in THF (10 ml) was added to a solution of the ynamine **3** (0.01 mol) in THF (5 ml) at −78° (cooled in Dry Ice–acetone bath) over a period of 1 hr. The solution was then allowed to warm to room temperature and filtered through anhydrous alumina, and the solvent was removed by evaporation under reduced pressure. The resulting solid (or oil) was crystallized from ether–petroleum ether (bp 30–60°) to afford the appropriate triazole (**7a–d**) or α-diazoamidine (**8e–f**).

General Procedure for the Reaction of Benzenesulfonyl Azides 6 with the Ynamine 4.—A solution of the azide **6** (1.4 mmol) in THF (10 ml) was added dropwise to a constantly stirred solution of the ynamine **4** (1.4 mmol) in THF (10 ml) at 0°. The reaction mixture was stirred at room temperature for about 1 hr and the solvent was removed under vacuum. The resulting brown-orange oil was crystallized from anhydrous ether to give the α-diazoamidines **9a–e**.

The melting points, yields, and elemental analyses of compounds **7a–d**, **8e–f**, and **9a–e** are recorded in Tables I and II.

Reaction of 7a with Acetic Acid.—When 1.5 g (0.00564 mol) of 1-benzenesulfonyl-4-methyl-5-*N,N*-diethylamino-1,2,3-triazole (**7a**) was treated with 5 ml of glacial acetic acid, the solution turned yellow, and it soon started to effervesce. After the yellow color had disappeared, the excess acetic acid was removed under pressure. The clear oil that remained was treated with an excess of saturated $NaHCO_3$ solution and extracted with two 10-ml portions of $CHCl_3$. The organic layer was dried (Na_2SO_4) and filtered, and the solvent was removed under reduced pressure to yield 1.09 g (73.5%) of a white solid which was recrystallized three times from ether to give an analytical sample of *N,N*-diethylamino-*N*-benzenesulfonylpropionamidine (**11**): mp 85.5–86.5; nmr ($CHCl_3$-*d*) δ 1.13 (t, 6, J = 7 cps, CH_3), 3.47 q, 4, J = 7 cps, CH_2), 5.30–6.89 (m, 3, vinyl hydrogens), 7.68 (m, 5, ArH).

Anal. Calcd for $C_{13}H_{18}N_2SO_2$: C, 58.61; H, 6.82; N, 10.52. Found: C, 58.39; H, 6.84; N, 10.47.

Hydrogenation of 11.—To a solution of 0.201 g (0.0075 mol) of **11** in 10 ml of ethyl acetate was added 0.2 g of 10% palladium on carbon. The solution was hydrogenated at atmospheric pressure and room temperature. The hydrogen uptake was 0.0076 mol and appeared to be complete at the end of 10 min. The solution was filtered and the solvent removed under reduced pressure to give a quantitative yield (0.203 g) of *N,N*-diethylamino-*N*-benzenesulfonylpropionamidine (**12**), mp 94–95°.

The analytical sample was obtained by three recrystallizations from ether: mp 95.5–96.5°; nmr ($CHCl_3$-*d*) δ 1.18 (m, 9, CH_3), 3.18 (m, 6, CH_2), 7.66 (m, 5, ArH).

Anal. Calcd for $C_{13}H_{20}N_2O_2S$: C, 58.23; H, 7.53; N, 10.45. Found: C, 58.22; N, 7.46; N, 10.22.

The Synthesis of *N,N*-Diethylamino-*N*-benzenesulfonylpropionamidine (12).—This compound was prepared according to the method of Pinner.[14] Equivalent amounts (0.1 mol) of absolute ethanol, propionitrile, and dry hydrogen chloride gas were allowed to react at 0°. After standing overnight, ethyl propionamidate hydrochloride (**13**) crystallized out from the solution. This was treated with an excess of diethylamine to give the *N,N*-diethylaminopropionamidine hydrochloride (**14**) which was then converted to the free amidine by treatment with 33%

(15) J. E. Leffler and Y. Tsuno, *J. Org. Chem.*, **28**, 902 (1963).

(16) R. Fuks and H. G. Viehe (private communication), *Chem. Ber.*, in press.

K_2CO_3 (aqueous). The amidine was then distilled, collecting the fraction between 179 and 181° (lit.[14] bp 181°).

To 1 g (0.0078 mol) of *N,N*-diethylaminopropionamidine was added 2.74 g (0.0156 mol) of benzenesulfonyl chloride and 10 ml of sodium hydroxide. The reaction mixture was heated on a steam bath for 5 min and extracted with chloroform. The chloroform layer was dried (Na_2SO_4) and evaporated to dryness under reduced pressure. The resulting white solid was recrystallized from ether three times to give the analytical sample of *N,N*-diethylamino-*N*-benzenesulfonylpropionamidine (**12**): mp 95.5–96.5°; nmr ($CHCl_3$-*d*) δ 1.18 (m, 9, CH_3), 3.18 (m, 6, CH_2), 7.66 (m, 5, ArH).

Anal. Calcd for $C_{13}H_{20}N_2O_2S$: C, 58.23; H, 7.53; N, 10.45. Found: C, 58.00; H, 7.51; N, 10.37.

Registry No.—**7a**, 25866-46-0; **7b**, 25866-47-1; **7c**, 25866-48-2; **7d**, 25907-88-4; **8e**, 25866-49-3; **8f**, 25907-89-5; **9a**, 25907-90-8; **9b**, 25907-91-9; **9c**, 25866-50-6; **9d**, 25957-51-1; **9e**, 25866-51-7; **11**, 25866-52-8; **12**, 25866-53-9.

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1,2,4-Triazoles. XXIV. Isomerization of *s*-Triazolo[4,3-*c*]quinazoline Derivatives[1]

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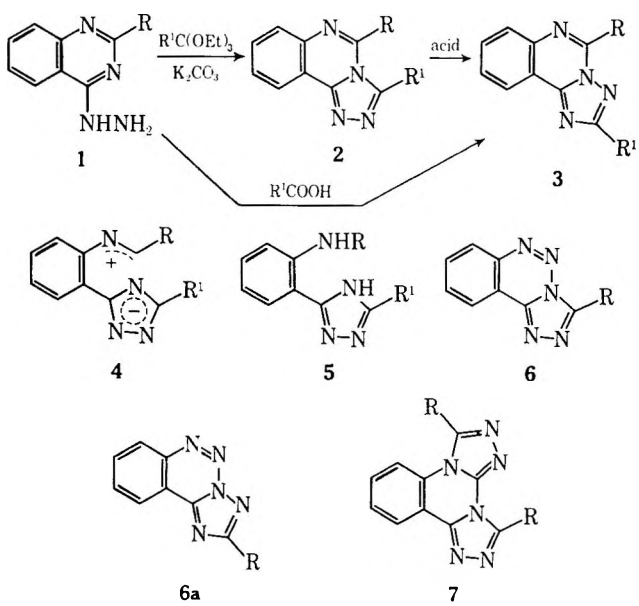
s-Triazolo[4,3-*c*]quinazolines, under the influence of acid or heat, underwent an extremely facile isomerization to *s*-triazolo[1,5-*c*]quinazolines. With alkali, ring opening occurred to 3-(2-aminophenyl)-*s*-triazoles which, with nitrous acid, gave the *s*-triazolo[4,3-*c*][1,2,3]benzotriazine system. Reduction of *s*-triazolo[1,5-*c*]quinazolines with sodium borohydride occurred at the 5,6 bond. Cyclization of 2,4-dihydrazinoquinazoline with ortho esters yielded bis-*s*-triazolo[4,3-*a*:4,3-*c*]quinazolines.

Isomerization in ring-fused *s*-triazoles induced by acid, base, or heat has been reported for several of these ring systems.[2] A particularly facile isomerization was observed with derivatives of the *s*-triazolo[4,3-*a*]-pyrimidine[3a] and *s*-triazolo[4,3-*c*]pyrimidine[3b] systems, and we now report an even more facile isomerization of the *s*-triazolo[4,3-*c*]quinazoline system to the *s*-triazolo[1,5-*c*]quinazoline system.

The synthesis of a fused *s*-triazole in which the 3,4 side of the *s*-triazole moiety is involved in the fusion is possible from a suitable 2-heterylhydrazine and carboxylic acids or ortho esters.[4] Thus, reaction of 4-quinazolylhydrazine (**1**, R = H) with aliphatic acids or ortho esters should give 3-substituted *s*-triazolo[4,3-*c*]quinazolines (**2**). We have now found that reaction of the hydrazine (**1**) with aliphatic acids always yielded the *s*-triazolo[1,5-*c*]quinazolines (**3**) by an extremely facile *in situ* rearrangement of the [4,3-*c*] system (**2**). This rearrangement could also be effected by gentle warming of the isomer **2** with carboxylic acids or by heating above the melting point.

It was possible to obtain the *s*-triazolo[4,3-*c*]quinazoline system (**2**) from the hydrazine and ortho esters as long as the reaction was carried out in the presence of potassium carbonate (Table I). Omission of the potassium carbonate always resulted in a mixture of the two isomers being formed, no doubt owing to traces of the appropriate acid (detected by glc) in the redistilled ortho esters. With triethyl orthopropionate, however, isomerization of the expected [4,3-*c*] system did not occur over a 16-hr reaction period, but the isomerization was essentially complete over a 48-hr period in the absence of potassium carbonate.



Substituents in the 2 position of the quinazoline nucleus exerted a predictable effect on the isomerization. 2-Methylquinazolin-4-ylhydrazine (**1**, R = CH_3) and ortho esters–potassium carbonate should yield 5-methyl-*s*-triazolo[4,3-*c*]quinazolines (**2**, R = CH_3), but in all cases isomerization occurred with such ease that only mixtures of the two isomers could be isolated. On the other hand, 2-phenylquinazolin-4-ylhydrazine (**1**, R = Ph) underwent ring closure with ortho esters–potassium carbonate to 5-phenyl-*s*-triazolo[4,3-*c*]quinazolines (**2**,

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(2) C. F. H. Allen, H. R. Beilfuss, D. M. Burness, G. A. Reynolds, J. F. Tinker, and J. A. VanAllan, *J. Org. Chem.*, **24**, 779, 787, 793, 796 (1959); C. F. H. Allen, G. A. Reynolds, J. F. Tinker, and L. A. Williams, *ibid.*, **25**, 361 (1960); K. Sirakawa, *J. Pharm. Soc. Jap.*, **78**, 1395 (1958); **79**, 903, 1487 (1959); **80**, 956, 1542 (1960); G. W. Miller and F. L. Rose, *J. Chem. Soc.*, 3357, 3369 (1965); K. T. Potts, H. R. Burton, and S. K. Roy, *J. Org. Chem.*, **31**, 265 (1966); K. T. Potts and S. W. Schneller, *J. Heterocycl. Chem.*, **5**, 485 (1968).

(3) (a) J. A. Bee and F. L. Rose, *J. Chem. Soc. C*, 2031 (1966); (b) G. W. Miller and F. L. Rose, *ibid.*, 5642 (1963).

(4) K. T. Potts, *Chem. Rev.*, **61**, 87 (1961).

Table I

R¹	R	Mp, °C	Yield, %	Nmr data,[b] chemical shift, τ (ppm) R¹	P.	Uv data, $\lambda_{max}^{CH_3OH}$, nm (log ε)	Mass spectral data,[c] M⁺
Some s-Triazolo[4,3-c]quinazolines (2)[a]							
H	H	213–214	80	0.5	0.6	240 (4.60)	170
CH_3	H	231–232	80	7.2	0.6	250 (4.66)	184
Et	H	187–188	90	6.8	0.6	240 (4.58)	198
H	Ph	205–206[d]	80	0.6	1.3–2.5	245 (4.7) 290 (4.2)	246
Et	Ph	168–169	70	6.7	1.3–2.5	245 (4.6) 290 (4.1)	274
Some s-Triazolo[1,5-c]quinazolines (3)							
H	H	109–110	75	1.4	0.6	240 (4.39)	170
CH_3	H	129–130	80	7.4	0.6	240 (4.79)	184
Et	H	86–87	65	7.2	0.6	240 (4.62)	198
H	Ph	184–185	87	1.4	1.3–2.5	245 (3.96)	246

[a] Satisfactory analytical values (±0.35 for C, H, and N) were reported for all compounds in this table: Ed. [b] Determined in $CDCl_3$. [c] Determined at 70 eV. [d] Lit.[5] mp 204–206°.

R = Ph; R¹ = H) without isomerization, thus substantiating an earlier claim[5] to the synthesis of **2** (R = Ph; R¹ = H). Isomerization of **2** (R = Ph) and its 3-alkyl derivatives to the corresponding isomeric system **3** was readily effected by extended reflux in acid solution.

These data indicate that in a reported synthesis[6] of 3-phenyl-s-triazolo[4,3-c]quinazoline (**2**, R = H; R¹ = Ph) by the cyclization of 4-benzhydrazidoquinazoline isomerization to the corresponding [1,5-c] system might have occurred. As the product isolated was stable to long reflux in acid solution, it appears that isomerization had actually occurred in the initial preparation and that the product should be regarded as 2-phenyl-s-triazolo-[1,5-c]quinazoline (**3**, R = H; R¹ = Ph).

The facility with which the above isomerizations occurred made it important to synthesize a representative s-triazolo[1,5-c]quinazoline derivative by an unambiguous route. Usual procedures for obtaining [1,5] fused s-triazole systems, such as dehydrogenation of suitable amidines or ring closure of 1,2-diaminopyridinium salts with acyl chlorides,[7] were precluded by the unavailability of the required precursors. However, a recent synthesis[8] of 2-amino-5-methyl-s-triazolo[1,5-c]quinazoline (**3**, R = CH_3; R¹ = NH_2), from aminoguanidine and 4-oxo-4H-3,1-benzoxazine provided a suitable route to the desired product. Deamination[9] of **3** (R = CH_3; R¹ = NH_2) with hypophosphorous acid gave a product identical with that obtained by ortho ester or acid ring-closure of 2-methylquinazolin-4-ylhydrazine (Table I). The spectral characteristics of the isomeric system (Table I) clearly differentiate between the respective structures. In particular, the high field chemical shifts of the 2 substituents in 2-substituted s-triazolo[1,5-c]quinazolines when compared with the chemical shifts of the corresponding 3 substituents in 3-substituted s-triazolo-[4,3-c]quinazolines readily enable assignments to the particular isomeric system to be made.

The above isomerization can be regarded as involving a covalent-type hydration of the 5,6 double bond of **2** followed by ring opening and subsequent ring closure at N-1 of the s-triazole nucleus. As the isomerization can also be effected by dry heat (more slowly), an alternative mechanistic hypothesis involving a zwitterionic intermediate such as **4**, may also be postulated.

This isomerization is essentially a variation of the Dimroth rearrangement and recent studies have shown[10] that in the quinazolines such isomerizations occur with extreme ease in the presence of alkali. Thus, the action of base on s-triazolo[4,3-c]quinazolines and also on s-triazolo[1,5-c]quinazolines was of particular interest.

Treatment of s-triazolo[4,3-c]quinazoline (**2**, R = R¹ = H) with hot aqueous sodium hydroxide gave 3-(2-aminophenyl)-s-triazole (**5**, R = R¹ = H) whose structure was confirmed by deamination to 3-phenyl-s-triazole. That the reaction involved an initial attack of hydroxide ion at the 6 position, rather than abstraction of the 6 proton which was observed in the conversion of s-triazolo[3,4-a]phthalazine into 3-(2-cyanophenyl)-s-triazole,[11] was established by the isolation of 3-(2-benzamidophenyl)-s-triazole (**5**, R = CO Ph; R¹ = H) by the action of hot base on 5-phenyl-s-triazolo-[4,3-c]quinazoline (**2**, R = Ph; R¹ = H). It appears that under these rearrangement conditions hydrolysis of the intermediate amide is faster than ring closure to the isomeric [1,5-c] system. The latter system also underwent analogous ring-opening reactions with a variety of substituents in the nucleus.

3-(2-Aminophenyl)-s-triazole (**5**, R = R¹ = H), on reaction with nitrous acid, gave s-triazolo[4,3-c]-[1,2,3]benzotriazine (**6**), a new heterocyclic ring system. The same product was also obtained from 4-(1,2,3)-benzotriazinylhydrazine and ethyl orthoformate. The available data does not exclude representation of this product as s-triazolo[1,5-c][1,2,3]benzotriazine (**6a**) which would be formed by ring closure of the intermediate diazo compound at N-1 of the s-triazole nucleus. If the latter structure were correct, it could only be formed from 1,2,3-benzotriazin-4-ylhydrazine by ring opening and rearrangement of the initial s-triazolo-[4,3-c][1,2,3]benzotriazine isomer (**6**). Though no isomerizations of ring-fused s-triazole systems reported to date have involved fission and re-formation of N–N

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(11) K. T. Potts and C. A. Lovelette, *Chem. Comm.*, 845 (1968); *J. Org. Chem.*, **34**, 3221 (1969).

bonds, it should be noted that solutions of condensed *v*-triazines have been found to be in equilibrium with the corresponding diazo isomer.[12] In **6** a similar situation can be readily envisaged, and the assignment of this structure can only be regarded as tentative at this stage. This internal diazonium cyclization reaction is a convenient route to heterocycles of this type and several examples of analogous ring systems have been described in the literature.[13]

The 5,6 double bond of 2-methyl-*s*-triazolo[1,5-*c*]quinazoline was found to be the site of reduction with sodium borohydride. The product, 5,6-dihydro-2-methyl-*s*-triazolo[1,5-*c*]quinazoline was readily identified from its nmr spectrum which showed methylene protons at τ 4.51 and an exchangeable NH proton at τ 4.25.

2,4-Dihydrazinoquinazoline (**1**, R = $NHNH_2$) is a suitable precursor for the synthesis of the bis-*s*-triazolo[4,3-*a*:4,3-*c*]quinazoline system (**7**). Ring closure readily occurred with ortho esters and this is the first example of a tetracyclic system derived from quinazoline. Though possibilities exist for isomerization during the reaction, only one product was obtained. Ready hydrolysis of **7** occurred with hot, dilute acid yielding 2,4-dihydrazinoquinazoline, thus confirming the assigned structure. Unlike the tricyclic systems **2** and **3**, the tetracyclic nucleus was stable to hot alkali.

Experimental Section[14]

The hydrazinoquinazolines were prepared by established procedures.[15] Minor variations in reaction work-up, especially the use of two-phase systems (water-chloroform at 0° for 3 hr) for the decomposition of the intermediate chloroquinazoline-phosphoryl chloride complexes, resulted in significant increases in overall yields.

Cyclization of 4-Quinazolinylhydrazines. A. With Ortho Esters–Potassium Carbonate.—The hydrazine (1.0 g), triethyl orthoformate (50 ml) and anhydrous potassium carbonate (0.5 g) were heated under reflux for 30 min. The product precipitated on cooling and, after recrystallization from ethanol, *s*-triazolo[4,3-*c*]quinazoline separated as fine, colorless needles: 0.6 g (64%); mp 213–214°; ir (KBr) 3050 (C–H), 1610 (C=N), 1525 (C=C) cm^{-1}.

The products prepared by this general procedure are described in Table I and their ir characteristics were consistent with those described above.

B. With Aliphatic Acids.—The hydrazine (1.0 g) was heated under reflux with formic acid (50 ml) for 30 min. After evaporation of excess acid, the residue crystallized from ethanol and *s*-triazolo[1,5-*c*]quinazoline was obtained as fine, colorless needles: 0.5 g (53%); mp 113–114°; ir (KBr) 3050 (C–H), 1610 (C=N), 1510 (C=C) cm^{-1}. Table I shows products prepared by this general procedure.

Isomerization of the *s*-Triazolo[4,3-*c*]quinazoline to the *s*-Triazolo[1,5-*c*]quinazoline System. A. By Acid.—The *s*-triazolo[4,3-*c*]quinazoline was refluxed in the corresponding aliphatic acid for 30 min. The acid was removed under reduced pressure and the product recrystallized from ethanol. The products were identical with those prepared by method B above.

B. By Heat.—The *s*-triazolo[4,3-*c*]quinazolines were heated above their melting points and, after cooling to room temperature, purified as above.

Ring Opening of *s*-Triazolo[4,3-*c*]quinazolines with Alkali.—*s*-Triazolo[4,3-*c*]quinazoline (or the [1,5-*c*] isomer) (1.0 g) and aqueous KOH (10%, 50 ml) were heated under reflux for 1 hr. After neutralization, the reaction mixture was extracted with ether, the ether extract dried (Na_2SO_4) and the residue left after evaporation of the ether recrystallized from benzene to give 3-(2-aminophenyl)-*s*-triazole as colorless needles: 0.45 g (50%); mp 144–145°; ir (KBr) 3400 (NH_2), 3100 (NH), 1610 (C=N), 1560 (C=C) cm^{-1}; $\lambda_{max}^{CH_3OH}$ 220 nm (log ϵ 3.51), 253 (3.10), 320 (2.75); nmr (CH_3CN) τ 4.0 (b, 2, NH_2), 3.40–2.20 (m, 4, aromatic), 1.78 (s, 1, H_5); mass spectrum, M^+, *m/e* (rel intensity) 164 (100).

Anal. Calcd for $C_8H_8N_4$: C, 59.97; H, 5.04; N, 34.97. Found: C, 60.28; H, 5.01; N, 34.73.

In a similar fashion, treatment of the appropriate *s*-triazolo-[4,3-*c*]- or -[1,5-*c*]quinazolines gave the following products.

3-(2-Aminophenyl)-5-methyl-*s*-triazole: colorless needles (85%); mp 153–154°; ir (KBr) 3400 (NH_2), 3150 (NH), 3050 (C–H), 1610 (C=N), 1570 (C=C) cm^{-1}; $\lambda_{max}^{CH_3OH}$ 219 nm (log ϵ 4.63), 250 (4.11), 318 (3.78); nmr (CH_3CN) τ 7.60 (s, 3, 5-CH_3), 4.05 (b, 2, NH_2), 3.5–2.3 (m, 4, aromatic); mass spectrum M^+, *m/e* (rel intensity) 124 (100).

Anal. Calcd for $C_9H_{10}N_4$: C, 61.96; H, 5.70; N, 32.05. Found: C, 62.03; H, 5.79; N, 32.06.

3-(2-Aminophenyl)-5-phenyl-*s*-triazole: colorless needles (90%); mp 189–190°; ir (KBr) 3370 (NH_2), 3100 (NH), 1610 (C=N), 1560 (C=C) cm^{-1}; $\lambda_{max}^{CH_3OH}$ 210 nm (log ϵ 4.73), 230 (4.80), 260 (4.50), 320 (3.94); nmr (CH_3CN) τ 2.3–2.0 (m, aromatic); mass spectrum, M^+, *m/e* (rel intensity) 235 (100).

Anal. Calcd for $C_{14}H_{12}N_4$: C, 71.17; H, 5.12; N, 23.71. Found: C, 71.29; H, 5.26; N, 23.75.

Treatment of 3-(2-Aminophenyl)-5-methyl-*s*-triazole with Nitrous Acid.—A mixture of sulfuric acid (20 ml, 8 *N*) and water (10 ml) at −10° was treated with sodium nitrite (0.57 g) added over 15 min followed by hypophosphorous acid (3 ml). Maintaining the temperature below −10°, 3-(2-aminophenyl)-5-methyl-*s*-triazole (2.0 g, 0.1 mol) was added in small portions with continuous stirring. After 2 hr at −10°, the reaction mixture was warmed at 60° for 2 hr and then neutralized with KOH solution. The 3-methyl-*s*-triazolo[4,3-*c*][1,2,3]benzotriazine that separated was recrystallized from benzene–petroleum ether (bp 60–80°) forming colorless needles: 1.4 g (75%); mp 163–164°; ir (KBr) 3075 (C–H), 1610 (C=N), 1580 (C=C) cm^{-1}; $\lambda_{max}^{CH_3OH}$ 248 nm (log ϵ 4.52), 290 (3.20); nmr ($CDCl_3$) τ 7.40 (s, 3, 3-CH_3), 2.2–1.3 (m, 4, aromatic); mass spectrum M^+, *m/e* (rel intensity) 185 (44).

Anal. Calcd for $C_9H_7N_5$: C, 58.37; H, 3.81; N, 37.82. Found: C, 58.17; H, 3.71; N, 38.11.

3-Phenyl-5-methyl-*s*-triazole was extracted with chloroform from the slightly basic reaction mixture and crystallized from benzene as colorless needles: mp 163–164° (lit.[16] mp 166°).

Similarly, ***s*-triazolo[4,3-*c*][1,2,3]benzotriazine** crystallized from benzene as colorless needles: yield 90%; mp 135–136°; ir (KBr) 3100 (C–H), 1620 (C=N), 1590 (C=C) cm^{-1}; $\lambda_{max}^{CH_3OH}$ 238 nm (log ϵ 4.81), 280 (4.00); nmr ($CDCl_3$) τ 2.2–1.3 (m, aromatic); mass spectrum M^-, *m/e* (rel intensity) 170 (45).

Anal. Calcd for $C_8H_5N_5$: C, 56.15; H, 2.92; N, 40.94. Found: C, 55.95; H, 2.79; N, 41.17.

Cyclization of 1,2,3-Benzotriazin-4-ylhydrazine with Ortho Esters.—The above hydrazine[17] (1.0 g) was refluxed in triethyl orthoformate (25 ml) with K_2CO_3 for 1 hr. The product precipitated upon cooling and was recrystallized from ethanol. The product was identical in every respect with that prepared above.

General Procedure for the Preparation of Bis-*s*-triazolo-[4,3-*a*:4,3-*c*]quinazolines.—2,4-Dihydrazinoquinazoline (2.0 g, 0.01 mol) and triethyl orthoformate (40 ml) were heated under reflux for 1 hr. The excess triethyl orthoformate was removed under reduced pressure and the residue was purified by sublimation *in vacuo* [180° (0.1 mm)]: 1.2 g (60%); mp 341–342°; ir (KBr) 3050 (C–H), 1600 (C=N), 1480 (C=C) cm^{-1}; $\lambda_{max}^{CH_3OH}$ 240 nm; mass spectrum M^+, *m/e* (rel intensity) 210 (100).

(12) C. Temple, Jr., C. L. Kussner, and J. A. Montgomery, *J. Org. Chem.*, **32**, 2241 (1967).

(13) I. E. Balaban and H. King, *J. Chem. Soc.*, **127**, 2801 (1925), T. N. Ghosh, *J. Indian Chem. Soc.*, **14**, 411 (1937); G. B. Bachman and F. M. Cowen, *J. Org. Chem.*, **13**, 89 (1948).

(14) Spectral characterization of products was carried out on the following instrumentation: ir, Perkin-Elmer Model 337 spectrophotometer; uv, Cary Model 14 spectrophotometer; nmr, Varian A-60 spectrometer using TMS as internal standard; mass spectra, Hitachi Perkin-Elmer RMU 6E mass spectrometer, using the direct inlet probe at ~150° and 70 eV. All evaporations were done under reduced pressure using a rotavap apparatus and mps were taken in capillaries. Microanalyses were by Galbraith Laboratories, Inc., Knoxville, Tenn., and Instranal Laboratories, Rensselaer, N. Y.

(15) M. Claesen and H. Vanderhaeghe, *Bull. Soc. Chim. Belg.*, **68**, 220 (1959).

(16) D. R. Liljegren and K. T. Potts, *J. Chem. Soc.*, 518 (1961).

(17) C. Grundmann, Jr. and H. Ulrich, *J. Org. Chem.*, **24**, 272 (1959).

Anal. Calcd for $C_{10}H_6N_6$: C, 57.13; H, 2.87; N, 39.98. Found: C, 56.93; H, 2.84; N, 39.85.

Similarly, **3,7-dimethylbis-*s*-triazolo[4,3-*a*:4,3-*c*]quinazoline** was purified by sublimation *in vacuo* [160° (0.1 mm)]: 1.9 g (80%); mp 315–316°; ir (KBr) 3125 (C–H), 1610 (C=N), 1525 (C=C) cm^{-1}; $\lambda_{max}^{CH_3OH}$ 240 nm; nmr ($CDCl_3$) τ 7.39 (s, 3, CH_3), 7.31 (s, 3, CH_3), 2.6–1.5 (m, 4, aromatic); mass spectrum M^+, *m/e* (rel intensity) 238 (100).

Anal. Calcd for $C_{12}H_{10}N_6$: C, 60.49; H, 4.23; N, 35.27. found: C, 60.25; H, 4.25; N, 35.24.

3,7-Diethylbis-*s*-triazolo[4,3-*a*:4,3-*c*]quinazoline was also purified by sublimation *in vacuo* [150° (0.1 mm)]: 1.7 g (65%); mp 258–259°; ir (KBr) 2980 (C–H), 1600 (C=N), 1580 (C=C) cm^{-1}; $\lambda_{max}^{CH_3OH}$ 240 nm; mass spectrum M^+, *m/e* (rel intensity) 266 (100).

Anal. Calcd for $C_{14}H_{14}N_6$: C, 63.14; H, 5.29; N, 31.56. Found: C, 63.22; H, 5.22; N, 31.74.

Reaction of Bis-*s*-triazolo[4,3-*a*:4,3-*c*]quinazoline with Dilute Acid.—Bis-*s*-triazolo[4,3-*a*:4,3-*c*]quinazoline (2.0 g, 0.008 mol) and 10% HCl (40 ml) were heated under reflux for 0.5 hr. The solvent was removed under reduced pressure. The residue crystallized from ethanol as fine, yellow needles. The product was identical in every respect with an authentic sample of 2,4-dihydrazinoquinazoline: 1.5 g (90%); mp 226–227° dec (lit.[15] mp 226–227° dec); ir 3450 (NH_2), 3050 (NH), 1650 (C=N), 1620 (NH), 1560 (C=C) cm^{-1}.

Sodium Borohydride Reduction of 2-Methyl-*s*-triazolo[1,5-*c*]quinazoline.—The quinazoline (1.0 g, 0.006 mol), methanol (50 ml), and excess sodium borohydride (1.6 g) were stirred at room temperature for 17 hr. The reaction mixture was evaporated to dryness under reduced pressure, and the crude residue was dissolved in water and the insoluble material filtered. The solution was then extracted with chloroform, dried (Na_2SO_4), and removed under reduced pressure. The crude product crystallized from benzene as fine, colorless needles: 0.6 g (60%); mp 150–151°; ir (KBr) 3200 (NH), 1640 (C=N), 1600 (NH), 1550 (C=C) cm^{-1}; $\lambda_{max}^{CH_3OH}$ 230 nm (log ϵ 3.19); nmr ($CDCl_3$) τ 7.58 (s, 3, 2-CH_3), 4.51 (s, 2, $-CH_2-$), 3.3–2.1 (m, 4, aromatic), 4.25 (b, 1, –NH); mass spectrum M^+, *m/e* (rel intensity) 186 (100).

Anal. Calcd for $C_{10}H_{10}N_4$: C, 64.50; H, 5.41; N, 30.09. Found: C, 64.28; H, 5.50; N, 29.87.

Registry No.—**2** (R^1 = H; R = H), 234-74-2; **2** (R^1 = Me; R = H), 25518-06-3; **2** (R^1 = Et; R = H), 25518-07-4; **2** (R^1 = H; R = Ph), 6506-59-8; **2** (R^1 = Et; R = Ph), 25518-09-6; **3** (R^1 = H; R = H), 234-74-2; **3** (R^1 = Me; R = H), 25518-11-0; **3** (R^1 = Et; R = H), 25518-12-1; **3** (R^1 = H; R = Ph), 25518-13-2; **5** (R^1 = R = H), 25518-14-3; **5** (R^1 = Me; R = H), 25568-69-8; **5** (R^1 = Ph; R = H), 25518-15-4; **6**, 25518-16-5; **6** (R = Me), 25518-17-6; **7**, 25518-18-7; **7** (R′ = R = Me), 25518-19-8; **7** (R^1 = R = Et), 25518-20-1; 5,6-dihydro-2-methyl-*s*-triazolo[1,5-*c*]quinazoline, 27111-63-3.

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Mesoionic Compounds. XI. Mesoionic Compounds of the 1,2,3-Triazole Series[1]

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Cyclization of ethyl N-methyl-N-arylazoaminoacetates with thionyl chloride gave anhydro-3-aryl-4-hydroxy-1-methyl-1,2,3-triazolium hydroxides. The corresponding N-methyl-N-arylazoaminoacetonitriles also underwent ready cyclization to anhydro-4-acetylimino-3-aryl-1-methyl-1,2,3-triazolium hydroxides with acetyl chloride, followed by treatment with base. Several cycloaddition reactions as well as chemical and spectral characteristics of this mesoionic system are described. In contrast to other mesoionic systems, protonation occurred readily at the exocyclic oxygen atom which was also the site of alkylation with triethyloxonium fluoroborate.

Since introduction of the original concept of mesoionic compounds,[2] comparatively few new systems have been described. As part of a general study of this interesting class of compounds, we have been investigating the synthesis of new types[3a] and now report our studies which have led to new mesoionic compounds of the 1,2,3-triazole series.[3b]

Cyclodehydration procedures have usually been used in the synthesis of mesoionic systems[4] and a variation of this approach was found to be effective in the 1,2,3-triazole system. Condensation of benzenediazonium chloride (**1**, R = Ph) with ethyl sarcosinate under carefully controlled conditions gave ethyl N-methyl-N-phenylazoaminoacetate (**2**, R = Ph) in 53% yield. Attempts to condense benzene–diazonium chloride with sarcosine itself under analogous conditions were unsuccessful, thus precluding the usual cyclodehydration of an appropriately substituted acid to the mesoionic system. Cyclization of the ester (**2**, R = Ph) with thionyl chloride–pyridine readily gave anhydro-4-hydroxy-3-phenyl-1-methyl-1,2,3-triazolium hydroxide (**4**, R = Ph) together with a small amount of a sulfur-containing product which has been identified as the sulfide (**6**). This sulfide was also obtained by the action of thionyl chloride–pyridine on the amide (**3**) as well as from the mesoionic system (**4**) and sulfur monochloride. Its structure was evident from analytical data which established the molecular formula as $C_{18}H_{16}N_6SO_2$ and from spectral data where the nmr spectrum was similar in all respects to that of **4** except that the 5-proton was absent. Use of *p*-toluenediazonium chloride in this reaction gave analogous products.

Analytical and spectral data clearly showed that ring closure to these mesoionic compounds had occurred. Particularly important in this respect were the ν_{CO} at 1650 cm^{-1} in the infrared spectra and a sharp singlet at

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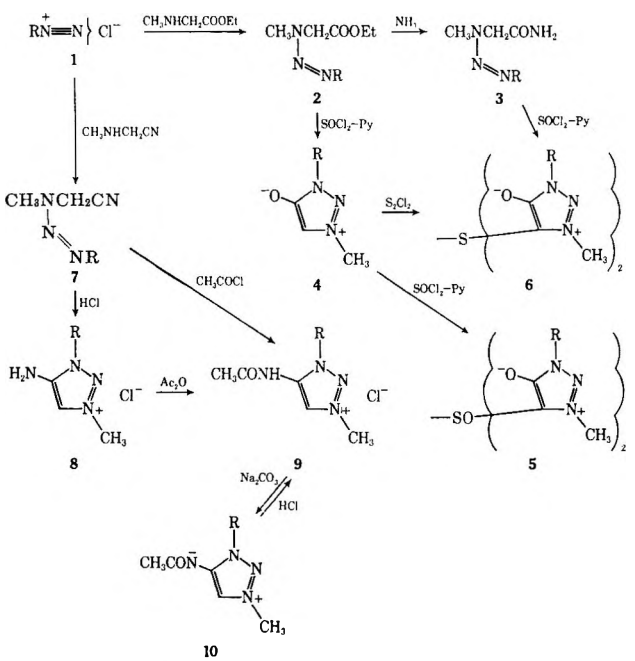
(2) F. L. Warren, *J. Chem. Soc.*, 1100 (1938); A. Schonberg, *ibid.*, 824 (1938); W. Baker and W. D. Ollis, *Quart. Rev. (London)*, **11**, 15 (1957).

(3) (a) *E.g.*, K. T. Potts and U. P. Singh, *Chem. Commun.*, 569 (1969); K. T. Potts, U. P. Singh, and E. Houghton, *ibid.*, 1128 (1969); K. T. Potts, E. Houghton, and U. P. Singh, *ibid.*, 1129 (1969); (b) anhydro-1,3-dimethyl-4-hydroxy-1,2,3-triazolium hydroxide has recently been obtained by methylation of 1-methyl-1,2,3-triazol-5-one [M. Begtrup and C. Pedersen, *Acta Chem. Scand.*, **20**, 1555 (1966); M. Begtrup and P. A. Kristensen, *ibid.*, **23**, 2733 (1969)].

(4) F. H. C. Stewart, *Chem. Rev.*, **64**, 129 (1964).

τ 3.34 attributable to the 5 proton in the nmr spectra, values consistent with those observed in other mesoionic systems.[3]

Condensation of benzenediazonium chloride with N-methylaminoacetonitrile gave N-methyl-N-phenylazoaminoacetonitrile (**7**, R = Ph). This nitrile, with dry hydrogen chloride, underwent cyclization to 4-amino-1-methyl-3-phenyl-1,2,3-triazolium chloride (**8**, R = Ph), a system analogous to the sydnone imines.[4] Like the latter, **8** could not be converted into the corresponding free base, but with acetic anhydride gave 4-acetamido-1-methyl-3-phenyl-1,2,3-triazolium chloride (**9**, R = Ph) which was also obtained directly from the nitrile (**7**) and acetyl chloride. Treatment of **9** with base gave the mesoionic compound anhydro-4-acetimino-1-methyl-3-phenyl-1,2,3-triazolium hydroxide (**10**, R = Ph) in which delocalization of the exocyclic negative charge over the acetimino group imparts stability to the system. An analogous series of products was obtained when *p*-toluenediazonium chloride was used in this reaction sequence. Analytical and spectral data established that ring closure of **7** to the salts **8** and **9** had occurred. In the infrared spectrum of **9**, the ν_{NH} at 3300–3200 cm^{-1} and ν_{CO} at 1650 cm^{-1} can be assigned to the exocyclic acetamido group and the disappearance of the –NH– absorption, together with a shift of ν_{CO} to 1600 cm^{-1}, provide excellent evidence for the assignment of structure **10** to the product obtained from **9** and base.



In contrast to other five-membered mesoionic systems with exocyclic oxygen atoms, anhydro-4-hydroxy-1-methyl-3-*p*-tolyl-1,2,3-triazolium hydroxide (**4**, R = *p*-$CH_3C_6H_4$) with dry hydrogen chloride in benzene protonates at the exocyclic oxygen atom giving 4-hydroxy-1-methyl-3-*p*-tolyl-1,2,3-triazolium chloride (**11**, R = *p*-$CH_3C_6H_4$). This conversion is quite apparent from the infrared spectra of the products, especially the disappearance of the ν_{CO} at 1650 cm^{-1} in **4** and the appearance of a very broad ν_{OH} at 2100 cm^{-1} in **11**. Similarly, a singlet at τ 2.02 in the nmr spectrum of **11** which exchanges with D_2O is indicative of an hydroxyl group, while the 5 proton in **11** occurs at τ 2.24 in contrast to τ 3.30 for the corresponding proton of **4**. In mesoionic compounds of the *s*-triazole series,[5] only those with an exocyclic sulfur atom are protonated under comparable conditions and it is only with six-membered mesoionic systems that protonation of the exocyclic oxygen has been observed.[6] On heating **11** *in vacuo* at 60°, it readily lost hydrogen chloride regenerating the mesoionic compound **4**, a behavior similar to that observed with the *s*-triazolium salts mentioned above.[5] No loss of methyl chloride occurred, as often has been observed on heating of heterocyclic quaternary salts,[7] and the regeneration of **4** would be expected to be assisted by its considerable resonance stabilization inherent in the mesoionic concept.[8] The elimination of hydrogen chloride also occurred with base and, indeed, the mesoionic compound itself is extremely stable to alkali, being recovered unchanged after refluxing with 10% sodium hydroxide solution for 24 hr. This ready salt formation and stability to alkali were extremely important in the procedure used for the isolation of the mesoionic compound (see below).

Attempts to methylate the exocyclic oxygen atom with methyl iodide were unsuccessful, results consistent with those reported for other five-membered mesoionic systems containing exocyclic oxygen atoms. However, reaction of **4** (R = *p*-$CH_3C_6H_4$) with triethyloxonium fluoroborate gave in good yield[9] 4-ethoxy-1-methyl-3-*p*-tolyl-1,2,3-triazolium fluoroborate (**12**, R = *p*-$CH_3C_6H_4$) which was quite stable and which was characterized as its picrate and iodide. This behavior is in direct contrast to that of anhydro-1,3-dimethyl-4-hydroxy-1,2,3-triazolium hydroxide[3b] which underwent ready reaction with methyl iodide.

Nmr data provided compelling evidence for structure **12**, with an ethyl group [τ 8.58 (t, 3, J = 7.0 Hz, $-CH_2-CH_3$; 5.49 (q, 2, J = 7.0 Hz, $-CH_2-CH_3$], an N–CH_3 group [τ 5.65 (s, 3)], a *p*-tolyl group [τ 7.58 (s, 3, C–CH_3), 2.53 (AB d, 2, J = 9.0 Hz); 2.30 (AB d, 2, J = 9.0 Hz], and a singlet proton at τ 1.28 (5-H). Both the N–CH_3 group and the 5 proton had undergone large downfield shifts (0.38 ppm and 2.02 ppm, respectively) owing to the conversion of the system into a 1,2,3-triazolium salt.

Hot hydrobromic acid on **12** regenerated the mesoionic system **4**, showing that no skeletal rearrangement had occurred. Surprisingly, heating **12** above its melting point did not regenerate the mesoionic system though this procedure has been effective in similar conversions.

As has been found with the sydnones,[4] bromination of **4** readily gave anhydro-5-bromo-4-hydroxy-1-methyl-3-*p*-tolyl-1,2,3-triazolium hydroxide (**14**, R = *p*-$CH_3C_6H_4$), obtained initially as the salt **13** (R = *p*-$CH_3C_6H_4$). Furthermore, reaction with thionyl chloride gave the sulfoxide (**5**).

Attempts to use polyaza mesoionic systems as 1,3 dipoles in cycloaddition reactions have been relatively

(5) K. T. Potts, S. K. Roy, and D. P. Jones, *J. Org. Chem.*, **32**, 2245 (1967); *J. Heterocycl. Chem.*, **2**, 105 (1965).

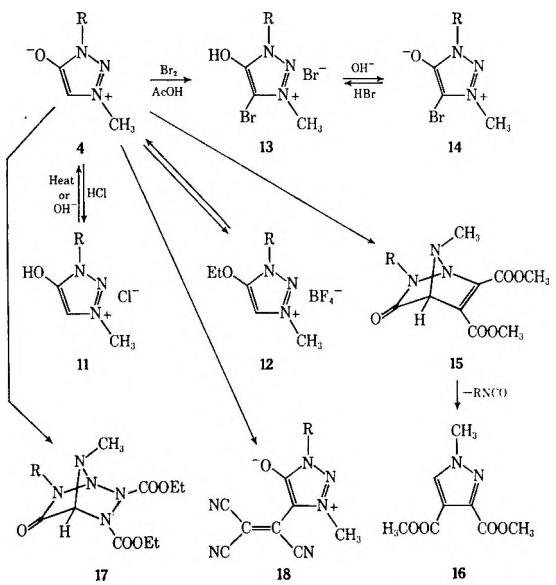
(6) S. A. Harris, T. J. Webb, and K. Folkers, *J. Amer. Chem. Soc.*, **62**, 3198 (1940); K. Mecklenborg and M. Orchin, *J. Org. Chem.*, **23**, 1591 (1958).

(7) *Heterocycl. Compounds*, **7**, 93 (1957).

(8) In the *s*-triazole series, 3,5-di(methylthio)-1,4-diphenyl-*s*-triazolium iodide, on treatment with pyridine, lost methyl iodide and gave the mesoionic anhydro-5-methylthio-3-mercapto-1,4-diphenyl-*s*-triazolium hydroxide (unpublished observations).

(9) D. E. Ames and B. Novitt, *J. Chem. Soc. C.*, 2355 (1969).

unsuccessful[10,11a] except in the case of the sydnones.[11] However, the 1,2,3-triazole system has now been found to undergo cycloaddition reactions with acetylenic and reactive olefinic-type dipolarophiles. Anhydro-4-hydroxy-1-methyl-3-*p*-tolyl-1,2,3-triazolium hydroxide (**4**, R = *p*-$CH_3C_6H_4$) on reflux with dimethyl acetylenedicarboxylate for 120 hr gave methyl 1-methylpyrazole-3,4-dicarboxylate (**16**), presumably *via* an intermediate such as **15**. The *p*-tolyl isocyanate eliminated during the reaction was identified as the corresponding urea. Reaction of the mesoionic compound **4** with ethyl azodicarboxylate in refluxing xylene for 1 hr gave a stable cycloadduct (**17**) from which *p*-tolyl isocyanate was not eliminated. This shows the importance of the double bond in the intermediate cycloadduct **15** in assisting aromatization. The structure of **17**, ethyl 7-methyl-



5-oxo-6-*p*-tolyl-1,2,3,6,7-pentaazabicyclo[2.2.1]heptane-2,3-dicarboxylate, was established from analytical and spectral data. The molecular formula $C_{16}H_{21}N_5O_5$ has to accommodate three carbonyl groups [ν_{CO} 1725 (b), 1670 cm^{-1}] two of which are present as nonequivalent ethyl ester groups from the nmr data [τ 8.83 (t, 3, J = 7.0 Hz), 8.77 (t, 3, J = 7.0 Hz), 5.91 (q, 2, J = 7.0 Hz), 5.76 (q, 2, J = 7.0 Hz)], a *p*-tolyl group [τ 7.63 (s, 3, C–CH_3), 2.76 (AB d, 2, J = 8.5 Hz) and 2.05 (AB d, 2, J = 8.5 Hz)], and an N–CH_3 group [τ 5.85 (s, 3)], together with a single aromatic-type proton (τ 0.18) which exchanged with D_2O under neutral conditions over a period of $\sim$ 72 hr. This bridgehead proton was broadened, probably by coupling with the bridge N–CH_3 group, a similar effect having been observed in the 1:1 cycloadduct of dimethylacetylene dicarboxylate and anhydro-4-hydroxy-2-methylcinnolinium hydroxide.[9] The above structural elements indicated by the nmr data are those present in the original reactants and are consistent with the formation of a 1:1 adduct.

Tetracyanoethylene underwent a ready reaction with the mesoionic compound. The dark red product obtained was found to have a molecular formula of $C_{15}H_{10}N_6O$ and, besides a strong –CN absorption at 2225 cm^{-1}, a strong carbonyl absorption at 1680 cm^{-1} was present in the infrared spectrum. Nmr data indicated the absence of the 5 proton of the original mesoionic compound and the structure of the product appears to be best represented as anhydro-4-hydroxy-1-methyl-3-*p*-tolyl-5-(1,2,2-tricyanoethyl)-1,2,3-triazolium hydroxide (**18**, R = *p*-$CH_3C_6H_4$). It is most likely that steric factors prevent cyclization in the 1,3-dipolar sense and that an "ene" type reaction product[12] that can readily lose hydrogen cyanide during the reaction to give **18** is formed. A similar type of product has also been observed in the reaction of andydro-5-hydroxy-3-methyl-2-phenylthiazolium hydroxide with tetracyanoethylene.[13]

Experimental Section[14]

Ethyl N-Methyl-N-phenylazoaminoacetate (**2**, **R** = **Ph**).—Aniline (9.3 g, 0.1 mol), dissolved in concentrated hydrochloric acid (20 ml) and water (20 ml) at −10°, was treated with a solution of sodium nitrite (7.2 g) in water (50 ml). After diazotization was complete, sodium acetate (20 g) in water (100 ml) was added, followed by the addition with stirring of ethyl sarcosinate hydrochloride (15.0 g, 0.1 mol) in water (50 ml) keeping the temperature below 0°. After 1 additional hr the yellow oil which separated was extracted with ether, the ether extract was washed twice with 10% sodium carbonate solution (10 ml each) and dried (Na_2SO_4). After removal of the ether, the residual oil was distilled under reduced pressure resulting in a pale yellow mobile oil: 12.0 g (53%); bp 122–123° (0.5 mm); ir (liq film) 3000, 2950, 2900 (m) (CH), 1750 (s) (CO), 1600 (w) (N=N) cm^{-1}; uv max (CH_3OH) 308 sh nm (log ϵ 4.07), 283 (4.12), 224(3.95), 218 sh (3.92); nmr ($CDCl_3$) τ 8.74 (t, 3, J = 7.5 Hz, CH_3 of ethyl), 6.58 (s, 3, N—CH_3), 5.78 (qt, 2, J = 7.5 Hz, –CH_2 of ethyl), 5.55 (s, 2, –N—CH_2), 2.62 (m, 5, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 221 (8), 105 (43), 78 (16), 77 (100), 51 (12), 44 (23), 43 (21).

Anal. Calcd for $C_{11}H_{15}N_3O_2$: C, 59.73; H, 6.78; N, 19.00. Found: C, 59.60; H, 6.95; N, 19.15.

Similarly, **ethyl N-methyl-N-*p*-tolylazoaminoacetate** (**2**, R = *p*-$CH_3C_6H_4$) was obtained from *p*-toluenediazonium chloride in 85% yield as a pale yellow oil: bp 126° (0.5 mm), solidifing on cooling and crystallizing from petroleum ether as colorless, irregular prisms: mp 31–32°; ir (liq film) 2990, 2925 (m) (CH), 1750 (s) (CO), 1590 (w) (N=N) cm^{-1}.; uv max (CH_3OH) 313 nm (log ϵ 4.10), 285 (4.14), 227 (3.96), 222 sh (3.93); nmr ($CDCl_3$) τ 8.71 (t, 3, J = 7.5 Hz, CH_3 of ethyl), 7.65 (s, 3, C—CH_3), 6.6 (s, 3, N—CH_3), 5.78 (qt, 2, J = 7.5 Hz, CH_2 of ethyl), 5.56 (s, 2, –N—CH_2), 2.86 (AB d, 2, J = 9.0 Hz, aromatic), 2.64 (AB d, 2, J = 9.0 Hz, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 235 (8), 120 (13), 119 (22), 92 (11), 91 (100), 65 (16), 44 (19), 43 (9), 42 (44).

Anal. Calcd for $C_{12}H_{17}N_3O_2$: C, 61.28; H, 7.25; N, 17.86. Found: C, 61.39; H, 7.37; N, 17.70.

N-Methyl-N-phenylazoaminoacetamide (**3**, **R** = **Ph**).—The ester (**2**; R = Ph) (2.0 g) was stirred overnight with concentrated ammonium hydroxide (50 ml). The colorless product which had separated was recrystallized from benzene forming colorless plates: 1.2 g (70%); mp 132–133°; ir (KBr) 3325, 3175 (s) (NH_2), 2960, 2910 (m) (CH), 1650 (s) (CO), 1590 (w) (N=N) cm^{-1}; uv max (CH_3OH) 304 nm (log ϵ 4.09), 284 (4.12), 224 (3.94), 218 sh (3.92); mass spectrum (70 eV) *m/e* (rel intensity) 192 (9), 106 (4), 105 (46), 78 (9), 77 (100), 51 (13), 50 (3), 44 (15), 43 (6).

(10) K. T. Potts and D. N. Roy, *Chem. Commun.*, 1061 (1968); unpublished observations.

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(13) Unpublished observations.

(14) Spectral characterization of products was carried out on the following instrumentation: ir, Perkin-Elmer Model 337 spectrophotometer; uv, Cary Model 14 spectrophotometer; nmr, Varian A-60 spectrometer using TMS as internal standard; mass spectra, Hitachi Perkin-Elmer RMU 6E spectrometer, using the direct inlet probe at ~150°. All evaporations were done under reduced pressure using a Rotavap apparatus and melting points were taken in capillaries. Microanalyses were by Galbraith Laboratories Inc., Knoxville, Tenn., and Instranal Laboratories, Rensselaer, N. Y.

Anal. Calcd for $C_9H_{12}N_4O$: C, 56.25; H, 6.25; N, 29.16. Found: C, 56.31; H, 6.32; N, 29.02.

Similarly, **N-methyl-N-p-tolylazoaminoacetamide** (**3**, R = p-$CH_3C_6H_4$) crystallized from benzene as colorless needles: 1.5 g (76%); mp 143–144°; uv max (CH_3OH) 313 nm (log ϵ 4.11), 287 (4.15), 227 (3.95), 222 sh (3.94); mass spectrum (70 eV) m/e (rel intensity) 206 (11), 120 (4), 119 (32), 92 (10), 91 (100), 65 (18), 44 (8).

Anal. Calcd for $C_{10}H_{14}N_4O$: C, 58.23; H, 6.84; N, 27.17. Found: C, 58.05; H, 6.71; N, 27.27.

N-Methyl-N-phenylazoaminoacetonitrile (**7**, **R = Ph**).—Aniline (9.3 g, 0.1 mol), dissolved in concentrated hydrochloric acid (20 ml) and water (20 ml), was cooled to −10° and a solution of sodium nitrite (7.2 g) in water (50 ml) was added dropwise with stirring. After the addition was completed, cooling and stirring were continued for 1 hr, and a solution of sodium acetate (20 g) in water (100 ml) added bringing the pH to 7. N-Methylaminoacetonitrile hydrochloride (10.6 g, 0.1 mol) in water (20 ml) was added; cooling and stirring were continued for 1 additional hr during which solid separated. The reaction mixture was extracted with ether; the ether extract was washed with 10% sodium carbonate solution (twice, 10 ml each) and dried (Na_2SO_4). The residue on removal of the ether was recrystallized from benzene–petroleum ether (bp 60–80°) affording colorless needles of the nitrile: 6.0 g (35%); mp 31–33°; ir (KBr) 3060, 2975, 2950 (m) (CH), 2250 (m) (CN), 1600 (m) (N=N) cm^{-1}; uv max (CH_3OH) 283 nm (log ϵ 4.15), 224 (4.01), 218 sh (3.97); nmr ($CDCl_3$) τ 6.69 (s, 3, N—CH_3), 5.51 (s, 2, –N—CH_2), 2.62 (m, 5, aromatic); mass spectrum (70 eV) m/e (rel intensity) 174 (12), 105 (28), 78 (18), 77 (100), 51 (17), 42 (12).

Anal. Calcd for $C_9H_{10}N_4$: C, 61.87; H, 5.74; N, 32.19. Found: C, 62.05; H, 5.73; N, 31.92.

In a similar fashion **N-methyl-N-p-tolylazoaminoacetonitrile** (**7**, **R** = p-$CH_3C_6H_4$) was obtained from p-toluenediazonium chloride in 35% yield. It crystallized from benzene–petroleum ether as colorless needles: mp 56–57°; ir (KBr) 3020, 2910 (m) (CH), 2250 (w) (CN), 1590 (m) (N=N) cm^{-1}; uv max (CH_3OH) 284 nm (log ϵ 4.14), 227 (4.01), 222 (4.00); nmr ($CDCl_3$) τ 7.66 (s, 3, C—CH_3), 6.66 (s, 3, N—CH_3), 5.50 (s, 2, N—CH_2), 2.8 (AB d, 2, J = 9.0 Hz, aromatic), 2.59 (AB d, 2, J = 9.0 Hz, aromatic); mass spectrum (70 eV) m/e (rel intensity) 188 (11), 119 (24), 91 (100), 77 (5), 65 (20), 42 (8).

Anal. Calcd for $C_{10}H_{12}N_4$: C, 63.83; H, 6.38; N, 29.79. Found: C, 63.96; H, 6.50; N, 29.92.

Anhydro-4-hydroxy-1-methyl-3-phenyl-1,2,3-triazolium Hydroxide (**4**, **R = Ph**).—Ethyl N-methyl-N-phenylazoaminoacetate (**2**, R = Ph) (2.0 g) in pyridine (3 ml) at 5° was treated dropwise with redistilled thionyl chloride (1.3 g) with stirring. After 10 hr at room temperature the reaction mixture was poured into ice water and extracted with chloroform. The chloroform was distilled and the residue triturated with small portions of acetone whence the product solidified. It crystallized from benzene as colorless plates of the sulfide **6** (R = Ph): 30 mg; mp 236–237°; ir (KBr) 3075–2990 (w) (CH), 1675 (s) (sh), 1650 (s) (CO), 1585 (m) (N=N) cm^{-1}; uv max (CH_3OH) 303 nm (log ϵ 4.15), 228 (4.32); nmr ($CDCl_3$) τ 5.62 (s, 3, N—CH_3), 2.58–2.08 (m, 5, aromatic); mass spectrum (70 eV) m/e (rel intensity) 380 (48), 218 (11), 206 (18), 188 (44), 105 (28), 78 (26), 77 (100).

Anal. Calcd for $C_{18}H_{16}N_6O_2S$: C, 56.74; H, 4.21; N, 22.10; S, 8.42. Found: C, 56.67; H, 4.12; N, 22.11; S, 8.69.

The above aqueous phase was concentrated on a rotatory evaporator, basified with ammonium hydroxide, and extracted with chloroform. After removal of the chloroform the residue was dissolved in benzene and chromatographed on neutral alumina. The colorless crystalline product obtained on elution with chloroform crystallized from benzene giving the mesoionic compound **4** (R = Ph) as colorless needles: 150 mg; mp 94–96°; ir (KBr) 3425 (m) (OH), 3150 (m) (CH), 1650 (s) (CO), 1590 (m) (N=N) cm^{-1}; uv max (CH_3OH) 298 nm (log ϵ 3.82), 237 (3.62), 203 (3.88); nmr ($CDCl_3$) τ 6.08 (s, 3, N—CH_3), 3.34 (s, 1, 5-H), 2.6–2.05 (m, 5, aromatic); mass spectrum (70 eV) m/e (rel intensity) 175 (100), 105 (32), 78 (14), 77 (62), 51 (38).

Anal. Calcd for $C_9H_9N_3O \cdot 0.5\ H_2O$: C, 58.69; H, 5.43; N, 22.82. Found: C, 58.84; H, 5.41; N, 22.81.

Similarly, **anhydro-4-hydroxy-1-methyl-3-p-tolyl-1,2,3-triazolium hydroxide** (**4**, **R** = p-$CH_3C_6H_4$) crystallized from benzene–petroleum ether as colorless needles: 400 mg (28%); mp 141–143°; ir (KBr) 3080 (m) (CH), 1660 (s) (CO), 1520 (m) (N=N) cm^{-1}; uv max (CH_3OH) 298 nm (log ϵ 3.98), 241 (3.90); nmr ($CDCl_3$) τ 7.62, (s, 3, C—CH_3), 6.03 (s, 3, N—CH_3), 3.3 (s, 1, 5-H), 2.72 (AB d, 2, J = 8.5 Hz, aromatic), 2.1 (AB d, 2, J = 8.5 Hz, aromatic); mass spectrum (70 eV) m/e (rel intensity), 189 (70), 119 (9), 91 (100), 65 (23), 42 (33).

Anal. Calcd for $C_{10}H_{11}N_3O$: C, 63.48; H, 5.86; N, 22.21. Found: C, 63.61; H, 5.91; N, 22.07.

Associated with this mesoionic compound was the sulfide **6** (R = p-$CH_3C_6H_4$) which crystallized from benzene as colorless needles: mp 268°; ir (KBr) 3040–2920 (w) (CH), 1650 (s) (CO), 1505 (m) (N=N) cm^{-1}; uv max (CH_3OH) 322 nm (log ϵ 4.28), 215 (4.33); nmr ($CDCl_3$) τ 7.73 (s, 3, C—CH_3), 5.7 (s, 3, N—CH_3), 3.07 (AB d, 2, J = 9.0 Hz aromatic), 2.33 (AB d, 2, J = 9.0 Hz, aromatic); mass spectrum (70 eV) m/e (rel intensity) 408 (8), 232 (6), 220 (9), 202 (17), 119 (13), 91 (100), 65 (21).

Anal. Calcd for $C_{20}H_{20}N_6O_2S$: C, 58.80; H, 4.94; N, 20.58; S, 7.84. Found: C, 59.18; H, 4.70; N, 20.37; S, 7.40.

Reaction of Thionyl Chloride with N-Methyl-N-p-tolylazoaminoacetamide (**3**, **R** = p-$CH_3C_6H_4$).—The above amide (2.0 g) in pyridine (2 g) at ~0° was treated with thionyl chloride (1.1 g). After several hours the reaction mixture was poured into water and the yellow solid which separated recrystallized from benzene. It formed colorless needles of the sulfide **6** (R = p-$CH_3C_6H_4$): 40 mg, mp 267–268°. The mixture melting point with the sulfide **6** (R = p-$CH_3C_6H_4$) prepared above was not depressed and the two products had identical infrared spectra. Reaction of the mesoionic compound (**4**) with sulfur monochloride in methylene chloride gave the same product.

Reaction of Thionyl Chloride with Anhydro-4-hydroxy-1-methyl-3-p-tolyl-1,2,3-triazolium Hydroxide (**4**, **R** = p-$CH_3C_6H_4$).—The mesoionic compound (200 mg) in pyridine (2 ml) at 5° was treated with thionyl chloride (150 mg). A colorless product separated within 20 min and stirring was continued for 2 hr at room temperature. The reaction mixture was poured into water and the solid which separated recrystallized from chloroform–petroleum ether, forming colorless, irregular prisms of the sulfoxide **5** (R = p-$CH_3C_6H_4$): mp 250–255° dec; ir (KBr) 3050 (w) (CH), 1655 (s) (CO), 1510 (m) (N=N) cm^{-1}; uv max (CH_3OH) 327 nm (log ϵ 4.20), 217 (4.31), 203 (4.35); nmr ($CDCl_3$) τ 7.65 (s, 3, C—CH_3), 5.58 (s, 3, N—CH_3), 2.76 (AB d, 2, J = 9.0 Hz, aromatic), 2.2 (AB d, 2, J = 9.0 Hz, aromatic); mass spectrum (70 eV) m/e (rel intensity) 408 (9), 232 (3), 220 (38), 202 (15), 119 (28), 92 (16), 91 (100), 65 (30), 43 (46), 41 (28), 39 (30).

Anal. Calcd for $C_{20}H_{20}N_6O_3S$: C, 55.60; H, 4.75; N, 19.80. Found: C, 56.07; H, 4.54; N, 19.34.

4-Hydroxy-1-methyl-3-p-tolyl-1,2,3-triazolium Chloride (**11**, **R** = p-$CH_3C_6H_4$).—A solution of the mesoionic compound **4** (R = p-$CH_3C_6H_4$) (1.0 g) in benzene (20 ml) was saturated with dry hydrogen chloride at about 0°. The product which separated was recrystallized from ethanol–ether, forming colorless, irregular prisms: 1.1 g (100%); mp 195–198°; ir (KBr) 3080 (m) (CH), 2100 (broad, m) (OH), 1600 (s) (N=N), 1575 (s) (C=C) cm^{-1}; nmr (DMSO-d_6) τ 7.62 (s, 3, C—CH_3), 5.85 (s, 3, N—CH_3), 2.63 (AB d, 2, J = 8.0 Hz, aromatic), 2.27 (AB d, 2, J = 8.0 Hz, aromatic), 2.24 (s, 1, 5-H), 2.02 (s, 1, 4-OH, exchanged with D_2O).

Anal. Calcd for $C_{11}H_{12}ClN_3O$: C, 53.21; H, 5.32; N, 18.62. Found: C, 53.40; H, 5.36; N, 18.87.

When the above chloride was heated *in vacuo* for 6 hr, or passed through a column of neutral alumina and the product eluted with methanol, the mesoionic compound **4** (R = p-$CH_3C_6H_4$) was obtained.

4-Ethoxy-1-methyl-3-p-tolyl-1,2,3-triazolium Fluoroborate (**12**, **R** = p-$CH_3C_6H_4$).—The mesoionic compound **4** (R = p-$CH_3C_6H_4$) (1.0 g) in dichloromethane (10 ml) and triethyloxonium fluoroborate[15] (1.0 g) in dichloromethane (20 ml) were kept overnight at room temperature and the reaction mixture then diluted with dry ether (200 ml). The colorless product which separated on cooling crystallized from absolute ethanol–ether as colorless rhombs: 1.5 g (95%); mp 81–83°; ir (KBr) 3150, 3000 (m) (CH), 1620 (s) (N=N), 1060 (broad, s) (COC) cm^{-1}; uv max (CH_3OH) 252 nm (log ϵ 4.00).

Anal. Calcd for $C_{12}H_{16}BF_4N_3O$: C, 47.21; H, 5.24; N, 13.77. Found: C, 47.07; H, 5.27; N, 13.67.

The picrate, prepared in ethanol, crystallized from ethanol as yellow needles, mp 165°.

Anal. Calcd for $C_{18}H_{19}N_6O_8$: C, 48.31; H, 4.28; N, 18.78. Found: C, 48.29; H, 4.13; N, 18.83.

(15) H. Meerwein, *Org. Syn.*, **46**, 113 (1966).

When the above fluoroborate (400 mg) was refluxed with HBr (15 ml of 48%) for 2 hr, the red reaction mixture basified with 10% sodium hydroxide solution and the alkaline solution extracted with chloroform, the product obtained was shown to be anhydro-4-hydroxy-1-methyl-3-*p*-tolyl-1,2,3-triazolium hydroxide.

Anhydro-5-bromo-4-hydroxy-1-methyl-3-*p*-tolyl-1,2,3-triazolium Hydroxide (14, R = *p*-$CH_3C_6H_4$).—The mesoionic compound 4 (R = *p*-$CH_3C_6H_4$) (100 mg) in acetic acid (5 ml) was cooled and bromine (200 mg) in acetic acid (2 ml) added dropwise with stirring. After 2 hr at room temperature the excess acid was removed on a rotatory evaporator, water and a solution of sodium carbonate added, and the solution extracted with chloroform. The residue left after removal of the chloroform was dissolved in benzene, chromatographed on neutral alumina and eluted with a chloroform–methanol mixture (97:3). It crystallized from benzene–petroleum ether as colorless needles: 90 mg (68%); mp 135°; ir (KBr) 1650 (s) (CO), 1505 (m) (N=N) cm^{-1}; uv max (CH_3OH) 310 nm (log ϵ 4.26), 248 (4.03), 202 (4.34); nmr ($CDCl_3$) τ 7.60 (s, 3, C—CH_3), 5.98 (s, 3, N—CH_3), 2.7 (AB d, 2, J = 8.5 Hz, aromatic), 2.08 (AB d, 2, J = 8.5 Hz, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 270 (2.5), 269 (22), 268 (2.5), 267 (22), 119 (11), 91 (100), 65 (13).

Anal. Calcd for $C_{10}H_{10}BrN_3O$: C, 44.78; H, 3.73; N, 15.67. Found: C, 44.92; H, 3.81; N, 15.54.

Reaction of 4 with Dimethyl Acetylenedicarboxylate.—The mesoionic compound 4 (R = *p*-$CH_3C_6H_4$) (200 mg) and dimethyl acetylenedicarboxylate (140 mg) in benzene (5 ml) were heated under reflux for 120 hr. The reaction mixture was poured into water and next morning evaporated to dryness on a rotatory evaporator. The residue was leached with benzene and the small amount of undissolved material was identified as di-*p*-tolylurea, mp 267°, not depressed on admixture with an authentic specimen.

The benzene solution was evaporated and the residue recrystallized from benzene–petroleum ether affording colorless needles of methyl 1-methylpyrazole-3,4-dicarboxylate: 150 mg (75%), mp 68–69°. This product was identical in all respects with an authentic sample of the pyrazole.[16]

Reaction of 4 with Ethyl Azodicarboxylate.—The mesoionic compound 4 (R = *p*-$CH_3C_6H_4$) (100 mg) and ethyl azodicarboxylate (100 mg) in xylene (5 ml) were refluxed for 1 hr. Removal of the xylene on a rotatory evaporator and recrystallization of the residue from benzene–petroleum ether afforded the cycloadduct ethyl 7-methyl-5-oxo-6-*p*-tolyl-1,2,3,6,7-pentaazabicyclo[2.2.1]heptane-2,3-dicarboxylate (17, R = *p*-$CH_3C_6H_4$) as colorless needles: 130 mg (72%); mp 172–173°; ir (KBr) 3175, 3000 (m) (CH), 1725 (s) (CO), 1670 (s) (CO) cm^{-1}; uv max (CH_3OH) 304 nm (log ϵ 4.03), 245 (3.58), 201 (4.30); nmr ($CDCl_3$) τ 8.83 (t, 3, J = 7.0 Hz, CH_2—CH_3), 8.77 (t, 3, J = 7.0 Hz, CH_2—CH_3), 7.63 (s, 3, C—CH_3), 5.85 (s, 3, N—CH_3), 5.91 (q, 2, J = 7.0 Hz, CH_2—CH_3), 5.76 (q, 2, J = 7.0 Hz, CH_2—CH_3), 2.76 (AB d, 2, J = 8.5 Hz, aromatic), 2.05 (AB d, 2, J = 8.5 Hz, aromatic), ~0.18 (s, 1, CH); mass spectrum (70 eV) *m/e* (rel intensity) 363 (15), 290 (19), 245 (8), 230 (12), 218 (33), 203 (7), 189 (27), 133 (10), 119 (15), 104 (8), 92 (12), 91 (100), 78 (17), 77 (9), 65 (15), 57 (13).

Anal. Calcd for $C_{16}H_{21}N_5O_5$: C, 52.88; H, 5.83; N, 19.28. Found: C, 52.95; H, 5.92; N, 19.18.

Reaction of 4 with Tetracyanoethylene.—The mesoionic compound 4 (R = *p*-$CH_3C_6H_4$) (200 mg) and tetracyanoethylene (140 mg) in xylene (5 ml) were heated under reflux for 6 hr. The dark red solid which separated on cooling was recrystallized from chloroform–petroleum ether giving deep red plates of anhydro-4-hydroxy-1-methyl-5-(1,2,2-tricyanoethyl)-3-*p*-tolyl-1,2,3-triazonium hydroxide 18 (R = *p*-$CH_3C_6H_4$): 205 mg (55%); mp 210–211°; ir (KBr) 2225 (m) (CN), 1690 (s) (CO), 1530 (s) (N=N) cm^{-1}; uv max(CH_3OH) 362 nm (log ϵ 4.00), 243 (3.91), 203 (4.01); nmr (DMSO-d_6) τ 7.58 (s, 3, C—CH_3), 5.62 (s, 3, N—CH_3), 2.55 (AB d, 2, J = 8.5 Hz, aromatic), 2.20 (AB d, 2, J = 8.5 Hz, aromatic); mass spectrum (70 eV) *m/e* (rel intensity) 290 (33), 119 (8), 92 (8), 91 (100), 65 (19).

Anal. Calcd for $C_{15}H_{10}N_6O$: C, 62.06; H, 3.47; N, 28.95. Found: C, 61.79; H, 3.50; N, 28.42.

4-Amino-1-methyl-3-phenyl-1,2,3-triazolium Chloride (8, R = Ph).—Dry hydrogen chloride was passed into a solution of N-methyl-N-phenylazoaminoacetonitrile (2.0 g) in anhydrous ether (20 ml) for 20 min during which a colorless product separated. It crystallized from ethanol–ether as colorless, irregular prisms and was extremely hygroscopic. It was characterized as the picrate which crystallized from methanol as yellow needles, mp 176–177°.

Anal. Calcd for $C_{15}H_{13}N_7O_7$: C, 44.67; H, 3.22; N, 24.31. Found: C, 44.84; H, 3.26; N, 24.47.

4-Amino-1-methyl-5-*p*-tolyl-1,2,3-triazolium chloride (8, R = p-$CH_3C_6H_4$) was likewise extremely hygroscopic and was also characterized as the picrate which crystallized from methanol as yellow needles, mp 190–191°.

Anal. Calcd for $C_{16}H_{15}N_7O_7$: C, 46.05; H, 3.59; N, 23.51. Found: C, 46.10; H, 3.64; N, 23.45.

Anhydro-4-acetimino-1-methyl-3-phenyl-1,2,3-triazolium Hydroxide (10, R = Ph). A. From 7 (R = Ph) and Acetyl Chloride.—The nitrile (2.5 g) in benzene (50 ml) was treated dropwise at room temperature with acetyl chloride (1.5 g) and, after ~1 hr, a brown solid had separated. After warming the reaction mixture gently for an additional hour, the brown product was collected and recrystallized several times from ethanol–ether, forming colorless irregular prisms which darken on standing and have a wide melting point range: ir (KBr) 3300–3200, (s) (NH), 3140, 3050 (s) (CH), 1650 (s) (CO), 1600 (s) (N=N) cm^{-1}. This product was assigned the structure 4-acetamido-1-methyl-3-phenyl-1,2,3-triazolium chloride (9, R = Ph) and was characterized as the picrate which separated from methanol as yellow needles: mp 194–195°.

Anal. Calcd for $C_{17}H_{15}N_7O_8$: C, 45.83; H, 3.37; N, 22.02. Found: C, 46.01; H, 3.49; N, 21.90.

The above chloride was dissolved in water and the solution basified with ammonium hydroxide. The solution was extracted with chloroform, the chloroform extract was dried (Na_2SO_4) and, after removal of the chloroform, the residue was recrystallized from benzene (charcoal) forming colorless needles of 10 (R = Ph): 0.6 g (20%); mp 177–178; ir (KBr) 3175 (m) (CH), 1600 (s) (CO), 1550 (s) (N=N) cm^{-1}; uv max (CH_3OH) 303 nm (log ϵ 3.91), 228 (4.08); nmr ($CDCl_3$) τ 7.83 (s, 3, -CO-CH_3), 5.84 (s, 3, N—CH_3), 2.47–1.94 (m, 5, aromatic), 1.37 (s, 1, 5-H); mass spectrum (70 eV) *m/e* (rel intensity) 216 (28), 202 (11), 201 (100), 188 (5), 123 (6), 92 (5), 77 (15), 51 (6), 43 (15).

Anal. Calcd for $C_{11}H_{12}N_4O$: C, 61.10; H, 5.55; N, 25.92. Found: C, 60.99; H, 5.60; N, 25.76.

B. From 8 and Acetic Anhydride.—The chloride 8 (R = Ph) (1.0 g) and acetic anhydride (5.0 ml) were heated on the water bath for 2 hr and, on cooling, a brown product separated. Excess acetic anhydride was removed under reduced pressure on the steam bath and the residue dissolved in a small volume of water and basified with ammonium hydroxide. After work-up as above, colorless needles of 10 (R = Ph), mp 177–178°, were obtained.

In the above fashion **anhydro-4-acetimino-1-methyl-3-*p*-tolyl-1,2,3-triazolium hydroxide (10, R = *p*-$CH_3C_6H_4$)** was obtained as colorless needles from methanol–benzene (charcoal): 30%, mp 214–215°; ir (KBr) 3175, 2925 (m) (CH), 1600 (s) (CO), 1550 (N=N) cm^{-1}; uv max (CH_3OH) 303 nm (log ϵ 3.94), 245 (4.11); nmr ($CDCl_3$) τ 7.85 (s, 3, -$COCH_3$), 7.6 (s, 3, C—CH_3), 5.85 (s, 3, N—CH_3), 2.67 (AB d, 2, J = 9.0 Hz, aromatic), 2.1 (AB d, 2, J = 9.0 Hz, aromatic), 1.43 (s, 1, 5-H); mass spectrum (70 eV) *m/e* (rel intensity) 230 (25), 216 (12), 215 (100), 123 (25), 119 (4), 91 (40), 65 (24), 43 (55), 42 (13).

Anal. Calcd for $C_{12}H_{14}N_4O$: C, 62.62; H, 6.08; N, 24.35. Found: C, 62.48; H, 6.16; N, 24.19.

The corresponding salt, 4-acetamido-1-methyl-3-*p*-tolyl-1,2,3-triazolium chloride, obtained from 7 (R = *p*-$CH_3C_6H_4$) and acetyl chloride was hygroscopic and could not be purified satisfactorily. It was characterized as the picrate which crystallized from methanol as yellow needles: mp 178–179°.

Anal. Calcd for $C_{18}H_{17}N_7O_8$: C, 47.07; H, 3.70; N, 21.35. Found: C, 47.27; H, 3.73; N, 21.19.

Registry No.—2 (R = Ph), 21600-46-4; 2 (R = *p*-$CH_3C_6H_4$), 25677-19-4; 3 (R = Ph), 25725-99-9; 3 (R = *p*-$CH_3C_6H_4$), 25677-20-7; 4 (R = Ph), 15284-64-7; 4 (R = *p*-$CH_3C_6H_4$), 25677-22-9; 5 (R = *p*-$CH_3C_6H_4$), 25677-23-0; 6 (R = Ph), 25677-24-1; 6 (R = *p*-$CH_3C_6H_4$), 25677-25-2; 7 (R = Ph), 25677-26-3;

(16) K. T. Potts and U. P. Singh, *Chem. Commun.*, 66 (1969).

7 (R = *p*-$CH_3C_6H_4$), 25677-27-4; 8 (R = Ph), 25726-00-5; 8 [R = *p*-$CH_3C_6H_4$ (picrate)], 25677-28-5; 9 [R = Ph (picrate)], 25677-29-6; 10 (R = Ph), 25677-30-9; 10 (R = *p*-$CH_3C_6H_4$), 25677-31-0; 10 [R = *p*-$CH_3C_6H_4$ (picrate)], 25677-32-1; 11 (R = *p*-$CH_3C_6H_4$), 25677-33-2; 12 (R = *p*-$CH_3C_6H_4$), 25676-99-7; 12 [R = *p*-$CH_3C_6H_4$ (picrate)], 25677-34-3; 14 (R = *p*-$CH_3C_6H_4$), 25677-35-4; 17 (R = *p*-$CH_3C_6H_4$), 25677-36-5; 18 (R = *p*-$CH_3C_6H_4$), 25677-37-6.

Acknowledgments. —The award of a grant from the National Science Foundation (NSF GP 6905) for the purchase of the mass spectrometer used in this study is gratefully acknowledged.

An Intramolecular Facilitated Acylation of a Tertiary Hydroxyl Group in a Perhydrobenzo[*b*]quinolizinetetrol[1,2]

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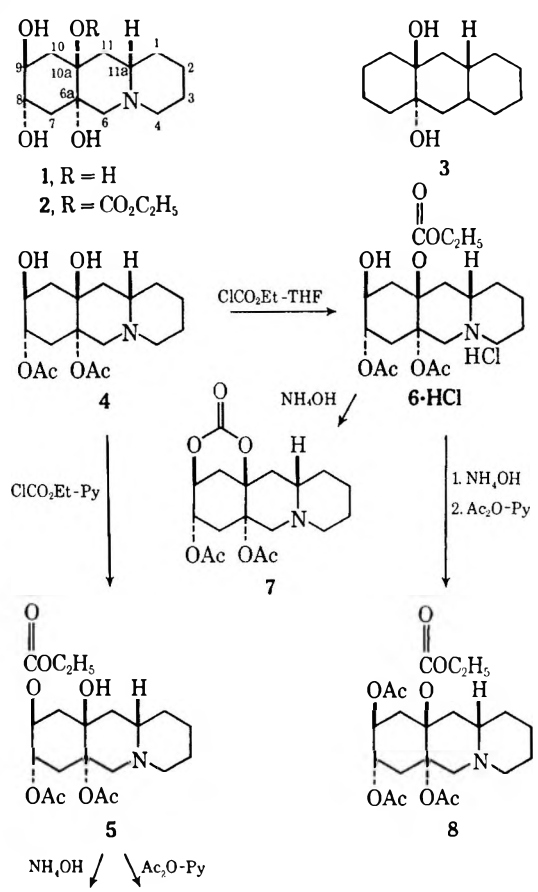
During the structure elucidation of 1,3,4,6,6a,7,8,9,10,10a,11,11a-dodecahydro-2H-benzo[*b*]quinolizine-6a,8,9-10a-tetrol (**1**), a selective acylation of the tertiary 10a-hydroxyl was observed. This reaction has been examined in more detail on the 6a,8-diacetate derivative **4**. It has been found that the acylation is solvent dependent. In pyridine, the secondary 9-hydroxyl is acylated with difficulty. In chloroform and tetrahydrofuran, the 10a-ethyl carbonate is obtained. Evidence is given for postulating that the acylation occurs directly by attack on the tertiary 10a-hydroxyl with an assist by the secondary *cis*-9-hydroxyl and by what appears to be a long-range field effect of the ring nitrogen.

In an earlier paper,[3] the novel facile acylation of a tertiary hydroxyl group bearing a 1,3-diaxial juxtaposition to both a secondary hydroxyl and a nitrogen lone pair of electrons was reported. The compound under investigation was 1,3,4,6,6a,7,8,9,10,10a,11,11a-dodecahydro-2H-benzo[*b*]quinolizine-6a,8,9,10a-tetrol (**1**), and the tertiary hydroxyl was located at position 6a.[4] During the stereochemical elucidation of the all-axial tetrol **1**, it was decided that one approach would be to form bridged structures of the two pairs of *cis*-1,3-diaxial hydroxyl groups. One method is to form a carbonate bridge using ethyl chloroformate.[5]

Treatment of tetrol **1** in tetrahydrofuran (THF) yielded the 10a-ethyl carbonate **2**.[3] Fieser has reported on the use of ethyl chloroformate as an alcohol protecting group. He called the reaction cathylation and the products cathylates. He also noted that no carbonates (cathylates) would form if the hydroxyl group was axial.[6] Thus here is ethyl chloroformate acylating an axial tertiary hydroxyl group. Because of the unusual nature of this acylation, it was decided to investigate this reaction further.

In studying the properties of this reaction in more detail, two items of information became apparent: (1) the C-9 secondary hydroxyl is necessary and (2) the reaction is solvent dependent. There was no reaction when diol **3** was the starting material.[3] Use of pyridine gave a mixture of products when **1** was the starting material, presumably owing to partial acylation of any of the four possible hydroxyls and in any combination. In order to eliminate two of the four possible hydroxyls, it was decided to use the known 6a,8-diacetate[3] (**4**) as the starting material.



Acylation of the 6a,8-diacetate (**4**) in tetrahydrofuran yielded the 6a,8-diacetate tertiary 10a-ethyl carbonate (**6**) in low yield. It was not possible to isolate

(1) This work was presented before the Medicinal Chemistry Section of the Academy of Pharmaceutical Sciences at the annual meeting of the American Pharmaceutical Association, Montreal, Quebec, May 1969, Abstracts, p 88.

(2) Financial support by the General Research Fund of the Oregon State University Graduate School is gratefully acknowledged.

(3) S. M. Kupchan, J. H. Block, and A. C. Isenberg, *J. Amer. Chem. Soc.* **89**, 1189 (1967).

(4) All asymmetric synthetic products described are racemic mixtures. Only one optical antipode for each is drawn for convenience of representation and discussion. In the representation of the quinolizidine derivatives the electron pair on nitrogen is understood to project downward, and a heavy bond to the 11a hydrogen indicates the *trans*-quinolizidine configuration.

(5) L. Hough, J. E. Priddle, and R. S. Theobold, *Advan. Carbohyd. Chem.*, **15**, 91 (1960).

(6) L. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y. 1959, pp 192, 217–219, 221, 241, 836.

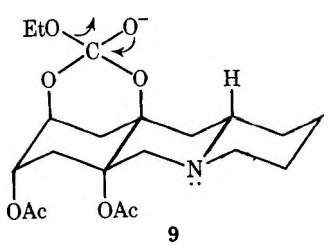
this compound as the thin layer chromatograms always indicated the presence of starting material. However, it was still possible to characterize the structure. The nmr spectrum showed the typical signals for an ethoxy moiety: quartet at δ 4.10 (J = 7 cps) and triplet at δ 1.28 (J = 7 cps). There was no downfield shift of the C-9 carbinol proton as would be expected had the C-9 hydroxyl been acylated.[7,8] Acetylation with acetic anhydride in pyridine yielded the already known 6a,8,9-triacetate 10a-ethyl carbonate (**8**). Treatment of **6** in mild base yielded the already known cyclic carbonate diacetate **7**.[3]

In contrast, acylation of the 6a,8-diacetate **4** with ethyl chloroformate in pyridine yielded the C-9 secondary carbonate **5**. This reaction went with difficulty requiring long periods of heating and 2–3 additions of ethyl chloroformate. This is consistent with previous observations reporting the difficulty of acylating an axial hydroxyl group with this reagent.[6] The carbonate's location on the secondary position is shown by the downfield shift of the C-9 equatorial carbinol proton[9] from δ 3.99 to the δ 5 region, failure to form a cyclic carbonate in mild base, and the lack of any hydroxyl groups capable of being acylated by acetic anhydride in pyridine.

No acylation occurred when the reaction solvent was *tert*-butyl alcohol or dioxane. Some product would form in chloroform. However, proper concentration of solvent is critical, and it may be that the concentrations, particularly of dioxane, were incorrect.

While it is not possible to postulate a definite mechanism, it is possible to reject some possibilities and speculate on others. It appears from the present evidence that the acylation is a direct attack on the C-10a tertiary hydroxyl. The tertiary position at both C-6a and 10a are hindered. The migration of an acetate from position 6a to a *cis*-hydroxyl at position 8 has been demonstrated[3] as has a similar migration from position 5 to position 3 in the cholestane series.[10] There is no reason to doubt that the hydroxyl at C-10a is any less hindered than that at C-6a.

The migration of an acetate presumably goes through an orthoacetate intermediate. In an analogous manner, the 10a-ethyl carbonate probably migrates to the secondary C-9 hydroxyl under basic conditions. In contrast with the migration of an acetate group, the ethyl carbonate contains the ethoxy leaving group (see intermediate **9**) resulting in a cyclic carbonate rather



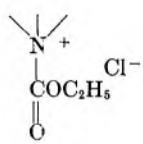
9

than the 9-ethyl carbonate **5**. The latter compound would not form the 9,10a-cyclic carbonate **7** when treated with mild base which is predicted as there is no driving force for a migration from the less hindered C-9 position to the more hindered C-10a position.

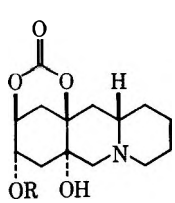
At first one might think that under the harsher conditions of the acylation in pyridine there might have been an acylation at the C-10a position followed by migration to the C-9 position. Refluxing of **6** in pyridine showed no changes in the infrared spectrum as compared to the starting material and no thin layer chromatogram (tlc) evidence for the presence of **5**. Tlc did show traces of the cyclic carbonate 6a,8-diacetate **7** which would be consistent if any migration were to occur from the C-10a position to C-9. Also refluxing the 10a-ethyl carbonate **2** in THF showed no further reaction. In addition, compound **5** does not react further with additional ethyl chloroformate in THF, dioxane, or pyridine.

Further evidence of the hindrance at position 10a is the nmr spectrum of the original 10a-ethyl carbonate **2** which shows the normal splitting pattern for an ethoxy group compared with that of the 6a,8,9-triacetate 10a-ethyl carbonate (**8**) in which the expected methylene quartet shows additional splitting.[3] This would indicate hindered rotation of the methylene group resulting in each methylene proton being in a nonequivalent environment.

A possible mechanism for the facilitated acylation would be the formation of an acylonium intermediate of the type involving the ring nitrogen which would then



acylate an alcoholic function. This intermediate would be consistent with the observation that lower yields of 10a-ethyl carbonate result when the pK_a of the ring nitrogen is decreased. However, it must still be kept in mind that only the C-10a alcohol is acylated even when tetrol **1** is the starting material. Thus the unique character of position 10a must always be considered when postulating a mechanism. In the case of the 9,10a-cyclic carbonate (**10**), no acylation of the C-6a or C-8 hydroxyl occurred with ethyl chloroformate in THF, while acylation did occur in pyridine producing 8-ethyl carbonate 9,10a-cyclic carbonate **11**.[3] Further, whenever triethylamine was present, all that was obtained was triethylamine hydrochloride and no acylated product.



10, R = H
11, R = COOEt

An alternative mechanism is based on the fact that the C-10a tertiary hydroxyl is in a unique position in that it is in a *trans*-1,4 relationship to the nitrogen lone pair of electrons. It appears that the ring nitrogen and the C-10a hydroxyl exert a long range field effect on

(7) R. U. Lemieux, R. K. Kullnig, W. J. Bernstein, and W. G. Schneider, *J. Amer. Chem. Soc.*, **80** 6098 (1958).
(8) J. N. Schoolery and M. T. Roger, *ibid.*, **80**, 5121 (1958).
(9) See E. W. Garbisch, Jr., *J. Org. Chem.*, **27**, 4249, (1962), and ref 7 for discussions of the use of W_H (width of the signal at one-half the peak height) in determining the conformation of carbinol protons.
(10) B. W. Sands and A. T. Rowland, *Steroids*, **4**, 175 (1964).

each other. Whenever there is an acyl group on the C-10a hydroxyl, the pK_a of the ring nitrogen decreases by at least 0.9 pK_a units.[3] Further, the yield of tertiary carbonate apparently decreases as the pK_a of the ring nitrogen decreases. Thus, the reaction of ethyl chloroformate in tetrahydrofuran with tetrol **1** (pK_a' = 8.14) produces yields of 50% **2** compared with no more than 9% **6** when the 6a,8-diacetate **4** (pK_a' = 6.98) is the starting material. Other long range field effects involving the ring nitrogen in the benzo[*a*]-quinolizine series have also been observed. In these compounds and appropriate model systems, the carbonyl frequency (infrared) of a ketone in a 1,4 relationship to a ring nitrogen would shift 15–25 cm^{-1} to higher wavenumbers whenever the ring nitrogen was protonated. Also the hydrates of some of these ketones were nearly as stable as chloral hydrate when the ring nitrogen was protonated.[11]

The role of the secondary C-9 hydroxyl is also essential as shown by the inability of the 6a,10a-diol **3** to be acylated by ethyl chloroformate in THF. In carbon tetrachloride, intramolecular hydrogen bonding between two *cis*-1,3-diaxial alcohols is quite pronounced.[12a,b] From infrared evidence, it was concluded that in *cis*-1,3-diols of certain bicyclononenes, hydrogen bonding between the hydrogen of the secondary hydroxyl and the oxygen of the tertiary hydroxyl was more favorable than the alternate possibility by a factor of two.[12a] In *cis*-3α,5α- and 3β,5β-cholestanediols, infrared and stereochemical evidence was given showing that hydrogen bonding of the tertiary 5-hydroxyl to the secondary 3-hydroxyl predominated. Since the perhydrobenzo[*b*]quinolizines are analogous to the cholestane-3α,5α-diol and hydrogen bonding of the secondary C-9 hydroxyl hydrogen to the oxygen of the C-10a tertiary hydroxyl would result in a steric repulsion between the C-10a hydroxyl hydrogen and the C-11a hydrogen (analogous to repulsion between the 5α-hydroxyl hydrogen and the 7α hydrogen in cholestane), it would appear probable that the C-10a hydroxyl hydrogen bonds to the C-9 hydroxyl oxygen.

It may be that the ring nitrogen has further weakened the O–H bond of the C-10a tertiary hydroxyl group permitting a direct acylation at the C-10a position. As the reaction proceeds, the generated hydrochloric acid protonates the ring nitrogen of the more basic unreacted starting material which, as the hydrochloride salt, is no longer susceptible to acylation. When the 6a,8-diacetate hydrochloride **4**·HCl was the starting material, there was no evidence of any acylation occurring. Pyridine may solvate both the C-9 and C-10a hydroxyls breaking the intramolecular hydrogen bonds with the result that acylation occurs at the C-9 secondary hydroxyl.

Intramolecular facilitated acylations have interest as potential enzyme models particularly for the esteratic enzymes where an acylated enzyme is an intermediate. It is plausible that at the enzyme's active site, there are long range effects due to the side chains of the amino acids being in a proper spatial relationship with each other. Rigid polyfunctional molecules of the benzo[*b*]quinolizine type provide a means of studying such potential long range actions.

(11) L. Novak, P. Sohar, and Cs. Szantay, *Acta Chim. Acad. Sci. Hung.*, **54**, 161 (1967).

(12) (a) R. West, J. J. Korst, and W. S. Johnson, *J. Org. Chem.*, **25**, 1976 (1960); (b) F. Dalton, J. I. McDougall, and G. D. Meakins, *J. Chem. Soc.*, 4068 (1963).

Experimental Section

Melting points were determined in unsealed capillaries on a Hoover-Thomas apparatus and are corrected. Infrared spectra were obtained on a Beckman Model IR-8 spectrophotometer in mineral oil. Nmr spectra were obtained on a Varian A-60 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard.[13] Thin layer chromatograms prepared with silica gel G (Brinkmann) were developed in a $CHCl_3$–CH_3OH (7:3) solvent system. Visualization was by iodine vapor. Skellysolve B refers to a petroleum ether fraction boiling at 60–68°. Microanalyses were performed by Dr. F. B. Strauss, Oxford, England.

1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2H-benzo[*b*]-quinolizine-6a,8,9,10a-tetrol 6a,8-Diacetate 9-Ethyl Carbonate (5).—To a solution of 50 ml of pyridine and 0.5 g of **4** cooled in an ice bath was added slowly 10 ml of ethyl chloroformate. The mixture thickened and then liquified upon warming to room temperature. The solution was then refluxed for 4.5 hr and recooled, 7 ml of ethyl chloroformate added, and the solution allowed to come to room temperature again. Two hours later the solution was recooled, 5 ml of ethyl chloroformate added, and the solution let stand overnight at room temperature. After the second addition of ethyl chloroformate, a solid remained in the flask even after warming to room temperature. Also, there would be some effervescence occurring as the ethyl chloroformate was being added to the cooled mixture to the extent that the reaction flask should be only loosely stoppered while the reaction mixture stands. After standing overnight, the mixture was cooled in an ice bath and ice was added to the flask. Ammonium hydroxide (7 *N*) was added until pH 8–9 (pHydrion paper). The basic mixture was extracted with chloroform (three 30-ml portions.) The chloroform extracts were dried over anhydrous magnesium sulfate and removed under reduced pressure. The residue was treated with benzene and distilled under reduced pressure removing the pyridine as an azeotrope. Treatment of the semisolid residue with Skellysolve B caused solidification yielding 0.465 gm of one spot material. The crude material was dissolved in 30 ml of ethyl acetate and boiled with Norit; the mixture was filtered. The filtrate was concentrated to 15 ml and Skellysolve B added. Upon cooling, crystalline material totaling 0.3 g, mp 170–173° dec, was obtained. The infrared spectrum showed hydroxyl at 3460 cm^{-1} and carbonyl at 1735 and 1705 cm^{-1}. The nmr spectrum showed significant signals at δ 5.08 (W_H = 7 cps) and δ 4.86 (W_H = 7 cps) for a total of 2 H consistent for acylated equatorial carbinol protons, δ 4.16 q (J = 7 cps, 2 H) and δ 1.29 t (J = 7 cps) consistent for ethoxy, and loss of one proton at δ 3 when shaken with D_2O. It was characterized as the hydrochloride salt recrystallized from chloroform–ethyl acetate, mp 231–232° dec. The infrared spectrum of **5**·HCl shows hydroxyl at 3200 cm^{-1} and carbonyl at1738 cm^{-1}.

Anal. Calcd for $C_{20}H_{32}O_8NCl$: C, 53.39; H, 7.17; N, 3.11; Cl, 7.88. Found: C, 53.18; H. 6.97; N, 2.95; Cl, 7.56.

Treatment of 6a,8-Diacetate 9-Ethyl Carbonate (5) with Mild Base.—Compound **5** (0.077 g) was dissolved in 13 ml of methyl alcohol and 17 ml of water added. Ammonium hydroxide (7 *N*) was added to pH 8–9 (pHydrion paper) and the solution allowed to stand at room temperature for 15 min. The solution was then extracted with chloroform (three 10-ml portions). The chloroform extracts were dried over anhydrous magnesium sulfate and then removed under reduced pressure yielding 0.04 gm. The infrared spectrum showed no decrease in hydroxyl as would be predicted if the 6a,8-diacetate 9,10a-cyclic carbonate (**7**) was formed. Just the opposite was observed. The spectrum showed new hydroxyl at 3330 cm^{-1} and decrease of carbonyl at 1705 cm^{-1} pointing to a solvolysis of the 9-ethyl carbonate. The thin layer chromatogram was consistent for this conclusion.[14]

1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2H-benzo[*b*]-quinolizine-6a,8,9,10a-tetrol 6a,8-Diacetate 10a-Ethyl Carbonate Hydrochloride (6·HCl).—A solution of 1040 ml of THF, 2.62 g of 6a,8-diacetate (**4**), and 104 ml of ethyl chloroformate was stirred for 2 hr and then allowed to stand overnight. A precipi-

(13) We thank Dr. Elliot Marvel of the Department of Chemistry, Oregon State University, for obtaining these nmr spectra.

(14) See ref 3 for a discussion of the intramolecular facilitated solvolysis of an acetate located at position 9.

tate appeared within 15 min after addition of the ethyl chloroformate. Filtration of the reaction mixture yielded 1.74 g of material characterized as 6a,8-diacetate hydrochloride **4**·HCl, mp 269.5–270° dec, by mixture melting point and comparison with the infrared spectrum of an authentic sample produced by adding diethyl ether saturated with hydrogen chloride gas to an ether solution of 6a,8-diacetate **4** and recrystallizing from ethyl alcohol–ethyl acetate. The infrared spectrum showed hydroxyl at 3340 and 3130 cm^{-1} and carbonyl at 1745 cm^{-1}.

Anal. Calcd for $C_{17}H_{28}O_6NCl$: C, 54.04; H, 7.47; N, 3.71; Cl, 9.47. Found: C, 54.14; H, 7.40; N, 3.65; Cl, 9.81.

The tetrahydrofuran filtrate was evaporated under reduced pressure and the residue suspended in ethyl acetate and filtered yielding 0.656 g, mp 202° dec.[15] The infrared spectrum showed hydroxyl at 3290 cm^{-1} and carbonyl at 1738 cm^{-1} and also indicated the product was a mixture containing about 50% 6a,8-diacetate hydrochloride **4**·HCl. Further characterization was done on the free amine.

1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2H-benzo[*b*]quinolizine-6a,8,9,10a-tetrol 6a,8-Diacetate 10a-Ethyl Carbonate (6).—The mixture of hydrochloride salts of **4** and **6** (0.051 gm) was dissolved in 10 ml of water in a separatory funnel and ice added. Chloroform (10 ml) followed by 7 *N* ammonium hydroxide to pH 8–9 (pHydrion paper) was then added and the mixture strongly agitated. The chloroform phase was removed and the aqueous phase extracted twice more with chloroform (10 ml portions). The chloroform extracts were dried over anhydrous magnesium sulfate and then removed under reduced pressure. The viscous residue solidified upon treatment with Skellysolve B. The presence of 6a,8-diacetate **4** starting material was shown by thin layer chromatography. The infrared spectrum showed hydroxyl at 3490 cm^{-1} and carbonyl at 1760, 1735, and 1715 cm^{-1}. The nmr spectrum showed significant signals at δ 4.98 (W_H = 8 cps, C-8 equatorial carbinol proton) and δ 3.91 (W_H = 8 cps, C-9 equatorial carbinol proton). The latter partially blocked the quartet at δ 4.10 (J = 7 cps), but the triplet at δ 1.28 (J = 7cps) confirmed the presence of ethoxy.

Characterization of 6. A. Formation of 1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2H-benzo[*b*]quinolizine-6a,8,9,10a-tetrol 6a,8,9-Triacetate 10a-Ethyl Carbonate (8).—Using reported procedures,[3] the mixture of compounds **4** and **6** was acetylated yielding a mixture of 6a,8,9-triacetate[3] and **8**. Several recrystallizations from Skellysolve B yielded an almost one spot material whose infrared spectrum was identical in all respects with that of the known material.[3]

B. Formation of 1,3,4,6,6a,7,8,9,10,10a,11,11a-Dodecahydro-2H-benzo[*b*]quinolizine-6a,8,9,10a-tetrol 6a,8-Diacetate 9,10a-Carbonate (7).—The mixture of compounds **4**·HCl and **6**·HCl (0.38 g) was dissolved in 10 ml of water and 7 *N* ammonium hydroxide added until pH 8–9 (pHydrion paper). The mixture became cloudy but cleared up again with the addition of more water. The solution was allowed to stand at room temperature for several minutes and then extracted with chloroform (three 10-ml portions). The chloroform extracts were dried over anhydrous magnesium sulfate and then removed under reduced pressure. The residue was chromatographed on silica gel (J. T. Baker). The desired cyclic carbonate diacetate was eluted with chloroform. Crystallization from Skellysolve B yielded 0.016 gm, mp 170°, of material whose infrared spectrum was identical with that of the known compound.[3] Further elution of the column with $CHCl_3$–CH_3OH (9:1) yielded the 6a,8-diacetate **4**.

Registry No.—**4**, 25683-77-6; **4**·HCl, 25683-78-7; **5**, 25683-79-8; **5**·HCl, 25683-80-1.

(15) The total yields do not add up to 100% of starting material. The proportions of each product reported here are similar in both large and small scale experiments. Addition of an ethereal solution of hydrogen chloride which should convert all basic nitrogenous material to hydrochloride salts had no effect on the yields. Since the starting material is a tertiary amine, there is probably decomposition of the type reported for tertiary amines in the presence of chloroformates. *Cf.* J. D. Hobson and J. G. McClusky, *J. Chem. Soc. C*, 2015 (1967).

Vinylpyrazoles

S. TROFIMENKO

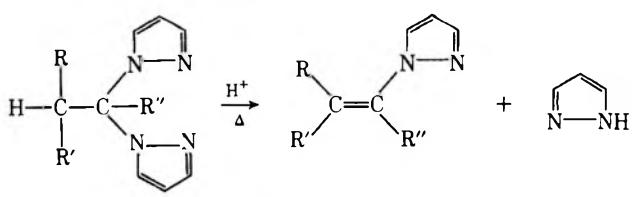
Contribution No. 1684 from the Central Research Department, Experimental Station, E. I. du Pont de Nemours and Company, Wilmington, Delaware 19898

Received April 10, 1970

1-Vinylpyrazole and its vinyl-substituted analogs have been prepared by acid-catalyzed cracking of geminal bis(1-pyrazolyl)alkanes. 1-Vinylpyrazole polymerizes under free-radical initiation to a high polymer; the extent of polymerization diminishes with increasing substitution on the vinyl group. The various 1-vinylpyrazoles do not behave as enamines. Shielding effects of a 1-pyrazolyl substiuent on the gem, cis, and trans vinyl protons have been determined.

In the area of pyrazole chemistry there are few examples of 1-pyrazolyl olefins. Apart from the addition products of pyrazole to acetylenedicarboxylic ester,[1,2] and the 1-vinylpyrazoles obtained by the high-pressure reaction of acetylene with 3,5-dimethylpyrazole and 3-methyl-5-phenylpyrazole,[3] some 1-propenylpyrazoles have been synthesized by the pyrolysis of certain α,β-unsaturated azines.[4] A general synthesis of 1-pyrazolyl olefins has been lacking.[4a]

During our work with geminal poly(1-pyrazolyl)alkanes[5] which are available from the reaction of pyrazole with acetals or ketals, a convenient way was found for synthesizing the parent 1-vinylpyrazole and its analogs containing various alkyl substituents on the vinyl group. The method consists of heating geminal bis(1-pyrazolyl)alkanes which contain β hydrogens in the presence of a strong acid such as *p*-toluenesulfonic. Around 200° fragmentation to pyrazole and an olefin occurs. The pyrolysis products are removed as formed



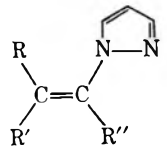
by distillation at atmospheric or reduced pressure and they can be separated with ease.

The cyclic and acyclic 1-pyrazolyl olefins prepared by this method (Table I) are water-insoluble liquids possessing an "olefinic" odor. Their structure assignment rests, apart from the mode of formation and full

(1) E. Benary, H. Meyer, and K. Charisius, *Ber.*, **59**, 108 (1926).
(2) R. M. Acheson and P. W. Poulter, *J. Chem. Soc.*, 2138 (1960).
(3) N. O. Jones, British Patent 887,365 (1962); *Chem. Abstr.*, **57**, 1077*h* (1962).
(4) R. L. Stern and J. G. Krause, *J. Org. Chem.*, **33**, 212 (1968).
(4a) NOTE ADDED IN PROOF.—The synthesis of 1-vinylpyrazole from 1-(2-hydroxyethyl)pyrazole has also been reported: I. I. Grandberg and G. J. Sharova, *Khim. Geterotsikl. Soedin.*, **2**, 325 (1968); *Chem. Abstr.*, **69**, 96564*k* (1968).
(5) S. Trofimenko, *J. Amer. Chem. Soc.*, **92**, 5118 (1970).

TABLE I

COMPOUNDS OF STRUCTURE



Compd[a]	R	R	R''	Bp, °C (mm)	Yield, %	$n^{25}D$	Uv, λ_{max} (ϵ)	Nmr $J_{RR'}$ Hz	$J_{R'R''}$ Hz	$J_{RR''}$, Hz	ν_R, τ	$\nu_{R'}$, τ	$\nu_{R''}$, τ
1	H	H	H	139–140 (atm)	39	1.5138[b]	250 (13,150)	0.9	8.7	15.6	4.55	5.28	3.01
2	H	H	CH_3	154–155 (atm)	46	1.5118	249 (11,000)	0	0.6	1.3	4.75	5.43	7.78
3	CH_3	H	H	167–169 (atm)[c]	62[c]	1.5139[c]	249[c] (10,600)	7.3	9.3	1.9	8.03	4.80	3.28
4	H	CH_3	H					6.9	1.5	13.9	4.01	8.25	3.22
5	CH_3	H	C_2H_5	108 (14)[d]	47[d]	1.4990[d]	242[d] (8100)	7.1	1.2	1.4	8.42	4.68	7.53 (CH_2)
6	H	CH_3	C_2H_5					7.2	0.6	0	4.35	8.27	7.35 (CH_2) 9.02 (CH_3)
7	H	H	C_2H_5					0	0	1.2	4.80	5.38	7.35 (CH_2) 8.86 (CH_3)
8	H	CH_3	CH_3	54 (6.0)[e]	84[e]	1.5082[e]	245[e] (8330)	7.2	0	1.2	4.18	8.26	7.85
9	CH_3	H	CH_3					7.2	1.3	1.2	8.33	4.78	7.85
10	CH_3	CH_3	H	75–76 (19)	56	1.5065	243 (10,800)	0	1.4	1.4	8.25	8.20	3.40
								Nmr data[f]					
11	H	$-(CH_2)_3-$		57 (0.6)	73	1.5462	253 (12,000)	2 d (unres) 2.76; "t" (1.9 and 2.4) 4.10; m 4.24, m 7.92, m 8.26, m 8.74 [2:1:1:2:2:4]					
12	H	$-(CH_2)_4-$		69 (0.6)	78	1.5412	250 (10,200)	2 d (unres) 2.84; "t" (1.8 and 2.4) 4.13; quint (J = 2.2 Hz) 4.62; m 7.5–8.7 [2:1:1:6][f]					

[a] Satisfactory C, H, and N analyses (±0.3%) were obtained for all compounds: Ed. [b] d^{25} = 0.9902 g/ml. [c] A 19:81 mixture of **3** and **4**. [d] A 17:83 mixture of **5** and **6**. [e] An 18:69:13 mixture of **7**, **8**, and **9**. [f] Listed are multiplicity (J) τ [peak ratio].

elemental analysis, on their nmr spectra. These indicated, in each case, the presence of a 1-substituted pyrazole ring and of the appropriate olefinic moiety. While in some instances unambiguous assignment could be made based on the magnitude of coupling constants alone, in others, particularly those involving cis–trans pairs, use had to be made of additive shielding increments.

In 1-vinylpyrazole (**1**) the three vinylic hydrogens appear at τ 3.01, 4.55, and 5.28 and were assigned to the gem, cis, and trans[6] hydrogens respectively on the basis of their coupling constants (J^{cis}_{H-H} = 8.7 and J^{trans}_{H-H} = 15.6 Hz) which were in the expected range for vinylic protons.[7,8] The corresponding values for 1-vinyl-3,5-dimethylpyrazole were found to be 8.8 and 15.3 Hz, respectively.

1-(2-Propenyl)pyrazole (**2**) had the vinylic hydrogens at τ 4.75 and 5.43. Here, geminal coupling was zero, while J_{H-CH_3} values were small (0.6 and 1.3 Hz) and not a distinguishing feature. However, considering the additive shielding parameters of alkyl groups[9,10] namely, −0.45 (gem), +0.22 (cis), and +0.28 ppm (trans), and starting with the chemical shifts of conclusively identified vinylic hydrogens in 1-vinylpyrazole, the cis and trans hydrogens in **2** should be at about τ 4.8 and 5.5, respectively. This correlates well with the observed 4.75 and 5.43 peaks and makes assignment possible.

From precursors capable of giving cis–trans mixtures such mixtures were obtained. For instance, fragmentation of 1,1-bis(1-pyrazolyl)propane produced the cis and trans isomers, **3** and **4**. Although they were not separated by distillation, their mixture could be analyzed by nmr again taking advantage of the cis and trans coupling constants. The major component (81%) was the trans isomer, **4**, as established from it J_{H-H} which was 13.9 Hz, while J^{cis}_{H-H} of the minor component was 9.3 Hz. This compares well with corresponding values in *N*,*N*-diethyl-1-propenylamine which have been reported as 13.7 and 8.6 Hz.[11]

Another example of a single product consisting of a cis–trans mixture was 1-[3-(2-pentenyl)]pyrazole (**5** and **6**) derived from 3,3-bis(1-pyrazolyl)pentane. Here, the coupling constants were of no help in identifying the isomers. On the other hand, by the use of additive shielding increments values of τ 4.3 and 4.9 were predicted for the cis and trans vinyl hydrogens. Accordingly, the vinyl peaks at 4.35 and 4.68 were assigned to the cis (**5**) and trans (**6**) isomers, respectively, which were present in 17:83 ratio. Of interest was the absence of trans H—CH_2 coupling, while $J^{cis}_{H-CH_2}$ was 1.2 Hz. The cis and trans couplings of CH_3 and CH_2 were 0.6 and 1.4 Hz, respectively.

A more complicated product mixture arose from 2,2-bis(1-pyrazolyl)butane, where two modes of eliminating pyrazole are possible. The product mixture consisted of 1[2-(2-butenyl)]pyrazoles and 1-[2-(1-butenyl)]pyrazole (**7**) in 82:18 ratio. These compo-

(6) Gem, cis, and trans will be used in reference to the 1-pyrazolyl substituent unless stated otherwise.

(7) Frank A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York, N. Y., 1969, p 358 ff.

(8) "High Resolution Nuclear Magnetic Resonance Spectroscopy," J. W. Einsley, J. Feeney, and L. H. Sutcliffe, Ed., Vol. 2, Pergamon Press, N. Y., 1966, p 1137.

(9) U. E. Matter, C. Pascual, E. Pretsch, A. Pross, W. Simon, and S. Sternhell, *Tetrahedron*, **25**, 691 (1969).

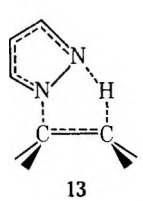
(10) S. W. Tobey, *J. Org. Chem.*, **34**, 1281 (1969).

(11) J. Sauer and H. Prahl, *Tetrahedron Lett.*, 2863 (1966).

nents were not separable by simple fractional distillation, although the lower-boiling cut was enriched in **7** and one of the 1-[2-(2-butenyl)]pyrazole isomers (**9**, *vide infra*). As with **5** and **6**, the cis–trans isomers were identified on the basis of the chemical shift of the vinyl proton: the one at τ 4.18 belonged to **8** while that at 4.78 to **9**. From that assignment the identity of the other peaks was deduced. The **8**:**9** ratio was 84:16, the trans isomer being again the major component. Just as in the case of **5**, the trans H-CH_2 coupling in **7** was zero, but $J^{cis}_{H-CH_2}$ was 1.2, whereas $J^{cis}_{H-CH_3}$ and $J^{trans}_{H-CH_3}$ were about equal (1.2–1.3 Hz).

Compounds **10**, **11**, and **12** presented no structure assignment problems as in each case only one product could be formed containing a vinyl hydrogen of established stereochemistry. The various chemical shifts and coupling constants for the vinyl substituents are listed in Table I. In general, the chemical shifts of all the vinyl protons were close to the positions predicted by the "additive" method, when 1-vinylpyrazole was used as standard. From the twelve examples of 1-vinylpyrazoles reported to this paper we have derived, using the relationship $\delta_{C=C-H}$ (in τ) = 4.75 + Z_{gem} + Z_{cis} + Z_{trans} and the reported additive increments for alkyl groups,[9] the appropriate additive increments for the 1-pyrazolyl substituent. They are −1.77 ± 0.05 for gem, −0.32 ± 0.14 for cis, and +0.37 ± 0.17 Hz[12] for trans and thus they differ not only in the magnitude of the shift but also in the direction for the cis substituent from those reported for NR_2 groups[9] where both cis and trans substituents cause upfield shifts.

The three cis–trans isomer pairs, **2** and **3**, **5**, and **6**, and **8** and **9** all show the trans isomer to be the major (over 80%) component of the mixture. This may be rationalized as follows: the cracking out of pyrazole is unlikely to proceed through a cyclic transition state, **13**, since in the absence of acid the geminal bisalkanes can



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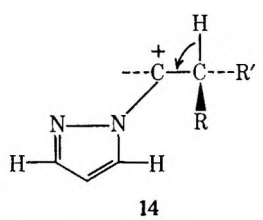

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be distilled at even higher temperatures without decomposition. Hence, the reaction probably proceeds *via* 2-*N*-protonation of a pyrazolyl group followed by dissociation to yield the carbonium ion **14** of sufficient lifetime to permit some rotation around the C–C bond. The conformation which minimizes nonbonding interactions between pyrazolyl 3,5 hydrogens and the R,R′ substituents will be that which has the bulkier substituent R′ remote from the pyrazolyl group. Such a geometry would lead preferentially, after loss of proton, to the trans isomers (for R′ = alkyl, R = H).

Vinylpyrazole and substituted vinylpyrazoles do not resemble enamines in reactivity. This is in accord with nonavailability of electrons from the 1 nitrogen to stabilize dipolar structures of transition states such as those commonly invoked to account for the reactivity of enamines. Vinylpyrazoles coexist with pyrazole and show no tendency to add it back. Shelf-life of vinylpyrazoles is good and no polymerization in the neat liquid is observed even after 2 years.

Polymerization of these monomers has been effected with azo initiators, although the rate and extent of polymerization depend on the nature of the substituents on the vinyl group. Thus, while neat 1-vinylpyrazole polymerizes almost explosively, 1-(2-propenyl)-pyrazole polymerizes to a lesser extent and the more heavily substituted analogs even less so. In dilute benzene solution 1-vinylpyrazole has been cleanly polymerized to polymers of mol wt 150,000–330,000. Transparent stretchable and orientable films have been cast from 17% methanolic solutions of poly-1-vinylpyrazole.

Experimental Section

The geminal bis(1-pyrazolyl)alkanes[5] and 1-vinyl-3,5-dimethylpyrazole[3] were prepared by published procedures. The nmr spectra were determined routinely on a Varian A-60 spectrometer, using 10% solution of the compound in carbon tetrachloride with internal tetramethylsilane as standard. In some instances, wher signals overlapped, their separation (for the determination of *J* values only) was effected by the use of a Varian HA-100 or Varian HR-220 spectrometer, or by employing a neat sample. The chemical shifts changed for some compounds significantly (up to 0.5 ppm) on going from a CCl_4 solution to a neat sample, for others (*e.g.*, 1-vinylpyrazole) not at all.

Synthesis of 1-Vinylpyrazole and of Substituted Analogs.—A general procedure for the preparation of 1-vinylpyrazole and of substituted 1-vinylpyrazoles consists of heating a geminal bis(1-pyrazolyl)alkane to 200–220° in the presence of about 1 g/mol of *p*-toluenesulfonic acid and distilling the two products, pyrazole and 1-pyrazolyl olefin. Pressure may be reduced for distillation of the higher boiling 1-pyrazolyl olefins but it should be adjusted so that the pot temperature remains around 200°. The distillate may contain, in addition, some unreacted geminal dipyrazolylalkane. The three components may be separated by a variety of methods. Pyrazole (bp 185°) plus 1-vinylpyrazole (bp 138°) can be separated by fractional distillation through an efficient column. In some systems much of the pyrazole crystallizes and the olefin may be dissolved in petroleum ether in which pyrazole is sparingly soluble. The petroleum ether extract is then washed with water to remove any pyrazole and the last traces of pyrazole are destroyed by the addition of sodium or calcium hydride to the concentrated organic phase prior to distillation. The olefin is easily separated from the geminal bis(1-pyrazolyl)alkane by fractional distillation. Throughout the purification, the composition of the mixture may be conveniently monitored by nmr.

The procedure is illustrated by a specific example. Other compounds prepared in this fashion are listed in Table I. In the case of vinylpyrazole and propenylpyrazoles some product was lost through polymerization in the pot.

1-Cyclohexenylpyrazole.—A mixture of 195 g (0.9 mol) of 1,1-bis(1-pyrazolyl)cyclohexane and 0.9 g of *p*-toluenesulfonic acid was stirred and heated until pyrazole starting distilling at atmospheric pressure. At this point distillation was continued at reduced pressure, the pressure being adjusted so that the pot temperature remained at 200–210°, until the pot was practically dry. The distillate, a part of which had solidified, was stirred with petroleum ether and the mixture was filtered. There was obtained 40 g (66%) of pyrazole. The filtrate was extracted three times with 500 ml of water (to remove any remaining pyrazole) and was then stripped. The residual oil was distilled *in vacuo*, after some calcium hydride was added, and the heart cut was obtained in 104 g (78%) yield. Its properties are listed in Table I.

Polymerization of 1-Vinylpyrazole.—Exactly 50.0 ml (49.5 g) of pure 1-vinylpyrazole in 200 ml of benzene was stirred at 75–80°. About 4–5 mg of azobisisobutyronitrile was added and stirring was continued for 30 min. When the solution became quite viscous, another 100 ml of benzene and 4 mg of initiator was added and this was repeated 30 min later. The viscous solution was poured into rapidly stirred 2.2 l. of hexane. The resulting

(12) These are root mean square deviations.

fibrous solid was filtered, washed thoroughly with hexane, and dried. It was then cut into small pieces and shredded in a blender under hexane. Filtration and subsequent drying at 100° (1 mm) gave 46.8 g (94.7%) of snow-white polymer: DTA, small endotherms at 80° and 117°, degradation endotherm peaks at 450°; TGA, 5% weight loss at 381°, 94.7% loss at 500°; inherent viscosity (0.1% in $CHCl_3$) 1.62.

Anal. Calcd for $(C_5H_6N_2)_n$: C, 63.8; H, 6.43; N, 29.8. Found: C, 63.5; H, 6.47; N, 29.7; mol wt (osmometric in dioxane), 148,500.

In similar experiments polymers with inherent viscosities of 3.13 and 1.76 and apparent mol wt of 250,000–360,000 were obtained.

Poly(2-propenylpyrazole).—To a solution of 50 ml of 1-(2-propenyl)pyrazole in 100 ml of benzene was added about 4 mg of azobisisobutyronitrile and the solution was stirred at 80° for 30 min. Another 4 mg of initiator was added and this was repeated after another 20 min. After a total of 3 hr at 80°, the thick solution was poured into 2 l. of stirred hexane. A solid which precipitated was filtered, washed with hexane, and dried *in vacuo*. The polymer was obtained in 32-g (67%) yield.

Anal. Calcd for $(C_6H_8N_2)_n$: C, 66.6; H, 7.46; N, 25.9. Found: C, 65.7; H, 7.44; N, 26.2.

Registry No.—**1**, 20173-98-2; **2**, 25834-28-0; **3**, 25834-29-1; **4**, 25834-30-4; **5**, 25834-31-5; **6**, 25834-32-6; **7**, 25834-33-7; **8**, 25834-34-8; **9**, 25834-35-9; **10**, 25834-36-0; **11**, 25834-37-1; **12**, 25834-38-2; 1-vinylpyrazole polymer, 25823-41-0; poly(2-propenylpyrazole), 25823-42-1.

Cleavage of Pyridyl Methyl Ethers and Reactions of 3-Halopyridines with Sodium Methoxide

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2-, 3- and 4-methoxypyridine and also anisole are readily cleaved to their hydroxy arenes and methyl ether in an SN2 reaction by sodium methoxide in methanol. At 164.7° the methoxpyridines react at relative rates 1.0:1.1:2.8, respectively. Using CD_3OD–D_2O as solvent and nmr analysis, it was possible to distinguish between CH_3OCD_3 and CH_3OD reaction products and thereby show that deuterioxide ion does not compete with methoxide ion in the cleavage of 3-methoxypyridine. With 4-methoxypyridine, methoxyl group exchange is faster than the formation of 4-hydroxypyridine. 3-Methoxypyridine undergoes hydrogen–deuterium exchange in the order H-4 > H-5 > H-2; no exchange at H-6 was observed. Hydrogen–deuterium exchange took place at H-3,5 but not at H-2,6 of 4-methoxypyridine. At 218°, 3-chloro- and 3-bromopyridine react with sodium methoxide to give 3-methoxypyridine which then undergoes ether cleavage. The concentrations of all pyridines in the consecutive reactions were followed by nmr. The ratios of the second-order rate constants for methoxy dehalogenation and ether cleavage at 218° are 0.53 and 0.75, respectively. Reactions leading to hydroxy compounds are of preparative value. No evidence was found for the formation of 3,4-pyridyne by dehydro halogenation of the halopyridines.

The preferred general method of cleaving ethers continues to involve the use of a strong acid.[1,2] Cleavage of ethers by bases, however, is regarded more as a curiosity, if not as an undesirable side reaction.[3] It has been suggested that cleavage of ethers by alcoholic KOH is of no preparative value.[4]

We wish to report the results of some preparative and kinetic studies of the methoxide ion induced cleavage of pyridyl methyl ethers. These studies were designed to (1) show that the cleavage reaction is of preparative value, (2) provide evidence for the expected SN2 mechanism, (3) obtain a measure of the ability of the aryl group to influence reactivity, (4) determine whether in a methanol–water mixture hydroxide ion competes with methoxide ion, and (5) determine the ability of a polar, aprotic solvent to influence the rate of ether cleavage.

We also report that 3-chloro- and 3-bromopyridine undergo methoxy dehalogenation at rates slightly slower than the accompanying ether cleavage.

Results and Discussion

Ether Cleavage.—3-Methoxypyridine undergoes cleavage by sodium methoxide in methanol and also in dimethyl sulfoxide (DMSO). That the anion of 3-hydroxypyridine was being formed was established by comparison with an authentic sample. The formation of methyl ether was established by mass spectrometry; this substance was distilled at 0° from a DMSO reaction mixture and characterized by its mass spectrum. It was possible to follow the disappearance of the methoxypyridine quantitatively using nmr because peaks of 3-hydroxypyridine anion are shifted upfield with respect to the starting material.

In principle, 3-methoxypyridine may undergo a cleavage reaction involving not only methoxide ion but also hydroxide ion.[5] Hydroxide ion is present in methanol–sodium methoxide when the methanol is not anhydrous[6] (eq 1). Since it is difficult to remove all

$$CH_3O^- + H_2O \rightleftharpoons CH_3OH + OH^- \quad (1)$$

traces of water from methanol, we attempted to determine whether hydroxide ion was responsible for a part of the cleavage. This was done using CD_3OD–CD_3ONa and CD_3OD–CD_3ONa–D_2O. Use of a deuterio rather than a proteo solvent makes it possible to employ nmr to identify cleavage products containing a methoxyl group. In proteo methanol signals for these products overlap with those of the solvent.

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(1) R. L. Burwell, *Chem. Rev.*, **54**, 615 (1954).

(2) E. Staude and F. Patat in "The Chemistry of the Ether Linkage," S. Patai, Ed., Interscience, New York, N. Y., 1967, Chapter 2.

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(4) L. Brandsma and J. F. Arens, in "The Chemistry of the Ether Linkage," S. Patai, Ed., Interscience, New York, N. Y., 1967, Chapter 13.

(5) Cleavage of 3-methoxypyridine by methoxide ion was first observed in our laboratory by Dr. Larry S. Helmick.

(6) J. Hine and M. Hine, *J. Amer. Chem. Soc.*, **74**, 5266 (1952).

Equations 2–7 give possible reactions between methoxypyridine and CD_3O^- and OD^-. In principle both of these oxide bases may react with the heterocyclic ether at either the saturated or ring carbon to give cleavage products. Reactions of methoxide-d_3 ion at

$$PyOCH_3 + CD_3O^- \longrightarrow PyO^- + CH_3OCD_3 \quad (2)$$

$$PyOCH_3 + CD_3O^- \longrightarrow PyOCD_3 + CH_3O^- \quad (3)$$

$$PyOCD_3 + CD_3O^- \longrightarrow PyO^- + CD_3OCD_3 \quad (4)$$

$$PyO^*CH_3 + OD^- \longrightarrow PyO^{*-} + CH_3OD \quad (5)$$

$$PyO^*CH_3 + OD^- \longrightarrow PyO^- + CH_3O^*D \quad (6)$$

$$PyOCD_3 + OD^- \longrightarrow PyO^- + CD_3OD \quad (7)$$

the saturated carbon are given in eq 2 and 4 and at the ring carbon in eq 3. Note that this latter reaction results in the formation of a new pyridyl methyl ether, one containing a CD_3O group; methoxy group exchange has taken place. Reaction of deuterioxide ion at the saturated carbon is given in eq 5 and at the ring carbon in eq 6, the symbol * serving to distinguish between the ether and deuterioxide ion oxygen atoms. Reaction of deuterioxide ion with the CD_3O ether in eq 7 may take place at the saturated or ring carbon.

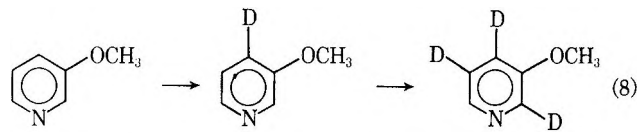
Reactions involving the methoxide ion may lead to methanol and methyl ether products while the deuterioxide (hydroxide) ion leads only to methanol. Each of these two products may be detected by nmr when CD_3OD serves as solvent; the latter peak was found to be 4.5 Hz downfield from the ether signal. However, quantitative analysis of each product is not possible, largely because signals lie within the multiplet of the residual CD_2HOD present in the solvent. Moreover, any CD_3OCD_3 and CD_3OD produced in reactions such as those in eq 4 and 7 are not measured by proton magnetic resonance.

The cleavage of 3-methyoxypyridine in CD_3OD–CD_3ONa was observed in two separate experiments. In the first no D_2O was added to the solvent. In the second 1.5 equiv (relative to the pyridine) of D_2O were added in order to ensure that the methanol was wet.

In both experiments at 164.7° as the signal of the methyl group of $PyOCH_3$ diminished, a signal due to CH_3OCD_3 appeared. No signal indicating the formation of CH_3OD could be detected, even after most of the substrate was consumed.

In order to show that the new signal appearing was due to CD_3OCH_3 and not to CH_3OD, the mixture was frozen in liquid nitrogen, the nmr tube opened, and CH_3OD injected in an amount corresponding to about 10% of the original quantity of heterocyclic ether. The nmr spectrum of this mixture clearly revealed the presence of the added methanol. Thus, even in the presence of added water no detectable reaction occurs between 3-methoxypyridine and deuterioxide ion. The stoichiometry of the ether cleavage reaction is given by eq 2.

The CD_3OD experiments also provide information about the ability of 3-methoxypyridine to deprotonate to give carbanions. Hydrogen–deuterium exchange was observed at positions 2, 4, and 5. That the most reactive site in 3-methoxypyridine is H-4 has been demonstrated.[7] H–D exchange at H-4 exceeds cleavage in rate but exchange at H-2 and H-5 is competitive with cleavage. Assignments of positions undergoing H–D exchange were based on chemical shifts and by changes in the spin coupling patterns.[8] Since substrate and base are consumed by ether cleavage, no attempt was made to obtain rate constants for hydrogen exchange. Rather, a rate constant ratio was obtained from a log–log plot of the percentage of hydrogen at H-5 *vs.* the percentage at H-2. Thus H-5 undergoes exchange 1.9 times as fast as H-2. Exchange was not observed at H-6. The order of introduction of deuterium into 3-methoxypyridine by means of methoxypyridyl anion formation is given in eq 8.



(8)

These H–D exchange results indicate that a methoxyl group exerts similar effects on the reactivity of ortho and meta positions. This is seen by comparison with H–D exchange data for pyridine. Under the same conditions pyridine undergoes H–D exchange at positions (H-3,5) meta to nitrogen 9.3 times as fast as at positions (H-2,6) ortho to nitrogen.[9] In 3-methoxypyridine a position (H-5) meta to both nitrogen and the methoxyl group is only 1.9 times as reactive as a position (H-2) ortho to both of these. That is, the effect of the ortho methoxy group is only 4.9 times as large as that of the meta methoxy group, assuming additivity of effects.

In proteo methanol only the cleavage of the ether linkage of 3-methoxypyridine is observable. Kinetic studies using CH_3OH–CH_3ONa were carried out under second-order conditions, CH_3ONa generally being in excess (Table I). Results from runs at two different base concentrations at 190.7° indicate that the second-order rate constant increases with increasing base concentration. This is not unexpected. Concentration is not the proper "acidity function" to be employed at high concentrations of methoxide ion.[10] Results from studies employing similar base concentrations at three temperatures give a linear Arrhenius plot; ΔH^* is

TABLE I

RATES OF CLEAVAGE OF PYRIDYL METHYL ETHERS BY SODIUM METHOXIDE

Substituted pyridine	Temp,[a] °C	Solvent	[CH_3ONa],[b] M	10^4k_2, M^{-1} sec^{-1}
3-OCH_3	164.7	CH_3OH	0.968	0.47
3-OCH_3	190.7	CH_3OH	0.893	3.6
3-OCH_3	190.7	CH_3OH	0.488	2.2
3-OCH_3	218	CH_3OH	0.769	22.
3-OCH_3	164.7	CH_3OH–DMSO[c]	1.08[d]	6.4[d]
3-OCH_3	164.7	DMSO	Satd[e]	...[f]
4-OCH_3	164.7	CH_3OH	0.968	1.2
2-OCH_3	164.7	CH_3OH	0.968	0.42

[a] ±0.5°. [b] Corrected for thermal expansion. [c] 1:2.3 (v/v) CH_3OH–DMSO. [d] Uncorrected for thermal expansion. [e] Suspension of CH_3ONa in DMSO. [f] Pseudo-first-order rate constant is 5.6×10^{-4} sec^{-1}.

(7) I. F. Tupitsyn, N. N. Zatsepina, A. V. Kirova, and Yu. M. Kapustin, *Reakts. Sposobnost Org. Soedin.*, **5**, 243 (1968).

(8) For an illustration of the method, see J. A. Zoltewicz and G. M. Kaufman, *Tetrahedron Lett.*, 337 (1967).

(9) J. A. Zoltewicz, C. L. Smith, and G. Grahe, *J. Amer. Chem. Soc.*, **91**, 5501 (1969).

(10) C. H. Rochester, *Quart. Rev. (London)*, **20**, 511 (1966).

29.9 ± 1.1 kcal/mol and ΔS^* is −11 ± 2 eu. The negative entropy term also suggests an S_N2 mechanism.

Addition of dimethyl sulfoxide (DMSO) to the methanolic reaction mixture resulted in an increase in the rate of cleavage of 3-methoxypyridine by methoxide ion. In a 1:2.3 (v/v) mixture of CH_3OH–DMSO at 164.7° cleavage was about 14 times as fast as in neat methanol. Cleavage of this ether by sodium methoxide also was observed in neat DMSO. Rates of cleavage in the mixed solvent and in neat DMSO were essentially the same; the concentration of sodium methoxide in the mixed solvent was about 1 *M*. It is interesting to note that, although the sodium methoxide is not very soluble in DMSO, a good pseudo-first-order rate plot for cleavage was observed. We interpret this to mean that, in spite of the consumption of sodium methoxide in the cleavage reaction, essentially a constant concentration of this base is maintained in solution, provided that solid base is present. A suspension of sodium methoxide in DMSO appears to be a useful reagent for the cleavage of ethers. This mixture is an alternative to homogeneous CH_3ONa–CH_3OH.

2- and 4-methoxypyridine were cleaved by CH_3ONa–CH_3OH at 164.7°. That the anions of 2- and 4-hydroxypyridine[11] were products was determined by comparison with authentic materials. Rate constants are given in Table I.

The cleavage of 4-methoxypyridine was also studied in CD_3OD–CD_3ONa at 164.7° containing 1.5 equiv of added D_2O. Both CH_3OCD_3 and CH_3OD products were found. In addition considerable exchange of the methoxyl group of the pyridyl ether resulted. For example, the amounts of CH_3O, CD_3O, and DO (sodium salt) pyridine present at one point during the reaction were 26, 53, and 21%, respectively, and later 9, 58, and 33%. Methoxy group exchange is faster than ether cleavage. Because CH_3OD is liberated by methoxy group exchange (eq 3), we are unable to rule out the possible formation of this product by the action of OD^- (eq 5 and 6).

Our data on the cleavage of 3-methoxypyridine and on the reaction of 3-bromopyridine in methanol–water, described below, indicate that attack of hydroxide ion is not competitive with attack of methoxide ion on a saturated or an unsaturated carbon.[13] Note that this comparison involves both nucleophiles attacking carbon in the same state of hybridization. Whether cleavage of 4-methoxypyridine by hydroxide ion attack at the ring carbon is competitive with methoxide ion attack at the saturated carbon is not clear. The 2- and 4-methoxypyridines are likely to show similar reactivities toward both oxide ion nucleophiles.

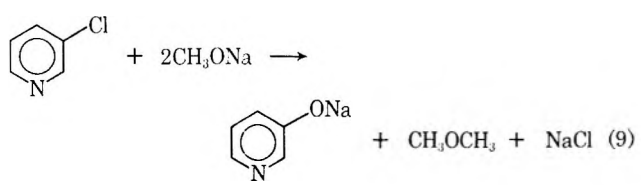
In general, it seems likely that in methanol–water mixtures some methyl aryl ethers may undergo cleavage by preferential reaction with the methoxide ion at the saturated carbon while others may undergo reaction with hydroxide ion at the unsaturated carbon, methoxide ion giving rise to methoxyl group exchange. Experiments similar to ours using CD_3OD may be useful to help determine the pathways being followed.

3-Methylthiopyridine in CH_3ONa–CH_3OH at 165° did not undergo detectable cleavage. Under the conditions employed, 3-methoxypyridine would have reacted completely. Thio ethers are said to be less reactive than their ether counterparts.[1,4]

Anisole underwent cleavage in 1 *M* CH_3ONa–CH_3OH at 218°; the reaction was essentially complete after 24 hr. Overlap of the phenolate ion protons with those of anisole precluded an accurate nmr kinetic study. Phenol was recovered in 70% yield as its 2,4,6-tribromo derivative after heating anisole at reflux in CH_3OH–CH_3ONa–DMSO. By contrast anisole is reported to be cleaved to a small degree in alcoholic KOH at 180–200°.[14] The facility of cleavage of the four methyl ethers investigated is 4-pyridyl > 3-pyridyl > 2-pyridyl > phenyl. For the 4-, 3-, and 2-methoxypyridines relative reactivity ratios at 164.7° are 2.8:1.1:1.0, respectively. This order qualitatively correlates with the acidity of the hydroxypyridines. Room temperature pK_a values are 7.80, 8.36, and 8.66, respectively.[15,16] Moreover, phenol is the least acidic of the four compounds considered and anisole is the least reactive ether.

3-Methylthiopyridine is less reactive than any of the three methoxypyridines although 3-mercaptopyridine with a pK_a = 4.8[17] is more acidic than any of the hydroxypyridines. However, the carbon affinity of sulfur is greater than the carbon affinity of oxygen.[18]

Consecutive Methoxy Dehalogenation and Ether Cleavage.—Comparison of our rate constant (2.2×10^{-3} M^{-1} sec^{-1}, 218°) for the cleavage of 3-methoxypyridine with that (5.1×10^{-4} M^{-1} sec^{-1}, 220°) reported for the formation of 3-methoxypyridine from 3-chloropyridine in methanol[19] suggested that the dehalogenation reaction was more complicated than previously realized. This comparison prompted us to attempt the conversion of 3-chloropyridine to 3-hydroxypyridine in CH_3ONa–CH_3OH according to eq 9. A 70% yield resulted. The reaction constitutes a convenient, one-



step conversion and appears to be superior to an older method giving low yields and employing a halopyridine, copper sulfate, and aqueous alkali.[20]

In view of these results a kinetic study was undertaken to redetermine the rate constant for methoxy dechlorination. Equimolar quantities of 3-chloropyridine and sodium methoxide were allowed to react at 218° and the reaction was followed by nmr. The

(11) Although 2- and 4-"hydroxy"-pyridines exist largely as their pyridone tautomers,[12] we employ the hydroxy nomenclature for the sake of clarity and emphasis. Cleavage of hydroxy derivatives are being considered.

(12) A. R. Katritzky and J. M. Lagowski, *Advan. Heterocycl. Chem.*, **1**, 339 (1963).

(13) For additional information, see J. F. Bunnett and G. T. Davis, *J. Amer. Chem. Soc.*, **76**, 3011 (1954).

(14) R. Stoermer and B. Kahlert, *Chem. Ber.*, **34**, 1812 (1901).

(15) These values refer to dissociation of the hydroxypyridine tautomer.

(16) K. Schofield, "Hetero-Aromatic Nitrogen Compounds. Pyrroles and Pyridines," Plenum Publishing Co., New York, N. Y., 1967, pp 148, 152–154.

(17) This value refers to dissociation of the thiol tautomer.[16]

(18) J. Hine and R. D. Weimar, Jr., *J. Amer. Chem. Soc.*, **87**, 3387 (1965).

(19) M. Liveris and J. Miller, *J. Chem. Soc.*, 3486 (1963).

(20) H. Maier-Bode, *Chem. Ber.*, **69**, 1534 (1936).

H-2,6 multiplets of 3-chloro- and 3-methoxypyridine and the H-4,5 multiplets of the anion of 3-hydroxypyridine are clearly separated from other aromatic ring hydrogen signals. The centers of these multiplets are ound at τ 1.5, 1.8, and 3.1, respectively. This favorable situation allowed the concentrations of all pyridine species to be determined as a function of time. The results shown in Figure 1 indicate that 3-chloropyridine is converted to 3-methoxypyridine which in turn reacts to yield the anion of 3-hydroxypyridine. The concentrations of chloropyridine and hydroxypyridine anion tend toward a common value. This is estimated to be 38% of the initial pyridine concentration. The amount of methoxypyridine rises to a maximum of about 28% and then decreases to about 24%.

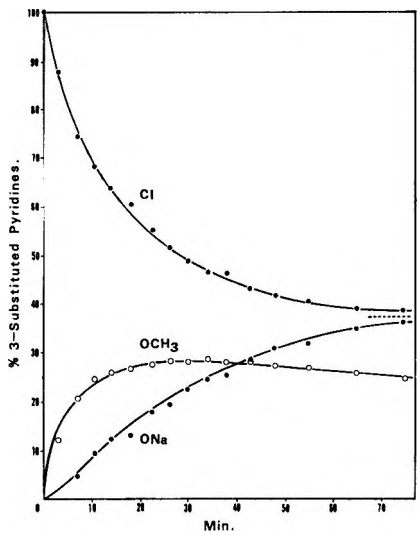


Figure 1.—Plots of the molar percentages of 3-substituted pyridines in the reaction of 3-chloropyridine with sodium methoxide in methanol at 218° as a function of time. Concentrations of starting material, 3-methoxypyridine intermediate, and the sodium salt of 3-hydroxypyridine were followed by nmr. Reactants were present initially at the same concentration, 0.381 *M*. The dashed line indicates a limiting value.

This concentration–time dependence is characteristic of a reaction system consisting of two competitive, consecutive, irreversible, second-order reactions. It is to be noted that when equimolar quantities of two starting materials A and B are employed, starting material A and a product resulting at the end of the two-step sequence approach the same limiting concentration as reactant B is consumed. Moreover, the maximum amount of intermediate formed is independent of the relative concentrations of reactants used.

Knowing the concentration ratios in the consecutive reactions, it is possible to obtain the rate-constant ratio for the two reactions. Two different methods were employed;[21,22] both gave essentially the same results. At 218° methoxy dechlorination of 3-chloropyridine has a second-order rate constant which is 0.53 times as large as that for cleavage of 3-methoxypyridine by methoxide ion. Since the ether cleavage rate constant was determined separately (Table 1), the rate constant for dechlorination is calculated to be $1.2 \times 10^{-3} M^{-1}$ sec^{-1}.

Treating the reaction of 3-chloropyridine with CH_3ONa–CH_3OH as a simple second-order reaction generates a curved rate plot. However, a linear region corresponding to about 50% reaction of the chloropyridine does result. This portion of the plot gives a rate constant, $1.0 \times 10^{-3} M^{-1}$ sec^{-1}, in good agreement with that obtained from the consecutive reaction treatment above. Our value is about twice as large as the previously reported value.[19] This may be due in part to the relative weight given to the points in constructing a second-order plot; the points later in the reaction giving rise to a smaller apparent constant. Salt effects may be another factor, since different salt concentrations were employed.

The reaction of 3-bromopyridine with CH_3ONa–CH_3OH at 218° also gave rise to 3-methoxypyridine and the anion of 3-hydroxypyridine. When equimolar amounts of the initial reactants were employed, the concentration of 3-bromopyridine and the anion of 3-hydroxypyridine tended to a limiting value of 35%. The concentration of 3-methoxypyridine rose to a maximum of 32% and then decreased to about 30%. The rate constant ratio of the first to the second reaction is 0.75. Hence, the rate constant for methoxy debromination is 40% as large as that for methoxy dechlorination (Table II). This result indicating a lack of an "element effect" in the dehalogenation reactions is good evidence for the expected aromatic, nucleophilic substitution mechanism.[23]

TABLE II

KINETICS OF METHOXY DEHALOGENATION OF 3-HALOPYRIDINES IN METHANOL AT 218°

Halogen[a]	$[CH_3ONa]$,[b] M	10^4k, M^{-1} sec^{-1}
Cl	0.381	1.2
Br	0.433	1.7

[a] Same concentration as sodium methoxide. [b] Corrected for thermal expansion.

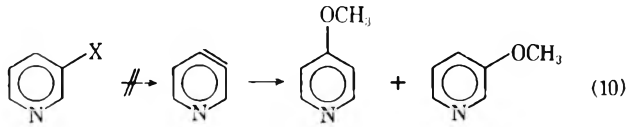
Curiously, 3-bromopyridine and methanolic KOH are reported to give 3-methoxypyridine in 87% yield but experimental details are lacking.[24] In an attempt to repeat this at 165° using a 5% excess of potassium hydroxide in methanol we found the amount of 3-methoxypyridine to rise to a maximum value of 36% after 9 hr and then decrease. The hydroxypyridine anion was the other product and was present to a lesser extent than the methoxypyridine. Note that these results show that the rate of hydroxide ion attack at the unsaturated carbon is less than the rate for methoxide ion.[13]

Noteably methoxy dehalogenation of 2- and 4-chloropyridines occurs rapidly enough so that ether cleavage is not a serious side reaction.[19]

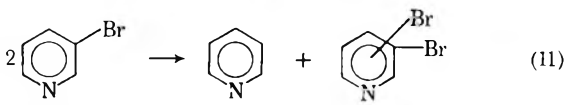
Our results also eliminate 3,4-pyridyne[25] formation

(21) P. R. Wells, *J. Phys. Chem.*, **63**, 1978 (1959).
(22) W. G. McMillan, *J. Amer. Chem. Soc.*, **79**, 4838 (1957).
(23) J. F. Bunnett, E. W. Garbisch, Jr., and K. M. Pruitt, *ibid.*, **91**, 6746 (1969).
(24) E. Koenigs, H. C. Gerdes, and A. Sirot, *Chem. Ber.*, **61**, 1022 (1928).
(25) For reviews, see T. Kaufmann, *Angew. Chem., Int. Ed. Engl.*, **4**, 543 (1965); H. J. den Hertog and H. C. van der Plas, *Advan. Heterocycl. Chem.*, **4**, 121 (1965).

(eq 10) and halogen transfer,[26] as serious competing reactions of 3-halopyridines with sodium methoxide.



(10)



(11)

Although the 4 anions of 3-halopyridines are formed in CH_3ONa–CH_3OH,[32] there is no evidence among the reaction products of 3,4-pyridyne formation. All of the pyridine components present in the reaction mixture are accountable in terms of 3-halo-, 3-methoxy-, and the anion of 3-hydroxypyridine to within an uncertainty of about 7%. This was determined by nmr using *tert*-butyl alcohol as a reference standard. This uncertainty reflects the combined uncertainty in the four nmr measurements. Moreover, 3- and 4-methoxypyridines are expected to result from the reactions of 3,4-pyridyne (eq 10). These ethers would undergo cleavage as well. If the anion of 4-hydroxypyridine were formed, it would have been detected among the substituted pyridines, using its H-3,5 signals centered at τ 3.6. Signals at this chemical shift were not detected during the reactions of 3-halopyridines. Moreover, the H-2,6 signals of pyridine, a product of halogen transfer, also could not be detected. Since these pyridine signals overlap with those of halopyridine starting material, removal of the halopyridine was required. This was achieved when excess sodium methoxide was employed. Thus our experiments set an upper limit of about 7% to the degree of 3,4-pyridyne formation and to halogen transfer which might occur during the reactions of 3-chloro- and 3-bromopyridine with CH_3ONa–CH_3OH at 218°.

In summary, pyridyl methyl ethers are cleaved by methoxide ion in an SN2 reaction. Methoxy dehalogenations of 3-halopyridines are complicated by this cleavage reaction.[32a]

Experimental Section

Materials.—Anisole, 2-methoxy- and 3-hydroxypyridine, and 2- and 4-pyridone were commercially available. Methanol-d_4 containing about 0.5% CD_2HOD was obtained from Merck Chemical Division. 3-Thiomethoxy-[33] and 3-[34] and 4-methoxypyridine[35] were prepared. Methanol was dried by distillation from magnesium methoxide, *tert*-butyl alcohol from potassium *tert*-butoxide. Sodium methoxide solutions were prepared by dissolving freshly cut sodium in dry methanol under dry nitrogen; solutions were standardized as before.[36] Dimethyl sulfoxide was dried over molecular sieves. Solutions were protected from air by serum stoppers and transfers were made by syringe.

Cleavage of Anisole by Sodium Methoxide in Methanol–DMSO.—To a mixture of 10 ml of methanol and 40 ml of dimethyl sulfoxide were added 5.4 g (0.050 mol) of anisole and 5.4 g (0.1 mol) of commercial powdered sodium methoxide. After heating at reflux for 18 hr, the solution was concentrated at atmospheric pressure to 0.5 volume and then diluted with water and acidified with hydrochloric acid. The filtered solution was treated with aqueous bromine and the phenol was isolated as 2,4,6-tribromophenol (12 g, 70%), mp 93–95° (lit.[37] mp 95–96°).

Preparation of 3-Hydroxypyridine from 3-Chloropyridine and Sodium Methoxide–Methanol.—A mixture of 1.2 g (0.0094 mol) of 3-chloropyridine and 20 ml of a saturated solution of sodium methoxide in methanol was heated in a metal bomb at 230° (metal bath temperature) for 4 hr. On cooling, the mixture was carefully diluted with water, neutralized with dilute hydrochloric acid, and evaporated under reduced pressure to a small volume. 3-Hydroxypyridine was recovered by filtration. Evaporation of the mother liquor to dryness and extraction of the residue with acetone gave a further crop; the combined yield of 3-hydroxypyridine, mp 126–128° (lit.[38] mp 124.5°), was 0.60 g (70%).

Kinetic Procedure. I. Cleavage of Methoxypyridines by Sodium Methoxide.—The reaction solution for a typical run was prepared by syringing aliquots of sodium methoxide, *tert*-butyl alcohol reference compound, dimethyl sulfoxide for mixed solvents runs, and the methyl ether into a 2-ml volumetric flask and diluting to mark with dry methanol. In the case of neat dimethyl sulfoxide, excess powdered sodium methoxide was employed. Ether concentrations were generally 0.3–0.4 *M* after mixing. An aliquot of this solution was placed into a nitrogen-filled nmr tube which was then sealed. After an nmr spectrum was obtained, the tube was suspended in a constant-temperature vapor bath (mesitylene, 164.7°; benzonitrile, 190.7°; naphthalene, 218°). The spectrum of the cooled sample was obtained on a Varian A-60A spectrometer and integrated.

The ratio of the areas of the H-2,6 peaks of 3- and 4-methoxypyridine and the H-6 peaks of the 2-methoxypyridine to the area of the reference compound provides a measure of the extent of reaction. These signals of the ether reactant do not overlap with signals from the product. Ratios used in plots were based on an average of six or more integration sweeps, caution being taken to avoid saturation effects.

When the methoxide ion concentration exceeded the ether concentration, kinetic plots were constructed by plotting the logarithm of $[CH_3ONa]/[PyOCH_3]$ against time. Second-order constants were obtained from the slope of the best visual line through the points. Good straight lines were obtained.

When the initial concentrations of methoxide ion and ether were the same, the nmr area ratios of standard to substrate were plotted against time.

Concentrations are corrected for thermal expansion by multiplying concentrations at room temperature by the ratio of the density of methanol at the reaction temperature to that at room temperature.[39] Results are given in Table I.

The amount of sodium methoxide consumed during kinetic runs was determined by titration. To an aliquot of a reaction mixture was added 2.00 ml of 0.999 *M* hydrochloric acid. The acidic solution then was potentiometrically titrated with 0.195 *M* sodium hydroxide. Three equivalence points were observed. The first due to titration of excess hydrochloric acid, the second to pyridinium ions, and the third to hydroxypyridine. The equivalence point for the latter was not sharp, however. From

(26) Halogen transfer has been observed to take place in pyridines,[27] benzenes,[28] thiophenes,[29] isothiazoles,[30] and imidazoles,[31] amide ion frequently serving as a catalyst. Bromine atom transfer is faster than transfer of a chorine atom.

(27) M. J. Pieterse and H. J. den Hertog, *Recl. Trav. Chim. Pays-Bas*, **81**, 855 (1962).

(28) C. E. Moyer, Jr., and J. F. Bunnett, *J. Amer. Chem. Soc.*, **85**, 1891 (1963); J. F. Bunnett and D. J. McLennan, *ibid.*, **90**, 2190 (1968).

(29) M. G. Reinecke and H. W. Adickes, *ibid.*, **90**, 511 (1968); S. Gronowitz and B. Holm, *Acta Chem. Scand.*, **23**, 2207 (1969).

(30) D. A. deBie and H. C. van der Plas, *Tetrahedron Lett.*, 3905 (1968).

(31) D. A. deBie and H. C. van der Plas, *Recl. Trav. Chim. Pays-Bas*, **88**, 1246 (1969).

(32) J. A. Zoltewicz and C. L. Smith, *Tetrahedron*, **25**, 4331 (1969).

(32a) NOTE ADDED IN PROOF.—A useful method of cleaving substituted anisoles involves thioethoxide ion in *N*,*N*-dimethylformamide: G. I. Feutrill and R. N. Mirrington, *Tetrahedron Lett.*, 1327 (1970). 1-Ethyl-2-methoxy-5-nitropyridinium salts undergo ether cleavage reactions with a variety of nucleophiles: T. Severin, D. Bätz, and H. Lerche, *Chem. Ber.*, **103**, 1 (1970).

(33) J. A. Zoltewicz and C. Nisi, *J. Org. Chem.*, **34**, 765 (1969).

(34) D. A. Prins, *Recl. Trav. Chim. Pays-Bas*, **76**, 58 (1957).

(35) E. Spinner and J. C. B. White, *Chem. Ind. (London)*, 1784 (1967).

(36) J. A. Zoltewicz and G. M. Kauffman, *J. Org. Chem.*, **34**, 1405 (1969).

(37) "Handbook of Chemistry and Physics," R. C. Weast, S. M. Selby, and C. D. Hodgman, Ed., 46th ed, Chemical Rubber Co., Cleveland, Ohio, 1965, p c-470.

(38) O. Fischer and E. Renouf, *Chem. Ber.*, **17**, 1896 (1884).

(39) J. Timmermans, "Physico-Chemical Constants of Pure Organic Compounds," Vol. I, Elsevier, New York, N. Y., 1950, p 303.

these data and the degree of ether cleavage it is possible to calculate the amount of sodium methoxide remaining prior to acidification. Concentrations agreed to within a few per cent of expected values, assuming the stoichiometry of eq 2.

The methods employed to investigate ether cleavage reactions in CD_3OD–CD_3ONa were similar to those employed when the solvent was proteo methanol. In the case of 4-methoxypyridine, methoxy group exchange was observed. The extent of this exchange was determined by comparison of the nmr area of the CH_3O group in the pyridyl ether with the H-2,6 area of this ether. The H-2,6 area provides a measure of CH_3O and CD_3O substrate while the CH_3O signal provides a measure of substrate not having undergone methoxyl group exchange. Even though hydrogen–deuterium exchange does take place at H-3,5 of 4-methoxypyridine, none was detected at H-2,6. The combined areas of H-2,6 of 4-methoxypyridine and of H-2,6 of the anion of 4-hydroxypyridine relative to added *tert*-butyl alcohol internal standard were constant throughout ether cleavage and hydrogen exchange.

II. 3-Chloro- or 3-Bromopyridine and Sodium Methoxide–Methanol. Consecutive, Competing Reactions.—Methods were similar to those given above with the following modifications. Equimolar quantities (Table II) of halopyridine and methanolic sodium methoxide were heated at 218° in sealed nmr tubes. The disappearance of the halo compound was followed by observing its H-2,6 signals centered at τ 1.5, the 3-methoxypyridine H-2,6 signals at τ 1.8 and the H-4,5 signals of the anion of 3-hydroxypyridine centered at τ 3.1. *tert*-Butyl alcohol τ 8.8 served as a reference standard.

The sum of the nmr areas at τ 1.5, 1.8, and 3.1 provides a measure of the total amount of the three pyridines and the ratio of one of the three areas to the total represents the fractional amount of that pyridine present. In Figure 1 these fractions, as percentages, are given as a function of time for the chloropyridine reaction. Similar curves were obtained for the bromopyridine reaction. Some difficulty was encountered with nmr determinations of the chloro reaction mixture, owing to the precipitation of NaCl. Vigorous shaking of the sample tube prior to determinations proved to be beneficial. Sodium bromide was soluble at ambient temperatures.

3-Halopyridine, 3-methoxypyridine, and the anion of 3-hydroxypyridine approach limiting concentrations as the concentration of sodium methoxide tends to zero. For the 3-chloropyridine the limiting percentages are estimated to be 38, 24, and 38, respectively. For 3-bromopyridine these percentages are 35, 30, and 35, respectively.

The ratio of the second-order rate constants for methoxy dehalogenation and methyl ether cleavage was estimated in two ways, the method of Wells[21] employing concentration ratios at the end of the reaction and the method of McMillan[22] employing concentration ratios for arbitrary degrees of reaction. Both methods gave results in agreement. For 3-chloropyridine the ratio of the rate constants for methoxy dehalogenation and ether cleavage is 0.53, for 3-bromopyridine 0.75. Thus, methoxy debromination is about 40% faster than methoxy dechlorination. It is to be noted that the sodium halide is incompletely soluble at the reaction temperature.

In a control experiment 3-methoxypyridine was heated with NaCl in methanol at 218°. After 10 hr some 28% of the methoxypyridine had reacted but no attempt was made at characterization. Note that in the above kinetic experiments the reaction time did not exceed 90 min.

Registry No.—2-Methoxypyridine, 1628-89-3; 3-methoxypyridine, 7295-76-3; 4-methoxypyridine, 620-08-6; sodium methoxide, 124-41-4; anisole, 100-66-3; 3-chloropyridine, 626-60-8; 3-bromopyridine, 626-55-1.

Acknowledgment.—We gratefully acknowledge partial support of this research by the National Science Foundation (GP-9488).

Basicities and H–D Exchange of Pyrazine N-Oxides

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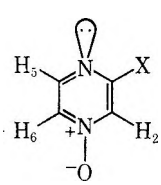
The hydrogen–deuterium exchange rates of H_2 and H_6 in some 3-substituted pyrazine 1-oxides have been correlated with σ constants, and the log of the H_2 exchange rates have been shown to be linearly related to the pK_a's of these compounds. The implication of these results upon the intermediacy of an ylide-like intermediate are discussed.

Base-catalyzed H–D exchange in pyridine N-oxide, its 3-chloro- and 3,5-dichloro derivatives have recently been described by Zoltewicz and Kauffman.[1,2] These studies showed that the 2,6 positions exchange more rapidly than the 3,5 positions, which in turn are more susceptible to H–D exchange than the 4 position. Similar, but qualitative, studies on pyridazine N-oxides showed that the protons undergo stepwise deuteration at the 6, 5, 4, and finally at the 3 position.[3]

We now wish to report the base-catalyzed H–D exchanges of the parent and of some substituted pyrazine N-oxides initiated with the aim of elucidating the effects that an additional heteroatom and different ring substituents have upon these exchange processes.

The considerable exchange-rate enhancement caused by replacement of the $=C_4-H$ function in a pyridine N-oxide by a $=N_4$ (formation of a pyrazine N-oxide) is evident from the following observations: The proton α to the N-oxide and chloro groups (H_2) in 3-chloropyrazine 1-oxide exchanges with a half-life of approximately 4 min, at 31° and in 0.0025 *N* NaOD. This compares with a half-life of 40 min for the exchange of H_2 in 3-chloropyridine N-oxide under more severe conditions (0.045 *N* NaOD and at 74°).

Because of the facility with which the pyrazine N-oxides undergo H–D exchange, they lend themselves admirably to this type of study. Furthermore, the presence of the additional heteroatom in these compounds (N_4) offers an "internal" reference standard with respect to the effect that a substituent (X in structure **1**) has upon the σ C_2–H bond in comparison with the similarly placed lone pair of electrons on N_4.



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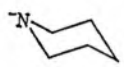
(1) J. A. Zoltewicz and G. M. Kauffman, *Tetrahedron Lett.*, 337 (1967).
(2) J. A. Zoltewicz and G. M. Kauffman, *J. Org. Chem.*, **34**, 1405 (1969).
(3) Y. Kawazoe, M. Ohnishi, and Y. Yoshioka, *Chem. Pharm. Bull.*, **12**, 1384 (1964).

TABLE I

SECOND-ORDER RATE CONSTANTS FOR H-D EXCHANGE IN NaOD-D_2O[a] AND pK_A's OF SOME 3-X-PYRAZINE 1-OXIDES

-X	Compd no.[b]	k_{H_2}, (l. mol^{-1} min^{-1})	k_{H_6}, (l. mol^{-1} min^{-1})	pK_A[c]
-CN	1	$2.8 \pm 0.2 \times 10^2$	...[d]	−1.12
-Cl	2	$7.5 \pm 0.3 \times 10$	9.9×10^{-1}	−1.05
$-OCH_3$	3	4.3 ± 0.1	2.1×10^{-2}	−0.45
$-NH_2$	4	$2.3 \pm 0.2 \times 10^{-1}$	1.1×10^{-3}	1.50, −1.92[e]
-H	5	$1.6 \pm 0.1 \times 10^{-1}$	1.6×10^{-1}	0.05
	6	$6.4 \pm 0.5 \times 10^{-1}$	7.1×10^{-4}	1.34, −1.80[e]
$-CH_3$	7	$4.6 \pm 0.4 \times 10^{-2}$	5.8×10^{-2}	0.46
$-N(CH_3)_2$	8	$3.3 \pm 0.2 \times 10^{-2}$	4.5×10^{-4}	1.34, −1.77[e]

[a] The various concentrations of NaOD used were 1.0–0.0025 *M*, and each compound was studied at more than two base concentrations. The pyrazine N-oxide concentrations employed varied from 0.5–0.05 *M*. [b] See Figure 1. [c] It is estimated that these values, obtained at room temperature, are accurate to ±20% and are based on the H_0 values used in ref 6. [d] Compound hydrolyzes before H_6 exchange occurs. [e] The second pK_A corresponds to that involving protonation of the pyrazine ring nitrogen atom. Since these values are obtained from the species where the external ring nitrogen is protonated, they cannot be used for the correlation with the rate constants.

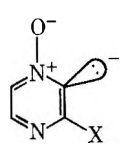
TABLE II

UV SPECTRAL DATA OF SOME 3-X-PYRAZINE 1-OXIDES

		Solvent				
		H_2O		H_2SO_4		
Compd	Substituent X	λ_{max} ($\epsilon \times 10^3$)[a]	λ_{min} ($\epsilon \times 10^3$)	λ_{max} ($\epsilon \times 10^3$)	λ_{min} ($\epsilon \times 10^3$)	H_2SO_4, *N*
5	H	213 (7.44) 263 (12.53)	230 (1.14)	228 (10.23) 285 (12.55)	245 (1.03)	7.28
7	CH_3	215 (12.05) 262 (12.77) 288 sh[a] (4.11) 297 sh (2.99)	234 (2.02)	232 (10.25) 285 (14.10)	247 (1.71)	4.79
3	OCH_3	212 (18.40) 260 (10.60) 302 (4.65)	234 (2.85) 283 (2.52)	202 (14.86) 221 sh (6.02) 281 (9.52) 305 sh (7.41)	250 (1.83)	15.29
4	NH_2[b]	232 (24.06) 260 (7.75) 331 (4.14)	251 (7.13) 289 (0.48)	225 (19.10) 278 (7.99) 338 (4.90)	250 (3.51) 305 (2.71)	7.30
8	$N(CH_3)_2$[c]	202 (9.25) 252 (30.75)	213 (4.70)	208 (6.56) 241 (21.40) 279 (7.84)	216 (5.76) 261 (5.42) 309 (1.23)	4.79
6	Piperidino[d]	205 (9.35) 256 (32.46)	217 (2.94)	211 (5.87) 246 (24.39) 277 (7.41)	218 (5.55) 270 (7.12) 309 (1.25)	4.79
2	Cl	222 (12.68) 226 (12.63) 293 sh (3.05) 303 sh (2.11)	239 (2.52)	203 (15.53) 238 (7.58) 282 (10.05) 300 sh (9.57)	221 (4.62) 255 (2.71)	35.53
	$CONH_2$	225 (17.10) 265 (9.70) 300 sh (2.02)	243 (5.33)	208 (18.51) 277 (6.02)	250 (1.60)	35.53
1	CN	229 (22.45) 272 (11.63) 310 sh (2.16)	246 (3.26)	204 (16.26) 244 (10.71) 250 sh (9.47) 290 (8.91) 315 sh (2.98)	216 (5.19) 260 (2.81)	29.31

[a] sh = shoulder. [b] The second protonation appears to be complete at 35.53 *N* H_2SO_4 with λ_{max} 221 (20.80), 348 (6.04); λ_{min} 270 (0.00). [c] The second protonation appears to be complete at 35.53 *N* H_2SO_4 with λ_{max} 236 (17.57). [d] The second protonation appears to be complete at 35.53 *N* H_2SO_4 with λ_{max} 236 sh (15.63), 244 (16.95).

Table I lists the rate constants for the exchange of H-2 in various pyrazine N-oxides of general structure **1**. These constants were obtained in the same manner as we have previously described for the H–D exchange reactions in some polyazaindenes,[4] and are first order in deuterioxide and N-oxide concentration. If we are dealing with the generation of an anion or ylide-like[1,2,4] intermediate such as **2**,[5] resulting from a σ bond cleavage, we would expect that there should exist a linear



2

free-energy relationship between the H–D exchange rates of H_2 and the σ_I parameters. Figure 1 shows the

(4) W. W. Paudler and L. S. Helmick, *J. Org. Chem.*, **33**, 1087 (1968).

(5) Since these reactions occur in aqueous media, the N-oxide function is almost certainly involved in hydrogen bonding with the solvent. This would tend to facilitate the formation of an ylide.

TABLE III

UV DATA USED IN THE DETERMINATION OF THE pK_A's FOR SOME 3-X-PYRAZINE 1-OXIDES

Substituent	λ_{used},[a] $\epsilon \times 10^3$ (solvent)[b]
H	263, 12.25 (H_2O); 4.96 (7.28 *N* H_2SO_4); 9.77 (0.97 *N* H_2SO_4)
OCH_3	260, 10.66 (H_2O); 3.70 (15.29 N H_2SO_4); 6.38 (7.30 *N* H_2SO_4)
$N(CH_3)_2$	279, 2.65 (H_2O); 7.81 (4.79 *N* H_2SO_4); 6.15 (0.21 *N* H_2SO_4)
Piperidino	280, 3.85 (H_2O); 7.29 (4.79 *N* H_2SO_4); 6.27 (0.21 *N* H_2SO_4)
NH_2	278, 1.99 (H_2O); 8.03 (7.30 *N* H_2SO_4); 6.87 (0.21 *N* H_2SO_4)
Cl	260, 11.40 (H_2O); 3.18 (35.53 *N* H_2SO_4); 11.25 (0.46 *N* H_2SO_4)
CN	270, 11.56 (H_2O); 4.43 (29.31 *N* H_2SO_4); 9.25 (15.29 *N* H_2SO_4)
$CONH_2$	265, 9.69 (H_2O); 3.73 (35.53 *N* H_2SO_4); 5.33 (15.29 *N* H_2SO_3)
CH_3	262, 12.45 (H_2O); 4.84 (4.79 *N* H_2SO_4); 9.63 (0.46 *N* H_2SO_4)

[a] The λ_{used} values represent those values where the change in ϵ is greatest in going from the nonprotonated to the protonated pyrazine N-oxides. [b] The ϵ values given correspond, respectively, to the nonprotonated, totally protonated, and partially protonated species. The totally protonated species was judged to be present when no change in ϵ was observed upon further increasing the hydrogen ion concentration of the solvent. Examples of uv spectra of pyrazine and derivatives can be found in ref 6.

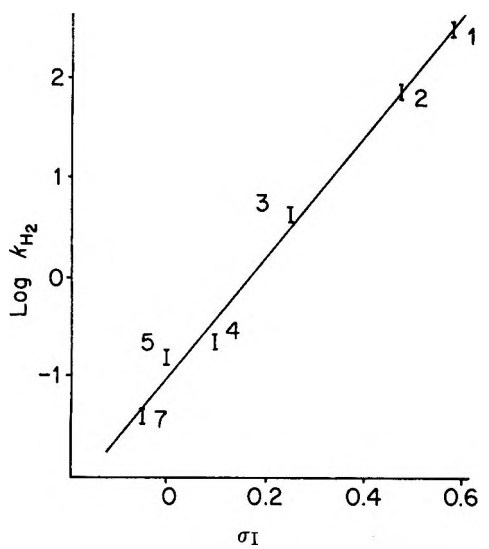
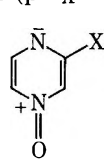


Figure 1.—Hammett correlation for base-catalyzed H_2–D_2 exchange of some 3-X-pyrazine 1-oxides (see Table I for compound identification).

quite satisfactory correlation obtained with these substituent constants, which take only the inductive effect of the substituent X into account.

A comparison of the equilibria involved in the formation of the anion (2) with that taking place in the N protonation of these pyrazine 1-oxides leads one to suggest that there should also exist a linear correlation between the p*K* and the log of the exchange rates of these compounds. If such a correlation does indeed exist, it would offer convincing evidence for the suggested H–D exchange mechanism. Furthermore, a study of the p*K*'s of these compounds also would yield some insight into the electronic effects of an N-oxide function in an aromatic system.

The strong base-weakening effect of an N-oxide group upon a *para*-situated sp^2 nitrogen atom is exemplified by a comparison of the p*K* of pyrazine ($pK_A = 0.65$)[6] with that of pyrazine N-oxide ($pK_A = 0.05$). Thus, there is



3

no significant contribution of resonance structures such as **3** to the ground state of pyrazine N-oxide.

The major effect that a 3 substituent has upon the basicity of the nonoxidized nitrogen atom ($\dot{N}_4$) in 3-substituted pyrazine 1-oxides appears to involve the inductive contribution of the substituents only (*cf.* Figure 1).[7] Thus, a correlation between the exchange rates and the basicities clearly exists. In fact there is a satisfactory linear correlation between the log k_{H_2} and the pK_A values of various 3-substituted pyrazine 1-oxides (*cf.* Figure 2). These correlations offer strong support to the idea that the H–D exchanges in pyrazine N-oxides, and probably also in other related systems (*cf.* polyazaindenes)[4] occur *via* ylide-like intermediates.

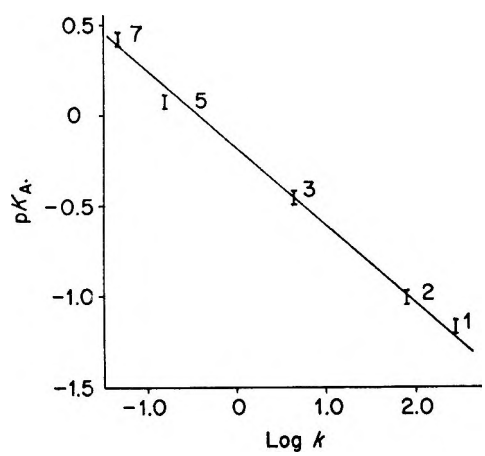


Figure 2.—pK_A correlation for base-catalyzed H_2–D_2 exchange of some 3-X-pyrazine 1-oxides (see Table I for compound identification).

Because of the distance between H_6 and the substituent X, any effect that X has upon the exchange rate would be considerably muted. An examination of the appropriate rate constants (*cf.* Table I), shows these considerations to be valid. The factors influencing the exchange rates of H_6 in these derivatives are not yet clear and must await the results of further studies on other heterocyclic ring systems.

(6) A. S. Chia and R. F. Trimble, Jr., *J. Phys. Chem.*, **65**, 863 (1961).

(7) These pK_A effects also confirm that N-4 in pyrazine 1-oxides is more basic than the oxygen atom.

Experimental Section[8]

Preparation of the N-Oxides.—The various N-oxides were prepared by procedures available in the literature.[9-11] The purity of the compounds was ascertained by tlc (alumina plates, developing solvents varied from benzene to benzene–ethyl acetate mixtures), mass spectroscopy, and melting points.

Determination of pK_A Values.—All of the pK_A's were determined spectrophotometrically (Cary 14 instrument) using seven different solutions at various H_2SO_4 concentrations. The procedure used was that described by Chia and Trimble.[6] Tables II and III list some of the pertinent uv data.

Determination of Rate Constants.—The appropriate N-oxide was weighed into an nmr tube and 0.4 ml of D_2O was added. The solution was then allowed to come to 31°, and the HA-100 instrument was adjusted. An initial spectrum and integration was then obtained. Addition of 0.1 ml of the appropriate concentration of aqueous NaOD at 31° was then added with shaking. The total time elapsed between addition of the base until the first spectrum is obtained was between 45 to 60 sec. This, as a referee pointed out, and we are certainly aware of it, allows us to get four points for the rapidly exchanging H_2 of the cyano compound. Nevertheless, the data on five different runs are reproducible within the limits indicated in Table I and cover between two and three half-lives.

In all of the other compounds, 10–15 points, covering at least two-half lives, were obtained.

(8) Nmr spectra were obtained with a Varian HA-100 spectrometer. Mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6E instrument equipped with a solid sample injector. The ionizing voltage employed was 80 V. Elemental analyses were done by Mrs. K. Decker of this department.

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(11) A. S. Elina, I. S. Musatova, and G. P. Sirova, *Khim. Geterotsikl. Soedin.*, 725 (1968).

Registry No.—**1**, 25594-31-4; **2**, 6863-76-9; **3**, 23902-69-4; **4**, 6863-77-0; **5**, 2423-65-6; **6**, 13134-48-0; **7**, 25594-37-0; **8**, 13134-49-1.

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Bis(trifluoromethyl)thioketene. I. Synthesis and Cycloaddition Reactions

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Bis(trifluoromethyl)thioketene has been synthesized by cracking its dimer prepared from diethyl malonate, thiophosgene, and sulfur tetrafluoride. It is stable enough to be distilled, handled, and stored without special precautions, yet is highly reactive. A tetramer and polymer have been prepared. Described here are reactions of the thioketene with (a) thiocarbonyl compounds to form dithietanes, (b) olefinic compounds and quadricyclenes to yield thietanes, (c) carbodiimides and azines to give 1,3-thiazetidines, (d) 2,3-dimethylbutadiene to form a 2H-thiopyran, and (e) norbornadienes to yield 2,6 adducts. 1,3-Dipolar additions of the thiocarbonyl group take place with diazomethane, benzonitrile oxide, and nitrones. Like nitrones, aryl oximes also give 1,4,2-oxathiazolidines. Two molecules of the thioketene combine with sulfur to form a dithiolane and trithiolane.

Organic chemistry has often been characterized as a mature science; yet some simple types of structures are scarcely known. Monomeric thioketenes have been sought for many years. Thioketene formulas appear in the literature as early as 1877,[1] but such compounds were soon realized to be some multiple of the simple formula.[2,3] Staudinger and coworkers unsuccessfully attempted to prepare a thioketene.[4,5] Dimers of aromatic thioketenes have been reported by Schönberg and coworkers[6] and the desaurins[7] can be regarded as thioketenes dimers. Dicyano- and carbomethoxycyanothioketene have not been isolated, but have been trapped as 1,3-[8a] and 1,4-dipolar[8b] adducts. Cyanothioketene has been postulated as an intermediate in the formation of dithiafulvenes from thioamides and chlorocyanoacetylene.[8c] Acidification of $C_6H_5C{\equiv}CSNa$ gave a polymer[9] which may have been derived from phenylthioketene, though this possibility was not mentioned. Subsequently, lithium salts of acetylenic thiols were treated with thiols and with amines to form thio esters and thioamides.[10-12a] Thioketenes were proposed as intermediates in the reaction sequence. Allylbutylthioketene was shown to be an intermediate in the rearrangement of allylthio-1-hexyne by trapping with an amine as a thioamide.[12b] Arylthioketenes have been suggested as intermediates in the photolysis of aryl-substituted 1,2,3-thiadiazoles,[13] and the thermal rearrangement of a dimethylthioketene dimer probably proceeds through the monomer.[14] Attempts to obtain dimethylthioketene by decomposi-

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(2) H. Bergreen, *ibid.*, **21**, 337 (1888).

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(5) H. Staudinger, "Die Ketene," Ferdinand Enke, Stuttgart, 1912, p 128.

(6) A. Schönberg, E. Frese, and K. Brosowski, *Chem. Ber.*, **95**, 3077 (1962).

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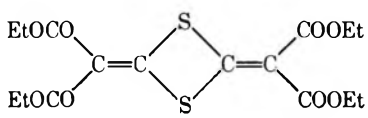
(13) W. Kirmse and L. Horner, *Justus Liebigs Ann. Chem.*, **614**, 4 (1958).

(14) E. U. Elam and H. E. Davis, *J. Org. Chem.*, **32**, 1562 (1967).

tion of cycloadducts of aryl isothiocyanates and 1-dialkylamino-2-methylpropenes were unsuccessful.[15a] No thioketenes were detected in the reaction of atomic sulfur with acetylenes.[15b]

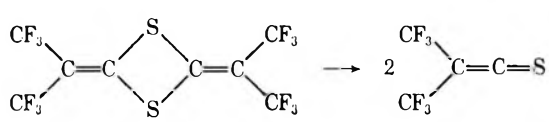
Reports of isolable thioketenes have been few. Carbon subsulfide,[16] S=C=C=C=S, might be included here. The synthesis of thioketene itself by the pyrolysis of *t*-butyl ethynyl sulfide was reported by Howard.[17] Thioketene could be collected without solvent at −196° but polymerized on warming to −80°. When collected and maintained in cyclohexene at −80°, it could be kept for several hours. The subject of this article, the reactive bis(trifluoromethyl)thioketene[18] (**3**), was announced in 1966. Since then, the hindered di-*t*-butylthioketene[19] and the ylide, $(C_6H_5)_3P{=}C{=}C{=}S$,[20] have been reported.

Synthesis.—Bis(trifluoromethyl)thioketene has been synthesized by preparing and cracking its dimer. From diethyl sodiomalonate and thiophosgene, tetraethyl 1,3-dithietane-$\Delta^{2,\alpha:4,\alpha'}$-dimalonate (**1**) was prepared



1

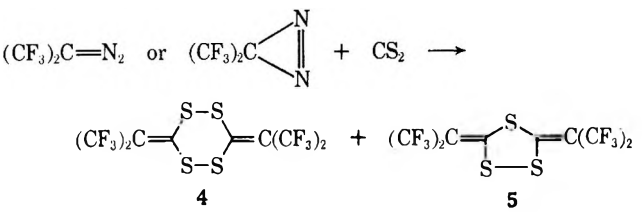
in 70% yield. This is an old compound but had been assigned a different structure.[3] Heating the tetraester with sulfur tetrafluoride in the presence of hydrogen fluoride[21] produced 2,4-bis[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]-1,3-dithietane (**2**), the dimer



2 **3**

of bis(trifluoromethyl)thioketene. This process was carried out in two steps. If a large amount of hydrogen fluoride was employed, the ester was converted to tar. When a small amount of hydrogen fluoride was used, only two or three of the ester groups were converted to CF_3. However, this partially fluorinated, deactivated mixture of dithietanes could be heated with additional hydrogen fluoride and sulfur tetrafluoride to form **2** in 75% yield.

The dimer is also available through other syntheses. Reaction of bis(trifluoromethyl)ketene[22a] with triphenylphosphine sulfide at 200° formed the dimer in 60% yield. Similar reactions, which probably proceed through a four-membered ring intermediate, have been reported to give only polymeric sulfur products with diphenylketene[4] and chloral.[22b] The decomposition of 2-diazo-1,1,1,3,3,3-hexafluoropropane[23] or 3,3-bis(trifluoromethyl)-3H-diazirine[24a] in carbon disulfide at 150–175° produced the cyclic polysulfides, **4** and **5**.[24b]



4 **5**

Presumably, bis(trifluoromethyl)carbene is formed and adds to carbon disulfide. The adduct then dimerizes to **4** and this, by loss of an atom of sulfur, forms **5**. These compounds are converted into the thioketene dimer by abstraction of sulfur with triphenylphosphine. A similar reaction with carbon disulfide has been reported for diazodiphenylmethane.[6] However, 3,3-bis(chlorodifluoromethyl)-3H-diazirine failed to undergo the reaction because the intermediate carbene rearranged to $CF_2{=}CClCF_2Cl$ by a 1,2 shift of a chlorine atom. Recently, the thioketene dimer has been synthesized by reaction of perfluoroisobutylene with potassium sulfide[25] and the reaction of $(CF_3)_2C{=}C{=}P(C_6H_5)_3$ with sulfur.[26]

Studies with a mass spectrometer equipped with a preheater showed bis(trifluoromethyl)thioketene dimer to be stable to 400°. At 600° the spectrum indicated the presence of 75% of bis(trifluoromethyl)thioketene, 21% of dimer, and 2% of perfluoroisobutylene. For laboratory production of the thioketene, the dimer was sublimed at 1-mm pressure through a platinum tube packed with quartz rings and heated to 750°. This produced the distilled monomer in 70% yield. The pyrolysis could also be carried out at 650° by distilling the dimer through the tube at atmospheric pressure but this formed a small foreshot containing carbon disulfide, tetrakis(trifluoromethyl)allene,[27] and perfluoroisobutylene, identified by mass spectrometry.

Monomeric bis(trifluoromethyl)thioketene (**3**) is a reddish orange liquid, bp 52–53°, with spectral absorptions at 5.61 μ (1783 cm^{-1}), 503 mμ (ϵ 8.5), and 239 mμ (ϵ 5590). It is a compound of gratifying reactivity, yet stable enough to distil, handle, and store without special precautions. It may be kept at 25° in glass

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(22) (a) D. C. England and C. G. Krespan, *ibid.*, **87**, 4019 (1965); I. L. Knunyants, Y. A. Cheburkov, and M. D. Bargamova, *Izv. Akad. Nauk. SSSR, Ser. Khim.* 1389 (1963); *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1265 (1963); Y. A. Cheburkov, E. I. Mysov, and I. L. Knunyants, *ibid.*, 1432 (1963). (b) H. Sohr and K. Lohs, *Z. Chem.*, **7**, 153 (1967).

(23) D. M. Gale, W. J. Middleton, and C. G. Krespan, *J. Amer. Chem. Soc.*, **88**, 3617 (1966); C. G. Krespan and W. J. Middleton, U. S. Patent 3,242,166 (1966); E. P. Mochalina and B. L. Dyatkin, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 926 (1965); *Bull Acad. Sci. USSR, Div. Chem. Sci.*, 899 (1965).

(24) (a) R. B. Minasyan, E. M. Rokhlin, N. P. Gambaryan, Y. V. Zeifman, and I. L. Knunyants, *ibid.*, 746 (1965). (b) Compounds **4** and **5** have been used to prepare iridium and platinum complexes of bis(trifluoromethyl)thioketene and 1,1-bis(trifluoromethyl)ethene-2,2-dithiolate: M. Green, R. B. L. Osborn, and F. G. A. Stone, *J. Chem. Soc. A*, 944 (1970).

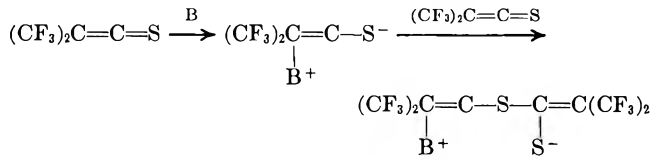
(25) C. G. Krespan and D. C. England, *J. Org. Chem.*, **33**, 1850 (1968).

(26) G. H. Birum and C. H. Matthews, *ibid.*, **32**, 3554 (1967).

(27) D. C. England and C. G. Krespan, *J. Amer. Chem. Soc.*, **88**, 5582 (1966).

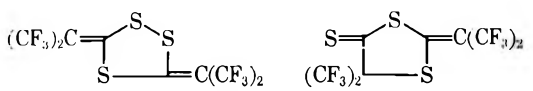
bottles for many months with little dimerization. In contrast, hexafluorothioacetone at 25° dimerizes in several hours.[28]

Dimerization of the thioketene back to **2** is brought about rapidly by catalytic amounts of Lewis bases such as tertiary amines and various nitrogen-, oxygen-, and sulfur-containing molecules that do not otherwise react with the thioketene. Presumably, this occurs through the mechanism



Loss of B results in dimer if the catalysis is carried out above about −20°. At lower temperatures, polymer is formed through addition of more units of the monomer. The thioketene is polymerized by adding it to acetone at −80°. The white polymer is insoluble in all solvents tried and melts at 245° with cracking back to the monomer. The infrared spectrum shows C=C absorption at 1575 cm^{-1}. A tetramer has also been prepared from the thioketene, but before discussing this, a description of the reaction of the thioketene with sulfur is necessary.

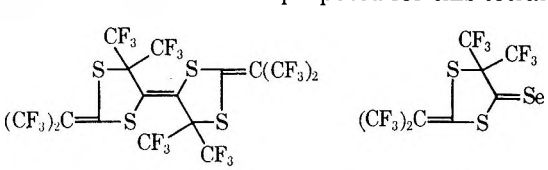
Reaction with Sulfur.—When the thioketene is heated with sulfur at 200°, two adducts, **5** and **6**, are formed in which two molecules of the thioketene are combined



5 **6**

with one atom of sulfur. Compound **5** is the same product as obtained from the reaction of 2-diazo-1,1,1,-3,3,3-hexafluoropropane with carbon disulfide. Its ^{19}F nmr spectrum has two close quadruplets at −8.60 and −7.72 ppm referred to $ClCF_2CF_2Cl$ as standard, and infrared C=C absorption at 1550 cm^{-1}. The magenta color of **6** is indicative of the thiocarbonyl group. The ^{19}F nmr shows an A_3B_3 pattern at −7.75 ppm arising from $(CF_3)_2C{=}C$ attached to two sulfur atoms, which are in turn attached to differing groups, and a singlet at +1.63 ppm from the ring CF_3 groups. Infrared C=C absorption is at 1577 cm^{-1}. Alternative structures with a five-membered ring containing C=S would have a 3-carbon sequence in the ring and would show well-separated quadruplets in the ^{19}F nmr. Both **5** and **6** are converted to the thioketene dimer and sulfur on standing in acetone solution.

Bis(trifluoromethyl)thioketene Tetramer.—When the thioketene and selenium were heated together at 200°, a 30% yield of a sparingly soluble bis(trifluoromethyl)thioketene tetramer, mp 130–130.5°, was formed along with a low yield of a purplish liquid mixture. The structure **7** is proposed for this tetramer.

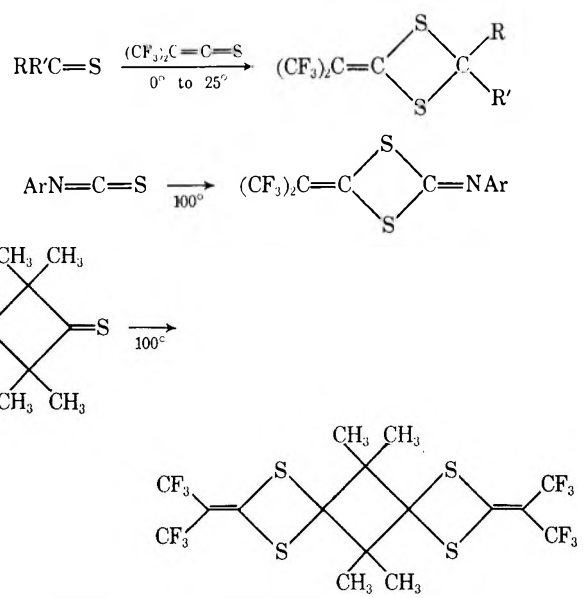


7 **8**

(28) W. J. Middleton, E. G. Howard, and W. H. Sharkey, *J. Org. Chem.*, **30**, 1375 (1965).

The ^{19}F nmr spectrum consists of a singlet for the CF_3 groups attached to the ring and an A_3B_3 pattern indicative of $(CF_3)_2C{=}C$ attached to two sulfur atoms which are attached to two differing groups. The central, symmetrically *trans*-substituted double bond does not show in the ir but is revealed in the Raman spectrum at 1520 cm^{-1}. The $(CF_3)_2C{=}C$ group shows characteristic absorption at 1576 cm^{-1} in the ir and Raman spectra. The melting point and sparing solubility of the compound also indicate a symmetrical structure. These data would also fit an alternative structure consisting of two fused six-membered rings with the double bond between the two common carbon atoms but this structure seems unlikely from the method of synthesis. The tetramer may form from the intermediate production of **8** which is the analog of **6**, obtained from the thioketene and sulfur. Thermal loss of selenium then might occur with formation of the ethylene, just as certain thiones lose sulfur to form ethylenes when heated.[29] However, refluxing the sulfur analog **6** (bp 191°) alone or in the presence of metals did not remove the more strongly bound sulfur to give the tetramer.

Dithietanes.—Just as bis(trifluoromethyl)thioketene will combine with itself to form a dithietane, so it will unite with a diversity of other thiocarbonyl compounds to form dithietanes in high yield. The types of operable compounds are illustrated by Table I. The structure of the products is shown by a singlet in the ^{19}F nmr spectrum and C=C absorption in the ir.

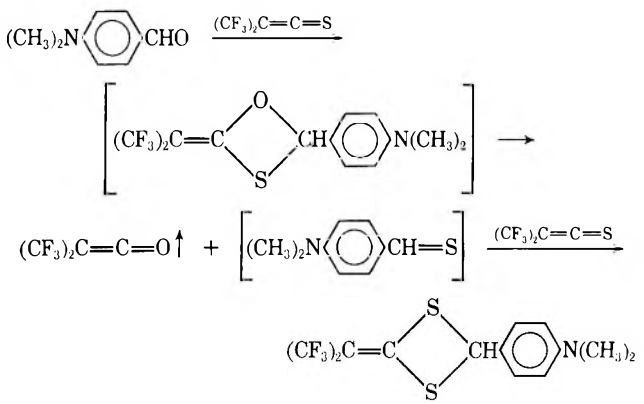


The dithietanes vary widely in stability. The least stable is the one formed from yellow *o*-phenylene trithiocarbonate (Table I, no. 12). The white dithietane is obtained at 10° but on standing at 25° it dissociates back into its components. The compound from methyl methylxanthate (no. 9) is not stable enough to distil at reduced pressure. The dithietane from $(C_6H_5)_2C{=}S$ dissociates at 140°. The remaining compounds did not reveal instability during purification.

Sulfur–Oxygen Exchange with Carbonyl Compounds.—Though the thioketene unites with thiocarbonyl compounds to form dithietanes, it does not combine with ordinary carbonyl compounds to form oxathie-

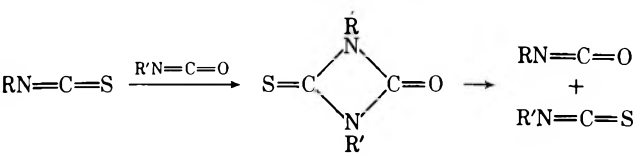
(29) E. Campaigne, *Chem. Rev.*, **39**, 50 (1946).

tanes. However, in an unexpected reaction with the electron-rich carbonyl compound *p*-dimethylaminobenzaldehyde at 10°, $(CF_3)_2C{=}C{=}O$ was evolved and



a dithietane was formed. Intermediate formation of the oxathietane is postulated with spontaneous dissociation of this into $(CF_3)_2C{=}C{=}O$ and *p*-dimethylaminothiobenzaldehyde. The latter then combines with the thioketene to form the dithietane shown above. The reaction also takes place with *p*-diethylaminobenzaldehyde, *p*-dimethylaminocinnamaldehyde, and *p*,*p*′-bis(dimethylamino)benzophenone. Thus, the latter gives the same dithietane as the corresponding thioketone.

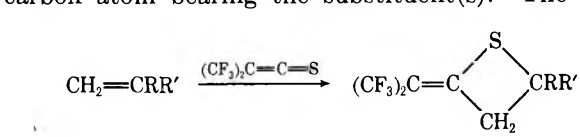
Sulfur–oxygen exchange also takes place between isothiocyanate and isocyanate esters at 200°.[30] This has been represented as occurring through the following sequence.

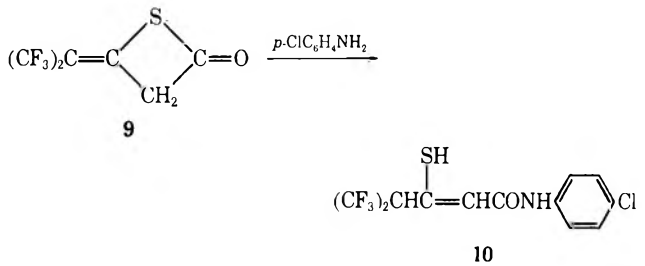


The possibility that a 1,3-oxathietane might be involved seems not to have been evaluated for this reaction or for $COS \rightleftharpoons CO_2 + CS_2$.

Thietanes.—The facile reaction of the thioketene with thiocarbonyl compounds to form dithietanes is equaled by its addition to certain olefin types to form thietanes. Methyleneadamantane, styrenes, ketene, and methylketene are operable as well as the electron-rich unsaturates comprising vinyl ethers, sulfides, and esters, and N-vinylcarbazole. The scope of the reaction appears greater than that of hexafluorothioacetone which is reported to form thietanes with vinyl ethers and sulfides.[31] Under photochemical conditions, the relatively unreactive thiobenzophenone will also yield thietanes with certain olefins.[32]

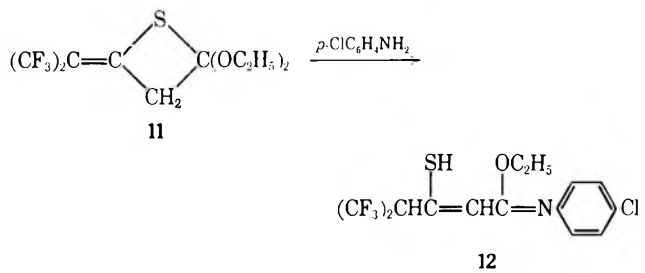
Examples of unsaturates that give thietanes are listed in Table II. The direction of cycloaddition is such that the sulfur atom becomes attached to the carbon atom bearing the substituent(s). The structures have been assigned by a combination of chemical and nmr methods in two cases while in the remaining examples nmr comparisons have been used. At 0°, ketene forms the β-thiolactone **9** which reacts with *p*-chloroaniline to yield an enethiol. For **9**, the ^{19}F nmr





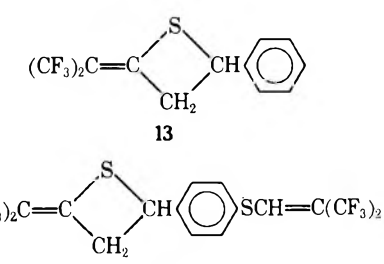
shows two quadruplets with the components of the low-field one characteristically split into apparent triplets by the CH_2 group. The CH_2 group shows a band with multiple splitting. For **10**, the ^1H nmr reveals a septuplet at 3.72 ppm [$(CF_3)_2CH$] and singlets at 6.31 (=CH), 7.44 (hydrogen-bonded SH), and 9.38 (NH). Hydrogen bonding of SH with either N or O would form a six-membered ring.

The adduct from ketene acetal also reacts with *p*-chloroaniline. The ^{19}F nmr of **11** again has two quadruplets with the components of the low-field one split to apparent triplets. The ^1H nmr for **12** has singlets at 6.25 (=CH) and 14.95 (hydrogen-bonded SH). Further data appear in the Experimental Section.



With *cis*-1,2-dimethoxyethylene (Table II, no. 16), stereospecific cycloaddition takes place as judged from the nmr spectrum in $CDCl_3$ which shows a doublet (J = 5.2 Hz) at 5.52 ppm for Hα to S and a broad multiplet at 5.20 from splitting by F for the other ring proton. *trans*-1,2-Dimethoxyethylene caused dimerization of the thioketene and did not form a cycloadduct.

Styrene gave the normal product **13** with the usual nmr pattern and in addition a 1:2 adduct (**14**). The $(CF_3)_2C{=}CH{-}S{-}$ group, encountered frequently in the chemistry of the thioketene, shows a diagnostic quadruplet (J = 1.4 Hz) for H at about 7.4 ppm in the nmr spectrum.

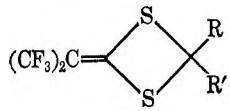


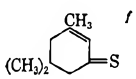
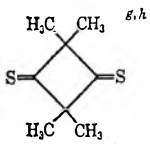
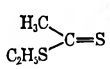
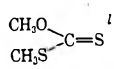
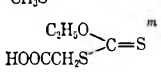
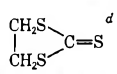
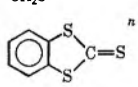
Unsaturates containing a double bond that can shift, including dimethylketene, undergo an "ene" reaction

(30) L. C. Case, *Nature*, **183**, 675 (1959); W. E. Erner, *J. Org. Chem.*, **29**, 2091 (1964).
(31) W. J. Middleton, *ibid.*, **30**, 1395 (1965).
(32) A. Ohno, Y. Ohnishi, and G. Tsuchihashi, *J. Amer. Chem. Soc.*, **91**, 5038 (1969), and references therein.

TABLE I

2,2-SUBSTITUTED 4-[2,2,2-TRIFLUORO-1-(TRIFLUOROMETHYL)ETHYLIDENE]-1,3-DITHIETANES[a,b]

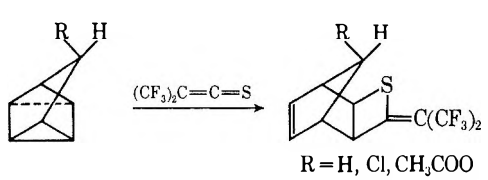


No.	Reactant, RR'C=S	Product mp or bp (mm), °C	Recrystn solvent	Yield, %
1	$(C_6H_5)_2C{=}S$[c]	59–59.5	CH_3OH	77
2	$[p\text{-}(CH_3)_2NC_6H_4]_2C{=}S$[d]	137–138	Cyclohexane	73
3	$(CF_3)_2C{=}S$[e]	126–127 $n^{25}D$ 1.3669		53
4	 [f]	77 (0.3) $n^{25}D$ 1.4848		74
5	 [g,h]	255	C_6H_6	82
6	 [i]	44 (0.2) $n^{25}D$ 1.4819		95
7	$(CH_3O)_2C{=}S$[j]	50–51	Hexane	73
8	$(C_6H_5O)_2C{=}S$[k]	42–42.5	CH_3OH	78
9	 [l]	Liquid, dec $n^{25}D$ 1.4869		High
10	 [m]	88.3–90	Cyclohexane	50
11	 [d]	85.5–86.5	CH_3OH	87
12	 [n]	Solid, dec		96
13	$C_6H_5N{=}C{=}S$[d]	46–47	CH_3OH	49
14	$p\text{-}ClC_6H_4N{=}C{=}S$[o]	48.5–49	CH_3OH	54
15	$p\text{-}O_2NC_6H_4N{=}C{=}S$[d]	62.5–63	CH_3OH	37
16	$m\text{-}O_2NC_6H_4N{=}C{=}S$[d]	53–53.5	CH_3OH	51
17	$p\text{-}C_6H_5N{=}NC_6H_4N{=}C{=}S$[p]	118–119	C_2H_5OH	71
18	$3,4,5\text{-}(CH_3O)_3C_6H_2N{=}C{=}S$[q]	89.7–90.5	Hexane	73
19	$p\text{-}S{=}C{=}NC_6H_4N{=}C{=}S$[r]	158.2–158.4	CCl_4	45
20	1-Naphthyl-N=C=S[d]	128.5–128.7	CH_2Cl_2-EtOH	79

[a] Disclosed in part in M. S. Raasch, U. S. Patents 3,336,334, 3,337,586, 3,355,446 (1967). [b] Ed. note: Satisfactory analytical data (±0.35%) for C, H, and S were reported for all compounds except no. 9 and 12 which were not analyzed and no. 6 (Calcd: C, 30.57. Found: C, 31.11) and no. 7 (Calcd: H, 2.01. Found: H, 2.45). [c] B. F. Gofton and E. A. Braude in "Organic Syntheses," Coll. Vol. IV, N. Rabjohn, Ed., Wiley, New York, N. Y., 1963, pp 927–928. [d] Distillation Products Industries, Rochester, N. Y. [e] Reference 28. [f] D. E. Winkler and S. A. Ballard, U. S. Patent 2,437,985 (1948). [g] R. D. Lipscomb, U. S. Patent 3,297,765 (1967); joint experiment with Dr. Lipscomb. [h] Reference 14. [i] C. S. Marvel, P. deRadzitsky, and J. J. Brader, *J. Amer. Chem. Soc.*, **77**, 5997 (1955). [j] M. Delepine, *Bull. Soc. Chim. Fr.*, [4] **7**, 409, 727 (1910). [k] H. Eckenroth and K. Kock, *Ber.*, **27**, 1369 (1894). [l] I. B. Douglas and W. J. Evers, *J. Org. Chem.*, **29**, 419 (1964). [m] E. Biilmann, *Justus Liebigs Ann. Chem.*, **339**, 355 (1905). [n] R. Huisgen and V. Weberndörfer, *Experientia*, **17**, 566 (1961). [o] G. M. Dyson *in* "Organic Syntheses," Coll. Vol. I, 2nd ed, H. Gilman and A. H. Blatt, Ed., Wiley, New York, N. Y., 1941, p 165. [p] C. E. Bolser and E. B. Hartshorn, *J. Amer. Chem. Soc.*, **45**, 2349 (1923). [q] Prepared by Dr. J. C. Kauer of these laboratories by the method of ref *o;* mp 67–68° (hexane). [r] G. J. M. van der Kirk, C. W. Pluygers, and G. deVries, *Recl. Trav. Chim. Pays-Bas*, **74**, 1262 (1955).

with the thioketene instead of thietane formation. This will be discussed in a future publication.

Adducts with Quadricyclenes.—Polycyclic thietanes are obtained when the thioketene adds to quadricyclenes. As is the case with the addition of other unsaturates to quadricylene,[33] the reaction stereospecifically gives an adduct with the thietane ring in the *exo* position. The lack of splitting in the nmr spectrum for the bridgehead protons indicates *endo* protons at the thietane ring bridgeheads.[34]



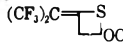
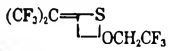
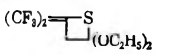
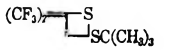
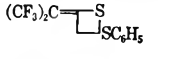
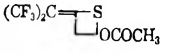
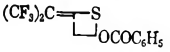
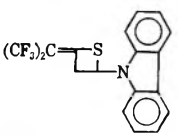
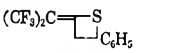
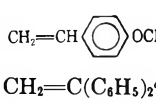
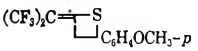
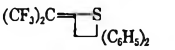
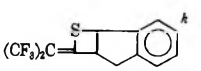
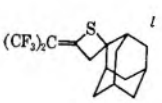
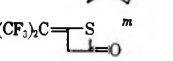
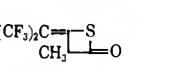
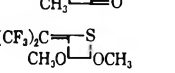
In the case of compounds with a substituent on the bridge, a configuration with the substituent *anti* to the thietane ring seems most likely for steric reasons. However, this was not established by nmr for these

(33) C. D. Smith, *J. Amer. Chem. Soc.*, **88**, 4273 (1966).

(34) E. W. C. Wong and C. C. Lee, *Can. J. Chem.*, **42**, 1245 (1964), and sources cited in ref 33.

TABLE II

2-SUBSTITUTED 4-[2,2,2-TRIFLUORO-1-(TRIFLUOROMETHYL)ETHYLIDENE]THIETANES[n,o]

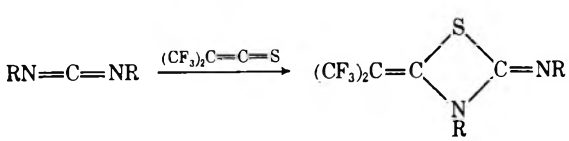
No.	Reactant	Reaction conditions	Product	Recrystn from, or $n^{25}D$	Bp (mm) or mp, °C	Yield, %
1	$CH_2=CHOC_2H_5$[a]	10–25°		1.4173	70–72 (7)	90
2	$CH_2=CHOCH_2CF_3$[b]	10–25°		1.3893	79–82 (11)	80
3	$CH_2=C(OC_2H_5)_2$[c]	10–25°, pentane		1.4202	73–74 (1.65)	81
4	$CH_2=CHSC(CH_3)_3$[d]	10–25°		1.4583	114 (10)	61
5	$CH_2=CHSC_6H_5$[e]	10–25°		1.5198	72 (0.06)	81
6	$CH_2=CHOCOCH_3$[a]	100°, 15 hr		1.4180	93–96 (11)	25
7	$CH_2=CHOCOC_6H_5$[f]	100°, 16 hr		C_6H_{12}	102–102.6	46
8	N-Vinylcarbazole[f]	25°, CH_2Cl_2, 4 hr		C_2H_5OH	152–153	80
9	$CH_2=CHC_6H_5$[a]	100°, 15 hr		1.4946	67 (0.2)	26
10		10–25°		1.5060	98 (0.1) 23–24	69
11	$CH_2=C(C_6H_5)_2$[c]	100°, 15 hr		CH_3OH	59–59.1	64
12	Indene[a]	25°, 16 hr		CH_3OH	134–137 (7) 76–77	53
13	2-Methyleneadamantane[g]	100°, 15 hr		CH_3OH	78–79 (0.05) 39.5–40.5	40
14	$CH_2=C=O$[h]	0°, CH_2Cl_2, 15 hr		1.4181	151–153	44
15	$CH_3CH=C=O$[i]	0–25°, Et_2O, 2 hr		1.4130	63–66 (29)	33
16	*cis*-$CH_3OCH=CHOCH_3$[j]	10–25°, C_6H_{12}		C_6H_{12}	104–105 (15) 42–43	94

[a] Distillation Products Industries, Rochester, N. Y. [b] Air Reduction Co., Inc., Ohio Medical Products Division, Riverton, N. J. [c] S. M. McElvain and D. Kuniger in "Organic Syntheses," Coll. Vol. III, E. C. Horning, Ed., Wiley, New York, N. Y., 1955, pp 506–508. [d] J. F. Arens and T. Doornbos, *Recl. Trav. Chim. Pays-Bas*, **75**, 481 (1956). [e] W. E. Parham, F. D. Blake, and D. R. Theissen, *J. Org. Chem.*, **27**, 2415 (1962). [f] Borden Chemical Co., Monomer Polymer Laboratories, Philadelphia, Pa. [g] P. von R. Schleyer and R. D. Nicholas, *J. Amer. Chem. Soc.*, **83**, 182 (1961); suggested by Dr. G. H. Berezin, Du Pont Co. [h] S. Andreades and H. D. Carlson, *Org. Syn.*, **45**, 50 (1965). [i] P. G. Blake and K. J. Hole, *J. Phys. Chem.*, **70**, 1464 (1966); A. D. Jenkins, *J. Chem. Soc.*, 2563 (1952). [j] B. R. O'Connor, *J. Org. Chem.*, **33**, 1991 (1968). [k] 2-[2,2,2-Trifluoro-1-(trifluoromethyl)ethylidene]indano[2,1-*b*]thietane. [l] 4′-[2,2,2-Trifluoro-1-(trifluoromethyl)ethylidene]spiroadamantane[2,2′]thietane. [m] 3-Mercapto-5,5,5-trifluoro-4-(trifluoromethyl)-3-pentenoic acid β-thiolactone. [n] Disclosed in part in M. S. Raasch, U. S. Patent, 3,468,908 (1969). [o] Ed. note: Satisfactory analytical data (±0.35%) for C, H, and S were reported for all compounds except no. 2 (Calcd: C, 30.01; H, 1.57. Found: C, 30.74; H, 2.06), no. 7 (Calcd: C, 45.61. Found: C, 46.03), no. 8 (Calcd: C, 55.80; H, 2.86. Found: C, 55.47; H, 3.35), no. 10 (Calcd: C, 47.55; H, 46.98), no. 12 (Calcd: C, 50.31; H, 2.60. Found: C, 50.79; H, 2.99), no. 14 (Calcd: C, 30.51; H, 0.85. Found: C, 30.93; H, 1.45).

crystalline adducts as the bridge proton and the vinylene protons do not show the marked interaction that occurs in simple 7-substituted norbornenes with such a configuration.[35]

1,3-Thiazetidines.—The thioketene cycloadds to carbodiimides to form 1,3-thiazetidines, a little-known class of compounds.[36]

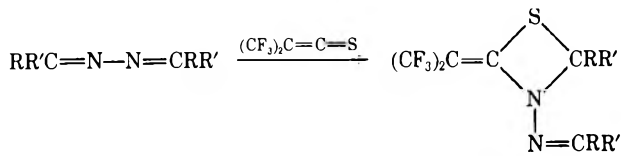
The reaction has been carried out with di-*p*-tolyl-, diisopropyl-, and dicyclohexylcarbodiimide. The products have spectral properties similar to those of the thietanes in that the ^{19}F nmr spectrum shows a pair of quadruplets and the ir has absorption at about 1628 cm^{-1} for the exocyclic double bond. Pyrolysis of the ditolyl compound at 240° caused splitting to *p*-tolyl isothiocyanate, a further proof of structure.



(35) E. I. Snyder and B. Franzus, *J. Amer. Chem. Soc.*, **86**, 1166 (1964).

(36) Many of the reports of 1,3-thiazetidines in the literature are incorrect. However, the reactions of thiocarbanilides with phosgene, thiophosgene, and diiodomethane do give 1,3-thiazetidines.

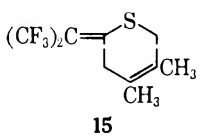
Less stable adducts were obtained from benzalazine and cyclohexanoneazine. The addition was reversed when the benzalazine adduct was heated at 120° with the formation of benzalazine and the thioketene dimer. The cyclohexanoneazine adduct was unstable at 25°.



The thioketene forms 2:1 adducts with Schiff bases. These will be discussed in a future article.

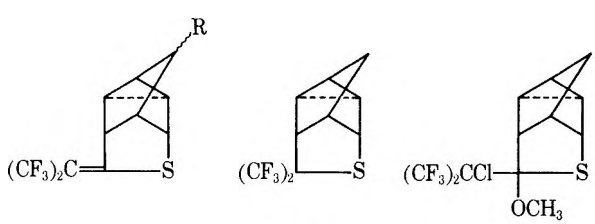
Diels–Alder Adducts.—The thiocarbonyl group of the thioketene readily acts as a dienophile, though the rate of reaction is not so great as for hexafluorothioacetone.[37] Differences in mode of reaction also occur. Whereas thietane formation takes place between the thioketene and styrene, hexafluorothioacetone undergoes a Diels–Alder reaction with styrene involving the vinyl group and a ring double bond. Other thiocarbonyl compounds have also been reported to form Diels–Alder adducts.[37–39]

Illustrative of the Diels–Alder reaction is the addition of the thioketene to 2,3-dimethylbutadiene to form **15**.



15

Addition to 2,5-Norbornadiene.—The addition of olefinic compounds across the 2,6-positions of norbornadiene[40–42] finds a counterpart in the chemistry of the thioketene as the thiocarbonyl group adds to these positions to form the structure **16**, a new polycyclic system. Apparently, thiocarbonyl compounds have not been added to norbornadiene previously, and the reaction has been extended by using hexafluorothioacetone to form **17**.



16a, R = H
b, R = $OC(CH_3)_3$
c, R = Cl

17

18

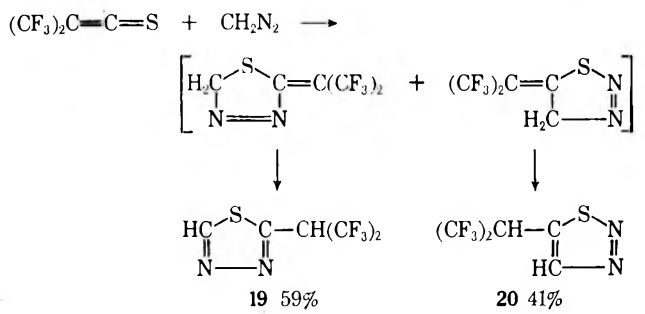
When a 7-monosubstituted norbornadiene is used, two stereoisomers are possible as products depending on whether the substituent is *syn* or *anti* to sulfur. The reaction proceeds with 7-*t*-butoxy- and 7-chlorononorbornadiene but the stereochemistry has not been established. The chloro product consisted of isomers in a ratio of 65:35 by glpc.

(37) W. J. Middleton, *J. Org. Chem.*, **30**, 1390 (1965).
(38) A. Schönberg and B. König, *Chem. Ber.*, **101**, 725 (1968).
(39) K. Yamada, M. Yoshioka, and N. Sugiyama, *J. Org. Chem.*, **33**, 1240 (1968).
(40) E. F. Ullman, *Chem. Ind. (London)*, 1173 (1958).
(41) D. E. Applequist and D. C. England, U. S. Patent 2,940,984 (1960).
(42) R. C. Cookson, J. Dance, and J. Hudec, *J. Chem. Soc.*, 5416 (1964), and references therein.

Chlorine can be readily added to the double bond of **16a** by means of sulfuryl chloride. Treatment of the product with methanol displaces the reactive chlorine atom α to the sulfur atom with methoxyl to form **18**. Such additions and displacements would probably be operable with the other types of thioketene adducts also.

1,3-Dipolar Additions.—The thiocarbonyl group of bis(trifluoromethyl)thioketene participates in 1,3-dipolar additions[43] to form sulfur heterocycles containing other heteroatoms. Described here are 1,3 cycloadditions to diazomethane, benzonitrile oxide, and nitrones. Because of certain similarities, additions to hydrogen azide and aryl oximes are also included in this section.

A. Addition to Diazomethane.—Diazomethane adds to the thiocarbonyl group in both directions without loss of nitrogen. The presumed intermediate products then undergo a prototropic shift to form the more stable thiadiazoles (**19** and **20**) containing conjugated

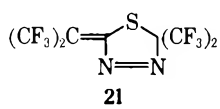


19 59%

20 41%

double bonds. The isomers were separated by glpc. The nmr spectra show the presence of $(CF_3)_2CH$, and, for **20**, coupling between the protons of the two CH groups.

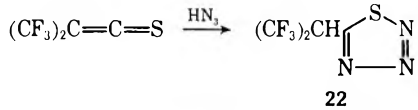
In the case of the reported addition of bis(trifluoromethyl)diazomethane to the thioketene to form **21**, such a prototropic shift cannot take place.[44]



21

Addition of diazomethane to the thioketene is similar to its reaction with aryl isothiocyanates to form 5-anilino-1,2,3-thiadiazoles,[45] but the reaction of diazo compounds with other thiocarbonyl compounds,[46a] including hexafluorothioacetone,[46b] is accompanied by loss of nitrogen.

B. Addition to Hydrogen Azide.—A solid, highly volatile 1,2,3,4-thiatriazole (**22**), the first aliphatic



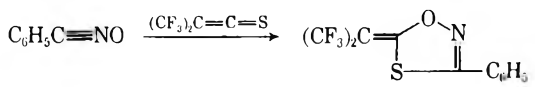
22

(43) R. Huisgen, *Angew. Chem.*, **75**, 604, 742 (1963); *Angew. Chem., Int. Ed. Engl.*, **2**, 565, 633 (1963); *Helv. Chim. Acta*, **50**, 2421 (1967). R. Huisgen, R. Grashey, and J. Sauer in "The Chemistry of Alkenes," S. Patai, Ed., Interscience, New York, N. Y., 1964, pp 806–878.
(44) W. J. Middleton, *J. Org. Chem.*, **34**, 3201 (1969).
(45) H. von Pechmann and A. Nold, *Ber.*, **29**, 2588 (1896); M. Tisler, M. Hrovat, and N. Machiedo, *Croat. Chem. Acta*, **34**, 183 (1962).
(46) (a) A. Schönberg, B. König, and E. Singer, *ibid.*, **100**, 767 (1967); M. Sander, *Chem. Rev.*, **66**, 319 (1966). (b) W. J. Middleton and W. H. Sharkey, *J. Org. Chem.*, **30**, 1384 (1965).

derivative of this heterocycle to be stable at 25°,[47] is formed from the thioketene and hydrogen azide. The compound may result from the formation and cyclization of $(CF_3)_2CHC(=S)N_3$ rather than by direct cycloaddition. The compound decomposes with a puff at 100° with deposition of sulfur, and presumably with the formation of nitrogen and $(CF_3)_2CHCN$.

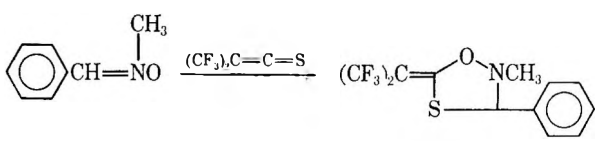
Aryl azides form 1:1 and 1:2 adducts with the thioketene. These will be reported in a future publication.

C. Addition to Benzonitrile Oxide.—A 1,4,2-oxathiazole results from reaction of the thioketene with benzonitrile oxide.



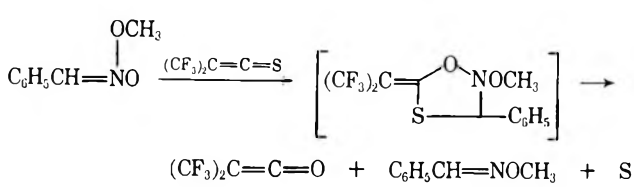
This addition is analogous to the trapping reaction used for dicyanothioketene and carbomethoxycyanothioketene.[8a] A number of aromatic thiocarbonyl compounds have also been added to nitrile oxides to form 1,4,2-oxathiazoles.[48] Carbon disulfide reacts with 2,4,6-trimethylbenzonitrile oxide in a more complex fashion but the initial product is thought to be a 1,4,2-oxathiazole.[49]

D. Addition to Nitrones.—What appears to be the first preparation of a 1,4,2-oxathiazolidine results from the addition of the thioketene to N-methyl-α-phenylnitrone. The ir spectrum has a band at 1618 cm^{-1} for



the exocyclic C=C and the ^{19}F nmr spectrum shows an A_3B_3 pattern consistent with $(CF_3)_2C{=}C$ attached to O and to S. The compound decomposes in a few days at 25°.

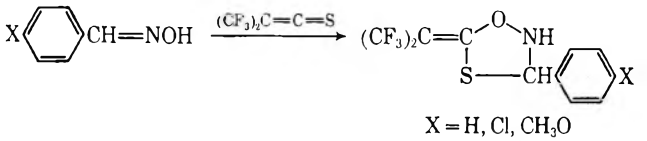
In the case of N-methoxy-α-phenylnitrone, the oxathiazolidine decomposed as formed according to the equation



All three products were identified. In effect, this is another exchange reaction in which the sulfur of the thioketene is exchanged for oxygen.

The addition of $C_6H_5N{=}C{=}S$ to nitrones is reported to occur across the N=C bond.[50]

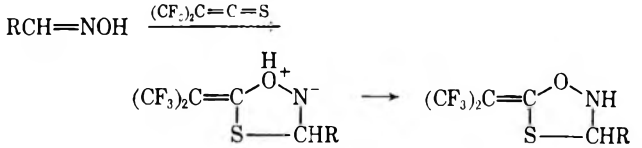
E. Addition to Aryl Oximes.—Like nitrones, aryl oximes also form 1,4,2-oxathiazolidines with the thioketene. In this case they are unsubstituted on the nitrogen atom. These white, crystalline products



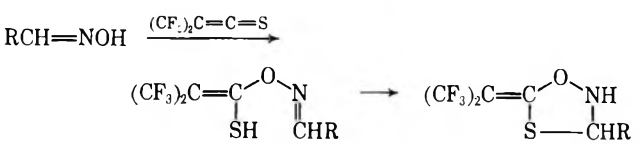
precipitate out when the thioketene is added to a solution of the oxime in dichloromethane and petroleum ether at 10°. They may be filtered off and allowed to dry briefly, but after about 30 min at 25° the phenyl and *p*-chlorophenyl compounds go pffft and disappear in a cloud of vapor. The *p*-anisyl analog undergoes this change after about 5 min. The compounds can be stored at −80°.

Though they are unstable, the phenyl and *p*-chlorophenyl compounds can be characterized by working rapidly. The ^{19}F nmr spectrum of the phenyl compound, for example, shows an A_3B_3 pattern comparable with that from the nitrone adducts. The ^1H nmr has a doublet (J = 12 Hz) at 6.05 ppm for CH and a doublet for NH (J = 12 Hz) at 6.53. When the solution is shaken with D_2O, the NH doublet disappears and the CH doublet is converted to a singlet. The ir spectrum shows bands at 3185 cm^{-1} for NH and 1621 for the exocyclic double bond.

Oximes can be alkylated on either nitrogen or oxygen but there is no physical evidence that they exist in part in the nitrone form. However, the reaction still could be represented as a 1,3 addition.[51]



Alternatively, the reaction course[52] might simply be



Decomposition of the phenyl derivative in dichloromethane gives benzonitrile and a compound, $C_{15}H_9F_{12}NOS$, whose structure is being investigated.

Experimental Section

The ^1H nmr spectra were determined on a Varian A-60 instrument using tetramethylsilane as external standard. The ^{19}F nmr spectra were measured on a Varian A-56/60 instrument using 1,2-difluoro-1,1,2,2-tetrachloroethane as a standard in a capillary tube placed in the sample tube. With this standard, nearly all values for the compounds of this article fall within 1000 Hz downfield from the standard. This standard is 3800 Hz (67.4 ppm) upfield from chlorotrifluoromethane. Raman spectra were measured on Cary Model 81 Laser, ir on Perkin-Elmer Model 21, and uv on Cary 14 spectrometers. Melting and boiling points are uncorrected.

Tetraethyl 1,3-Dithietane-$\Delta^{2,\alpha:4,\alpha'}$-dimalonate[3] (1).—Into a 5-l., three-necked, round-bottomed flask, fitted with a mechanical stirrer and a large capacity reflux condenser, were placed 700 g (4.38 mol) of diethyl malonate and 1600 ml of tetrahydrofuran.

(47) K. A. Jensen and C. Pedersen, "Advances in Heterocyclic Chemistry," Vol. III, A. R. Katritsky, Ed., Academic Press, New York, N. Y., 1964, pp 263–284.

(48) R. Huisgen, W. Mack and E. Anneser, *Angew. Chem.*, **73**, 656 (1961).

(49) W. O. Foye and J. M. Kauffman, *J. Org. Chem.*, **31**, 2417 (1966).

(50) R. Huisgen, *Angew. Chem.*, **75**, 626 (1963); *Angew. Chem., Int. Ed. Engl.*, **2**, 588 (1963). R. Grashey, R. Huisgen, and H. Leitermann, *Tetrahedron Lett.*, No. 12, 9 (1960).

(51) In the addition of two molecules of dimethyl acetylenedicarboxylate to acetone oxime, N-alkenylation of the oxime with one molecule is proposed as the first step with 1,3 addition to the nitrone so formed as the second step: E. Winterfeldt and W. Krohn, *Angew. Chem.*, **79**, 722 (1967); *Angew. Chem., Int. Ed. Engl.*, **6**, 709 (1967).

(52) Proposed by one of the referees.

Sodium hydride (189 g of 55.6% in oil, 4.38 mol) was placed in a 500-ml erlenmeyer flask which was then connected to the large flask with Gooch tubing. During 1 hr, the sodium hydride was added to the tetrahydrofuran solution in portions and the Gooch tubing was clamped shut with a hemostat between additions. After all the sodium hydride was added, the condenser and Gooch tubing were removed and the flask was fitted with a thermometer and dropping funnel. Thiophosgene (252 g, 2.19 mol) dissolved in 200 ml of tetrahydrofuran was added through the dropping funnel during 75 min while the temperature of the reaction mixture was maintained at 18–22° with an ice bath. After all the thiophosgene had been added, the ice bath was removed and stirring was continued for 15 min. Then 1500 ml of distilled water was added and the product was filtered off on a suction funnel. The filter cake was washed with about 1 l. of ether, or until the yellow color was gone. The cake was then slurried with 1000 ml of water, refiltered, and washed with 4 to 6 l. of distilled water, or until no chloride ion was found in the rinse. The cake was rinsed with 200 ml of alcohol and then spread out to air dry. Final drying was done at 90° for 16 hr in a vacuum oven. The yield was 300–320 g (68–72.5%), mp 179–180°. Except for an off-white color, the compound is essentially pure and may be used without recrystallization for the reaction with SF_4. After recrystallization from dioxane, the compound melted at 180–181°: ir 1511 (C=C), 1672, 1689 cm^{-1} (C=O). Small amounts have been recrystallized from 70% nitric acid.

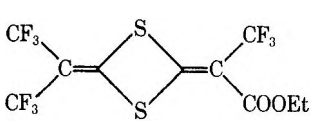
The tetramethyl ester[7b] can be prepared in the same way, but dimethyl sodiomalonate precipitates from tetrahydrofuran whereas the diethyl ester stays in solution.

2,4-Bis[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]-1,3-dithietane (2).—Tetraethyl 1,3-diethietanedimalonate (150 g) was placed in a 1-l. "Hastelloy" C bomb which was then cooled in a Dry Ice–methanol bath and evacuated. The bomb was charged with 25 g of hydrogen fluoride and 310 g of water-white sulfur tetrafluoride. Heating was carried out at 125° for 2 hr, 150° for 2 hr, and 200° for 4 hr. The bomb was then allowed to cool overnight. The next morning it was vented, the valve was closed, and the bomb was cooled in a Dry Ice–methanol bath. Without prior evacuation, the bomb was charged with 85 g of HF and 310 g of SF_4 and heating was resumed, 150° for 2 hr and 200° for 4 hr. The bomb was cooled to 35–40°, vented, and unloaded into a polyethylene bottle. The product was carefully poured onto ice and the crystals containing tar were washed with water, 10% sodium carbonate solution, and water again. The crystals were steam distilled, filtered off, and placed on paper towels. Because of the volatility of the product, it was not allowed to air dry more than about 1 hr. The product was then dissolved in warm dichloromethane, dried with anhydrous magnesium sulfate, filtered warm, and crystallized by reducing in volume and cooling. The yield was 100–108 g (69–75%) in three crops: mp 84°; bp 170°; ir 1616 cm^{-1} (C=C); ^{19}F nmr (CCl_4) −8.30 ppm (s). While almost any organic solvent can be used for recrystallization, a solvent boiling higher than dichloromethane causes loss of product by volatilization when boiled. The SF_4 used should be pure, water-white. Otherwise, the preparation may fail. Chlorine is suspect as a deleterious impurity.

Anal. Calcd for $C_8H_{12}S_2$: C, 24.75; F, 58.74; S, 16.52. Found: C, 24.96; F, 58.28; S, 16.83.

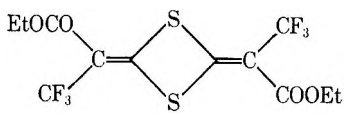
Partial Fluorination of Tetraethyl 1,3-Dithietane-$\Delta^{2,\alpha:4,\alpha'}$-dimalonate.—Preliminary experiments with the SF_4 treatment yielded partially fluorinated products from which three compounds were isolated and characterized. No attempt has been made to improve the yield of these.

Tetraethyl 1,3-dithietane-$\Delta^{2\,\alpha:4,\alpha'}$-dimalonate (1, 50 g), 50 g of HF, and 150 g of SF_4 were heated in a 400-ml Hastelloy shaker tube for 2 hr each at 110, 125, 140, and 150°. The HF was allowed to evaporate from the product, water was cautiously added, and the mixture was made just basic with sodium hydroxide. The mixture was steam distilled and the oil that came over was collected with dichloromethane and dried ($MgSO_4$). The solid left after evaporation of the solvent was recrystallized from methanol to give 6.2 g which was sublimed at 100° to yield ethyl 3,3,3-trifluoro-2-{4-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]-1,3-dithietane-2-ylidene}propionate: mp 49–50°; ir 1577 (conjugated C=C), 1631 [$(CF_3)_2C$=C], 1685 cm^{-1} (C=O); ^{19}F nmr ($CDCl_3$) −8.72 [A_3B_3 pattern, $(CF_3)_2C$=], 9.60 ppm (s, CF_3).



Anal. Calcd for $C_{10}H_5F_9O_2S_2$: C, 30.62; H, 1.28; F, 43.69; S, 16.36. Found: C, 30.85; H, 1.28; F, 42.92; S, 16.20.

1 (20 g), 12 g of HF, and 60 g of SF_4 were heated to 140° in a 145-ml shaker tube. At this point, the reaction flashed to 181°. It was cooled to 140° and continued there for a total of 8 hr. The product was poured onto ice and the tarry precipitate was rinsed with water and ethanol. About 2 g of the tris(trifluoromethyl) compound described above was sublimed out. The residue was extracted with hot ethanol and the solution was decolorized and boiled down to give 5.1 g of crystals, mp 126–140°. Four recrystallizations from ethanol yielded 2.6 g of 2,4-bis[2,2,2-trifluoro-1-(ethoxycarbonyl)ethylidene]-1,3-dithietane: mp 153.5–154.5°; ir 1580 (C=C), 1701 cm^{-1} (C=O); ^{19}F nmr ($CDCl_3$) −8.81 ppm (s). The high melting point and single band in the ir are indicative of the *trans*, symmetrical structure.



Anal. Calcd for $C_{12}H_{10}F_6O_4S_2$: C, 36.36; H, 2.54; F, 28.77; S, 16.18. Found: C, 36.25; H, 2.66; F, 28.81; S, 16.05.

From the mother liquor was isolated 0.32 g of a compound, mp 97–98°, of the same composition but with stronger ir absorption, evidently the *cis* form: ^{19}F nmr ($CDCl_3$) −9.28 ppm (s).

Synthesis of 2 from Bis(trifluoromethyl)ketene.—Bis(trifluoromethyl)ketene (4.0 g, 0.025 mol) and 5.88 g (0.02 mol) of triphenylphosphine sulfide were heated in a Carius tube at 200° for 5 hr. The product was steam distilled to give 2.3 g (59%) of 2, identified by melting point and mixture melting point. Perfluoroisobutylene and triphenylphosphine sulfide failed to react at 200°.

Reaction of 2-Diazo-1,1,1,3,3,3-hexafluoropropane with Carbon Disulfide.—2-Diazo-1,1,1,3,3,3-hexafluoropropane[23] (11 g, 0.062 mol) and 20 ml (0.33 mol) of carbon disulfide were heated in an 80-ml Hastelloy bomb at 175° for 12 hr. Distillation of the product gave 2.55 g (20%) of 3,5-bis[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]-1,2,4-trithiolane (5): bp 91–93° (15 mm); $n^{25}D$ 1.4519; ir 1553 cm^{-1}; ^{19}F nmr (neat) −7.60, −8.65 ppm (quadruplets).

Anal. Calcd for $C_8F_{12}S_3$: C, 22.86; F, 54.25; S, 22.90. Found: C, 22.57; F, 54.13; S, 23.34.

When the above reaction was run at 150° instead of 175°, a small amount of 3,6-bis[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]-*s*-tetrathiane (4) was isolated, which indicates this is the precursor to the 1,2,4-trithiolane. 2-Diazo-1,1,1,3,3,3-hexafluoropropane (5 g, 0.028 mol) and 10 ml (0.16 mol) of carbon disulfide were heated at 150° for 8 hr. Distillation of the product gave 1.77 g, bp 90–109° (15 mm), in 2 cuts. Crystals separated from the higher cut. Filtration and crystallization twice from methanol yielded 150 mg of the s-tetrathiane, mp 44.3–44.5°. From the pot residue, 160 mg more was obtained (4.9% total yield): ir 1565 cm^{-1} (C=C, simple spectrum indicative of symmetrical molecule); ^{19}F nmr (CCl_4) −11.1 ppm (s, no impurities evident).

Anal. Calcd for $C_5F_{12}S_4$: C, 21.24; F, 50.41; S, 28.36. Found: C, 20.78; F, 49.29; S, 28.71.

Reaction of 3,3-Bis(trifluoromethyl)-3H-diazirine with Carbon Disulfide.—3,3-Bis(trifluoromethyl)-3H-diazirine[24] (5 g, 0.028 mol) and 15 ml of carbon disulfide were heated in an 80-ml Hastelloy bomb for 8 hr. Distillation of the product gave 2.17 g (37%) of 5, bp 87–89° (13 mm), $n^{25}D$ 1.4520. Analytical and spectral data agree with those above for 5.

Conversion of the Cyclic Polysulfides to Bis(trifluoromethyl)-thioketene Dimer (2).—Mixing 5 with a 1.2 mol equiv of triphenylphosphine produced an exothermic reaction. After the mixture was heated at 100°, it was steam distilled to give an 80% yield of 2 identified by melting point and mixture melting point. Similarly 4 was converted to 2.

3,3-Bis(chlorodifluoromethyl)-3H-diazirine.—In a 500-ml flask fitted with magnetic stirrer and reflux condenser, 200 ml of 5.25% NaOCl (0.14 mol), 2 g of NaOH and 14 g (0.065 mol) of 1,3-dichloro-1,1,3,3-tetrafluoro-2,2-propanediamine[53] were stirred

(53) W. J. Middleton and C. J. Krespan, *J. Org. Chem.*, **30**, 1398 (1965).

at 25° for 20 hr. The temperature did not rise more than 1°. The flask was then connected to a Dry Ice trap and the product was pulled off under water vacuum. The product was dried ($MgSO_4$) and distilled using an oil bath to give 6.6 g (48%) of the diazirine: bp 57°; $n^{25}D$ 1.3363; ir 1640 cm^{-1} (N=N); uv max (isooctane) 293.5 mμ (ε 58), 303.5 (60); ^{19}F nmr (neat) −6.30 ppm (s).

Anal. Calcd for $C_3Cl_2F_4N_2$: Cl, 33.61; F, 36.02; N, 13.28. Found: Cl, 33.29; F, 35.60; N, 13.59.

When a few drops of the compound were heated over a flame in a small test tube, the compound exploded and broke the tube. When dropped onto a melting point block heated to 280°, the compound decomposed with a muted pop. This behavior is in contrast to that of 3,3-bis(trifluoromethyl)-3H-diazirine[54] which is reported to show no tendency to detonate. The above procedure is an adaptation of the one used to prepare the perfluoro analog.[24]

Decomposition of 3,3-Bis(chlorodifluoromethyl)-3H-diazirine.—3,3-Bis(chlorodifluoromethyl)-3H-diazirine (8 g) and 20 ml of carbon disulfide were heated at 175° for 10 hr in an 80-ml Hastelloy bomb. Distillation of the product gave 6.10 g, bp 36°, apparently an azeotrope of carbon disulfide and the fluoro olefin, 2.60 g, bp 36–46.5°, and the rest at 46.5°. Fluorine nmr of the 36°-cut showed only $CF_2=CClCF_2Cl$. Gas chromatography of this cut over 20% Kel-F ester on 60–80 mesh firebrick at 25° gave an area per cent of 36.6 for carbon disulfide (4.9 min retention time), 63.3 for the olefin (10.45 min), and 3 trace peaks of 0.03 or less. This indicated that the 36° cut contained about 56% of theory of the olefin. The cut was subjected to preparative scale gas chromatography under similar conditions to give an isolated yield of 2,3-dichloro-1,1,3,3-tetrafluoropropene[55] of 53%: bp 45°; $n^{25}D$ 1, 3450; ir 1743 cm^{-1} (C=C, gas phase); nmr −14.8 (d, J = 32 Hz, split to doublets, J = 8 Hz, CF_2Cl), 6 peaks at 9.5 to 11.1 and 5 at 11.8 to 12.5 ppm ($CF_2=$). The other distillation cuts were not examined.

Anal. Calcd for $C_3F_4Cl_2$: Cl, 38.77; F, 41.56. Found: Cl, 38.71; F, 41.58.

Bis(trifluoromethyl)thioketene (3).—The apparatus for cracking 2 consisted of a 0.5-in. platinum tube 24-in. long with the middle 12-in. packed with 3-mm sections of 6-mm quartz tubing. The ends of the tube were silver-soldered to stainless steel 18/9 spherical inner joints. Two porcelain-jacketed copper-Constantan thermocouples were taped to the tube with glass cloth electrical tape and the tube was mounted in a 12-in. flexible-band, ceramic-insulated heater. The tube was clamped at an angle of 30° with the horizontal to a ring stand. The lower end was connected by way of an external 18/9 spherical point to a glass trap cooled with liquid nitrogen and connected to an oil pump. The upper end of the pyrolysis tube was attached to an external 18/9 spherical joint on the side arm of a 100-ml distilling flask. The neck and side arm of the flask and the upper end of the pyrolysis tube were wrapped with heating tape to keep these parts above the melting point of the dimer. A Glas-Col heater was mounted beneath the flask. One thermocouple was attached to a Honeywell Pyr-O-Vane temperature controller with Powerstat and the other was connected to a potentiometer for checking the temperature.

The distilling flask was charged with 80 g of dimer 2, the pyrolysis tube was heated to 750°, and the pressure was reduced to *ca.* 1 mm with the oil pump. With the aid of the heater on the distilling flask, the dimer was sublimed through the pyrolysis tube during about 3 hr, or at such a rate that little dimer collected in the receiving trap. Nitrogen was then admitted and the trap was allowed to warm to room temperature. The trap contents were filtered or decanted from dimer if present and the mobile, reddish orange bis(trifluoromethyl)thioketene was then distilled: bp 52–53°; mp −55° (yellow solid); $n^{25}D$ 1.3495; d^{25}_4 1.462, dipole moment 1.95 D; ir and Raman 1783 cm^{-1} (5.61 μ); visible max (isooctane) 503 mμ (ε 8.5); uv max (isooctane) 239 mμ (ε 5590);[56] ^{19}F nmr (neat) −9.15 ppm (s). The still pot contained some dimer and a complex, liquid mixture. After correction was made for recovered dimer, the yield was 69–72%.

Anal. Calcd for C_4F_6S: C, 24.75; F, 58.74; S, 16.52. Found: C, 24.95; F, 58.65; S, 16.54.

In a single inhalation toxicity test, four rats were exposed to 5 ppm of the thioketene for 4 hr. No deaths occurred. The compound is thus less toxic than phosgene which kills at 5 ppm and is not comparable to the extemely toxic perfluoroisobutylene. The sample for this test was purified by glpc over 2.5% Kel-F ester on firebrick. The thioketene so obtained was less stable, but it is uncertain whether this was caused by introduction of a dimerization catalyst from the column, or removal of an inhibitor. The thioketene was restabilized by shaking with 1 drop of sulfuric acid and redistilling for the toxicity test.

Reaction of Bis(trifluoromethyl)thioketene with Sulfur.—Bis(trifluoromethyl)thioketene (23.3 g, 0.12 mol) and 4.23 g (0.13 mol) of sulfur were sealed in a glass tube and heated at 200° for 6 hr. The magenta liquid was decanted from 2.52 g of sulfur and distilled to give 18 g (71%) of a mixture, bp 83–111° (27 mm). Cuts, bp 90–100° (27 mm), were purified by glpc over 25% Dow-Corning FS 1265 on firebrick at 150°. The main fraction, 70–75% of the total product, was a magenta liquid: bp 191°; $n^{25}D$ 1.4570; ir 1577 cm^{-1} (C=C); visible max (isooctane) 528 mμ (ε 52.5); uv max (isooctane) 333 mμ (ε 12,000), 240 (10,880); ^{19}F nmr (neat) 1.63 (s, $2CF_3$), −7.75 ppm [A_3B_3 pattern, $(CF_3)_2C=$]. This compound is **6**, 5,5-bis(trifluoromethyl)-2-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]-1,3-dithiolane-4-thione.

Anal. Calcd for $C_8F_{12}S_3$: C, 22.86; S, 22.90. Found: C, 23.22; S, 23.05.

Distillation cuts boiling at 100–111° (27 mm) were chromatographed on the same column. Compound **5** came off later than **6** and was pale orange: $n^{25}D$ 1.4520; ir 1550 cm^{-1}; ^{19}F nmr (neat) −7.71, −8.60 ppm (quadruplets). These data and the elemental analysis are in agreement with those for the product (**5**) obtained from carbon disulfide and $(CF_3)_2C=N_2$.

Bis(trifluoromethyl)thioketene Tetramer (7).—Bis(trifluoromethyl)thioketene (15 g) and 6 g of selenium were sealed in a glass tube and heated at 200° for 5 hr. The solids were filtered from a purplish liquid mixture (*ca.* 3 g) and rinsed with a little dichloromethane. The solids were then extracted with acetone and the solution was boiled down to the crystallization point to give 4.5 g (30%) of tetramer, *trans*-2,2′-bis[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]-5,5,5′,5′-tetrakis(trifluoromethyl)-$\Delta^{4,4'}$-bi-1,3-dithiolane: mp 130–130.6°; ir 1575 cm^{-1} [$(CF_3)_2C=C$]; Raman 1575 [$(CF_3)_2C=C$], 1520 cm^{-1} (central C=C); ^{19}F nmr ($CHCl_3$) −5.90 (s, $2CF_3$), −9.60 ppm [A_3B_3 pattern, $(CF_3)_2C=$]. The white color indicates absence of C=S.

Anal. Calcd for $C_{16}F_{24}S_4$: C, 24.75; S, 16.52; mol wt, 776. Found: C, 25.09; S, 16.72; mol wt, 791 (in $CHCl_3$ by vapor pressure osmometer).

Dithietanes.—Thiocarbonyl compounds no. 1, 2, 4, and 6–12 in Table I were dissolved in about 2 ml/g of dichloromethane and the solution was stirred and occasionally cooled with ice to maintain the temperature at 10–25° while an equivalent of bis(trifluoromethyl)thioketene was added. Reaction was rapid and completion was indicated by the disappearance of the color of the thioketene. No. 3 was used neat at 0° with a reaction time of 3 hr. No. 5 was sealed in a glass tube with 2 ml/g of hexane and 2 equiv of the thioketene and heated at 100° for 15 hr. No. 12–20 were sealed in glass tubes, neat if liquid or with dichloromethane if solid, together with 1 equiv of the thioketene, and heated at 100° for 15 hr. Solvent was removed from the products and they were then recrystallized or distilled as indicated in Table I. All the compounds are colorless, which shows absence of C=S in the structure. In accord with the assigned structure the ^{19}F nmr spectrum shows a singlet for $(CF_3)_2C=C$ attached to the two sulfur atoms. For the dithietane from $(CF_3)_2C=S$ (Table I, no. 3) this occurs at −7.15 ppm (neat). For the rest of the compounds, neat or in solution in $CDCl_3$ or CCl_4, the singlet falls in the range of −8.51 to −9.95 ppm. The C=C ir absorption for the compounds occurs around 1613–1637 cm^{-1}.

Reaction with *p*-Dialkylaminobenzaldehydes.—*p*-Dimethylaminobenzaldehyde (2.24 g, 0.015 mol) dissolved in 20 ml of dichloromethane was placed in a simple, magnetically stirred still whose outlet was connected to a trap containing 2.80 g (0.03 mol) of aniline in dichloromethane. To the still was added dropwise 5.82 g (0.03 mol) of bis(trifluoromethyl)thioketene. Bis(trifluoromethyl)ketene evolved and was captured by the aniline. After the end of the addition, the dichloromethane in the pot was distilled into the trap. The sparingly soluble 3,3,3-trifluoro-2-(trifluoromethyl)propionanilide isolated from the trap amounted to 2.32 g (57%). After recrystallization from benzene it had mp 170.5–171° which showed no depression with a sample

(54) D. M. Gale, W. J. Middleton, and C. G. Krespan, *J. Amer. Chem. Soc.*, **88**, 3617 (1966).

(55) W. T. Miller, U. S. Patent 2,733,277 (1956).

(56) "UV Atlas of Organic Compounds," Vol. I, Plenum Press, New York, N. Y., 1966, p B13/3.

prepared from $(CF_3)_2C{=}C{=}O$[22] and aniline (lit.[57] mp 168–169°).

The product in the still pot was recrystallized from hexane (decolorizing charcoal) to give 4.15 g (77%) of 2-(*p*-dimethylaminophenyl)-4-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]-1,3-dithietane: mp 148–149°; ir 1600 cm^{-1} [$(CF_3)_2C{=}C$]; ^{19}F nmr (CCl_4) −9.95 ppm (s); ^1H nmr (CCl_4) 3.05 (s, $2CH_3$), 5.45 (s, CH), 7.09 ppm (center of aromatic A_2B_2 pattern).

Anal. Calcd for $C_{13}H_{11}F_6NS_2$: C, 43.44; H, 3.09; S, 17.85. Found: C, 43.75; H, 3.55; S, 17.95.

The diethylamino homolog was made in the same way in 28% yield: mp 81–82° from methanol; ^{19}F nmr (CCl_4) −10.10 ppm (s).

Anal. Calcd for $C_{15}H_{15}F_6NS_2$: C, 46.50; H, 3.90; S, 16.55. Found: C, 47.15; H, 3.97; S, 16.73.

Reaction with *p*-Dimethylaminocinnamaldehyde.—To 0.88 g (0.005 mol) of powdered *p*-dimethylaminocinnamaldehyde (Aldrich Chemical Co., recrystallized from methanol) suspended in 10 ml of hexane (which gives better results than dichloromethane) was added 1.94 g (0.01 mol) of bis(trifluoromethyl)thioketene. After 1 hr the solid was filtered off and recrystallized from methanol (decolorizing charcoal) to give 1.14 g (59%) of 2-(*p*-dimethylaminostyryl)-4-[2,2,2-trifluoro-1-(trifluoromethyl)-ethylidene]-1,3-dithietane: mp 136–137°; ir 1613 (=CH), 1563, 1534, 1490 (C=C), 971 cm^{-1} (*trans* CH=CH); ^{19}F nmr (CCl_4) −10.10 ppm (s).

Anal. Calcd for $C_{15}H_{13}F_6NS_2$: C, 46.73; H, 3.40; N, 3.63. Found: C, 46.76; H, 3.42; N, 3.45.

Reaction with 4,4′-Bis(dimethylamino)benzophenone.—The reaction was carried out as with *p*-dimethylaminobenzaldehyde and gave a 64% yield of 2,2-bis(*p*-dimethylaminophenyl)-4-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]-1,3-dithietane recrystallized from cyclohexane. After being recrystallized again from cyclohexane and from CCl_4, it melted at 135–136°, showed no depression in mixture melting point with dithietane no. 2, Table I, and had the same ^1H nmr as that product.

Anal. Calcd for $C_{21}H_{20}F_6N_2S_2$: C, 52.70; H, 4.21; S, 13.40. Found: C, 52.48; H, 4.22; S, 13.53.

Thietanes.—Conditions for preparing thietanes appear in Table II. A temperature of 10–25° indicates that the unsaturate was stirred and cooled in ice while 1 equiv of the thioketene was added dropwise. The reaction was complete at the end of the addition. Reactions at 100° were run in sealed glass tubes. The ^{19}F nmr spectra of the compounds in CCl_4, $CDCl_3$, or neat are similar and consist of two quadruplets, one at −7.7 to −9.7 ppm and the second at 1.2–1.6 ppm higher field. Components of the low field quadruplet are split to apparent triplets (J = ~2.6 Hz) for those thietanes containing a CH_2 group. For compounds no. 12 and 16, Table II, which contain a CH group adjacent to $(CF_3)_2C{=}C$, the low-field quadruplet components are split to doublets. Splitting in the high-field quadruplets is poorly defined or not evident. In the ^1H nmr spectrum, the CH_2 groups appear as broadened peaks with multiple splitting. Ir absorption for the exocyclic double bonds is at 1640–1670 cm^{-1}.

In the case of styrene (Table II, no. 9), which forms two products, the crude product from 7.76 g (0.04 mol) of the thioketene, 7.28 g (0.07 mol) of styrene, and 0.05 g of hydroquinone was diluted with methanol and 4.7 g of polymer was filtered off. The methanol was boiled from the filtrate and the residue was diluted with a small amount of petroleum ether. Crystals of the 2:1 thioketene:styrene adduct were filtered off and recrystallized from hexane to yield 2.54 g (26%) of 2-[2,2,2-trifluoromethyl)ethylidene]-4-{*p*-[3,3,3-trifluoro-2-(trifluoromethyl)propenylthio]phenyl}thietane (**14**): mp 75.5–76.5°; ir 3058 (=CH), 1621, 1577, 1481 (C=C), 853 cm^{-1} (*para*-disubstituted aromatic); ^{19}F nmr (CCl_4) −4.31, −7.00 [quadruplets, $(CF_3)_2C{=}CH{-}S{-}$], −10.8, −13.4 ppm (quadruplets); ^1H nmr (CCl_4) 2.00, 3.08, 3.57, 3.85 (AB pattern, latter 2 peaks split to doublets, CH_2), 4.44 (center of 2 doublets, thietane ring CH), 7.27 (4 aromatic H), 7.38 ppm [quadruplet for $(CF_3)_2C{=}CH$, J = 1.6 cps].

Anal. Calcd for $C_{16}H_8F_{12}S_2$: C, 39.02; H, 1.64; S, 13.03. Found: C, 39.20; H, 1.76; S, 12.94.

The 2-phenyl-4-[2,2,2-trifluoro-1-trifluoromethyl)ethylidene]-thietane in the filtrate from the above 2:1 adduct was distilled as indicated in Table II: ir 1653 (exocyclic C=C), 1595, 1499 cm^{-1} (aromatic C=C); ^{19}F nmr (neat) −7.45, −8.80 ppm (quadruplets, J = 7 cps, split to triplets, J = 2.6 cps, the low field one more clearly so); ^1H nmr (neat) 3.40 (multiplet, CH_2), 4.20 (2 doublets, CH), 6.93 ppm (s, C_6H_5). The pot residue yielded 0.6 g more (6%) of the 2:1 adduct.

Supplemental evidence on the structure of the indene adduct (Table II, no. 12) was obtained by desulfurization. The adduct (4 g), 150 ml of absolute ethanol, and 20 g of Raney nickel were refluxed for 4 hr. The product was filtered and distilled to give 2.36 g (65%) of 2-[3,3,3-trifluoro-2-(trifluoromethyl)propenyl]-indan: bp 92° (7 mm); mp 31–32° from methanol; ir 1675 cm^{-1} (linear C=C); ^{19}F nmr (neat) −2.14, −8.60 ppm (quadruplets); ^1H nmr (neat) 1.85–2.9 (multiplets, $2CH_2$), 3.12 (apparently a broad sextet and indicative of one proton split about equally by 5 protons, which would be consistent for the 2 proton of the indan nucleus in the proposed structure), 6.36 (d, =CH of substituent), 6.76 ppm (aromatic peak).

Anal. Calcd for $C_{13}H_{10}F_6$: C, 55.71; H, 3.60; F, 40.68. Found: C, 55.22; H, 3.83; F, 40.90.

2-(*p*-Methoxyphenyl)-4-[2,2,2-trifluoro-1-(trifluoromethyl)-ethylidene]thietane (Table II, no. 10) was converted to its 1,1-dioxide by heating 6.56 g (0.02 mol) in 25 ml of acetic acid with 6.2 ml (0.06 mol) of 30% hydrogen peroxide for 2 hr. Excess peroxide was destroyed by adding 5% Ru on C and the solvent was then evaporated from the filtered solution. Methanol was added to the cooled residue and the crystalline sulfone was filtered off and recrystallized from hexane to yield 4.7 g (72%), mp 97–97.5°.

Anal. Calcd for $C_{13}H_{10}F_6SO_3$: C, 43.33; H, 2.80; S, 8.90. Found: C, 43.29; H, 2.83; S, 9.03.

Synthesis of 10.—To 2.36 g (0.01 mol) of product no. 14, Table II, in 10 ml of dichloromethane was added 1.28 g of *p*-chloroaniline in 10 ml of dichloromethane. After 1 hr the solvent was evaporated and the residue was recrystallized from carbon tetrachloride to give 3.0 g (82%) of *p*-chloro-5,5,5-trifluoro-3-mercapto-4-(trifluoromethyl)-2-pentenanilide: mp 162.5–163°; ir 3226 (NH), 3040 (=CH), 1629, 1532 (*sec* amide), 1597, 1580, 1490 (C=C), 816 cm^{-1} (*para*-disubstituted aromatic band); ^1H nmr ($CDCl_3$) 3.72 [septuplet, $(CF_3)_2CH$], 6.31 (s, SH), 7.44 (s, =CH), 7.48 (A_2B_2 pattern, *p*-C_6H_4), 9.38 ppm (s, NH, removed by D_2O).

Anal. Calcd for $C_{12}H_8ClF_6NOS$: 39.63; H, 2.22; S, 8.82; mol wt, 364. Found: C, 39.49; H, 2.40; S, 8.66; mol wt, 389 (in $CHCl_3$ by vapor pressure osmometer).

Synthesis of 12.—On mixing 3.10 g (0.01 mol) of product no. 3, Table II, and 1.28 g (0.01 mol) of *p*-chloroaniline, the mixture became hot, liquified, and then crystallized. Recrystallization from ethanol gave 3.46 g (88%) of ethyl N-(*p*-chlorophenyl)-5,5,5-trifluoro-3-mercapto-4-(trifluoromethyl)-2-pentenimidate: mp 114–114.5°; ir 3067 (=CH), 3012, 2985, 2915 (C–H), 2558 (broad, hydrogen-bonded SH), 1645, 1575, 1560, 1499 (olefinic C=C, C=N, aromatic C=C), 831 cm^{-1} (*para*-disubstituted) aromatic; ^1H nmr (CCl_4) 1.46 (t, CH_3), 4.14 [quadruplet of ethyl CH_2 and septuplet of $(CF_3)_2CH$ superimposed], 7.20 (s, C_6H_4), 14.95 ppm (s, SH, removed by D_2O); ^{19}F nmr −2.62 ppm (d, J = 8 Hz).

Anal. Calcd for $C_{14}H_{12}F_6ClNOS$: C, 42.91; H, 3.09; S, 8.18. Found: C, 42.91; H, 3.24; S, 8.20.

Quadricyclene Adduct.[58]—To 7 g (0.076 mol) of quadricyclene (tetracyclo[3.2.0.$0^{2,7}$.$0^{4,6}$]heptane)[59] in 10 ml of dichloromethane was added dropwise 15 g (0.077 mol) of bis(trifluoromethyl)-thioketene. The temperature was kept at about 30° by cooling with ice. After the color of the thioketene had disappeared, the product was distilled to give 19.9 g (91%) of 4-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]-3-thiatricyclo[4.2.1.$0^{2,5}$]non-7-ene: bp 93° (9 mm); $n^{25}D$ 1.4655; ir 3077 (=CH), 2944, 2899 (saturated C–H), 1631 (exocyclic C=C), 1567 cm^{-1} (cyclic C=C); ^1H nmr (neat) 1.76 (center of AB pattern, bridge CH_2), 2.83 (s, 2 H, norbornene bridgeheads), 2.93 (s, H α to S), 3.33 [broad peak, H next to $(CF_3)_2C{=}C$ with splittings by F], 5.95 ppm (m, CH=CH); ^{19}F nmr (neat) −7.28, −9.30 ppm (quadruplets, components of latter split to doublets). A crude product prepared in CCl_4 had the same spectrum.

Anal. Calcd for $C_{11}H_8F_6S$: C, 46.15; H, 2.82; S, 11.20. Found: C, 46.51; H, 2.90; S, 11.42.

The compound did not isomerize when refluxed for 15 min at 226°.

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7-Chloroquadricyclene Adduct.—The thioketene (8.73 g, 0.045 mol) was added to 7-chloroquadricyclene[60] (5.60 g, 0.045 mol) with occasional cooling. After the mixture had stood for 16 hr, it was scratched to induce crystallization and recrystallized from methanol to give 9.72 g (68%) of the 9-chloro derivative of the previous compound in four crops: mp 67–68°; ^{1}H nmr ($CDCl_3$) 3.25 (m, norbornene bridgehead protons plus H α to S), 3.67 (broad peak, H on the other thietane bridgehead with splittings by F), 4.95 (s, with evidence of splitting, bridge H), 6.20 ppm (m, CH=CH); ^{19}F nmr (CCl_4) −7.65, −9.80 (quadruplets, components of latter split to doublets).

Anal. Calcd for $C_{11}H_7ClF_6S$: C, 41.20; H, 2.20; S, 10.00. Found: C, 41.60; H, 2.36; S, 9.93.

7-Acetoxyquadricyclene Adduct.—To 5.60 g (0.037 mol) of 7-acetoxyquadricyclene[61] in 5 ml of dichloromethane was added 9.70 g (0.05 mol) of the thioketene with cooling. After 16 hr the mixture was cooled and 2.5 g of the thioketene dimer was filtered off. Distillation of the filtrate gave 8.85 g (66%) of the 9-acetoxy compound, bp 80–82° (0.12 mm), n^{25}D 1.4689. The product solidified in part and recrystallization from petroleum ether left 4.8 g: mp 44–45°; ^{1}H nmr ($CDCl_3$) 2.0 (s, CH_3), 3.25 (m, norbornene bridgehead protons plus H α to S), 3.58 (broad peak, H on the other thietane bridgehead, with splitting by F), 5.60 (s, broadened with indications of splitting, bridge H), 6.15 ppm (m, CH=CH); ^{19}F nmr (CCl_4) −7.75, −9.92 (quadruplets, components split to doublets).

Anal. Calcd for $C_{13}H_{10}F_6O_2S$: C, 45.34; H, 2.93; S, 9.31. Found: C, 45.31; H, 3.04 S, 9.30.

1,3-Thiazetidines. A. Di-*p*-tolylcarbodiimide Adduct.—To 6.66 g (0.03 mol) of di-*p*-tolylcarbodiimide in 25 ml of dichloromethane was added 6 g (0.03 mol) of bis(trifluoromethyl)thioketene. After 16 hr the solvent was allowed to evaporate and the residue was recrystallized from methanol to give 10.6 g (85%) of 3-*p*-tolyl-2-(*p*-tolylimino)-4-[2,2,2-trifluoro-1-(trifluoromethyl)-ethylidene]-1,3-thiazetidine: mp 83–84°; ir 1733 (C=N), 1629 (exocyclic C=C), 1603, 1511 (aromatic C=C), 820 cm^{-1} (*para*-disubstituted aromatic band); ^{19}F nmr ($CDCl_3$) −10.0, −14.1 ppm (quadruplets).

Anal. Calcd for $C_{19}H_{14}F_6N_2S$: C, 54.80; H, 3.39; S, 7.70; mol wt, 416. Found: C, 55.00; H, 3.42; S, 7.73; mol wt, 371 (ebullioscopic in 1,2-dichloroethane).

The above compound (5 g) was heated under reflux at 240° for 5 min. The product was steam distilled to give 2.2 g of *p*-tolyl isothiocyanate as an oil. Reaction of this with *p*-toluidine gave 4,4′-dimethylthiocarbanilide, identified by mp 178–180° and mixture melting point with an authentic sample.

B. Dicyclohexylcarbodiimide Adduct.—This thiazetidine was prepared and worked up in 92% yield as described for the *p*-tolyl analog: mp 56–56.5°; ir 1748 (C=N), 1626 cm^{-1} (C=C); ^{19}F nmr −10.9, 15.3 ppm (quadruplets, J = 8 Hz).

Anal. Calcd for $C_{17}H_{22}F_6N_2S$: C, 50.41; H, 5.54; S, 8.01; mol wt, 400. Found: C, 49.91; H, 5.28; S, 7.85; mol wt, 381, 369 (ebullioscopic in 1,2-dichloroethane).

C. Diisopropylcarbodiimide Adduct.—The thioketene was added directly to 1 equiv of the carbodiimide with cooling in ice. Distillation gave an 88% yield of the thiazetidine: bp 47–48° (0.15 mm); n^{25}D 1.4450; ^{1}H nmr (neat) 0.95 (d), 1.24 (d), 2.88, 3.79 ppm (centers of septuplets); ^{19}F nmr −9.80, −14.2 ppm (quadruplets).

Anal. Calcd for $C_{11}H_{14}F_6N_2S$: C, 41.25; H, 4.41; S, 10.01. Found: C, 41.42; H, 4.46; S, 10.50.

D. Benzalazine Adduct.—To 5.24 g (0.025 mol) of benzalazine in 50 ml of benzene was added 4.85 g (0.025 mol) of bis-(trifluoromethyl)thioketene. After 16 hr, the solution was treated with decolorizing charcoal and the benzene was allowed to evaporate. The sticky mass of crystals remaining was washed with petroleum ether until free of benzalazine. The residual white crystals were recrystallized from methanol to give 1.6 g (19%) of 3-benzylideneamino-2-phenyl-4-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]-1,3-thiazetidine: mp 136–138°; ir 3086, 3049 (=CH), 1653 (exocyclic C=C), 1610, 1567, 1504 (aromatic C=C), 785, 690 cm^{-1} (monosubstituted aromatic bands); ^{1}H nmr ($CDCl_3$) 6.37 (s, CH of thiazetidine ring), 7.2–7.7 ppm (m, C_6H_5 + C_6H_5CH=, this position for the CH is considered more likely for a 1,2 adduct than for a 1,4 adduct); ^{19}F nmr −12.1, −14.8 ppm (quadruplets, J = 8 Hz).

Anal. Calcd for $C_{18}H_{12}F_6N_2S$: C, 53.74; H, 3.01; S, 7.97; mol wt, 402. Found: C, 53.84; H, 3.05; S, 7.73; mol wt, 369 (ebullioscopic in 1,2-dichloroethane).

E. Cyclohexanoneazine Adduct.—Cyclohexanoneazine[62] (5.78 g, 0.03 mol) dissolved in 25 ml of petroleum ether was maintained at 10–15° while 8.0 g (0.04 mol) of bis(trifluoromethyl)thioketene was added. The solvent was allowed to evaporate and the residue was washed with cold methanol to leave 5.5 g of crystals of 3-cyclohexylideneamino-2-[2,2,2-trifluoro-1-(trifluoromethyl)-ethylidene]-1,3-thiaazaspiro[3.5]nonane. A small amount of this unstable compound could be recrystallized from nitromethane if done quickly, mp 99.5–100.5°, ir 1613 cm^{-1} (C=C).

Anal. Calcd for $C_{16}H_{20}F_6N_2S$: C, 49.72; H, 5.22; S, 8.30. Found: C, 49.65; H, 5.11; S, 8.29.

Addition to 2,3-Dimethylbutadiene.—Addition of 7.76 g (0.04 mol) of the thioketene to 3.61 g (0.044 mol) of 2,3-dimethylbutadiene with cooling in ice and distillation gave 9.3 g (84%) of 5,6-dihydro-3,4-dimethyl-6-[2,2,2-trifluoro-1-(trifluoromethyl) ethylidene]-2H-thiopyran (**15**): bp 96–98° (9 mm); n^{25}D 1.4503; ir 1570 (exocyclic C=C), 1376 cm^{-1} (C–CH_3); ^{1}H nmr (neat) 1.56 (s, $2CH_3$), 3.05 ppm (s, broadened, $2CH_2$); ^{19}F nmr −9.43, −13.0 ppm (quadruplets).

Anal. Calcd for $C_{10}H_{10}F_6S$: C, 43.47; H, 3.65; S, 11.60. Found: C, 43.69; H, 3.39; S, 11.28.

Norbornadiene Adduct.—2,5-Norbornadiene (3.68 g, 0.04 mol) and 7.76 g (0.04 mol) of bis(trifluoromethyl)thioketene were sealed in a glass tube and heated at 100° for 16 hr. The red liquid obtained was distilled at 106–110° (10 mm) and then crystallized in part. The crystals were filtered off and recrystallized from methanol to give 3.73 g (33%) of hexahydro-2-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]-3,5,6-metheno-2H-cyclopenta[*b*]thiophene[58] (**16a**) in 3 crops: mp 53–53.5°; ir 1608 cm^{-1} (C=C); ^{1}H nmr (CCl_4) 1.25 to 1.75 (m, 3 cyclopropane H), 1.85 (s, CH_2, 2.39 (broadened peak, 1 H), 3.37 (m, 1 H), 3.52 ppm (quartet, 1 H); ^{19}F nmr −9.31, −11.9 ppm (quadruplets). The nmr shows absence of =CH.

Anal. Calcd for $C_{11}H_8F_6S$: C, 46.15; H, 2.82; S, 11.20. Found: C, 46.43; H, 3.14; S, 10.99.

The foreshot from the distillation contained a small amount of an unsaturated purple thione. Although not obtained analytically pure by glpc, nmr and ir indicated that the compound was the result of the addition of the C=C bond of the thioketene across the 2,3 positions of norbornadiene.

Norbornadiene Adduct Sulfone.—The above compound (2.86 g, 0.01 mol) was heated at 100° for 4 hr with 20 ml of acetic acid and 3 ml of 30% hydrogen peroxide. Water (20 ml) was then slowly added and crystals separated. After cooling, the crystals were filtered off (3.02 g, 95%) and recrystallized from methanol containing a little water to give 2.93 g of the 1,1-dioxide, mp 124.5–125°; ir 1669 cm^{-1} (C=C).

Anal. Calcd for $C_{11}H_8F_6O_2S$: C, 41.52; H, 2.53; S, 10.08. Found: C, 41.54; H, 2.74; S, 10.01.

7-*t*-Butoxynorbornadiene Adduct.—7-*t*-Butoxy-2,5-norbornadiene[63] (13.02 g, 0.08 mol) and 15.52 g (0.08 mol) of the thioketene were heated in a sealed glass tube at 100° for 15 hr. The mixture was cooled, 5 ml of dichloromethane was added, and 6.9 g of the thioketene dimer was filtered off. The filtrate was distilled at 70° (0.05 mm) and the crystals in the distillate were rinsed with methanol cooled in Dry Ice. Recrystallization from methanol left 4.48 g (16%) of 4-*t*-butoxyhexahydro-2-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]-3,5,6-metheno-2H-cyclopenta[*b*]thiophene (**16b**) in three crops, all melting at 72–73°: ^{1}H nmr (CCl_4) 1.2 [s, $(CH_3)_3$], 1.55 (m, 3 H), 2.20, 3.35 (broadened peaks, each 1 H), 4.02 ppm (m, 2 H); ^{19}F nmr −9.15, −11.9 ppm (quadruplets, components of latter split to doublets).

Anal. Calcd for $C_{15}H_{16}F_6OS$: C, 50.26; H, 4.50; S, 8.95. Found: C, 50.36; H, 4.60; S, 8.82.

Removal of methanol from the original rinse left 2.35 g of liquid which may have contained some of the other stereoisomer.

7-Chloronorbornadiene Adduct.—7-Chloro-2,5-norbornadiene (9 g, 0.07 mol) and 27 g of the thioketene were sealed in a glass tube and heated at 100° for 15 hr. The thioketene dimer (9 gm) was filtered off and rinsed with dichloromethane. Distillation of the filtrate gave 9.37 g (41%) of the 4-chloro compound (**16c**): bp 68–69° (0.15 mm); n^{25}D 1.4872; ^{1}H nmr (neat) 1.9 (m, 3 H),

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2.61 (s, 1 H), 3.5–4.4 ppm (m, 3 H); ^{19}F nmr −8.65, −10.4 ppm (quadruplets). The spectra do not show clear evidence of two isomers, but glpc over fluorosilicone on firebrick demonstrated a purity of 99.5% and an isomer ratio of 35:65 with retention times of 6.9 and 8.5 min.

Anal. Calcd for $C_{11}H_7ClF_6S$: C, 41.20; H, 2.20; S, 10.00. Found: C, 41.38; H, 2.37; S, 10.29.

Norbornadiene–Hexafluoroacetone Adduct (17).—A 200-ml flask with a thermometer in a side arm was equipped with a magnetic stirrer and a dropping funnel cooled with Dry Ice. The flask was cooled with an ice–salt bath and charged with 12 g (0.13 mol) of norbornadiene and 50 ml of dichloromethane. Through the dropping funnel was added in rapid drops 23 g (0.13 mol) of hexafluorothioacetone[28] in 50 ml of dichloromethane while the temperature in the flask was maintained at 8–10°. The thioketone was almost immediately decolorized. Distillation gave 8.7 g (25%) of 2,2-bis(trifluoromethyl)hexahydro-3,5,6-metheno-2H-cyclopenta[*b*]thiophene (**17**): bp 60° (1.5 mm); n^{25}D 1.4405; ^{1}H nmr (neat) 1.57 (m, 3 H), 1.80 (s, CH_2), 2.8 (m, H), 3.35 ppm (s, broad, 1 H); ^{19}F nmr −3.58, +2.62 ppm (quadruplets, J = 11 Hz).

Anal. Calcd for $C_{10}H_8F_6S$: C, 43.80; H, 2.94; S, 11.69. Found: C, 44.21; H, 3.26; S, 11.73.

Chlorination of 16a.—16a (1 g, 0.035 mol) and 0.47 g (0.0035 mol) of sulfuryl chloride formed a clear solution when mixed. Sulfur dioxide was evolved and the product crystallized on scratching. This was 2-chloro-6-[1-chloro-2,2,2-trifluoro-1-(trifluoromethyl)ethyl]hexahydro-3,5,6-metheno-2H-cyclopenta[*b*]-thiophene. The compound is sensitive to moisture. Warming with methanol caused replacement of Cl α to S with CH_3O. Cooling the methanol in Dry Ice caused 0.88 g (72%) of 2-methoxy compound (**18**) to crystallize out: mp 44.7–45.5°; ir no C=C; ^{1}H nmr (CCl_4) 1.48, 1.58 (2 peaks, 1st broadened, 2nd a triplet, 5 H), 2.43, 2.61 (broad peaks, each 1 H), 3.16 (1 H), 3.50 ppm (s, CH_3).

Anal. Calcd for $C_{12}H_{11}ClF_6OS$: C, 40.86; H, 3.14; Cl, 10.05. Found: C, 40.97; H, 3.21; Cl, 10.21.

Addition to Diazomethane.—A solution of 1.8 g (0.043 mol) of diazomethane[64] in 150 ml of ether was cooled in ice and 9.7 (0.05 mol) of bis(trifluoromethyl)thioketene was added dropwise with stirring. After all had been added, the ether was boiled off, the residue was cooled, and some of the thioketene dimer was filtered off and rinsed with dichloromethane. Distillation of the filtrate and rinse gave 8.0 g (79%) of two isomers, bp 65–67° (10 mm), n^{25}D 1.4000. The isomers were revealed by the ^{19}F nmr spectrum which showed a doublet at +1.06 ppm (59%) and another at 0 ppm (41%), both arising from $(CF_3)_2CH$. Separation was accomplished by glpc over 20% DC-200 silicone oil on Chromosorb P at 125°. Isomer **19** came at 11.7 min and **20** at 14.2 min. Compound **19** is 2-[2,2,2-trifluoro-1-(trifluoromethyl)-ethyl]-1,3,4-thiadiazole: n^{25}D 1.4004; ir 3115 (=CH), 1626, 1490 cm^{-1}; ^{1}H nmr (neat) 5.3 septuplet, $(CF_3)_2CH$], 8.8 ppm (s, no splitting, ring proton); ^{19}F nmr +1.03 ppm (d). Compound **20** is 5-[2,2,2-trifluoro-1-(trifluoromethyl)ethyl]-1,2,3-thiadiazole: n^{25}D 1.4002; ^{1}H nmr (neat) 5.4 ppm [septuplet, $(CF_3)_2CH$]; ir 3096 (=CH), 1458 cm^{-1}; ^{1}H nmr (neat) 5.4 [septuplet, $(CF_3)_2CH$], 9.7 ppm (d, J = 1 Hz, ring proton, shows CH–C=CH structure in this isomer); ^{19}F nmr −0.05 ppm (d).

Anal. Calcd for $C_5H_2F_6N_2S$: C, 25.43; H, 0.85; S, 13.57. Found for **19**: C, 25.53; H, 0.80; S, 13.87. Found for **20**: C, 25.71; H, 0.78; S, 13.73.

Hydrogen Azide Adduct.—To a mixture of 3.9 g (0.06 mol) of sodium azide, 4 ml of water, and 25 ml of dichloromethane was added 3 g (0.03 mol) of sulfuric acid with magnetic stirring at 10° or less. Sodium sulfate (6 g) was added for drying, and 19 ml (0.045 mol) of solution was decanted. To this was added 5.82 g (0.03 mol) of the thioketene with stirring and occasional cooling to keep the temperature at 20–30°. The solvent was allowed to evaporate at 25° to give 7.1 g (100%) of 5-[2,2,2-trifluoro-1-(trifluoromethyl)ethyl]-1,2,3,4-triazole (**22**). This very volatile solid was recrystallized from pentane: mp 60.5–61°; ir double bonds not evident, no evidence of azide; ^{1}H nmr (CCl_4) 5.32 ppm (septuplet); ^{19}F nmr −1.26 ppm (d).

Anal. Calcd for $C_4HF_6H_3S$: C, 20.26; H, 0.43; S, 13.53. Found: 20.58; H, 0.59; S, 13.43.

Benzonitrile Oxide Adduct.—To benzonitrile oxide in ether, prepared from 6.8 g (0.044 mol) of benzoyl chloride oxime[65] was added 8.5 g (0.044 mol) of the thioketene with cooling in ice. Evaporation of the ether gave 10.75 g of crystals which were recrystallized from methanol to give 9.3 g (68%) of 3-phenyl-5-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]-1,4,2-oxathiazole in two crops: mp 98–99°; ir 3106, 3049 (=CH), 1618 (exocyclic C=C) 1587, 1548, 1497 (C=N and aromatic C=C), 770–715 cm^{-1} (monosubstituted aromatic); ^{1}H nmr (CCl_4) 7.5 ppm (m, C_6H_5); ^{19}F nmr −9.6 ppm (A_2B_3 pattern).

Anal. Calcd for $C_{11}H_5F_6NOS$: C, 42.18; H, 1.61; S, 10.24. Found: C, 42.51; H, 1.88; S, 10.34.

N-Methyl-α-phenylnitrone Adduct.—To 4.05 g (0.03 mol) of N-methyl-α-phenylnitrone[66] dissolved in 15 ml of dichloromethane and cooled in ice was added 5.82 g (0.03 mol) of the thioketene with stirring. The solvent was allowed to evaporate and the residue (9.7 g) was recrystallized from hexane to give 8.85 g (90%) of 2-methyl-3-phenyl-5-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]-1,4,2-oxathiazolidine: mp 49.5–5.5; ir 1613 (exocyclic C=C), 1497 cm^{-1} (aromatic C=C); ^{1}H nmr (CCl_4) 2.95 (s, CH_3), 5.83 (s, CH), 7.60 ppm (s, C_6H_5); ^{19}F nmr −10.7 ppm (A_3B_3 pattern). Had the unlikely reverse addition across the thiocarbonyl group taken place, the ^{19}F nmr would show two well-separated quadruplets, and the CH would reveal coupling with F.

Anal. Calcd for $C_{12}H_9F_6NOS$: C, 43.76; H, 2.76; S, 9.73. Found: C, 43.70; H, 2.64; S, 9.68.

Reaction with N-Methoxy-α-phenylnitrone.—To 5.3 g (0.035 mol) of N-methoxy-α-phenylnitrone[67] in 10 ml of dichloromethane was added 6.8 g (0.035 mol) of the thioketene while cooling in ice to keep at 20°. During the addition the solution became cloudy as sulfur began to separate and gas was evolved. This gas was identified as $(CF_3)_2C{=}C{=}O$ by passing it into a solution of aniline in dichloromethane to form $(CF_3)_2CHCONHC_6H_5$, mp 171–172°, identical with an authentic sample. At the end of the reaction, 0.3 g of gummy sulfur was removed from the solution. The dichloromethane was boiled off and from the cooled residue 0.15 g of sulfur crystallized out. The liquid residue was distilled to give 2.33 g (49%) of O-methylbenzaldoxime, bp 79–82° (15 mm), n^{25}D 1.5410, identified by comparison of its nmr spectrum with that of an authentic sample prepared from methoxyamine and benzaldehyde.

Benzaldoxime Adduct.—A solution of 3.63 g (0.03 mol) of *syn*-benzaldoxime in 6 ml of dichloromethane and 24 ml of petroleum ether was cooled in ice and 5.82 g of the thioketene was added with stirring. The white, beautifully crystalline 3-phenyl-5-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]-1,4,2-oxathiazolidine separated and was filtered off and rinsed with petroleum ether to yield 7.4 g (78%). If the compound is allowed to stand at 25° for about 30 min, it starts to turn yellow and suddenly disappears in a cloud of smoke with a hissing sound. It can be stored at −80° and showed ir 3185 (NH), 1621 (exocyclic C=C), 1587, 1499 (aromatic C=C), 770–715 cm^{-1} (monosubstituted aromatic).

Anal. Calcd for $C_{11}H_7F_6NOS$: C, 41.90; H, 2.24; S, 10.17. Found: C, 42.15; H, 2.33; S, 10.20.

By working rapidly, the nmr spectra in $CDCl_3$ were obtained: 6.05 (d, CH, J = 12 Hz), 6.53 (d, NH, J = 12 Hz), 7.48 ppm (s, C_6H_5) (when the solution was shaken with D_2O, the NH doublet disappeared and the CH doublet was converted to a singlet); ^{19}F nmr −10.4 ppm (A_3B_3 pattern as in the nitrone adducts).

***p*-Chlorobenzaldoxime Adduct.**—To 1.56 g (0.01 mol) of *syn*-*p*-chlorobenzaldoxime[68] in 15 ml of cold dichloromethane was added 1.94 g (0.01) of the thioketene. Petroleum ether (3.5 ml) was added and the solution was cooled in Dry Ice. The 3-*p*-chlorophenyl derivative was filtered off and washed with petroleum ether to yield 1.6 g (31%). It had about the same instability as the phenyl compound and a closely similar ^{1}H nmr spectrum.

Anal. Calcd for $C_{11}H_6ClF_6NOS$: S, 9.17. Found: S, 8.84.

Anisaldoxime Adduct.—The reaction was carried out as described for benzaldoxime. The 3-*p*-anisyl compound was much less stable and existed at 25° for only 5 min before suddenly decomposing.

(64) J. A. Moore and D. E. Reed, *Org. Syn.*, **41**, 16 (1961).

(65) G. W. Perold, A. P. Steyn, and F. V. K. von Reiche, *J. Amer. Chem. Soc.*, **79**, 462 (1957).

(66) O. L. Brady, F. P. Dunn, and R. F. Goldstein, *J. Chem. Soc.*, 2390 (1926).

(67) F. Arndt and J. D. Rose, *ibid.*, 6 (1935).

(68) H. Erdmann and E. Schwechtern, *Justus Liebigs Ann. Chem.*, **260**, 63 (1890).

Registry No.—Table I—1, 14970-97-9; 2, 14970-98-0; 3, 14971-00-7; 4, 24515-92-0; 5, 24515-93-3; 6, 18795-65-8; 7, 18795-63-6; 8, 18795-64-7; 9, 24515-97-7; 10, 18795-66-9; 11, 18795-62-5; 12, 24516-00-5; 13, 18174-52-2; 14, 18174-53-3; 15, 24516-03-8; 16, 24516-04-9; 17, 18174-54-4; 18, 19323-42-3; 19, 24514-62-3; 20, 18174-55-5; Table II—1, 23592-26-9; 2, 23592-27-0; 3, 23592-28-1; 4, 23592-30-5; 5, 23592-38-3; 6, 23592-31-6; 7, 23592-32-7; 8, 24514-71-4; 9, 23592-33-8; 10, 23592-34-9; 11, 23592-35-0; 12, 24514-75-8; 13, 23592-40-7; 14, 23592-36-1; 15, 23592-37-2; 16, 24514-79-2; **1**, 7555-16-0; **2**, 7445-61-6; ethyl 3,3,3-trifluoro-2-{4-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]-1,3-dithietane-2-ylidene}propionate, 24515-27-3; 2,4-bis[2,2,2-trifluoro-1-(ethoxycarbonyl)ethylidene]-1,3-dithietane, 24515-15-9; **3**, 7445-60-5; **4**, 7555-17-1; **5**, 7592-88-3; 3,3-bis(chlorodifluoromethyl)-3H-diazirine, 24515-31-9; **6**, 24515-32-0; **7**, 24553-67-1; 2-(*p*-dimethylaminophenyl)-4-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]-1,3-dithietane, 15008-38-5; 2-(*p*-diethylaminophenyl)-4-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]-1,3-dithietane, 14970-99-1; 2-(*p*-dimethylaminostyryl)-4-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]-1,3-dithietane, 24515-35-3; **14**, 24515-36-4; 2-[3,3,3-trifluoro-2-(trifluoromethyl)propenyl]indan, 24515-37-5; 2-(*p*-methoxyphenyl)-4-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]thietane 1,1,-dioxide, 23592-41-8; quadricyclene adduct with bis(trifluoromethyl)-thioketene, 19438-57-4; 7-chloroquadricyclene adduct with bis(trifluoromethyl)thioketene, 24515-17-1; 7-acetoxyquadricyclene adduct with bis(trifluoromethyl)thioketene, 24515-18-2; 3-*p*-tolyl-2-(*p*-tolylimino)-4-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]-1,3-thiazetidine, 24515-56-8; dicyclohexylcarbodiimide adduct with bis(trifluoromethyl)thioketene, 24515-57-9; diisopropylcarbodiimide adduct with bis(trifluoromethyl)thioketene, 24515-58-0; 3-benzylideneamino-2-phenyl-4-[2,2,2-trifluoro-1-(trifluoromethyl)-ethylidene]-1,3-thiazetidine, 24515-59-1; 3-cyclohexylideneamino-2-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]-1,3-thiaazaspiro[3.5]nonane, 24515-60-4; **15**, 7527-44-8; **16a**, 20877-47-8; **16a** dioxide, 20877-48-9; **16b**, 19441-45-3; **16c**, 20877-50-3; **17**, 24515-71-7; **18**, 24515-72-8; **19**, 24515-73-9; **20**, 24515-74-0; **22**, 24515-76-2; 3-phenyl-5-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]-1,4,2-oxathiazole, 24515-77-3; 2-methyl-3-phenyl-5-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]-1,4,2-oxathiazolidine, 24515-78-4; 3-phenyl-5-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]-1,4,2-oxathiazolidine, 24515-80-8; 3-*p*-chlorophenyl-5-[2,2,2-trifluoro-1-(trifluoromethyl)ethylidene]-1,4,2-oxathiazolidine, 24515-81-9.

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Small Charged Rings. XII.[1] Aziridinium Ring Opening by Carboxylic Acids[2]

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Polycyclic aziridinium salts have been found to react with carboxylic acids at elevated temperatures to give compounds possessing amine salt and ester functionality. The monocyclic aziridinium salt 5-azoniadispiro[4.0.5.1]dodecane perchlorate (**1**) was found to rearrange thermally before carboxylic acid addition occurred. The bicyclic aziridinium salt, 1,6-dimethyl-1-azoniabicyclo[4.1.0]heptane perchlorate (**4**), reacted with carboxylic acids, probably *via* a β-amino tertiary carbonium ion intermediate, to form an ammonium ester (**5**). The tri- and tetracyclic aziridinium salts, 1-azoniatricyclo[4.4.1.0^{1,6}]undecane perchlorate (**6**) and 1-azoniatetracyclo[7.3.2.0^{1,13}.O^{5,13}]tetradecane perchlorate (**8**), reacted "abnormally" at the aziridinium methylene to give ammonium esters of primary alcohols, *e.g.*, 6-acetoxymethyl-1-azabicyclo[4.4.0]decane perchlorate (**7a**) and 13-acetoxymethyl-1-azatricyclo[7.3.1.0^{5,13}]tridecane perchlorate (**9a**), respectively. The position of carboxylic acid reaction with the aziridinium ring was determined by following the nmr chemical shift of the methylene protons from the original aziridinium ring to the ammonium ester product, and then to the corresponding free amine ester.

Discovery of the reaction of diazomethane with ternary iminium perchlorates and fluoroborates to form aziridinium salts has made a variety of substituted aziridinium salts readily available and has permitted investigation of their chemistry.[3] Previous papers in the series have described the reaction of 1,1,2,2-tetrasubstituted aziridinium salts. The aziridinium salts have been found to undergo ring opening by solvolysis-type reaction at the more substituted ring carbon;[3b] nucleophilic displacement at the less hindered, less substituted ring carbon;[3b] thermal rearrangement;[3b] and ring opening and expansion *via* cycloaddition of aldehydes,[4] ketones,[5] nitriles,[6] and nitrones.[7] The solvolytic ring opening, ring expansion, and thermal

(1) For the preceding article in this series, see N. J. Leonard and D. A. Durand, *J. Org. Chem.*, **33**, 1322 (1968).

(2) We are pleased to acknowledge the support of the National Science Foundation by Research Grant GP-8407X.

(3) For pertinent references and general summaries of work in this field, see (a) N. J. Leonard, *Rec. Chem. Progr.*, **26**, 211 (1965), and (b) D. R. Crist and N. J. Leonard, *Angew. Chem.*, **81**, 953 (1969); *Angew Chem., Int. Ed. Engl.*, **8**, 962 (1969).

(4) N. J. Leonard, E. F. Kiefer, and L. E. Brady, *J. Org. Chem.*, **28**, 2850 (1963).

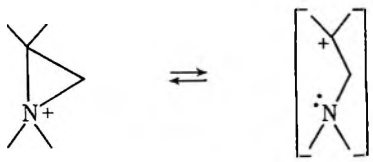
(5) N. J. Leonard, J. V. Paukstelis, and L. E. Brady, *ibid.*, **29**, 3383 (1964).

(6) N. J. Leonard and L. E. Brady, *ibid.*, **30**, 817 (1965).

(7) N. J. Leonard, D. A. Durand, and F. Uchimaru, *ibid.*, **32**, 3607 (1967).

rearrangement reactions appear to proceed *via* β-amino tertiary carbonium ion intermediates where sterically possible (Scheme I). We have now found that the

SCHEME I



aziridinium ring is opened with carboxylic acids, *e.g.*, acetic acid and benzoic acid, and we have tested the course of the reaction by means of a series of sterically graduated aziridinium salts.

The series of aziridinium salts selected included 5-azoniadispiro[4.0.5.1]dodecane perchlorate (**1**),[8] 1,6-dimethyl-1-azoniabicyclo[4.1.0]heptane perchlorate (**4**),[9] 1-azoniatricyclo[4.4.1.0^{1,6}]undecane perchlorate (**6**),[8] and 1-azoniatetracyclo[7.3.2.0^{1,13}.0^{5,13}]tetradecane perchlorate (**8**).[8] Attempts at bringing about reaction of compound **1** with the representative carboxylic acids were conducted at 70° for 14 hr in glacial acetic acid and in a 2-nitropropane solution of benzoic acid. Even under these moderated conditions only thermal rearrangement products **2** and **3**[10] were obtained.[3b] When solutions of compounds **4**, **6**, and **8** in glacial acetic acid were heated at reflux, ammonium ester products **5a**, **7a**, and **9a**, respectively, were produced. Mixtures of compounds **6** and **8** with benzoic acid, when heated for 10 min at 135° and 20 min at 145°, respectively, gave the corresponding products, **7b** and **9b**. Evidence of reaction of **4** with benzoic acid was obtained from nmr spectra, but a pure product, **5b**, analogous to that obtained with acetic acid, was not isolated.

In general, the products produced by carboxylic acid addition were characterized by microanalysis and by their infrared and proton magnetic resonance spectra. For the ammonium ester products, the position of attachment of the carboxylate group was determined by examining the change in the pmr chemical shift of the methylene protons from the original aziridinium ring to the ammonium ester product, and then to the corresponding tertiary amine ester liberated from this salt. These data are presented in Table I. The methylene protons originally in the aziridinium ring of **4**, when traced to **5a**, exhibited a doublet at τ 6.42 in the nmr spectrum. This changed to an AB system centered at 7.23 when **5a** was converted to the free amine. The shift of 0.81 ppm is of the order expected[8] for an α_{N^+}-CH_2 to α_N-CH_2 conversion and compares favorably with the 1.02 ppm upfield shift of the other α-methylene group during the same conversion. By contrast, the resonances of the former aziridinium methylene protons, when traced to **7a**, **7b**, **9a**, and **9b**, fell between τ 5.03 and 5.45. Conversion to free amine in each of these cases caused the chemical shifts of the methylene groups to move upfield by only 0.14–0.17 ppm. The lower field signals of the methylene groups in this family of salts is evidence for their attachment to oxygen, and the relatively small change in chemical shift upon liberation of the free amines confirms the assigned structures.

(8) N. J. Leonard, K. Jann, J. V. Paukstelis, and C. K. Steinhardt, *J. Org. Chem.*, **28**, 1499 (1963).

(9) The preparation from the iminium salt was similar to that for 6-ethyl-1-methyl-1-azoniabicyclo[4.1.0]heptane perchlorate in ref 8. For the preparation of the iminium salt precursor, 1,2-dimethyl-3,4,5,6-tetrahydropyridinium perchlorate, see N. J. Leonard and F. P. Hauck, Jr., *J. Amer. Chem. Soc.*, **79**, 5279 (1957).

(10) P. C. Kelley, Ph.D. Thesis, University of Illinois, 1965.

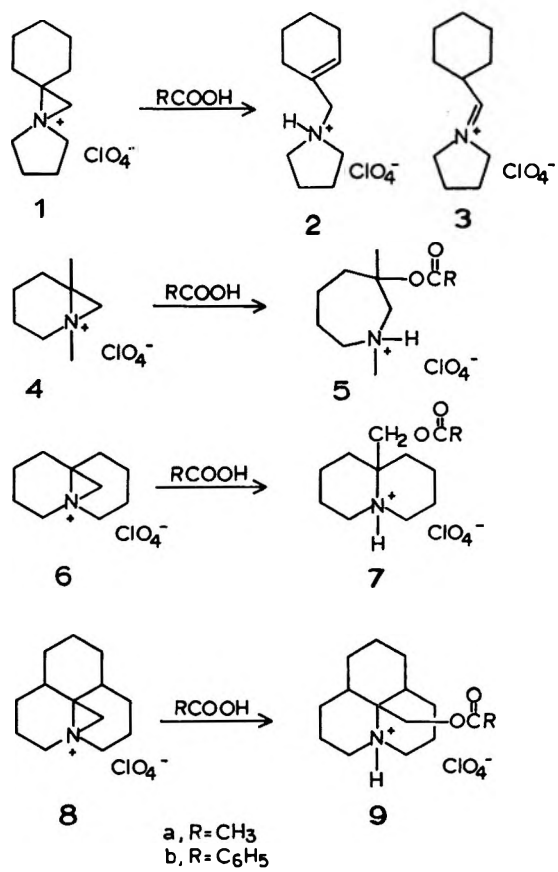
TABLE I

PRODUCTS OF CARBOXYLIC ACID REACTION WITH AZIRIDINIUM SALTS

Compd	Yield, %	Pmr of α-CH_2[a,b] Salt	Free amine
5a	53	6.42(d)[c]	7.08, 7.38[d]
7a	64	5.45[e]	5.62
7b	72	5.17[e]	5.33
9a	55	5.28	5.44
9b	69	5.03	5.17

[a] Former aziridinium methylene group. [b] Chemical shifts, τ (methylene chloride, TMS). [c] J = 4.5 Hz. [d] AB system, J_{AB} = 14 Hz. [e] In CF_3COOH.

The diversity of products resulting from the heating of the selected aziridinium salts with carboxylic acids seems inconsistent at first inspection. Thus, compound **1** does not yield an ammonium ester but instead gives thermal rearrangement products **2** and **3**. Compound **4** gives the product of reaction of acetic acid at the more substituted aziridinium carbon atom, which corresponds to the normal position for solvolytic ring opening. Compounds **6** and **8** give products of reaction of acetic and benzoic acids at the less substituted aziridinium carbon. This variety of products may be explained by considering β-aminocarbonium ion intermediates in equilibrium with the aziridinium salt.

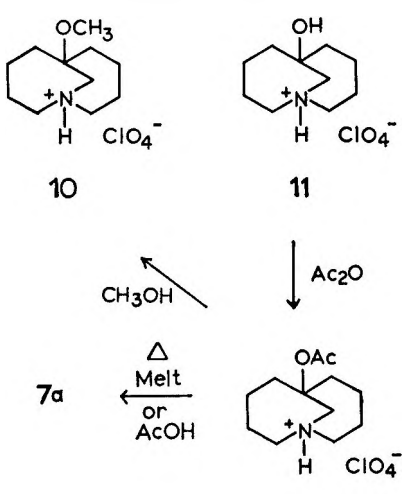


The solvolysis of 5-azoniadispiro[4.0.5.1]dodecane perchlorate (**1**) in methanol (65°) and ethanol (78°) to yield the corresponding N-[1-methoxy(ethoxy)cyclo-

hexylmethyl]pyrrolidine perchlorates[11] and the thermolysis of **1** in the melt (145°) to give a mixture of ene–ammonium (**2**) and iminium (**3**) salts[10] are best explained as proceeding through the β-amino tertiary carbonium ion derived from opening of the strained aziridinium ring. In acetic acid and benzoic acid, even when the temperature was maintained as low as possible (70°) to give appreciable reaction, the products isolated were not the corresponding N-[1-(acetoxy- or benzoyloxy)cyclohexylmethyl]pyrrolidine perchlorates but rather the products, **2** and **3**, of hydrogen migration in the proposed β-amino tertiary carbonium ion intermediate. The experiments do not preclude formation of the acetoxy and benzoyloxy compounds during the reaction, since any reversal by an E1 elimination would proceed through the same carbonium ion.

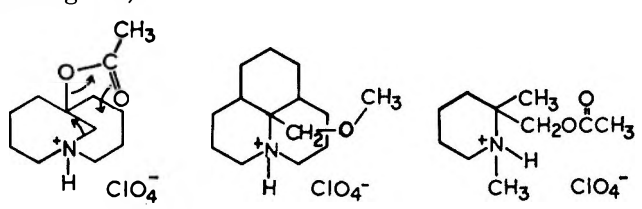
The bicyclic aziridinium salt **4** did not undergo thermal rearrangement as readily as **1**. The major product obtained from **4** and glacial acetic acid at reflux was 3-acetoxy-1,3-dimethyl-1-azacycloheptane perchlorate (**5a**), the structure of which was determined spectroscopically as described above. This may be regarded as the *normal* solvolysis product; methanolysis of the homolog, 6-ethyl-1-methyl-1-azoniabicyclo[4.1.0]heptane perchlorate, had produced an analogous product, 3-ethyl-3-methoxy-1-methyl-1-azacycloheptane perchlorate.[8]

With respect to the methanolysis product of **6**, namely, 6-methoxy-1-azabicyclo[4.4.1]undecane perchlorate (**10**),[8] the acetolysis product of **6**, 6-acetoxymethyl-1-azabicyclo[4.4.0]decane perchlorate (**7a**) is *abnormal*, that is, the acetoxyl group ends up attached to the former aziridinium carbon that was less substituted. For comparison, 6-acetoxy-1-azabicyclo[4.4.1]undecane perchlorate (**12**) was synthesized by



treatment of 6-hydroxy-1-azabicyclo[4.4.1]undecane perchlorate (**11**)[8] with acetic anhydride.[12] This isomer was converted to **7a** by heating in the melt (170°) for 1–2 min; moreover, **12** was also converted, approximately 64% in 30 min., to **7a** in refluxing glacial acetic acid. This suggests that the initial aziridinium ring opening of **6** in methanol or acetic acid leads to the bicyclo[4.4.1]undecane system under kinetic control. When the methanol product **10** is obtained, the methoxyl group is not readily displaced under the reaction conditions. If the acetoxy product **12** is formed, however, the acetoxyl group can be displaced by partial dissociation of the salt, ionization, and participation of the neighboring amino nitrogen.[13] As shown by the conversion of **12** to **7a**, at least under the stated reaction conditions, **7a** is the thermodynamically more stable acetoxy isomer. As further indication of the ionization of the [4.4.1]acetate (**12**) and the intermediacy of **6**, the reaction of **12** in refluxing methanol was observed to give 6-methoxy-1-azabicyclo[4.4.1]undecane perchlorate (**10**) (nmr determination), as in the direct methanolysis of **6**. By contrast, 6-methoxy-1-azabicyclo[4.4.1]undecane perchlorate remained unchanged when refluxed in glacial acetic acid for 30 min.

Logical mechanistic sequences can be developed for these interconversions based on the equilibration of the aziridinium ion in **6** with the related, solvated β-amino-carbonium ions. In the transition state leading to rapid ring opening at the more substituted carbon, cleavage of the N^+–C bond may be well advanced toward β-amino tertiary carbonium ion formation. In the transition state leading to ring opening at the less substituted carbon, appreciable covalent bonding to the solvent-reactant may be taking place with cleavage of the N^+–C bond, possibly assisted by proton transfer from carboxylic acid to nitrogen. Full development of the new C–O bond completes the solvolysis process.[14,15] The driving force for the observed conversion of **12** to **7a** appears to be relief of strain energy in going from the bridged dual seven-membered ring system to the fused six-membered rings of the azadecalin system. Ionization of acetate **12** permits the conversion, whereas this pathway would not occur as readily with the methoxy compound **10**. A logical mechanism has been described above for the conversion of **12** to **7a** through **6**. Another distinct possibility lies in the participation of acetoxyl as a neighboring group[16] (*e.g.*, through **13**).



(11) N. J. Leonard and K. Jann, *J. Amer. Chem. Soc.*, **84**, 4806 (1962).

(12) R. A. Johnson, M. E. Herr, H. C. Murray, and G. S. Fonken, *J. Org. Chem.*, **33**, 3187 (1968).

(13) (a) C. F. Hammer and S. R. Heller, *Chem. Commun.*, 919 (1966); (b) R. C. Fuson and C. L. Zirkle, *J. Amer. Chem. Soc.*, **70**, 2760 (1948).

(14) The aziridinium and β-amino carbonium ion solvates may be cognate to ion-pair intermediates [see R. A. Sneen and J. W. Larsen, *J. Amer. Chem. Soc.*, **91**, 362 (1969), and references therein], but the forces of interaction here are between cations or developing carbonium ions and, for example, alcohols or carboxylic acids.

(15) The overall situation is somewhat complicated by the fact that in the solvated β-amino-*t*-carbonium ion first formed by ring opening of **6** the unshared electron pair on nitrogen may be *endo*. Scale molecular models indicate that this form is more strained than the N-inverted form in which the unshared pair is *exo* with respect to the methylene bridge. Strained ring systems having sp^2 hybridization at the bridgehead, including S = 9, [4.4.1] types [(a) F. S. Fawcett, *Chem. Rev.*, **47**, 219 (1950)], have been previously described [see (b) T. L. Westman and R. D. Stevens, *Chem. Commun.*, 459 (1965), and references therein; (c) A. C. Cope, R. J. Cotter, and G. G. Roller, *J. Amer. Chem. Soc.*, **77**, 3590 (1955); (d) K. Biemann, G. Büchi, and B. H. Walker, *ibid.*, **79**, 5558 (1957); (e) W. J. McMurray, Ph.D. Thesis, University of Illinois, 1963]. Although an equilibrium may disfavor the electron-pair–*endo* form, it is apparent from the experiments that this does not prevent interconversion from one bicyclic system to the other.

(16) (a) S. Winstein, E. Grunwald, R. E. Buckles, and C. Hanson, *J. Amer. Chem Soc.*, **70**, 816 (1948); (b) S. Winstein, E. Grunwald, and L. L. Ingraham, *ibid.*, **70**, 821 (1948).

The ring system in **8** provides an extreme case where methanolysis and acetolysis both follow the abnormal course. Thus, 1-azoniatetracyclo[7.3.2.0^{1,13}.0^{5,13}]tetradecane perchlorate (**8**) yielded 13-methoxymethyl-1-azatricyclo[7.3.1.0^{5,13}]tridecane perchlorate (**14**) in refluxing methanol,[8] 13-acetoxymethyl-1-azatricyclo[7.3.1.0^{5,13}]tridecane perchlorate (**9a**) in refluxing glacial acetic acid, and 13-benzoyloxymethyl-1-azatricyclo[7.3.1.0^{5,13}]tridecane perchlorate (**9b**) when heated with benzoic acid at 145°. In this case there is not only steric resistance to formation of the β-amino-*t*-carbonium ion but probably steric hindrance to its capture by the methanol or carboxylic acid. With these restrictions imposed, the methoxy or acyloxy group becomes attached to the methylene aziridinium carbon, probably through a transition state in which there is appreciable covalent bonding to the solvent-reactant. The possibility of direct displacement by acetate[17] or benzoate on the less hindered methylene carbon depends upon the availability of the carboxylate anion arising from self-ionization. The self-ionization product of glacial acetic acid, as determined by conductivity measurements, has been found to be 2.1×10^{-13} at 105.7°[18] and 2.5×10^{-13} at 25°.[19] Potentiometric measurements gave the value 3.5×10^{-15} at 25°.[20] Thus, the very low acetate ion concentration available probably means that acetate does not play a significant role in the reaction **8** → **9a**. Moreover, no products of methylene attack were observed for **1** and **4** with acetic acid alone. In the case of 1,6-dimethyl-1-azoniabicyclo[4.1.0]heptane perchlorate (**4**) it was possible to obtain some of the isomeric 2-acetoxymethyl-1,2-dimethylpiperidine salt (**15**) of **5a** when **4** was treated with glacial acetic acid containing anhydrous sodium acetate. The added acetate was a requirement for the observation of this type of product (nmr determination) from **4**, whereas it was not in the cases of the tricyclic (**6**) and tetracyclic (**8**) aziridinium salts. Consequently, the only obligatory reagent for the abnormal aziridinium ring opening in these special systems (**6** and **8**) to give products such as **7** and **9** appears to be the carboxylic acid.

Experimental Section[21]

5-Azoniadispiro[4.0.5.1]dodecane perchlorate (**1**), **1-azoniatricyclo[4.4.1.0^{1,6}]undecane perchlorate** (**6**), **and 1-azoniatetracyclo[7.3.2.0^{1,13}.0^{5,13}]tetradecane perchlorate** (**8**) were prepared as described previously[8] by the addition of ethereal diazomethane to the corresponding iminium perchlorate in methylene chloride at 0°. The aziridinium salts were stored in a vacuum desiccator at room temperature. 1,6-Dimethyl-1-azoniabicyclo[4.1.0]heptane perchlorate (**4**) was prepared in a similar manner from 1,2-dimethyl-3,4,5,6-tetrahydropyridinium perchlorate:[9] mp 151.5–153°; yield 84%; no O—H, $^{+}$N—H, or C=N^{+} absorptions in the infrared spectrum; pmr (CH_2Cl_2) τ 6.42 (br t, 2, J = 6.0 Hz, CH_2N^{+}), 6.78 and 7.04 (AB system of doublets, 2, J_{AB} = 5.0 Hz, aziridinium methylene), 6.85 (s, 3, CH_3N^{+}), 7.86 (br t, 2, J = 6.0 Hz, CH_2C), and 8.27 (br s, 7, CH_3C and 4 ring protons).

Anal. Calcd for $C_8H_{16}ClNO_4$: C, 42.48; H, 7.08; N, 6.19. Found: C, 42.33; H, 7.01; N, 6.33.

Thermal Rearrangement Products from 5-Azoniadispiro[4.0.5.1]dodecane Perchlorate (**1**) **in the Presence of Acetic Acid and Benzoic Acid.**—Solutions of 1.00 g (3.76 mmol) of 5-azoniadispiro[4.0.5.1]dodecane perchlorate (**1**)[11] in 5 ml of glacial acetic acid and the same quantity of aziridinium salt plus 3.0 g of benzoic acid in 10 ml of 2-nitropropane were heated at 70° for 14 hr. Both solutions were then poured into a large volume of stirred ether and the resulting precipitates were triturated with additional ether. Both semisolid products were dissolved in small volumes of methylene chloride, reprecipitated in stirred ether, and triturated with ether. The characteristic odor of aldehyde could be detected in both crude products.[10] Cyclohexanecarboxaldehyde would arise from the hydrolysis of the iminium salt **3**, produced by thermal rearrangement of the aziridinium salt. The nmr spectra (CH_2Cl_2) of the crude products showed no proton resonances attributable to benzoyl or acetyl groups. However, evidence for the presence of the ene–ammonium salt **2**, the other thermal rearrangement product,[10] was indicated by the broad resonances at about τ 2.3 for N^{+}–H and at τ 3.98 for the olefinic protons in both spectra.[22]

General Procedure of the Aziridinium Salt–Carboxylic Acid Reaction. Preparation of 6-Benzoyloxymethyl-1-azabicyclo[4.4.0]decane Perchlorate (**7b**).—A mixture of 0.50 g (2.0 mmol) of 1-azoniatricyclo[4.4.1.0^{1,6}]undecane perchlorate (**6**) and 1.00 g (8.1 mmol) of benzoic acid was heated at 135° for 10 min with attendant darkening of the melt. After cooling, the solid was triturated several times with ether before dissolution in methylene chloride and precipitation by addition to ether with stirring. The solid was recrystallized from acetonitrile–ether to give 0.52 g (72%) of tan prisms. Two further recrystallizations gave colorless prisms: mp 218–220° ν_{max}^{Nujol} 3090 and 1710 cm^{-1}; pmr (CF_3CO_2H), τ 1.90 and 2.48 (2 m, 5, Ar hydrogens), 5.17 (s, 2, CH_2O), 6.42 (br s, 4, $CH_2N^{+}CH_2$), and 8.00 (br s, 12, ring methylenes).

Anal. Calcd for $C_{17}H_{24}ClNO_6$: C, 54.54; H, 6.42; N, 3.74. Found: C, 54.69; H, 6.31; N, 3.86.

A portion of the perchlorate salt was converted to the free amine by treatment with aqueous potassium carbonate and extraction with methylene chloride. The combined extracts were dried, filtered, and concentrated *in vacuo*. The nmr spectrum was definitive for **6-benzoyloxymethyl-1-azabicyclo[4.4.0]decane**: pmr (CH_2Cl_2) τ 2.03, 2.52 (2 m, 5, Ar hydrogens) 5.33 (s, 2 CH_2O), 7.00–7.70 (v br m, 4 CH_2NCH_2), and 8.00–8.80 (v br m, 12 ring methylenes).

In a similar manner the products given below were obtained.

From a solution of 0.66 g (2.9 mmol) of 1,6-dimethyl-1-azoniabicyclo[4.1.0]heptane perchlorate (**4**) in 10 ml of glacial acetic acid heated at reflux for 3 hr there was obtained from ethanol-ether 440 mg (53%) of **3-acetoxy-1-3-dimethyl-1-azacycloheptane perchlorate** (**5a**). A colorless, analytically pure sample, prisms, had mp 113.5–115°; ν_{max}^{Nujol} 3120 amd 1710 cm^{-1}; pmr (CH_2Cl_2), τ 6.42 (br d, 4, J = 4.5 Hz, $CH_2N^{+}CH_2$), 6.96 (d, 3, J = 5.0 Hz, $N^{+}CH_3$), 7.60–8.35 (v br m, 6, ring methylenes), 7.86 (s, 3, CH_3CO_2), and 8.50 (s, 3, CCH_3). When the reaction was run in acetic acid with anhydrous sodium acetate present some of the 2-acetoxymethyl-1,2-dimethylpiperidine salt was formed in addition to **5a**.

Anal. Calcd for $C_{10}H_{20}ClNO_6$: C, 41.96; H, 6.99; N, 4.90. Found: C, 42.12; H, 6.98; N, 4.92.

The free amine obtained gave an nmr spectrum confirming the structure as **3-acetoxy-1,3-dimethyl-1-azacycloheptane**: pmr (CH_2Cl_2) τ 7.08 and 7.38 (AB system of doublets, 2, J_{AB} = 14 Hz, NCH_2C), 7.30–7.60 (br m, 2, CH_2N), 7.65 (s, 3, NCH_3), 8.06 (s, 3, CH_3CO_2), 8.0–8.5 (br m, 6, ring methylenes), and 8.55 (s, 3, CH_3C).

From a solution of 0.50 g (2.0 mmol) of 1-azoniatricyclo[4.4.1.0^{1,6}]undecane perchlorate (**6**) in 2.0 ml of glacial acetic acid heated at reflux for 30 min there was obtained in two crops from ethanol 390 mg (64%) of light tan needles of **6-acetoxymethyl-1-azabicyclo[4.4.0]decane perchlorate** (**7a**). Two further recrystallizations gave an analytically pure sample: mp 183–184.5°; ν_{max}^{Nujol} 3135 and 1760 cm^{-1}; pmr (CF_3CO_2H), τ 3.35 (v br m, 1, $N^{+}H$), 5.45 (s, 2, CH_2O), 6.45 (br m, 4, $CH_2N^{+}CH_2$), 7.63 (s, 3, CH_3), and 8.03 (br m, 12 ring methylenes).

(17) H. R. Snyder and J. H. Brewster, *J. Amer. Chem. Soc.*, **71**, 291 (1949).
(18) R. J. L. Martin, *Aust. J. Chem.*, **18**, 321 (1965).
(19) I. M. Kolthoff and A. Willman, *J. Amer. Chem. Soc.*, **56**, 1007 (1934).
(20) S. Bruckenstein and I. M. Kolthoff, *ibid.*, **78**, 2974 (1956).
(21) All melting points are corrected. Infrared spectra were obtained with a Perkin-Elmer Model 337 grating spectrophotometer. Microanalyses were performed by Mr. Josef Nemeth and his staff. Nuclear magnetic resonance spectra were obtained on a Varian Associates Model A-60, A-60A or 56-60A spectrometer using tetramethylsilane as an internal standard. In the nuclear magnetic resonance data, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, v = very, and br = broad.
(22) Further discussion is reserved for a complete paper on thermal rearrangements.

Anal. Calcd for $C_{12}H_{22}ClNO_6$): C, 46.15; H, 7.05; N, 4.49. Found: C, 46.29; H, 6.93; N, 4.46.

The free amine obtained gave an nmr spectrum definitive for **6-acetoxymethyl-1-azabicyclo[4.4.0]decane**: pmr (CH_2Cl_2), τ 5.62 (s, 2, CH_2O), 7.00–7.75 (v br m, 4, CH_2NCH_2), 7.98 (s, 3, CH_3), 8.17–8.80 (br m, 12, ring methylenes).

A solution of 1.00 g (3.4 mmol) of 1-azoniatetracyclo[7.3.2.$0^{1,13}$.-$0^{5,13}$]tetradecane perchlorate (**8**) in 5 ml of glacial acetic acid heated at reflux for 30 min yielded 660 mg (55%) of tan needles of **13-acetoxymethyl-1-azatricyclo[7.3.1.$0^{5,13}$]tridecane perchlorate** (**9a**) from ethanol–ether. Three further recrystallizations gave an analytically pure sample: mp 206–208°; ν_{max}^{Nujol} 3160 and 1760 cm^{-1}; pmr (CH_2Cl_2) τ 5.28 (s, 2, CH_2O), 6.67 (br m, 4, CH_2N^+-CH_2), 7.70–8.80 (v br m, 16, ring methylenes), and 7.85 (s, 3, CH_3CO_2).

Anal. Calcd for $C_{15}H_{25}ClNO_6$: C, 51.28; H, 7.12; N, 3.99. Found: C, 51.53; H, 7.42; N, 4.00.

An nmr spectrum of the free amine confirmed the structure of **13-acetoxymethyl-1-azatricyclo[7.3.1.$0^{5,13}$]tridecane**: pmr (CH_2-Cl_2) τ 5.44 (s, 2, CH_2O), 7.20–7.70 (br m, 4, CH_2NCH_2), 7.90–8.90 (v br m, 16, ring methylenes), and 7.97 (s, 3, CH_3CO_2).

A mixture of 0.50 g (1.7 mmol) of 1-azoniatetracyclo[7.3.2.-$0^{1,13}0^{5,13}$]tetradecane perchlorate (**8**) and 1.0 g of benzoic acid heated at 145° for 20 min yielded 490 mg (69%) of tan needles of **13-benzoyloxymethyl-1-azatricyclo[7.3.1.$0^{5,13}$]tridecane perchlorate** (**9b**). A second recrystallization afforded an analytically pure sample of light tan needles: mp 198.5–200.5°; ν_{max}^{Nujol} 3050 and 1710 cm^{-1}; pmr (CH_2Cl_2) τ 1.98 and 2.47 (2 m, 5, Ar), 5.03 (s, 2, CH_2O), 6.60 (br m, 4, $CH_2N^+CH_2$) and 7.50–8.70 (v br m, 16, ring methylenes).

Anal. Calcd for $C_{20}H_{28}ClNO_6$: C, 57.97; H, 6.76; N, 3.38. Found: C, 57.97; H, 6.62; N, 3.57.

The nmr spectrum of the free amine confirmed the structure of **13-benzoyloxymethyl-1-azatricyclo[7.3.1.$0^{5,13}$]tridecane**: pmr (CH_2Cl_2), τ 1.94 and 2.52 (2 m, 5, Ar), 5.17 (s, 2, CH_2O), 6.95–7.67 (v br m, 4, CH_2NCH_2), and 7.82–8.90 (v br m, 16, ring methylenes).

6-Acetoxy-1-azabicyclo[4.4.1]undecane Perchlorate (12).—A solution of 0.50 g (1.85 mmol) of 6-hydroxy-1-azabicyclo[4.4.1]-undecane perchlorate (**11**)[8] in 10 ml of acetic anhydride was heated on a steam bath for 1 hr. The solvent was evaporated *in vacuo* to give light yellow crystals. The product was triturated with ether before recrystallization from ethanol to give light tan platelets: mp 163–164° (dec); yield 0.35 g (61%); ν_{max}^{Nujol} 3110 and 1690 cm^{-1}; pmr (CF_3COOH) τ 5.78 and 6.15 (2 d, 2, J = 3.0 Hz, CCH_2N^+ of *cis* and *trans* isomers respectively), 6.43 (br m, 4, $CH_2N^+CH_2$), 7.76 and 7.82 (2 s, 3, $CH_3C{=}O$ of *trans* and *cis* isomers respectively),[14b] and 7.94 (br s, 12, remaining ring methylenes).

Anal. Calcd for $C_{12}H_{22}ClNO_6$: C, 46.15; H, 7.05; N, 4.49. Found: C, 46.31; H, 7.04; N, 4.50.

Conversion of 6-Acetoxy-1-azabicyclo[4.4.1]undecane Perchlorate (12) to 6-Acetoxymethyl-1-azabicyclo[4.4.0]decane Perchlorate (7a).—A solution of 150 mg of 6-acetoxy-1-azabicyclo-[4.4.1]undecane perchlorate (**12**) in 5 ml of glacial acetic acid was heated at reflux for 30 min. The solvent was evaporated *in vacuo* and the solid was triturated with ether. The product was dissolved in methanol and slowly added to a large volume of stirred ether. The product was then triturated with ether and dried *in vacuo*. The nmr spectrum (CF_3COOH) exhibited signals corresponding to 64% conversion of **12** to **7a**. The conversion was also carried out in the molten state. A sample of 100 mg of **12**, mp 163–164°, was heated at 170° for 1–2 min with a darkening of the melt. The nmr spectrum of the melt showed signals corresponding to essentially complete conversion of **12** to **7a**.

Reaction of 6-Acetoxy-1-azabicyclo[4.4.1]undecane Perchlorate (12) with Methanol.—A solution of 200 mg of 6-acetoxy-1-azabicyclo[4.4.1]undecane perchlorate (**12**) in 20 ml of methanol was heated at reflux for 2 hr. The solvent was evaporated *in vacuo* and an nmr spectrum (CF_3CO_2H) of the colorless solid was obtained. The spectrum was marked by the appearance of a sharp singlet at τ 6.60 (OCH_3), a decrease in the intensity of the signal arising from the acetyl group, and the appearance of a doublet at τ 6.18. Integration of the spectrum indicated approximately 47% conversion to 6-methoxy-1-azabicyclo[4.4.1]undecane perchlorate (**10**) under the stated conditions. 6-Methoxy-1-azabicyclo[4.4.1]undecane perchlorate was unchanged, as judged by nmr, when heated for 30 min at reflux in glacial acetic acid.

Registry No.—**4**, 25516-26-1; **5a**, 25568-58-5; **5a** free amine, 25516-17-0; **7a**, 25516-18-1; **7a** free amine, 25516-19-2; **7b**, 25516-20-5; **7b** free amine, 25516-21-6; **9a**, 25516-22-7; **9a** free amine, 25516-23-8; **9b**, 25516-24-9; **9b** free amine, 25568-59-6; **12**, 25529-23-1.

Small Charged Rings. XIII.[1] Abnormal Ring Expansion of Polycyclic Aziridinium Salts[2]

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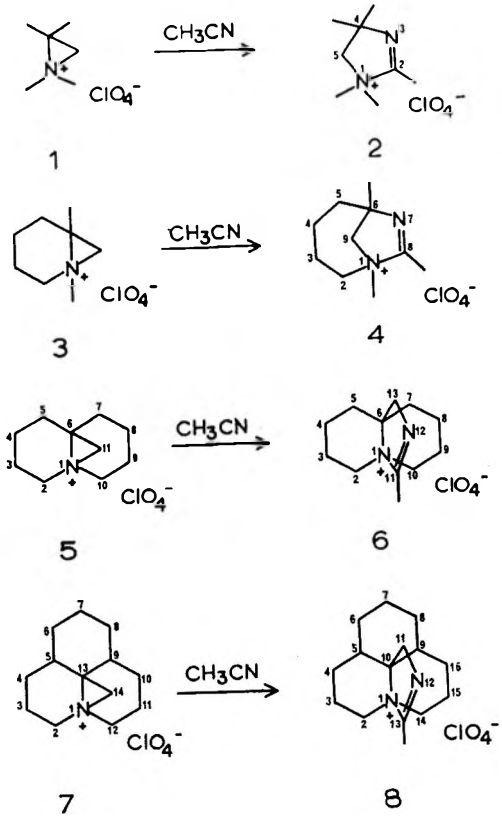
Abnormal ring expansion products are formed when the tri- and tetracyclic aziridinium salts, 1-azoniatricyclo-[4.4.1.0^{1,6}]undecane perchlorate (**5**) and 1-azoniatetracyclo[7.3.2.0^{1,13}.0^{5,13}]tetradecane perchlorate (**7**), are caused to react with acetonitrile to give 11-methyl-12-aza-1-azoniatricyclo[4.4.3.0^{1,6}]tridec-11-ene perchlorate (**6**) and 13-methyl-12-aza-1-azoniatetracyclo[7.4.3.0^{1,10}.0^{5,10}]hexadec-12-ene perchlorate (**8**), respectively, and when **5** is caused to react with the nitrone, 5,5-dimethyl-Δ^1-pyrroline 1-oxide, to give 5,5-dimethyl-7-oxa-6-aza-1-azoniatetracyclo[7.4.4.0^{1,9}.0^{2,6}]heptadecane perchlorate (**16**). By contrast, the mono- and bicyclic aziridinium salts 1,1,2,2-tetramethylaziridinium perchlorate (**1**) and 1,6-dimethyl-1-azoniabicyclo[4.1.0]heptane perchlorate (**3**) react with acetonitrile to give normal ring expansion products, 1,1,2,4,4-pentamethylimidazolinium perchlorate (**2**) and 1,6,8-trimethyl-7-aza-1-azoniabicyclo[4.2.1]non-7-ene perchlorate (**4**), respectively, and with the nitrone to give the normal products, 3,3,5,5,9,9-hexamethyl-2-oxa-1-aza-5-azoniabicyclo[4.3.0]nonane perchlorate (**14**) and 1,5,5,8-tetramethyl-7-oxa-6-aza-1-azoniatricylo[6.4.1.0^{2,6}]tridecane perchlorate (**15**), The acetonitrile ring expansion products of the normal and abnormal reactions are substituted imidazolinium salts, and the nitrone adducts contain the oxadiazinium ring system. Normal ring expansion reaction involves the 1,2 bond breaking of a 1,1,2,2-tetrasubstituted aziridinium salt while abnormal ring expansion involves 1,3 bond breaking. Compounds **1** and **3** react with benzaldehyde and acetone to give normal ring expansion products but **5** would not react with either reagent. The structures of the products of aziridinium ring expansion were established by spectroscopic methods and by spectroscopic and chemical identification of their degradation products. Some of the compounds (*e.g.*, **6**, **8**, **16**) fall into the structural category of "propellanes."

Previous papers in this series[3] have described the ring expansion reactions of aziridinium salts. Aldehydes[4] and ketones[5] react to form substituted oxazolidinium salts, nitriles[6] to form substituted imidazolinium salts, and stable nitrones[7] to give 1:1 ring-expanded adducts with formation of an oxadiazinium ring. These ring expansions appear to proceed by reaction of the polar or dipolar species with the more substituted of the two possible β-aminocarbonium ion intermediates developable from the aziridinium salt. Thus, in the normal ring expansion of aziridinium salts, the heteroatom of the polar (aldehyde, ketone, nitrile) or dipolar (nitrone) species reacts at the more substituted carbon of the aziridinium ring. We have now observed cases of *abnormal* ring expansion in which the nitrogen atom of a nitrile and the oxygen atom of a nitrone react at the less substituted aziridinium carbon. We recognize that the designation abnormal does not represent abnormality of the chemical process as much as it represents a lack of adherence to predictability on the basis of our past experience. Nevertheless, we find this categorization more arresting than the designation 1,3 bond breaking. The aziridinium salts that underwent abnormal ring expansion were those that also had been found to give abnormal solvolysis products with carboxylic acids, *i.e.*, compounds in which the acyloxy group becomes attached to the former aziridinium carbon that was less substituted. The conditions and steric requirements for abnormal solvolysis have been described in the preceding article.[1]

A series of sterically graduated aziridinium salts was selected for the ring expansion reaction in order to compare normal and possible abnormal products and to determine the structural requirements for any abnormal ring expansion. The following compounds satisfied these criteria: 1,1,2,2-tetramethylaziridinium perchlorate (**1**),[5] 1,6-dimethyl-1-azoniabicyclo[4.1.0]heptane perchlorate (**3**),[1] 1-azoniatricyclo[4.4.1.0^{1,6}]undecane perchlorate (**5**),[8] and 1-azoniatetracyclo[7.3.2.-0^{1,13}.0^{5,13}]tetradecane perchlorate (**7**).[8] Acetonitrile



(1) For preceding article in this series, see N. J. Leonard and D. B. Dixon *J. Org. Chem.*, **35**, 3483 (1970).

(2) We are pleased to acknowledge the support of the National Science Foundation by Research Grant GP-8407X.

(3) For reference and a summary of work in this field, see (a) N. J. Leonard, *Rec. Chem. Progr.*, **26**, 211 (1965); (b) D. R. Crist and N. J. Leonard, *Angew. Chem.*, **81**, 953 (1969); (c) D. R. Crist and N. J. Leonard, *Angew. Chem., Int. Ed. Engl.*, **8**, 962 (1969).

(4) N. J. Leonard, E. F. Kiefer, and L. E. Brady, *J. Org. Chem.*, **28**, 2850 (1963).

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(6) N. J. Leonard and L. E. Brady, *ibid.*, **30**, 817 (1965).

(7) N. J. Leonard, D. A. Durand, and F. Uchimaru, *ibid.*, **32**, 3607 (1967).

(8) N. J. Leonard, K. Jann, J. V. Paukstelis, and C. K. Steinhardt, *J. Org. Chem.*, **28**, 1499 (1963).

and the nitrone, 5,5-dimethyl-Δ^1-pyrroline 1-oxide, were caused to react with this set of aziridinium salts.

When heated in acetonitrile at reflux for 3 hr, aziridinium salts **1** and **3** were found to give the normal ring expanded products, 1,1,2,4,4-pentamethylimidazolinium perchlorate (**2**) and 1,6,8-trimethyl-7-aza-1-azoniabicyclo[4.2.1]non-7-ene perchlorate (**4**), respectively. However, aziridinium salts **5** and **7** were found to react with acetonitrile at reflux during 68 and 38 hr, respectively, to give abnormal ring expansion products as the isolable products, namely, 11-methyl-12-aza-1-azoniatricyclo[4.4.3.$0^{1,6}$]tridec-11-ene perchlorate (**6**) and 13-methyl-12-aza-1-azoniatetracyclo-[7.4.3.0.$^{1,15}0^{5,10}$]hexadec-12-ene perchlorate (**8**). The yields were unfortunately variable throughout the series. Evidence of imidazolinium ring formation in all four products consisted of satisfactory microanalyses, the presence of infrared absorption maxima between 1690 and 1710 cm^{-1} arising from the C=N function, and the appearance of a three-proton resonance between τ 7.28 and 7.59 in the nmr spectrum of each compound.

The nmr spectra of products **2**, **4**, **6**, and **8** permitted the assignments of the products to the normal or abnormal category. The resonances of the former aziridinium methylene protons in the spectrum of product **2** appeared as a singlet at τ 6.02 while the resonance of the corresponding methylene protons in product **4** appeared as an AB system of doublets centered at τ 6.09. The resonance of the other methylene protons adjacent to charged nitrogen in **4** appeared at τ 6.22. The chemical shifts of these former aziridinium methylene protons appear where expected for methylene protons adjacent to charged nitrogen.[8] The chemical shifts and their proximity to the chemical shift of the α-methylene protons not in the imidazolinium ring of product **4** confirm the assignment of structures **2** and **4** as normal ring expansion products.

The resonances of the former aziridinium methylene protons in the nmr spectra of products **6** and **8** appeared as quartet signals at τ 5.72 and 5.62, respectively. The resonances of the two methylene groups adjacent to charged nitrogen but not in the imidazolinium ring appeared at τ 6.35 and 6.20, respectively. The chemical shift of 0.4 ppm to lower field for the imidazolinium methylene protons in products **6** and **8** from those in **2** and **4** suggests [6,8] that the methylene group in **6** and **8** is α to the sp^2 nitrogen and β to the quaternary nitrogen, indicating that these two compounds are abnormal ring expansion products possessing the assigned structures.

Important details in the nmr spectrum of **6** include the quartet at τ 5.72, J = 1.9 Hz, assigned to the imidazolinium methylene protons, and a triplet at τ 7.28, J = 1.9 Hz, assigned to the methyl protons. Similar features are found in the spectrum of **8** at τ 5.62, J = 2.0 Hz, and 7.33, J = 2.0 Hz. It was suspected that this multiplicity arose from long-range coupling between the imidazolinium methylene and the methyl protons through five bonds.[9] Spin-spin decoupling at 100 MHz confirmed the existence of long-range coupling in compound **6**. Irradiation at τ 5.72 converted the signal at τ 7.28 to a sharp singlet with $W_{1/2}$ = 2.0 Hz compared to $W_{1/2}$ = 4.5 Hz before irradiation. In like manner, irradiation at τ 7.28 converted the signal at τ 5.72 to a sharp singlet with $W_{1/2}$ = 2.5 Hz compared with $W_{1/2}$ = 6.0 Hz before irradiation. The tricyclic ring system in **6** and tetracyclic ring system in **8** hold the imidazolinium ring in the rigid conformation required for long-range coupling through the C=N portion of the ring. Coupling through five bonds of a homoallylic system has been found to be of magnitude 1.2 to 2.8 Hz in acyclic systems and 1.9 to 3.0 Hz in cyclic systems.[9] Homoallylic systems in which nitrogen has replaced one of the sp^2 carbons have exhibited long range coupling constants of 1.0 to 5.5 Hz.[10-13] Thus, the values of 1.9 and 2.0 Hz for the coupling constants observed in the spectra of **6** and **8** are in the range of those found in similar systems.

Further verification of the structures of the normal and abnormal ring expansion products was considered desirable, and chemical degradations of **2** and **6** were carried out as representatives of each series. One approach was to attempt to hydrogenate 1,1,2,4,4-pentamethylimidazolinium perchlorate (**2**) with Adams catalyst in glacial acetic acid. The result was somewhat unexpected since the major product was 2-acetamido-N^1,N^1-dimethyl-2-methylpropylamine (**11**) perchlorate and the overall result was the replacement of the $\gtrless C—CH_3$ fragment with an acetyl group attached to the nitrogen which originated from the nitrile. Because this reaction formally represented the addition of 1 mol of water to **2**, the necessity of hydrogen and catalyst was suspect; indeed, a control experiment showed that the same conversion could be accomplished efficiently with acetic acid alone. The base, N-(1,1-dimethylamino-2-methylprop-2-yl)acetamide, was identified by microanalysis, infrared spectrum, and nmr spectrum, which showed a signal at τ 8.13 characteristic of acetyl methyl protons. Lithium aluminium hydride reduction of **2** in tetrahydrofuran resulted in reductive opening of the imidazolinium ring to N^1,N^1-dimethyl-N^2-ethyl-2-methyl-1,2-diaminopropane (**9**), characterized as the dipicrate. This hydride reduction method of structure determination was considered less satisfactory because of low conversions and problems in the derivatization of diamine products. We therefore returned to amino amide products for identification. N-(2-Dimethylamino-2-methylprop-1-yl)acetamide (**10**), the isomer of **11**, was prepared (30% yield) *via* a direct displacement on the less hindered, methylene carbon of the aziridinium ring of **1** by acetamide anion, prepared by treatment of acetamide with sodium hydride. This constitutes a new S_N2-type ring opening of aziridinium salts. The compound exhibited an nmr signal characteristic of the acetyl methyl group. There is a distinct difference in the chemical shift and coupling of the methylene protons in the two isomers, **10** and **11**, with the former showing a doublet, J = 5.0 Hz, at τ 6.89, and the latter a singlet at τ 7.58. Both spectra were obtained for methylene chloride solutions. The characteristic chemical shift of methylene adjacent

(9) (a) For a review of long-range coupling, see S. Sternhell, *Rev. Pure Appl. Chem.*, **14**, 15 (1964); (b) also M. Barfield and B. Chakrabarti, *Chem. Rev.*, **69**, 757 (1969).

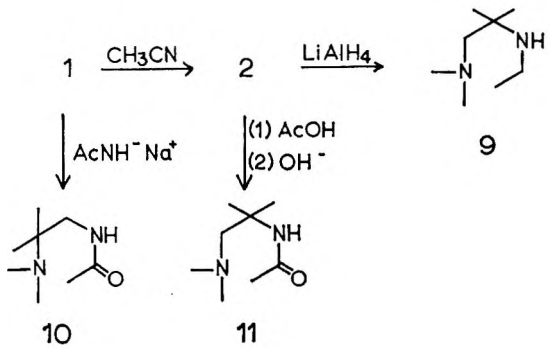
(10) M. A. Weinberger and R. Greenhalgh, *Can. J. Chem.*, **41**, 1038 (1963).

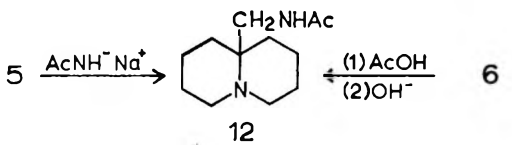
(11) M. D. Mehter, D. Muller, and E. F. Mooney, *J. Chem. Soc.*, 6695 (1965).

(12) G. O. Dudek, *J. Amer. Chem. Soc.*, **85**, 694 (1963).

(13) N. J. Leonard and J. V. Paukstelis, *J. Org. Chem.*, **28**, 3021 (1963).

to amide nitrogen[14] and the spin–spin coupling by the amide proton produces a definitive signal for that grouping in **10**. These amino amides firmly established the structure of the imidazolinium perchlorate **2** and provided models for the degradation products of **6**.



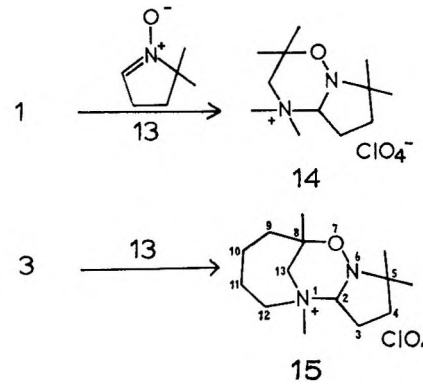


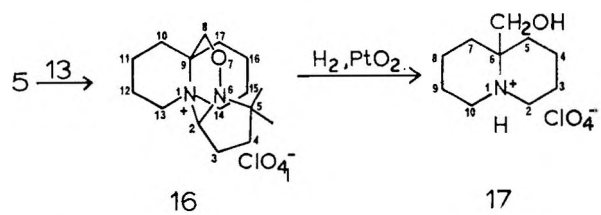
The structure of compound **6** was verified in the following way. A derivative of compound **5** was prepared for comparison by utilizing the direct displacement by acetamide anion upon the aziridinium ring methylene. Compound **12**, 6-acetamidomethyl-1-azabicyclo[4.4.0]decane, was produced in 30% yield and was found to give a satisfactory microanalysis and an infrared spectrum very similar to that of **10**. The nmr spectrum of **12** was distinguished by the signals for the acetyl protons at τ 8.06 and the methylene protons at τ 6.57, a doublet, J = 5.5 Hz, as expected. Compound **6** was then hydrolyzed in acetic acid as was done with **2**. The nmr spectrum of the product after conversion to the free base was identical with that of **12**, along with the infrared spectrum, mass spectrum, melting point, and mixture melting point.

An investigation of the nitrone ring expansion reaction utilizing the above aziridinium salts gave normal and abnormal type adducts parallel to those in the acetonitrile ring expansion reaction. It has been previously reported that aziridinium salt **1** underwent normal ring expansion when treated with 5,5-dimethyl-Δ^1-pyrroline 1-oxide (**13**) to give 3,3,5,5,9,9-hexamethyl-2-oxa-1-aza-5-azoniabicyclo[4.3.0]nonane perchlorate (**14**).[7] Aziridinium salt **3** likewise gave the normal product 1,5,5,8-tetramethyl-7-oxa-6-aza-1-azoniatricyclo[6.4.1.$0^{2,6}$]tridecane perchlorate (**15**). The structure of adduct **14** has been established previously by means of chemical degradation.[7] A comparison of the nmr spectra of **14** and **15** in dimethyl sulfoxide-d_6 and in methylene chloride served to prove that **15** is a normal ring expansion product. The resonance of the methine proton adjacent to both nitrogens appeared at τ 5.64 in **14** and 5.52 in **15**. The resonance of the former aziridinium methylene appeared as an AB system in both compounds centered at τ 6.58 in **14** and at 6.45 in **15** (CH_2Cl_2). The signals for the N-methyl protons appeared at τ 6.81 and 6.98 in **14** and 6.82 (3 H) in **15**.

(14) L. M. Jackman, "Applications of Nuclear Magnetic Spectroscopy in Organic Chemistry," Pergamon Press, London, 1959, p 56.

The resonances of the *gem* dimethyl groups of the pyrrolidine ring appeared at τ 8.81 and 8.95 in **14** and 8.68 and 8.87 in **15**. The similar resonances of these groups confirm that compound **15** contains a 1,2,4-oxadiazinium ring and is a normal ring expansion product.



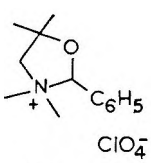


By contrast, when the tricyclic aziridinium salt, 1-azoniatricyclo[4.4.1.$0^{1,6}$]undecane perchlorate (**5**) was treated with 5,5-dimethyl-Δ^1-pyrroline 1-oxide (**13**), the product of abnormal ring expansion, 5,5-dimethyl-7-oxa-6-aza-1-azoniatetracyclo[7.4.4.$0^{1,9}$.$0^{2,6}$]heptadecane perchlorate (**16**) was isolated. The nmr spectrum of **16** was compared with that of adduct **15**. Evidence for the existence of a 1,2,4-oxadiazinium ring in **16** was obtained from comparison of the signals of the *gem* dimethyl protons of the pyrrolidine ring of **16** at τ 8.69 and 8.80 with those of **15** at τ 8.68 and 8.87. In addition, the methine proton adjacent to both nitrogens gave a signal at τ 4.66 in **16** compared with 5.52 in **15**. Apparently the conformation of an abnormal tetracyclic product acts to deshield the methine proton with respect to the conformation of the normal tricyclic product **15**. Verification that **16** was an abnormal ring expansion product was obtained by examination of the resonance of the former aziridinium methylene protons. This signal in **16** appeared as an AB system of doublets centered at τ 5.83 while in **15** the AB system was centered at 6.45. This chemical shift for **15** is reasonable for methylene protons adjacent to oxygen but not for methylene protons adjacent to charged nitrogen. Chemical evidence for the abnormal product **16** was obtained by catalytic hydrogenolysis. When **16** dissolved in 1:1 methanol–acetic acid was treated with Adams' catalyst under hydrogen there was obtained 6-hydroxymethyl-1-azabicyclo[4.4.0]decane perchlorate (**17**), identified by analysis, infrared spectrum, and nmr spectrum. The former aziridinium methylene signal in the nmr spectrum appears at τ 5.80 in **17**. Upon conversion to the free amine, the methylene signal moved upfield to τ 6.50.[8] In comparison, the resonance of the former aziridinium methylene of the isomeric 6-hydroxy-1-azabicyclo[4.4.1]undecane perchlorate appeared at τ 6.41 and shifted to τ 6.90 upon liberation of the free amine.[8] Also, compound **17** has a melting

point of 191–193°, whereas the [4.4.1] isomer had a melting point of 98–99°.

Attempts at formation of a nitrone adduct by reaction of aziridinium salt **7** with 5,5-dimethyl-Δ^1-pyrroline 1-oxide (**13**) were not successful. A heat of mixing or reaction was observed but no crystalline material could be isolated.

Expansion of the aziridinium ring by reaction of compounds **1**, **3**, and **5** with benzaldehyde was also examined. Compounds **1** and **3** gave the normal ring expansion products,[4] 2-phenyl-3,3,5,5-tetramethyloxazolidinium perchlorate (**18**) and 1,6-dimethyl-8-phenyl-7-oxa-1-azoniabicyclo[4.2.1]nonane perchlorate (**19**), respectively. Attempts at the preparation of the



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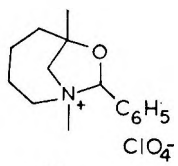

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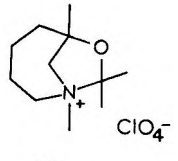

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benzaldehyde adduct of aziridinium salt **5** did not result in the isolation of a product, and the presence of a ring-expanded product could not be detected in the nmr spectra of the crude reaction mixtures. The structure of the normal ring expanded product **19** was determined by chemical degradation. Lithium aluminum hydride reduction[4] of **19** in tetrahydrofuran resulted in the formation of 3-benzyloxy-1,3-dimethyl-1-azacycloheptane perchlorate, the same product being obtained by solvolysis of the aziridinium salt **3** in benzyl alcohol at 80°.

Compounds **1** and **3** also formed normal ring expansion products with acetone[5] to give 2,2,3,3,5,5-hexamethyloxazolidinium perchlorate (**20**) and 1,6,8,8-tetramethyl-7-oxa-1-azoniabicyclo[4.2.1]nonane perchlorate (**21**), respectively, whereas the formation of an acetone adduct of compound **5** could not be detected by nmr spectroscopy, even after attempted reaction in sealed tubes at elevated temperatures.

It has been observed that mono- and bicycloaziridinium salts react to form normal ring expanded products while the tri- and tetracyclic aziridinium salts selected react to form abnormal ring expanded products. These statements obtain for the compounds which can actually be isolated, and they are not meant to be exclusive. They also hold at the level of nmr detectability in the crude reaction mixtures obtained for most of the combinations. The formation of abnormal products can be explained if one visualizes the β-amino-*t*-carbonium ion that could be an intermediate in the normal ring expansion reaction. Acetonitrile and nitrone **13** are considerably different in regard to their bulk and their degree of nucleophilicity toward aziridinium salts. Consequently, the ring expansion reaction should be considered separately for each reactant.

In the transition state for 1,2 bond breaking the process may be well advanced toward β-amino-*t*-carbonium ion formation, especially for mono- and bicyclic aziridinium salts **1** and **3**. This concept of the transition state for the aziridinium ring opening should be applicable to product formation by either a one-step cycloaddition process or a two-step addition, ring-closure process, the difference between the two processes being the orientation of the solvent–reactant molecules in the intermediate and the degree of covalent bonding by the solvent–reactant to carbon and to nitrogen. In the case of the tricyclic aziridinium salt **5**, as we have seen from preceding papers,[1,8] initial aziridinium ring opening can lead to the bicyclo[4.4.1]undecane system under kinetic control. *endo* addition of acetonitrile with respect to the methylene bridge appears subject to steric constraint at the tertiary carbon, and the CH_3—$C^+{\equiv}N$— group may be lost before ring closure to the even more strained tricyclic[4.4.2.$1^{1,6}$] system (isomeric with **6**) can result. *exo* addition of acetonitrile with respect to the methylene bridge would result in a species which is prevented sterically from ring closure to nitrogen. In the case of the tetracyclic aziridinium salt **7** there is not only greater steric resistance to formation of the β-amino-*t*-carbonium ion but greater steric hindrance to its capture by acetonitrile. The transition state for 1,3 bond breaking may be pictured as containing appreciable covalent bonding to the solvent–reactant as the N^+–CH_2 bond is cleaved. Covalent bond formation with acetonitrile followed by ring closure or possibly cycloaddition across the 1,3 bond provides the abnormal ring expansion product.

The nitrone ring expansion reactions occur more readily than those with acetonitrile. Heat is evolved on mixing **1**, **3**, or **5** with **13**, the reaction proceeds at ambient temperature, it does not require more than 100% excess of nitrone as solvent–reactant, and high yields are obtained. Where steric hindrance is minimal, as with **1** and **3**, nucleophilic displacement occurs at the more reactive position (as with water, methanol, and acetic acid) and the new ring is formed. When steric hindrance becomes significant, as in **5**, displacement occurs at the less reactive, but more accessible, methylene carbon. There may be a reversible addition to the substituted aziridinium carbon of **5** from the *exo* direction, but the intermediate would be sterically prevented from formation of a new 1,2,4-oxadiazinium ring, as in the nitrile case. Applying the same steric considerations, the normal and abnormal ring expansion reactions may also proceed by concerted cycloaddition.

Experimental Section[15]

1,1,2,4,4-Pentamethylimidazolinium Perchlorate (**2**).—A solution of 2.22 g (11.1 mmol) of 1,1,2,2-tetramethylaziridinium perchlorate (**1**)[5] in 10 ml of acetonitrile was heated at reflux for 3 hr under a slow stream of nitrogen. The solvent was removed *in vacuo* and the resulting oil crystallized upon cooling. After trituration with ether and recrystallization from ethanol the feather-like colorless crystals had mp 168.5–169.5°; yield 0.93 g (35%); ν_{max}^{Nujol} 1710 cm^{-1} (C=N); pmr (CF_3COOH) τ 6.02 (s,

(15) Melting points are corrected. Nuclear magnetic resonance spectra were obtained on a Varian Associates A-60, A-60A, A-56/60, or HA-100 spectrometer using tetramethylsilane as an internal reference. We thank Mr. Robert L. Thrift for his assistance with the nmr spectra. Infrared spectra were obtained on a Perkin-Elmer Model 337 grating spectrophotometer. Microanalyses were performed by Mr. Josef Nemeth and his staff. In nuclear magnetic resonance data, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, v = very, and br = broad.

2, CH_2N^+), 6.41 [s, 6, $(CH_3)_2N^+$] 7.38 (s, 3, $CH_3C{=}N$), and 8.36 [s, 6, $(CH_3)_2C$].

Anal. Calcd for $C_8H_{17}ClN_2O_4$: C, 39.83; H, 7.05; N, 11.62. Found: C, 40.24; H, 7.09; N, 11.50.

1,6-Dimethyl-1-azoniabicyclo[4.1.0]heptane Perchlorate (3).[1]—An excess of ethereal diazomethane was added in portions to a solution of 0.50 g (2.36 mmol) of 1,2-dimethyl-3,4,5,6-tetrahydropyridinium perchlorate[16] in 40 ml of stirred methylene chloride cooled at 0°. The solution was stirred 30 min, the excess diazomethane was evaporated with warm water, and the remaining solvent was evaporated *in vacuo*. The colorless solid was taken up in methylene chloride, ether was added to the cloud point, and the solution was allowed to stand at −20° until crystals formed. The cold solvent was removed under a blanket of nitrogen with a fritted glass filterstick and the colorless needles obtained were dried *in vacuo*: mp 151.5–153°; yield 0.45 g (84%); no OH, N^+H, or $C{=}N^+$ absorptions in the infrared spectrum; pmr (CH_2Cl_2) τ 6.42 (br t, 2, J = 6.0 Hz, CH_2N^+), 6.78 and 7.04 (AB system of doublets, 2, J_{AB} = 5.0 Hz, aziridinium methylene), 6.85 (s, 3, CH_3N^+), 7.86 (br t, 2, J = 6.0 Hz, CH_2C), and 8.27 (br s, 7, CH_3C and 4 ring protons).

Anal. Calcd for $C_8H_{16}ClNO_4$: C, 42.48; H, 7.08; N, 6.19. Found: C, 42.33; H, 7.01; N, 6.33.

1,2,6-Trimethyl-1-azoniabicyclo[4.1.0]heptane Perchlorate.—A slight excess of ethereal diazomethane was added to a stirred solution of 0.50 g (2.21 mmol) of 1,2,6-trimethyl-3,4,5,6-tetrahydropyridinium perchlorate[16] in 40 ml of CH_2Cl_2 cooled in an ice bath. The solution was stirred for 30 min and the solvent was evaporated *in vacuo* to yield 0.53 g (100%) of light yellow powder. The product was dissolved in CH_2Cl_2 and ether added to the cloud point of the solution. The solution was allowed to stand 2 days at −20°, and the product was collected by filterstick removal of the cold solvent under a nitrogen atmosphere, small colorless prisms: mp 161–162°; pmr (CH_2Cl_2) τ 6.15–6.55 (m, 1, CH), 6.72 and 7.23 (AB system of doublets, J_{AB} = 5 Hz, assigned to aziridinium methylene protons in one of the two diastereomeric racemates), 6.87 and 7.02 (2 s, 3, N^+CH_3 of each racemate), 7.02 (center of overlapping AB system assigned to aziridinium methylene protons in the second racemate), 7.88 (br m, 2, CCH_2), 8.22 and 8.27 (2 s, 3, CCH_3 of each racemate), 8.22 (br m, 4, $CH_2CH_2CH_2$), 8.53 and 8.59 (2 d, 3, J = 7.0 Hz, for $CHCH_3$ of each racemate).

Anal. Calcd for $C_9H_{18}ClNO_4$: C, 45.00; H, 7.50; N, 5.83. Found: C, 45.30; H, 7.56; N, 6.02.

1,6,8-Trimethyl-7-aza-1-azoniabicyclo[4.2.1]non-7-ene Perchlorate (4).—A slight excess of ethereal diazomethane was added to a solution of 0.50 g (2.36 mmol) of 1,2-dimethyl-3,4,5,6-tetrahydropyridinium perchlorate[16] in 40 ml of stirred methylene chloride cooled to 0°. The solution was stirred 30 min, the solvent was removed *in vacuo*, and the colorless solid was taken up in 10 ml of redistilled acetonitrile. The acetonitrile solution was heated at reflux under a slow stream of nitrogen for 3 hr. The acetonitrile was evaporated *in vacuo*, and the product was recrystallized from ethanol to yield 0.31 g (49%) of colorless prisms. Three recrystallizations from ethanol furnished analytically pure material: mp 118.5–120°; ν_{max}^{Nujol} 1700 cm^{-1} ($C{=}N$ band); pmr (CH_2Cl_2) τ 5.60 and 6.57 (AB system of doublets, 2, J_{AB} = 13 Hz, N^+CH_2C), 6.22 (br m, 2, $CH_2CH_2N^+$), 6.47 (s, 3, N^+CH_3), 7.59 (s, 3, $CH_3C{=}N$), 8.17 (br s, 6, $CH_2CH_2CH_2$), and 8.52 (s, 3, CH_3C).

Anal. Calcd for $C_{10}H_{19}ClN_2O_4$: C, 44.94; H, 7.12; N, 10.49. Found: C, 45.25; H, 7.14; N, 10.63.

1,2,6,8-Tetramethyl-7-aza-1-azoniabicyclo[4.2.1]non-7-ene Perchlorate.—A slight excess of ethereal diazomethane was added to a stirred solution of 0.50 g (2.21 mmol) of 1,2,6-trimethyl-3,4,5,6-tetrahydropyridinium perchlorate[16] in 30 ml of methylene chloride cooled by an ice bath. The solution was stirred 30 min, and the solvent was removed *in vacuo*. The colorless solid was dissolved in 10 ml of redistilled acetonitrile, and the solution was heated at reflux for 20 hr. Upon cooling, a slight turbidity was removed by filtration, and the product was precipitated by addition to a large volume of stirred ether. The oily product was taken up in methylene chloride, reprecipitated, and washed with ether. The product was then dissolved in hot ethanol. The cooled solution deposited colorless prisms in two crops: first crop 0.163 g, mp 116–119°; second crop 0.165 g, mp 115–122°; total yield 0.328 g (53%); ν_{max}^{Nujol} 1690 cm^{-1} ($C{=}N$); pmr (CH_2Cl_2) τ 5.67 and 6.61 (AB system of doublets, J_{AB} = 12 Hz, imidazolinium methylene protons of one racemate), 5.83 and 6.94 (AB system of doublets, J_{AB} = 13 Hz, imidazolinium methylene protons of other racemate), 6.05 (br m, $CHCH_3$), 6.57 and 6.72 (2 s, 3, N^+CH_3 of racemate), 7.63 (s, 3, $CH_3C{=}N$), 8.24 (br s, 6, $CH_2CH_2CH_2$), 8.47 (d, 3, J = 7.0 Hz, $CHCH_3$), 8.56 (s, 3, CH_3C).

Anal. Calcd for $C_{11}H_{21}ClN_2O_4$: C, 46.98; H, 7.49; N, 9.96. Found: C, 47.13; H, 7.52; N, 10.16.

11-Methyl-12-aza-1-azoniatricyclo[4.4.3.$0^{1,6}$]tridec-11-ene Perchlorate (6).—A solution of 0.75 g (2.98 mmol) of 1-azoniatricyclo[4.4.1.$0^{1,6}$]undecane perchlorate (5)[8] in 20 ml of acetonitrile under a slow stream of nitrogen was heated at reflux for 68 hr. The solvent was removed *in vacuo*, and the reddish oil obtained was dissolved in approximately 75 ml of hot ethanol. Upon cooling, some noncrystalline material precipitated and was removed by filtration. The ethanol solution was then concentrated *in vacuo* to about 20 ml, heated, and allowed to stand. Reddish yellow prisms were collected in 250-mg yield. The combined product was then recrystallized from methanol to give two crops of yellow prisms: mp (both crops) 221–237° with charring; yield 159 and 32 mg, respectively (total, 22%). Further recrystallization from methanol yielded analytically pure light yellow prisms: mp 241–244° dec; ν_{max}^{Nujol} 1690 cm^{-1} ($C{=}N$); pmr (CF_3COOH) τ 5.72 (q, 2, J = 1.9 Hz, $CCH_2N{=}$), 6.00–6.70 (m, 4, $CH_2N^+CH_2$), 7.28 (t, 3, J = 1.9 Hz, CH_3), and 7.98 (v br s, 12, remaining ring methylenes).

Anal. Calcd for $C_{12}H_{21}ClN_2O_4$: C, 49.15; H, 7.17; N, 9.56. Found: C, 49.28; H, 7.30; N, 9.38.

13-Methyl-12-aza-1-azoniatetracyclo[7,4.3.$0^{1,10}$.$0^{5,10}$]hexadec-12-ene Perchlorate (8).—A solution of 0.70 g (2.4 mmol) of 1-azoniatetracyclo[7.3.2.$0^{1,13}$.$0^{6,13}$]tetradecane perchlorate (7)[8] in 10 ml of anhydrous acetonitrile was heated at reflux for 36 hr. The reddish solution obtained was poured into a large volume of stirred ether and the precipitate was triturated with ether to give a dark red semisolid. Attempted crystallization from ethanol was unsuccessful. The ethanol was evaporated *in vacuo*, the oil obtained was treated with aqueous potassium carbonate, and the mixture was extracted several times with ether. The mixture was then extracted with methylene chloride, and the extracts were dried over anhydrous potassium carbonate. The solvent was evaporated *in vacuo* and the residual yellow oil was recrystallized twice from ethanol–ether, yield 75 mg (9%) of light yellow needles of analytically pure product: mp 213–214.5°; ν_{max}^{Nujol} 1710 cm^{-1}; pmr (CF_3CO_2H) τ 5.62 (q, 2, J = 2.0 Hz, CCH_2N), 6.20 (br m, 4, $CH_2N^+CH_2$), 7.33 (t, 3, J = 2.0 Hz, CH_3), and 8.05 (br m, 16, remaining ring methylenes).

Anal. Calcd for $C_{15}H_{25}ClN_2O_4$: C, 54.05; H, 7.51; N, 8.41. Found: C, 54.18; H, 7.76; N, 8.33.

Lithium Aluminum Hydride Reduction of 1,1,2,4,4-Pentamethylimidazolinium Perchlorate (2). N^1,N^1-Dimethyl-N^2-ethyl-2-methyl-1,2-diaminopropane (9) Dipicrate.—To a cooled, stirred mixture of 1.00 g (26 mmol) of lithium aluminum hydride in 50 ml of tetrahydrofuran was added in one portion 1.00 g (4.15 mmol) of 1,1,2,4,4-pentamethylimidazolinium perchlorate (2). The mixture was allowed to warm to ambient temperature and then heated at reflux for 16 hr. The heating bath was removed, and 1.0 ml of water was added dropwise, followed by 1.0 ml of 15% sodium hydroxide and then 3.0 ml of water. The mixture was then heated at reflux for 2 hr. Upon cooling, the precipitate was removed by filtration and washed with ether. The combined solutions were dried over anhydrous potassium carbonate followed by evaporation of the solvents *in vacuo*. The product was dissolved in a small amount of ethanol, an adequate amount of a saturated ethanolic solution of picric acid was added, and the solution was heated (steam bath) for a short time. Yellow prisms were obtained upon cooling which were recrystallized from ethanol containing a slight excess of picric acid: mp 207–210°; yield 0.152 g (6%); pmr (CH_2Cl_2) τ 6.28 (s, 2, CCH_2N^+), 6.83 (q, 2, J = 7.5 Hz, CH_2CH_3), 6.87 [s, 6, $(CH_3)_2N^+$], 8.37 [s, 6, $(CH_3)_2C$], and 8.64 (t, 3, J = 7.5 Hz, CH_3CH_2).

Anal. Calcd for $C_{20}H_{26}N_8O_{14}$: C, 39.87; H, 4.32; N, 18.60. Found: C, 40.04; H, 4.43; N, 18.52.

N-1-(2-Dimethylamino-2-methylpropyl)acetamide (10).—A solution of 0.59 g (10 mmol) of acetamide in 5 ml of dry dimethylformamide was added dropwise to a stirred mixture of 0.40 g (10 mmol) of a 60% mineral oil dispersion of sodium hydride in 10 ml of dry dimethylformamide, and the mixture was stirred for 1.5 hr under nitrogen. A solution of 2.12 g (10.6 mmol) of 1,1,2,2-tetramethylaziridinium perchlorate (1)[4] in 5 ml of dry dimethyl-

(16) N. J. Leonard and F. P. Hauck, Jr., *J. Amer. Chem. Soc.*, **79**, 5279 (1957).

formamide was then added dropwise to the mixture, and the suspended material disappeared during addition. The solution was stirred an additional 3 hr before the solvent was removed *in vacuo*. The viscous oil was dissolved in water, and the solution was saturated with potassium carbonate. The solution was extracted with chloroform, and the combined extracts were dried over anhydrous potassium carbonate before being evaporated *in vacuo*. The product was distilled *in vacuo*: bp 71° (0.20 mm); yield 0.47 g (30%); ν_{max}^{film} 3290, 3070, 1655, and 1545 cm^{-1}; pmr (CH_2Cl_2) τ ~3.50 (v br m, 1, NH), 6.89 (d, 2, J = 5.0 Hz, $CH_2NHC{=}O$), 7.82 [s, 6, $(CH_3)_2N$], 8.07 (s, 3, $CH_3C{=}O$), and 9.02 [s, 6, $(CH_3)_2C$].

Anal. Calcd for $C_8H_{18}N_2O$: C, 60.76; H, 11.39; N, 17.72. Found: C, 60.49; H, 10.98; N, 17.81.

Reaction of 1,1,2,4,4-Pentamethylimidazolinium Perchlorate (2) with Acetic Acid. N-(1,1-Dimethylamino-2-methylprop-2-yl)acetamide (11).—The reaction was first run as an attempted reduction of 1,1,2,4,4-pentamethylimidazolinium perchlorate (2) in commercial glacial acetic acid with platinum and hydrogen, but it was later found that the identical product was obtained when the platinum and hydrogen were omitted. A 0.10-g (0.4 mmol) sample of 1,1,2,4,4-pentamethylimidazolinium perchlorate (2) was stirred with 7.5 ml of glacial acetic acid at ambient temperature for 3 hr. The solvent was removed by evaporation in vacuo at 50°. The residue was dissolved in 6 ml of absolute ethanol and the solvent was removed, leaving 98 mg (91%) of 2-acetamido-N^1,N^1-dimethyl-2-methylpropylamine (11) perchlorate as a white powder. The perchlorate salt was recrystallized from ethanol as colorless prisms of **2-acetamido-N^1,N^1-dimethyl-2-methylpropylamine perchlorate**: mp 120–121°; ν_{max}^{Nujol} 3350, 3060, 1665, and 1550 cm^{-1}; pmr (CF_3COOH) τ 2.43 (br s, 1, $NHC{=}O$), 6.38 (d, 2, J = 4 Hz, N^+CH_2), 6.84 [d, 6, J = 5 Hz, $(CH_3)_2N^+$], 7.67 (s, 3, $CH_3C{=}O$), 8.36 [s, 6, $(CH_3)_2C$].

Anal. Calcd for $C_8H_{19}ClN_2O_5$: C, 37.07; H, 7.34; N, 10.81. Found: C, 37.13; H, 7.39; N, 10.83.

The reaction appeared to proceed slightly faster in 2:1 acetic acid–water and the purity of the product was not affected.

A portion of the salt was dissolved in water, and the solution was saturated with sodium bicarbonate. The solution was extracted with methylene chloride, and the extracts were dried over anhydrous potassium carbonate. The solvent was evaporated *in vacuo* to yield the free base, **N-(1,1-dimethylamino-2-methylprop-2-yl)acetamide (11)**, possessing the following pmr (CH_2Cl_2): τ ~3.55 (v br m, 1, $NHC{=}O$), 7.58 (s, 2, CH_2), 7.70 [s, 6, $(CH_3)_2N$], 8.13 (s, 3, $CH_3C{=}O$), and 8.71 [s, 6, $(CH_3)_2C$].

ε-Acetamidomethyl-1-azabicyclo[4.4.0]decane (or 10-Acetamidomethylquinolizidine) (12).—A solution of 0.234 g (3.97 mmol) of acetamide in 5 ml of dry dimethylformamide was added dropwise to a stirred suspension of 0.159 g (3.97 mmol) of a 60% mineral oil dispersion of sodium hydride in 10 ml of dry dimethylformamide. The suspension was stirred overnight under nitrogen, and a solution of 1.00 g (3.97 mmol) of 1-azoniatricyclo[4.4.-1.$0^{1,6}$]undecane perchlorate (5)[8] in 5 ml of dry dimethylformamide was added dropwise with the suspended material disappearing during addition. The mixture was stirred for an additional 2 hr. The solvent was evaporated *in vacuo*, and the oily product was dissolved in a small portion of water. The aqueous solution was saturated with sodium bicarbonate and extracted with four portions of chloroform. The combined extracts were dried over anhydrous potassium carbonate, and the chloroform was evaporated under a stream of nitrogen. The product was sublimed at 80° (0.25 mm) to give 0.25 g (30%) of a wet looking solid. The product was washed with two small portions of ether and resublimed at 60° (0.20 mm): prisms; mp 120–122.5°; ν_{max}^{Nujol} 3250, 3070, 1635, and 1565 cm^{-1}; pmr (CH_2Cl_2) τ 3.64 (v br m, 1, $NHC{=}O$), 6.57 (d, 2, J = 5.5 Hz, CH_2NH), ~7.37 (br m, 4, CH_2NCH_2), 8.06 (s, 3, $CH_3C{=}O$), and ~8.53 (br m, 12, remaining ring methylenes).

Anal. Calcd for $C_{12}H_{22}N_2O$: C, 68.57; H, 10.48; N, 13.33. Found: C, 68.35; H, 10.43; N, 13.32.

Attempted Catalytic Reduction of 11-Methyl-12-aza-1-azoniatricyclo[4.4.3.$0^{1,6}$]tridec-11-ene Perchlorate (6).—A solution of 140 mg of compound 6 in 75 ml of glacial acetic acid with 50 mg of platinum oxide was shaken under 3 atm hydrogen at ambient temperature for 15 hr. The catalyst was removed by filtration, and the solvent evaporated *in vacuo*. The tacky product was dissolved in hot ethanol which yielded upon cooling 31 mg of starting material. Ether was added to the filtrate to produce a small amount of flocculent material which was removed by filtration. The ethanol was removed *in vacuo*, and the remaining oil was dissolved in water. The aqueous solution was saturated with potassium carbonate and extracted with methylene chloride. The combined extracts were dried over anhydrous potassium carbonate followed by evaporation of the solvent *in vacuo*. The solid product was sublimed, washed with two small portions of ether, and sublimed again. The product obtained was identical with 6-acetamidomethyl-1-azabicyclo[4.4.0]decane (12) (see above) judged by infrared and nmr spectra and identical melting point (121–123.5°) and mixture melting point (120.5–123.5°).

Anal. Calcd for $C_{12}H_{22}N_2O$: C, 68.57; H, 10.48; N, 13.33. Found: C, 68.75; H, 10.44; N, 13.33.

To show that acetic acid alone was sufficient to effect the reaction a 5.2 mg (0.02 mmol) sample of 6 was treated with 1.0 ml of acetic acid and the mixture was allowed to stand at 38–42° for 4 days. The solvent was then removed by evaporation and the residue was treated with 1 ml of ethanol–xylene (1:1). The ir spectrum of the residue after evaporation had $\nu_{max}^{CH_3OH}$ 1670 cm^{-1}. The product was then dissolved in 10 ml of methanol and treated with 1 ml of basic ion-exchange resin (Dowex 1X-2, 100-200 mesh, OH^- form, which had been washed with methanol prior to use), and the mixture was allowed to stand at ambient temperature for 1.5 hr. The resin was removed by filtration, and the residue after evaporation, 3.0 mg (81%), was identical with 12 as judged by superimposable infrared spectra, mass spectra which had the same fragmentation patterns, and melting point (120.5–123.5°).

5,5-Dimethyl-Δ^1-pyrroline 1-oxide (13) was prepared by reductive cyclization of the corresponding γ-nitroaldehyde according to the method of Bonnett, Brown, Clark, Sutherland, and Todd.[17] The nitrone was stored at −20° under nitrogen.

Reaction of 1,6-Dimethyl-1-azoniabicyclo[4.1.0]heptane Perchlorate (3) with 5,5-Dimethyl-Δ^1-pyrroline 1-Oxide (13).—To 1.00 g (8.85 mmol) of 5,5-Dimethyl-Δ^1-pyrroline 1-oxide (13) was added in portions 1.00 g (4.42 mmol) of 1,6-dimethyl-1-azoniabicyclo[4.1.0]heptane perchlorate (3) with the evolution of heat. The reactants were mixed thoroughly during the addition, and the mixture was allowed to stand at ambient temperature for 5 days. The semisolid mixture was triturated with ethyl acetate to give a colorless solid. Recrystallization from acetonitrile–ether afforded 1.02 g (68%) of colorless prisms of **1,5,5,8-tetramethyl-7-oxa-6-aza-1-azoniatricyclo[6.4.1.$0^{2,6}$]tridecane perchlorate (15)**. A further recrystallization afforded an analytical sample: mp 157–158°; no infrared maxima corresponding to O–H or N^+–H; pmr (CH_2Cl_2) τ 5.52 (t, 1, N^+CHN), 5.9–6.2 (br, m, 1 $CHHN^+$), 5.98 and 6.92 (AB system of doublets, 2, J_{AB} = 14 Hz, N^+CH_2C), 6.4–6.8 (br, m, 1, $CHHN^+$), 6.82 (s, 3, CH_3N^+), 7.5–8.4 (complex multiplet, 10, remaining ring methylenes), 8.68 (s, 3, CH_3C), and 8.68 and 8.87 (2 s, 6 $(CH_3)_2C$].

Anal. Calcd for $C_{14}H_{27}ClN_2O_5$: C, 49.56; H, 7.96; N, 8.26. Found: C, 49.79; H, 7.95; N, 8.16.

Reaction of 1-Azoniatricyclo[4.4.1.$0^{1,6}$]undecane Perchlorate (5) with 5,5-Dimethyl-Δ^1-pyrroline 1-Oxide (13).—To 1.12 g (9.9 mmol) of 5,5-dimethyl-Δ^1-pyrroline 1-oxide (13) was added 1.24 g (4.9 mmol) of 1-azoniatricyclo[4.4.1.$0^{1,6}$]undecane perchlorate (5) in portions with the evolution of heat. The reactants were thoroughly mixed until the viscous mixture solidified within 15 min. After allowing it to stand at ambient temperature for 20 hr, the mixture was triturated with ethyl acetate to yield a solid product. Two recrystallizations from acetonitrile–ether gave 1.04 g (58%) of thick colorless prisms of analytically pure **5,5-dimethyl-7-oxa-6-aza-1-azoniatetracyclo[7.4.4.$0^{1,9}0^{2,6}$]heptadecane perchlorate (16)**: mp 122.5–124.5°; no infrared maxima corresponding to O–H or N^+–H; pmr (CD_3CN) τ 4.66 (br t, 1, J = 3.5 Hz, N^+CHN), 5.21 and 6.44 (AB system of doublets, 2, J_{AB} = 6.5 Hz, CCH_2O), 5.48 (complex t, 1, J = 13 Hz, $CHHN^+$), 5.95 (complex t, 1, J = 13 Hz, $CHHN^+$), 6.97 (complex t, 2, J = 13 Hz, N^+CH_2), 7.2–8.6 (complex multiplet, 16, remaining ring methylenes), and 8.69 and 8.80 [2 s, 6, $(CH_3)_2C$].

Anal. Calcd for $C_{16}H_{29}ClN_2O_5$: C, 52.60; H, 7.95; N, 7.67. Found: C, 52.77; H, 8.04; N, 7.63.

Reduction of the Nitrone Adduct of 1-Azoniatricyclo[4.4.1.$0^{1,6}$]undecane Perchlorate (5).—A solution of 250 mg (0.68 mmol) of 5,5-dimethyl-7-oxa-6-aza-1-azoniatetracyclo[7.4.4.$0^{1,9}.0^{2,6}$]heptadecane perchlorate (16) in 50 ml of 1:1 methanol–acetic acid was shaken at ambient temperature under 3 atm of hydrogen for 30 hr in the presence of 50 mg of Adams catalyst. The

(17) R. Bonnett, R. F. C. Brown, V. M. Clark, I. O. Sutherland, and Sir A. Todd, *J. Chem. Soc.*, 2094 (1959).

catalyst was removed by filtration and washed with fresh solvent. Evaporation of the solvent *in vacuo* yielded an oil which was recrystallized to give 70 mg (37%) of colorless prisms from 2-propanol–ether, **6-hydroxymethyl-1-azabicyclo[4.4.0]decane perchlorate (17)**: mp 191–193°; ν_{max}^{Nujol} 3510 and 3105 cm^{-1}; pmr (CF_3CO_2H) τ 5.80 (s, 2, CH_2O), 6.46 (br m, 4, $CH_2N^+CH_2$), and 8.03 (br s, 12, remaining ring methylenes).

Anal. Calcd for $C_{10}H_{20}ClNO_5$: C, 44.44; H, 7.41; N, 5.19. Found: C, 44.65; H, 7.40; N, 5.25.

A portion of the product was treated with aqueous potassium carbonate, and the free amine was extracted with methylene chloride. The solution was dried over anhydrous potassium carbonate and concentrated *in vacuo* to obtain an nmr spectrum of **6-hydroxymethyl-1-azabicyclo[4.4.0]decane**: pmr (CH_2Cl_2) τ 6.50 (s, 2, CH_2O), 7.26 (complex multiplet, 4, CH_2NCH_2), and 8.52 (br s, 12, remaining ring methylenes).

5,5-Dimethyl-1-ethoxy-Δ^1-pyrrolinium Fluoroborate.—This compound was made as an nmr model for the occurrence of single C–O bond formation with **13** rather than cycloaddition. A solution of 3.36 g (30 mmol) of 5,5-dimethyl-Δ^1-pyrroline 1-oxide (**13**) in 10 ml of dry methylene chloride was added to a cooled solution of 5.65 g (30 mmol) of triethyloxonium fluoroborate in 30 ml of dry methylene chloride. After 10 min the solvent was evaporated *in vacuo*. The oil initially obtained solidified to give 6.5 g (94%) of crude material. The product was recrystallized from ethanol–ether at −20°. The solvent was removed under a blanket of nitrogen with a filter stick: waxy needles; mp 52–52.5°; pmr (CF_3COOH) τ 1.73 (br t, 1, J = 2.0 Hz, CH=N^+), 5.47 (q, 2, J = 7.0 Hz, CH_2CH_3), 6.74 (t of d, 2, $J_{3,4}$ = 7.5 Hz, $J_{2,3}$ = 2.0 Hz, CH_2C=), 7.59 (t, 2, J = 7.5 Hz, CH_2C), 8.33 [s, 6, $(CH_3)_2C$], and 8.46 (t, 3, J = 7.0 Hz, CH_2CH_3).

Anal. Calcd for $C_8H_{16}BF_4NO$: C, 41.92; H, 6.99; N, 6.11. Found: C, 42.22; H, 7.22; N, 6.16.

2-Phenyl-3,3,5,5-tetramethyloxazolidinium Perchlorate (18).—A solution of 0.95 g (4.75 mmol) of 1,1,2,2-tetramethylaziridinium perchlorate (**1**) in 5 ml of benzaldehyde was heated at 60° under a nitrogen atmosphere for 24 hr. Upon cooling, the solution was poured into 200 ml of rapidly stirred ether, the ether was decanted, and the sticky product was triturated with ether. The product was dissolved in a small amount of methylene chloride, and the precipitation process was repeated. Recrystallization from ethanol yielded 0.76 g (57%) of colorless prisms: mp 130.5–131.5°; nmr (CH_2Cl_2) τ 2.47 (s, 5, C_6H_5), 4.00 (s, 1, ArCH), 6.21 (apparent d, 2, J = 2.5 Hz, CH_2N^+), 6.78 and 7.27 [singlets, 6, $(CH_3)_2N^+$) and 8.38 [s, 6, $(CH_3)_2C$].

Anal. Calcd for $C_{13}H_{20}ClNO_5$: C, 50.98; H, 6.54; N, 4.58. Found: C, 50.85; H, 6.64; N, 4.83.

1,6-Dimethyl-8-phenyl-7-oxa-1-azoniabicyclo[4.2.1]nonane Perchlorate (19).—A slight excess of ethereal diazomethane was added to a solution of 0.50 g (2.36 mmol) of 1,2-dimethyl-3,4,5,6-tetrahydropyridinium perchlorate[8] in 40 ml of stirred methylene chloride cooled to 0°. The solution was stirred 30 min, the solvent was evaporated *in vacuo*, and the colorless solid was taken up in 5 ml of benzaldehyde. The benzaldehyde solution was heated at 60° under a nitrogen atmosphere for 20 hr. After cooling, the solution was slowly poured into 200 ml of rapidly stirred ether with precipitation of a colorless solid. The solid was washed with ether and recrystallized from ethanol: colorless prisms; mp 172–173°; yield 0.46 g (59%); pmr (dimethyl sulfoxide-d_6) τ 2.37 (s, 5, C_6H_5), 3.88 (s, 1, ArCH), 5.64 and 6.32 (AB system of doublets, 2, J_{AB} = 12.5 Hz, N^+CH_2C), 6.68 and 6.82 (singlets, 3, N^+CH_3), 7.05 (m, 2, $CH_2CH_2N^+$), 8.15 (br s, 6, $CH_2CH_2CH_2$), and 8.47 (s, 3, CH_3C).

Anal. Calcd for $C_{16}H_{22}ClNO_5$: C, 54.22; H, 6.63; N, 4.22. Found: C, 54.24; H, 6.63; N, 4.29.

3-Benzyloxy-1,3-dimethyl-1-azacycloheptane Perchlorate.—A solution of 0.50 g (2.2 mmol) of 1,6-dimethyl-1-azoniabicyclo-[4.1.0]heptane perchlorate (**3**) in 5 ml of benzyl alcohol was heated at 80° for 22 hr.[4] After cooling, the solution was poured into 150 ml of stirred ether containing 4 drops of ethanolic perchloric acid (1:1). The colorless solid obtained was washed several times with ether before being recrystallized twice from 2-propanol: colorless prisms; mp 106–107°; yield 0.53 g (72%); ν_{max}^{Nujol} 3110 cm^{-1} (N^+H); pmr (CH_2Cl_2) τ 2.63 (m, 5, Ar), 5.48 (s, 2, $ArCH_2$), 6.30–6.85 (m, 4, $CH_2N^+CH_2$), 7.08 (s, 3, N^+CH_3), 7.70–8.50 (m, 6, $CH_2CH_2CH_2$), 8.73 (s, 3, CH_3C).

Anal. Calcd for $C_{15}H_{24}ClNO_5$: C, 53.89; H, 7.18; N, 4.19. Found: C, 54.13; H, 7.29; N, 4.28.

Reduction of 1,6-Dimethyl-8-phenyl-7-oxa-1-azoniabicyclo-[4.2.1]nonane Perchlorate (19).—A mixture of 0.120 g (3.16 mmol) of lithium aluminum hydride in 50 ml of tetrahydrofuran was cooled in an ice bath with stirring, and to the mixture was added in one portion 1.00 g (3.0 mmol) of 1,6-dimethyl-8-phenyl-7-oxa-1-azoniabicyclo[4.2.1]nonane perchlorate (**19**). The mixture was allowed to warm to ambient temperature and then was heated at reflux for 3 hr. The mixture was allowed to cool, and 0.12 ml of water, then 0.12 ml of 15% sodium hydroxide, and then 0.36 ml of water were carefully added. The resulting white suspension was heated at reflux for 1 hr, cooled, and removed by filtration. The white residue was washed with ether, and the combined solutions were dried with anhydrous magnesium sulfate. The dried solution was titrated with ethanolic perchloric acid (1:1) to the congo red end point, and the precipitate was washed with ether. The product was recrystallized twice from 2-propanol to give colorless prisms: mp 106.5–107.5°; mmp (with identical solvolysis product) 106–107°; yield 0.67 g (67%); ν_{max}^{Nujol} 3110 cm^{-1} (N^+H); pmr (CH_2Cl_2) identical with that of the product of the solvolysis reaction.

Anal. Calcd for $C_{15}H_{24}ClNO_5$: C, 53.89; H, 7.18; N, 4.19. Found: C, 53.95; H, 7.33; N, 4.31.

1,6,8,8-Tetramethyl-7-oxa-1-azoniabicyclo[4.2.1]nonane Perchlorate (21).—A solution of 0.50 g (2.2 mmol) of 1,6-dimethyl-1-azoniabicyclo[4.1.0]heptane perchlorate (**3**) in 10 ml of anhydrous acetone was heated at reflux for 21 hr under a nitrogen atmosphere. The solution was then poured into a large volume of stirred ether and the precipitate was triturated with ether. An nmr spectrum of the crude product indicated incomplete reaction. The mixture was dissolved in ethanol and heated at reflux for 30 min to open the ring of the aziridinium salt remaining. The ethanol was evaporated *in vacuo* and the oil was treated with aqueous potassium carbonate. The aqueous suspension was first extracted with ether followed by extraction with methylene chloride. The methylene chloride extracts were dried over anhydrous potassium carbonate, and the solvent was evaporated *in vacuo*. The oily product was recrystallized twice from ethanol–ether to give an analytically pure sample: mp 178–179°; yield 73 mg (12%); no OH or N^+H maxima in the infrared spectrum; pmr (CH_2Cl_2) τ 5.87 and 6.18 (AB system of doublets, 2, J_{AB} = 13 Hz, N^+CH_2C), 6.2–6.6 (br m, 2, $CH_2CH_2N^+$), 6.82 (s, 3, CH_3N^+), 7.8–8.4 (br m, 6, remaining ring methylenes), 8.27 [s, 6, $(CH_3)_2C$], and 8.49 (s, 3, CCH_3).

Anal. Calcd for $C_{11}H_{22}ClNO_5$: C, 46.48; H, 7.75; N, 4.93. Found: C, 46.44; H, 7.77; N, 4.76.

Registry No.—**2**, 25516-25-0; **3**, 25516-26-1; **4**, 25516-27-2; **6**, 25568-60-9; **8**, 25568-61-0; **9** dipicrate, 25516-28-3; **10**, 25516-29-4; **11**, 25516-30-7; **12**, 25641-44-5; **15**, 25568-62-1; **16**, 25568-63-2; **17**, 25516-31-8; **17** free amine, 25516-32-9; **18**, 25516-33-0; **19**, 25516-34-1; **21**, 25516-35-2; 1,2,6-trimethyl-1-azoniabicyclo[4.1.0]heptane perchlorate, 25568-64-3; 1,2,6,8-tetramethyl-7-aza-1-azoniabicyclo[4.2.1]non-7-ene perchlorate, 25516-38-5; 2-acetamido-N^1,N^1-dimethyl-2-methylpropylamine perchlorate, 25516-36-3; 5,5-dimethyl-1-ethoxy-Δ^1-pyrrolinium fluoroborate, 25-529-24-2; 3-benzyloxy-1,3-dimethyl-1-azacycloheptane perchlorate, 25516-37-4.

Ring Tautomerism of o-Mercaptohydrocinnamonitriles. 2-Amino-4*H*-1-benzothiopyrans[1a,b]

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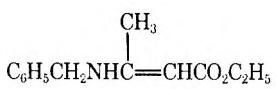
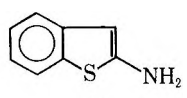
Received March 24, 1970

The formation of the thiochromenes, ethyl 2-amino-4*H*-1-benzothiopyran-3-carboxylate (**5c**) and 2-amino-4*H*-1-benzothiopyran-3-carbonitrile (**6c**), enamine ring tautomers of the substituted *o*-mercaptohydrocinnamonitriles, **5a** and **6a**, respectively, is described. Corresponding failure in the preparation of the parent *o*-mercaptohydrocinnamonitrile (**4a**) or either of its ring tautomers (**4b**, **4c**) from *o*-(benzylthio)hydrocinnamonitrile (**17**) is also reported. This latter failure, as well as thiochromene formation, is rationalized on the basis of the relative stability of exocyclic and endocyclic double bonds in six-membered rings. The preparation of the nitriles (**22a,b**) used in the formation of **5c** and **6c**, respectively, is also reported, as are two approaches (Scheme I) to *o*-(benzylthio)hydrocinnamonitrile (**17**), which was required for the attempted synthesis of the system **4**. In the latter case, the undesired formation of 2,3-dihydrobenzo[*b*]thiophene (**12**) from 2-(*o*-benzylthio)phenethyl alcohol (**9**) is described and compared with the recently discovered heterocyclization of *cis*-γ-benzylthiocrotononitrile to 2-aminothiophene (process **20**).

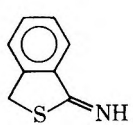
Imine–enamine tautomerism in various systems has been under investigation in recent years,[2] and generally the enamine predominates. For example, Dudek and Volpp[2a] demonstrated an enamine structure for ethyl β-benzylaminocrotonate (**1**). Systems exist, however, where the imine becomes tautomerically significant as a result of appropriate structural modifications. The 2-nitrogen substituted benzothiophenes illustrate this concept. Although the benzo[*b*]thiophene **2** has the expected 2-enamine structure,[3] the corresponding dihydrobenzo[*c*]thiophene **3** has an imino group in the 2 position.[4] This imino tautomer **3a** is favored because the alternative enamine would require the less stable *o*-quinoidal ring system (**3b**).



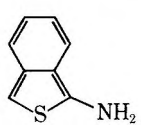
1



2

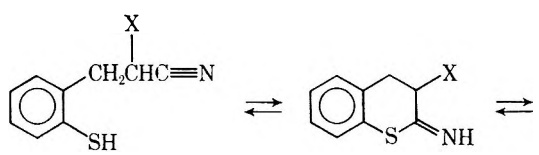


3a



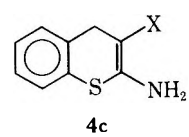
3b

We now wished to shift our attention from the five-membered ring of benzothiophenes to the six-membered ring of thiochromans **4–6b** and thiochromenes **4–6c**. Here a question to be answered was how readily would ring tautomerism, involving nitrile and thiol groups, occur? Because of the correlative work of Brown,[5] who observed that the formation or retention of an exocyclic double bond in a six-membered ring does not occur so readily as for a five-membered ring, we speculated that, in system **4**, the chain tautomer, *o*-mercaptohydrocinnamonitrile (**4a**), would prevail. However, it seemed plausible that location of an appropriate substituent (*e.g.*, X = $CO_2C_2H_5$ or CN) on the α carbon atom would result in ring tautomerism. This would follow because the carbon–nitrogen exocyclic double bond would be isomerized into the stable endocyclic position as a result of conjugation with the substituent X (**5c**, **6c**).



4a, X = H
5a, X = $CO_2C_2H_5$
6a, X = CN

4b



4c

All of these arguments have proven to be accurate. First, experiments to form **4b** or **4c** from *o*-(benzylthio)-hydrocinnamonitrile (**17**)[6] were unsuccessful, as indicated by recovery of starting material. Since the five-membered ring systems, 2,3-dihydro-3,3-dimethyl-2-iminobenzo[*b*]thiophene and 2-aminobenzo[*b*]thiophene (**2**), formed instantly in quantitative yields under the same conditions, these differences are significant and reflect the difficulty in the formation of an exocyclic double bond in a six-membered ring. A further attempt to remove the benzyl group of **17**, involving anhydrous aluminum bromide, which previously had been found to be a useful reagent for this purpose,[7] also failed. Although the chain tautomer of this system, *o*-mercaptohydrocinnamonitrile (**4a**), might eventually have been obtained, experimentation was discontinued in favor of work on the substituted *o*-mercaptohydrocinnamonitriles (**5a**, **6a**).

The synthesis of *o*-(benzylthio)hydrocinnamonitrile (**17**), the key precursor in the experiments just outlined,

* To whom correspondence should be addressed.

(1) (a) Presented as part of the Organic Chemistry Program at the 24th Annual Northwest Regional Meeting of the American Chemical Society, Salt Lake City, Utah, June 12, 1969. (b) For preceding paper VIII on Tautomerism, see D. L. Eck and G. W. Stacy, *J. Hetercycl. Chem.*, **6**, 147 (1969). (c) Dow Research Assistant, summer 1966; National Science Foundation Summer Fellow, 1967. (d) National Science Foundation Summer Fellow, 1963; National Science Foundation Cooperative Fellow, 1963–1964.

(2) (a) G. O. Dudek and G. P. Volpp, *J. Amer. Chem. Soc.*, **85**, 2697 (1963); (b) J. Dabrowski and J. Terpinski, *Tetrahedron Lett.*, **49**, 1363 (1965); (c) H. Bredereck, G. Simchen, R. Wahl, and F. E. Effenberger, *Chem. Ber.*, **101**, 512 (1968); (d) H. Ahlbrecht, *Tetrahedron Lett.*, **42**, 4421 (1968).

(3) G. W. Stacy, F. W. Villaescusa, and T. E. Wollner, *J. Org. Chem.*, **30**, 4074 (1965).

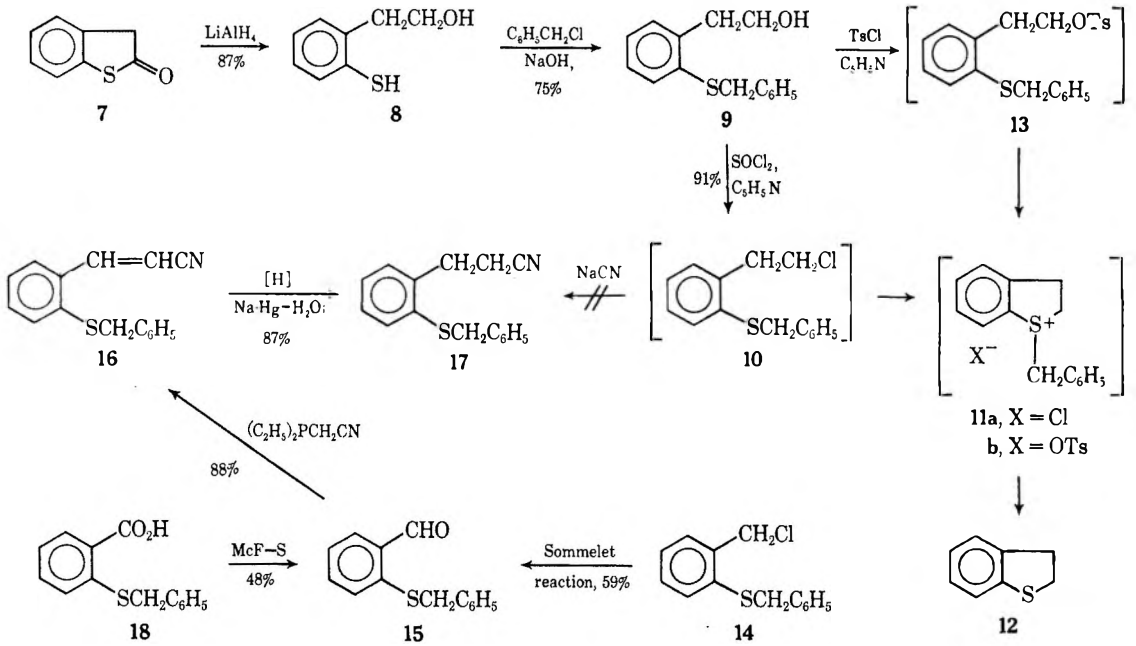
(4) (a) A. W. Day and S. Gabriel, *Ber.*, **23**, 2478 (1890); (b) G. W. Stacy, A. J. Papa, F. W. Villaescusa, and S. C. Ray, *J. Org. Chem.*, **29**, 607 (1964).

(5) H. C. Brown, *ibid.*, **22**, 439 (1957).

(6) This was an attempted application of our new method of forming tautomeric mercaptonitriles: G. W. Stacy and D. L. Eck, *Tetrahedron Lett.*, 5201 (1967); also see ref 1b.

(7) G. W. Stacy and T. E. Wollner, *J. Org. Chem.*, **32**, 3082 (1967).

SCHEME I

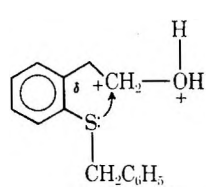


is presented in Scheme I. Problems were involved in the sequence explored, and some unanticipated results were uncovered. Because of the availability of benzo[*b*]thiophen-2(3*H*)-one (**7**) by oxidation of 2-benzo[*b*]thienyllithium,[8] we were attracted to the prospective series leading from **7** to benzyl *o*-(2-chloroethyl)-phenyl sulfide (**10**) and then to *o*-(benzylthio)hydrocinnamonitrile (**17**). This approach depended on the facile reduction of the thiolactone **7** to *o*-mercaptophenethyl alcohol (**8**) by lithium aluminum hydride in 87% yield. In the next step, selective alkylation of sulfur in the presence of the hydroxyl group of **8** with benzyl chloride under alkaline conditions to give **9** proved no problem. However, treatment of **9** with thionyl chloride did not give the intermediate chloride **10**, but instead 2,3-dihydrobenzo[*b*]thiophene (**12**) in 91% yield. Benzyl chloride also was isolated from the reaction mixture in 80% yield. The same products were also obtained employing alternative conditions, such as phosphorus pentaehloride in carbon tetrachloride or concentrated hydrochloric acid. An attempt to prepare tosylate **13** was no more successful; 2,3-dihydrobenzo[*b*]thiophene (**12**) again was formed.

Such cyclization probably occurs through a cyclic sulfonium intermediate **11** by interaction of sulfur with electron-deficient carbon (process **19**). Of related interest is the *S*-methyl series;[9] unlike our *S*-benzyl series, here *o*-methylthiophenethyl alcohol reacts with hydrochloric acid to yield a chloride. However, the fact that the ortho isomer reacts 620 times more rapidly than the para isomer is consistent with a cyclic sulfonium intermediate. Indeed, a substance claimed to be a chloroplatinate salt of the sulfonium chloride was isolated.

The postulate of a sulfonium intermediate is supported further by the high yields of benzyl chloride obtained in the several experiments studied. Comparable observations were made relevant to the formation of perhydrobenzofurans under similar conditions.[10] The special role of the five-membered cyclic sulfonium intermediate also becomes more apparent when one considers the usual difficulty in cleavage of benzyl sulfides.[11]

Finally, it should be noted that our recently discovered heterocyclization of benzylthionitriles[1b] follows a parallel course and a similar high yield when a five-membered ring is involved. In the conversion of **9** to **12**, an electron deficiency is created on the hydroxyl-bearing carbon atom by protonation, as in the case of hydrochloric acid, or by combination, as with tosyl chloride. The electron-deficient carbon atom then interacts with nucleophilic sulfur in the cyclization process (**19**). In the parallel reaction of *cis*-γ-benzylthiocrotonitrile,[1b] the carbon atom of the nitrile group becomes electron deficient by virtue of protonation of the nitrogen atom and then interacts with electron-dense sulfur (process **20**).



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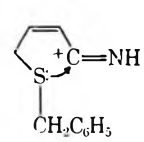


20

The synthesis of **17** was eventually accomplished through a sequence involving a Wittig-type reaction[12] with *o*-(benzylthio)benzaldehyde (**15**) followed by reduction of cinnamonitrile **16** with sodium amalgam, both processes taking place in high yield. The prerequisite aldehyde **15** was prepared most conveniently by the Sommelet reaction; the McFadyen and Stevens method was less satisfactory for this purpose.

(8) G. van Zyl, D. C. DeJongh, V. L. Heasley, and J. W. van Dyke, *J. Org. Chem.*, **26**, 4942 (1961).

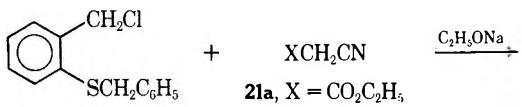
(9) G. M. Bennett and M. M. Hafez, *J. Chem. Soc.*, 652 (1941).

(10) (a) S. E. Cantor and D. S. Tarbell, *J. Amer. Chem. Soc.*, **86**, 2902 (1964); (b) G. R. Gray, F. C. Hartman, and R. Baker, *J. Org. Chem.*, **30**, 2020 (1965).

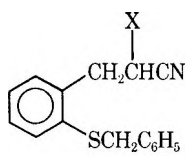
(11) D. S. Tarbell and D. P. Harnish, *Chem. Rev.*, **49**, 1 (1951).

(12) W. S. Wadsworth and W. D. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1961).

We next investigated our premise that introduction of an appropriate substituent (*e.g.*, **5** and **6**) would promote ring tautomerism through conjugation. The required nitriles (**22a,b**) were prepared by alkylation of ethyl cyanoacetate (**21a**) or malononitrile (**21b**), respectively, by benzyl α-chloro-*o*-tolyl sulfide (**14**). These intermediates (**22a,b**) then were heterocyclized by the action of aluminum bromide in benzene followed by hydrolysis to produce the desired thiochromenes (**5c**, **6c**).



14



22

Spectroscopic evidence for the 2-aminothiochromene structural assignment was conclusive. For example, the infrared spectrum of ethyl 2-amino-4*H*-1-benzothiopyran-3-carboxylate (**5c**) had two strong bands in the N—H stretch region at 3470 and 3310 cm^{-1}; the spectrum showed no evidence for absorption bands in the C≡N and C=N regions which would be required by the tautomers **5a** and **5b**, respectively. There was a strong ester carbonyl band at 1650 cm^{-1}. The nmr spectrum provided additional evidence with five areas of absorption at δ 7.1–7.3, 6.4, 4.0–4.3 (q), 3.5, and 1.2–1.4 (t) with an area ratio of 4:2:2:2:3. The two-proton peak at 6.4 corresponds to the amino function, while the peak at 3.5 can be assigned to the methylene group in the 4 position. The stability of the enamine structures **5c** and **6c** relative to the imino structure agrees with Dudek's[2b] findings for β-benzylaminocrotonate and Brown's[5] observations on exocyclic double bonds. It is also in keeping with observed reluctance of nitrogen to form a double bond when alternative single bond formation is possible.[13]

Experimental Section

All melting points are corrected while boiling points at reduced pressures are uncorrected. The microanalytical work was performed by Galbraith Laboratories, Knoxville, Tenn. The infrared spectra were determined on Beckman IR-5 and IR-8 spectrophotometers and assignments were based on data cited by Bellamy,[14] if not otherwise stated. The spectra of liquids were run as neat films with sodium chloride optics. Nmr spectra were determined by a Varian A-60 spectrometer using carbon tetrachloride or deuterated chloroform as the solvent and tetramethylsilane as the internal standard. The chemical shift in parts per million is followed in parentheses by the splitting pattern: cm = complex multiplet, q = quartet, d = doublet, singlets being otherwise assumed, and the number of protons found by integration follows. Routine work-up of experimental procedures unless otherwise stated involves extraction with ethyl ether, washing the combined extracts with sodium chloride solution, drying over anhydrous magnesium sulfate, and finally removal of the ether to give a distillable or crystallizable residue.

o-Mercaptophenethyl Alcohol (8).—To a stirred suspension of 1.90 g (0.05 mol) of lithium aluminum hydride in 100 ml of anhydrous ether under nitrogen was added dropwise a solution of 3.60 g (0.024 mol) of benzo[*b*]thiophene-2(3*H*)-one (**7**)[15] in 75 ml of anhydrous ether over a period of 20 min. The mixture was stirred at room temperature for 4 hr, and then 40 ml of water was added carefully with cooling to decompose excess lithium aluminum hydride, after which was added dropwise 125 ml of 10% sulfuric acid with continued cooling. The phases were separated, and the aqueous phase was extracted with ether (two 100-ml portions). After work-up, the viscous residue was vacuum distilled to yield 3.20 g (87%): bp 93–96° (0.08 mm); $n^{25}D$ 1.5959; ir 3360 (OH), 2562 cm^{-1} (SH).

Anal. Calcd for $C_8H_{10}OS$: C, 62.30; H, 6.54; S, 20.79. Found: C, 62.36; H, 6.70; S, 20.86.

o-(Benzylthio)phenethyl Alcohol (9).—A solution of 2.60 g (0.017 mol) of **8** in 2 ml of 95% ethanol was added dropwise to a stirred solution of 0.80 g (0.02 mol) of sodium hydroxide in 10 ml of 95% ethanol to which 1 ml of water was added (nitrogen). The solution was stirred 0.5 hr at room temperature and then 2.28 g (0.018 mol) of benzyl chloride was added dropwise. The mixture was stirred and refluxed for 6 hr and then filtered. The ethanol was removed under reduced pressure, and the residue taken up in 50 ml of ether. After work-up, distillation of the viscous liquid yielded 2.10 g (75%): bp 147–151° (0.05 mm); $n^{25}D$ 1.6146; ir 3360 cm^{-1} (OH).

Anal. Calcd for $C_{15}H_{16}OS$: C, 73.73; H, 6.60; S, 13.12. Found: C, 73.89; H, 6.66; S, 13.28.

Formation of 2,3-Dihydrobenzo[*b*]thiophene (12) from 9.—To a solution of 3.00 g (0.0123 mol) of **9** in 3 ml of dry pyridine was added dropwise with cooling (under nitrogen) 1.60 g (0.0134 mol) of thionyl chloride. After the addition, the mixture was stirred at 65° for 12 hr, and then 50 ml of cold water was added and the mixture was extracted with chloroform (three 30-ml portions). After work-up, the residue was fractionally distilled yielding two main fractions: an 80% yield of benzyl chloride [bp 80–83° (16 mm), ir identical with that of an authentic sample]; and 1.50 g (90%) of 2,3-dihydrobenzo[*b*]thiophene (**12**) [bp 108–110° (16 mm), $n^{25}D$ 1.6184].

Anal. Calcd for C_8H_8S: C, 70.54; H, 5.92; S, 23.54. Found: C, 70.23; H, 5.72; S, 23.27.

Similar results were obtained by using other reagents: phosphorus pentachloride in carbon tetrachloride gave 47% **12** and 50% benzyl chloride, concentrated hydrochloric acid gave 72% **12** and 68% benzyl chloride, and tosyl chloride–pyridine gave 69% **12**.

The **sulfone of 2,3-dihydrobenzo[*b*]thiophene (12)** was prepared by oxidation with 30% hydrogen peroxide in glacial acetic acid to give a 79% yield of product, mp 91–92.5° (lit.[16] mp 91.5–92°).

Anal. Calcd for $C_8H_8SO_2$: C, 57.12; H, 4.79; S, 19.06. Found: C, 57.19; H, 4.71; S, 18.82.

o-(Benzylthio)benzaldehyde (15) from Benzyl α-Chloro-*o*-tolyl Sulfide (14) by the Sommelet Reaction.—A solution of 12.42 g (0.05 mol) of benzyl α-chloro-*o*-tolyl sulfide[3] and 9.11 g (0.065 mol) of hexamethylenetetramine in 150 ml of chloroform was heated under reflux for 2 hr with 100 ml of 20% hydrochloric acid. The mixture was cooled and extracted with ether (three 100-ml portions). Work-up yielded 6.75 g (59%) of pale yellow solid, mp 69–74°. This material could be employed without further purification in the preparation of **16**. A sample was recrystallized twice from absolute ethanol to yield colorless needles: mp 75–76°; ir ($CHCl_3$) 2700 (aldehyde C–H), 1690 cm^{-1} (C=O); nmr (CCl_4) δ 10.14 (1, CHO), 7.22–7.05 (cm, 9, benzene rings), 3.93 (2, CH_2).

Anal. Calcd for $C_{14}H_{12}OS$: C, 73.60; H, 5.31; S, 14.04. Found: C, 73.70; H, 5.18; S, 13.94.

A **2,4-dinitrophenylhydrazone** recrystallized from ethyl acetate–ethanol gave orange needles, mp 199–200°.

Anal. Calcd for $C_{20}H_{16}N_4O_4S$: C, 58.95; H, 3.72; N, 13.75. Found: C, 58.73; H, 3.81; N, 13.68.

o-Benzylthiobenzaldehyde (15) from o-(Benzylthio)benzoic Acid (18) by the McFadyen and Stevens Method.—A mixture of 34.0 g (0.08 mol) of crude 1-(*o*-benzylthiobenzoyl)-2-*p*-tolysulfonylhydrazide (see below) in 250 ml of freshly distilled ethylene glycol was heated to 160°, and then 18 g (0.80 mol) of

(13) (a) A. Albert and J. N. Phillips, *J. Chem. Soc.*, 1294 (1956); (b) K. L. Morgan, *ibid.*, 1461 (1952).

(14) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd ed, Wiley, New York, N. Y., 1958.

(15) Prepared in 30% yield by oxidation of benzo[*b*]thienyllithium in the presence of an alkyl Grignard reagent (ref 8).

(16) R. Fricke and G. Spilker, *Ber.*, **88**, 1589 (1952).

anhydrous sodium carbonate was added. The mixture was heated until evolution of gas ceased (2–3 min). The soluion was cooled slightly and then diluted with 2 l. of hot water. Work-up of the mixture produced a red oil which crystallized on standing, mp 67–71°. If the oil was distilled under reduced pressure, it gave a yellow liquid which readily crystallized: bp 144–150° (0.08 mm); mp 69–71°. The infrared absorption spectrum of this substance was identical with that of a sample prepared by the Sommelet reaction.

1-(*o*-Benzylthiobenzoyl)-2-*p*-tolylsulfonylhydrazide.—To a stirred solution of 19.0 g (0.072 mol) of *o*-(benzylthio)benzhydrazide[17] in 225 ml of dry pyridine, was slowly added 15.5 g (0.082 mol) of *p*-toluenesulfonyl chloride, while the temperature was maintained below 10°. The mixture was allowed to warm to room temperature and stirred for 3 hr, after which it was then heated at 75° for 1 hr. The hot mixture was poured into a mixture of 350 ml of hydrochloric acid and 500 g of ice. The yellow precipitate which formed was collected, washed several times with ether, and dried to yield 38.0 g of pale yellow crystals, mp 146–172°. A sample of the material (2.0 g) was recrystallized three times from a mixture of heptane–ethyl acetate to yield 1.0 g of colorless plates, mp 145.5–146°.

Anal. Calcd for $C_{21}H_{20}N_2O_3S$: C, 61.13; H, 4.89; S, 15.55. Found: C, 60.92; H, 4.89; S, 15.43.

***o*-(Benzylthio)cinnamonitrile (16).**—While the temperature was maintained below 10°, 17.7 g (0.10 mol) of methylcyanodiethyl phosphate[18] was added dropwise to a stirred suspension of 2.40 g (0.10 mol) of sodium hydride in 50 ml of 1,2-dimethoxyethane (freshly dried over calcium hydride). The mixture then was stirred at room temperature until all the sodium hydride had dissolved (1 hr). A solution of 22.8 g (0.10 mol) of *o*-(benzylthio)-benzaldehyde (**15**) in 100 ml of 1,2-dimethoxyethane was then added dropwise while the temperature was kept below 0°. After the addition had been completed, the mixture was stirred at room temperature for 4 hr during which time a gummy precipitate formed; it was then poured into 1 l. of cold water. Work-up gave an orange oil which solidified on standing to give 22.3 g (88%) of a light brown mass, mp 64–73°. Although this material was satisfactory for subsequent use, an analytical sample was recrystallized twice from heptane to give colorless needles: mp 89–90°; ir (CCl_4) 2220 cm^{-1} (CN); nmr (CCl_4) δ 3.90 (2, CH_2), 5.41–5.70 (d, 1, CH), 7.52–7.81 (d, 1, CH), 7.09–7.77 (cm, 9, benzene rings).

Anal. Calcd for $C_{15}H_{13}NS$: C, 76.45; H, 5.22; S, 12.91. Found: C, 76.22; H, 5.44; S, 12.91.

***o*-(Benzylthio)hydrocinnamonitrile (17).**—A solution of 10.06 g (0.04 mol) of **16** in 300 ml of ethanol was poured into 100 ml of water to form a fine suspension. Then 200 g of 2% sodium amalgam was added, and the mixture was stirred at 45–50° for 3 hr. The mixture was poured into 500 ml of water and worked up in the usual way. The residual oil solidified on standing to give a pale yellow product, 10.05 g (98%), mp 48–53°. The solid was recrystallized from hexane to give 8.86 g (87%) of colorless needles, mp 53–55°. A sample was further recrystallized from hexane to give mp 54–55°; ir (CCl_4) 2260 cm^{-1} (CN); nmr (CCl_4) δ 2.14–2.38 (t, 2, CH_2), 2.47–2.98 (t, 2, CH_2), 3.94 (2, CH_2), 7.08–7.36 (cm, benzene rings).

Anal. Calcd for $C_{16}H_{15}NS$: C, 75.95; H, 5.93; S, 12.62. Found: C, 75.81; H, 6.07; 12.43.

Attempted Formation of the Tautomeric System 4. A. Treatment of 17 with Hydrogen Chloride.—A solution of 2.51 g (0.01 mol) of **17** in 40 ml of anhydrous ether was cooled to Dry Ice bath temperatures. The solution was saturated with anhydrous hydrogen chloride and then allowed to slowly warm to room temperature. After the mixture had stood for 3 days with occasional addition of hydrogen chloride, the ether was removed to give an oil, the infrared spectrum of which was the same as the unreacted starting material.

B. With Aluminum Bromide.—To a cooled solution of 8.00 g (0.03 mol) of anhydrous aluminum bromide in 20 ml of anhydrous benzene was added a solution of 5.06 g (0.02 mol) of **17** in 40 ml of anhydrous benzene. The mixture was then stirred for 30 hr at room temperature after which 75 ml of water was added dropwise, and the benzene layer was removed. The aqueous phase was extracted with ether (two 50-ml portions), and work-up produced 2.48 g of an intractable orange oil.

Ethyl *o*-(Benzylthio)-α-cyanohydrocinnamate (22a).—To a solution of 0.23 g (0.01 g atom) of sodium metal in 40 ml of absolute ethanol was added slowly 2.26 g (0.02 mol) of ethyl cyanoacetate (nitrogen). The resulting solution was stirred for 0.5 hr at room temperature and then 2.49 g (0.01 mol) of **14** was added dropwise. The mixture was refluxed for 2 hr and the sodium chloride removed by filtration. The ethanol was removed under reduced pressure, and the residue taken up in 50 ml of ether. Work-up gave a residue, which was molecularly distilled at 200° (0.05 mm) yielding 1.61 g (50%): $n^{25}D$ 1.5669; ir 2250 (C≡N), 1725 cm^{-1} (ester C=O).

Anal. Calcd for $C_{19}H_{19}NO_2S$: C, 70.12; H, 5.89; S, 9.61. Found: C, 70.04; H, 6.01; S, 9.61.

This compound was also prepared by alkylation with sodium hydride in either dimethyl sulfoxide or dimethylformamide in crude yields of over 90%.

[*o*-(Benzylthio)benzyl]malononitrile (22b).—The same procedure was used as in the preparation of **22b** as for **22a** with the exception that malononitrile was substituted for ethyl cyanoacetate. After work-up the residue was molecularly distilled at 220° (0.05 mm) to produce 2.0 g (72%) of a yellow oil, ir 2260 cm^{-1} (C≡N).

Anal. Calcd for $C_{17}H_{14}N_2S$: C, 73.34; H, 5.07; S, 11.52. Found: C, 73.04; H, 5.15; S, 11.62.

Ethyl 2-Amino-4*H*-1-benzothiopyran-3-carboxylate (5c).—To a cooled, stirred solution of 4.0 g (0.015 mol) of anhydrous aluminum bromide in 20 ml of dry benzene (nitrogen) was added a solution of 3.25 g (0.01 mol) of crude **22a** in 10 ml of dry benzene. During the addition, a very thick syrup formed causing irratic stirring; however, stirring was continued for 12 hr, and then the contents were poured into 150 ml of ice water. After the usual type of work-up, the residue was vacuum distilled yielding 1.0 g (43%) of a viscous oil which solidified on standing: bp 135–140° (0.08 mm); mp 59.5–61.5°. Recrystallization from pentane yielded 0.55 g (29%): mp 61–61.5°; ir (10% $CHCl_3$) 3470, 3310, (N—H), 1650 cm^{-1} (ester C=O); nmr ($CHCl_3$) δ 7.1–7.3 (cm, 4, benzene rings), 6.4 (2, NH_2), 4.0–4.3 (q, 2, CH_2), 3.5 (2, CH_2), 1.2–1.4 (t, 3, CH_3).

Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; S, 13.63. Found: C, 61.29; H, 5.74; S, 13.47.

Treatment of an ether solution of **5c** with dry hydrogen chloride resulted in the separation of **the hydrochloride of 5c**, mp 120–125° dec.

Anal. Calcd for $C_{12}H_{14}ClNO_2S$: C, 53.03; H, 5.19; Cl, 13.05. Found: C, 52.75; H, 5.16; Cl, 13.23.

2-Amino-4*H*-1-benzothiopyran-3-carbonitrile (6c).—To a cooled, stirred solution of 4.0 g (0.015 mol) of anhydrous aluminum bromide in 20 ml of anhydrous benzene was added dropwise (under nitrogen) a solution of 2.70 g (0.01 mol) of crude **22b** in 10 ml of anhydrous benzene. During the addition, two phases formed and the mixture became dark red. The mixture was stirred 13 hr at room temperature and then cooled while 100 ml of water was added. After the work-up, the residue was distilled, bp 180–188° (0.01 mm); the product solidified and was sublimed three times and then washed with pentane to yield 0.75 g (40%): mp 95–100° (a well-defined melting point could not be obtained since the compound sublimed from 90–100°); ir (10% $CHCl_3$) 3470, 3380 (N—H), 2180 cm^{-1} (C≡N); nmr ($CHCl_3$) δ 4.7 (2, NH_2), 3.4 (2, CH_2).

Anal. Calcd for $C_{10}H_8N_2S$: C, 63.80; H, 4.28; S, 17.03. Found: C, 64.00; H, 4.34; S, 16.90.

Registry No.—**5c**, 25866-37-9; **5c** HCl, 25866-38-0; **6c**, 25907-84-0; **8**, 25866-39-1; **9**, 25866-40-4; **12**, 4565-32-6; **15**, 24852-71-9; **15** 2,4-DNP, 25907-86-2; **16**, 25866-42-6; **17**, 25866-43-7; **22a**, 25866-44-8; **22b**, 25866-45-9; 1-(*o*-benzylthiobenzoyl)-2-*p*-tolylsulfonylhydrazide, 25907-87-3.

(17) In this McFadyen and Stevens sequence some known intermediates were prepared. *o*-(Benzylthio)benzhydrazide was formed from ethyl *o*-(benzylthio)benzoate in 92% yield, mp 163–164° (lit. mp 164°). (a) F. Gialdi, R. Ponce, and A. Barruffini, *Farmaco, Ed. Sci.*, **15**, 856 (1960) [*Chem. Abstr.*, **55**, 21040 (1960)]. Ethyl *o*-(benzythio)benzoate was prepared as colorless needles in 90% yield, mp 68.5–69° (lit. mp 68°). (b) W. J. Barry and I. L. Finer, *J. Chem. Soc.*, 138 (1954). Finally, the initial intermediate in the series, *o*-(benzylthio)benzoic acid (**18**), was obtained by alkylation of *o*-mercaptobenzoic acid (Aldrich) by benzyl chloride in quantitative yield, mp 188.5–189° (lit. mp 189°). (c) H. Apitzsch, *Ber.*, **46**, 3102 (1913).

(18) N. D. Dawson and A. Burger, *J. Amer. Chem. Soc.*, **74**, 5313 (1952).

Acknowledgment.—We wish to thank the Research Committee of Washington State University for partial support of this work, as well as the donors of the Petroleum Research Fund, administered by the American Chemical Society, for a grant 2403-A1, 4.

Peracid Oxidation of Ene–Lactams. A Synthesis of Macrocyclic Imides

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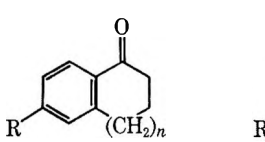
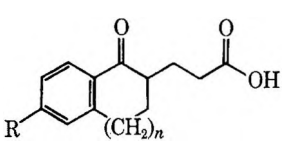
The substituted propionic acids **2a–c** prepared by conventional procedures were converted to the amides **3a–d**, which were ring closed in presence of *p*-toluenesulfonic acid to the unsaturated lactams **4a–d**. On peracid oxidation of **4a**, the ketone **5** was obtained. The oxidation of **4b–d** yielded with oxygen insertion the products **7a–c**. The structures of these compounds were proven by alkaline degradation. The mechanism of the peracid oxidation is discussed.

In our earlier work on the synthesis of medium-ring benzoic acid lactones,[1] we oxidized cyclic enol ethers with an excess of *m*-chloroperbenzoic acid. In some instances we observed a deviation from the normal reaction pathway leading to cyclic carbonates instead of the expected lactones. A mechanism for this insertion of an extra oxygen atom was proposed. The present paper deals with the peracid oxidation of ene–lactams which provides a synthetic approach to a novel class of macrocyclic imides.

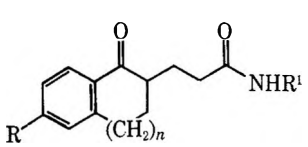
Ketones **1a–c** were converted into the corresponding formyl derivatives with ethyl formate in the usual manner. These compounds were reacted with ethyl acrylate in the presence of triethylamine to generate propionic acid esters which were transformed to the acids **2a–c**. These were converted to the amides **3a–d** which in turn were cyclized with *p*-toluenesulfonic acid in boiling toluene to yield the cyclic ene–lactams **4a–d**.



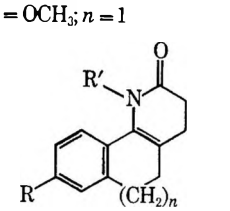
1a, R = H; $n = 2$
b, R = H; $n = 1$
c, R = OCH_3; $n = 1$



2a, R = H; $n = 2$
b, R = H; $n = 1$
c, R = OCH_3; $n = 1$

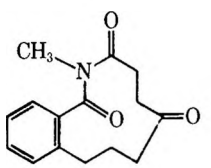


3a, R = H; $R^1 = CH_3$; $n = 2$
b, R = R^1 = H; $n = 1$
c, R = H; $R^1 = CH_3$; $n = 1$
d, R = OCH_3; $R^1 = CH_3$; $n = 1$

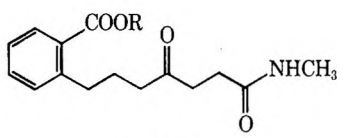


4a, R = H; $R^1 = CH_3$; $n = 2$
b, R = R^1 = H; $n = 1$
c, R = H; $R^1 = CH_3$; $n = 1$
d, R = OCH_3; $R^1 = CH_3$; $n = 1$

Oxidation of the ene–lactam **4a** with an excess of *m*-chloroperbenzoic acid led, in good yield, to a product whose analytical and spectral data corroborated with structure **5**. On alkaline treatment of this ketone, the benzoic acid **6a** was obtained, which was characterized as its methyl ester **6b**.

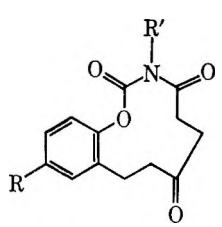


5



6a, R = H
b, R = CH_3

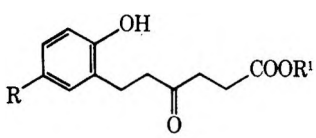
In contrast, the oxidation of the ene–lactam **4b** under the same conditions led to a compound containing an extra oxygen (molecular ion at *m/e* 247). Its elemental analysis confirmed the formula $C_{13}H_{13}NO_4$. The infrared, ultraviolet, and nmr spectra were in complete agreement with the assigned structure **7a**. Similar oxidation of the lactams **4c** and **d** led to the isolation of the macrocyclic imides **7b** and **c**, respectively.



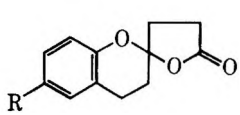
7a, R = H; R^1 = H
b, R = H; $R^1 = CH_3$
c, R = OCH_3; $R^1 = CH_3$

The structures of these compounds were proven by alkaline degradation.

Treatment of the ketones **7a** and **b** with aqueous methanolic sodium hydroxide yielded the phenolic acid **8a**. The compound **7c**, under identical conditions, led to **8b**.



8a, R = H; R^1 = H
b, R = OCH_3; R^1 = H
c, R = OCH_3; $R^1 = CH_3$



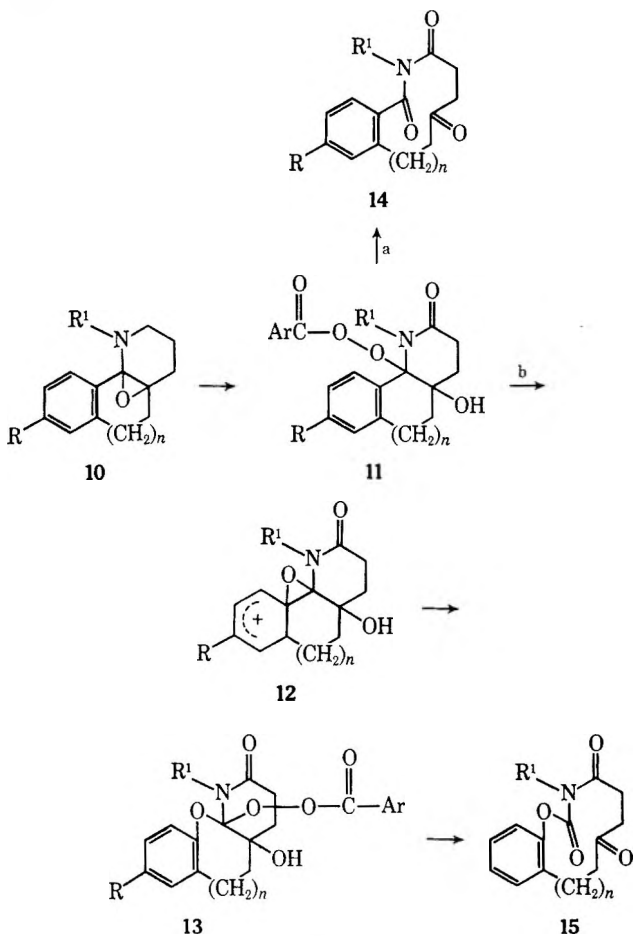
9a, R = H
b, R = OCH_3

(1) (a) H. Immer and J. F. Bagli, *J. Org. Chem.*, **33**, 2457 (1968); (b) J. F. Bagli and H. Immer, *Can. J. Chem.*, **46**, 3115 (1968).

The acid **8a** was dehydrated on treatment with acetic anhydride to a product, which showed in its infrared spectrum a carbonyl band at 1780 cm^{-1}. The ultraviolet spectrum was characteristic for an isolated benzene ring. The mass spectral data and the elemental analysis were in agreement with structure **9a**. Analogous reaction of the methoxy derivative **8b** yielded **9b**. The acid **8a** was readily synthesized by an aldol condensation of O-hydroxybenzaldehyde and levulinic acid,[2] followed by hydrogenation of the resulting unsaturated acid.

Discussion

The results obtained can best be accommodated by the mechanism proposed for the oxidation of enol ethers.[1]



The initially formed epoxide **10** is opened by *m*-chloroperbenzoic acid.[3] The electron deficiency at the benzylic oxygen atom in the perester **11** causes: (a) fragmentation to form the product **14** (n = 2), and (b) formation of the phenonium ion **12** (n = 1), which is attacked by another mole of peracid to form **13**. This perester leads through fragmentation to the product **15**.

The substrates **4b–d** react exclusively *via* pathway b, regardless of the presence of an electron donating group (as in **4d**), stabilizing the phenonium ion.[4] The substitution at the nitrogen does not change the course of the reaction (compare **4b** and **4d**). The substrate **4a**, on the other hand, leads through pathway a to **6**. Everything else being equal, but the size of the central ring the conformational differences must account for the different reaction pathways.[5] Similar results were already obtained in the oxidation of enol ethers.[1] The cases presented here, however, show a much higher degree of specificity and provide a striking example of the very subtle steric demands for phenonium-ion participation.

Experimental Section[6]

Ketopropionic Acids. 1,2,3,4-Tetrahydro-1-oxo-2-naphthalenepropionic acid (2b) was prepared *via* the formyl compound followed by condensation with ethyl acrylate and base hydrolysis, mp 108–110° (lit.[7] 108–110°).

1,2,3,4-Tetrahydro-6-methoxy-1-oxo-2-naphthalenepropionic acid (2c) was prepared using the above procedure and had mp 134–135° (lit.[8] 128–130°). **2,3,4,5-Tetrahydro-1-oxo-1H-benzocycloheptene-2-propionic acid (2a)** was synthesized when 2,3,4,5-tetrahydro-1-oxo-1H-benzocycloheptene (8 g) in dry benzene (200 ml) and ethyl formate (20 ml) were cooled in ice. Sodium hydride (6 g) was added gradually and the mixture stirred at room temperature for 3 days under nitrogen. The acidic **2,3,4,5-tetrahydro-2-hydroxymethylene-1H-benzocycloheptene-1-one** (9.8 g) was isolated in the usual manner. The crude formyl ketone (4.23 g) was stirred with ethyl acrylate (5.6 ml) in methanol (20 ml) in presence of triethylamine (0.93 ml) at 40° for 4 days. The mixture was diluted with ether, washed with sodium carbonate (5%), then with saturated sodium chloride, the ether was extract dried, and the solvent was removed. The residue was distilled to yield (91%) the ethyl ester of the acid **2a** (4.75 g): bp 140–145° (0.2 mm); $\nu_{max}^{CHCl_3}$ 1727, 1665 cm^{-1}.

Anal. Calcd for $C_{16}H_{20}O_3$ (260): C, 73.82; H, 7.74. Found: C, 73.35; H, 7.56.

Hydrolysis in aqueous methanolic potassium hydroxide gave the acid **2a**, in quantitative yield: mp 82–83°; $\nu_{max}^{CHCl_3}$ 1700, 1675, and 1600 cm^{-1}.

Anal. Calcd for $C_{14}H_{16}O_3$ (232): C, 72.39; H, 6.94. Found: C, 72.64; H, 6.89.

Preparation of Acid Amides. A. From Acid Chlorides.—To a suspension of the sodium salt of acid **2b** (11 g) in benzene (150 ml) containing a few drops of pyridine, oxalyl chloride (18 ml) was added dropwise under ice cooling. The mixture was allowed to reach room temperature and stirred for 45 min. After filtration, the solvent was removed to yield the corresponding acid chloride (checked by infrared).

The above acid chloride was dissolved in dry benzene (55 ml) and methyl amine passed for 30 min. The clear solution was diluted with benzene, washed with water, dried, and the solvent was removed to yield (77.5%) **1,2,3,4-tetrahydro-N-methyl-1-oxo-2-naphthalenepropionamide (3c)** (8.2 g). A sample crystallized from methanol–ether: mp 93–94°; $\nu_{max}^{CHCl_3}$ 3470, 3355, 1672, and 1605 cm^{-1}; λ_{max} 246 mμ (13,700); nmr δ 8.0 (*ortho* aromatic proton[9]), 7.33 (3 H, aromatic), δ 2.82 (3 H, N-methyl doublet).

Anal. Calcd for $C_{14}H_{17}O_2N$ (231): C, 72.70; H, 7.41; N, 6.06. Found: C, 72.93; H, 7.3; N, 5.93.

1,2,3,4-Tetrahydro-1-oxo-2-naphthalenepropionamide (3b) was obtained in a similar manner using ammonia in place of methyl amine: mp 147–148°, $\nu_{max}^{CHCl_3}$ 34 00, 3500, 1676, and 1600 cm^{-1}; λ_{max} 247 mμ (10,550); nmr δ 8.0 (*ortho* aromatic proton), 7.32 (3 H, aromatic).

(2) S. H. Zaheer, I. K. Kacker, and N. S. Rao, *Chem. Ber.*, **89**, 351 (1956).

(3) The occurrence of this opening under the prevailing mild conditions can be explained by invoking participation of phenonium ion. For examples, see R. Huisgen, *Angew. Chem.*, **69**, 341 (1957).

(4) These results are in contrast to those obtained upon oxidation of enol ethers (see ref 1a). A comparison on rigid mechanistic ground is invalidated by the functional and conformational differences in the heterocyclic ring.

(5) The same tendency is reflected in the formolysis of 1,2-benzylcyclenyl-3-methyl tosylates of different ring size (see ref 3).

(6) All experimental conditions were the same as described in ref 14 of our earlier communication (see ref 1a), except that silica gel (0.05–0.2 mm Merck) was employed for column chromatography. Nmr were recorded in deuteriochloroform.

(7) W. E. Bachmann and G. D. Johnson, *J. Amer. Chem. Soc.*, **71**, 3463 (1949).

(8) A. A. Akhrem and I. G. Zavelskaya, *Izv. Akad. Nauk SSSR*, 1637 (1960).

(9) "*ortho* proton" refers to the proton *ortho* to the carbonyl substituent.

Anal. Calcd for $C_{13}H_{15}O_2N$ (217): C, 71.87; H, 6.96; N, 6.45. Found: C, 71.97; H, 6.75; N, 6.85.

1,2,3,4-Tetrahydro-6-methoxy-N-methyl-1-oxo-2-naphthalenepropionamide (3d) prepared in the same way had mp 139–140°; $\nu_{max}^{CHCl_3}$ 3450, 3330, 1715, and 1600 cm^{-1}; λ_{max} 224 (12,200), 272 mμ (15,650); nmr δ 7.98 (*ortho* aromatic proton), 6.79 (3 H, aromatic), 3.83 (3 H, O-methyl), 2.82 (3 H, N-methyl doublet).

Anal. Calcd for $C_{15}H_{19}O_3N$ (261.3): C, 68.94; H, 7.33. Found: C, 68.93; H, 7.12.

B.—Another procedure used for amides is examplified in the preparation of **2,3,4,5-tetrahydro-N-methyl-1-oxo-1H-benzocycloheptene-2-propionamide (3a)**. To a solution of carbonyldiimidazole (2.32 g) in tetrahydrofuran (18 ml) was added a solution of acid **2a** (2.52 g) and the mixture stirred for 2 min, monomethylamine was bubbled through for 30 min, the reaction mixture was diluted with ether, washed with water, dried and the solvent was removed. The crude product was passed through silica gel (300 g) and was eluted with ethyl acetate–benzene 4:1, to yield (75.5%) crystals (2.05 g). Crystallization from methylene chloride–ether gave a sample with mp 72–73°; ν_{max}^{Nujol} 3260, 1672, 1635, and 1595 cm^{-1}; λ_{max} 246 mμ (7400); nmr δ 7.8–7.1 (4 H, aromatic), 2.78 (3 H, N-methyl, doublet).

Anal. Calcd for $C_{15}H_{19}O_2N$ (245): C, 73.44; H, 7.81; N, 5.71. Found: C, 73.77; H, 7.65; N, 5.76.

Preparation of Lactams.—The lactams were generally prepared in 80–90% yield by refluxing the toluene solution of the acid amide in presence of *p*-toluene sulfonic acid over a period of 2–4 hr, using a Dean-Stark, water separator. **3,4,5,6-Tetrahydro-1-methylbenzo[*h*]quinolin-2(1H)-one (4c)** had mp 113–115°; $\nu_{max}^{CHCl_3}$ 1660 cm^{-1}; λ_{max} 281 mμ (8450); nmr δ 7.19 (4 H aromatic), 3.2 (3 H, N-methyl singlet).

Anal. Calcd for $C_{14}H_{15}ON$ (213.2): C, 78.84; H, 7.09; N, 6.57. Found: C, 78.93; H, 6.96; N, 6.51.

3,4,5,6-Tetrahydrobenzo[*h*]quinolin-2(1H)-one (4b) crystallized from chloroform–ether and had mp 181–183°; $\nu_{max}^{CHCl_3}$ 3400, 1674 cm^{-1}; λ_{max} 292 mμ (5700).

Anal. Calcd for $C_{13}H_{13}ON$ (199): C, 78.36; H, 6.58; N, 7.03. Found: C, 78.07; H, 6.58; N, 7.14.

3,4,5,6-Tetrahydro-8-methoxy-1-methylbenzo[*h*]quinolin-2-(1H)-one (4d) had mp 78–80°; $\nu_{max}^{CHCl_3}$ 1650, 1600 cm^{-1}; λ_{max} 231 (19,300), 287 (13,200); nmr δ 7.2–6.6 (3 H, aromatic), 3.83 (3 H, O-methyl) 3.18 (3 H, N-methyl).

Anal. Calcd for $C_{15}H_{17}O_2N$ (243.3): C, 74.05; H, 7.04; N, 5.76. Found: C, 73.75; H, 6.94; N, 5.58.

1,3,4,5,6,7-Hexahydro-1-methyl-2H-benzo[6,7]cyclohepta-[1,2-*b*]pyridine-2-one (4a) crystallized from ether–petroleum ether had mp 100–101°; ν_{max}^{Nujol} 1660 cm^{-1}; λ_{max} 252 (6400); nmr δ 7.2 (4 H, aromatic, multiplet), 2.9 (3 H, N-methyl, singlet).

Anal. Calcd for $C_{15}H_{17}ON$ (227): C, 79.26; H, 7.50; N, 6.16. Found: C, 79.23; H, 7.68; N, 6.30.

Peracid Oxidation.—A typical oxidation procedure was as follows. To a suspension of *m*-chloroperbenzoic acid (9.5 g) in methylene chloride (40 ml) was added a solution of lactam (3.9 g) in methylene chloride so as to maintain gentle reflux. The mixture was stirred for 1 hr (the time varied from one to 4 hr for different substrates). The reaction mixture was cooled in an ice bath, and was filtered. The residue was crystallized from benzene to yield (62.4%) the **5,6,8,9-tetrahydro-1,3-benzoxazecycloundecane-2,4,7(3H)-trione (7a)**: 3 g; mp 137–138°; $\nu_{max}^{CHCl_3}$ 1762, 1705 cm^{-1}; λ_{max} 262 mμ (620); nmr δ 7.1 (4 H, aromatic).

Anal. Calcd for $C_{13}H_{13}O_4N$ (247): C, 63.15; H, 5.30; N, 5.66. Found: C, 63.34; H, 5.23; N, 5.50.

5,6,8,9-Tetrahydro-3-methyl-1,3-benzoxazecycloundecane-2,-4,7(3H)-trione (7b) yielded 47% and was crystallized from methanol–ether: mp 139–140°, $\nu_{max}^{CHCl_3}$ 1748, 1710, and 1675 cm^{-1}; λ_{max} 257 mμ (430); nmr δ 7.18 (4 H, aromatic). The mass spectrum showed *m/e* 261 (M^+), 248 ($M - 18$)$^+$.

Anal. Calcd for $C_{14}H_{15}O_4N$ (261): C, 64.36; H, 5.79; N, 5.36. Found: C, 64.30; H, 5.80; N, 5.33.

5,6,8,9-Tetrahydro-11-methoxy-3-methyl-1,3-benzoxazecycloundecane-2,4,7(3H)-trione (7c) yielded 37.2% and was crystallized from chloroform–hexane: mp 169–171°; $\nu_{max}^{CHCl_3}$ 1748, 1712, and 1675 cm^{-1}; λ_{max} 275 (2180); 282 mμ (2050); nmr δ 6.87 (3 H, aromatic), 3.78 (3 H, O-methyl) and 3.28 (3 H, N-methyl). The mass spectrum showed *m/e* 291 (M^+), 273 ($M - 18$)$^+$.

Anal. Calcd for $C_{15}H_{17}O_5N$ (291): C, 61.85; H, 5.88; N, 4.81. Found: C, 61.73; H, 5.57; N, 4.62.

4,5,8,9-Tetrahydro-2-methyl-1H-2-benzazacycloundecane-1,-3,6(2H,7H)-trione (5) yielded 63.5% and was crystallized from acetone–isopropyl ether to give crystals: mp 107–108°; ν_{max}^{Nujol} 1700, 1670 cm^{-1}; λ_{max} 225 mμ (10,500); nmr δ 7.3 (4 H, aromatic), 3.1 (3 H, N-methyl, singlet)

Anal. Calcd for $C_{15}H_{17}O_3N$ (259): C, 69.48; H, 6.61; N, 5.4. Found: C, 69.50; H, 6.49; N, 5.33.

O-(6-Carboxy-4-oxohex-5-enyl)benzoic Acid (8a). **A.**—To a suspension of ketone **7a** (0.52 g) in methanol (6 ml) was added a solution of sodium hydroxide (0.24 g) in water (1.5 ml). The reaction mixture was stirred for 45 min at room temperature. The mixture was then diluted with ether and extracted with water. The water layer acidified and reextracted with ether. After the usual work up the crude product was crystallized from methanol–ether to give in 72.5% yield the acid **8a**: mp 120–121°; ν_{max}^{Nujol} 3200 1700, 1580 cm^{-1}; λ_{max} 275 (2420) neutral, and 295 mμ (3700) alkaline; nmr δ 6.8 (4 H, aromatic). The mass spectrum showed *m/e* 204 ($M - 18$)$^+$.

Anal. Calcd for $C_{12}H_{14}O_4$ (222): C, 64.85; H, 6.35. Found: C, 64.76; H, 6.76.

B.—The above acid was synthesized by hydrogenation of O-(6-carboxy-4-oxohex-5-enyl)benzoic acid[2] (2.9 g) in methanol in presence of 5% palladium on charcoal (0.2 g). The product obtained from hydrogenation was identical in all respects with that synthesized by procedure A.

O-[6-(N-methylcarbamido)-4-oxohexyl]benzoic Acid Methyl Ester (6b).—To a solution of ketone (**5**) 0.25 g in methanol (4 ml), was added a solution of sodium hydroxide (3 ml, 10%) and the mixture was stirred for 10 min. The methanol was removed, and the residue was diluted with water. The aqueous solution was washed with chloroform, and acidified with 10% hydrochloric acid. Reextraction with chloroform yielded after work up an acid (0.256 g). The acid was directly esterified with diazomethane. The resulting crude ester was purified by passing through a column of silica gel and eluting with 60% ethyl acetate–benzene. The ester had mp 84–85°; $\nu_{max}^{CHCl_3}$ 3440, 1730, 1710, 1675 cm^{-1}; λ_{max} 267 mμ (362); nmr 7.25 (4 H, aromatic), 2.97 (3 H, N-methyl doublet).

Anal. Calcd for $C_{16}H_{21}O_4N$ (291): C, 65.96; H, 7.27; N, 4.56. Found: C, 65.82; H, 7.30; N, 4.87.

3,4-Dihydro-2-hydroxy-2H-benzopyran-2-propionic Acid γ-Lactone (9a).—To a solution of acid **8a** (0.2 g) in acetic anhydride (3 ml) sodium acetate (5 mg) was added. The solution was stirred for 5 min. The mixture was diluted with methanol, and the solvent was evaporated. The residue taken in ether, and worked up as usual to yield 0.18 g of product, crystallized from chloroform–hexane to yield **9a**: mp 102–104°; $\nu_{max}^{CHCl_3}$ 1780, 1600 cm^{-1}; λ_{max} 270 (1490) 276 mμ (1530); nmr δ 7.01 (4 H, aromatic). The mass spectrum showed *m/e* 204 $(M)^+$, 160 $(M - 44)^+$.

Anal. Calcd for $C_{12}H_{12}O_3$ (204): C, 70.58; H, 5.92. Found: C, 70.91; H, 5.66.

3,4-Dihydro-2-hydroxy-6-methoxy-2H-benzopyran-2-propionic Acid γ-Lactone (9b).—To a suspension of ketone **7c** (0.4 g) in methanol (5 ml) was added a solution of sodium hydroxide (0.15 g) in water (1.5 ml). The reaction mixture was stirred for 30 min under nitrogen. It was then diluted with ether and the aqueous layer was acidified. The acid **8b** was isolated and characterized by infrared spectrum. The above acid (0.35 g) was directly treated with acetic anhydride (3 ml) and stirred for 1 hr. The product (0.25 g) was isolated as described in the above experiment. Crystallization from chloroform–hexane gave 0.18 g of compound **9b**: mp 103–104°, $\nu_{max}^{CHCl_3}$ 1775, 1600 cm^{-1}; λ_{max} 290 mμ (2820); nmr δ 6.75 (3 H, aromatic), 3.78 (3 H, O-methyl); 2.55 (8 H, multiplet).

Anal. Calcd for $C_{13}H_{14}O_4$ (234): C, 66.66; H, 6.02. Found: C, 66.76; H, 5.81.

Registry No.—**2a,** 25743-83-3; **2a** (ethyl ester), 25661-99-8; **3a,** 25662-00-4; **3b,** 25662-01-5; **3c,** 25662-02-6; **3d,** 25662-03-7; **4a,** 25662-04-8; **4b,** 25662-05-9; **4c,** 25662-06-0; **4d,** 25662-07-1; **5,** 25662-08-2; **6b,** 25662-09-3; **7a,** 25662-10-6; **7b,** 25662-11-7; **7c,** 25662-12-8; **8a,** 25665-48-9; **9a,** 3243-89-8; **9b,** 25665-49-0.

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Alkaline Transformations Among Glucose, Fructose, and Mannose

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The kinetic parameters of the aldose–ketose transformation in dilute alkali are obtained by measuring the ultraviolet absorption of the acid derived (1.0 *M* HCl, 80.0°, 10.0 hr) hydroxymethylfurfural (HMF, λ_{max} 283 nm) which is proportional to the concentration of fructose in alkali with time when the original solution contained only the single hexoses, glucose, mannose, or fructose. An analog computer is utilized to evaluate a proposed kinetic model for the aldose–ketose transformation. The rate constants obtained are used to calculate the apparent heats of activation, entropy factors, bimolecular rate constants, and the hexose pK_a's. Ultraviolet chromophores were observed at 310 and 270 nm in the alkaline solution. These chromophores were dependent on the hexose concentration, the alkaline concentration, and the atmosphere (air, nitrogen, or oxygen) under which the reactions were conducted.

The Lobry de Bruyn–Alberda van Ekenstein alkaline interconversion among aldoses and ketoses[1,2] has been extensively studied in the hexose system of fructose, glucose, and mannose with regard to possible mechanisms and intermediates.[3] However, kinetic data were not obtained with the exception of the very recent paper by MacLaurin and Green[4] who used one set of conditions. Our present study evaluates the kinetic parameters of the interconversions among these hexoses for a series of alkaline concentrations and temperatures.

A fraction of the glucose in alkaline solution should be converted to fructose and mannose to achieve the equilibrium, and conversely.[1,2] Since an accurate method was available to measure fructose by acidic transformation (1.0 *M* HCl, 80.0°, 10.0 hr) to hydroxymethylfurfural (HMF),[5] the conversion of glucose and mannose to fructose and the loss of fructose was measured under varying conditions of temperature and alkali concentration. Haworth and Jones[6] had used essentially the same techniques of sequential alkali and acid treatment to convert glucose to HMF, but they did not attempt to quantify or study the kinetics of the alkaline conversion.

Experimental Section

Materials and Equipment.—Glucose, fructose, and mannose were obtained from Distillation Products Industries. All other chemicals were of analytical reagent grade.

A Beckman Model DU spectrophotometer, slit width 0.1 mm, was used to measure the absorbance of HMF at 283 nm. Absorbance spectra were obtained from a Cary Model 15 recording spectrophotometer. The kinetic data from the three hexoses were analyzed by the use of an EAI Model TR-48 analog computer.

Fructose Analysis.—Fructose was analyzed by the method of Garrett and Blanch.[5] A 5.0-ml aliquot of an alkaline hexose solution (0.003–0.030 *M*) was acidified to 1.0 *M* HCl and maintained for 10.0 hr at 80.0°. An aliquot was cooled and appropriately diluted. The absorbance of HMF was measured at 283 nm against a water blank.

Kinetic Procedures.—Alkaline solutions (235.0 ml) were prepared so that the desired alkaline strength (0.001, 0.002, 0.004, 0.007, 0.01, 0.02, 0.10, 0.20. 0.40, or 0.60 *M* NaOH) would be obtained after dilution to 250.0 ml. These solutions were preheated to the desired temperatures (25.0, 35.0, 40.0, 50.0, or 95°) in a constant temperature water bath. Aliquots (15.0 ml) of the 0.10 *M* hexose solutions (glucose, fructose, or mannose) were added to the preheated alkaline solutions and shaken; 5.0-ml samples were immediately and subsequently taken. These alkaline samples were acidified (20.0 ml of 1.30 *M* HCl) and stored (5°) until convenient to place in the 80.0° temperature bath for 10.0 hr. On removal from the 80.0° bath, the samples were cooled and appropriately diluted, and the absorbance read at 283 nm against a water blank. The above procedure was conducted under ambient atmospheric conditions.

In addition some of the alkaline solutions were purged for 15 min with oxygen-free nitrogen before the addition of the hexose and purged for 5 min after each sample was taken. Care was taken to tighten the glass stoppers after each purging sequence to minimize the amount of air in contact with the solutions. These nitrogen purged solutions were analytically monitored in parallel with the solutions under ambient atmospheric conditions.

Glucose–Fructose Alkaline Equilibrium Mixtures.—Mixtures of glucose and fructose (Table I) were prepared which were representative of the equilibrium established between the two hexoses at specific alkaline concentrations (0.20, 0.40, and 0.60 *M* NaOH) at 35.0°. A 15.0-ml aliquot from each of the appropriately prepared standard mixtures was put into 235.0 ml of the desired preheated NaOH solution. Initially and periodically thereafter, 5.0-ml aliquots from each of the three alkaline solutions were added to 20.0 ml of 1.30 *M* HCl. Each acidic solution was then heated at 80.0° for 10.0 hr, sampled, cooled and appropriately diluted, and the HMF absorbance read at 283 nm against a water blank.

Chromophores from Hexoses in Alkali.—The cell compartment of a Cary Model 15 spectrophotometer with a Cary automatic sample changer attachment was equilibrated at 40.0°. The cell compartment was continuously purged with oxygen-free nitrogen or oxygen as desired.

Alkaline solutions (80.0 ml) were prepared so that the desired alkaline strength (0.20, 0.40, or 0.60 *M* NaOH) would be obtained after dilution to 100.0 ml. These alkaline solutions were preheated to 40.0°. Glucose or fructose solutions (20.0 ml) were prepared so that the desired hexose concentration (0.002, 0.004, 0.006, or 0.008 *M*) would be obtained after addition to the 80.0 ml of preheated alkaline solution. On addition of the hexose solution to the alkaline solution, these solutions were shaken, immediately sampled, and placed in one of the Cary cells. Four of the five cells were used for these hexose samples; the fifth contained a blank of the specific alkaline solution being tested without hexose.

Results and Discussion

Kinetics.—The Lobry de Bruyn–Alberda van Ekenstein transformation of glucose (Figure 1), mannose (Figure 2), and fructose (Figure 3) was studied at various alkali concentrations at 35.0°. Periodic samples were taken from these alkaline reaction solutions and analyzed for the amount of HMF derived from the fructose present by acidifying (1.0 *M* HCl, 80.0°, 10.0 hr) and measuring the absorbance of the HMF produced.

The effects of temperature on acid-derived HMF at a constant alkaline concentration for glucose (Figure 4), mannose (Figure 5), and fructose (Figure 6) were also

(1) C. A. Lobry de Bruyn and W. Alberda van Ekenstein, *Recl. Trav. Chim. Pays-Bas*, **14**, 203 (1895).

(2) C. A. Lobry de Bruyn and W. Alberda van Ekenstein, *ibid.*, **16**, 262 (1897).

(3) J. C. Speck, Jr., *Advan. Carbohyd. Chem.*, **13**, 63 (1958).

(4) D. J. MacLaurin and J. W. Green, *Can. J. Chem.*, **47** (21), 3947 (1969).

(5) E. R. Garrett and J. Blanch, *Anal. Chem.*, **39**, 1109 (1967).

(6) W. H. Haworth and W. G. M. Jones, *J. Chem. Soc.*, 667 (1944).

TABLE I

EXPERIMENTAL AND CALCULATED APPARENT FIRST-ORDER RATE CONSTANTS FOR THE LOSS OF HMF ABSORBANCE DERIVED FROM THE ALKALINE DECOMPOSITION OF AN EQUILIBRIUM MIXTURE[a] OF GLUCOSE, G, AND FRUCTOSE, F, WITH TIME AT 35.0°

			10^4k_1 (sec^{-1})[b]			k_{app}	
10^4[G][a]	10^4[F][a]	[NaOH], *M*	k_1	k_2	k_3	Calcd[c]	Expt[d]
5.29	6.71	0.20	0.542	0.692	0.186	0.104	0.100
6.20	5.80	0.40	0.711	0.658	0.303	0.146	0.155
6.70	5.30	0.60	0.844	0.669	0.436	0.193	0.180

[a] The specified mixtures of G and F were those ratios of G:F that would exist at equilibrium. [b] These are the rate constants obtained from HMF yields with time under similar conditions on the assumption of the model

$$G \underset{k_1}{\overset{k_2}{\rightleftharpoons}} F \xrightarrow{k_3} P$$

where P represents degradation products. [c] The apparent rate constant is calculated from $k_{app} = k_3/(1 + k_1/k_2)$. [d] The apparent rate constant is determined experimentally from the slope of plots of log [HMF] *vs.* time.

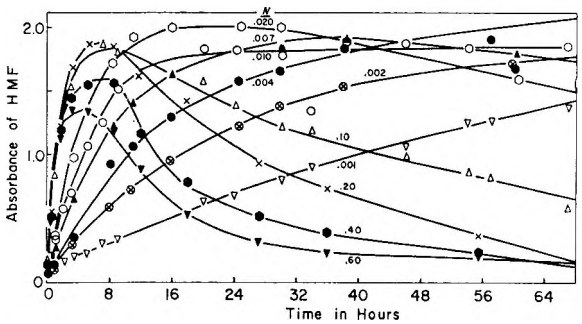


Figure 1.—Effects of NaOH concentration on the HMF absorbance derived (1.0 *M* HCl, 80.0°, 10.0 hr) from 0.006 *M* glucose at 35.0° as a function of time.

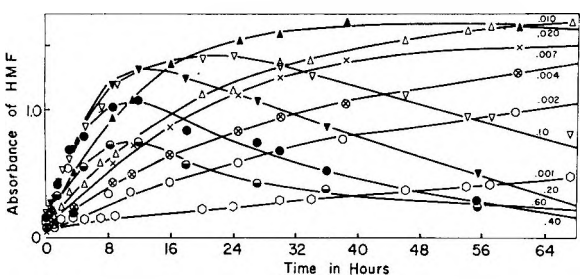
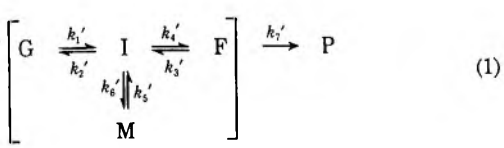


Figure 2.—Effects of NaOH concentration on the HMF absorbance derived (1.0 *M* HCl, 80.0°, 10.0 hr) from 0.006 *M* mannose at 35.0° as a function of time.

studied. The degradation of the hexoses was too fast at 95° to monitor the conversion among the hexoses.

The generally accepted theory for the Lobry de Bruyn–Alberda van Ekenstein transformation implicates an enediol intermediate. A theoretically acceptable model[7] would be the following



(1)

where glucose (G), mannose (M), and fructose (F) are in equilibrium with the intermediate (I) and where one or all species can degrade to other products (P). This intermediate has never been isolated[3] and may be assumed to be present only in small quantities. Under

(7) E. A. Davidson, "Carbohydrate Chemistry," Holt, Rinehart and Winston, New York, N. Y., 1967, pp 185–191.

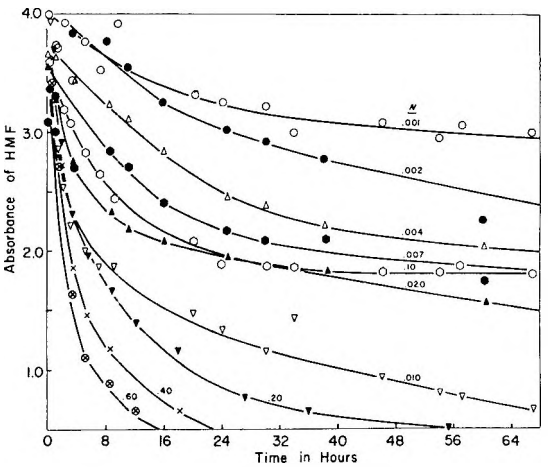
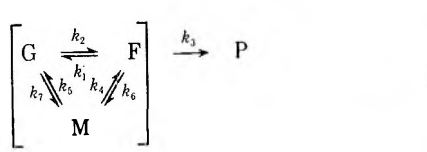


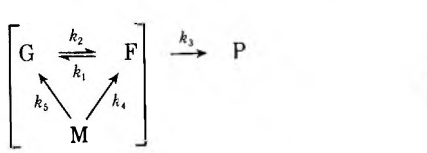
Figure 3.—Effects of NaOH concentration on the HMF absorbance derived (1.0 *M* HCl, 80.0°, 10.0 hr) from 0.006 *M* fructose at 35.0° as a function of time.

these conditions $k_2' > k_1'$, $k_4' > k_3'$, $k_6' > k_5'$ and a kinetically equivalent model of eq 1 would be



(2)

This is essentially the model used by MacLaurin and Green.[4] Wolfrom and Lewis[8] stated that only small amounts of mannose (about 2%) could be recovered from an equilibrium mixture when starting with either glucose or fructose. Miyada[9] stated that he was unable to detect any mannose when starting with glucose or fructose in alkaline solutions. This would suggest that eq 2 could be simplified to the following



(3)

If it is postulated that only the fructose degrades to other products or if the achievement of the glucose–fructose equilibrium and the loss of mannose is fast

(8) M. L. Wolfrom and W. L. Lewis, *J. Amer. Chem. Soc.*, **50**, 837 (1928).

(9) D. S. Miyada, The Lobry de Bruyn Transformation of D-Glucose and 3,4,6-Trimethyl-D-Fructose, Ph.D. Dissertation, Michigan State University, East Lansing, Mich., 1953.

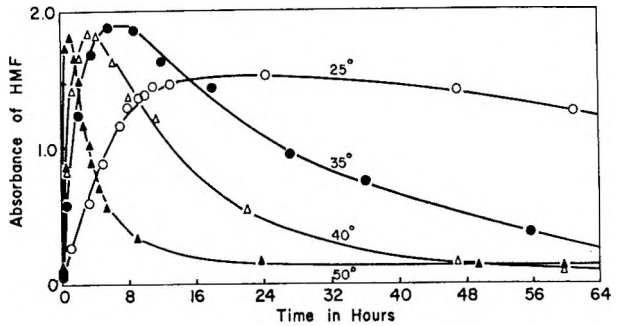


Figure 4.—Effects of temperature on the HMF absorbance derived (1.0 *M* HCl, 80.0°, 10.0 hr) from 0.006 *M* glucose solution in 0.20 *M* NaOH as a function of time.

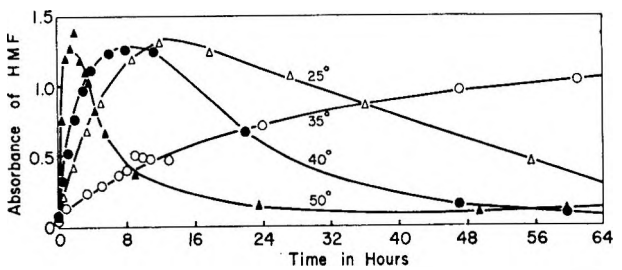
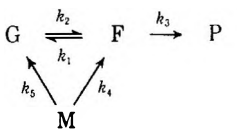


Figure 5.—Effects of temperature on the HMF absorbance derived (1.0 *M* HCl, 80.0°, 10.0 hr) from 0.006 *M* mannose solution in 0.20 *M* NaOH as a function of time.

compared to the production of other products, the model of eq 3 can be written



(4)

MacLaurin and Green[4] estimated rate constants for the degradation of mannose and glucose to other products but they were 36 times smaller in magnitude than that for the conversion of fructose to other products.

The analog computer was programmed to test the consistency of the data with eq 4. The differential equations based on eq 4 are

$$-\mathrm{d[G]}/dt = k_2[\mathrm{G}] - k_1[\mathrm{F}] - k_5[\mathrm{M}] \quad (5)$$

$$-\mathrm{d[M]}/dt = (k_4 + k_5)[\mathrm{M}] \quad (6)$$

$$\mathrm{d[F]}/dt = k_2[\mathrm{G}] + k_4[\mathrm{M}] - k_1[\mathrm{F}] - k_3[\mathrm{F}] \quad (7)$$

$$\mathrm{d[P]}/dt = k_3[\mathrm{F}] \quad (8)$$

The HMF yields were proportional to the fructose present. These yields were determined as a function of time for the same concentrations of glucose (G) and fructose (F) at a given alkali concentration and temperature. The curves were fitted by the programmed analog computer based on the model of eq 4. Appropriate values for the k_1, k_2, and k_3 constants were chosen for this fitting. These constants were maintained in the analog computer program and the k_4 and k_5 values were adjusted to fit the HMF data obtained from the reaction of the same concentration of mannose (M) under the same conditions as a function of time. This did not assume a finite amount of mannose when equilibrium was achieved.

Typical plots of the fitting of such data obtained at

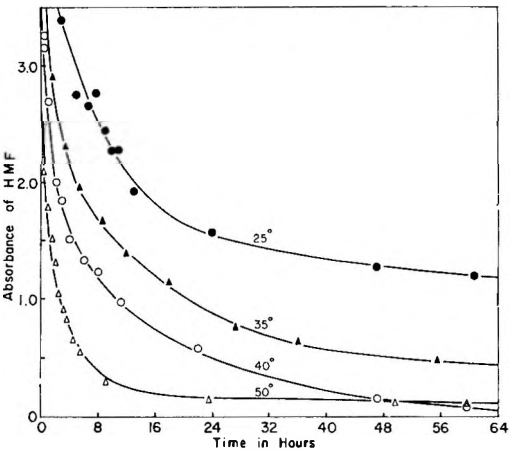


Figure 6.—Effects of temperature on the HMF absorbance derived (1.0 *M* HCl, 80.0°, 10.0 hr) from 0.006 *M* fructose solution in 0.20 *M* NaOH as a function of time.

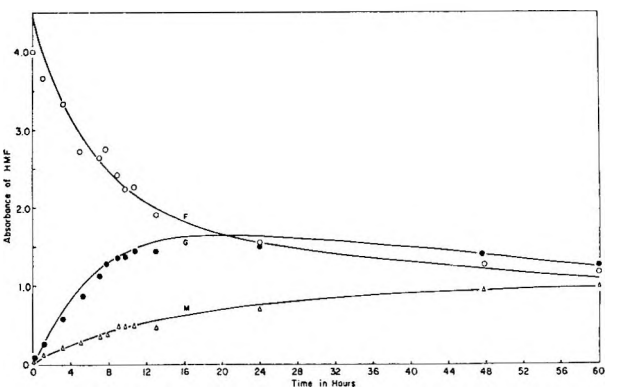
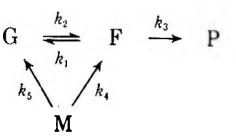


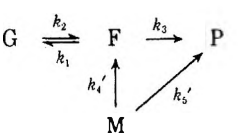
Figure 7.—Absorbance of HMF derived (1.0 *M* HCl, 80.0°, 10.0 hr) from 0.006 *M* hexose (glucose, G, fructose, F, or mannose, M) in 0.20 *M* NaOH at 25.0° as a function of time. The drawn curves were generated from the analog computer program for



the same temperature and alkaline concentration are given in Figure 7. The obtained rate constants are summarized in Table II.

The rate constants for the interconversions were all greater than that for the degradation of fructose in the cases studied in contrast to the one set of high alkaline conditions studied by MacLaurin and Green.[4]

The rate constants, k_3 and k_4 (Table II), obtained by analog computer fitting of the data are approximately equal for the higher concentrations at 35.0°, and at 40.0 and 50.0°. Although this is inconsistent with the assumption that the loss of mannose is fast compared to the production of other products (eq 4), the model of eq 4 is still valid if the major route of sugar degradation is *via* fructose. If mannose is assumed to degrade directly to other products, eq 4 may be rewritten



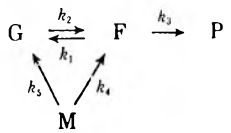
(9)

TABLE II

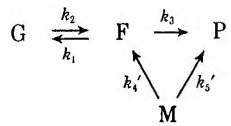
APPARENT FIRST-ORDER RATE CONSTANTS OBTAINED FROM THE ANALOG COMPUTER FITTING OF HYDROXYMETHYLFURFURAL ABSORBANCE (1.0 *M* HCl, 80.0°, 10 HR.) DERIVED FROM ANALYSES OF THE REACTION OF ALKALINE SOLUTIONS OF 0.006 *M* GLUCOSE, FRUCTOSE, AND MANNOSE WITH TIME[a]

			$10^4 k_i$ (sec^{-1})						
°C	[NaOH]	pH[b]	k_1	k_2	k_3	k_4	k_5	k_4'[c]	k_5'[c]
25.0	0.20	13.16	0.194	0.186	0.0528	0.0472			
35.0	0.001	10.68	0.0169	0.0206		0.00472			
35.0	0.002	10.99	0.0478	0.0466	0.00175	0.0189			
35.0	0.004	11.24	0.0658	0.0808	0.00908	0.0329			
35.0	0.007	11.48	0.0933	0.138	0.0132	0.0591			
35.0	0.01	11.66	0.176	0.198	0.0107	0.0763	0.0151		
35.0	0.02	11.95	0.174	0.308	0.0261	0.119			
35.0	0.10	12.56	0.479	0.588	0.102	0.193	0.0283		
35.0	0.20	12.86	0.542	0.692	0.186	0.189	0.0794	0.247	0.00847
35.0	0.40	13.13	0.711	0.658	0.303	0.200	0.108	0.272	0.00333
35.0	0.60	13.30	0.844	0.669	0.436	0.167	0.0444	0.206	0.0272
40.0	0.20	12.70	1.278	1.517	0.303	0.472	0.0583	0.532	0.0150
50.0	0.20	12.42	4.222	4.389	1.489	2.083	0.542	2.272	0.0316

[a] Fitted in accordance with the model



[b] The pH was calculated from $pH = pK_w + \log [a_{OH^-}]$. [c] Alternate fittings in accordance with the model



This did not change significantly the fit of the mannose data and may be considered as a kinetically equivalent model. A typical curve is given in Figure 8 and the data is presented in Table II.

The validity of eq 4 was reinforced by following the HMF production from a mixture of glucose and fructose in the proportions anticipated at equilibrium in a given concentration of alkali at a given temperature; *i.e.*, [F]:[G] = $k_2:k_1$ (Table I). It was anticipated that a typical first-order plot should be obtained for the production of HMF as a function of time in alkali. In this case, eq 4 has reduced to

$$G \underset{k_1}{\overset{k_2}{\rightleftharpoons}} F \xrightarrow{k_3} P \qquad (10)$$

The total hexose concentration of the equilibrium mixture would be

$$[H] = [G] + [F] \qquad (11)$$

At equilibrium

$$k_1[F] = k_2[G] \qquad (12)$$

The differential equation for the disappearance of the total hexose is

$$-d[H]/dt = k_3[F] \qquad (13)$$

Equations 11 and 12 may be substituted into eq 13 and

$$-d\{[F] + (k_1/k_2)[F]\}/dt = k_3[F] \qquad (14)$$

On rearrangement of eq 14

$$-d[F]/dt = [k_3/(1 + k_1/k_2)][F] = k_{app}[F] \qquad (15)$$

On integration

$$\ln [F] = \ln [F_0] - [k_3/(1 + k_1/k_2)]t = \ln [F_0] - k_{app}t \qquad (16)$$

Since the derived HMF absorbance is proportional to the fructose (F) present, the plot of ln [HMF absorbance] *vs.* time for the reaction of this equilibrium mixture should give a straight line with a slope equal to $[k_3/(1 + k_1/k_2)]$ (eq 16). A good correlation (Table I) between the slopes using the k_i values obtained from the analog computer data of Table II for the specific equilibrium conditions tested supports the validity of eq 10.

The apparent first-order rate constants (Table II) in the Lobry de Bruyn–Alberda van Ekenstein transformation were functions of hydroxide ion activity, a_{OH^-}. In all cases but that of k_3, the slopes of such plots decreased with increasing a_{OH^-}. The hydroxide ion activity was calculated from

$$a_{OH^-} = \gamma[NaOH] \qquad (17)$$

where the NaOH values were experimental and the activity coefficients, γ, were obtained from the literature[10] and interpolated from the constructed curve of γ *vs.* [NaOH] for 35.0°.

The dependence of the apparent first-order rate constant (k_i) on the hydrogen ion activity may be given by

$$k_i = (k_{OH^-})(a_{OH^-})(f) \qquad (18)$$

(10) H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," 3rd ed, Reinhold, New York, N. Y., 1958, p 729.

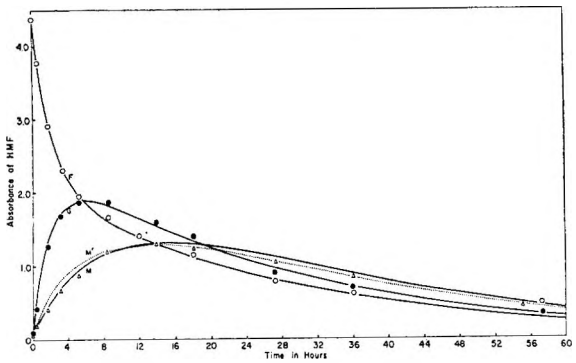
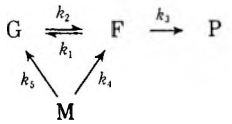
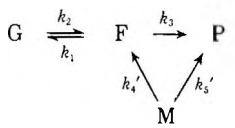


Figure 8.—Absorbance of HMF derived (1.0 *M* HCl, 80.0°, 10.0 hr) from 0.006 *M* hexose (glucose, G, fructose, F, mannose, M) in 0.20 *M* NaOH at 35.0° as a function of time. The solid lines were generated from the analog computer program



and the dotted line was generated from a similar program



where k_{OH^-} is the bimolecular rate constant and f is the fraction of the hexose in the undissociated form. The logarithm of eq 18 is

$$\log k_i = \log k_{OH^-} + \log a_{OH^-} + \log f \quad (19)$$

Since

$$\log a_{OH^-} = -pOH \quad (20)$$

and

$$-pOH = pH - pK_w \quad (21)$$

eq 19 becomes

$$\log k_i = \log k_{OH^-} + pH - pK_w + \log f \quad (22)$$

When only the uncharged species is present in a pH range, the plot of log k_i *vs.* pH should be a straight line with a slope of unity within that range. This is the case with k_3 for the entire pH range studied (Figure 9).

However, the slope is unity for k_1, k_2, and k_4 (Figure 9) only during the lower pH regions and the curves bend over in the higher pH regions. This is indicative of hydroxyl ion attack on two different species and eq 18 must be modified to

$$k_i = (k_{OH^-})(a_{OH^-})(f_U) + (k_{OH^-})(a_{OH^-})(f_D) \quad (23)$$

where f_U is the fraction undissociated and f_D is the fraction dissociated. The hydroxyl ion attack on the undissociated species is kinetically equivalent to water attack on the anion.[11] The possibility of a further hydroxyl ion attack on the dissociated species might be seen from the deviation from a subsequent plateau at the higher pH values of curve k_1 in Figure 9. The k_{OH^-}' can be roughly estimated from these two points as 2.29×10^{-4} l./mol sec (Table III, footnote c).

(11) E. R. Garrett, *J. Amer. Chem. Soc.*, **79**, 3401 (1957).

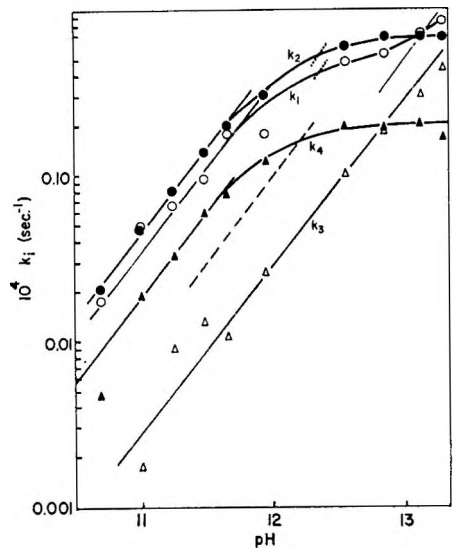


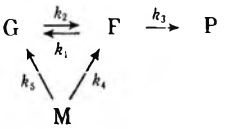
Figure 9.—Semilogarithmic plots of the apparent rate constants, k_i, at 35.0° obtained from the analog computer program for the aldose–ketose transformation against pH. The dashed line, drawn parallel to and at half the nonlogarithmic values of the ordinates of the log k −pH line of unit slope, intersects the log k − pH profile at the pK_a for that hexose.

TABLE III

THERMODYNAMIC AND KINETIC CONSTANTS FOR THE APPARENT FIRST-ORDER RATE CONSTANTS FITTED BY THE ANALOG COMPUTER PROGRAM[a]

k_i	ΔH_a[b]	log P[b]	$10^4 k_{OH^-}$[c]	ΔS^*[d]
k_1	24.1	14.9	16.1	4.75
k_2	24.2	15.0	20.7	5.67
k_3	25.4	15.3	1.34	4.15
k_4	28.6	17.6	8.44	18.1

[a] Based on the model



The individual values of the k_i are given in Table I. [b] Calculated from the slope and intercept of Arrhenius plots in accordance with log k_i = log P − $(\Delta H_a/2.303R)(1/T)$ where ΔH_a is in kcal/mol. [c] Calculated from the intercepts of log k_i *vs.* pH at 35.0° from the pH range where the plots are of unit slope (Figure 9) and conform to the expression log k_i = log k_{OH^-} − pK_w + pH where k_{OH^-} is in l./mol sec. A k_{OH^-} can be estimated for hydroxide ion attack on the ionized sugar for the k_1 case on the premise that $k_1 = k_{OH^-}a_{OH^-}f_U + k'_{OH^-}a_{OH^-} - f_D$ where f_U and f_D are the undissociated and dissociated fractions, respectively. This can be estimated from the approach to unit slope at the higher pH values for the log k_1 *vs.* pH plot (Figure 9) and k_{OH}' is 2.29×10^{-4} l./mol sec. [d] Calculated from $\Delta S^* = 2.3R$ [log k_{OH^-} − log (kT/h) + $(\Delta H_a - RT)(2.3\,RT)$], with units of eu.

However, in light of the data at 1.0 *N* NaOH on this system by MacLaurin and Green,[4] the likelihood of OH^- attack on the ionized species is small and the deviation may be assigned to a slight aberration in the data. Thus it is most probable that $k_{OH}' \sim 0$ and eq 18, 19, and 22 are valid.

In the region where the slope of the curve from the log k *vs.* pH plot approaches unity, the hexose exists mainly as the uncharged species and $f_U = 1$. Thus the log k_{OH^-} values (Table III) can be calculated from corresponding pH and log k_i values on the straight line of

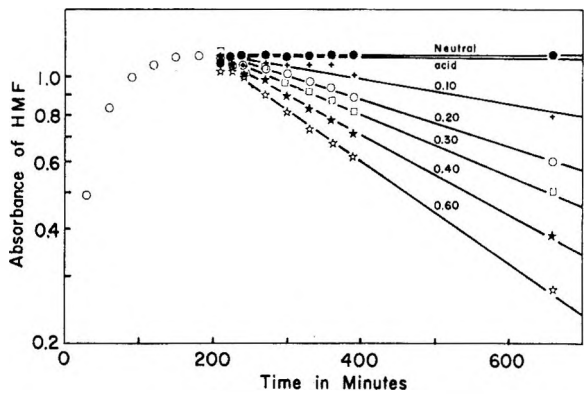


Figure 10.—Semilogarithmic plots of the absorbance of HMF derived (1.0 *M* HCl, 80.0°, 10.0 hr) from a 0.004 *M* glucose solution in 0.20 *M* NaOH at 40.0° in which the alkaline concentration was varied after 3.5 hr against time. The curves are labeled as to [NaOH].

unit slope (eq 22). The pK_w values at 35.0° were obtained from the literature.[10] A line may be drawn parallel to, and at half the nonlogarithmic values of the ordinates of the log k − pH line of unit slope. The intersection of this line and the log k − pH profile occurs at the apparent pK_a for that hexose. An example (dashed line) is presented in Figure 9 for k_4.

At a specific pH, the hydroxyl ion activity and the fractional amount of the hexose as an ionic species are fixed and the k_i for the pH can be calculated from eq 22. These calculated k_i values will coincide with the data when the pK_a has been properly designated. The curves (Figure 9) that are drawn are calculated from eq 22 and their agreement with the experimental values is apparent.

The determined kinetic pK_a values at 35.0° are consistent with the values of Izatt and coworkers[12] (Table IV).

TABLE IV
CALCULATED AND LITERATURE pK_a VALUES FOR THE TESTED HEXOSES

Hexose	Calcd pK_a	Lit. pK_a[a]
Glucose	12.36	12.46
Mannose	12.23	12.08
Fructose	12.44	12.27

[a] Reference 12.

The dependencies of rate constants on the absolute temperature were determined from the appropriate plot of data obtained at four temperatures (Table II) for 0.006 *M* hexose in 0.20 *M* NaOH in accordance with the Arrhenius' equation

$$\log k_i = -(\Delta H_a/2.303R)(1/T) + \log P \quad (24)$$

where the apparent first-order rate constants, k_i, are in sec^{-1}. The Arrhenius energy of activation, ΔH_a (Table III), was calculated from the slopes of these curves. From the absolute rate equation[13]

$$k_{OH^-} = (kT/h)e^{(\Delta S^*/R)}e^{-(\Delta H_a - RT)/RT} \quad (25)$$

or

$$\Delta S^* = 2.303R[\log k_{OH^-} - \log (kT/h) + (\Delta H_a - RT)/(2.303RT)] \quad (26)$$

(12) R. M. Izatt, J. H. Rytting, L. D. Hansen, and J. J. Christensen, *J. Amer. Chem. Soc.*, **88**, 2641 (1966).

(13) W. J. Moore, "Physical Chemistry," 3rd ed, Prentice-Hall, Englewood Cliffs, N. J., 1963, p 297.

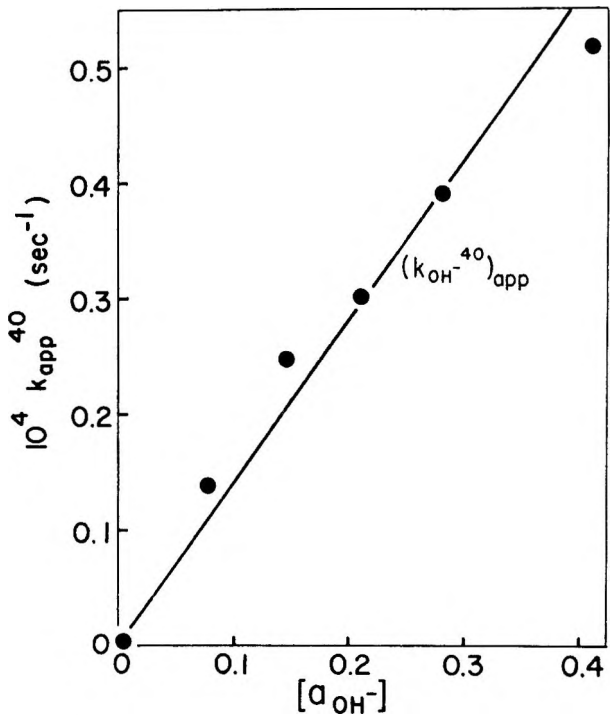


Figure 11.—Plot of the apparent rate constants, $k_{app}{}^{40}$, for the loss of HMF derived from fructose equilibrated with glucose in 0.20 *M* NaOH at 40.0° against the hydroxyl ion activity, a_{OH^-}.

the entropy of activation, ΔS^*, was obtained (Table III) where k = Boltzmann constant, h = Planck constant, R = gas constant in cal/mol °K, and T = temperature in °K.

The small positive entropy values for k_1, k_2, and k_3 indicate that the transition states have degrees of randomness similar to the original hexose. However, the high positive entropy value for k_4 is indicative of a less ordered transition state.[14]

The maximum conversion to fructose at 40.0° in 0.20 *M* NaOH occurs when glucose is allowed to react for 3.5 hr. The alkalinity of this reacting solution was varied at this time. In addition, the production of acid-derived HMF (1.0 *M* HCl, 80.0°, 10.0 hr) was followed with time for the reaction at 40.0° of one aliquot neutralized and one aliquot acidified to 0.20 *M* HCl. The first-order plots of these HMF absorbances after 3.5 hr were linear (Figure 10) and the apparent first-order rate constants, $k_{app}{}^{40}$, were a linear function of the alkaline concentration (Figure 11). The apparent bimolecular rate constant, $(k_{OH^-}{}^{40})_{app}$, was obtained from the slope of the curve in Figure 11 and was 1.40×10^{-4} l./mol sec at 40.0°.

Since the yield of HMF was invariant with time in the neutral and acid solutions (Figure 10), the established equilibrium among the hexoses must be stabilized under these nonalkaline conditions The $(k_{OH^-}{}^{40})_{app}$ value was converted to 35.0°, $(k_{OH^-}{}^{35})_{app} = 0.744 \times 10^{-4}$ l./mol sec, by a variation of eq 24; *i.e.*,

$$\log (k_{OH^-}{}^{35})_{app} = \log (k_{OH^-}{}^{40})_{app} - (\Delta H_a/2.303R)(1/T^{35} - 1/T^{40}) \quad (27)$$

where the superscripts refer to the temperatures involved and the ΔH_a (Table III) is 25.4 kcal/mol. This

(14) A. N. Martin, "Physical Pharmacy," Lea and Febiger, Philadelphia, Pa., 1964, pp 652–655.

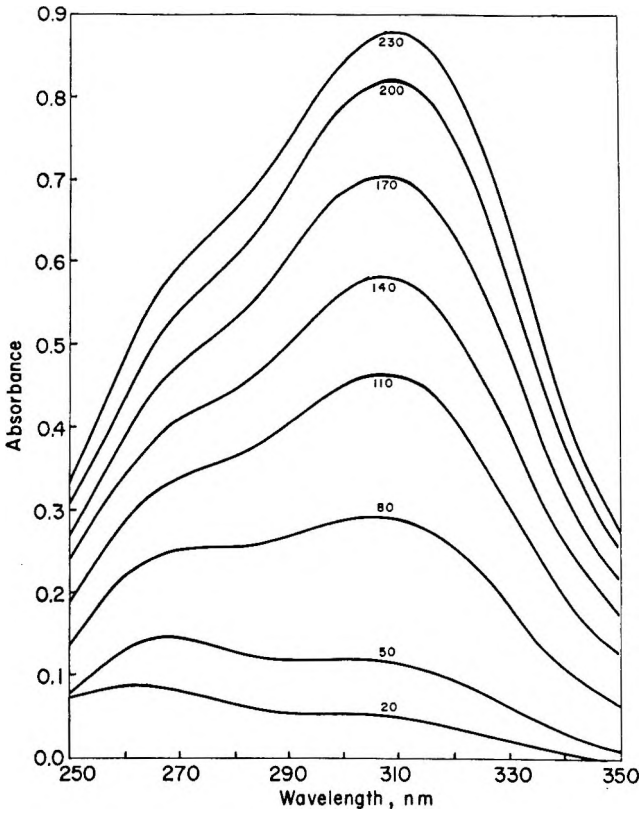


Figure 12.—Absorbance spectra of 0.008 *M* glucose in 0.20 *M* NaOH at 40.0°. The curves are labeled in minutes from time of mixing of the NaOH and glucose.

value compared favorably to the $(k_{OH^-}{}^{35})_{app}$ of 0.754 × 10^{-4} l./mol sec calculated from eq 15

$$(k_{OH^-}{}^{35})_{app} = k_{OH_3^-}/(1 + k_{OH_1^-}/k_{OH_2^-}) \quad (28)$$

where the $k_{OH_i^-}$ values were obtained from Figure 9 and listed in Table III.

Alkaline Chromophores—Two ultraviolet absorbance maxima (λ_{max} at 270 and 310 nm) appeared when the hexoses (glucose or fructose) were treated in alkaline solution. The relative absorbances of these two chromophores appeared to be concentration dependent in the early stages of the reaction. In 0.20 *M* NaOH at 40.0° the absorbance of the 270-nm chromophore was predominant in a 0.002 *M* glucose solution. The absorbances of the two chromophores were about equal in a 0.004 *M* glucose solution, and the absorbance of the 310-nm chromophore was predominant in a 0.008 *M* glucose solution (Figure 12). However, with time the 270-nm chromophore became predominant in all three cases as the 310-nm chromophore disappeared.

An explanation for the hexose concentration effect on the chromophoric response was that the 310-nm chromophoric species was being formed by a first-order process from the hexose and subsequently was converted by a zero-order process to the 270-nm chromophoric species. This may be represented by

$$G \xrightarrow{k_1} A_{310} \xrightarrow{k_0} A_{270} \quad (29)$$

where A_{310} and A_{270} represent the species that have their λ_{max} at 310 and 270 nm, respectively.

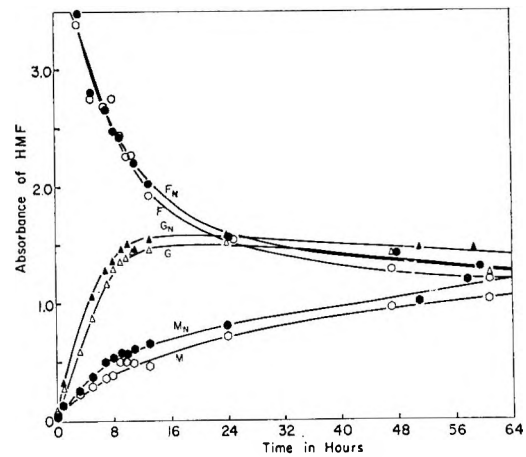


Figure 13.—Comparisons of the derived HMF absorbance between nitrogen purged (H_N) and nonpurged (H) solutions of 0.006 *M* hexose (glucose, G, fructose, F, or mannose, M) in 0.20 *M* NaOH at 25.0° as a function of time.

The pH of the hexose solution also affected the magnitude of the absorbance of the chromophores. The absorbance spectra when monitored at several pH values after a 0.004 *M* glucose solution was reacted in 0.20 *M* NaOH at 40.0° for 3.5 hr showed a decrease in absorbance of the 270-nm chromophore with lower pH.

The atmospheric conditions under which the alkaline hexose solutions were reacted drastically affected the pattern of chromophoric response. For a 0.004 *M* fructose solution in 0.20 *M* NaOH at 40.0°, the absorbance of the two chromophores was about equal under normal atmospheric conditions. However, under nitrogen atmosphere or when the fructose solution has been purged with nitrogen as well as reacted under nitrogen atmosphere, the absorbance of the 310-nm chromophore was predominant to such an extent that the absorbance contributed by the 270-nm chromophore was negligible. In contrast, when the fructose solution was purged with oxygen and reacted under oxygen atmosphere, the absorbance of the 270-nm chromophore was predominant and the absorbance contribution of the 310-nm chromophore was negligible.

An explanation for the atmospheric influence on the chromophoric response could be that the conversion of the 310-nm to the 270-nm chromophoric species was an oxidative step. This can be represented by

$$G \longrightarrow A_{310} \xrightarrow{[O]} A_{270} \quad (30)$$

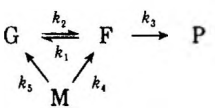
Tremendous differences were noticed in the absorbance of the alkaline chromophores with the atmosphere (nitrogen purged or unpurged) of the solution. However, the amount of fructose produced from glucose or mannose or remaining from fructose was seemingly unaffected by a difference in nitrogen or air atmosphere (Figure 13 for 25.0°) when the fructose was monitored by the acid derived absorbance of HMF. This would indicate that the alkaline chromophores were not representative of an intermediate in the aldose–ketose transformation but were the result of a degradative reaction of the hexose.

The time of maximum achievement of the 310-nm chromophore was about 6 hr, whereas, under the same conditions (0.20 *M* NaOH, 40.0°), the production of

fructose from glucose was 3.5 hr as monitored by the formation of HMF (1.0 *M* HCl, 80.0°, 10.0 hr) from the fructose produced.

Conclusions

The progress of this aldose–ketose transformation can be followed by monitoring the amount of fructose (1.0 *M* HCl, 80.0°, 10.0 hr) in solution with time as a function of temperature and alkaline concentration. The solutions initially contained either glucose, fructose, or mannose and the yield of fructose can be monitored from each. From the three curves generated, the analog computer can be utilized to simultaneously analyze the data according to the model



(4)

This model assumes that any intermediate in the aldose–ketose transformation is short lived and immediately forms one of the hexoses. Another assumption is that the glucose–fructose equilibrium is fast compared to the degradation to other products. A third assumption is that negligible amounts of mannose are formed from either glucose or fructose. From the rate constants obtained from the analog computer plots, the thermodynamic and kinetic parameters can be defined.

If these curves from glucose, fructose, and mannose are generated under oxygen free conditions, very little or no differences in the amount of fructose present with time is observed. This would indicate that the aldose–ketose transformation is not dependent on oxidation.

The alkaline hexose solution gives rise to two ultraviolet chromophore maxima, one at 270 nm and the other at 310 nm. The relative magnitudes of these two chromophores are affected by the concentration of hexose, concentration of alkali, and absence or presence of oxygen. The 270-nm chromophore is predominant in the lower hexose concentration range (0.002 *M* hexose) and the 310-nm chromophore is predominant in the higher range (0.008 *M* hexose). Under nitrogen atmosphere (oxygen free), the 270-mn chromophore is nonexistent while the 310-nm chromophore is greatly exaggerated. Under oxygen atmosphere, the 270-nm chromophore is predominant with the 310-nm chromophore appearing only briefly and to a limited extent. In normal atmosphere (air), there appears to be an isosbestic point around 284 nm which indicates a one to one transfer between the absorbing species. Under normal conditions the 310-nm chromophore begins to recede after about 6 hr and the 270 nm begins to dominate. Compilation of the existing data suggests the following model

$$\text{hexose} \longrightarrow A_{310} \xrightarrow{[O]} A_{270} \longrightarrow X$$

where A_{310} and A_{270} represent the species that have their λ_{max} at 310 and 270 nm, respectively.

The alkaline chromophores may not be involved in the Lobry de Bruyn–Alberda van Ekenstein transformation. Several factors may support this view. First, the time of maximum production of fructose from glucose is 3.5 hr in 0.20 *M* NaOH at 40.0°, whereas the maximum absorbance of the 310-nm chromophore is not achieved until about 6 hr under the same conditions. Secondly, nitrogen purging has little effect on the production of fructose from glucose, whereas the alkaline chromophores are drastically affected by the absence or presence of oxygen.

Registry No.—Glucose, 50-99-7; fructose, 57-48-7; mannose, 3458-28-4.

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A New Synthesis of the Antibiotic Phosphonomycin

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A new, total synthesis of the antibiotic phosphonomycin is described. Thermal rearrangement of di-*t*-butyl 2-propynyl phosphite yields the di-*t*-butyl propadienylphosphonate ester. A selective hydrogenation, followed by acid-catalyzed cleavage of the *t*-butyl groups, affords *cis*-propenylphosphonic acid in high yield. This olefin acid is epoxidized and the product is resolved in essentially one step to furnish phosphonomycin.

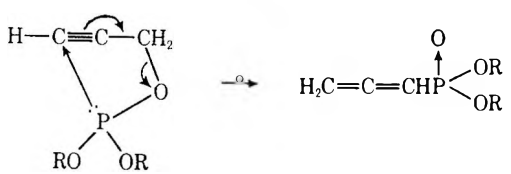
Phosphonomycin is a promising new antibiotic of unusual structure originally isolated from fermentation broths of *Streptomyces fradiae*. It has been found to be orally effective against both Gram-positive and Gram-negative infections in mice. Its bactericidal mode of action is *via* irreversible binding to the enzyme pyruvate–uridine diphospho-N-acetylglucosamine, thereby inhibiting cell wall synthesis.[1]

Phosphonomycin has been shown to be (−)-(1*R*,2*S*)-1,2-epoxypropylphosphonic acid. Proof of structure was obtained by synthesis together with a chemical determination of the absolute configuration.[2]

We wish to describe a different total synthesis of phosphonomycin which is simple and elegant, and which affords the antibiotic in much higher yield. Our approach is based on a five-step *in situ* preparation of *cis*-propenylphosphonic acid followed by a one-step epoxidation and resolution. The overall sequence leading to (−)-*cis*-1,2-epoxypropylphosphonic acid as its mono-(+)-α-phenethylammonium salt is shown in Scheme I.

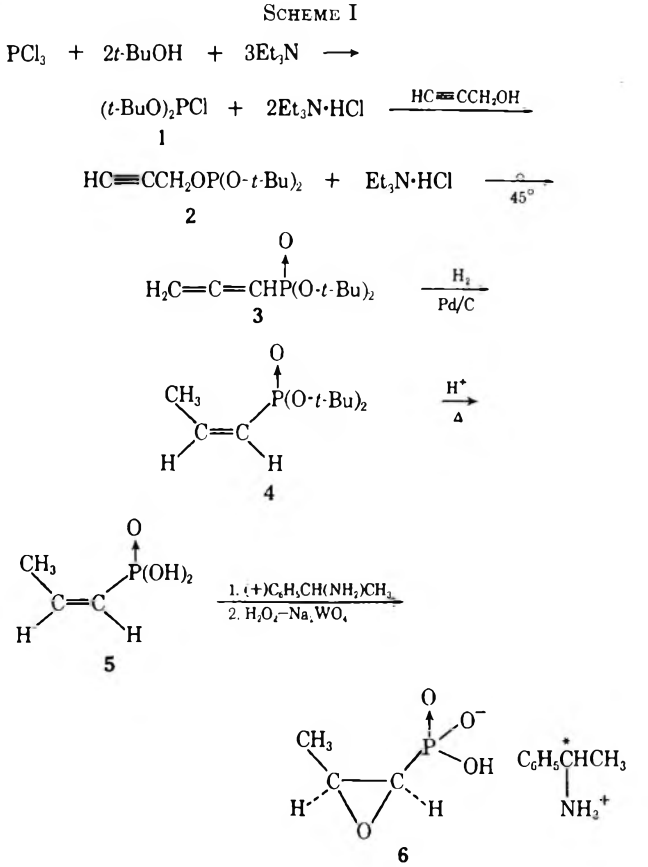
Di-*t*-butyl phosphorochloridite (**1**) was prepared by adding 2 equiv of *t*-butyl alcohol to a benzene solution of phosphorus trichloride containing triethylamine as hydrogen chloride acceptor. Propargyl alcohol was then added at 5–10° to form di-*t*-butyl 2-propynyl phosphite (**2**). Immediately after the addition was completed, the reaction mixture was analyzed by infrared spectroscopy. Absorption bands at 3.00 and 4.65 μ characterized the mixed phosphite **2**. In addition, a doublet at 5.08, 5.14 μ indicated its partial rearrangement to the allene **3**.

The thermal rearrangement of 2-alkynyl phosphites to 1,2-alkadienyl phosphonates has been the subject of intensive study in recent years.[3] The reaction has been shown to be of first order and follows an intramolecular pathway of the SNi′ type.



We have found that when R = *t*-butyl, the nucleophilicity of the trivalent phosphorus atom is so enhanced that even at 0° rearrangement slowly takes place. The acetylene → allene rearrangement was completed *in situ* by heating the reaction mixture at 45° for 2 hr to afford di-*t*-butyl propadienylphosphonate (**3**). Longer heating periods, even at reflux temperature (80–82°), did not cause the prototropic further rearrangement of **3** to the α,β-propynyl phosphonate ester.[3]

SCHEME I



The heavy precipitate of triethylamine hydrochloride salt was removed at this stage by extraction into water. The benzene phase containing allene **3** was dried and then hydrogenated at 15 psi with Pd–C catalyst. The reduction in benzene solution was extremely selective and stereospecific, with hydrogen attacking only the terminal double bond of the allene moiety to give the *cis* olefin.[4] This selectivity was confirmed by a reduction with D_2 which showed that more than 96% of the deuterium had entered the β,γ positions. In addition, the hydrogenation conveniently stopped when 1 equiv of hydrogen was taken up to give di-*t*-butyl *cis*-pro-

(1) D. Hendlin, E. O. Stapley, M. Jackson, H. Wallick, A. K. Miller, F. J. Wolf, T. W. Miller, L. Chaiet, F. M. Kahan, E. L. Foltz, H. B. Woodruff, J. M. Mata, S. Hernandez, and S. Mochales, *Science*, **166**, 122 (1969).

(2) B. G. Christensen, W. J. Leanza, T. R. Beattie, A. A. Patchett, B. H. Arison, R. E. Ormond, F. H. Kuehl, Jr., G. Albers-Schonberg, and O. Jardetzky, *ibid.*, **166**, 123 (1969).

(3) See V. Mark in "Mechanisms of Molecular Migrations," Vol. II, B. S. Thyagarajan, Ed., Interscience, New York, N. Y., 1969, p 319, for leading references.

(4) After completion of our work, the selective hydrogenation of 1,2-diene phosphonic esters in alcohol solution with 5% Pd–$CaCO_3$ was reported by A. A. Petrov, B. I. Ionin, and V. M. Ignatyev, *Tetrahedron Lett.*, 15 (1968).

penylphosphonate (4). Continuation of the reduction for several hours longer resulted in no further absorption of hydrogen. The rapid removal of the two *t*-butyl groups was accomplished by refluxing the benzene solution containing 4 with a strong acid catalyst. A particularly elegant procedure is to use *cis*-propenylphosphonic acid as catalyst to avoid contaminating the product with a foreign acid. Removal of solvent leaves *cis*-propenylphosphonic acid (5) in 81% overall yield. This was the first intermediate isolated after five *in situ* chemical reactions.

We have found that *t*-butyl is an especially advantageous blocking group and deserves to be more widely used in organophosphorus chemistry. We estimate the combined yield of di-*t*-butyl phosphorochloridite (1) and mixed phosphite (2) to be extremely high, in the range of 90–95%. Furthermore, acid catalyzed cleavage of both *t*-butyl groups in phosphonate ester 4 is a very clean and rapid reaction, requiring moderate temperatures and with the blocking groups leaving the reaction medium as gaseous isobutylene. The deblocking process can also be carried out thermally, after a short induction period, by heating the neat di-*t*-butyl phosphonate ester to 100°, and maintaining that temperature during the strongly endothermic process. In either case, the rate of gas evolution accelerates as the reaction proceeds because the product being formed is itself a strong acid which can serve as catalyst.

When ethyl and isopropyl were used as blocking groups in this synthesis, the yield and purity of *cis*-propenylphosphonic acid was decidedly lower. This was due in part to a poorer yield at the mixed phosphite (of type 2) stage, as well as partial attack at the olefinic and C–P bonds of ester 4 by the hot aqueous hydrochloric acid required to cleave these alkyl groups.

Conversion of *cis*-propenylphosphonic acid (5) to phosphonomycin was accomplished in essentially one step, as follows. Slightly more than 1 equiv of a mixture of resolving base, (+)-α-phenethylamine, and triethylamine was added to a propanol solution of *cis*-propenylphosphonic acid to attain the desired pH range for epoxidation. The warm solution was then treated with hydrogen peroxide, with sodium tungstate as catalyst.[2,5] After 1 hr at 50–55°, the epoxidation was complete. Cooling the reaction mixture produced a crystalline precipitate of (+)-α-phenethylammonium (−)-*cis*-1,2-epoxypropylphosphonate (6) which was found to be 92% optically pure. The undesired triethylammonium salt of the (+) isomer remained in solution. A single recrystallization from aqueous propanol afforded phosphonomycin (salt) of 100% optical purity. The yield in this combined epoxidation and resolution step was 32.5%, or 65% based only on the (−) form.

Experimental Section[6]

Di-*t*-butyl Propadienylphosphonate (3).—A stirred solution of phosphorus trichloride (68.7 g, 0.50 mol) in anhydrous benzene (750 ml) was cooled to 5° under N_2, and then triethylamine (154.4 g, 1.525 mol) was added at 5–10° over a 20-min period. After stirring for 20 min more, a solution of *t*-butyl alcohol (74.1 g, 1.00 mol) in anhydrous benzene (74 ml) was added dropwise, with good agitation, while maintaining the reaction temperature between 5 and 10° with an ice–methanol bath. The thick reaction mixture containing di-*t*-butyl phosphorochloridite[7] (1) was stirred for 1.5 hr at 5–10°, and then a solution of propargyl alcohol (28.0 g, 0.50 mol) in benzene (40 ml) was added at 5–10° over a 30-min period. When the addition was complete, a filtered aliquot was analyzed by infrared spectroscopy: bands at 3.00 (HC≡) and 4.65 μ (HC≡C) characterized the product, di-*t*-butyl 2-propynyl phosphite (2), while a doublet at 5.08, 5.14 μ indicated its partial rearrangement to 3.

After stirring for 1 hr at 5–10°, the mixture was warmed to 40–45° and kept at that temperature for 2 hr to complete the rearrangement. The reaction mixture was then cooled to room temperature and water (185 ml) was added in portions. The triethylamine hydrochloride precipitate dissolved, and the aqueous layer was separated and reextracted with benzene (50 ml). The combined benzene layers were dried over sodium sulfate (60 g) to afford a solution of di-*t*-butyl propadienylphosphonate (3) which was used directly in the next step. An analytical sample was obtained by distillation: bp 54–56° (0.1 mm); ir (neat) 5.08, 5.14 (C=C=C), 7.90 (P→O), 9.62 (P–O–C), and 12.10 μ (=CH_2).

Anal. Calcd for $C_{11}H_{21}O_3P$: C, 57.31; H, 9.11; P, 13.33. Found: C, 57.06; H, 9.32; P, 12.97.

Di-*t*-butyl *cis*-Propenylphosphonate (4).—The dried benzene solution containing 3 was treated with 5.0 g of 5% Pd–C and reduced at 16–18° in a jacketed steel vessel equipped with "Magnadrive" stirrer (1500 rpm) at a constant 15 psi of H_2. The theoretical amount of H_2 was taken up in 1–1.5 hr. The catalyst was removed by filtration and the filtrate (1.15 l.) containing 4 was used directly for the deblocking step. The infrared showed a strong band at 6.14 μ characteristic of the *cis* olefin, while absence of the allene doublet at 5.0–5.2 μ indicated the completeness of the reduction. An analytical sample was obtained by distillation: bp 45–46° (0.1 mm); ir (neat) 6.14 (*cis* C=C), 7.98 (P→O), and 9.62 μ (P–O–C).

Anal. Calcd for $C_{11}H_{23}O_3P$: C, 56.38; H, 9.89; P, 13.22. Found: C, 56.54; H, 10.09; P, 13.18.

***cis*-Propenylphosphonic Acid (5). A.**—A 500-ml flask, equipped with motor stirrer, thermometer, addition funnel, and a short distilling head with horizontal condenser connected to a receiver with a gas outlet tube, was charged with *cis*-propenylphosphonic acid (5 g) as catalyst and a 50-ml aliquot of the benzene solution containing 4. The two-phase mixture was heated to reflux whereupon cleavage of the *t*-butyl groups began, liberating more of acid 5 and isobutylene gas which exited from the system. The remaining portion (1.1 l.) of the benzene solution of 4 was then added over 100 min, with simultaneous distillation of benzene to maintain the reaction mixture between 50 and 150 ml by balancing the addition and distillation rates. When the addition was complete, the remaining benzene was removed *in vacuo* to afford crude 5 of sufficient purity to be used in the next step. This brown oil (which sometimes crystallized) weighed 56.9 g net, having C=C content of 87% by Br_2 titration. The overall yield, therefore, from propargyl alcohol to 5 was 81%. A pure sample (hygroscopic) was prepared by recrystallization of the monobenzylammonium salt, mp 155–157°, followed by ion exchange on Amberlite IR-120 resin: mp 55–57°.

Anal. Calcd for $C_3H_7O_3P$: C, 29.52; H, 5.78; P, 25.38. Found: C, 29.48; H, 5.89; P, 25.54.

B.—Neat di-*t*-butyl ester 4 was treated with a catalytic amount of concentrated hydrochloric acid (1 ml acid/50 g ester), and heated on the steam bath in the hood until evolution of isobutylene ceased (30 min). Gas evolution was slow in the beginning, but became extremely vigorous toward the end. The weight yield of crude acid 5 was similar to that obtained by method A, but the purity was somewhat lower.

(+)-α-Phenethylammonium (−)-*cis*-1,2-Epoxypropylphosphonate (6).—*cis*-Propenylphosphonic acid having C=C purity of 83% (148 g, 1.00 mol "pure") was dissolved in propanol (800 ml). To the stirred solution was added (+)-α-phenethylamine[8] (80.5 g, 0.665 mol), followed by enough triethylamine (56 g,

(5) G. B. Payne and P. H. Williams, *J. Org. Chem.*, **24**, 54 (1959).

(6) Melting points were determined with a Thomas–Hoover Uni-Melt apparatus in unsealed capillary tubes and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 621 grating infrared spectrophotometer. We are grateful to Mr. R. N. Boos and associates for microanalyses, and Mr. J. Gilbert and colleagues for all other assays. Solvents were dried to less than 0.1 mg/ml of H_2O over molecular sieves. All reagents used had less than 1.5 mg/ml of H_2O as determined by Karl Fischer assay.

(7) V. Mark and J. R. Van Wazer, *J. Org. Chem.*, **29**, 1006 (1964).

(8) Practical grade of 95% optical purity from Norse Laboratories, Santa Barbara, Calif.

0.553 mol) to reach a pH of 5.8–5.9. The resulting warm solution was treated in one portion with sodium tungstate dihydrate (5.0 g, 0.015 mol) and disodium ethylenediaminetetraacetic acid (1.0 g) dissolved together in 15 ml of warm (65–70°) water. Hydrogen peroxide (1.53 mol, 157 ml of a 30% solution) was then added dropwise with stirring over a 15-min period while maintaining the temperature between 40 and 55°. After the addition was complete, the reaction was kept at 50–55° for 1 hr to complete the epoxidation. The solution was then cooled to −5° over a 30-min period to initiate crystallization. After stirring for 2 hr at −5°, the product was filtered and the cake washed with cold propanol (four 50-ml portions). This salt when dried weighed 106 g, and was about 92% optically pure. To complete the resolution, the salt was dissolved in 770 ml of hot (75–80°) propanol. The slightly turbid solution was charcoal treated (2.5 g) and filtered while hot through a preheated funnel. To the hot filtrate was added 80 ml of warm (60–70°) water. Crystallization of the monohydrate began within a few minutes. After stirring the mixture at 0° for 2 hr the product was filtered, washed with cold propanol (three 25-ml portions), and dried *in vacuo* at 45°. The yield of phosphonomycin salt **6** was 90.1 g (32.5%): mp 132–134° dec; $[\alpha]^{25}{}_{405}$ −2.6° (*c* 5, H_2O) or +18.7° (*c* 3, DMF); Karl Fischer 6.6% (theory 6.5%); equiv wt 278.7 (theory 277.3).

Anal. Calcd for $C_{11}H_{18}NO_4P \cdot H_2O$: C, 47.64; H, 7.27; N, 5.05; P, 11.17. Found: C, 47.66; H, 7.00; N, 5.29; P, 11.09.

Registry No.—**3**, 25383-48-6; **4**, 25383-05-5; **5**, 25383-06-6; **6**, 25383-07-7; phosphonomycin, 23155-02-4.

Alkaloids of *Sceletium* Species.[1] III.[2] The Structures of Four New Alkaloids from *S. strictum*

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The isolation and structures of four new alkaloids, mesembrenol (**5**, R = Me; R′ = H), *O*-acetylmesembrenol (**5**, R = Me; R′ = Ac), 4′-*O*-demethylmesembrenol (**5**, R = R′ = H), and 4′-*O*-demethylmesembranol (**4**, R = H) are reported. The position of the phenolic hydroxyl in 4′-*O*-demethylmesembranol is determined by the application of a radioisotope dilution method. A discussion of the circular dichroism and nuclear magnetic resonance spectra of (+)-mesembrenone (**2**) and the nmr spectra of related alcohols mesembrenol and 6-epimesembrenol (**7**) is presented in providing information on the conformational preference of ring C in which it is shown that the equivalent forms of the half-chair, as represented in structures **2a**, **5a**, and **7a**, is preferred.

Certain *Sceletium* species (*Fam. Aizoaceae*) are used for the preparation of the drug known as *Channa* or *Kougoed*. Previous studies on *S. namaquense*, *S. tortuosum*, and *S. anatomicum* have led to the isolation and characterization of the alkaloids mesembrine (**1**), mesembrenone (**2**), and mesembranol (**4**, R = Me).[4]

Structural Studies.—In the course of a study of the biosynthesis of these alkaloids we have examined the major alkaloids of *Sceletium strictum* L. Bol.[5] Preliminary examination of the total alkaloid fraction by gas liquid chromatography (glpc) on several columns (see Experimental Section) showed it to contain one major component and several minor constituents. The major component proved to be a new alkaloid, mesembrenol (**5**, R = Me; R′ = H), $C_{17}H_{23}NO_3$, mp 145°, $[\alpha]_D$ +90°, which could be isolated on occasions by crystallization of the total alkaloid fraction from acetone but was usually obtained only after chromatography over alumina. The infrared spectrum of mesembrenol shows absorption bands at 3630 and 3450 cm^{-1} characteristic of an alcoholic hydroxyl group and the presence of this group was substantiated by the formation of an O-acetyl derivative (**5**, R = Me; R′ = Ac). An N-methyl, two aromatic methoxyls, three aromatic hydrogens and two olefinic hydrogens signals are present in the nmr spectrum and a comparison with the spectra of mesembranol and mesembrine suggested it could be assigned as a member of the octahydroindole class of mesembrine-type alkaloids. This conclusion is supported by the mass spectrum which shows a molecular ion at *m/e* 289, and an intense peak at *m/e* 219. A detailed study of the mass spectra of the mesembrine alkaloids[6] has established that alkaloids of this ring system which possess a 3a-dimethoxyphenyl substituent all show a prominent peak at *m/e* 219 which is attributed to an ion of structure **6** (R = Me). The occurrence of the *m/e* 219 ion in the mass spectrum of mesembrenol implies that the double bond and hydroxyl group have to be situated in ring B and their placement as shown in structure **5** (R = Me, R′ = H) is provided by its oxidation to (±)-mesembrenone (**2**) with Jones reagent. The racemic nature of the product in this reaction is not exceptional and occurs as a consequence of the acidic conditions of the reaction which lead to the intervention of an equilibrium involving the protonated form of **2** and the symmetrical dienone **3**.

Elucidation of the remaining structural features of (+)-mesembrenol, namely, the stereochemistry of the C-6 hydroxyl and the absolute configuration was established by the hydrogenation of the new base to (−)-mesembranol (**4**, R = H; R′ = Me). The relative and absolute stereochemistry of the latter has been firmly established by a recent X-ray analysis of 6-epimesembranol methiodide.[2]

(1) Supported by the National Science Foundation Grant GB4361 and the National Institutes of Health through Grant AM13977-01 and a Research Career Program Award 1K04GM42342-01 to P. W. J.

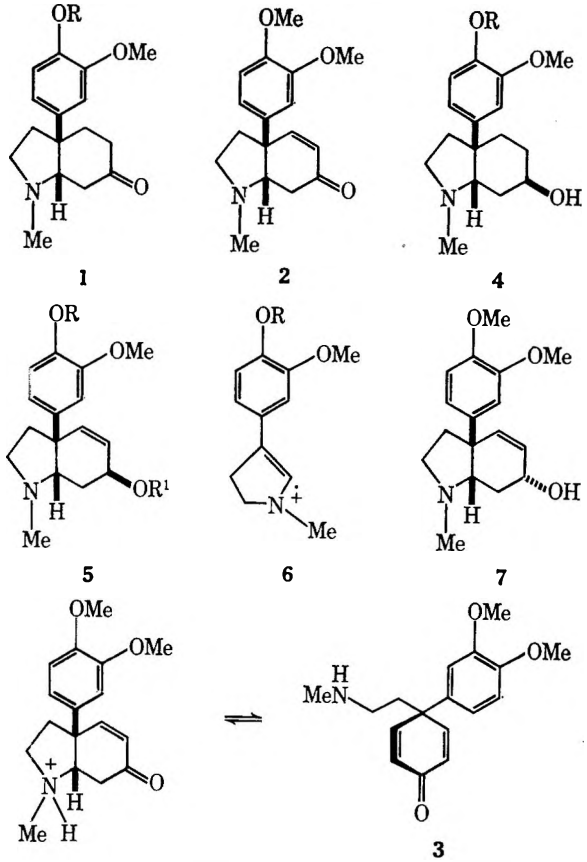
(2) See P. Coggon, D. S. Farrier, P. W. Jeffs, and A. T. McPhail, *J. Chem. Soc. A*, in press, for paper II in this series.

(3) (a) National Science Foundation Undergraduate Research Participant, 1967; (b) National DefenseE ducation Act Fellow, 1966–1969, Du Pont Fellow, 1969–1970; (c) National Aeronautics and Space Administration Act Fellow, 1965–1968.

(4) For a review, see A. Popelak and G. Lettenbauer, "The Alkaloids," Vol. IX, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1968, p 467.

(5) Identified by Dr. L. Bolus, Bolus Herbarium, University of Cape Town, South Africa, through the courtesy of Mr. Herre, Stellenbosch, South Africa.

(6) P. W. Jeffs and N. Martin, unpublished observations.



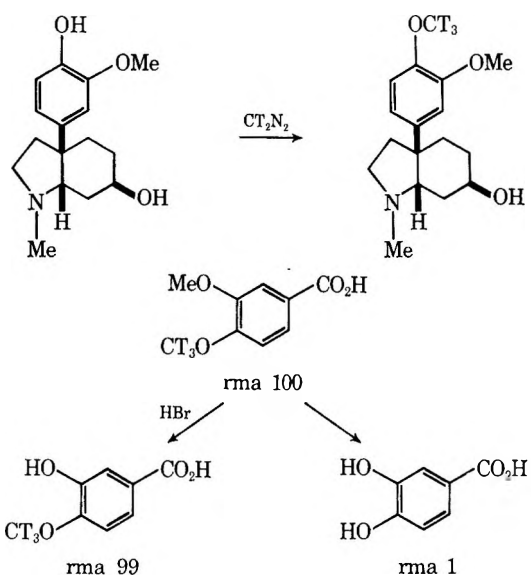
The presence of the known alkaloids mesembrenone, mesembrine, and mesembranol was indicated by glpc analysis and each alkaloid could be isolated by chromatography over alumina. In addition, O-acetylmesembrenol (**5**, R = Me; R′ = Ac) was obtained on occasions and in one instance proved to be the major alkaloid. The more polar fractions from the chromatographic separation gave a crystalline product, mp 200–203° which consisted of a mixture of two new bases (glpc). The phenolic nature of these two new alkaloids was evident by their solubility in sodium hydroxide solution and this was used to advantage in separating them from nonphenolic bases. Attempts to separate the phenolic alkaloids by column chromatography were unsuccessful, however, fractional crystallization of the mixture from methanol gave a pure compound, mp 219.5–220°. The mass spectrum of this compound has a parent ion at *m/e* 275 corresponding to the molecular formula $C_{16}H_4NO_3$ and an intense peak at *m/e* 205. The latter is 14 mass units less than ion **6** (R = Me) found in the mass spectra of mesembrine-type alkaloids possessing a dimethoxyphenyl ring; this fact, in conjunction with its phenolic character suggested that this alkaloid is an O-demethylmesembrenol. This was substantiated by the methylation of the phenolic base to (+)-mesembrenol on treatment with diazomethane and its structure and stereochemistry is therefore defined with the exception of the location of the phenolic hydroxyl group.

Catalytic hydrogenation of the phenolic alkaloid mixture affords a single compound, mp 201°, which is homogeneous by glpc and corresponds to the second component in the original mixture. Alternatively, preparative layer chromatography of mother liquor fractions of the phenolic alkaloid fraction which were enriched in this second component led to its isolation in pure form. The mass spectrum of this compound shows a parent ion at *m/e* 277 corresponding to $C_{16}H_{23}NO_3$ and it is converted to (−)-mesembranol with diazomethane. These results establish that the two phenolic alkaloids are an O-demethylmesembranol and an O-demethylmesembrenol in which the phenolic hydroxyl is located at the same site in both compounds.

In principle, a distinction between the two possible structures 4′-O-demethylmesembranol (**4**, R = H) and 3′-O-demethylmesembranol for the phenolic alkaloid, mp 201°, may be made on the basis of either of two criteria: (1) the number of deuteria introduced into the aromatic ring under conditions of base or acid catalyzed exchange, or (2) ethylation of the phenolic hydroxyl followed by drastic oxidation of the product to a substituted benzoic acid. Attempts to effect deuterium exchange under basic conditions gave equivocal results and the small amount of material available precluded the use of ethylation and oxidative degradation because of the low yield expected in this reaction. To circumvent these difficulties, application of a radio-dilution method was used to locate the site of the phenolic hydroxyl group.

A few milligrams of the phenolic alkaloid, which had been previously equilibrated with tritium oxide, was treated with diazomethane-T_2 and the product isolated by dilution with inactive mesembranol. Vigorous oxidation of the radioactive mesembranol afforded radio-labeled veratric acid which was isolated from the oxidation by adding inactive acid as a carrier. Treatment of the labeled veratric acid with hydrobromic acid under carefully controlled conditions gave isovanillic acid,[7] which in turn was converted to protocatechuic acid. No loss of label occurred in the conversion of veratric acid to isovanillic acid whereas the protocatechuic acid isolated was essentially inactive. Similarly, the transformation of labeled veratric acid directly to protocatechuic acid could also be achieved with hydrogen bromide under the appropriate conditions (see Experimental Section). A summary of this degradation scheme is presented in Chart I, and the results clearly demonstrate that all of the tritium label

CHART I



(7) A. Lovecy, R. Robinson, and S. Sugasawa, *J. Chem. Soc.*, 818 (1930).

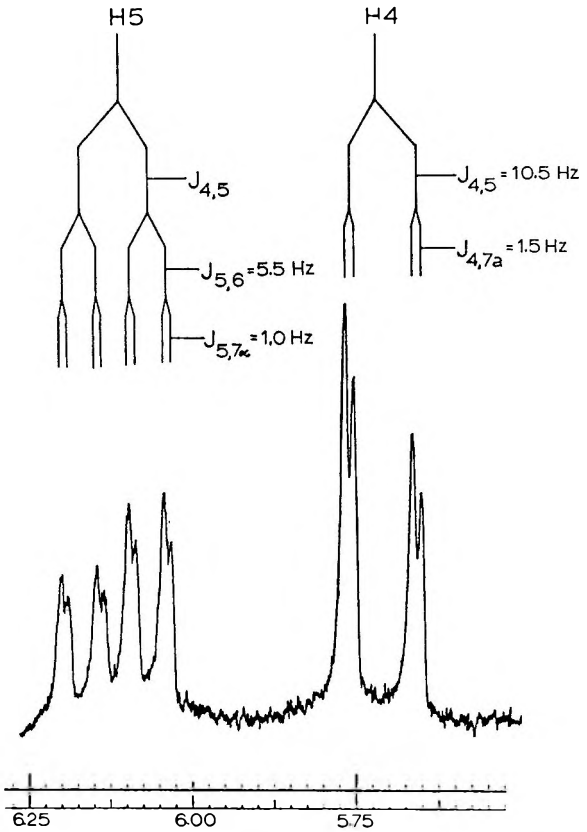
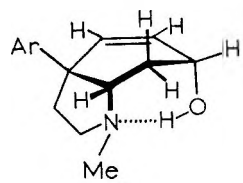


Figure 1.—Nmr spectrum of olefinic hydrogen region of 6-epimesembrenol.

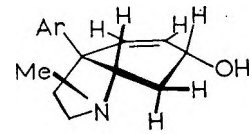
in the veratric acid obtained from the oxidation reaction is located in the 4-O-methyl group of the acid. In view of the demonstrated relation between the phenolic bases, the location of the tritiomethyl group in the veratric acid derived from one serves to establish the structures of both alkaloids as 4′-O-demethylmesembranol (**4**, R = H) and 4′-O-demethylmesembrenol (**5**, R = R′ = H), respectively.

Nmr and CD Spectral Studies.—Previous studies[8] of mesembranol, 6-epimesembranol, and the related ketone, mesembrine, have shown that the preferred ground-state conformations of these alkaloids are those in which ring B exists in the particular chair conformation in which the aryl substituent occupies the quasi-axial position. In view of this rather unexpected finding it was appropriate to examine the conformational features of the unsaturated analogs mesembrenol, 6-epimesembrenol (**7**) and mesembrenone.

The 6-epimesembrenol required for this study was obtained by reduction of (±)-mesembrenone with lithium aluminum hydride in tetrahydrofuran. In our hands this reduction afforded the 6-epi alcohol **7** as the major product together with mesembrenol. The latter, which was obtained in its racemic form, mp 124°, was identified by spectral comparisons with those obtained for the optically active form.[9] 6-Epimesembrenol was characterized from its nmr spectrum (*vide infra*) and by its oxidation to mesembrenone with manganese dioxide. The ir spectrum of **7** in carbon tetrachloride solution shows no absorption attributable to a free OH-stretching mode but instead a strong broad, concentration-independent, bonded OH absorption occurs at 3385 cm^{-1} over the concentration range 1.78 × 10^{-2} M to 1.78 × 10^{-3} M. Since no trace of any free OH-stretching absorption band was detected, 6-epimesembrenol must exist almost exclusively in the intramolecularly hydrogen bonded N–HO half-chair conformation **7a**. The existence of any significant concentration of the alternate form **7b** therefore may be confidently excluded from consideration.



7a



7b

The semirigid nature for conformation **7a** of 6-epimesembrenol provides a convenient model for an nmr study the results of which might be expected to afford information useful in diagnosing the conformational features of mesembrenol and mesembrenone.

Examination of the nmr spectrum of 6-epimesembrenol shows the following features which are pertinent to the conformational aspects of its structure. The signals from the two olefinic hydrogens appear (see Figure 1) as a 4-line pattern (C-4 H) and an 8-line (C-5 H) pattern centered at δ 5.73 and 6.12, respectively. The magnitudes of $J_{5,6}$ = 5.5 Hz and $J_{4,6}$ = 0 Hz (first order analysis) are fully consistent with conformation **7a**. Examination of a Drieding model shows that in this conformation the value of the dihedral angle which C-6 H makes with the hydrogens at C-4 and C-5 approaches 0°, resulting in a situation which is known to give rise to maximum vicinal and minimum allylic coupling.[10] On the other hand **7b** would be predicted to give rise to a small $J_{5,6}$ and a maximum $J_{4,6}$ in view of the 90° dihedral angle relationship of the C-6 H with the hydrogens at C-4 and C-5 present in this conformation.

Double resonance (nmdr) experiments show that the fine splitting observed in the C-4 H signal is due to long range coupling to the C-7a hydrogen signal which is located at δ 2.55. Since in this latter decoupling experiment the 8-line pattern of the C-5 hydrogen resonance signal remains unchanged, the fine splitting present in it has to be ascribed to coupling to one of the C-7 hydrogens. In view of the known stereospecificity[10] of ^4J couplings, this is most reasonably assigned to the C-7α hydrogen in which its stereochemical relation to the C-5 hydrogen is a distorted "W" arrangement.

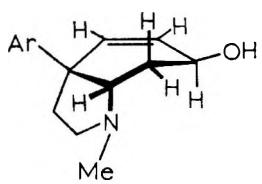
A similar analysis of the nmr spectrum of mesembrenol provides clear evidence that it too exists in the analogous ring C half-chair conformation **5a** like that found in the 6-epi alcohol. This occurs despite the fact that it lacks the advantage of the stabilizing effect which the intramolecular hydrogen bond undoubtedly confers on this conformation in 6-epimesembrenol. Inspection of the olefinic hydrogen pattern shows only a small splitting between the C-5 and C-6 hydrogen sig-

(8) P. W. Jeffs, R. L. Hawks, and D. S. Farrier, *J. Amer. Chem. Soc.*, **91**, 3831 (1969).

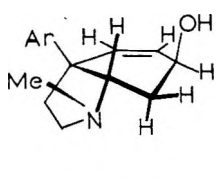
(9) Bodendorf and Krieger [*Arch. Pharm. (Weinheim)*, **290**, 441 (1957)] have reported that the reduction of (+)-mesembrenone with $LiAlH_4$ in ether affords (+)-mesembrenol, mp 117°, as the only product in 60% yield. Their results were reported without any implications of stereochemical detail.

(10) For a recent summary, see S. Sternhell, *Quart. Rev. (London)*, **23**, 236 (1969).

nals in the spectrum (Figure 2), and the appearance of this pattern as a quartet of uneven triplets may be accounted for by the fortuitous near equivalence in the line separations in the spectrum which originate from the four coupling constants $J_{5,6}$, $J_{4,6}$, $J_{4,7a}$, and $J_{5,7\alpha}$. The small and similar values of $J_{5,6}$ and $J_{4,6}$ are best accommodated by conformation **5a** in which the dihedral angle between the C-6 and the C-4 hydrogens is ~90°. The alternative conformation **5b** would be anticipated to give rise to quite different values for these couplings. Furthermore, it was possible to demonstrate that the long range coupling of the hydrogens at C-4 and C-7a found in the epi alcohol **7a** also exists in an analogous manner in mesembrenol from the observation that the upper pair of triplets resulting from the C-4 hydrogen signal could be collapsed to a double doublet by a nmdr experiment involving irradiation at the resonance position of the C-7a hydrogen at δ 2.33. The lower doublet of triplets of the C-5 hydrogen signal in this pattern remained essentially unchanged in this experiment and its multiplicity may be accounted for by the presence of a small long-range coupling of the C-5 hydrogen to the C-7α hydrogen which is similar in magnitude to $J_{5,6}$.



5a



5b

In approaching the question of the conformation of mesembrenone, consideration of the magnitude of $J_{5,6}$ so useful in the case of the mesembrenols is not available and an alternative to the nmr method was sought. Fortunately, the application of circular dichroism (CD) provides a potential means of ascertaining the preferred conformation. Previous studies have shown that the chirality in an optically active nonplanar cyclohexenone may be correlated with the sign of the Cotton effect arising from the n → π* or π → π* transition of the enone chromophore. Since mesembrenone is obtained as the racemate in the usual isolation procedure it was necessary to devise conditions for preparing optically active mesembrenone of known absolute configuration for CD studies.

Oxidation of (+)-mesembrenol offered a simple route to the desired product. In devising this reaction due cognizance had to be taken of the expected ease of racemization of the product under anything but neutral conditions; the use of the neutral oxidant manganese dioxide appeared to fulfill these requirements. (+)-Mesembrenone (**2**) was obtained when a solution of (+)-mesembrenol in carefully purified chloroform was stirred over manganese dioxide and the reaction terminated as soon as the oxidation was complete as evidenced by glpc analysis. The optical purity of the product was ascertained by converting it to mesembrine. A comparison of its ord spectrum with that of natural mesembrine indicated that the mesembrenone was 80% optically pure.[11]

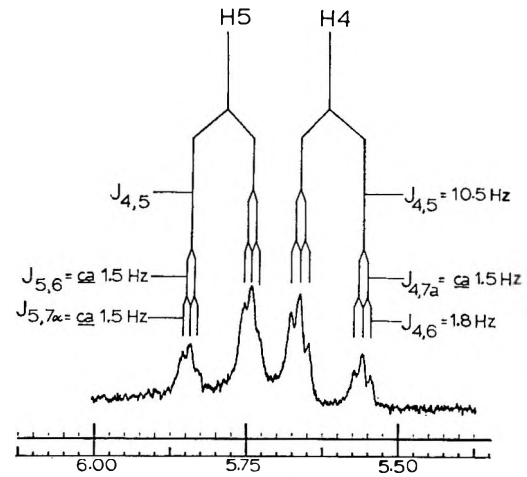
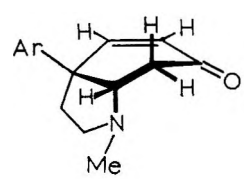


Figure 2.—Nmr spectrum of olefinic hydrogen region of mesembrenol.

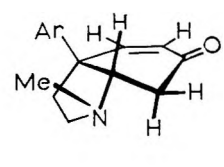
The experimental conditions for the preparation of (+)-mesembrenone are quite critical and even small deviations led to a product which was either completely or essentially racemic. In this connection it is pertinent to mention that some measure of the ease with which (+)-**2** undergoes racemization may be gathered from the observations that (+)-**2** in ethanol was racemized on standing at room temperature overnight or by brief heating to ~ 50° for 5 min.

The CD spectrum of (+)-mesembrenone recorded in chloroform showed a negative maximum at 334 mμ attributable to the Cotton effect resulting from n → π* transition of the enone chromophore. It is interesting to note that observation of this band in the electronic absorption spectrum is precluded by virtue of being submerged beneath the 'tail' resulting from the intense band at 278 mμ associated with the veratrole chromophore.

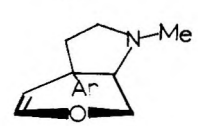
A negative Cotton effect for the n → π* transition of the enone chromophore in a structure possessing the absolute stereochemistry represented by structure **2** necessitates that the direction of chirality be as in **2a**.[12] This can be seen more clearly from a comparison of the octant projections of **2a** and **2b** from which it is obvious



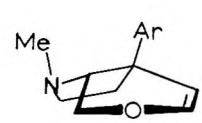
2a



2b



2a



2b

(11) This value should be regarded as the minimum value for optical purity of the mesembrenone since, in view of the ease with which this compound undergoes racemization, it is conceivable that some racemization occurred during its hydrogenation to mesembrine. Attempts to minimize this possibility were made by carrying out the reaction at 0°, with an excess of catalyst to ensure rapid reduction (15-min catalyst contact).

(12) W. B. Whalley, *Chem. Ind. (London)*, 1024 (1962). G. Snatzke, *Tetrahedron*, **21**, 413 (1965); 421 (1965); 439 (1965).

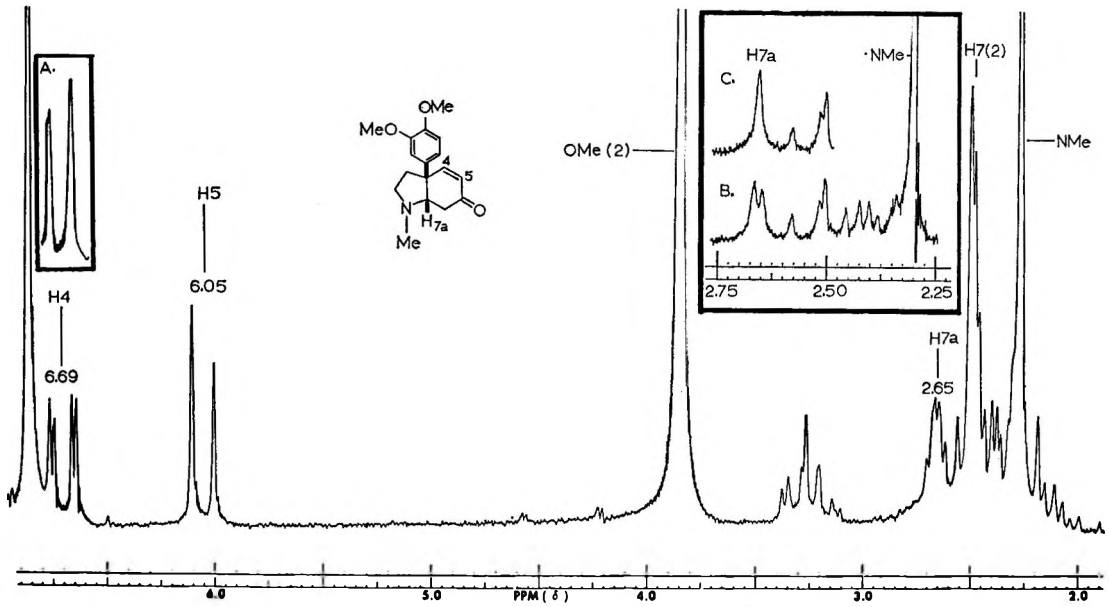


Figure 3.—Nmr spectra of mesembrenone and 5,7,7-d_3 mesembrenone with associated spin decoupling studies. A. Decoupling of C-4 hydrogen resonance by irradiation at C-7a hydrogen resonance frequency (δ 2.65). B. C-7 hydrogen signal in 5,7,7-d_3-mesembrenone. C. Decoupling of C-7a hydrogen signal in 5,7,7-d_3-mesembrenone by irradiation of the C-4 hydrogen resonance (δ 6.69).

that Cotton effects of opposite sign are predicted for these two conformations. A correlation exists[13] between the magnitude of the CD maximum and the deviation from coplanarity in the enone chromophore and the value of $[\theta] = -5060°$ calculated for optically pure (+)-mesembrenone is slightly larger than the molecular ellipticity values found for Δ^4-3-keto steroids[14] which range from $[\theta] = -4290$ to $-4719°$. In consonance with these observations, a comparison of Dreiding models of mesembrenone and the steroid systems shows that the cyclohexenone ring in the alkaloid has a somewhat larger degree of deformation from coplanarity.

Some further support for the above conformational assignment is available from the nmr spectrum of mesembrenone (Figure 3) which shows that the C-4 proton is long-range coupled just as in the case of the alcohols **4a** and **7a**. Nmdr studies demonstrate that the hydrogen involved in this long-range coupling is located at δ 2.65 (A). Assignment of this signal to the C-7a hydrogen resonance can be made from a comparison of its appearance in the mesembrenone spectrum where it occurs as a rough quartet to its appearance in the 5,7,7-d_3-mesembrenone spectrum in which it is a simple doublet (B). The doublet nature in the 5,7,7-d_3-mesembrenone spectrum is shown to be due to its long-range coupling to the C-4 hydrogen by the appropriate nmdr experiment (C). The long-range couplings of the C-4 and C-7a hydrogens and the C-5 and C-7α hydrogens in the mesembrenols is therefore paralleled in mesembrenone. This fact, together with the similarity in magnitude of the long-range coupling constants in these three compounds provides corroborative evidence for the conformation of mesembrenone as **2a**.

In summary, the spectral evidence indicates that the preferred ground-state conformations of mesembrenol and 6-epimesembrenol correspond to the equivalent half-chair ring C conformation as represented by structures **5a** and **7a**, respectively. Similarly, mesembrenone adopts the analogous ring C half-chair conformation rather than the alternative form **2b**.

Experimental Section

Melting points were taken on a Thomas-Hoover capillary apparatus and are corrected. Infrared spectra were recorded on Perkin-Elmer Models 137, 237, and 621 recording spectrophotometers. The nmr spectra were recorded at 60 MHz on a Varian A60 and at 100 MHz on a Varian HA 100 nmr spectrometer.[15] Glpc analyses were carried out on an F and M Model 402 high efficiency gas chromatograph with dual flame ionization detectors. Mass spectra[16] were obtained on an MS-902 mass spectrometer using a direct inlet system and operated with an ionization energy of 70 eV. CD and ORD spectra were obtained on a Jasco ORD–CD spectropolarimeter. Radioactive samples, dissolved in 10 ml of a stock solution prepared by mixing 1.2 l. of *p*-dioxane, 200 ml of 1,2-dimethoxyethane, 178 ml of water, 9.6 g of diphenyloxazole, and 0.24 g of *p*-bis[2-(5-phenyloxazolyl)]benzene, were counted on a Nuclear Chicago Unilux 1 liquid scintillation system.

Isolation of the alkaloids of *S. strictum* has been carried out in several different ways; the procedure described below is representative.

Three-year-old plants of *Sceletium strictum* L. bol. grown from seed were harvested in May and homogenized with 95% ethanol (4 l. in a Waring Blendor and the resulting suspension was heated on a steam bath for 1 hr prior to standing overnight. The solution was filtered and the filter cake (dry weight 151 g) extracted in a Soxhlet with CH_3OH. The combined extracts were concentrated to ~600 ml *in vacuo* and the resulting solution was treated with excess Na_2CO_3 before extracting with $CHCl_3$ (five 400-ml portions). After the $CHCl_3$ solution had been concentrated to ~1 l. it was extracted with 1 *N* HCl (six 300-ml portions). The combined HCl extracts were basified and reextracted with $CHCl_3$ (seven 200-ml portions). Removal of the $CHCl_3$ left 3.9 g of crude alkaloids. A further 0.12 g of alkaloid fraction was obtained by a repetition of the extraction procedure using

(13) G. Snatzke, "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," G. Snatzke, Ed., Heyden and Son, London, 1967, p 208.

(14) L. Velluz and M. Legrand, *Angew. Chem.*, **73**, 603 (1961).

(15) Obtained at North Carolina State University, Raleigh, and at the Environmental Health Laboratories, U. S. Public Health Service, Research Triangle Park, through the courtesy of Dr. Zelman Gaibel.

(16) Recorded through the cooperation of the Research Triangle Mass Spectrometry Center which is sponsored by a Special Facilities Grant No. FR-0330-01, National Institutes of Health.

$CHCl_3$:CH_3OH (3:1) to afford a total alkaloid fraction of 4.02 g (2.6% based on dry weight).

A sample of the crude alkaloid fraction was analyzed by glpc on two columns and the results are shown in Table I in which the relative retention times for identifiable alkaloids are given with respect to mesembrenol.

TABLE I

Alkaloid	SE-30[a]	Carbowax 20M[b]
Mesembrine	1.11	0.76
Mesembrenone	1.17	1.00
Mesembranol	1.00	0.87
Mesembrenol	1.00	1.00
O-Acetylmesembrenol	1.41	0.71
4′-O-Demethylmesembrenol	0.94	1.55
4′-O-Demethylmesembranol	0.94	1.65

[a] Glass column (8 ft × 0.25 in.) containing 3% SE 30 on Aeropak 30 (100–120 mesh) at a column temperature of 220°. [b] Glass column (8 ft × 0.25 in.) containing 4% Carbowax 20M on Aeropak 30 (100–120 mesh) as column temperature of 250°.

Chromatography of the crude alkaloid fraction (4.02 g) over neutral alumina (200 g, activity II) using a linear gradient of benzene (2 l.) against ethyl acetate (2 l.), 300 ml of ethyl acetate–C_2H_5OH (4:1) and finally 500 ml of CH_3OH. A total of 360 15-ml fractions were collected and the components of these fractions were analyzed by glpc using both Carbowax 20M and SE-30 columns under conditions specified in Table I. Fractions were combined as follows on the basis of the glpc results: 1–60, non-alkaloidal material (14 mg); 61–72, unidentified component (7 mg); 73–84, mesembrenone (32 mg); 85–87, mixture (1:1) mesembrine–mesembrenone (13 mg); 88–140, mesembrine (101 mg); 141–170, mesembrenol (285 mg); 171–326, mesembrenol–mesembranol (90:10) (871 mg); 327–360 mesembrenol, mesembranol, 4′-O-demethylmesembrenol, and 4′-*O*-demethylmesembranol (2.62 g).

The material from the combined fractions 327–360 was partitioned between $CHCl_3$ and 10% NaOH solution, the organic layer separated and the nonphenolic alkaloids (1.33 g) recovered from the $CHCl_3$. Glpc analysis of this material showed several unidentified minor components and peaks attributable to mesembranol and mesembrenol. The crude phenolic alkaloid fraction (0.75 g) consisted of two major components (glpc) and several minor alkaloids (<10%). (+)-**Mesembrenol** was purified by recrystallization from ethyl acetate or acetone to give colorless prisms: mp 140°; $[\alpha]^{25}D$ +91° (*c* 0.0176, $CHCl_3$); $\nu_{max}^{CHCl_3}$ 3630, 3450 cm^{-1} (OH), ratio of the intensity of the former to the latter peak increased on dilution; λ_{max}^{EtOH} 230 mμ (ε 9210), 279 (3515), 284 (2990); mass spectrum *m/e* 289 (M^+) (8.8), 219 (54), 70 (100); nmr δ 6.84 (m, 3 H, aromatic hydrogens), 5.70 (2 H, center quartet of triplets, H-4 and H-5), 4.30 (m, 1 H, C-6 H), 3.76 and 3.80 (s, each 3 H, OCH_3), and 2.30 (s, 3 H, NCH_3).

Anal. Calcd for $C_{17}H_{23}NO_3$: C, 70.56; H, 8.01; N, 4.84. Found: C, 70.48; H, 7.99; N, 4.83.

The **O-acetyl** derivative prepared in the usual way was obtained as an oil which was purified by chromatography in benzene over alumina (activity II) to afford an oil: ν_{max} 1740 (C=O), 1235 cm^{-1}; nmr δ 6.92 (m, 3 H, aromatic H), 5.80 (s, 2 H, H-4 and H-5), 5.92 and 3.86 (s, each 3 H, OCH_3), and 2.05 (s, 3 H, NCH_3).

A sample was purified by glpc for analysis using an 8-ft SE-30 column at 220°. The spectral and chromatographic properties of this sample were identical with a compound which was isolated from six-month-old *S. strictum* plants.

Anal. Calcd for $C_{19}H_{25}NO_4$: *m/e* 331.1783. Found: *m/e* 331.1777.

Chromic Acid Oxidation of (+)-Mesembrenol.—Mesembrenol (54 mg) was dissolved in 10 ml of acetone and the solution cooled to −10°. Chromic acid[17] (3 drops) was added to the solution of mesembrenol which was stirred and maintained at −10° for 20 min after the addition was complete. The excess chromic acid was destroyed by the addition of ~2 ml of a 1:1 mixture of isopropanol–acetone and the solvents removed *in vacuo*. The residue obtained was dissolved in 10 ml of water and basified with Na_2CO_3, and the aqueous solution extracted with $CHCl_3$. The crude product recovered from the $CHCl_3$ extract showed a single component on glpc analysis which corresponded to mesembrenone. Chromatography of the product over neutral alumina (activity III 20g) in 9:1 benzene–ethyl acetate afforded 35 mg of pure (±)-mesembrenone, $[\alpha]_{300}$ 0°, in the first 150 ml of solvent. The hydrochloride prepared from this sample crystallized from methanol–ether as plates, mp 190–195° (dec), which proved identical with an authentic sample of (±)-mesembrenone hydrochloride.

Manganese Dioxide Oxidation of (+)-Mesembrenol.—(+)-Mesembrenol (25.2 mg) was dissolved in 5 ml of $CHCl_3$ (which had been purified immediately before use by two passes through a column of basic alumina) and the solution cooled to 0° in an ice bath. Manganese dioxide (77 mg) was added to the solution and stirring continued for 25 hr at which point glpc analysis of the reaction mixture showed a 55% conversion of the mesembrenol to mesembrenone. An additional 75 mg of MnO_2 was then added and stirring continued for 1.5 hr at which time the mesembrenol remaining constituted less than 1% of the reaction mixture by glpc analysis. The reaction mixture was filtered to remove MnO_2 and the solvent was removed by a nitrogen stream at room temperature. Drying was completed at 25° *in vacuo* to yield (+)-mesembrenone (23 mg) as an oil: CD $[\theta]_{305}$ 0°, $[\theta]_{334}$ −4060°, $[\theta]_{310}$ 0° (*c* 1.072 mg/ml, ethanol). A significant decrease in the negative maxima in the CD spectrum was observed when ethanolic solutions were allowed to stand at room temperature. One sample which was allowed to stand for 24 hr was completely racemized. Similarly, an oxidation reaction carried out as specified above gave (+)-mesembrenone of very low optical purity (~5%) when removal of the $CHCl_3$ solvent was carried out at 50° on a Rotovac.

The optical purity of the sample of (+)-mesembrenone, $[\theta]_{334}$ −4060°, was established by its catalytic reduction to (+)-mesembrine as follows. A sample (20 mg) of (+)-mesembrenone was dissolved in 2 ml of ethyl acetate, which had been purified by passing through a column of basic alumina (activity I) immediately before use, and introduced into a stirred suspension of 40 mg of 10% palladium on carbon in 3 ml of ethyl acetate which had been cooled to 0°. The mixture was stirred under a hydrogen atmosphere at 1 atm and the progress of the reaction followed by glpc analysis; reduction was found to be complete in 10 min. After removal of the catalyst the usual work-up afforded (+)-mesembrine (~19 mg) as an oil. A small sample of this material was converted to the hydrochloride, mp 204–207°, and an independent comparison of the optical purity of the free base and the hydrochloride was made by a comparison of the molecular ellipticities of natural (+)-mesembrine and its hydrochloride. The average value obtained for the optical purity of the (+)-mesembrine from the hydrogenation of (+)-mesembrenol was 80%.

Catalytic Hydrogenation of Mesembrenol.—A solution of mesembrenol (26 mg) in 10 ml of CH_3OH was stirred over PtO_2 (4 mg) in an atmosphere of hydrogen until no more hydrogen was absorbed. After filtering the solution free of the catalyst, the solvent was removed to leave a residue which showed a single component on glpc corresponding to mesembranol. Crystallization of the residue from acetone gave (−)-mesembrenol as white prisms, mp 145–145.5°. This material was shown to be identical in every respect with an authentic sample of (−)-mesembranol by comparison of melting point, mixture melting point, tlc, glpc, and mass spectrum. The CD spectrum showed a plain negative curve identical with that of natural (−)-mesembranol.

4′-O-Demethylmesembrenol.—The crude phenolic alkaloid fraction, obtained either from the total alkaloid fraction by extraction with NaOH solution or from the NaOH soluble fraction of material enriched in the phenolic alkaloids *via* chromatography, crystallized from ethyl acetate as prisms, mp 200–203°. Glpc analysis of this material showed it was a two-component mixture. A sample (30 mg) of this mixture of CH_3OH (2 ml) was treated with an excess of an ethereal solution of CH_2N_2. Removal of the solvent and excess CH_2N_2 left a solid which on analysis by glpc showed two peaks corresponding to mesembranol and mesembrenol. The identity of the methylation products was confirmed by chromatographic separation over alumina, the fraction eluted with benzene–$CHCl_3$ (3:1) being identical with authentic (+)-mesembrenol while the later fraction eluted with benzene–$CHCl_3$ (1:3) was identical with authentic (−)-mesembranol.

Repeated fractional crystallization of the phenolic alkaloid mixture from CH_3OH afforded 4′-*O*-demethylmesembrenol as colorless prisms: mp 219–220°; $[\alpha]^{25}_{300}$ +533° (*c* 0.83 mg/ml, C_2H_5OH); λ_{max}^{EtOH} 225 mμ (log ε 3.44), 280 (3.44); $\lambda_{max}^{0.1\ N\ NaOH}$ 246

(17) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

(3.96), 295 (3.59); mass spectrum *m/e* 275 (M^+) (22), 205 (65), 70 (100), and 45 (90).

Anal. Calcd for $C_{16}H_{21}NO_3$: *m/e* 275.1521. Found: *m/e* 275.1540.

A solution of the phenolic alkaloid (~3 mg) in 1 ml of CH_3OH on treatment with excess ethereal CH_2N_2 afforded (+)-mesembrenol, mp 143–144°, identified by chromatographic and spectral comparisons with an authentic sample.

4′-*O*-Demethylmesembranol. A.—Mother liquors from the solution from which 4′-*O*-demethylmesembrenol had been obtained were subjected to preparative layer chromatography on silica gel H using $CHCl_3$–CH_3OH (3:1) and applying a double-pass technique. The two bands which appeared at R_f 0.61 and 0.32 gave 4′-*O*-demethylmesembrenol, mp 219°, and 4′-*O*-demethylmesembranol respectively. The latter crystallized from CH_3OH as prisms: mp 201°; $[\alpha]^{25}_{30}$ −199° (c 0.71, C_2H_5OH); λ_{max}^{EtOH} 229 (3.62), 280 (3.38); $\lambda_{max}^{0.1\ N\ NaOH}$ 245 (3.89), 294 (3.53; mass spectrum *m/e*, 277 (60), 205 (89), 204 (66), 70 (100).

Anal. Calcd for $C_{16}H_{23}NO_3$: *m/e* 277.1678. Found: *m/e* 277.1680.

B.—A mixture of the phenolic alkaloids (14 mg) in 10 ml of CH_3OH was stirred under an atmosphere of hydrogen in the presence of 10% palladium on carbon (10 mg) for 3 hr. The catalyst was filtered off and the filtrate concentrated to afford crystals (~6 mg), mp 201°, which were identical by chromatographic (tlc, glpc) and mass spectral comparisons with the 4′-*O*-demethylmesembranol obtained above.

Tritiomethylation of 4′-*O*-Demethylmesembranol.—To ~5 mg of 4′-O-demethylmesembranol in 0.2 ml of CH_3OH, 0.2 ml of tritiated water [activity 1 Ci/g] was added. This solution was mixed with a solution of CH_2N_2 in 10 ml of tetrahydrofuran containing 0.2 ml of tritiated water [20 μCi/g] and the mixture was kept for 10 days at 0–5°. Inactive mesembranol (12 mg) was added to the reaction mixture as a carrier and the product obtained after removal of the solvents was purified by chromatography over alumina to afford [*4′-O-methyl-*^{3}*H*]-mesembranol of high specific activity, 43.6 μCi/mmol.

$KMnO_4$ Oxidation of [*4′-O-Methyl-*^{3}*H*]-Mesembranol.—The tritium-labeled alcohol from the above experiment was dissolved in a mixture of dioxane (5 ml) and 5% aqueous Na_2CO_3 (15 ml). Potassium permanganate (3%) was added dropwise to this solution at reflux until the clear supernatant layer was distinctly pink. The refluxing was continued for a total of 70 min and the mixture cooled and treated with solid $NaHSO_3$ until clear. Veratric acid (25 mg) was added as a carrier and the solution acidified with concentrated hydrochloric acid before extracting with $CHCl_3$ (five 20-ml portions). A Na_2CO_3 extraction of the $CHCl_3$ concentrate, followed by acidification of the aqueous extract and reextraction with $CHCl_3$ (three 60-ml portions) and ether (six 60-ml portions), gave, on removal of solvents, a solid residue. Crystallization of this residue from C_2H_5OH gave veratric acid (14 mg), mp 180–182°, which was radioactive. Two recrystallizations gave radiochemically pure material 3.06×10^{-1} μCi/mmol.

Sequential Demethylation of Radiolabeled Veratric Acid.—A suspension of the labeled veratric acid (14 mg) in 0.1 ml of 48% HBr was heated under reflux. A clear solution was obtained after 2.5 min and heating was continued for a further 3 min until a solid precipitated. The solution was cooled, diluted with an equal volume of water, and filtered. The residue was washed with three 0.5-ml portions of water and dried to give 8 mg of isovanillic acid, mp 243–247°, which was radioactive (3.03×10^{-1} μCi/mmol). This sample was mixed with 0.5 ml of 48% HBr and heated under gentle reflux for 25 min, during which time an additional 0.2 ml of HBr was added after 15 min. On cooling the solution to room temperature a crystalline precipitate of protocatechuic acid formed which was filtered and washed with water to give ~3.5 mg, mp 194–196°. This sample showed only weak activity (3.00×10^{-2} μCi/mmol). Insufficient material was available to attempt to crystallize this sample to constant activity.

Demethylation of [*4′-O-Methyl-*^{3}*H*]-Vanillic Acid to Protocatechuic Acid.—Radio-labeled veratric acid (3.06×10^{-1} μCi/mmol ~2 mg, was heated under gentle reflux with 0.8 ml of 48% HBr for 35 min. The sample was cooled and the crystalline protocatechuic acid was filtered off and washed thoroughly with water. A sample of this material (mp 196–198°) showed only very low activity (2.86×10^{-3} μCi/mmol).

$LiAlH_4$ Reduction of (±)-Mesembrenone.—(±)-Mesembrenone (2.10 g) in 25 ml of dry tetrahydrofuran was added dropwise to a stirred solution of 3.0 g $LiAlH_4$ in 60 ml of tetrahydrofuran. Stirring was continued for 2 hr and the reaction was quenched with 10% aqueous NH_4Cl. Work-up of the reaction mixture yielded a yellow oil (2.03 g) which, by gas chromatographic analysis, was shown to be a mixture of 6-epimesembrenol and mesembrenol in a 65:35 ratio.

The oil was dissolved in benzene and placed on a dry-packed alumina column (Woelm grade II, 75 cm × 1.6 cm). Elution was carried out by a gradient solvent system, benzene–25% benzene in ethyl acetate (2.5 l.). A total of 250 20-ml fractions were collected. The progress of the column was monitored by glpc analysis on a Carbowax 20M column operated as indicated in Table I. Fractions 15–85 contained (±)-6-epimesembrenol (1.1 g), 86–96 contained mixtures of both alcohols (~400 mg), and 97–250 contained (±)-mesembrenol. **(±)-6-Epimesembrenol**, an oil, exhibited the following spectral properties: $\gamma_{max}^{CCl_4}$ 3385 cm^{-1} unchanged over concentration range 1.78×10^{-2} *M* to 1.78×10^{-3} *M*; mass spectrum *m/e* 289 (M^+) (12), 250 (21), 219 (24), 144 (64), 70 (100); nmr δ (m, 3 H, aromatic hydrogens), 6.12 (8-line pattern, 1 H, H-4, $J_{4,5}$ = 10.5, $J_{5,6}$ = 5.5, $J_{5,7\alpha}$ = 1.0 Hz), 5.73 (d, 1 H, H-5, $J_{4,5}$ = 10.5, $J_{4,7a}$ 1.5 Hz), 4.00 (m, 1 H, C-6), 3.82 and 3.80 (m, each 3 H, OCH_3 aromatic), and 2.40 (s, 3 H, NCH_3). A sample of the alcohol **7** (10 mg) in $CHCl_3$ afforded (±)-mesembrenone on stirring with MnO_2 (100 mg) for 4 hr. The spectral and chromatographic properties of the product were identical with an authentic sample of mesembrenone. (±)-6-Epimesembrenol was purified for analysis by glpc.

Anal. Calcd for $C_{17}H_{23}NO_3$: *m/e* 289.1678. Found: *m/e* 289.1675.

(±)-Mesembrenol crystallized from acetone as prisms, mp 122–124.5° (lit.[9] mp 117°). Its spectral properties and chromatographic properties were identical in every respect with that of natural (+)-mesembrenol.

Anal. Calcd for $C_{17}H_{23}NO_3$: *m/e* 289.1678. Found: *m/e* 289.1675.

Deuteration of (±)-Mesembrenone.—(±)-Mesembrenone (90 mg) was dissolved in 5 ml of dry dioxane to which 200 mg of sodium was added. Deuterium oxide (5 ml) was next added dropwise and the solution refluxed 18 hr. The dioxane and deuterium oxide were then removed by distillation *in vacuo*, and the residue recharged with 5 ml of dioxane, 200 mg of sodium, and 5 ml of deuterium oxide as above. Reflux was initiated and continued for 10 hr and the solvents were removed as before. The residue was taken up in $CHCl_3$. This was washed once with 2 ml of water and dried over anhydrous $MgSO_4$. The drying agent was then filtered off, the $CHCl_3$ removed from the residue in a nitrogen stream, and final drying accomplished *in vacuo*. The light yellow oil weighed 43 mg. Glpc analysis was consistent with mesembrenone. Nmr indicated that deuteration at C-5 and C-7 (**2**) was complete.

Registry No.—**2**, 25516-12-5; **4** (R = H), 25516-13-6; **5** (R = R′ = H), 25516-14-7; **5** (R = Me; R′ = H), 25516-15-8; **5** (R = Me; R′ = Ac), 25516-16-9; **7**, 25568-56-3.

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The Absolute Configuration of Indolmycin

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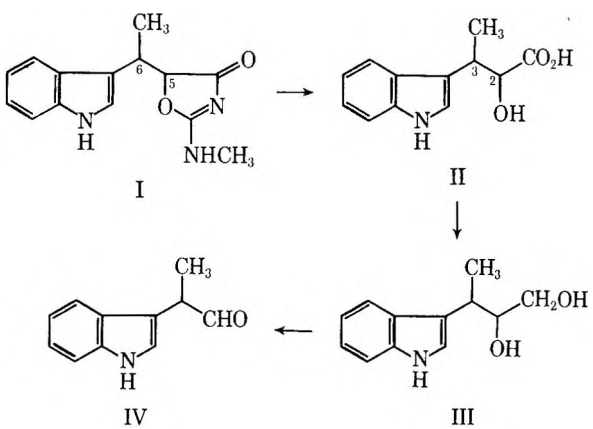
Synthesis of the enantiomer of α-indolmycenic acid from (−)-*trans*-2,3-epoxybutyric acid establishes the absolute configuration of the antibiotic indolmycin as 5*S*,6*R*. The absolute configuration of the plant growth hormone (*S*)-(+)-α-(3-indolyl)propionic acid, assigned earlier by the quasiracemate method, has been confirmed by direct correlation with α-indolmycenic acid.

Indolmycin (**1**), an antibiotic isolated[1] from an African strain of *Streptomyces albus*, is of interest for its antimicrobial activity[2] against strains of staphylococci which are resistant to many commercially available antibiotics. The structure was elucidated in a careful study by Schach von Wittenau and Els,[3] who also were able to deduce the relative configuration and to accomplish a total synthesis of the antibiotic. The ordinarily intimate relationship of biological activity to configuration of chiral molecules prompted this study of the absolute configuration of indolmycin.

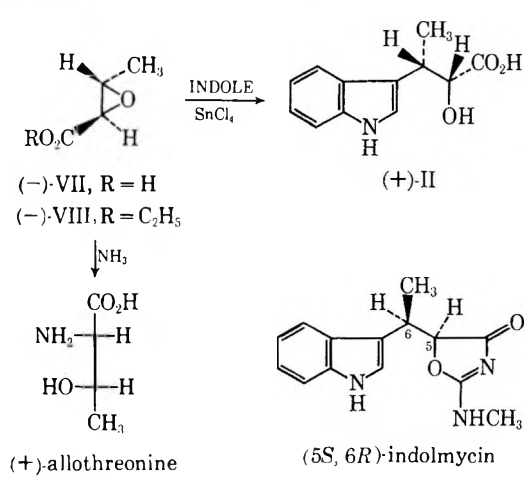
Alkaline hydrolysis of indolmycin was reported[3] to yield a mixture of (−)-α-indolmycenic acid (II) and its epimer at the carbinol carbon C-2, β-indolmycenic acid. Reduction with lithium aluminum hydride afforded glycol III, which was cleaved with periodate to the optically active aldehyde IV. The relative configuration at the two asymmetric centers was deduced from the behavior of indolmycin and its 5 epimer on acid hydrolysis, and confirmed by synthesis of racemic II from indole and *trans*-ethyl-2,3-epoxybutyrate. Consequently, any of the degradation products II–IV could be used for determination of absolute configuration by correlation with a compound of known configuration.



The paucity of optically active compounds of rigorously established configuration containing a 3-indole substituent attached to the asymmetric center limited efforts to use aldehyde IV in a correlation scheme; preliminary attempts to prepare (+)- or (−)-IV by reduction of derivatives of α-(3-indolyl)propionic acid (VI) or by oxidation of 2-(3-indolyl)propan-1-ol (V) were frustrated by low yields and racemization. We turned therefore to direct synthesis of indolmycenic acid (II) from a compound of known configuration, and chose (−)-*trans*-2,3-epoxybutyric acid (VII) for this purpose.

(−)VII, $[\alpha]^{25}D$ −74.8°, was prepared by resolution of the racemic acid with brucine according to the procedure of Harada and Oh-hashi.[4] These workers established the absolute configuration of (−)-VII as (2*R*,3*S*) by nucleophilic opening of the epoxide ring with ammonia to give (+)-(2*S*,3*S*)-allothreonine.[5] Levorotatory VII was converted to the ethyl ester (VIII) by reaction of the silver salt with ethyl iodide. The stannic chloride catalyzed reaction between (±)-VIII and indole was reported by Schach von Wittenau and Els[3] to yield only (±)-α-indolmycenic acid (II) and none of the diastereoisomer; it may be pictured as nucleophilic displacement with inversion at C-3 of the coordinated epoxide. Regardless of detailed mechanism, the configuration at C-2 in α-indolmycenic acid must be the same as that in VIII.

Indole reacted with (−)-VIII in carbon tetrachloride at −10°, with stannic chloride as catalyst, to give α-indolmycenic acid ethyl ester, which was hydrolyzed to the crystalline optically active acid II, $[\alpha]D$ +7.8°. The synthetic acid gave infrared and nmr spectra identical with those of the hydrolysis product of indolmycin, but the rotation was the opposite of that reported. Since dextrorotatory II prepared by synthesis from (−)-VII must have the (2*R*,3*S*) configuration, (−)-II is the (2*S*,3*R*) isomer and indolmycin correspondingly has the (5*S*,6*R*) configuration.



α-(3-Indolyl)propionic Acid.—The establishment of absolute configuration of indolmycin also permitted an unambiguous chemical corroboration of the absolute configuration of α-(3-indolyl)propionic acid ("indoleisopropionic acid") (VI), a plant growth hormone.

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(3) M. Schach von Wittenau and H. Els, *J. Amer. Chem. Soc.*, **83**, 4678 (1961); **85**, 3425 (1963).

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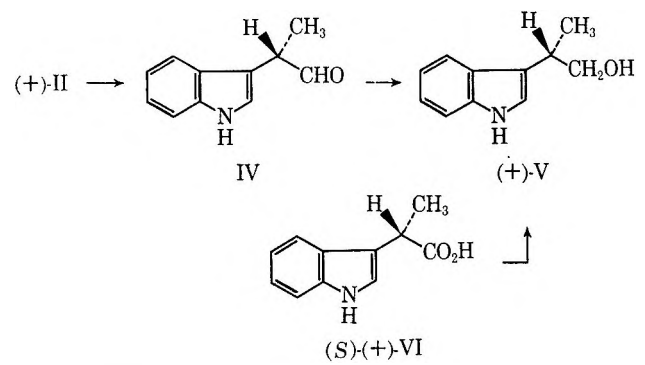
Acid VI is the higher homolog of a long-known plant growth regulator, indoleacetic acid (heteroauxin) and has been shown in a number of studies[6,7] to have auxin activity often equal to or surpassing that of indoleacetic acid. The dextrorotatory isomer has been isolated[8] both in the free state and as its mannitol ester from the sclerotia and saprophytic cultures of the ergot fungus *Claviceps purpurea*. The biosynthesis of VI from tryptophan and methionine has been the subject of a recent investigation.[9]

The enantiomers of VI show clear differences in hormonal activity, the (+) isomer being more active in most tests;[7] this finding has been attributed to differences in diffusion velocity in the plant.[7a] The effect of configuration on auxin activity may be important for the understanding of the growth-regulating mechanism, and the configuration of optically active VI has been the subject of earlier investigations. Sjöberg[10] used the quasiracemate method to deduce the (*S*) configuration for (+)-VI, employing α-(1-naphthyl) propionic acid as the reference standard, and later[11] came to the same conclusion on the basis of comparison of ORD curves of VI and related acids.

To permit a rigorous assignment by chemical interconversions, α-(3-indolyl) propionic acid (VI) was prepared and resolved with brucine. Reduction of (+)-VI, $[\alpha]_D$ +106°, with diborane gave (+)-2-(3-indolyl)propan-1-ol (V), $[\alpha]_D$ +28°. This alcohol was then prepared independently from (+)-α-indolmycenic acid (II). Following the degradation scheme of Schach von Wittenau and Els,[3] (+)-II was reduced to glycol III with lithium aluminum hydride. Periodate cleavage of III afforded α-(3-indolyl)propionaldehyde (IV) which was immediately reduced with lithium aluminum hydride. The reduction product,



(+)-V, was identical with the alcohol derived from (+)-VI. This correlation of (+)-VI with (+)-(2*R*,3*S*)-II confirms the (*S*) configuration assigned earlier to (+)-VI.

Experimental Section

trans-**2,3-Epoxybutyric Acid (VII).**—Acid VII was prepared by epoxidation of sodium crotonate with hydrogen peroxide and sodium tungstate, according to the procedure of Payne and Williams.[12] The acid had mp 82–85° (lit.[12] mp 83°). Partial resolution with brucine was achieved by the published procedure.[4] The levorotatory acid had mp 53–56°, $[\alpha]^{25}_D$ −74.8° (c = 1, benzene); lit.[4] mp 61°, $[\alpha]^{25}_D$ −82.5° (c 0.59, benzene).

(−)-**Ethyl** *trans*-**2,3-Epoxybutyrate (VIII).**—A solution of 5.95 g of the brucine salt of (−)-VII, mp 175° dec, $[\alpha]^{25}_D$ −24.4° (*c* = 1.5, H_2O), in 30 ml of water was treated with 12 ml of 1 *N* sodium hydroxide solution and filtered to remove brucine. To the filtrate was added a solution of 2.04 g of silver nitrate in 6 ml of water followed by 40 ml of methanol. After cooling, the precipitated silver salt (1.23 g), mp 180–182°, was collected and dried *in vacuo*.

A mixture of the silver salt (1.68 g) and ethyl iodide (1.5 ml) in 50 ml of benzene was refluxed 40 min under nitrogen, then cooled and filtered. Distillation of the filtrate gave the ester[13] as a colorless oil: bp 110° (30 mm); 0.68 g; $[\alpha]^{25}_D$ −23.5° (c 2, CCl_4); ν CCl_4 1750 cm^{-1}; nmr (CCl_4) δ 1.3, t, 3 H, 1.35, d, 3 H, 3.1, m, 2 H, 5.2 q, 2 H.

(+)-α-**Indolmycenic Acid (II).**—To a solution of 0.68 g of (−)-VIII and 1.3 g indole in 10 ml of carbon tetrachloride, cooled to −10°, a solution of 1.0 ml of anhydrous stannic chloride in 6 ml of carbon tetrachloride was added dropwise with stirring. After stirring 40 min at −10°, the mixture was poured into concentrated sodium bicarbonate solution and stirred for 1 hr until all gummy material was dissolved. The organic layer was separated, dried, and concentrated and the residual oil chromatographed on Florisil, eluting first with benzene, then with chloroform. Concentration of the combined chloroform fractions gave 0.80 g of reddish oil, which was hydrolyzed by 1.5-hr reflux under nitrogen with 12 ml of 10% sodium hydroxide. The solution was cooled, washed with ether, acidified with dilute sulfuric acid, and extracted with two 30-ml portions of ether. Concentration of the dried extracts left a solid residue, which was recrystallized from water. α-Indolmycenic acid (II) was isolated as a pale yellow solid: mp 175–176°, $[\alpha]^{25}_D$ +7.80° (*c* 2, CH_3OH); lit.[3] mp 181–182°, $[\alpha]^{25}_D$ −10° (*c* 2, CH_3OH). The infrared and nmr spectra were identical with those of the (−) acid.[14]

α-**(3-Indolyl)propionic Acid (VI).**—The racemic acid VI was prepared both by hydrolysis[7a] of α-(3-indolyl)propionitrile, itself prepared by the reaction of the indole Grignard reagent with α-bromopropionitrile, or by the base-catalyzed reaction of indole with lactic acid;[15,16] the latter method is far more practical. In a typical run, a 300 ml Monel autoclave was charged with 58 g of indole, 59 g of 85% aqueous lactic acid, and 45 g of 85% potassium hydroxide. The mixture was heated at 220° for 18 hr, cooled to 90°, and taken up in 250 ml of water. After washing with ether the alkaline solution was acidified to pH 1 with 12 *N* hydrochloric acid and extracted with ether. The extracts were washed with water, dried, and concentrated, leaving an oil which crystallized on standing. Recrystallization from chloroform gave 60.4 g (64%) of colorless solid, mp 105–106° (lit.[7b] mp 111–112°).

Anal. Calcd for $C_{11}H_{11}NO_2$: C, 69.55; H, 5.82; N, 7.41. Found: C, 69.37; H, 5.90; N, 7.32.

The acid was resolved with brucine according to the procedure of Sjöberg.[6b] (+)-VI had mp 136–137°, $[\alpha]^{23}_D$ 106° (benzene); lit.[5b] mp 138–140°, $[\alpha]^{23}_D$ 106.2° (benzene).

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(12) G. B. Payne and P. H. Williams, *J. Org. Chem.*, **24**, 54 (1959).

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(14) We thank Dr. M. Schach von Wittenau, Chas. Pfizer and Co., for his kindness in sending us samples of the indolmycenic acids.

(15) H. E. Johnson and D. G. Crosby, *J. Org. Chem.*, **28**, 1246 (1963).

(16) We are grateful to Dr. B. Franko-Filipic and Mr. W. McCarthy, FMC Corporation, Princeton, N. J., for their help in running large-scale preparations.

2-(3-Indolyl)propan-1-ol (V). **A.**—Racemic V was prepared by lithium aluminum hydride reduction of methyl α-(3-indolyl)-propionate (prepared from (±)-VI and diazomethane) in tetrahydrofuran. Work-up gave (±)-V as a pink, viscous oil, bp 155° (0.1 mm). The *p*-nitrobenzoate melted at 117°.

Anal. Calc for $C_{18}H_{16}N_2O_4$: C, 66.65; H, 4.97; N, 8.64. Found: C, 66.66; H, 5.05; N, 8.59.

B.—A solution of 3.7 g of (+)-VI in tetrahydrofuran was reduced with 40 ml of a 1 *M* solution of diborane in tetrahydrofuran at room temperature for 2.5 hr. The mixture was poured onto ice and saturated with salt. The organic layer was washed with 5% sodium bicarbonate, dried, and distilled, yielding (+)-2-(3-indolyl)propan-1-ol:[17] bp 135° (0.1 mm); lit.[17] bp 145° (0.15 mm), $[\alpha]^{22}D$ +28.1° (c 2.5, CH_3OH).

C.—Following the procedure of Schach von Wittenau and Els,[3] 120 mg of (+)-α-indolmycenic acid, $[\alpha]D$ +7.8°, was reduced with lithium aluminum hydride in ether, and the resulting glycol (III) cleaved with sodium periodate. The crude α-(3-indolyl)-propionaldehyde(IV) showed carbonyl absorption at 1720 cm^{-1}. The aldehyde was not further characterized, but reduced directly with lithium aluminum hydride in ether. After the usual work-up, 55 mg of (+)-V was obtained, $[\alpha]^{26}D$ +20° (*c* 2.7, CH_3OH), which showed tlc behavior and infrared spectra identical with those of the alcohol obtained in parts A and B. The alcohols from both parts B and C showed plain positive ORD curves from 300–600 nm.

(17) R. A. Robinson, U. S. Patent 2,908,691; *Chem. Abstr.*, **56**, 3455 (1962).

Registry No.—(+)-II, 25834-21-3; (±)-V, 25834-22-4; (±)-V *p*-nitrobenzoate, 25834-23-5; (−)-VIII, 25834-24-6; (−)-VIII Ag salt, 25834-25-7; indolmycin, 23369-88-2.

Acknowledgments.—This research was supported by an unrestricted grant from Hoffmann-La Roche, Inc., to whom the authors express their appreciation. We thank Mr. Raymond Danforth for his skillful assistance in the preparation and resolution of acid VI and for studies on alternative approaches to determination of configuration of indolmycin.

Synthesis of D-Dihydrosphingosine[1]

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A stereospecific synthesis of D-dihydrosphingosine is recorded. The reaction of 6-benzyloxycarbonylamino-2,2-dimethyl-5-formyl-3a,5,6,6a-tetrahydro-D-ribofuro[2,3-*d*]dioxolane (**6**), prepared in three steps from 3-amino-3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (**3**), with the Wittig reagent, prepared from tetradecyltriphenylphosphonium bromide (**2**) is described. The product, a mixture of cis and trans olefins (**8**), was deacetonated, and the resulting glycol was cleaved with sodium metaperiodate and then reduced with sodium borohydride to give crystalline 2-benzyloxycarbonylamino-D-*erythro*-Δ⁴-octadecene-1,3-diol (**11**). Hydrogenation of **11** over palladium on charcoal reductively deblocked the amine and saturated the olefin to give D-dihydrosphingosine (**12**).

D-Sphingosine (2-amino-1,3-dihydroxy-D-*erythro*-octadec-4-ene) and D-dihydrosphingosine (2-amino-1,3-dihydroxy-D-*erythro*-octadecane) are bases which serve as the backbone for the structures of cerebrosides, gangliosides, sphingomyelin, etc. Abnormal amounts of cerebroside derivatives have been observed in leukodystrophy,[2] Niemann–Pick and Tay–Sachs diseases,[3] etc. Unusual concentrations of sphingomyelin have been found in cataracts.[4]

Evidence is accumulating that sphingosine and dihydrosphingosine derivatives can act as prophylactics against certain laboratory induced diseases in animals. Thus intradermal injections containing cerebrosides offered significant protection against experimental allergic encephalomyelitis in rabbits.[5] Injection of ganglioside–cerebroside complexes offered relief from the symptoms of tetanus toxin in mice.[6] The suggestion was made[6] that such a technique might be of prophylactic value in human tetanus.

Biochemical studies using sphingosine derivatives isolated from natural sources were made difficult by the questionable purity of such materials. The syntheses of sphingosine[7] and dihydrosphingosine[8] reported have inevitably led to racemic mixtures which must then be resolved in order to obtain the desired optically active material.

Carbohydrates offer a wide assortment of extensively functionalized starting materials with known absolute configuration. By the attachment of a long alkyl chain to the appropriate amino sugar, the synthesis of optically pure sphingosine derivatives and analogs becomes a relatively simple procedure. A series of papers by Gigg, *et al.*,[9] describes the use of a Wittig condensation of an amino sugar derived from glucosamine with the ylide prepared from triphenylphosphine and tridecyl bromide to give D-phytosphingosine(4-hydroxydihydrosphingosine). The absence of a double bond in phytosphingosine circumvented the problem of cis *vs.* trans isomers of the Wittig product. For this same reason, the synthesis of D-dihydrosphingosine by a Wittig condensation was investigated initially and is reported here.

A logical starting material for the synthesis of D-dihydrosphingosine (and D-sphingosine) is the readily available 3-amino-3-deoxy-1,2:5,6-di-O-isopropylidene-

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(1) This investigation was supported by Public Health Service Research Grant No. NS-07776 from the National Institute of Neurological Diseases and Stroke.

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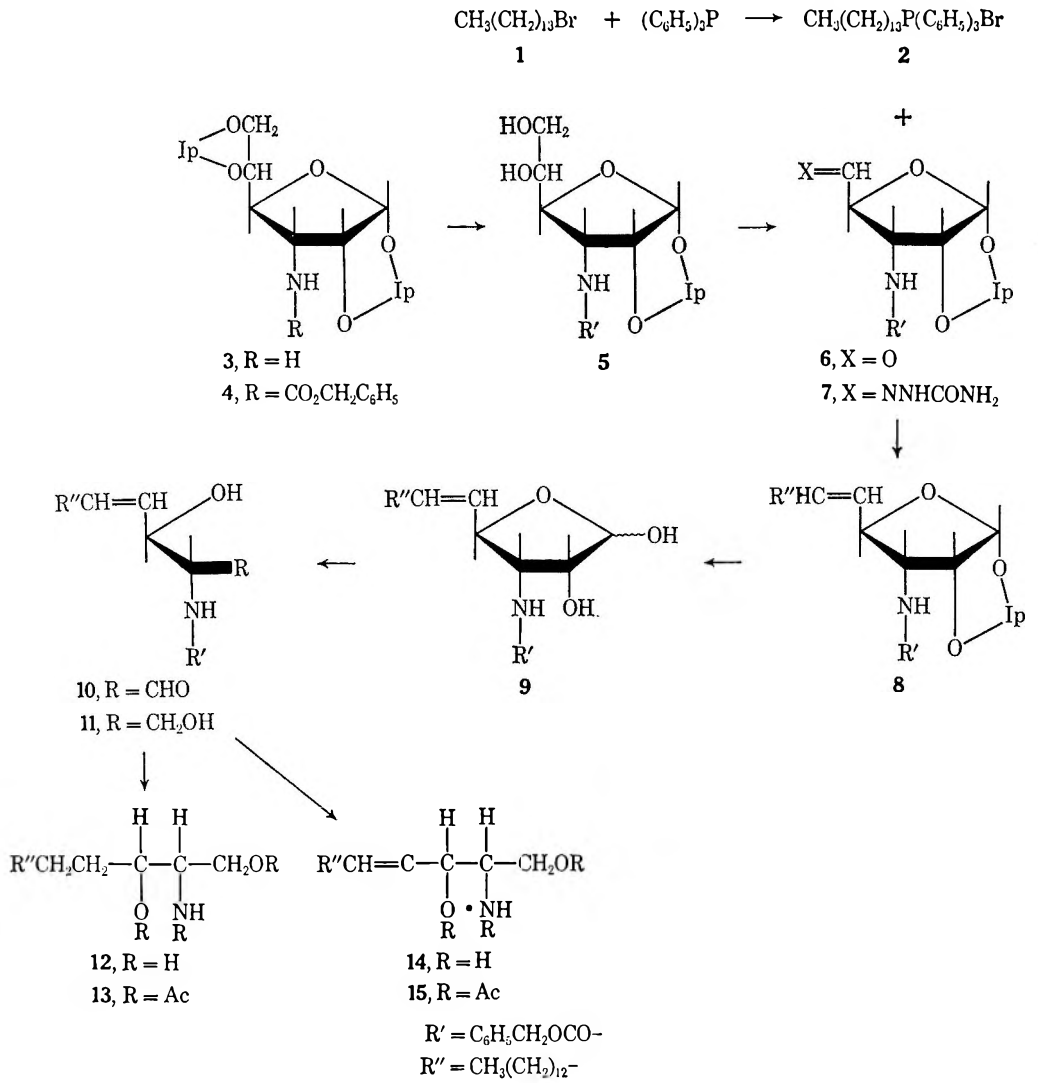
(5) B. Niedieck and U. Kuck, *Z. Immunitaetsforsch. Allerg. Klin. Immunol.*, **133**, 43 (1967).

(6) J. Mellanby, H. Mellanby, D. Pope, and W. E. Van Heyningen, *J. Gen. Microbiol.*, **54**, 161 (1969).

(7) (a) C. A. Grob and F. Gadient, *Helv. Chim. Acta*, **40**, 1145 (1957); (b) D. Shapiro, H. Segal, and H. M. Flowers, *J. Amer. Chem. Soc.*, **80**, 1194 (1958).

(8) (a) E. N. Zoonkova, K. I. Eller, V. I. Tsetlin, B. I. Mitsner, and N. A. Preobrazhenskii, *Zh. Org. Khim.*, **2**, 2184 (1966); (b) W. Stoffel, and G. Sticht, *Hoppe-Seyler's Z. Physiol. Chem.*, **348**, 1561 (1967).

(9) J. Gigg, R. Gigg, and C. D. Warren, *J. Chem. Soc.*, 1872 (1966), and subsequent papers.



α-D-allofuranose (**3**),[10] because the degradative removal of carbons 1 and 6 results in a 4-carbon fragment with the necessary functional groups in the desired D-erythro configuration. The amine function of **3** was blocked by a reaction with benzyl chloroformate in pyridine to give 3-benzyloxycarbonylamino-3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (**4**). Selective removal of the 5,6-isopropylidene group using aqueous acetic acid gave 3-benzyloxycarbonylamino-3-deoxy-1,2-O-isopropylidene-α-D-allofuranose (**5**) as a syrup. Cleavage of the glycol of **5** by means of sodium metaperiodate yielded 6-benzyloxycarbonylamino-2,2-dimethyl-5-formyl-3a,5,6,6a-tetrahydro-D-ribofuro[2,3-*d*]dioxolane (**6**) as an oil, characterized as the crystalline semicarbazone (**7**).

The Wittig reagent necessary for the condensation was prepared starting from the reaction of tetradecyl bromide (**1**) with triphenylphosphine to give crystalline tetradecyltriphenylphosphonium bromide (**2**). Treatment of **2** with 1 mol equiv of phenyllithium in ether–hexane generated the Wittig reagent. To this was added a solution of the aldehyde **6** in dry benzene and the reaction was refluxed for 21 hr to give, on work-up and chromatographic purification, a 30% yield of 6-benzyloxycarbonylamino-2,2-dimethyl-5-(1-pentadecenyl)-3a,5,6,6a-tetrahydro-D-ribofuro[2,3-*d*]dioxolane (**8**) of the mixed cis and trans configuration from which the cis isomer could be isolated pure by crystallization. The cis assignment was based on the fact that the infrared spectrum of the recrystallized Wittig product showed no absorption band at 10.3 μ.[11] It was not necessary to separate the cis from trans isomers, since the final hydrogenation would convert both to dihydrosphingosine (**12**)

Deacetonation of the mixed cis–trans olefin, **8**, using aqueous acetic acid gave a quantitative yield of 1,2 diol (**9**). Treatment of **9** with sodium metaperiodate cleaved the 1,2-glycol. Sodium borohydride reduction of the resulting aldehyde (**10**) gave crystalline 2-benzyloxycarbonylamino-D-*erythro*-Δ⁴-octadecene-1,3-diol (**11**). Hydrogenation of **11** using 10% palladium on charcoal yielded crystalline D-dihydrosphingosine (**12**), which was characterized as its sulfate. Acetylation of **12** using acetic anhydride in pyridine gave a crystalline triacetate (**13**) which had the same melting point, infrared spectrum, and optical rotation as a sample of D-dihydrosphingosine triacetate which was prepared from commercially available D-sphingosine. The mixture melting point of the two samples of triacetate showed no depression. This synthesis represents a more direct proof of structure by synthesis of dihydrosphingosine. The previous proof by synthesis de-

(10) (a) K. Freudenberg and F. Brauns, *Ber.*, **55**, 3233 (1922); (b) M. L. Wolfrom, F. Shafizadeh, and R. K. Armstrong, *J. Amer. Chem. Soc.*, **80**, 4885 (1958).

(11) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1954, p 31.

scribed by Gigg and coworkers[9] was indirect, in that they synthesized phytosphingosine and demonstrated the identity of their synthetic product with that of phytosphingosine prepared from naturally occurring sphingosine.

It is interesting to note that the Wittig reaction between the aldehyde (6) and the ylide derived from the phosphonium bromide (2) gave an olefin (8) which appeared to be a mixture of cis and trans isomers with the cis isomer predominant. There was undoubtedly a significant amount of the trans isomer, since the infrared spectrum of the material obtained after chromatography showed significant absorption at 10.3 μ. In the recrystallized samples of 8, this absorption was absent, hence the cis assignment.

For this synthesis to be useful in the synthesis of D-sphingosine, the Wittig reaction conditions must be altered so that the trans isomer of 8 will predominate. This aspect is currently under investigation.

Experimental Section[12]

3-Benzyloxycarbonylamino-3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (4).—A solution of 8.0 g (31 mmol) of 3-amino-3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (3)[10] in 130 ml of dry pyridine was cooled to 0° under nitrogen, and then 21.8 ml (124 mmol) of benzyl chloroformate was added dropwise with stirring and continued cooling. The mixture was stored at 0–5° for 18 hr, and then 4 ml of water was added dropwise with stirring to decompose the excess benzyl chloroformate. After *ca.* 0.5 hr at room temperature, the mixture was partitioned between 200 ml each of chloroform and saturated aqueous sodium bicarbonate. The layers were separated and the aqueous fraction was extracted with two additional portions of chloroform. The chloroform extracts were washed with water, combined, dried, and evaporated to dryness *in vacuo* to give 20.6 g of brown oil.

The oil was extracted with 100 ml of boiling cyclohexane. The cyclohexane solution was decanted and cooled to give 7.8 g (64%) of product as white crystals, mp 74–76°. The thin layer chromatography showed one spot at R_f 0.87 using solvent A. Recrystallization from 20 ml of cyclohexane gave the analytically pure product: mp 74–76°; λ_{max}^{Nujol} 5.80 (C=O), 8.60 μ (gem dimethyl); $[\alpha]^{20}D$ +55° (*c* 0.49, chloroform).

Anal. Calcd for $C_{20}H_{27}O_7N$: C, 61.1; H, 6.92; N, 3.56. Found: C, 61.1; H, 6.79; N, 3.54.

6-Benzyloxycarbonylamino-2,2-dimethyl-5-formyl-3a,5,6,6a-tetrahydro-D-ribofuro[2,3-*d*]dioxolane (6).—A solution of 5.9 g of 3-benzyloxycarbonylamino-3-deoxy-1,2:5,6-di-O-isopropylidene-α-D-allofuranose (4) in 145 ml of 75% aqueous acetic acid was heated at 60° under a nitrogen atmosphere for 20 min and then was cooled to −10° in an ice–salt bath. A solution of 5 *N* aqueous sodium hydroxide was added dropwise with vigorous stirring until pH 7 was obtained, and then the mixture was extracted with three 100-ml portions of chloroform. The combined chloroform extracts were washed with water, dried, and evaporated to dryness *in vacuo* to give a quantitative yield of 3-benzyloxycarbonylamino-3-deoxy-1,2-O-isopropylidene-α-D-allofuranose (5) as a colorless oil.

Thin layer chromatography showed one spot with R_f 0.30 and 0.19 in solvents A and B, respectively.

A stirred solution of 5.6 g (16 mmol) of 5,6-diol (5) in 85 ml of 50% aqueous methanol was treated with 3.45 g (16 mmol) of sodium metaperiodate under a nitrogen atmosphere. The reaction was stirred at room temperature for 1 hr by which time a white precipitate had separated. The reaction was filtered and the filtrate was extracted with three 200-ml portions of chloroform. The chloroform layers were washed with water, and then dried and evaporated to dryness *in vacuo* to give a quantitative yield of product 6 as a colorless oil: λ_{max}^{film} 5.85 (C=O), 8.60 μ (gem dimethyl).

Thin layer chromatography using solvent B showed one spot at R_f 0.37.

The semicarbazone 7 prepared by the procedure of Shriner and Fuson,[13] was recrystallized from ethanol and had mp 197–198°, $[\alpha]^{22}D$ +59° (*c* 0.50, methanol).

Anal. Calcd for $C_{17}H_{22}N_4O_6$: C, 54.0; H, 5.86; N, 14.8. Found: C, 54.3; H, 5.97; N, 14.7.

Tetradecyltriphenylphosphonium Bromide.—A mixture of 10.0 g (0.36 mol) of 1-bromotetradecane and 9.5 g (0.36 mol) of triphenylphosphine was heated at 140° under a nitrogen atmosphere for 5 hr. The reaction formed a solid gel when it was cooled. The gel was dissolved in 50 ml of dried (over molecular sieves) acetone and 120 ml of dry diethyl ether was added. The solution was cooled at 0° and then filtered to give 15.3 g (78%) of product (2) as white crystals, mp 91–94°. The analytical sample was prepared by recrystallization from acetone–ether to give white crystals with mp 94–96°.

Anal. Calcd for $C_{32}H_{44}BrP$: C, 71.2; H, 8.22; Br, 14.8. Found: C, 71.5; H, 8.36; Br, 14.7.

6-Benzyloxycarbonylamino-2,2-dimethyl-5-(1-pentadecenyl)-3a,5,6,6a-tetrahydro-D-ribofuro[2,3-*d*]dioxolane (8).—To a stirred solution of 9.44 g (17.5 mmol) of tetradecyltriphenylphosphonium bromide in 625 ml of dry benzene under a nitrogen atmosphere was added 8.93 ml of phenyllithium solution (17.6 mmol). The mixture was stirred for 10 min, and then a solution of 5.2 g (16.2 mmol) of fresly prepared aldehyde 6 in 50 ml of dry benzene was added. The reaction was heated at reflux for 21 hr, and then the benzene was evaporated to dryness *in vacuo* to yield 19.9 g of residue as a brown oil. Thin layer chromatography (solvent B) showed no trace of aldehyde (6) and the oil gave a negative test for reducing sugar using Benedict's reagent.

The residue was dissolved in 10 ml of dry benzene and was applied to a column which contained 143 g of silica gel. The column was developed with 275 ml of benzene and then 1000 ml of 10% diethyl ether in benzene. The ether–benzene fraction was evaporated to dryness *in vacuo* to give 2.4 g (30%) of product (8) as an oil which crystallized on standing and was satisfactory for the next step.

Thin layer chromatography using solvent C showed two spots at R_f 0.75 and 0.70, presumably the cis and trans isomers of 8: λ_{max}^{film} 5.85 (carbonyl), 6.65 (amide II), 8.6 (gem dimethyl), 10.3 μ (weak, trans-disubstituted olefin).

Recrystallization of the crystalline mixture from 30 ml of methanol gave 444 mg of product, mp 72–73°, which was homogeneous on thin layer chromatography in solvent C with R_f 0.75: λ_{max}^{Nujol} 5.85 (carbonyl), 6.6 (amide II), 8.6 μ (gem dimethyl).

The absence of infrared absorption at 10.3 μ is consistent with the assignment of a cis configuration, $[\alpha]^{20}D$ −4° (*c* 0.48, chloroform).

Anal. Calcd for $C_{30}H_{47}NO_5$: C, 71.8; H, 9.44; N, 2.79. Found: C, 72.1; H, 9.46; N, 2.89.

2-Benzyloxycarbonylamino-D-*erythro*-Δ⁴-octadecene-1,3-diol (11).—A solution of 2.0 g of mixed cis–trans isomers (8) in 100 ml of 80% aqueous acetic acid was heated at reflux under a nitrogen atmosphere for 3 hr. The solution was evaporated to dryness *in vacuo* to give 1.68 g of crude diol 9 as a brown oil. Thin layer chromatogaphy in solvent C showed no trace of starting material.

To a solution of the above diol (1.68 g, *ca.* 3.64 mmol) in 400 ml of methanol under a nitrogen atmosphere was added 1.07 g (5.0 mmol) of sodium metaperiodate. The mixture was stirred at room temperature for 16 hr and then was filtered. The filter cake was washed with methanol and the combined filtrate and washings were evaporated to dryness *in vacuo*. The residue was partitioned between chloroform and water. The chloroform extract was washed with water, dried, and evaporated to dryness *in vacuo* to give a 100% yield of the aldehyde 10 as an oil.

A solution of 1.25 g (2.9 mmol) of the above aldehyde (10) in 180 ml of methanol was cooled to 0° under a nitrogen atmosphere, and then a solution of 109 mg (2.9 mmol) of sodium borohydride in 60 ml of methanol was added dropwise with stirring. The reaction was stirred for 16 hr and then was evaporated to dryness *in vacuo* to yield a brown oily residue which was partitioned be-

(12) Melting points are corrected. Organic solutions were dried using anhydrous magnesium sulfate. Thin layer chromatograms were run on silica gel HF (E. Merck A. G. Darmstadt). Spots were detected using iodine vapor. Solvent systems used for developing the chromatograms were: A, ethyl acetate–diethyl ether (1:3); B, ethyl acetate–chloroform (1:1); C, 10% diethyl ether in benzene; D, 10% benzene in ether. Silica gel chromatography was carried out using Gallard Schlesinger reagent grade silica gel (90–200 mesh).

(13) R. L. Shriner and R. C. Fusion, "The Systematic Identification of Organic Compounds," Wiley, New York, N. Y., 1948, p 170.

tween 200 ml each of water and chloroform. The layers were separated and the aqueous phase was extracted with three additional portions of chloroform. The chloroform layers were washed with water, dried, and evaporated to dryness *in vacuo* to yield 0.98 g of an oil which solidified. Thin layer chromatography in solvent D showed a number of spots with a major one at R_f 0.75.

Trituration of the oil with cold hexane gave 123 mg of product with mp 63–66°, $[\alpha]^{20}D$ −6° (*c* 0.26, chloroform). Thin layer chromatography in solvent D showed one spot at R_f 0.75: λ_{max}^{Nujol} 5.95 (carbonyl), 6.5 (amide II), 10.3 μ (weak, trans-disubstituted olefin).

Anal. Calcd for $C_{26}H_{43}NO_4$: C, 72.0; H, 10.0; N, 3.23. Found: C, 71.8; H, 10.2; N, 3.39.

2-Amino-D-*erythro*-octadecane-1,3-diol (12) (D-Dihydrosphingosine).—A solution of 105 mg (0.24 mmol) of 2-benzyloxycarbonylamino-D-*erythro*-Δ^4-octadecene-1,3-diol (11) in 2.7 ml of glacial acetic acid was hydrogenated at atmospheric pressure and room temperature using 68 mg of 10% palladium on charcoal for 20 hr. The hydrogenation mixture was filtered and the filtrate was evaporated to dryness *in vacuo* to yield 82 mg of product as a white solid which was characterized as the sulfate.[14] Recrystallization from glacial acetic acid gave crystals, mp 150° dec, λ_{max}^{Nujol} 6.5 μ (NH).

Anal. Calcd for $C_{33}H_{80}N_2O_8S$: C, 61.7; H, 11.5; N, 4.0. Found: C, 61.7; H, 11.3; N, 4.12.

Lesuk, *et al.*,[14] reported that the sulfate slowly darkened on heating and finally melted at 265° dec. Thus the melting point does not appear to be a reliable criterion for identification.

D-Dihydrosphinogosine Triacetate (13).—Acetylation of crude D-dihydrosphingosine using acetic anhydride in pyridine gave crystals, mp 90–93°, $[\alpha]^{19}D$ +16° (*c* 0.5 in chloroform), which had the same infrared spectrum as authentic dihydrosphingosine triacetate[8b] and which gave no melting point depression when a mixture melting point was determined with a sample of authentic dihydrosphingosine triacetate which had been prepared from commercially available D-sphingosine sulfate. D-dihydrosphingosine triacetate is reported to have mp 98°, $[\alpha]D$ +17° (*c* 1.4, chloroform).[15]

Registry No.—**2**, 25791-20-2; **4**, 25791-21-3; **6**, 25834-61-1; **7**, 25791-22-4; **8**-*cis*, 25791-23-5; **8**-*trans*, 25834-62-2; **11**, 25834-63-3; **12**, 764-22-7; **12** sulfate, 25791-25-7.

(14) A. Lesuk and R. J. Anderson, *J. Biol. Chem.*, **139**, 457 (1941).

(15) C. A. Grob, E. F. Jenny, and H. Utzinger, *Helv. Chim. Acta*, **34**, 2249 (1951).

12α-Etiojerva-1,4-diene-3,17-dione

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Microbiological oxidation of the 12α-pregnajervane **1f** produces the title compound **4a** whose structure was proven unambiguously by an alternate synthesis from the same starting material. This route involves successive Baeyer–Villiger oxidation, oxidation of the 3-hydroxyl group (→ **2e**, R′ = Ac), selenium dioxide oxidation of the A ring (→ **4e**, *R′* = Ac), saponification of the acetate, and oxidation of the resulting 17-hydroxyl group. The stereochemistry of the C-17 substituents is discussed.

Microbiological oxidation of saturated pregnanes has proved a useful method to prepare the corresponding A ring unsaturated derivatives.[1] Since analogous compounds in the 12α-etiojervane series were of interest for biological evaluation, the 12α-pregnajervane[2,3] (**1f**) (R = H) was submitted to bacterial oxidation. The chief product (~30%) was not the dienone **4f** although the desired A ring grouping was present (uv and nmr analysis). An overoxidation (Scheme I) of a type familiar in the pregnanes[1] had occurred, yielding a tetracycle in which the 17-acetyl group had been degraded to the 17 ketone (without epimerization at C-13). The gross structure **4a** was suggested by the presence of a saturated carbonyl band at 5.83 μ and the absence of the acetyl signal near 125 Hz.

Structural confirmation of the fermentation product was accomplished without difficulty since a similar compound, the 17β-hydroxy-1,4-diene (**4e**, R′ = H, 13α-CH_3) had been prepared earlier in the 12α,13α-etiojervane series by an unambiguous chemical synthesis.[3a] Oxidation of the hydroxyl group in the latter compound afforded a material spectrally very similar to the fermentation product, but differing in its optical rotation (+162° *vs.* −86°). The difference between the two compounds, a result of the stereochemistry at C-13, was resolved by treating the less stable 13β-methyl derivative (**4a**) with base, generating the more stable 13α-methyl compound **4b**.[4]

When the activity of the unstable dienone **4a** as an aldosterone-blocking agent was discovered,[5] additional supplies of this compound and its derivatives were required. The moderate yields of the dienedione **4a** from fermentation and the limited success of early attempts to utilize it chemically led to the exploration of its chemical synthesis.

Although the starting ketone **1c** has the 13-methyl in the desired configuration, side chain degradation by Beckmann rearrangement of its oxime, even under carefully controlled conditions, caused epimerization at C-13.[3a] Attempted utilization of this accessible 13α epimer **1b** by hydrogenation of its enol diacetate (Δ^{17}) yielded, after saponification, largely hydrogenolyzed materials containing little of the desired 17β-diol **1e** (R = R′ = H).

Conversion of the unsaturated ketone **1a** (Δ^{12})[3a] to the desired 13β-methyl compound was attempted by hydrogenation over several palladium catalysts; however, the preponderant product in each case was the stable 13α-methyl derivative.[6] Use of platinum catalysts, in an effort to reduce both the olefinic and the car-

(1) W. Charney and H. L. Herzog, "Microbial Transformations of Steroids," Academic Press, New York, N. Y., 1967.

(2) The term "etiojervane" and "pregnajervane" represent 17aβ-methyl-*C*-nor-D-homo-18-nor-5α,13β-androstane and its pregnane analog, respectively. See F. C. Chang and R. C. Ebersole, *Tetrahedron Lett.*, 3521 (1968).

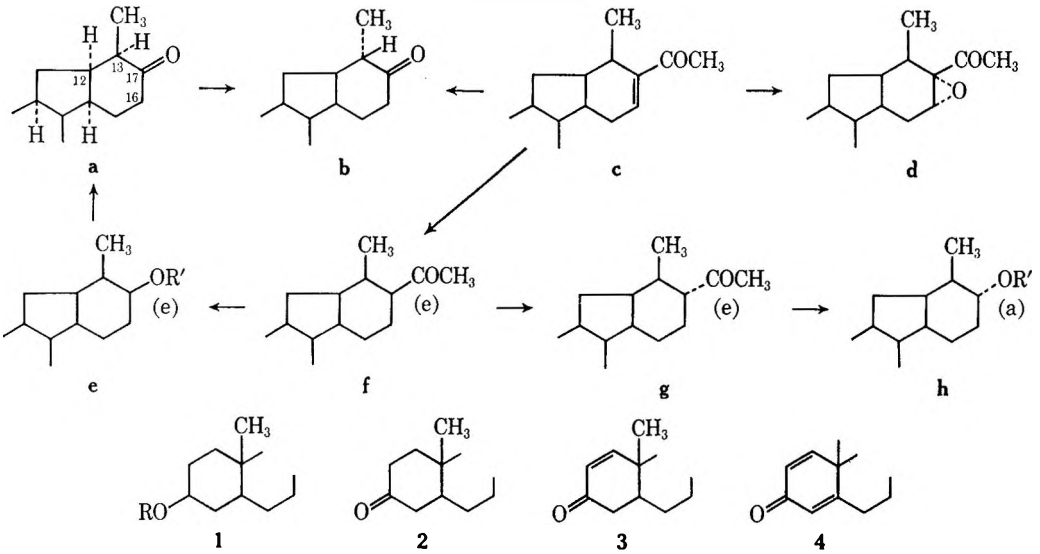
(3) (a) W. F. Johns and I. Laos, *J. Org. Chem.*, **30**, 123 (1965); (b) W. F. Johns, *ibid.*, **29**, 2545 (1964).

(4) A similar epimerization of the 13-methyl group is described in ref 3a.

(5) Private communication from Dr. L. Hofmann of these laboratories. The activities of this and related compounds will be included in a future communication.

(6) A recent communication reports formation of the 13β-methyl derivatives in this way, success apparently a result of the difference in catalysts employed: *cf.* H. Mitsuhashi and N. Kawahara, *Tetrahedron*, **21**, 1215 (1965).

SCHEME I



R, R′ = H, Ac, CHO

bonyl groups before C-13 epimerization occured, led mainly to hydrogenolyzed materials.

Reduction of the carbonyl group of **1a** (Δ^{12}) with lithium tri-*tert*-butoxyaluminohydride was a very slow reaction; subsequent catalytic reduction of the Δ^{12} double bond afforded the desired 13β-methyldiol **1h** (R′ = H) as well as hydrogenolysis products. The 17α configuration of the hydroxyl group in the final product (as well as in its unsaturated precursor) was demonstrated by its spectral identity with the known diol (see below). A successful concurrent attempt to produce diol **1h** was achieved by lithium aluminum hydride reduction of the 16,17 epoxide **1d**,[3a] periodate cleavage of the resulting 17,20-diol, and lithium alumium hydride reduction of the 17 ketone. Neither of these sequences proceeded in sufficiently high yields to warrant their further utilization.

Although initial studies[3a] of the Baeyer–Villiger oxidation of the 17β-pregnajervane **1f** to the 17β-acetate **1e** (R′ = Ac) with hot performic acid met with only moderate success, the yields were improved considerably by the use a large excess of *m*-chloroperbenzoic acid.[7] The 17α-pregnajervane **1g** was obtained from the β isomer by treatment with base and predominated (~20:1) in the resulting equilibrium mixture. This compound smoothly underwent *m*-chloroperbenzoic acid oxidation to yield a new acetate **1h** (R′ = Ac) clearly different from that derived from the β-acetyl derivative. The possibility of preoxidation isomerization of the β-acetyl side chain is thus ruled out.[8] Both the 17α- and 17β-acetates (**1e**, **1h**) from these two oxidations were hydrolyzed to their respective diols (**1e**, **1h**, R = R′ = H) and these in turn were oxidized to a single diketone **2a**, showing the pairs to be epimeric only at C-17.

A relatively unstrained D ring conformation, in which the 13-methyl group and the 17α substituent are equatorial, is postulated for both C-17 acetates **1e** and **1h**. This assignment is in agreement with the relative sharpness and position of the nmr signals for their respective C-17 protons. The ORD curve of the parent 17α-acetyl derivative **1g**[9] shows a weak positive Cotton effect; octant rule analysis indicated no change in D ring conformation from that in **1h**, if it is assumed that the 20-carbonyl group lies between C-18 and the 16β hydrogen. This assumption is reasonable both from inspection of the molecular model and by analogy to the normal steroids.[10] The strong positive Cotton effect seen in the ORD spectrum of the unstable 17β-acetyl compound **1f**[11] indicates a conformational change in which C-18 is now axial, again assuming that the carbonyl group lies between C-18 and the 16β hydrogen. This change results from an interaction of the axial 17β-acetyl group with C-19 which is stronger than that between the axial 13-methyl and C-19.

The 17β-diacetate **1e** (R = R′ = Ac), the immediate product of the Baeyer–Villiger oxidation of **1f** (R = Ac), could not easily be hydrolyzed to the 17-monoacetate **1e** (R = H; R′ = Ac), a compound required for further A ring transformations. Selective oxidation of the corresponding 3,17β-diol **1e** (R = R′ = H) afforded the unwanted 3-hydroxy 17-ketone **1a** (although the 3,17α-diol **1h** did give the useful 3-keto-17α-ol **2h**). A more fruitful route entailed Baeyer–Villiger oxidation of the 3-formate derivatives. These were formed without epimerization at C-17 by a brief contact of either 3-hydroxy compound (**1f**, **1g**) in formic acid at room temperature, or alternatively, by hydrogenation of **1c** (R = CHO). The oxidation product from either formate, a mixed ester, was selectively hydrolyzed by a simple passage of the crude product over an alumina column[12] to yield the desired 3-hydroxy-17-acetates (**1e** or **1h**).

Oxidation of the 3-hydroxy group proceeded smoothly and each of the epimeric ketoacetates **2e**, **2h** (R′ = Ac) were characterized by saponification to the correspond-

(7) Dr. P. B. Sollman, of these laboratories, is to be thanked for having developed this procedure. See the Experimental Section for precautions necessary to ensure the safe isolation of the product from this mixture.

(8) These results amend the incorrect configurational designation of the Baeyer–Villiger product given in ref 3a.

(9) Professor W. Klyne, Westfield College, University of London, is to be acknowledged for providing the ORD measurements of these compounds as well as for a helpful discussion relating to their interpretation.

(10) N. L. Allinger, P. Crabbé, and G. Perez, *Tetrahedron*, **22**, 1615 (1966).

(11) A recent communication describes similar configurational assignments: H. Suginome, N. Sato, and T. Masamune, *Tetrahedron Lett.*, 2671 (1969).

(12) See W. F. Johns and D. M. Jerina, *J. Org. Chem.*, **28**, 2922 (1963), and references cited terein.

ing ketols **2e**, **2h** (R′ = H). The 17α derivative thus produced was identical with that obtained above. Oxidation of either hydroxy ketone afforded the 13β-methyl diketone **2a** in good yield.

Selenium dioxide oxidation of the 17β-acetate **2e** (R′ = Ac) effected introduction of the desired 1,4-diene system in only moderate yields. The chief by-products were the Δ¹ derivative **3e** (R′ = Ac) and intractable selenium-containing tars; none of the Δ⁴ derivative was seen. Conversion of the Δ¹ derivative to additional dienone was possible in modest yields by further treatment with selenium dioxide. Dichlorodicyanoquinone oxidation of either the Δ¹ derivative **3e** (R′ = Ac) or the corresponding saturated ketone **2e** (R′ = Ac) yielded virtually none of the dienone **4e** (R′ = Ac). Removal of selenium from the intractable by-products was attempted with ammonium sulfide treatment[13] alone or preceded by saponification of the 17-acetate, but little improvement in yield resulted. The 17α-acetate **2h** (R′ = Ac) similarly provided a fair yield of the 1,4-dienone **4h** (R′ = Ac), accompanied by the Δ¹ ketone **3h** (R′ = Ac).

An alternative pathway for conversion of the Δ¹-etiojervane **3e** (R′ = Ac) to the corresponding 1,4-diene **4e** (R′ = Ac) was investigated by use of 17β-acetoxyandrost-1-en-3-one as a model compound. Cupric bromide bromination[14] of this compound followed by base catalyzed elimination of the resultant 4-bromine atom afforded 40% of the desired 17β-acetoxyandrosta-1,4-dien-3-one. The limited yields of this sequence coupled with the success of an alternative route led to abandonment of this scheme.

The 17β-acetate **4e** was saponified to provide the corresponding 17 alcohol. This compound in turn was oxidized with the chromium trioxide–pyridine to yield the dienedione **4a**, identical in all respects with the initially described fermentation product.

Experimental Section[15]

3,17-Diacetoxy-12α-etiojerv-13-ene (1e, Δ¹³, R = R′ = Ac).—Aqueous perchloric acid (70%, 0.3 ml) was added to 3 ml of acetic anhydride at 5°. The resulting solution was added to a solution of 0.50 g 3β-hydroxy-12α,13α-etiojervan-17-one (**1b**, R = H)[3a] in 30 ml of benzene and 10 ml of carbon tetrachloride. The solution was allowed to come to room temperature. After 4 hr, ice was added and the product was isolated by extraction with carbon tetrachloride in a standard manner (washing consecutively with water and with aqueous potassium bicarbonate, drying over magnesium sulfate, and concentrating at a temperature below 50°). Recrystallization of the crude product from hexane gave 0.29 g of the enol diacetate: mp 101–102°; 5.74 μ; 45 (19-CH_3), 89 (C=CCH_3), 120 (3-OAc), 126 (17-OAc) Hz.

Anal. Calcd for $C_{23}H_{34}O_4$: C, 73.76; H, 9.15. Found: C, 73.96; H, 9.33.

Hydrogenation of this enol acetate over a variety of catalysts effected at best a slow reduction affording a preponderance of hydrogenolyzed product. After base hydrolysis of the crude hydrogenation products, no homogeneous sample of a diol could be obtained. Similarly, hydrogenolysis was seen when the unsaturated ketone **1a** (R = H, Δ¹²)[3a] was reduced over platinum catalyst.

Etiojerv-12-ene-3β,17α-diol 3-Acetate (1h, Δ¹², R = Ac; R′ = H).—A solution of 0.5 g of the unsaturated ketone **1a** (Δ¹², R = Ac) in 40 ml of tetrahydrofuran at 5° was treated with 1.5 g of lithium tri-*tert*-butoxyaluminohydride. After 18 hr the solution was poured into water and the product was extracted with methylene chloride. The crude product was purified by preparative thin layer chromatography yielding 355 mg of crystalline material which was recrystallized from acetone–hexane to give 180 mg of the unsaturated alcohol **1h** (R = Ac; R′ = H[12]): mp 133–135°; 2.75, 5.78 μ; 47 (19-CH_3), 102 (18-CH_3), 248 (m, 17-H) Hz.

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.98; H, 9.68.

This compound was oxidized with manganese dioxide to the starting unsaturated ketone **1a** (Δ¹², R = Ac).

12α-Pregnajervane-3β,17α,20-triol.—A solution of 1.0 g of the oxide **1d** (R = Ac) in 50 ml of tetrahydrofuran was added to a slurry of 0.7 g of lithium aluminum hydride in 100 ml of tetrahydrofuran. The mixture was stirred at room temperature for 18 hr and at reflux for 2 hr. The solution was cooled and diluted slowly and consecutively with 20 ml of ethyl acetate, 2 ml of water, and 2 ml of 10% aqueous potassium hydroxide. The mixture was filtered through Super-Cel and the resulting solution was concentrated to dryness. The residue was recrystallized from methylene chloride–ethyl acetate to yield 0.30 g of the triol, hydrated with 0.25 mol equiv of water: mp 200–205°; 2.75 μ; 48 (19-CH_3), 52 and 59 (18-CH_3) Hz.

Anal. Calcd for $C_{21}H_{36}O_3 \cdot 0.25\ H_2O$: C, 73.96; H, 10.79. Found: C, 73.99; H, 10.39.

Treatment of 65 mg of this triol in 4 ml of methanol and 0.2 ml of pyridine with 0.1 g of paraperiodic acid in 1 ml of water for 1.5 hr at room temperature provided, after dilution with water and filtration of the resulting precipitate, 32 mg of the pure 13β-methyl ketone **1a** (R = H) (by spectral comparison).[3a]

3β-Hydroxy-12α,17α-pregnajervan-20-one (1g, R = H).—A solution of 6 g of the saturated ketone **1f** (R = H) in 100 ml of methanol and 10 ml of 10% aqueous potassium hydroxide was heated at reflux in an atmosphere of nitrogen for 0.5 hr, and was cooled and diluted with excess 1% aqueous hydrochloric acid. The resulting precipitate was filtered, washed with water, and dried; it had $[\alpha]_D$ −46°, corresponding to 5% of the 17β derivative. Recrystallization from aqueous acetone gave 4.6 g of the pure 17α-acetyl derivative **1g** (R = H): mp 136–137°; 2.75, 5.84 μ; ORD (*c* 1.97 mg/ml, MeOH) $[\phi]^{tr}_{343}$ −415, $[\phi]^{pk}_{300}$ +300°; inflection 250 mμ (ε 3195); α −35°; $[\alpha]_D$ −52°.[9,16]

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 79.35; H, 10.57.

Separation of this material from its epimer by thin layer, paper, or gas chromatography in a number of systems was not possible. Its ir and nmr spectra were essentially indistinguishable from those of the unstable β epimer **1f** (R = H). Attempted formation of the enol acetate of the β-acetyl derivative **1f** (R = H) with iso-propenyl acetate and *p*-toluenesulfonic acid led to mixtures containing minor amounts of enol acetate mixed with starting material and dark polymers.

The 3-acetate of the 17α-acetyl derivative **1g**, prepared with acetic anhydride and pyridine, failed to crystallize but exhibited the proper nmr absorption (3-OAc, 122; 17-$COCH_3$, 128 Hz). Again the nmr and ir spectra were very similar to those of the β epimer.

3β-Formyloxy-12α,17α-pregnajervan-20-one (1g, R = CHO).—The alcohol **1f** (34.5 g) was dissolved in 300 ml of formic acid. After 1 hr the stirred solution was slowly diluted with water. The resulting precipitate was recrystallized from aqueous methanol to yield 35.0 g of the formate **1g** (R = CHO): mp 95–96°; 5.80 μ; 45 and 52 (18-CH_3), 50 (19-CH_3), 483 (HCO_2) Hz; $[\alpha]_D$ − 53°.

Anal. Calcd for $C_{22}H_{34}O_3$: C, 76.26; H, 9.89. Found: C, 75.93; H, 9.81.

3β-Formyloxy-12α-pregnajervan-20-one (1f, R = CHO).—The alcohol **1f** (R = H, 26 g) dissolved in 150 ml of formic acid for 1 hr and diluted with water, afforded 26 g of the formate, mp 92 − 94°, after recrystallization from aqueous acetone: 5.81 μ; 45 and 51 (18-CH_3), 50 (19-CH_3), 483 (HCO_2) Hz; $[\alpha]_D$ +44°.

(13) A successful utilization of this procedure in the normal pregnanes has been described: M. Kocor and M. Maczka, *Bull. Acad. Pol. Sci.*, **14**, 347 (1966); *Chem. Abstr.*, **65**, 18651c (1966).

(14) See, *e.g.*, P. B. Sollman and R. M. Dodson, *J. Org. Chem.*, **26**, 4180 (1961); L. C. King and G. K. Ostrum, *ibid.*, **29**, 3459 (1964).

(15) We wish to thank Dr. J. W. Ahlberg and staff for the analyses and spectra reported. The infrared spectra were determined in chloroform, ultraviolet spectra in methanol, and rotations in chloroform (1%). Nmr spectra were determined in deuteriochloroform on a Model A-60 spectrometer, Varian Associates, Inc, at 60 Hz, using tetramethylsilane as an internal standard (Δν = 0). $W_{1/2}$ denotes peak width at half-height.

(16) This compound was first prepared by Mr. I. Loas, of these laboratories. The 17β-acetyl derivative displayed α = +116; see ref 3a.

Anal. Found: C, 76.40; H, 9.91.

3β-Formyloxy-12α-pregnajerv-16-en-20-one (1c, R = CHO), prepared by dissolving 1c (R = H) in formic acid for 1 hr, was recrystallized from aqueous acetone: mp 158–163°; 5.80, 6.00 μ; 235 mμ (10,600).

Anal. Calcd for $C_{22}H_{32}O_3$: C, 76.70; H, 9.36. Found: C, 76.60; H, 9.62.

12α-Etiojervane-3β,17α-diol 3-Formate 17-Acetate (1h, R = CHO; R′ = Ac). Procedure A.—The formate 1g (R = CHO, 4.8 g) in 80 ml of methylene chloride was treated with 3 g of *m*-chloroperbenzoic acid. After 6 days, 10 g of calcium hydroxide[17] was added to the solution and the mixture was stirred for 0.5 hr. The mixture was filtered and the solvent distilled. The residue was crystallized from pentane and recrystallized from aqueous acetone to yield 1.63 g of the formate **1h** (R = CHO, R′ = Ac): mp 102–106°; 5.78 μ; $[\alpha]_D$ −66°.

Anal. Calcd for $C_{22}H_{34}O_4$: C, 72.89; H, 9.45. Found: C, 73.21; H, 9.65.

The mother liquors of this reaction on chromatography[18] showed some of the starting material to be present. To effect complete reaction and circumvent the prolonged reaction times a modified procedure ("B") was developed.

B.—The formate 1g (43 g, R = CHO) and 100 g of *m*-chloroperbenzoic (70% pure) were dissolved in 0.5 l. of methylene chloride with stirring. After 22 hr the mixture was diluted with 3 l. of methylene chloride and added to a well-stirred slurry of 200 g of calcium hydroxide in 1 l. of methylene chloride over a 30-min period. (This method of work-up is required to avoid a very vigorous decomposition of the excess peracid). After 1 hr the mixture was filtered and the product isolated as above yielding a comparable yield of the 17α-acetate **1h** (R = CHO, R′ = Ac) with none of the starting material in evidence.

Baeyer–Villiger Oxidation of the 17β-Acetyl 3-Formate 1f.—Both procedures A and B were successfully employed on the 17β-acetyl derivative 1f (R = CHO) but the product failed to crystallize, even after chromatography. In procedure A, appreciable amounts of starting material were found after 14 days of reaction time. Boiling the reaction mixture was relatively ineffective in increasing the rate of reaction.

An earlier method used performic acid at 75° for 2 hr. The material balance was low and, under these conditions, the reaction incomplete. Basic hydrolysis of the product yielded the known 17β-diol **1e**[19] in good yield.

12α-Etiojervane-3β,17β-diol Diacetate (1e, R = Ac; R′ = Ac).—The *m*-chloroperbenzoic acid oxidation (procedure A) yielded after 3 days, from 3.2 g of the starting acetate 1f (R = Ac), a product which crystallized from pentane to yield 1.6 g of the diacetate **1e** (R = R′ = Ac): mp 107–111°; 5.78 μ; 50 (19-CH_3), 50 and 57 (18-CH_3), 122 (OAc), 280 (m, 3β-H), 298 (m, 17α-H) Hz; $[\alpha]_D$ 0°.

Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.36; H, 9.64. Found: C, 73.15; H, 9.41.

Saponification of this compound with base afforded the known 17β-diol **1e** in good yield.

12α-Etiojervane-3β,17α-diol Diacetate (1h, R = R′ = Ac).—The 3-acetate 1g (2.0 g) was treated with *m*-chloroperbenzoic acid (procedure A) and after 2 days yielded a product crystallized from ether and recrystallized from methylene chloride–hexane to give 0.18 g of the 17α-diacetate **1h** (R = R′ = Ac): mp 107–109°; 5.78 μ; 48 (19-CH_3), 52 and 57 (18-CH_3), 122 (OAc), 270–290 (3α,17β-H's) Hz; $[\alpha]_D$ −67°.

Anal. Found: C, 73.63; H, 9.58.

12α-Etiojervane-3β,17α-diol (1h, R = R′ = H). A. Hydrolysis of the Diacetate 1h. Procedure C.—A solution of 0.12 g of the diacetate **1h** (R = R′ = Ac) in 10 ml of methanol and 1 ml of 10% aqueous potassium hydroxide was heated at reflux for 1 hr, the methanol was distilled, and the reaction mixture was diluted with water. The resulting precipitate was collected on a filter and washed with water. Recrystallization from ether give the pure 17α-diol **1h**: mp 178–181°; 2.75 μ; 47 (19-CH_3), 56 and 63 (18-CH_3), 198–230 (17β-H, 3α-H) Hz.

Anal. Calcd for $C_{19}H_{32}O_2$: C, 78.03; H, 11.03. Found: C, 77.92; H, 10.94.

For comparison, the 3β,17β-diol **1e**[19] had the following nmr signals: 48 (19-CH_3), 56 and 63 (18-CH_3), 200–225 (3α-H), 225–235 (17α-H) Hz.

B. Hydrogenation of the Unsaturated Alcohol 1h (Δ^{12}, **R = Ac; R′ = H**).—The acetate **1h** (Δ^{12}, R = Ac; R′ = H; 0.11 g) in 50 ml of acetic acid containing 0.1 g of 5% rhodium–alumina was shaken with hydrogen at 40 psi for 6 hr. The mixture was filtered and the filtrate concentrated to dryness. The residue was saponified (procedure C) to afford a semicrystalline product which was recrystallized to yield 41 mg of the 3β,17α-diol **1h**, mp 172–176°, identical by ir, nmr, and tlc comparisons with the above sample.

Selective Oxidation of the 3β,17α-diol 1h.—Jones reagent[20] (0.25 ml, 4 *N* chromic acid solution) was added to a solution of 300 mg of the 17α-diol **1h** in 50 ml of acetone at 10°. After 10 min the product was extracted with methylene chloride, yielding as the principal product (nmr, ir, and tlc analysis), the 3β-hydroxy 17-ketone **1a**. With excess oxidizing reagent the known 3,17-diketone **2a**[3a] was formed.

12α-Etiojervane-3β,17β-diol 17-Acetate (1e, R = H; R′ = Ac). Procedure D. A. Alumina-Catalyzed Hydrolysis.—The 3-formate 17β-acetate **1e** (43 g) was chromatographed on 3 kg of Merck Alumina. Early eluates afforded 0.5 g of a crude ester mixture. Elution with 10% ethyl acetate–benzene afforded 34.4 g of material which was recrystallized from acetone–hexane to give 24.6 g of the 3-alcohol **1e** (R = H, R′ = Ac): mp 92–94°; 2.75, 5.79 μ; 48 (19-CH_3), 51 and 58 (18-CH_3), 214 (m, 3α-H), 298 (m, $W_{1/2}$ = 10 Hz, 17α-H) Hz.

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.40; H, 10.25. Found: C, 75.28; H, 10.04.

B. Potassium Carbonate Hydrolysis.—A solution of 1.82 g of the diacetate **1e** (R = R′ = Ac) in 20 ml of methanol and 10 ml of water containing 0.75 g of potassium carbonate were mixed at 15°. After 7 hr, the solution was diluted with water. The product was extracted with methylene chloride and purified by chromatography yielding material which was crystallized from ether–hexane to afford 0.65 g of the 17β-acetate **1h** (R = H, R′ = Ac), mp 92–94°, described above.

12α-Etiojervane-3β,17α-diol 17-Acetate (1h, R = H; R′ = Ac).—A brief alumina chromatograph (procedure D) afforded, from 31 g of the pure formate **1h** (R = CHO, R′ = Ac), 21.5 g of the recrystallized (acetone–hexane) 3-alcohol 17-acetate **1h** (R = H, R′ = Ac): mp 129–131°; 2.72, 5.76 μ; 48 (19-CH_3), 51 and 58 (18-CH_3), 214 (m, 3α-H), 280 (m, $W_{1/2}$ = 19 Hz, 17β-H) Hz.

Anal. Found: C, 75.69; H, 10.23.

17β-Acetoxy-12α-etiojervan-3-one (2e, R′ = Ac). Procedure E.—A solution of 0.63 g of the monoacetate **1e** (R = H, R′ = Ac) in 20 ml of acetone at 5° was treated with 1 ml of 4 *N* chromic acid solution (Jones reagent).[20] After 0.5 hr at ambient temperature the solution was diluted with water and 1 ml of 2-propanol. The product was extracted with methylene chloride and chromatographed. The material eluted with 2% ethyl acetate–benzene consisted of 0.56 g of the 17β-acetate **2e** which solidified slowly (recrystallization failed): 5.82 μ; 53 and 59 (18-CH_3), 61 (19-CH_3), 301 (m, 17α-H, $W_{1/2}$ = 11 Hz) Hz.

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 76.01; H, 9.88.

17α-Acetoxy-12α-etiojervan-3-one (2h, R′ = Ac).—Oxidation of the alcohol **1h** (R = H, R′ = Ac) by use of procedure E yielded a crystalline product on dilution of the reaction mixture with water. From 15.5 g of the starting alcohol, there was obtained 14.6 g of the pure ketone **2h** (R′ = Ac): mp 104–105°; 5.78 μ; 52 (19-CH_3), 52 and 59 (18-CH_3), 280 (m, $W_{1/2}$ = 18 Hz, 17β—H) Hz.

Anal. Found: C, 75.57; H, 9.62.

17β-Hydroxy-12α-etiojervan-3-one (2e, R′ = H).—Saponification of 0.35 g of the 17β-acetate **2e** (procedure C) afforded directly a crystalline product, recrystallized from acetone–hexane to yield 0.19 g of the 17β-alcohol **2e**: mp 121–124°; 2.73, 5.84 μ; 58 and 64 (18-CH_3), 60 (19-CH_3), 232 (m, $W_{1/2}$ = 10 Hz, 17α-H) Hz; $[\alpha]_D$ +31°.

Anal. Calcd for $C_{19}H_{30}O_2$: C, 78.57; H, 10.41. Found: C, 78.52; H, 10.41.

Reacetylation of the hydroxy compound afforded the 17β-acetate **2e** in good yield.

(17) H. B. Henbest and B. Nicholls, *J. Chem. Soc.*, 4608 (1957).

(18) The chromatographies described in this paper were routinely run on a weight of silica gel 60 times that of the weight of the product being separated. We thank Mr. R. T. Nicholson and staff for their competent execution of these chromatograms.

(19) This compound, with the C-17 configuration incorrectly assigned, appears in ref 3a: *cf.* the discussion above.

(20) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

17α-Hydroxy-12α-etiojervan-3-one (2h, R′ = H).—Saponification of 0.85 g of the 17α-acetate **2h** (procedure C) afforded an amorphous product which was crystallized from ether and recrystallized from acetone–cyclohexane to yield the 17α alcohol **2h**: mp 150–153°; 2.72, 5.82 μ; 58 (19-CH_3), 58 and 64 (18-CH_3) Hz; $[\alpha]D$ −10°.

Anal. Found: C, 78.50; H, 10.43.

17β-Acetoxy-12α-etiojervane-1,4-dien-3-one (4e, R′ = Ac). Procedure F.—Selenium dioxide (0.3 g) was added to a solution of 0.9 g of the ketone **2e** (R′ = Ac) in 20 ml of *tert*-butyl alcohol and 0.1 ml of pyridine. The solution was boiled under an atmosphere of nitrogen. The same quantities of pyridine and selenium dioxide were added after 24 and 48 hr. After a total of 4 days, the solution was cooled and filtered, using methylene chloride to wash the insoluble precipitate. The combined solutions were concentrated to near dryness and then diluted with water and extracted with ethyl acetate. The extract was washed with water, potassium bicarbonate, water, cold ammonium sulfide solution, cold ammonium hydroxide, and again with water. The product obtained (0.90 g) was chromatographed. Elution with 5% ethyl acetate–benzene afforded 0.10 g of amorphous 17β-acetoxy-12α-etiojervan-1-en-3-one (**3e**, R′ = Ac): 5.78, 5.97 μ; 230 mμ (9900); 53 and 60 (18-CH_3), 62 (19-CH_3) 347 and 357 (C_1 H), 418 and 428 (C_2 H) Hz.

Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.06; H, 8.95.

Attempts to convert the ketone **3e** (R′ = Ac) to 1,4-diene by retreatment with selenium dioxide under similar conditions or by use of dichlorodicyanoquinone in refluxing benzene led to additional dienone **4e** (R′ = Ac), but the yields were erratic and generally low.

Continued elution of the above chromatographic column gave crude fractions (0.51 g) recrystallized from acetone–hexane to afford 0.34 g of the dienone **4e** (R′ = Ac): mp 135–137° as a hemiacetonate; 5.78, 6.00, 6.16 μ; 243 mμ (16,600); 53 and 59 (18-CH_3), 73 (19-CH_3), and C=CH signals at 365, 376, 378, 412, and 422 Hz.

Anal. Calcd for $C_{21}H_{28}O_3 \cdot {}^1/_2C_3H_6O$: C, 75.59; H, 8.74. Found: C, 75.75; H, 8.47.

In other runs, removal of selenium from the product was attempted by boiling the dark product in ethanol containing aqueous ammonium sulfide.[13] The product was isolated, reacetylated with pyridine–acetic anhydride, and rechromatographed. The yields after such treatment (or retreatment of chromatographed portions) were not noticeably improved. Also, saponification of the entire product followed by chromatography gave no increase in yield.

17β-Acetoxyandrosta-1,4-dien-3-one from 17β-Acetoxyandrostan-1-en-3-one.—A solution of 0.75 g of 17β-acetoxyandrost-1-en-3-one and 2 g of cupric bromide in 200 ml of tetrahydrofuran was heated at reflux under nitrogen for 20 hr. The colorless solution was consecutively distilled to half volume, diluted with water, and extracted with methylene chloride. The resulting unstable bromide in 20 ml of dimethylformamide was added to 40 ml of boiling dimethylformamide containing 2 g of magnesium oxide. After 2 hr the mixture was cooled and filtered. The solvent was removed *in vacuo* and the residue extracted with methylene chloride. The resulting dark oil was chromatographed on silica and yielded first 90 mg of starting material followed by 0.29 g (40%) of the 1,4-diene, spectrally identical with an authentic sample.

17α-Acetoxy-12α-etiojerva-1,4-dien-3-one (4h, R′ = Ac).—The acetate **2h** (R′ = Ac, 0.63 g) was oxidized with selenium dioxide (procedure F). After 20 hr the product was isolated and chromatographed on silica, yielding, besides some starting material, 0.20 g of crude 1,4-diene, which was recrystallized from acetone–hexane to yield the pure compound: mp 112–114°; 5.78, 6.01 μ; 242 mμ (14,100).

Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.42; H, 8.48.

17β-Hydroxy-12α-etiojerv-1-en-3-one (3e, R′ = H). Procedure G.—A solution of 0.8 g of the ester **3e** (R′ = Ac) in 30 ml of *tert*-butyl alcohol containing 5 ml of 10% aqueous potassium hydroxide was heated at reflux with stirring under an atmosphere of nitrogen for 1 day. The solvent was distilled and the product isolated by methylene chloride extraction. Chromatography yielded fractions (0.18 g) eluted with 15% ethyl acetate–benzene which were recrystallized from acetone–hexane to yield 0.10 g of the 17β-alcohol **3e** as a hemiacetonate: mp 79–87°; 2.72, 5.95 μ; 230 mμ (8900); 59 and 66 (18-CH_3), 62 (19-CH_3), 345 and 355 (C_1 H), 417 and 422 (C_2 H) Hz.

Anal. Calcd for $C_{19}H_{28}O_2 \cdot {}^1/_2C_3H_6O$: C, 77.56; H, 9.84. Found: C, 77.71; H, 9.81.

17β-Hydroxy-12α-etiojervane-1,4-dien-3-one (4e, R′ = H).—The acetate (**4e**, R′ = Ac, 0.9 3 g) was saponified (procedure G) in 3 hr yielding, after recrystallization from methylene chloride–hexane, 0.44 g of the dienone: mp 125–127°; 2.75, 6.07, 6.18 μ; 244 mμ (16,400); 58 and 66 (18-CH_3), 73 (19-CH_3) Hz; $[\alpha]D$ +41°.

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.77; H, 9.26.

Acetylation of this material afforded in good yield the acetate **4e** (R′ = Ac).

12α-Etiojerva-1,4-diene-3,17-dione (4a). A. Fermentation.[21]—*Nocardia sp.* ATCC No. 19534 was innoculated into a sterile nutrient mixture of 6 g of beef extract and 10 g of peptone in 2 l. of distilled water, and the mixture was incubated with agitation and aeration for 25 hr at room temperature. A solution of 1.37 g of the acetate **1f** (R = Ac) in 32 ml of acetone and 32 ml of methanol was added and the mixture was incubated for 40 hr. The mixture was then extracted with methylene chloride and the product (0.80 g) was chromatographed. Starting material (0.18 g) was eluted with 1% ethyl acetate–benzene. Elution with 30% ethyl acetate–benzene afforded 0.32 g of material, recrystallized from methylene chloride–hexane, to yield 0.16 g of the dienedione **4a**: mp 176–180°; 5.82, 5.99 μ; 242 mμ (16,800); 58 and 63 (18-CH_3), 72 (19-CH_3), 364 (C_4 H), 373 and 374 (C_1 H), 406 and 411 (C_2 H) Hz; $[\phi]^{pk}_{255}$ +17,800; $[\phi]^{tr}_{309}$ 5680; α +235°;[9] $[\alpha]D$ −86°.

Anal. Calcd for $C_{19}H_{24}O_2$: C, 80.24; H, 8.57. Found: C, 79.99; H, 8.36.

B. Oxidation of the 17β-Alcohol (4e, R′ = H).—A solution of 0.14 g of the 17β alcohol **4e** in 5 m of pyridine was added to a slurry of 0.2 g of the Sarett reagent[22] prepared from 0.2 g of chromium trioxide. After 10 min at 5° the solution was allowed to warm to room temperature. After 1.5 hr the mixture was diluted with water and the product extracted with ether. The material was recrystallized from methylene chloride–cyclohexane to yield 95 mg of the dione **4a**, mp 169–176°, identical in the ir and nmr with the above material.

12α,13α-Etiojervane-1,4-diene-3,17-dione (4b). A. Base-Catalyzed Epimerization.—The dione (**4a**, 40 mg) was treated with base (procedure C) for 3 hr. The solvent was blown off in a stream of nitrogen and the product isolated by methylene chloride extraction. The material was recrystallized from ether to yield the 13α-dione **4b**, mp 122–124°, mmp (with starting material) 100–110°; both ir and nmr spectra were very similar with those of **4a**; $[\alpha]D$ +162°.

Anal. Found: C, 80.00; H, 8.38.

B. Chromic Acid Oxidation.—The alcohol **4e** (R′ = H, 13α-CH_3) was oxidized with chromic acid (procedure E). The mixture was diluted with water and the product extracted with methylene chloride. The material crystallized and was recrystallized to afford the diketone **4b** identical with that produced above.

Registry No.—**1c** (R = CHO), 26019-85-2; **1e** (Δ^{13}, R, R′ = Ac), 26019-86-3; **1e** (R = R′ = Ac), 26019-87-4; **1f** (R = CHO), 26019-88-5; **1g** (R = H), 26094-16-6; **1g** (R = CHO), 26019-89-6; **1h** (Δ^{12}, R = Ac; R′ = H), 26019-90-9; **1h** (R = CHO, R′ = Ac), 26019-91-0; **1h** (R, R′ = Ac), 26019-92-1; **1h** (R, R′ = H), 26019-93-2; **1e** (R = H, R′ = Ac), 26019-94-3; **2e** (R′ = Ac), 26019-95-4; **2e** (R′ = H), 26019-96-5; **2h** (R′ = Ac), 26019-97-6; **2h** (R′ = H), 26019-98-7; **3e** (R′ = Ac), 26019-99-8; **3e** (R′ = H), 22785-13-3; **4a**, 22785-14-4; **4b**, 26020-02-0; **4e** (R′ = Ac), 22785-06-4; **4e** (R′ = H), 22785-11-1; **4b** (R′ = Ac), 26020-05-3; 12α-pregnajervane-3β,17α,20-triol, 26020-06-4.

(21) We are indebted to Dr. R. D. Muir and staff, of these laboratories, who ran this fermentation.

(22) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953).

Acknowledgment.—The competent technical assistance of Mrs. Barbara Tucker is gratefully acknowledged. The author wishes to thank Dr. Robert R. Burtner for the initial suggestion to explore fermentation of the pregnajervanes and for his valued counsel during the course of this work. The preparation of large quantities of intermediates was capably carried out by Mr. R. Salzmann.

The Synthesis of Model Compounds for Maleylacetoacetic Acid. Maleylacetone[1]

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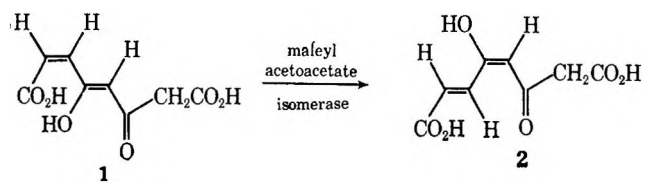
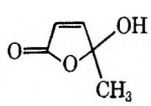
Configurationally labile maleylacetone has been prepared by the careful hydrolysis of 4-acetonylidenebut-2-ene-4-olide (*Z*) and shown to exist as a mixture of closed "pseudo" acid **4a** and open enol acid **4b** in chloroform and benzene and as "pseudo" acid in water. Ultraviolet and nmr spectra of the acids and anions are reported along with dissociation constants of the acid.

In the course of our study of *cis* to *trans* isomerizations we became interested in the mechanism of the enzymatic conversion of maleylacetoacetic acid (**1**) to fumarylacetoacetic acid (**2**). This *cis* to *trans* isomerization occurs in nature in the metabolism of aromatic amino acids.[2]



1 **2**

The study of this mechanism involves the synthesis and investigation of model compounds of **1** having similar but simpler structures. The first and simplest model compound prepared and its mechanism of isomerization studied was *cis*-β-acetylacrylic acid (**3**) which exists as the cyclic "pseudo" acid but as an

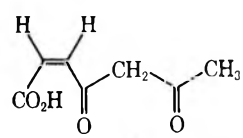


3

acyclic carboxylate anion.[3] The geometrical isomerization is catalyzed by thiocyanate ion which we consider to be a model for glutathione, the coenzyme needed for the enzyme-catalyzed isomerization of maleylacetoacetate. The role of the enzyme in this reaction is more obscure. The enzyme, we have suggested,[4] might catalyze the formation of a Schiff base between maleylacetoacetate and itself. The Schiff base, being more basic, would have a larger fraction protonated than the substrate and this in turn would enhance nucleophilic attack by glutathione thereby to catalyze isomerization.

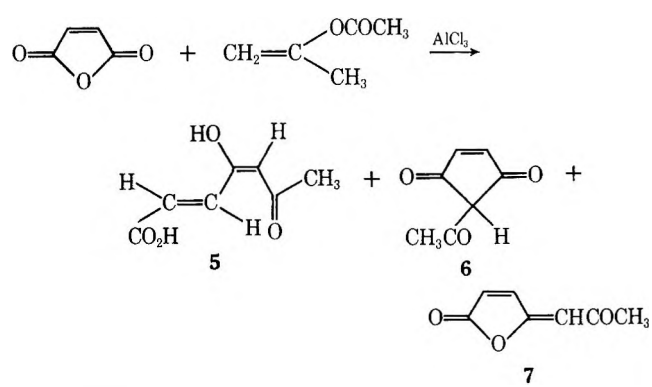
The anion of **3** was examined as to its ability to form Schiff bases with amines.[4] The predominant reaction, unfortunately, appears to be conjugate addition. Those amines possessing an α-nucleophilic atom such as hydroxylamine or semicarbazide, however, do form Schiff bases and the reactivity of the α,β-unsaturated semicarbazone towards thiocyanate was studied. Conjugate addition of amines to the γ,δ double bond in **1** might be less favorable because of the greater delocalization of positive charge and so it was of interest to see the effect of the introduction of an additional keto group, β to the original α′,β′-unsaturated carbonyl group of our first model compound. Moreover, such a molecule would be closer in structure to the natural substrate (**1**) and would be a more accurate model for studying other aspects of the chemistry of **1**.

A compound having the β-diketone moiety α to the *cis* double bond yet being simpler than maleylacetoacetic acid is maleylacetone (**4**). Maleylacetone has



4

previously been reported to have been isolated in 87% purity as a product of the enzymatic oxidation of homogentisic acid.[5] In addition, **4** has been suggested by Nilsson as a probable intermediate in the formation of fumarylacetone (**5**), 2-acetylcyclopentene-1,3-dione (**6**), and 4-acetonylidenebut-2-ene-4-olide (**7**), from the



5 **6** **7**

(1) Research carried out at Brookhaven National Laboratory under contract with the U. S. Atomic Energy Commission.

(2) W. E. Knox in "The Enzymes," Vol. 2, P. D. Boyer, H. Lardy, and K. Myrbäck, Ed., Academic Press, New York, N. Y., 1960, pp 282–289.

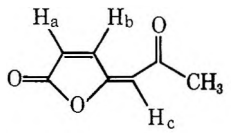
(3) (a) S. Seltzer and K. D. Stevens, *J. Org. Chem.*, **33**, 2708 (1968); (b) K. D. Stevens and S. Seltzer, *ibid.*, **33**, 3922 (1968).

(4) C. Santiago and S. Seltzer, in preparation.

(5) D. I. Crandall, *et al.*, *J. Biol. Chem.*, **235**, 3011 (1960), reported that in the isolation of maleylacetoacetic acid from the enzymatic oxidation of homogentisic acid nonenzymatic decarboxylation occurred to give maleylacetone.

aluminum chloride catalyzed condensation of maleic anhydride and isopropenyl acetate.[6]

We reinvestigated the condensation of isopropenyl acetate with maleic anhydride as a possible synthetic route to maleylacetone. By carrying out the condensation in methylene chloride at room temperature we were able to isolate a butenolide (**8**) isomeric with Nilsson's 4-acetonylidenebut-2-ene-4-olide. The two isomeric butenolides, **7** and **8**, differ in stereochemistry about the *exo* double bond. On examination of their nmr spectra it was possible to determine the structure



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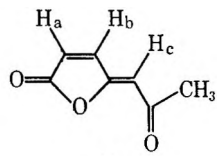
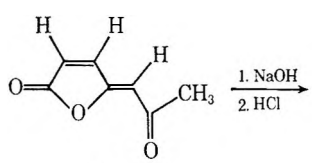


8

of each isomer. The coupling constant of the *exo* vinyl hydrogen (H_c) and H_a was 1.8 Hz in **7** and 0.8 Hz in **8**. Since larger couplings have been observed for protons with *trans* relationships over many bonds than those with *cis* relationships,[7] the structural assignments of 4-acetonylidenebut-2-ene-4-olide (*Z*), **8**, and 4-acetonylidenebut-2-ene-4-olide (*E*), **7**, were made.[8] When **8** is heated in chloroform for 4 hr, 27% of it is converted to **7**. We were not able to isolate **7** following Nilsson's reaction conditions and work-up.[9]

Butenolide **8**, when treated with 1 *N* sodium hydroxide dissolved within a few minutes at room temperature to give an orange solution which upon acidification in the cold followed by rapid extraction with methylene chloride gave maleylacetone as a mixture of the closed "pseudo" acid (**4a**) and open enol acid (**4b**). The aqueous phase of the reaction mixture deposits fumarylacetone (**5**) after standing for several hours at room temperature. The ratio of **4a** to **4b** varies from 3:1 to 15:1 in different reaction mixtures, the former ratio being observed more frequently. We have not determined the cause of the variability of the relative



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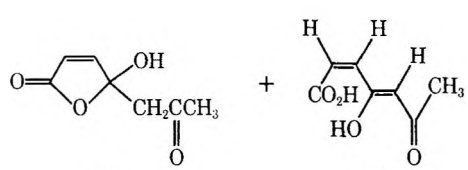
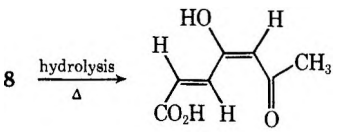


4a **4b**

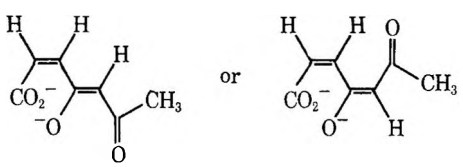
amounts of closed and open acids but suggest that it may be due to variations in both the pH after acidification in the hydrolysis step and the time lapse between acidification and extraction. Owing to the marked tendency for *cis* to *trans* isomerization to occur in maleylacetone, it was not possible to separate the two isomers. Maleylacetone can be stored at −6° for several weeks without appreciable isomerization in fumarylacetone. However, in aqueous solution or to chloroform, isomerization is rapid. For example, when **8** is hydrolyzed and the reaction mixture heated at 100° for a few minutes, fumarylacetone crystallizes from the solution.



6

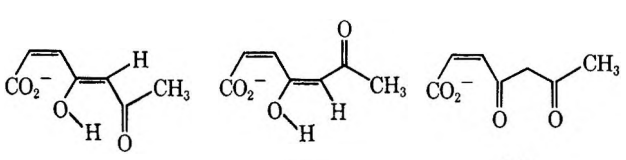
The ratio of **4a** and **4b** was determined from the nmr spectra. The ratio of the two isomers does not vary in chloroform-*d* or benzene-d_6. In water or deuterium oxide, however, maleylacetone exists exclusively as the "pseudo" acid **4a**.

The nmr spectra of the mono and dianions were taken. The dianion was prepared by dissolving the butenolide, **8**, in excess 1 *N* sodium hydroxide. The nmr spectrum showed two singlets in the vinyl region with relative areas of 2:1 Thus the *cis* vinyl protons have the same chemical shift and the presence of a third vinyl proton supports the enolate structure **9**.



9

Acidification of the basic solution gives a solution which has an nmr spectrum identical with that of maleylacetone in water. The monoanion was prepared by adding sodium bicarbonate to a solution of maleylacetone in deuterium oxide (pD of solution 8.34). The spectrum showed two different quartets (J = 12.5 Hz) and two different methyl singlets of equal intensity. The uv spectrum at pH 8.34 exhibits a strong maximum at 312 nm indicating an extended conjugated system as in the enol forms **10a** and **10b**. Since the nmr



10a **10b** **10c**

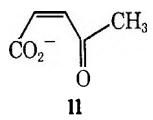
spectra were taken in D_2O, the observation of an additional vinyl proton at C-5 was precluded by its rapid exchange with the solvent. Along with the uv maximum at 312 nm there is also a double humped maximum at 212 and 243 nm which is reminiscent of the uv

(6) M. Nilsson, *Acta Chem. Scand.*, **18**, 441 (1964).

(7) T. Schaefer, *J. Chem. Phys.*, **36**, 2235 (1962); R. T. Hobgood, Jr., and J. H. Goldstein, *J. Mol. Spectrosc.*, **12**, 76 (1964).

(8) Recently, J. E. Blackwood and coworkers [*J. Amer. Chem. Soc.*, **90**, 509 (1968)] introduced this nomenclature for the unambiguous specification of stereoisomerism about a double bond.

(9) Nilsson isolated butenolide **7** as a neutral compound in the reaction of maleic anhydride with isopropenyl acetate. The work-up involved separating **6** and **7** by extracting **6** from the organic phase with 2 *M* sodium hydroxide. Since **7**, like **8**, reacts with base to give maleylacetone, it would appear that it would only be possible to isolate **7** as a neutral compound if the extraction with base were carried out so rapidly that the hydrolysis of **7** is incomplete. Possibly this is the reason that we were not able to isolate **7** under Nilsson's reaction conditions.



11

spectrum of *cis*-β-acetylacrylate ion (**11**). Its spectrum has the same appearance with equal maxima at about 210 and 230–250 nm (ε ~6000).[3a] The uv and nmr spectra of the monoanion of maleylacetone in water are consistent with a mixture of enol (**10a** and/or **10b**) and keto (**10c**) forms. Since only two methyl singlets could be detected at 60 MHz it is impossible at this time to determine which enol **10a** or **10b** is present in greater quantity in aqueous solution.

These results can be compared with the keto–enol equilibrium of acetylacetone. In water at ambient temperatures, there is approximately 80% of the keto form.[10] Additional conjugation might be expected to increase the quantity of enol as it does in maleylacetone.

The pK_a values of maleylacetone as determined by titration with base are 4.2 and 9.4. The first ionization constant was also determined to be 3.95 by standard spectrophotometric techniques. The difference between this value and the value obtained for pK_{a_1} by titration (4.2) is probably due to the fact that the spectrophotometric pK_a determination was carried out at a constant ionic strength while the titration was not. The uv spectra of maleylacetone between pH 2 and 6.43 show an isosbestic point at 210 nm consistent with a pH-dependent equilibrium between an acid and its anion and a pH-independent equilibrium between two or more forms of monoanion.

The ultraviolet spectra of maleylacetone at pH 0.99, 6.43, and 13 are given in the Experimental Section.

The mass spectrum (see Experimental Section) of maleylacetone is consistent with its assigned structure. A portion of its spectrum shows strong similarities to that for 4-acetonylidenebut-2-ene-4-olide (*Z*). This may be due to the loss of water in the heated inlet system or after formation of the parent (*m/e* 156) ion.

Experimental Section[11]

4-Acetonylidenebut-2-ene-4-olide (*Z*) (**8**).—To a stirred slurry of 60 g (0.45 mol) of aluminum chloride in 400 ml of methylene chloride was added 20 g (0.204 mol) of maleic anhydride. The mixture was stirred at room temperature for 30 min and 20 g (0.20 mol) of isopropenyl acetate was added over a period of ~5 min. The reaction mixture was stirred for 5 hr at room temperature, and added to 500 ml of 2 *N* HCl with sufficient ice to maintain the temperature below 10°. The dark viscous complex was decomposed by stirring. The organic phase was separated and the acid extracted with methylene chloride (total methylene chloride, 200 ml). The organic phases were combined, filtered through Celite, and washed with 200 ml of 5% Na_2CO_3 (in three portions) followed by 50 ml of saturated NaCl. The organic phase was dried with anhydrous $MgSO_4$ and evaporated at room temperature. Two recrystallizations of the yellow semisolid residue from CCl_4 (20 ml) and treatment with carbon at the last recrystallization gave 0.9–1.2 g (3.3–4.3%) of pale yellow needles of **8**: mp 79–81°; uv max (cyclohexane) 280 nm (ε 19,600); ir (KBr) 1780 (vs), 1700 (s), and 1640 cm^{-1} (s); nmr ($CDCl_3$) δ 2.58 (s, 3 H, CH_3), 5.58 (s, 1 H, vinyl), 6.46 and 7.53 (q, 2 H, J = 5.5 Hz). The mass spectrum (80 eV) showed *m/e* (rel intensity) 138 (33), 123 (100), 95 (31), and 69 (30).

Anal. Calcd for $C_7H_6O_3$: C, 60.86; H, 4.37. Found: C, 61.11; H, 3.98.

4-Acetonylidenebut-2-ene-4-olide (*E*) (**7**).—The preparation of **7** was carried out using the same quantities and procedure as used in the preparation of **8**. However, when the crude semisolid was allowed to stand at −6° for 2 days, 0.45 g (1.15%) of a light tan solid, mp 100.5–101.5° (lit.[6] mp 97–101°), is obtained after recrystallization from carbon tetrachloride. The nmr spectrum of this compound is identical with that reported by Nilsson.[6]

Maleylacetone (**4**).—To 1.274 g (0.0092 mol) of butenolide **8** was added 25 ml of 1 *N* NaOH. The solid dissolved within a few minutes to give an orange solution which was washed with 10 ml of methylene chloride. The basic phase was cooled and acidified with concentrated HCl, and rapidly extracted with 40 ml of methylene chloride. The combined organic phases were washed with 10 ml of saturated NaCl solution and dried over anhydrous $MgSO_4$. A small amount of carbon was added, the solution filtered, and the solvent removed at room temperature at reduced pressure leaving 0.512 g (36%) of a pale yellow oil, which partially solidifies when stored at −6° for several days. The nmr spectrum showed that maleylacetone is a mixture of "pseudo" acid and open acid with the ratio variable between different reactions. The nmr spectrum ($CDCl_3$) showed δ 2.30 (s, 3 H, CH_3), 2.9–3.2 (q, 2 H, J = 16 Hz, CH_2 adjacent to asymmetric center), 6.12 and 7.35 (q, 2 H, J = 5.5 Hz, ring protons), and 7–8 (broad OH) for "pseudo" acid, **4a**, and 2.24 (s, 3 H, CH_3), 5.79 (s, 1 H, C-5 vinyl), 6.38 (s, 2 H, C-2 and C-3 vinyls), and 7–8 (broad OH) for the open acid **4b**. The position of the OH signal is variable and frequently a very broad signal is observed. The nmr spectrum (benzene-d_6) showed δ 1.70 (s, 3 H, CH_3), 2.1–2.8 (q, 2 H, J = 16 Hz, CH_2 adjacent to asymmetric center), 5.70 and 6.78 (q, 2 H, J = 5.5 Hz, ring protons) due to **4a** and δ 1.52 (s, 3 H, CH_3), 4.9 (s, 1 H, C-5 vinyl), and 5.58 and 6 (q, 2 H, J = 13 Hz, C-2 and C-3 vinyls) due to **4b**. Irradiation of the downfield half of the vinyl quartet of **4a** caused the upfield half of the quartet to collapse to a singlet thus fully exposing the previously obscured quartet of **4b**. The OH protons were not obvious in benzene-d_6 probably due to its absorption occurring over a wide area of the spectrum. The nmr spectrum in H_2O (reference, H_2O taken as 5 ppm from TMS) showed δ 2.22 (s, 3 H, CH_3), 3.28 (s, 2 H, CH_2), and 6.22 and 7.5 (q, 2 H, J = 5.5 Hz, ring protons) due to **4a** which appears to be the only isomer in this solvent. The ir spectrum (neat) showed 4000–3000 (broad, OH) and 1744–1704 cm^{-1} (d, C=O's). The mass spectrum (80 eV) showed *m/e* (relative intensity) 156 (51), 138 (21), 123 (86), 111 (100), 99 (28), 95 (42), 85 (32), and 69 (31). The uv spectrum showed $\lambda_{max}^{pH\ 0.99}$ 195 nm (ε 9300); $\lambda_{max}^{pH\ 6.43}$ 312 (ε 9300), 243 (4400), 212 (4100); $\lambda_{min}^{pH\ 6.43}$ 265 (ε 3300), 225 (4000); $\lambda_{max}^{pH\ 13}$ 323 (ε 14,000), 235 (4500); $\lambda_{min}^{pH\ 13}$ 270 (ε 1600).

Anal. Calcd for $C_7H_8O_4$: C, 53.84; H, 5.16. Found: C, 53.61; H, 5.25.

Molecular distillation of the pale yellow maleylacetone at 0.5 μ at 25° afforded a colorless viscous oil with identical nmr and ir spectra as described above.

Anal. Calcd for $C_7H_8O_4$: C, 53.84; H, 5.16. Found: C, 53.47; H, 5.47.

The aqueous phase, after standing for several hours at room temperature deposited 0.234 g (16% based on **8**) of fumarylacetone (**5**): mp 162–165° (lit.[6] mp 158–160°); uv max (0.1 *N* $HClO_4$) 312 nm (ε 14,000) [lit.[12] uv max (0.1 *N* HCl) 315 nm (ε 13,500)]; nmr (acetone-d_6) 2.24 (s, 3 H, CH_3), 6.04 (s, 1 H, C-5 vinyl), 6.60 and 7.00 (q, 2 H, J = 16 Hz, C-2 and C-3 vinyls), 4–5 (broad, 2 H, OH's).

Fumarylacetone (**5**).—To 0.41 g (0.00296 mol) of butenolide **8** was added 5.5 ml of 1 *N* NaOH. After the solid had dissolved, the orange solution was acidified with concentrated HCl and heated for 3 min on a steam bath. On cooling the solution deposited 0.19 g (41%) of light tan needles, mp 162–166° (lit.[6] mp 158–160°).

Disodium Salt of Maleylacetone (**9**).—To 0.056 g (0.00041 mol) of **8** was added about a threefold excess of 1 *N* NaOH and

(10) J. Powling and H. J. Bernstein, *J. Amer. Chem. Soc.*, **73**, 4353 (1951).

(11) All melting points were determined on a Reichert melting point block and are uncorrected. Uv spectra were recorded on a Cary 14 spectrophotometer. Infrared spectra were run on a Perkin-Elmer 337 spectrophotometer and nmr spectra were taken on a Varian A-60 instrument with TMS as internal standard unless otherwise specified. The mass spectrum was recorded on a Hitachi Perkin-Elmer RMU-7 mass spectrometer and pH measurements were made on an Orion Model 801 digital pH meter standardized at pH 4 and 7. Microanalyses were performed by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y.

(12) C. Kisker and D. I. Crandall, *Tetrahedron*, **19**, 701 (1963).

the nmr spectrum taken. The nmr spectrum (reference, water taken as 5 ppm from TMS) showed δ 2.38 (s, 3 H, CH_3), 5.55 (s, 1 H, C-5 vinyl), 6.34 (s, 2 H, C-2 and C-3 vinyls). The above solution was acidified with concentrated HCl and the nmr spectrum of the resulting solution was identical with that of maleylacetone in water. A similar experiment with butenolide **7** was carried out in order to show that it was also hydrolyzed to form maleylacetone.

Monosodium Salt of Maleylacetone (10).—To 0.038 g (0.00024 mol) of maleylacetone in 0.5 ml of D_2O was added 0.054 g (0.00064 mol) of $NaHCO_3$. After CO_2 evolution had ceased the nmr spectrum was taken and showed (reference, HOD taken as 5 ppm from TMS) δ 2.48 (s, 3 H, CH_3), 2.57 (s, 3 H, CH_3), 6.33 and 6.58 (q, 2 H, J = 12.5 Hz, C-2 and C-3 vinyls), 6.5 and 6.76 (q, 2 H, J = 12.5 Hz, C-2 and C-3 vinyls). The pD of this solution was 8.34. The solution from the nmr tube was diluted to 1 l., the pH adjusted to 7.99 with $NaHCO_3$ and HCl, and the uv spectrum run (λ_{max} 312 nm).

Titration of Maleylacetone.—Maleylacetone (0.16176 g, 0.001036 mol) in 20 ml of water was titrated with 0.1219 N NaOH using a glass electrode. The pH was measured after each 0.2 ml addition of base. The first neutralization equivalent required 8.40 ml of NaOH (0.001024 mol). The pK_a's were determined from the pH at addition of half an equivalent of base, the first two ionization constants being 4.2 and 9.4.

Dissociation Constants.—Nine acetic acid–sodium acetate buffer solutions containing lithium perchlorate were prepared to give solutions in which the sum of the acetic acid and sodium acetate concentrations was 0.01 M and the ionic strength was 0.1 M when diluted with a stock solution of maleylacetone. An Orion Model 801 digital pH meter standardized at pH 4 and 7 was used to determined the pH of each solution. Uv spectra were recorded on a Cary 14 spectrophotometer at 25° for each buffer solution containing 2.24×10^{-4} M maleylacetone. The reference cell contains buffer. Complete ionization was assumed at pH 6.43 (*i.e.*, $[anion]_{6.43} = [acid]_0$). Ratios of $[anion]_{pH}/[acid]_0$ were determined at 312 nm and taken as $O.D._{pH}/O.D._{6.43}$. A plot of these ratios gave pK_a = 3.95 when $[anion]_{pH}/[acid]_0$ = 0.5.

Registry No.—**4a**, 25517-95-7; **4b**, 25568-65-4; **7**, 25527-98-4; **8**, 25527-99-5; **9**, *cis,cis* (disodium salt), 25568-66-5; **9**, *cis,trans* (disodium salt), 25528-00-1; **10a** (monosodium salt), 25528-01-2; **10b** (monosodium salt), 25528-02-3; **10c** (monosodium salt), 25528-03-4.

Acknowledgment.—We wish to thank Dr. David Christman for recording the mass spectra.

The Prévost Reaction with 5-Substituted 5-Allylbarbituric Acids

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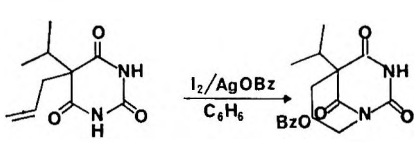
Received March 31, 1970

The Prévost reaction utilizing 5-substituted 5-allylbarbituric acids produced furopyrimidines by intramolecular O-alkylation. These compounds could be hydrolyzed readily in the presence of acid or converted to esters by treatment with the corresponding alcohol in the presence of acid.

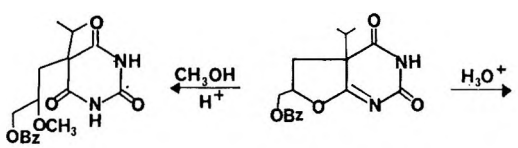
Meltzer and Lewis[2] reported the conversion of 5-isopropyl-5-allylbarbituric acid (**1**) to a bicyclic product **2** by the use of the "dry" Prévost reaction.[3]

In attempting to duplicate the work of Meltzer and Lewis in these laboratories, it was found that the product which they obtained had been assigned an erroneous structure and was not **2**, as they depicted.

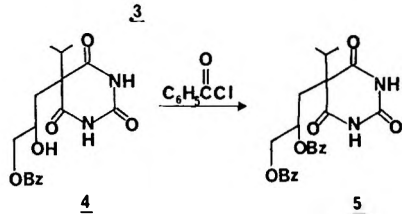


1 **2**

On examination, the cyclized product proved to be an O-alkylated structure, 4(a)-isopropyl-6-benzoyloxymethyl-5H,6H-furo[2,3-*d*]-$\Delta^{1,7a}$-2,4(3H)-pyrimidinedione (**3**). The infrared spectrum of **3** showed intense absorption at 1625 cm^{-1} (>C=N– stretching frequency).[4] The mass spectrum of **3** gave a molecular ion at *m/e* 330, consistent with its ascribed formula. The enol–ether, **3**, underwent facile conversion to 5-isopropyl-5-(2-hydroxy-3-benzoyloxypropyl) barbituric acid (**4**) during acid hydrolysis. The dibenzoate, **5**, was prepared by the treatment of **4** with benzoyl chloride



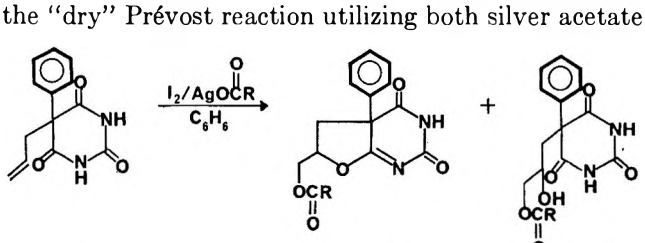
6 **3**



4 **5**

in pyridine. The alcohol methine proton in **4** was shifted from nmr δ 4.50 (3-proton multiplet) to 5.60 in the acylated product **5**. Compound **3** yielded a methyl ether, **6**, on treatment with methanol in the presence of acid (ether methine proton shifted 1.0 ppm downfield relative to the alcohol, **4**).

5-Phenyl-5-allylbarbituric acid (**7**) was subjected to the "dry" Prévost reaction utilizing both silver acetate



7 **8** **9**

a) R = CH_3

b) R = C_6H_5

(1) Taken in part from the dissertation presented by R. A. Robinson, July 1969, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

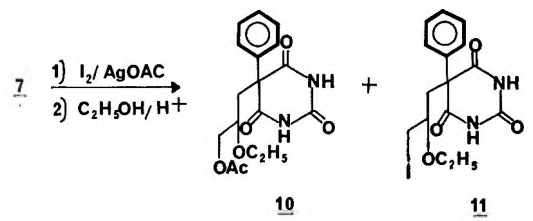
(2) R. I. Meltzer and A. D. Lewis, *J. Org. Chem.*, **21**, 256 (1956).

(3) C. V. Wilson, *Org. React.*, **9**, 360 (1957).

(4) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, San Francisco, Calif., 1962, p 39.

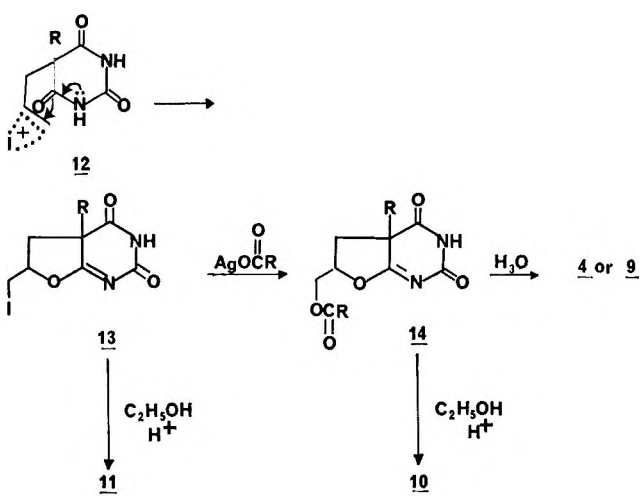
and silver benzoate. The corresponding furopyrimidines, **8a** and **8b**, and the corresponding hydrolysis products, the hydroxy esters, **9a** and **9b**, were isolated from the reactions. Both **8a** and **8b** were readily hydrolyzed to the hydroxy esters **9a** and **9b** in the presence of acid. The formation of **9a** and **9b** in the Prévost procedure can be attributed to partial hydrolysis of the furopyrimidines during chromatographic purification on silica gel.

Acid-catalyzed ethanolysis of a mixture resulting from the treatment of **7** with iodine and silver acetate afforded two compounds, 5-phenyl-5-(2-ethoxy-3-acetoxypropyl)barbituric acid (**10**) and an iodo ether (**11**).



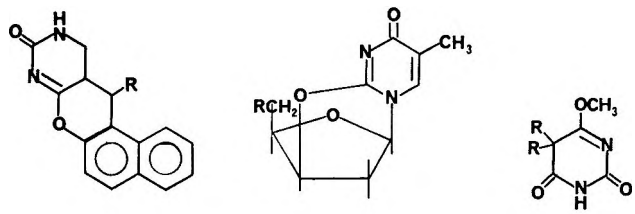
Nmr decoupling studies established the chemical shifts of the ether methylene and methine protons (δ 4.35–4.80) of **10**. The iodo ether was assigned structure **11** based on elemental analysis and spectral similarities (nmr) to **10**.

A plausible mechanism for the formation of the observed products involves the initial formation of an iodonium intermediate **12**, followed by neighboring



group participation of the imide electrons to form an intermediate iodine-containing furopyrimidine, **13**. The esterified product **14** would then be obtained by displacement of the primary iodo group by acetate anion. Acid-catalyzed ethanolysis of **13** and **14** would lead to the observed products, **10** and **11**.

The use of silver salts, particularly in solvents of low polarity, has been shown to favor alkylation in many ambident heterocyclic systems.[5–7] An anhydrothymidine analog, **15**, has been isolated *via* intramolecular alkylation with silver or alkali salts.[8,9] Other cyclic,



16,[10] and noncyclic, **17**,[11] enol ethers similar to the system reported in this paper have also been reported.

Experimental Section[12]

4(a)-Isopropyl-6-benzoyloxymethyl-5H,6H-furo[2,3-*d*]-$\Delta^{1,7a}$ 2,4(3H)-pyrimidinedione (3).—Silver benzoate (11.50 g, 0.05 mol) was suspended in 200 ml of C_6H_6. Iodine (6.35 g, 0.025 mol) (in 100 ml of C_6H_6) was added and the suspension stirred at room temperature for 15 min. To the suspension was added 5-isopropyl-5-allylbarbituric acid (**1**) (5.25 g, 0.025 mol) (suspended in 200 ml of hot C_6H_6), and the reaction was stirred and refluxed for 2 hr, cooled to room temperature, and filtered *in vacuo*. The benzene was removed and the residue chromatographed on silica gel. The column was eluted with $CHCl_3$ to afford a mixture of benzoic acid and **1** followed by 2.28 g (28%) of **3**: mp 170–172° [Me_2CO–petroleum ether (60–68°)] (lit.[1] mp 172–173.5°); ir (KBr) 3250, 1720, 1690, 1625 cm^{-1}; nmr (DMSO-d_6) 1.00 (6 H, triplet, CH_3), 2.00–2.41 (2 H, multiplet, CH_2), 2.50 (DMSO-d_5 and isopropyl methine), 4.46–4.70 (2 H, multiplet, CH_2OBz), 5.08–5.50 (1 H, multiplet, CH), 7.50–7.75 (3 H, aromatic), 7.91–8.10 (2 H, multiplet, *ortho*-aromatic), 10.96 (1 H, broad singlet, >NH).

Anal. Calcd for $C_{17}H_{18}N_2O_5$: C, 61.81; H, 5.49; N, 8.48. Found: C, 61.90; H, 5.60; N, 8.47.

5-Isopropyl-5-(2-hydroxy-3-benzoyloxypropyl)barbituric Acid (4).—To a solution of 0.100 g (0.303 mmol) of **3** in 5 ml of Me_2CO was added 4 drops of CF_3CO_2H and 2 ml of H_2O. The solution was warmed on a steam bath for 10 min and allowed to stand for 8 hr. The solvent was removed *in vacuo* and the H_2O azeotroped with several portions of C_6H_6. The residue was triturated with Et_2O and the solid material recrystallized from Et_2O–petroleum ether (60–68°) to give **4** (0.088 g, 84%): mp 178–181°; ir (KBr) 3450, 3220, 2910, 1740–1690; nmr (CF_3CO_2H) 0.96–1.33 (6 H, multiplet, CH_3), 1.96–3.00 (3 H, multiplet, CH_2 and isopropyl methine), 4.40–4.66 (3 H, multiplet, CH_2OBz and HCOH), 7.33–7.80 (3 H, multiplet, aromatic), 7.93–8.80 (2 H, multiplet, *ortho*-aromatic).

Anal. Calcd for $C_{17}H_{20}N_2O_6$: C, 58.61; H, 5.79; N, 8.04. Found: C, 58.58; H, 5.94; N, 7.98.

5-Isopropyl-5-(2,3-dibenzoyloxypropyl)barbituric Acid (5).—A solution of **4** (0.200 g, 0.575 mmol) in 15 ml of pyridine and BzCl (0.085 g, 0.575 mmol) was heated at 60° for 2 hr. The reaction mixture was cooled to room temperature, poured into an iced solution of dilute HCl, and extracted with Et_2O. The Et_2O extracts were washed with H_2O, dried ($MgSO_4$), and evaporated *in vacuo* to give an oil which was chromatographed on Silicar CC-4 (Mallinckrodt). The column was eluted with 60%

(5) N. Kornblum, R. A. Smiley, R. K. Blackwood, and D. C. Iffland, *J. Amer. Chem. Soc.*, **77**, 6269 (1955).

(6) G. C. Hopkins, J. P. Jonak, H. Minnemeyer, and H. Tieckelmann, *J. Org. Chem.*, **32**, 4040 (1967).

(7) G. C. Hopkins, J. P. Jonak, H. Tieckelmann, and H. J. Minnemeyer, *ibid.*, **31**, 3969 (1966).

(8) J. J. Fox and N. C. Miller, *J. Org. Chem.*, **28**, 936 (1963).

(9) J. P. Horowitz, J. Chua, J. A. Urbanski, and M. Noel, *ibid.*, **28**, 942 (1963).

(10) W. J. Doran, "Medicinal Chemistry," Vol. IV, F. F. Blicke and R. H. Cox, Ed., Wiley, New York, N. Y., 1959, p 143.

(11) J. A. Snyder and K. P. Link, *J. Amer. Chem. Soc.*, **75**, 1881 (1953).

(12) All melting points were taken on the Thomas–Hoover capillary melting point apparatus and are corrected. Analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind., by Weiler and Strauss Microanalytical Laboratory, Oxford, England, and on an F & M Model 185, University of Kansas. Infrared spectra were recorded on Beckman IR-8 and IR-10 spectrophotometers. Nuclear magnetic resonance spectra were recorded on A-60, A-60A, and HA-100 analytical spectrophotometers with tetramethylsilane as a standard. Nuclear magnetic resonance data are reported as δ values (parts per million). Molecular weights were determined on the Finnigan 1015 mass spectrometer.

Et_2O–40% Skellysolve B to yield **5** (0.036 g, 14%): mp 170–172° (Me_2CO–Skellysolve B); nmr (CF_3CO_2H) 9.03–1.13 (6 H, multiplet, CH_3), 2.06–3.00 (3 H, multiplet, CH_2 and isopropyl methine), 4.40–4.63 (2 H, multiplet, CH_2OBz), 5.26–5.82 (1 H, multiplet, HCOBz), 7.43–7.75 (6 H, multiplet, aromatic), 7.83–8.16 (4 H, multiplet, *ortho*-aromatic).

Anal. Calcd for $C_{24}H_{24}N_2O_7$: C, 63.71; H, 5.35; N, 6.19. Found: C, 63.98; H, 5.19; N, 6.22.

5-Isopropyl-5-(2-methoxy-3-benzoyloxypropyl)barbituric Acid (6).—A solution of 0.200 g (0.606 mmol) of **3** in 10 ml of absolute MeOH was treated in the manner previously described for **29** to give 0.160 g (83%) of **6**: mp 178–180.5°. [Me_2CO–petroleum ether (60–68°)]; nmr (CF_3CO_2H) 1.00–1.43 (6 H, multiplet, CH_3) 2.16–3.26 (3 H, multiplet CH_2 and isopropyl methine), 4.16 (3 H, singlet, OCH_3), 4.40–4.83 (2 H, multiplet, CH_2OBz), 5.33–5.96 (1 H, multiplet, $CHOCH_3$), 7.33–7.86 (3 H, multiplet aromatic) 7.90–8.33 (2 H, multiplet, *ortho*-aromatic).

Anal. Calcd for $C_{18}H_{22}N_2O_6$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.89; H, 5.84; N, 7.71.

4(a)-Phenyl-6-benzoyloxymethyl-5H,6H-furo[2,3-*d*]-$\Delta^{1,7a}$-2,4(3H)-pyrimidinedione (8b).—A suspension of AgOBz (4.70 g, 20.5 mmol), iodine (2.60 g, 10.2 mmol) and 5-phenyl-5-allylbarbituric acid (**7**) (2.50 g, 10.2 mmol) in 600 ml of anhydrous C_6H_6 was prepared according to the procedure outlined for **3**. The reaction was refluxed with stirring for 90 min and cooled to room temperature. Filtration and removal of the C_6H_6 *in vacuo* afforded a residue which was taken up in $CHCl_3$ and passed through silica gel (90% $CHCl_3$–10% 2-propanol). An oil was obtained which was chromatographed on Silicar CC-4 (Mallinckrodt). Elution with 90% petroleum ether (60–68°)–10% Et_2O yielded a mixture of **7** and benzoic acid. Increasing the Et_2O concentration to 40% gave **7** followed by 0.687 g 5-phenyl-5-(2-hydroxy-3-benzoyloxypropyl)barbituric acid (**9b**): mp 199–201° (Me_2CO–Skellysolve B); ir (KBr) 3450, 3210, 1750–1700; nmr (CF_3CO_2H) 3.00–3.60 (2 H, multiplet, CH_2), 4.50–4.80 (3 H, multiplet, CH_2–OBz, CHOH), 7.35–7.80 (8 H, multiplet, aromatic), 8.05–8.30 (2 H, multiplet, *ortho*-aromatic).

Anal. Calcd for $C_{20}H_{18}N_2O_6$: C, 62.82; H, 4.74; N, 7.32. Found: C, 6.282; H, 4.66; N, 7.25.

Further elution with 100% Et_2O gave 0.653 g (18%) of the furopyrimidine (**8b**), recrystallized from Me_2CO–petroleum ether (60–68°): mp 185–186.5°; ir (KBr) 3185, 1720, 1630; nmr (DMSO-d_6) 2.80–3.10 (2 H, multiplet, CH_2), 4.50–5.20 (3 H, CH_2OBz, -CHO'), 7.20–7.75 (8 H, multiplet, aromatic), 7.95–8.20 (2 H, multiplet, *ortho*-aromatic), 11.08 (1 H, broad singlet, >NH).

Anal. Calcd for $C_{20}H_{16}N_2O_6$: C, 65.93; H, 4.43; N, 7.69. Found: C, 66.03; H, 4.54; N, 7.61.

Treatment of **8b** with CF_3CO_2H, H_2O, and Me_2CO, as described for **4**, gave **9b** [ir and tlc (Silicar CC-4) (40% Et_2O–petroleum ether 60–68°) were identical with **9b** isolated from the reaction].

4(a)-Phenyl-6-acetoxymethyl-5H,6H-furo[2,3-*d*]-$\Delta^{1,7a}$-2,4-(3H)-pyrimidinedione (8a).—A suspension of AgOAc (4.08 g, 24.6 mmol), I_2 (3.12 g, 12.3 mmol), and **32** (3.00 g, 12.3 mmol) in 600 ml of dry C_6H_6 was prepared according to the method outlined for **8b**. The reaction was stirred and refluxed for 90 min, cooled and purified as described for the isolation of **8b**. Elution with 50% Et_2O–50% petroleum ether (60–68°) gave a mixture of **7** and a halogen containing compound. The column was eluted with 100% Et_2O to afford 0.245 g of the hydroxy acetate (**9a**): mp 200–202° [Me_2CO–petroleum ether (60–68°)]; ir (KBr) 3450, 3210, 1750–1700; nmr (CF_3CO_2H) 2.25 (3 H, singlet, CH_3), 2.70–3.25 (2 H, multiplet, CH_2), 4.20–4.68 (3 H, multiplet, CH_2OAc, CHOH), 7.45 (5 H, singlet, aromatic).

Anal. Calcd for $C_{15}H_{16}N_2O_6$: C, 56.24; H, 5.04; N, 8.75. Found: C, 56.45; H, 5.10; N, 8.74.

Further elution with 100% Et_2O gave 0.368 g (10%) of the furopyrimidine (**8a**): mp 160–164° [Me_2CO–petroleum ether (60–68°)]; ir (KBr) 3200, 1750, 1700, 1650; nmr (DMSO-d_6) 2.05 (3 H, singlet, CH_3), 2.65–2.90 (2 H, multiplet, CH_2), 4.15–4.81 (3 H, CH_2OAc, CHO–), 7.30–7.55 (5 H, multiplet, aromatic), 11.03 (1 H, broad singlet, NH).

Anal. Calcd for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.67; N, 9.27. Found: C, 59.40; H, 4.59; N, 9.07.

Compound **8a** was converted to **9a** by acid hydrolysis as described for **3** and **8b** (ir and tlc were superimposable with **9a** isolated from the reaction mixture).

5-Phenyl-5-(3-acetoxy-2-ethoxypropyl)barbituric Acid (10).—A suspension of silver acetate (6.80 g, 0.041 mol), iodine (5.17 g, 0.020 mol), and **7** (5.00 g, 0.020 mol) in 500 ml of dry C_6H_6 was prepared in the manner described for the synthesis of **3**. The reaction was stirred and refluxed for 2 hr, cooled to room temperature, and filtered *in vacuo*. After removal of solvent the residue was taken up in 600 ml of abs EtOH and filtered. A few drops of concentrated HCl were added which resulted in the formation of a precipitate. The mixture was filtered and the EtOH removed *in vacuo* (80°). During evaporation of the solvent, the reaction turned black. The residue was taken up in $CHCl_3$ and chromatographed on silica gel. The column was eluted with 85% $CHCl_3$–15% EtAc to yield 0.940 g of a yellow oil which was taken up in Et_2O. A crystalline solid, 0.690 g, mp 202–205° [Et_2O–petroleum ether (60–68°)] (positive Beilstein), was assigned structure **11**: nmr (CF_3CO_2H) 1.50 (3 H, triplet), 2.80–3.80 (3 H, multiplet), 4.35–4.80 (3 H, multiplet), 7.50 (4 H, singlet, aromatic).

Anal. Calcd for $C_{15}H_{17}N_2O_4I$: C, 43.28; H, 4.12; N, 6.73. Found: C, 43.48; H, 4.09; N, 6.65.

Further elution gave 1.29 g of an oil, resistant to further purification attempts, followed by 0.770 g of **10**, a white solid: mp 234–236° (EtOH); nmr (DMSO-d_6) 1.00 (3 H, triplet, CH_3), 2.00 (3 H, singlet, CH_3), 2.55–3.10 (2 H, multiplet), 3.25–4.45 (5 H, multiplet), 7.30 (5 H, singlet, aromatic).

Anal. Calcd for $C_{17}H_{20}N_2O_6$: C, 58.61; H, 5.79; N, 8.04. Found: C, 58.42; H, 5.45; N, 8.03.

Registry No.—**3**, 25568-67-6; **4**, 25517-96-8; **5**, 25517-97-9; **6**, 25517-98-0; **8a**, 25517-99-1; **8b**, 25518-00-7; **9a**, 25518-01-8; **9b**, 25518-02-9; **10**, 25518-03-0; **11**, 25518-04-1.

Acknowledgment.—The authors gratefully acknowledge support of this project by the National Institutes of Health Grants GM-9254.

Oxidative Degradation of Resin Acids[1]

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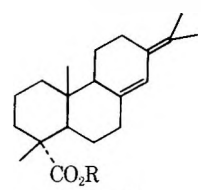
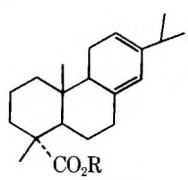
Received April 6, 1970

Lemieux oxidation of **1b** afforded **3b** in 50% yield, but the Lemieux oxidation of **2b** gave varying yields of **4b** and **5**. Procedures for the exhaustive ozonolysis of **1b** and **2b** have been standardized to afford the important synthetic intermediates, **3b** and **4b**, in 55–60% yields. Partial ozonolysis of **1b** afforded **6**, **8a**, and **10a**. The evidence for structures **8a** and **10a** is presented. RuO_4–$NaIO_4$ oxidation of **6**, **1b**, and **2b** gave **3b**, **3b**, and **4b** in excellent yields.

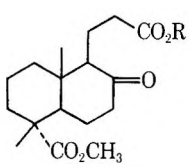
Chemical degradation products of resin acids have proven useful in elucidating the stereochemistry of certain natural products possessing the resin acids A/B ring stereochemistry.[2] A study of the biosynthesis of resin acids necessitated the development of efficient degradation procedures which could eventually be utilized to locate the labeled atoms in the radioactive resin acids. The quest for a simple method of effecting a one-step cleavage of the conjugated diene system in neoabietic acid (**1a**) and levopimaric acid (**2a**) to obtain the important bicyclic keto acids **3a** and **4a**, prompted us to carry out a systematic investigation of the oxidative degradation of resin acids.



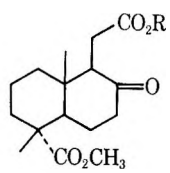
1a, R = H
b, R = CH_3



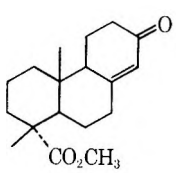
2a, R = H
b, R = CH_3



3a, R = H
b, R = CH_3



4a, R = H
b, R = CH_3



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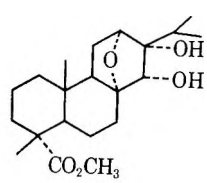

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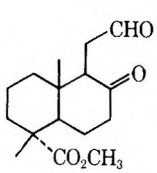

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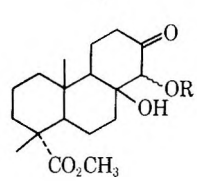
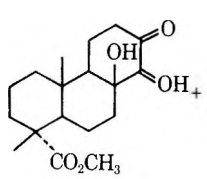


8a, R = H
b, R = $COCH_3$



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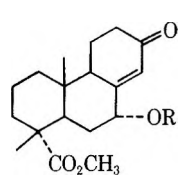


10a, R = H
b, R = $COCH_3$

Since the Lemieux–von Rudloff oxidation[3] of the enone ester **6** afforded the keto acid ester **3a** in 84% yield,[4] we were encouraged to study the reaction conditions best suitable for oxidizing **1b** and **2b**. While our work was in progress, Apsimon and coworkers reported[5] the Lemieux–von Rudloff oxidation of nonconjugated vinyl groups of methyl pimarate and methyl sandaracopimarate. Treatment of **1b** with potassium permanganate–sodium metaperiodate and aqueous dioxane for 48 hr afforded the keto acid ester **3a** in about 50% yields. When **2b** was subjected to the above treatment, varying yields of **4a** and **5**[6] were obtained. Although the dihydroxy oxide **5** can be converted to **4a** by using Jones reagent, the tedious purification required for the dioxane (see Experimental Section) and the varying yields of the keto acid ester **4a**, suggested a reinvestigation of the ozonolysis of **1b** and **2b**.

Exhaustive ozonolysis of **1b** in ethyl acetate at −70°, followed by work-up according to the procedure of Bailey,[7] afforded an oil, which on Jones oxidation[8] gave an acidic fraction in consistent yields of 60–65%. Methylation of this acid fraction with ethereal diazomethane and column chromatography over silica gel afforded the pure keto diester **3b** in 55% yield as a pale yellow oil, $C_{18}H_{28}O_5$: ν_{max} 1730 and 1710 cm^{-1}; nmr ($CDCl_3$) τ 6.3 and 6.33 (two carbomethoxyls), 7.5–7.8 (C-7 methylene), 8.86 (C-4 methyl), and 9.2 (C-10 methyl).

Earlier workers in this laboratory had reported[9] that drastic ozonolysis of **2b** gave the keto acid ester **4a** in yields varying from 20–45%. However, ozonolysis of **2b** in ethyl acetate at −70°, followed by work-up of Bailey and Jones oxidation, gave an acidic fraction in consistent yields of 60–70%. The acid fraction could be crystallized with some difficulty to afford the pure keto acid ester **4a**, mp 173–175°, but it was easier to purify the acid fraction by methylation with diazomethane and column chromatography over silica gel. The pure keto diester **4b** was obtained in 57–60% yields as a pale yellow oil, $C_{17}H_{26}O_5$: ν_{max} 1735 and 1710 cm^{-1}; nmr ($CDCl_3$) τ 6.29 and 6.32 (two carbomethoxyls), 7.5–7.9 (C-7 methylene), 8.78 (C-4 methyl), and 9.24 (C-10 methyl).

(1) S. W. Pelletier, K. N. Iyer, C. W. J. Chang, and A. Ogiso, *Tetrahedron Lett.*, **35**, 3819 (1968).

(2) See, *e.g.*, K. W. Gopinath, T. R. Govindachari, P. C. Parthasarathy, and N. Vishwanathan, *Helv. Chim. Acta*, **44**, 1040 (1961).

(3) R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1701 (1955).

(4) A. Ogiso and S. W. Pelletier, *Chem. Commun.*, 94 (1967).

(5) J. W. ApSimon, A. S. Y. Chau, W. G. Craig, and H. Krehm, *Can. J. Chem.*, **45**, 1439 (1967).

(6) H. Kanno, W. H. Schuller, and R. V. Lawrence, *J. Org. Chem.*, **31**, 4138 (1966).

(7) P. S. Bailey, *J. Amer. Chem. Soc.*, **78**, 3811 (1956).

(8) K. Bowden, I. M. Heilbron, E. R. H. Jones, and C. L. Weedon, *J. Chem. Soc.*, 39 (1946).

(9) S. W. Pelletier, L. B. Hawley, Jr., and K. W. Gopinath, *Chem. Commun.*, 96 (1967).

When the Jones oxidation step is omitted, the yields of **3b** and **4b** are lowered and this decrease in yield is more pronounced in the case of **4b**. It appears that one of the products of ozonolysis may be the ketoaldehyde ester **7** which would afford **4a** on Jones oxidation.

Partial ozonolysis of **1b**, which has been reported[10] to give the enone ester **6** in yields varying from 37–55%, afforded a viscous yellow oil. Purification of this oil by column chromatography over Florisil and preparative thick layer chromatography over silica gel gave the desired enone ester **6**, mp 127–128°, and two more polar products, compounds A and B, respectively.

Efforts to improve the yields of **6** using either potassium iodide–sodium thiosulfate,[7] or methyl sulfide[11] to decompose the ozonide succeeded in affording consistent yields of 60–65% of **6** and the amounts of compounds A and B were significantly reduced.

Compound A [mp 173–174°; $[\alpha]_D$ 11.5°; $C_{18}H_{28}O_5$; ν_{max} 3525, 3470, 3405, 1740, and 1728 cm^{-1}; nmr τ 8.94, 8.76 (two C methyls), 6.22 (carbomethoxyl), and 6.15 (one proton on a carbon bearing a hydroxyl group)] exhibited a major peak in its mass spectrum at m/e 323 (M − 1) attributable to the stable oxonium ion[12] **9**. The spectral data coupled with the fact that acetylation of compound A afforded only a monoacetate [mp 256–259°; $C_{20}H_{30}O_6$; ν_{max} 3460, 1755, 1735, 1724, and 1240 cm^{-1}] prompted us to assign structure **8a** to compound A, which may have been formed by epoxidation of the C_8–C_{14} double bond of **1b**, cleavage of the isopropylidine moiety, and opening of the epoxide. Epoxidation of double bonds during ozonolysis and subsequent opening of the epoxide has ample precedence.[13]

Compound B crystallized from ether–hexane as long needles, mp 153–154°, and exhibited ν_{max} 3440, 1705, 1680, 1640, 1620, and 1260 cm^{-1}, indicating the presence of a hydroxyl group and a conjugated ketone, whereas the ultraviolet absorption at 241 mμ and its high extinction coefficient (14,500) suggested the presence of basic enone structure in **6**. That hydroxylation may have occurred at either of the allylic positions at C-7 or C-9 was suggested by an elemental analysis corresponding to a $C_{18}H_{26}O_4$ formula. Evidence for the hydroxyl function at C-7 was obtained from the nmr spectrum, which showed a 1 H doublet at τ 4.03 (J = 2.5 cps) attributable to an α proton on a >C=C—C(=O)— function, the hydroxyl proton at τ 5.43 which was successfully exchanged upon deuteration, and the proton geminal to the hydroxyl as a 1 H triplet at τ 5.65. The three proton singlets at τ 9.15, 8.77, and 6.28 could be rationally ascribed to the C-10 methyl, C-4 methyl, and the C-4 carbomethoxyl, respectively. Further evidence for the secondary nature of the hydroxyl group was obtained from the acetate which was obtained under mild conditions, and the nmr spectrum of the acetate which showed a triplet at τ 4.57 (J = 3 cps) assignable to the proton geminal to the acetate group. In addition, compound B, which has a deshielded C-14 olefinic proton (τ 4.03) relative to that of **6** (τ 4.31), has its C-14 proton further downfield (τ 3.92) in the acetate.

Sarett oxidation of compound B gave an oil which exhibited absorption in the ultraviolet at ν_{max} 261 mμ characteristic of an emicisoid enedione moiety.[14] On the basis of all this evidence, we propose structures **10a** and **10b** for compound B and its acetate, respectively. Compound B may have arisen from **1b** by an allylic hydroxylation during ozonolysis and work-up. The stereochemistry of the hydroxyl group has been deduced from the nmr spectra of **6**, **10a**, and **10b**. Dreiding models show that the hydroxyl group, with an α-axial configuration has its geminal equatorial proton coupling with the C-6 methylene protons which form dihedral angles of 60° with respect to the C-7 proton. The observed coupling constant of 3 cps does not favor a β-equatorial hydroxyl configuration since an axial C-7 H, axial C-6 H vicinal coupling of 8–14 cps was not observed in the nmr spectrum.

A recent paper by Caspi, *et al.*,[15] utilizing ruthenium tetroxide–sodium metaperiodate in aqueous acetone for the efficient degradation of α,β-unsaturated and cross-conjugated ketones to the corresponding keto acids in high yields prompted us to investigate the utility of this reagent for the oxidative degradation of **6**, **1b**, and **2b**. The RuO_4–$NaIO_4$ oxidation of **6** proceeded smoothly to afford the keto acid ester **3a** in yields of about 80%. As mentioned previously, it was easier to purify the product as the keto diester **3b**. Oxidation of **1b** and **2b** afforded the keto diesters **3b** and **4b** in 70–77% yield. However, owing to the rather high cost of the ruthenium dioxide used and the tedious work-up, ozonolysis appears to be method of choice for degradation of **1b** and **2b** to the keto acid esters **3a** and **4a**, respectively, on a preparative scale.

Experimental Section

General Procedures.—Melting points are corrected and were taken on a hot stage equipped with a microscope and polarizer. Finely powdered samples were placed on the stage 15° below the melting point and the temperature was raised at a rate of about 4°/min. Ultraviolet spectra were determined in 95% ethanol on a Perkin-Elmer Model 202 spectrophotometer and infrared spectra on Perkin-Elmer Model 137, 237, or 457 spectrophotometers. Nuclear magnetic resonance (nmr) spectra were taken on Varian A-60 or HA-100 spectrometers in deuteriochloroform, unless otherwise stated, with tetramethylsilane as an internal standard. Ozonolyses were carried out using a Welsbach Model T-23 laboratory ozonator. Optical rotations were taken on a Perkin-Elmer Model 141 polarimeter. Gas phase chromatography was conducted using a Varian Aerograph 1520 chromatograph. The columns used were 4% QF-1 and 5% SE-30.

Purification of Dioxane.—After commercial dioxane had been purified according to the procedure outlined by Fieser,[16] the purified dioxane was treated at room temperature with small amounts of aqueous potassium permanganate till the solution was not decolorised. Considerable difficulty was encountered with certain batches of dioxane which consumed permanganate at a slow rate over several days and this method proved too tedious for practical use.

Lemieux Oxidation of the Enone Ester 6.—To a solution of 145 mg of the enone ester **6** in 50 ml of dioxane cooled at 15–20° was added a solution of 750 mg of $NaIO_4$, 50 mg of $KMnO_4$, and 25 mg of Na_2CO_3 in 30 ml of water. The mixture was stirred for 45 hr at room temperature. After excess reagent was decomposed by the

(10) G. C. Harris and T. F. Sanderson, *J. Amer. Chem. Soc.*, **70**, 339 (1948); A. W. Burgstahler and L. R. Worden, *ibid.*, **86**, 96 (1964).

(11) J. J. Pappas, W. P. Keaveney, E. Gancher, and M. Berger, *Tetrahedron Lett.*, **36**, 4273 (1966).

(12) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Interpretation of Mass Spectra of Organic Compounds," Holden-Day, San Francisco, Calif., 1964, p 28.

(13) P. S. Bailey, *Chem. Rev.*, **58**, 945 (1958).

(14) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," Pergamon Press, London, 1964, p 61.

(15) D. M. Piatak, H. B. Bhat, and E. Caspi, *J. Org. Chem.*, **34**, 112 (1969).

(16) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath, Boston, 1957, p 285.

careful addition of 5% H_2O_2 with ice cooling, the mixture was evaporated to remove the dioxane. The aqueous layer was extracted with chloroform followed by ether and both organic layers were extracted with 5% NaOH. The combined alkaline extract was acidified with concentrated HCl and extracted with ether. Evaporation of the ether gave an oil which was chromatographed on silica gel. Elution with chloroform gave 132 mg of an oil. The oil, the keto acid ester **3a**, and its methyl ester **3b** each showed a single spot on tlc with solvent systems of $CHCl_3$–MeOH (10:1) and benzene–ethyl acetate (5:1), respectively. The keto acid ester **3a** could not be induced to crystallize. It showed ν_{max} ($CHCl_3$) at 3400–2900 broad, 1715, 1212, 1255 cm^{-1}. Its nmr spectrum showed singlets at τ 9.23, 8.80, and 6.28.

Oxidation of Methyl Neoabietate.—To a solution of methyl neoabietate, derived from 450 mg of neoabietic acid (253 mμ, ϵ 25,600) by the standard methylation with diazomethane in ether, and 250 mg of sodium carbonate in 100 ml of dioxane and 20 ml of water was added a solution of 3.2 g of sodium metaperiodate and 150 mg of potassium permanganate in 50 ml of water at 15–20°. The mixture was stirred for 45 hr at room temperature. The reaction mixture should retain the color of permanganate during the reaction period. After excess reagent was decomposed by the addition of 5% hydrogen peroxide under ice cooling, almost all of the dioxane was evaporated *in vacuo*. The aqueous solution was acidified with concentrated hydrochloric acid and extracted with chloroform followed by ether. The organic layers were extracted with 5% sodium hydroxide. The organic layer was washed with water, dried over sodium sulfate, and evaporated to give 220 mg of a mixture of neutral compounds. The combined alkaline extract was washed with ether, acidified with concentrated hydrochloric acid, and extracted with ether thoroughly. The ether extract was washed with water, dried over sodium sulfate, and evaporated to give 320 mg of an oil. The acidic oil was chromatographed on 5 g of silica gel and elution with chloroform gave 235 mg of the pure ketoacid ester **3**. The infrared spectrum and behavior of this product on thin layer chromatography were identical with that of the keto acid ester derived from the enone ester **6**.

Lemieux Oxidation of Methyl Levopimarate.—To a solution of methyl levopimarate (obtained from 500 mg of levopimaric acid) in 120 ml of purified dioxane containing 300 mg Na_2CO_3, was added a solution of 4.9 g of $NaIO_4$ and 250 mg of $KMnO_4$ in 60 ml of water. The mixture was stirred at room temperature for 45 hr. Work-up as for the Lemieux oxidation of methyl neoabietate afforded an acid fraction (140 mg) and a neutral fraction (322 mg).

The acid fraction was methylated and the resulting oil was essentially homogeneous since an injected sample showed a single peak on vpc (4% QF-1). The dimethyl ester was passed through a column of silica gel and eluted with chloroform to afford the keto diester **4a** as a pale yellow oil (126 mg).

The neutral fraction consisted essentially of the dihydroxy ether **5**: mp 182–183°; ν_{max} (Nujol) 3400 (OH), 1725 (CO_2CH_3), 1075 (COC); τ 9.20 and 8.93 (isopropyl), 9.17 (C-10 Me), 6.66 (C-12 H), 5.93 (C-14 H).

Anal. Calcd for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35. Found: C, 68.77; H, 9.32.

Oxidation of the Dihydroxy Oxide 5.—To a solution of 75 mg of the dihydroxy ether **5** in 1 ml of acetic acid was added a solution of 450 mg of lead tetraacetate in 10 ml of acetic acid and 1 ml of water. The solution was allowed to stand overnight at room temperature. The reaction mixture was poured into water and extracted with ether. The ether extract was washed with water, dried over Na_2SO_4 and evaporated to give an oil. The crude oil was oxidized with Jones[1] reagent to give 25 mg of the keto acid ester **4a**, which was separated by silica gel chromatography and identified by comparison with an authentic sample of **4a** as obtained previously.

Exhaustive Ozonolysis of Methyl Neoabietate.—In typical runs, 1-g batches of neoabietic acid[17] in 25 ml of anhydrous ether were methylated with ethereal diazomethane and the solvent removed by flash evaporation. The resulting methyl ester **1b** in 25 ml of ethyl acetate was ozonized at −70° for 1 hr under the following conditions: 90 V, flow rate 0.02 ft^3/min, 5-lb pressure.

The reaction flask was removed from the Dry Ice bath and allowed to come to room temperature. KI solution (10 ml, 1%) was added to decompose the ozonide and the reaction mixture was washed three times with saturated aqueous sodium thiosulfate and once with brine. The organic layer was separated and taken to dryness, and the residue dissolved in acetone. To the cooled stirred solution, Jones[1] solution was added dropwise and the reaction was allowed to proceed for 1–2 hr.

Extraction with ether and separation into neutral and basic fractions with cooled 5% aqueous sodium hydroxide yielded neutral fractions weighing 0.28–0.41 g and acidic fractions comprising the keto acid ester **3a** weighing 0.63–0.77 g.

Generally, further purification by chromatography using silica gel (30 g) and chloroform elution was carried out. Homogeniety of the sample was checked by tlc on silica gel G with a solvent system consisting of 10% MeOH in $CHCl_3$ and by gpc of the dimethyl ester on 5% SE-30 and 4% QF-1 columns with a flame ionization detector.

Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.38; H, 8.92.

Exhaustive Ozonolysis of Methyl Levopimarate (2b).—An ethereal solution of 1 g of levopimaric acid was treated with ethereal diazomethane and the solvent was removed *in vacuo*. The resulting methyl ester **2b** in 25 ml of ethyl acetate was ozonized at −70° for 1 hr under the following conditions: 90 V, flow 0.02 ft^3/min, 5-lb pressure.

The reaction flask was removed from the Dry Ice bath and allowed to come to room temperature, 10 ml of 1% KI was added to decompose the ozonide, and then the liberated iodine was removed by washing with sodium thiosulphate. The organic layer was washed with water (four 10-ml portions), dried ($NaSO_4$), and evaporated to dryness. The residue was dissolved in acetone, cooled to 0°, and treated with Jones reagent for 2 hr. Usual work-up followed by separation into acid and neutral fractions with cold 5% NaOH afforded neutral fractions weighing 0.26–0.35 g and acid fractions from 0.62–0.72 g.

The acid fraction was methylated with diazomethane and chromatographed over 20 g of silica gel. Elution with chloroform afforded the pure keto diester (0.57–0.61 g) as a pale yellow oil: ν_{max} 1738, 1710 cm^{-1}; τ 6.29 and 6.32 (two carbomethoxyls), 7.5–7.9 (C-7 CH_2–), 8.78 (C-4 Me), 9.24 (C-10 Me).

Anal. Calcd for $C_{17}H_{26}O_5$: C, 65.78; H, 8.44. Found: C, 65.61; H, 8.45.

Partial Ozonolysis of Methyl Neoabietate. Method A.—Four grams of neoabietic acid in 50 ml of anhydrous ether was methylated with diazomethane in ether. After evaporation to dryness the methyl ester **1b** in 75 ml of methylene chloride was subjected to ozonolysis at −70° under the following conditions: 90 V, flow 0.02 ft^3/min, 6-lb pressure, 25 min.

The reaction mixture was allowed to come to room temperature, 5 g of powdered zinc and 25 ml of glacial acetic acid were added and the mixture was stirred for 2–3 hr. The zinc dust was collected and washed with methylene chloride, the filtrate carefully neutralized with aqueous saturated sodium bicarbonate and the layers separated. The organic layer was washed with brine and dried over anhydrous sodium sulfate. Evaporation to dryness gave an oil which on standing in ether gave successive crops of crystals of the enone ester **6**, totaling 0.88 g, mp 126–128° (lit.[10] mp 127–128°).

The mother liquor was chromatographed on florisil eluting with chloroform. After the enone ester was eluted, the dihydroxy ketone **8a**, was collected and crystallized as fine needles from hexane–ether: mp 173–174°; $[\alpha]_D$ +11.5; for ir and nmr see text. Prominent mass peaks occurred at M^+ 324 (16%) and *m/e* 323 (84%).

Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.33; H, 8.64.

The column was further eluted with 5% methanol in chloroform. The eluent was evaporated to give an oil which was spread on silica gel HF thick-layer plates (2 mm) and developed using 2% MeOH–$CHCl_3$. Separation of the less mobile band relative to the dihydroxy ketone **8a** and washing the adsorbent in a glass sintered funnel with ethyl acetate afforded the hydroxy–enone ester **10a** which crystallized from ether–hexane: mp 153–154°; $[\alpha]_D$ −101° ($CHCl_3$); for nmr and ir see text; λ_{max} (EtOH) 241 mμ (ϵ 14,500).

Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.63; H, 8.66.

Method B.[18]—Ozone was bubbled through a solution of methyl neoabietate (1 g) in 25 ml of ethyl acetate at −75° for 6 min. The reaction mixture was allowed to attain room temperature. The ozonide was decomposed by the addition of 25 ml of a 1% solution of potassium iodide and a few drops of acetic acid. The organic layer was then washed with a solution of sodium thiosul-

(17) V. M. Loeblich and R. V. Lawrence, *J. Org. Chem.*, **21**, 610 (1956).

(18) We thank Mr. S. W. Page for conducting these experiments.

fate, and then with brine. The sodium sulfate–dried organic extract afforded 1.048 g of an oil which was dissolved in 4 ml of chloroform and spread on a 4-mm thick 200 × 400 mm silica gel plate. Development of the plate with chloroform and visualization by a uv lamp showed 3 main bands. The least polar compound, the enone ester **6**, was obtained as a crystalline solid, mp 126–127°, in 65% yield. Compounds **8a** and **10a** were isolated in 3 and 0.6%, respectively.

Method C.[18]—The ozonolysis was conducted exactly as in method B but the ozonide was treated at −75° with 3 ml of methyl sulfide and the resulting mixture was stirred at room temperature for 3 hr. Removal of solvent afforded an oil (1.026 g) which on preparative thick layer chromatography afforded the enone ester **6**, mp 125–127°, in a 67% yield. Compounds **8a** and **10a** were found to be present in very small amounts (from tlc) and were not isolated.

Acetylation of the Ketodiol Ester (8a).—To an ice-cooled flask containing 40 mg of the ketodiol ester suspended in 1 ml of acetic anhydride (98%) was added 0.5 ml of pyridine (dried over KOH). After the diol had dissolved, the flask was removed from the ice bath and kept at room temperature for 17 hr. The crystals were collected, washed with water, and dried to give 30 mg of the monoacetate **8b**, mp 241–248°. The filtrate was extracted with ether and this fraction yielded an additional 10 mg, mp 247–253°.

The analytical sample was recrystallized from methylene chloride–carbon tetrachloride: mp 258–259°; ν_{max} 3460 (OH), 1755 (ketone flanked by acetoxyl), 1735 (ester), 1724, 1240 (acetate) cm^{-1}.

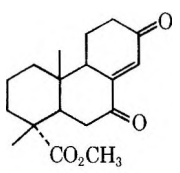
Anal. Calcd for $C_{20}H_{30}O_6$: C, 65.55; H, 8.25. Found: C, 65.62; H, 8.39.

Acetylation of the Hydroxyenone Ester.—To 30 mg of hydroxy-enone ester **10a** dissolved in 0.6 ml of acetic anhydride (98%) and cooled in an ice bath was added 0.02 ml of pyridine. After standing overnight (22 hr) the mixture was poured onto ice. Extraction with ether and drying (Na_2SO_4) the ether extract, followed by evaporation to dryness *in vacuo* yielded an oil. Dry benzene was added and the oil was evaporated to dryness again to remove residual pyridine and acetic acid.

Preparative thick layer chromatography on silica gel HF, eluting with 2% MeOH–$CHCl_3$, gave the acetate–enone ester **10b** as the more mobile band. The acetate–enone ester **10b** obtained as an oil, 20 mg, was crystallized from hexane–ether: mp 143–144°; ν_{max} (CCl_4) 1740, 1685, 1635, 1230 cm^{-1}; nmr absorptions appeared at τ 9.12 (C-10 Me), 8.79 (C-4 Me), 6.31 (CO_2Me), 3.92 [doublet, J = 25 cps, C=CHC(=O)—], 565 (triplet, J = 3 cps, —CHO—), 7.92 (OAc).

Anal. Calcd for $C_{20}H_{28}O_5$: C, 68.94; H, 8.10. Found: C, 68.95; H, 8.33.

CrO_3–Pyridine Oxidation of 10a.—A solution of 30 mg of **10a** in 1 ml of pyridine was added to a cooled solution of 35 mg of CrO_3 in 1 ml of pyridine and the reaction mixture was allowed to stand at room temperature for 18 hr. The reaction was terminated by the addition of 2 ml of 2 *N* sulfuric acid and 5 ml of a saturated solution of sodium bisulfite. The mixture was diluted with 25 ml of water and extracted with ether (five 10-ml portions). The ether extract was washed with water (three 5-ml portions), dried over sodium sulfate, and evaporated to dryness *in vacuo* to give an oil whose tlc showed the presence of starting material and a less polar compound. The less polar compound was obtained by preparative chromatography. The compound (5.5 mg) failed to crystallize, ν_{max} 1735 and 1685 cm^{-1}, λ_{max} 260 mμ. On the basis of these spectral characteristics the oxidation product appears to be the enedione (I).



I

RuO_4–$NaIO_4$ Oxidation of the Enone Ester (6).—A solution of 500 mg of the enone ester **6** in 25 ml of acetone was added dropwise to a stirring yellow suspension of ruthenium tetroxide (generated by adding a solution of 1.0 g of sodium metaperiodate in 20 ml of water to a black suspension of 100 mg of ruthenium dioxide in 45 ml of acetone). Small portions of a solution of 4 g of $NaIO_4$ in 50 ml of aqueous acetone were added at periodic intervals when the reaction mixture turned dark in color. The reaction mixture was stirred at room temperature for 24 hr and the reaction was terminated by the addition of 15 ml of isopropyl alcohol. The dark colored mixture was filtered through a well-packed column (150 × 40 mm) of Celite 545. In later experiments we found that a column of sand worked efficiently. The column was washed well with 150–175 ml of acetone to ensure complete recovery of organic material. The clear filtrate and washings were combined and evaporated to dryness *in vacuo*. The residue was taken up in 100 ml of water and extracted five times with 30-ml portions of ether. The combined ether extract was washed with 5% sodium hydroxide (five 15-ml portions), and then with water six 20-ml portions). The ether extract was dried over sodium sulfate and evaporated to dryness *in vacuo* to afford a neutral fraction (48 mg) whose tlc indicated that it is a complex mixture.

The combined 5% NaOH extract was acidified with 6*N* hydrochloric acid and the product was taken up in ether (six 35-ml portions). The ether extract was washed with water (four 20-ml-portions), dried over magnesium sulfate, and evaporated to dryness *in vacuo* to obtain the acidic fraction (476 mg). The acidic fraction was methylated with ethereal diazomethane and the resulting ester was purified by column chromatography using silica gel. The pure keto diester **3a** was obtained as a pale yellow oil (424 mg) identical in all respects with the product of exhaustive ozonolysis of **1b**.

RuO_4–$NaIO_4$ Oxidation of Methyl Neoabietate (1b).—A solution of 516 mg of methyl neoabietate in 30 ml of acetone was added dropwise to a stirring yellow suspension of RuO_4 (generated by adding a solution of 1.8 g of $NaIO_4$ in 20 ml of water to a black suspension of 200 mg of RuO_2 in 45 ml of acetone). The experiment was conducted as the oxidation of **6**. Usual work-up afforded pure **3b** in 72–75% yield. The neutral fraction (10–15%) was a complex mixture (from tlc) and was not investigated further.

RuO_4–$NaIO_4$ Oxidation of Methyl Levopimarate (2b).—The experimental conditions used were similar to those used in the oxidation of **1b**. Thus, 515 mg of **2b** afforded 76–79% of pure **4b** and 10–12% of a neutral fraction which was essentially the dihydroxy oxide **5**.

Registry No.—**1b**, 3310-97-2; **2b**, 3513-69-7; **3b**, 25594-16-5; **4b**, 25594-17-6; **5**, 25594-18-7; **8a**, 25594-19-8; **8b**, 25565-15-5; **10a**, 25594-20-1; **10b**, 25594-21-2.

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Reaction of Endocyclic α,β-Unsaturated γ-Lactones with Thiols[1]

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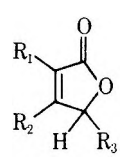
The reactions of the α,β-unsaturated lactones, $\Delta^{\alpha,\beta}$butenolide (1), α-methyl-$\Delta^{\alpha,\beta}$-butenolide (2), β-methyl-$\Delta^{\alpha,\beta}$-butenolide (3), and γ-methyl-$\Delta^{\alpha,\beta}$-butenolide (4) with the thiols, 1-propanethiol, α-toluenethiol, L-cysteine, and N-acetyl-L-cysteine methyl ester were investigated. The products were identified as the thio ethers resulting from Michael-type addition of the thiols across the conjugated carbonyl systems. The dissociations of the L-cysteine adducts were followed kinetically and their instability contrasted with an exocyclic α-methylene lactone thiol adduct.

The reaction of α,β-unsaturated lactones with thiols has been suggested to play a key role in several biological growth-regulatory phenomena. The selective growth-inhibitory action of δ-hexenolactone on certain animal tissures was shown to be antagonized by cysteine.[4] Spectrophotometric and colorimetric studies showed that direct and reversible reaction took place between the lactone and the thiol grouping, and it was proposed that δ-hexenolactone exerts its effect on cellular proliferation mainly through its reactivity with sulfhydryl groups essential to enzyme function. Similar studies of a variety of unsaturated lactone antibiotics led to similar proposals concerning their mode of action.[5-7] The inhibition of plant growth by protoanemonin,[8] heliangine,[9] and vernolepin[10] is prevented by BAL and other sulfhydryl compounds, and has been attributed to reaction of the inhibitors with sulfhydryl enzymes. Very recently, a study of the reactions of tumor-inhibitory α-methylene lactones with model biological nucleophiles revealed that thiols were the most reactive of the nucleophiles investigated, and that successive thiol addition to bis unsaturated lactones resulted in a marked diminution in the biological activity of the adducts.[11] The tumor-inhibitory α-methylene lactones were shown to inhibit the sulfhydryl enzyme, phosphofructokinase, and evidence was presented to indicate that the inhibition resulted from their reaction with the sulfhydryl groups of the enzyme.[12] A possible relationship between the carcinogenicity of certain unsaturated lactones and their reactivity with sulfhydryl cell components or metabolites has been suggested.[13,14] However, the advisability of using such data as criteria for predicting the carcinogenicity of lactones has been questioned following a more recent study.[15]

In the course of our continuing studies of the reactions of unsaturated lactones with model biological nucleophiles, we have investigated the reactions of substituted endocyclic α,β-unsaturated γ-lactones with thiols. In 1945, Cavallito and Haskell reported the formation of an amphoteric compound by reaction of cysteine with γ-methyl-$\Delta^{\alpha,\beta}$-butenolide (4), but the product was not identified.[6] The same authors reported that β-methyl-$\Delta^{\alpha,\beta}$-butenolide (3) showed no measurable reaction with cysteine, and that the lactone could be recovered quantitatively unchanged. The product, 4c, of S-alkylation of cysteine by 4 has recently been isolated and characterized by Black.[16] We report herein the results of a study of the addition of various thiols to α-methyl-, β-methyl-, and γ-methyl-$\Delta^{\alpha,\beta}$-butenolides, and the isolation and characterization of the previously elusive cysteine adducts of α-methyl-, and β-methyl-$\Delta^{\alpha,\beta}$-butenolides.

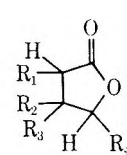


1, $R^1 = R^2 = R^3 = H$

2, $R^1 = CH_3$; $R^2 = R^3 = H$

3, $R^1 = R^3 = H$; $R^2 = CH_3$

4, $R^1 = R^2 = H$; $R^3 = CH_3$



1a, $R^1 = R^2 = R^4 = H$; $R^3 = SCH_2CH_2CH_3$

2c, $R^1 = CH_3$; $R^2 = R^4 = H$; $R^3 = SCH_2CH<^{NH_3^+}_{COO^-}$

3c, $R^1 = R^4 = H$; $R^2 = CH_3$; $R^3 = SCH_2CH<^{NH_3^+}_{COO^-}$

4a, $R^1 = R^2 = H$; $R^3 = SCH_2CH_2CH_3$; $R^4 = CH_3$

4b, $R^1 = R^2 = H$; $R^3 = SCH_2C_6H_6$; $R^4 = CH_3$

4c, $R^1 = R^2 = H$; $R^3 = SCH_2CH<^{NH_3^+}_{COO^-}$; $R^4 = CH_3$

4d, $R^1 = R^2 = H$; $R^3 = SCH_2CH<^{NHCOCH_3}_{COOCH_3}$; $R^4 = CH_3$

Treatment of $\Delta^{\alpha,\beta}$-butenolide (1), α-methyl-$\Delta^{\alpha,\beta}$-butenolide (2), β-methyl-$\Delta^{\alpha,\beta}$-butenolide (3), and γ-methyl-$\Delta^{\alpha,\beta}$-butenolide (4) with the thiols, 1-propanethiol, α-toluenethiol, L-cysteine, and N-acetyl-L-cysteine methyl ester, made possible an evaluation of the effect of a methyl substituent on the reactivity of the

(1) Tumor Inhibitors. LVII. Part LVI: S. M. Kupchan, R. M. Smith, Y. Aynehchi, and M. Maruyama, *J. Org. Chem.*, **35**, 2891 (1970). This work was supported by grants from the National Institutes of Health (HE-12957 and CA-11718) and the American Cancer Society (T-275).

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butenolide toward S-alkylation in a Michael-type reaction.

The results are summarized in Table I. It is apparent that a methyl substituent in the α or β position markedly reduces the reactivity of the butenolide toward Michael-type addition of thiols. The low reactivity of **3** with cysteine is interesting in view of the earlier observation that treatment of strophanthidin (a β-substituted butenolide) with an excess of cysteine did not affect its ultraviolet absorption.[17] The apparent failure of strophanthidin to undergo facile addition of sulfhydryl compounds *in vitro* has been interpreted as rendering improbable the hypothesis that such reactions may play a role in the mode of action of cardiotonic steroids. However, the possibility that polyfunctional enzymatic interactions *in vivo* could favor the addition reaction cannot be excluded from consideration.

TABLE I

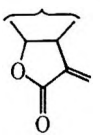
THIOL ADDUCTS OF SUBSTITUTED $\Delta^{\alpha,\beta}$-BUTENOLIDES

Lactone	Thiol[a]	Conditions[b]	Product	Yield, %
1	a	3	**1a**	65
2	a	3, 4	None	
2	c	1	**2c**	38
2	d	7	None	
3	a	3, 5, 7	None	
3	b	6	None	
3	c	2	**3c**	12
3	d	7	None	
4	a	3	**4a**	20
4	b	3	**4b**	44
4	c	1	**4c**[c]	94
4	d	7	**4d**	60

[a] a, $HSCH_2CH_2CH_3$. b, $HSCH_2C_6H_5$. c, $HSCH_2CH<^{NH_3}_{COO^-}$. d, $HSCH_2CH<^{NHCOCH_3}_{COOCH_3}$. [b] 1: pH 7, adjusted to pH with NaOH solution, room temperature, 18 hr. 2: pH 7.4, adjusted to pH with NH_4OH, room temperature, 4 days. 3: pH 7.4, phosphate buffer, 40°, 20 hr. 4: pH 7.4, phosphate buffer, 40°, 7 days. 5: pH 8, phosphate buffer, 60°, 7 days. 6: pH 8, phosphate buffer, 40°, 20 hr. 7: Triethylamine as base, in ether, room temperature, 14 hr. [c] See ref 16.

Cysteine appears to be the most reactive of the thiols investigated. Both the α-methyl- and β-methylbutenolides, **2** and **3**, were found to form adducts only with cysteine and to be unreactive toward N-acetylcysteine methyl ester, 1-propanethiol, and α-toluenethiol within the pH range studied (pH 6–8). The greater reactivity of cysteine may be attributable to the marked acidity of cysteine's sulfhydryl group ($pK_a = 8.5$).[18]

In the preparation of the endocyclic cysteine adducts (**2c**, **3c**, and **4c**), considerable manipulative difficulties were encountered which suggested an inherent instability, and, in fact, successful preparative procedures were developed only after considerable experimentation. This behavior contrasted with the cysteine adduct formed upon reaction of the exocyclic unsaturated γ-lactone function (**5**) present in many sesquiterpene lactones including elephantopin (**6**).[11] The following results indicate that the adducts of the endocyclic compounds (**2**, **3**, and **4**) are indeed much less stable and tend to undergo retro-Michael reactions much more readily than adducts of exocyclic analogs.



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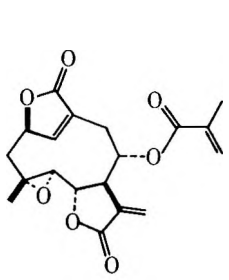

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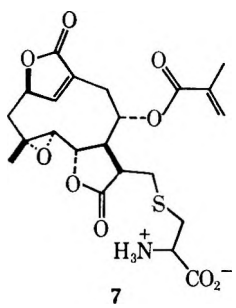

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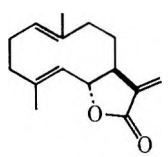

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The rate of formation of cysteine from the adducts could be monitored under irreversible conditions by means of the thiol reagent 2,2′-dipyridyl disulfide. The endocyclic cysteine adducts **2c**, **3c**, and **4c** underwent retro-Michael reaction at 25° and pH 7.4 with first-order rate constants of 34×10^{-6}, 125×10^{-6}, and 3.0×10^{-6} sec^{-1}, respectively, whereas the rate of dissociation of the exocyclic monocysteine adduct (**7**) of elephantopin was immeasurably slow. Indeed there was no evidence of reversal under such conditions for any of the cysteine adducts of the exocyclic unsaturated γ-lactones.

It is also noteworthy that the exocyclic unsaturated lactone in **6** reacted much faster with cysteine than the endocyclic lactones **2**, **3**, or **4**. The second-order rate constant for the reaction of elephantopin and 1 mol of cysteine at 25° has been reported as 2600 l. mol^{-1} min^{-1}.[11] In contrast the most reactive of the endocyclic lactones, **4**, has been reported to react with cysteine (0.67 *M*) at room temperature and pH 7 in 15 min to afford a 90% yield of adduct **4c**.[15] A second-order rate constant of approximately 1–10 l. mol^{-1} min^{-1} can be associated with this process.[19] This suggests a rate ratio of exocyclic to endocyclic unsaturated lactones of the order of 10^3.

The enhanced reactivity of the exocyclic unsaturated compounds toward thiols compared with that of the endocyclic compounds may find explanation in several factors. The terminal carbon of an exocyclic methylene group should have a lower steric requirement than the corresponding carbon of any of the endocyclic compounds studied. Furthermore, the polarization of the conjugated carbonyl system would be expected to be greater in the exocyclic methylene compounds than in the endocyclic compounds. The inductive effects of

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(19) For a second-order equimolar reaction, $k_2t = {}^1/_A - {}^1/_{A_0}$. Hence k_2 corresponds to approximately 1–10 l. mol^{-1} min^{-1} if this reaction is 90–99% complete after 15 min, since $A_0 = 0.67$ *M*. This is in agreement with a published value of 2.2 l. mol^{-1} min^{-1} [14] for the loss of thiol in the presence of lactone **4**.

the alkyl substituents would be expected to decrease the electrophilic character of the β carbon and thus diminish the reactivity of the endocyclic compounds toward nucleophilic attack. This effect should be most marked in the β-methylbutenolide (3) which is the least reactive of all.

The greater stability of the exocyclic adducts, once formed, may be rationalized if the retro-Michael process involves the initial loss of a proton from the α-carbon, for the loss of a tertiary proton is both sterically and inductively less favorable than the loss of a secondary proton. The α-methylbutenolide adduct (2c) may be so stabilized, but the subsequent loss of thiol anion from each of the endocyclic derivatives may be associated with a concomitant release of I strain[20] as ionization occurs, thus leading to an enhanced dissociation relative to the exocyclic case.

An entirely analogous situation exists in the interactions of amines with α,β-unsaturated lactones. Of the endocyclic compounds only the γ-methylbutenolide (4) has been investigated;[21] addition of dimethylamine has been shown to occur in solution, although the instability of the product precluded isolation and further characterization. In contrast, the exocyclic unsaturated lactone present in costunolide (8) has been shown to react with dimethylamine to give a stable Michael adduct.[22]

In a study of the relative nucleophilic reactivities of amino groups and mercaptide ions in addition reactions with α,β-unsaturated compounds, Friedman, *et al.*,[23] found that, at comparable pK_a values and steric environments, sulfur anions are about 280 times more reactive than amino groups. Our results with the amino thiol, cysteine, are in good agreement, for only thiol addition was observed. All the cysteine adducts formed gave negative spot tests on tlc for a thiol group, although some dissociation in aqueous solution was noted.

Further studies of the Michael-type addition of thiols to unsaturated lactones are in progress, and will be reported in due course.

Experimental Section

Infrared spectra were determined on a Beckman Model IR-5A recording spectrophotometer. Ultraviolet spectra were recorded on a Beckman Model DK-2A spectrophotometer fitted with a thermostated cell compartment and a variable timer interlocked with a repetitive scanning attachment to give fully automatic operation. Nmr spectra were determined on Varian A-60A and HA-100 spectrometers. Evaporations were carried out at temperatures less than 40° under reduced pressure. All melting points were determined on a Thomas–Hoover capillary melting point apparatus and are corrected. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. For the mass spectral data, the authors thank the Purdue Mass Spectrometry Center.

Buffers.—The buffers employed were those of Sorensen and Palitzch, described by Kolthoff and Rosenblum.[24]

Deoxygenated Water.—Distilled water was redistilled under deoxygenated nitrogen from potassium permanganate–sodium hydroxide (2 g, 2 g/l.). High purity nitrogen was deoxygenated by bubbling through a solution of pyrogallol [potassium hydroxide (25 g), pyrogallol (100 g), water (250 ml)], and then through a solution of sodium vanadate (*vide infra*).

Sodium Vanadate Solution.[25]—Zinc (125 g) was amalgamated by treatment with 10% mercurous nitrate (125 ml) containing a few drops of concentrated nitric acid. The zinc was washed with water and placed in a gas washing bottle. A solution of 0.1 *M* sodium metavanadate (Alfa Inorganics) in 2 *M* sulfuric acid was added. Nitrogen was bubbled through the yellow-green solution, which became dark blue in a few hours and was then ready for use. A constant flow of nitrogen was maintained through the solution until the color changed to muddy brown, indicating a loss of effectiveness.

Preparative Layer Chromatography on "Avicel."—"Avicel" (American Viscose Corp., Newark, Del.) chromatoplates were prepared (1.25 mm thick) according to Wolfrom's procedure.[26,27] Each chromatoplate was used to separate 50–75 mg of a mixture. The chromatoplates were developed with ethyl acetate:acetic acid:formic acid:water (18:3:1:4, v/v), a system which gave good separation of cystine, cysteine, and the various adducts. Since the butenolide–cysteine adducts usually could not be visualized by uv irradiation, the bands were detected by spraying two narrow strips of the plate with 0.2% ethanolic ninhydrin solution. After the ninhydrin color had developed, the desired band was removed from the plate. The material was eluted with deoxygenated water, and the eluate was lyophilized to give the desired adduct as a powder.

$\Delta^{\alpha,\beta}$-Butenolide (1).—The butenolide 1 was prepared according to the procedure of Price and Judge.[28]

Formation of the $\Delta^{\alpha,\beta}$-Butenolide–1-Propanethiol Adduct: 3-Thiopropyl-4-hydroxybutanoic Acid Lactone (1a).—An aqueous buffered solution (100 ml, pH 7.4) of $\Delta^{\alpha,\beta}$-butenolide (1, 250 mg, 0.003 mol) and 1-propanethiol (0.35 ml, 0.0037 mol, Aldrich) was stirred at 40° for 18 hr. The aqueous solution was extracted with chloroform (five 50-ml portions). The combined chloroform extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residual oil was distilled, bp 95–98° (0.2 mm), to yield a clear, colorless oil (1a, 303 mg, 65%): ir λ_{max}^{film} 5.63 μ (lactone carbonyl); nmr ($CDCl_3$) τ 9.02 (3 H, t, J = 7 Hz, $-CH_2CH_3$), 8.8–7.9 (2 H, m, $-CH_2CH_3$), 7.8–6.8 (4 H, m, $-CH_2S-$ and $-CH_2CO_2-$), 6.5–5.3 (3 H, m, *n*-PrSCHCH$_2$O); mass spectrum (75 eV) *m/e* (rel intensity) 160 M^+ (35.5), 102 (62), 85 (22), 84 (20), 74 (11), 73 (34), 61 (15.5), 60 (100), 59 (40), 58 (29).

Anal. Calcd for $C_7H_{12}O_2S$: C, 52.49; H, 7.55; S, 19.98. Found: C, 52.30; H, 7.58; S, 19.89.

α-Methyl-$\Delta^{\alpha,\beta}$-butenolide (2).—The butenolide 2 was prepared according to the reported procedure.[29]

Formation of the α-Methyl-$\Delta^{\alpha,\beta}$-butenolide–L-Cysteine Adduct: 2-Methyl-3-(2-amino-2-carboxyethylthio)-4-hydroxybutanoic Acid Lactone (2c).—A solution of the butenolide 2 (500 mg, 0.005 mol) and cysteine hydrochloride monohydrate (438 mg, 0.0025 mol) in water (15 ml) was adjusted to pH 7.0 with 2 *N* sodium hydroxide solution and kept under a nitrogen atmosphere for 24 hr. The solution was extracted with ether (three 250-ml portions), and the combined ether extracts were dried ($MgSO_4$) and concentrated under reduced pressure to yield recovered butenolide 2 (255 mg, 0.0025 mol). The aqueous solution was concentrated under reduced pressure, and absolute ethanol was added to effect solution of all the precipitated material. The aqueous ethanol solution was cooled, and the white, noncrystalline solid which formed was collected by centrifugation to give the adduct 2c. Concentration of the mother liquors yielded a second crop, which was shown by its infrared spectrum to be identical with the first material isolated. The total yield of 2c was 205 mg (38%): mp 188–190° with some softening beforehand and effervescence at the melting point; ir λ_{max}^{KBr} 5.56 μ (lactone carbonyl); nmr (D_2O) τ 8.40 (3 H, d, J = 7 Hz, α-CH_3), 7.4–6.8 (2 H, m, $-C(CH_3)HCHSR$), 6.8–6.6 (2 H, $-SCH_2-$), 6.5–5.5 (3 H, m, SCH_2CH- and $-SCHCH_2O-$); mass spectrum (75 eV) *m/e* (rel intensity) 219 M^+ (2.5), 174 (5.0), 146 (8.0), 101 (9.3), 100 (7.5),

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99 (16), 98 (48), 89 (11), 76 (32), 75 (32), 74 (100), 70 (6.2), 69 (47).

Anal. Calcd for $C_8H_{13}NO_4S$: C, 43.83; H, 5.98; N, 6.39; S, 14.45. Found: C, 43.62; H, 5.91; N, 6.49; S, 14.25.

β-Methyl-$\Delta^{\alpha,\beta}$-butenolide (3).—The butenolide **3** was prepared according to reported procedures.[30-32]

Formation of the β-Methyl-$\Delta^{\alpha,\beta}$-butenolide–L-Cysteine Adduct: 3-(2-Amino-2-carboxyethylthio)-3-methyl-4-hydroxybutanoic Acid Lactone (3c).—A solution of cysteine hydrochloride (158 mg, 0.001 mol) and the butenolide **3** (98 mg, 0.001 mol) in deoxygenated water (1 ml) was adjusted to pH 7.4 with concentrated ammonium hydroxide, while kept under a stream of nitrogen. The flask was sealed and kept at room temperature for 4 days, and then the solution was lyophilized to give a white powder. The powder was dissolved in a minimum of water and chromatographed on "Avicel." A band, R_f 0.45–0.65, was removed and eluted with ice water. The water eluates were immediately frozen and lyophilized to give a white powder. The powder was dissolved in MeOH (4 ml) and precipitated by addition of ethyl acetate (20 ml). The precipitate was collected by filtration and washed with ethyl acetate to give, after drying, a white powder (**3c**, 26 mg, 12.0%): mp 203–205° dec; ir λ_{max}^{KBr} 5.62 μ (lactone carbonyl); mass spectrum (75 eV) *m/e* (rel intensity) 219 M^+ (0.23), 98 (43.7), 76 (11.9), 74 (17.6), 69 (100), 68 (17.6), 56 (17.9).

Anal.[33] Calcd for $C_8H_{13}NO_4S$: C, 43.81; H, 5.98; N, 6.38; S, 14.62. Found: C, 39.54 (43.4 corrected); H, 5.31 (5.8 corrected); N, 6.03 (6.6 corrected); S, 13.03 (14.3 corrected).

Adduct **3c** was found to decompose very rapidly in water at room temperature to give cysteine and the starting butenolide.

γ-Methyl-$\Delta^{\alpha,\beta}$-butenolide (4).—The butenolide **4** was prepared from α-angelica lactone (Aldrich) according to the reported procedure.[34]

Formation of the γ-Methyl-$\Delta^{\alpha,\beta}$-butenolide–1-Propanethiol Adduct: 3-Propylthio-4-hydroxypentanoic Acid Lactone (4a).—An aqueous buffer solution (125 ml, pH 7.4) of the γ-methylbutenolide (0.5 g, 0.005 mol) and 1-propanethiol (0.38 g, Aldrich) were mixed and stirred at 40° for 20 hr. The solution was extracted with ether, and the combined ethereal extracts were dried over anhydrous $MgSO_4$. Concentration of the ethereal solution under reduced pressure yielded an oil which was purified on freshly activated silica gel GF_{254} plates. The plates were eluted with ether:hexane (1:1), and a band R_f 0.4 (visualized with uv light), was removed and eluted with ether. Concentration of the ether eluate yielded a clear, colorless oil (**4a**, 166 mg, 20%): ir $\lambda_{max}^{CHCl_3}$ 5.58 μ (saturated lactone carbonyl); nmr ($CDCl_3$) τ 9.02 (3 H, t, CH_3CH_2–), 8.55 (3 H, d, J = 6 Hz, CH_3CHO), 8.7–8.1 (2 H, m, $CH_3CH_2CH_2S$–), 7.6–7.0 (4 H, m, $-CH_2S$ and $-CH_2CO_2$–), 7.0–6.7 (1 H, m, –SCH–), 5.8–5.4 (1 H, quintet, J = 6 Hz, CH_3CHO); mass spectrum (75 eV) *m/e* (rel intensity) 174 M^+ (27.6), 102 (87.5), 99 (17.3), 98 (17.3), 73 (20.7), 61 (17.3), 60 (100), 59 (18.4), 55 (20.7).

Anal. Calcd for $C_8H_{14}O_2S$: C, 55.16; H, 8.10; S, 18.37. Found: C, 55.29; H, 8.08; S, 18.49.

Formation of the γ-Methyl-$\Delta^{\alpha,\beta}$-butenolide–α-Toluenethiol Adduct: 3-Benzylthio-4-hydroxypentanoic Acid Lactone (4b).—This adduct was prepared as described for the 1-propanethiol adduct (**4a**) to yield after chromatography a clear, colorless oil (**4b**, 44%): ir $\lambda_{max}^{CHCl_3}$ 5.62 (saturated lactone carbonyl), 6.65–7.70 μ (aromatic); nmr ($CDCl_3$) τ 8.73 (3 H, d, J = 6 Hz, $-CHCH_3^a$), 8.0–6.9 (3 H, m, $-SCHCH_2CO_2$–), 6.25 (2 H, s, $-SCH_2C_6H_5$), 5.9–5.4 (1 H, m, CH_3CH^bO–), 2.75 (5 H, s, aromatic protons); H^a and H^b shown to be coupled by double irradiation experiments (J = 6 Hz); mass spectrum (75 eV) *m/e* (rel intensity) 222 M^+ (43.7), 150 (15.6), 121 (42), 92 (26), 91 (100), 77 (7.3), 65 (30.2).

Anal. Calcd for: $C_{12}H_{14}O_2S$: C, 64.85; H, 6.35; S, 14.40. Found: C, 64.88; H, 6.36; S, 14.46.

While this work was in progress, adduct **4b**, 3-benzylthio-4-hydroxypentanoic acid lactone, was independently prepared in a nonaqueous medium by Jones and Young.[15]

Formation of the γ-Methyl-$\Delta^{\alpha,\beta}$-butenolide–L-Cysteine Adduct: 3-(2-Amino-2-carboxyethylthio)-4-hydroxypentanoic Acid Lactone (4c).—This adduct was prepared according to the procedure published by Black.[16] The product was obtained in 94% yield as a crystalline solid, mp 179–180° dec (lit 193–197° dec).[9]

Anal. Calcd for $C_8H_{13}NO_4S$: C, 43.81; H, 5.98; N, 6.38; S, 14.62; M, 219. Found: C, 43.62; H, 5.89; N, 6.53; S, 14.55; M (mass spectrum), 219.

N-Acetyl-L-cysteine Methyl Ester (d).—A solution of N-acetyl-L-cysteine (1.0 g, 0.006 mol, K & K Laboratories) in methanol (20 ml) was mixed with an ethereal solution of diazomethane. The reaction was monitored by tlc (silica gel, ether), and addition of diazomethane was stopped when only a trace of N-acetyl-L-cysteine remained. (Addition of an excess of diazomethane made the product difficult to purify.) The product was recrystallized from ether–petroleum ether to yield the methyl ester (**d**, 0.79 g, 73%): mp 78–80.5°, and after sublimation [45–50° (bath temperature)(0.01 mm)] mp 81–82° (lit.[35] 79–80°); ir λ_{max}^{KBr} 3.08 (–NHCO–), 3.92 (sh, –SH), 5.78 μ (ester).

Formation of the γ-Methyl-$\Delta^{\alpha,\beta}$-butenolide–N-Acetyl-L-cysteine Methyl Ester Adduct: 3-(2-Acetylamino-2-carbomethoxyethylthio)-4-hydroxypentanoic Acid Lactone (4d).—A solution of N-acetyl-L-cysteine methyl ester (583 mg, 0.0033 mol), γ-methyl-$\Delta^{\alpha,\beta}$-butenolide (339 mg, 0.0033 mol, 96% pure), and triethylamine (6 drops) in ether (8 ml) was allowed to stand at room temperature for 14 hr. Two layers resulted, and the ethereal layer (upper) was pipetted from the tube. The lower layer was distilled at 205° (bath temperature) and 0.075 mm to yield the adduct **4d** (556 mg, 60%): $[\alpha]^{28}D$ +46° (c 1.01, $CHCl_3$); ir λ_{max}^{film} 6.63 (saturated lactone), 5.74, 5.97 μ (amide); nmr ($CDCl_3$) τ 8.55 [3 H, d, J = 6 Hz, $-CH(CH_3^a)O$–], 7.93 (3 H, s, $-NHCOCH_3$), 6.21 (3 H, s, $-CO_2CH_3$), 5.65 [1 H, quintet, J = 6.5 Hz, $-CH^b(CH_3)O$–], 5.20 [1 H, 6 line multiplet, $-CH(NHCOCH_3)$], 2.85 (1 H, m, –NHCO–); H^a and H^b were shown to be coupled by double irradiation experiments.

Anal. Calcd for $C_{11}H_{17}NO_5S$: C, 47.99; H, 6.23; N, 5.09; S, 11.64. Found: C, 47.84; H, 6.38; N, 5.20; S, 11.52.

Retro-Michael Reaction Kinetic Measurements. Procedure.—The L-cysteine adduct (~1 μmol) was dissolved in phosphate buffer solution (pH 7.4, 1 ml). A calculated volume (~ 360 μl) was added to a 1-cm cuvette, and diluted with more buffer (thermostated at 25°) to give a final concentration of adduct of 10^{-4} M. The cuvette was placed in the thermostated cell holder of the uv spectrophotometer and the reaction was started by the addition of a sufficient quantity (~36 μl) of a freshly prepared solution of 2,2′-dipyridyl disulfide[36] in tetrahydrofuran (22.0 mg in 10 ml) to give an equimolar reaction mixture.

The uv absorption of the solution was measured automatically over the range 300–400 mμ at appropriate time intervals. The rate of liberation of cysteine was measured by monitoring the very fast and irreversible reaction with 2,2′-dipyridyl disulfide to give 2-thiopyridone (λ_{max} 343 mμ, ε 7780). The infinity values were calculated from known starting concentrations since the observed infinity readings were found to be low.

α-Methyl-$\Delta^{\alpha,\beta}$-butenolide–L-Cysteine Adduct.—Adduct **2c** (0.235 mg/ml, 335 μl), in the presence of 2,2′-dipyridyl disulfide (1.0×10^{-4} M) underwent irreversible retro-Michael reaction in buffered 1% tetrahydrofuran solution. The first-order plot of the kinetic data tapered off with time at about 30% reaction; however, the rate constant, $k_1 = 3.4 \times 10^{-5}$ sec^{-1}, calculated from the straight initial portion of the plots was reproducible to about ±10%.

β-Methyl-$\Delta^{\alpha,\beta}$-butenolide–L-Cysteine Adduct.—Adduct **3c** (0.239 mg/ml, 412 μl), at an initial concentration of 1.25×10^{-4} M, underwent dissociation in the presence of 2,2′-dipyridyl disulfide (1.25×10^{-4} M) with $k_1 = 1.25 (\pm 0.17) \times 10^{-4}$ sec^{-1}.

γ-Methyl-$\Delta^{\alpha,\beta}$-butenolide–L-Cysteine Adduct.—Adduct **4c** (0.250 mg/ml, 400 μl), at an initial concentration of 1.27×10^{-4} M, underwent dissociation in the presence of 2,2′-dipyridyl disulfide (1.27×10^{-4} M) with $k_1 = 3.0 (\pm 0.25) \times 10^{-6}$ sec^{-1}.

Elephantopin–Monocysteine Adduct.—The preparation of this compound (**7**) has been described elsewhere.[11] The adduct **7** was prepared in a 4% tetrahydrofuran–buffer solution (pH 7.4) by allowing an equimolar mixture of L-cysteine (1.0×10^{-4} M) and elephantopin (**6**) to react to completion. After 60 min the con-

(30) W. J. Conradie, C. F. Garbers, and P. S. Steyn, *J. Chem. Soc.*, 594 (1964).

(31) J. M. Stewart and D. W. Woolley, *J. Amer. Chem. Soc.*, **81**, 4951 (1959).

(32) C. H. Hoffman, *ibid.*, **79**, 2316 (1957).

(33) The analysis was corrected for 9.8% ash. Attempts to free **3c** from ash using a Bio-Gel column (a successful procedure in these laboratories for purifying stable, high molecular weight, cysteine adducts) were unsuccessful.

(34) J. Thiele, R. Tischbein, and E. Lossow, *Justus Liebigs Ann. Chem.*, **319**, 144 (1902).

(35) J. B. Jones and D. C. Wigfield, *Can. J. Chem.*, **44**, 2517 (1966).

(36) D. R. Grassetti and J. F. Murray, Jr., *Arch. Biochem. Biophys.*, **119**, 41 (1967).

centration of free cysteine was negligible. The solution of adduct **7** (10^{-4} *M*) was placed in a cuvette and 2,2′-dipyridyl disulfide (36 μl., 10^{-2} *M* solution in tetrahydrofuran) was added to give an equimolar mixture. The ultraviolet absorption of the solution was then measured at various times. However, there was no change in the absorption; *i.e.*, there was no thiopyridone produced.

Registry No.—**1**, 497-23-4; **1a**, 25516-01-2; **2**, 22122-36-7; **2c**, 25516-03-4; **3**, 6124-79-4; **3c**, 25516-05-6; **4**, 591-11-7; **4a**, 25516-07-8; **4b**, 25516-08-9; **4c**, 6417-06-7; **4d**, 25516-10-3; 1-propanethiol, 107-03-9; α-toluenethiol, 100-53-8; L-cysteine, 52-90-4; N-acetyl-L-cysteine methyl ester, 7652-46-2.

Synthesis of D-1-Hydroxy-2-amino-3-ketooctadecane-4,5-^{3}H Hydrochloride[1a]

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N-Trifluoroacetyl- and N-carbobenzoxydihydrosphingosines were oxidized to their corresponding keto analogs with chromic anhydride in pyridine and converted to D-1-hydroxy-2-amino-3-ketooctadecane hydrochloride. It was found from the ease of removal of the N-protective groups that the N-carbobenzoxy compound provided the best yield of the ketoamine salt. N-Carbobenzoxydihydrosphingosine-4,5-^{3}H carried through the same reaction sequence yielded D-1-hydroxy-2-amino-3-ketooctadecane-4,5-^{3}H hydrochloride. The N-acetyl, O,N-diacetyl, and 2,4-dinitrophenylhydrazone derivatives of the ketoamine base were prepared for purposes of characterization. The presence of two forms of D-1-hydroxy-2-acetamido-3-ketooctadecane was suggested by the finding of one band on thin layer chromatography and two bands on gas–liquid chromatography.

During our investigation of the *in vitro* biosynthesis of long-chain bases by *Hansenula ciferri*, it was necessary to have D-1-hydroxy-2-amino-3-ketooctadecane[1b] which has been shown to be an intermediate in the biosynthesis of dihydrosphingosine.[2-4] The preparation of D-1-hydroxy-2-acetamido-3-ketooctadecane was reported[5] in which the secondary hydroxyl group of N-acetyldihydrosphingosine, D-*erythro*-1,3-dihydroxy-2-acetamidooctadecane,[6] was oxidized with chromic anhydride in pyridine.[7] It was thought that the free ketoamine or its salt could be obtained by this procedure if the oxidation were performed on the appropriate N-substituted base. N-Trifluoroacetyl- and N-carbobenzoxydihydrosphingosines were selected for this purpose because the trifluoroacetyl group could be cleaved easily under mild alkaline conditions at room temperature, whereas the carbobenzoxy function could be removed by hydrogenolysis.

Oxidation of N-trifluoroacetyldihydrosphingosine gave the expected D-1-hydroxy-2-trifluoroacetamido-3-ketooctadecane in about 35% yield. However, upon treatment with K_2CO_3, little or no free ketoamine was obtained, unlike reaction with the unoxidized parent compound which yielded the free base. The ketoamine hydrochloride was prepared in 24% yield from the N-trifluoroacetyl keto derivative by refluxing with 1.5 *N* HCl in aqueous ethanol. By comparison, oxidation of N-carbobenzoxydihydrosphingosine gave yields of about 45% of the respective keto analog (Scheme I, B, C); reduction over palladium in ethanol containing sufficient hydrochloric acid to neutralize the generated free base resulted in 95% yields of ketoamine hydrochloride. When the N-carbobenzoxy keto compound was reduced in glacial acetic acid, dihydrosphingosine was obtained whose identity was proved by infrared spectroscopy and by the melting point of its N-acetyl derivative. Thin layer chromatography of the ketoamine hydrochloride in chloroform:methanol (95:5) showed a single component, R_F 0.40; gas–liquid chromatography of the trimethylsilyl derivative was unsuccessful. The free ketoamine was obtained by treatment of the hydrochloride with $KHCO_3$ in aqueous methanol followed by extraction into ether and removal of solvent; it changed color rapidly from white to yellow after crystallization from petroleum ether. The yellow ketoamine melted at 49–54°. Thin layer chromatography disclosed one major component, R_F 0.42, along with five minor ones, R_F 0.69, 0.76, 0.83, 0.89, and 0.93. It was concluded that N-carbobenzoxydihydrosphingosine was the substrate of choice for preparation of the ketoamine hydrochloride because of the ease of removal of the protective group and the better overall yield.

The overall yield of D-1-hydroxy-2-amino-3-ketooctadecane-4,5-^{3}H hydrochloride was 30%; the radioactive yield based on N-carbobenzoxydihydrosphingosine-4,5-^{3}H was 15% (Scheme I). Since little or no tritium activity was observed on carbon atoms 1 to 3 in previous preparations[8] of dihydrosphingosine-4,5-^{3}H, the loss of 10.4 μCi after oxidation of N-carbobenzoxydihydrosphingosine (35.9 μCi/mg) to N-carbobenzoxy keto compound (25.5 μCi/mg) was attributed to an impurity of high specific activity which was removed from the keto compound but cochromatographed with N-carbobenzoxydihydrosphingosine-4,5-^{3}H during purification on the silicic acid column, and to removal of tritium on carbon atom 4 by exchange.

Proof that oxidation had occurred at the secondary hydroxyl group was obtained by treating an acetic acid

(1) (a) This investigation was supported in part by Public Health Service Research Grant No. NB 06300-04 from the National Institutes of Neurological Diseases and Stroke. (b) As this work was being prepared for publication, P. B. Mendershausen and C. C. Sweeley, *Biochemistry*, **8**, 2633 (1969), reported the micropreparation of the ketoamine free base from N-carbobenzoxydihydrosphingosine. However, the complete chemical characterization of this compound was not made. Since our efforts were directed at preparing sufficient material to be stored for varying periods of time during radioactive studies, it was decided to isolate the ketoamine as a salt.

(2) R. N. Brady, S. J. DiMari, and E. E. Snell, *J. Biol. Chem.*, **244**, 491 (1969).

(3) P. E. Braun and E. E. Snell, *ibid.*, **243**, 3775 (1968).

(4) (a) W. Stoffel, D. Le Kim, and G. Sticht, *Z. Physiol. Chem.*, **349**, 664 (1968); (b) *ibid.*, **349**, 1637 (1968).

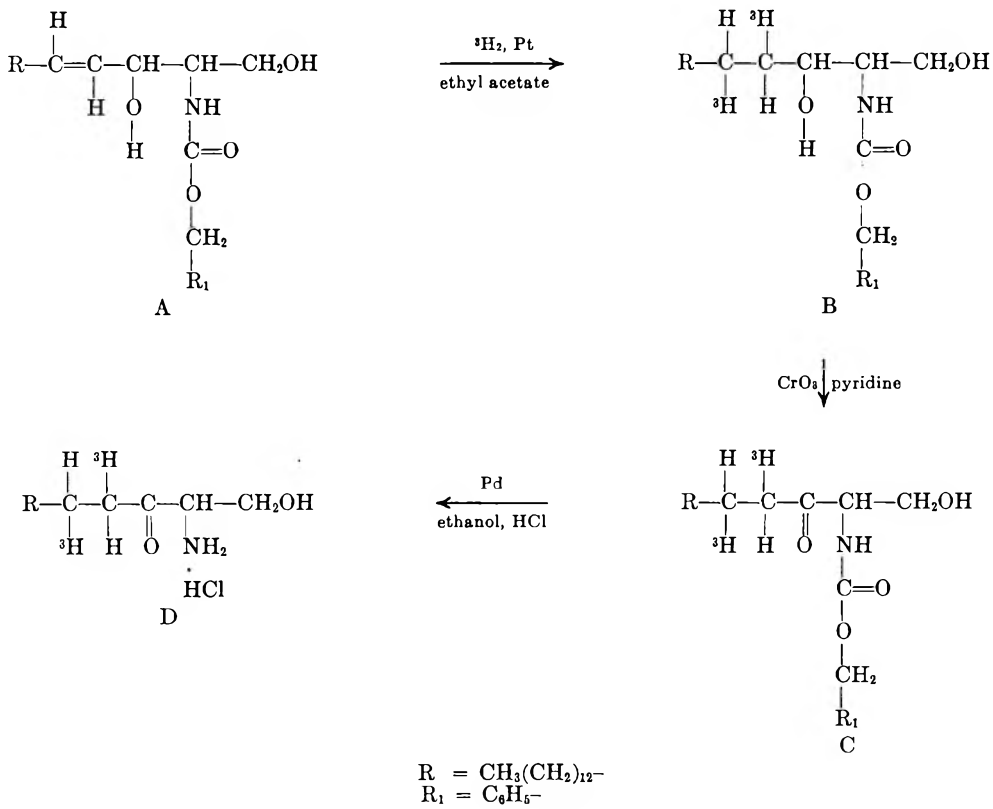
(5) R. C. Gaver and C. C. Sweeley, *J. Amer. Chem. Soc.*, **88**, 3643 (1966).

(6) H. E. Carter and Y. Fujino, *J. Biol. Chem.*, **221**, 879 (1956).

(7) G. I. Poos, G. E. Arth, R. E. Beyler, and L. H. Sarett, *J. Amer. Chem. Soc.*, **75**, 422 (1953).

(8) B. Weiss and R. L. Stiller, *J. Biol. Chem.*, **242**, 2903 (1966).

SCHEME I



solution of the ketoamine hydrochloride with lead tetraacetate. The major cleavage component was palmitic acid. This would be the product, along with a molecule each of formic acid and formaldehyde, if a vicinal ketoamine structure were present;[9] palmitaldehyde and two molecules of formic acid would be obtained if the primary hydroxyl had been oxidized. Treatment of the ketoamine hydrochloride with periodic acid gave an insoluble precipitate, with about 10% oxidation, similar to that which is obtained with dihydrosphingosine and periodic acid.

Thin layer chromatography in several solvent systems of D-1-hydroxy-2-acetamido-3-ketooctadecane showed one component, but gas–liquid chromatography of the trimethylsilyl derivative revealed two components, a major one at 12.5 min and a minor one at 25.5 min. The identity of the minor component could not be accounted for as the trimethylsilyl derivative of either N-acetylsphingosine or N-acetyldihydrosphingosine which had retention times of 27.5 and 31.5 min, respectively. Storage at room temperature under anhydrous conditions as well as successive passage through silicic acid columns disclosed, upon gas–liquid rechromatography, that the formerly minor component had increased to become the major one. A single component was still obtained by thin layer chromatography. Since gas–liquid chromatography–mass spectrometry was not available to aid in the determination of the structure of these components, it is postulated that gradual cyclization of the acetamido keto compound gives a substituted oxazolidine which would yield a ditrimethylsilyl derivative. Since ditrimethylsilyl-2-acetamidosphingosine has a retention time of 27.5 min, the oxazolidine may be the form that emerges at 25.5 min. The 12.5-min component, therefore, would be the monotrimethylsilyl derivative of the keto form.

(9) E. L. Jackson, *Org. React.*, **2**, 341 (1944).

Experimental Section

Thin layer chromatography was conducted as previously described[10] on plates coated with either Adsorbosil-1 (Applied Science Laboratories) or silica gel G (Brinkmann Instruments Company) and developed with chloroform:methanol (95:5) or chloroform:methanol:ammonia (40:10:1).[11] Bands were detected by exposure to iodine vapor. In experiments where the bands were to be analyzed by gas–liquid chromatography, or for radioactivity, a parallel run was made with exposure to iodine and used as a guide for removal of unexposed bands to avoid contamination of the sample by iodine. The silicic acid with the adsorbed compound was removed from the plate and was treated successively with 5-ml portions of chloroform:methanol (2:1) and twice with methanol at room temperature. After removal of solvent below 55° from the combined extracts, the residue was dried over phosphorus pentoxide and reacted with the trimethylsilyl reagent.[12]

Columns, 2.5 × 20 cm, were prepared with Mallinkrodt silicic acid which was washed several times with chloroform:methanol (2:1) and activated by heating 24 hr at 120°. The packed column was washed with several hundred milliliters of chloroform until the silicic acid showed no change in translucency.

The trimethylsilyl derivatives of the bases were analyzed by gas–liquid chromatography on 2.5% Se-30 on Gas Chrom Q, mesh 100–200. The column and injector and detector temperatures were maintained at 210, 270, and 240°, respectively. To 2.0 mg of base was added 0.5 ml of the trimethylsilyl reagent; after centrifugation of the reaction mixture, 1–2 μg samples of the supernatant were taken for analysis.

Infrared spectra were obtained on KBr disks with a Perkin-Elmer infrared spectrophotometer. Sphingosine was isolated as the sulfate from hydrolysates of bovine sphingolipids.[13] Dihydrosphingosine was prepared by hydrogenation of sphingosine over platinum in ethanol. The N-acetyl- and N-carbobenzoxy-

(10) B. Weiss and R. L. Stiller, *J. Lipid Res.*, **6**, 159 (1965).
(11) K. Sambasivarao and R. H. McCluer, *ibid.*, **4**, 437 (1963).
(12) H. E. Carter and R. C. Gaver, *ibid.*, **8**, 391 (1967).
(13) H. E. Carter, W. P. Norris, F. J. Glick, G. E. Phillips, and R. Harris, *J. Biol. Chem.*, **170**, 269 (1947).

dihydrosphingosines were prepared as previously described.[13,14] Fatty acids were esterified with diazomethane[15] and analyzed as reported earlier.[16]

Tritrifluoroacetyldihydrosphingosine (I).—Trifluoroacetic anhydride, 12.6 g (60 mmol), was added to 4.5 g (15 mmol) of dihydrosphingosine suspended in 150 ml of dry ethyl acetate; the base dissolved as the reaction proceeded. The organic layer was washed with water until neutral and the solvent removed. The residue, dried over phosphorus pentoxide, was crystallized from petroleum ether (Skellysolve B, bp 60–70°): yield 4.2 g; mp 104–106°; infrared absorption 1785 and 1220 (ester) (s), 1725 and 1535 (secondary amide) (s), and 1175 cm^{-1} (carbon–fluorine) (s); hydroxyl absorption was absent.

Anal. Calcd for $C_{24}H_{36}O_5NF_9$ (589.3): C, 48.87; H, 6.16. Found: C, 48.57; H, 6.01.

N-Trifluoroacetyldihydrosphingosine (II).—To 1.0 g of compound I in 75 ml of methanol was added 1.0 g of $KHCO_3$ in 48 ml of water. The mixture was stirred gently at 60° for 1 min, allowed to stand 12 hr at room temperature, and then treated twice with 125-ml portions of ether. The combined ether extracts were washed; the solvent was removed. The dried residue was crystallized from acetonitrile: yield 615 mg; mp 129–130° (The product gave a negative ninhydrin reaction in 95% ethanol.); infrared absorption 1700 and 1560 (secondary amide) (s), 1180 (carbon–fluorine) (s), 1115 (secondary hydroxyl) (m), 1075 and 1050 cm^{-1} (doublet, primary hydroxyl) (s).

Anal. Calcd for $C_{20}H_{38}O_3NF_3$ (397.3): C, 60.41; H, 9.64; N, 3.52; F, 14.35. Found: C, 60.42; H, 9.82; N, 3.58; F, 14.17.

Dihydrosphingosine.—Compound II, 50 mg in 4 ml of methanol, was treated with 50 mg of K_2CO_3 in 2 ml of water; the turbid reaction mixture was stirred gently at 60° for 1 min and allowed to stand 24 hr at room temperature. After removing the product with ether which was then washed and concentrated, the dried residue was crystallized from petroleum ether, yield 31 mg, mp 74–76°. The product gave a positive reaction with ninhydrin.

D-1-Hydroxy-2-trifluoroacetamido-3-ketooctadecane (III).—Dry chromic anhydride, 1.0 g (10 mmol), was added to a solution of 1.0 g (2.51 mmol) of compound II in 30 ml of dry pyridine surrounded by an ice bath; the reaction mixture was stirred magnetically. After 1 hr in the ice bath and another at room temperature, the reaction mixture was poured into an ice–water mixture and the product was removed by two extractions with 200-ml portions of ether:ethyl acetate (1:1). The organic layer was washed with water, filtered, and concentrated. The dried residue was dissolved in chloroform and loaded on a silicic acid column which was developed successively with 200 ml portions of chloroform, 1% methanol in chloroform, and methanol. The eluates were concentrated to dryness. The residue from chloroform was crystallized from petroleum ether (bp 60–70°): yield 355 mg; mp 72–74°; infrared absorption 1710 (carbonyl) (s), 1525 (secondary amide) (m), 1170 (carbon–fluorine) (s), and 1060 cm^{-1} (primary hydroxyl) (m).

Anal. Calcd for $C_{20}H_{36}O_3NF_3$ (395.3): C, 60.72; H, 9.18; N, 3.54; F, 14.42. Found: C, 60.03; H, 9.27; N, 3.65; F, 14.47.

Unreacted compound II, 180 mg, was recovered from the 1% methanol in chloroform eluate; the methanol eluate yielded an oil, 107 mg.

D-1-Hydroxy-2-amino-3-ketooctadecane Hydrochloride (IV).—Compound III, 100 mg, was refluxed 4 hr in 3 ml of 1.5 *N* HCl in 84% ethanol. The reaction mixture was lyophilized and dried over KOH and phosphorus pentoxide. The residue, washed several times by suspension in hot petroleum ether with centrifugation, was dissolved in 2 ml of ethanol; the precipitate that formed upon chilling the solution was collected by centrifugation after addition of 8 ml of petroleum ether: yield 19 mg; mp 97–98° (The product gave positive ninhydrin and chloride tests and reduced an alkaline copper tartrate solution.); infrared absorption 1725 (carbonyl) (s), 1615 and 1290 (NH_3^+) (m), and 1060 cm^{-1} (primary hydroxyl) (m).

Anal. Calcd for $C_{18}H_{38}O_2NCl$ (335.8): C, 64.32; H, 11.41; N, 4.17; Cl, 10.57. Found: C, 64.38; H, 11.16; N, 4.13; Cl, 10.78.

D-1-Hydroxy-2-carbobenzoxamido-3-ketooctadecane (V).—Dry chromic anhydride, 1.0 g (10 mmol), was added to 1.0 g (2.3 mmol) of N-carbobenzoxydihydrosphingosine in 30 ml of dry pyridine surrounded by an ice bath. The reaction mixture was processed as in the preparation of compound III and the product was separated on a silicic acid column. The residue from the chloroform eluate was crystallized from petroleum ether: yield 435 mg; mp 61–63°; infrared absorption 1720 (carbonyl) (s), 1690 and 1540 (secondary amide) (m), 1280 (ester) (s), and 1060 cm^{-1} (primary hydroxyl) (m). Thin layer and gas–liquid (retention time 127 min) chromatographies showed a single component.

Anal. Calcd for $C_{26}H_{43}O_4N$ (433.6): C, 71.95; H, 10.00; N, 3.23. Found: C, 71.61; H, 10.00; N, 3.18.

Unreacted starting material, 253 mg, was recovered from the 1% methanol in chloroform eluate. Thin layer and gas–liquid (retention time 15 min) chromatographies showed a single component.

D-1-Hydroxy-2-amino-3-ketooctadecane Hydrochloride (VI).—Compound V, 218 mg, was hydrogenated over 50 mg of palladium oxide in 125 ml of ethanol containing 0.5 ml of 1 *N* HCl (1 ml of concentrated HCl + 11 ml of ethanol); the solution was stirred magnetically 4 hr at room temperature. After filtration of the reaction mixture and washing of the catalyst with hot ethanol, the combined filtrates were concentrated and the residue, dissolved in a minimal volume of hot ethanol, was precipitated by addition of four volumes of petroleum ether, yield 146 mg, mp 97–98°. Tests for chloride, ninhydrin, and reduction of alkaline copper tartrate as well as the infrared spectrum and elementary analyses were the same as those obtained for compound IV. Thin layer chromatography showed a single component.

3-Hydroxy Diastereoisomers of Dihydrosphingosine Acetate.—Compound V, 218 mg, was hydrogenated over 50 mg of palladium oxide in 25 ml of glacial acetic acid in the same manner as described for the preparation of compound VI. After filtration of the reaction mixture and washing of the catalyst with hot ethanol, the combined filtrates were concentrated. Ethanol was added to the residue several times with distillation each time and the product, dried over KOH and phosphorus pentoxide, was washed by suspension in hot petroleum ether with centrifugation, yield 161 mg. Tests were positive for ninhydrin and acetate but negative for the reduction of alkaline copper tartrate. A portion of the acetate salt was converted to the N-acetyl derivative which melted at 128–131°; the same derivative of the natural *erythro* base melted at 125°.

Lead Tetraacetate Oxidation.—To 34 mg (0.1 mmol) of compound IV in 6 ml of glacial acetic acid was added with gentle warming 89 mg (0.2 mmol) of lead tetraacetate. After 2 hr at room temperature, 4 ml of methanol were added; 3 hr later, the reaction mixture was treated three times with 20-ml portions of ethyl acetate:*n*-heptane (1:1) after the addition of 5 ml each of water and 30% nitric acid. The combined extracts were washed with H_2O, filtered, and concentrated. The dried residue was crystallized from petroleum ether, yield 21 mg, mp 57°. Authentic palmitic acid melted at 58°. The infrared spectra of both samples were identical as were the retention times of their methyl esters on gas–liquid chromatography.

Derivatives of Compound VI. N-Acetyl (VII).—To 34 mg of compound VI in 6 ml of ether:ethyl acetate (1:1) was added 0.1 ml of acetic anhydride followed by 400 mg of $KHCO_3$ in 10 ml of water. After further addition of 50 ml of ether, the organic layer was washed and the solvent removed. The dried residue was crystallized from 10 ml of *n*-heptane, yield 32 mg, mp 104–105°. This product was identical with that obtained from the chromic anhydride oxidation of N-acetyldihydrosphingosine, as determined by thin layer and gas–liquid chromatographies and their infrared spectra.

Anal. Calcd for $C_{20}H_{39}O_3N$ (341.3): C, 70.32; H, 11.52; N, 4.10. Found: C, 70.79; H, 11.69; N, 4.04.

3-Hydroxy Diastereoisomers.—Compound VII, 30 mg, was treated with 8 mg of $NaBH_4$ in 10 ml of methanol containing 0.1 ml of NaOH. After 1 hr the reaction mixture was poured into an equal volume of ice water. The precipitate, removed by centrifugation, was dried and crystallized from *n*-heptane, yield 11 mg, mp 112–118°.

O,N-Diacetyl.—To 51 mg of compound VII in 2 ml of dry pyridine were added 0.1 ml of acetic anhydride; the product was removed with ether after addition of an equal volume of water. The organic layer was washed and concentrated and the residue was crystallized from petroleum ether, yield 48 mg, mp 95–96°. Infrared absorption for ester was present at 1750 and 1230 cm^{-1}.

(14) B. Weiss, *J. Amer. Chem. Soc.*, **79**, 5553 (1957).

(15) K. S. Tenny, S. C. Gupta, R. F. Nystrom, and F. A. Kummerow, *J. Amer. Oil Chem. Soc.*, **40**, 172 (1963).

(16) B. Weiss, *Biochemistry*, **3**, 1288 (1964).

Anal. Calcd for $C_{22}H_{41}O_4N$ (383.3): C, 68.87; H, 10.78; N, 3.65. Found: C, 68.99; H, 10.72; N, 3.75.

2,4-Dinitrophenylhydrazone.—Compound VI, 34 mg, was refluxed 5 min with 30 mg of 2,4-dinitrophenylhydrazine in 4 ml of methanol containing 0.1 ml of 6 *N* HCl. After cooling to room temperature the reaction mixture was centrifuged. The precipitate was crystallized from methanol, yield 27 mg, mp 138–141°.

Anal. Calcd for $C_{24}H_{42}O_5N_5Cl$ (515.3): C, 55.86; H, 8.22; N, 13.58. Found: C, 55.55; H, 8.21; N, 13.43.

Compound VII, 51 mg, treated in the same manner as compound VI with 2,4-dinitrophenylhydrazine, yielded 38 mg of derivative, mp 165°. The anticipated hydrazone corresponding to $C_{26}H_{43}O_6N_5$ (521.3) with calculated values for C, 59.85, H, 8.31, and N, 13.43 was not obtained; instead, the values for C, 55.37, H, 6.53, and N, 17.59 were found suggesting an empirical formula of $C_{26}H_{36}O_7N_7$ (557.3). The product showed one component on thin layer chromatography.

D-1-Hydroxy-2-carbobenzoxamido-3-ketooctadecane-4,5-^{3}H (VIII).—To 1.4 mg (22.8 mC) of N-carbobenzoxydihydrosphingosine-4,5-^{3}H[8] in 50 ml of methanol were added 434 mg of N-carbobenzoxydihydrosphingosine; the solution was concentrated and the residue was dried over phosphorus pentoxide. The product was dissolved in 30 ml of pyridine, chilled and treated with 435 mg of dry chromic anhydride. The remainder of the procedure, including column chromatography on silicic acid, was the same as that employed in the preparation of compound V, yield 138 mg (32%), mp 63°; recovered radioactivity 3.5 mCi, 15%; specific activity 25.5 μCi/mg (11.1 mCi/mmol).

The yield of N-carbobenzoxydihydrosphingosine-4,5-^{3}H recovered from the 1% methanol in chloroform was 150 mg (35%), mp 105–106°. Radioactive yield 5.4 mCi, 24%; specific activity 35.9 μCi/mg.

D-1-Hydroxy-2-amino-3-ketooctadecane-4,5-^{3}H Hydrochloride.[17]—Compound VIII, 138 mg, was hydrogenated and the product was isolated in the same manner as that described for the preparation of compound VI, yield 93.4 mg (87%), mp 96–98°; Recovered radioactivity 3.3 mCi, 14%; specific activity 35.7 μCi/mg (11.9 mC/mmol). The product was stored in the dark *in vacuo* over phosphorus pentoxide.

Registry No.—I, 25515-49-5; II, 25515-50-8; dihydrosphingosine, 764-22-7; III, 25515-52-0; IV, 25515-53-1; V, 25515-54-2; VI (2,4-dinitrophenylhydrazone), 25515-57-5; dihydrosphingosine acetate (diastereoisomers), 25528-34-1; VII, 25515-55-3; VII (3-hydroxy diastereoisomers), 13552-12-0; VII (O,N-diacetyl), 25515-56-4; VIII, 25568-74-5; D-1-hydroxy-2-amino-3-ketooctadecane-4,5-^{3}H (HCl), 25515-58-6.

(17) Preliminary studies showed that this compound was an efficient precursor in the biosynthesis of phytosphingosine by growing cultures of the yeast *Hansenula ciferrii*.

Carbodiimide–Sulfoxide Reactions. VIII.[1] Reactions of Oximes and Hydroxylamines[2]

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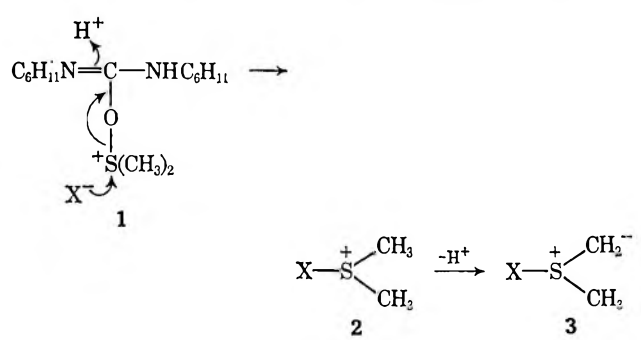
The reaction of benzophenone oxime with dimethyl sulfoxide and dicyclohexylcarbodiimide in the presence of trifluoroacetic acid leads to formation of α,α-diphenyl-*N*-(thiomethoxymethyl)nitrone (**5**) and the isomeric *O*-(thiomethoxymethyl)benzophenone oxime (**6**). The relative amounts of **5** and **6** depend upon the reaction conditions and, using pentadeuterio-**5**, intramolecular rearrangement into pentadeuterio-**6** has been demonstrated. Similar formation of a nitrone and oxime ether occurred using fluoren-9-one oxime, but certain aliphatic oximes led to complex reaction mixtures. Reactions of several 17-oximino steroids led to the formation of D-homolactams and of unsaturated nitriles *via* first- and second-order Beckmann rearrangements, the latter being unusual with these compounds. Both *syn* and *anti* isomers of *p*-bromobenzaldoxime gave *p*-bromobenzonitrile and α-*p*-bromophenyl-*N*-(thiomethoxymethyl)nitrone in different proportions. *N*-Phenylhydroxylamine gave azoxybenzene, presumably *via* oxidation to nitrosobenzene, and *N*,*N*-dibenzylhydroxylamine gave α-phenyl-*N*-benzylnitrone in high yield. Mechanisms for these reactions are presented.

Previous papers in this series have described mild acid-catalyzed reactions of dimethyl sulfoxide (DMSO) and dicyclohexylcarbodiimide (DCC) with alcohols,[4] phenols,[5] and active methylene compounds.[1] In each case the observable reactions can be explained by nucleophilic attack of the functional group upon an initial DMSO–DCC adduct (**1**), giving an oxysulfonium salt, or related derivative, (**2**) which can readily lose a proton



giving a sulfonium ylide (**3**). The latter can then directly rearrange or undergo further reactions.

The mildness of these reactions suggests that other nucleophilic functional groups might also react with **1** leading to many possible types of reaction. In this paper we describe the reactions of several different types of oximes and hydroxylamines while in subsequent publications a wide range of other functional groups are considered.[6]

Benzophenone oxime (**4**) was found to react rapidly with DMSO and DCC in the presence of 0.5–1.0 equiv of anhydrous orthophosphoric acid, omission of any of these reagents blocking the reaction. Unlike the reactions described previously, however, free trifluoro

(1) For part VII, see A. F. Cook and J. G. Moffatt, *J. Amer. Chem. Soc.*, **90**, 740 (1968).

(2) This and related work was presented as part of the Eleventh National Medicinal Chemistry Symposium of the American Chemical Society, Quebec, Canada, June 1968.

(3) Syntex Postdoctoral Fellow, 1964–1965.

(4) (a) K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **87**, 5661, 5670 (1965); (b) A. H. Fenselau and J. G. Moffatt, *ibid.*, **88**, 1762 (1966).

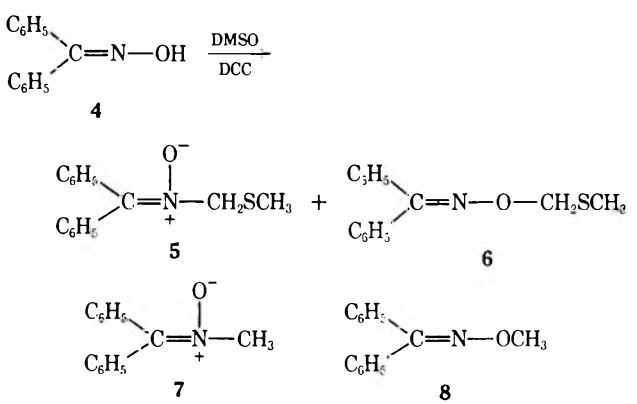
(5) (a) M. G. Burdon and J. G. Moffatt, *ibid.*, **88**, 5855 (1966); (b) M. G. Burdon and J. G. Moffatt, *ibid.*, **89**, 4725 (1967).

(6) U. Lerch and J. G. Moffatt, unpublished results.

acetic acid (TFA) gave a somewhat cleaner reaction mixture with no necessity for adding pyridine.

A preparative reaction between **4** and 3 mol equiv of DCC in a 1:1 mixture of DMSO and benzene containing 0.5 mol equiv of trifluoroacetic acid rapidly gave one major, polar product and one minor, nonpolar product together with traces of unreacted **4** and benzophenone. Chromatography on a column of silicic acid quite readily separated these components and led to the isolation, in crystalline form, of the two new products in yields of 74 and 3%. Both compounds gave elemental analyses corresponding to the molecular formula $C_{15}H_{15}NOS$ and their monomeric nature was confirmed by mass spectrometry. On the basis of the evidence presented below these compounds are shown to be α,α-diphenyl-*N*-(thiomethoxymethyl)nitrone (**5**) and *O*-(thiomethoxymethyl)benzophenone oxime (**6**), respectively.

The structure of **5** was deduced from its spectral properties and by degradation.[7] Its nmr spectrum clearly demonstrated the presence of a thiomethoxymethyl group and, unlike the oxime ether, two of the aromatic protons are deshielded by roughly 0.7 ppm due to the proximity of the polar oxygen atom. In addition, the ultraviolet spectrum closely resembles that of an authentic sample of α,α-diphenyl-*N*-methylnitrone (**7**)[8] which showed λ_{max} 234 mμ (ε 12,100) and 295 (11,200) and the infrared spectra of **5** and **7** showed very similar N → O stretching frequencies at 1250 cm^{-1}.



Treatment of **5** with very dilute hydrochloric acid in aqueous methanol led to rapid hydrolysis giving benzophenone, formaldehyde, and an odoriferous sulfur compound, presumably methyl mercaptan. A rough kinetic study by following changes in the ultraviolet spectrum indicated that the hydrolysis of **5** is about six times as fast as that of *N*-methylnitrone **7**. Desulfurization of **5** with a sponge nickel catalyst[9] gave the known crystalline *N*-methylnitrone **7** in 20% yield together with 37% benzophenone (presumably *via* simply hydrolysis of **5** or **7**) and 34% unreacted **5**.

The isomeric *O*-(thiomethoxymethyl) oxime (**6**) was also characterized by its nmr spectrum and by the similarity of its ultraviolet spectrum to that of *O*-methylbenzophenone oxime[8] **8** (λ_{max}^{MeOH} 231 mμ, ε 13,200; λ_{max} 260 mμ, ε 10,800) which was prepared from benzophenone and methoxylamine. Final proof of the structures of **5** and **6** came from an independent synthesis of both compounds *via* alkylation of the sodium salt of benzophenone oxime with chloromethyl methyl sulfide. Alkylation of such ambident anions is known to lead to both nitrones and *O*-alkyl oximes[7] and a systematic study of the factors affecting the site of alkylation has been made.[10] In most cases *O*-alkylation is somewhat favored[10] but in the above reaction roughly equal amounts of **5** (38%) and **6** (47%) were obtained. This ratio is, however, in marked contrast to that obtained in the DMSO–DCC reaction in which the nitrone was the preponderant product. Very recently Kerr and Wilson[11] have briefly reported the formation of **5** from benzophenone oxime with DMSO and DCC but **6** was apparently not obtained.

A number of small experiments were carried out in order to determine the effects of controlled variations in reaction conditions. The product distributions, as estimated by thin layer chromatography are recorded in Table I. From Table I it can be seen that, as in the oxidation of alcohols,[4] optimal results require the use of more than 1 mol equiv of DCC (experiments 1–3) and a larger than stoichiometric amount of DMSO (experiments 4 and 5). The nature of the cosolvent and the reaction time are also reflected in the relative proportions of **5** and **6**, the relative proportion of the ether **6** being lower in the presence of nonpolar diluents such as benzene or ether (reactions 3 and 7). An increase in the proportion of the oxime ether at the expense of the nitrone is also apparent when the reaction time is prolonged (reactions 8–10 and 12–13), especially when using phosphoric acid, but it is not significant under the standard conditions using TFA and benzene as a diluent (reaction 3). The same products are formed, although in somewhat different proportions, in reactions using TFA, anhydrous phosphoric acid,

TABLE I

PRODUCT DISTRIBUTION USING DIFFERENT REACTION CONDITIONS[a]

Expt	Variable feature	Oxime 4	Benzophenone	Nitrone 5	Oxime ether 6
1	1 equiv, DCC (16 hr)	32	24	42	2
2	2 equiv, DCC (16 hr)	6	8	79	7
3	3 equiv, DCC (16 hr)	9	11	75	5
4	1 equiv, DMSO (3 hr)	81	4	12	3
5	2 equiv, DMSO (3 hr)	58	6	31	5
6	Pure DMSO (3 hr)	22	18	39	21
7	DMSO–ether (1:1) (1 hr)	5	11	67	9
8	DMSO–DMF (1.5 hr)[b]	13	11	67	9
9	DMSO–DMF (5 hr)[b]	14	14	52	20
10	DMSO–DMF (20 hr)[b]	20	13	30	37
11	1.0 equiv, H_3PO_4 (1.5 hr)	4	20	41	34
12	0.5 equiv, H_3PO_4 (1.5 hr)	4	19	59	18
13	0.5 equiv, H_3PO_4 (24 hr)	6	16	31	47

[a] Standard conditions used 3 mol equiv of DCC and 0.5 equiv of trifluoroacetic acid in DMSO–benzene (1:1). Only deviations from this standard mixture are indicated in the Table. The product distributions (%) were determined by quantitative tlc using chloroform–ethyl acetate (4:1) followed by measurement of ultraviolet absorption. [b] 0.8 mol equiv of trifluoroacetic acid was used.

(7) The chemistry of nitrones has recently been reviewed: (a) J. Hamer and A. Macaluso, *Chem. Rev.*, **64**, 473 (1964); (b) G. R. Delpiene and M. Lamchen, *Quart. Rev. (London)*, **19**, 329 (1965).

(8) L. Semper and L. Lichtenstadt, *Ber.*, **51**, 928 (1918).

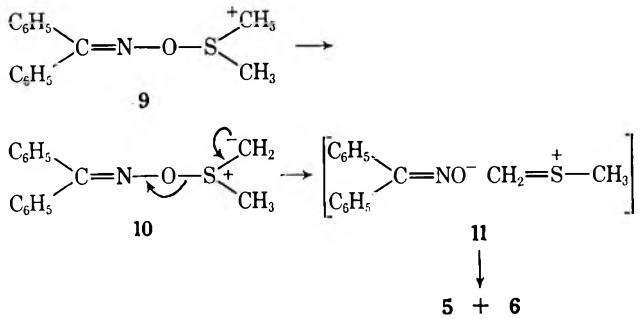
(9) Davidson Chemical Division of W. R. Grace and Co., Cincinnati, Ohio.

(10) P. A. S. Smith and J. E. Robertson, *J. Amer. Chem. Soc.*, **84**, 1197 (1962).

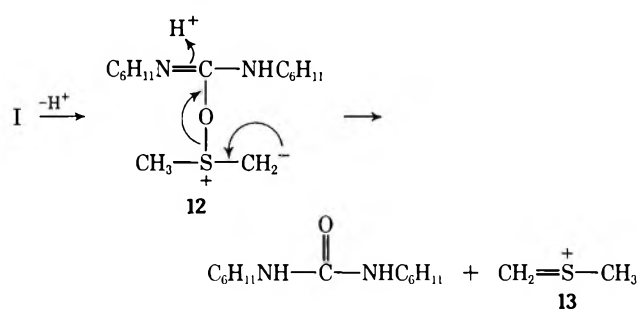
(11) D. A. Kerr and D. A. Wilson, *Tetrahedron Lett.*, 2885 (1968).

pyridinium trifluoroacetate, and dichloroacetic acid. No reaction, however, was observed using toluenesulfonic acid.

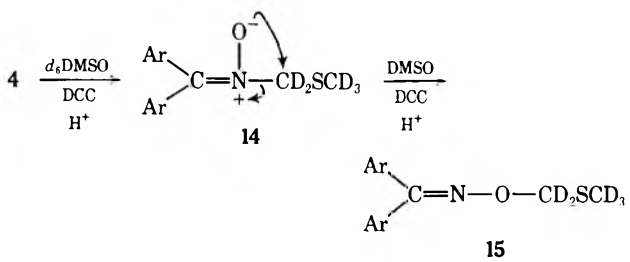
The most probable mechanism of the reactions above appears to involve nucleophilic attack of the oxime oxygen upon the DMSO–DCC adduct (**1**) with formation of an oxysulfonium salt (**9**) which readily loses a proton with formation of the sulfonium ylide (**10**). There is no proton in **10** available for abstraction in the oxidation of alcohols[4b] and the nature of the products precludes an intramolecular rearrangement with attack by the carbanion on carbon or nitrogen as in the reactions of phenols.[5] The ylide **10** appears, rather, to dissociate into the ion pair (**11**) which then recombines into the nitrone (**5**) and the ether (**6**) *via* alkylation by the electrophilic methylene methyl sulfonium ion at nitrogen or oxygen, respectively.



The alternate possibility that the methylene methyl sulfonium ion (**13**) arises *via* decomposition of the ylide (**12**) derived by proton loss from the DMSO–DCC adduct (**1**) appears unlikely. In previous work it has been shown that the ion **13**, generated by different reactions, is indeed a powerful electrophile which rapidly alkylates phenols and phenol ethers.[5b,12] Anisole, however, undergoes no observable reaction with DMSO, DCC, and anhydrous phosphoric acid[5a] which indicates that the conversion **1** → **12** → **13** does not take place under the usual reaction conditions. Initial reaction of **1** with the oxime thus appears to be a prerequisite for the observed reactions.

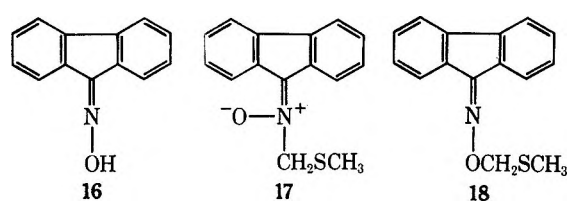


The observed increase with time of the relative proportion of oxime ether relative to nitrone suggests the possibility of a direct interconversion of these isomers. The thermal rearrangement of certain nitrones to the isomeric oxime ethers has been described by Cope, *et al.*,[13] and indeed it was found that heating a sample of **5** under nitrogen at 150° for 2 hr led to the formation of a mixture of benzophenone, benzophenone oxime, and the oxime ether (**6**) as judged by thin layer chromatography. A direct chemical isomerization of the nitrone to the oxime ether was also directly demonstrated. Thus, reaction of the crystalline nitrone **5** with DMSO, DCC, and anhydrous phosphoric acid for 40 hr at room temperature was shown to lead to the formation of 38% of the isomeric oxime ether (**6**) as well as 32% unreacted **5** and 30% benzophenone presumably arising from simple hydrolysis of **5**. The conversion **5** to **6** appears to absolutely require the presence of DMSO, DCC, and acid since in the absence of any one of these reagents greater than 90% of the nitrone remained unchanged and only a little benzophenone was formed. When the pentadeuterionitrone (**14**) from **4**, DMSO-d_6, DCC, and TFA was reacted with nondeuterated DMSO, DCC, and anhydrous phosphoric acid as above, the resulting oxime ether (**15**) was still predominantly deuterated; integration of the nmr signals at 5.23 and 2.22 ppm indicating the presence of only 9 and 18% protons in the $-NCH_2S$ and $-SCH_3$ groups, respectively. It is thus clear that the conversion of **5** to **6** is an essentially intramolecular process which could be explained by the type of mechanism (**14** → **15**) that has been used for the equivalent thermal rearrangement.[13] A radical dissociation–recombination mechanism has also been recently proposed for the thermal rearrangement of certain nitrones.[14] A mechanism that explains the necessary roles of DMSO, DCC, and a proton source remains obscure.



It might also be mentioned that α,α-diphenyl-*N*-methylnitrone (**7**) did not undergo any noticeable rearrangement under comparable conditions, only starting material and a little benzophenone being formed. The oxime ether (**6**) was completely stable under these conditions.

Fluoren-9-one oxime (**16**) underwent a very similar reaction with DMSO, DCC, and TFA giving the thiomethoxymethylnitrone (**17**) and the oxime ether (**18**) in yields of 71 and 5%, respectively. Some unreacted oxime was also recovered and traces of a very unstable, rather polar product were isolated but not examined further. Unlike **5**, the nitrone (**17**) showed very little tendency to rearrange into the oxime ether (**18**) upon reaction with DMSO, DCC, and acid.



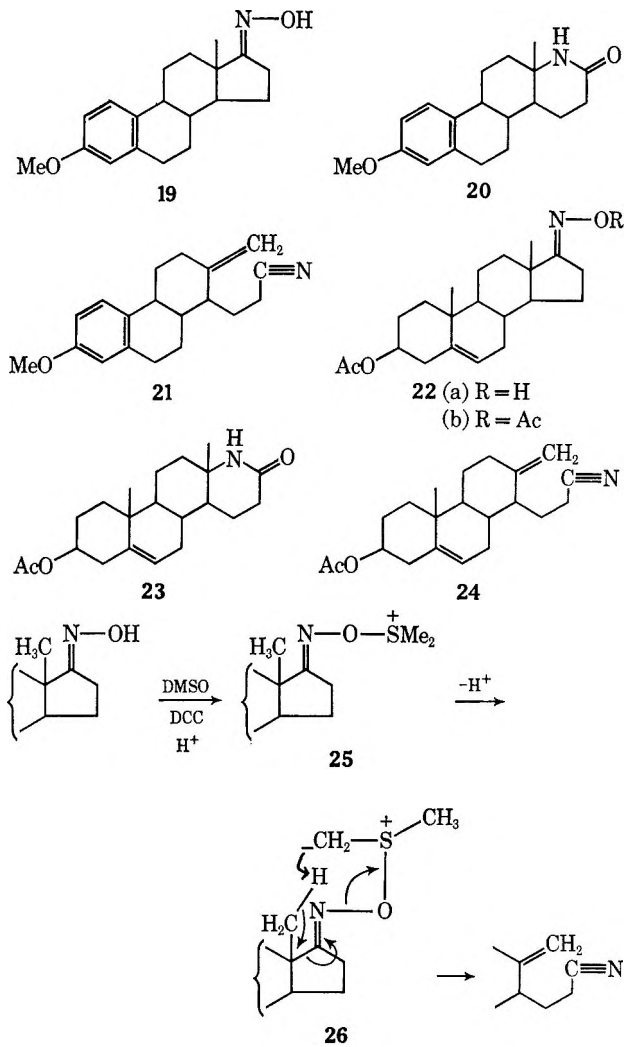
(12) K. E. Pfitzner, J. P. Marino, and R. A. Olofson, *J. Amer. Chem. Soc.*, **87**, 4658 (1965).

(13) A. C. Cope and A. C. Haven, *ibid.*, **72**, 4896 (1950).

(14) E. J. Grubbs, J. A. Villaneal, J. D. McCullough, and J. S. Vincent, *ibid.*, **89**, 2234 (1967).

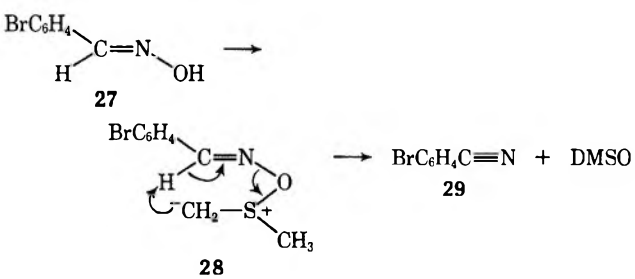
Several oximes containing aliphatic residues were also examined (*e.g.*, cyclohexanone, acetophenone, and tetralone oximes) and shown by tlc to lead to complex, and difficulty separable, mixtures containing six or more compounds including those expected from Beckmann rearrangements. Thus, acetanilide was shown to be a major product from the reaction of acetophenone oxime. More clear-cut examples of Beckmann rearrangements were found using several 17-oximino steroids as models. Reaction, for example, of estrone methyl ether oxime (**19**) with DMSO, DCC, and TFA led to the very rapid formation of two products in roughly equal amounts. Following chromatography on silicic acid, these were shown to be the known 13α-amino-3-methoxy-13,17-secoestra-1,3,5(10)-trien-17-oic-13,17-lactam (**20**)[15] which was isolated in 39% yield, and 3-methoxy-13,17-secoestra-1,3,5(10),13(18)-tetraenoic nitrile (**21**), the result of a second-order Beckmann rearrangement,[16] in 41% yield. The structure of **21** is based upon its elemental analysis, the presence of a nitrile band at 2250 cm^{-1} in its infrared spectrum, its nmr spectrum which shows the absence of an 18-methyl group and the presence of the methylene group as two 1-proton singlets at 4.56 and 4.85 ppm. The formation of equal amounts of lactam **20** and nitrile **21** is interesting since a number of 17-oximino steroids have been subjected to Beckmann rearrangement under a variety of conditions with formation, generally in high yield, of only the corresponding lactams. The only mention of second-order products that we have found was the formation of a 6% yield of a seco nitrile from adrenosterone 17-oxime upon rearrangement with 4-acetamidobenzenesulfonyl chloride in pyridine[17] and the very recent report of the formation in 9% yield of the $\Delta^{13(14)}$ tetrasubstituted olefin isomer of **21** from **19** and chlorosulfonic acid.[18] We suggest that the formation of the oxysulfonium salt (**25**), which provides an excellent leaving group for a normal Beckmann rearrangement, is followed by ylide formation (**26**) in the usual way. The availability of the ylide anion for an intramolecular proton abstraction from C_{18} then explains the anomolous formation of the unsaturated nitrile. Even though such a cyclic mechanism requires an eight-membered cyclic transition state, molecular models suggest that such an intermediate is readily accommodated. A similar reaction with 3-β-acetoxy-17-oximinoandrost-5-ene (**22a**) led to the formation of the lactam (**23**)[19] and the unsaturated nitrile (**24**) in yields of 21 and 61%, respectively.

Once again the requirements for these reactions have been checked and it was shown that the formation of **20** and **21** from **19** proceeded rapidly (within 30 min) only in the presence of DMSO, DCC, and TFA. The acid could be replaced by anhydrous orthophosphoric or by dichloroacetic acids but in both cases the reaction was less satisfactory. Reactions in which DMSO was replaced by DMF or benzene led to the formation of *traces* of lactam **20** but no nitrile, suggesting that some activation of the oxime, presumably *via* formation of an isourea ether, is possible with DCC and acid alone.



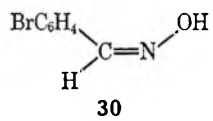
In the absence of DCC or of acid, however, no detectable reaction occurred. As has been reported earlier for the case of benzophenone oxime,[11] reaction of **22a** with DMSO and acetic anhydride led only to the quantitative formation of the *O*-acetyl oxime (**22b**).

Aldoximes behaved in quite a different way. Thus, the *syn* (**27**) and *anti* (**30**) isomers of *p*-bromobenzaldoxime were prepared in crystalline form by the isomerization method of Brady and Dunn[20] and separately subjected to the usual reaction. In both cases two products were rapidly formed and shown to be *p*-bromobenzonitrile (**29**) and α-*p*-bromophenyl-*N*-thiomethoxymethylnitrone (**31**). The *syn*-oxime (**27**) gave



crystalline nitrile and nitrone in yields of 68 and 39% while the *anti*-oxime gave a larger proportion of nitrile (84% isolated) with relatively little nitrone. This result is perhaps somewhat surprising since formation of

(15) B. M. Regan and F. N. Hayes, *J. Amer. Chem. Soc.*, **78**, 639 (1956).
(16) (a) L. G. Donaruma and W. Z. Heldt, *Org. React.*, **2**, 1 (1960); (b) C. A. Grob and P. W. Schiess, *Angew. Chem., Int. Ed. Engl.*, **6**, 1 (1967).
(17) W. Nagata, M. Narisada, and T. Sugasawa, *J. Chem. Soc. C*, 648 (1967).
(18) A. Cervantes, P. Crabbé, J. Iriarte, and G. Rosenkrantz, *J. Org. Chem.*, **33**, 4294 (1968).
(19) S. Kaufman, *J. Amer. Chem. Soc.*, **73**, 1779 (1951).
(20) O. L. Brady and F. P. Dunn, *J. Chem. Soc.*, **123**, 1785 (1923).



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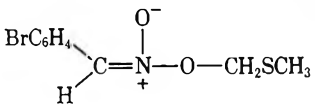

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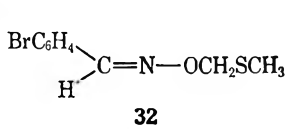


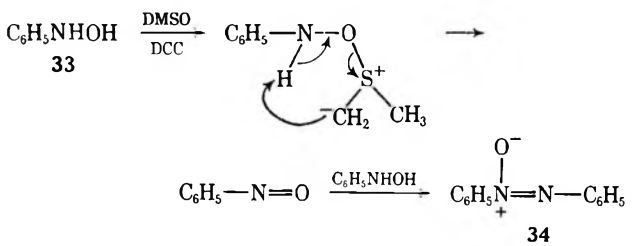
32

the nitrile could be expected to occur *via* an intramolecular proton abstraction mechanism (**27** → **30**) *via* the ylide **28**, a process that would be favored by *syn* stereochemistry. Formation of the nitrone (**31**, for which no stereochemical assignment can be made since only a single isomer has been isolated) presumably involves a dissociation and recombination mechanism *via* an ion pair similar to **11** and might be expected to be favored by *anti*-stereochemistry.

The assignment of configurations to **27** and **30** is based upon the usual preferential formation of the *syn* isomer which can then be transformed into the less stable, higher melting *anti* form[20] and is confirmed by nmr spectroscopy, the vinyl proton of **27** occurring at lower field (8.19 ppm) than that of **30** (7.46 ppm).[21] Alkylation of both **27** and **30** with chloromethyl methyl sulfide and sodium hydride in benzene gave roughly equal amounts of the nitrone **31** identical with that from the DMSO–DCC reaction, and the isomeric oxime ether **32**. In neither case was there any indication of geometrical isomers, presumably the thermodynamically more stable form being formed. Hydrolysis of **31** with hydrochloric acid in methanol gave mainly the *syn*-oxime (**27**) rather than the parent carbonyl compound as had been found with **5**.

While quantitative experiments have not been done, owing in part to the volatility of the products and the lability of the isomeric oximes, benzaldehyde oxime has been shown to react in a similar way giving mainly benzonitrile and a small amount of α-phenyl-*N*-thiomethoxymethylnitrone.

Reactions of a few hydroxylamines with DMSO and DCC have also been studied. *N*-Phenylhydroxylamine[22] (**33**) reacted rapidly under the usual conditions giving azoxybenzene (**34**) in 54% yield presumably *via* initial oxidation of **33** to nitrosobenzene followed by reaction with excess **33**. Several other minor products were not investigated further.



34

The reaction of *N*,*N*-dibenzylhydroxylamine (**35**) with DMSO, DCC, and TFA took a different course giving crystalline α-phenyl-*N*-benzylnitrone (**38**) in 84% yield together with minor amounts of benzaldehyde (isolated as its dinitrophenylhydrazone) and *N*-benzylbenzamide. We suggest that the initially formed

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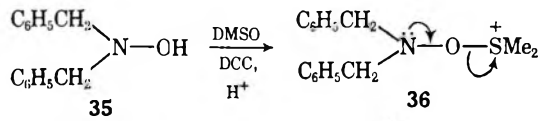

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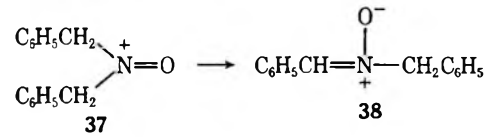

37 38

oxysulfonium ion (**36**) collapses with intervention of the unshared electrons on nitrogen to give the nitroso cation (**37**) and dimethyl sulfide. A prototropic shift then converts (**37**) into the protonated nitrone which is isolated as the free base (**38**). A very similar conversion of a nitroso compound into a nitrone by alkylation with an oxonium salt has recently been described by Baldwin, *et al.*[23]

The formation of both benzaldehyde and *N*-benzylbenzamide could result from hydrolysis or rearrangement of the nitrone **38**, both types of reaction being well known.[7]

Experimental Section

General experimental methods are as previously described.[1]

Reactions of Benzophenone Oxime.—Trifluoroacetic acid (0.75 ml, 10 mmol) was added to a cooled solution of benzophenone oxime (2.00 g, 10.1 mmol) and DCC (6.2 g, 30 mmol) in anhydrous DMSO (20 ml) and benzene (20 ml) under nitrogen. After 2 hr at 25°, the mixture was poured into ice water and the resulting precipitate was well washed by trituration with benzene. The combined filtrates and benzene washings were extracted several times with water, dried (Na_2SO_4), and evaporated leaving 3.39 g of a yellow semisolid which was chromatographed on a column containing 150 g of Merck silicic acid. Elution with benzene gave 80 mg (3%) of *O*-(thiomethoxymethyl)benzophenone oxime (**6**) with mp 49–49.5° from benzene–hexane: λ_{max}^{MeOH} 231 mμ (ε 14,600), 261 (12,000); nmr ($CDCl_3$) 2.20 ppm (s, 3, SCH_3), 5.22 (s, 2, OCH_2S), 7.4 (br s, 10, Ar); mass spectrum (70 eV) *m/e* 257 (M^+), 211 (M − CH_2S), 194, 180 (M − C_6H_5), 77 (C_6H_5), 61 (CH_3SCH_2).

Anal. Calcd for $C_{15}H_{15}NOS$: C, 70.01; H, 5.88; N, 5.43; S, 12.46. Found: C, 70.19; H, 5.97; N, 5.44; S, 12.63.

Continued elution with chloroform–ethyl acetate (4:1) gave small amounts of benzophenone (8%) and unreacted **4** (8%) and elution with ethyl acetate gave **5** contaminated with some dicyclohexylurea (2.66 g). The solid was triturated with benzene and the soluble portion crystallized from aqueous methanol giving 1.85 g (74%) of α,α-diphenyl-*N*-(thiomethoxymethyl)-nitrone (**5**): mp 92–92.5°; λ_{max}^{MeOH} 236 mμ (ε 13,200), 300 (12,400); ir (KBr) 1250 cm^{-1} (C=N^+–O^-); nmr ($CDCl_3$) 2.43 ppm (s, 3, SCH_3), 4.75 (s, 2, NCH_2S), 7.3 (m, 8, Ar), 8.0 (m, 2, Ar); mass spectrum (70 eV) *m/e* 257 (M^+), 196 (M − CH_2SCH_3), 62 (CH_2SCH_3).

Anal. Calcd for $C_{15}H_{15}NOS$: C, 70.01; H, 5.88; N, 5.43; S, 12.46. Found: C, 70.17; H, 5.87; N, 5.43; S, 12.61.

Alkylation of Benzophenone Oxime.—Benzophenone oxime (5.0 g, 25.4 mmol) and a suspension of pentane washed sodium hydride (from 1.6 g, 35 mmol of a 53% suspension in mineral oil) were stirred in benzene at 80° under nitrogen for 20 min. After cooling, chloromethyl methyl sulfide (5.1 g, 53 mmol) was added, and the mixture was refluxed for 30 min. The mixture was filtered and the filtrate was evaporated to dryness leaving 6.51 g of a yellow oil that was chromatographed on a column containing 270 g of Merck silicic acid. Elution with benzene gave 3.04 g (47%) of **6** with mp 49–49.5° from benzene–hexane and identical spectral properties with those above. Elution with chloroform and with chloroform–ethyl actate (1:1) gave 0.47 g (10%) of benzophenone and 2.3 g (38%) of **5** of mp 92–92.5° and identical with that above.

Acidic Hydrolysis of 5.—A solution of 139 mg (0.54 mmol) of **5** in 3.5 ml of 85% methanol containing 0.05 ml of concentrated

(23) J. E. Baldwin, R. G. Pudussery, B. Sklarz, and M. K. Sultan, *Chem. Commun.*, 1361 (1968).

hydrochloric acid was kept at 35° for 30 min. Evaporation of the solvent left a solid residue that was sublimed (50°, (0.1 mm)] giving 85 mg (91%) of benzophenone of mp 48° and giving a 2,4-dinitrophenylhydrazone of mp 235–238°. A similar hydrolysis mixture was directly treated with acidic 2,4-dinitrophenylhydrazine solution giving a mixture of the dinitrophenylhydrazones of benzophenone and formaldehyde which were separated and identified by tlc using chloroform.

Desulfurization of 5.—A mixture of 281 mg of **5** and 0.5 g of Davidson sponge nickel[10] was stirred in benzene at 50° for 5 hr. Chromatography of the filtered and evaporated mixture on a column of silicic acid using benzene–chloroform(4:1) gave 81 mg (41%) of benzophenone, and elution with chloroform–ethyl acetate (4:1) gave 95 mg (34%) of unreacted **5** followed by 46 mg (20%) of α,α-diphenyl-*N*-methylnitrone: mp 101.5–102° from hexane (lit.[8] mp 102–103°); λ_{max}^{MeOH} 234 mμ (ε 12,100), 295 (11,200); ir (KBr) 1250 cm^{-1}; nmr ($CDCl_3$) 3.7 ppm (s, 3, NCH_3), 7.4 (m, 8, Ar), 8.0 (m, 2, Ar).

α,α-Diphenyl-*N*-(pentadeuteriothiomethoxymethyl)nitrone (14).—The reaction between **4** (196 mg, 1 mmol), DCC (168 mg, 3 mmol), and TFA (0.04 ml, 0.5 mmol) in a mixture of d_6-DMSO (0.25 ml) and benzene (0.25 ml) was carried out essentially as with nondeuterated DMSO. Preparative tlc using chloroform–ethyl acetate (4:1) gave three main bands corresponding to **5**, unreacted **4**, and a little benzophenone. Elution of the slowest band gave 0.17 g of crystalline solid which was dissolved in benzene leaving 60 mg of dicyclohexylurea. Crystallization of the benzene soluble portion from hexane gave 96 mg (37%) of **14**: mp 93–95°; ir (KBr) almost identical with that of **6**; nmr ($CDCl_3$) 7.4 ppm (m, 8, Ar), 8.0 (m, 2, Ar), no resonance below 7 ppm; mass spectrum (70 eV) *m/e* 262 (M^+), 196 ($Ar_2C{=}NO^+$), 66 ($CD_2SCD_3^+$).

Reaction of 14 with DMSO–DCC–H_3PO_4.—The pentadeuterionitrone (**14**, 84 mg, 0.33 mmol), DCC (206 mg, 1 mmol), and anhydrous orthophosphoric acid (0.15 mmol) were dissolved in DMSO (0.2 ml) and ethyl acetate (0.2 ml). After 16 hr at 25°, the mixture was worked up with ethyl acetate and purified by preparative tlc using benzene. Elution of the fastest uv-absorbing band (same mobility as **6**) gave 15 mg of chromatographically homogeneous **15**: ir ($CDCl_3$) 1490, 1445, 1325, 1305, 980, 695 cm^{-1} almost identical with **6**; nmr ($CDCl_3$) 7.35 ppm (br s, 10, Ar), 5.23 (s, 0.2, OCH_2S), 2.12 (s, 0.4, SCH_3).

Reaction of Fluoren-9-one Oxime with DMSO–DCC.—A reaction between fluoren-9-one oxime (1.95 g, 10 mmol), DCC (6.18 g, 30 mmol), and TFA (0.375 ml, 5 mmol) in a mixture of DMSO (10 ml) and benzene (10 ml) for 24 hr at 25° was worked up with ethyl acetate. Evaporation and trituration of the residue with ether gave 1.22 g (48%) of pure crystalline **17** which was recrystallized from ethanol: mp 154–155°; λ_{max}^{MeOH} 238 mμ (ε 36,000), 256 (27,700), 341 (16,300), 356 (17,600); nmr ($CDCl_3$) 2.50 ppm (s, 3, SMe), 5.35 (s, 2, NCH_2S), 7.3 (m, 5, Ar), 7.6 (m, 2, Ar), 8.2 (m, 1, Ar); mass spectrum *m/e* 255 (M^+), 61 ($CH_2SCH_3^+$).

Anal. Calcd for $C_{15}H_{13}NOS$: C, 70.56; H, 5.13; N, 5.49; S, 12.56. Found: C, 70.72; H, 5.18; N, 5.34; S, 12.58.

The mother liquors from **17** were purified by preparative tlc using ether–hexane (3:1) giving four bands. The fastest band contained 135 mg (5%) of the oxime ether **18** as a homogeneous syrup that was crystallized from cold hexane with mp 49–50°: λ_{max}^{MeOH} 218 mμ (ε 22,600), 223 (22,600), 247 (36,100), 256 (47,100), 308 (10,500), 360 (1900); nmr ($CDCl_3$) 2.26 ppm (s, 3, SCH_3), 5.40 (s, 2, OCH_2S), 7.3 (m, 6, Ar), 7.7 (m, 1, Ar), 8.2 (m, 1, Ar).

Anal. Calcd for $C_{16}H_{13}NOS$: C, 70.56; H, 5.13; N, 5.49. Found: C, 70.78; H, 4.97; N, 5.29.

The second band contained some unreacted **16** and the third band a further 0.60 g (total yield 1.82 g, 71%) of **17** identical with that above.

Reaction of Estrone Methyl Ether Oxime (19).—Estrone methyl ether oxime[15] (0.96 g, 3.2 mmol), DCC (1.85 g, 9 mmol), and TFA (0.15 ml, 2 mmol) were reacted for 16 hr in a mixture of DMSO (10 ml) and benzene (10 ml). The worked-up mixture was purified by chromatography on a column containing 200 g of silicic acid. Elution with benzene gave 430 mg (48%) of nitrile **21** that was homogeneous by tlc[24] and vpc but which has not been obtained in crystalline form: λ_{max}^{MeOH} 277 mμ (ε 1800), 286 (1700); nmr ($CDCl_3$) 3.71 ppm (s, 3, OCH_3), 4.56 (s, 1, C=CH_2), 4.85 (s, 1, C=CH_2), 6.58 (s, 1, C_4H), 6.74 (q, $J_{1,2}$ = 9 Hz, $J_{2,3}$ = 2 Hz, 1, C_2H), 7.13 (d, $J_{1,2}$ = 9 Hz, 1, C_1H), no methyl singlet in 1.1–1.2 ppm range; ir (neat) 2250 cm^{-1} (C≡N).

Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24; N, 4.98. Found: C, 80.95; H, 8.22; N, 5.15.

Continued elution with chloroform gave 120 mg (12%) of unreacted **19** and elution with chloroform–ethyl acetate (3:1) gave 370 mg (40%) of lactam **20**: mp 218–220° (lit.[15] mp 222–224°); λ_{max}^{MeOH} 277 mμ (ε 2000), 287 (1800); ir (KBr) 1665 cm^{-1} (CONH); nmr ($CDCl_3$) 1.17 ppm (s, 3, $C_{19}H$), 3.74 (s, 3, OCH_3), 6.64 (s, 1, C_4H), 6.70 (br d, 1, C_2H), 7.20 (d, $J_{1,2}$ = 9 Hz, 1, C_1H), 7.32 (s, 1, NH).

Anal. Calcd for $C_{19}H_{25}NO_2$: C, 76.22; H, 8.42; N, 4.68. Found: C, 76.04; H, 8.64; N, 4.51.

Reaction of 3-β-Acetoxy-17-oximinoandrost-5-ene (22).—The reaction of **22** (1.04 g, 3 mmol, mp 177–179°),[19] DCC (1.85 g, 9 mmol), and TFA (0.15 ml, 2 mmol) in a mixture of DMSO (5 ml) and benzene (5 ml) was worked up as above and chromatographed on a column containing 200 g of silicic acid. Elution with chloroform gave 633 mg (61%) of the nitrile **24** as a syrup that slowly crystallized (mp 104–106°) on standing. After recrystallization from methanol the mp 105–106°: ir (KBr) 2245 cm^{-1} (C≡N), 1740 (OAc); nmr ($CDCl_3$) 0.93 ppm (s, 3, $C_{18}H$), 2.00 (s, 3, OAc), 4.55 (s, 1, C=CH_2), 4.85 (s, 1, C=CH_2), 5.40 (d, 1, C_6H).

Anal. Calcd for $C_{21}H_{29}NO_2$: C, 77.02; H, 8.93; N, 4.28. Found: C, 76.91; H, 9.22; N, 4.31.

Continued elution with a gradient of ethyl acetate in chloroform gave dicyclohexylurea followed by 218 mg (21%) of lactam **23** with mp 292–293° (lit.[19] mp 295–298°): ir (KBr) 1735 cm^{-1} (OAc), 1680 (CONH); nmr ($CDCl_3$) 1.01 ppm (s, 3, $C_{19}H$), 1.17 (s, 3, $C_{18}H$), 2.02 (s, 3, OAc), 4.6 (m, 1, C_3H), 5.40 (m, 1, C_6H), 7.35 (s, 1, NH).

Anal. Calcd for $C_{21}H_{31}NO_3$: C, 73.00; H, 9.05; N, 4.05. Found: C, 73.19; H, 9.14; N, 3.92.

Reaction of 22 with DMSO and Acetic Anhydride.—A solution of **22** (173 mg, 0.5 mmol) in DMSO (1.5 ml) and acetic anhydride (1.0 ml) was kept at room temperature for 24 hr during which time a crystalline product separated. The mixture was poured over ice giving the crystalline oxime acetate (172 mg, 90%) with mp 184–186° from methanol: ir (KBr) 1735, 1755, 1770 cm^{-1}; nmr ($CDCl_3$) 0.99 ppm (s, 3, $C_{18}H$), 1.02 (s, 3, $C_{19}H$), 2.00 (s, 3, OAc), 2.12 (s, 3, OAc), 5.4 (m, 1, C_6H).

Anal. Calcd for $C_{23}H_{33}NO_4$: C, 71.29; H, 8.58; N, 3.61. Found: C, 71.14; H, 9.06; N, 3.61.

Reaction of *syn*-*p*-Bromobenzaldoxime (27).—The *syn* oxime (**27**) (2.74 g, 13.7 mmol), with mp 112–113° (lit.[25] mp 110–111°), DCC (4.5 g, 22 mmol), and TFA (0.2 ml, 2.7 mmol) were reacted for 2.5 hr in a mixture of DMSO (15 ml) and benzene (20 ml). The mixture was worked up with benzene giving 2.85 g of a yellow solid which was sublimed [50° (0.1 mm)] giving 1.70 g (68%) of pure *p*-bromobenzonitrile (**29**) of mp 111–112° (lit.[26] mp 112.5°): λ_{max}^{MeOH} 240 mμ (ε 20,800); ir (KBr) 2230 cm^{-1} (C≡N). Upon raising the temperature of the sublimation[27] to 90°, 1.02 g (29%) of the pure nitrone **32** was obtained with mp 102.5–103.5°: λ_{max}^{MeOH} 302 mμ (ε 23,100); nmr ($CDCl_3$) 2.32 ppm (s, 3, SCH_3), 4.85 (s, 2, NCH_2S), 7.76 (s, 1, HC=N), 7.52 (d, *J* = 8 Hz, 2, Ar), 8.15 (d, *J* = 8 Hz, 2, Ar).

Anal. Calcd for $C_9H_{10}NOSBr$: C, 41.55; H, 3.88; N, 5.39; S, 12.33. Found: C, 41.74; H, 4.02; N, 5.26; S, 12.55.

Hydrolysis of 203 mg of **32** with 90% methanol (5 ml) containing 0.1 ml of 2 *N* hydrochloric acid at 25° for 4 hr gave mainly the *syn* oxime (**27**) which was isolated by thin layer chromatography using chloroform.

***anti*-*p*-Bromobenzaldoxime (30).**—Hydrogen chloride was bubbled for 15 min through a vigorously stirred solution of the *syn* oxime (**27**) (4.0 g) in ether. The resulting precipitate was collected by filtration, washed with ether, and dissolved in water. A 2 *N* solution of sodium hydroxide was then added until the mixture was pH 9 and the resulting crystalline residue (3.1 g, 78%) was collected by filtration and washed with water. Thin layer chromatography using $CHCl_3$–ethyl acetate (4:1) showed a single spot with a mobility smaller than that of **27**: mp 134–135°

(24) The product was distinctly different from the isomeric $\Delta^{13(14)}$ compound recently described by Cervantes, *et al.*[19] We are grateful to Dr. Crabbé for a sample of their compound.

(25) A. Hantzsch, *Z. Phys. Chem.*, **13**, 510 (1894).

(26) A. Korczynski and B. Fandrich, *C. R. Acad. Sci.*, **183**, 421 (1926).

(27) Alternatively, the reaction was worked up by chromatography on silicic acid, **29** and **32** being eluted with benzene and with chloroform–ethyl acetate (1:3), respectively. After crystallization from benzene–hexane, the products were identical with those above.

(lit.[28] mp 157° by a different method); nmr (DMSO-d_6) 7.46 ppm (s, 1, HC=N), 7.63 (d, J = 9 Hz, 2, Ar), 7.97 (d, J = 9 Hz, 2, Ar), 11.82 (s, 1, OH).

Reaction of *anti*-*p*-Bromobenzaldoxime (30).—A mixture of **30** (2.74 g), DCC (4.5 g), and TFA (0.20 ml) was reacted for 2.5 hr in DMSO (20 ml) and benzene (20 ml). After the usual work-up sublimation at 50° (0.1 mm) gave 2.10 g (84%) of nitrile **29** identical with that above. The residue (400 mg) contained a roughly 5:3 mixture of *p*-bromobenzaldehyde and nitrone **32** by quantitative tlc but isolation was not attempted.

Alkylation of *p*-Bromobenzaldoxime with Chloromethyl Methyl Sulfide. A.—Pentane washed sodium hydride (65 mg) was added to a stirred solution of the *syn* oxime (**27**) (417 mg) in benzene (20 ml). After 10 min at 25° the mixture was heated to 70° for 10 min, and cooled while chloromethyl methyl sulfide (1 ml) was added in several portions. After 15 min at 50° the yellow solution was filtered and evaporated *in vacuo* leaving 520 mg of a yellow oil which was purified by chromatography on a column of silicic acid. Elution with benzene–chloroform (4:1) gave 225 mg (42%) of *O*-(thiomethoxymethyl)-*p*-bromobenzaldoxime (**32**) which was sublimed at 70° (0.1 mm) with mp 61–62°: λ_{max}^{MeOH} 267 mμ (ε 19,100); 298 (3400); nmr ($CDCl_3$) 2.27 ppm (s, 3, SCH_3), 5.24 (s, 2, OCH_2S), 7.45 (s, 4, Ar), 8.04 (s, 1, HC=N).

Anal. Calcd for $C_9H_{10}NOSBr$: C, 41.55; H, 3.88; N, 5.39; S, 12.33. Found: C, 41.73; H, 3.97; N, 5.42; S, 12.57.

Traces (45 mg total) of unreacted oxime and *p*-bromobenzaldehyde were eluted with chloroform–ethyl acetate (1:1) and 217 mg (40%) of nitrone (**32**) was obtained with chloroform–ethyl acetate (1:5). After sublimation at 90° (0.1 mm) this material was identical with **32** obtained from the DMSO–DCC reaction.

B.—A reaction identical with A was carried out except that the *anti* oxime (**30**) was used. The products were identical with those from the *syn* oxime by melting point and by nmr and ir spectra.

Reaction of *N*-Phenylhydroxylamine (33).—Trifluoroacetic acid (0.075 ml, 1 mmol) was added to a solution of freshly prepared *N*-phenylhydroxylamine[22] (1.11 g, 10 mmol) and DCC (6.0 g, 29 mmol) in a mixture of DMSO (15 ml) and benzene (15 ml). The initially pale yellow solution rapidly became green, then yellow, and finally red. After 14 hr the mixture was diluted with benzene and excess DCC was destroyed by addition of oxalic acid (20 mmol). After filtration, the solution was extracted three times with water, dried, and evaporated leaving 1.06 g of an oil that was chromatographed on a column containing 100 g of silicic acid. The major product (540 mg, 54%) was eluted with a gradient of chloroform in benzene (20–80%) and was followed by small amounts of four unidentified compounds. The product crystallized upon storage giving *trans*-azoxybenzene as yellow needles of mp 34.5–35.5° (lit.[29] mp 36°): λ_{max}^{MeOH} 230 mμ (ε 9100), 259 (7800), 320 (14,700) (virtually identical with lit.[30] values); nmr ($CDCl_3$) 7.23–7.66 (m, 6, Ar), 8.01–8.41 (m, 4, Ar).

Reaction of *N*,*N*-Dibenzylhydroxylamine (35).—A solution of *N*,*N*-dibenzylhydroxylamine (2.13 g, 10 mmol), DCC (4.2 g, 20 mmol), and trifluoroacetic acid (0.1 ml, 1.3 mmol) in DMSO (10 ml) and ether (10 ml) was kept at 25° for 1 hr. The mixture was then diluted with chloroform, filtered, extracted several times with water, dried (Na_2SO_4), and evaporated leaving a clear syrup. Crystallization from benzene gave 1.76 g (84%) of α-phenyl-*N*-benzylnitrone (**38**) with mp 81–83° (lit.[31] mp 82–83°): λ_{max}^{MeOH} 294 mμ (ε 20,300), 222 sh (9800); nmr ($CDCl_3$) 5.03 ppm (s, 2, $ArCH_2N$), 7.2–7.6 (m, 9, Ar), 8.1–8.4 (m, 2, Ar and HC=N); ir (KBr) 1590 cm^{-1}.

Chromatography of the mother liquors in silicic acid gave benzaldehyde (310 mg, 10% as the 2,4-dinitrophenylhydrazone) and a small amount of *N*-benzylbenzamide of mp 102–104° which was identical in every way with an authentic sample.

Registry No.—**5,** 19133-01-8; **6,** 25056-49-9; **14,** 25056-50-2; **15,** 25055-75-8; **17,** 25055-76-9; **18,** 25055-77-0; **20,** 20678-99-3; **21,** 25062-42-4; **22b,** 7675-95-8; **23,** 2232-16-8; **24,** 25062-45-7; **29,** 623-00-7; **30,** 25062-46-8; **32,** 25055-79-2; **38,** 3376-26-9.

(28) C. Kjellin and K. G. Kuglenstjerna, *Ber.*, **30** (1899).

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(30) G. M. Badger and R. G. Buttery, *ibid.*, 2156 (1953).

(31) H. E. DeLaMare and G. M. Coppinger, *J. Org. Chem.*, **28,** 1068 (1963).

Carbodiimide–Sulfoxide Reactions. IX.[1] Synthesis of 2′- and 3′-Keto Derivatives of Cytidine

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Reaction of N^4-acetylcytidine with an excess of chlorotriphenylmethane in pyridine at 90° gives both the 2′,5- and 3′,5′-dityrityl derivatives and a small amount of N^4-acetyl-2′,3′,5′-tritritylcytidine. Each compound could be deacetylated and then related to the corresponding uridine derivatives by deamination. Efficient oxidation of the isomeric N^4-acetyl ditritylcytidines could be achieved using either the dimethyl sulfoxide–dicyclohexylcarbodiimide or the dimethyl sulfoxide–acetic anhydride methods giving the corresponding 2′- and 3′-ketocytidine derivatives. Subsequent detritylation using hydrogen chloride in chloroform gave N^4-acetyl-2′(or 3′)-ketocytidines. Oxidation of free 2′,5′- or 3′,5′-ditritylcytidines could also be accomplished using the DMSO–DCC method. Borohydride reduction of the various compounds was studied, the 2′ ketones giving nucleosides with the arabinose and ribose configurations in a ratio of 4:1 while the 3′ ketones gave xylosyl and ribosyl derivatives in a ratio of 3:2. Reduction of the free N^4-acetyl-2′- and -3′-ketocytidines with sodium borohydride-^{3}H provides a facile route to cytosine nucleosides with the arabinose, xylose, and ribose configurations containing a tritium label at specific positions of the sugar.

The development of mild methods for the oxidation of alcohols based upon the reactions of dimethyl sulfoxide (DMSO) activated by dicyclohexylcarbodiimide (DCC),[3] acetic anhydride,[4] or phosphorus pentoxide[5] has led to many syntheses of otherwise difficulty accessible keto sugar derivatives.[6] In an earlier paper in this series,[7] we have described the oxidation in good yield of 2′,5′-di-*O*-trityluridine (**1**) and of 3′,5′-di-*O*-

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(1) For part VIII, see A. H. Fenselau, E. H. Hamamura, and J. G. Moffatt, *J. Org. Chem.*, **35**, 3546 (1970).

(2) Syntex Postdoctoral Fellow, 1967–1968.

(3) K. E. Pfitzner and J. G. Moffatt, *J. Amer. Chem. Soc.*, **85**, 3027 (1963); 5661 (1965); **87**, 5670 (1965).

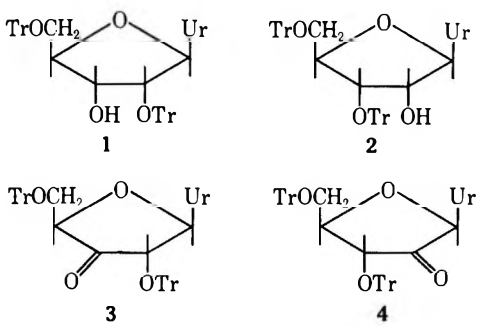
(4) J. D. Albright and L. Goldman, *ibid.*, **89**, 2416 (1967).

(5) K. Onodera, S. Hirano, and N. Kashimura, *Carbohyd. Res.*, **6**, 276 (1968).

(6) For reviews, see (a) J. S. Brimacombe, *Angew. Chem., Int. Ed. Engl.*, **8**, 401 (1969). (b) J. G. Moffatt in "New Oxidation Reactions," D. J. Trecker, Ed., Marcel Dekker, New York, N. Y., 1970, in press.

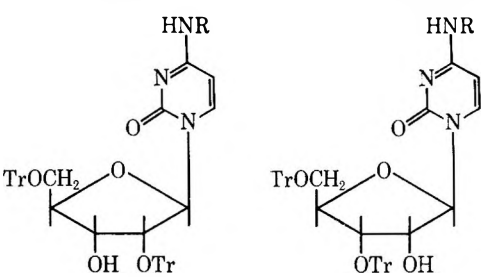
(7) A. F. Cook and J. G. Moffatt, *J. Amer. Chem. Soc.*, **89**, 2697 (1967).

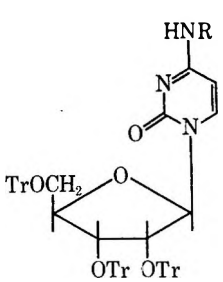
trityluridine (2) to the corresponding dityrityl ketonucleosides, **3** and **4**, respectively.



In this paper we describe an extension of this work to the synthesis of derivatives of cytidine and the use of these compounds as intermediates in facile syntheses of cytosine ribosides, arabinosides, and xylosides bearing isotopic labels in specific positions of the sugar.

In view of the great alkaline lability of 2′- and 3′-ketonucleosides,[7] the appropriate di-*O*-trityl derivatives of cytidine appear to be the most satisfactory starting materials for oxidation. The reaction of N^4-acetylcytidine[8] with 3 equiv of chlorotriphenylmethane in pyridine at 90° was found to give roughly equal amounts (33 and 25%) of N^4-acetyl-2′,5′-di-*O*-tritylcytidine (**5a**) and N^4-acetyl-3′,5′-di-*O*-tritylcytidine (**6a**), together with a small amount of N^4-acetyl-2′,3′-5′-tri-*O*-tritylcytidine (**7a**). The isomeric dityrityl compounds are readily distinguished by thin layer chromatography. Mizuno and Sasaki[9] have briefly described the tritylation of N^4-acetylcytidine but only reported the isolation of **5a**. Each compound was deacetylated by treatment with ammonium hydroxide giving crystalline 2′,5′-di-*O*-tritylcytidine (**5b**), 3′,5′-di-*O*-tritylcytidine (**6b**), and 2′,3′,5′-tri-*O*-tritylcytidine (**7b**), respectively. The structural assignments were confirmed by deamination of **5b**, **6b**, and **7b** with isoamyl nitrite and acetic acid



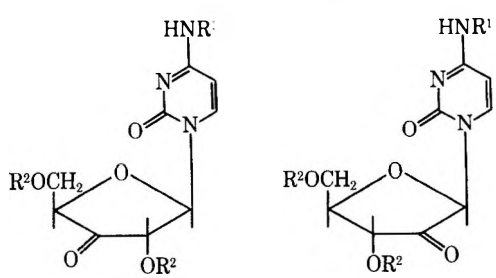


giving 2′,5′-di-*O*-trityluridine, 3′,5′-di-*O*-trityluridine, and 2′,3′,5′-tri-*O*-trityluridine all of which were identical with authentic samples[7] in their physical properties and spectroscopic behavior.

Oxidation of the *N*-acetyl nucleosides, **5a** and **6a**, was readily achieved using either the DMSO–acetic anhydride[4] or the DMSO–DCC[3] methods. Using the former method we have found it convenient to carry out the oxidation at 60° for 4 hr rather than at room temperature for an extended period. There was no observable formation of either acetate esters or thiomethoxy methyl ethers during oxidation of these compounds. Both methods of oxidation were very efficient, the reaction of **5a**, for example, giving the desired ketone, N^4-acetyl-1-(2′,5′-di-*O*-trityl-β-D-*erythro*-pentofuran-3-ulosyl)cytosine (**8a**),[10] in yields of 87 and 86%. The product was readily crystalline and the presence of the 3′-keto function was demonstrated by a carbonyl band at 1780 cm^{-1} in the infrared spectrum in addition to those normally present at roughly 1720 and 1675 cm^{-1} in the alcohol **5a**. The rather high frequency of the 3′-carbonyl group is similar to those previously observed for other ketofuranosides.[5,7]

Formation of the ketone also leads to striking alterations in the nmr spectra. Whereas in the alcohol **5a** all the sugar protons are well separated and resolved, the 1′, 2′, and 4′ protons of **8a** are superimposed as a signal at 4.7 ppm. In deuteriobenzene these three protons are resolved, both $C_{1'}H$ and $C_{2'}H$ appearing as singlets. The large shift of the anomeric proton from 6.75 ppm in **5a** to 4.7 ppm in **8a** is particularly striking.

In a similar way, the oxidation of N^4-acetyl-3′,5′-di-*O*-tritylcytidine (**6a**) to N^4-acetyl-1-(3′,5′-di-*O*-trityl-β-D-*erythro*-pentofuran-2-ulosyl)cytosine (**9a**)[10] was readily achieved using the DMSO–acetic anhydride method, the homogeneous product being obtained in 81% yield following preparative thin layer chromatography. Crystalline **9a** was obtained from ethanol as a hydrate and while covalent hydration of the 2′-keto function is a likely possibility, a new carbonyl band was present at 1780 cm^{-1} in its infrared spectrum. Whether or not the carbonyl group was covalently hydrated, the absence of a $C_{2'}$ proton was indicated by the appearance of the $C_{1'}$ proton as a singlet in the nmr spectrum whereas the $C_{1'}$ proton of the alcohol **6a** was a doublet with $J_{1',2'} = 5$ Hz. Drying the sample *in vacuo* at 80° apparently only partially removed this water.



The oxidation of the isomeric ditritylcytidines **5b** and **6b** containing free 4-amino functions was also accom-

(8) K. A. Watanabe and J. J. Fox, *Angew. Chem., Int. Ed. Engl.*, **5**, 579 (1966).

(9) Y. Mizuno and T. Sasaki, *Tetrahedron Lett.*, 4579 (1965).

(10) For simplicity we trivially refer to this compound (**8a**) as N^4-acetyl-3′-keto-2′,5′-di-*O*-tritylcytidine and use a similar nomenclature for related ketonucleosides elsewhere in this paper.

plished. In these cases, the use of the DMSO–acetic anhydride method was not feasible since concomitant acetylation of the amino function occurred, oxidation of **6b** giving the N^4-acetyl ketone (**9a**) in 76% yield. These oxidations were also attempted using DMSO and phosphorus pentoxide[5] at 60° and, while the desired products were formed, there were also considerable amounts of several by-products including detritylated materials. Oxidation of **5b** and **6b** could, however, be successfully achieved using the DMSO–DCC method. A number of model experiments indicated that dichloroacetic acid was perhaps the preferred proton source and that disappearance of the starting material was essentially complete using either 0.5 or 1.2 equiv of this acid. Examination of the reaction mixtures using tlc, however, showed that, in addition to the desired product (**8c** or **9c**), a major, much less polar, product was present to various extents in different experiments. Attempted isolation of this material led to partial breakdown to the desired ketone. The nonpolar product had a uv spectrum with λ_{max}^{MeOH} 307 mμ similar to an N^4-acetylcytidine derivative and its seems likely to be the N^4-dichloroacetyl derivative of the desired ketone. Brief treatment with very dilute methanolic ammonium hydroxide cleaved the acyl function without effecting the rest of the molecule and in this way crystalline **9c** was isolated in 71% yield.

Attempted hydrolysis of the trityl groups from the dityityl ketones (**8a**, **8c**, **9a**, or **9c**) with acetic acid led to complete decomposition predominantly *via* glycosidic cleavage. On the other hand, treatment of **8a** or **9a** with roughly 3 mol equiv of anhydrous hydrogen chloride in chloroform at 0° led to precipitation of the free N^4-acetyl-3′- and -2′-ketocytidines (**8b** and **9b**) in good yields and contaminated with only traces of impurities. As was found in the uridine series, these compounds are unstable and tend to decompose upon prolonged storage or upon attempted purification by preparative tlc on cellulose. Neither compound was obtained in crystalline form and both undoubtedly exist as ketone hydrates since they do not show carbonyl absorptions other than those present in N^4-acetylcytidine in their ir spectra. As obtained, they were, however, essentially homogeneous by paper chromatography and electrophoresis, both having electrophoretic mobilities greater than that of N^4-acetylcytidine in pH 6.0 borate.[11] The structures of the compounds are clearly defined by the reduction experiments which follow. Attempted detritylation of the free amino ketones (**8c** and **9c**) using hydrogen chloride was unsuccessful owing to immediate formation of an insoluble hydrochloride.

As was shown in the uridine series,[7] both the 2′- and 3′-ketocytidine derivatives are very unstable under basic conditions, rapidly undergoing glycosidic cleavage. By a combination of spectral and chromatographic studies it could be shown that the ditrityl-2′- or 3′-ketones with or without an N^4-acetyl group were completely degraded within 10 min at room temperature in 0.01 N methanolic sodium hydroxide. The detritylated materials (**8b** and **9b**) were extremely unstable and decomposed instantly under comparable conditions.

(11) J. F. Codington, R. Fecher, and J. J. Fox, *J. Amer. Chem. Soc.*, **82**, 2794 (1960).

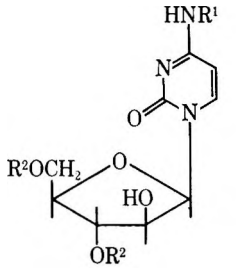
The optical rotatory dispersion (ORD) spectra of the various ketocytidine derivatives deserve some comment. Thus, all of the reported compounds (**8a–c**, **9a–c**) show positive Cotton effects as expected for pyrimidine β-nucleosides.[12] Also, the spectra of these compounds are roughly symmetrical and, in the case of the 2′-ketones (**9a–c**), show crossover at close to the λ_{max} of the ultraviolet spectra (*e.g.*, 390 mμ for **9a** and 255 mμ for **9c**). In the case of 3′-keto-2′,5′-di-*O*-tritylcytidine (**8c**), however, the spectrum is strongly shifted to longer wavelengths, crossover now occurring at 312 mμ which is roughly 50 mμ beyond the λ_{max} of 263 mμ. A somewhat similar, although less impressive, shift is found with **8a** which shows crossover at 319 mμ as compared with that of 300 mμ with the 2′-keto isomer (**9a**). These effects are not observed with **8b** and **9b** presumably because these compounds are known to be hydrates of the ketones. A similar effect was previously noted in the uridine series[7] where the ORD spectra of 3′-keto derivatives were markedly shifted toward longer wavelengths relative to their 2′-keto counterparts. It thus seems to be a general phenomenon that 3′-ketonucleosides exhibit Cotton effects in which the carbonyl group plays an important role relative to the heterocyclic base.

The borohydride reduction of the various ketones has been examined in some detail since, as will be seen, this provides a facile route to cytosine nucleosides labeled with tritium at specific positions of the sugar. The presence or absence of an N^4-acetyl group appears to have little effect upon the direction of reduction. Thus, reduction of either N^4-acetyl-2′-keto-3′,5′-ditritylcytidine or of the related 4-amino compound **9c** with sodium borohydride in ethanol–benzene gave products with arabinose and ribose configurations in a ratio of 4:1. These yields were determined by quantitative borate electrophoresis[11] following deacetylation with methanolic ammonium hydroxide and detritylation with acetic acid. Preparative reduction of **9a** showed that quite extensive loss of the N^4-acetyl group occurred concomitantly, but pure N^4-acetyl-1-(3′,5′-di-*O*-trityl-β-D-arabinofuranosyl)cytosine (**10a**) could be isolated by direct crystallization from the reaction mixture and shown to be pure by borate electrophoresis after removal of the protecting groups. If, subsequently, the deacetylation was completed by treatment of the reduction mixture with methanolic ammonium hydroxide, the expected 1-(3′,5′-di-*O*-trityl-β-D-arabinofuranosyl)cytosine (**10b**) and 3′,5′-di-*O*-tritylcytidine (**6b**) could be separated by preparative thin layer chromatography and isolated in crystalline form. Similar reduction of **9c** gave the same two compounds in isolated yields of 71 and 20%. The purity of each compound could be confirmed by detritylation followed by borate electrophoresis.

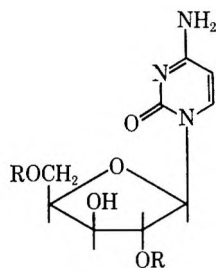
Reduction of the 3′-ketones (**8a** and **8c**) were also very similar and gave products with xylose and ribose configurations in a ratio of 3:2. Once again quite extensive deacetylation accompanied reduction of **8a**. In a preparative experiment, the deacetylation was completed by treatment with ammonium hydroxide prior to preparative thin layer chromatography which

(12) (a) T. R. Emerson, R. J. Swan, and T. L. V. Ulbricht, *Biochemistry*, **6**, 843 (1967); (b) T. Nishimura, B. Shimizu, and I. Iwai, *Biochim. Biophys. Acta*, **157**, 221 (1968).

clearly separated 1-(2′,5′-di-*O*-trityl-β-D-xylofuranosyl)-cytosine (**11a**) and 2′,5′-di-*O*-tritylcytidine (**5b**) which were isolated crystalline in yields of 55 and 37%.



10a, R^1 = Ac; R^2 = trityl
b, R^1 = H; R^2 = trityl
c, R^1 = R^2 = H



11a, R = trityl
b, R = H

For the preparation of nucleosides containing specific tritium labels in the sugar, it was considered desirable to minimize the number of chemical manipulations following introduction of the isotope. Accordingly, the reduction of the detritylated N^4-acetyl-2′- and -3′-ketocytidines (**9b** and **8b**) was examined. Treatment of **8b** or **9b** with sodium borohydride in water led to almost complete cleavage to cytosine presumably due to the extreme lability of these compounds under mildly alkaline conditions. In ethanol, however, little cytosine was formed and there was little indication of reduction of the cytosine ring.[13] Accordingly, **9b** was reacted in ethanol with a small excess of sodium borohydride-^{3}H and the crude product was then treated with ammonium hydroxide to complete removal of the N^4-acetyl group. A considerable amount of cytosine was formed and was most efficiently removed by preparative thin layer chromatography. The nucleoside band was further fractionated on a column of Dowex-1 (OH^-) resin according to Dekker[14] giving homogeneous cytidine-2′-^{3}H and 1-(β-D-arabinofuranosyl)cytosine-2′-^{3}H (**10c**) with specific activities of 0.58 and 0.54 mCi/μmol, respectively. Both compounds were homogeneous and identical with authentic samples in a variety of chromatographic and electrophoretic systems.

In a similar way the reduction of **8b** with sodium borohydride-^{3}H followed by deacetylation gave cytidine-3′-^{3}H and 1-(β-D-xylofuranosyl)cytosine-3′-^{3}H (**11b**).[15] In this case it was not necessary to remove cytosine by preparative thin layer chromatography and the two labeled nucleosides were clearly separated by chromatography on Dowex-1 (OH^-) resin. We were unable to obtain a satisfactory separation of these compounds using 30% methanol as eluent as recommended by Dekker[14] but got excellent separation using 20% methanol. Once again, the products were chromatographically and electrophoretically homogeneous. It should be pointed out that the total recovery of labeled nucleosides from reduction of **8b** and **9b** was only 26 and 40%. Since formation of cytosine was not a problem during reduction of these compounds with nonisotopic borohydride, it is not unlikely that some decomposition of the isotopic reagent had taken place prior to its use leading to some unreacted ketones which would decompose upon alkaline treatment. In retrospect, it is likely that reduction of the protected ketones **8c** or **9c** would provide better overall yields of the labeled nucleosides. In spite of these somewhat reduced yields obtained, this method provides a very direct and simple route for the preparation of biologically interesting nucleosides bearing specific isotopic labels.

(13) N. Miller and P. A. Cerutti, *J. Amer. Chem. Soc.*, **89**, 2767 (1967).
(14) C. A. Dekker, *ibid.*, **87**, 4028 (1965).
(15) We are grateful to Dr. J. J. Fox for an authentic sample of **11b**. J. J. Fox, N. Yung, I. Wempen, and I. L. Doerr, *ibid.*, **79**, 5060 (1957).

Experimental Section

General experimental methods are similar to those described previously.[1] Isotope counting was done using a Packard Tri-Carb liquid scintillation spectrometer using the scintillation fluid described by Herberg.[16]

Tritylation of N^4-Acetylcytidine.—N^4-Acetylcytidine (15 g, 52 mmol)[8] was added to a stirred solution of chlorotriphenylmethane (56.2 g, 157 mmol) in anhydrous pyridine (150 ml) at 90°. The clear solution that resulted after roughly 10 min was heated for a further 5 hr and then cooled and poured into 1.5 l. of well-stirred ice water. The resulting precipitate was dissolved in chloroform, extracted with 5% sodium bisulfate and water, dried ($MgSO_4$), and evaporated. The residue (70 g) was dissolved in benzene and applied to a 9 × 6 cm column of silicic acid which was then washed with benzene (2 l.) until no further triphenylmethanol (total 29.8 g) was eluted. Subsequent elution with chloroform–ethyl acetate (1:2) gave a mixture (30 g) of di- and tritrityl derivatives while elution with ethyl acetate gave a mixture (4 g) of unreacted N^4-acetylcytidine and monotrityl derivatives. The chloroform–ethyl acetate eluate was crystallized from chloroform–ether (using seed crystals previously obtained following preparative tlc) to give 9.54 g of pure N^4-acetyl-2′,5′-di-*O*-tritylcytidine (**5a**). The mother liquors were evaporated and the residue (19.6 g) was chromatographed on a column containing 700 g of silicic acid using chloroform–ethyl acetate (1:2). Following a small amount of triphenylmethanol, the first peak from the column was impure N^4-acetyl-2′,3′,5′-tri-*O*-tritylcytidine (**7a**) which was finally purified by preparative tlc using three consecutive developments with chloroform–ethyl acetate (2:1). The final product (1.2 g, 2%) was crystallized from benzene–ether with mp 265–266°: λ_{max}^{MeOH} 304 mμ (ε 5800), 250 (sh, 13,400); $[\alpha]^{23}D$ −10° (*c* 0.1, $CHCl_3$); ORD positive Cotton effect with peak at 324 mμ (Φ) +15,600°), crossover at 305 mμ and a trough at 250 mμ (Φ −44,000°); nmr ($CDCl_3$) 2.27 ppm (s, 3, NAc), 2.3 (m, 1, $C_{5'a}H$), 2.71 (m, 1, J_{gem} = 11 Hz, $C_{5'b}H$), 3.45 (d, 1, $J_{2',3'}$ = 4.5 Hz, $C_{3'}H$), 4.0 (m, 1, $C_{4'}H$), 4.59 (q, 1, $J_{1',3'}$ = 8 Hz, $J_{2',3'}$ = 4.5 Hz, $C_{2'}H$), 6.53 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 6.8–7.5 (m, aromatic and $C_{1'}H$), 7.77 (d, 1, $J_{5,6}$ = 8 Hz, C_6H).

Anal. Calcd for $C_{68}H_{57}N_3O_6$: C, 80.67; H, 5.68; N, 4.15. Found: C, 80.76; H, 5.73; N, 4.31.

Continued elution then almost completely separated the ditrityl isomers **5a** and **6a**. The overlapping fractions were separated by preparative tlc using chloroform–ethyl acetate (1:2). Both isomers were then chromatographically homogeneous and distinct from one another. The faster isomer (**5a**, total yield 13.4 g, 33%) was readily recrystallized from ethanol or chloroform–hexane as fine needles which sintered and melted at 170–180° (reported[9] sintering and melting at 168–180°): λ_{max}^{MeOH} 305 mμ (ε 5400), 250 (sh, 13,100); $[\alpha]^{23}D$ +104° (c 0.1, $CHCl_3$); ORD (MeOH) positive Cotton effect with a peak at 330 mμ (Φ + 28,400°), crossover at 304 mμ and a trough at 250 mμ (Φ −41,000°); nmr ($CDCl_3$) 1.62 ppm (br s, 1, $C_{3'}OH$), 2.31 (s, 3, NAc), 2.84 (br d, 1, $J_{2',3'}$ = 5 Hz, $C_{3'}H$), 3.10 (q, 1, J_{gem} = 11 Hz, $J_{4',5'a}$ = 3 Hz, $C_{5'a}H$), 3.23 (q, 1, J_{gem} = 11 Hz, $J_{4',5'b}$ = 2 Hz, $C_{5'b}H$), 4.02 (br s, 1, $C_{4'}H$), 4.52 (q, 1, $J_{1',2'}$ = 7.5 Hz, $J_{2',3'}$ = 5 Hz, $C_{2'}H$), 6.75 (d, 1, $J_{1',2'}$ = 7.5 Hz, $C_{1'}H$), 6.97 (d, 1, $J_{5,6}$ = 7.5 Hz, C_5H), 6.1–7.6 (m, 30, aromatic), 8.00 (d, 1, $J_{5,6}$ = 7.5 Hz, C_6H), 10.25 (br s, 1, NH).

Anal. Calcd for $C_{49}H_{43}N_3O_6$: C, 76.43; H, 5.63; N, 5.46. Found: C, 76.05; H, 5.76; N, 5.48.

The more polar isomer (**6a**, total yield 10.1 g, 25%) was a white solid which has not been obtained in crystalline form: λ_{max}^{MeOH} 300 mμ (ε 5700), 250 (sh, 13,600); $[\alpha]^{23}D$ +40° (c 0.1, $CHCl_3$); ORD positive Cotton effect with a peak at 318 mμ (Φ +11,300°), crossover at 304 mμ and a trough at 255 mμ (Φ −34,200°); nmr ($CDCl_3$) 1.88 ppm (br s, 1, $C_{2'}OH$), 2.27

(16) R. J. Herberg, *Anal. Chem.*, **32**, 43 (1960).

(s, 3, NAc), 2.90 (q, 1, J_{gem} = 11 Hz, $J_{4',5'a}$ = 3 Hz, $C_{5'a}H$), 3.33 (q, 1, J_{gem} = 11 Hz, $J_{4',5'b}$ = 2 Hz, $C_{5'b}H$), 3.60 (m, 1, $C_{4'}H$), 3.90 (t, 1, $J_{1',2'} = J_{2',3'}$ = 5 Hz, $C_{2'}H$, superimposed upon NH), 4.18 (q, 1, $J_{2',3'}$ = 5 Hz, $J_{3',4'}$ = 3 Hz, $C_{3'}H$), 6.06 (d, 1, $J_{1',2'}$ = 5 Hz, $C_{1'}H$), 7.0–7.6 (m, 30 aromatic and C_6H), 8.05 (d, 1, $J_{5,6}$ = 7.5 Hz, C_6H), 9.94 (br s, 1, NH).

Anal. Calcd for $C_{40}H_{43}N_3O_6$: C, 76.43; H, 5.63; N, 5.46. Found: C, 75.90; H, 5.74; N, 5.37.

2′,5′-Di-*O*-tritylcytidine (5b).—Concentrated ammonium hydroxide (80 ml) was added to a solution of (**5a**) in chloroform (50 ml) and acetone (100 ml). Methanol was added until a clear solution resulted and this was stored overnight. Crystalline **5b** (4.11 g, 89%) was collected with mp 180–182° unchanged upon recrystallization from benzene–acetone: λ_{max}^{MeOH} 270 mμ (ε 8000), λ_{max}^{MeOH,H^+} 278 mμ (11,000); $[\alpha]^{23}D$ +117° (*c* 0.1, $CHCl_3$); ORD (MeOH) positive Cotton effect with peak at 292 mμ (Φ +35,400°), crossover at 272 mμ and a trough at 230 mμ (Φ −55,000°); nmr (DMSO-d_6) 2.5 ppm (m, 1, $C_{3'}H$), 2.9 (br s, 2, $C_{5'}H_2$), 3.80 (br s, 1, $C_{4'}H$), 4.15–4.35 (m, 2, $C_{2'}H$ and $C_{3'}OH$), 5.36 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 6.42 (d, 1, $J_{1',2'}$ = 7 Hz, $C_{1'}H$), 7.0–7.6 (m, 30 aromatic and C_6H).

Anal. Calcd for $C_{47}H_{41}N_3O_5$: C, 77.54; H, 5.68; N, 5.78. Found: C, 77.36; H, 5.67; N, 6.02.

Treatment of **5a** (100 mg) in DMSO (2 ml) and benzene (0.2 ml) with isoamyl nitrite (0.1 ml) and glacial acetic acid (0.05 ml) at 25° for 2 days followed by preparative tlc using chloroform–ethyl acetate (10:1) gave crystalline 2′,5′-di-*O*-trityluridine (49 mg, 52%) that was chromatographically and physically identical with an authentic sample.[7] No 3′,5′-di-*O*-trityluridine was formed.

3′,5′-Di-*O*-tritylcytidine (6b).—Concentrated ammonium hydroxide (100 ml) was added to a solution of **6a** (5 g) in chloroform (10 ml) and methanol (200 ml), giving an initially clear solution. After 12 hr at 25°, crystalline **6b** (4.04 g, 87%) was removed and had mp 225–226° unchanged upon recrystallization from methanol: λ_{max}^{MeOH} 270 mμ (ε 8700), λ_{max}^{MeOH,H^+} 285 mμ (13,400); $[\alpha]^{23}D$ +48° (*c* 0.1, $CHCl_3$); ORD (MeOH) positive Cotton effect with a peak at 289 mμ (Φ +10,800°), crossover at 276 mμ and a trough at 236 mμ (Φ −29,000°); nmr ($CDCl_3$) 2.76 ppm (q, 1, J_{gem} = 11 Hz, $J_{4',5'a}$ = 4 Hz, $C_{5'a}H$), 3.22 (q, 1, J_{gem} = 11 Hz, $J_{4',5'b}$ = 2 Hz, $C_{5'b}H$), 3.43 (m, 1, $C_{4'}H$), 3.80 (t, 1, $J_{1',2'} = J_{2',3'}$ = 5 Hz, $C_{2'}H$), 4.12 (q, 1, $J_{2',3'}$ = 5 Hz, $J_{3',4'}$ = 3 Hz, $C_{3'}H$), 5.35 (*d*, 1, $J_{5,6}$ = 8 Hz, C_5H), 5.99 (d, 1, $J_{1',2'}$ = 5 Hz, $C_{1'}H$), 6.9–7.5 (m, 30, aromatic), 7.72 (d, 1, $J_{5,6}$ = 8 Hz, C_6H).

Anal. Calcd for $C_{47}H_{41}N_3O_5$: C, 77.54; H, 5.68; N, 5.78; Found: C, 77.36; H, 5.74; N, 5.92.

Treatment of **6b** (100 mg) with isoamyl nitrite and acetic acid as above gave 43 mg (46%) of chromatographically homogeneous 3′,5′-di-*O*-trityluridine that was identical with an authentic sample by tlc and by infrared and nmr spectroscopy.

2′,3′,5′-Tri-*O*-tritylcytidine (7b).—Concentrated ammonium hydroxide (5 ml) was added to a solution of **7a** (400 mg) in methanol (50 ml) and the solution was heated under reflux for 2 hr. Preparative tlc using three developments with CCl_4–acetone (2:1) cleanly separated the product from unreacted **7a**. Elution and crystallization from methanol–water gave 70 mg of pure **7b** with mp 241–244°: λ_{max}^{MeOH} 277 mμ (ε 13,100); ORD (MeOH) positive Cotton effect with a peak at 302 mμ (Φ +32,500°) and crossover at 278 mμ; nmr ($CDCl_3$) 1.84 ppm (br s, 2, NH_2), 2.64 (d, 1, $J_{2',3'}$ = 5 Hz, $C_{3'}H$), 2.98 (br s, 2, $C_{5'}H_2$), 3.89 (d, 1, *J* = 1 Hz, $C_{4'}H$), 4.36 (q, 1, $J_{1',2'}$ = 7 Hz, $J_{2',3'}$ = 5 Hz, $C_{2'}H$), 4.39 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 6.74 (d, 1, $J_{1',2'}$ = 7 Hz, $C_{1'}H$), 6.8–7.6 (m, 45 aromatic and C_6H).

Anal. Calcd for $C_{66}H_{55}N_3O_5$: C, 81.70; H, 5.72; N, 4.33. Found: C, 81.77; H, 6.11; N, 4.63.

Treatment of **7b** (50 mg) with isoamyl nitrite (0.04 ml) and acetic acid (0.02 ml) in dioxane (2 ml) for 14 days led to roughly 50% deamination to 2′,3′,5′-tri-*O*-trityluridine which was isolated by preparative tlc using chloroform–ethyl acetate (10:1) and shown to be identical with an authentic sample.[7]

N^4-Acetyl-3′-keto-2′,5′-di-*O*-tritylcytidine (8a). **A.**—A solution of **5a** (1.55 g, 2 mmol) and acetic anhydride (2 ml) in DMSO (20 ml) and anhydrous benzene (5 ml) was kept at 60° for 4 hr. The solution was then diluted with ethyl acetate, extracted once with 5% sodium bicarbonate and twice with water, dried ($MgSO_4$), and purified by preparative tlc on four 1-m long plates using carbon tetrachloride–acetone (2:1). Elution of the major band gave 1.37 g (87%) of chromatographically homogeneous **8a** which could be crystallized from methanol–acetone as needles which melted with decomposition at 196–198°, partially recrystallized and did not remelt below 300°: λ_{max}^{MeOH} 302 mμ (ε 6500), 250 (sh 16,600); $[\alpha]^{23}D$ +40° (*c* 0.1, $CHCl_3$); ORD (MeOH) positive Cotton effect with a peak at 331 mμ (Φ +10,800°), crossover at 319 mμ and a trough at 300 mμ (Φ −15,100°); ν_{max} (KBr) 1780, 1730, 1660 cm^{-1}; nmr ($CDCl_3$) 1.84 ppm (s, 3, NAc), 3.4 (m, 2, $C_{5'}H_2$), 4.5–4.8 (m, 3, $C_{1'}H$, $C_{2'}H$, $C_{4'}H$), 6.45 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 6.5–7.5 (m, 31, aromatic and C_6H), 10.12 (s, 1, NH).

Anal. Calcd for $C_{49}H_{41}N_3O_6$: C, 76.63; H, 5.38; N, 5.48. Found: C, 76.54; H, 5.34; N, 5.63.

B.—Dichloroacetic acid (0.02 ml, 0.25 mmol) was added to a solution of **5a** (385 mg, 0.5 mmol) and DCC (309 mg, 1.5 mmol) in a mixture of benzene (5 ml) and DMSO (5 ml) and kept overnight at 25°. The mixture was diluted with ethyl acetate and a solution of oxalic acid (1.5 mmol) in methanol (0.5 ml) was added. After 30 min the solution was filtered, extracted with 5% sodium bicarbonate and then twice with water, dried ($MgSO_4$), and evaporated to dryness. The residue was dissolved in acetone (5 ml), filtered to remove a small amount of dicyclohexylurea, and evaporated. Crystallization of the residue from ether gave 330 mg (86%) of pure **8a** identical with that above.

3′-Keto-N^4-acetylcytidine (8b).—An anhydrous solution of hydrogen chloride in chloroform (6.2 ml of 0.27 *N*, 1.7 mmol) was added to a solution of **8a** (389 mg, 0.5 mmol) in chloroform (10 ml) and kept for 1 hr at 0°. After addition of ether (30 ml) the white precipitate was collected by centrifugation in a tube protected by a serum cap and washed three times with fresh ether. After drying *in vacuo* over phosphorus pentoxide and potassium hydroxide pellets **8b** (160 mg) was obtained as a very hygroscopic white powder which moved as a single spot just faster than N^4-acetylcytidine and gave a positive test with dinitrophenylhydrazine spray on borate electrophoresis (1 *M* boric acid, pH 6.0).[11] It also gave an intense spot upon paper chromatography using 1-butanol–H_2O (86:14) with only traces of impurities present: λ_{max}^{MeOH} 297 mμ (ε 7100), 248 (13,400), 213 (16,200); λ_{max}^{MeOH,H^+} 314 mμ (ε 13,400), 230 (sh, 8100) and 214 (12,100); $[\alpha]^{23}D$ +81° (*c* 0.1, $CHCl_3$); ORD (MeOH) positive Cotton effect with a peak at 315 mμ (Φ +9300°), crossover at 290 mμ and a trough at 250 mμ (Φ −16,000°); ν_{max} (KBr) 1715, 1600 cm^{-1}; nmr (DMSO-d_6) 2.13 ppm (s, 3, NAc), 3.68 (br d, 2, $J_{4',5'}$ = 3 Hz, $C_{5'}H_2$), 4.3 (m, 1, $C_{4'}H$), 4.34 (d, 1, $J_{1',2'}$ = 7.5 Hz, $C_{2'}H$), 6.14 (d, 1, $J_{1',2'}$ = 7.5 Hz, $C_{1'}H$), 7.26 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 8.35 (d, 1, $J_{5,6}$ = 8 Hz, C_6H).

Anal. Calcd for $C_{11}H_{13}N_3O_6 \cdot 2H_2O$: C, 41.36; H, 5.37; N, 13.15. Found: C, 40.99; H, 5.41; N, 12.49.

2′-Keto-3′,5′-di-*O*-trityl-N^4-acetylcytidine (9a). **A.**—Acetic anhydride (2 ml) was added to a solution of **6a** (1.54 g, 2 mmol) in DMSO (19 ml) and kept at 60° for 2 hr. The reaction was worked up as for **8a** and purified by preparative tlc on four plates using carbon tetrachloride–acetone (2:1). Elution of the major ultraviolet absorbing band gave 1.24 g (81%) of homogeneous **9b** as a granular foam that could be crystallized from ethanol and melted with decomposition at 158–160°: λ_{max}^{MeOH} 300 mμ (ε 6000), 249 (15,600); λ_{max}^{MeOH,H^+} 316 mμ (ε 14,900); $[\alpha]^{23}D$ +37° (*c* 0.1, $CHCl_3$); ORD positive Cotton effect with a peak at 315 mμ (Φ +4400°), crossover at 300 mμ and at rough at 256 mμ (Φ −21,700°); ν_{max} (KBr) 1780, 1730, 1660 cm^{-1}; nmr ($CDCl_3$) 2.06 ppm (s, 3, NAc), 2.72 (m, 1, $C_{5'a}H$), 3.02 (m, 1, $C_{5'b}H$), 4.15 (m, 1, $C_{4'}H$), 4.45 (d, 1, $J_{3',4'}$ = 5 Hz, $C_{3'}H$), 5.60 (s, 1, $C_{1'}H$), 7.0–7.5 (m, 31, aromatic and C_6H), 7.58 (d, 1, $J_{5,6}$ = 8 Hz, C_6H).

Anal. Calcd for $C_{49}H_{41}N_3O_6 \cdot H_2O$: C, 74.88; H, 5.51; N, 5.35. Found: C, 74.95; H, 5.40; N, 5.35.

B.—A solution of **6b** (500 mg) and acetic anhydride (0.5 ml) in DMSO (10 ml) was kept at 60° for 4 hr. The mixture was then partitioned between ethyl acetate and water and the organic phase was extracted with cold aqueous sodium bicarbonate and then water. It was then purified by preparative tlc using carbon tetrachloride–acetone (3:1) and the major band was eluted and crystallized from acetone–methanol giving 380 mg (76%) of essentially pure **9a** with mp 155–160° dec.

2′-Keto-N^4-acetylcytidine (9b).—A solution of **9a** (1.49 g, 1.94 mmol) in chloroform (5 ml) was cooled to 0° and a solution of anhydrous hydrogen chloride in chloroform (20 ml of 0.41 *N*, 8.2 mmol) was added in four portions over 15 min. After 1 hr at 0° the mixture was diluted with ether (50 ml) and the white precipitate was collected by centrifugation. It was then washed three times with ether and dried *in vacuo* over potassium hy-

droxide giving 0.46 g of **9b** as a hygroscopic powder which gave a single, dinitrophenylhydrazine positive spot similar to **8b** on borate electrophoresis and paper chromatography: λ_{max}^{MeOH} 299 mμ (ε 6700), 248 (13,200), 214 (15,300); λ_{max}^{MeOH,H^+} 315 mμ (ε 14,400), 230 (sh, 8200), 215 (9900); $[\alpha]^{23}D$ +95°; ORD (MeOH) positive Cotton effect with a peak at 318 mμ (Φ +8900°), crossover at 295 mμ and a trough at 250 mμ (Φ −21,200°); ν_{max} (KBr) 1720, 1600 cm^{-1}; nmr (DMSO-d_6) 2.13 ppm (s, 3, NAc), 3.5–4.0 (m, 5, $C_4'H$, $C_5'H_2$, $C_3'OH$ and $C_5'OH$), 4.41 (d, 1, $J_{3',4'}$ = 8 Hz, $C_3'H$), 5.48 (s, 1, $C_1'H$), 7.24 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 4.19 (d, 1, $J_{5,6}$ = 8 Hz, C_6H). Elemental analysis indicated that the sample was roughly a dihydrate but acceptable figures were not obtained for all elements. The ultraviolet and ORD values quoted above are based upon this hydrate.

3′-Keto-2′,5′-di-*O*-tritylcytidine (8c).—Dichloroacetic acid (0.1 ml, 1.2 mol) was added to a solution of **5b** (727 mg, 1 mmol) and DCC (618 mg, 3 mmol) in benzene (5 ml) and DMSO (20 ml) and the mixture was stored overnight. The mixture was worked up as above for **8a** (method B) and purified by preparative tlc using carbon tetrachloride–acetone (2:1) giving two bands, one moving somewhat faster than the starting material and the other near the solvent front. Elution of the slower band gave 370 mg (51%) of chromatographically homogeneous **8c** which could be crystallized from methanol with mp 142–144°: λ_{max}^{MeOH} 263 mμ (sh, ε 8600), λ_{max}^{MeOH,H^+} 285 (11,300); $[\alpha]^{23}D$ +35° (*c* 0.1, $CHCl_3$); ORD (MeOH) positive Cotton effect with a peak at 332 mμ (Φ +9800°), crossover at 312 and a trough at 286 mμ (Φ −13,700°); nmr (DMSO-d_6) 3.3 (m, 2, $C_5'H_2$), 4.5 (m, 2, $C_2'H$ and $C_4'H$), 4.95 (d, 1, $J_{1',2'}$ = 2.5 Hz, $C_1'H$), 5.49 (d, 1, $J_{5,6}$ = 7 Hz, C_5H), 6.66 (d, 1, $J_{5,6}$ = 7 Hz, C_6H); 7.05 (br s, 2, NH_2), 7.1–7.4 (m, 30, aromatic).

Anal. Calcd for $C_{47}H_{39}N_3O_5$: C, 77.76; H, 5.42; N, 5.79. Found: C, 77.55; H, 5.57; N, 5.76.

Elution of the fast band gave 390 mg of a material that had already partially decomposed to **8c**. Preparative tlc using chloroform–ether (10:1) separated some crystalline 1-dichloroacetyl-1,3-dicyclohexylurea of mp 147–148° (lit.[17] mp 146–148°) but was accompanied by extensive decomposition of the fast band to **8c**. Elution and crystallization of the resulting band on the origin gave a further 140 mg (total yield 70%) of **8c** identical with that above.

2′-Keto-3′,5′-di-*O*-tritylcytidine (9c).—Dichloroacetic acid (0.1 ml, 1.2 mmol) was added to a solution of **6b** (727 mg, 1 mmol) and DCC (618 mg, 3 mmol) in a mixture of benzene (10 ml) and DMSO (10 ml). After storage overnight, the reaction was worked up as described for **8a** (method B). After the oxalic acid treatment and aqueous extraction tlc using chloroform–methanol (10:1) showed the presence of **9c** and a fast-moving compound in a ratio of roughly 1:3. The solvent was evaporated and the residue dissolved in methanol (10 ml). Concentrated ammonium hydroxide (0.4 ml) was added and after 5 min the solvent was rapidly removed and the residue was purified by preparative tlc using chloroform–methanol (10:1). Elution of the major band gave 0.62 g of homogeneous **9c** that was crystallized from acetone–methanol giving 514 mg (71%) of needles with mp 153–154°: λ_{max}^{MeOH} 268 mμ (sh, 8400), λ_{max}^{MeOH,H^+} 283 mμ (13,100); $[\alpha]^{25}D$ +75° (c 0.1, $CHCl_3$); ORD (MeOH) positive Cotton effect with a peak at 273 mμ (Φ +10,700°), crossover at 255 and a trough at 238 mμ (Φ −4400°); ν_{max} (KBr) 1780, 1650 cm^{-1}; nmr (DMSO-d_6) 5.47 ppm (s, 1, $C_1'H$), 5.79 (d, 1, $J_{5,6}$ = 7 Hz, C_5H), 7.0–7.4 (m, aromatic), 7.72 (d, 1, $J_{5,6}$ = 7 Hz, C_6H).

Anal. Calcd for $C_{47}H_{39}N_3O_5$: C, 77.76; H, 5.42; N, 5.79. Found: C, 77.70; H, 5.21; N, 6.36.

Reduction of 3′-Keto-2′,5′-di-*O*-trityl-N^4-acetylcytidine (8a).—A solution of **8a** (200 mg, 0.26 mmol) in benzene (2 ml) was diluted with ethanol (10 ml) and sodium borohydride (5 mg, 0.13 mmol) was added. After storage in the dark for 20 min, the solvent was evaporated and the residue partitioned between chloroform and water. The chloroform phase was evaporated to dryness and the residue dissolved in a mixture of chloroform (5 ml) and methanol (10 ml). Concentrated ammonium hydroxide (2 ml) was added and after 3 hr at 20°, the solvent was evaporated and the residue purified by preparative tlc using carbon tetrachloride–acetone (1:1). Two bands resulted and elution of the slower one (74 mg) followed by crystallization from ethanol gave 70 mg (37%) of 2′,5′-di-*O*-tritylcytidine (**5b**) that was identical to an authentic sample. Elution of the faster band (120 mg) followed by crystallization from ethanol gave 104 mg (55%) of 1-(2′,5′-di-*O*-trityl-β-D-xylofuranosyl)cytosine (**11a**) which melted at 178–180°, resolidified, and remelted at roughly 250° (dec): λ_{max}^{MeOH} 267 mμ (ε 7700), λ_{max}^{MeOH,H^+} 288 mμ (ε 11,400); $[\alpha]^{23}D$ +37° (*c* 0.28, $CHCl_3$); ORD (MeOH) positive Cotton effect with a peak at 290 mμ (Φ +11,600°), crossover at 272 mμ and a trough at 250 mμ (Φ − 8200°); nmr (DMSO-d_6) 2.79 ppm (m, 2, $C_5'H_2$), 5.00 (d, 1, $J_{H,OH}$ = 4 Hz, $C_3'OH$), 5.68 (d, 1, $J_{5,6}$ = 7.5 Hz, C_5H), 6.25 (s, 1, $C_1'H$), 7.2–7.5 (m, 30, aromatic), 7.57 (d, 1, $J_{5,6}$ = 7.5 Hz, C_6H).

Anal. Calcd for $C_{47}H_{41}N_3O_5$: C, 77.56; H, 5.68; N, 5.77. Found:[18] C, 76.92; H, 5.68; N, 5.76.

Reduction of 2′-Keto-3′,5′-di-*O*-tritylcytidine (9c).—Sodium borohydride (6 mg, 0.16 mmol) was added to a solution of **9c** (200 mg, 0.28 mmol) in a mixture of benzene (2 ml) and ethanol (10 ml). After 20 min the solvent was evaporated and the residue partitioned between chloroform and water. The organic phase was dried and separated into two bands by preparative tlc using chloroform–2-propanol (9:1). Elution of the faster band gave 41 mg (20%) of 3′,5′-di-*O*-tritylcytidine that was identical with an authentic sample after crystallization from methanol. Elution of the slower band gave 143 mg (71%) of 1-(3′,5′-di-*O*-trityl-β-D-arabinofuranosyl)cytosine (**10b**) which was crystallized from acetone as needles of mp 265–266°: λ_{max}^{MeOH} 271 mμ (ε 9400); $[\alpha]^{23}D$ +110° (*c* 0.23, $CHCl_3$); ORD (MeOH) positive Cotton effect with a peak at 288 mμ (Φ +14,600°), crossover at 272 mμ, and a trough at 235 mμ (Φ −30,900°); nmr ($CDCl_3$) 5.30 ppm (d, 1, $J_{5,6}$ = 7.5 Hz, C_5H), 6.18 (d, 1, $J_{1',2'}$ = 2 Hz, $C_1'H$), 7.57 (d, 1, $J_{5,6}$ = 7.5 Hz, C_6H).

Anal. Calcd for $C_{47}H_{41}N_3O_5$: C, 77.56; H, 5.68; N, 5.77. Found: C, 77.78; H, 5.18; N, 6.27.

N^4-Acetyl-1-(3′,5′-di-*O*-trityl-β-D-arabinofuranosyl)cytosine (10a).—A solution of **9a** (150 mg, 0.2 mmol) in benzene (2 ml) and ethanol (15 ml) was treated with sodium borohydride (4 mg) for 20 min. After work-up as above, tlc showed that quite extensive deacetylation had occurred. Direct crystallization of the chloroform extracts from ethanol gave 23 mg of the pure N^4-acetyl arabinoside **10a** with mp 272–274°: λ_{max}^{MeOH} 300 (ε 8500), 245 mμ (sh, 16,000); λ_{max}^{MeOH,H^+} 313 mμ (14,200); ORD (MeOH) positive Cotton effect with a peak at 316 mμ (Φ +5500°), crossover at 302 mμ and a trough at 250 mμ (Φ −39,000°).

Anal. Calcd for $C_{49}H_{43}N_3O_6$: C, 76.43; H, 5.63; N, 5.46. Found: C, 76.07; H, 5.95; N, 5.38.

Deacetylation with ammonium hydroxide–methanol followed by detritylation with 80% acetic acid gave only arabinosylcytosine as judged by borate electrophoresis.

A comparable reduction of **9a** (100 mg) in which deacetylation was completed by treatment with concentrated ammonium hydroxide in methanol prior to preparative tlc as in the reduction of **8a** gave 67 mg (70%) of **10b** and a small amount of **6b**.

Reduction of 2′-Keto-N^4-acetylcytidine with $NaBH_4$-^3H.—A solution of sodium borohydride-^3H (50 mCi, specific activity 2.3 mCi/μmol) in ethanol (0.5 ml) was added to a solution of 2′-keto-N^4-acetylcytidine (13.7 mg, 36 μmol) in ethanol (1 ml) and the mixture was kept at room temperature for 4 hr. A little Dowex 50 (H^+) resin was then added, the mixture was filtered, and the resin was washed with 1 *N* ammonium hydroxide. The filtrates were evaporated and the residue was deacetylated by overnight storage in methanol (1 ml) and concentrated ammonium hydroxide (1 ml). After evaporation of the solvent, the residue was chromatographed on two 20 × 20 cm preparative tlc plates using 2-propanol–ethyl acetate–water (23:65:12) to separate the labeled nucleosides from cytosine. The radioactive region was eluted with methanol, evaporated, and applied to a 1 × 20 cm column of Dowex 1 (OH^-) resin equilibrated with methanol–water (3:7). Elution with the same solvent gave a symmetrical peak containing 3.0 μmol (8.4%) of cytidine-2′-^3H with a specific activity of 0.58 mCi/μmol. Continued elution with a linear gradient (0–0.1 *M*) of triethylammonium bicarbonate in 30% methanol (2 l.) then gave a second peak containing 11.5 μmol (32%) of 1-(β-D-arabinofuranosyl)cytosine-2′-^3H with a specific activity of 0.54 mCi/μmole. The pooled peaks were evaporated to dryness and then coevaporated several times with methanol to remove residual bicarbonate. Both peaks were homogeneous and identical with authentic standards

(17) M. G. Burdon and J. G. Moffatt, *J. Amer. Chem. Soc.*, **88**, 5855 (1966).

(18) In several preparations of this compound we have consistently obtained low carbon analyses.

by borate electrophoresis at pH 6, electrophoresis in 1 *M* acetic acid, and by paper chromatography in 1-butanol–acetic acid–water (4:1:1).

Reduction of 3′-Keto-N^4-acetylcytidine with $NaBH_4$-^3H.—A reaction between 3′-keto-N^4-acetylcytidine (17.3 mg, 41 μmol) and sodium borohydride-^3H (50 mCi, 2.3 mCi/μmol) was carried out as with the 2′ ketone above. After deacetylation, the mixture was evaporated to dryness and directly applied to a 2 × 45 cm column of Dowex-1 (OH^-) resin equilibrated with methanol–water (1:4). Continued elution with the same solvent gave two well resolved peaks centered about fractions 230 and 290 (15 ml each). The first of these contained cytidine-3′-^3H (3.5 μmol, 8.5%) with a specific activity of 0.62 mCi/μmol, while the second contained 7 μmol (17.1%) of 1-(β-D-xylofuranosyl)cytosine-3′-^3H with a specific activity of 0.54 mCi/μmol. Both products were homogeneous and identical with authentic samples by the electrophoretic and chromatographic systems above.

Registry No.—**5a**, 6698-19-7; **5b**, 6614-56-8; **6a**, 25787-17-1; **6b**, 25767-18-2; **7a**, 25787-19-3; **7b**, 25787-20-6; **8a**, 25787-21-7; **8b**, 25787-22-8; **8c**, 25787-23-9; **9a**, 25787-24-0; **9b**, 25787-25-1; **9c**, 25787-26-2; **10a**, 25787-27-3; **10b**, 25787-28-4; **11a**, 25834-65-5.

Notes

Evidence for a Carbenoid Intermediate in the Corey–Winter Alkene Synthesis[1,2]

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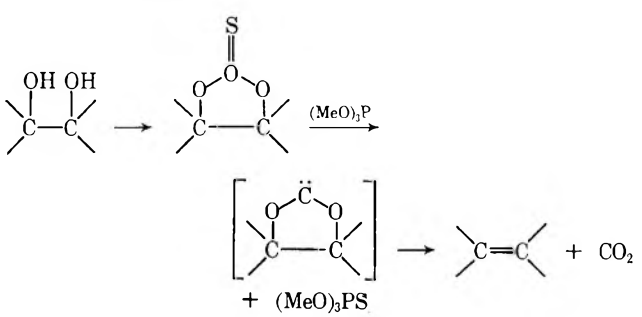
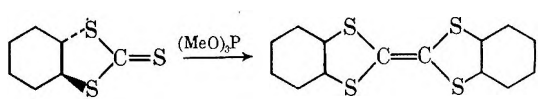
The synthesis of alkenes by treatment of cyclic 1,2-thionocarbonates with a phosphite ester (Corey–Winter alkene synthesis[3]) has proved to be a useful route to unsaturated sugar derivatives.[4–7] It was postulated[3] that the reaction proceeds through a carbene intermediate that is unstable with respect to the alkene and carbon dioxide.



Corey and coworkers[8] extended this synthesis to the preparation of alkenes from trithiocarbonates. The synthetic route permits preparation of highly strained alkenes in good yield. When formation of an alkene is impossible, as with *trans*-cyclohexane-1,2-dithiol 1,2-thionocarbonate, coupling products are obtained. These observations led the authors[8] to propose a



concerted, cycloelimination mechanism for the product-forming step. More recently Corey and Märkl[9] have isolated phosphorus ylides from the reaction of cyclic 1,3-trithiocarbonates with alkyl phosphites, and have been able to inhibit alkene formation from the cyclic 1,2-trithiocarbonates by adding an excess of benzaldehyde to the reaction mixture. Under the latter conditions the product is a ketene dithioacetal formed by a Wittig reaction of the intermediate ylide with the aldehyde. Some systems led only to alkenes, even when an excess of aldehyde was present. It was postulated[9] that ylide intermediates were formed in each case, at least with the trithiocarbonate precursors, and that competitive decomposition of the ylide to alkene, or reaction of the ylide with aldehyde, determined the product obtained.

We now present direct evidence to support the hypothesis of a carbene intermediate in the conversion of the thionocarbonate of a 1,2-diol into an alkene. The 5,6-thionocarbonate (**1**) of 1,2-*O*-isopropylidene-α-D-glucofuranose when treated with refluxing trimethyl phosphite for 70 hr gave, in addition to the 5,6-alkene **2** (isolated crystalline in 75% yield) as earlier reported,[5] a second product (**3**), isolated crystalline in 1% yield after column chromatography of the mother liquors from crystallization of **2**. Compound **3** proved to be identical in all respects with 1,2-*O*-isopropylidene-α-D-glucofuranose 3,5,6-orthoformate,[10] an authentic sample of which was prepared in 94% yield by condensation of 1,2-*O*-isopropylidene-α-D-glucofuranose with triethyl orthoformate.

(1) Part XI in the series Synthesis and Reactions of Unsaturated Sugars. For part X, see D. M. Clode, D. Horton, M. H. Meshreki, and H. Shoji, *Chem. Commun.*, 693 (1969).

(2) Supported, in part, by the Agricultural Research Service, U. S. Department of Agriculture, Grant No. 12-14-100-9201(71) (OSURF Project 2573) administered by the Northern Utilization Research and Development Division, Peoria, Ill.

(3) E. J. Corey and R. A. E. Winter, *J. Amer. Chem. Soc.*, **85**, 2677 (1963).

(4) D. Horton and W. N. Turner, *Tetrahedron Lett.*, 2531 (1964).

(5) D. Horton and W. N. Turner, *Carbohyd. Res.*, **1**, 444 (1966); D. Horton, J. K. Thomson, and C. G. Tindall, Jr., *Methods Carbohyd. Chem.*, **6**, in press.

(6) E. L. Albano, D. Horton, and T. Tsuchiya, *Carbohyd. Res.*, **2**, 349 (1966).

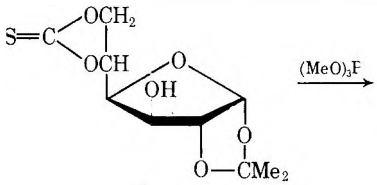
(7) D. Horton and C. G. Tindall, Jr., *Abstr. Pap. Amer. Chem. Soc. Meeting*, **158**, CARB6 (1969).

(8) E. J. Corey, F. A. Carey, and R. A. E. Winter, *J. Amer. Chem. Soc.*, **87**, 934 (1965).

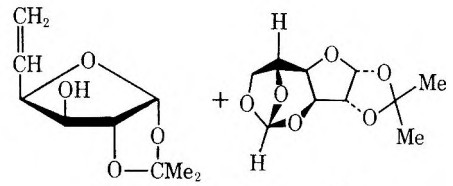
(9) E. J. Corey and G. Märkl, *Tetrahedron Lett.*, 3201 (1967).

(10) K. Freudenberg and W. Jacob, *Ber.*, **80**, 325 (1947); E. J. Hedgley and O. Mérész, *Proc. Chem. Soc.*, 399 (1964).

The structure of **3** is fully supported by 100-MHz nmr spectral assignments verified by spin decoupling, and by mass spectrometry; a major ion having *m/e* 215 corresponding to loss of a methyl radical from the molecular ion is observed. Full spectral details are recorded in the Experimental Section, where 100-MHz nmr data verified by spin decoupling are also recorded for the thionocarbonate **1**, together with mass spectral data.

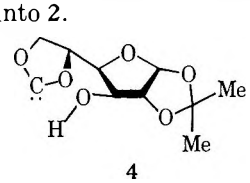


1



2 major **3** minor

The formation of the orthoformate **3** as a side product in the conversion of thionocarbonate **1** into alkene **2** can be attributed to the intramolecular insertion of a carbene intermediate (**4**) into the O–H bond of the hydroxyl group at C-3, and provides strong evidence that the same carbene **4** is an intermediate in formation of the alkene **2**. It would be difficult to reconcile the observed formation of **3** as a side product if a reaction intermediate of the ylide type were involved in the conversion of **1** into **2**.



4

Experimental Section

General Methods.—Nmr spectra were measured at 100 MHz, and chemical shifts refer to an internal standard of tetramethylsilane (τ 10.00); the latter also provided a lock signal. Signal assignments were verified by spin decoupling. Deuteration was performed by adding 1 drop of deuterium oxide to the prepared sample. Mass spectra were recorded by C. R. Weisenberger with an AEI MS-902 high-resolution, double-focusing spectrometer with an accelerating potential of 8 kV, an ionizing potential of 70 eV, and a direct-insertion probe with an inlet temperature of 250°. Thin layer chromatography (tlc) was performed with 0.25-mm layers of silica gel G (E. Merck, Darmstadt, Germany) activated at 120° as the adsorbent and sulfuric acid as the indicator.

1,2-*O*-Isopropylidene-α-D-glucofuranose 5,6-Thionocarbonate (1).—This compound was prepared as described previously,[5] mp 205–206°, $[\alpha]^{20}D$ −18° (c 1, acetone); 100-MHz nmr data in acetone-d_6 τ 3.98 (1-proton doublet, $J_{1,2}$ = 3.4 Hz, H-1), 4.62 (1-proton, symmetrical eight-line multiplet, $J_{4,5}$ = 2.6 Hz, H-5), 5.26 (2-proton, apparent doublet, $J_{5,6} \sim 8$ Hz, H-6,6′), 5.37 (1-proton triplet, $J_{3,4}$ = 3.5 Hz, H-4), 5.46 (1-proton doublet, $J_{2,3} \sim 0$ Hz, H-2), 5.68 (1-proton, broad peak, becoming a doublet after deuteration, H-3), 7.12 (1-proton, broad peak, disappears on deuteration, OH), 8.58, 8.75 (3-proton singlets, CMe_2); mass spectral data (relative peak intensity and assignment in parentheses) *m/e* 262 (1, M^+), 247 (1, M − CH_3), 187 (65, M − CH_3 − CH_3CO_2H), 159 (6), 129 (9), 127 (18), 101 (9), 100 (4), 86 (42), 85 (90), 73 (20), 71 (15), 69 (34), 68 (5), 60 (100, $CH_3CO_2H \cdot^+$), 59 (100, $CH_3COCH_3H^+$), 58 (20), 57 (27), 56 (5), 55 (25), 45 (14), 44 (10), 43 (60, CH_3CO^+).

Reaction of 1 with Trimethyl Phosphite.—The following is an adaptation of an earlier procedure.[5] A solution of **1** (5.0 g, 19 mmol) in freshly distilled trimethyl phosphite (20 ml) was heated to reflux under an atmosphere of nitrogen. The bath temperature was maintained for 60 hr at 150°, during which time the mixture ceased to reflux. The solution was cooled and poured into 250 ml of 1 *M* aqueous sodium hydroxide and the mixture was stirred vigorously until a permanently basic, homogeneous solution resulted. The solution was extracted with four 250-ml portions of chloroform, and the dried (magnesium sulfate) extract was evaporated to a colorless syrup (2.78 g) that crystallized spontaneously. Tlc of the product (3:1 dichloromethane–ether) showed a major component (**2**), R_f 0.5, and a minor component (**3**), R_f 0.9. The solid was dissolved in the minimum volume of ether, and Skellysolve[11] C (50 ml) was added. The solution was then concentrated at 15–20° until it became slightly turbid, whereupon it was seeded with **2** and refrigerated for 12 hr, to give **5,6-dideoxy-1,2-*O*-isopropylidene-α-D-*xylo*-hex-5-enofuranose (2)**, yield 1.92 g (in two crops). The residual mother liquors were chromatographed on a column (3 × 30 cm) of silica gel (type 7734, 70–325 mesh ASTM, E. Merck) with 3:2 petroleum ether (bp 60–110°)–ether as eluent. The first product to be eluted was **1,2-*O*-isopropylidene-α-D-glucofuranose 3,5,6-orthoformate (3)**, yield 50 mg (0.22 mmol, 1%), identical with an authentic sample of **3** by mixture melting point and ir and nmr spectra. Further elution of the column gave an additional 0.62 g of **2**, total yield of **2** 2.54 g (13 mmol, 72%), mp 61–65°, $[\alpha]^{20}D$ −60° (c 2, chloroform).

1,2-*O*-Isopropylidene-α-D-glucofuranose 3,5,6-Orthoformate (3).—Into a 25-ml flask was placed 1,2-*O*-isopropylidene-α-D-glucofuranose (5.0 g, 22.6 mmol) and triethyl orthoformate (3.4 ml, 22.6 mmol) and 1 ml of acetic acid. The mixture was heated under an atmosphere of nitrogen for 4 hr at 120°. The cooled mixture was evaporated and three 15-ml portions of toluene were evaporated from the residue to remove acetic acid. Sublimation of the resultant solid at 0.05 Torr and 120° gave a white powder that was recrystallized from ethyl acetate to give pure **3**, yield 4.9 g (21.2 mmol, 94%), mp 201–203°, $[\alpha]^{20}D$ −41.5° (c 0.3, chloroform); R_f 0.9 (3:1 dichloromethane–ether); nmr data in chloroform-*d* τ 3.94 (1-proton doublet, $J_{1,2}$ = 3.2 Hz, H-1), 4.03 (1-proton singlet, orthoformate CH), 5.22 (1-proton, broad multiplet, width 12 Hz, H-5), 5.44 (1-proton doublet, $J_{2,3} \sim 0$ Hz, H-2), 5.65 (1-proton doublet, $J_{3,4}$ = 3.0 Hz, H-3), 5.92 (1-proton doublet and 1-proton multiplet, $J_{6,6'}$ = 8.0 Hz, $J_{5,6} \sim 0$, H-6, H-4), 6.11 (1-proton quartet, $J_{5,6}$ = 4.6 Hz, H-6′), 8.52, 8.78 (3-proton singlets, CMe_2); mass spectral data (relative intensities and assignments given in parentheses) *m/e* 215 (60, M − CH_3), 187 (<1, M − CH_3CO), 159 (<1, M − 71), 155 (<1, M − CH_3 − CH_3CO_2H), 129 (70), 127 (20), 114 (5), 113 (15), 101 (20), 100 (50), 85 (85), 71 (10), 69 (21), 61 (11), 59 (41, $CH_3COCH_3H^+$), 43 (100, CH_3CO^+).

For this compound prepared by a different procedure the following constants have been reported:[10] mp 201–203°, $[\alpha]D$ −40.9° (chloroform), τ 3.90 (H-1), 3.99 (orthoformate CH).

Fusion of **3** (1 g) with triphenylacetic acid (0.1 g) at 210° led to quantitative recovery of unchanged **3**, which sublimed from the reaction vessel and no conversion[12] into **2** was observed.

Registry No.—**1**, 25356-81-4; **3**, 3891-47-2.

(11) Petroleum ether fractions, bp 90–97°, Skelly Oil Co., Kansas City, Mo.

(12) G. Crank and F. W. Eastwood, *Aust. J. Chem.*, **17**, 1392 (1964).

The Synthesis of Cherylline

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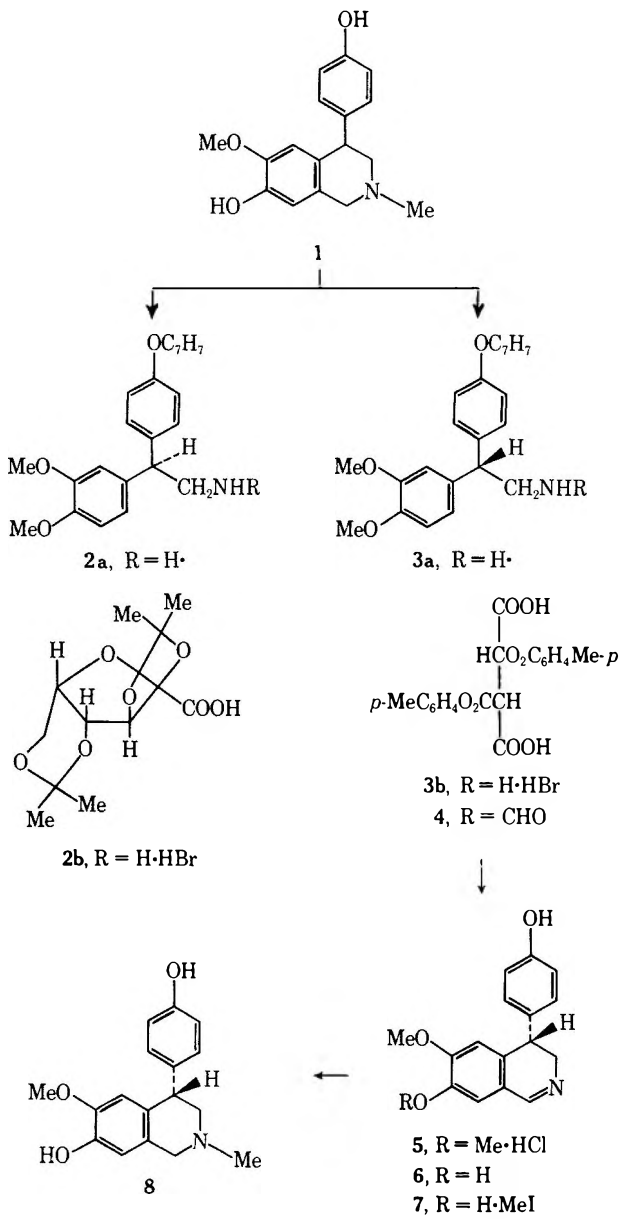
The isolation, structure, and *S* configuration of cherylline (**8**), a new representative of the rare phenolic *Amaryllidaceae* alkaloids, was recently reported[1] and

(1) A. Brossi, G. Grethe, S. Teitel, W. C. Wildman, and D. T. Bailey, *J. Org. Chem.*, **36**, 1100 (1970).

followed by a synthesis of (±)-cherylline.[2] We now describe the first total synthesis of the alkaloid **8** as well as its unnatural isomer.[3]

Resolution of the (±)-phenethylamine **1**[2] with (−)-diacetone-2-keto-L-gulonic acid[4] in 2-propanol afforded the diastereomeric salt **2a** (Scheme I). Treatment of

SCHEME I



the resulting mother liquors (as the free base) with (−)-di-O-*p*-toluoyl-D-tartaric acid in acetone provided the diastereomeric salt **3a**. Each of these was converted to the corresponding crystalline hydrobromides **2b** and **3b**[5] whose ORD and CD spectra were exact mirror images.

Reaction of the (−)-phenethylamine **3b** with methyl formate provided the (−)-N-formyl derivative **4** which was subjected to Bishler–Napieralski cyclization followed by debenzylation with concentrated hydrochloric acid at 25° to give the (−)-6,7-dimethoxydihydroisoquinoline **5**. Selective O-demethylation[6,7] of **5** with 48% hydrobromic acid at 100° for 6 hr yielded the (−)-6-methoxy-7-hydroxy derivative **6** which was converted with methyl iodide into the corresponding (−)-quaternary **7**. All of these levoratatory intermediates exhibited positive Cotton effects in their ORD spectra. However, sodium borohydride reduction of **7** was accompanied by inversion of the Cotton effects to afford (−)-cherylline (**8**) whose physical and spectral properties were identical with natural cherylline.[1,8] By the same reaction sequences, the (+)-phenethylamine **2b** was transformed into the unnatural isomer of cherylline.

Experimental Section[9]

(+)-2(*R*)-2-(4-Benzyloxyphenyl)-2-(3,4-dimethoxyphenyl)-ethylamine diacetone-2-keto-L-gulonate (2a) and Hydrobromide 2b.—An aqueous solution of 28.4 g (0.064 mol) of **1**·HBr[2] was rendered alkaline with 10% sodium hydroxide and extracted with methylene chloride, and the extract was evaporated. The residual oil and 18.7 g (0.064 mol) of (−)-diacetone-2-keto-L-gulonic acid hydrate[4] were dissolved in 185 ml of 2-propanol and stored at 25° for 17 hr. The crystals were filtered, dried (24.6 g), and recrystallized first from a mixture of 100 ml of methanol and 600 ml of 2-propanol, and then from a mixture of 75 ml of methanol and 300 ml of 2-propanol to give 13.2 g (64% based on 0.032 mol) of **2a**: mp 144–145°; $[\alpha]_D$ −5.2°.

Anal. Calcd for $C_{23}H_{25}NO_3 \cdot C_{12}H_{18}O_7$ (637.73): C, 65.92; H, 6.80. Found: C, 65.98; H, 6.80.

An aqueous solution of 12.8 g (0.02 mol) of **2a** was made alkaline with 10% sodium hydroxide and the free base was extracted with methylene chloride. The extract was rendered acidic with ethanolic hydrogen bromide and evaporated, and the residue was crystallized twice from acetonitrile, to give 7.5 g (84%) of **2b**: mp 123–125°; $[\alpha]_D$ +6.5°, $[\alpha]_{365}$ +21.0°; ORD (c 0.501, MeOH) $[\Phi]_{700}$ +16.4°, $[\Phi]_{589}$ +22.6°, $[\Phi]_{290}$ +355° (tr), $[\Phi]_{277}$ +800° (pk), $[\Phi]_{250}$ −1330° (tr), and $[\Phi]_{230}$ +6240° (pk); CD $[\theta]_{300}$ 0, $[\theta]_{287}$ −700, $[\theta]_{274}$ 0, $[\theta]_{270}$ +350, $[\theta]_{259}$ 0, and $[\theta]_{240}$ −17,600.

Anal. Calcd for $C_{23}H_{25}NO_3 \cdot HBr$ (444.39): C, 62.17, H, 5.90. Found: C, 62.42; H, 5.75.

(−)-2(*S*)-2-(4-Benzyloxyphenyl)-2-(3,4-dimethoxyphenyl)-ethylamine Di-O-*p*-tolucyl-D-tartrate (3a) and Hydrobromide (3b).—The 2-propanol mother liquors, obtained from the crystallization of crude **2a**, were evaporated, the residue dissolved in water, rendered alkaline with 10% sodium hydroxide, and extracted with methylene chloride. The organic extract was washed with 2% sodium hydroxide and evaporated. The residual oil (8.2 g) and 8.7 g (24.2 mmol) of (−)-di-O-*p*-toluoyl-D-

(2) A. Brossi and S. Teitel, *Tetrahedron Lett.*, 417 (1970).

(3) Presented in part by one of us (A. B.) at the Third Natural Products Symposium in Mona, Jamaica, Jan 5–9, 1970.

(4) T. Reichstein and A. Grüssner, *Helv. Chim. Acta*, **17**, 311 (1934). Its potential as a resolving agent was first recognized by our colleagues, Drs. W. Leimgruber and E. Mohacsi of these laboratories.

(5) The optical purity of these two isomers could be better judged at $[\alpha]_{365}$ where the rotations were enhanced over those at $[\alpha]_D$.

(6) Based on the preferential O-demethylation of the 7-methoxy group in 6,7-dimethoxy-3,4-dihydroisoquinoline with mineral acid as reported by H. Bruderer and A. Brossi, *Helv. Chim. Acta*, **48**, 1945 (1965).

(7) The partial ether cleavage of dimethoxy-substituted 3,4-dihydroisoquinolines and the application in certain alkaloid syntheses was presented by one of us (A. B.) at the 13th Symposium on the Chemistry of Natural Products, Sapporo, Japan, Sept 25–27, 1969, pp 177–186 of abstract, and will be detailed by A. Brossi and S. Teitel in a forthcoming publication.

(8) We are grateful to Professor W. C. Wildman of Iowa State University for providing us with a sample of natural cherylline.

(9) All melting points (corrected) were taken in open capillary tubes with a Thomas–Hoover melting apparatus. All thin layer chromatography employed silica gel G plates which were developed for 12–15 cm and detected with Dragendorff's reagent. The ultraviolet spectra were measured in ethanol with a Cary recording spectrophotometer Model 14M. Nuclear magnetic resonance spectra were obtained with a Varian Associates Model A-60 or HA-100 spectrophotometer using, unless noted otherwise, DMSO-d_6 as solvent and tetramethylsilane as internal reference. Chemical shifts are reported in δ with following abbreviations: (s) singlet, (m) multiplet, (t) triplet, (b) broad. Optical rotations were measured with a Perkin-Elmer polarimeter Model 141 using a 1% solution in methanol at 25°. Rotatory dispersion curves were determined at 23° with a Durrum-Jasco spectrophotometer Model 5 using 1 cm, 0.1 cm, or 0.1 mm cells. Circular dichroism curves were measured on the same instrument and are expressed in molecular ellipticity units [θ]. The mass spectra were taken with a CEC 21-110 mass spectrometer at 70 eV using a direct insertion probe. Extracts of products in organic solvents were washed with water and dried over anhydrous sodium sulfate.

tartaric acid were dissolved in 100 ml of acetone; the solution was stored at 25° for 20 hr. The crystals were filtered and recrystallized twice from acetone to give 12 g (50% based on 0.032 mol present in 1) of **3a**: mp 184–185°; $[\alpha]$D −79.0°.

Anal. Calcd for $C_{23}H_{25}NO_3 \cdot C_{20}H_{18}O_8$ (749.78): C, 68.88; H, 5.78. Found: C, 68.63; H, 5.79.

Conversion of 7.5 g (0.01 mol) of **3a** by the procedure given for the preparation of **2b** afforded, after two crystallizations from acetonitrile, 3.8 g (86%) of **3b**: mp 122–124°; $[\alpha]$D −6.5°, $[\alpha]_{365}$ −20.9°; ORD and CD mirror images of **2b**.

Anal. Calcd for $C_{23}H_{25}NO_3 \cdot HBr$ (444.39): C, 62.17; H, 5.90. Found: C, 62.22; H, 5.55.

(−)-2(*S*)-N-[2-(4-Benzyloxyphenyl)-2-(3,4-dimethoxyphenyl)-ethyl Formamide (4).—An aqueous solution of 7.3 g (16.4 mmol) of **3b** was rendered alkaline with sodium hydroxide and extracted with methylene chloride, and the extract evaporated. The residue was dissolved in 200 ml of methyl formate and heated at 60–65° under 20 atmospheres of nitrogen for 24 hr. The volatiles were evaporated and the residue dissolved in benzene and chromatographed over 45 g of silica gel. The benzene and benzene–ethyl acetate (80:20) eluates (700 mg) were discarded and the benzene–ethyl acetate (50:50) eluates were collected and evaporated to give 5.8 g (90%) of **4** as a colorless oil: bp 140° (0.02 mm); n^{25}D 1.5699; uv max 226 mμ (ε 22,360), 278 (5010), 284 (4420) (sh); nmr ($CDCl_3$) δ 3.82 (s, 6, OCH_3), 5.00 (s, 2, OCH_2), 5.58 (b, 1, NH), 6.60–7.50 (m, 7, aromatic), 7.34 (s, 5, C_6H_5), and 8.05 (s, 1, CHO); ORD and CD spectra the same as given for **3b**, within experimental error.

Anal. Calcd for $C_{24}H_{25}NO_4$ (391.45): C, 73.63; H, 6.44. Found: C, 73.55; H, 6.54.

(−)-4(*S*)-6,7-Dimethoxy-4-(4-hydroxyphenyl)-3,4-dihydroisoquinoline Hydrochloride (5).—A mixture of 16.4 g (42 mmol) of **4** and 18.6 ml of phosphorus oxychloride in 300 ml of acetonitrile was stirred and refluxed for 1 hr and evaporated under reduced pressure. The residue was suspended in 5% sodium hydroxide and extracted with ethyl acetate, and the extract evaporated. The residual oil (18 g) was dissolved in 150 ml of benzene, 150 ml of concentrated hydrochloric acid was added and the mixture was stirred vigorously at 25° for 15 hr and evaporated under reduced pressure. The residue was crystallized from a mixture of ethanol and ether to give 8.1 g (58%) of **5**·HCl: mp 221–222°; uv max 233 mμ (ε 19,350), 252 (15,000) (sh), 286 (5550), 310 (7400), and 363 (5150); nmr δ 3.80 (s, 3, OCH_3), 3.82 (s, 3, OCH_3), 4.06 (m, 2, CH_2), 4.48 (t, 1, J = 7 Hz, CH), 6.73, 6.90 (AA'BB', 4, aromatic), 6.87, 7.63 (2 s, 2, CH-7, 8), 9.08 (s, 1, CH=N), 9.55 (b, 1, OH or NH); $[\alpha]$D −139.5°; ORD (*c* 0.337, CH_3OH) $[\Phi]_{700}$ −309°, $[\Phi]_{589}$ −444°, $[\Phi]_{400}$ −495° (pk), $[\Phi]_{350}$ −13,870° (tr), $[\Phi]_{306}$ +8420° (pk), $[\Phi]_{272}$ −3960° (sh), $[\Phi]_{254}$ −17,330° (tr), and $[\Phi]_{330}$ +24,760° (pk); CD $[\theta]_{416}$ 0, $[\theta]_{376}$ +6530, $[\theta]_{356}$ 0, $[\theta]_{329}$ −16,990, $[\theta]_{302}$ 0, $[\theta]_{292}$ +3920, $[\theta]_{283}$ 0, $[\theta]_{272}$ −2610, $[\theta]_{266}$ −1310, $[\theta]_{244}$ −42,470, $[\theta]_{232}$ 0, and $[\theta]_{228}$ +16,340.

Anal. Calcd for $C_{17}H_{17}NO_3 \cdot HCl$ (319.79): C, 63.85; H, 5.67. Found: C, 64.06; H, 5.85.

(−)-4(*S*)-7-Hydroxy-4-(4-hydroxyphenyl)-6-methoxy-3,4-dihydroisoquinoline (6).—A solution of 11.0 g (34.5 mmol) of **5** in 300 ml of 48% hydrobromic acid was stirred at 100° for 6 hr and evaporated under reduced pressure. The residue was dissolved in water, neutralized with sodium bicarbonate, and extracted with ethyl acetate (four 125-ml portions). The extracts were evaporated and crystallized from a mixture of ethanol and ether to give 7.4 g (80%) of **6**: mp 207–208°; uv max 233 mμ (ε 30,700), 280 (8400), and 318 (5000); nmr δ 3.65 (s, 3, OCH_3-6), 6.45, 6.82 (s, 2, CH-5,8), 8.60, 6.86 (AA'BB', 4, CH-2',3',5',6'), 8.12 (b, 1, CH-1), and 9.03 (b, 2, OH); $[\alpha]$D −222.4°, ORD (*c* 0.507, 0.1 *N* HCl in CH_3OH) $[\Phi]_{700}$ −334°, $[\Phi]_{589}$ −468°, $[\Phi]_{406}$ +2390° (pk), $[\Phi]_{344}$ −10,620° (tr), $[\Phi]_{305}$ +10,360° (pk), $[\Phi]_{254}$ −10,090° (tr), and $[\Phi]_{230}$ +35,060° (pk); CD $[\theta]_{430}$ 0, $[\theta]_{280}$ +5260, $[\theta]_{360}$ 0, $[\theta]_{328}$ −16,480, $[\theta]_{302}$ 0, $[\theta]_{290}$ +2450, $[\theta]$ −2800 (sh), $[\theta]_{244}$ −30,140, $[0]_{231}$ 0, and $[0]_{228}$ +4210.

Anal. Calcd for $C_{16}H_{15}NO_3$ (269.29): C, 71.36; H, 5.61. Found: C, 71.22; H, 5.79.

(−)-4(*S*)-7-Hydroxy-4-(4-hydroxyphenyl)-6-methoxy-2-methyl-3,4-dihydroisoquinolinium Iodide (7).—A solution of 5.0 g (18.5 mmol) of **6** and 26 ml of methyl iodide in 300 ml of methanol was stored at 25° for 24 hr and evaporated. The residue was crystallized from a mixture of methanol and ether to give 5.3 g (69%) of **7**: mp 242–243°; uv max 215 mμ (ε 29,100), 251 (20,600), 280 (5900), 312 (10,000), and 370 (7300); nmr δ 3.63 (s, 3, $^+NCH_3$), 3.79 (s, 3, OCH_3), 4.08 (m, 2, CH_2), 4.53 (t, 1, J = 8 Hz, CH), 6.72, 6.99 (AA'BB', 4, aromatic), 6.75, 7.28 (2s, 2, CH-5,8), 9.15 (s, 1, CH=N), and 9.50 (b, 2, 2 OH), $[\alpha]$D −88.9°; ORD (*c* 0.746, CH_3OH) $[\Phi]_{700}$ −304°, $[\Phi]_{589}$ −430°, $[\Phi]_{410}$ +1100° (pk), $[\Phi]_{348}$ −11,020° (tr), $[\Phi]_{308}$ +7440° (pk), $[\Phi]_{270}$ −5510° (sh), $[\Phi]_{259}$ −23,140° (tr), and $[\Phi]_{230}$ +7710° (pk); CD $[\theta]_{430}$ 0, $[\theta]_{380}$ +5450, $[\theta]_{356}$ 0, $[\theta]_{330}$ −13,820, $[\theta]_{306}$ 0, $[\theta]_{296}$ +3270, $[\theta]_{288}$ 0, $[\theta]_{270}$ −6540 (sh), $[\theta]_{246}$ −32,020, $[\theta]_{234}$ 0, and $[\theta]_{230}$ +14,540.

Anal. Calcd for $C_{17}H_{18}INO_3$ (411.24): C, 49.65; H, 4.41. Found: C, 49.64; H, 4.48.

(−)-4(*S*)-7-Hydroxy-4-(4-hydroxyphenyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (8).—To a stirred solution of 4.11 g (10 mmol) of **7** in 300 ml of methanol was added 6 g of sodium borohydride over 1 hr. After stirring for 3 hr, the reaction mixture was evaporated and the residue dissolved in water, acidified with 6 *N* hydrochloric acid, neutralized with sodium bicarbonate, and extracted with ethyl acetate. The organic extract was evaporated and the residue crystallized from ether to afford 2.3 g (81%) of **8**: mp 216–217°; uv max 225 mμ (ε 16,400) (sh), 282 (4800), and 293 (3000) (sh); nmr δ 2.27 (s, 3, NCH_3), 3.42 (s, 2, CH_2-1), 3.54 (s, 3, OCH_3), 3.97 (t, 1, J = 6 Hz, CH-4), 6.28, 6.51 (2 s, 2, CH-5,8), 6.67, 6.97, (AA'BB', 4, aromatic), and 8.97 (b, 2, OH); mass spectrum *m/e* (rel intensity) 285 (29), 242 (100), 241 (87), 227 (25), 225 (65), 211 (55), 210 (37), 199 (12), 197 (14), 182 (17), 181 (32), 169 (13), 165 (15), 153 (18), 152 (19); compound **8** was identical in thin layer chromatographic behavior with natural cherylline[8] in the following solvent systems, acetonitrile–concentrated ammonium hydroxide (90:10), chloroform–methanol (70:30), chloroform–methanol–diethylamine (92:3:5), methanol–acetic acid (1:1); $[\alpha]$D −71.9° [lit.[1] $[\alpha]^{26}$D −69° (*c* 0.2, CH_3OH)]; ORD (*c* 0.249, CH_3OH) $[\Phi]_{700}$ −131°, $[\Phi]_{589}$ −189°, $[\Phi]_{295}$ −12,150° (tr), $[\Phi]_{278}$ +16,040° (pk), $[\Phi]_{258}$ +2520° (tr), $[\Phi]_{242}$ +9170° (pk), and $[\Phi]_{229}$ −13,750° (tr); CD $[\theta]_{306}$ 0, $[\Phi]_{290}$ −17,570, $[\theta]_{280}$ 0, $[\theta]_{275}$ +3860, $[\theta]_{256}$ +640, $[\theta]_{240}$ +12,860, $[\theta]_{235}$ 0, and $[\theta]_{225}$ −22,290; identical within experimental error, in ORD and CD with natural cherylline.[1]

Anal. Calcd for $C_{17}H_{19}NO_3$ (285.33): C, 71.56; H, 6.71. Found: C, 71.27; H, 6.66.

(+)-4(*R*)-7-Hydroxy-4(4-hydroxyphenyl)-6-methoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (Unnatural Cherylline, Antipode of 8).—This was obtained from **2b** by the methods described for the conversion of **3b** into **8** *via* the dextrorotatory antipodes of **4**, **5**, **6**, and **7**: mp 214–215° (from ether); identical in tlc, uv, and nmr with **8**; ORD and CD mirror images of **8**.

Anal. Calcd for $C_{17}H_{19}NO_3$ (285.33): C, 71.56; H, 6.71. Found: C, 71.63; H, 6.76.

Registry No.—**2a**, 25528-07-8; **2b**, 25528-08-9; **3a**, 25528-09-0; **3b**, 25515-38-2; **4**, 25641-45-6; **5**, 25515-39-3; **6**, 25515-40-6; **7**, 25515-41-7; (−)-(*S*)-**8**, 23367-61-5; (+)-(*R*)-**8**, 25515-34-8.

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A New Ylide from Tetrakis(trifluoromethyl)cyclopentadienone and Triphenylphosphine

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The reaction between hexafluorobut-2-yne and chlorobis(carbonyl)rhodium dimer gives good yields of tetrakis(trifluoromethyl)cyclopentadienone.[1] When

(1) R. S. Dickson and G. Wilkinson, *J. Chem. Soc.*, 2699 (1964).

solutions containing this dienone and triphenylphosphine are mixed at room temperature, the yellow color of the dienone is immediately discharged and from the reaction a compound of stoichiometry $C_{27}H_{15}F_{12}OP$ is obtained in excellent yield. The product of the reaction is considered to be a new ylide, tetrakis(trifluoromethyl)cyclopentadienonetriphenylphosphorane (I), on the basis of the following spectral data.

Tetrakis(trifluoromethyl)cyclopentadienone shows bands in the infrared at 1684 (C=C stretch) and 1718, 1761 cm^{-1} (C=O stretch),[1] but this new compound shows only two bands at 1502 and 1582 cm^{-1}, which can be assigned to the aromatic double bonds, the keto bands being no longer present. In addition, the spectrum shows a strong band at 1107 cm^{-1} which is expected for the structure shown because of the presence of a quaternary triphenylphosphonium group.[2]

The ^{19}F nmr spectrum of the compound at 56.4 MHz shows two resonances of equal area separated by 43.7 Hz, but at 94.1 MHz these are now separated by 79 Hz. The peaks are therefore two separate resonances centered at −11.4 and −12.2 ppm and correspond closely to the reported nmr spectrum of tetrakis(trifluoromethyl)cyclopentadienone itself which shows two resonances at −7.9 and −10.1 ppm.[1] This similarity of the spectra shows that the triphenylphosphine must have combined with the dienone through the oxygen atom since addition to carbon in a Michael manner would give a compound with four nonequivalent CF_3 groups. Each of the peaks is too complex for good resolution but ^{19}F–^{19}F homonuclear spin decoupling on each of the resonances causes them to collapse to singlets showing that the splitting is due entirely to ^{19}F–^{19}F coupling with the ^{31}P–^{19}F coupling being immeasurably small. This evidence strongly supports the structure proposed since the nmr should show two resonances for equivalent pairs of CF_3 groups, and it would also show a small ^{19}F–^{31}P coupling, because the P atom is as far away from the fluorines as possible. The uv spectrum of the ylide is also markedly different from the initial dienone. This new compound shows an absorption at 307 mμ (ε 780) whereas the dienone shows a band at 342 mμ (ε 360).

This reaction differs from that found between hexafluoroacetone and triphenylphosphine; in this case with hexafluoroacetone two molecules of the ketone add to one molecule of the phosphine to give a 5-membered ring phospholane compound.[3] The ylide is favored in the reaction with tetrakis(trifluoromethyl)cyclopentadienone because of two features: transfer of an electron pair into the ring causes the formation of the aromatic cyclopentadienide ring; and the electron transfer is further favored by the electron-withdrawing CF_3 groups substituent on the cyclopentadienone.

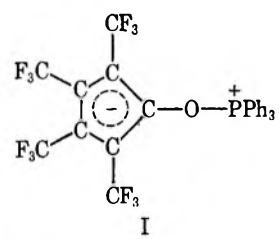
A similar adduct has been obtained with the same dienone and 1,2-bis(diphenylphosphino)ethane except then the stoichiometry now shows that two molecules of dienone have added to each molecule of the diphosphine. The dienone does not react with triphenylarsine or triphenylstilbine, but it has been reported to give colorless compounds with amines.[1] Further investigation of this reaction has shown that these compounds are amine hydrofluorides formed by defluorination of the dienone.

(2) F. S. Ramirez and S. Levy, *J. Amer. Chem. Soc.*, **79**, 67 (1957).
(3) R. F. Stockel, *Tetrahedron Lett.*, 2833 (1966).

Experimental Section

Infrared spectra were recorded on a Grubb–Parson's spectromaster. Nuclear magnetic resonance spectra were obtained on Varian V-4311 and HA-100 spectrometers operating at 56.4 and 94.1 MHz, respectively, and chemical shifts are given relative to benzotrifluoride as internal reference. Ultraviolet spectra were recorded on a Perkin-Elmer 350 spectrometer. Mass spectra were recorded on a MS9 spectrometer. Microanalyses were performed by A. Bernhardt, Mülheim, Ruhr, and molecular weights were obtained by Mechrolab osmometer operating at 36°.

Tetrakis(trifluoromethyl)cyclopentadienonetriphenylphosphorane (I).—When a yellow solution of tetrakis(trifluoromethyl)cyclopentadienone (0.12 g, 1 mol) in CH_2Cl_2 was added to a solution of triphenylphosphine (0.15 g, 1.7 mol) in the same solvent, the color was immediately discharged. The solution was boiled and MeOH was added dropwise until colorless crystals formed. The compound was recrystallized from CH_2Cl_2–MeOH in a similar way to give 0.17 g (80%) of the required product: mp 219–224°; ir (Nujol mull) 1582, 1502, 1276, 1211, 1107, 1043, 934, 752, 699 cm^{-1}; nmr (CH_2Cl_2) φ −11.4 (m), −12.2 (m); uv (CH_2Cl_2) 307 mμ (ε 780). *Anal.* Calcd for $C_{27}H_{15}F_{12}OP$: C, 52.6; F, 37.1; mol wt, 614.06687. Found: C, 52.2; F, 36.8; mol wt, 619 ($CHCl_3$ osmometer), 614.0668 (mass spectrograph). The compound is soluble in $CHCl_3$ but insoluble in MeOH.



I

Registry No.—I, 25396-73-0.

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Preparation and Photolysis of 3-Azido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose[1]

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The photochemistry of organic azides has been of interest in the last several years. One application has been made to carbohydrates in that methyl 2,3,4-tri-*O*-acetyl-6-azido-6-deoxy-α-D-glucopyranoside has been photolyzed and hydrolyzed to yield the 6-aldehydo derivative.[2] We have found that the introduction of carbonyl functions into secondary positions of sugars may be accomplished by photolysis of the appropriate secondary azide to the corresponding imino derivative which is readily converted to the ketone.

(1) This work was supported by the Corn Refiners Association Inc., Journal Paper No. 3938 of the Purdue Agricultural Experiment Station, Lafayette, Ind. 47907.
(2) D. Horton, A. E. Luetzow, and J. C. Wease, *Carbohyd. Res.*, **8**, 366 (1968).

The substrate was 3-azido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose, obtained in 40% yield from 1,2:5,6-di-*O*-isopropylidene-3-*O*-(*p*-tolysulfonyl)-α-D-glucofuranose by nucleophilic displacement with sodium azide in hexamethylphosphoramide.[3] Synthesis of this azide was recently reported by this laboratory[4] using dimethylformamide as the solvent for the tolysulfonyloxy displacement. The disadvantage of the method was the 15 days required for disappearance of the starting material. In hexamethylphosphoramide, however, the reaction time is reduced to 18 hr. After extracting the products from the reaction mixture, silica gel column chromatography separates the azide from an olefinic by-product, 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*erythro*-hex-3-enofuranose.

When a benzene solution of the azide is exposed to ultraviolet radiation for 18 hr, the starting material completely disappears, as indicated by the absence of azide absorption at 2150 cm^{-1}. The syrup obtained after concentration of the reaction mixture is refluxed with aqueous ether to convert the photoproduct, presumably the imine, to the ketone hydrate, isolated in 34% yield. The hydrate is a crystalline compound,[5] whereas the ketone, 1,2:5,6-di-*O*-isopropylidene-α-D-*ribo*-hexofuran-3-ulose, is a syrup.

An authentic sample of the ketone was prepared according to the method of Sowa and Thomas,[6] by oxidation of 1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose with methyl sulfoxide in the presence of acetic anhydride. This ketone on conversion to the hydrate was identical with the photoproduct derivative.

Experimental Section

Irradiations with unfiltered ultraviolet light were conducted using a Hanovia 200-W low-pressure mercury lamp (654A36) inserted into a water cooled quartz immersion well. Melting points were measured on a Fisher-Johns apparatus and are corrected. Infrared spectra were obtained with a Perkin-Elmer Model 337 spectrophotometer.

3-Azido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose.—To a solution of 1,2:5,6-di-*O*-isopropylidene-3-*O*-(*p*-tolysulfonyl)-α-D-glucofuranose (4.14 g, 0.01 mol) in 50 ml of hexamethylphosphoramide heated to 120° is added, with stirring, sodium azide (5.2 g, 0.08 mol). After 18 hr the reaction mixture is cooled to 25° and transferred with the aid of 25 ml of water to a Friedrich liquid–liquid extractor and extracted with 250 ml of hexane. After 12 hr, the hexane extract is washed 4 times with 250-ml portions of water to remove the small remaining quantity of hexamethylphosphoramide. The hexane extract is dried over anhydrous sodium sulfate and filtered. The filtrate is concentrated to a syrup and chromatographed over a silica gel column (4 × 65 cm) using benzene–ethyl acetate (20:1 v/v) as eluent. Only two carbohydrate components are present in the reaction mixture and in the column eluate as determined by thin layer chromatography using benzene–ethyl acetate (6:1 v/v) as irrigant. The column fractions containing the faster moving olefin component are combined and concentrated to a syrup, whereupon the residue spontaneously crystallized (0.75 g, 31%). It is recrystallized from hexane to give 3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-*erythro*-hex-3-enofuranose, mp 51° (lit.[7] mp 51°). The ir spectrum in Nujol shows a strong olefinic band at 1650 cm^{-1}. The slower moving azide fractions from the column are then collected and concentrated to a syrup. This is dissolved in 10 ml of hexane and left at 0° for 24 hr, whereupon 3-azido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose crystallizes as long needles: mp 38–39°; $[\alpha]^{25}D$ +72° (c 1.0, chloroform); yield 1.14 g (40%).

Photolysis of 3-azido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranose.—The above azide (4.85 g) in 1 l. of benzene was irradiated 18 hr after which the solution was concentrated and refluxed with aqueous ether (50 ml). After concentrating to dryness, the syrup was applied to a silica gel column and eluted with chloroform–acetone (15:1 v/v). Progress was followed by tlc and the fraction containing the ketone hydrate crystallized from ether–hexane: mp 113–114°; $[\alpha]^{25}D$ +45° (c 1.0, chloroform); yield 1.6 g (34%). R_f and ir values and mixture melting point were identical with those of an authentic sample. Elemental analysis agreed with calculated values.

Registry No.—3-Azido-3-deoxy-1,2:5,6-di-*O*-isopropylidene-α-D-allofuranonse, 21870-78-0.

(3) Y. Ali and A. C. Richardson, *J. Chem. Soc.*, 1764 (1968).
(4) U. G. Nayak and R. L. Whistler, *J. Org. Chem.*, **34**, 3819 (1969).
(5) P. J. Beynon, P. M. Collins, P. T. Doganges, and W. G. Overend, *J. Chem. Soc.*, 1131 (1966).
(6) W. Sowa and G. H. S. Thomas, *Can. J. Chem.*, **44**, 836 (1966).
(7) K. Freudenberg and F. Brauns, *Ber.*, 3233 (1922).

Synthesis of N-Carbobenzoxyamino Acid and Peptide Pentafluorophenyl Esters as Intermediates in Peptide Synthesis

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Recently we have shown that peptide bond formation, by use of active esters in the presence of triethylamine under conditions where oxazolones are not known to form, led to racemization *via* α-hydrogen abstraction.[1] Kinetic studies demonstrated the superiority of the pentafluorophenyl ester in the synthesis of peptides, where racemization by α-hydrogen abstraction can occur. N-Carbobenzoxy-S-benzyl-L-cysteine active esters were studied as to their relative rates of racemization and coupling, and it was found that the pentafluorophenyl ester could be coupled in better than 90% yield in 5 min with virtually no racemization.[2] Previous work had shown that there is no racemization when N-carbobenzoxyglycyl-L-phenylalanine pentafluorophenyl ester is coupled with glycine ethyl ester in the Anderson test.[3] The high reactivity of the pentafluorophenyl esters[2] indicates that these compounds can be used in the synthesis of peptide active esters in a variation of the mixed anhydride procedure. Thus a N-protected amino acid pentafluorophenyl ester can be coupled with a slowly reacting amino acid active ester, such as *p*-nitrophenyl ester, to yield N-protected dipeptide active ester.[2b] This variation of the "backing-off procedure"[4] can be helpful in preparing optically pure intermediates for high-molecular-weight sequential polypeptides. Peptide pentafluorophenyl esters can be prepared either by the "pentafluorophenol complex"[5] or through the mixed anhydride procedure;[6]

(1) (a) J. Jovacs, G. L. Mayers, R. H. Johnson, and U. R. Ghatak, *Chem. Commun.*, 1066 (1968); (b) Symposium Monograph of The First American Peptide Symposium, Yale University, 1968 (in press).
(2) (a) J. Kovacs, G. L. Mayers, R. H. Johnson, R. E. Cover, and U. R. Ghatak, *Chem. Commun.*, 53 (1970); (b) J. Kovacs, G. L. Mayers, R. H. Johnson, R. E. Cover, and U. R. Ghatak, *J. Org. Chem.*, **35**, 1810 (1970).
(3) L. Kisfaludy and J. Kovacs, Proceedings of the 8th European Peptide Symposium, Noordwijh, 1966, Macmillan, New York, N. Y., 1967.
(4) M. Goodman and K. C. Steuben, *J. Amer. Chem. Soc.*, **81**, 3980 (1959).
(5) J. Kovacs, L. Kisfaludy, and M. Q. Ceprini, *ibid.*, **89**, 183 (1967).
(6) (a) J. R. Vaughn, Jr., *ibid.*, **73**, 3547 (1951); (b) T. Wieland and H. Bernhard, *Justus Liebigs Ann. Chem.*, **572**, 190 (1951); (c) R. A. Boissonnas, *Helv. Chim. Acta*, **34**, 874 (1951).

TABLE I

N-CARBOBENZOXYAMINO ACID PENTAFLUOROPHENYL ESTERS

PFPOH ester	Registry no.	Method of prep- aration	Purification solvent	Mp, °C	$[\alpha]^{22}D$, deg	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
Z-Ala	25516-39-6	B	Hexane	84.0–85.0	−22.41 (*c* 2.12, EtOAc)	$C_{17}H_{12}NO_4F_5$	52.45	3.11	3.60	52.48	3.52	3.87
Z-Val	25529-25-3	A	EtOH–H_2O	50–51.5	−12.30 (*c* 2.00, EtOAc)	$C_{19}H_{16}NO_4F_5$	54.70	3.80	3.40	54.96	4.11	3.72
Z-DL-Val	17543-46-3		EtOH–H_2O	88–90						54.9	4.00	3.50
Z-Lys | Z	25529-27-5	A	$CHCl_3$–hexane	105–107	8.58 (*c* 2.25, EtOAc)	$C_{28}H_{25}N_2O_6F_5$	57.93	4.34	4.83	58.10	4.46	5.29
Z-Try	17543-50-9	A	$CHCl_3$–hexane	124–125	−26.4 (*c* 2.05, EtOAc)	$C_{25}H_{17}N_2O_4F_5$	59.53	3.40	5.55	60.02	3.38	5.94
Z-Met	17543-51-0	A	EtOH	104–106	−18.7 (*c* 2.00, EtOAc)	$C_{19}H_{16}NO_4SF_3$	50.78	3.59	3.12	50.41	3.94	3.20
Z-Phe	17543-49-6	A	EtOH	98–100	−26.67 (*c* 2.00, EtOAc)	$C_{23}H_{16}NO_4F_5$	59.40	3.60	3.00	59.54	3.71	3.26
Z-Ser	25529-31-1	A	EtOH	142.5–143.5	−16.25 (*c* 2.00, EtOAc)	$C_{17}H_{12}NO_5F_5$	50.38	3.00	3.46	50.33	3.11	3.49
Z-DL-Ser	17543-47-4		EtOH	140.5–141						50.50	3.20	3.70
Z-Pro	17543-45-2	B	Hexane–C_6H_6	Oil	−55.05 (*c* 2.00, EtOAc)	$C_{19}H_{14}NO_4F_5$	54.95	3.39	3.37	55.20	3.70	3.60
Z-Leu	25529-34-4	B	Hexane	Oil	−17.7 (*c* 2.00, EtOAc)	$C_{20}H_{18}NO_4F_5$	55.68	4.20	3.25	55.69	4.39	3.30
Z-Glu | O-Bu-*t*	25529-35-5	B	Hexane–C_6H_6	85–87	−16.5 (*c* 2.03, EtOAc)	$C_{23}H_{22}NO_6F_5$	54.87	4.41	2.99	54.73	4.54	2.78
Z-Ileu	25529-36-6	B	Hexane–C_6H_6	Oil	−13.5 (*c* 2.00, EtOAc)	$C_{20}H_{18}NO_4F_5$	55.68	4.20	3.25	55.53	4.15	3.12
Z-Glu | NH_2	17543-48-5	A	EtOH–H_2O	116–118	−10.94 (*c* 2.01, EtOAc)	$C_{19}H_{15}N_2O_5F_5$	51.20	3.40	6.30	51.59	3.68	6.55
Z-Asp-BZL	17543-13-4	A	EtOH	95.5–96	−9.85 (*c* 2.01, EtOAc)	$C_{25}H_{18}NO_6F_5$	57.37	3.46	2.68	57.10	3.52	2.83
Z-Arg | NO_2	17543-52-1	A	EtOH	98–99	−12.6 (*c* 2.15, EtOAc)	$C_{20}H_{13}N_5O_6F_5$	46.30	3.50	13.50	46.66	3.90	13.57
Z-Gly	16748-79-1	A	EtOH–H_2O	86–87		$C_{16}H_{10}NO_4F_5$	51.25	2.70	3.70	51.43	2.80	3.99
Z-Cys | BZL	25529-39-9	A	EtOAc–pentane	85–86	−25.6 (*c* 2.00, EtOAc) −40.0 (*c* 2.05 THF) −24.95 (*c* 2.00, $CHCl_3$)	$C_{24}H_{18}NO_4SF_5$	56.36	3.55	2.74	56.40	3.61	2.84
Z-Asp-O-*t*-Bu	25529-40-2	B	Hexane–C_6H_6	76.5–77.5	−43.1 (*c* 2.00, $CHCl_3$)	$C_{22}H_{20}NO_6F_5$	53.99	4.22	2.93	53.12	4.04	3.16

thus N-carbobenzoxyglycine was coupled with S-benzyl-L-cysteine pentafluorophenyl ester to give the corresponding dipeptide active ester. Such peptide pentafluorophenyl esters are very important for the synthesis of sequential polypeptides.[2]

The above considerations suggested the merit of reporting the preparation of several important N-carbobenzoxy-L-amino acid pentafluorophenyl esters. Similar to the pentachlorophenyl esters,[7] N-carbobenzoxyamino acid pentafluorophenyl esters were most conveniently prepared by the use of dicyclohexylcarbodiimide. Several of the pentafluorophenyl ester derivatives were difficult to prepare in a pure state since these esters are low melting, very soluble in all organic solvents, and hydrolyze in the presence of water. However, this does not reduce their usefulness in peptide synthesis since the crude ester can be used in coupling to give the corresponding optically pure peptides in high yield.[8] To obtain the latter esters analytically pure, the synthesis and purification had to be carried out using anhydrous reagents and solvents in an inert atmosphere. Table I summarizes the reaction conditions for the preparation of N-carbobenzoxyamino acid pentafluorophenyl esters with the corresponding physical constants and analysis.

Experimental Section

Melting points were taken on a Thomas–Hoover melting point apparatus in open capillaries and are uncorrected. Optical rotations were determined on a Rudolph spectropolarimeter Model 80. Infrared spectra were taken on a Beckman IR-8. Elemental analysis were performed by Schwartzkopt Microanalytical Laboratory, Woodside, N. Y., or Alfred Bernhardt Mikroanalytisches Laboratorium, West Germany.

Reagents.—Hexane (reagent grade) was treated with sulfuric acid and passed through a column of basic alumina (Woelm aluminum oxide activity grade I). Ethyl acetate (reagent grade) was placed over anhydrous potassium carbonate for several days, filtered, and distilled from phosphorus pentoxide. Chloroform (reagent grade) was washed with sulfuric acid, six times with half its volume of water, dried over anhydrous calcium chloride for at least 24 hr, filtered, and distilled from phosphorous pentoxide. Benzene (thiophene free, Fisher Scientific) was distilled from sodium. Silica gel (Merck) (0.05–0.20 mm) was heated at least 4 hr at 100° and cooled in an inert anhydrous atmosphere before use. Pentafluorophenol was obtained from Aldrich and used as supplied.

Synthesis of Amino Acid Pentafluorophenyl Esters. Method A.—An N-protected amino acid (10 mmol) and pentafluorophenol (10 mmol) were dissolved in 75 ml of ethyl acetate and the solution was cooled to 0°. Dicyclohexylcarbodiimide (10 mmol), dissolved in 10 ml of ethylacetate, was added, and the reaction mixture was stirred at 0°. After 1 hr the dicyclohexylurea was removed by filtration and the solvent was removed *in vacuo*. The resulting N-protected amino acid pentafluorophenyl ester was recrystallized from the appropriate solvent. The recrystallization solvent and physical data are reported in Table I.

Method B.—The synthesis described in method A and the isolation of the pentafluorophenyl ester was carried out in an inert atmosphere using anhydrous solvents. Since these esters were difficult to purify by recrystallization because of their high solubility in organic solvents, it was necessary to purify them for analysis by column chromatography in silica gel. To avoid hydrolysis during the chromatography the silica gel and all glassware were heated in the oven at 100° for at least 4 hr and then quickly removed to an inert atmosphere to cool. After removal of the dicyclohexylurea by filtration and removal of the solvent *in vacuo*, the residue was dissolved in 5 ml of hexane and placed on the silica gel column. The column was prepared with 20 g of silica gel suspended in hexane (13 × 2 cm). The eluates were collected and monitored by thin layer chromatography. Fractions that contained the pentafluorophenyl ester were combined and evaporated to dryness. The solid residues were triturated with pentane and filtered. All samples prepared in this manner gave one spot on thin layer chromatography and were shipped under nitrogen for analysis.

N-Carbobenzoxyglycyl-L-phenylalanine Pentafluorophenyl Ester.—To a solution of dicyclohexylcarbodiimide (0.206 g, 1

(7) J. Kovacs, M. Q. Ceprini, C. A. Duprez, and G. N. Schmit, *J. Org. Chem.*, **32**, 3696 (1967).

(8) For example, crude N-carbobenzoxy-nitro-arginine pentafluorophenyl ester can be coupled to valyl-tyrosyl-isoleucyl-histidyl-prolyl phenylalanine methyl or *t*-butyl ester in 90% yield: unpublished work of U. R. Ghatak and V. R. Giannasio.

mmol) in 4 ml of ethyl acetate, pentafluorophenol (0.558 g, 3 mmol) in 4 ml of ethyl acetate was added at 0°, and after 5 min N-Carbobenzoxyglycyl-phenylalanine (0.356 g, 1 mmol) in 20 ml of ethyl acetate was added. After the reaction mixture was stirred for 1 hr at 0°, the dicyclohexylurea was filtered and the mother liquor evaporated to dryness. The resulting oil was dissolved in ethyl acetate and residual dicyclohexylurea was filtered. After removal of the solvent *in vacuo*, the dipeptide active ester was obtained in 92% yield (0.482 g), mp 96–98°. For analysis it was crystallized from ethanol–water: mp 96–98°, $[\alpha]^{23}D$ −10.5° (*c* 1.0, $CHCl_3$). This compound prepared by the "backing-off" procedure gave the same physical constants.

Anal. Calcd for $C_{25}H_{19}N_2O_5F_5$: C, 57.47; H, 3.67; N, 5.36. Found: C, 57.23; H, 3.86; N, 5.69.

N-Carbobenzoxyglycyl-S-benzyl-L-cysteine Pentafluorophenyl Ester.—N-Carbobenzoxyglycine (1.045 g, 5 mmol) was dissolved in 13 ml of ethyl acetate containing (0.55 ml, 5 mmol) N-methyl morpholine, and isobutyl chloroformate (0.7 ml, 5.3 mmol) was added at −20°. After stirring the reaction mixture at −20° for 15 min, *S*-benzyl-L-cysteine pentafluorophenyl ester hydrobromide (2.289 g, 5 mmol), which had been prepared in the usual manner from the corresponding N-carbobenzoxy derivative, and triethylamine (0.7 ml, 5 mmol) were added. After stirring the reaction mixture for 30 min at −20° and 1 hr at 0°, it was diluted with 13 ml of ethyl acetate and washed with 13 ml of 1 *N* hydrochloric acid, 15 ml of 5% sodium bicarbonate solution, twice with 20 ml of 1 *N* hydrochloric acid, thrice with 20 ml of water, and dried over anhydrous sodium sulfate. The solvent was removed *in vacuo* and the oily residue (3.39 g, 60%) was dissolved in ether and placed in the freezer. The crystalline product was filtered and washed with ether and pentane, yield 2.50 g (44%), mp 74–80°. Recrystallization from ether–pentane raised the mp to 84–85°, $[\alpha]^{22}D$ −30.74° (*c* 2.04, ethyl acetate).

Anal. Calcd for $C_{26}H_{21}O_5N_2SF_5$: C, 54.93; H, 3.72; N, 4.93; S, 5.64. Found: C, 54.73; H, 3.75; N, 5.20; S, 6.04.

Registry No.—N-Carbobenzoxyglycyl-L-phenylalanine pentafluorophenyl ester, 14131-93-2; N-carbobenzoxyglycyl-S-benzyl-L-cysteine pentafluorophenyl ester, 25529-42-4.

Acknowledgment.—This work was supported by grants from the National Institutes of Health, Public Health Service (G.M. 06579 and 08795). We wish to thank Professor H. Horan for the infrared spectra.

Reduction of Olefins Using Sodium–Hexamethylphosphoramide–*t*-Butyl Alcohol[1]

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Nonconjugated alkenes and polyalkylated aromatic compounds are resistant to reduction by dissolving metals in liquid ammonia.[3-6] Solutions of lithium in certain alkylamines reduce some nonconjugated monoolefins and alkylbenzenes, but reaction is slow and yields are variable.[7] During the course of other work, we found that solutions of sodium hexamethylphosphoramide (HMPA) containing *t*-butyl alcohol were capable of effecting reduction of hexamethylbenzene not only to 1,2,3,4,5,6-hexamethylcyclohexa-1,4-diene, but also to the corresponding hexamethylcyclohexene and -hexane.[8,9] The observation of the latter products suggested that HMPA–sodium–*t*-butyl alcohol might be effective in reducing other unactivated alkenes. Here we wish to describe experiments indicating that this reducing mixture provides a convenient and general method of saturating even tetraalkyl substituted carbon–carbon bonds.[11]

Table I lists the yields of products detected on reaction of several representative unsaturated compounds with ~2–4 equiv of sodium in HMPA–*t*-butyl alcohol at room temperature over periods of 6–24 hr. The yields of reduced product in these reactions are generally high. The relatively low yields observed for the reduction of norbornene and 3,3,6,6-cyclohexa-1,4-diene represent isolated yields, and should be considered minimum values: with attention to detail during the work-up procedures, it should be possible to increase these numbers significantly. Similarly, the conversion

TABLE I

REDUCTION OF OLEFINS WITH SODIUM–HEXAMETHYLPHOSPHORAMIDE–*t*-BUTYL ALCOHOL

Starting material	Product	Yield, %[a]
1-Hexene	*n*-Hexane	98
Methylenecyclohexane	Methylcyclohexane	100
trans-3-Hexene	*n*-Hexane	97
Cyclohexene	Cyclohexane	99
Norbornene	Norbornane	73[b]
		>40[b,c]
1-Methylcyclohexane	Methylcyclohexene	100
	*trans*-Decalin	91
	cis-Decalin	3
	*trans*-Hexahydroindan	(73)[d]
	cis-Hexahydroindan	(27)[d]
3-Hexyne	Hexane	79
	trans-3-Hexene	14
Norcarane	1-Methylcyclohexane	Trace[e]

[a] Unless noted otherwise, yields were determined by glpc using internal standard techniques. Products were identified by comparison of mass spectra with those of authentic samples. [b] Isolated yield. [c] No effort was made to maximize this yield (see Experimental Section). [d] Relative yields. [e] >95% norcarane was observed at the end of the reaction. 1-Methylcyclohexane (<1%) was identified by glpc retention time only.

(1) Supported in part by the National Institutes of Health, Grant GM 16020.

(2) National Science Foundation Trainee, 1965–1966; National Institutes of Health Predoctoral Fellow, 1966–1969.

(3) A. J. Birch, *Quart. Rev. (London)*, **4**, 69 (1950); A. J. Birch and H. Smith, *ibid.*, **12**, 17 (1958).

(4) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, Chapter 3.

(5) T. J. King, *J. Chem. Soc.*, 898 (1951).

(6) H. Boer and P. M. Duinker, *Rec. Trav. Chim. Pays-Bas*, **77**, 346 (1958); J. D. Brooks, R. A. Durie, and H. Silberman, *Aust. J. Chem.*, **17**, 55 (1964).

(7) For examples, see (a) R. A. Benkeser, C. Arnold, R. F. Lambert, and O. H. Thomas, *J. Amer. Chem. Soc.*, **77**, 6042 (1955); (b) R. A. Benkeser, R. E. Robinson, D. M. Sauve, and O. H. Thomas, *ibid.*, **77**, 3230 (1955); (c) R. A. Benkeser, *et al.*, *J. Org. Chem.*, **29**, 1313 (1964); (d) R. A. Benkeser, M. L. Burrous, J. J. Hazdra, and E. M. Kaiser, *ibid.*, **28**, 1094 (1963); (e) R. A. Benkeser, J. J. Hazdra, R. F. Lambert, and P. W. Ryan, *ibid.*, **24**, 854 (1959).

(8) G. M. Whitesides and W. J. Ehmann, *J. Amer. Chem. Soc.*, **91**, 3800 (1969).

(9) The initial stimulus to examine sodium–HMPA–*t*-butyl alcohol as a reducing system originated in studies of the reduction of α,β-unsaturated ketones carried out by Dr. Roger Giese and Professor H. O. House in this department.[10] We are indebted to Drs. Giese and House for advice concerning this system.

(10) K. W. Bowers, R. W. Giese, J. Grimshaw, H. O. House, N. H. Kolodny, K. Kronberger, and D. K. Roe, *J. Amer. Chem. Soc.*, **92**, 2783 (1970); H. O. House, R. W. Giese, K. Kronberger, J. P. Kaplan, and J. F. Simeone, *ibid.*, **92**, 2800 (1970).

(11) For reviews of HMPA as a solvent for reductions, see H. Normant, *Angew. Chem., Int. Ed. Engl.*, **6**, 1046 (1967); H. Normant, *Bull. Chim. Soc. Fr.*, 791 (1968); H. Normant, T. Cuvigny, J. Normant, and B. Angelo, *ibid.*, 1561 (1965); and ref 10.

of 3-hexyne to *n*-hexane could have been improved by the use of additional sodium. However, reduction of the cyclopropyl ring of norcarane does not appear to be practical under these reaction conditions.

The ratios of products containing *cis* and *trans* ring junctures obtained on reduction of $\Delta^{9,10}$-octalin and 4,5,6,7-tetrahydroindan indicate that, at least in these cases, the reductions are nonstereospecific. For comparison, the equilibrium ratio of *cis*- to *trans*-decalin at room temperature is 5:95,[12] and the corresponding ratio for hexahydroindan is 39:61.[13] Hence, the product mixtures formed in these two reductions lie close to equilibrium mixtures. It seems unlikely that *cis* and *trans* isomers of decalin or hexahydroindan interconvert under these conditions. Thus, the carbanions or organosodium compounds that are presumed to be intermediates in the reductions react, either by virtue of the stereochemistry of their formation or of their subsequent equilibration, to give directly a nearly thermodynamic product distribution.

These reductions in HMPA offer a potentially attractive method of incorporating deuterium into organic molecules. The reduction of olefins using a deuterated alcohol (*e.g.*, *t*-butyl alcohol-O-*d*) should permit deuteration without the isomerization and scrambling common to catalytic reductions or the expense of deuterated diborane and similar reducing agents. To test the practicality of deuterium incorporation by reduction in HMPA, $\Delta^{9,10}$-octalin and 3,3,6,6-tetramethylcyclohexadiene were allowed to react with sodium–HMPA–*t*-butyl alcohol-O-*d* (93% d_1, 7% d_0). The observed deuterium incorporation into the *trans*-decalin and 1,1,4,4-tetramethylcyclohexane were 1.71 and 1.80 deuterium atoms per olefinic bond, respectively; after correction for the isotopic purity of the *t*-butyl alcohol-O-*d*, these incorporations become 1.84 and 1.94 deuterium atoms per olefinic bond. Although the hydrogen incorporated into these products may indicate that attack of carbanion or radical on HMPA occurs to some extent, it seems more probable that it reflects isotopic fractionation resulting from a kinetic isotope effect in protonation of intermediate carbanions by alcohol.[14] Regardless, reduction by sodium–HMPA–*t*-butyl alcohol-O-*d* holds clear promise as a method of introducing deuterium into certain classes of molecules.

Experimental Section[15]

General Methods.—All reactions were carried out in flame-dried glassware under an inert atmosphere of prepurified nitrogen using standard techniques for handling oxygen- and water-sensitive compounds.[16] Tetrahydrofuran was dried by distillation from lithium aluminum hydride under a nitrogen atmosphere. Hexamethylphosphoramide (Fisher Scientific Company) was purified by stirring with sodium at room temperature until a dark blue color persisted and distilling [65° (0.2 Torr)] through a 10-cm Vigreux column. Reagent grade *t*-butyl alcohol was dried by distillation from calcium hydride. Unless otherwise specified, all reagents were obtained commercially and used without further purification.

Reductions. General Procedure.—Similar procedures were used for all of the small-scale reductions described in Table I. A representative procedure is that for 1-hexene. A mixture of 150 mg (6.5 mg-atoms) of sodium cut into small pieces, 18 ml of HMPA, and 0.1141 g (1.4 mmol) of 1-hexene, containing 0.148 g of cyclohexane as an internal glpc standard, was stirred at room temperature until a blue color appeared. To the blue solution was added a 0.3-ml portion of *t*-butyl alcohol; two additional 0.3-ml portions were added at 1.5 hr intervals. After the blue color vanished, (~6 hr) the solution was poured into 80 ml of water and extracted with 5 ml of decane. The decane was washed with 50 ml of water and dried ($MgSO_4$). Analysis by glpc using a β,β'-oxidipropionitrile on Chromosorb W column showed 0.115 g (98%) of hexane and 0.0052 g (4%) of 1-hexene.

Reduction of norbornene illustrates the procedure used for larger scale reactions. A mixture of 5.8 g (0.25 g-atom) of sodium and 100 ml of HMPA was stirred until a blue color appeared and 20 g (0.27 mol) of *t*-butyl alcohol was added in one portion. After the sodium–HMPA–alcohol solution had been allowed to stir for 5 min at room temperature, a solution of 9.4 g (0.10 mol) of norbornene in 10 ml of HMPA was added slowly over a period of 6 hr at such a rate that the blue color of the HMPA solution never completely disappeared.[17] After completion of the addition, the mixture was stirred for 12 hr, poured into 400 ml of ice water, and extracted with two 20-ml portions of pentane. The organic phase was then distilled through a 10-cm vacuum-jacketed column to yield 7.0 g (73%) of norbornene having bp 105.5–106.5° and mp 86.5–87.5°, and ir spectrum identical with that of an authentic sample. Glpc analysis of the pentane extract, using UC-W98 on Chromosorb W column, showed no trace of unreacted norbornene.

2,2,5,5-Tetramethylcyclohexa-1,3-dione.—A mixture of 60 g (0.43 mol) of 5,5-dimethylcyclohexa-1,3-dione (dimedone), 100 g (0.72 mol) of potassium carbonate, and 500 ml of methanol was heated at reflux temperature until carbon dioxide evolution had ceased (*ca.* 30 min). The mixture was cooled to 0° and 140 g (0.99 mol) of iodomethane was added slowly over 1 hr. The mixture was heated at reflux temperature for 1 hr, cooled, and poured into 1 l. of water. The water was extracted three times with 500-ml portions of ether and the ether solution dried ($MgSO_4$) and concentrated under vacuum. The residue was crystallized from hexane to yield 40 g (55%) of 2,2,5,5-tetramethylcyclohexa-1,3-dione having mp 96–97°, lit.[18] mp 98°.

2,2,5,5-Tetramethylcyclohexa-1,3-diol.—To a slurry of 16 g (0.42 mol) of lithium aluminum hydride in 500 ml of dry tetrahydrofuran was added 33 g (0.2 mol) of 2,2,5,5-tetramethylcyclohexa-1,3-dione in 250 ml of tetrahydrofuran over a period of 1 hr. After the addition was complete, the solution was heated to reflux for 1 hr, cooled, and excess LAH was decomposed by cautious addition of ethyl acetate. The mixture was made acidic with 20% aqueous hydrochloric acid, the layers were separated, and the solvent was removed under vacuum. The residue was dissolved in 1 l. of ether, washed with 500 ml of water, dried ($MgSO_4$), and the ether was removed under vacuum to yield 30 g (90%) of 2,2,5,5-tetramethylcyclohexa-1,3-diol having mp 185–190°; lit.[19] mp for the *trans* isomer 105–107°; for the *cis* isomer 201–206°.

3,3,6,6-Tetramethylcyclohexadiene.—A solution of 25 g (0.15 mol) of 2,2,5,5-tetramethylcyclohexa-1,3-diol and 150 g (0.79 mol) of *p*-toluenesulfonyl chloride in 450 ml of pyridine was refluxed for 20 hr, poured over ice, and extracted with three 100-ml

(12) G. Chiurdoglu and J. L. Jaminet, *Bull Soc. Chim. Belges*, **62**, 448 (1953).

(13) K. R. Blanchard and P. von R. Schleyer, *J. Org. Chem.*, **28**, 247 (1963).

(14) Y. Pocker and J. H. Exner, *J. Amer. Chem. Soc.*, **90**, 6764 (1968).

(15) Melting points were determined using a Thomas–Hoover capillary melting point apparatus and are uncorrected. Boiling points are uncorrected. Nmr spectra were run on a Varian T-60 spectrometer. Infrared spectra were taken in sodium chloride cells using a Perkin-Elmer Model 237B grating spectrophotometer. Mass spectra were determined on a Hitachi Perkin-Elmer RMU-6D mass spectrometer. Product mixtures were analyzed by glpc on an F & M Model 810 flame ionization instrument. Products were identified by collecting samples by glpc using an F & M Model 720 instrument equipped with a thermal conductivity detector, and comparing the mass spectra of the collected samples with the spectra of authentic compounds. Microanalysis was performed by Midwest Microlab, Inc., Indianapolis, Ind.

(16) D. F. Shriver, "The Manipulation of Air-sensitive Compounds," McGraw-Hill, New York, N. Y., 1969.

(17) If the norbornene were added too rapidly to the reducing mixture, the blue color would vanish temporarily, but would return shortly after the addition of norbornene was stopped. If the addition of norbornene were continued after the blue color had vanished, the solution would eventually turn yellow and the blue color would not return, even upon stirring for several days. Sodium did not dissolve appreciably in this yellow solution and the reduction proceeded very slowly, if at all. The same phenomena were noted when the reaction was carried out by the addition of *t*-butyl alcohol to sodium in a solution of norbornene in HMPA.

(18) T. G. Halsall and D. B. Thomas, *J. Chem. Soc.*, 2431 (1956).

(19) F. W. Grant, R. W. Gleason, and L. H. Bushwellen, *J. Org. Chem.*, **30**, 290 (1965).

portions of ether. The ether was washed with 150 ml of 10% aqueous hydrochloric acid, dried ($MgSO_4$), and concentrated by distillation through a 50-cm Vigreux column. The residue was then distilled through a 50-cm Teflon annular spinning-band column to yield 5.0 g (27%) of 3,3,6,6-tetramethylcyclohexadiene. The ir spectrum was in agreement with that of an authentic sample;[20] nmr ($CDCl_3$) δ 5.38 (s, 4, vinyl CH) and 1.01 ppm (s, 12, CH_3).

t-**Butyl Alcohol-O-*d*.**—To 33 g (0.25 mol) of potassium *t*-butoxide under nitrogen was added very carefully 7.0 ml (0.35 mol) of deuterium oxide (Columbia Organic Chemicals, 99.8% *d*). The crude *t*-butyl alcohol-O-*d* was removed by bulb to bulb distillation under vacuum and was then distilled from calcium hydride to yield 15 g (82%) of *t*-butyl alcohol, having isotopic composition[21] 93.0% d_1 and 7.0% d_0.[10,22]

1,1,4,4-Tetramethylcyclohexane-2,3,5,6-*d*$_4$.—A mixture of 1.0 g (44 mg-atom) of sodium and 25 ml of HMPA were stirred at room temperature until a deep blue color appeared. To the solution was then added 0.55 ml (*ca.* 0.5 g, 3.7 mmol) of 3,3,6,6-tetramethylcyclohexadiene and 4 ml of *t*-butyl alcohol-O-*d*. The mixture was stirred overnight and poured into 100 ml of an ice water slush. The aqueous phase was immediately extracted with 25 ml of fluorotrichloromethane and the organic layer was separated, dried ($MgSO_4$), and concentrated by distillation of the solvent through a 20-cm Vigreux column. The 1,1,4,4-tetramethylcyclohexane in the residue was collected using glpc (UC-W98 on Chromosorb W) to yield 0.21 ml of pure product having mass spectral isotopic composition (10 eV) 66.2% d_4, 28.6% d_3, and 5.2% d_2.

Characterization was accomplished by preparation of undeuterated 1,1,4,4-tetramethylcyclohexane using $(CH_3)_3COH$ as the proton source: nmr ($CFCl_3$) δ 1.25 (s, 8, CH_2) and 0.88 ppm (s, 12, CH_3).

Anal. Calcd for $C_{10}H_{20}$: C, 85.63; H, 14.37. Found: C, 85.68; H, 14.37.

Registry No.—Hexamethylphosphoramide, 680-31-9; *t*-butyl alcohol, 75-65-0; sodium, 7440-23-5.

Acknowledgments.—We are indebted to Dr. H. O. House for a sample of $\Delta^{9,10}$-octalin, and Drs. Jon Engstrom and F. D. Greene for a sample of tetrahydroindan.

(20) Sadtler Catalogue, spectrum no 30757.

(21) Benzene-free phenylmagnesium bromide was prepared by the addition of 50 ml of toluene to *ca.* 10 mmol of phenylmagnesium bromide in 5 ml of ether and distillation of the mixture until glpc analysis showed that no ether or benzene remained in the resulting toluene suspension of phenyl Grignard reagent. The isotopic composition of the *t*-butyl alcohol-O-*d* was determined by reaction of the Grignard reagent with *t*-butyl alcohol-O-*d*, isolation of a sample of the resulting benzene by distillation, further purification by collection from glpc, and mass spectral isotopic analysis. Less than 1 equiv of *t*-butyl alcohol-O-*d* per equivalent of phenyl Grignard reagent was used to minimize the influence of any deuterium kinetic isotope effect in the hydrolysis on the accuracy of the analysis.

(22) A superior preparation of *t*-butyl alcohol-O-*d* has been published recently: A. T. Young and R. D. Guthrie, *J. Org. Chem.*, **35**, 852 (1970).

Preferential O$^-$-5 *vs.* O$^-$-6 Cyclization in a Neighboring Group Reaction[1]

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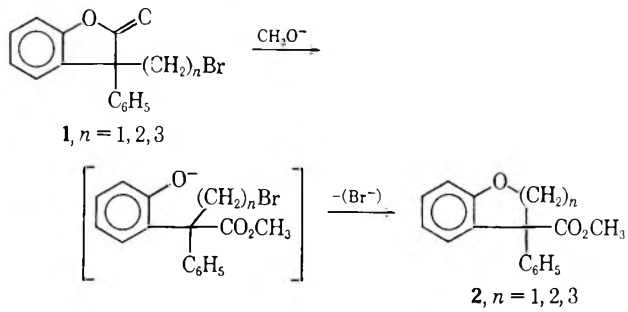
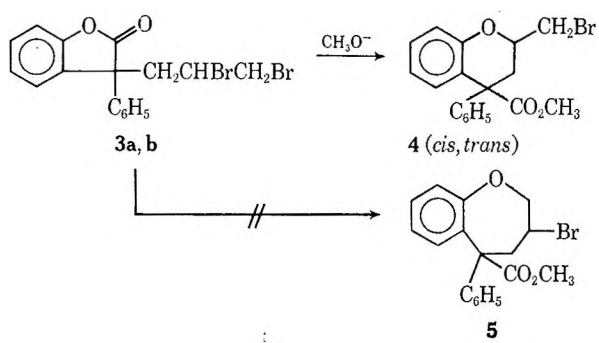
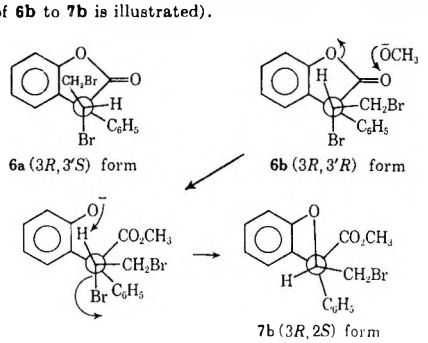
A previous report[2] described the methoxide ion induced rearrangement of the three homologous benzofuranones **1** to the corresponding methyl esters, **2**. The first two members of this series (n = 1, 2) rearrange with extraordinary rapidity (reaction can be conducted under titration conditions), but the third member (n = 3) rearranges more slowly.



It was not surprising, therefore, to find[3] that the dibromide **3** rearranges exclusively by O$^-$-6 cyclization to the chroman derivative **4**. No detectable amounts of the corresponding tetrahydrobenzoxepin **5** (O$^-$-7 cyclization) are found. Furthermore, halide displacement occurs stereospecifically, one diastereomer of **3** giving *cis*-**4** and the other, exclusively, *trans*-**4**.



We now find that O$^-$-5 is favored over O$^-$-6 cyclization in this system, and that displacement again is stereospecific. One diastereomer of the dibromide **6a** (mp 109–110°) affords the *trans* bromo ester **7a**, mp 102–103° (82% yield), and the other, **6b** (mp 117–118°), gives the *cis* ester **7b** as an oil which converts to the lactone **8** on distillation.[4] With benzylamine, **7b** (but not **7a**) gives the lactam **9**. The structures shown for these compounds are compatible with their elemental analyses, infrared spectra and nmr spectra. In addition, the complex ABX spin systems observed for the



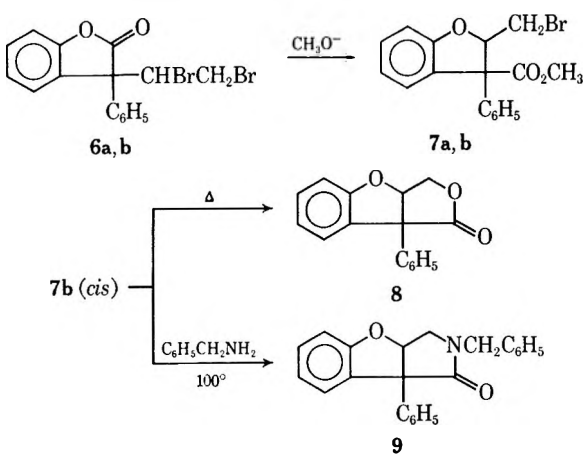
(1) Paper XIV in the series, "Neighboring Group Reactions." For paper XIII, see H. E. Zaugg and R. J. Michaels, *J. Org. Chem.*, **31**, 1332 (1966).

(2) H. E. Zaugg, R. W. DeNet, and R. J. Michaels, *ibid.*, **26**, 4821 (1961).

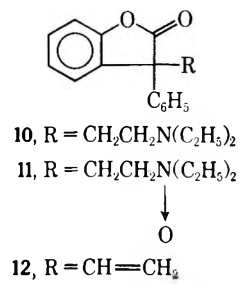
(3) H. E. Zaugg, R. W. DeNet, and E. T. Kimura, *J. Med. Chem.*, **5**, 430 (1962).

(4) Assuming that intramolecular bromide displacement in **6a** and **6b** occurs exclusively with inversion, their relative configurations can be assigned as follows, each structure representing a single mirror image (conversion of **6b** to **7b** is illustrated).

–OCHCH$_2$– group in compounds **7a**, **8**, and **9** have been fitted successfully to theoretical nmr spectra (see the Experimental Section).



The dibromides **6** were prepared by a sequence starting from the diethylaminoethylbenzofuranone **10**.[5] Treatment with hydrogen peroxide led to the amine oxide **11** (90%),[6] which, on dry distillation, afforded the vinylbenzofuranone **12** (35–40%). Bromine added readily to **12** to give a mixture of the dibromides **6a** and **b** which were separated by fractional crystallization.



Experimental Section[7]

Peroxide Oxidation of 3-(β-Diethylaminoethyl)-3-phenyl-2-benzofuranone (10).—To a stirred solution of **10**[5] (freshly distilled) (50 g, 0.162 mol) in ethanol (600 ml) was added 30% hydrogen peroxide (40 ml). After standing at room temperature for 1 week, the product **11** (50 g, 90%) was collected at the filter and dried: mp 177–179° dec; ir (Nujol) no peak at 1790 cm^{-1} (lactone C=O); insoluble in water and all common organic solvents; soluble in DMF and DMSO.

Anal. Calcd for $C_{20}H_{25}NO_4$: C, 69.95; H, 7.34. Found: C, 69.88; H, 7.59.

3-Phenyl-3-vinyl-2-benzofuranone (12).—A 15-g portion of the N-oxide **11** was heated in an oil bath in a round-bottom flask equipped for short-path distillation under reduced pressure (0.5–1.5 mm). When the bath temperature reached 180° distillation began, and continued until 205° was reached and 10.5 g of crude product had been collected: bp 125–175° (0.5–1.5 mm), n^{25}D 1.58. The combined crude product from three such runs was taken up in dry ether (100–150 ml), filtered from insoluble material (2.5 g), washed successively with dilute aqueous HCl and water, and dried (MgSO$_4$). Filtration and removal of the ether by distillation afforded a residual oil (13.5 g) that was distilled under reduced pressure giving the vinyl compound **12** (11.7 g, 38%): bp 130–135° (0.8 mm); n^{25}D 1.5869; ir (CHCl$_3$) 1790 cm^{-1} (lactone C=O); nmr $\left(\begin{matrix}H_A\\R\end{matrix}\!>C=C<\!\begin{matrix}H_B\\H_C\end{matrix}\right)$ δ 6.34 (q, 1, J_{AB} = 10 Hz, J_{AC} = 17 Hz, H$_A$), 5.41 (d, 1, J_{AB} = 10 Hz, J_{BC} < 1 Hz, H$_B$), 5.24 (d, 1, J_{AC} = 17 Hz, J_{BC} < 1 Hz, H$_C$).

Anal. Calcd for $C_{16}H_{12}O_2$: C, 81.33; H, 5.13; O, 13.54. Found: C, 81.40; H, 4.89; O, 13.48.

From the cold trap of the original pyrolytic distillation was isolated N,N-diethylhydroxylamine, bp 120–122° (atm), n^{25}D 1.4173, identified by elemental analysis and conversion to its oxalate, mp 134–136° (lit.[8] mp 136–137°).

3-(1′,2′-Dibromoethyl)-3-phenyl-2-benzofuranones (6a and 6b).—To a stirred solution of the vinylbenzofuranone **12** (15.4 g, 0.0652 mol) in chloroform (200 ml) was added dropwise a solution of bromine (10.5 g, 0.0655 mol) in chloroform (100 ml). The reaction was illuminated by a 40-W light bulb during the addition and for 16 hr thereafter. The chloroform was removed by distillation and the thick amber-colored residue (26 g) was triturated with methanol (50–100 ml). After standing for 2 hr the crystallized product (16.2 g, mp 98–102°) was collected at the filter and dried. Two more recrystallizations from methanol gave **6a** (11.5 g, 45%): mp 109–110°; essentially homogeneous by tlc (hexane–ether–acetone, 90:5:5, R_f 0.46); ir (CHCl$_3$) 1800 cm^{-1} (lactone C=O).

Anal. Calcd for $C_{16}H_{12}Br_2O_2$: C, 48.52; H, 3.05; Br, 40.35; O, 8.08. Found: C, 48.54; H, 3.04; Br, 40.55; O, 8.30.

The filtrate from the original methanol trituration was concentrated to dryness and the residue (9.5 g) was taken up in a minimum quantity of benzene, decolorized with charcoal, and treated with 4–5 volumes of hexane. Refrigeration for several days yielded **6b** (2.8 g, 11%), mp 116–118°. A sample was recrystallized again from a benzene–hexane mixture: mp 117–118° (mmp with **6a**, 85–90°); homogeneous by tlc (hexane–ether–acetone, 90:5:5, R_f 0.35); ir (CHCl$_3$) 1800 cm^{-1} (lactone C=O).

Anal. Calcd for $C_{16}H_{12}Br_2O_2$: C, 48.52; H, 3.05; Br, 40.35; O, 8.08. Found: C, 48.26; H, 2.81; Br, 40.04; O, 8.11.

Methyl *trans*-2-Bromomethyl-2,3-dihydro-3-phenyl-3-benzofurancarboxylate (7a).—To a stirred suspension of **6a** (2.5 g, 0.0063 mol), mp 109–110°, in methanol (60 ml), containing phenolphthalein indicator, was added dropwise a solution of sodium methoxide (from 0.15 g, 0.0065 g-atom of Na) in methanol (30 ml). Initial reaction was rapid as shown by the nearly instantaneous decolorization of the indicator after the addition of each drop. The rate slowed considerably, however, near the end of the addition (1.5 hr). The basic mixture was stirred overnight at room temperature and crystallized product (1.1 g, mp 101–102°) was collected at the filter and dried. The filtrate was concentrated to dryness and the residue was taken up in a mixture of ether and water. On drying and concentrating the ether layer a glassy residue (1 g) was obtained which crystallized (0.7 g, mp 99–100°) on trituration with methanol to give a total yield of 1.8 g (82%). Two recrystallizations from methanol afforded 1.58 g of pure **7a**: mp 102–103°; ir (CHCl$_3$) 1730 cm^{-1} (ester C=O); nmr δ 7.1 (m, 9, ArH), 5.62 (m, 1, J_{AX} = 10.3 Hz, J_{BX} = 3.2 Hz, –OCH$_X$–), 3.82 (s, 3, OCH$_3$), 3.15 (m, 1, J_{AB} = 11 Hz, J_{BX} = 3.2 Hz, BrCH$_B$–), 2.80 (m, 1, J_{AB} = 11 Hz, J_{AX} = 10.3 Hz, BrCH$_A$–).

Anal. Calcd for $C_{17}H_{15}BrO_3$: C, 58.81; H, 4.35; Br, 23.01; O, 13.83. Found: C, 58.77; H, 4.38; Br, 22.75; O, 13.81.

Methyl *cis*-2-Bromomethyl-2,3-dihydro-3-phenyl-3-benzofurancarboxylate (7b) and 3,4-Benzo-2,7-dioxa-5-phenylbicyclo[3.3.0]-octan-6-one (8).—When the foregoing procedure was applied to the dibromide **6b** (3.0 g), mp 117–118°, an oil (2.6 g) was obtained that resisted attempts at crystallization. Its infrared spectrum showed that the lactone carbonyl group (1800 cm^{-1}) in **6b** had been converted entirely to an ester group (1740 cm^{-1}). Other spectral details also resembled those of the isomeric bromo ester **7a**. However, when the oil (**7b**) was distilled under reduced pressure, the distillate [1.7 g, bp 160–162° (0.5–1 mm)] exhibited (ir) the partial conversion to still another carbonyl compound. A second distillation [1.2 g, bp 155–157° (0.5 mm)] effected complete conversion to this material which solidified and was recrystallized twice from ether–hexane to afford 0.75 g (39% yield from **6b**) of the lactone **8**: mp 91–92°; ir (CHCl$_3$) 1775 cm^{-1} (lactone C=O); nmr δ 7.1 (m, 9, ArH), 5.42 (m, 1, J_{AX} = 2.6 Hz, J_{BX} = 5.4 Hz, ArOCH$_X$–), 4.68 (m, 1, J_{AB} = 11.1 Hz,

(5) A. W. Weston and W. B. Brownell, *J. Amer. Chem. Soc.*, **74**, 653 (1952).

(6) The structure assigned to **11** is uncertain. Microanalysis indicates the addition of the elements of one molecule of water to those required for structure **11**. Since lactone carbonyl absorption is not readily detectable in the infrared (Nujol), the true structure may be more accurately represented as the corresponding hydroxy acid.

(7) Melting points and boiling points are uncorrected. Spectra were recorded on a Perkin-Elmer Model 521 infrared spectrophotometer and on a Varian A-60 nmr spectrometer. Chemical shifts (all in CDCl$_3$) are expressed in δ values relative to tetramethylsilane in solution.

(8) W. R. Dunstan and E. Goulding, *J. Chem. Soc.*, **75**, 800 (1899).

J_{BX} = 5.4 Hz, $-CH_BOCO-$), 4.55 (m, 1, J_{AB} = 11.1 Hz, J_{AX} = 2.6 Hz, $-CH_AOCO-$).

Anal. Calcd for $C_{16}H_{12}O_3$: C, 76.17; H, 4.80; O, 19.03. Found: C, 76.33; H, 4.84; O, 19.05.

7-Aza-3,4-benzo-7-benzyl-2-oxa-5-phenylbicyclo[3.3.0]octan-6-one (9).—A sample of the mixed bromo esters **7a** and **7b** (1.8 g of an oil obtained from the mixed dibromides **6**) was treated with benzylamine (10 ml) and heated on the steam bath for 16 hr. Excess amine was removed by distillation (<100°) under reduced pressure. The residue was treated with dry ether and the insoluble benzylamine hydrobromide (0.8 g, mp 220–223°) was removed by filtration. The filtrate was washed with dilute HCl and water and solid product (0.45 g, mp 165–167°) was recovered from the concentrated extract. One recrystallization from ethanol afforded pure lactam **9**: mp 167–168°; ir ($CHCl_3$) 1635 cm^{-1} (lactam C=O); nmr δ 7.1 (m, 14, ArH), 5.16 (m, 1, J_{AX} = 4.6 Hz, J_{BX} = 7.6 Hz, $-OCH_X-$), 4.77 (d, 1, J_{CD} = 14.5 Hz, $C_6H_5CH_CN-$), 4.37 (d, 1, J_{CD} = 14.5 Hz, $C_6H_5CH_DN-$), 3.71 (m, 1, J_{AB} = 12 Hz, J_{BX} = 7.6 Hz, ring-CH_B-N–), 3.52 (m, 1, J_{AB} = 12 Hz, J_{AX} = 4.6 Hz, ring-CH_A-N–).

Anal. Calcd for $C_{23}H_{19}NO_2$: C, 80.91; H, 5.61; N, 4.11; O, 9.37. Found: C, 80.74; H, 5.60; N, 4.29; O, 9.50.

When a sample of the pure *trans*-bromo ester **7a**, mp 102–103°, was submitted to the foregoing procedure, none of the lactam **9** was detectable (ir) in the product. Instead, a liquid amino ester was produced from which a crude solid hydrochloride could be derived. However, this salt resisted all attempts at purification for more precise characterization.

Registry No.—**6a**, 25236-51-5; **6b**, 25236-52-6; **7a**, 25282-55-7; **7b**, 25236-53-7; **8**, 25236-54-8; **9**, 25236-55-9; **12**, 25236-56-0.

Acknowledgments.—We are indebted to Mrs. Evelyn Baker for the tlc tests of purity, to Mrs. Ruth Stanaszek for the nmr spectra, to Dr. Milton Levenberg for calculations of some of the theoretical nmr spectra, to Mr. Victor Rauschel for the microanalyses, and to Mr. Wm. Washburn for the infrared spectra.

Concerning the "Conjugation" of Cyclopropyl with an Adjacent Activated Olefinic Group. An Electrochemical Approach

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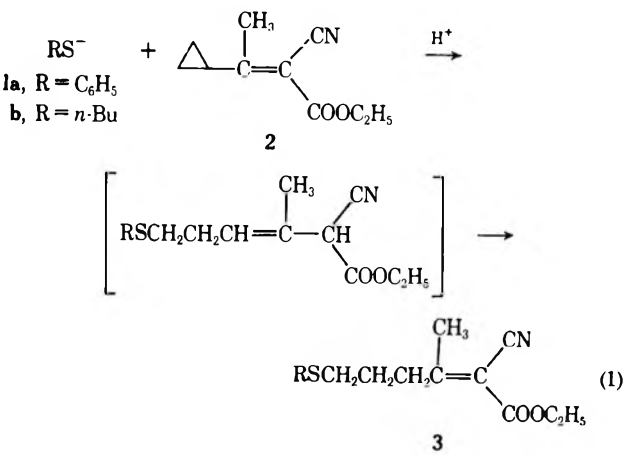
The possibility of conjugation between a cyclopropyl group and a carbon double bond has gained much attention.[1] While the data from uv spectroscopy indicated an affirmative answer for the excited state,[2] the interpretation of the results of hydrogenating such systems catalytically[3] or by sodium in liquid ammonia[4] is ambiguous. The report[1] that mercaptide ion (**1**) reacted with ethyl 2-cyano-3-cyclopropyl-2-butenoate (**2**) to yield a product (**3**) resulting from a formal 1,6 addition was rationalized as resulting from nucleophilic attack upon a conjugated system including the cyclopropyl group. Attempts to use a variety of secondary amines as nucleophiles failed.

(1) J. M. Stewart and D. R. Olsen, *J. Org. Chem.*, **33**, 4534 (1968), and references cited therein.

(2) M. J. Jorgenson and T. Leung, *J. Amer. Chem. Soc.*, **90**, 3769 (1968).

(3) E. F. Ullman, *ibid.*, **81**, 5386 (1959); M. T. Wuesthoff and B. Rickborn, *J. Org. Chem.*, **33**, 1311 (1968).

(4) H. M. Walborsky and J. B. Pierce, *ibid.*, **33**, 4102 (1968).



(1)

Since it is well known that extension of the conjugation of activated olefins[5] leads to a substantial anodic shift in the reduction potential of the olefins[6] and since reductive coupling in such a system is largely through the ω position,[5] it would be interesting to compare the behavior of **2** and its 3-*n*-propyl (**4**) analog,[7] ethyl 2-cyano-3-methyl-2-hexenoate, under electrolytic conditions and to assess by this means the contribution of the cyclopropyl group to conjugation. While **4**, because of steric conditions, would not be expected to undergo reductive coupling at the 3 position, **2** could reductively couple if opening of the cyclopropyl ring made available an unhindered position.

Polarographic studies (Table I) showed that the cyclopropyl group, even when adjacent to an electron-withdrawing group (**6**, **7**) is not electroreducible. The substances $RC(CH_3)=C(CN)COOC_2H_5$ were, as expected, reducible; however, changing R from ethyl (**5**) to *n*-propyl (**4**) to cyclopropyl (**2**) had virtually no effect upon the half-wave potential. This shows that only the activated olefinic group is involved in the reduction.

Compounds **2**, **4**, and **5** showed only one reduction wave in anhydrous DMF or in 10% aqueous DMF.[8] That this was a one-electron wave was demonstrated unequivocally for **4** which is capable at most of undergoing a two-electron reduction under these conditions: addition of phenol, a more effective proton donor than water, to the polarographic solution virtually doubled the wave height. The same result was then also observed with **2**. The ability of the first reduction species, an anion radical, to escape protonation by water in many cases is not a new phenomenon (*cf.* ref 10). The failure to obtain a second reduction wave for **2** and **4** as well as the complete irreversibility of the reduction of even **4** in DMF (exhibited in cyclic voltammetry at the fastest practical sweep rates, 20 V/sec) remain unexplained.[11] They indicate an extremely rapid follow-

(5) M. M. Baizer and J. D. Anderson, *J. Electrochem. Soc.*, **111**, 226 (1964).

(6) Compare, *e.g.*, the half-wave potentials (V. *vs.* saturated calomel electrode) of the following pairs: acrylonitrile, −1.9, 1-cyano-1,3-butadiene, −1.5; ethyl acrylate, −1.8, ethyl sorbate, ~−1.5; benzalfluorene, −1.67, cinnamylidenefluorene, −1.46.

(7) The uv maximum of **2** ($\lambda_{max}^{CH_3CN}$ 257 mμ, log ε 3.99) showed an auxochromic shift with respect to **3** ($\lambda_{max}^{CH_3CN}$ mμ, log ε 3.87) of +25 Δλ; this is similar to the results with other cyclopropyl olefinic esters.[2]

(8) A similar one-wave reduction was obtained for ethyl 2-cyanosorbate.[9]

(9) J. P. Petrovich, M. M. Baizer, and M. R. Ort, *J. Electrochem. Soc.*, **116**, 743 (1969).

(10) J. Simonet and M. Morenas, *C. R. Acad. Sci., Ser. C*, **269**, 42 (1969).

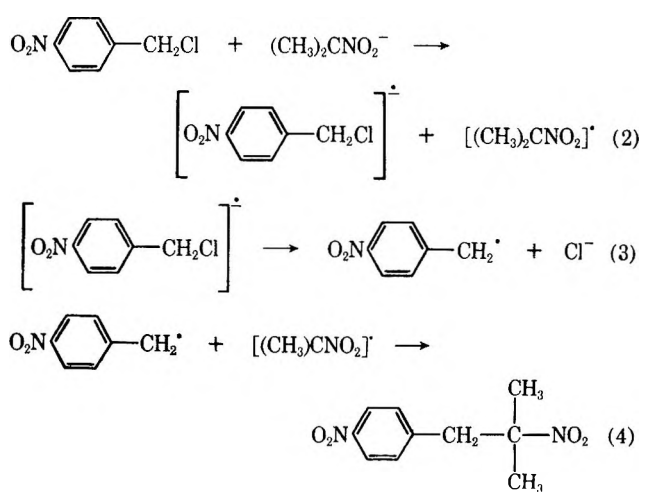
(11) Under these conditions diethyl fumarate showed completely reversible anion radical formation.

up reaction of the anion radicals, perhaps fragmentation or reaction with solvent or disproportionation; the elucidation of these phenomena is not critical to the argument presented below.

Macroelectrolysis of **4** (Table II) under conditions which have successfully yielded reductively coupled products from a variety of activated olefins[12] yielded the saturated derivative, ethyl 2-cyano-3-methyl hexanoate (**8**) but no hydro dimer. About 25% of **4** was simultaneously cleaved hydrolytically to methyl *n*-propyl ketone (**9**) and cyanoacetic ester (**10**) in a reversal of the method of synthesis. Macroelectrolysis of **2** (Table III) with partial conversion yielded **9**, **8**, **4**, and the products of hydrolytic cleavage **6** and **10**; there was no hydrodimer. Since **6** is not electroreducible, **9** must have arisen by reduction of **2** followed by hydrolysis. The formation of **4** as the major product is interesting. Heterogeneous catalytic hydrogenation with Raney nickel[13] and homogeneous catalysis using Wilkinson's catalyst[14] have been used successfully to reduce selectively the double bond of vinylcyclopropanes. The electrochemical method appears to offer a means of cleaving and reducing the cyclopropyl group and leaving the double bond intact.

The absence of an anodic shift in the polarographic reduction of **2** compared to **4** and the failure of **2** to yield any hydrodimer on electroreduction suggest that the reported reaction (eq 1) of mercaptide with **2**, which we have verified, may not be the result of a nucleophilic reaction but rather a conjugate electron-transfer–radical combination reaction. It is becoming increasingly recognized that this type of sequence obtains in many cases which formally appear to be nucleophilic reactions.[15]

In a reaction (eq 2–4) elucidated by Kerber, *et al.*,[16]



there is an electron-transfer step (eq 2), an intervening chemical reaction (eq 3) and finally a radical combination (eq 4). The 2-nitropropane radical gave a partially resolved esr spectrum but no dimer presumably because it and the *p*-nitrobenzyl radical are present in the same solvent cage and interact according to eq 4.

If the process of eq 1 proceeds by a similar route, the electron-transfer step would yield mercaptide radical and the anion radical of **2**. Cyclic voltammetry indicated that the latter was extremely unstable; macroelectrolyses showed that it does not dimerize. Obtaining a resolved spectrum for this anion radical was therefore, hopeless, but an esr signal (*vide infra*) for mercaptide radical was observed in the course of the reaction.

In the case of the anion radical of **2**, the intervening chemical reaction corresponding to eq 3 above is ring opening and protonation yielding $\cdot CH_2CH_2CH_2C(CH_3)=C(CN)COOC_2H_5$. Combination of this radical with mercaptide radical completes the sequence. No disulfide was found indicating that here too, the final reaction may have occurred in a solvent cage.

Further support for the above proposal was sought by examining the reaction of phenyl mercaptide with **4**. It was anticipated that since addition of mercaptide (anion or radical) to the 3 position of **4** was sterically disfavored, if phenyl mercaptide radical were formed as a result of an electron transfer to **4**, it would have ample opportunity to dimerize. This was indeed the case: when **4** was treated with benzenethiol and a small quantity of sodium ethoxide in refluxing ethanol for 6 hr with careful exclusion of air there was a fifteenfold increase in the quantity of diphenyl disulfide obtained from a blank run without **4**; vpc analysis indicated formation of a miniscule amount of a second product definitely not **8**. The electron-transfer step may be reversible (*cf.* ref 16): extension of the reaction period to 16 hr yielded only 4.8 times the amount of diphenyl disulfide formed in a blank run under identical conditions.

Experimental Section

Materials.—Methyl cyclopropyl ketone **6** (Aldrich Chemical Co., Inc.) was used as received. Ethyl 2-cyano-3-cyclopropyl-2-butenoate **2**,[1] the analogous 3-ethyl **5** and 3-*n*-propyl derivatives **4**,[17] and ethyl 2-cyano-3-*n*-propylbutanoate **8** were prepared according to the literature.

In our hands, the preparation of **2** always yielded more of the solid isomer (methyl/cyano *cis*[1]) than reported. Only the solid isomer was used in this work. Cyclopropyl cyanide **7** was prepared from 4-bromo- rather than 4-chlorobutyronitrile by essentially a literature procedure.[18] Attempts to reduce only the double bond of **2** by palladium–charcoal in ethanol, Raney nickel,[13] or diimide[19] failed. The DMF used in polarographic solutions was purified as described;[9] when used in macroelectrolyses the final purification through a molecular sieve was omitted. Tetra-*n*-butylammonium iodide (polarographic grade, Southwestern Analytical Chemicals) was used as received. Tetra-*n*-heptylammonium iodide (Eastman Organic Chemicals) was recrystallized from ethyl acetate. Tetraethylammonium *p*-toluenesulforate (Aldrich Chemical Co., Inc.) was recrystallized from acetone.

Equipment.—The polarograph was a Sargent Model XXI. The dropping mercury electrode constants were $m = 1.08$ mg/sec, $t = 6.2$ sec, $m^{2/3}t^{1/6} = 1.455$. Standard polarographic H cells were used throughout. The polarograms were recorded against a saturated calomel electrode as the reference using 0.1 *M* supporting electrolyte in dimethylformamide as solvent. Cell resistances were around 1000 ohms and no correction was made for *ir* drop in the cell. The cells used for macroelectrolyses

(12) M. M. Baizer, J. D. Anderson, J. H. Wagenknecht, M. R. Ort, and J. P. Petrovich, *Electrochim. Acta*, **12**, 1377 (1967).

(13) M. T. Wuesthoff and B. Rickborn, *J. Org. Chem.*, **33**, 1311 (1968).

(14) C. H. Heathcock and S. R. Poulter, *Tetrahedron Lett.*, 2755 (1969).

(15) K. A. Bilevich and O. Yu. Okhlobystin, *Russ. Chem. Rev.*, **37**, 954 (1968); K. A. Bilevich, N. N. Pubnov, and O. Yu. Okhlobystin, *Tetrahedron Lett.*, 3465 (1968).

(16) R. C. Kerber, G. W. Urry, and N. Kornblum, *J. Amer. Chem. Soc.*, **87**, 4520 (1965). See also F. J. Smentowski, *ibid.*, **85**, 3036 (1963).

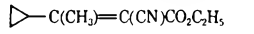
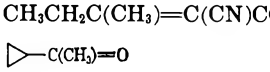
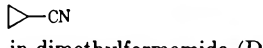
(17) A. C. Cope, C. M. Hofmann, C. Wyckoff, and E. Hardenbergh, *ibid.*, **63**, 3452 (1941).

(18) G. M. Lampman, D. A. Horne, and G. D. Hager, *J. Chem. Eng. Data*, **14**, 396 (1969).

(19) J. W. Hamersma and E. I. Snyder, *J. Org. Chem.*, **30**, 3985 (1965).

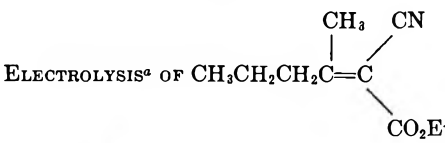
TABLE I

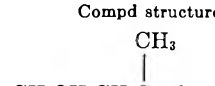
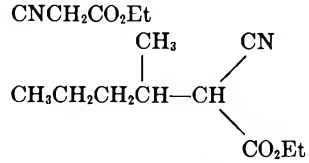
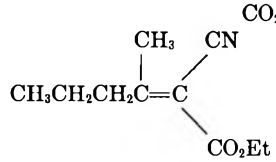
POLAROGRAPHIC DATA

Compd No.	Structure	Anhydrous DMF $-E_{1/2}$[a]	Anhydrous DMF Id[b]	DMF with proton donor $-E_{1/2}$	DMF with proton donor Id[b]
2		1.72	1.35[c]	1.68[d]	1.07
				1.71[e]	2.73
4	$CH_3CH_2CH_2C(CH_3)=C(CN)CO_2C_2H_5$	1.75	1.32	1.70[d]	1.07
				1.75[e]	2.45
5	$CH_3CH_2C(CH_3)=C(CN)CO_2C_2H_5$	1.74	1.36	1.70[d]	1.08
6		No wave			No wave[d]
7		No wave			No wave[d]

[a] $E_{1/2}$ (V) *vs.* sce in dimethylformamide (DMF) with 0.1 *M* tetraheptylammonium iodide. [b] Id = height wave (mm) × sensitivity (μa/mm)/concentration (mmol/l. × $m^{2/3}t^{1/6}$) (see Experimental Section); concentration of depolarizer ~1.5 × 10^{-3} *M*. [c] Substance produced "maximums". [d] With 10% H_2O. [e] With phenol in 0.1 *M* tetrabutylammonium iodide.

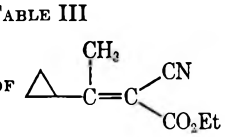
TABLE II

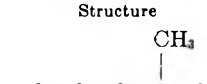
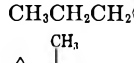
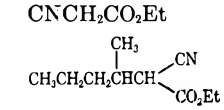
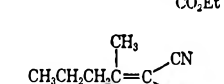
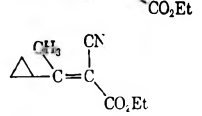
ELECTROLYSIS[a] OF 

Catholyte: Depolarizer, mol	Salt, g	DMF, ml	H_2O, ml	HOAc, ml	Products recovered: Compd no.	Compd structure	mmol	A hr equiv
0.100	10.0	50	5	1.0	9		26	
					10	$CNCH_2CO_2Et$	23	
					8		21	1.12
					4		33.4	

[a] Conditions: mercury cathode, 23°, 0.5 A for 150 min.

TABLE III

ELECTROLYSIS[a] OF 

Catholyte: Depolarizer, mol	Salt, g	DMF, ml	H_2O, ml	HOAc, ml	Products recovered: Compd No.	Compd Structure	mmol	A hr equiv
0.100	10.0	50	5	1.0	9		4.2	0.225
					6		9.7	
					10	$CNCH_2CO_2Et$	13.9	
					8		1.39	0.149
					4		6.80	0.365
					2		61.5	

[a] Conditions: mercury cathode, 23°, 0.8 A for 225 min.

with mercury cathodes were the one previously described[20] and also a scaled-down version cathode area 38.4 cm², catholyte volume ~75 ml. The vpc analyses were performed on a Varian Series 1200, Hi-Fi III gas chromatograph (single column, single flame ionization detector). The two columns used were both 6-ft, 1/8 in. diameter stainless steel packed respectively with 10% Carbowax 20M on 80–100 mesh Chromosorb W (NAW) and 3% SE-30 on 100–200 mesh Varaport 30.

The esr spectra were obtained using a Varian V-4502 spectrometer equipped with a 12 in. magnet. The modulation frequency was 100 kHz. The Varian rapid scan cavity was used in conjunction with the Varian rapid scan unit and the C-1024 time averaging computer. The microwave frequency under experimental conditions was measured with a Hewlett–Packard X350A wavemeter and was 9.544 GHz. The sweeps were calibrated using a basic aqueous solution of potassium peroxylamine disulfonate (g = 2.0055, a = 13 G) and were found to be satisfactorily linear.

Procedures.—The macroelectrolyses were carried out under the conditions summarized in Tables II and III. The mercury was then separated from the catholyte and the latter diluted with water and thoroughly extracted with methylene chloride. The extracts were washed and dried over anhydrous magnesium sulfate. The analyses were performed as follows. The excess methylene chloride was carefully removed from the products using a rotary evaporator and a vacuum pump (10 mm), keeping the water bath at room temperature. When most of the CH_2Cl_2 had been removed, the temperature of the water bath was increased to 50° and the vacuum increased to 5 mm. The low boiling products were collected in two Dry Ice–acetone traps in series.

The above distillate typically contained the ketones and methylene chloride. These products were analyzed neat at 70° using 10% Carbowax 20M.

The residue from the above stripping, which contained the bulk of the products, was analyzed (20% in acetone) using 10% Carbowax 20M, programmed from 120 to 220° at 10° min^{-1}. Relative retention times and relative response factors were calculated using diethyl malonate as an internal standard. Components were qualitatively determined by subsequent injection of authentic samples prepared independently.

For determining the esr spectra, separate solutions of 1.65 g of **1** (with R = C_6H_5) in 5 ml of ethanol (with 0.025 g of sodium) and of 2.25 g of **2** in 20 ml of ethanol were mixed under exclusion of oxygen. The sample tubes were sealed under nitrogen and heated for a few minutes at 50–70° before they were transferred to the esr cavity at room temperature. A well-resolved five-line spectrum was detected under the proper modulation conditions (optimum conditions about 0.75 peak to peak modulation). The spectra were very weak and required many hours of data accumulation. Typically, accumulation of 900 scans over 8 hr gave a signal to noise ratio of about 12. The intensity ratios of the peaks varied with the modulation amplitude, pointing to the fact that the peaks were of different widths and shapes and contained unresolved features; at 0.75 G peak to peak modulation the ratio was 1:1.6:2.6:1. Because of the weakness of the signals it was not possible to resolve additional structure by lowering the modulation amplitude. The same five-line spectrum (although much weaker) was also obtained when **2** was excluded, but oxygen was allowed to come into contact with the solution. This observation, together with the explanations that follow, lead us to attribute the spectrum to the phenylmercaptyl radical. The g factor was found to be 2.030. This value is close to the isotropic g value of 2.040 attributed by Zandstra and Michaelsen[21] to phenylmercaptyl radical produced during the pyrolysis of diphenyldisulfide. This assignment has been criticized by Schmidt[22] who found a much smaller g factor (isotropic g = 2.007) for the supposed phenylmercaptyl radical produced by uv irradiation of diphenyl disulfide. It should be noticed that in both references the radicals were observed in a frozen matrix, and that therefore no hyperfine structure was detected that could support the assignments. On the other hand, the hyperfine structure of phenoxyl radical has been resolved by Stone and Waters[23] who reported the following hyperfine constants: $a_{2,6}$ = 6.65 G, a_4 = 10.1 G, $a_{3,5}$ = 1.8 G. Our spectrum can be interpreted in terms of hyperfine constants $a_{2,6}$ = 2.7 G, a_4 = 5.4 G, $a_{3,5}$ = 1.0 G. The splitting with the 3,5 hydrogens was too small to be resolved, but from the observed linewidth an upper limit of about 1 G was estimated for $a_{3,5}$. Compared to the phenoxy radical, the much smaller hyperfine constants observed in our case are consistent with the fact that in mercaptyl radicals the spin density is concentrated on the sulfur atom most of the time.[21]

(20) M. M. Baizer, *J. Electrochem. Soc.*, **111**, 215 (1964).
(21) P. J. Zandstra and J. D. Michaelsen, *J. Chem. Phys.*, **39**, 933 (1963).
(22) U. Schmidt, *Organosulfur Chem.*, 75 (1967).
(23) T. J. Stone and W. A. Waters, *J. Chem. Soc.*, 213 (1964).

Registry No.—**2**, 17407-28-2; **4**, 25528-05-6; **5**, 25528-06-7.

The Cyclization of Epoxy Olefins. VIII. Attempted π Routes to Bridged Bicyclic Systems[1]

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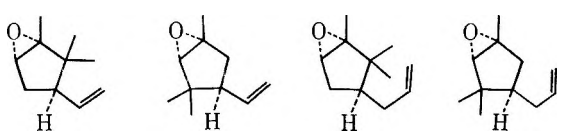
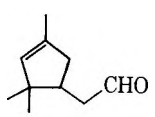
Received January 20, 1970

In a previous report[3] on work in the area of epoxide cyclizations we described attempts to form the bornane skeleton by closure of **1**. These experiments led only to noncyclic rearrangement products. As suggested previously,[3,4] the transition state for cyclization of compounds like **1** appears to allow for little overlap between the orbitals of the double bond and the ring carbon atom. In addition, one of the rearrangement reactions of **1** has as a strong driving force the relief of the crowding of groups on three adjacent positions of a cyclopentane ring. In order to investigate these factors we chose to examine the reactivities of three related epoxy olefins **2**, **3**, and **4**.



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

In structure **2** the propensity of the α-campholene system for rearrangement[5] has been eliminated since this compound no longer features 1, 2, 3 ring substitution. In addition, opening of the epoxide ring of **2** in either a cyclization or a ketone forming reaction should occur at the tertiary center which in this case is insulated from the *gem*-dimethyl group. With **3** the steric difficulties encountered with **1** in bringing an olefinic carbon and a ring carbon within bonding distance should be diminished. Compound **4** in turn embodies both structural variations discussed for **2** and **3**.

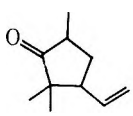


5

(1) This work was supported in part by the National Institutes of Health, Grant No. GM 11728. (b) The previous paper in this series is D. J. Goldsmith and C. F. Phillips, *J. Amer. Chem. Soc.*, **91**, 5862 (1969).
(2) Coca Cola Research Fellow, 1963–1965.
(3) D. J. Goldsmith and C. J. Cheer, *J. Org. Chem.*, **30**, 2264 (1965).
(4) L. J. Dolby and R. H. Iwamoto, *ibid.*, **30**, 2420 (1965).
(5) (a) F. Tieman, *Chem. Ber.*, **29**, 3006 (1896); (b) E. R. Buchman and H. Sargent, *J. Org. Chem.*, **7**, 140 (1942).

Compounds 2 and 4 were prepared from iso-α-campholenealdehyde[6] (5); the former by the method previously described[1] for 1, and the latter by addition of methylene triphenylphosphorane to the aldehyde and subsequent epoxidation of the more highly substituted double bond. Epoxy olefin 3 was prepared from α-campholenealdehyde by the same Wittig reaction, epoxidation sequence. The stereochemistry of these compounds follows from the previously described[1,7] results for epoxidation of cyclopentenyl systems.

When 2 was subjected to cyclizing conditions[8] with anhydrous stannic chloride in benzene a single product, ketone 6, was obtained. Thus no cyclization had occurred with 2 as well as with 1 and rearrangement of the



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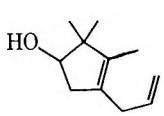

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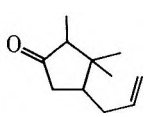
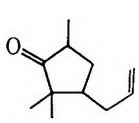


8

appended groups on adjacent positions of the cyclopentane ring could not be solely responsible for the indisposition of the 4-vinylcyclopentene oxide system to form bicyclic products.

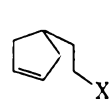
A molecular model of the second epoxy olefin 3 indicates that little or no angle strain is required to make the potential bonding orbitals of the olefinic carbon and the epoxide carbon assume a parallel relationship. Despite this consideration, however, when 3 was treated with stannic chloride in benzene solution no cyclization product was obtained. The products of the reaction were analogous in structure to those obtained from 1.[3] Thus preparative glpc of the crude reaction mixture yielded 54% (relative yield) of alcohol 7 which displayed in its nmr spectrum multiplets at 4.78, 4.97, and 5.50 ppm corresponding to three vinyl hydrogens plus a signal at 1.52 ppm for a vinyl methyl group. The second product obtained in 42% relative yield was a ketone. Both the nmr spectrum and the infrared spectrum indicated that the terminal vinyl group was present in this product also and by analogy with the ketonic product from 1[3] the structure 8 was assigned.

The final epoxy olefin in this series, 4, also yielded no bicyclic products from treatment of the epoxide with acid. The only product from the reaction of 4 with stannic chloride in benzene was the ketone 9.



9

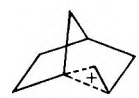
The "π route" to bicyclic systems has been the subject of considerable investigation.[9] Most of the reported cases, however, are of the cyclopentenyl ethyl type; that is the cationic center is exocyclic to the ring and the cyclization reaction proceeds through a bicycloheptyl cation as in i to ii.



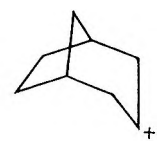
i

ii

The system exemplified by epoxy olefins 5 and 6 in which the participating π bond is exocyclic was expected to cyclize *via* a cation which can be represented in a general way by either the bridged structure iv or the classical structure v.



iii



iv

The fact that no cyclization of either 5 or 6 occurs suggests that either these ions lack the stability associated with bridged ions of the type exemplified by ii or that steric factors continue to play a larger role in these reactions than assumed. In support of this it is interesting to note that rearrangement of 2-*exo*-norbornylcarbinyl amine by nitrous acid deamination affords only 18% of 18 while the corresponding *endo* derivative yields none of this type of product.[10,11] This rearrangement when it does occur must proceed *via* an ion related to iv or v. The failure of the *endo* case to yield 18 was ascribed by Benson and Willner[11] to the necessity for a "boat conformation in the rearrangement of this isomer. They also noted, however, that the predominant rearrangement pathway of the *exo* compound also involves boatlike conformations. Thus, factors other than this simple conformational one must be important in production of bridged cations like iv.[11]

Experimental Section[12]

1,3,3-Trimethyl-4(2′-hydroxyethyl)cyclopentene.—Reduction of iso-α-campholenealdehyde, 5[6] (45.0 g, 0.29 mol), with sodium borohydride (30.0 g, 0.78 mol) in 600 ml of ethanol by standard methods afforded 42.5 g (93%) of the alcohol: bp 63.5–64.5° (0.56 mm); n^{23}D 1.4689; ir (neat) 3300, 1750, 1058, and 828 Cm^{-1}; nmr (CCl_4) δ 0.80 (s, 3), 1.00 (s, 3) 1.52 (s, 3), 3.52 (t, 2, J = 6 Hz), 4.38 (s, 1), 5.03 (m, 1).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 1176. Found: C, 77.61; H, 11.70.

1,3,3-Trimethyl-4-(2′-acetoxyethyl)cyclopentene.—The alcohol from above (39 g, 0.25 mol) was converted to the corresponding acetate with acetic anhydride (200 ml) and sodium acetate (20.0 g, 0.25 mol) employing standard methods: bp 63° (0.3 mm); n^{23}D 1.4540; ir (neat) 1730, 1650, 1238, 1043, and 829 cm^{-1}.

Anal. Calcd for $C_{12}H_{20}O_2$: C, 73.42; H, 10.27. Found: C, 73.53; H, 10.43.

1,3,3-Trimethyl-4-vinylcyclopentene.—The preceeding acetate was pyrolyzed as described previously[3] using a modified Johnson pyrolysis column.[13] In a typical run 20 g of acetate was pyrolyzed under the following conditions: oil bath, 180–185°; pyrolysis column, 465–475°; fractionating column, 70–80° (155–160 mm). The yield after redistillation of the product was 10.0 g of diene: bp 91.5–94.5° (163 mm); n^{22}D 1.4513; ir (neat) 3060, 1640, 1650, 1370, 1000, 914, and 828 cm^{-1}; nmr (CCl_4) δ 0.78 (s, 3), 0.98 (s, 3), 1.63 (s, 3), 2.23 (m, 3), 5.0 (m, 2), 5.75 (m, 2).

Anal. Calcd for $C_{10}H_{16}$: C, 88.16; H, 11.84. Found: C, 88.42; H, 11.76.

(6) M. P. Hartshorn and A. F. A. Wallis, *Chem. Ind. (London)*, 1878 (1963).
(7) H. B. Henbest, *Proc. Chem. Soc.*, 159 (1963).
(8) D. J. Goldsmith, *J. Amer. Chem. Soc.*, **84**, 3913 (1962).
(9) G. D. Sargent, *Quart. Rev. (London)*, **20**, 301 (1966).
(10) K. Alder and R. Reubke, *Chem. Ber.*, **91**, 1525 (1959).
(11) J. A. Berson and D. Willner, *J. Amer. Chem. Soc.*, **86**, 609 (1964).
(12) Boiling points are uncorrected. Nmr spectra were obtained at 60 MHz, with tetramethylsilane as an internal reference.
(13) K. S. Williamson, R. T. Keller, G. S. Fonken, J. Szmuszkovicz, and W. S. Johnson, *J. Org. Chem.*, **27**, 1612 (1969).

1,3,3-Trimethyl-4-vinylcyclopentene 1,2-Oxide (2).—To a cold stirred solution of 4 g (0.029 mol) of the diene from above there was added in a dropwise manner 55.2 ml of a solution of monoperphthalic acid in ether (0.029 mol). After an additional 3 hr of reaction at room temperature the mixture was worked up in the usual way[3] to yield 3.2 g of oxide 2 which eluted as a single substance on Carbowax 20M and Apiezon L glpc columns: $n^{22}D$ 1.4502; ir (neat) 3050, 1635, 998, 910, and 838 cm^{-1}; nmr (CCl_4) δ 0.72 (s, 3), 0.99 (s, 3), 1.35 (s, 3), 1.80 (m, 3), 2.71 (s, 1), 4.73 (m, 1), 4.97 (m, 1), 5.41 (m, 1).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.60. Found: C, 79.12; H, 10.55.

Reaction of Epoxide 2 with Stannic Chloride.—Stannic chloride (0.20 ml) was added to a solution of 2 (1.0 g, 0.0065 mol) in 25 ml of benzene and the mixture stirred for 10 hr at room temperature. The reddish reaction mixture was then poured into ice water, shaken vigorously, and extracted with ether. Removal of the solvent after drying over sodium sulfate afforded 0.8 g of material which showed only a single glpc peak on Apiezon L and Carbowax 20M columns. Purification by preparative glpc yielded 6: $n^{24}D$ 1.4522; ir (CCl_4) 3050, 1730, 1683, and 920 cm^{-1}; nmr (CCl_4) δ 0.83 (s, 3), 0.98 (s, 3), 1.12 (d, 3, J = 7 Hz), 2.22 (m, 4), 4.88 (m, 1), 5.11 (m, 1), 5.58 (m, 1).

Anal. Calcd for $C_{10}H_{16}O$: C, 78.89; H, 10.60. Found: C, 78.93; H, 10.56.

2,3,3-Trimethyl-4-allylcyclopentene.—α-Campholenealdehyde (10.0 g, 0.065 mol) in 50 ml of ether was added rapidly to 225 ml of a solution of methylene triphenylphosphorane (prepared from 16.6 g, 0.049 mol of triphenylmethyl phosphonium bromide and 35 ml, approx 0.05 mol, of n-butyllithium) maintained at 0–5°. After 10 min 150 ml of water was added to the creamy suspension. Removal of the solvent after extraction of the aqueous layer with ether and drying afforded 8.6 g of crude product. Distillation through an 18-in. spinning-band column yielded 3.6 g (36%) of pure diene: bp 68–71 (21 mm); $n^{23}D$ 1.4581; ir (neat) 3050, 3000, 1640, 1355, 911, and 800 cm^{-1}; nmr (CCl_4) δ 0.77 (s, 3), 0.97 (s, 3), 1.57 (m, 3), 4.88 (m, 1), 5.00 (m, 1), 5.12 (m, 2), 5.52 (m, 1).

Anal. Calcd for $C_{11}H_{18}$: C, 87.92; H, 12.07. Found: C, 87.99; H, 12.16.

2,2,2-Trimethyl-4-allylcyclopentene 1,2-Oxide (3).—The epoxidation of the allylcyclopentene from above was carried out as described for 2 to yield 3 (97%): $n^{23}D$ 1.4556; ir (neat) 3050, 1635, 1358, 910, and 846 cm^{-1}; nmr (CCl_4) δ 0.72 (s, 3), 0.95 (s, 3), 1.22 (s, 3), 3.02 (m, 1), 4.73 (m, 1), 4.96 (m, 1), 5.42 (m, 1).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.73; H, 11.01.

Reaction of 3 with Stannic Chloride.—Treatment of 3 (1.0 g) with stannic chloride in benzene in the manner described above for 2 afforded 0.95 g of dark oil. Analytical glpc on Apiezon L at 160° showed two major components and one minor one with retention times of 8.5, 11.0, and 9.5 min, and in the proportions 54%, 42%, and 4% respectively. The minor component could not be isolated.

Preparative glpc on Apiezon L afforded the 54% component, 2,3,3-trimethyl-4-allylcyclopentanone, 8, as an oil: $n^{22}D$ 1.4651; ir (CCl_4) 3080, 1740, 1638, and 920 cm^{-1}; nmr (CCl_4) δ 0.70 (s, 3), 0.95 (s, 3), 0.96 (d, 3), 4.87 (m, 1), 5.10 (m, 1) 5.65 (m, 1).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.29; H, 10.85.

Isolation of the 42% component by preparative glpc afforded 2,3,3-trimethyl-1-allylcyclopenten-4-ol, 7: $n^{22}D$ 1.4816; ir (CCl_4) 3600, 3050, 1630, 1057, 992, and 915 cm^{-1}; nmr (CCl_4) δ 0.90 (s, 3), 0.96 (s, 3), 1.52 (m, 3), 3.72 (m, 1), 4.78 (m, 1), 4.97 (m, 1), 5.50 (m, 1).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.63; H, 10.69.

1,3,3-Trimethyl-4-allylcyclopentene.—Application of the previously described procedure for addition of methylene triphenylphosphorane to campholenealdehyde to 5 afforded the title compound: bp 60–61° (17 mm); $n^{24}D$ 1.4521; ir (neat) 3050, 1635, 1645, 995, 911, and 825 cm^{-1}; nmr (CCl_4), 0.80 (s, 3), 1.0 (s, 3), 1.62 (m, 3), 4.78 (m, 1), 5.02 (m, 1), 5.45 (m, 1).

Anal. Calcd for $C_{11}H_{18}$: C, 87.92; H, 12.07. Found: C, 87.94; H, 12.11.

1,3,3-Trimethyl-4-allylcyclopentene 1,2-Oxide (4).—Epoxidation of the diene from above by the previously described procedure[3] afforded 4, purified by preparative glpc: $n^{23}D$ 1.4500; ir (neat) 3030, 1635, 1359, 996, 913, and 840 cm^{-1}; nmr (CCl_4) δ 0.72 (s, 3), 0.98 (s, 3), 1.30 (s, 3), 4.72 (m, 1), 4.97 (m, 1), 5.42 (m, 1).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.43; H, 11.01.

Reaction of 6 with Stannic Chloride.—Treatment of 4 (0.5 g) with stannic chloride in benzene by the previously described procedure afforded 0.45 g of 9. The material was purified by preparative glpc on Apiezon L at 160°: $n^{22}D$ 1.4536; ir (CCl_4) 3050, 1725, 1635, 1242, 920, and 865 cm^{-1}; nmr (CCl_4) δ 0.80 (s, 3), 0.96 (s, 3), 1.06 (d, 3, J = 7 Hz), 4.87 (m, 1), 5.10 (m, 1), 5.60 (m, 1).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.91. Found: C, 79.35; H, 10.68.

Registry No.—1,3,3-Trimethyl-4-(2′-hydroxyethyl)-cyclopentene, 4605-50-9; 1,3,3-trimethyl-4-(2′-acetoxyethyl)cyclopentene, 25527-89-3; 1,3,3-trimethyl-4-vinylcyclopentene, 25527-90-6; **2**, 25515-35-9; **3**, 25515-36-0; **4**, 25515-37-1; 1,3,3-trimethyl-4-allylcyclopentene, 25527-91-7; **6**, 25527-92-8; 2,3,3-trimethyl-4-allylcyclopentene, 25527-93-9; **7**, 25527-94-0; **8**, 25527-95-1; **9**, 25527-96-2.

Reduction of Cyclic Anhydrides with $NaBH_4$. Versatile Lactone Synthesis

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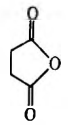
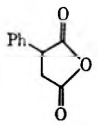
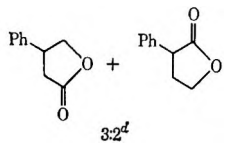
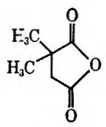
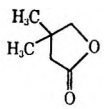
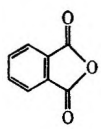
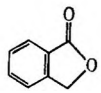
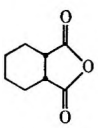
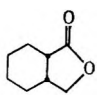
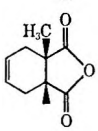
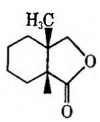
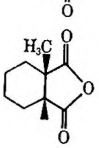
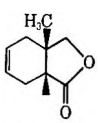
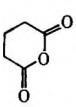
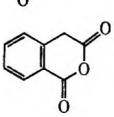
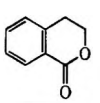
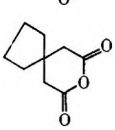
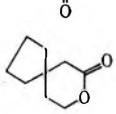
Received March 13, 1970

Over 20 years ago Chaikin and Brown[1] reported that, with $NaBH_4$, acid anhydrides show only slight reduction on prolonged heating. Since then, only two isolated examples of the $NaBH_4$ reduction of cyclic anhydrides have appeared in the literature.[2,3] More recently, the $NaBH_4$ reduction of mixed carboxylic-carbonic anhydrides[4] and thiophthalic anhydride[5] have been recorded. We have examined the reduction of a number of cyclic anhydrides with this reagent and have found that δ and γ lactones can be isolated in good to excellent yields (51–97%). This procedure is more convenient and more versatile than the previoulsy reported methods using $LiAlH_4$[6] or $LiAlH(O\text{-}t\text{-}Bu)_3$.[6a] The steric course of the $NaBH_4$ reduction of 5-membered unsymmetrical cyclic anhydrides is identical with that observed with $LiAlH_4$[6a] or Na–EtOH.[7] In most instances hydride attack takes place principally at the carbonyl group adjacent to the more highly substituted carbon atom. Thus, the reduction of *cis*-1-methylcyclohexane-1,2-dicarboxylic acid anhydride (I) to

(1) S. W. Chaikin and W. G. Brown, *J. Amer. Chem. Soc.*, **71**, 122 (1949).
(2) B. E. Cross, R. H. B. Galt, and J. R. Hanson, *J. Chem. Soc.*, 5052 (1963).
(3) W. R. Vaughan, C. T. Goetschel, M. H. Goodrow, and C. L. Warren, *J. Amer. Chem. Soc.*, **85**, 2282 (1963).
(4) Y. G. Perron, L. B. Crast, J. M. Essery, R. R. Fraser, J. C. Godfrey, C. T. Holdrege, W. F. Minor, M. E. Neubert, R. A. Partyka, and L. C. Cheney, *J. Med. Chem.*, **7**, 483 (1964).
(5) R. H. Schlessinger and I. S. Ponticello, *Chem. Commun.*, 1013 (1969).
(6) (a) J. J. Bloomfield and S. L. Lee, *J. Org. Chem.*, **32**, 3919 (1967). (b) B. E. Cross and J. C. Stewart, *Tetrahedron Lett.*, 3589 (1968).
(7) R. P. Linstead and A. F. Millidge, *J. Chem. Soc.*, 478 (1936).

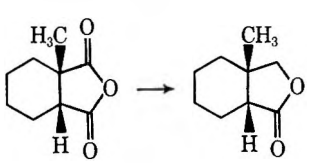
TABLE I

LACTONES PRODUCED FROM THE $NaBH_4$ REDUCTION OF CYCLIC ANHYDRIDES

Starting anhydride	Registry no.	Product[a]	Method[b]	% yield	Mp or bp (mm), °C	Lit. mp or bp (mm), °C
	108-30-5		B-2	51	184–194 (760)	202–203 (760)[c]
	1131-15-3	 3:2[d]	A-1	67	171–173 (13)	113–122 (0.1)[e]
	17347-61-4		A-2	74	79–82 (13)	207–208 (760)[c]
	85-44-9		B-1	97	71–73	72–73[f]
	13149-00-3		A-1	76	123–125 (13)	72–77 (0.5)[e]
	25357-31-7		A-1	65	127–131 (13)	68–72 (0.1)[e]
	14679-27-7		A-1	80	120–123 (13)	51–61 (0.07)[e]
	108-55-4		A-2	67	110–113 (13)	102–104 (7)[g]
	703-59-3		A-2	55	177–178 (13)	176 (20)[h]
	5662-95-3		A-2	68	138–147 (13)	*i*

[a] Ir and nmr spectra were consistent with the structures assigned. [b] See Experimental Section. [c] A. Windaus and F. Klanhart, *Ber.*, **54** [B], 58 (1921). [d] The 3:2 ratio of lactones was identical with that found by Bloomfield and Lee[6] in their $LiAlH_4$ reduction experiments. [e] Reference 6. [f] J. H. Gardner and C. A. Naylor Jr., *Org. Syn.*, **16**, 71 (1936). [g] S. F. Friess, *J. Amer. Chem. Soc.*, **71**, 2571 (1949). [h] J. Colonge and P. Boisde, *C. R. Acad. Sci.*, **239**, 1047 (1954). [i] No mp recorded: N. A. Klitgaard, *Dan. Tidsskr. Farm.*, **42**, 84 (1968); *Chem. Abstr.*, **71**, 3021j (1969).

lactone II was accomplished with either $NaBH_4$, $LiAlH_4$,[6a] $NaBH(OMe)_3$, or Na–EtOH.[7]



I II

In only one case was exclusive reduction at the carbonyl adjacent to the less sterically crowded carbon atom of a 5-membered cyclic anhydride observed. This exception was the report by Vaughan, *et al.*,[3] that camphoric anhydride was reduced to α-campholide by $NaBH_4$. We repeated this work, and nmr analysis of the reduction product confirmed the structure assignment. The results of our $NaBH_4$ reduction experiments are compiled in Table I. Yields are of distilled product.

Experimental Section

General Procedures for the $NaBH_4$ Reduction of Cyclic Anhydrides to Lactones.—Unless otherwise stated in Table I, all lactones were shown to be one pure isomer by glpc using a Hewlett-Packard research chromatograph, Model 5751B, equipped with glass columns packed with 3% OV 17 on 100–120 mesh Gas-Chrom Q.

A mixture of 2.0 g (0.05 mol) of $NaBH_4$ in 10 ml of THF (method A-1) or DMF (method B-1) was stirred and cooled in an ice bath while 0.05 mol of anhydride in 40 ml of THF (DMF) was added in 5 min. The ice bath was removed and stirring was continued for 1 hr. (Method A-1 and B-1) 6 *N* HCl (20 ml) was added cautiously and the mixture was concentrated. Water (100 ml) was added and the mixture was extracted with 50 ml of Et_2O. The Et_2O extract was dried (Na_2SO_4), concentrated, and distilled giving the desired lactone. (Method A-2 and B-2) Ethanolic 10 *N* HCl (10 ml) was added and the resulting mixture was heated on a steam bath 1 hr, filtered, concentrated, and distilled giving the desired lactone.

Reduction of *cis*-1-Methylcyclohexane-1,2-dicarboxylic Acid Anhydride with $NaBH(OMe)_3$.—Method A-1 was used; only the 0.05 mol of $NaBH_4$ was replaced by 0.10 mol of $NaBH(OMe)_3$. The yield was 78% of *cis*-2-methyl-2-hydroxymethylcyclohexane carboxylic acid γ-lactone (II).

Reduction of *cis*-1-Methylcyclohexane-1,2-dicarboxylic Acid Anhydride with Na and EtOH.—The procedure reported by Linstead and Millidge[7] was used. The yield of II was 35%.

Registry No.—NaBH4, 16940-66-2.

Decabromo-3,3′-dihydrofulvalene

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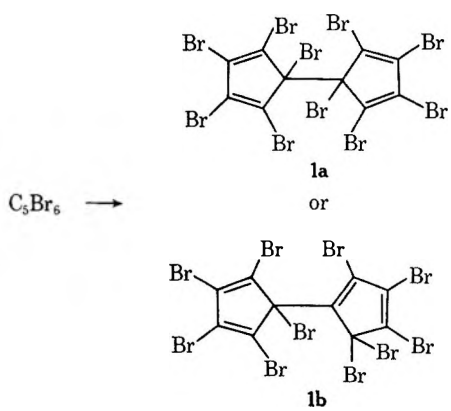
Hydrocarbons and Monomers Research Laboratory, The Dow Chemical Company, Midland, Michigan 48640

Received December 29, 1969

West and Kwitowski[2] recently reported the isolation of $C_{10}Br_{10}$ (1), mp 139–140°, from the reactions of hexabromocyclopentadiene (C_5Br_6) with copper(I) bromide or various metals. Possible structures for this dihydrodecabromofulvalene were noted as **1a** or **1b**.



1a

1b

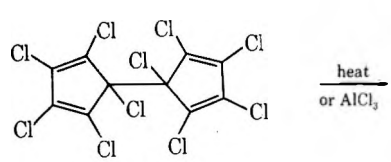
In a more recent report Smith and West[3] describe the isomerization of the chlorine compound $C_{10}Cl_{10}$, mp 121° (2), to three new isomers which were assigned the structures **3**, **4**, and **5** by nqr analysis.

Work in our laboratories on the chemistry of hexabromocyclopentadiene has led us to the isolation of $C_{10}Br_{10}$, mp 140.5–142°, from two reaction sequences and prompts us to report its occurrence and to assign it a structure.

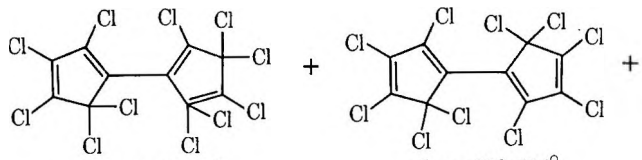
(1) To whom inquiries should be addressed.

(2) R. West and P. T. Kwitowski, *J. Amer. Chem. Soc.*, **90**, 4697 (1968).

(3) R. M. Smith and R. West, *J. Org. Chem.*, **35**, 2681 (1970); see also V. Mark and E. O'Neil, *ibid.*, in press. We thank Dr. West for a prepublication copy of his manuscript. *Cf.* R. M. Smith and R. West, Abstracts, 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 1969, ORGN 60.

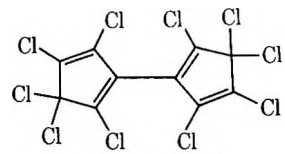


2, mp 121°



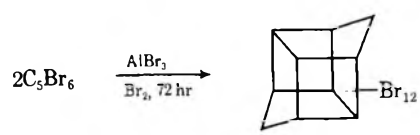
4, mp 81–82°

5, mp 113–114°



3, mp 110–111°

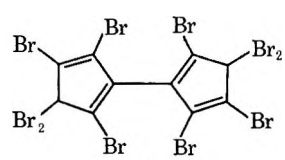
The reaction of C_5Br_6 with metallic copper in 95% ethanol at 45° results in a mixture of $C_{10}Br_{10}$ and C_5Br_6 separable on a silica column to give an 85% yield of $C_{10}Br_{10}$ (**1**), mp 140.5–142°. In a preparation of $C_{10}Br_{12}$ (**6**), mp 340–350° dec, from C_5Br_6[4] the reaction



6

was stopped at the end of 45 hr. The "recovered" C_5Br_6 possessed a melting point range of 111–115° and was separable into C_5Br_6 and pure $C_{10}Br_{10}$ (**1**). This eutectic "recovered C_5Br_6" appears to be the same as West's 1:1 complex of C_5Br_6 and $C_{10}Br_{10}$, mp 108–109°.[2]

Compound **1** has three bands in the carbon–carbon double bond region in the infrared (1626, 1579, 1550 cm^{-1}). Examination of the ir spectra of the various $C_{10}Cl_{10}$ isomers[5] reveals that only one of these, **3**, shows this three peak pattern. Not only are the carbon–carbon double bond regions for **1** and **3** virtually identical, there is a gross similarity of the entire infrared spectra for these compounds which is not noted with the other $C_{10}Cl_{10}$ isomers. This suggests that the skeletal structures and double bond locations for **1** and **3** are the same; *i.e.*, structure **7** is proposed as the structure of



7

$C_{10}Br_{10}$, mp 140.5–142°. This structure also appears chemically to be the most logical choice, since, of all the possible dicyclopentadienyl structures, this stands out as being the least sterically crowded molecule and, therefore, most certainly the most thermodynamically stable. This point gains credence by the fact that all

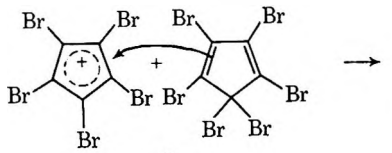
(4) C. W. Roberts and M. B. Chenoweth, U. S. Patent 3,212,973 (Oct 19, 1965).

(5) E. D. Weil, U. S. Patent 3,219,710 (Nov 23, 1965).

syntheses of **1** have been under conditions where one might expect to obtain the most stable isomer.

Compound **1** reacts in bromine in the presence of aluminum tribromide to give $C_{10}Br_{12}$ (**6**), mp 340–350° dec, identical with the compound prepared directly from C_5Br_6.

The formation of **1** and its reaction to form **6** may be explained as follows. In the presence of aluminum bromide the pentabromocyclopentadienyl cation (**8**) is undoubtedly formed. Attack on this by a molecule of C_5Br_6 followed by elimination of bromonium ion (assisted by $AlBr_4^-$ to give Br_2) leads either to **9** or a symmetrical structure, **10**, depending on which bromine is



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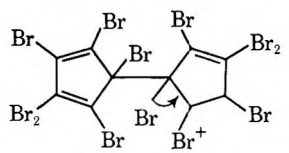

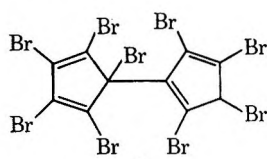

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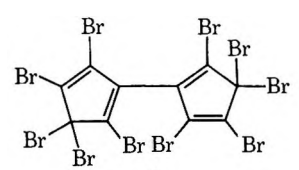
lost. In the presence of aluminum bromide, **9** or **10** may isomerize to the most thermodynamically stable isomer, **7**. The bromines on **7** are free to move from position to position in the presence of aluminum bromide, *i.e.*, all of the possible dicyclopentadienyl structures are in a state of dynamic equilibrium under these conditions. While this equilibrium apparently strongly



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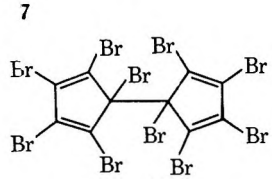

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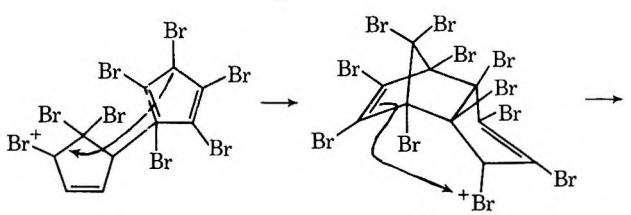

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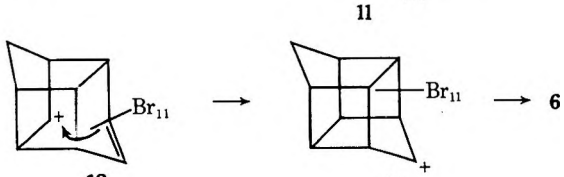
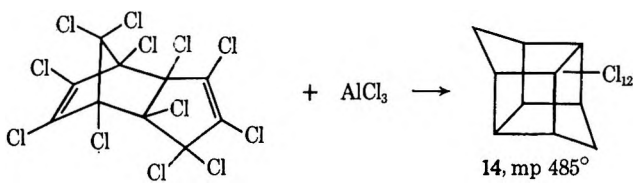


12 **13**

favors structure **7**, it is not necessary that a given isomer be present in high concentration for it to be seriously considered as the only one involved in a particular reaction. Thus isomer **10**, though probably present only in very low concentration is used in the proposed mechanism for the formation of **6** because it is the only isomer for which straightforward pathways can easily be envisioned to give **6**.[6] Structure **11** is attractive as an intermediate in the overall reaction both because of the simplicity of the mechanism when it is employed and because of its apparent precedent in the reaction shown below.[7]



14, mp 485°

Experimental Section

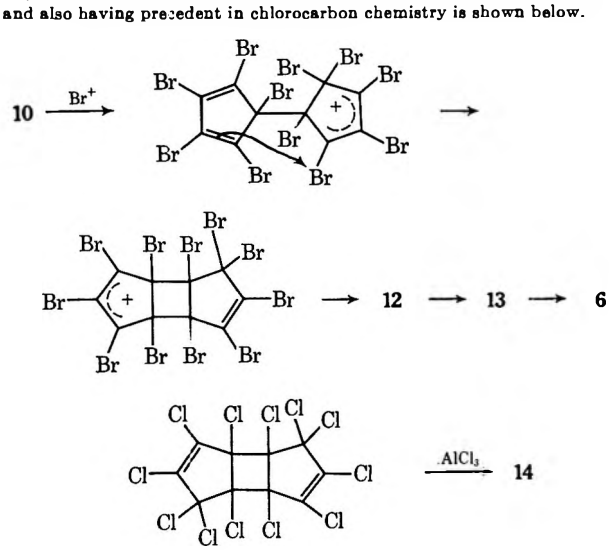
Infrared spectra were obtained with a Beckman IR-9 spectrometer. The mass spectra were obtained on a CEC-21-110B (direct probe) instrument. The isotope peaks observed match the relative abundances calculated for the naturally occurring isotopes.

Hexabromocyclopentadiene was prepared both by Straus'[8] method and by a modification of West's procedure,[2] the latter being preferred. Recrystallization from *n*-hexane or methanol yielded yellow crystalline product, mp 86.5–88°, with an infrared spectrum identical with a known pure standard.

Preparation of $C_{10}Br_{10}$ (7) from Hexabromocyclopentadiene.— A mixture of 43.2 g (0.08 mol) of C_5Br_6, 100 ml of absolute ethanol, 50 ml of benzene, and 5 ml of H_2O was placed in a 500 ml erlenmeyer flask equipped with a magnetic stirring bar, thermometer, and nitrogen purge. The stirred mixture was heated to 45° when it became homogenous. To the solution was added 5.08 g of copper (0.08 g-atom) in the form of copper–bronze (pigment grade) during 5 min; 10 min after addition was complete the copper powder appeared to have reacted. The mixture was stirred at 40–45° for 16 hr and the solvent evaporated under reduced pressure at a bath temperature no higher than 45°. The total residue (48 g) was treated with three 200-ml portions of methylene chloride and the combined solutions extracted with two 100-ml portions of 0.1 *N* sulfuric acid and three 200-ml portions of H_2O. The organic layer was dried over anhydrous $MgSO_4$ and the solvent evaporated to give 42 g of crude product.

(6) E. T. McBee, J. D. Idol, and C. W. Roberts, *J. Amer. Chem. Soc.*, **77**, 4375 (1955).

(7) A second attractive mechanistic possibility, pointed out by a referee, and also having precedent in chlorocarbon chemistry is shown below.



(8) F. Straus, L. Kollek, and W. Heyn, *Ber.*, **63B**, 1868 (1930).

Thin layer chromatography (silica–heptane) indicated a mixture of C_5Br_6 and $C_{10}Br_{10}$. The 42 g was dissolved in 400 ml of *n*-heptane (400 ml) and run through a silica (Davison 922 grade, 200–325 mesh) gel column. The first fraction gave 5.0 g of recovered C_5Br_6, while the main fraction gave 27.4 g of $C_{10}Br_{10}$, mp 140.5–142°, an 85% yield based on recovered C_5Br_6: ir (Nujol) 1626, 1579, 1550, 1287, 1183, 1148, 1099, 1000, and 692 cm^{-1}; uv λ_{max}^{hexane} 333 nm (log ϵ 3.28); mass spectrum showed a molecular ion peak at *m/e* 910 (calcd for $C_{10}Br_{10}$, *m/e* 910). The mass spectrum itself is intersting in that it shows only ions resulting from the consecutive loss of bromine all the way from $C_{10}Br_{10}^+$ to C_{10}^+; each of these ions also had a doubly charged partner, which in most cases was the more intense.

Anal. Calcd for $C_{10}Br_{10}$: C, 13.07; Br, 86.93. Found: C, 13.20; Br, 86.80.

Isolation of $C_{10}Br_{10}$ (7) from the Preparation of Dodecabromopentacyclo[5.3.0.0^{2,6}.0^{3,9}.0^{4,8}]decane (6).—Hexabromocyclopentadiene (473 g, 0.875 mol) was placed in a 3-l., three-necked, round-bottomed flask equipped with a nitrogen inlet, a reflux condenser connected successively to a calcium chloride drying tube and a water scrubber, and a stirrer. Bromine (800 ml) was added and to the resulting solution was added 105 g of aluminum bromide. After refluxing for 45 hr water was added dropwise to destroy the aluminum bromide and the bromine was removed by steam distillation. The dark brown viscous oil remaining after removal of the bromine was treated with hot hexane leaving a dark brown solid. Recrystallization of the solid from THF–hexane gave about 120 g of pure $C_{10}Br_{12}$, mp 340–350° dec. The hexane washings proved to be a mixture of C_5Br_6, another similar compound (later identified as $C_{10}Br_{10}$, **7**) and an intractable tar. This last component was effectively removed by running the entire solution through a column of silica gel. After three recrystallizations of a sample of this material from 95:5 hexane–benzene a material was obtained having the physical appearance of C_5Br_6 but melting at 111–115°.[2] Mass spectrographic analysis of this material showed that it was a mixture of C_5Br_6 and a second component that was identified as $C_{10}Br_{10}$. The $C_{10}Br_{10}$ was obtained in pure form by removal of the C_5Br_6 by sublimation at 105° and 0.1 mm for 15 hr followed by recrystallization of the residue from 1:1 benzene–hexane. The material thus obtained was homogeneous to mass spectroscopy ($C_{10}Br_{10}$), was shown by ir to be free of C_5Br_6 and melted at 140–142°. Infrared and uv spectra were identical with those of **7** above.

Preparation of 6 from 7.—Compound **7** (5 g) was dissolved in bromine (20 ml) and 3 g of aluminum bromide was added. The mixture was stirred under reflux for 72 hr, cooled, water slowly added, and the bromine removed by steam distillation. Filtration of the residue gave a red solid that was added to 50 ml of benzene; after stirring for about 10 min the white solid (5.1 g) was collected by filtration. The solid thus obtained was shown by infrared analysis to be $C_{10}Br_{12}$ (**6**), yield 87%, mp 340–350° dec.

Registry No.—**7**, 25568-68-7.

Acknowledgment.—The authors are grateful to R. Nyquist for determining infrared spectra, L. Shadoff for the mass spectral data, and L. Swim for elemental analyses.

Novel "Meisenheimer" Complexes. Alkyl-2,4,6-trinitrocyclohexadienate Anions

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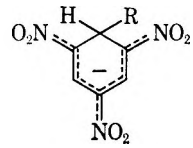
Received March 30, 1970

1,3,5-Trinitrobenzene (TNB) reacts with a variety of anionic bases to yield brightly colored solutions of species known as "Meisenheimer" compounds (σ complexes), **1**, where R = –OH, $-OCH_3$, $-CH_2COCH_3$, $-CH_2NO_2$, –CN).[2–5] Such structures have been postulated as intermediates in nucleophilic aromatic substitution reactions, and, in a few instances, stable adducts have been isolated.[2–5] We report here the preparation, isolation, and initial investigation of salts of new complexes of this type in which *alkyl* groups are coordinated to the ring (**1**, R = CH_3 or *n*-C_4H_9).



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Alkyl-2,4,6-trinitrocyclohexadienate anions (**1**, R = CH_3 or *n*-C_4H_9) are readily prepared by adding TNB to solutions of the appropriate tetraalkylboron salts (see Experimental Section below). The visible spectra of these compounds are typical of TNB anion complexes (Table I).[3] The positions and intensities of the bands are very similar in a variety of polar and nonpolar solvents.

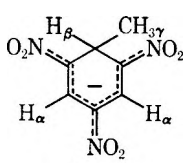
Table I

Absorption Maxima for Acetonitrile Solutions of Complexes of Structure 1

R	Cation	λ_1, mμ	ϵ_1,[a] l. mol^{-1} cm^{-1}	λ_2, mμ	ϵ_2,[a] l. mol^{-1} cm^{-1}
CH_3	$As^+(Ph)_4$	470	31,600	572	14,900
n-C_4H_9	$N^+(Me)_4$	474	31,800	568	14,800
n-C_4H_9	$As^+(Ph)_4$	474	31,500	568	14,700

[a] Spectra obtained immediately after mixing; estimated errors <5% (see Experimental Section).

Nmr Spectra. A. Tetraphenylarsonium Methyl-2,4,6-trinitrocyclohexadienate (2).—The nmr spectrum



$As^+(Ph)_4$ **2**

of an acetonitrile-d_3 solution of the compound obtained from the reaction of tetraphenylarsonium tetramethylboride and TNB is consistent with structure **2** (see Table II).[6] The resonance frequencies and splitting

Table II

Nmr Chemicals Shifts ($-\delta$) and Coupling Constants (cps) for Compounds 2[a] and 3[a]

Compd	H_α	H_β	H_γ	$J_{H_\alpha-H_\beta}$	$J_{H_\beta-H_\gamma}$	Cation protons
2	8.24	4.64	1.14	0.75 ± 0.05	6.2 ± 0.1	7.75[b]
3	8.39	4.84	...[c]	0.75 ± 0.05	4.2 ± 0.1	3.08[b]

[a] Salts are ~0.1 *M* in acetonitrile-d_3. A small impurity peak which was shown to be water was detected at 2.1 ppm. [b] Multiplet. [c] Butyl protons appear as a broad multiplet extending from ~0.8 to 1.9 ppm.

(1) National Science Foundation Predoctoral Fellow, 1969–1970.

(2) M. R. Crampton, *Advan. Phys. Org. Chem.*, **7**, 211 (1969).

(3) E. Buncel, A. R. Norris, and K. E. Russell, *Quart. Rev. Chem. Soc.*, **22**, 123 (1968).

(4) R. Foster and C. A. Fyfe, *Rev. Pure Appl. Chem.*, **16**, 61 (1966).

(5) C. A. Fyfe, *Can. J. Chem.*, **46**, 3047 (1968).

(6) Integrated intensities of the resonance absorptions agree with the proposed peak assignments.

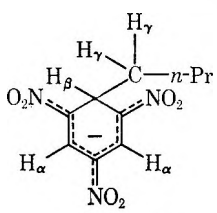
TABLE III
ANALYTICAL DATA[a]

Compd		Found, % C	Found, % H	Found, % N	Calcd, % C	Calcd, % H	Calcd, % N	Mp, °C
$N^+(Me)_4$	(TNB-butyl)$^-$	48.46	6.87	15.99	48.83	7.02	16.27	206.5–207.5
$As^+(Ph)_4$	(TNB-butyl)$^-$	61.98	4.87	6.16	62.48	4.94	6.34	120–122
$As^+(Ph)_4$	(TNB-methyl)$^-$	61.24	4.42	6.95	60.89	4.29	6.87	166–167

[a] Analyses were performed by Baron Consulting Co., Orange, Conn. 06477.

pattern observed for the ring protons are typical for "Meisenheimer" complexes.[2-4] The fact that the γ-methyl protons are shifted slightly downfield from the methyl resonance frequency of methylcyclohexane is probably due to the anisotropy of the nearby NO_2 groups. The observed coupling constants and chemical shifts do not change significantly in other solvents. Addition of TNB to an acetonitrile-d_3 solution of **2** does not affect the nmr spectrum of the complex, indicating exchange of methyl anion between the complex and TNB must occur slowly (if at all!) at 40°.[7]

B. Tetramethylammonium Butyl-2,4,6-trinitrocyclohexadienate (3).—The nmr spectrum of this compound shows absorptions which can be assigned to the protons in **3** (see Table II).[6] The proton resonances of



$N^+(Me)_4$ **3**

the anion do not change significantly when tetraphenylarsonium is substituted for tetramethylammonium.

Ir Spectra.—The most significant features of the infrared spectrum of the (TNB-butyl)$^-$ complex in deuteriochloroform are the presence of two very strong bands at 1219 and 1159 cm^{-1} and the complete absence of bands at 1550 and 1345 cm^{-1}, the characteristic stretching frequencies of the NO_2 group in TNB.[8] In analogy with Norris' investigation of the TNB–cyanide complex, we assign the intense bands at 1219 and 1159 cm^{-1} to the antisymmetric and symmetric NO_2 stretching frequencies of the complex.[8] This assignment is consistent with Norris' suggestion that the effect of delocalization of negative charge is to decrease the NO bond order, thus shifting the NO_2 stretching frequencies to lower energy.

Support for this point of view is provided by the following experiment: on acidification (HCl gas) of a deuteriochloroform solution of the (TNB-butyl)$^-$ complex the purple color fades to yellow; new intense bands at 1545 and 1350 cm^{-1} appear in the infrared spectrum of the acidified solution; and in addition, the previously observed NO_2 stretches are now completely absent. The nmr spectrum of the acidified solution indicates 2,4,6-trinitrobutylbenzene is a decomposition product. Similar color changes are obtained if the (TNB-methyl)$^-$ complex is studied.

Experimental Section

Nmr spectra were recorded at 60 and 100 MHz on Varian spectrometers. Chemical shifts relative to internal tetramethylsilane were determined by the usual side-band techniques. Visible spectra were recorded using matched 1-cm quartz cells in a Cary 14 spectrometer, and infrared spectra were measured in 0.1-mm path length sodium chloride cells in a Beckman IR-12 spectrometer.

Preparation of Compounds.—The preparation of **3** is illustrative of the general synthetic procedure; a solution of TNB (0.60 g, 2.8 mmol) in 10 ml of acetone was added dropwise with stirring to a solution of tetramethylammonium tetrabutylboride[9] (0.34 g, 1.1 mmol) in 10 ml of acetone under nitrogen. After addition was completed the resulting purple solution was stirred for 0.5 hr. Excess ether (~100 ml) was added to the reaction mixture, which was subsequently stored at 0° for 4 hr. The precipitated purple solid (0.29 g, 70%) was filtered, washed with ether, and recrystallized from an ethanol–ether mixture.

The preparation of the (TNB-methyl)$^-$ complex was similar, except in order to achieve good yields it became necessary to stir the solutions for a much longer period (~12 hr) prior to the addition of ether.[10]

The salts appear to be relatively stable in air but were stored under nitrogen as a precautionary measure. The color of dilute solutions of the complexes fades in about 1 hr when they are exposed to light. Spectroscopic measurements were made on freshly prepared solutions and reproducibility was excellent. Analytical data are recorded in Table III.

Registry No.—**1**, R = n-C_4H_9, cation = $As^+(Ph)_4$, 25448-31-1; **2**, 25448-32-2; **3**, 25448-33-3.

Acknowledgments.—The author gratefully acknowledges the interest and support of Professor I. D. Kuntz throughout the course of this study. Thanks are also due to Professor P. von R. Schleyer and Mr. M. Hendrick who read and commented on the manuscript of this paper.

(7) This result is quite general for "Meisenheimer" complexes.[2,3]
(8) A. R. Norris and H. F. Shurvell, *Can. J. Chem.*, **47**, 4267 (1969).
(9) R. Damico, *J. Org. Chem.*, **29**, 1971 (1964).
(10) Trialkylboron compounds, which burn spontaneously in air, appear to be side products of these reactions. It is advisable to carry out these syntheses in a well-ventilated hood.

Mechanistic Aspects of the Wallach Transformation of Azoxybenzenes

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Received March 5, 1970

In strong sulfuric acid solutions, azoxybenzenes are converted to *p*-hydroxyazobenzenes in a process known as the Wallach transformation.[2] The exact dependence of the reaction rate on the acidity of the medium is unknown and appears to differ measurably for differently substituted azoxybenzenes,[3] but it is evident that more than one proton is transferred to the azoxybenzene

(1) Deceased.
(2) E. Buncel in "Mechanisms of Molecular Migrations," Vol. 1, B. S. Thyagarajan, Ed., Interscience, New York, N. Y., 1968.
(3) D. Duffey and E. C. Hendley, *J. Org. Chem.*, **33**, 1918 (1968).

prior to or during a rate-limiting step most probably involving N–O bond scission.

Mechanisms proposed for the Wallach reaction differ mainly in whether nucleophilic attack at a *para* position occurs before or after the rate-limiting step. If bisulfate ion or another suitable nucleophile attacks before the N–O bond cleaves, then evidence is needed for an equal probability of attack at the nonequivalent *para* positions to explain the nearly equal appearance of hydroxyl at either position in the product.[4,5]

Miller and Parker[6] have reported Hammett σ parameters of 0.769 and 0.595 for the displacement of chloride by hydroxide at the 4 and 4′ positions[7] where both substrates were activated toward nucleophilic attack by a nitro group *ortho* to the chlorine. With *p*-bromoazoxybenzenes the relative ease of nucleophilic displacement of bromide from the 4 and 4′ positions is found to depend on the reaction conditions, and, under some conditions, the two positions are equally susceptible to attack.

In Table I it is seen that both 4- and 4′-bromoazoxybenzene are considerably less reactive in butanol than in ethanol, and a considerably greater difference between the reactivities of the two isomers is also observed in butanol than in ethanol. In aqueous ethanol the order of reactivity is apparently reversed although the difference is probably not significant. A trend of decreasing difference in reactivity with increasing ion-solvating power or polarity is thus evident. This trend indicates a likelihood that in aqueous sulfuric acid solution the nonequivalent *para* positions in azoxybenzene may be equally susceptible to nucleophilic attack.

TABLE I
INFLUENCE OF THE MEDIUM ON RATE OF NUCLEOPHILIC DISPLACEMENT[a]

Solvent	90% ethanol	Ethanol	1-Butanol
Initial base concn, *M*	3.56	0.52	0.08
Reaction time	12 hr	12 hr	10 days
4′-Bromoazoxybenzene	93	55	26[b]
4-Bromoazoxybenzene	89	67	74
4-Bromonitrobenzene	75[c]	72	
Bromobenzene	<1		

[a] Reported as per cent reacted. [b] After 34 days. [c] After 6 hr.

The expected products of the reaction of 4- and 4′-bromoazoxybenzene with hydroxide in aqueous ethanol, namely, 4- and 4′-hydroxyazoxybenzene, were synthesized by another route[8] and found to be unstable under the reaction conditions necessitating an estimate of the extent of reaction by the formation of bromide ion and the decrease in base concentration. In Table II the increase in reaction rate for 4′-bromoazoxybenzene that accompanies an increase in initial base concentration is indicative that the initial reaction is bimolecular as expected.

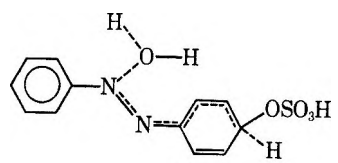
TABLE II
EFFECT OF INITIAL BASE CONCENTRATION ON BROMIDE LIBERATION FROM 4′-BROMOAZOXYBENZENE[a]

Initial base concn, *M*	0.89	1.78	3.56
% reacted	19	52	93[b]

[a] Reaction conditions: 90 vol % ethanol, 25 hr at 117°. [b] After 12 hr.

Under normal conditions of the Wallach reaction, *i.e.*, greater than 75% sulfuric acid, most azoxybenzenes exist in the form of their conjugate acids in which the oxygen is apparently protonated.[9] Whether it is oxygen or nitrogen that is protonated, however, does not alter the high probability that the rings are activated toward attack even by such comparatively poor nucleophiles as bisulfate ion or perhaps water in the less acidic media.

If the Wallach transformation involves nucleophilic attack prior to breaking the N–O bond, there would seem a distinct possibility that the loss of a proton from a phenyl ring, aromatization, and N–O cleavage would be concerted as pictured in the intermediate **1**. Such a situation would lead to a primary kinetic isotope effect when the *para* hydrogens are replaced by deuterium.



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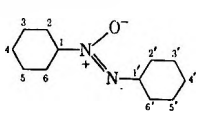
To test this possibility azoxybenzene-d_{10} was synthesized and its reaction rate compared to that of natural azoxybenzene in the same medium (95% sulfuric acid by weight) and at the same temperature (25°). Calculation of the Wallach reaction rate constants in solvents of 90% or greater sulfuric acid is complicated somewhat by a slower sulfonation reaction undergone by the *p*-hydroxyazobenzene.[10]

The reacting system was treated as two consecutive pseudo-first-order reactions[11] for which the time dependence of absorbance at a given wavelength is given by

$$\epsilon_1 A_0\left[\frac{k_1}{k_2 - k_1}(e^{-k_1 t} - e^{-k_2 t})\right] + \epsilon_2 A_0\left[1 + \frac{1}{k_1 - k_2}(k_2 e^{-k_1 t} - k_1 e^{-k_2 t})\right]$$

where ϵ_1 and ϵ_2 are the molar extinction coefficients of the conjugate acid of *p*-hydroxyazobenzene and its sulfonation product, A_0 is the initial concentration of azoxybenzene, k_1 is the rate constant of the Wallach reaction, and k_2 is the rate constant for the sulfonation reaction. The parameters ϵ_1, ϵ_2, and k_2 were all measured independently, but A_0 was only known as approximately 20 μM. Tables III and IV show reasonably good agreement of the calculated and observed absorbances measured at 464 nm for k_1 values of 3.42×10^{-4} and 3.58×10^{-4} sec^{-1} for the deuterated and

(4) M. M. Shemyakin, V. I. Maimind, and B. K. Vaichunaite, *Chem. Ind. (London)*, 755 (1958).
(5) L. C. Behr and E. C. Hendley, *J. Org. Chem.*, **31**, 2715 (1966).
(6) J. Miller and A. J. Parker, *Aust. J. Chem.*, **11**, 302 (1958).
(7) The positions of azoxybenzene are numbered as shown.



A

(8) A. Angeli, *Atti Accad. Naz. Lincei*, **23** [I], 557 (1914).
(9) C.-S. Hahn and H. H. Jaffé, *J. Amer. Chem. Soc.*, **84**, 949 (1962).
(10) P. H. Gore and G. K. Hughes, *Aust. J. Sci. Res., Ser. A*, **3**, 136 (1950). W. M. J. Strachan and E. Buncel, *Can. J. Chem.*, **47**, 4011 (1969).
(11) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1961, Chapter 8.

TABLE III
WALLACH REARRANGEMENT OF NATURAL AZOXYBENZENE IN 95% SULFURIC ACID AT 25°[a]

Time, sec	Absorbance at 464 nm, Obsd	Absorbance at 464 nm, Calcd
0	0.000	0.000
180	0.045	0.043
480	0.113	0.109
840	0.184	0.179
1260	0.253	0.253
1800	0.328	0.332
2520	0.411	0.416
3480	0.494	0.500
22,320	0.776	0.757
77,640	0.846	0.853

[a] $A_0 = 20.0\ \mu M$; $\epsilon_1 = 34{,}700\ M^{-1}\ cm^{-1}$; $\epsilon_2 = 45{,}900\ M^{-1}\ cm^{-1}$; $k_1 = 3.58 \times 10^{-4}\ sec^{-1}$; $k_2 = 1.67 \times 10^{-5}\ sec^{-1}$.

TABLE IV
WALLACH REARRANGEMENT OF AZOXYBENZENE-d_{10} IN 95% SULFURIC ACID AT 25°[a]

Time, sec	Absorbance at 464 nm, Obsd	Absorbance at 464 nm, Calcd
0	0.000	0.000
120	0.022	0.024
300	0.055	0.059
540	0.103	0.102
800	0.161	0.161
1380	0.230	0.233
1800	0.282	0.281
2340	0.338	0.336
3360	0.421	0.419
4140	0.469	0.466
5700	0.541	0.530
6900	0.579	0.562
11,880	0.664	0.624
18,300	0.699	0.650
85,500	0.779	0.753

[a] $A_0 = 17.5\ \mu M$; $\epsilon_1 = 3.47 \times 10^4\ M^{-1}\ cm^{-1}$; $\epsilon_2 = 4.59 \times 10^4\ M^{-1}\ cm^{-1}$; $k_1 = 3.42 \times 10^{-4}\ sec^{-1}$; $k_2 = 1.67 \times 10^{-5}\ sec^{-1}$.

natural azoxybenzene, respectively. A 2% change in either A_0 or k_1 gives noticeably poorer fits. This gives $k_H/k_D = 1.05 \pm 0.05$ which was experimentally indistinguishable from unity. In 80.5% sulfuric acid at 75° k_H/k_D was found to be 1.00 ± 0.05. The probable absence of a primary isotope effect is thus demonstrated.

The observations reported here therefore show that nucleophilic attack during or before a rate-limiting step cannot be excluded as a mechanistic possibility for the Wallach transformation, but the rate-limiting step does not seem to include loss of an aromatic proton.

Experimental Section

Materials.—4- and 4′-bromoazoxybenzene were prepared by previously described methods.[12] Azoxybenzene-d_{10} (mp 36°) was prepared by reduction[13] of nitrobenzene-d_5 which in turn had been prepared from benzene-d_6 (Merck Sharpe and Dome Ltd.). Deuterium content was estimated as 98+% for the azoxybenzene by comparison of pmr peak areas with those of dilute solutions of natural azoxybenzene. The spectrum of the deuterated azoxybenzene above 300 nm and the pK_a of its conjugate acid were the same as for natural azoxybenzene.

Bromide Displacement.—Portions (10 ml) of 0.036 M solutions of the bromine compounds were sealed in ampoules after nitrogen flushing. The ampoules were heated in boiling water for several minutes and then placed in a 117° oven. After heating, the ampoule contents were diluted with water, the alcohols were removed with the water pump, and the residue was acidified to pH 5 with standard perchloric acid and titrated for halide ion by Mohr's method. Blank samples containing only solvent and base were run for each solvent system and found to be stable.

Wallach Reaction Kinetics.—Approximately 20 μM solutions of the azoxybenzene were placed in a jacketed tube with water thermostated at the desired temperature circulated through the outer jacket. The tube was placed in a calibrated Coleman Jr. spectrometer set at 464 nm. In Tables III and IV the background absorbance of 0.136 has been subtracted from the observed absorbances. The runs in 80.5% sulfuric acid were performed as described previously.[3]

Registry No.—4′-Bromoazoxybenzene, 16054-48-1; 4-bromoazoxybenzene, 16109-68-5; azoxybenzene, 495-48-7; azoxybenzene-d_{10}, 25244-28-4.

Acknowledgment.—The authors thank Mr. Stephen H. Farish for computational assistance.

(12) L. C. Behr, *J. Amer. Chem. Soc.*, **76**, 3672 (1954).
(13) A. Lachman, *ibid.*, **24**, 1180 (1902).

Critical Micelle Concentrations of Optically Active and Racemic 2-Octylammonium and 2-Octyltrimethylammonium Ions

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Our demonstration that the stereochemical course of alkanol formation *via* the classical amine–nitrous acid deamination reaction can be moderated by the presence of alkylammonium ion micelles[2] forms part of a rapidly growing interest in the control of organic reaction chemistry by micellar phases.[3] The rational design of micellar agents now assumes special importance.

The dependence of the critical micelle concentration (cmc), defined as "the saturation concentration of singly dispersed species,"[4] on such parameters of molecular structure as chain length and branching, number, type, and location of ionic "head" groups, chain unsaturation, gegenion identity and charge type, and related factors, has been well studied.[5] Studies of chiral micellar agents, and especially of the effect of possible diastereomeric and enantiomeric interactions on the cmc are, however, not common. Beckett and coworkers reported that the cmc's of some racemic and optically active N-alkyl-N,N-dimethylalanine hydrobromides were identical.[6] In a preliminary trial we had found apparent differences in the cmc's of racemic and optically active 2-octylammonium perchlorate in 1.5 M aqueous sodium perchlorate at pH 4.[7]

It did seem possible that micellar agents composed of a single enantiomer might "fit" together more or less

(1) NDEA Fellow, 1968–1970.
(2) R. A. Moss and D. W. Reger, *J. Amer. Chem. Soc.*, **91**, 7539 (1969).
(3) See E. H. Cordes and R. B. Dunlap, *Accounts Chem. Res.*, **2**, 339 (1969).
(4) See K. Shinoda, T. Nakagawa, B-I. Tamamushi, and T. Isemura, "Colloidal Surfactants," Academic Press, New York, N. Y., 1963, p 4.
(5) Reference 4, particularly Chapter 1.
(6) A. H. Beckett, G. Kirk, and A. S. Virji, *J. Pharm. Pharmacol., Suppl.*, **19**, 71 (1967).
(7) Reference 2, Note 14.

readily than the corresponding racemic modification. D and L amino acids apparently differ in their "fit" to the surface of D-N-alkyl-N,N-dimethylalanyl betaines.[8,9] The likelihood that many investigations of micellar control of organic reaction stereochemistry will be forthcoming, impelled us to give further scrutiny to our preliminary observation and to report the results at this time.

Cmc's of racemic and optically active (89–94% optically pure) 2-octylammonium bromide (at pH 1.5) and 2-octyltrimethylammonium bromide were determined in water and in 1.5 *M* aqueous sodium bromide. The cmc of 2-octylammonium perchlorate was determined in 1.5 *M* and 2.0 *M* aqueous sodium perchlorate at pH 1.5. Cmc's were taken as the "break points" of graphs of log (micellar agent concentration) *vs.* observed surface tension obtained with a DuNouy tensiometer. All measurements were made on solutions in a thermostatted cell at 31° and were reproducable to ±0.3 dynes/cm. The cmc values recorded in Table I each represent the average of at least three

TABLE I

CMC'S OF RACEMIC AND OPTICALLY ACTIVE 2-OCTYLAMMONIUM AND 2-OCTYLTRIMETHYLAMMONIUM IONS

Case	Micellar agents[a]	Solvent	Cmc (mol/l.)	% avg dev
1	2-OTA-Br	H_2O	0.325	6.8
	2-OTA-Br*	H_2O	0.362	2.5
2	2-OTA-Br	1.5 *M* aqueous NaBr	0.148	2.7
	2-OTA-Br*	1.5 *M* aqueous NaBr	0.146	6.1
3	2-OA-Br	1.5 *M* aqueous NaBr[b]	0.129	1.6
	2-OA-Br*	1.5 *M* aqueous NaBr[b]	0.128	2.4
4	2-OA-ClO_4	1.5 *M* aqueous $NaClO_4$[b]	0.0499	1.8
	2-OA-ClO_4*	1.5 *M* aqueous $NaClO_4$[b]	0.0516	1.9
5	2-OA-ClO_4	2.0 *M* aqueous $NaClO_4$[b]	0.0417[c]	0.2
	2-OA-ClO_4*	2.0 *M* aqueous $NaClO_4$[b]	0.0427[d]	0.7

[a] OTA = octyltrimethylammonium, OA = octylammonium. An asterisk denotes the optically active samples. [b] pH 1.5. [c] The cmc is unchanged at pH 4.0. [d] Use of 100% optically pure 2-OTA-Br in cases 1 and 2 gave values within the experimental errors.

measurements on *separately prepared* micellar solutions. The cmc of racemic 2-octylammonium bromide in water (pH 1.5) was determined as 0.34 *M*. Under these conditions, surface tension–log (concentration) graphs for the optically active salt did not exhibit sharp "breaks." The graphs were satisfactory in the other cases examined, and free of minima, though the "break" became sharper at lower cmc values.[10]

Differences, such as they are, between the cmc's of the racemic and optically active ions lie just at the border of combined experimental error (*e.g.*, case 1). Within the accuracy of our measurements, therefore, the racemic and optically active species have essentially identical cmc's. We consider that our earlier, contrary observation[7] was most likely due to an inadequately purified racemic 2-octylammonium ion sample, which may have exhibited a depressed cmc.[11] The present results, together with previous work,[6] suggest that a continued search for "fit" problems accompanying micellization of racemic, as opposed to optically active micellar agents, might concentrate on molecules in which the center of chirality is located well into the hydrophobic portion of the micellar agent. The effect of chirality at the "head" group (with regard to cmc) is probably mitigated by the water molecules and gegenions which "insulate" the "head" groups from each other in the micelle.

(8) A. H. Beckett, G. Kirk, and A. S. Virji, *J. Pharm. Pharmacol.*, **19**, 827 (1967).

(9) This case is obviously not analogous with the title problem, since it involves diastereomeric solubilization interactions rather than enantiomeric micellization interactions. The situations are, nonetheless, conceptually akin.

(10) A recent application of the surface tension cmc determination method, including a sample graph, may be found in L. R. Romstead and E. H. Cordes, *J. Amer. Chem. Soc.*, **90**, 4404 (1968). For other references, see ref 4, p 11.

Experimental Section

Materials.—Racemic 2-aminooctane (K & K) was purified by distillation. Distillate was monitored by gas chromatography (gc) on a 10 ft × 0.25 in., 10% SE-30 on GCR (45–60) column at 122°. When necessary, more rigorous purification was afforded by distillation over a Nester–Faust Teflon annular spinning-band column. Only 2-aminooctane of gc purity (>99%) was used in further work.

Optically active 2-aminooctane was obtained from the racemate by the method of Mann and Porter[12,13] and had $\alpha^{24}D$ −2.38° (*l* 0.5 dm, neat), corresponding to an optical purity of at least 89%.[14] A second batch of resolved amine had $\alpha^{22}D$ −2.51° (*l* 0.5 dm, neat) and was at least 94% optically pure. The two active amine samples were used without distinction in cmc determinations.

2-Octyltrimethylammonium bromide was prepared from 2-aminooctane by the procedure of Clarke[16] (which gave 2-octyldimethylamine) followed by quaternization with methyl bromide. The 2-octyldimethylamine (bp 37–38°, 1.35 Torr) was produced in 72% yield and showed traces of (presumably) 2-aminooctane and 2-octylmethylamine by gc. It was not further purified, but was converted to the quaternary salt by the following, generalized procedure. 2-Octyldimethylamine, an equal volume of dry ethanol, and 1.75 equiv of methyl bromide (Matheson) were sealed into a pressure tube[17] and shaken overnight at *ca.* 25°. Ethanol and excess methyl bromide were then evaporated. The crystals were washed well with anhydrous ether and then dissolved in the minimum necessary volume of hot methanol. Several volumes of dry ether were added to the cooling methanol solution so as to drive out the salt in a fine form. The salt was collected and triturated with dry ether. The entire process was then repeated twice. Crystals obtained in this way were suitable for cmc determinations, as judged by the absence of minima in their surface tension–log (concentration) graphs.[18] 2-Octyltrimethylammonium bromide was thus obtained in a (purified) yield of 50%. It decomposed at 259–260° (sealed capillary tube) after discoloring above 220°.

Anal. Calcd for $C_{11}H_{26}BrN$: C, 52.38; H, 10.39; Br, 31.68; N, 5.55. Found: C, 52.21; H, 10.57; Br, 31.56; N, 5.32.[19]

(11) The argumentation and conclusions of ref 2 are unaffected by the present findings.

(12) F. G. Mann and J. W. G. Porter, *J. Chem. Soc.*, 456 (1944).

(13) We thank Mr. C. Talkowski for the amine resolution.

(14) F. G. Mann and J. Reid, *J. Chem. Soc.*, 3384 (1950), report $\alpha^{19}D$ −2.66° (*l*. 0.5 dm, neat) for scrupulously dried amine. Traces of water are known to depress this value to $\alpha^{19}D$ −2.55°.[15] Our amine samples were dried by distillation from sodium just prior to polarimetry and optical purities are therefore based on the former value.

(15) A. Streitwieser, Jr., and W. D. Schaeffer, *J. Amer. Chem. Soc.*, **78**, 5597 (1956).

(16) H. T. Clarke, H. B. Gillespie, and S. Z. Weisshaus, *ibid.*, **55**, 4571 (1933).

(17) Methyl bromide was introduced as a liquid at −70°. The reaction is exothermic. Reagents should be mixed at low temperature and allowed to warm after the pressure tube has been sealed.

(18) Alternative purification methods such as recrystallizations from acetone, ethylacetate, or alcohol–ether did not yield material satisfactory for cmc determinations.

(19) Analysis by Micro-Tech Laboratories, Skokie, Ill. Infrared and nmr spectra were in accord with structure.

Optically active 2-octyltrimethylammonium bromide was prepared from resolved 2-aminooctane in an identical manner. From 2-aminooctane, $\alpha^{24}D$ −2.377° (88.6% optically pure), the optically active salt obtained had $\alpha^{23}D$ +3.18° (c 1.0 *M* in methanol, 0.5 dm).

Cmc Determinations.—All solutions of the ammonium salts were prepared in "Lecktrostill Steam Distilled Water," resistivity >1.5 × 10^6 ohm cm (Electrified Water Co., Newark, N. J.). Stock solutions were water, 1.5 *M* aqueous NaBr, 1.5 *M* aqueous NaBr (acidified to pH 1.5 with HBr solution which had been preadjusted to 1.5 *M* in bromide ion), and 1.5 *M* and 2.0 *M* aqueous $NaClO_4$ (acidified to pH 1.5 with $HClO_4$). Solutions of the amine or the ammonium salt were prepared (above the cmc) using these stock solutions. 2-Octylamine solutions were preadjusted to pH 1.5 with aqueous HBr (1.5 *M* in bromide) before bringing to dilution with bromide stock solution. A similar procedure was used in the perchlorate experiments.

Surface tension was determined in a cell thermostatted at 31° by a Haake constant-temperature circulating pump. An aliquot of the amine or the ammonium ion solution (at a concentration above the cmc) was successively diluted by addition of 0.50-ml portions of the appropriate stock solution from an accurate buret (±0.01 ml). Stirring was accomplished after each dilution with a micro stirring bar and the surface tension corresponding to the then present concentration[20] was measured with a DuNuoy tensiometer.[21] Cmc values were then determined from graphs of observed surface tension *vs.* log (concentration). Average cmc values, determined from at least three separately prepared micellar solutions appear in Table I.

Registry No.—(±)-2-OA-Br, 25474-24-2; (−)-2-OA-Br, 25474-25-3; (±)-2-OTA-Br, 25474-26-4; (+)-2-OTA-Br, 25474-27-5; (±)-2-OA-ClO_4, 25474-28-6.

Acknowledgments.—We thank the National Institutes of Health (Gm-13585) and the National Science Foundation (GP-12645) for financial support.

(20) The volume additivity demanded by this procedure was demonstrated to ±0.01 ml by parallel control experiments for cases 1, 2, and 4 of Table I.

(21) The average deviation from the mean of a series of 12 surface tension readings taken either on water or a micellar solution was ±0.3 dynes/cm.

The Structure of the Adduct from Diphenylketene and Triethyl Phosphite

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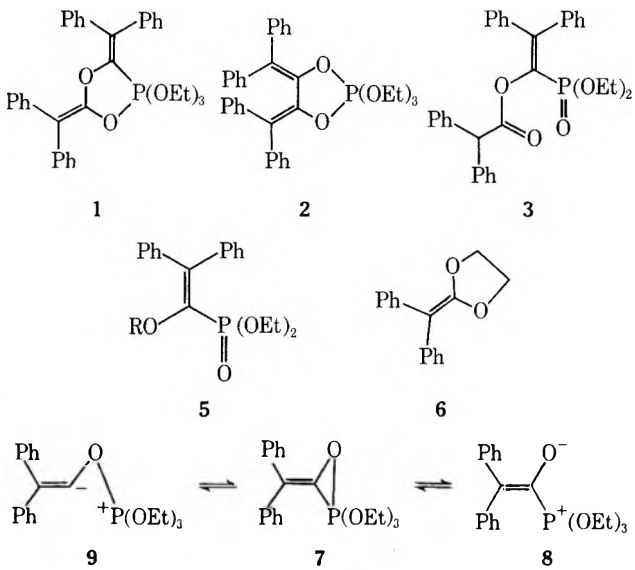
During the course of work on the interaction of trivalent phosphorus with carbonyl derivatives we have examined the 2:1 adduct of diphenylketene and triethyl phosphite.[2] The structure of this substance, which undergoes a high-temperature deoxygenation rearrangement to diphenylacetylene,[2] has been the subject of some speculation;[3] and we here describe a solution to this problem.

The adduct, $C_{34}H_{35}PO_5$, prepared as previously described[2] showed a medium strength band at 1660 cm^{-1} in the infrared (solid and solution) and the nmr spectrum, which contained only phosphorus-bound ethoxyl and aryl protons, underwent an irreversible change at 90°. In accordance with previous speculative suggestions for the presence of pentacoordinate phosphorus atom in this molecule, the ^{31}P magnetic resonance spectrum showed a chemical shift of +55 ppm relative to 85% H_3PO_4, without solvent dependence.[4] However "freezing out" of discrete pseudorotational structures could not be observed in the proton spectrum of the ethoxyl ligands down to −114°.[4,5] At this stage two structures, **1** and **2**, seemed in accord with the evidence, neither of which possessed a carbonyl function, *vide supra*. Distinction between these two possibilities was made on the basis of hydrolytic behavior, for in moist air or in wet ether the adduct was converted into the enol ester (**3**), ν_{max} 1760 cm^{-1}, and ethyl diphenylacetate (**4**). That **4** was a further ethanolysis product of **3**



was demonstrated by the observation that methanol, with a trace of sodium methoxide, converted **3** into methyl diphenylacetate. More vigorous hydrolysis of **3** gave almost 2 mol of diphenylacetic acid. Confirmation of the enol ester structure **3** was achieved by synthesis. Thus the Arbuzov product from diphenylacetyl chloride and triethylphosphite was the stable enol phosphonate (**5**, R = H), from its composition and positive ferric chloride test.[6] The enolic hydroxyl group of **5** (R = H), exchangeable with deuterium oxide, was acetylated to the acetate **5** (R = $COCH_3$), ν_{max} 1760 cm^{-1}, and methylated (diazomethane) to the ether **5** (R = CH_3). Treatment of **5** (R = H) with diphenylketene yielded the phosphonate **3**, identical in infrared, ultraviolet and nmr spectra with the originally isolated substance. The hydrolytic conversion of the adduct to **3** then enables the assignment **1** to be proposed for this substance and rejection of alternative **2**, since the latter could not readily yield an enol ester **3** under simple hydrolytic conditions. As a close ultra-

(1) Alfred P. Sloan Fellow, 1969–1970.

(2) T. Mukaiyama, H. Nambu, and M. Okamoto, *J. Org. Chem.*, **27**, 3651 (1962).

(3) R. F. Hudson, "Structure and Mechanism in Organophosphorus Chemistry," Academic Press, New York, N. Y., 1965, p 197; A. J. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus," Elsevier, New York, N. Y., 1967, p 88.

(4) F. Ramirez, *Accounts Chem. Res.*, **1**, 168 (1968).

(5) F. H. Westheimer, *ibid.*, **1**, 70 (1968).

(6) An analogous enolic compound has recently been described by Richard N. McDonald and Donald G. Hill, *Chem. Commun.*, **12**, 671 (1969).

violet model for the chromophore of **1** we prepared the glycol acetal (**6**) of diphenylketene which showed λ_{max} 272 mμ (ε 20,000) in reasonable accord with the broad maximum at 257 mμ (ε 40,000) noted for the adduct. The hypsochromic shift in **1** is apparently due to the presence of the pentavalent phosphorus in the five-membered ring. Whilst the detailed mechanisms of reaction of trivalent phosphorus with carbonyl groups is as yet unclear[4] a rationale of the formation of **1** may be obtained through the intermediacy of a initial 1:1 adduct (**7**), which in its open form (**8**) undergoes a simple 1,3 dipolar addition to another mole of ketene, providing the 1,4,2-dioxyphospholane structure **1**. We have observed no change in the ^{31}P chemical shift (chloroform solution) up to 90°, at which temperature an irreversible thermal decomposition takes place, thus eliminating an isomerization to a 1,3,2-dioxyphospholane structure **2**, as reported in some systems by Ramirez.[4] The thermolysis to acetylene is probably reversal of the last step followed by decomposition of **7** to dipole **9**. Decomposition of **9** to diphenylacetylene and triethylphosphate is a reaction which finds close analogy in the tolane synthesis.[7]

Experimental Section[8]

All reactions were performed under deoxygenated dried prepurified nitrogen. Melting points were measured on a Kofler hot stage and are uncorrected. Ultraviolet spectra were recorded on a Coleman-Hitachi 124 double-beam spectrometer. Infrared spectra were recorded on a Perkin Elmer 257 spectrophotometer. ^1H nmr spectra at room temperature were measured on a Varian A-60A spectrometer with tetramethylsilane as internal reference. Variable temperature ^1H and ^{31}P nmr spectra were obtained from a Varian HA-100 spectrometer equipped with a V6040 temperature control and a probe fitted with a thermocouple for measuring the temperature. In the HR mode at operating frequency 40.5 MHz ^{31}P nmr spectra were calibrated by the sideband technique using a Hewlett-Packard variable audiooscillator and P_4O_6 as external reference. Mass spectra were measured on a AEI MS9 mass spectrometer.

Adduct 1. 3,5-Bis(diphenylmethylene)-1,4,2-dioxatriethoxyphospholane.—Dry triethyl phosphite (0.912 g) reacted exothermally when added dropwise to freshly distilled diphenylketene (2.142 g) in 2 ml Et_2O. Evaporation yielded yellow crystalline **1**: mp 85–100°; uv max (C_6H_{12}) 257 mμ (ε 40,000); ir (C_6H_6, C_6H_{12}, $CHCl_3$, CH_2Cl_2, Nujol) 1660 (C=C), 1600 cm^{-1}; ^1H nmr (CS_2) σ 0.85 (m, 6), 3.68 (m, 4), 7.15 (m, 20); ^{31}P nmr ppm relative to 85% H_3PO_4 (0 ppm) (C_6H_6, CH_2Cl_2, $CHCl_3$) +55; mass spectrum (70 eV) *m/e* (relative intensity) 240 (4), 182 (3), 167 (16), 105 (7), 77 (4).

Hydrolysis of Adduct.—Stirring in a moist air stream produced an oily product mixture. Separation by column chromatography (silica gel) gave **3** and ethyl diphenylacetate. **1** when stirred with wet ether under dry nitrogen gave the same products after evaporation and chromotography.

Methanolysis of 3.—A solution of **3** in MeOH containing a little sodium methoxide was refluxed for 2 hr. Evaporation yielded methyl diphenylacetate, recrystallized from EtOH: mp 57–58°; identical with an authentic specimen.

Hydrolysis of 3.—An ethereal solution of **3** (0.372 g) when stirred for 3 hr with 5 ml 4 *N* NaOH, acidified with HCl and extracted with Et_2O yielded diphenylacetic acid (0.257 g) upon evaporation: mp 140–143°; identical with an authentic specimen.

2,2-Diphenylethylenol-1-(ethyl)phosphonate (5) (R = H).—Triethyl phosphite (0.72 g) in 20 ml was added dropwise to a solution of diphenylacetyl chloride (1.0 g) in 30 ml Et_2O. The solution was refluxed under dry nitrogen for 3 hr. After solvent evaporation, the product was recrystallized from benzene and hexane: mp 99–103°; uv max (95% EtOH) 260 mμ (ε 20,000) with 1 drop 4 *N* NaOH 300 mμ; ir (Nujol) 3400–3100 (b, OH), 1490 (m, C=C), 1200 (b, P=O), 980 (b, P–O–C) after D_2O treatment and recrystallization 2500–2200 cm^{-1} (b, OD); ^1H nmr ($CDCl_3$) σ 1.15 (m, 6), 3.95 (m, 4), 6.72 (bs, 1) function of concentration, 7.31 (s, 10) after D_2O treatment broad singlet disappears; ^{31}P nmr (benzene) ppm relative to 85% H_3PO_4 −9; mass spectrum (70 eV) *m/e* (relative intensity) 332 (1), 304 (2), 194 (12), 167 (27), 137 (1).

Anal. Calcd for $C_{18}H_{21}O_4P$: C, 65.05; H, 6.37; P, 9.32. found: C, 64.91; H, 6.44; P, 9.48.

1-(Acetoxy)-2,2-diphenylethylene(ethyl)phosphonate (5) (R = $COCH_3$).—A solution of **5** (R = H) (1.20 g) in 25 ml Ac_2O plus a trace of NaOAc when heated at 40° for five hours yielded the crude oil after evaporation of excess Ac_2O. Purification of **5** (R = $COCH_3$) was accomplished by preparative tlc on aluminia GF, eluted with $CHCl_3$: ir (neat) 1760 (s, C=O), 1260 (s), 1220 (b) 1130 (s), 1040 (b); nmr (CCl_4) σ 1.11 (m, 6), 1.93 (s, 3) 3.88 (m, 4) 7.20 (d, 10); mass spectrum (25 eV) *m/e* (relative intensity) 346 (18), 332 (15), 317 (10), 209 (10), 194 (61), 167 (26), 149 (10), 121 (10), 111 (10), 105 (16), 93 (10), 43 (24).

2,2-Diphenylethylene-1-(ethyl)phosphonate Methyl Ether (5) (R = CH_3).—An ethereal solution (27 ml) of CH_2N_2 (0.315 g) was added to **5** (R = H) (2.50 g). After stirring at 0° for 3 hr followed by evaporation of Et_2O, the oil **5** (R = CH_3) was isolated in 63% yield: uv max (C_6H_{14}) 260 mμ (ε 10,000); nmr (CCl_4) σ 1.05 (m, 6), 3.42 (s, 3), 3.85 (m, 4), 7.20 (m, 10); mass spectrum (25 eV) *m/e* (relative intensity) 346 (20), 317 (10), 209 (10), 167 (14), 121 (10). Although spectral properties were in full agreement with those expected for these new compounds, **5** (R = CH_3) (R = $COCH_3$), elemental analysis was not attempted.

1-(Diphenylacetoxy)-2,2-diphenylethylene(ethyl)phosphonate (3).—Triethylamine (1.12 g) in 15 ml C_6H_6 added dropwise into diphenylacetyl chloride (2.56 g) in 15 ml C_6H_6 generated diphenylketene in solution and Et_3NHCl. **5** (R = H) (3.70 g) in 20 ml C_6H_6 was added to above reaction mixture. After 10 hr at 60°, filtration and evaporation of C_6H_6 yielded the oil **3**. Purification was accomplished by column chromatography (silica gel) eluted with $CHCl_3$ followed by preparative tlc (silica gel GF254) doubly eluted with $CHCl_3$: uv max (C_6H_{14}) 257 mμ (ε 11,000); ir (neat) 3100–2900 (m, CH), 1760 (s, C=O), 1665 (w, C=C), 1600 (w), 1255 (b), 1110 (b), 1020 (b, P–O–C), 745 (s), 690 cm^{-1} (s); ^1H nmr (CCl_4) σ 1.03 (m, 6), 3.83 (m, 4), 4.95 (s, 1), 7.20 (m, 20); ^{31}P nmr (C_6H_6) ppm relative to 85% H_3PO_4 −7; mass spectrum (70 eV) 331 (1), 233 (8), 182 (108), 165 (27), 105 (268), 77 (186).

Anal. Calcd for $C_{32}H_{31}O_5P$: C, 72.99; H, 5.93; P, 5.88. Found: C, 73.00; H, 6.07; P, 5.66.

This material was identical in all spectral and chromatographic properties with the compound obtained by hydrolysis of **1**, *vide supra*.

Diphenylketene Ethylene Acetal (6).—This acetal was prepared by a modification of the procedure of Gulbins.[9] Instead of generating diphenylketene *in situ* from azibenzil, it was formed as described by Taylor.[10] The Et_3NHCl was filtered off, followed by addition of ethylene carbonate and a trace of LiCl. After 3.5 hr at 180°, distillation yielded the acetal which was recrystallized from C_6H_{14}: bp 150–155° (0.12 mm), mp 141–144° [lit. bp 174–175° (0.3 mm), mp 149–151°]; uv max (C_6H_{14}) 272 mμ (ε 20,000); ir (Nujol) 1650 (s, C=C), 1600 (w), 1050 cm^{-1} (sb, C—O—C); nmr ($CDCl_3$) σ 4.23 (s, 4), 7.25 (s, 10); mass spectrum (70 eV) 238 (9), 165 (15), 105 (4), 77 (3).

Registry No.—**1**, 25577-16-6; **3**, 25577-17-7; **5** (R = H), 25577-18-8; **5** (R = CH_3), 25577-19-9; **5** (R = $COCH_3$), 17474-77-0.

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(7) A. A. Bothner-By, *J. Amer. Chem. Soc.*, **77**, 3293 (1955); J. G. Pritchard and A. A. Bothner-By, *J. Phys. Chem.*, **64**, 1271 (1960).

(8) Elemental analyses were performed by the Midwest Microlab Inc., Indianapolis, Ind. 46226.

(9) K. Gulbins and K. Hamann, *Chem. Ber.*, **94**, 3287 (1961).

(10) Reported in L. F. Fieser and M. Fieser, "Reagents for Organic Syntheses," Wiley, New York, N. Y., 1967, p 344.

The *ortho* Claisen Rearrangement. IX. The Effect of Solvent on the Substituent Effect[1,2]

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The rate of the *ortho* Claisen rearrangement is subject to both solvent[1a,3] and substituent[1a,d,e,h,3] effects. Electron-donating groups and polar solvents increase the rate of the reaction. In view of this sensitivity of the rearrangement to both solvent and structure, a determination of the relation of solvent change to substituent effect might permit conclusions about the relative importance of solvent and substituents in stabilizing the transition state.

In order to investigate this problem, the rates of rearrangement of four allyl *p*-X-phenyl ethers in three solvents, tetradecane, carbitol, and 28.5% ethanol–water, were compared. The relevant experimental data are summarized in Table I. Rate constants at the common temperature of 181° were obtained by interpolation and extrapolation and are shown in Table II. The rate constants were correlated by using Hammett's equation and σ^+ values. The reaction constants, ρ, in each solvent are included in Table II.

Table II shows that there is only a small change in ρ with solvent variations that produce an overall rate effect of 22- to 39-fold. This implies that the internal electronic demands of the reaction site on the substituents remains about the same in all solvents. Since solvent effects are intermolecular in nature while substituent effects are intramolecular and more closely associated with the reaction center, it might have been anticipated that medium effects on the reaction constant would not be large. The variation in ρ is in the direction expected—as solvent polarity increases and the energy of the transition state is lowered, a smaller stabilizing contribution from the substituents is required and so ρ is smaller.

TABLE I
RATE CONSTANTS AND ACTIVATION PARAMETERS FOR REARRANGEMENT OF ALLYL *p*-X-PHENYL ETHERS

		$k \times 10^5$ (sec^{-1})			
X	Solvent	T_1	T_2	$\Delta H^{\ddagger a,b}$	$\Delta S^{\ddagger b,c}$
NO_2	Tetradecane	0.166 ± 0.002[d]	0.972 ± 0.026[e]	33.9	−10.5
	Carbitol[f]	1.03 ± 0.09[g]			
	28.5% EtOH–H_2O	0.732 ± 0.012[h]	4.09 ± 0.01[i]	28.3	−15.6
Br	Tetradecane	0.439 ± 0.003[d]	2.25 ± 0.05[e]	30.5	−16.2
	Carbitol[f]	2.48 ± 0.06[g]	9.46 ± 0.3[e]	29.8	−14.8
	28.5% EtOH–H_2O	1.14 ± 0.03[h]	6.11 ± 0.13[i]	27.6	−16.4
CH_3	Tetradecane	0.728 ± 0.002[f]	3.30 ± 0.02[e]	33.1	−9.8
	Carbitol[f]	4.71 ± 0.04[f]	18.8 ± 0.2[e]	30.3	−12.6
	28.5% EtOH–H_2O	2.23 ± 0.01[h]	10.7 ± 0.3[i]	26.2	−18.5
OCH_3	Tetradecane	2.13 ± 0.01[d]	11.8 ± 0.1[e]	33.0	−7.7
	Carbitol[f]	8.66 ± 0.09[g]	35.7 ± 0.1[e]	29.9	−12.1
	28.5% EtOH–H_2O	5.82 ± 0.16[h]	29.3 ± 0.1[i]	26.5	−15.8

[a] In kcal/mol [b] The average deviation of ΔH is ±0.2 kcal/mol and that of ΔS is ±0.3 eu. [c] In cal/(deg mol). [d] T = 177.7 ± 0.1°. [e] T = 199.7 ± 0.1°. [f] $EtOCH_2CH_2OCH_2CH_2OH$. [g] T = 180.9 ± 0.1°. [h] T = 170.7 ± 0.1°.

TABLE II
RATES OF REARRANGEMENT OF ALLYL *p*-X-PHENYL ETHERS AT 181°

	$k \times 10^5$ (sec^{-1})[a]					
Solvent	NO_2	Br	CH_3	OCH_3	ρ^b	r^c
Tetradecane	2.34	5.98	7.94	28.3	−0.67	0.97
Carbitol[d]	10.3	27.7	44.2	91.6	−0.61	0.99
28.5% EtOH–H_2O	90.9	134	233	621	−0.53	0.95

[a] T = 181.0°. [b] Reaction constant obtained with σ^+ values. [c] Correlation coefficient. [d] $EtOCH_2CH_2OCH_2CH_2OH$.

Experimental Section

Preparation of Allyl *p*-X-Phenyl Ethers.—These compounds were prepared by the procedure previously described.[1a] Immediately prior to final distillation, the allyl ether was dissolved in Skellysolve B and chromatographed on a column of activity grade I alumina using Skellysolve B as eluent. The solvent in the eluate was evaporated and the residue was distilled. The physical properties of the products agreed with those recorded in the literature.[1a]

Solvents.—Tetradecane and carbitol were separately distilled through a 45-cm Vigreux column. Center cuts having boiling ranges of less than a degree were selected for the kinetic measurements. The 28.5% ethanol–water solvent was prepared by diluting 30.0 ml of absolute ethanol to 100.0 ml with water.

Kinetic Measurements.—The spectrophotometric procedure previously described[1a] was employed.

Registry No.—Allyl *p*-nitrophenyl ether, 1568-66-7; allyl *p*-bromophenyl ether, 25244-30-8; allyl *p*-methylphenyl ether, 23431-48-3; allyl *p*-methoxyphenyl ether, 13391-35-0.

(1) Previous papers in this series: (a) W. N. White, D. Gwynn, R. Schlitt, C. Girard, and W. Fife, *J. Amer. Chem. Soc.*, **80**, 3271 (1958); (b) W. N. White and B. E. Norcross, *ibid.*, **83**, 1968 (1961); (c) *ibid.*, **83**, 3265 (1961); (d) W. N. White and W. K. Fife, *ibid.*, **83**, 3846 (1961); (e) W. N. White and C. D. Slater, *J. Org. Chem.*, **26**, 3631 (1961); (f) *ibid.*, **27**, 2908 (1962); (g) W. N. White and E. F. Wolfarth, *ibid.*, 3509 (1961); (h) W. N. White, C. D. Slater, and W. K Fife, *ibid.*, **26**, 627 (1961); (i) W. N. White and E. F. Wolfarth, *ibid.*, **35**, 2196 (1970).

(2) This investigation was supported by Grants G-7345 and GP-1970 from the National Science Foundation.

(3) H. L. Goering and R. R. Jacobsen, *J. Amer. Chem. Soc.*, **80**, 3277 (1958).

An Inhibitor-Initiated Polymerization of N-Vinylcarbazole

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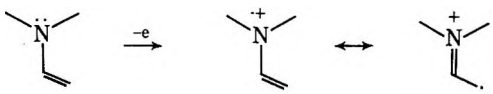
In the course of our study of organic redox reactions as a means of generating free radicals in solution, we have noticed N-vinylcarbazole to be one of the most effective reductants among the amines, and this can be attributed at least in part to the formation of the cation radical which can be resonance stabilized.[1]



There have been a number of reports in the literature about the atypical nature of this particular cation–radical intermediate. For example, both ionic and free-radical inhibitors usually exert little or no effect on the polymerization of N-vinylcarbazole when electron acceptors such as tetracyanoethylene and *p*-chloranil are used as initiators.[2,3] It is believed that the formation of the cation radical was involved in the initial step of the process. Also, it was reported more recently that when ferric ion is used as the oxidant in the presence of oxygen, it led to the formation of a dimer of N-vinylcarbazole, *trans*-1,2-dicarbazylcyclobutane.[4]

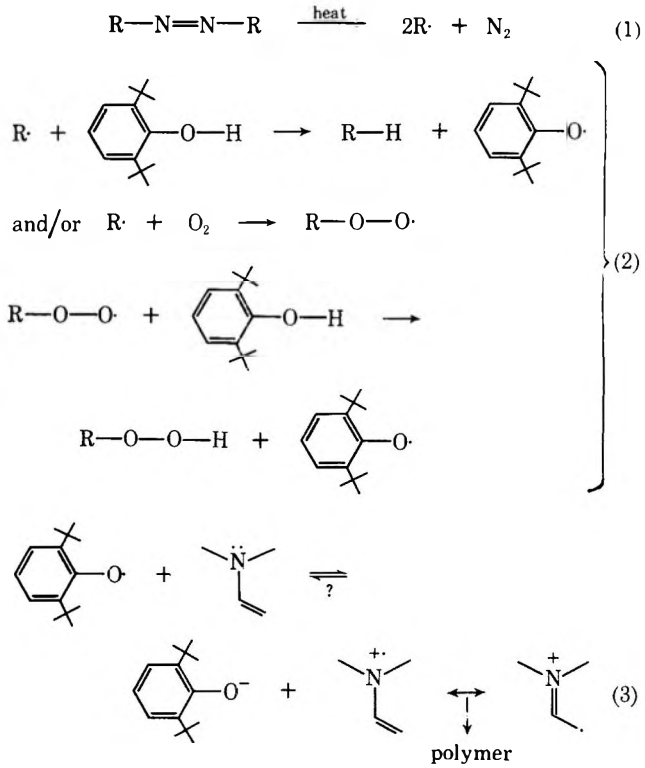
In this note we wish to report our more recent findings that highly hindered phenols such as 2,6-di-*t*-butylphenol and 2,4-di-*t*-butylphenol, usually inhibitors of free-radical chain process, do not retard but rather accelerate the polymerization of N-vinylcarbazole in methanol to result in the formation of lower molecular weight poly-*n*-vinylcarbazole when azobisisobutyronitrile was used as initiator.

When a solution containing 2 g (1×10^{-2} mol) of N-vinylcarbazole and 0.02–0.2 g (1×10^{-4}–1×10^{-3} mol) of 2,6-di-*t*-butylphenol and 0.05 g ($\sim 3 \times 10^{-4}$ mol) of azobisisobutyronitrile in 50 ml of methanol was heated under nitrogen atmosphere at 50° for 5 hr, it produced a gummy precipitate, weighing from 1.2 to 1.5 g. Trituration of the gummy solid in benzene afforded white solid melting at a wide range from 150–250°. Infrared spectrum of the solid resembles that of poly-N-vinylcarbazole. There is no unsaturation as bromination in carbon tetrachloride and permanganate oxidation tests were negative. Exploratory molecular weight determination by Rast method gave a value of ~510, indicating this is probably a mixture of low molecular weight polymers. This may also explain the appreciable solubility of this solid in benzene, whereas high molecular weight poly-N-vinylcarbazole obtained commercially dissolves only slightly in benzene and toluene at room temperature.

(1) C.-H. Wang, *Chem. Ind. (London)*, 751 (1964).
(2) L. P. Ellinger, *ibid.*, 1982 (1963).
(3) H. Scott, T. P. Konen, and M. M. Labes, *Polym. Lett.*, **2**, 689 (1964).
(4) C.-H. Wang, C. C. Sizman, and K. Stevenson, *J. Org. Chem.*, **35**, 2045 (1970).

In accompaning experiments under identical conditions, the one without the phenol afforded only a small amount, ~0.2 g, of polymer at the end of 5 hr; the one with the phenol (1×10^{-4} mol) but without azo compound produced no trace of polymer after 5 hr. In another run, the reaction with azo compound, 2,6-di-*t*-butylphenol and N-vinylcarbazole, each of the same amount as in the previous experiment, in methanol was carried out in open air with vigorous stirring at 50°, it yielded about the same amount of polymers at the end of 5 hr, whereas the blank run without phenol produced no polymeric substance.

The effect of hindered phenols in free-radical polymerization of N-vinylcarbazole is indeed unusual and hard to explain. One conjecture, based on the aforementioned information, will be that there is an interaction between the isobutyronitrile radical and/or the isobutyronitrile–peroxy radical and the phenol to result in the formation of the phenoxy radical which in turn undergoes a redox process with N-vinylcarbazole as indicated in the following equations.



The interaction between alkylperoxy radical and phenols to afford the alkyl hydroperoxide and the phenoxy radicals is well documented.[5] The direct hydrogen abstraction from the phenol by isobutyronitrile radical may parallel the reaction between benzhydryl radical and thiophenol.[6] The constancy in the yield of polymer in various runs containing 2,6-di-*t*-butylphenol from 1×10^{-4} to 1×10^{-3} mol might suggest that reaction 2 is the principal path for the consumption of the isobutyronitrile radical and also that in the polymerization process, the atypical cation radical intermediate, insensitive toward various scavengers, is involved. Consideration of the rate of decomposition of azobisiso-

(5) A. F. Bickel and E. C. Kooyman, *J. Chem. Soc.*, 2215 (1956).
(6) C.-H. Wang and S. G. Cohen, *J. Amer. Chem. Soc.*, **79**, 1924 (1957).

butyronitrile at 50° gives pertinent information. The rate of decomposition of this azo compound at 80° is $\sim 1.7 \times 10^{-4}$ mol^{-1} sec^{-1} and E_A is ~30 kcal/mol.[7] At 50° the rate constant is estimated to be $\sim 3.5 \times 10^{-6}$ mol^{-1} sec^{-1}. Thus the initial highest concentration of isobutyronitrile radical or the isobutyronitrile-peroxy radical in the presence of oxygen in these experiments is about 4×10^{-8} mol/l. which is negligibly small compared to the concentration of phenols in any of the experiments.

Simple phenols are less effective as initiators in this process than the hindered ones, indicating probably that the hindered phenoxy radicals are more stable and capable of existing long enough to undergo the redox reaction with N-vinylcarbazole. The nature of the redox initiated polymerization of N-vinylcarbazole *via* a cation radical is poorly understood at the present time, except it differs from ordinary radical initiated polymerization process *via* a carbon radical whereas the former process is insensitive toward oxygen and phenoxy radicals as well as other inhibitors mentioned earlier.

Experimental Section[8]

Chemicals.—N-Vinylcarbazole, mp 65–67°, was obtained from Matheson Coleman and Bell; 2,6-di-*t*-butylphenol, mp 35–37°, 2,4-di-*t*-butylphenol, mp 24–26°, phenol, mp 40–41°, and azobisisobutyronitrile, mp 103° dec, were obtained from Eastman. Methanol anhydrous AR was obtained from Mallinckrodt.

Polymerization of N-Vinylcarbazole.—(a) A solution of 2 g (1×10^{-2} mol) of N-vinylcarbazole and 0.02 g (1×10^{-4} mol) of 2,6-di-*t*-butylphenol and 0.05 g ($\sim 3 \times 10^{-4}$ mol) of azobisisobutyronitrile in 50 ml of methanol was heated under nitrogen atmosphere at 50° for 5 hr. The reaction mixture produced a yellowish gummy mass. Upon drying the solid weighed 1.2 g. The solid was triturated with benzene and turned into a yellowish white solid, melting at a wide range from 150 to 250°. The infrared spectrum in KBr possesses the following bands at 3030, 1650, 1600, 1560, 1500, 1450, 1240, 750, 720 cm^{-1}, resembling that of poly-*n*-vinylcarbazole.[9] This solid did not decolorize either bromine in carbon tetrachloride or permanganate solution in acetone–water medium.

In the blank runs, the one without azoisobutyronitrile produced no polymer while the one without 2,6-di-*t*-butylphenol afforded ~0.2 g of polymeric material of comparable property with that from experiment a.

(b) In two parallel experiments, the conditions and reagents were maintained the same as in (a) except that the amount of 2,6-di-*t*-butylphenol was increased to 0.04 g (2×10^{-4} mol) and 0.2 g (1×10^{-3} mol). The reaction proceeded as in (a) and the products were worked up in the same manner as in (a). The yields of the polymeric products in these two runs were 1.2 g and 1.5 g, respectively.

(c) When 2,4-di-*t*-butylphenol was used instead of 2,6-di-*t*-butylphenol as in (a), the reaction produced a polymeric substance resembling that from (a) weighing 1.1 g. With phenol, on the other hand, no polymer was obtained. However, when the reaction with phenol was heated at 50° for a longer time (20 hr), a trace amount of polymeric substance was obtained. Identification of this trace amount of substance was not attempted.

(d) Reaction a was repeated by carrying out the procedure in open air with vigorous stirring instead of under nitrogen atmosphere. It yielded a polymeric substance weighing 1.1 g. However, with azobisisobutyronitrile but no 2,6-di-*t*-butylphenol in open air, the yield of a polymeric substance was practically nil at the end of 5 hr.

Registry No.—N-Vinylcarbazole, 1484-13-5.

(7) F. W. Lewis and M. S. Matheson, *J. Amer. Chem. Soc.*, **71**, 747 (1949).
(8) Melting points are not corrected. Spectral analysis was performed in the analytical laboratories of Arthur D. Little, Inc., Cambridge, Mass.
(9) Reference polymer from General Aniline and Film Corp., Union, N. J.

The Diels–Alder Reaction of N-Vinylphthalimide with Isoprene and 9-Methoxyanthracene

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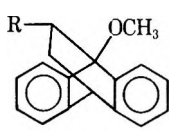
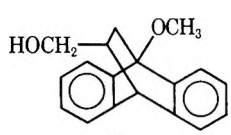
Received April 17, 1970

N-Vinylphthalimide (1) has been available commercially for over a decade and numerous accounts of its use as a monomer have been published, but its potential as a dienophile in the Diels–Alder reaction seems to be limited to the report of adduct formation with anthracene and hexachlorocyclopentadiene.[3] So far no unsymmetrically substituted diene has been condensed with it in order to study its regiospecificity in this reaction. Since vinylamine, like vinyl alcohol, is unavailable for use in a Diels–Alder reaction, the use of **1** potentially offers two step syntheses of various amines such as 11-amino-9,10-dihydro-9,10-ethanoanthracene. This pharmacologically interesting amine has so far been prepared only by a four-step synthesis from anthracene.[4]

9-Methoxyanthracene when condensed with acrylic acid, methyl acrylate, acrylonitrile, and acrylamide gives an adduct corresponding to **2**, but allyl alcohol, having no conjugated system, gives rise to **3**.[5]

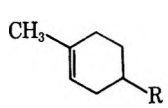


2

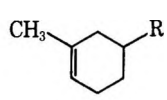


3

Isoprene, like other 2-substituted butadienes, gives rise to mainly the "para" adduct **4** rather than the isomeric adduct corresponding to **5** when condensed



4



5

with acrylic acid, acrolein,[6] methyl acrylate, acrylyl chloride, acrylamide,[7] styrene, 2-vinylpyridine,[8] etc.

Recently, the reaction of methyl acrylate with isoprene was reported to give a 7:1 ratio of the two adducts corresponding to **4** and **5**, respectively, when the reaction was run at either room temperature or at 120°.[9] When the reaction occurred in benzene at 7–12° and was catalyzed by aluminum chloride, a 19:1 ratio was obtained with the "para" adduct again predominating.[9]

Supposedly the aluminum chloride complexes with the carbonyl oxygen of the methyl acrylate and intensifies the positive charge on the β-carbon atom of the

(1) National Institutes of Health, Predoctoral Fellow, 1966–1967.
(2) Supported by the Office of Naval Research.
(3) K. Kato and M. Yoshida, *Nippon Kugaku Zasshi*, **87**, 1098 (1966).
(4) S. Wazonek and J. V. Hallum, *J. Org. Chem.*, **18**, 288 (1953).
(5) J. S. Meek, P. A. Monroe, and C. J. Bouboulis, *ibid.*, **28**, 2572 (1963).
(6) E. Lehman and W. Paasche, *Ber.*, **66B**, 1068 (1935).
(7) D. R. Wilgus, Ph.D. Thesis, University of Colorado, 1951.
(8) J. S. Meek, R. T. Merrow, and S. J. Cristol, *J. Amer. Chem. Soc.*, **74**, 2667 (1952).
(9) T. Inukai and T. Kojima, *J. Org. Chem.*, **31**, 1121 (1966).

acrylate moiety. This increases that carbon's attraction for the more electron rich carbon atom (C-1) in the isoprene molecule and leads to the higher ratio of the "para" adduct.

In N-vinylphthalimide delocalization of the unshared electron pair on the nitrogen atom should make the β-carbon atom of the vinyl group negative, but this effect would be counteracted by delocalization involving the carbonyl groups as well as by the inductive effects of the oxygen atoms. These effects do not lead to a clear cut prediction of the major adduct to be expected with 9-methoxyanthracene, although with isoprene one would expect an adduct corresponding to **4** as the major product since no dienophile has yet given a major adduct corresponding to **5**.

The Diels–Alder reaction of 1- and 9-methoxyanthracene went readily at 200° and only one adduct was isolated. Its pmr spectrum revealed a doublet for the bridgehead proton which showed it was the nonvicinal adduct corresponding to **3**.

Isoprene and **1** gave a crystalline adduct which was dehydrogenated to N-*p*-tolylphthalimide. The adduct was also synthesized from the known methyl acrylate–isoprene adduct.

It appears that 9-substituted anthracenes are more sensitive to steric and electronic effects governing orientation than are 2-substituted butadienes and that **1** behaves like an unconjugated dienophile in its condensation with 9-methoxyanthracene.

Experimental Section

N-(9-Methoxy-9,10-dihydro-9,10-ethanoanthracene-11-yl)phthalimide.— **1** (1 g) and 1.3 g of 9-methoxyanthracene[6] were fused at 200° for 50 hr. The mixture was then dissolved in ethanol, filtered, and then concentration gave 0.43 g of colorless solid, mp 200–203°. The pmr spectrum ($CDCl_3$) showed a doublet at 4.4 ppm (J = 2.5 Hz) for the bridgehead proton.

Anal. Calcd for $C_{25}H_{19}NO_3$: C, 78.72; H, 5.02. Found: C, 78.57; H, 4.92.

When anthracene and **1** were condensed in a similar fashion a 60% yield of N-(9,10-dihydro-9,10-ethanoanthracen-11-yl)phthalimide, mp 183–185°, was obtained. Recrystallizations from benzene–petroleum ether gave an analytically pure sample, mp 196–197° (lit.[3] 180–181°).

N-(1-Methyl-4-cyclohexenyl)phthalimide.—**1** (10 g), 4 g of isoprene and 0.1 g of hydroquinone dissolved in 15 ml of acetone were heated in a rocking autoclave at 175–185° for 28 hr. Extraction of the product with 250 ml of hot ethanol left 3.7 g of apparently polymeric material, mp 175–230° dec. From the extract 1.77 g (13%) of white crystals were obtained. Recrystallization gave the analytical sample, mp 141–143°.

Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.99; H, 6.21; N, 5.68.

The methyl acrylate adduct of isoprene[7] on treatment with hydrazine gave a product which by means of a Curtius reaction was converted into an amine which gave a phthalimide, mp 139–140°, that was identical with the adduct of **1** and isoprene.

When 1.2 g of the N-vinylphthalimide–isoprene adduct was heated for 80 min at 297–358° with 0.1 g of 10% palladium on charcoal, hydrogen was evolved. Fractional crystallization from ethanol then gave 0.19 g of white crystals, mp 201–203°. A mixture of this product and N-*p*-tolyphthalimide,[10] mp 202–203°, melted at 202–203° while a mixture of this product and N-*m*-tolyphthalimide,[10] mp 171–173°, melted at 160–185°.

Registry No.—**2** (R = phthalimido), 25577-21-3; **4** (R = phthalimido), 25577-22-4; N-vinylphthalimide, 3485-84-5; isoprene, 78-79-5; 9-methoxyanthracene, 2395-96-2.

(10) J. B. Lingle and H. F. Roeker, *J. Amer. Chem. Soc.*, **30**, 1882 (1908).

The Effect of Pressure on Some Sterically Hindered Solvolysis Reactions[1]

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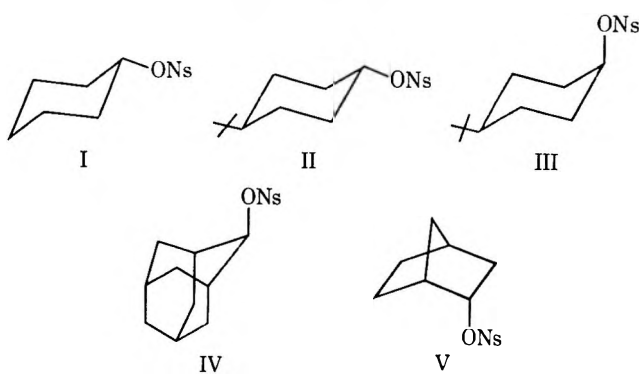
In several earlier publications[2–4] we have shown that the activation volume of a solvolysis reaction may depend somewhat on the occurrence of participation. In at least some of the reactions for which participation has been claimed, steric hindrance has been proposed[5] as an alternative explanation of the rate ratio of epimeric substrates, and since steric hindrance evidently also has small effects on the activation volume, at least in the Menshutkin reaction,[6,7] we considered it desirable to study the pressure-promoted hydrolysis of the following closely related nosylates.



In these reactions the formation of an ion pair should be unhindered for I and II and hindered for IV and V. In I, the leaving group is expected to depart from an equatorial position. In II, the 4-*tert*-butyl group forces it to leave from that position. In IV, the rigid adamantyl ring system forces it to leave from the axial position; hindrance is then provided by the axial 3- and 5-hydrogen atoms. In V, hindrance has been considered to be exerted by the 6-*endo*-hydrogen atom.[5] We hoped that a large difference between the pressure coefficients of II and III would furthermore enable us to calculate the effect of pressure on A, a measure of the size of the nosyloxy group.[8] The results are shown in Table I.

The absolute ΔV^* values are somewhat larger than those observed in earlier studies; the reason for this is that the more precise conductance method employed here allows its determination from observations over a smaller range (1 kbar) and with smaller pressure intervals (see ref 6 for a full discussion of this point).

The observations clearly do not show a correlation between ΔV^* and steric hindrance. While the ΔV^* values for I and II do seem to be slightly less negative

* Author to whom correspondence should be addressed.

(1) Paper XXI in the Series "Chemical Reactions Under High Pressure."
(2) W. J. le Noble and B. L. Yates, *J. Amer. Chem. Soc.*, **87**, 3515 (1965).
(3) W. J. le Noble, B. L. Yates, and A. W. Scaplehorn, *ibid.*, **89**, 3751 (1967).
(4) W. J. le Noble and B. Gabrielsen, *Tetrahedron Lett.*, **1**, 45 (1970).
(5) See, *e.g.*, H. C. Brown, *Chem. Brit.*, 199 (1966).
(6) For a review of this topic, see W. J. le Noble, *Prog. Phys. Org. Chem.*, **5**, 207 (1967), and several papers quoted there.
(7) W. J. le Noble and Y. Ogo, *Tetrahedron*,, in press.
(8) S. Winstein and N. J. Holness, *J. Amer. Chem. Soc.*, **77**, 5562 (1955).

TABLE I

EFFECT OF PRESSURE[a] ON THE SOLVOLYSIS RATE CONSTANTS[b] OF SEVERAL NOSYLATES IN AQUEOUS ACETONE AT 25°

I		II		III		IV		V	
p	10^5k_1	p	10^5k_1	p	10^5k_1	p	10^5k_1	p	10^5k_1
0.001	5.60	0.001	2.39	0.001	12.30	0.001	0.367	0.001	2.22
0.072	6.19	0.155	2.74	0.076	13.33	0.100	0.397	0.083	2.40
0.151	6.52	0.244	2.99	0.236	15.14	0.193	0.431	0.178	2.55
0.211	6.82	0.325	3.07	0.402	16.97	0.350	0.478	0.215	2.62
0.311	7.30	0.481	3.50	0.563	18.89	0.517	0.514	0.390	2.93
0.381	7.76	0.640	3.93	0.636	19.98	0.668	0.551	0.455	3.06
0.448	8.04	0.763	4.28	0.721	21.21	0.777	0.588	0.541	3.14
0.555	8.54	0.881	4.66	0.849	22.60			0.599	3.29
0.692	9.34							0.801	3.50
0.857	10.17								
ΔV_0^{*c} =	−20.0		−20.5		−21.6		−20.6		−21.0

[a] In kbar. [b] In sec^{-1}. [c] In cm^3/mol.

than those of III–V, the differences are very small and almost certainly within the limit of error, estimated to be ±0.3 cm^3/mol. We conclude that the difference between the ΔV^* values of V and its epimer[2,3] is not due to steric hindrance. Such effects might be demonstrated in more severely hindered solvolyses, but many such reactions are characterized by extensive concomitant rearrangement, so that participation and charge delocalization begin to cloud the picture, and in others the steric rate retardation is so great that the accurate conductance measurements employed here can no longer be used, at least not under the same conditions.

Experimental Section

The nosylate esters used were prepared by adding about 0.1 mol of *p*-nitrobenzenesulfonyl chloride to an equimolar amount of the alcohol at −10°, stirring for 0.5 hr, and adding a cold solution of 100 ml of concentrated hydrochloric acid and 500 ml of water. The mixture was extracted several times with ether and the combined extracts were dried with anhydrous magnesium sulfate and evaporated to small volume. The residue was decolorized and crystallized from ether; the yields were in the 50–70% range. The structures were verified by nmr; the analytical data are shown in Table II.

TABLE II

ANALYTICAL DATA OF THE NOSYLATE ESTERS

Alkyl group	Mp, °C	Calcd, % C	Calcd, % H	Found, % C	Found, % H
Cyclohexyl (I)	77.0–77.2	50.51	5.29	50.33	5.32
trans-4-*tert*-Butylcyclohexyl (II)	101.0–101.4	56.29	6.79	56.57	6.91
cis-4-*tert*-Butylcyclohexyl (III)	95.2–97.8	56.29	6.79	56.28	6.79
2-Adamantyl (IV)	137–139	56.96	5.67	56.89	5.88
2-*endo*-Norbornyl (V)	102.3–103.3	52.52	5.095	2.36	5.06

The conductance cell was similar to that used by Whalley.[9] Platinum tubing[10] (0.5 mm diameter) was used for the leads going through the Pyrex walls to avoid the problem[11] of frequent breakage due to the compressibility difference between Pyrex and platinum; in hundreds of pressure applications we did not experience a single breakage. The cells were conditioned with dilute solutions of *p*-nitrobenzenesulfonic acid in aqueous acetone and stored in the same solution when not in use. A mercury pool in the bottom of the cell provided the means for separating the solution from the pressure transmission fluid. The electrodes were about 1 cm apart and 4 mm in diameter; they were welded to the leads and platinized by the procedure of Jones and Bolinger.[12] The cell was suspended inside the pressure vessel[13] from a closure in such a way that the electrodes were connected *via* small cups sealed into a cell and filled with mercury, and prongs protruding from the closure. The prongs were slightly conical and insulated from the closure by means of conical lava sleeves; these sleeves in turn were made leak proof by means of an epoxy resin. The pressure was measured by means of a calibrated Bourdon gauge and could be held constant to about 1 bar more or less indefinitely. The temperature of the pressure vessel was controlled at 25.00 ± 0.02°. The resistances were measured by means of a Leeds and Northrup bridge (1553), Hewlett-Packard wide range oscillator and Model 102B oscilloscope, and a Rhode and Schwartz amplifier (121221-2). A frequency of 1500 Hz proved best for our apparatus. About 3 mg of the ester was employed in each run with 50 ml of solvent; the solvent composition was 55:45 acetone and water by weight. At least 10 pairs of observations were made after 1 hr was allowed for temperature equilibrium. The data were treated by the Guggenheim method to yield the rate constants;[14] the latter were obtained from the data by computer. The correlation coefficient was always larger than 0.999; reproducibility between completely independent runs was usually much better than 1%.

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Registry No.—I, 788-92-1; II, 25662-47-9; III, 25662-48-0; IV, 25665-65-0; V, 25716-02-3.

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The Aqueous Dichromate Oxidation of Primary Alcohols

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The oxidation of primary alcohols to aldehydes is often difficult to accomplish in good yields because the aldehydes are themselves easily converted to carboxylic acids under oxidative conditions. The methods avail-

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able to accomplish such transformations have recently been reviewed.[1] Of these methods the most attractive involve either the use of chromium trioxide in pyridine or argentic picolinate in aqueous solutions.[1,2] However, both of these methods are subject to certain limitations; the CrO_3–pyridine complex is hazardous to prepare and product isolation is sometimes difficult while argentic picolinate is an expensive reagent and time consuming in its preparation.

Sodium dichromate on the other hand is a readily available and inexpensive reagent that is known to have a high oxidation potential under acidic conditions or at elevated temperatures.[3,4] Under acidic conditions the oxidation of primary alcohols to aldehydes often gives unsatisfactory yields because of the formation of substantial amounts of carboxylic acids or esters[5,6] unless the aldehyde can be distilled from the reaction mixture as it forms.[7,8] However, it is known that aldehyde oxidation proceeds *via* the aldehyde hydrate[9] (eq 1) and,

$$RCH_2OH \xrightarrow{Cr^{VI}} RCH \overset{O}{\parallel} \xrightarrow[H^+]{H_2O} RCH(OH)_2 \xrightarrow{Cr^{VI}} RCO_2H \quad (1)$$

since the hydration reaction is acid catalyzed, it occurred to us that it might be sufficiently retarded under neutral conditions to make carboxylic acid formation negligibly slow. Consequently, we undertook a study of the oxidation of various types of alcohols by neutral aqueous sodium dichromate at high temperatures. This procedure has previously been used with good success for the oxidation of arene side chains.[10,11] However, since alcohols are more readily attacked by oxidants than are hydrocarbons, we were able to work under much less vigorous conditions. In fact, although the oxidation of arenes requires the use of a high temperature, high pressure reactor,[11] we found that some alcohols could be oxidized in refluxing aqueous dichromate solutions.

As the results presented in Table I indicate, this reaction gives good yields for all benzyl alcohols but much less satisfactory yields for aliphatic alcohols. Hence the value of the reaction lies in its obvious selectivity for α-phenyl alcohols and the ability to use conditions that are completely safe and easy to achieve. Furthermore, product isolation through extraction from the aqueous solution into ether is a relatively simple process.

A preliminary kinetic study into the relative rates of oxidation of benzyl alcohol and benzaldehyde was also completed and in agreement with our expectations it was found that the alcohol was oxidized approximately 18 times as fast as the aldehyde. At the pH of these kinetic experiments (5.6, phosphate buffer) the aldehyde hydrate is probably present in only minute concentrations thus preventing second stage oxidation to benzoic acid.

TABLE I

PRODUCTS OBTAINED FROM THE OXIDATION OF ALCOHOLS WITH AQUEOUS SODIUM DICHROMATE

Alcohol[a]	Product	Conversion, %[b]	Yield, %[c]
Benzyl alcohol[d]	Benzaldehyde	25	66
Benzyl alcohol	Benzaldehyde	70	85
Benzyl alcohol[e]	Benzaldehyde	79	78
	Benzoic Acid	7	7
p-Methoxybenzyl alcohol	*p*-Methoxybenzaldehyde	70	81
p-Methylbenzyl alcohol	*p*-Methylbenzaldehyde	48	79
p-Fluorobenzyl alcohol	*p*-Fluorobenzaldehyde	53	68
p-Chlorobenzyl alcohol	*p*-Chlorobenzaldehyde	36	85
m-Methoxybenzyl alcohol	*m*-Methoxybenzaldehyde	51	90
m-Chlorobenzyl alcohol	*m*-Chlorobenzaldehyde	27	96
p-Nitrobenzyl alcohol	*p*-Nitrobenzaldehyde	65	76
	p-Nitrobenzoic acid	10	10
o-Nitrobenzyl alcohol	*o*-Nitrobenzaldehyde	39	86
	o-Nitrobenzoic acid	1	1
β-Naphthylmethanol	β-Naphthaldehyde	65	82
Cinnamic alcohol	Cinnamaldehyde	87	91
α-Phenylethanol[f]	Acetophenone	50	96
α-Phenylethanol[e]	Acetophenone	84	86
β-Phenylethanol		None	None
2-Propanol	Acetone	4	13
Cyclohexanol	Cyclohexanone	2	27
Cyclohexanol[g]	Cyclohexanone	14	58
Cyclohexanol[h]	Cyclohexanone	10	35
1-Heptanol[h]	Heptanal	7	17
Allyl alcohol[i]	Acrolein	9	32
2-Methyl-2-propenol[i]	2-Methylpropenal	10	21
1-Hexen-3-ol[j]	1-Hexen-3-one	11	39

[a] Unless otherwise indicated a 1:1 mol ratio of $Na_2Cr_2O_7$ to alcohol (usually 0.10 mol of each component in 100 ml of water) was held at reflux temperature (98°) for 3 hr. [b] Conversion is based on the total amount of material recovered and indicates the extent to which the reaction has proceeded under these conditions. Total recovery varied from 80 to 99%. [c] Yield as based on unrecovered starting material. [d] A molar ratio of $Na_2Cr_2O_7$ to alcohol of 0.5 was used at 50° for 14 hr. [e] Time increased to 9 hr. [f] Time decreased to 2 hr. [g] Time increased to 6 hr. [h] Time increased to 24 hr. [i] 50° for 2 hr. [j] Time decreased to 1.5 hr.

Experimental Section

Equimolar ratios of sodium dichromate and alcohol (0.1 mol of each) were mixed with 100 ml of water and refluxed in a 250-ml round-bottomed flask equipped with a magnetic stirrer and reflux condenser. Usually the alcohol was not completely soluble in the refluxing mixture and with some alcohols (*e.g.*, *p*-methylbenzyl alcohol), acetone (1–5 ml) was added to prevent sublimation onto the reflux condenser. After 3 hr the mixture was cooled, diluted with 100 ml of water, the pH was adjusted to 9 with 1.0 *M* NaOH, and the mixture was extracted three times with 100-ml portions of ether. The aqueous portion was then acidified with 3 *M* H_2SO_4 and again extracted three times with 100-ml portions of ether. The ether extracts were dried over $MgSO_4$, concentrated, and analyzed by use of gas–liquid chromatography and a Varian A-60A nmr spectrophotometer equipped with a digital voltage monitor to integrate the proton signals.

Registry No.—Sodium dichromate, 10588-01-9.

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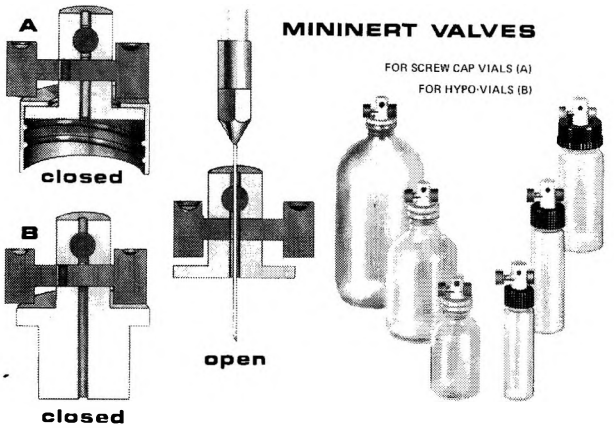

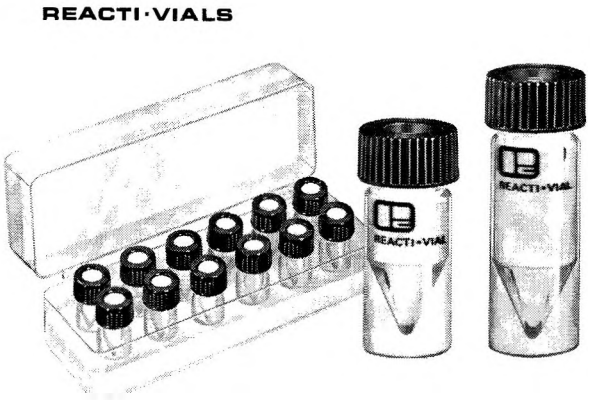

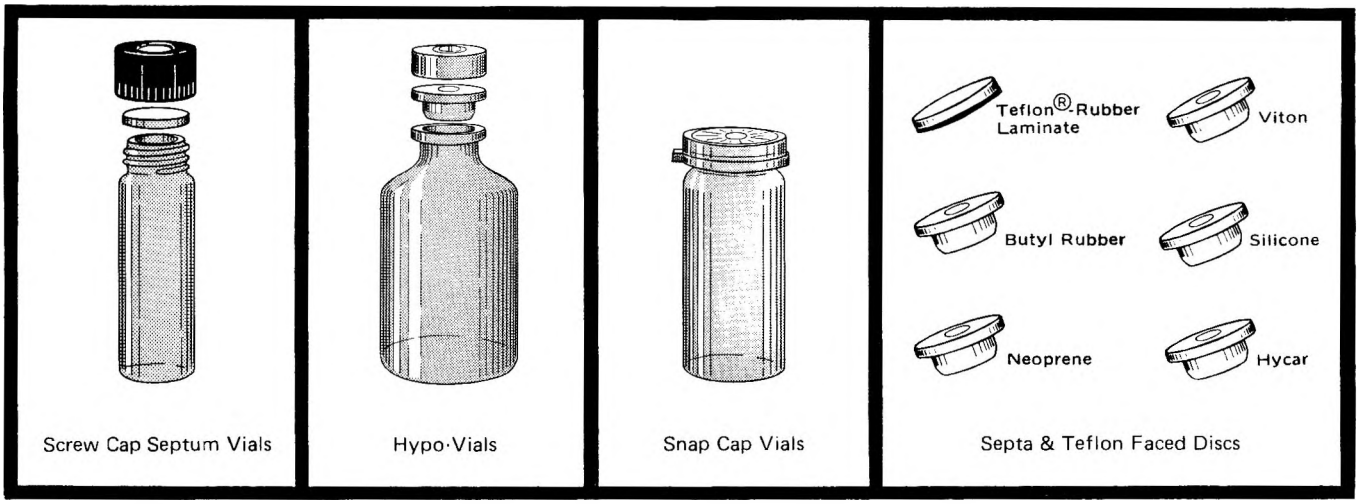

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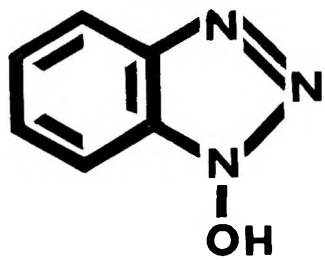

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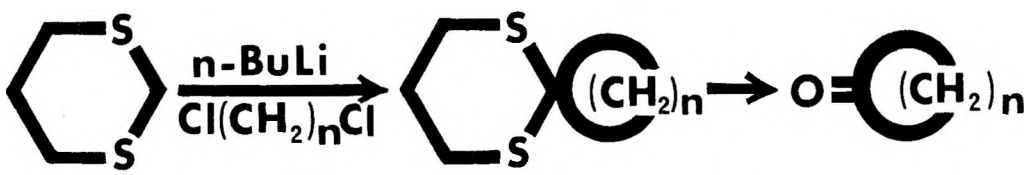

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