VOLUME 37 JANUARY 14, 1972 NUMBER 1 JOCEAH

THE JOURNAL OF Organic Chemistry

PUBLISHED BIWEEKLY BY THE AMERICAN CHEMICAL SOCIETY

THE JOURNAL OF Organic Chemistry

Published biweekly by the American Chemical Society at 20th and Northampton Streets, Easton, Pennsylvania

Published biweekly by the American Chemical Society at 20th and Northampton Sts., Easton, Pa. 18042. Second-class postage paid at Washington, D. C., and at additional mailing offices.

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Volume 37

JANUARY–APRIL 1972

(Pages 1–1280)

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JOCEAH 37(1) 1–154 (1972)

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(In nmr descriptions, s = singlet, d = doublet, t = triplet, m = multiplet.)

"The ethereal extract was dried ($MgSO_4$), concentrated, and distilled giving 10.23 g (65%) of the acetoxy ketone 12: bp 82–83° (2.9 mm); n_D^{25} 1.4266 [lit.[6] bp 80–82° (3 mm); n_D^{25} 1.4261]; d_4^{25} 0.823; $[\alpha]_D^{25}$ 0.0° (c 6, CH_3OH); uv max (95% EtOH) 275 nm (ε 21); ir (CCl_4) 1725 (C=O), 1740 cm^{-1} (ester C=O); nmr (CCl_4) δ 3.98 (t, 2, J = 6 Hz, CH_2OAc), 2.43 (t, 2, J = 6 Hz, CH_2CO), 2.07 (s, 3), 1.97 (s, 3), and 1.6 (m, 4); mass spectrum (70 eV) m/e (rel intensity) 158 (5), 143 (5), 115 (6), 100 (50), 99 (11), 98 (100), 85 (10)."

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THE JOURNAL OF Organic Chemistry®

VOLUME 37, NUMBER 1

JANUARY 14, 1972

The Acid-Catalyzed Isomerization of Thujopsene

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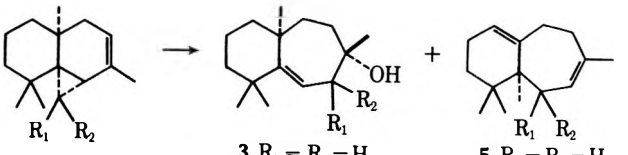
Received June 17, 1971

The acid-catalyzed isomerization of (−)-thujopsene (**1**) under nonaqueous conditions proceeds principally *via* the isolable spiro olefin intermediates α- and β-chamigrene (**8** and **9**) to a complex mixture of isomeric tricyclic olefins. The major component of this complex mixture is rigorously shown to be 7,10-ethano-4,4,7-trimethyl-1(9)-octalin (**10**).

The tricyclic sesquiterpene (−)-thujopsene is known to occur widely in genera belonging to the natural order Cupressales.[1] Originally isolated from Hibawood oil,[2] it has subsequently been shown to be present also in American cedarwood oil.[3] The first correct structure for thujopsene was deduced by Erdtman and Norin[4] and subsequent stereospecific total syntheses[5] of its racemate and evidence from chemical degradation[6] has confirmed the earlier[4] structural assignment. The absolute configuration of (−)-thujopsene was initially assigned by Enzell[7] and later confirmed by Dauben and Oberhansli[8] and the naturally occurring sesquiterpene is thus known to possess structure **1**.

With the structure of (−)-thujopsene well established, attention has focused on the chemistry of this unusual molecule, especially protonation with appropriate acid catalysts to the rearrangement-prone cyclopropylcarbinyl cation system. Thujopsene (**1**) treated with aqueous oxalic acid was reported by Nagahama[9] to give an unidentified hydrocarbon and widdrol (**3**). Dauben and Friedrich[10,11] reported that treatment of thujopsene with perchloric acid in aqueous dioxane afforded primarily widdrol (**3**) and a bicyclic diene identified as 1,4,11,11-tetramethylbicyclo[5.4.0]undeca-3,7-diene (**5**). Subsequent isomerization studies[12-14] employing racemic dideuteriothujopsene (**2**) afforded dideuteriowiddrol (**4**) and dideuterated bicyclic diene **6** with the deuterium label in the final products on different carbon atoms. These authors presented a mechanism which accounted for the divergent pathways observed. Further acid treatment[11,13] of diene **5** afforded a tricyclic hydrocarbon identified as 2,2,3,7-tetramethyltricyclo[5.2.2.0^{1,6}]undec-3-ene (**7**).



1, $R_1 = R_2 = H$
2, $R_1 = R_2 = D$
3, $R_1 = R_2 = H$
4, $R_1 = R_2 = D$
5, $R_1 = R_2 = H$
6, $R_1 = R_2 = D$

Recently Itô and coworkers[15] have reported similar results in their studies on the perchloric acid–aqueous dioxane isomerizations of thujopsene (**1**) and, in addition, identified small amounts of β-chamigrene (**9**) and a tricyclic hydrocarbon assigned structure **10** but whose structure was not rigorously proved.

We have found that the acid-catalyzed isomerization of (−)-thujopsene (**1**) under nonaqueous conditions affords as the major initial products the isolable spiro olefin intermediates α- and β-chamigrene (**8** and **9**).[16,17] Subsequent rearrangement affords an isomeric series of principally two tricyclic olefins which we shall here designate as olefin A and olefin B. We will discuss later the rigorous structure proof of olefin B and its formulation as 7,10-ethano-4,4,7-trimethyl-1(9)-octalin (**10**).

(1) T. Norin, *Acta Chem. Scand.*, **15**, 1676 (1961).
(2) M. Yano, *J. Soc. Chem. Ind. Jap.*, **16**, 443 (1913); S. Uchida, *ibid.*, **31**, 501 (1928).
(3) J. Runeberg, *Acta Chem. Scand.*, **14**, 1288 (1960).
(4) H. Erdtman and T. Norin, *Chem. Ind. (London)*, 622 (1960); T. Norin, *Acta Chem. Scand.*, **15**, 1676 (1961); S. Forsen and T. Norin, *ibid.*, **15**, 592 (1961).
(5) W. G. Dauben and A. C. Ashcraft, *J. Amer. Chem. Soc.*, **85**, 3673 (1963); G. Buchi and J. D. White, *ibid.*, **86**, 2884 (1964); K. Mori, M. Ohki, A. Kobayashi, and M. Matsui, *Tetrahedron*, **26**, 2815 (1970).
(6) T. Norin, *Acta Chem. Scand.*, **17**, 738 (1963).
(7) C. Enzell, *ibid.*, **16**, 1553 (1962).
(8) W. G. Dauben and P. Oberhansli, *J. Org. Chem.*, **30**, 3947 (1965).
(9) S. Nagahama, *Bull. Chem. Soc. Jap.*, **33**, 1467 (1960).
(10) W. G. Dauben and L. E. Friedrich, *Tetrahedron Lett.*, 1735 (1967).
(11) L. E. Friedrich, Dissertation No. 67-8559, University Microfilms, Inc., Ann Arbor, Mich.
(12) W. G. Dauben and L. E. Friedrich, *Tetrahedron Lett.*, 2675 (1964).
(13) W. G. Dauben and L. E. Friedrich, Abstracts of the International Union of Pure and Applied Chemistry, Fifth International Symposium on the Chemistry of Natural Products, London, July 8–13, 1968, pp 296–297.
(14) W. G. Dauben and E. I. Aoyagi, *Tetrahedron*, **26**, 1249 (1970).
(15) S. Itô, M. Yatagai, and K. Endo, *Tetrahedron Lett.*, 1149 (1971); S. Itô, M. Yatagai, K. Endo, and M. Kodama, *ibid.*, 1153 (1971).
(16) S. Itô, K. Endo, T. Yoshida, M. Yatagai, and M. Kodama, *Chem. Commun.*, 186 (1967).
(17) Y. Ohta and Y. Hirose, *Tetrahedron Lett.*, 2483 (1968).

TABLE I

Entry	Acid	Acid/thujopsene wt ratio[a]	T, °C	Time, hr	Yield, %, hydrocarbons	7	11[b]	10[b]	9	5	8	Unidentified[c]
					Thujopsene							
1	Formic (90%)	0.1	100	1	96	0	0	0	28	8	55	9
2	Polyphosphoric	0.02	40	3	93	2	0	0	29	13	53	3
3	Polyphosphoric	0.4	40	3	89	11	28	42	0	0	9	10
4	Phosphoric (100%)	0.4	40	3	93	7	5	18	6	11	46	7
5	Perchloric (70%)	0.4	40	3	90	17	30	44	0	0	2	7
6	Sulfuric (98%)	0.4	40	3	93	34	21	29	0	0	7	9
					Chamigrenes[d]							
7	Polyphosphoric	0.4	40	3	95	13	24	37	0	0	13	13
8	Sulfuric (98%)	0.4	40	3	90	18	28	42	0	0	1	11
9	Perchloric (70%)	0.4	40	3	89	17	29	42	0	0	1	11

[a] Entry 1 contains no acetic acid; for the other entries a 1:1 wt ratio of thujopsene to acetic acid was employed. [b] Analysis on a Carbowax 20M column. Analysis on a liquid crystal or an SF-96 column shows that these two components are actually five compounds in a 5:30:12:18:35 ratio. [c] Entries 3 and 5–9 contain approximately 5% cuparene (**13**) reported under unidentified hydrocarbons. [d] The distilled mixture obtained from entry 1 was used in these isomerizations.

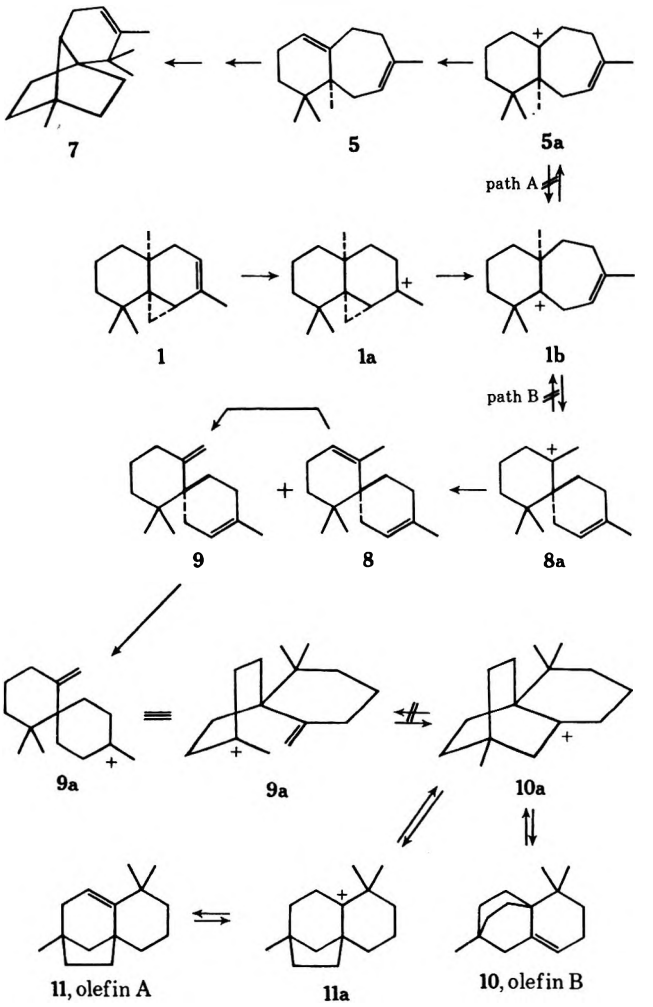
Our general acid isomerization conditions employed were various concentrations of strong mineral acids in acetic acid. Acetic acid, although not a sufficiently strong acid to isomerize thujopsene at the temperatures employed, served as a useful solvent in which to conduct the desired isomerizations. These conditions led to high yields of distilled isomerized olefin products and to low amounts (less than 5%) of acetate byproducts. The reaction mixtures were analyzed directly by gas chromatography and mass spectrometry, and individual components were subsequently purified *via* spinning-band distillation and identified by comparison of spectral data with authentic samples where available. Some of our pertinent results are summarized in Table I.

Treatment of (−)-thujopsene with formic acid (entry 1) or low ratios of polyphosphoric acid in acetic acid (entry 2) led principally to the optically active α- and β-chamigrenes (**8** and **9**) with only a minor amount of the bicyclic diene **5** reported by previous workers[10,11,15] as the principal product under aqueous acid conditions.

The chamigrene mixture above when treated with higher ratios of strong mineral acid in acetic acid (entries 7–9) led to the formation of the tricyclic olefin mixture **7**, **10**, and **11**. Almost identical ratios were obtained when (−)-thujopsene itself was subjected to the same conditions (entries 3 and 5), while sulfuric acid (entry 6) afforded a somewhat higher amount of tricyclic olefin **7**. Tricyclic olefin **7** is optically active, whereas olefins **10** and **11** are both inactive. Reactions interrupted at partial conversion (entry 4) showed that the β-chamigrene (**9**) disappeared far more rapidly than the α-chamigrene (**8**) and that tricyclic olefin **10** was formed more rapidly than olefin **11**.

Although these results would seem to imply the involvement of a rapid **9** → **10** conversion and a slow **8** → **11** conversion, the rearrangement pathway is best accommodated *via* a slow **8** → **9** isomerization followed by a rapid **9** → **10** conversion and a subsequent slow **10** → **11** isomerization as outlined in Scheme I. Protonation of (−)-thujopsene (**1**) leads to the bicyclic cation **1b** *via* cyclopropyl ring opening of initially formed cation **1a**. Cation **1b** is a key intermediate in this sequence

SCHEME I



since two divergent rearrangement pathways are possible. Path A affords cation **5a** *via* angular methyl migration and generation of bicyclic diene **5** by subsequent proton loss. This pathway has already been shown to hold for diene **5** by the deuterium labeling studies[12–14] which led to the dideuteriodiene **6** from dideuteriothujopsene (**2**). Alternatively, path B would

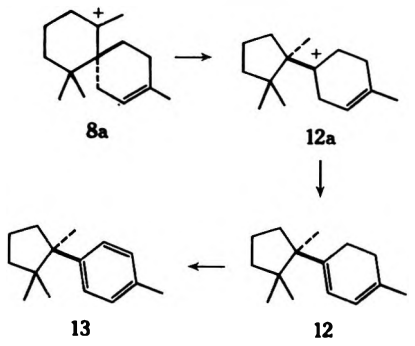
afford the spiro cation **8a** *via* ring contraction from cation **1b**, subsequent proton loss generating both α-chamigrene (**8**) and β-chamigrene (**9**).

Bicyclic diene **5** is reported[11] to be optically active and we also find that both the α- and β-chamigrenes (**8** and **9**) generated under our conditions retain high optical purity of the same sign of rotation as the chamigrenes isolated from natural sources.[16,17] These results imply highly stereoselective bond migrations during the isomerization process. Itô and coworkers[15] likewise report that the β-chamigrene (**9**) isolated under their conditions retains high optical purity.

Subsequent rearrangements of diene **5** eventually lead to tricyclic olefin **7** reported[11,13] and confirmed by us to be optically active. The α-chamigrene (**8**) slowly isomerizes to β-chamigrene (**9**) which, known from its chemistry to preferentially react at the less hindered trisubstituted double bond,[16] readily generates cation **9a**. Cyclization of cation **9a** to tricyclic cation **10a** then affords inactive (no asymmetric center) tricyclic olefin **10**. These findings are substantiated by the observations of Itô and coworkers[15] that β-chamigrene (**9**) upon further mild isomerization affords the tricyclic hydrocarbon **10** as the major product.

Several minor components of unknown structures are combined in Table I under the heading unidentified hydrocarbons. For entries 3 and 5–9 we have shown approximately 50% of these unidentified components to be identical with the known hydrocarbon cuparene (**13**).[18] The formation of this optically active hydrocarbon undoubtedly arises *via* cuprenene **12**, known[19] to readily aromatize to cuparene (**13**) as outlined in Scheme II. This product also exhibits a high degree

SCHEME II

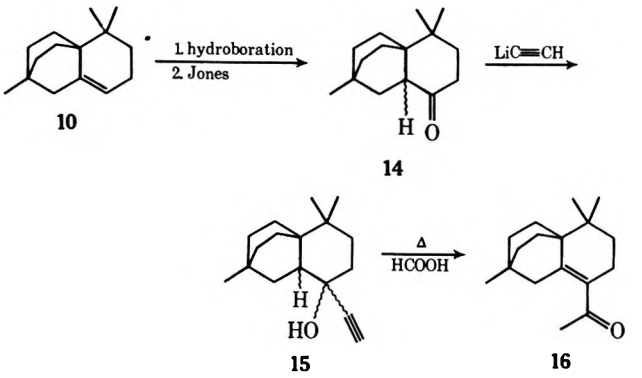


of optical purity again pointing to stereoselective bond migrations during the isomerization process.

Olefins A and B were separated free from contamination by each other *via* careful spinning-band distillation; however, nmr evidence indicated that neither component was pure. A column was eventually found which showed that the 40:60 mixture of product olefins A and B contained at least five components in a 5:30:12:18:35 ratio. Separate acid treatment of either olefin A or B afforded identical mixtures of the same five components.

In view of the complexity of the above equilibrium mixture we concentrated our efforts on the structure elucidation of olefin B since this component was the one initially formed from β-chamigrene (**9**) and also was the major (35%) component of the equilibrium mixture. A spinning-band prepared sample of olefin B (judged by nmr to be 65–70% pure, but free from olefin A) was utilized in subsequent transformations as outlined in Scheme III. Ketone **14** was readily prepared *via* hydroboration–oxidation of olefin **10** and Jones[20] oxidation of the resulting secondary alcohol mixture. Treatment of ketone **14** with lithium acetylide afforded the tertiary alcohol derivative **15** which smoothly rearranged upon heating in formic acid to the methyl ketone known[21] to possess structure **16**. The structure of olefin B is thus rigorously shown to be the tricyclic olefin 7,10-ethano-4,4,7-trimethyl-1(9)-octalin (**10**).

SCHEME III



We have as yet no definitive proof for the structure of olefin A, the 30% equilibration component, but prefer structure **11**. Spectral evidence is not unequivocal and other reasonable structures can be postulated. No attempts have been made to elucidate the structures of the remaining minor equilibration components.

The factors which govern the ratio of path A to path B (Scheme I) are not clearly understood. We confirm earlier observations[11,15] that thujopsene treated with dilute perchloric acid in aqueous dioxane affords predominantly the bicyclic diene **5** (path A) with only minor amounts of α- and β-chamigrene. Our conditions utilizing acetic acid or formic acid as solvent greatly favor the path B products and we observe in general only minor amounts (~15%) of products derived *via* path A.

Indirect evidence strongly suggests that the initial products (**8** and **9**) from path B do not lead to any products (**5**) from path A and vice versa. The known amount of path A derived products (Table I, entry 1, olefins **7** and **5**) of thujopsene treated with formic acid is roughly the same as that obtained when this mixture is further isomerized with stronger acids (entries 7–9). Some deviation is to be expected since the fate of the undefined components (7%) is unknown. Furthermore, sulfuric acid–acetic acid treatment of thujopsene (entry 6) affords significantly more products from path A than when the chamigrene mixture (entry 8) is employed under the same conditions. This latter result implies a difference in the fate of initially formed cation **1b** (path A *vs.* path B ratio) and not that cations **8a** and **5a** themselves interconvert *via* the intermediacy of cat-

(18) C. Enzell and H. Erdtman, *Tetrahedron*, **4**, 361 (1958).
(19) W. G. Dauben and P. Oberhansli, *J. Org. Chem.*, **31**, 315 (1966).
(20) K. Bowden, I. M. Heilbron, E. R. H. Jones, and B. C. L. Weedon, *J. Chem. Soc.*, 39 (1946).
(21) H. U. Daeniker, A. R. Hochstetler, K. Kaiser, G. C. Kitchens, and J. F. Blount, *J. Org. Chem.*, **36**, 6 (1971).

ion **1b**, which would predict identical product ratios in entries 6 and 8.

More direct evidence on this question was obtained by the isomerization of a sample of α-chamigrene (containing 4% of an unidentified component but no bicyclic diene **5**) with sulfuric acid–acetic acid. Detailed analysis of the product showed only 1.5% of tricyclic olefin **7** derived from path A, the remaining products identified as the olefin A and B mixture (93%), cuparene (**13**, 3.5%), and an unidentified component (2%). Cation **8a** must of necessity be involved in this transformation in order to convert to cation **9a** for further cyclization, but virtually no conversion to cation **1b** and entry to the path A products is observed. Similar results have recently been reported[15] for the further isomerization of β-chamigrene (**9**).

Olefin **7** clearly does not arise from the olefin A and B mixture since isomerization of a sample of olefin B (**10**) under our standard conditions afforded no tricyclic olefin **7** or any of the chamigrenes, implying no appreciable reversal to cation **9a** from cation **10a**. Furthermore, Dauben and Friedrich[13] have already shown that bicyclic diene **5** is converted to tricyclic olefin **7** in 70% yield upon further isomerization and thus implying minimal crossover of this path A product to the path B products observed under our conditions.

Closer inspection of the results of the previously reported[11,15] isomerizations under aqueous acid conditions shows that the initial reaction of thujopsene is hydration to widdrol (**3**) and that the isomerized products may actually arise from the solvolysis of this tertiary alcohol. Both compounds, however, should afford the same intermediate cations and lead to the same products under identical treatment. Indeed, treatment of widdrol (**3**) with sulfuric acid–acetic acid gave the same product mixture as obtained directly from thujopsene showing that under nonaqueous conditions the path B products again predominate.

The difference in behavior between the two sets of isomerization conditions (strong acid in aqueous *vs.* nonaqueous media) apparently lies in subtle solvation effects on the intermediate cations **1a** and **1b** which lead to path A preference in aqueous acid and to path B preference in nonaqueous acid. Thus by appropriate choice of conditions a number of different isomerization olefins can be obtained as the major products.

Experimental Section

Materials and Equipment.—(−)-Thujopsene was readily obtained in 99% purity by careful fractional distillation of Hiba wood oil through a 2-ft Goodloe column: bp 67–68° (0.5 mm); $n^{20}D$ 1.5050; $[\alpha]^{25}D$ −92.5° (neat).

Spectra were recorded using a Perkin-Elmer 457 grating ir spectrophotometer, Varian A-60A nmr spectrometer, and a Perkin-Elmer 270 double-focusing mass spectrometer. Spinning-band separations were accomplished with a Nester-Faust NFA-100 autoannular Teflon spinning-band column. Vapor phase chromatography (vpc) was carried out with an F & M 720 equipped with a 2 m × 0.25 in. copper column packed with 15% Carbowax 20M on Chromosorb P (column A) or a Beckman GC-5 equipped with a 500 ft × 0.03 in. SF-96 coated stainless steel capillary column (column B). The retention times (T_r) on these columns of the olefins identified in this study relative to α-chamigrene (**8**) are summarized in Table II.

Formic Acid Treatment of (−)-Thujopsene (1).—A mixture of thujopsene (120 g) and 90% formic acid (12 g) was heated at 100° for 1.0 hr, then cooled and poured into 100 ml of water, and extracted with benzene. The organic extracts were washed with water, sodium bicarbonate solution, and water. The solvent was removed under reduced pressure and distilled affording 115 g (96%) of hydrocarbon mixture, bp 65–75° (0.5 mm), $[\alpha]^{25}D$ −21° (neat). Analysis of this mixture by gas chromatography gave the composition in Table I, entry 1.

TABLE II

Olefin	T_r (column A)	T_r (column B)
Tricyclic olefin **7**	0.62	0.79
Thujopsene (**1**)	0.64	0.81
Olefin A (**11**)	0.72	0.83,[a] 0.87[a]
Olefin B (**10**)	0.82	0.90,[a] 0.91,[a] 0.94[a]
β-Chamigrene (**9**)	0.90	0.89
Bicyclic diene **5**	1.00	0.99
α-Chamigrene (**8**)	1.00	1.00
Cuparene (**13**)	1.30	1.18

[a] These five components are present in the olefin A–olefin B mixture; the peak with T_r = 0.87 is pure olefin A (**11**) and that with T_r = 0.94 is pure olefin B (**10**). The structures of the peaks with T_r = 0.83, 0.90, and 0.91 are unknown.

(−)-β-Chamigrene (9).—A sample of the hydrocarbon mixture above (100 g) was separated *via* careful spinning-band distillation and the progress of the distillation monitored by vpc. A sample of β-chamigrene in 95% purity exhibited the following characteristics: bp 109–110° (5 mm); $n^{20}D$ 1.5105; $[\alpha]^{25}D$ −52° (neat) [lit.[16] $[\alpha]^{15}D$ −52.7° ($CHCl_3$)]; ir (neat) 1638, 1388, 1368, 890, 804 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 5.30 (m, 2, $W_{h/2}$ = 8 Hz), 4.88 (m, 1, $W_{h/2}$ = 4 Hz), 4.54 (d, 1, J = 2 Hz), 1.58, 0.87, 0.88 (s, 3 each); mass spectrum 204 (26), 189 (79), 119 (60), 107 (65), 105 (72), 93 (100). These spectral data are identical with those reported[16] for (−)-β-chamigrene isolated from natural sources.

Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.31; H, 12.00.

(−)-α-Chamigrene (8).—Continued fractionation of the above hydrocarbon mixture afforded α-chamigrene in 93% purity and exhibited the following characteristics: bp 111–112° (5 mm); $n^{20}D$ 1.5145; $[\alpha]^{25}D$ −11° (neat) [lit.[17] $[\alpha]D$ −14.5° ($CHCl_3$)]; ir (neat) 1655, 1072, 830, 810, 800, 760 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 5.37 (m, 2, $W_{h/2}$ = 15 Hz), 1.65, 1.63 (s, 3 each), 0.89, 0.84 (s, 3 each); mass spectrum 204 (38), 136 (82), 133 (36), 121 (100), 119 (74), 105 (44), 93 (58), 91 (41). These spectral data correspond to those reported[17] for (−)-α-chamigrene isolated from natural sources.

Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 87.98; H, 11.96.

Polyphosphoric Acid–Acetic Acid Treatment of (−)-Thujopsene (1).—A mixture of polyphosphoric acid (200 g) and acetic acid (500 g) was agitated at 40° while thujopsene (500 g) was fed in over 10 min. After 3 hr the reaction mixture was poured into water (1 l.) and extracted well with benzene. The organic layers were successively washed with water, sodium carbonate solution, and brine. The solvent was removed under reduced pressure to afford 500 g of crude product which by vpc analysis had the composition given in Table I, entry 3. This material was distilled through a 2-ft Goodloe column and a total of 446.9 g (89%) of hydrocarbon fractions, bp 51–89° (0.5 mm), was obtained. Identical isomerization procedures with other mineral acids in acetic acid gave the results summarized in Table I.

2,2,3,7-Tetramethyltricyclo[5.2.2.0^{1,6}]undec-3-ene (7).—Fractions of the above distillation enriched in the desired isomer were further purified by spinning-band distillation and the progress of the distillation was monitored by vpc. A minor component in the early distillation fractions was isolated in pure form: bp 97–98° (5 mm); $n^{20}D$ 1.4996; $[\alpha]^{25}D$ −64° (neat); ir (neat) 1651, 1068, 1056, 1023, 838, 792 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 5.26 (m, 1, $W_{h/2}$ = 7 Hz), 1.67 (s, 3), 1.01, 0.97, 0.87 (s, 3 each); mass spectrum 204 (38), 189 (100), 175 (36), 119 (93), 105 (39), 95 (50), 91 (38). Comparison with an authentic sample[11] of 2,2,3,7-tetramethyltricyclo-[5.2.2.0^{1,6}]undec-3-ene (**7**) proved that the two samples were identical.

Olefin A (11).—Continued spinning-band distillation afforded samples of olefin A which exhibited the following characteristics: bp 100–101° (5 mm); $n^{20}D$ 1.5075; $[\alpha]^{25}D$ 0° (neat); ir (neat) 1664, 1188, 1102, 1070, 985, 960, 840, 795, 662 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 5.23 (m, 1, $W_{h/2}$ = 9 Hz), 0.99, 0.87, 0.83 (s, 3 each); mass spectrum 204 (31), 189 (27), 175 (100), 133 (20), 119 (35), 105 (39), 95 (20).

Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.24; H, 11.81.

7,10-Ethano-4,4,7-trimethyl-1(9)-octalin (10).—Continued spinning-band distillation afforded samples of olefin B free from olefin A which exhibited the following characteristics: bp 103–104° (5 mm); $n^{20}D$ 1.5085; $[\alpha]^{25}D$ 0° (neat); ir (neat) 1670, 1135, 1070, 960, 838, 815, 770 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 5.26 (m, 1, $W_{h/2}$ = 8 Hz), 0.80 (s, 3), 0.78 (s, 6), impurity singlets at 1.00 and 1.02 (approximately 30% impurity by integral); mass spectrum 204 (42), 189 (40), 175 (100), 148 (25), 133 (25), 119 (50), 105 (55), 95 (25), 91 (29).

Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.07; H, 11.76.

Cuparene (13).—A minor higher boiling component formed during the above isomerization was also isolated and exhibited the following characteristics: bp 75–76° (0.5 mm); $n^{20}D$ 1.5137; $[\alpha]^{25}D$ +46.5° (neat) [lit.[17] $[\alpha]^{25}D$ +65.3° (neat)]; ir (neat) 1892, 1785, 1510, 1463, 1018, 809, 720, 544 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 2.30, 1.25, 1.07, 0.56 (s, 3 each), 7.10, 7.24 (AB quartet, 4, J_{AB} = 8.5 Hz); mass spectrum 202 (25), 145 (59), 132 (100), 131 (65), 119 (51), 105 (38). The spectral data are identical with that reported[17] for cuparene isolated from natural sources.

7,10-Ethano-4,4,7-trimethyl-1-decalone (14).—A solution (110 ml) of 1 *M* BH_3 in tetrahydrofuran was placed under nitrogen and cooled to 5°; a 10.4-g (100 mmol) sample of olefin B (judged by nmr to contain 70% of olefin 10) was added over 10 min. The resulting solution was stirred at 25° for 20 hr, cooled to 5°, treated successively with 10 ml of water, 80 ml of 10% aqueous NaOH, and 80 ml of 30% aqueous H_2O_2, and then stirred at 35° for 3.5 hr. The mixture was extracted with hexane, and the organic portion was washed with water and dried over anhydrous magnesium sulfate. The solvent was removed to afford 22.0 g of a waxy solid, ir (neat) 3360 cm^{-1}. This crude alcohol mixture was dissolved in 200 ml of acetone, cooled to 5°, and treated with 21 ml of standard Jones[20] reagent. After 20 min, isopropyl alcohol (5 ml) was added and the mixture filtered. The salts were dissolved in water and extracted with hexane. The combined organic extracts were washed with sodium bicarbonate solution and brine and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue distilled affording 18.5 g (84%) of principally ketone **14**: bp 110–112° (0.5 mm); $n^{25}D$ 1.5072; $[\alpha]^{25}D$ 0° (neat); ir (neat) 1707 (C=O), 1143, 1004 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 1.17, 0.86, 0.81 (s, 3 each); mass spectrum 220 (100), 191 (59), 164 (32), 135 (35), 121 (37), 81 (46). This material solidified upon standing. A sample recrystallized from hexane exhibited mp 51–52° (lit.[15] mp 48°).

The 2,4-dinitrophenylhydrazone was prepared and exhibited mp 191–192° after four recrystallizations from ethanol.

Anal. Calcd for $C_{21}H_{28}N_4O_4$: C, 62.98; H, 7.05; N, 13.99. Found: C, 63.00; H, 7.35; N, 14.24.

1-Acetyl-7,10-ethano-4,4,7-trimethyl-1(9)-octalin (16).—Lithium acetylide–ethylenediamine complex (15.0 g, 0.15 mol) was suspended in anhydrous benzene (35 ml) and anhydrous tetrahydrofuran (35 ml) and heated to 40°. To this suspension was added ketone **14** (17.0 g, 0.076 mol) at a rate to maintain the temperature between 40 and 45°. The mixture was stirred for 3 hr and cooled and water (30 ml) added and stirred at 50° for 1 hr. The solution was filtered and washed with benzene and brine, and the solvent was removed. The crude product (20 g) showed ir absorptions at 3500 (OH) and 3330 (≡CH) expected for alcohol **15**, as well as a carbonyl at 1707 cm^{-1} of unreacted ketone **14**, and was judged to contain 40% of ketone **14** by integration of the nmr spectra. A sample of the above crude mixture (9.0 g) was heated at 100° for 3 hr with 90% formic acid (30 ml) and water (2.5 ml). The solution was cooled, poured into water (200 ml), and extracted with benzene. The combined organic extracts were washed with sodium bicarbonate solution and brine. The solvent was removed and the residue distilled to afford 6.1 g of material, bp 110–125° (0.1 mm). Analysis by vpc showed two peaks in a 40:60 ratio which were separated by preparative vpc. The minor component was identical with starting ketone **14**. The major component possessed spectral properties identical with an authentic sample[21] of 1-acetyl-7,10-ethano-4,4,7-trimethyl-1(9)-octalin (**16**).

Acid-Catalyzed Isomerization of α-Chamigrene (8).—A sample of α-chemigrene (**8**, 0.50 g, 96% pure by vpc, containing no bicyclic diene **5**) was vigorously agitated with 98% sulfuric acid (0.20 g) and acetic acid (0.50 g) for 3 hr at 40°. The mixture was cooled, diluted with water, and extracted with hexane. The organic extracts were washed with sodium bicarbonate solution and the solvent was removed under reduced pressure. Short-path distillation afforded 0.45 g of colorless oil, bp 90–100° (0.4 mm). Analysis by vpc (column B) and mass spectroscopy gave the following composition: **7** (1.5%), olefin A and B (5 components, 93%), **13** (3.5%), unidentified component (2%).

Acid-Catalyzed Isomerization of Widdrol (3).—A sample of widdrol[9] (**3**, 1.5 g) was vigorously agitated with acetic acid (2.0 g) and 98% sulfuric acid (0.80 g) at 40° for 3 hr. The mixture was cooled, diluted with water, and extracted with hexane. The organic extracts were washed with sodium bicarbonate solution and the solvent was removed under reduced pressure. Short-path distillation afforded 1.2 g of colorless oil, bp 90–100° (0.4 mm). Analysis by vpc (column A) gave the following composition: **7** (33%), olefins A and B (5 components, 60%), **13** (4%), unidentified components (3%).

Registry No.—**1**, 470-40-6; **7**, 32391-40-5; **8**, 19912-83-5; **9**, 18431-82-8; **10**, 32391-43-8; **11**, 32391-44-9; **13**, 16982-00-6; **14**, 32391-46-1; **14**, 2,4-DNPH, 32391-47-2.

The Acetylation of Thujopsene

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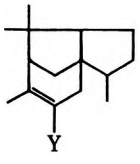
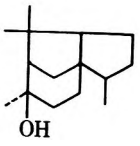
Received June 17, 1971

The acetylation of the hydrocarbon fraction of American cedarwood oil with acetic anhydride–polyphosphoric acid affords two major products, acetylcedrene (2) derived from (−)-α-cedrene and 1-aceto-7,10-ethano-4,4,7-trimethyl-1(9)-octalin (6) derived from (−)-thujopsene (5) by prior isomerization to octalin 8 and subsequent acetylation. The structure of ketone 6 was established by X-ray analysis of the ethylene thioketal derivative.

American cedarwood oil, one of the most economical and abundant sources of sesquiterpenes, is an important oil for the fragrance industry in the United States. The structures of the two best known constituents of this oil, α-cedrene (1) and cedrol (3), were finally determined by Stork and coworkers[1,2] more than a century after their initial isolation. Subsequent more detailed investigation of the hydrocarbon portion of this oil[3] has shown that in addition to α-cedrene an almost equal amount (40–50%) of thujopsene (5) is present, along with small amounts (5–15%) of β-cedrene (4) and a number of other sesquiterpenes.



1, Y = H
2, Y = $COCH_3$



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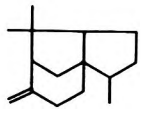

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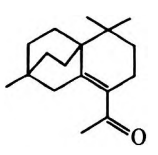
Among the numerous derivatives of American cedarwood oil which are utilized in perfumery is a ketonic mixture obtained by the acetylation of the hydrocarbon fractions of this oil with acetic anhydride or acetyl chloride and catalysts such as zinc chloride, aluminum chloride, or boron trifluoride. This product possesses a warm woody odor and is sold under various trade names within the fragrance industry. These findings prompted us to investigate an alternate acetylation procedure employing acetic anhydride with polyphosphoric acid as the catalyst. Under these conditions a product similar to the earlier ketonic mixture but with a greatly enhanced odor value was obtained. No structure elucidations of the components of this mixture have previously been reported and we present here the results of our work in this area.

Acetylation of either pure α-cedrene (1) or β-cedrene (4) afforded as the sole ketonic product the acetyl derivative 2 which possessed a weak odor of no special interest. Since ketone 2 was identical with the major ketone found in the mixture obtained by acetylation of the hydrocarbon fraction of American cedarwood oil, we suspected that the odor components sought after were instead acetylthujopsene derivatives. Confirmation of this hypothesis was readily obtained by acetylation of pure (−)-thujopsene (5) into a mixture of hydrocarbons and ketones containing no acetylcedrene (2) and possessing a strong woody odor.

Analysis of the ketonic portion by gas chromatography revealed the presence of seven major components which were designated in order of elution as isomers A (8%), B (7%), C (3%), D (9%), E (8%), F (13%), and G (52%). Mass spectroscopy showed that each of these components was isomeric and corresponded to a molecular formulation of $C_{17}H_{26}O$. These isomers were subsequently obtained in varying degrees of purity *via* careful spinning-band distillation. In view of the complexity of this mixture we concentrated our initial efforts at structure elucidation on the major (52%) component. This component fortunately possessed a powerful woody-musk-ambergris odor far greater than the other six isomers and could readily be obtained in 95% purity *via* distillation.

The ir spectrum showed an intense conjugated carbonyl absorption at 1672 cm^{-1} and also a strong unusual double bond absorption at 1587 cm^{-1}. Elemental analysis and mass spectral data supported a $C_{17}H_{26}O$ molecular formula which combined with ir data demanded that a tricyclic structure be retained. The nmr spectrum although showing three methyl singlets at δ 0.78, 0.78, and 0.85 and a methyl ketone singlet at δ 2.22, clearly had no vinyl hydrogens or vinyl methyl groups and could therefore not be derived from direct acetylation of the thujopsene skeleton. Moreover, although the thujopsene initially charged was optically active, the product ketone was inactive, as were the recovered unacetylated hydrocarbons.

We consequently elected to elucidate unambiguously the structure of the liquid major acetylation product of thujopsene *via* an X-ray crystal structure determination on a suitable solid derivative. A number of derivatives were prepared and the ethylene thioketal derivative was selected. Proof that this derivative was valid for structure determination was provided by Corey's[4] mild hydrolysis procedure which regenerated a ketone identical with that utilized for the original derivatization. The single crystal X-ray structure analysis showed that the derivative possessed structure 7



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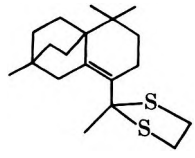


7

(1) G. Stork and R. Breslow, *J. Amer. Chem. Soc.*, **75**, 3291 (1953); *ibid.*, **75**, 3292 (1953).

(2) G. Stork and F. H. Clarke, *ibid.*, **77**, 1072 (1955); *ibid.*, **83**, 3114 (1961).

(3) J. Runeberg, *Acta Chem. Scand.*, **15**, 592 (1961).

(4) E. J. Corey and D. Crouse, *J. Org. Chem.*, **33**, 298 (1968).

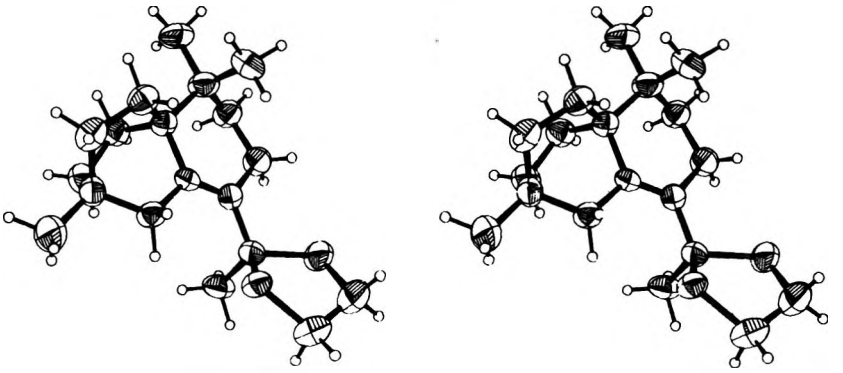
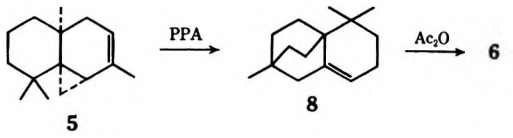


Figure 1.—Stereodrawing showing the conformation of **7** in the solid state. The ellipsoids represent the thermal motions of each atom at the 50% probability level. The drawing was prepared by a computer program written by C. K. Johnson of the Oak Ridge National Laboratory.

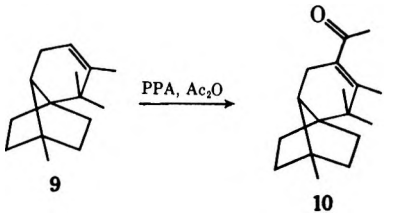
(Figure 1) and the parent ketone must therefore be formulated as **6**.

The hydrocarbon mixture which was recovered under the acetylation conditions contained no thujopsene but could be reacetylated to afford the same ketonic mixture as previously obtained directly from thujopsene, implying that isomerization preceded acetylation.



The results of our investigation of the acid-catalyzed isomerization of thujopsene[5] proved that indeed this was true and that the acetylated products arose from this complex mixture of hydrocarbons. Ketone **6** therefore arises by acetylation of the tricyclic olefin **8** formed from thujopsene under the reaction conditions.

Dauben and Friedrich[6] have previously reported the formation of tricyclic hydrocarbon **9** from per-



chloric acid–acetic acid treatment of thujopsene. Treatment of this hydrocarbon under our acetylation conditions afforded a single ketonic product which was found to be identical with the 9% component (isomer D) in the original acetylthujopsene mixture and is thus assigned structure **10**.

Ketone **6**, the major acetylthujopsene product, appears to be the first known example of a tricyclic compound of this type possessing a strong musk odor. All other known tricyclic musks with an acetyl group[7] also contain an aromatic ring.

(5) H. U. Daeniker, A. R. Hochstetler, K. Kaiser, and G. C. Kitchens, *ibid.*, **36**, 1 (1971).

(6) W. G. Dauben and L. E. Friedrich, Abstracts of the International Union of Pure and Applied Chemistry, Fifth International Symposium on the Chemistry of Natural Products, London, July 8–13, 1968.

(7) T. F. Wood, *Givaudanian*, Sept (1969); *ibid.*, March–April, (1970).

Experimental Section

Materials and Equipment.—(−)-Thujopsene (**5**) was obtained in 99% purity by careful fractional distillation of Hibawood oil through a 2-ft Goodloe column: bp 67–68° (0.5 mm); $n^{20}D$ 1.5050; $[\alpha]^{25}D$ −92.5° (neat). (−)-α-Cedrene (**1**) was obtained in 99% purity by dehydration of (+)-cedrol (**3**) by the method of Teisseire, *et al.*:[8] bp 64° (0.3 mm); $n^{20}D$ 1.4978; $[\alpha]^{25}D$ −88° (neat).

Spectra were recorded on a Perkin-Elmer 457 grating ir spectrophotometer, a Beckman Acta III uv spectrophotometer, a Varian A-60A nmr spectrometer, and a Perkin-Elmer 270 double-focusing mass spectrometer. Spinning-band separations were accomplished with a Nester-Faust NFA-100 autoannular Teflon spinning-band column. Vapor phase chromatography (vpc) was carried out with an F & M 720 equipped with a 2 m × 0.25 in. copper column packed with 15% Carbowax 20M on Chromosorb P. Combustion analyses were determined by Schwartzkopf Microanalytical Laboratory, Woodside, N. Y.

Acetylcedrene (2).—Acetic anhydride (400 g) was added with cooling to polyphosphoric acid (480 g) with efficient agitation over 10 min. Methylene dichloride (200 ml) was added, followed by (−)-α-cedrene (**1**, 204 g) with cooling over 10 min, which was agitated at 25° for 2 hr and then at 50° for 3 hr. The mixture was poured onto 1000 g of ice, warmed to 50° for 0.5 hr, and extracted with methylene dichloride. The combined organic extracts were washed with water, sodium carbonate solution, and brine. The solvent was removed at reduced pressure affording 210 g of crude product. This mixture was fractionally distilled affording 66.0 g of recovered α-cedrene and 99.0 g (59% based on reacted α-cedrene) of acetylcedrene (**2**), bp 98–105° (0.4 mm), which contained by vpc 81% of the desired component and 19% of five minor components. A pure sample of acetylcedrene (**2**) was obtained by careful spinning-band distillation: bp 84–86° (0.01 mm); $n^{20}D$ 1.5152; $[\alpha]^{25}D$ −38.5° (neat); ir (neat) 1672 (C=O), 1600 (conj C=C), 1230, 1198, 1160, 1130, 1085, 1020, 970, 935, 640, 600 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 2.20 (s, 3), 1.98 (s, 3), 1.02, 0.98 (s, 3 each), 0.90 (d, 3, J = 8 Hz); mass spectrum 246 (11), 161 (36), 119 (20), 69 (20), 43 (100).

Anal. Calcd for $C_{17}H_{26}O$: C, 82.87; H, 10.64. Found: C, 82.78; H, 10.72.

1-Aceto-7,10-ethano-4,4,7-trimethyl-1(9)-octalin (6).—Acetic anhydride (400 g) was added to polyphosphoric acid (480 g) with efficient agitation and cooling over 10 min. Methylene dichloride (200 ml) was added, followed by (−)-thujopsene (**5**, 204 g) with cooling over 10 min, which was agitated at 25° for 2 hr and then at 50° for 2 hr. The mixture was poured onto 1000 g of ice, warmed to 50° for 0.5 hr, and extracted with methylene dichloride. The combined organic extracts were washed with water, sodium carbonate solution, and brine. The solvent was removed at reduced pressure and the residue was distilled on a still head to afford 171 g of distillate, bp 70–150° (0.2 mm). The distillate was fractionally redistilled affording 63 g of the recovered isomerized hydrocarbon mixture[6] and 104 g (61% based on hydrocarbons consumed) of a ketonic mixture, bp 115–135° (0.2 mm). This ketonic material was comprised of seven components by vpc

(8) P. Teisseire, M. Plattier, W. Wojnarowski, and G. Ourisson, *Bull. Soc. Chim. Fr.*, 2749 (1966).

and designated as isomers A (8%), B (7%), C (3%), D (9%), E (8%), F (13%), and G (52%) in order of elution. The identical mixture was also formed when the recovered isomerized hydrocarbons[5] were reacetylated under the above conditions. The major component of the ketonic mixture was obtained in pure form by careful spinning-band distillation and exhibited the following properties: bp 92–93° (0.05 mm); n^{20}D 1.5265; $[\alpha]^{25}$D 0.0° (neat); λ_{max}^{MeOH} 257 nm (ϵ 6750); ir (neat) 1672 (C=O), 1587 (conj C=C), 1247, 1239, 1175, 940 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 2.21 (s, 3), 0.85 (s, 3), 0.79 (s, 6); mass spectrum 246 (43), 218 (31), 203 (58), 161 (32), 43 (100), 41 (36).

Anal. Calcd for $C_{17}H_{26}O$: C, 82.87; H, 10.64. Found: C, 82.79; H, 10.71.

Ethylene Thioketal Derivative of 1-Aceto-7,10-ethano-4,4,7-trimethyl-1(9)-octalin (7).—A sample of ketone **8** (1.0 g), acetic acid (10 ml), ethanedithiol (1.1 ml), and boron trifluoride etherate (1.1 ml) was allowed to stand at 25° for 3.5 hr. Water (50 ml) was added and the mixture was extracted with hexane. The organic phase was washed with water, 5% aqueous NaOH, and water and dried ($MgSO_4$). The solvent was removed and the residue crystallized from hexane to afford 950 mg (72%) of thioketal **7**: mp 74–75°; ir (KBr) 1279, 1142, 1129, 1035, 1019, 853 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 3.28 (s, 4), 1.90 (s, 3), 0.88 (s, 3), 0.77 (s, 6); mass spectrum 322 (2), 261 (100), 232 (24), 217 (30), 175 (25), 106 (27), 59 (28). An additional slow recrystallization from hexane afforded crystals suitable for an X-ray crystal structure determination, mp 76–77°.

Anal. Calcd for $C_{19}H_{30}S_2$: C, 70.72; H, 9.38; S, 19.89. Found: C, 70.91; H, 9.17; S, 20.08.

Hydrolysis of Thioketal 7.—The procedure of Corey and Crouse was employed.[4] A mixture of thioketal **7** (75 mg), acetonitrile (2.3 ml), water (0.12 ml), $HgCl_2$ (134 mg), and $CdCO_3$ (88 mg) was stirred under N_2 at 50° for 6.5 hr. The mixture was then evaporated to dryness, benzene added, and the mixture filtered. The benzene solvent was removed affording 45 mg of yellow oil. The ir, nmr, and mass spectra were identical with those of ketone **8**, the major product from the acetylation of thujopsene, from which the thioketal derivative **7** had been prepared.

4-Aceto-2,2,3,7-tetramethyltricyclo[5.2.2.0^{1,6}]undec-3-ene (10).—The procedure previously outlined for the preparation of ketone **6** was employed with olefin **9** (10.0 g), acetic anhydride (19.6 g), and polyphosphoric acid (23.5 g). After the same work-up procedure the residue was distilled affording 4.8 g of recovered olefin **9** and 5.4 g of desired ketone product, bp 132–135° (0.5 mm). A sample of the major (70%) ketonic product was isolated by preparative vpc and exhibited the following properties: n^{20}D 1.5155; ir (neat) 1690 (C=O), 1615 (conj C=C), 1240, 1225, 1205 cm^{-1}; $\delta_{TMS}^{CDCl_3}$ 2.33 (s, 3), 1.72 (s, 3), 1.03 (s, 3), 1.00 (s, 3), 0.93 (s, 3); mass spectrum 246 (16), 231 (35), 203 (25), 133 (17), 119 (17), 95 (15), 43 (100). The spectral properties were identical with those of isomer D isolated from the acetylation of thujopsene by the above procedure.

Anal. Calcd for $C_{17}H_{26}O$: C, 82.87; H, 10.64. Found: C, 82.90; H, 10.57.

X-Ray Analysis of 7.—The ethylene thioketal derivative **7** crystallizes as well-formed prisms from hexane. The crystal data are a = 11.530 (8), b = 9.246 (6), c = 16.873 Å (10), β = 92.08 (6)°, space group $P2_1/a$, d_{obsd} = 1.19 g cm^{-3} (flotation in aqueous KI), d_{calcd} = 1.19 g cm^{-3} for Z = 4. The intensity data were measured by a moving crystal–moving detector method on a Hilger-Watts Model Y290 four-circle diffractometer. Nickel filtered Cu Kα radiation and pulse height discrimination were used. A total of 3586 independent reflections were measured ($2\theta < 140°$) of which 2345 were unobservably weak and were not included in the structure analysis. The crystal used for data collection was approximately 0.12 × 0.15 × 0.22 mm. The function minimized in the least-squares refinement was $\Sigma w\left||F_o| - |F_c|\right|^2$ where $w = 1/(11.8 + |F_o| + 0.012|F_o|^2)$. Standard atomic scattering curves were used for S, C,[9] and H.[10] The refinement calculations were made with a local modification of the program ORFLS.[11]

The structure of **7** was solved by the heavy atom method. A difference Fourier calculated after three cycles of full matrix least squares (anisotropic temperature factors for all atoms) clearly showed all the hydrogen atoms. Refinement was continued by block diagonal least squares (9 × 9 blocks for the anisotropic atoms, 4 × 4 blocks for the hydrogen atoms) until the shifts in all parameters of the heavier atoms were less than $^1/_4$ of their standard deviations ($^1/_2$ of a standard deviation for the hydrogens). A difference Fourier based on the final parameters showed no features greater than 0.15 e Å^{-3} in magnitude. The final conventional unweighted R factor is 5.1%.[12]

Registry No.—**2**, 32388-55-9; **5**, 470-40-6; **6**, 32388-56-0; **7**, 32388-57-1; **10**, 32388-58-2.

(9) D. T. Cromer and J. T. Waber, *Acta Crystallogr.*, **18**, 104 (1965).

(10) R. F. Stewart, E. R. Davidson, and W. T. Simpson, *J. Chem. Phys.*, **42**, 3175 (1965).

(11) W. R. Busing, K. O. Martin, and H. A. Levy, Report ORNL-TM-305, Oak Ridge National Laboratory, Oak Ridge, Tenn., 1962.

(12) Listings of structure factors, coordinates, and thermal parameters for **7** will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Reprint Department, ACS Publications, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

Thujopsene Rearrangements. The Cyclopropylcarbinyl System[1-3]

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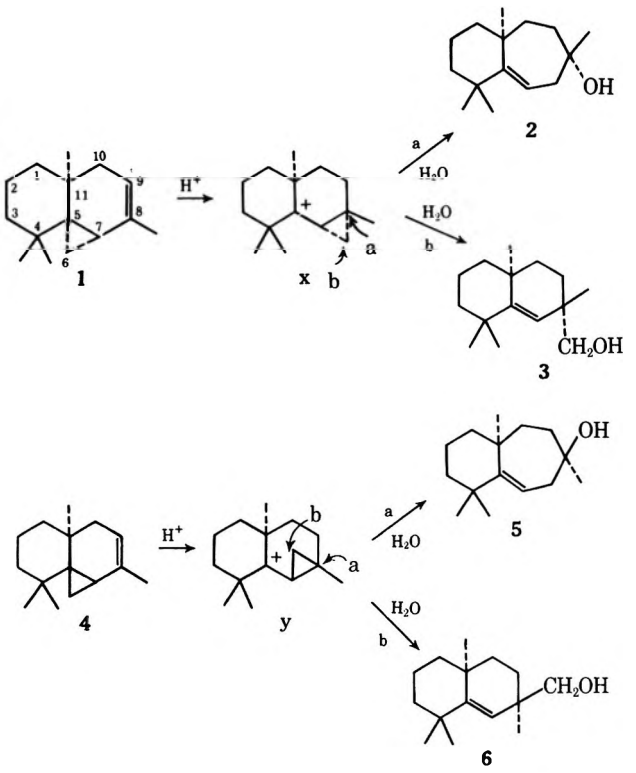
Received May 10, 1971

The earlier findings of the retention of the stereochemical integrity of the cyclopropylcarbinyl grouping in the isomeric *cis*- and *trans*-thujopsene in the early stages of the acid-catalyzed rearrangement of these sesquiterpenes have been extended. Upon longer reaction under mild acid conditions, *cis*-thujopsene (**1**) rearranged directly to **7** with concomitant ring enlargement and angular methyl group migration. The pathway for this conversion was established using 6,6-dideuterio-*cis*-thujopsene. In contrast to these results, *trans*-thujopsene (**4**) yielded the conjugated diene **8**, a compound resulting from ring enlargement but no angular methyl migration. The structures of these two rearrangement products were established by degradation and by synthesis. The mechanistic pathways for these conversions are discussed and it is shown that a combination of factors, all related to the steric configuration of the ring juncture, are responsible for the retention of the identity of the two initially formed stereoisomeric cyclopropylcarbinyl cations.

Part A

The development of organic chemical mechanistic theory and the development of the understanding of biosynthetic mechanisms have stimulated the postulation of biogenetic schemes for a variety of natural products. The sesquiterpenes have received much attention due to their wide occurrence and their variety of structures.[7] In turn, these biogenetic postulates have stimulated study of the transformation of one natural product to another using laboratory reagents. In recent years, the reactions of the tricyclic sesquiterpene thujopsene (**1**)[8] have attracted much interest since its postulated biogenesis involved a cyclopropylcarbinyl–cyclopropylcarbinyl rearrangement.[9] This sesquiterpene, in addition to being a major constituent of cedar wood oil[10] and of Japanese Hibawood oil,[11] also occurs in the oils of practically all of the Cupressales.[12]

Thujopsene contains a cyclopropylcarbinyl grouping and it is this functionality which is mainly responsible for the complex chemical personality it possesses. For example, under mild acid conditions (0.02 *M* $HClO_4$ in 80% aqueous dioxane) this grouping rearranges to give two homoallylic alcohols, the naturally occurring widdrol (**2**) *via* path a and the *cis*-neopentyl-type alcohol **3** *via* path b.[2] Using thujopsene labeled with deuterium in the methylene position of the cyclopropane ring, it has been shown that the rearrangement goes through a cyclopropylcarbinyl–cyclopropylcarbinyl rearrangement to give an intermediate, such as x,[2] and that such a rearrangement proceeds with retention of configuration. This result indicates that the interconversion must involve either a series of 1,2 shifts *via* a puckered cyclobutonium ion or direct bonding at the small lobe of the back bond of the cyclopropane ring and go in one step.[2]



In earlier work in this laboratory,[2,13] a sterospecific synthesis of the thujopsene nucleus had been developed and, thus, it was possible to prepare *trans*-thujopsene (**4**), the stereochemical designation referring to the ring juncture. When **4** was allowed to react under the above mild acid conditions, the major alcohols formed were *epi*-widdrol (**5**) and the *trans*-neopentyl-type alcohol **6**. These materials can be derived from the *trans*-cyclopropylcarbinyl intermediate y in the same manner as discussed for the cis intermediate. In these two isomeric series there is a finite amount of leakage between the ions x and y but in the main series each stereoisomeric cation maintains its stereochemical integrity in this series of interconversions at this early stage of the rearrangement process.

(1) This work was partially supported by Grant No. GP-8700 from the National Science Foundation.

(2) For previous papers in this study, see W. G. Dauben and L. E. Friedrich, *Tetrahedron Lett.*, 2675 (1964); W. G. Dauben and L. E. Friedrich, *ibid.*, 1735 (1967); W. G. Dauben and E. I. Aoyagi, *Tetrahedron*, **26**, 1249 (1970).

(3) A portion of this work appeared in the Abstracts, IUPAC 5th International Symposium on the Chemistry of Natural Products, F-13, London, England, July 8–13, 1968, p 296.

(4) National Science Foundation Predoctoral Fellow.

(5) Roche Anniversary Foundation Postdoctoral Fellow.

(6) National Institutes of Health Predoctoral Fellow.

(7) J. B. Hendrickson, *Tetrahedron*, **7**, 82 (1959); W. Parker, J. S. Roberts, and R. Ramage, *Quart. Rev., Chem. Soc.*, **21**, 331 (1967).

(8) The projection represents the absolute configuration of cis-thujopsene.

(9) W. G. Dauben and P. Oberhänsli, *J. Org. Chem.*, **31**, 315 (1966).

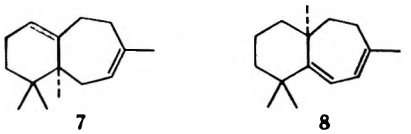
(10) J. Runeberg, *Acta Chem. Scand.*, **15**, 592 (1961).

(11) M. Yano, *J. Soc. Chem. Ind. Jap.*, **16**, 443 (1913); S. Uchida, *ibid.*, **31**, 501 (1928).

(12) H. Erdtman and T. Norin in "Progress in the Chemistry of Natural Products," Vol. 24, L. Zechmeister, Ed., Springer-Verlag, New York, N. Y., 1966, pp 206–287.

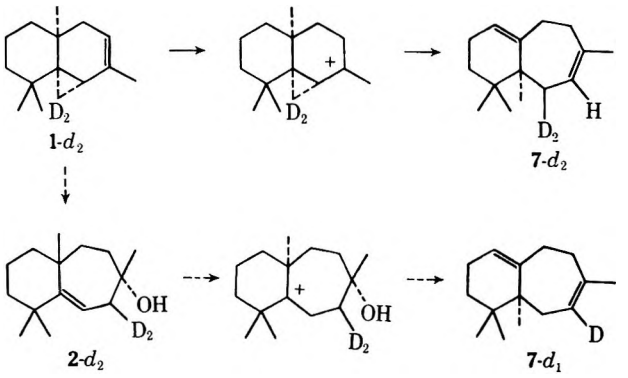
(13) W. G. Dauben and A. C. Ashcraft, *J. Amer. Chem. Soc.*, **85**, 3673 (1963).

When the acid-catalyzed reactions were allowed to proceed for an extended period, all of the products formed early in the reaction disappeared and *cis*-thujopsene yielded mainly hydrocarbon **7** and *trans*-thujopsene gave hydrocarbon **8**. Thus, it is found that the stereochemical difference of these two starting materials is still retained after destruction of the cyclopropylcarbinyl and related homoallyl systems. The retention of the stereochemical integrity of the two isomeric cyclopropylcarbinyl systems in *cis*- and *trans*-thujopsene is readily understood by evaluation of the changes in the geometry of the ring system required to bring about a stereochemical interconversion of the two isomeric cation systems. An understanding of the continued specificity found in this present investigation was gained by a study of the mechanism of formation of the rearranged hydrocarbon **7**.



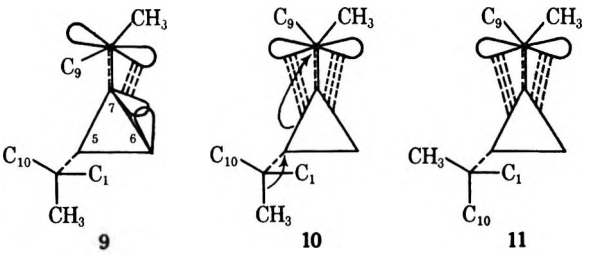
7 **8**

The presence of the bicyclo[5.4.0]undecane nucleus suggested that the rearranged diene **7** was derived from widdrol (**2**). However, it was possible that the methyl migration occurred concomitantly with the rearrangement of the cyclopropylcarbinyl cation to the homoallylic system (or possibly, a homoallylic cation was formed, followed by methyl migration). In order to establish the reaction pathway, *cis*-6,6-dideuteriothujopsene (**1**-d_2) was converted to the diene **7**. It was



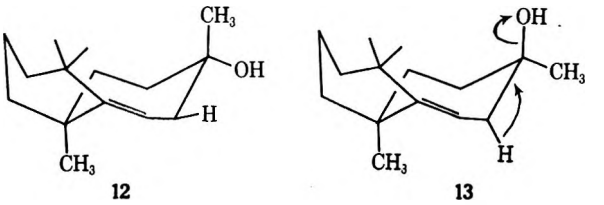
found that the product retained both deuterium labels and both vinyl hydrogen atoms. Also, the allylic region of its nmr spectrum was reduced in intensity. Therefore, the diene must be **7**-d_2 as expected from the direct formation from thujopsene and not **7**-d_1 required if widdrol **2**-d_2 was the direct precursor.

In *cis*-thujopsene (**1**), the unsymmetrical cyclopropylcarbinyl system **9** due to steric restraints within the molecule has the minimal energy and it is this cation which is involved in the cyclopropylcarbinyl–cyclopropylcarbinyl rearrangement leading to widdrol (**2**) and its related neopentyl-type alcohol **3**. A similar series of rearrangements (not shown) exist for *trans*-thujopsene from an unsymmetrical cyclopropylcarbinyl cation leading to *epi*-widdrol (**5**) and the neopentyl-type alcohol **6**. These series of interconversions are reversible and with the continuous re-formation of a carbonium ion, the slightly more energetic bisected cyclopropylcarbinyl cations **10** and **11**, ions which are



higher in energy in this series due to ring strain, not to lesser p–π overlap, may participate in the overall reaction. This bisected ion now makes the cleavage of the C-5–C-7 bond a competitive reaction. In the case of *cis*-thujopsene, the angular methyl group, as illustrated in **10**, is in the exact position for a trans coplanar transition state for migration of the methyl group leading to the rearranged diene **7**. As is seen in the bisected cation **11** from *trans*-thujopsene, the carbon best situated for migration is part of the left-hand ring and in rearranging would yield a spiran with a five-membered ring. This latter process must be sufficiently energy demanding so as not to compete with the other reactions.

These other reactions are related to widdrol and *epi*-widdrol. As seen in the projection **13**, the most stable



conformation of *epi*-widdrol places the tertiary hydroxyl group in an axial conformation. Such a conformational arrangement permits facile elimination to yield the conjugated diene **8**. That this reaction is more favored than the skeletal rearrangement to yield a spiran is quite understandable. The most stable conformation of widdrol is depicted as **12** and this conformation places the tertiary hydroxyl group in an equatorial conformation which is less prone to elimination. Thus a combination of factors, all related to the steric nature of the ring juncture, permits *cis*- and *trans*-thujopsene to retain their identity in all these rearrangement processes.

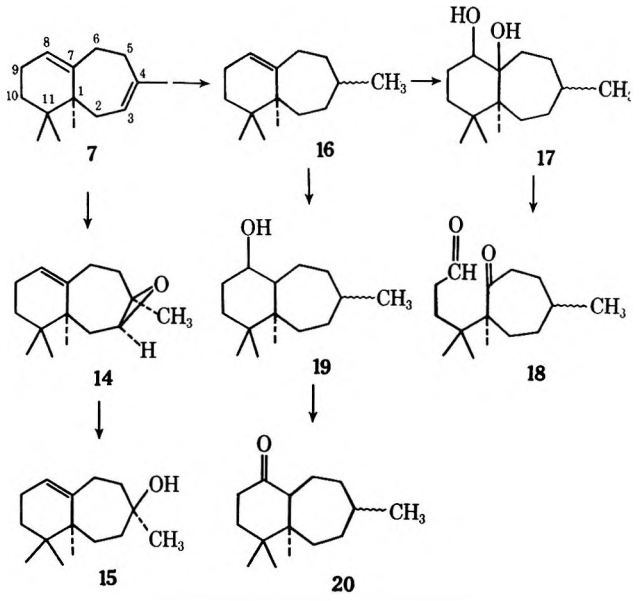
Part B

The hydrocarbon **7** was shown to have a molecular composition of $C_{15}H_{24}$, isomeric with *cis*-thujopsene, by the appearance of a molecular ion at *m/e* 204 in its mass spectrum. The nmr spectrum was extremely different from those of all previously reported compounds studied in that a multiplet at δ 1.8–2.5, corresponding to eight allylic methylene protons, was found. The additional resonances at δ 5.28 for two protons, a maximum in the ultraviolet spectrum at 192 nm (ϵ 13,900), and an infrared spectral absorption at 822 cm^{-1} indicated the presence of two nonconjugated, trisubstituted double bonds.[14] These features taken in conjunction with the molecular composition showed that **7** must be a bicyclic diene in which one of the double bonds was derived from one of the carbocyclic rings of thujopsene. The nmr spectrum of the diene also estab-

(14) R. A. Micheli and T. H. Applewhite, *J. Org. Chem.*, **27**, 345 (1962).

lished the presence of three quaternary methyl groups and a vinyl methyl group.

Reaction of diene **7** with 0.9 equiv of *m*-chloroperbenzoic acid gave epoxide **14** whose nmr spectrum showed one vinyl hydrogen and four quaternary methyl absorptions. This result indicates that the methyl-substituted double bond in **7** is less hindered than the other trisubstituted double bond. It is of passing interest that the alcohol **15** formed by $LiAlH_4$ reduction of epoxide **14** was also isolated in 0.5% yield directly from the acid-catalyzed reaction mixture of thujopsene. Since in **15** the hydroxyl group and the angular methyl group must be trans to one another due to the stereochemistry of the epoxide, this alcohol must have resulted from hydration of the diene **7** rather than from a methyl migration in widdrol. Furthermore, in 1958,

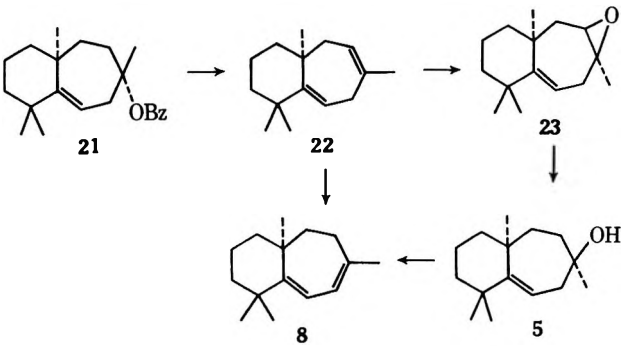


Tanaka and Yamashita[15] reported that a tertiary alcohol was formed from the reaction of *cis*-thujopsene with 50% sulfuric acid in acetic acid, followed by hydrolysis of the acetates. Since the physical constants of their alcohol were similar to those of **15**, it is most likely that the two alcohols are the same compound.

The bicyclo[5.4.0]undecane skeleton of **7** was established by the following series of reactions. The lesser hindered double bond of this diene was preferentially hydrogenated to yield a 6:1 mixture of dihydro and tetrahydro products. The dihydro product **16** was purified by preparative vpc and it was a mixture of the epimeric methyl compounds. The dihydro mixture reacted slowly with osmium tetroxide to yield diol **17**, the slow hydroxylation reaction confirming the hindered nature of the C-7–C-8 double bond. The diol was cleaved with lead tetraacetate to yield the keto aldehyde **18**. Its infrared spectrum (ir max at 2810, 2710, 1729, 1693 cm^{-1}) indicated the presence of an aldehyde and a ketone and the primary nature of the aldehyde was established by the presence of a one hydrogen triplet (J = 2 Hz) resonance at δ 9.41 in the nmr spectrum. The absorption at 1693 cm^{-1} is indicative of a seven-ring ketone.

The size of the other ring in diene **7** was determined by hydroboration and oxidation of the dihydro derivative **16** to yield alcohol **19** and ketone **20**, respectively. The 1706-cm^{-1} absorption of **20** is characteristic of a six-ring ketone. Thus, the foregoing data establish that diene **7** contains a bicyclo[5.4.0]undecadiene skeleton in which the more hindered double bond is situated endocyclic to the six-membered ring and exocyclic to the seven-membered ring. Taking into account the nmr data with regard to allylic methylene groups, the two double bonds must be placed as shown in **7**. The placement of the vinylic methyl group and the three quaternary methyl groups clearly follows from mechanistic considerations.

The structure of diene **8** derived from *trans*-thujopsene was established on the basis of the following information. Its mass spectrum (parent peak m/e 204) clearly established that the hydrocarbon was isomeric with starting *trans*-thujopsene. An absorption maximum at 262 nm established the presence of an *s-cis*-1,3-diene, the infrared spectrum indicated only trisubstituted double bonds (840 cm^{-1}), and the nmr spectrum established the presence of only one vinyl methyl group but two vinyl protons and three quaternary methyl groups. These data suggested the structure **8**, a diene formed directly from *epi*-widdrol **5**. This assignment was confirmed by the synthesis of **8** from widdrol benzoate (**21**). Pyrolysis of **21** in *N,N*-



dimethylaniline gave the nonconjugated diene **22**, the absence of skeletal rearrangement being shown by conversion to the epoxide **23** which, in turn, upon reduction with $LiAlH_4$ yielded *epi*-widdrol. The nonconjugated diene was converted to the conjugated diene **8** by treatment with potassium *tert*-butoxide in dimethyl sulfoxide.

Experimental Section

Melting points were taken with a Büchi Schmelzpunktbestimmungsapparatus or on a Fisher-Johns melting point apparatus and are uncorrected. Glpc were conducted either with Varian-Aerograph Models A-90-P, 600, or 204 B or with Hewlett-Packard Model 402. Nmr spectra were taken with Varian spectrograph Models A-60, T-60, or HR-100, using TMS as an internal standard. The mass spectra were obtained using a modified CRC Type 21-103C mass spectrometer, a Varian M-66 cycloidal mass spectrometer, or a Finnigan quadrupole mass spectrometer. Combustion analyses and high-resolution mass spectra were performed by the Microanalytical Laboratory, College of Chemistry, University of California, Berkeley, Calif.

Isomerization of *cis*-Thujopsene to Diene 7.—A solution of 150 g of *cis*-thujopsene, 300 ml of 0.1 *M* aqueous perchloric acid, and 1200 ml of dioxane was heated under reflux for 27 hr. The cooled sclution was neutralized with aqueous sodium carbonate, most of the dioxane removed under reduced pressure, and the residual mixture extracted with petroleum ether. The organic extract was washed with aqueous potassium bicarbonate and with water and dried, and the solvent removed under reduced

(15) J. Tanaka and I. Yamashita, *Bull. Osaka Ind. Res. Inst.*, **9**, 5 (1958).

pressure. A pentane solution of the residual oil was filtered through 150 g of Woelm neutral alumina (activity I) to yield after removal of the solvent 130 g of a brown oil, glpc analysis (DEGS, 128°) of which indicated that diene **7** comprised 54% of the mixture.

The oil was distilled through a 24-in. spinning-band column and the central fraction, 42 g, bp 149–150° (9.5 mm), containing 71% of **7** was further purified by preparative glpc (20% NPGS, Chromosorb P-HMDS, 20 ft × $^3/_8$ in., 168°) to yield material of 97% purity. The absence of α-chamigrene was confirmed by coinjection and by quantitative analysis of the nmr spectrum: $[\alpha]^{23}D$ +65.3° (*c* 0.209, $CHCl_3$); uv max (hexane) 192 nm (ϵ 13,900); ir max (neat) 822 cm^{-1}; nmr (CCl_4) δ 5.28 (2 H, m), 1.8–2.5 (8 H, m), 1.60 (3 H, sharp m), 0.94 (3 H, s), 0.87 (6 H, s).

Anal. Calcd for $C_{15}H_{24}$ (204.36): C, 88.16; H, 11.84. Found: C, 88.48; H, 11.62; *m/e* 204.

Epoxidation of Diene 7.—A solution of 100 mg (0.5 mmol) of 85% *m*-chloroperbenzoic acid in 2.5 ml of chloroform was added, dropwise, over a period of 5 min to a cooled solution (0°) of 204 mg (1.0 mmol) of diene **7** in 2.0 ml of chloroform. The solution was allowed to stand at 3° for 30 hr; a starch–iodide test indicated the absence of peracid but glpc analysis indicated 50% of starting material. An additional 80 mg (0.4 mmol) of *m*-chloroperbenzoic acid was added to the solution and allowed to react for an additional 2.5 hr. The solution was diluted with ether, washed with aqueous ferrous sulfate, potassium bicarbonate, and water, and dried, and the solvent was removed to yield 190 mg of an oil. Glpc analysis (10% SE-30, 160°) indicated the presence of four products in 10, 60, 20, and 10%, respectively, in order of elution.

The major material **14** was purified by preparative glpc (10% SE-30, Chromosorb P, HMDS, 162°, 5 ft × 0.75 in.). Reinjection of the collected product indicated a purity of greater than 95%: nmr (CCl_4) δ 5.23 (1 H, m), 2.60 (1 H, t, J = 5.5 Hz), 1.12 (3 H, s), 0.92 (3 H, s), 0.88 (3 H, 2), 0.87 (3 H, s); *m/e* 220.

$LiAlH_4$ Reduction of Epoxide 14.—A mixture of 13 mg of **14** and 37 mg of $LiAlH_4$ in 20 ml of glyme was heated under reflux for 9 hr and the mixture worked up in the usual fashion. The crude white solid alcohol was recrystallized from hexane: mp 118–121°; $[\alpha]^{23}D$ +106° (c 0.1118, $CHCl_3$); nmr (CCl_4) δ 5.28 (1 H, broad s), 1.12 (3 H, s), 0.97 (3 H, s), 0.92 (3 H, s), 0.88 (3 H, s).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.12; H, 11.79. Found: C, 81.17; H, 11.70.

Hydrogenation of Diene 7.—A mixture of 100 mg (0.49 mmol) of diene **7**, 20 mg of 20% palladium on charcoal, 5 ml of ethanol, and 2 ml of ethyl acetate was shaken under 1 atm of hydrogen at room temperature for 18 hr. Glpc analysis (DEGS, 102°) indicated an 86% yield of dihydro products **16** and 14% yield of a tetrahydro material; no starting diene remained. The dihydro products appeared to be an equal mixture of two isomers (at the methyl group) and they were collected together by preparative glpc (DEGS, 102°): nmr (CCl_4) δ 5.28 (1 H, m), 2.0 (4 H, m), 0.92 (6 H, s), 0.84 (6 H, s).

Anal. Calcd for $C_{15}H_{26}$: C, 87.30; H, 12.70. Found: C, 87.28; H, 12.72.

Osmylation of Dihydro Product 16.—A mixture of 204 mg (1.0 mmol) of dihydro product **16**, 270 mg (1.1 mmol) of osmium tetroxide, 250 μl of dry pyridine, and 30 ml of dry ether was allowed to stand at room temperature for 11 days. To the brown mixture was added several milliliters of 50% aqueous methanol which was saturated with sodium sulfide, the black precipitate filtered, and the filtrate diluted with ether. The ethereal solution was washed with aqueous sodium sulfide and water and dried, and the solvent was removed under reduced pressure to yield 175 mg of an oil which was chromatographed on 10 g of Woelm neutral alumina (activity II). Elution with 30 ml of petroleum ether and evaporation of the solvent yielded 99 mg (49%) of starting olefin **16**. Elution with 100 ml of diethyl ether afforded 44 mg of semicrystalline diol **17**: ir max (CCl_4) 3635, 3600, 3460 cm^{-1}; nmr (CCl_4) δ 3.68 (1 H, m). The crude material was used directly in the following experiment.

Cleavage of Diol 19.—A mixture of 44 mg (0.18 mmol) of crude diol **19**, 200 mg (0.45 mmol) of lead tetraacetate, and 10 ml of acetic acid was allowed to react at room temperature for 5 days. The mixture was poured onto crushed ice, extracted with petroleum ether, and processed in the usual manner to yield 37 mg of an oil. Glpc analysis (10% SE-30, 180°) of the crude material indicated that the major product comprised 75% of the mixture: ir max (CCl_4) 2810, 2710, 1729, 1693 cm^{-1}; nmr (CCl_4) δ 9.41 (1 H, t, J = 2 Hz). The keto aldehyde **18** was purified by preparative glpc (10% SE-30, 190°).

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.85; H, 10.98.

Hydroboration of Dihydro Product 16.—Diborane generated from 156 mg (4.12 mmol) of sodium borohydride and 0.85 ml of boron trifluoride–etherate in diethylene glycol was passed into a solution of 200 mg (0.97 mmol) of monoolefin **16** in 12 ml of tetrahydrofuran at 0° with a nitrogen sweep. The solution was allowed to stand at room temperature for 3 hr, and 0.5 ml of water was added slowly, followed by 1 ml of 3 *M* aqueous sodium hydroxide and 0.1 ml of 30% aqueous hydrogen peroxide. After 1 hr, an additional 0.5 ml of 3 *M* sodium hydroxide was added and the mixture allowed to stand for 30 min. The solvent was partially rotary evaporated, the remaining mixture extracted with ether, and the ethereal extract processed in the usual fashion to yield 160 mg of an oil. The crude product was chromatographed on 10 g of Woelm neutral alumina (activity II); elution with 25 ml of petroleum ether yielded 73 mg (37%) of starting material and elution with 50 ml of ether produced 70 mg (32%) of crystalline alcohol **19**: ir max (CCl_4) 3620, 3380 cm^{-1}; nmr (CCl_4) δ 3.66 (1 H, broad multiplet).

Anal. Calcd for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found: C, 82.20; H, 12.20.

Oxidation of Alcohol 19.—A solution of 65 mg (0.29 mmol) of alcohol **19** was oxidized at 0° with 0.2 ml of Jones reagent in the usual fashion. After 5 min, the mixture was processed to yield 65 mg of an oil which by glpc analysis (DEGS, 160°) indicated the major product comprised 80% of the mixture. The ketone **20** was purified by preparative glpc (DEGS, 161°): ir max (CCl_4) 1706 cm^{-1}; nmr (CCl_4) δ 2.1 (3 H, m).

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 80.80; H, 11.68.

Rearrangement of *cis*-6,6-Dideuteriothujopsene to Diene 7.—A solution of 0.95 g (4.9 mmol) of *cis*-6,6-dideuterothujopsene (1-d_2) in 9.6 ml of 80% aqueous dioxane–perchloric acid (prepared from 6.18 g of water, 24.72 g of dioxane, and 76 mg of 70% aqueous perchloric acid) was heated under reflux for 175 min under an atmosphere of nitrogen. The reaction mixture was worked up in the standard fashion and the 1.0 g of residual solid was chromatographed on 30 g of Woelm neutral alumina (activity II). Elution with 150 ml of hexane yielded 0.565 g of hydrocarbon fraction and elution with benzene yielded the alcohol fraction.

The hydrocarbon fraction was analyzed by glpc (10% KOH, 10% Carbowax, 163°, 5 ft × $^3/_8$ in.) and found to contain 38% unreacted dideuteriothujopsene and 43% of diene 7-d_2. The diene was purified by preparative glpc; its ir spectrum was practically identical with that of undeuterated **7** and its nmr spectrum was identical with the spectrum of the undeuterated diene except for several prominent absorptions in the allylic region, δ 1.8–2.5, which were reduced in intensity. The mass spectrum of the product indicated that the material was 87% dideuterated, as was the starting material.

Isomerization of *trans*-Thujopsene to Diene 8.—A solution of 260 mg (1.28 mmol) of *trans*-thujopsene in 2.6 ml of 80% aqueous dioxane was brought to reflux and 4.4 μl of 70% perchloric acid was added. The reaction solution was heated under reflux for 20 hr, cooled, neutralized, and extracted with hexane. The hexane solution was rotary evaporated, and the residue chromatographed on 5 g of neutral Woelm alumina (activity II) to give 170 mg of hydrocarbon mixture and 70 mg of *trans*-neopentyl type alcohol **6**. Glpc analysis of the hydrocarbon fraction showed the presence of three materials in a ratio of 3:1:1; the major material was purified by preparative glpc (10% TCNE, 120°) and was obtained in 85% purity: uv max (cyclohexane) 262 nm (ϵ 7500) with shoulders at 254 and 273 nm; nmr (CCl_4) δ 5.6 (2 H, distorted AB quartet), 1.78 (3 H, d), 1.13 (6 H, 2), 1.03 (3 H, s); mass spectrum *m/e* 204, 121, 119 (base peak), 105.

Widdrol Benzoate (21).—A solution of 5.5 g (24.8 mmol) of widdrol and 12.4 ml of benzoyl chloride in 120 ml of pyridine was heated on a steam bath for 4 hr, cooled, and diluted with 740 ml of 1 *N* hydrochloric acid. The mixture was extracted twice with hexane, and the hexane solution was washed with 100 ml of 2 *N* hydrochloric acid and 50 ml of aqueous sodium bicarbonate solution and dried. The solvent was rotary evaporated and the residual oil chromatographed on Woelm neutral alumina (activity II). Elution with hexane yielded 6.4 g of product which slowly solidified: ir max (CCl_4) 1712 cm^{-1};

nmr (CCl_4) δ 7.45–7.87 (3 H, m), 7.20–7.27 (2 H, m), 5.43 (2 H, q, J = 8 and 6 Hz), 2.53–2.78 (2 H, m), 1.57 (3 H, s), 1.20 (3 H, s), 1.09 (6 H, s).

Anal. Calcd for $C_{22}H_{30}O_2$: C, 80.94; H, 9.26. Found: C, 81.22; H, 9.01.

1,4,8,8-Tetramethyl[5.4.0]undeca-3,6-diene (22)—A mixture of 3.8 g of widdrol benzoate and 100 ml of freshly distilled *N,N*-dimethylaniline was heated under reflux for 40 hr, diluted with 500 ml of 2 *N* aqueous hydrochloric acid, and extracted three times with hexane. The hexane extract was washed with saturated aqueous sodium bicarbonate solution and dried, and the solvent was rotary evaporated to give 3.1 g of oily material. Glpc analysis (20% DEGS, Chromosorb P, HMDS, 130°, 5 ft × 0.25 in.) indicated three hydrocarbons in a ratio of 70, 25, and 5% yields. This crude material after filtration through Woelm neutral alumina (activity II) was used directly in the next experiment.

A 250-mg portion was chromatographed on 20 g of silica gel impregnated with 22% silver nitrate. Elution with 72 ml of hexane–benzene (9:1) afforded a total of 185 mg of the diene **22** in six fractions. The major product from the middle chromatography fraction was still impure as indicated by a low residual uv absorption in the 255–273-nm region. No further purification was attempted and the purified diene had the following properties: uv max (cyclohexane) 185 nm (ε 17,400), 254 (1120), 263 (1240), 273 (860); nmr (CCl_4) δ 5.17–5.83 (2 H, poorly formed quartet, J = 7 and 3 Hz), 3.17 (1 H, d, J = 20 Hz), 1.72 (3 H, narrow multiplet), 1.10 (3 H, s), 1.08 (3 H, s), 1.09 (3 H, s).

Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.20; H, 11.67.

1,4,8,8-Tetramethyl[5.4.0]undeca-4,6-diene (8).—To a solution of 2.0 g (72% pure) of diene **22** in 2 ml of dry benzene and 100 ml of dry dimethyl sulfoxide (distilled from calcium hydride) was added 3.1 g of potassium *tert*-butoxide. The dark red solution was stirred at room temperature for 6 hr, poured into water, and processed in the usual fashion. The crude product was chromatographed on 20 g of Woelm neutral alumina (activity II) to give 1.7 g (85%) of hydrocarbon mixture which upon glpc analysis showed two peaks (78 and 22%). The minor product has a retention time identical with starting diene **22**. The dominant reaction product was purified by preparative glpc; the retention time and all spectra were identical with those of diene **8** prepared from *trans*-thujopsene.

3β,4β-Oxa-1α,4α,8,8-tetramethylbicyclo[5.4.0]undec-6-ene (23).—A solution of 469 mg (2.24 mmol) of 82.5% *m*-chloroperbenzoic acid in 7 ml of chloroform was slowly added to a solution of 551 mg (2.70 mmol) of diene **22** (70% purity) in 5 ml of chloroform at 0°. The reaction was allowed to proceed for 3.5 hr at 0°, diluted with pentane, and worked up in the standard fashion. The crude product was chromatographed on 25 g of Woelm neutral alumina (activity II). Elution with 32 ml of hexane gave 100 mg of unreacted hydrocarbon; elution with hexane–ether (increasingly greater amounts of ether) gave two products. The first product was 70 mg (14%) of impure isomeric 6,7-oxa-3-ene: nmr (CCl_4) δ 5.13 (1 H, d, J = 8 Hz), 2.83 (1 H, t, J = 3 Hz), 2.43–2.75 (2 H, m), 2.00–2.38 (2 H, broad multiplet), 1.63 (3 H, narrow multiplet), 1.11 (6 H, s), 0.76 (3 H, s).

The second product was 248 mg (51%) of pure epoxide **23**: $[\alpha]_D$ +67° (*c* 16.9, $CHCl_3$); ir max (CCl_4) 1650, 840 cm^{-1}; nmr (CCl_4) δ 5.52 (1 H, q, J = 7, 4 Hz), 2.79 (1 H, q, J = 8, 7 Hz), 2.25–2.50 (1 H, m), 1.29 (6 H, s), 1.13 (3 H, s), 1.05 (3 H, s).

Anal. Calcd for $C_{15}H_{24}O$: C, 81.76; H, 10.98. Found: C, 81.87; H, 10.77.

***epi*-Widdrol (5).**—A mixture of 1.44 g (6.54 mmol) of epoxide **23**, 1.17 g (31 mmol) of $LiAlH_4$, and 125 ml of glyme was heated under reflux in a nitrogen atmosphere for 16 hr. The cooled mixture was diluted with ether and water carefully added until a clear organic layer was obtained. The organic layer was decanted and processed in the usual manner. The 1.47 g of crude product was 95% pure *epi*-widdrol (glpc, 10% KOH, 10% Carbowax 6000, 185°). A portion of the crude product (365 mg) was chromatographed on Woelm neutral alumina to yield *epi*-widdrol: mp 54–56°; $[\alpha]_D$ +132° (*c* 5.81, $CHCl_3$).

Registry No.—**1**, 32435-95-3; **4**, 32436-14-9; **5**, 25490-91-9; **7**, 32436-16-1; **8**, 32436-17-2; **14**, 32436-18-3; **15**, 32436-19-4; **16**, 32436-20-7; **17**, 32436-21-8; **18**, 32436-22-9; **19**, 32436-23-0; **20**, 32436-24-1; **21**, 32436-25-2; **22**, 32436-26-3; **23**, 32436-27-4; **23** 6,7-oxa-3-ene isomer, 32436-28-5.

A Stereoselective Nonannelation Synthesis of Eudalene Sesquiterpenes[1]

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Received May 17, 1971

A new stereoselective synthetic approach to the eudalene sesquiterpenes has been devised which does not utilize the Robinson annelation sequence. Clemmensen reduction of 5-methoxy-1-tetralonecarboxylic acid (**4**) gives 8-methoxytetralin-2-carboxylic acid (**5**), which on Birch reduction affords 3,4,5,6,7,8-hexahydronaphthalen-1(2*H*)-one-7-carboxylic acid (**3**) as the major product. Conjugate addition of lithium dimethyl cuprate to **3** gives a mixture of three stereoisomeric 4a-methyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1(2*H*)-one-7-carboxylic acids (**9**, **10**, and **11**). Treatment of the mixture of acids with methylenetriphenylphosphorane, followed by esterification, equilibration, and hydrolysis affords 4aβ-methyl-8-methylene-1,2,3,4,4a,5,6,7,8aα-decahydronaphthalene-2β-carboxylic acid (**12**), a compound which has previously been converted to β-eudesmol (**1**).

Although several syntheses of eudalene-type sesquiterpenes have been reported,[2] every successful synthetic approach has utilized the Robinson annelation sequence to construct the bicyclic skeleton characteristic of this group of natural products. Unfortunately, owing to the steric course of the annelation reaction, this approach necessitates multistep synthetic schemes with the stepwise introduction of the various substituents on the perhydronaphthalene ring system.[3]

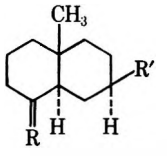
In order to circumvent these problems, we attempted to design a new, general synthesis of these sesquiterpenes which did not utilize the annelation reaction and which would permit stereochemical control at each step. Examination of the structure of β-eudesmol (**1**) reveals that this molecule is basically a 9-methyl-*trans*-decalin with an equatorial substituent

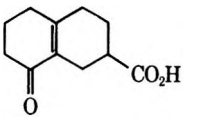
(1) (a) A preliminary communication describing a portion of this work appeared in *Tetrahedron Lett.*, 501 (1971). (b) Abstracted in part from the Ph.D. dissertation of M. L. Mole, Clemson University, May 1971. (c) Supported in part by Career Development Award GM-5433 from the National Institutes of Health.

(2) Earlier synthetic approaches to these sesquiterpenes are described: (a) C. H. Heathcock and T. R. Kelly, *Tetrahedron*, **24**, 1801 (1968); (b) J. A. Marshall, M. T. Pike, and R. D. Carroll, *J. Org. Chem.*, **31**, 2933 (1966); (c) J. A. Marshall and M. T. Pike, *ibid.*, **33**, 435 (1968); (d) D. C. Humber, A. R. Pinder, and R. A. Williams, *ibid.*, **32**, 2335 (1967); (e) J. M. Mellor and S. Munavelli, *Quart. Rev., Chem. Soc.*, **18**, 270 (1964).

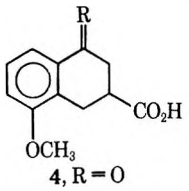
(3) The details of these stereochemical problems are particularly apparent in the syntheses described in ref 2a, b, and d.

at C-7 and any stereoselective synthesis must control the stereochemistry at these centers. A suitable precursor which permits this steric control is the keto acid **2** utilized earlier by Heathcock in a synthesis of eudesmol.[2a]

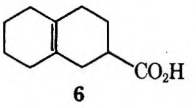




1, R = CH_2; R′ = $C(CH_3)_2OH$ — **3**
2, R = O; R′ = CO_2H
12, R = CH_2; R′ = CO_2H
14, R = α-OH; β-CH_3; R′ = $C(CH_3)_2OH$
15, R = β-OH; α-CH_3; R′ = $CH_2{=}CHCH_3$



4, R = O
5, R = H, H



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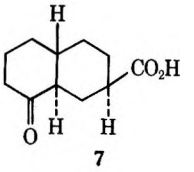

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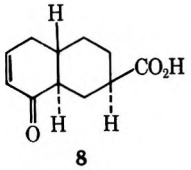

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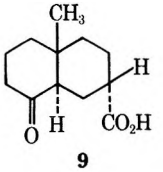

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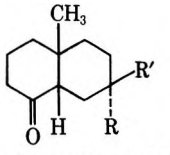
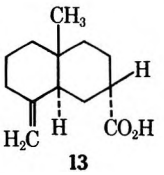


10, R = H; R′ = CO_2H
11, R = CO_2H; R′ = H



13

Although **2** was synthesized by these workers *via* a rather lengthy annelation sequence, it appeared to be also available from the unsaturated keto acid **3**, which in turn could be obtained by reduction of an aromatic compound.

A suitable starting point for the preparation of **3** seemed to be the readily available 5-methoxytetralone-3-carboxylic acid (**4**).[4] Clemmensen reduction of **4** afforded 8-methoxytetralin-2-carboxylic acid (**5**), which on Birch reduction followed by acid hydrolysis of the crude reaction products[5] gave a mixture of four acids. Separation of this mixture by chromatography gave an unsaturated acid, $C_{11}H_{16}O_2$, in 18% yield, plus three keto acids. The nmr spectrum of the unsaturated acid exhibits no vinyl protons and, assuming no unusual side reactions, it is almost certainly the octalin carboxylic acid, **6**.

Separation of the keto acids was effected by a combination of chromatography on silica gel and treatment with Girard's-T reagent. By this method a saturated keto acid, $C_{11}H_{16}O_3$ could be isolated in 9% yield and on the basis of the analytical data, rather featureless nmr spectrum, and appropriate carboxyl absorption in the infrared, this material must be 1-decalone-7-carboxylic acid (**7**). The major product of the reduction (25%) was an unsaturated acid, $C_{11}H_{14}O_3$, which shows no vinyl protons in the nmr, has the ultraviolet maximum expected for **3** (calcd λ_{max} 249, obsd 244), and shows α,β-unsaturated ketone carbonyl absorption in the infrared. Finally, a small quantity of a compound isomeric with **3** was obtained which shows vinyl protons at δ 5.83 and 6.72 and which has the ultraviolet absorption predicted for a monosubstituted α,β-unsaturated ketone (calcd λ_{max} 227, obsd 226). On the basis of these data this material must be keto acid **8**. The stereochemistry of compounds **7** and **8** was not investigated, but it is assumed that they have the more stable trans ring fusion with an equatorial carboxyl group.

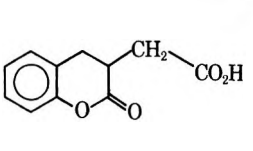
Glc data from several runs indicated that the product ratios were somewhat variable, but a typical reaction mixture consisted of 42% of **3**, 21% of **6**, 24% of **7**, 7% of **8**, 2% recovered starting material, **5**, and trace amounts of several other unidentified products.

Reaction of **3** with lithium dimethyl cuprate[6] gave a mixture of three saturated keto acids in a ratio of 4:3:2 (A, B, and C). On the basis of spectral data (see Experimental Section) and subsequent conversions these are three of the four possible isomers of the desired eudalene precursor, **2**. In addition to **2**, which has an equatorial carboxyl group, there is a trans isomer with an axial carboxyl group, **9**, and a pair of cis isomers, **10** and **11**. The principal isomer, A, could be isolated in pure form and, in order to gain some insight into the stereochemistry of these compounds, was subjected to equilibration studies.

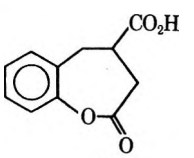
Treatment of the methyl ester of A with methanolic sodium methoxide gave a mixture of A and a new isomer, D, in a ratio of 3:5. Since these conditions should effect equilibration at both C-5 and C-7 (sesquiterpene numbering), D should be the most stable of the four isomers, almost certainly **2**, with the trans ring fusion and equatorial substituent at C-7. Not only is **2** expected to be the most stable of these isomers, but Heathcock has obtained this compound by equilibration of a mixture of **2** and **11**. Isomer A, which was obtained in pure form, is almost certainly one of the two compounds with a cis ring fusion, since it has been shown that there is relatively little energy difference between *cis*- and *trans*-10-methyl-1-decalone, while $\Delta G_{CO_2CH_3}$ is in excess of 1 kcal/mol.[7]

On the basis of the physical properties of A, it is dif-

(4) A. Sieglitz and C. Jordanides, *Justus Liebigs Ann. Chem.*, **702**, 94 (1967). The modified Friedel–Crafts cyclization of the benzylsuccinic anhydride described in the Experimental Section proceeds much more smoothly than the original procedure. In addition to a 45% yield of **4**, a significant quantity of a 1:1 mixture of lactones (i and ii) was obtained.



i



ii

The structures of i and ii were assigned on the basis of analytical and spectral data, and hydrolysis and methylation to the starting benzylsuccinic acid (see Experimental Section).

(5) H. L. Dryden, Jr., O. M. Webber, R. R. Burtner, and J. A. Cella, *J. Org. Chem.*, **26**, 3237 (1961).

(6) H. O. House, W. L. Respess, and G. M. Whitesides, *ibid.*, **31**, 3128 (1966).

(7) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Wiley, New York, N. Y., 1965, pp 231–232, 441. Assuming no complicating stereoelectronic factors, equilibration of the methyl esters of **2** and **9** should give approximately 80–85% **2**.

ferent from the cis keto acid prepared by Heathcock and to which stereoformula **11** can be assigned with a high degree of certainty;[2a] thus A must be assigned structure **10**. Of the two methyl singlets in the nmr spectrum of the isomerized mixture of esters, the most intense appeared at the same position as that reported for compound **2** by Heathcock and Kelly,[2a] strengthening the above assignment of configuration to D.

Some insight into the stereochemistry of isomers B and C follows from the equilibration of A as the free acid. This gave only A and B in a ratio of 3:1. Since the carboxylate anion would not be expected to equilibrate under the basic conditions of this isomerization, B must be epimeric with A at C-5 but retain the same stereochemistry at C-7. Consequently B is **9** and C is the cis acid reported earlier by Heathcock (**11**).

It has been noted that the reaction of both *cis*- and *trans*-1-decalones with methylene triphenylphosphorane in dimethyl sulfoxide leads predominantly to products with a trans ring fusion.[2b,8] Since β-eudesmol has this stereochemistry, the mixture of isomeric acids described above was subjected to these reaction conditions to give a mixture of three acids in a ratio of *ca.* 5:4:1. The major product could be isolated by direct crystallization and was not identical with acid **12**, a compound which has earlier been converted to β-eudesmol.[2a,b,9] On the basis of glc data the component present to the extent of 40% was the desired product, and by analogy with other systems the major product, **13**, was epimeric to **12** at C-7. This assignment of stereochemistry was verified when it was found that equilibration of the methyl ester of either the principal product of the Wittig reaction or the crude reaction mixture, followed by hydrolysis, gave **12**, identical in all respects with a sample prepared by Marshall's route.[2b,9]

Since acid **12** has been converted to β-eudesmol,[2b] and β-eudesmol has in turn been converted to cryptomeridiol[10] (**14**) and neointermediol[11] (**15**), the synthesis of **12** constitutes a formal total synthesis of these three sesquiterpenes. In addition, this is the first total synthesis of any eudalene sesquiterpene which does not utilize the Robinson annelation reaction, and this synthetic sequence may serve as a prototype for other syntheses in the sesquiterpene series.

Experimental Section[12]

o-Methoxybenzylidenesuccinic Acid.—This compound was prepared using a modification of Horning's procedure.[13] To 770 ml of *tert*-butyl alcohol was added 52 g of potassium and the mixture was mechanically stirred and heated at reflux under nitrogen for 4.5 hr. To the resulting heterogeneous mixture of potassium *tert*-butoxide and *tert*-butyl alcohol was added as quickly as possible 177 ml (184 g) of diethyl succinate in 100 ml of *tert*-butyl alcohol. Immediately 127 g of *o*-anisaldehyde in 100 ml of *tert*-butyl alcohol was added as rapidly as feasible without losing control of the vigorous reaction. The resulting heterogenous mixture was stirred and heated at reflux for 2 hr. After cooling, 1400 ml of water was added and 1600 ml of *tert*-butyl alcohol–water was removed by distillation (final head temperature, 99°). To the reaction mixture was added a solution of 120 g of potassium hydroxide in 400 ml of water and the dark solution was heated at reflux for 4 hr. The cooled mixture was washed with ether and, after heating on the steam bath to drive off any dissolved ether, concentrated hydrochloric acid was added carefully (vigorous foaming) until pH 1 was reached. After chilling in an ice bath for 3 hr, the precipitate was filtered, washed with water, air-dried, and finally dried *in vacuo* for 4 hr to give 199 g (90%) of brown solid. A 5.60-g portion of the crude product was triturated with a small portion of ether and recrystallized from 95% ethanol, giving 3.75 g of tan crystals, mp 186–201°. A second recrystallization gave 1.3 g of slightly colored material: mp 207–210.5° dec (lit. mp 208.5–211°);[13] ir 3.0–4.2, 5.82–5.96, 11.87–13.22 μ; nmr (DMSO-d_6) 3.38 (s, 2 H, CH_2), 3.87 (s, 3 H, OCH_3), 6.91–7.60 (m, 4 H, ArH), 7.90 (s, 1 H, vinyl H).

o-Methoxybenzylsuccinic Acid.—From 170 g of crude benzylidenesuccinic acid, catalytic hydrogenation by Horning's method[13] gave after crystallization from benzene 100 g (55% based on anisaldehyde) of reduced acid, mp 133–136°. A small sample was dissolved in ether and filtered, the solvent was removed, and the residue was recrystallized from benzene to give off-white crystals: mp 143–144° (lit. mp 142–145°);[13] ir 2.9–3.9, 5.90 μ; nmr 2.22–3.23 (m, 5 H, CH_2 and CH), 3.77 (s, 3 H, OCH_3), 6.72–7.35 (overlapping AB systems, 4 H, ArH).

o-Methoxybenzylsuccinic Anhydride.—To 63.6 g of *o*-methoxybenzylsuccinic acid, mp 133–136°, protected from atmospheric moisture, was added 54 ml of acetyl chloride. A vigorous reaction was apparent after 15 min and was allowed to continue for an additional 30 min; stirring and gentle reflux were then begun and continued for 2 hr. After standing at room temperature for 18 hr the excess acetyl chloride was removed *in vacuo* with warming on the steam bath. Three 15-ml portions of dry benzene were added and then removed *in vacuo* at steam bath temperature, leaving 58.8 g of brown, viscous anhydride, ir 5.34, 5.57 μ. When 0.300 g of this material was allowed to stand at −10° for several weeks it crystallized. The resulting solid was recrystallized from ether–hexane and a second recrystallization gave white crystals mixed with a brown solid. The solvent was decanted, and 0.100 g of white crystals (mp 67.5–68.5°) were separated and recrystallized from ether–hexane to give 0.070 g of *o*-methoxybenzylsuccinic anhydride: mp 68–69°; ir 5.34, 5.43, 5.61 μ; nmr δ 2.78 (d, J = 7.5 Hz, 2 H, $ArCH_2$), 2.98–3.67 (m, 3 H, $-CH_2CH-$), 3.85 (s, 3 H, OCH_3), 6.85–7.45 (m, 4 H, ArH).

Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.49. Found: C, 65.17; H, 5.44.

5-Methoxy-1-tetralonecarboxylic Acid (4).—The crude anhydride, 58.5 g, was dissolved in 880 ml of nitrobenzene and added over a 50-min period to a stirred solution of 103 g of aluminum chloride in 470 ml of nitrobenzene protected from atmospheric moisture. Stirring was continued for 5 min and a mixture of 500 g of ice and 500 ml of concentrated hydrochloric acid was added. After standing for 1.5 days, the nitrobenzene was removed by steam distillation. The hot solution was filtered, allowed to cool, and seeded. After standing overnight, the brown crystals were collected and dried *in vacuo* to give 26.6 g (45%) of crude material, mp 125–141°. For characterization, 0.350 g of the tetralone was purified by dissolution in 75 ml of 50% aqueous hydrochloric acid, filtering the hot solution, and chilling in an ice–water bath. The cloudy solution was filtered again and allowed to stand overnight. The crystals (0.055 g) were filtered and dried *in vacuo*. Recrystallization from water afforded 0.045 g of colorless needles: mp (softening) 139–143°, melt 143–144° (lit. mp 145°);[4] ir 5.80, 5.96 μ; nmr δ 2.84–3.59 (m, 5 H, CH_2, CH), 3.88 (s, 3 H, OCH_3), 7.08 (q, J = 8 and J = 1.5 Hz, 1 H, ArH), 7.33 (t, J = 8 Hz, 1 H, ArH), 7.70 (q, J = 8 and J = 1.5 Hz, 1 H, ArH).

The mother liquors from the first crystallization were extracted with ether (six 400-ml portions), the extracts were dried and filtered, and the solvent was removed *in vacuo*, leaving 22.5 g of

(8) M. D. Soffer and L. A. Burke, *Tetrahedron Lett.*, 211 (1970).

(9) We would like to thank Professor J. A. Marshall, Northwestern University, for a sample of this compound.

(10) M. Suminoto, H. I. Hirai, and K. Wada, *Chem. Ind.* (*London*), 780 (1963).

(11) V. B. Zalkow, H. Shaligram, and L. H. Zalkow, *ibid.*, 194 (1964).

(12) All melting points were determined on a Kofler hot-stage apparatus and uncorrected. Infrared spectra were taken as potassium bromide disks or liquid films on sodium chloride plates using a Perkin-Elmer Model 137 spectrophotometer and are reported in microns. Ultraviolet spectra were taken in methanol using a Perkin-Elmer Model 202 spectrophotometer and are reported as λ_{max} in millimicrons (log ε). Nuclear magnetic resonance spectra were obtained using a Varian Associates A-60 nuclear magnetic resonance spectrophotometer with deuteriochloroform as a solvent unless stated otherwise. All spectra are reported in parts per million relative to tetramethylsilane (δ). Gas–liquid chromatography was carried out on an F & M Model 810 analytical gas chromatograph using helium as the carrier gas at a flow rate of 35 ml/min through a ⅛ in. × 10 ft copper column of 10% QF1 on HP Chromosorb W (80–100 mesh). Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

(13) E. C. Horning and G. N. Walker, *J. Amer. Chem. Soc.*, **74**, 5147 (1952).

tan oil which subsequently crystallized. Recrystallization of 9.5 g from ether–hexane gives 2.9 g of lightly colored crystals. A second recrystallization from ether afforded material, mp 136–138°. Repeated recrystallization failed to improve the melting point. Recrystallization several times from benzene or sublimation did not improve the melting point, and tlc (silica gel G, benzene–ethyl acetate) showed two major spots (i and ii, ref 4) (0.74, 0.86): ir 5.67, 5.91 μ; nmr 2.58–3.16 (m, 5 H, CH_2, CH), 6.68–7.20 (m, 4 H, ArH), 9.00 (s, 1 H, CO_2H).

Anal. Calcd for $C_{11}H_{10}O_4$: C, 64.08; H, 4.89. Found: C, 63.88; H, 5.00.

A solution of 0.700 g of this material was heated at reflux under nitrogen in 3 ml of 20% aqueous sodium hydroxide, containing 0.32 ml of dimethyl sulfate. The solution was cooled, diluted with water, and washed twice with ether. The aqueous solution was acidified with concentrated hydrochloric acid to pH 1 and the cloudy solution was extracted with ether. The extracts were combined, washed once with water, dried, and filtered and the solvent was removed under reduced pressure, leaving 0.680 g of nearly colorless oil which crystallized on standing, mp 110–120°. Recrystallization from benzene afforded 0.503 g (62%) of tan crystals, mp 134–138°. The ir and nmr were identical with those of *o*-methoxybenzylsuccinic acid, mp 135–139°.

8-Methoxytetralin-2-carboxylic Acid (5).—The tetralonecarboxylic acid was reduced under the usual conditions of the Clemmensen reduction.[14] From 25.3 g of keto acid there was obtained 22.4 g (95%) of crude **5**, mp 136–141°. Recrystallization from 10% hydrochloric acid and then water gave the analytical sample: mp 142–143°; ir 5.88 μ; nmr δ 1.64–2.25 (m, 2 H, $ArCH_2CH_2$), 2.62–3.12 (m, 5 H, $ArCH_2$, CH), 3.80 (s, 3 H, OCH_3), 6.58–7.25 (m, 3 H, ArH).

Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.89; H, 6.84. Found: C, 69.92; H, 6.85.

3,4,5,6,7,8-Hexahydronaphthalen-1(2*H*)-one-7-carboxylic Acid (3).—A solution of 9.60 g of 8-methoxytetralin-2-carboxylic acid in 487 ml of dry ethanol was added with stirring to 390 ml of liquid ammonia. To this solution was added 45.8 g of sodium spheres in four portions. An additional 200 ml of ammonia was added after the third addition of sodium in order to maintain the blue color. After stirring for 8 hr the ammonia was evaporated and the ethanol was removed at reduced pressure and steam-bath temperature. Water was added and the solvent was removed to give a thick paste to which was added 1 l. of water. The solution was brought to pH 1 with concentrated hydrochloric acid and heated on the steam bath under a reflux condenser for 3 hr. After cooling in an ice bath, the mixture was extracted with ether, the extracts were dried and filtered, and the solvent was removed under reduced pressure, leaving approximately 8 g of yellow oil which crystallized. Analysis by glc of the methyl ester of the combined solids indicated there to be 53% of the desired enone. The crude solid was dissolved in benzene and chromatographed on a column of silica gel (Will, Grade 922, activated 6 hr at 140°). Elution with benzene–ethyl acetate (10:1) gave 1.53 g of an oil which crystallized on standing. Recrystallization from a small volume of hexane gave the analytical sample of **1,2,3,4,5,6,7,8-octahydro-2-naphthoic acid (6)**: mp 108–110°; ir 5.90 μ; nmr δ 1.36–2.85 (m, 15 H, CH and CH_2), 11.62 (s, 1 H, CO_2H).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.44; H, 8.81.

Elution with benzene–ethyl acetate (5:1) gave 1.72 g of a mixture of saturated and unsaturated ketones. A solution of 1.50 g of this mixture was dissolved in 33.8 ml of dry ethanol containing 4.93 ml of acetic acid and 4.93 g of dry Girard's-T reagent and heated at reflux for 3.5 hr. The solvent was removed and 70.3 ml of water was added. The pH was quickly adjusted to 5–6 with sodium carbonate and the solution was extracted with three portions of ether. The aqueous layer was allowed to stand for 12 hr at room temperature and extracted with four portions of ether. The pH was adjusted to 1 with concentrated hydrochloric acid and the solution was kept at room temperature for 11 hr and extracted with six portions of ether. After standing at room temperature another 48 hr and then at steam bath temperature for 2 hr, the solution was again extracted with ether and then continuously extracted with ether for 56 hr. The final extracts were filtered and dried and the solvent was removed to give 0.223 g of **4,4a,5,6,7,8-hexahydronaphthalen-1(1a*H*)-one-7-carboxylic acid (8)**. Recrystallization from ether–hexane gave the analytical sample: mp 152–156°; ir 3.28, 5.86, 6.00, 6.06 μ; uv λ_{max} 266 mμ (log ε 3.64); nmr δ 0.83–2.70 (m, 11 H, CH, CH_2), 5.83 (d, J = 10 Hz, 1 H, OCCH=), 6.72 (m, 1 H, OCCH=CH), 10.32 (s, 1 H, CO_2H).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.04; H, 7.34.

The intermediate fractions eluted with benzene–ethyl acetate (5:1) gave 0.830 g of **2,3,4,4a,5,6,7,8-octahydronaphthalen-1-(1a*H*)-one-2-carboxylic acid (7)**, which after repeated recrystallization from anhydrous ether, and finally ether–benzene, had mp 146–149°: ir 5.87 μ; nmr δ 1.1–2.6 (m, 15 H, CH and CH_2), 11.51 (s, 1 H, CO_2H).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.43; H, 8.33.

Treatment of this compound with ethereal diazomethane gave the oily methyl ester, characterized as the 2,4-dinitrophenylhydrazone, mp 179–181°, from aqueous methanol.

Anal. Calcd for $C_{18}H_{22}N_4O_6$: C, 55.38; H, 5.68; N, 14.35. Found: C, 55.47; H, 5.66; N, 14.37.

The final fractions eluted with benzene–ethyl acetate (5:1) gave 2.23 g of **3,4,5,6,7,8-hexahydronaphthalen-1(2*H*)-one-2-carboxylic acid (3)**. The analytical sample, mp 145–146°, was crystallized from dry ether: ir 2.9–3.8, 5.86, 6.19 μ; uv λ_{max} 244 mμ (log ε 4.18); nmr δ 1.25–2.82 (m, 15 H, CH and CH_2), 11.40 (s, 1 H, CO_2H).

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.27. Found: C, 68.11; H, 7.37.

The methyl ester (ir 5.75, 6.01 μ) was prepared with diazomethane and characterized as its 2,4-dinitrophenylhydrazone. Crystallization from methanol–ethyl acetate afforded bright red needles, mp 194.5–196.5°.

Anal. Calcd for $C_{18}H_{20}N_4O_6$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.50; H, 5.30; N, 14.18.

4a-Methyl-3,4,4a,5,6,7,8,8a-octahydronaphthalen-1(2*H*)-one-7-carboxylic Acid.—To a rapidly stirred mixture of 3.93 g of cuprous iodide in 79 ml of anhydrous ether at 0° under nitrogen was added slowly over a 10-min period, 15–17 ml of a 2 *N* ethereal solution of methyllithium. The solution was allowed to stir for 5 min, and 1 g of 3,4,5,6,7,8-hexahydronaphthalen-1(2*H*)-one-7-carboxylic acid (**3**) in 100 ml of dry ether was added and rinsed in with two 10-ml portions of the same solvent. The yellow, heterogenous mixture was stirred at 0° under nitrogen for 2 hr. The mixture was then slowly poured into a rapidly stirred solution of 530 ml of 1.2 *N* hydrochloric acid at 0°. When all the yellow color had disappeared and only the gray to tan precipitate of cuprous iodide remained, the heterogenous mixture was extracted repeatedly with ether. The extracts were dried and filtered and the solvent was removed under reduced pressure at steam bath temperature, leaving 1.08 g (100%) of a dark brown oil. Analysis by glc of the methyl ester of this oil showed three major components in a ratio of approximately 4:3:2 (A:B:C). The oil was dissolved in ethyl acetate–hexane (1:100) and filtered through 10 g of silica gel which had been activated at 140° for 6 hr. Ethyl acetate–hexane (1:99) was used for elution until the eluate was free of the purple color of iodine. Elution with ethyl acetate–hexane (1:95) gave 0.050 g of a light brown oil which was not characterized. Further elution with ethyl acetate–hexane (1:4) gave 0.940 g (87%) of light brown oil which crystallized and was used in the next step without further purification. One of the components of the reaction mixture was crystallized as follows. The crystalline residue from above was dissolved in 10 ml of ethyl acetate and added to 120 ml of hot cyclohexane. The solution was concentrated to 100 ml, and after standing a brown oil settled out. The supernatant liquid was decanted and concentrated to approximately 50 ml to give a mixture of brown oil and crystals. The supernatant liquid was decanted and the residue was triturated with small amounts of dry ether. The crystals (0.300 g) were dissolved in 5 ml of ethyl acetate and added to 20 ml of cyclohexane and the solution was concentrated to cloudiness. The solution was allowed to cool and seeded, and 0.110 g of light yellow crystals was collected. Another recrystallization afforded the analytical sample of **8aβ-methyl-3,4,4a,5,6,7,8,8aα-octahydronaphthalen-1(2*H*)-one-7-carboxylic acid (10)**: mp 152–154°; ir 3.0, 3.85, 5.88 μ; nmr δ 0.93 (s, 3 H, CH_3), 1.10–2.60 (m, 14 H, CH, CH_2), 11.12 (s, 1 H, CO_2H).

Anal. Calcd for $C_{12}H_{16}O_3$: C, 68.55; H, 8.63. Found: C, 68.51; H, 8.68. Analysis by glc of the methyl ester indicates that this compound represents 41% of the original reaction.

Equilibration Studies. A.—A solution of 0.010 g of 4aβ-methyl-3,4,4a,5,6,7,8,8aα-octahydronaphthalen-1(2*H*)-one-7-carboxylic acid (**10**) in 2 ml of 10% sodium hydroxide was heated on

(14) E. L. Martin, *J. Amer. Chem. Soc.*, **58**, 1438 (1936).

the steam bath for 1 hr. The reaction mixture was acidified with concentrated hydrochloric acid and extracted with four portions of ether. The extracts were dried, the solvent was removed, and the residual acid was converted to the methyl ester with diazomethane. Glc analysis indicated that there were two components present in the mixture in a ratio 3:1 (A:B). The retention time of the major component was the same as that of the starting acid, while that of the minor component was the same as that of the isomer present in intermediate amount in the original reaction mixture.

B.—Keto acid **10** was converted to the methyl ester with diazomethane and 0.010 g was heated at reflux for 16 hr in 2.0 ml of methanolic sodium methoxide. The methanol was removed, 5 ml of water was added, and the solution was acidified (pH 1) with conentrated hydrochloric acid. The turbid solution was extracted with ether, the extracts were dried over magnesium sulfate, and the solvent was removed to give 0.005 g (50%) of a mixture of esters. Glc analysis indicated that there were two components present in a ratio 3:5 (A:D). The retention time of the minor component was the same as that of the starting ester, while the major product was a new ester of longer retention time. The infrared spectrum of this mixture showed absorption at 5.75 and 5.83 μ while the nmr showed two singlets, at δ 0.81 and 0.91, of relative intensities of *ca.* 2.2:1.

4aβ-Methyl-8-methylene-1,2,3,4,4a,5,6,7,8,8aα-decahydronaphthalene-2α-carboxylic Acid (13).—To a solution of methylene triphenylphosphorane, from 4.40 g of methyltriphenylphosphonium bromide in 45 ml of dimethyl sulfoxide, was added 0.500 g of the mixture of isomeric acids, A, B, and C, described above in 10 ml of dimethyl sulfoxide. The deep orange solution was stirred and heated at 62–65° for 36 hr. After cooling to room temperature, the reaction mixture was poured into water, and the basic solution was brought to pH 1 with concentrated hydrochloric acid and extracted with ether. The extracts were washed with water and dried, and the solvent was removed under reduced pressure at steam bath temperature, leaving 2 g of a yellow oil. The oil was dissolved in anhydrous ether–hexane and filtered through a column of silica gel. Elution with hexane gave in the first fraction 0.030 g of a colorless oil which was not characterized. Elution with hexane–anhydrous ether (1:1) gave 0.415 g of yellow oil (84%) which crystallized on standing. Analysis by glc of the methyl ester of this material showed that it consisted of 40% of the desired acid (**12**), and 60% of a mixture of two other compounds in a ratio of *ca.* 6:1. Recrystallization from hexane gave the 2α-acid, **13**, as white crystals: mp 123–125°; ir 5.87, 6.06, and 11.29 μ; nmr δ 0.75 (s, 3 H), 1.27–2.50 (envelope, 13 H), 2.85 (m, 1 H), 4.46 (br s, 1H), 4.76 (br s, 1 H).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 75.18; H, 9.76.

When the Wittig reaction was carried out as described above utilizing the methyl esters instead of the mixed acids, a similar mixture of compounds was obtained.

4aβ-Methyl-8-methylene-1,2,3,4,4a,5,6,7,8,8aα-decahydronapthalene-2β-carboxylic Acid (12).—An ethereal solution of 0.150 g of the mixture of stereoisomeric methylene acids described above was treated with diazomethane for 15 min. The ether was evaporated and the resulting oil was heated at reflux for 2 hr with 1 ml of methanol containing 0.108 g of sodium methoxide and protected from atmospheric moisture. The methanol was removed under reduced pressure at steam bath temperature, water was added, and the solution was heated on the steam bath under nitrogen for 1 hr. After cooling to room temperature and acidifying to pH 1 with concentrated hydrochloric acid, the reaction mixture was extracted with ether. The extracts were washed once with water, dried, and filtered and the solvent was removed under reduced pressure, leaving 0.135 g (90%) of yellow oil which crystallized on standing. Crystallization of the acid from hexane at −10° afforded 0.067 g of tan crystals, mp 107–114°. Recrystallization from the same solvent gave 0.054 g of off-white crystals, mp change in crystalline from 95–117°, mp 117.5–118.5°; mmp with an authentic sample,[2b,9] change in crystalline from 95–115°, mp 115–117°. The infrared spectrum was identical with that of the authentic sample, as was the glc retention time of the methyl esters: nmr δ 0.75 (s, 3 H), 1.02–2.67 (envelope, 14 H), 4.47 (br s, 1 H), 4.73 (br s, 1 H) [lit. (in CCl_4) δ 0.75, 4.52, 4.78[2b]].

Registry No.—**3**, 32178-64-6; **3** methyl ester 2,4-DNP, 32298-25-2; **4**, 16035-97-5; **5**, 32178-63-5; **6**, 32298-28-5; **7**, 32298-80-9; **7** methyl ester 2,4-DNP, 32298-29-6; **8**, 32367-43-4; **10**, 32298-30-9; **12**, 32298-31-0; **13**, 32179-13-8; *o*-methoxybenzylidenesuccinic acid, 24289-96-1; *o*-methoxybenzylsuccinic acid, 32298-34-3; *o*-methoxybenzylsuccinic anhydride, 32298-35-4.

Studies on Resin Acids. VII. Isomerization of 19-Norabietatetraenes[1]

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Received June 23, 1971

The composition of the mixture of olefins obtained by lead tetraacetate decarboxylation of 4-epidehydroabietic acid (**4**) has been found to be very nearly the same as that obtained from dehydroabietic acid. Acid-catalyzed isomerization of this mixture of olefins leads to a mixture of 19-norabieta-4,8,11,13-tetraene (**2**) and 19-nor-5β-abieta-3,8,11,13-tetraene (**7**), in which the latter predominates. Hydroboration–oxidation of **7** gives 18-nor-5β-abieta-8,11,13-trien-3α-ol (**9**), which on oxidation affords the corresponding ketone **14**. The course of the isomerization of the olefin mixture is discussed.

In the course of the hydroboration–oxidation of the mixture of olefins obtained by lead tetraacetate decarboxylation of dehydroabietic acid, there was obtained, among other products, 19-norabieta-8,11,13-trien-7-one (**1**).[2] It was suggested that this ketone was probably derived from 19-norabieta-4,8,11,13-tetraene (**2**), but this was not confirmed[2] and in an effort to gain additional information concerning the origin of **1**, a convenient source of olefin **2** was sought. Although **2** has been isolated from the decarboxylation mixture by chromatography,[3] this substance constitutes less than 30% of that mixture.[2,3] Since it had been reported that lead tetraacetate decarboxylation of podocarpic acid methyl ether (**3**) gives a mixture of olefins which contains 63% of the analog of **2**,[4] this reaction was carried out on 4-epidehydroabietic acid (**4**).[1] This procedure gave, however, a mixture of 32% of **2**, 41% of 19-norabieta-4(18),8,11,13-tetraene (**5**), and 27% of 19-norabieta-3,8,11,13-tetraene (**6**). Repetition of the decarboxylation in the podocarpic acid series gave, in contrast to the original report,[4,5] a mixture containing 32% of the analog of **2** and 38 and 25% of the analogs of **5**

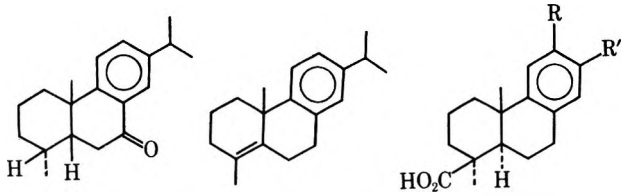
(1) Part VI: J. W. Huffman, *J. Org. Chem.*, **35**, 3154 (1970).

(2) J. W. Huffman, *ibid.*, **35**, 478 (1970).

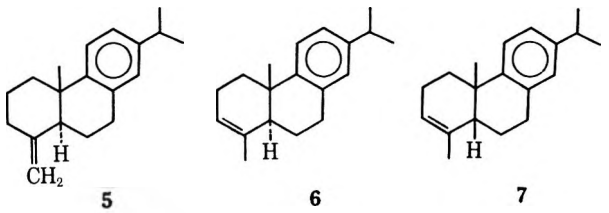
(3) C. R. Bennett, R. C. Cambie, R. A. Franich, and T. J. Fullerton, *Aust. J. Chem.*, **22**, 1711 (1969).

(4) C. R. Bennett and R. C. Cambie, *Tetrahedron*, **23**, 927 (1967).

(5) R. C. Cambie and W. A. Denny, *Aust. J. Chem.*, **22**, 1699 (1969), subsequently reported similar data, correcting their original report (ref 4).



1 2 3, R = OCH_3; R′ = H
4, R = H; R′ = $CH(CH_3)_2$



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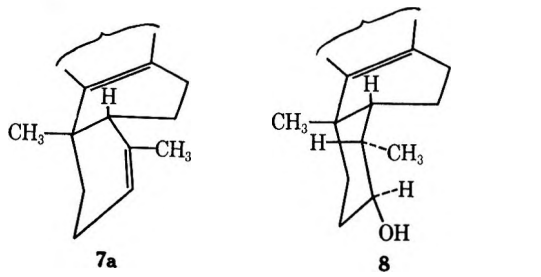

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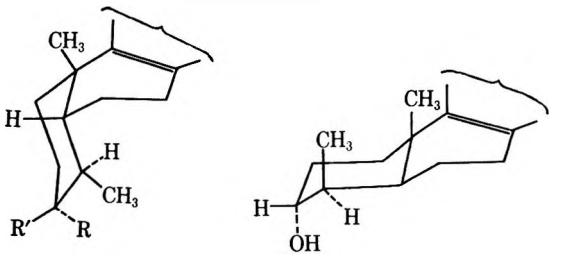
and **6**, respectively. The decarboxylation of dehydroabietic acid gives a mixture of **2**, **5**, and **6** in relative percentages of 27, 40, and 33,[2] and on the basis of Cambie's original data[4] and the obvious difference between them and these results, it was suggested that the lead tetraacetate decarboxylations proceed *via* a hot carbonium ion.[2] However, since it is apparent that very nearly the same percentages of isomeric olefins are obtained in these decarboxylations regardless of the stereochemistry at C-4, it seems probable that the reactions are proceeding by way of a classical, open carbonium ion.

It has been reported that the acid-catalyzed isomerization of the 19-norpodocarpatetraene mixture gives a 2:1 mixture of the 4- and 3-enes[5] and by analogy it was assumed that similar treatment of the norabietatetraenes[2,6a] would give a mixture rich in **2**, which would be amenable to either chemical or chromatographic separation techniques. The use of Cambie's conditions (*p*-toluenesulfonic acid–dioxane) gave little evidence of isomerization, and repetition of Cambie's isomerization of the norpodocarpatetraenes failed to give the reported results.[5] When the mixture of olefins from dehydroabietic acid was heated with *p*-toluenesulfonic acid in toluene there was obtained a mixture which contained from 30 to 50% of **2** with the balance of the mixture being an olefin which was different from either **5** or **6**. Attempted separation by silver nitrate–silica gel chromatography failed; however, selective epoxidation of **2**[5] or preparative glc gave a pure sample of the new compound. The mass spectrum of this material indicated that it was isomeric with **2**, **5**, and **6** (M^+ 254),[6b] and the nmr spectrum showed a vinyl proton signal at δ 5.33, a broadened singlet due to a vinyl methyl at δ 1.71, and an angular methyl signal at δ 1.27. The only structure consistent with these data is 19-nor-5β-abieta-3,8,11,13-tetraene (**7**), in which A and B rings have adopted a nonsteroidal conformation (**7a**).[7] Treatment of the norpodocarpatetraene mixture under similar conditions gives similar results.

In order to gain additional insight into the structure of **7**, and in particular its mode of formation, a mixture of **2** and **7** which was rich in **7** was subjected to hydroboration–oxidation. The principal product was a secondary alcohol, $C_{19}H_{28}O$, which showed a moderately shielded C-10 methyl singlet in the nmr at δ 1.17 and a carbinol proton as a multiplet at δ 3.12. Since the signals for the benzylic protons partially overlapped that of the carbinol proton, the acetate was prepared and this showed a very broad signal ($W_{1/2}$ = 23 Hz) at δ 4.50. The width of this signal indicates that proton is axial, and the vicinal coupling constant for the secondary methyl is 5 Hz, indicating that H-4 is also axial, with the secondary methyl group equatorial.[8a] Although both the nonsteroidal conformer of 19-nor-5β-abieta-8,11,13-trien-3β-ol (**8**) and the steroidal conformer of 18-nor-5β-abieta-8,11,13-trien-3α-ol (**9**) would have the hydroxyl and secondary methyl group equatorial, the angular methyl signal is at the same frequency as that of 18-norabieta-8,11,13-trien-3α-ol (**10**).[2] This indicates that the methyl group in both compounds has the same spatial relationship to the aromatic ring and that the hydroboration product of olefin is the 3α-ol (**9**), resulting from α attack of diborane on **7**. Examination of a model of **7** indicates that in the nonsteroidal conformation β attack is hindered by the angular methyl group. In the steroidal conformer the convex β face of ring A is relatively unhindered while the concave α side of the olefin is shielded by rings B and C. The



9, R = OH; R′ = H
13, R = R′ = H
14, R = R′ = O

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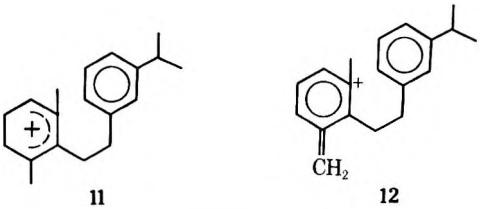

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(6) (a) J. W. Huffman and P. G. Arapakos, *J. Org. Chem.*, **30**, 1604 (1965). (b) We would like to thank the Research Triangle Institute for Mass Spectrometry, Research Triangle Park, N. C., for carrying out this determination.

(7) In the 5α isomer of **7** (**6**), the angular methyl signal appears at δ 1.05 (ref 2). The only way to explain the rather profound deshielding of the angular methyl in **7** is by some change in the spatial relationship between the angular methyl group and the aromatic ring. The steroidal conformation of **7** would have the angular methyl and the aromatic ring in nearly the same relationship as in **6**, and consequently the angular methyl signal would not be expected to be significantly different from that of **6**.

(8) (a) F. Johnson, N. A. Starkousky, and W. D. Gurowitz, *J. Amer. Chem. Soc.*, **87**, 3492 (1965). (b) S. P. Acharya and H. C. Brown, *J. Org. Chem.*, **35**, 3874 (1970), have used a similar argument in discussing the conformation of thujopsene. These authors discuss in some detail the theoretical justification for this approach in probing the conformational preferences of mobile systems.

stereochemical course of the hydroboration reaction provides confirmatory evidence for the nonsteroidal conformation of **7**.[8b]

In contrast to the highly stereoselective hydroboration of **7**, catalytic hydrogenation gave a mixture of two hydrocarbons. The nmr spectrum of the major product showed the high-field methyl singlet (δ 1.18) associated with a steroidal conformation[8b] while the C-10 methyl signal for the minor component of the mixture appeared at δ 1.40, indicating a nonsteroidal conformation for rings A and B. On the basis of these data the major isomer is 18-nor-5β-abieta-8,11,13-triene (**13**), with an equatorial secondary methyl group, while the minor product is the C-4 epimer with an equatorial methyl and nonsteroidal conformation.

Although the isomerization of the mixture of **2**, **5**, and **6** is *a priori* a straightforward acid-catalyzed olefin isomerization proceeding through a carbonium ion at C-4, an alternative path involving rupture of the 9-10 bond, followed by the recyclization in a manner similar to that suggested by Wenkert for the dehydroabietonitrile–isodeoxypodocarponitrile reaction could not be excluded.[9] It should be noted, however, that if this mechanism were operative, the intermediate would be either a symmetrical allylic carbonium ion (**11**) or a tertiary homoallylic carbonium ion (**12**, or the isomeric ion corresponding to **6**). If the former course correctly represented the reaction path, the product olefins would be a racemic mixture and if the latter mechanism were operative, the products would be enantiomeric with the natural resin acids. Consequently, alcohol **9** was oxidized to the corresponding ketone (**13**) under conditions which preclude isomerization at C-4.[10] The ketone thus obtained showed a C-10 methyl signal in the nmr at relatively high field (δ 1.26) indicating a steroidal conformation for the molecule, and the relatively small value of the vicinal coupling constant for the secondary methyl protons (J = 6 Hz) indicates that this methyl group is equatorial.[7] The rotatory dispersion curve of **13** showed a negative Cotton effect curve (amplitude −12.7) as predicted by the octant rule for the steroidal conformer of 18-nor-5β-abieta-8,11,13-tetraen-3-one (**14**). The structure of **14** would thus seem to exclude a breaking of the 9–10 bond during the isomerization and tends to support a simple carbonium ion mechanism.

During the course of several different isomerizations of the mixture of olefins from dehydroabietic acid, it was found that the relative percentages of **2** and **7** were somewhat variable. In an effort to follow the course of the reaction one run was carried out and the composition of the reaction mixture was monitored at various intervals. Initially there is a rapid conversion of **5** and a somewhat less rapid conversion of **6** to **2**, followed by a rather slow conversion of **2** to a mixture of **2** and **7**. Although no effort was made to carry this reaction to completion, after 25 hr the isomerization mixture contains 61% of **7**, 37% of **2**, 2% of **6**, and a trace of **5** and traces of three other compounds. Following the completion of this work Whitlock reported isomerization data for the deisopropyl analog of **2**, using *p*-toluenesulfonic acid–acetic acid.[11] These authors observed nearly the same ratio of **2** to **7** that we observe; however, they also obtained nearly 20% of three other isomeric olefins. These differences in product composition can probably be attributed to solvent differences, which would ultimately amount to a counterion effect.[12] Whitlock has attempted to explain the differences in his solvolysis results and olefin isomerizations in terms of conformational effects;[11] however, our results seem to favor the alternative explanation.

A priori it appears rather unusual that the major product of the isomerization of **2**, **5**, and **6** should be a cis-fused, trisubstituted olefin (**7**); however, examination of models indicates that in **2**, **5**, and **6** there are rather severe steric interactions between C-18 and C-6, which are relieved by isomerization to **7**.

Experimental Section[13]

Decarboxylation of Dehydroabietic Acid.—This reaction was carried out as described previously.[2,6] Analysis by nmr and glc gave the following results: **5**, 40%; **6**, 33%; **2**, 27%. Canonica, *et al.*, report 37, 34, and 29%, respectively.[14]

Decarboxylation of 4-Epidehydroabietic Acid (**4**).—This reaction was carried out in the same manner as that of dehydroabietic acid; analysis by nmr showed 41% 19-norabieta-4(18),8,11,13-tetraene (**5**), 27% 19-norabieta-3,8,11,13-tetraene (**6**), and 32% 19-norabieta-4,8,11,13-tetraene (**2**). The olefins were isolated as described earlier.[2,6]

Decarboxylation of o-Methylpodocarpic Acid (**3**).—Decarboxylation of *o*-methylpodocarpic acid and the isolation of the olefins were carried out as described previously.[2,6] Analysis by nmr and glc gave the following results: 38% 12-methoxy-19-norpodocarpa-4(18),8,11,13-tetraene; 26% 12-methoxy-19-norpodocarpa-3,8,-11,13-tetraene, and 32% 12-methoxy-4,8,11,13-tetraene. Cambie reports 39, 33, and 28%, respectively, from this reaction.[5]

Isomerization of 19-Norabietatetraenes.—To a solution of 5.24 g of the mixture of **2**, **5**,/and **6** obtained from the lead tetraacetate decarboxylation of dehydroabietic acid in 250 ml of toluene was added 0.45 g of *p*-toluenesulfonic acid and the mixture was heated at reflux 5 hr and then allowed to stand for 24 hr at room temperature. The precipitated toluenesulfonic acid was filtered off, the toluene was removed at reduced pressure, and the residue was taken up in hexane. The hexane solution was washed with 5% aqueous sodium hydroxide and water, dried, concentrated to a small volume, and filtered through a column of Merck acid-washed alumina. Elution with hexane gave 4.85 g (93%) of a mixture containing 63% of 19-norabieta-4,8,11,13-tetraene (**2**) and 37% of 19-nor-5β-abieta-3,8,11,13-tetraene (**7**), plus traces of other isomers. Attempted separation by chromatography on silver nitrate–silica gel[15] was unsuccessful, and the mixture was finally resolved by preparative glc to give pure (glc) **7** [nmr 1.27 (s, C-10 methyl), 1.71 (br s, C-4 methyl), 5.33 (m, H-3)] and pure (glc) **2**.

In one run, carried out as described above, aliquots were withdrawn at intervals and the course of the reaction was monitored by glc (Table I).

Isomerization of 12-Methoxy-19-norpodocarpatetraenes. A.—A solution of 1.00 g of the mixture of olefins from *o*-methylpodocarpic acid in 50 ml of toluene containing 0.10 g of *p*-toluenesulfonic acid was heated at reflux for 4 hr and allowed to stand at room temperature for 18 hr. The product was isolated as de-

(9) E. Wenkert and B. G. Jackson, *J. Amer. Chem. Soc.*, **80**, 211 (1958).

(10) (a) E. J. Corey and R. A. Sneen, *ibid.*, **78**, 6269 (1969); (b) J. W. Huffman, J. A. Alford, and R. R. Sobti, *J. Org. Chem.*, **35**, 473 (1970).

(11) H. W. Whitlock, Jr., and L. E. Overman, *J. Amer. Chem. Soc.*, **93**, 2247 (1971).

(12) D. J. Cram and M. R. V. Sahyun, *ibid.*, **85**, 1257 (1963).

(13) Melting points were determined on a Kofler hot stage and are uncorrected. Infrared spectra were taken as films or potasium bromide pellets on a Perkin-Elmer Model 137 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian Associates Model A-60 spectrometer using deuteriochloroform as a solvent and tetramethylsilane as an internal standard. Signals are reported in parts per million relative to this standard (δ). Optical rotatory dispersion curves were determined in methanol using a Jasco ORD/UV-5 spectropolarimeter. Analytical glc data were obtained using an F and M Model 810 chormatograph with 8 ft × 0.125 in. SE-30 on Chromosorb W or 10 ft × 0.125 in. OV-17 on Chromosorb W columns at temperatures of 225–240°.

(14) L. Canonica, B. Danieli, P. Manitto, and G. Russo, *Gazz. Chim. Ital.*, **98**, 699 (1968).

(15) T. Norin and L. Westfelt, *Acta Chem. Scand.*, **17**, 1828 (1963).

TABLE I

COURSE OF THE ISOMERIZATION OF 19-NORABIETATETRAENES

Time, hr	Compd, %			
	2	5	6	7
0	27	40	33	0
1	74	1	13	12
2	67	Trace	5	28
3	57	Trace	3	40
4	51	Trace	3	46
6	48	Trace	2	50
8	46	Trace	2	52
25	37	Trace	2	61

scribed above to give 0.493 g of a mixture which contained 54% 12-methoxy-19-nor-5β-podocarpa-3,8,11,13-tetraene [nmr δ 5.35 (m, H-4), 3.72 (OCH_3) (d, J = 1 Hz, C-4 methyl), and 1.28 (s, C-10 methyl)] and 46% 12-methoxy-19-norpodocarpa-4,8,11,13-tetraene [nmr δ 3.72 (s, OCH_3), 1.67 (br s, C-4 methyl), 1.37 (s, C-10 methyl)]. Cambie[4] reports signals at δ 3.68, 1.64, and 1.33 for this compound.

B.—The norpodocarpatetraene mixture was treated and the product was isolated as described by Cambie[5] to give a mixture which contained 36% 12-methoxy-19-norpodocarpa-4(18),8,11,-13-tetraene, 24% 12-methoxy-19-norpodocarpa-3,8,11,13-tetraene, and 40% 12-methoxy-4,8,11,13-tetraene.

Epoxidation of Isomerized Abietatetraenes.—To a solution of 2.84 g of a mixture of 2 (54%) and 7 (46%) in 125 ml of methylene chloride was added 1.41 g of *m*-chloroperbenzoic acid. The mixture was stirred at room temperature for 0.75 hr and then excess 10% aqueous sodium bisulfite was added. The organic layer was drawn off and washed with bisulfite solution and two portions of 10% aqueous sodium carbonate. After drying the solvent was removed to give 1.73 g of oil which was taken up in hexane and chromatographed on 80 g of Bio-Rad activity I neutral alumina. Elution with hexane gave 0.255 g of 7, homogeneous by glc. Elution with hexane–benzene mixtures gave 0.599 g of a mixture of epoxides, which was not investigated further.

Hydroboration of Isomerized Abietatraenes.—To a solution of 2.89 g of the mixture of 2 and 7, obtained as described above, in 25 ml of dry ether containing 1.00 g of lithium aluminum hydride and maintained at 0° was added dropwise a solution of 3.75 ml of boron trifluoride in 60 ml of ether. The reaction mixture was stirred for 2 hr at ambient temperature and sufficient ice was added to decompose the excess diborane. Saturated brine was added, the ethereal solution was decanted, and the aqueous phase was slurried with two portions of ether which were combined with the original organic phase. The ethereal solution was dried and the solvent was removed at reduced pressure with gentle warming. The residual alkylboranes were taken up in 120 ml of tetrahydrofuran to which was added 60 ml of 10% aqueous sodium hydroxide followed by 50 ml of 30% hydrogen peroxide. The reaction mixture was stirred at room temperature for 18 hr, and the aqueous layer was drawn off and extracted with two portions of ether. The combined organic layers were washed with water and dried and the solvent was removed to give 2.40 g of pale amber oil. Tlc (silica gel G, benzene–ethyl acetate, 8:1) indicated that the product was a mixture of at least three compounds with one predominating. On standing the oil partially crystallized and trituration with hexane gave 0.451 g of 18-nor-5β-abieta-8,11,13-trien-3α-ol (9). Recrystallization from hexane gave 0.350 g: mp 135–136°; nmr δ 1.11 (d, J = 5 Hz, C-4 methyl), 1.17 (s, C-10 methyl), and 3.12 (m, H-3).

The analytical sample, mp 138–139°, was crystallized from aqueous methanol.

Anal. Calcd for $C_{19}H_{28}O$: C, 83.77; H, 10.36. Found: C, 83.88; H, 10.25.

The acetate was prepared from 0.10 g of 9. This material would not crystallize: mass spectrum M^+ 314; nmr δ 0.93 (d, J = 5 Hz, C-4 methyl), 1.18 (s, C-10 methyl), 1.95 (s, CH_3CO), 4.50 (m, $W_{1/2}$ = 23 Hz, H-3).

The hexane solution remaining from the isolation of 9 was chromatographed on 90 g of Merck acid-washed alumina. Elution with hexane gave 0.102 g of a mixture of hydrocarbons while benzene–methylene chloride mixtures gave 0.443 g of oil. Later benzene–methylene chloride fractions afforded an additional 0.954 g of 9.

Hydrogenation of 19-Nor-5β-abieta-3,8,11,13-tetraene.—A solution of 0.152 g of 7 in 10 ml of ethanol containing 0.030 g of Adam's catalyst was hydrogenated at 50 psig. After filtering off the catalyst and removing the solvent there was obtained 0.108 g (71%) of nearly colorless oil. For characterization the product was taken up in hexane and filtered through a column of Bio-Rad neutral alumina. Glc indicated that the mixture contained 66% 18-nor-5β-abieta-8,11,13-triene (13) [nmr δ 0.92 (d, J = 5 Hz, C-4 methyl), 1.18 (s, C-10 methyl)] and 34% 19-nor-5β-abieta-8,11,13-triene [nmr δ 0.96 (d, J = 7 Hz, C-4 methyl), 1.40 (s, C-10 methyl)]; mass spectrum, M^+ 256.

18-Nor-5β-abieta-8,11,13-tetraen-3-one (14).—A solution of 0.20 g of 9 in 6 ml of benzene was added slowly with vigorous stirring to a chilled (5°) solution of 0.150 g of chromic acid and 1.50 g of sodium dichromate in 25 ml of acetic acid and 2 ml of water. The reaction was stirred at room temperature for 18 hr, the aqueous layer drawn off, the benzene solution washed thoroughly with water and dried, and the solvent removed to give 0.125 g (65%) of nearly colorless oil, which was homogeneous to tlc (silica gel G, benzene–hexane, 1:1): nmr δ 1.09 (d, J = 6 Hz, C-4 methyl), 1.26 (s, C-10 methyl); ORD $[\phi]_{400}$ +350°, $[\phi]_{302}$ −447°, $[\phi]_{294}$ 0°, $[\phi]_{282}$ +825°. For analysis 14 was converted to the 2,4-dinitrophenylhydrazone, mp 165–166°, from ethanol–ethyl acetate.

Anal. Calcd for $C_{25}H_{30}N_4O_4$: C, 66.65; H, 6.71; N, 12.44. Found: C, 66.86; H, 6.76; N, 12.58.

Registry No.—**2**, 23963-77-1; **5**, 22478-62-2; **6**, 22478-63-3; **7**, 32298-72-9; **9**, 32298-73-0; **9** acetate, 32298-74-1; **13**, 32298-75-2; **14**, 32298-76-3; **14** 2,4-dinitrophenylhydrazone, 32298-77-4; 12-methoxy-19-nor-5β-podocarpa-3,8,11,13-tetraene, 32298-78-5; 12-methoxy-19-nor-5β-podocarpa-4,8,11,13-tetraene, 32298-79-6; 19-nor-5β-abieta-8,11,13-triene, 32367-41-2.

Acknowledgments.—The spectropolarimeter was obtained through a National Science Foundation Research Instruments Grant. We thank T. F. Sanderson of Hercules, Inc., for a generous gift of dehydroabietonitrile and Dr. Reuben Sawdaye of this department for assistance with the glc experiments.

The Photochemistry of 1,1,2,2-Tetraphenylethane. A Di-π-ethane Reaction

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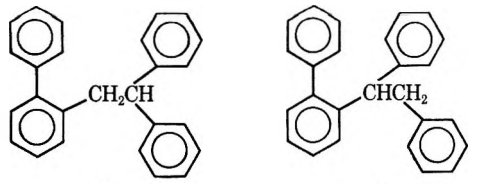
Received July 2, 1971

The photolysis of 1,1,2,2-tetraphenylethane (1) has been found to result in the formation of 1-(2-biphenylyl)-1,2-diphenylethane (6), biphenyl (3), and *cis*- and *trans*-stilbene (2 and 4). Mechanistic studies involving the photolysis of 1,1-diphenyl-2,2-ditolylethane (8) were conducted. The results from these studies require that three of the four photoproducts (2, 3, and 4) from irradiation of 1,1,2,2-tetraphenylethane (1) arise through an interaction of the number one positions of two benzene rings attached to adjacent carbon atoms. This type of reaction is termed a di-π-ethane reaction in analogy to the well-known di-π-methane rearrangement. The mode of formation of the fourth photoproduct is still unknown.

We have recently isolated 1,1,2,2-tetraphenylethane (1) as one of the photoproducts from the photolysis of benzophenone azine.[2] There was a clear indication from the products in this reaction that 1,1,2,2-tetraphenylethane (1) was itself photolabile. We have now investigated the photochemistry of 1 and wish to describe the unusual fragmentation and rearrangement processes it undergoes as well as to report the discovery of a new type of photochemical process, a di-π-ethane reaction.

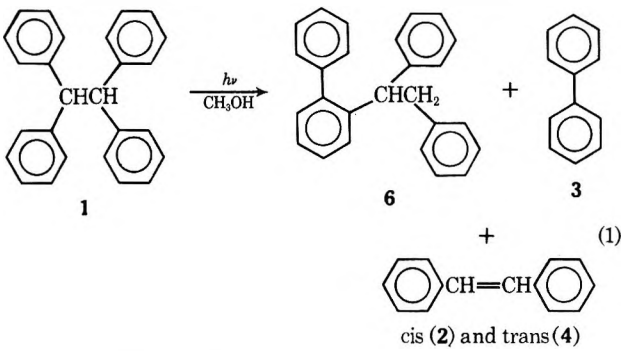
Results

Vycor-filtered irradiation of 3.00 mmol of 1,1,2,2-tetraphenylethane (1) in 1200 ml of methanol under nitrogen for 45 min with a 450-W Hanovia mercury vapor lamp caused the disappearance of 0.93 mmol of starting material as well as a yellowing of the reaction mixture. Distillation of the solvent and chromatography of the photolysis mixture on Florisil separated it into four fractions in addition to unreacted starting material. The three minor products were identified as *cis*-stilbene (2, 16%), biphenyl[3] (3, 10%), and *trans*-stilbene (4, 5%) by comparison with known samples. Structural assignment to the major photoproduct (65% yield, mp 79–81°) rests upon the following spectroscopic and chemical evidence. The major product was found to be isomeric with the starting material (1) by elemental analysis and molecular weight determination. The ir spectrum showed only absorptions characteristic of an alkyl aromatic system. The nmr spectrum (CCl_4) showed absorptions at τ 3.10 (19 H, m), 5.67 (1 H, t), and 6.81 (2 H, d). These data suggested that the photoproduct possessed a substituted biphenyl structure. The fact that the uv spectrum exhibited only end absorption was in accord with a biphenyl system which possessed an ortho substitution pattern.[4] Spectroscopic analysis, therefore, was consistent with two possible photoproduct structures, 2-(2-biphenylyl)-1,1-diphenylethane (5) and 1-(2-biphenylyl)-1,2-diphenylethane (6). Assignment of structure 6 to the major photoproduct was made on the basis of its synthesis from 1-bromo-1,2-diphenylethane and 2-bromobiphenyl in the presence of magnesium. The photochemical reaction of 1,1,2,2-tetraphenylethane (1) is described by eq 1.



5 6

Irradiation of 1,1,2,2-tetraphenylethane (1) under the same conditions as described above except for a longer photolysis time (3 hr) followed by the same chromatographic procedure resulted in similar yields of *cis*-stilbene (2, 16%), biphenyl[3] (3, 11%), and *trans*-stilbene (4, 7%); however, the yield of 1-(2-biphenylyl)-1,2-diphenylethane (6) was reduced to 22% and a new photoproduct was formed in 39% yield. The

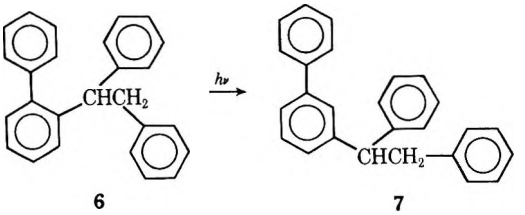


1 6 3 (1)

cis (2) and trans (4)

new photoproduct was also isomeric with the starting material (1) and nearly identical with 6 in ir and nmr spectral data [nmr (CCl_4) τ 2.85 (19 H, m), 5.79 (1 H, t), 6.66 (2 H, d)]; however, the uv spectrum exhibited a maximum at 251 nm (ε 10,000), indicating a biphenyl system which was not ortho-substituted. On the basis of this spectral information the most probable structure for the photoproduct was 1-(3-biphenylyl)-1,2-diphenylethane (7). Confirmation of this structural assignment was achieved by synthesis of 7 from 1-bromo-1,2-diphenylethane and 3-bromobiphenyl *via* a Grignard coupling reaction.

The two reactions of 1,1,2,2-tetraphenylethane (1) described above clearly suggested that 1-(2-biphenylyl)-1,2-diphenylethane (6) was an intermediate in the formation of 1-(3-biphenylyl)-1,2-diphenylethane



6 7

(1) Author to whom inquiries should be addressed.

(2) R. W. Binkley and J. Gorse, III, Abstracts, 161st National Meeting of the American Chemical Society, Los Angeles, Calif., 1971, No. ORGN 128.

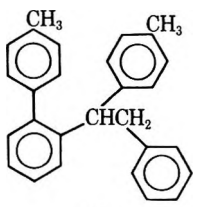
(3) The uv spectrum of the methanol distilled from the reaction mixture had an absorption spectrum identical with that of biphenyl; thus, it is likely that some biphenyl was lost during evaporation of the solvent.

(4) H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," Wiley, New York, N. Y., 1964, p 397.

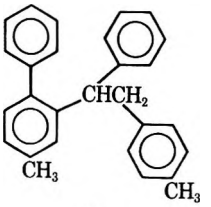
(7). Photolysis of 6 under the same conditions as 1 led quantitatively to 7.[5]

1,1-Diphenyl-2,2-ditolylethane (8) was irradiated using the same photolysis procedure as with 1. Chromatography on Florisil separated the reaction mixture into two mixtures of photoproducts. Preparative vpc analysis of the first photoproduct mixture separated it into 4-methylbiphenyl (9, 22%) and *cis*- and *trans*-4-methylstilbene (10, 16% and 11, 5%). No other stilbenes or methylbiphenyls were detected even though experiments with biphenyl, 2- and 3-methylbiphenyl, 4,4′-dimethylbiphenyl, and *cis*- and *trans*-4,4′-dimethylstilbene showed that they would have been in this mixture and would have been detected by vpc analysis.

The second fraction isolated from photolysis of 8 exhibited an nmr spectrum which was clearly a mixture of compounds related to 1-(2-biphenylyl)-1,2-diphenylethane (6). The nmr spectrum was consistent with an essentially equal combination of 12 and 13; unfortunately, however, this photolysis mixture proved to be an inseparable one. Vpc analysis resulted in decomposition. Adsorption chromatography using Florisil, silica gel, and alumina as well as several types of liquid–liquid partition chromatography were unsuccessful.

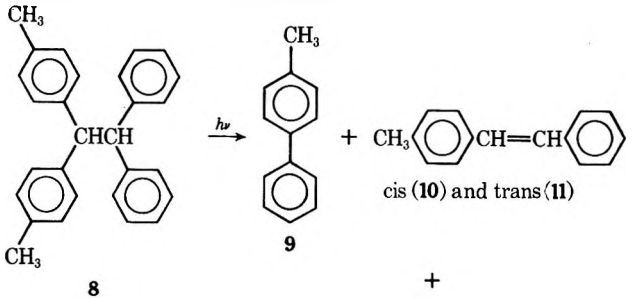


12



13

The photochemical reaction of 1,1-diphenyl-2,2-ditolylethane (8) is described in eq 2.



(2)

Discussion

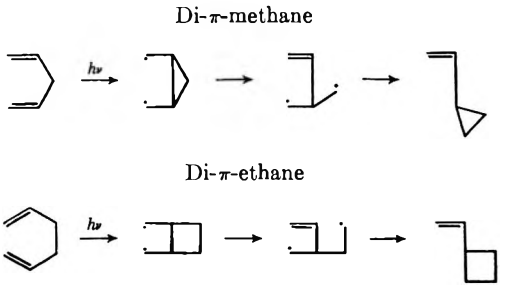
There are several interesting questions raised by the results from the photolysis of 1,1,2,2-tetraphenylethane (1). Perhaps the most intriguing of these deals with the mechanism of the reaction process, although a knowledge of the types of systems which will undergo this reaction is certainly of interest. Even though further experimentation is necessary before complete mechanistic determinations can be made, the results from this study give important insight into understanding this reaction and the new mechanistic process which controls it.

(5) This type of rearrangement has been studied by a number of workers. Most recent is the thorough examination of methylbiphenyls by V. Mende, J. L. Laseter, and G. W. Griffin, *Tetrahedron Lett.*, 3747 (1970).

In considering possible mechanisms for the photoreaction of 1,1,2,2-tetraphenylethane[6] (1), two fundamental reaction types, the di-π-methane and the di-π-ethane (Scheme I), appear possible. A di-π-methane

SCHEME I

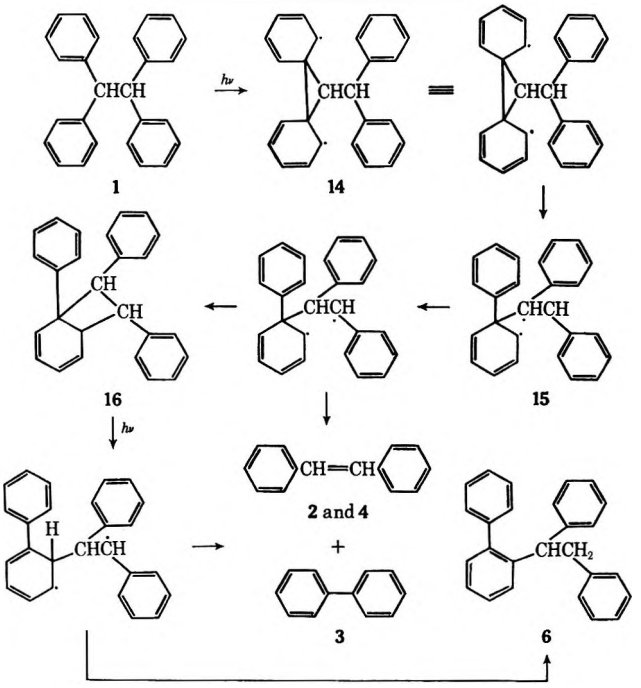
DI-π-METHANE AND DI-π-ETHANE REARRANGEMENT



reaction in this system (Scheme II) would be initiated

SCHEME II

DI-π-METHANE REARRANGEMENT FOR 1,1,2,2-TETRAPHENYLETHANE (1)



by bond formation between the substituted positions of two geminal benzene rings and lead to the intermediate 14. The diradical thus produced could stabilize itself by rearrangement to the cyclobutane 16, which upon further excitation would either fragment the two ring bonds to produce biphenyl (3) and *cis*- and *trans*-stilbene (2 or 4) or break only a single cyclobutane ring bond to lead, after hydrogen migration, to 1-(2-biphenylyl)-1,2-diphenylethane (6). It is worth noting that although the proposed reaction process (Scheme II) is identical with the di-π-methane rearrangement throughout the first segment of the reaction course, it takes a different turn at an intermediate stage. In the normal di-π-methane reaction the diradical 15 would have formed a norcaradiene

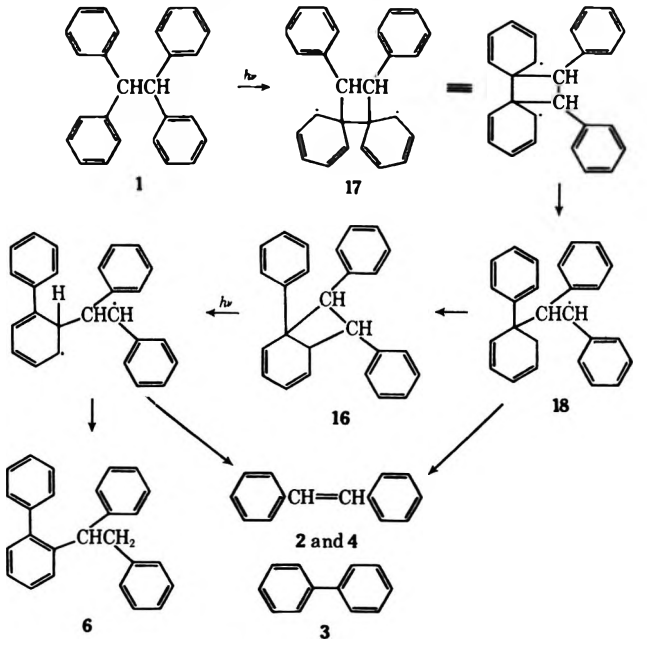
(6) The most extensive studies of the di-π-methane reaction have been by H. E. Zimmerman and A. C. Pratt, *J. Amer. Chem. Soc.*, **92**, 6267 (1970), and references cited therein.

structure; instead, however, it undergoes a phenyl migration before ring closure.

A second mechanistic possibility is shown in Scheme III. This process proposes a di-π-ethane reaction to

SCHEME III

DI-π-ETHANE REARRANGEMENT FOR 1,1,2,2-TETRAPHENYLETHANE (1)



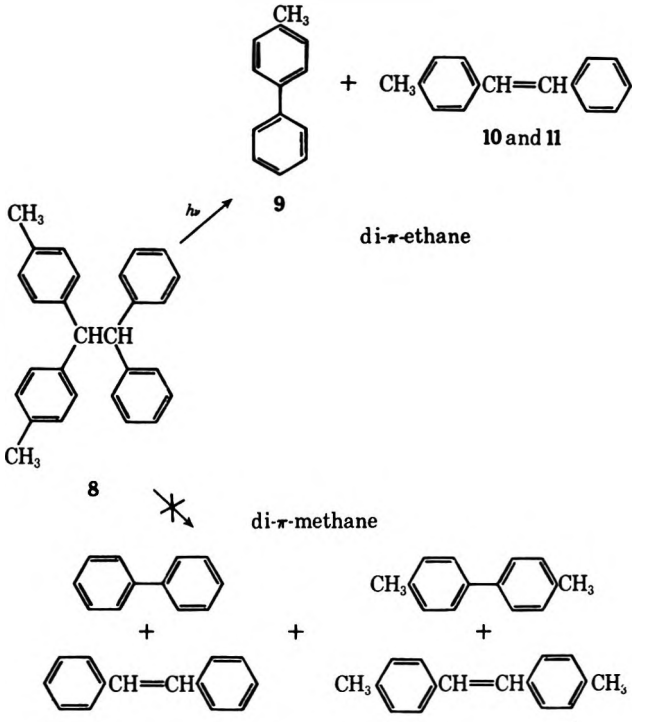
account for the transformations of 1,1,2,2-tetraphenylethane (1). Such a mechanism differs from the di-π-methane reaction in that it describes the interaction of π systems attached to adjacent carbon atoms. This type of interaction and rearrangement in the case of 1 leads through intermediate diradicals 17 and 18 to the cyclobutane derivative 16. Possible reaction of this intermediate (16) was discussed in the previous paragraph and is pictured in Scheme III.

A decision between the two proposed mechanistic pathways (di-π-methane and di-π-ethane) can be made for three of the four products (2, 3, and 4) from photolysis of 1 based upon the results from irradiation of 1,1-diphenyl-2,2-ditolylethane (8). Excitation of 8 yields 4-methylbiphenyl (9) as the only simple biphenyl and *cis*- and *trans*-4-methylstilbene (10 and 11) as the only stilbenes formed (Scheme IV). This result excludes the di-π-methane pathway but is completely consistent with the di-π-ethane proposal. Experimental difficulties (see Results) prevented any conclusion from being drawn regarding the mechanism of formation of the substituted biphenyl 6.

The apparent demonstration that a di-π-ethane type of interaction is taking place in the photolysis of 1 raises a number of questions related to the photochemistry of unsaturated systems. For example: What are the molecular structural requirements for a di-π-ethane reaction to occur? What factors control whether a di-π-methane or di-π-ethane reaction will take place in a particular system where both are possible? Is there a series of related reactions involving the photochemical interaction of π systems in which the two processes discussed here (the di-π-methane and di-π-ethane rearrangements) represent only the

SCHEME IV

PHOTOCHEMISTRY OF 1,1-DIPHENYL-2,2-DITOLYLETHANE



first two members? These and other questions are currently under investigation in our laboratories.

Experimental Section

Vycor-Filtered Irradiation of 1,1,2,2-Tetraphenylethane (1).—In a typical run 999 mg (3.00 mmol) of 1,1,2,2-tetraphenylethane[7] (1) in 1200 ml of methanol was irradiated for 45 min with a 450-W Hanovia high-pressure mercury-vapor lamp which had been lowered into a water-cooled quartz immersion well. Prepurified nitrogen was passed through the solution for 1 hr prior to irradiation and a slow stream of nitrogen was continued during photolysis.

After irradiation, the solvent was removed by distillation *in vacuo* below 25°, producing a distillate which exhibited the uv spectrum of biphenyl and leaving a residue consisting of crystals mixed with a yellow oil. The residual oil was chromatographed on a 90 × 2.5 cm Florisil column slurry packed in 1:9 ether–hexane; 60-ml fractions were collected. The column was eluted as follows: 0.5 l. of hexane, 0.5 l. of 1:49 ether–hexane, and 0.75 l. of 1:24 ether–hexane.

Fraction 7 afforded 15 mg (0.09 mmol) of crystalline biphenyl, mp 68–69°, identical in ir spectrum and giving no mixture melting point depression with a known sample.[7] Fractions 8 and 9 gave 27 mg (0.15 mmol) of *cis*-stilbene, identical in ir and nmr spectra with an authentic sample.[7] Fractions 10 and 11 produced 9 mg (0.06 mmol) of crystalline *trans*-stilbene, mp 118–122°, identical in ir spectrum and showing no mixture melting point depression with a known sample.[7] Fractions 14–18 yielded 234 mg of a clear oil which crystallized on standing to give a material melting at 69–81°. Identification of this material is described in the following paragraph. Fractions 21–25 afforded 690 mg (2.07 mmol) of unreacted 1,1,2,2-tetraphenylethane (1).

Recrystallization of fractions 14–18 from hexane afforded 204 mg (0.60 mmol) of colorless crystals identified as 1-(2-biphenylyl)-1,2-diphenylethane (6) on the basis of the following data: mp 79–81°; ir λ_{max}^{neat} 3.18–3.43 (s), 6.24 (s), 6.68 (s), 6.76 (s), 6.89 (s), 9.33 (m), 9.70 (m), 9.92 (m), 13.30 (vs), and 14.35 nm (vs); nmr (CCl_4) τ 3.10 (19 H, m), 5.67 (1 H, t), 6.81 (2, H, d).

Anal. Calcd for $C_{26}H_{22}$: C, 93.38; H, 6.62. Found: C, 93.39; H, 6.77.

1-(2-Biphenylyl)-1,2-diphenylethane (6) was synthesized from 1-bromo-1,2-diphenylethane[8] and 2-bromobiphenyl[9] in the pres-

(7) Aldrich Chemical Co., Milwaukee, Wis. 53233.
(8) E. S. Wallis and F. H. Adams, *J. Amer. Chem. Soc.*, **55**, 3849 (1933).
(9) G. Schultz, *Justus Liebigs Ann. Chem.*, **207**, 353 (1881).

ence of magnesium according to the procedure of Bachmann.[10] This material was found to be identical with the photoproduct, thus confirming the assignment of structure 6 to the major photoproduct from the photolysis of 1,1,2,2-tetraphenylethane (1).

Extended Vycor-Filtered Irradiation of 1,1,2,2-Tetraphenylethane (1).—The irradiation and isolation procedures were the same as those described above except that the irradiation time was extended to 3 hr.

Fraction 7 afforded 45 mg (0.30 mmol) of crystalline biphenyl, mp 67–69°. Fractions 8 and 9 gave 78 mg (0.42 mmol) of *cis*-stilbene, identified by ir spectroscopy. Fractions 10 and 11 produced 33 mg (0.19 mmol) of *trans*-stilbene, mp 119–120°. Fractions 14–18 yielded 240 mg of a crystalline material, mp 70–80°, recrystallized from hexane to give 198 mg (0.60 mmol) of 1-(2-biphenylyl)-1,2-diphenylethane (6), mp 79–80°. Fractions 19 and 20 afforded 352 mg of a clear oil whose identification is described in the following paragraph. Fractions 21–23 gave 99 mg (0.31 mmol) of unreacted 1,1,2,2-tetraphenylethane (1).

The unknown photoproduct from fractions 19 and 20 was identified as 1-(3-biphenylyl)-1,2-diphenylethane (7) on the basis of the following spectral data as well as its independent synthesis from 1-bromo-1,2-diphenylethane and 3-bromobiphenyl[11] in the presence of magnesium:[10] ir λ_{max}^{neat} 3.18–3.43 (s), 6.25 (s), 6.68 (s), 6.76 (m), 6.89 (s), 9.33 (m), 9.70 (m), 13.25 (vs), and 14.30 nm (vs); nmr (CCl_4) τ 2.85 (19 H, m), 5.79 (1 H, t), and 6.66 (2 H, d).

Vycor-Filtered Irradiation of 1-(2-Biphenylyl)-1,2-diphenylethane (6).—The irradiation and isolation procedures were the same as those described above except that the irradiation was conducted for only 5 min and 50 mg (0.15 mmol) of 6 was irradiated.

Fractions 19 and 20 afforded 45 mg of 1-(3-biphenylyl)-1,2-diphenylethane (7), identified by nmr spectroscopy.

Synthesis of 1,1-Diphenyl-2,2-ditolylethylene.—Magnesium (3.00 g, 0.125 g-atom) and benzhydrol bromide[7] (24.7 g, 0.125 mol) were added to 50 ml of anhydrous ether. After the initial reaction had subsided, the mixture was refluxed for 1 hr, followed by the dropwise addition of 21 g (0.100 mol) of 4,4′-dimethylbenzophenone in 100 ml of anhydrous ether and a second 1-hr reflux period. The ether was removed *in vacuo* below 25° and 25 ml of a 48% solution of hydrogen bromide in acetic acid was carefully added, precipitating a white solid. This solid was washed with water and recrystallized twice from chloroform–hexane to give 9.7 g of 1,1-diphenyl-2,2-ditolylethylene: mp 141–145°; nmr ($CDCl_3$) τ 3.05 (10 H, s), 3.18 (8 H, s), and 7.80 (6 H, s).

Anal. Calcd for $C_{28}H_{24}$: C, 93.30; H, 6.70. Found C, 93.41; H, 6.71.

Synthesis of 1,1-Diphenyl-2,2-ditolylethane.—1,1-Diphenyl-2,2-ditolylethylene (3 g) was reduced by the method of Bachman[10] to give 2.1 g of 1,1-diphenyl-2,2-ditolylethane: mp 129–130°; nnr ($CDCl_3$) τ 2.6–3.1 (18 H, m), 5.15 (2 H, s), and 7.88 (6 H, s).

Anal. Calcd for $C_{28}H_{26}$: C, 92.45; H, 7.55. Found: C, 92.40; H, 7.13.

Vycor-Filtered Irradiation of 1,1-Diphenyl-2,2-ditolylethane (8).—The irradiation and isolation procedures were the same as those described in the Vycor-filtered irradiation of 1,1,2,2-tetraphenylethane (1) except that 1.00 g of 8 was irradiated and the irradiation time was extended to 35 min.

Fractions 7–9 afforded 68 mg of a mixture of materials whose separation is described below. Fractions 10 and 11 yielded 10 mg (0.05 mmol) of *trans*-4-methylstilbene, mp 178° (lit.[12] mp 180°), identical with an authentic sample. Fractions 14–19 afforded a second mixture of compounds which, unfortunately, proved to be inseparable. Various types of absorption and partition chromatography were unsuccessful at separating this mixture. Fractions 22–27 gave 698 mg of unreacted starting material (8).

Preparative vpc analysis of fractions 7–9 on a 5 ft × 0.25 in. column packed with 20% SE-30 on Chromosorb P at 140° separated them into two components. The first of these represented 55% (37 mg, 0.22 mmol) of the mixture and was found by comparison with an authentic sample[7] to be 4-methylbiphenyl. The second component was found to be *cis*-4-methylstilbene (31 mg, 0.16 mmol) also by comparison with a known sample.[13] No other materials could be detected in this mixture.

Registry No.—1, 632-50-8; 6, 32298-37-6; 7, 32298-38-7; 8, 32298-39-8; 1,1-diphenyl-2,2-ditolylethylene, 32298-40-1.

Acknowledgment.—It is a pleasure to thank the National Science Foundation (GP 16664) for support of this research.

(10) W. E. Bachmann, *J. Amer. Chem. Soc.*, **55**, 3859 (1933).

(11) M. Gomberg and W. W. Bachman, *J. Amer. Chem. Soc.*, **46**, 2343 (1924).

(12) A. Ramart, *Ann. Chim. (Paris)*, [10] **8**, 315 (1938).

(13) *cis*-4-Methylstilbene was obtained by the Pyrex-filtered photoisomerization of the trans isomer in benzene.

Photoisomerization of Nopinone

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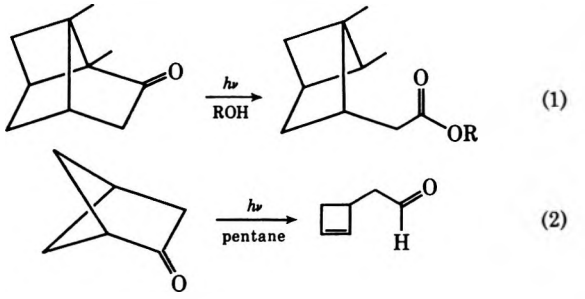
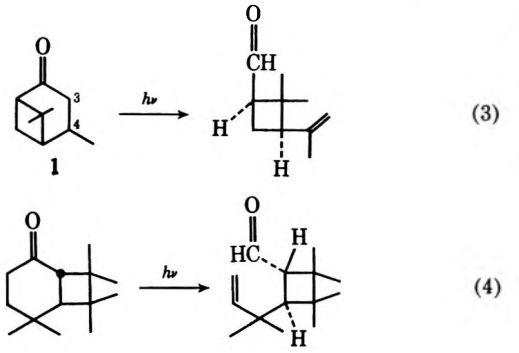
Received July 2, 1971

Irradiation of nopinone in methanol gives an 80:20 mixture of *cis*-1-formyl-2,2-dimethyl-3-vinylcyclobutane (**3**) and 3-(2′,2′-dimethyl-$\Delta^{3'}$-cyclobutenyl)-1-propanal (**7**). Irradiation in *tert*-butyl alcohol gives **3**, **7**, and 4-isopropenyl-5-hexenal (**4**).

Cycloalkanones are well known[1] to undergo photochemical α cleavage to give ketenes and/or unsaturated aldehydes. The direction of cleavage is preferentially toward the more highly substituted α-carbon atom. α-Ketocyclobutanes in bicyclic systems are considerably abnormal in this regard. Some, such as carvone camphor and bicyclo[2.1.1]hexan-2-one (eq 1 and 2),[2,3]



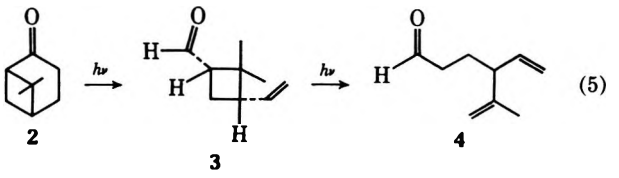
photochemically undergo α cleavage of the more substituted bond, but others, such as verbanone (**1**) (eq 3)[4] and 5,5,7,7,8,8-hexamethylbicyclo[4.2.0]octan-2-one (eq 4),[5] are reported to cleave the least substituted bond



α to the carbonyl. This abnormal α cleavage has been rationalized[4] for **1** by the fixed conformation causing excellent orbital overlap between the hydrogen at C-4 and the carbonyl group and resulting in hydrogen migration concurrent with α cleavage.

We wish to report the photochemistry of an analogous compound, nopinone (6,6-dimethylbicyclo[3.1.1]heptan-2-one) (**2**), including evidence that photocleavage of **2** occurs at both bonds α to the carbonyl to give a mixture of aldehydes.

Irradiation of **2** in methanol solution until 90–95% disappearance of starting material on glc gave one major product (75–80%) and a few very minor products. The major product was collected by preparative glc. Its spectral data (see Experimental Section) was consistent with *cis*-1-formyl-2,2-dimethyl-3-vinylcyclobutane (**3**), an analogous product to that found from verbanone. Irradiation of **2** in *tert*-butyl alcohol increased one of the minor products with a concurrent decrease in the amount of **3**. This product was also isolated by preparative glc and identified on the basis of spectral data (see Experimental Section) as 4-isopropenyl-5-hexenal (**4**), which is the normal Norrish II product of the primary photoproduct **3** (eq 5). This



was confirmed by isolation of **3** from a methanol irradiation of **2** and reirradiation in *tert*-butyl alcohol. Initially, 17% (glc) of **4** formed and then this percentage remained constant as the amount of polymeric material increased. Apparently, in methanol the initial aldehyde **3** forms a hemiacetal, thus preventing further light absorption. This increase in yield of an aldehydic photoproduct by the use of methanol as solvent has been observed before.[3]

Isolation of photoproduct **3** by careful spinning-band distillation gave material with an nmr spectrum not identical with that previously obtained by preparative glc. There were minor differences in the vinylic region, but the major change was the appearance of two methyl singlets at τ 8.83 and 8.91 in addition to the methyl singlets of **3** at τ 8.70 and 9.03. By nmr integration, the unknown:**3** ratio was 1:4.

At first we entertained the possibility that this product was *trans*-**3** since the relative nmr positions of the methyl singlets were consistent with those observed[6] for *cis*- and *trans-gem*-dimethylcyclobutane derivatives. Since the initial configuration of **3** must be cis due to the geometry of nopinone, the existence of *trans*-**3** would have to involve a rather unusual epimerization of a cyclobutyl ketone. This was not the case, as shown by independent synthesis of *cis*- and *trans*-1-acetyl-2,2-dimethyl-3-vinylcyclobutane (**5**) from *cis*-pinonic acid (Scheme I) and comparison of this material to a sample of **5** prepared from **3**. The synthesis was straightforward except for introduction of the terminal vinylic group. After several unsuccessful approaches,[7] the double bond was introduced with ease by pyrolysis of the *N*-oxide.[8]

(1) O. L. Chapman, *Advan. Photochem.*, **1**, 366 (1963).

(2) J. Meinwald, R. A. Schneider, and A. F. Thomas, *J. Amer. Chem. Soc.*, **89**, 70 (1967).

(3) J. Meinwald and R. A. Chapman, *ibid.*, **90**, 3218 (1968).

(4) T. Matsui, *Tetrahedron Lett.*, 3761 (1967).

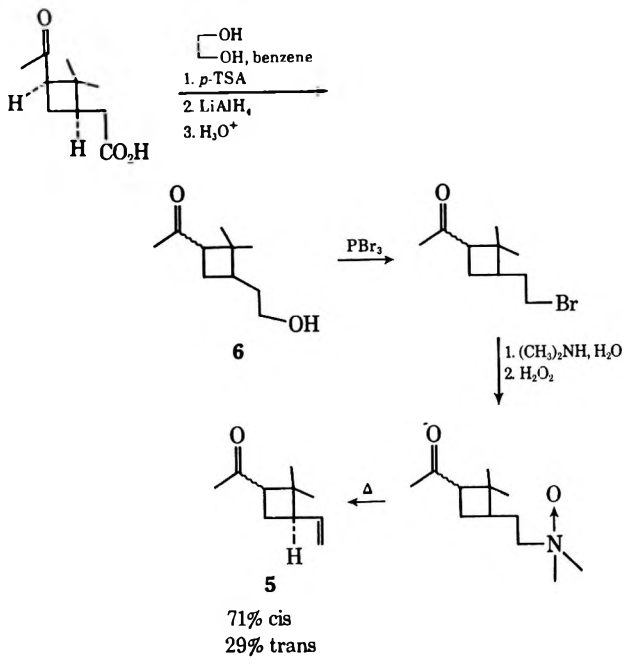
(5) P. J. Nelson, D. Ostrem, J. D. Lassila, and O. L. Chapman, *J. Org. Chem.*, **34**, 811 (1969).

(6) L. R. Subramanian and G. S. K. Rao, *Tetrahedron*, **25**, 1749 (1969).

(7) Attempts to form the double bond by elimination of the terminal bromide, tosylate, or trimethylammonium iodide were unsuccessful, as also were attempts to pyrolyze the ketoacetate or hydroxyacetate.

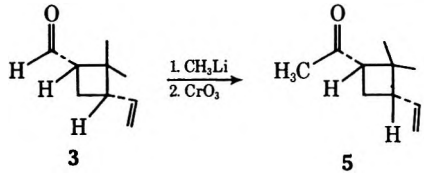
(8) A. C. Cope, D. C. McLean, and N. A. Nelson, *J. Amer. Chem. Soc.*, **77**, 1628 (1955).

SCHEME I



Epimerization of the acetyl group occurred during the conversion of *cis*-pinonic acid to keto alcohol **6**. The stereochemical assignment for the epimers of **5** is based on the nmr methyl region (singlets at τ 8.72 and 9.20, 71%; singlets at τ 8.85 and 9.00, 29%) and the fact that the cis epimer is the thermodynamically favored epimer of a 1,3-disubstituted cyclobutane.[9]

Reaction of **3**, containing 20% of the unknown, with methyllithium followed by Jones[10] oxidation (eq 6)

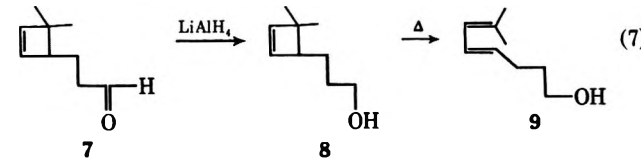


(6)

occurred without any epimerization and gave a ketonic mixture whose major component (79% by nmr) was identical with the sample of synthetic *cis*-**5**, thus proving the structure of photoproduct **3**. The minor ketone (21% by nmr) had methyl singlets in the nmr spectrum at τ 8.83 and 8.91, which were not identical with those of *trans*-**5**.

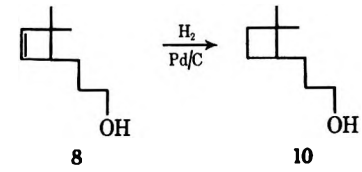
The unknown photoproduct was then assigned the structure of 3-(2′,2′-dimethyl-$\Delta^{3'}$-cyclobutenyl)-1-propanol (**7**) based on the results of a lithium aluminum hydride reduction of the nopinone photomixture. Glc analysis of this mixture on Carbowax 20M showed three alcohols in order of elution: A, 67%; B, 15%; C, 18%. After glc collection, A and B were identified as the alcohols corresponding to **3** and nopinol, respectively.

Compound C was identified as 7-methyl-4,6-octadien-1-ol (**9**) on the basis of the following spectral data: ir(neat) 3300–3400, 1052, 981, and 953 cm^{-1}; λ_{max}^{MeOH} 237 nm (ϵ 20,600); nmr (τ, ppm), 3.45–4.73 (three vinylic hydrogens), 8.26 (broad vinylic methyl singlet). This was the first indication by glc analysis that aldehyde **3** was impure and contained **7**. Apparently, aldehyde **7** and the methyl ketone corresponding to **7** do not survive the hot glc injector (250°), and alcohol **8** thermally rearranges to dienol **9** under the same conditions (eq 7).



(7)

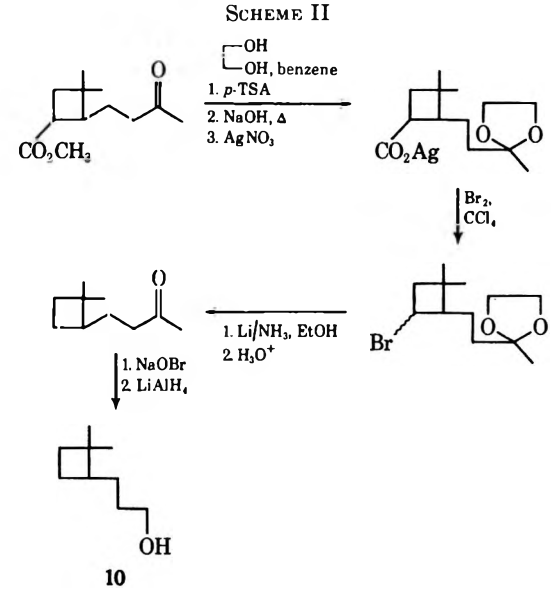
Hydrogenation of the mixture of alcohols over palladium on charcoal again gave three peaks on glc and the 3-(2′,2′-dimethylcyclobutyl)-1-propanol (**10**) (24% of the mixture) was isolated by preparative glc (eq 8).



(8)

The structural assignment was proven by comparison of the reduced photoproduct to a sample of **10** which had been synthesized by an independent route (Scheme II).

SCHEME II



We have no direct proof of the double bond position in **7**; however, the isolation of dienol **9** and the reasonable mechanism (Scheme III) for formation of **7** during the irradiation of **2** indicates that the double bond is positioned as shown in **7**.

The photoisomerizations of nopinone (**2**) can then be summarized as in Scheme III.[11] The major product arises from α cleavage on the least substituted side; however, the "normal" cleavage does occur to the extent of 20%. Probably, analogous cyclobutene aldehydes will be observed as minor products from irradiation of other bicyclic α-ketocyclobutanes.

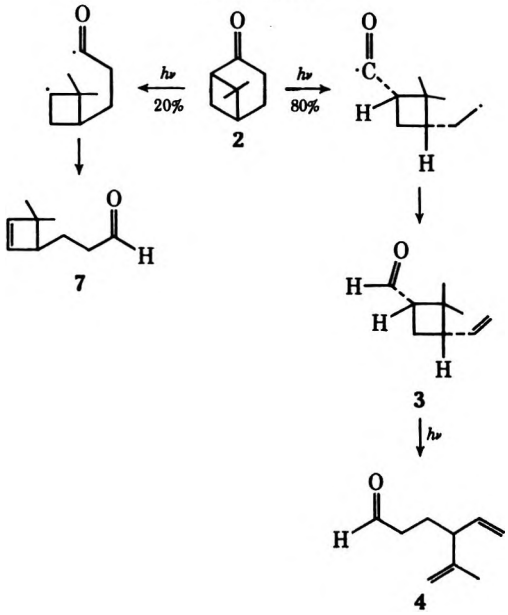
Photocleavage of bicyclo[3.1.1]-2-heptanones appears to be a facile reaction even though the bond with the lesser degree of substitution is broken. This was con-

(9) N. L. Allinger and L. A. Tushaus, *J. Org. Chem.*, **30**, 1945 (1965).

(10) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953).

(11) This mechanism denotes a diradical intermediate for both pathways, whereas in fact the hydrogen atom migration may be concerted with ring cleavage to give aldehyde **3** directly.

SCHEME III



firmed by measuring the quantum yields for ketone disappearance of bicyclo[3.1.1]-2-heptanones as compared to the yields measured by Wagner[12] for substituted cyclohexanones (Table I).

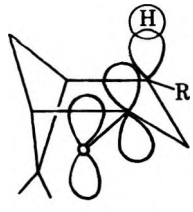
TABLE I
QUANTUM YIELDS FOR DISAPPEARANCE OF KETONES IN BENZENE

Ketone	Φ_{-K}
Nopinone	0.32[a]
Verbanone	0.40[a]
Cyclohexanone	0.20[b]
2-Methylcyclohexanone	0.46,[a] 0.50[b]
3-Methylcyclohexanone	0.083[b]

[a] 6–10% disappearance of ketone using 3000-Å Rayonet lamps. [b] Reference 12 using 3130 Å.

The quantum yields for nopinone and verbanone are intermediate to those of cyclohexanone (no α substitution) and 2-methylcyclohexanone (α substitution). It is interesting that a β-methyl group in the bicyclo[3.1.1]-2-heptanone system does not decrease Φ_{-K} as is the case for the cyclohexanone system (compare verbanone to 3-methylcyclohexanone).

The explanation[4] of Matsui that the rigid geometry of the bicyclo[3.1.1]-2-heptanone molecule allows excellent overlap of the carbonyl group and the sp^3 orbital of the β hydrogen (see structure a), such that hydrogen atom migration can occur before or at the same time as the ring cleavage, reasonably accounts for this efficient cleavage of the least substituted α bond. In addition, the release of molecular strain by α cleavage in the direction of the coplanar aligned hydrogen may play a role in increasing the quantum yield.



a

Experimental Section

Preparative irradiations were carried out with a 450-W medium pressure Hanovia mercury lamp in a quartz immersion probe. The filter was a glass cylinder of Corex (>255 nm) insertable between the lamp and the probe. Solutions were outgassed with argon before and during the irradiations.

Infrared spectra were taken as neat samples on a Perkin-Elmer 457 and absorptions are reported as inverse centimeters; uv spectra were taken on a Beckman Acta III; nmr spectra were taken on a Varian A-60A as chloroform-d_1 solutions and are reported as τ units relative to TMS (τ 10.0); and molecular weights were determined from mass spectra obtained with a Perkin-Elmer 270. Gas-liquid chromatography (glc) was done on a 10% Carbowax 20M (12 ft × 1/8 in.) column unless otherwise stated.

Nopinone (6,6-Dimethylbicyclo[3.1.1]heptan-2-one) (2).—Nopinone (2), prepared by ozonolysis[13] of β-pinene (Aldrich Chemical Co.), had the following spectral characteristics: mol wt 138; ir 1715 (s), 1461 (m), 1202 (m), 1030 (m); λ_{max}^{MeOH} 277 nm (ϵ 29); nmr 7.26–8.55 (8 H, multiplet), 8.65 (3 H, singlet, methyl H), 9.14 (3 H, singlet, methyl H).

Irradiation of Nopinone (2).—A solution of 3.00 g of nopinone (2) in 150 ml of methanol (0.145 *M*) was irradiated with Corex-filtered light until starting material was 90–95% gone (2.5–3.0 hr). Solvent was removed under reduced pressure, three runs were combined, and the residual oil was distilled at 15 mm pressure. The distillate (5.61 g) consisted, by glc, of one major component (75–80%) with 20–25% of three other components including unreacted 2. The major component was isolated pure by glc collection and was identified as *cis*-1-formyl-2,2-dimethyl-3-vinylcyclobutane (3): mol wt 138; ir 2870 (m), 2715 (m), 1718 (s), 1638 (m), 1000 (m), 918 (s); nmr (100 MHz) 0.18 (1 H, d, J = 2 Hz, aldehydic H), 4.07–4.49 (1 H, multiplet, vinylic H), 4.92 (1 H, sharp absorption with fine splitting, terminal methylene H), 5.00–5.12 (1 H, multiplet, terminal methylene H), 7.1–8.4 (4 H, multiplet, cyclobutyl H), 8.73 and 9.06 (6 H, two s, methyl H); nmr (60 MHz) methyl singlets at 8.70 and 9.03.

When the major component was isolated by careful spinning-band distillation [bp 53–56° (10 mm)], the nmr spectrum (60 MHz) had two additional methyl singlets (confirmed as singlets by 100-MHz spectrum) at 8.83 and 8.91. By integration, the ratio of the 8.70 and 9.03 singlets to the 8.83 and 8.91 singlets was 4:1. The 20% component was identified as 3-(2′,2′-dimethyl-$\Delta^{3'}$-cyclobutenyl)-1-propanal (7) by reduction and comparison to a synthetic sample of 3-(2′,2′-dimethylcyclobutyl)-1-propanol (see below).

When the irradiation was done in *tert*-butyl alcohol, the major glc peak, isolated by distillation, was the same 4:1 mixture of components as was formed during the methanol irradiation. However, extending the irradiation in *tert*-butyl alcohol resulted in an increase of a third product (retention time relative to 3 equalled 1.2) as well as a large increase in the amount of polymeric material. This compound was isolated by preparative glc and identified as 4-isopropenyl-5-hexenal (4): mol wt 138; ir 2715 (w), 1720 (s), 895 (m); nmr 0.29 (1 H, broadened singlet, aldehydic H), 3.93–4.64 (1 H, multiplet, vinylic H), 4.83–5.32 (4 H, multiplet, terminal methylene H), 7.15–7.83 (3 H, multiplet, allylic H and H α to carbonyl), 8.00–8.53 (5 H, multiplet with vinylic methyl H at 8.34 (doublet, J = 1 Hz)).

When a 4:1 mixture of 3 and 7, isolated by distillation of a nopinone–methanol irradiation, was reirradiated in *tert*-butyl alcohol, 17% of 4 formed initially and then remained at this percentage as the amount of polymeric material increased. After irradiation (1.50 g of 3 and 7, 150 ml of *tert*-butyl alcohol, 0.048 *M*, Corex filter, 3.5 hr), an nmr spectrum of the distillable portion (27%) of the oil showed the vinylic methyl group of 4 at τ 8.32.

Conversion of *cis*-1-Formyl-2,2-dimethyl-3-vinylcyclobutane (3) to *cis*-1-Acetyl-2,2-dimethyl-3-vinylcyclobutane (5).—A solution of 0.51 g (3.7 mmol) of 3 (containing *ca.* 20% of 7), isolated by spinning-band distillation of a nopinone irradiation mixture, in 50 ml of dry ether, was stirred under nitrogen at room tem-

(12) P. J. Wagner and R. W. Spoerke, *J. Amer. Chem. Soc.*, **91**, 4437 (1969).

(13) J. Meinwald and P. G. Gassman, *ibid.*, **82**, 5448 (1960).

perature and 5.0 ml of methyllithium–ether solution (*ca.* 2.3 *M*, 11 mmol) was added dropwise. The solution was heated under reflux for 3 hr and allowed to cool and stand overnight. An excess of saturated ammonium chloride solution was added dropwise, the layers were separated, and the aqueous layer was extracted with ether (three 50-ml portions). The combined ethereal extract was dried over magnesium sulfate, filtered, and concentrated.

The crude oil (0.57 g), which was not purified further, was identified as mainly 1-(1′-hydroxyethyl)-2,2-dimethyl-3-vinylcyclobutane on the basis of the following data: mol wt 154; ir 3350 (broad), no carbonyl stretching band; nmr 3.80–4.47 (1 H, multiplet, vinyl H), 4.82–5.26 (2 H, multiplet, terminal methyl H), 5.98–6.55 (1 H, multiplet, H geminal to OH), 7.34–8.80 (5 H, multiplet, methine, methylene, and hydroxyl H), 8.84–9.13 (9 H, multiplet, methyl H). Glc showed two major peaks (53–47%) assigned as diastereomers. These two peaks, each separately glc collected, gave essentially identical mass and nmr spectra.

The major impurity by glc, whose percentage varied from 0 to 20% with various runs, was glc collected and identified (mass spectrum, nmr) as the reduction product of **3**, *cis*-1-hydroxymethyl-2,2-dimethyl-3-vinylcyclobutane, by comparison with a sample obtained by lithium aluminum hydride reduction of **3**.

A solution of the above alcohol mixture (0.49 g, 3.2 mmol) in 15 ml of reagent acetone was oxidized at 0° with excess Jones reagent.[10] After work-up, the major component of the residual oil (0.38 g, 86% pure by glc) was identified as *cis*-1-acetyl-2,2-dimethyl-3-vinylcyclobutane (**5**) and was identical (ir, nmr, and mass spectra, glc retention time) to a synthetic sample of *cis*-**5** (see below).

The nmr spectrum of the oxidation product had two additional methyl singlets at τ 8.83 and 8.91 (21% by nmr integration). These singlets were at different positions than those of synthetic *trans*-**5** (see below) and were tentatively assigned as the methyl singlets of 4-(2′,2′-dimethyl-$\Delta^{3'}$-cyclobutenyl)-2-butanone from reaction of **7** with methyllithium followed by oxidation.

Conversion of 3-(2′,2′-Dimethyl-$\Delta^{3'}$-cyclobutenyl)-1-propanal (7) to 3-(2′,2′-Dimethylcyclobutyl)-1-propanol (10).—A mixture of 5.60 g of **3** and **7** (80% **3** and 20% **7** by nmr) containing some nopinone was reduced with excess lithium aluminum hydride. Glc of the residual oil showed three peaks in order of elution: A, 67%; B, 15%; C, 18%. The components were isolated by preparative glc on Carbowax 20M.

Alcohol A was identified as *cis*-1-hydroxymethyl-2,2-dimethyl-3-vinylcyclobutane on the basis of the following data: ir 3300–3400 (s), 1630 (m), 1004 (s), 992 (s), 905 (s); nmr 3.89–4.49 (1 H, multiplet, vinyl H), 4.88–5.28 (2 H, multiplet, terminal methylene H), 6.34–6.54 (2 H, three-peak multiplet, H α to OH), 7.07 (1 H, singlet, hydroxyl H), 7.30–8.65 (4 H, multiplet, methine and methylene H), 8.89 and 9.10 (6 H, two singlets, methyl H).

Alcohol B was identified as nopinol by comparison (nmr spectrum and glc retention time) to nopinol prepared by lithium aluminum hydride reduction of nopinone.

Alcohol C was identified as 7-methyl-4,6-octadien-1-ol on the basis of the following data: ir 3300–3400 (s), 1438 (s), 1052 (s), 981 (m), 953 (s); λ_{max}^{MeOH} 237 nm (ϵ 20,600); nmr 3.45–4.73 (3 H, multiplet, vinyl H), 6.39 (2 H, triplet, J = 6.5 Hz, H α to OH), 7.2 (1 H, broad absorption, hydroxyl H), 7.60–8.04 (2 H, multiplet, allylic H), 8.1–8.9 (8 H, multiplet with broad vinylic methyl singlet at 8.26). This product was not present in the mixture prior to glc collection as shown by the absence of the strong vinylic methyl absorption at τ 8.26 in the nmr spectrum of the crude reaction mixture after reduction.

A mixture of the above alcohols (2.91 g), 50 ml of absolute ethanol, and 0.2 g of 5% palladium on carbon was hydrogenated on a Parr shaker (30–50 psi) until hydrogen uptake ceased. After filtration and concentration, glc analysis of the residual oil (2.80 g) showed three peaks in order of elution: A, 71%; B, 24%; nopinol, 5%. Components A and B were isolated by preparative glc on Carbowax 20M.

Alcohol A was identified as 1-hydroxymethyl-2,2-dimethyl-3-ethylcyclobutane on the basis of the following data: mass spectrum, last peak at 124 (M − 18); ir 3300–3400 (s); nmr 6.36–6.57 (2 H, three-peak multiplet, H α to OH), 7.39 (1 H, singlet, hydroxyl H), 8.90 and 9.08 (two singlets, methyl H), 9.08 (triplet, J = 7 Hz, methyl H).

Alcohol B was identified as 3-(2′,2′-dimethylcyclobutyl)-1-propanol (10) by comparison (ir, nmr, and mass spectra, glc retention time) with an independently synthesized sample (see below).

Synthesis of 1-Acetyl-2,2-dimethyl-3-vinylcyclobutane (5).—A solution of 92.0 g (0.434 mol) of *cis*-pinonic acid (Aldrich), 124 g (2.0 mol) of ethylene glycol, 700 ml of benzene, and 0.4 g of *p*-toluenesulfonic acid was heated under reflux with a continuous water separator until the theoretical amount of water (0.9 mol) was collected. The solution was concentrated under reduced pressure, diluted with 200 ml of anhydrous ether, washed with half-saturated sodium carbonate solution, dried, filtered, and concentrated. The crude oil (137 g) was not purified further; the ir spectrum had a single carbonyl band at 1742 cm^{-1} (s) with no absorption for remaining ketone.

A solution of 137 g (0.5 mol, 1.0 equiv) of the ester ketal in ether was reduced with lithium aluminum hydride (17.8 g, 1.9 equiv) to give, after work-up with excess 10% sulfuric acid, a residual oil (61.4 g) which was identified as 1-acetyl-2,2-dimethyl-3-(2′-hydroxyethyl)cyclobutane: ir 3390 (s), 1700 (s), 1368 (m), 1181 (m), 1050 (s); nmr 6.43 (2 H, triplet, J = 6.5 Hz, H geminal to hydroxyl group), 6.90–7.53 (2 H, multiplet, H α to carbonyl and hydroxyl H), 7.83–8.60 [8 H, multiplet with acetyl methyl singlets at 7.93 (trans) and 7.97 (cis)], 8.70 (cis), 8.78 (trans), 9.00 (trans), and 9.13 (cis) (6 H, four singlets, methyl H). By integration of the nmr methyl singlets, the isomer ratio was 67% cis and 33% trans.

To a solution of 56.0 g (0.329 mol) of 1-acetyl-2,2-dimethyl-3-(2′-hydroxyethyl)cyclobutane in 3 l. of benzene was added, dropwise with stirring, 30.0 g (0.111 mol) of phosphorus tribromide. After addition, the solution was heated under reflux for 2 hr, allowed to cool, and quenched into 4 l. of ice and water. The layers were separated, the aqueous phase was extracted with benzene, and the combined organic phase was washed with half-saturated salt solution, dried, filtered, and concentrated. Distillation of the crude oil (67.4 g) gave pure 1-acetyl-2,2-dimethyl-3-(2′-bromoethyl)cyclobutane: 30.5 g (40% yield); bp 87–88° (0.5–1.0 mm); ir (CCl_4) 1706 (s), 1362 (m), 1351 (m), 1178 (m), 1042 (w); nmr 6.68 (2 H, triplet, J = 6.5 Hz, H geminal to bromine), 7.14 (1 H, misshapen triplet, J = 8–9 Hz, H α to carbonyl), 7.60–8.50 (8 H, multiplet with acetyl methyl singlet at 7.96), 8.68 (cis), 8.77 (trans), 8.98 (trans), and 9.11 (cis) (6 H, four singlets, methyl H). By integration of the nmr methyl singlets, the isomer ratio was 71% cis and 29% trans.

A solution of 30.5 g (0.131 mol) of 1-acetyl-2,2-dimethyl-3-(2′-bromoethyl)cyclobutane in 100 ml of methanol was added dropwise to a stirred solution of 300 ml of 40% dimethylamine in water. After addition, the solution was heated under reflux for 1 hr, allowed to cool, and diluted with 100 ml of ether and 100 ml of saturated salt solution. The layers were separated and the aqueous phase was extracted with ether. The combined organic phase was extracted with 10% sulfuric acid and the acidic extract was then basified with 20% sodium hydroxide solution. The basic layer was extracted with ether which was then dried, filtered, and concentrated to give 1-acetyl-2,2-dimethyl-3-(2′-*N*,*N*-dimethylaminoethyl)cyclobutane: 24.2 g (94% yield); ir (CCl_4) 2849 (m), 2801 (m), 1721 (s), 1466 (m), 1370 (m), 1357 (m), 1182 (m), 1043 (m); nmr 6.16–7.50 (3 H, multiplet, H geminal to nitrogen and α to carbonyl), 7.64–8.62 [14 H, multiplet with *N*,*N*-dimethyl singlet at 7.80 and acetyl methyl singlets at 7.95 (trans) and 7.97 (cis)], 8.72 (cis), 8.78 (trans), 9.01 (trans), and 9.13 (cis) (6 H, four singlets, methyl H). By integration of the nmr methyl singlets, the isomer ratio was 72% cis and 28% trans.

To a cold solution of 12.0 g (0.061 mol) of 1-acetyl-2,2-dimethyl-3-(2′-*N*,*N*-dimethylaminoethyl)cyclobutane in 100 ml of methanol was added, dropwise with stirring, 21.2 g (0.187 mol) of 30% hydrogen peroxide solution. After addition, the solution was stirred at room temperature for 25 hr, and then a small amount of platinum black was added and the mixture was stirred at room temperature for 2 days. The mixture was filtered and concentrated, and the residual material (8.20 g) was heated in an oil bath (from 120 to 200°) under vacuum, and the distillate, bp 51–64° (0.5 mm), collected from a short path condenser into a receiver cooled in a Dry Ice–acetone mixture. The distillate (two layers, 6.35 g) was diluted with ether and water, and the layers were separated. The organic layer was washed with cold dilute hydrochloric acid, washed with sodium carbonate solution, and then was dried, filtered, and concentrated to give pure 1-acetyl-2,2-dimethyl-3-vinylcyclobutane (**5**): 2.49 g (27% overall yield); mol wt 152; ir 1700 (s), 1634 (m), 1460 (s),

1361 (s), 1180 (s), 996 (s), 912 (s); nmr 3.97–4.59 (1 H, multiplet, vinylic H), 4.94 (1 H, broad singlet, terminal methylene H), 5.07–5.27 (1 H, multiplet, terminal methylene H), 6.93–8.44 [7 H, multiplet with acetyl methyl singlets at 7.97 (trans) and 8.00 (cis)], 8.72 (cis), 8.85 (trans), 9.00 (trans), and 9.20 (cis) (6 H, four singlets, methyl H). By integration of the nmr methyl singlets, the isomer ratio was 71% cis and 29% trans.

Anal. Calcd for $C_{10}H_{16}O$: C, 78.90; H, 10.59. Found: C, 78.62; H, 10.32.

Synthesis of 4-(2′,2′-Dimethylcyclobutyl)-2-butanone.—A solution of 31.0 g (0.15 mol) of 4-(2′,2′-dimethyl-4′-carbomethoxycyclobutyl)-2-butanone, obtained by esterification of the corresponding acid derived from ozonolysis of caryophyllene,[14] 18.0 g (0.29 mol) of ethylene glycol, 0.1 g of *p*-toluenesulfonic acid, and 150 ml of benzene was heated under reflux while using a continuous water separator. After the theoretical amount of water was collected, the solution was cooled and neutralized with 10% sodium hydroxide, and the product was isolated. The resulting ethylene ketal of 4-(2′,2′-dimethyl-4′-carbomethoxycyclobutyl)-2-butanone was not purified further: 33.8 g; nmr 6.09 (4 H, singlet, ketal H), 6.34 (3 H, singlet, methyl ester H), 8.71, 8.92, and 8.96 (9 H, three singlets, methyl H).

A mixture of 33.8 g (0.13 mol) of the above ketal, 5.2 g (0.13 equiv) of sodium hydroxide, and 50 ml of water was heated under reflux for 5 hr. Periodically, the pH was adjusted to 9–10 by the addition of small amounts of 10% sodium hydroxide solution. The mixture was allowed to cool and extracted with ether. The aqueous phase was returned to the flask and a solution of 24.0 g (0.14 equiv) of silver nitrate in 100 ml of water was added at room temperature. After addition, the mixture was stirred 1 hr and filtered, and the silver salt was washed with water and methanol and dried in the dark under vacuum to give 36.2 g of a pale gray powder.

The silver salt (36.0 g, 0.12 mol) was added portionwise over 0.5 hr to a stirred solution of 18.0 g (0.11 mol) of bromine in 100 ml of carbon tetrachloride at −15 to −20°. After addition, the mixture was stirred 0.5 hr at −15°, allowed to warm to room temperature, and filtered. The filtrate was washed with water, 10% sodium hydroxide solution, again with water, dried, and concentrated. An ir spectrum of the resultant oil (18.9 g) showed a strong carbonyl band; therefore, the above ketalization was repeated to give 19.0 g of the ethylene ketal of *cis*- and *trans*-4-(2′,2′-dimethyl-4′-bromocyclobutyl)-2-butanone: nmr 5.2–5.7 (1 H, multiplet, H α to Br), 6.05 (4 H, singlet, ketal H), 8.65, 8.68, 8.79, 8.82, 8.91, and 9.01 (9 H, six singlets, methyl H).

To a solution of the above bromide (19.0 g, 0.069 mol) and 5 ml of 1,2-dimethoxyethane in 500 ml of freshly distilled liquid ammonia, was added 1.0 g (0.14 equiv) of lithium in portions. After addition, the blue solution was stirred for 1 hr, and then 10 ml of absolute ethanol was added dropwise followed by the cautious addition of 8.0 g (0.15 equiv) of solid ammonium chloride. The ammonia was allowed to evaporate, the salts were dissolved in water, and the ethylene ketal of 4-(2′,2′-dimethylcyclobutyl)-2-butanone was isolated by extraction with ether: 9.63 g; nmr 6.07 (4 H, singlet, ketal H), 8.70, 8.95, and 9.00 (9 H, three singlets, methyl H).

A solution of the above ketal (9.60 g), 200 ml of acetone, 20 ml of water, and 3 ml of concentrated hydrochloric acid was heated under reflux for 2–3 hr and allowed to cool. The solution was neutralized with 10% sodium hydroxide, partially concentrated under reduced pressure, and diluted with water, and the organic material was isolated by extraction with ether. The residual oil (5.80 g) was chromatographed on 325 g of silica gel slurry-packed with hexane into a 2.5-cm i.d. column. The hexane and benzene eluted material (0.18 g) was discarded. Benzene–ether mixtures and ether eluted 85% pure 4-(2′,2′-dimethylcyclobutyl)-2-butanone: 3.73 g (16% overall yield); mol wt 154; ir 1709; nmr 7.89 (3 H, singlet, methyl α to carbonyl), 8.95 and 9.00 (6 H, two singlets, methyl H).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.77; H, 11.76.

Synthesis of 3-(2′,2′-Dimethylcyclobutyl)-1-propanol (10).—To a solution of 0.39 g (2.5 mmol) of 4-(2′,2′-dimethylcyclobutyl)-2-butanone, 10 ml of water, and 36 ml dioxane, cooled to 0°, was added dropwise, a solution of sodium hypobromite, prepared from 1.36 g (34 mequiv) of sodium hydroxide, 12 ml of water, 1.41 g (9 mmol) of bromine, and 8 ml of dioxane. After 3 hr at 0°, a solution of 0.56 g of sodium sulfite in 5.6 ml of water was added and the reaction mixture was poured into 15 ml of 10% sodium hydroxide solution and extracted with ether. The aqueous phase was acidified with concentrated hydrochloric acid to pH 1 and extracted with ether. The ethereal extract was washed with water, dried, and concentrated to give 3-(2′,2′-cyclobutyl)-propionic acid: 0.16 g; ir, 2500–3500 (broad), 1700 (s); nmr 0.75 (1 H, broad singlet, acidic H), 8.95 and 8.99 (6 H, two singlets, methyl H).

A solution of the above acid (0.16 g, 1 mmol) in 5 ml of anhydrous ether was added dropwise to a stirred mixture of 0.2 g (20 mequiv) of lithium aluminum hydride. After addition, the mixture was heated under reflux for 5 hr, allowed to cool, and then saturated ammonium chloride solution was added dropwise until the salts settled. The mixture was filtered, and the filtrate was diluted with ether, washed with 10% sodium hydroxide solution, washed with water, dried, and concentrated to give 0.09 g (26% overall yield) of 3-(2′,2′-dimethylcyclobutyl)-1-propanol (10): mass spectrum last peak at 124 (M − 18); ir 3200–3400 (s), 1460 (s), 1380 (m), 1365 (s), 1056 (s); nmr 6.3–6.6 (2 H, misshapen triplet, J = 5–6 Hz, H α to OH), 7.25 (1 H, broad singlet, hydroxyl H), 8.98 and 9.02 (6 H, two singlets, methyl H).

Anal. Calcd for $C_9H_{18}O$: C, 76.00; H, 12.76. Found: C, 76.07; H, 12.57.

Quantum Yields for Disappearance of Nopinone and Verbanone.—Quantum yields were determined according to the procedure of Wagner.[12] Solutions 0.20 M of each ketone in benzene containing octadecane as an internal standard were placed in 1.1-cm Pyrex tubes, degassed, sealed, and irradiated in parallel at 33° on a merry-go-round using 8-RUL 3000-Å Rayonet lamps. At this concentration, the ketones absorbed ≥99% of the 300-nm radiation. The amount of ketone that disappeared was measured by glc analysis (4% UCW 98, 12 ft × 1/8 in.) by comparing the ketone:standard area ratios before and after irradiation.

Two tubes containing 1.0 M acetone and 0.20 M *cis*-1,3-pentadiene in cyclohexane were irradiated in parallel with the above samples. The average yield of *trans*-1,3-pentadiene (9–10%) was measured on an 18 ft × 1/8 in. column packed with 10% GE-SE-54 using electronic peak integration. The quantum yield for the cis to trans isomerization, after being corrected for back reaction, is 0.555.[15] The quantum yields for disappearance (6–10%) of ketone were: 2-methylcyclohexanone, 0.46 (reported[12] 0.50); nopinone, 0.32 ± 0.02; verbanone,[16] 0.40 ± 0.02.

Registry No.—**2**, 24903-95-5; **3**, 32319-47-4; **4**, 32319-48-5; *cis*-**5**, 32319-49-6; *trans*-**5**, 32319-50-9; **7**, 32319-66-7; **9**, 32319-51-0; **10**, 32319-52-1; 1-(1′-hydroxyethyl)-2,2-dimethyl-3-vinylcyclobutane, 32319-53-2; *cis*-1-hydroxymethyl-2,2-dimethyl-3-vinylcyclobutane, 32319-54-3; *cis*-1-acetyl-2,2-dimethyl-3-(2′-hydroxyethyl)cyclobutane, 32319-55-4; *trans*-1-acetyl-2,2-dimethyl-3-(2′-hydroxyethyl)cyclobutane, 32319-56-5; 1-hydroxymethyl-2,2-dimethyl-3-ethylcyclobutane, 32380-98-6; *cis*-1-acetyl-2,2-dimethyl-3-(2′-bromoethyl)cyclobutane, 32319-57-6; *trans*-1-acetyl-2,2-dimethyl-3-(2′-bromoethyl)cyclobutane, 32319-58-7; *cis*-1-acetyl-2,2-dimethyl-3-(2′-*N*,*N*-dimethylaminoethyl)-cyclobutane, 32319-59-8; *trans*-1-acetyl-2,2-dimethyl-3-(2′-*N*,*N*-dimethylaminoethyl)cyclobutane, 32319-60-1; ethylene ketal, 4-(2′,2′-dimethyl-4′-carbomethoxycyclobutyl)-2-butanone, 32319-61-2; ethylene ketal, *cis*-4-(2′,2′-dimethyl-4′-bromocyclobutyl)-2-butanone, 32319-62-3; ethylene ketal, *trans*-4-(2′,2′-dimethyl-4′-bromocyclobutyl)-2-butanone, 32319-63-4; ethylene ketal, 4-(2′,2′-dimethylcyclobutyl)-2-butanone, 32319-64-5; 4-(2′,2′-dimethylcyclobutyl)-2-butanone, 32319-65-6.

Acknowledgments.—The authors would like to thank Dr. H. U. Daeniker and Professor W. G. Dauben for helpful discussions in regard to this research.

(14) L. Ruzicka and A. H. Wind, *Helv. Chim. Acta*, **14**, 423 (1931).

(15) A. A. Lamola and G. S. Hammond, *J. Chem. Phys.*, **43**, 2129 (1965).

(16) A. F. Regan, *Tetrahedron*, **25**, 3801 (1969).

Synthesis of Polyglutathione, Polyasparthione, and Related Sequential Polypeptides[1]

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Received June 10, 1971

Polypeptides with repeating sequence of glutathione, asparthione, and their α analogs have been synthesized. The protected polypeptides, poly(α-benzyl-L-glutamyl-*S*-benzyl-L-cysteinylglycine) (XIV), poly(α-benzyl-L-aspartyl-*S*-benzyl-L-cysteinylglycine) (XV), poly(γ-benzyl-L-glutamyl-*S*-benzyl-L-cysteinylglycine) (XVI), and poly(β-benzyl-L-aspartyl-*S*-benzyl-L-cysteinylglycine) (XVII), were prepared by self condensation of the corresponding tripeptide pentachlorophenyl esters IV, V, IX, or X and XII or XIII, respectively. The optically pure tripeptide active esters were obtained through the "backing off" method from the C-terminal glycine pentachlorophenyl ester. The *C*- and *S*-benzyl protecting groups from the polymers XIV, XV, XVI, and XVII have been removed with sodium–liquid ammonia to afford polyglutathione (XVIII), polyasparthione (XIX), polyisoglutathione (XX), and polyisoasparthione (XXI), with weight average molecular weights of 9000, 7000, 16,000, and 6000, respectively. Polyglutathione was investigated for radioprotective activity. Polyglutathione shows a growth stimulating effect on *B. subtilis*.

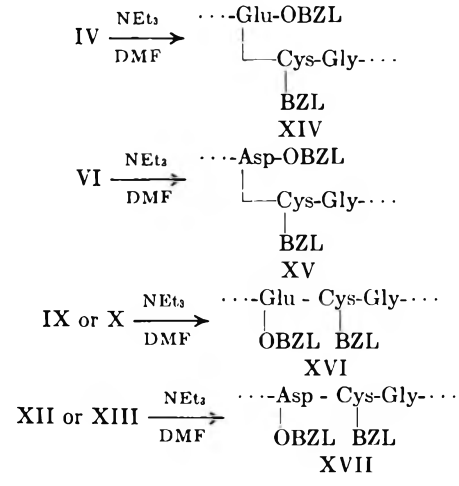
Glutathione[3] has a protective effect against radiation[4] and is considered to act as a detoxicant of hydrogen peroxide generated in cells.[5] It appeared possible that a high-molecular-weight sequential polypeptide containing the repeating unit of glutathione could be stored in the body as an active thiol-containing molecule for prolonged action. Although in recent years a number of sequential polypeptides containing trifunctional amino acids have been synthesized,[6] polypeptides having a repeating sequence of a naturally occurring biologically active peptide are unknown. This paper reports the synthesis of polyglutathione, polyasparthione, and the related α polymers by the pentachlorophenyl ester polymerization method.[6b,e,g-i]

The preparation of the tripeptide active esters IV and VI, which are needed for polycondensation, was achieved in high yields through stepwise lengthening of the peptide chain from the activated C-terminal amino acid, glycine pentachlorophenyl ester, by using the mixed anhydride (M.A.) coupling method, as shown in Scheme I.[7]

Syntheses of the α-tripeptide active esters IX, X and XII, XIII were achieved by using the *N-tert*-butyloxycarbonyl protecting group (Scheme II), since attempted removal of the *N*-benzyloxycarbonyl group from *N*-benzyloxycarbonyl-γ-benzyl-L-glutamyl-*S*-benzyl-L-cysteinylglycine pentachlorophenyl ester (VII), with hydrogen bromide led to a complex mixture.

The tripeptide active ester trifluoroacetate salts IX and XII partly polymerize on standing in solution or drying under vacuum above 50°.

The tripeptide active ester salts were polymerized[6g] in concentrated dimethylformamide solution in the presence of 2 equiv of triethylamine. While the polymerization of the ω-tripeptide active ester salts IV and VI yielded the corresponding polymers XIV and XV, respectively, in 70–80% yield, polymerization of the α-peptide active ester salts IX or X and XII or XIII gave the corresponding polymers XVI and XVII in the range of 55 and 39% yields, respectively.



The *C*- and *S*-benzyl protecting groups of the polymers XIV and XV were removed[8] with sodium–liquid ammonia. The complete removal[9] of the protecting benzyl groups was indicated by the absence of aromatic protons in the pmr spectra of the sodium salts of the deblocked polymers. Polyglutathione (XVIII) and polyasparthione (XIX) were isolated by acidification of the water-soluble sodium salts of the polymers and dialysis, with weight average molecular weights of 9000 and 7000, respectively, in the ultracentrifuge.[10] The iodo-

(1) Part of this investigation was presented at the 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 13–18, 1969, Abstract ORGN 176.

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(3) (a) S. P. Colowick, A. Lazarow, E. Racker, D. R. Schwarz, D. R. Stadtman, and H. Waelsch, "Glutathione," Proceedings of the Symposium held at Ridgefield, Conn., Nov 1953, Academic Press, New York, N. Y., 1954. (b) E. M. Crook, "Glutathione," Biochemical Society Symposium, No. 17, held at Senate House, University of London, February 15, 1958, Cambridge, England, University Press, 1959. (c) W. E. Knox in "The Enzymes," P. D. Boyer, H. Lardy, and J. Myrback, Ed., Vol. 2, 2nd ed, Academic Press, New York, N. Y., 1960, p 254.

(4) (a) H. M. Patt, E. B. Tyree, R. L. Straube, and D. E. Smith, *Science*, **110**, 213 (1949); (b) for a review see D. R. Hope, ref 3b, p 93.

(5) (a) P. Hochstein and G. Cohen, *Acta Biol. Med. Ger. Suppl.*, **3**, 292 (1964); (b) A. S. Hill, A. Haut, G. E. Cartwright, and M. M. Wintrobe, *J. Clin. Invest.*, **43**, 17 (1964); (c) H. S. Jacob, S. H. Ingbar, and J. H. Jandl, *ibid.*, **44**, 1187 (1965).

(6) (a) For a review see E. Katchalski and M. Sela, *Advan. Protein Chem.*, **13**, 243 (1958); (b) J. Kovacs and B. J. Johnson, *J. Chem. Soc.*, 6777 (1965); (c) A. T. Moore and H. N. Rydon, *Acta Chim. Hung.*, **44**, 103 (1965); (d) F. H. C. Stewart, *Aust. J. Chem.*, **18**, 887 (1965), and references cited therein; (e) J. Kovacs, R. Giannotti, and A. Kapoor, *J. Amer. Chem. Soc.*, **88**, 2282 (1966); (f) D. F. DeTar, F. F. Rogers, Jr., and H. Bach, *ibid.*, **89**, 3039 (1967), and earlier papers in this series; (g) J. Kovacs, G. N. Schmit, and U. R. Ghatak, *Biopolymers*, **6**, 817 (1968); (h) B. J. Johnson, *J. Chem. Soc. C*, 3008 (1968); (i) "Amino-acids, Peptides, and Proteins," Chem. Soc. Specialist Periodical Report, **1**, 143, 200 (1969); **2**, 169 (1970).

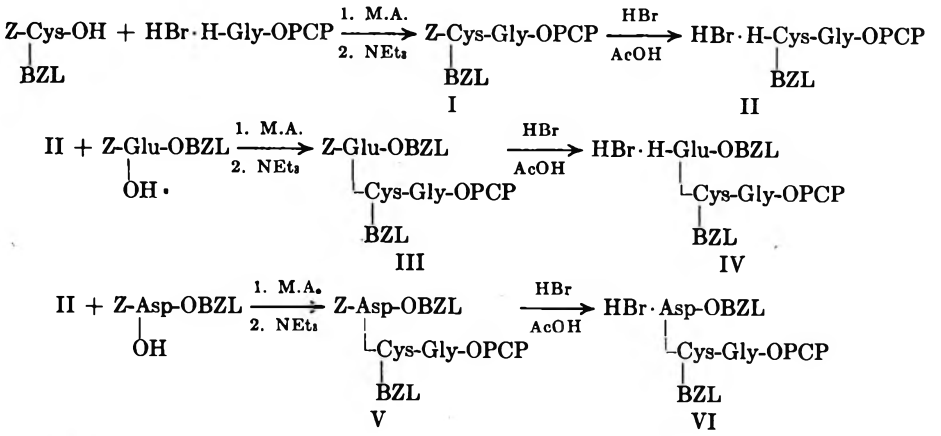
(7) Abbreviations follow the rules in "Abbreviated Designation of Amino-Acid Derivatives and Polypeptides" (Information Bulletin No. 25, IUPAC). Other abbreviations follow as used in "Peptides 1968," Proceedings of the 9th European Peptide Symposium, E. Bricas, Ed., Wiley, New York, N. Y., 1968.

(8) J. L. Wood and V. du Vigneaud, *J. Biol. Chem.*, **130**, 110 (1939).

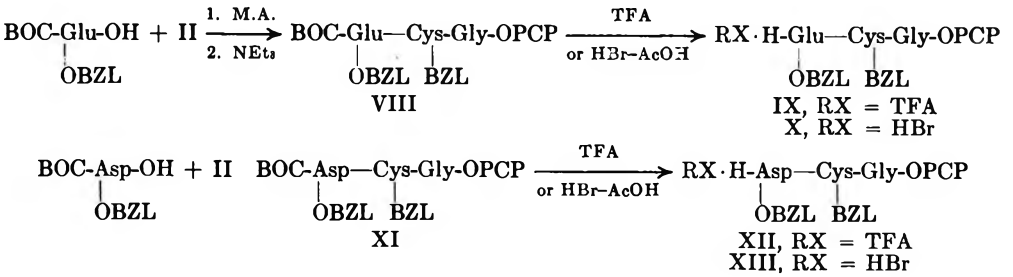
(9) *Cf.* A. Berger, J. Noguchi, and E. Katchalski, *J. Amer. Chem. Soc.*, **78**, 4483 (1956).

(10) H. K. Schachman, "Ultracentrifugation in Biochemistry," Academic Press, New York, N. Y., 1959.

SCHEME I



SCHEME II



metric titration of the thiol groups of dialyzed samples of the polymers XVIII and XIX indicated that only a

negligible amount of disulfide linkage had probably formed under the carefully controlled experimental conditions. Polyisoglutathione (XX) and polyisoasparthione (XXI) were obtained similarly with molec-

ular weights of 16,000 and 6000, respectively. Removal of the *C*- and *S*-benzyl protecting groups of the polymers XIV and XV with anhydrous hydrogen fluoride[11] gave less pure and of lower molecular weight polymers.

During the synthesis of the tripeptide active esters there is no danger of racemization.[12] Racemization of the base-sensitive cysteine residue could occur during polymerization. However, the model dipeptide, *N*-benzyloxycarbonyl-*S*-benzyl-L-cysteinylglycine ethyl ester, in the presence of 7 equiv of triethylamine in the tetrahydrofuran solution showed practically no racemization in 48 hr at room temperature.[13] This result suggests that no racemization of the cysteine residue occurred during polymerization of the tripeptides.

The antiradiation testing of polyglutathione (XVIII) and polyasparthione (XIX) was undertaken by Dr. T. R. Sweeney, Walter Reed Army Institute of Research, Walter Reed Army Medical Center, Washington, D. C. However, the physical properties of these polymers were unsatisfactory for detailed studies.[14] In addition, Dr. M. Pisano, Department of Biology at St. John's University, investigated the effect of polyglutathione (XVIII) on various microorganisms. Preliminary results disclosed a growth stimulation effect on *Bacillus subtilis* when polyglutathione was present in the medium at a concentration of 25 μg/ml. These results will be published in detail elsewhere in a subsequent paper.

(11) S. Sakakibara, Y. Shimonishi, Y. Kishida, M. Okada, and H. Sugihara, *Bull. Chem. Soc. Jap.*, **40**, 2164 (1967).

(12) J. Kovacs, L. Kisfaludy, M. Q. Ceprini, and R. H. Johnson, *Tetrahedron*, **25**, 2555 (1969).

(13) J. Kovacs, G. L. Mayers, R. H. Johnson, R. E. Cover, and U. R. Ghatak, *J. Org. Chem.*, **35**, 1810 (1970).

Experimental Section

Melting points were taken on a Thomas–Hoover apparatus and are uncorrected. The infrared spectra were taken in potassium bromide pellets on a Beckman IR-8 spectrophotometer and only the characteristic strong bands are recorded. The microanalyses were carried out by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y., and Drs. G. Weiler and F. B. Strauss, Oxford, England. Unless otherwise stated, all the analytical samples were dried over phosphorus pentoxide for 20 hr at 56° under high vacuum. The polymers were dried under the same conditions at 78°. Thin layer chromatography was carried out on precoated silica gel analytical plates F254 (Brinkman); unless otherwise stated spots were located by ultraviolet light or exposure to iodine vapor.

***N*-Benzyloxycarbonyl-*S*-benzyl-L-cysteinylglycine Pentachlorophenyl Ester (I).**—A well-stirred solution of 6.90 g (20 mmol) of *N*-benzyloxycarbonyl-*S*-benzyl-L-cysteine in 60 ml of dry tetrahydrofuran containing 2.20 ml (20 mmol) of *N*-methylmorpholine was cooled to −15° (Dry Ice–methanol) and 2.80 ml (21 mmol) of isobutyl chloroformate was added. After 15 min

(14) In a private communication Dr. Sweeney informed us that no satisfactory tests on these polymers could be performed due to their insolubility in biologically suitable vehicles. Both compounds, when placed in aqueous vehicles or suspending agents, form sticky gelatinous clungs which prevent their uniform dispersion in the vehicles. Consequently, more dose cannot be uniformly administered to the test animals through a hypodermic needle. However, one of the samples of polyglutathione (XVIII) was tested under these very unsatisfactory conditions and the following results were obtained in ICR female mice: acute LD_{50} (ip) > 1000 mg/kg; survival after 1000 R ^{60}Co γ radiation, 500 mg/kg, 15 min prerad, 15 mice, 67% survival; 250 mg/kg, 15 min prerad, 15 mice, 7% survival; control, 10 mice, 10% survival. These experiments are suggestive of some radioprotective activity.

8.58 g (22 mmol) of glycine pentachlorophenyl ester hydrobromide was added followed by 3.0 ml (21 mmol) of triethylamine in 60 ml of precooled tetrahydrofuran. Stirring at −10 to 0° was continued for 30 min followed by another 1.5 hr at 0°. The reaction mixture was diluted with 300 ml of cold water and the white solid peptide was filtered. The precipitate was thoroughly washed with 5% sodium bicarbonate solution, water, 1 *N* hydrochloric acid, water, two 100-ml portions of cold methanol, and finally with ether. White crystalline dipeptide was dried *in vacuo*; yield 12.20 g (93%), mp 189–191°. Recrystallization from tetrahydrofuran–ether afforded 10.15 g of the dipeptide I as fluffy needles, mp 190–191°, $[\alpha]^{22}D$ −31.8° (*c* 2.0, dimethylformamide). It showed a single spot in tlc in benzene–methanol–acetic acid (10:2:1); λ_{max} 5.63 (COOPCP), 5.92 (urethane), 6.08 (amide I), 6.52 (amide II), and doublet at 7.21 and 7.33 μ (pentachlorophenyl).

Anal. Calcd for $C_{26}H_{21}N_2O_5SCl_5$: C, 48.00; H, 3.25; N, 4.30; S, 4.93. Found: C, 48.03; H, 3.34; N, 4.20; S, 5.15.

S-Benzyl-L-cysteinylglycine Pentachlorophenyl Ester Hydrobromide (II).—*N*-Benzyloxycarbonyl-*S*-benzyl-L-cysteinylglycine pentachlorophenyl ester (I), 8 g (12.3 mmol), was pulverized and thoroughly mixed with 25 ml of dry acetic acid followed by the addition of 40 ml of 40% hydrogen bromide in acetic acid. The reaction mixture was shaken from time to time over a period of 20 min. After this time, 25 ml of acetic acid was added and the solid mass was dispersed by vigorous shaking. After 15 min the mixture was diluted with a large excess of dry ether, cooled overnight, and filtered. The light yellow hydrobromide salt was washed with dry ether and dried *in vacuo* over potassium hydroxide; yield 6.19 g (84%), mp 192–193° dec. Two recrystallizations from methanol–ether yielded 5.21 g of colorless needles; mp 193–194° dec; $[\alpha]^{22}D$ 11.3° (*c* 2, dimethylformamide); λ_{max} 3.44 (broad, $-NH_3^+$), 5.61 (COOPCP), 5.99 (amide I), 6.45 (amide II), and doublet at 7.22 and 7.35 μ (pentachlorophenyl); tlc in 1-butanol–pyridine–acetic acid–water (30:20:6:24) gave a single ninhydrin-positive spot.

Anal. Calcd for $C_{18}H_{16}N_2O_3SCl_5Br$: C, 36.18; H, 2.70; N, 4.69; S, 5.37. Found: C, 36.44; H, 2.61; N, 4.32; S, 5.79.

***N*-Benzyloxycarbonyl-α-benzyl-L-glutamyl-*S*-benzyl-L-cysteinylglycine Pentachlorophenyl Ester (III).**—*N*-Benzyloxycarbonyl-*L*-glutamic acid α-benzyl ester was coupled with the dipeptide hydrobromide II as described previously. The crude product (82.5%), mp 189–190°, was crystallized from tetrahydrofuran–ether to yield pure tripeptide III: mp 191–193°; tlc, single spot in methylene chloride–methanol (9:1); $[\alpha]^{22}D$ −26.15° (*c* 2, dimethylformamide).

Anal. Calcd for $C_{38}H_{34}N_3O_8SCl_5$: C, 52.46; H, 3.94; N, 4.83. Found: C, 52.11; H, 4.07; N, 4.78.

α-Benzyl-L-glutamyl-*S*-benzyl-L-cysteinylglycine Pentachlorophenyl Ester Hydrobromide (IV).—This compound was prepared using the procedure described for II in 92% yield, mp 148–150° dec. Crystallization from methanol–ether raised the melting point to 152–154° dec. It was recrystallized twice from the same solvent as colorless needles, mp 153–155° dec, $[\alpha]^{22}D$ −18.4° (*c* 2, dimethylformamide).

Anal. Calcd for $C_{30}H_{29}N_3O_6SCl_5Br$: C, 44.11; H, 3.58; N, 5.36. Found: C, 44.00; H, 3.40; N, 5.14.

***N*-Benzyloxycarbonyl-α-benzyl-L-aspartyl-*S*-benzyl-L-cysteinylglycine Pentachloroohenyl Ester (V).**—To the mixed anhydride prepared from 2.072 g (6 mmol) of *N*-benzyloxycarbonyl-L-aspartic acid α-benzyl ester in 30 ml of tetrahydrofuran, 0.67 ml (6 mmol) of *N*-methylmorpholine, and 0.84 ml (6.3 mmol) of isobutyl chloroformate at −15°, 3.588 g (6 mmol) of the dipeptide hydrobromide II was added, followed by 0.84 ml (6 mmol) of triethylamine in 30 ml of cold tetrahydrofuran. After 30 min at −10 to 0°, stirring at 0° was continued for 1 hr. The reaction mixture was worked up as described for I, yield 4.62 g (95%), mp 191–193°. Two recrystallizations from tetrahydrofuran–ether afforded the tripeptide V, mp 193–195°, $[\alpha]^{26}D$ −25.7° (*c* 2, dimethylformamide); tlc in methylene chloride–methanol (9:1) showed a single spot.

Anal. Calcd for $C_{37}H_{32}N_3O_8SCl_5$: C, 51.92; H, 3.77; N, 4.91; S, 3.74; Cl, 20.71. Found: C, 51.90; H, 3.95; N, 4.78; S, 3.94; Cl, 20.41.

α-Benzyl-L-aspartyl-*S*-benzyl-L-cysteinylglycine Pentachlorophenyl Ester Hydrobromide (VI).—This compound was prepared the usual way. It was recrystallized from methanol–ether in silky, colorless needles: yield 1.25 g (60%); mp 195–196° dec; $[\alpha]^{24}D$ −15.1° (*c* 2, dimethylformamide).

Anal. Calcd for $C_{29}H_{27}O_6N_3SCl_5Br$: C, 43.39; H, 3.39; N, 5.24; S, 3.99. Found: C, 43.19; H, 3.45; N, 5.34; S, 4.11.

***N*-Benzyloxycarbonyl-γ-benzyl-L-glutamyl-*S*-benzyl-L-cysteinylglycine Pentachlorophenyl Ester (VII).**—The mixed anhydride, prepared from 2.226 g (6 mmol) of *N*-benzyloxycarbonyl-L-glutamic acid γ-benzyl ester, was coupled with 3.588 g (6 mmol) of the dipeptide hydrobromide II, and the reaction mixture was worked up as described for the dipeptide I. The crude product was crystallized from tetrahydrofuran–ether to afford 4.30 g (82%) of VII: mp 203–205°; $[\alpha]^{23}D$ −21.8° (*c* 2, dimethylformamide); tlc showed a single spot in methylene chloride–methanol (9:1).

Anal. Calcd for $C_{36}H_{34}N_3O_8SCl_5$: C, 52.46; H, 3.94; N, 4.83. Found: C, 52.28; H, 3.80; N, 4.71.

***N*-*tert*-Butyloxycarbonyl-γ-benzyl-L-glutamyl-*S*-benzyl-L-cysteinylglycine Pentachlorophenyl Ester (VIII).**—Mixed anhydride coupling of *N*-*tert*-butyloxycarbonyl-L-glutamic acid γ-benzyl ester[15] and dipeptide hydrobromide II gave VIII in 73% yield, mp 150–151° with shrinking above 147°. Recrystallization from tetrahydrofuran–methanol gave gel, which was filtered, washed with ether, and dried to yield the product as a white powder: mp 151–153°, shrinking above 147°; $[\alpha]^{24}D$ −23.1° (*c* 2, dimethylformamide).

Anal. Calcd for $C_{35}H_{36}N_3O_8SCl_5$: C, 50.28; H, 4.34; N, 5.03; S, 3.83; Cl, 21.20. Found: C, 50.13; H, 3.94; N, 5.06; S, 4.18; Cl, 20.77.

γ-Benzyl-L-glutamyl-*S*-benzyl-L-cysteinylglycine Pentachlorophenyl Ester Trifluoroacetate (IX).—Pentachlorophenyl ester VIII, 1.52 g (1.8 mmol), was treated with 5 ml of cold anhydrous trifluoroacetic acid at room temperature for 40 min. Evaporation of the solvent *in vacuo* below 30° left colorless solid, 1.453 g (95%), mp 151–153° dec, which reprecipitated from methanol solution with ether: mp 151–153° dec; $[\alpha]^{24}D$ −12.45° (*c* 2, dimethylformamide).

Anal. Calcd for $C_{32}H_{29}N_3O_8SCl_5F_3$: C, 45.22; H, 3.44; N, 4.94; S, 3.77. Found: C, 45.64; H, 3.63; N, 5.09; S, 4.42.

γ-Benzyl-L-glutamyl-*S*-benzyl-L-cysteinylglycine Pentachlorophenyl Ester Hydrobromide (X).—The tripeptide VIII and HBr gave, after recrystallization from methanol–ether, hydrobromide X as fluffy white solid in 86% yield: mp 162–163° dec; $[\alpha]^{23}D$ −9.95° (*c* 2.01, dimethylformamide).

Anal. Calcd for $C_{30}H_{29}N_3O_6SCl_5Br$: C, 44.11; H, 3.58; N, 5.36; S, 3.92. Found: C, 43.41; H, 3.57; N, 5.20; S, 3.89.

***N*-*tert*-Butyloxycarbonyl-β-benzyl-L-aspartyl-*S*-benzyl-L-cysteinylglycine Pentachlorophenyl Ester (XI).**—The mixed anhydride prepared from 3.557 g (11 mmol) of *N*-*tert*-butyloxycarbonyl-L-aspartic acid β-benzyl ester[16] was coupled to 6.578 g (11 mmol) of dipeptide hydrobromide II. The tripeptide was worked up as described previously, to afford 8.75 g (90%) of XI, mp 164–166°. This was precipitated as gel from tetrahydrofuran–methanol. After drying 6.53 g of the pure tripeptide XI was obtained as a white powder: mp 168–169°; $[\alpha]^{23}D$ −26.3° (*c* 2.03, dimethylformamide); tlc in methylene chloride–methanol (9:1) gave a single spot.

Anal. Calcd for $C_{34}H_{34}N_3O_8SCl_5$: C, 49.68; H, 4.16; N, 5.11; S, 3.90; Cl, 21.56. Found: C, 50.05; H, 4.32; N, 5.30; S, 4.04; Cl, 21.90.

β-Benzyl-L-aspartyl-*S*-benzyl-L-cysteinylglycine Pentachlorophenyl Ester Trifluoroacetate (XII).—Pentachlorophenyl ester XI, 3 g (3.65 mmol), was treated with 10 ml of anhydrous trifluoroacetic acid; after 10 min crystalline white solid separated. The reaction mixture was diluted with ether and the precipitated solid was washed with ether and dried *in vacuo* over potassium hydroxide: yield 3.01 g (98%); mp 170° dec with charring; $[\alpha]^{24}D$ −17.3° (*c* 2, dimethylformamide).

Anal. Calcd for $C_{31}H_{27}N_3O_8Cl_5SF_3$: C, 44.54; H, 3.26; N, 5.03; S, 3.84. Found: C, 45.72; H, 3.15; N, 5.25; S, 4.31.

β-Benzyl-L-aspartyl-*S*-benzyl-L-cysteinylglycine Pentachlorophenyl Ester Hydrobromide (XIII).—This compound was obtained from pentachlorophenyl ester (XI), the usual way in 92% yield: mp 196–198° dec; $[\alpha]^{23}D$ −12 .6° (*c* 2, dimethylformamide).

Anal. Calcd for $C_{29}H_{27}N_3O_6SCl_5Br$: C, 43.39; H, 3.39;

(15) C. H. Li, B. Gorup, D. Chung, and J. Ramchandran, *J. Org. Chem.*, **28**, 178 (1963).

(16) E. Sandrin and R. A. Boissonnas, *Helv. Chim. Acta*, **46**, 1637 (1963)

N, 5.24; S, 3.99. Found: C, 43.39; H, 3.45; N, 5.37; S, 3.98.

Poly(α-benzyl-L-glutamyl-*S*-benzyl-L-cysteinylglycine) (XIV).—To a solution of 1.635 g (2 mmol) of α-benzyl-L-glutamyl-*S*-benzyl-L-cysteinylglycine pentachlorophenyl ester hydrobromide (IV) in 2 ml of purified dimethylformamide,[6g] 0.56 ml (4 mmol) of purified triethylamine[6g] was added and left on a shaker for 48 hr. The solid reaction mass was triturated with 150 ml ether and centrifuged. The residue was triturated with ether (three 100-ml portions), with methanol (two 100-ml portions), finally with ether and dried: yield 787 mg (84%); λ_{max} 5.78 (COOBZL), 6.09 (amide I), 6.55 μ (amide II), the pentachlorophenyl ester carbonyl band and the doublet completely disappeared.

Anal. Calcd for $(C_{24}H_{27}N_3O_5S)_\infty$: C, 61.38; H, 5.80; N, 8.95; S, 6.83. Found: C, 60.87; H, 5.66; N, 8.87; S, 6.97.

Poly(α-benzyl-L-aspartyl-*S*-benzyl-L-cysteinylglycine) (XV).—To a suspension of 803 mg (1 mmol) of α-benzyl-L-aspartyl-*S*-benzyl-L-cysteinylglycine pentachlorophenyl ester hydrobromide (VI) in 1.5 ml of dimethylformamide, 0.28 ml (2 mmol) of triethylamine was added and the mixture was left in a mechanical shaker for 48 hr. The polymer was worked up following the procedure described above to afford 330 mg (73%) of white powder.

Anal. Calcd for $(C_{23}H_{25}N_3O_5S)_\infty$: C, 60.65; H, 5.53; N, 9.22; S, 7.04. Found: C, 60.95; H, 5.73; N, 8.90; S, 7.22.

Poly(γ-benzyl-L-glutamyl-*S*-benzyl-L-cysteinylglycine) (XVI).

A. Polymerization of the Trifluoroacetate Salt IX.—γ-Benzyl-L-glutamyl-*S*-benzyl-L-cysteinylglycine pentachlorophenyl ester trifluoroacetate (IX) (850 mg) was polymerized and the product was worked up following the method described above to yield 254 mg (54%) of XVI.

Anal. Calcd for $(C_{24}H_{27}N_3O_5S\cdot H_2O)_\infty$: C, 59.12; H, 5.58; N, 8.62; S, 6.58. Found: C, 59.33; H, 5.68; N, 8.82; S, 7.40.

B. Polymerization of the Hydrobromide Salt X.—γ-Benzyl-L-glutamyl-*S*-benzyl-L-cysteinylglycine pentachlorophenyl ester hydrobromide (X) (2.45 g) was polymerized and worked up according to the method described previously. The polypeptide XVI was obtained as a white solid, yield 0.809 g (57%).

Anal. Found: C, 60.35; H, 5.37; N, 9.13; S, 7.52.

Poly(β-benzyl-L-aspartyl-*S*-benzyl-L-cysteinylglycine) (XVII).

A. Polymerization of the Trifluoroacetate Salt XII.—β-Benzyl-L-aspartyl-*S*-benzyl-L-cysteinylglycine pentachlorophenyl ester trifluoroacetate (XII) (1.67 g) gave polymer XVII following the usual procedure, yield 248 mg (27%).

Anal. Calcd for $(C_{23}H_{25}N_3O_6S\cdot H_2O)_\infty$: C, 58.33; H, 5.71; N, 8.87; S, 6.77. Found: C, 58.54; H, 5.61; N, 9.31; S, 7.29 (0.07% residue).

B. Polymerization of the Hydrobromide Salt XIII.—β-Benzyl-L-aspartyl-*S*-benzyl-L-cysteinylglycine pentachlorophenyl ester hydrobromide (XIII) (2.40 g) was polymerized to afford 537 mg (39%) of polymer XVII.

Anal. Calcd for $(C_{23}H_{25}O_5N_3S\cdot{}^1/_2H_2O)_\infty$: C, 59.47; H, 5.64; N, 9.05; S, 6.90. Found: C, 59.73; H, 5.32; N, 9.40; S, 7.46.

Removal of the *C*- and *S*-Benzyl Protecting Groups of the Polymers with Sodium–Liquid Ammonia. Polyglutathione (XVIII).—To a stirred suspension of 1.7 g of the polymer XIV in 200 ml of freshly distilled (from sodium) liquid ammonia, 800 mg of finely cut sodium was added. Each portion of sodium was added when the blue color had faded. At the end, the blue color was allowed to persist for 30 min, after which the excess of sodium was destroyed by the addition of a few crystals of ammonium chloride. The ammonia was allowed to evaporate under a stream of oxygen-free nitrogen (purified by passing through Fieser's solution) and the white residue was completely freed from ammonia in a vacuum desiccator over sulfuric acid. The residue was dissolved in 50 ml of freshly distilled water containing 1 ml of 1% ethylenediaminetetracetic acid sodium salt, adjusted to about pH 6 with acetic acid, and lyophilized. The residual white solid was taken in 25 ml of freshly distilled water, acidified with 2 *N* hydrochloric acid to about pH 3, and dialyzed against six 1000-ml portions of freshly distilled water under a nitrogen atmosphere, until free of chloride ion. After lyophilization the polymer XVIII was obtained as a fluffy white solid: yield 516 mg (59%); $\bar{M}_w$ = 9000 by sedimentation equilibrium. The sodium salt of the polymer XVIII in D_2O (10%) showed the complete absence of aromatic protons in the nmr (60 Mcps). The analytical sample was prepared by washing the polymer with water, absolute ethanol, and peroxide-free ether under an oxygen-free nitrogen atmosphere and dried.

Anal. Calcd for $(C_{10}H_{15}N_3O_5S)_\infty$: C, 41.52; H, 5.23; N, 14.52; S, 11.08; SH, 11.14. Found: C, 41.58; H, 5.85; N, 14.87; S, 10.65; SH, 9.48 by iodometric titration.

Polyasparthione (XIX).—The protecting benzyl groups from polymer XV (1.0 g) were removed in 200 ml of liquid ammonia with 350 mg of sodium. The reaction mixture was worked up following the conditions described for the preparation of XVIII. After dialysis and lyophilization, the polymer XIX was obtained as a fluffy white solid: yield 265 mg (60%); $\bar{M}_w$ = 7000 by sedimentation equilibrium.

Anal. Calcd for $(C_9H_{13}N_3O_5S)_\infty$: C, 39.27; H, 4.76; N, 15.26; S, 11.65; SH, 11.20. Found: C, 39.27; H, 5.16; N, 15.14; S, 11.54; SH, 10.29.

Polyisoglutathione (XX).—The polymer XVI (500 mg) was treated as above to obtain the free polymer XX in 58% yield; $\bar{M}_w$ = 16,000 by sedimentation equilibrium.

Anal. Calcd for $(C_{10}H_{15}N_3O_5S)_\infty$: C, 41.52; H, 5.23; N, 14.52; S, 11.08; SH, 11.14. Found: C, 41.72; H, 5.45; N, 13.92; S, 10.82; SH, 11.52.

Polyisoasparthione (XXI).—Polymer XVII (500 mg) gave, after similar treatment, 133 mg (60%) of XXI as a fluffy white solid, $\bar{M}_w$ = 6000 by sedimentation equilibrium.

Anal. Calcd for $(C_9H_{13}N_3O_5S)_\infty$: C, 39.27; H, 4.76; N, 15.26; S, 11.65; SH, 11.20. Found: C, 39.97; H, 5.37; N, 14.92; S, 11.26; SH, 10.82.

Removal of the *C*- and *S*-Benzyl Protecting Groups of the Polymers by Anhydrous Hydrogen Fluoride. Polyglutathione (XVIII).—To a stirred solution of 2 g of the polymer XIV in 15 ml of trifluoroacetic acid containing 2.5 ml of anisole, *ca.* 20 ml of anhydrous hydrogen fluoride was collected at Dry Ice–methanol bath temperature. The solution turned light yellow to red color. After stirring at −15 to 0° for 1 hr, the reaction mixture was stirred at room temperature for about 18 hr. The hydrogen fluoride was removed with a stream of oxygen-free nitrogen and the polymer was precipitated by addition of peroxide-free ether, centrifuged, washed with four 200-ml portions of ether to afford white amorphous polymer, and dried overnight at 78° (0.1 mm), yield 1.20 g, $\bar{M}_w$ = 5000 by sedimentation equilibrium.

Anal. Calcd for $(C_{10}H_{15}N_3O_5S)_\infty$: C, 41.52; H, 5.23; N, 14.52; S, 11.08. Found: C, 43.97; H, 4.88; N, 11.42; S, 9.01.

Polyasparthione (XIX).—Polymer XV was similarly treated with anhydrous hydrogen fluoride. The reaction mixture was worked up following the conditions as described for the preparation of XVIII. The polymer was obtained as white amorphous powder and dried at 78° (0.1 mm) overnight, yield 2.87 g, $\bar{M}_w$ = 4600 by sedimentation equilibrium.

Anal. Calcd for $(C_9H_{13}N_3O_5S)_\infty$: C, 39.27; H, 4.76; N, 15.26; S, 11.65. Found: C, 41.71; H, 5.06; N, 12.22; S, 9.44.

Weight-Average Molecular Weights.—Weight-average molecular weights were determined in the Spinco Model E analytical ultracentrifuge by the sedimentation equilibrium method in Tris buffer (pH 7.8). The calculations used were those given by Schachman.[10] Measurements were made at concentrations in the range of 0.7–1% at 22–24°, at a rotor speed of 16,000 rpm and a schlieren angle of 65°, assuming partial specific volume of 0.72.

Registry No.—I, 32296-65-4; II, 32296-66-5; III, 32296-79-0; IV, 32380-99-7: V, 32296-80-3; VI, 32296-81-4; VII, 32296-82-5; VIII, 32296-67-6; IX, 32296-68-7; X, 32296-69-8; XI, 32296-70-1; XII, 32296-71-2; XIII, 32296-72-3; XIV (polymer), 32270-57-8; XIV (repeating unit), 32355-52-5; XV (polymer), 32270-58-9; XV (repeating unit), 32355-53-6; XVI (polymer), 32270-59-0; XVI (repeating unit), 32355-54-7; XVII (polymer), 32270-60-3; XVII (repeating unit), 32355-55-8; XVIII (polymer), 32270-61-4; XVIII (repeating unit), 32355-57-0; XIX (poly-

mer), 32270-62-5; XIX (repeating unit), 32355-56-9; XX (polymer), 32270-63-6; XX (repeating unit), 32355-58-1; XXI (polymer), 32270-64-7; XXI (repeating unit), 32355-59-2.

Acknowledgment.—This work was supported by Grant No. G.M. 08795 from the National Institutes of Health, Public Health Service. We wish to thank Professor H. Horan for the infrared spectra.

Synthesis of *dl*-Hedycaryol[1]

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Received May 11, 1971

The synthesis of *dl*-hedycaryol (**5**) according to Scheme I is described. Dimethyl 4-hydroxyisophthalate (**1**) was hydrogenated over ruthenium dioxide and the resulting dimethyl hydroxycyclohexanedicarboxylate mixture **11** was acetylated. The acetate **12** was pyrolyzed at 260° in the presence of potassium acetate and the major product, dimethyl cyclohexene-2,4-dicarboxylate (**13**), was separated by distillation. Addition of methyllithium to **13** yielded the bis tertiary diol **15** which was selectively dehydrated to 2-(2-propenyl)-4-(2-hydroxy-2-propyl)-1-cyclohexene (**2**) by heating in dimethyl sulfoxide. Conversion of **2** to octalone **3** was effected by a previously established sequence: 1,4 cycloaddition of ethyl α-acetoxyacrylate, lithium aluminum hydride reduction, and sodium periodate oxidation. Direct angular methylation of **3** was effected by treatment with a mixture of sodium hydride and methyl iodide in dimethoxyethane (conditions corresponding to the reaction of kinetically generated enolates). The resulting octalone mixture **4** was correlated with γ-eudesmol (**41**) and epi-γ-eudesmol (**42**) by Wolff–Kishner reduction. From the reduction of the octalone mixture with lithium aluminum hydride a crystalline diol **43** was obtained which was converted to monotosylate **44** which yielded hedycaryol (**5**) upon treatment first with diborane and then with aqueous sodium hydroxide. The properties of synthetic *dl*-**5** match those reported for the natural *d* enantiomer.

Hedycaryol (**5**) is a biogenetically important sesquiterpene, isomeric with and derived from *trans,trans*-farnesol and the progenitor of a further set of sesquiterpene skeletal families, exemplified most directly by the eudesmols (hydronaphthalenes) and bulnesol and guaiol (hydroazulenes), related by acid-catalyzed cyclizations, and by elemol, related *via* the Cope rearrangement.[3]

Hedycaryol has a relatively recent history; although its biogenetic involvement as a 1,5-cyclodecadiene was appreciated in print in 1953,[4] the structure of the first sesquiterpene 1,5-cyclodecadiene was not established until 1959,[5] and hedycaryol itself was not isolated until 1968.[6] This article records the synthesis of *dl*-hedycaryol.

Synthetic Scheme.—The synthesis was planned and carried out according to the accompanying flow chart, in four main sections, A, B, C, and D (see Scheme I). This approach concedes to nature, at least temporarily, the exclusive ability to transform acyclic precursors directly to *trans,trans*-1,5-cyclodecadienes.[7] The present synthesis involves fragmentation of the appropriately functionalized and substituted hydronaphthalene precursor to the ten-membered ring of hedycaryol which is specifically a 1,5-dimethyl-*trans,trans*-1,5-cyclodecadiene bearing a 2-hydroxy-2-propyl chain at C-8. This was accomplished by Marshall's method:[8] hydroboration of octalyl tosylate **44** and subsequent generation of *dl*-hedycaryol at a relatively low temperature (65°) by fragmentation in the presence of base. Some care is necessary in planning and carrying out the synthesis because hedycaryol is relatively unstable thermally, rearranging to elemol (**6**) with a half-life of 3 hr at 100°,[6] and it is very susceptible to cyclization in the presence of acids.[9]

Sections B and C together exemplify the preparation of 9-methyl-$\Delta^{4(10)}$-1-octalones *via* 1,4 cycloaddition to a 1-isopropenylcyclohexene (B)[10] and subsequent angular methylation (C).[11] Section B involves the regiospecific but indirect 1,4-cycloaddition of ketene (which itself favors 1,2 cycloaddition).[12] This can be accomplished by the use of α-acetoxyacrylates and related substances.[10] Although the involvement of angular methylation as an essential part of the planned synthesis might be considered to be poor strategy, it may be noted that introduction of the angular methyl group by direct alkylation of $\Delta^{4(10)}$-1-octalones (β,γ-unsaturated) is a viable method, whereas direct angular methylation of 1-decalones is not. Moreover, prior incorporation of the methyl, using the same overall approach, can be summarily dismissed because of the failure of 1-methyl-2-isopropenylcyclohexenes to un-

(1) (a) The investigation was supported by Public Health Service Research Grants GM 09759, GM 14133, and GM 16338 from the Division of General Medical Sciences, U. S. Public Health Service. (b) The article is abstracted from the Ph.D. theses of C. E. S., University of Wisconsin, 1968, and H. C. K., Wesleyan University, 1971. The synthesis was first presented at the 155th National Meeting of the American Chemical Society, San Francisco, Calif., April 1968, Abstract P-2.

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(3) Sesquiterpene biogenetic relations are reviewed by W. Parker, J. S. Roberts, and R. Ramage, *Quart. Rev., Chem. Soc.*, **21**, 321 (1967).

(4) L. Ruzicka, A. Eschenmoser, and H. Heusser, *Experientia*, **9**, 357 (1953).

(5) J. B. Hendrickson, *Tetrahedron*, **7**, 82 (1959); V. Herout, M. Horak, B. Schneider, and F. Sorm, *Chem. Ind. (London)*, 1089 (1959).

(6) R. V. H. Jones and M. D. Sutherland, *Chem. Commun.*, 1229 (1968). Note the corrigendum, *ibid.*, 892 (1970).

(7) For an interesting, although unsuccessful, synthetic approach of this type see E. J. Corey and E. A. Broger, *Tetrahedron Lett.*, 1779 (1969).

(8) J. A. Marshall and G. L. Bundy, *Chem. Commun.*, 854 (1967).

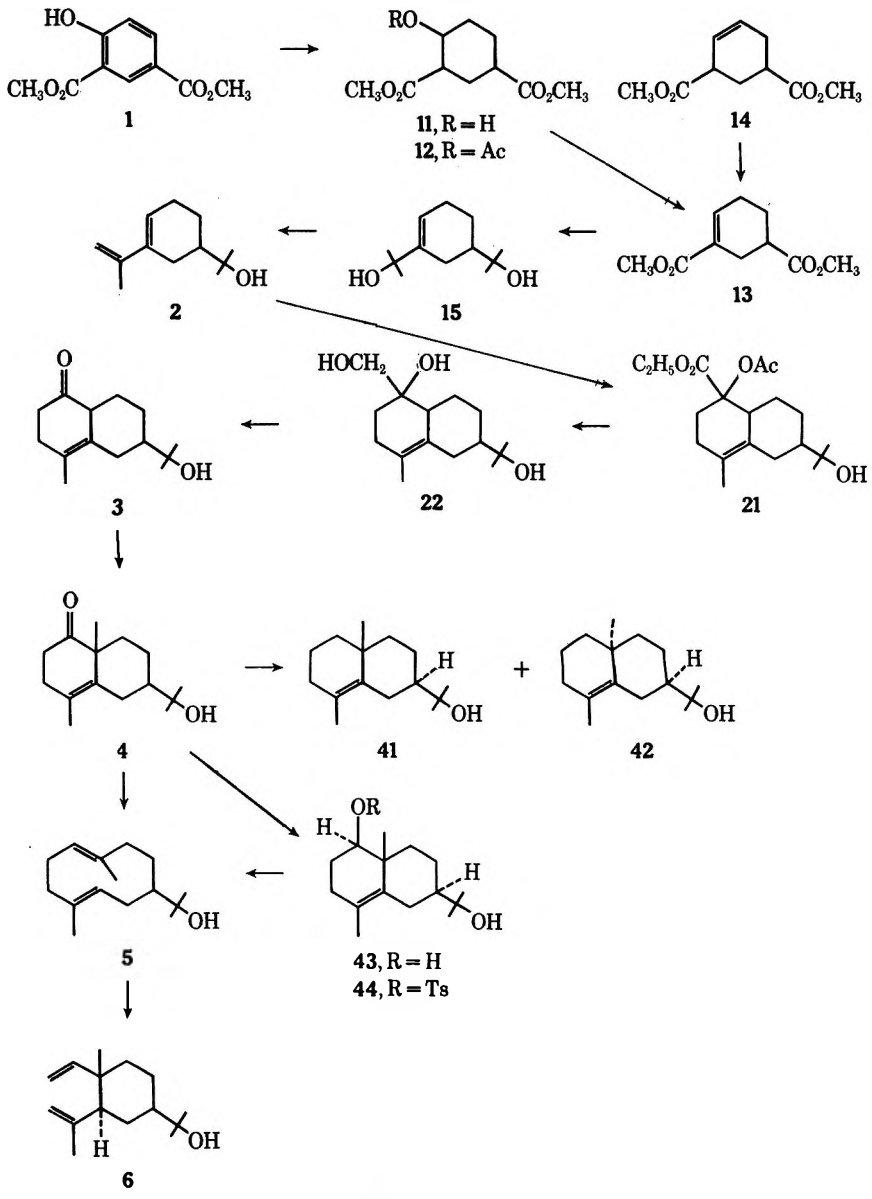
(9) The conversion of *d*-**5** to a mixture of eudesmols has been reported to occur upon refluxing a solution in ether containing 1% *p*-toluenesulfonic acid.[6] Our results provide an even more striking illustration of the sensitivity of **5** to acid, synthetic material suffering cyclization to the eudesmols in buffered acetic acid with a half-life of 15 min at 60°. The product of this reaction also consisted of a mixture of α-, β-, and γ-eudesmols; moreover, specific examination by glpc for the presence of bulnesol, which is biogenetically formed from **5** as are the eudesmols, by a simple acid-catalyzed cyclization (albeit anti-Markovnikov in the case of bulnesol), failed to detect any (<2%), and an intriguing problem of biogenetic simulation remains.

(10) P. S. Wharton and B. T. Aw, *J. Org. Chem.*, **31**, 3787 (1966).

(11) P. S. Wharton and C. E. Sundin, *ibid.*, **33**, 4255 (1968).

(12) See J. D. Roberts and C. M. Sharts, *Org. React.*, **12**, 1 (1962).

SCHEME I[a,b]



[a] The synthetic sequence is indicated by heavy arrows. [b] Relative stereochemistry is indicated only when dotted lines are present.

dergo synthetically useful 1,4-cycloaddition reactions.[13]

The four sections are considered in order A–D (Scheme I).

Section A (1 → 2) starts with an appropriately substituted compound, 4-hydroxyisophthalic acid, which is available as a by-product in the manufacture of salicylic acid. Hydrogenation of the dimethyl ester **1** at 100° in tetrahydrofuran over ruthenium dioxide yielded a mixture consisting of 35% of hydrogenolysis products, the isomeric dimethyl cyclohexane-1,3-dicarboxylates (**11**). On a large scale, separation of the products by distillation was accompanied by much lactonization, an unnecessary complication which was most efficiently avoided by acetylating the crude hydrogenation product prior to distillation. Furthermore, the acetate obtained in this way (**12**) could be converted directly to the conjugated diester, dimethyl cyclohexene-2,4-dicarboxylate (**13**), by heating to 260° in the presence of potassium acetate. The isomers of the unconjugated diester, dimethyl cyclohexene-3,5-dicarboxylate (**14**), were present in the neutral fraction of the pyrolysate but they comprised only 6% of the equilibrium mixture of unsaturated diesters at 200°, as shown in independent experiments, and they could be separated by fractional distillation, thus allowing the use of recycling procedures. Some acidic material was formed in the pyrolysis but this could also be recycled after esterification.

Conversion of the conjugated diester to a crystalline bis tertiary diol (**15**) was effected in high yield by treatment with methyllithium. Dehydration of the diol to isopropenylcyclohexene (**2**), an apparently simple transformation involving dehydration of the alcohol which is both tertiary and allylic but not of the simple tertiary alcohol, was accomplished with less ease than had been anticipated. Heating with pyridine-treated alumina[14] gave promising results which were, however, difficult to reproduce; and the desired product was always accompanied by varying amounts of isomeric diene, and trienes from bis dehydration, in addition to starting material. A simpler reproducible procedure consisted of heating the diol in dimethyl sulfoxide at

(13) See A. S. Onishschenko, "Diene Synthesis," Israel Program for Scientific Translation, Jerusalem, 1964, pp 418–419.

(14) E. von Rudloff, *Can. J. Chem.*, **39**, 1860 (1961).

130°.[15] The tertiary allylic alcohol suffered highly selective dehydration but the result was a mixture of dienes containing 80% of **2** and 20% of undesired isomeric diene. Attempts to reduce the amount of isomerization were to no avail. Furthermore, attempted separation of the mixture by distillation led to complete loss of **2** by isomerization, presumably induced by acidic impurities generated by dimethyl sulfoxide and retained in the product. In fact, contrary to report,[15] dehydration in dimethyl sulfoxide seemed to be acid-catalyzed because it was found that addition of 1,5-diazabicyclo[4.3.0]non-5-ene completely inhibited the reaction.

Sections B (2 → 3) and C (3 → 4).—By following procedures already described,[10,11] the mixture of dienes containing 80% of **2** was converted to **4**. A 1,4 cycloadduct **21** was first obtained by heating with ethyl α-acetoxyacrylate. Thereafter, excess acetoxyacrylate and most of the unreactive diene isomeric with **2** were removed *in vacuo* at 110° but it was not possible to distill the remaining glass because of accompanying dehydration. Direct reduction of the glass with lithium aluminum hydride in ether afforded, in 47% overall yield, a solid which must be predominantly one of the four possible diastereomeric *dl*-triols **22** and, in 40% yield, an oil consisting of an impure mixture of triol isomers. Careful oxidation of crystalline triol with sodium metaperiodate gave β,γ-unsaturated ketone **3**, which was immediately methylated with a mixture of 1.1 equiv of sodium hydride and excess methyl iodide in dimethoxyethane. (Some care is needed at this stage to obviate the disastrously irreversible isomerization of β,γ-unsaturated ketone **3** to the corresponding α,β-unsaturated ketone.) The crude product was chromatographed on alumina, a procedure which afforded, in 52% overall yield, a mixture consisting of diastereomers with the constitution of **4**. Wolff–Kishner reduction of crude ketonic product afforded a mixture of *dl*-γ-eudesmol (**41**, methyl cis to hydroxypropyl) and *dl*-epi-γ-eudesmol (**42**) in a ~80:20 ratio as determined by comparisons with authentic samples.[16]

Section D (4 → 5).—Reduction of the mixture of diastereomeric octalones (**4**) was carried out after analyzing reduction of the octalone similarly constituted but lacking the hydroxypropyl side chain;[17] in this case, lithium aluminum hydride in ether gave a mixture of major and minor alcohols (85:15) which were separated by preparative glpc and characterized by their nmr spectra, which showed signals at δ 3.35 and 3.33 ppm as broadened triplets with $W_{1/2}$ of 17 and 10 Hz, illustrative of the difference in cyclohexane systems expected for hydrogens on carbon bearing equatorial and axial oxygen, respectively.[18] Various other hydride–solvent systems were examined but they afforded almost no variation in the product ratio.

Subsequent reduction of **4** (87% *cis* diastereomer) with lithium aluminum hydride in dimethoxyethane at −15° gave a mixture of diols from which the expected major product (**43**) was obtained crystalline in 29% yield. Oxidation of this diol with chromic acid and subsequent Wolff–Kishner reduction yielded *dl*-γ-eudesmol only, the absence of *dl*-epi-γ-eudesmol showing that crystalline diol is stereochemically homogeneous at C-6 and C-9. The stereochemistry of the hydroxyl group at C-1 is equatorial according to the nmr signal at δ 3.47 ($W_{1/2}$ = 17 Hz).

Crystalline diol was converted to the corresponding monotosylate **44** in high yield and fragmentation of the tosylate to *dl*-hedycaryol (**5**) was then examined. After initial experiments with an old bottle of commercial diborane in tetrahydrofuran had afforded variable results, reproducibility was achieved with a previously unopened batch of the same reagent, a cautionary note perhaps worthy of comment although the nature of the problem was not determined.

Fragmentation of the boron-containing compounds was carried out with aqueous sodium hydroxide for 13 hr at 65°. The nmr spectrum of the resulting oil showed the presence of ~20% residual tosylate (which was inert to prolonged fragmentation conditions) and a yield of *dl*-hedycaryol, based on the unique absorption at δ 4.92 ppm, of 60%. Nmr and ir data showed that only a small amount of *dl*-elemol (**6**) had been formed, consistent with the established preference for an internal rather than peripheral mode of fragmentation.[8]

dl-Hedycaryol was isolated in 50% yield from the crude product *via* extraction of the oil with aqueous silver nitrate without addition of an organic solvent. Samples of *dl*-**5** isolated in this way could be distilled *in vacuo* over solid sodium hydroxide but no further purification was apparent; in both cases only small amounts (2–4%) of *dl*-**6** could be detected by nmr spectroscopy. It was not possible to assay the overall purity of synthetic *dl*-**5** directly by glpc because of the occurrence of thermal or acid-catalyzed rearrangements on all columns tested, but use was made of the thermal rearrangement in an indirect determination. After heating in cyclohexane at 130° for 16 hr, a sample of *dl*-**5** gave, with no material loss, *dl*-**6** of >96% purity as established by glpc. Spectroscopic data afforded by samples of synthetic *dl*-**5** match those reported for the natural *d* enantiomer.[19]

Experimental Section

Physical Data.—Melting points were determined using a Thomas Unimelt capillary melting point apparatus and are uncorrected. Boiling points are uncorrected. Analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich. Infrared spectra were obtained using a Perkin-Elmer Model 137 spectrophotometer. Nmr spectra were recorded using a Varian A-60A spectrometer employing tetramethylsilane as an internal reference. Spinning band distillations were performed using a 24-in. Nester–Faust NFT-50 Teflon spinning band column fitted with an automatic reflux ratio control. Gas–liquid phase chromatography (glpc) was performed on Varian Aerograph, Model A-90-P, and Perkin-Elmer, Model F-11, units, using packed and capillary stainless steel columns, respectively. Peak areas were calculated using a Disc chart integrator. The various columns used for glpc were: 5 ft × 0.25 in. 5% Carbowax 20M on Teflon 6 (1); 5% Carbowax 20M on 40–60 Chromosorb T (2); and 150 ft × 0.01 in. SF-96 (3).

Materials.—All solvents were dried and/or distilled before use with the exception of Mallinckrodt anhydrous ether. Magnesium sulfate was used as a drying agent. *n*-Butyllithium in

(15) V. J. Traynelis, W. L. Hergenrother, H. T. Hanson, and J. A. Valicenti, *J. Org. Chem.*, **27**, 2377 (1962); *ibid.*, **29**, 123 (1964).

(16) Authentic samples were generously supplied by Dr. J. A. Marshall, Northwestern University.

(17) Y. C. Poon, Ph.D. Thesis, Wesleyan University, 1971.

(18) See N. S. Bhacca and D. H. Williams, "Applications of Nmr Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 49–53.

(19) Copies of the ir and nmr spectra of hedycaryol-*d* were generously supplied by Dr. M. D. Sutherland.

hexane (Alpha) was titrated and found to be 2.54 *M* in total base and 2.44 *M* in butyllithium.

Dimethyl 4-hydroxyisophthalate (1) was prepared from the "brown dust" by-product of salicyclic acid production, generously supplied by the Hilton–Davis Chemical Co. In portions, *ca.* 4000 g of "brown dust" was extracted and then esterified and afforded, after work-up, 1716 g of brown crystals of 1, mp 96–98° (lit.[20] mp 97.5°). Crystallization from hexane failed to raise the melting point.

Dimethyl 4-Acetoxycyclohexane-1,3-dicarboxylate (12).—Into a 1400-ml capacity hydrogenation bomb was placed 300.5 g of crystalline dimethyl 4-hydroxyisophthalate, mp 96–98°, 16.5 g of ruthenium dioxide (62.5%, Engelhard), and enough tetrahydrofuran to half fill the bomb. The bomb was flushed with nitrogen, filled with hydrogen to a pressure of 1590 psi, and slowly heated, with shaking. The temperature was finally maintained at 100°. The bomb was refilled with hydrogen after 2 hr and again after 24 hr. After a total of 46 hr hydrogen uptake had become slow and the bomb was allowed to cool. Work-up gave 297.4 g of a light brown oil to which was added 320 g of pyridine and 277 g of acetic anhydride. After 10 days at room temperature work-up yielded 317 g of a light brown oil which was subjected to a spinning band distillation to remove 75.6 g of lower boiling components, bp to 85° (0.3 mm). The remaining oil was then subjected to a simple distillation which afforded 224.2 g of acetate (61% based on dimethyl 4-hydroxyisophthalate), bp 143° (0.4 mm).

Dimethyl Cyclohexene-2,4-dicarboxylate (13).—A mixture of 162.6 g of dimethyl 4-acetoxycyclohexane-1,3-dicarboxylate and 15.1 g of fused potassium acetate was heated at 260–265° under nitrogen in a round-bottom flask fitted with a distillation head. Over a period of 15 min 45.7 g of distillate was collected (theoretical yield of acetic acid, 37.8 g). After 17 min of heating a large amount of solid suddenly separated in the reaction flask. The flask was cooled, and the reaction mixture was worked up, affording 94.3 g (76%) of dark oil as the neutral fraction.

Combination of similar material from various runs gave a total of 270 g which was first simply distilled, affording 251.4 g of light yellow oil, bp 100–110° (0.9 mm). The distillate was subjected to spinning band distillation with the reflux ratio set at 100:1, giving 59.4 g up to a recorded head temperature of 67° (0.2 mm) before glpc analysis of the distillate showed that little or no dimethyl cyclohexene-3,5-dicarboxylate (14) remained in the pot. The remaining oil, from which 53.2 g had been removed, was subjected to a simple distillation, yielding 132.5 g of 13 (52% overall from starting acetate): bp 115–118° (0.2 mm); homogeneous by glpc analysis on column 2 at 223°; nmr (CCl_4) δ 6.92 (broad s, 1), 3.67 and 3.69 (two sharp s, 6), and 1.35–2.85 ppm (complex, 7).

2,4-Di(2-hydroxy-2-propyl)cyclohexene (15).—To a stirred solution of 4 mol of 2.16 *M* methyllithium in ether (Alpha) was added dropwise, over 1 hr, under nitrogen, and with cooling in an ice–water bath, a solution of 117.5 g (0.593 mol) of dimethyl cyclohexene-2,4-dicarboxylate, obtained as described above, in 320 ml of anhydrous ether. During the addition a fine white precipitate formed. After the addition was complete the ice bath was removed and the mixture was allowed to stir at room temperature for 7 hr. To the reaction mixture was then added dropwise over 20 min, with stirring and cooling in an ice–water bath, 100 ml of water. Further work-up yielded 117.6 g (97%) of a white powder: mp 114–121°; nmr (CCl_4) δ 5.7 (broad, 1.0) and 0.9–2.4 ppm (complex, showing equal intensity peaks at 1.20 and 1.30 ppm, 23.1).

Recrystallization from acetone raised the melting point to 121–122° and afforded an analytical sample.

Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.76; H, 11.41.

2-(2-Propenyl)-4-(2-hydroxy-2-propyl)-1-cyclohexene (2).—To 15.1 g of alumina (Woelm neutral, activity I) was added, with thorough mixing, first 1 ml of pyridine and then 49.2 g of 2,4-di(2-hydroxy-2-propyl)-1-cyclohexene, obtained as described above, mp 120–122°. The mixture was stirred for 3 hr at 170° and then cooled and repeatedly extracted with ether. Work-up and subsequent distillation at 0.2 mm yielded 3.24 g, bp 75–81°; 1.43 g, bp 82–83°; 11.79 g (49% based on unrecovered diol), bp 84–85°; and 2.44 g, bp 86–105°; with 13 g undistilled. The third fraction was shown to consist of 98% one component by glpc on column 1 at 190°: ir (film) 2.97, 6.11, 6.21 μ; uv max (EtOH) 234 nm (ϵ 16,400); nmr ($CDCl_3$) δ 5.89 (m, 1), 4.99 (m, 1), 4.85 (m, 1), 1.92 (s, 3), and 1.23 (s, 6). Preparative glpc on column 1 at 160° afforded an analytical sample.

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 79.78; H, 11.33.

Repeated extraction with hot acetone of both the alumina and the magnesium sulfate (used as a drying agent) afforded 19.9 g of a sticky solid which was combined with the distillation residue and crystallized from acetone; a total of 22.6 g (46%) of starting diol was recovered with mp above 115°.

***cis,cis*-1-Hydroxy-6-(2-hydroxy-2-propyl)-4,9-dimethyl-$\Delta^{4(10)}$-octalin** (43).—A solution of 49.6 g (0.250 mol) of 2,4-di-(2-hydroxy-2-propyl)cyclohexene (mp 115–120°) in 250 g of dimethyl sulfoxide (Aldrich) was heated under nitrogen at 130° for 1.5 hr. The resulting light yellow oil was successively cooled in an ice–water bath, poured into 1500 ml of water, and extracted three times with a total of 1000 ml of pentane. The combined pentane extracts were washed five times with water and once with brine. After drying, evaporation yielded 42.6 g (96.7%) of a yellow, viscous oil: nmr (CCl_4) δ 6.38 (broadened d, 0.17, J = 10 Hz), 5.6 and 5.8 (broad, total integration 1.21), 4.93 (broad, 1.00), 4.78 (broad, 1.0), 4.33 (broad, 0.09), and 0.8–2.9 (complex, with spikes at 1.17 and 1.86 ppm, 28.2).

A mixture of 74.6 g of material similarly obtained, 80.6 g (0.510 mol) of ethyl α-acetoxyacrylate,[21] and 1.4 g of 3,5-di-*tert*-butylcatechol (Aldrich) was heated at 110° under nitrogen for 38 hr, at which time the ir spectrum of the reaction mixture showed little further change. Heating of the crude product in a bath at 110° starting at 5 mm and ending at 0.2 mm yielded first 39.9 g of recovered ethyl α-acetoxyacrylate, bp to 76° (5 mm), and then 9.5 g, bp to 90° (1 mm). Undistilled was 111.4 g of a yellow glass showing weak nmr signals at δ 6.45 (broad), 6.28 (broad), 5.5 (very broad) and 4.72 ppm, consistent with the presence of ~11 mol % of isomerized diene and ~4 mol % of dehydrated adduct.

To a stirred mixture of 25.6 g (0.674 mol) of lithium aluminum hydride and 1100 ml of anhydrous ether was added dropwise a solution of the 111.4 g of yellow glass in 880 ml of anhydrous ether. After 6 hr of stirring at room temperature, 5.2 g (0.137 mol) of additional lithium aluminum hydride was added. After a total of 14 hr at room temperature, 100 ml of saturated aqueous magnesium sulfate was added dropwise with stirring, followed by 50 ml of water. After 1 hr 150 g of anhydrous magnesium sulfate was added. The mixture was filtered and the solid was washed with ether. The combined filtrates were dried and evaporated, yielding 34 g of a viscous, yellow oil. The solid salt mixture was then extracted several times with methanol and the methanol extracts were dried and evaporated. The resulting white solid was washed with water and then dried at reduced pressure, affording 35.3 g of triol 22. This was combined with similar material from another run, and the total of 49.6 g was recrystallized from 150 ml of methanol, yielding 22.9 g, mp 162–170°, of a first crop, and 7.2 g, mp 155–167°, of a second crop of white crystals.

To a stirred suspension of 21.4 g (84.3 mmol) of crystalline triol in 300 ml of methanol was added a solution of 20.0 g (93.5 mmol) of sodium metaperiodate in 100 ml of water. The mixture warmed slightly on mixing and a voluminous white precipitate rapidly formed, requiring the addition of another 100 ml of methanol to facilitate stirring. After 1 hr the mixture was poured into 800 ml of brine containing 6.3 g of dissolved sodium thiosulfate. The mixture was extracted with ether and the ether extracts were evaporated. In order to remove residual methanol the residual oil was twice treated with 50-ml portions of benzene and the solvent was removed both times, yielding a yellow oil: ir (film) 2.94, 5.87 (β,γ-unsaturated ketone) with a very small shoulder at 6.0 μ (α,β-unsaturated ketone).

To a mixture of sodium hydride (86 mmol from pentane washing of 3.912 g of sodium hydride dispersion, 50–55% in mineral oil), 20 ml of methyl iodide, and 20 ml of dimethoxyethane, stirred under nitrogen and cooled in an ice–water bath, was added, over 5 min, a solution of 18.73 g of yellow oil, obtained as described above (84 mmol based on 3) in 40 ml of dimethoxyethane. The ice bath was removed and the mixture was allowed to warm to room temperature and then remain for a total of 16 hr. Volatile compounds were then removed by evaporation and the residue

(20) A. S. Lindsey, *J. Chem. Soc.*, 3222 (1958).

(21) The ethyl ester was prepared by the procedure described for the methyl ester by J. Wolinsky, R. Novak, and R. Vasileff, *J. Org. Chem.*, **29**, 3596 (1964).

was dissolved in 20 ml of 80:20 ethanol–water, 2 *N* in potassium hydroxide, and the mixture was stirred at room temperature for 9 hr. Work-up yielded 19.9 g of a brown oil (100% based on monomethylation); glpc on column 2 at 200° showed three sets of components with retention times of <7 min (6%, dehydrated products), 7–14.5 min (75%, β,γ-unsaturated ketones), and 14.5–25 min (19%, α,β-unsaturated ketones). This oil was combined with material similarly obtained and the total, 29.1 g, was chromatographed on 1670 g of silica gel (Grace 60/200 mesh) in a 60 × 7 cm column. The oil was transferred to the column with a total of 100 ml of carbon tetrachloride (50 + 25 + 25 ml), and development and elution were effected in 22 fractions, 1–20 consisting of 1000-ml portions of 2:3 ether–hexane, yielding 21.7 g of recovered material, 21 of 4000 ml of the same solvent, yielding 0.59 g, and 22 of 4000 ml of ether, yielding 4.0 g. The total material recovery was 90%.

Fraction 13 yielded the following data: ir (film) 5.87 (strong) with 6.04 μ (very weak, α,β-unsaturated ketone contaminant); nmr (CCl_4) δ 0.9–2.9 (complex, with spikes at 1.16 and 1.18, and a broadened singlet at 1.71 ppm); glpc on column 2 at 190° one major peak at 8.3 min with a shoulder at 7.5 min (total 96%). Fractions 11–14 (totalling 13.7 g) were analyzed by glpc and were all found to consist of the same "peak plus shoulder" with no marked change in relative amounts of the two components which together accounted for no less than 95% of discernible peaks in all fractions. The major and minor components in fractions 11–14 corresponded to *dl*-1-oxo-γ-eudesmol and *dl*-1-oxo-epi-γ-eudesmol, respectively, in a combined yield of 44%.

From 410 mg of material similar to that of fraction 13 there was obtained 408 mg (93%) of crude oxime, mp 145–152°, which afforded an analytical sample after crystallization from ethanol–water and sublimation; mp 153–155°; nmr ($CDCl_3$) δ 1.68 (s, 3), 1.30 (s, 3), 1.30 (s, 3), and 1.23 (s, 6).

Anal. Calcd for $C_{15}H_{25}NO_2$: C, 71.67; H, 10.02; N, 5.57. Found: C, 71.68; H, 10.14; N, 5.57.

To a mixture of 0.837 g (22.1 mmol) of lithium aluminum hydride and 75 ml of dry dimethoxyethane, stirred under nitrogen with cooling in an ice–brine bath at −20 to −25°, was added dropwise over 45 min a solution of 4.88 g of fraction 13 obtained as described above in 60 ml of dimethoxyethane. The mixture was allowed to come to room temperature over 4 hr. After 14 hr at room temperature 0.231 g (6.08 mmol) of additional lithium aluminum hydride was added. After another 3 hr, work-up (using saturated magnesium sulfate solution) yielded 4.79 g (97.4%) of a gummy white solid which was crystallized from 25 ml of ether at −8°. The resulting white solid was recrystallized from cyclohexane and yielded 1.45 g (29%) of **43** as white plates: mp 124–125°; nmr ($CDCl_3$) δ 3.47 (broadened triplet, 1, J = 7.5 Hz) and 0.8–2.9 (complex, with spikes at 1.01 and 1.21 and broadened singlet at 1.60 ppm, total integration 25).

Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 11.00. Found: C, 75.48; H, 10.84.

Wolff–Kishner Reductions.—To a solution of 15.6 mg (0.656 mmol) of *cis,cis*-1-hydroxy-6-(2-hydroxy-2-propyl)-4,9-dimethyl-$\Delta^{4(10)}$-octalin (**43**), mp 121.5–124°, in 1 ml of acetone was added, *via* syringe, 18 μl of 8 *N* chromium trioxide in aqueous sulfuric acid.[22] The final traces of oxidant yielded a persistent orange color. Work-up yielded 14.6 mg (94%) of a light yellow oil.

A.—The 14.6 mg obtained as described above was mixed in a tube with 0.5 ml of triethylene glycol (Aldrich), 5 μl of acetic acid, and 20 μl of hydrazine hydrate. The mixture was heated under nitrogen at 75° for 21 hr. The tube was then cooled and 27.2 mg of potassium hydroxide was added. The tube was then bent and sealed and one end was immersed in a bath at 200° for 6.5 hr so that distillate collected in the other end. Work-up yielded 8.5 mg (62%) of an oil which, by glpc analysis on column 2 at 140°, consisted solely of *dl*-γ-eudesmol (**41**), retention time 16.8 min.

B.—In the same manner 89.0 mg of chromatography fraction 13, obtained as described above, yielded 65.4 mg (78%) of an oil consisting of 87% *dl*-γ-eudesmol (**41**) and 13% *dl*-epi-γ-eudesmol (**42**) by glpc analysis.[16]

C.—In the same manner 71.0 mg of the total crude reaction product, obtained in the methylation described above, yielded 57.6 mg (86%) of an oil. Glpc analysis of the ratio of *dl*-γ- to *dl*-epi-γ-eudesmol was rendered difficult by broadening and overlapping of peaks caused by the presence of other components, but a rough estimate of 15% *dl*-epi-γ-eudesmol in the mixture was made.

Tosylate of *cis,cis*-1-Hydroxy-6-(2-hydroxy-2-propyl)-4,9-dimethyl-$\Delta^{4,(10)}$-octalin (44).—To a solution of 2.343 g (9.85 mmol) of diol **43** in 5 ml of pyridine, cooled in an ice bath, was added 2.348 g (12.33 mmol) of *p*-toluenesulfonyl chloride. The mixture was warmed momentarily to room temperature to yield a clear solution which was then stored at 5° for 28 hr. Ten drops of water were then added and the mixture was shaken intermittently for 1 hr at room temperature. Work-up yielded 3.14 g (97%) of a white foam which gave 2.76 g (81%), mp 62–68°, from 10 ml of ether at −8°. Material with this melting point was suitable for subsequent reactions; it could be recrystallized from ether and an analytical sample of **44** was thereby obtained: mp 67–70°; nmr (CCl_4) δ 4.35 ppm (broadened t, 1, J = 7.9 Hz).

Anal. Calcd for $C_{22}H_{32}O_4S$: C, 67.31; H, 8.22; S, 8.17. Found: C, 67.22; H, 8.38; S, 8.11.

***dl*-Hedycaryol (5).**—To 5 ml (5 mmol) of a solution of diborane in tetrahydrofuran (Alpha), stirred under nitrogen and cooled in an ice–water bath, was added dropwise over 12 min a solution of 204.8 mg (0.522 mmol) of tosylate **44**, mp 62–68°, in 9 ml of tetrahydrofuran. After 1.5 hr the ice bath was removed, and the solution was allowed to stand at room temperature for 7 hr; 0.24 ml of water was added dropwise and then 10 ml of 5 *N* aqueous sodium hydroxide. The resulting two-phase mixture was heated at 65° for 13 hr, with stirring under nitrogen. Work up (no acid washes) yielded 127.6 mg (theoretical 116.2 mg) of a clear oil: nmr (CCl_4) δ 7–8 (AB, residual tosylate, 1.12), 4.93 (broad, characteristic of hedycaryol, normalized to 2.0), and 0.6–2.9 (complex, with spikes at 1.17, 1.48, and 2.44 ppm, total integration 38.6). The oil was stirred with and then separated from several portions of 20% aqueous silver nitrate solution (total 9 ml). The residual oil was taken up in 5 ml of ether and extracted with 2 ml of silver nitrate solution as the ether was gently evaporated under a stream of nitrogen. This procedure was repeated on the remaining gummy material. The combined aqueous silver nitrate extracts were washed once with ether before 20 ml of concentrated aqueous ammonia was added. The resulting milky suspension was extracted several times with ether and the combined ether extracts, after further work-up, afforded 59.8 mg (51%) of *dl*-hedycaryol: nmr (CCl_4) δ 4.93 (broad, 2) and 0.8–2.6 (complex, with a sharp signal at 1.17, less sharp signals at 1.48 and 1.57, total integration, theoretically 24, 25.7). A weak signal at 0.97 ppm revealed the presence of no more than 4% of *dl*-elemol. In the presence of a pellet of sodium hydroxide, a 47.6-mg sample of similar material obtained from another run was subjected to short-path distillation at 0.2 mm from an oil bath at 90–95°: 33.3 mg of distillate was collected; ir (film) and nmr (CCl_4) spectra matched those of the natural isomer.[19]

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 81.18; H, 11.65.

A solution of 52 mg of *dl*-hedycaryol (distilled) in 1 ml of cyclohexane was heated at 130° for 16 hr in a sealed tube which had been subjected to a pretreatment involving an ammonia rinse. Evaporation of solvent gave a quantitative recovery of material with an ir matching that obtained from an authentic sample of *l*-elemol;[23] nmr (CCl_4) δ 5.79 (A of AMX, 1.00, J_{AM} = 10.1, J_{AX} = 18.0 Hz), 4.5–5.1 (complex, 3.83), and 0.85–2.5 (complex, with sharp signals at 1.70, 1.15, and 0.97 ppm, total integration 21.7); glpc analysis on column 2 at 137° revealed a major component (>95.6%) at 17.9 min with minor components at 15.5 (<0.4%) and 23.0 and 25.5 min (total <4%).

Registry No.—**2**, 32319-37-2; **4** oxime, 32319-38-3; **5**, 32319-39-4; **12**, 32319-40-7; **13**, 32319-41-8; **15**, 32319-42-9; **22**, 32319-43-0; **43**, 32319-44-1; **44**, 32319-45-2.

(22) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2555 (1953).

(23) An ir spectrum of *l*-elemol was generously supplied by Dr. T. G. Halsall, Oxford University.

A Novel Protecting Group for the Synthesis of 7α-D-Pentofuranosylhypoxanthines[1]

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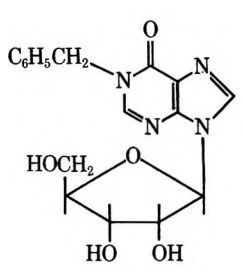
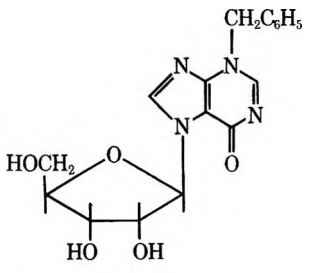
Received June 6, 1971

A new protecting group, the 1-oxy-2-picolyl (OP) group, has been studied and found to be quite stable both to alkaline or acid treatment but readily removable by treatment by acetic anhydride at room temperature. It was found that this protecting group was useful in cases where the benzyl protecting group does not work well. By the use of this protecting group, 3-benzyluracil (XII) and 7-benzylhypoxanthine (XIX) have been prepared which were not obtainable by direct alkylation of their respective parent heterocycles. This OP group has been successfully applied to the synthesis of 7-α-D-arabinofuranosylhypoxanthine (XXIV).

The benzyl group is a useful protecting group for hydroxyl, sulfhydryl, amino, and imino functions.[2] Removal of the benzyl blocking group is usually achieved by catalytic hydrogenation or by sodium and liquid ammonia treatment. However, difficulties have been reported[3] in removing nitrogen-linked benzyl groups from purine nucleoside derivatives. Montgomery, *et al.*,[3c] reported that catalytic debenzylation of 1-benzylinosine (I) and 3-benzyl-7-ribofuranosylhypoxanthine (II) was slow and incomplete resulting in a low yield of the debenzylation product. Anderson and coworkers[4] have also reported that 1-benzyl-3-carbomethoxypyrrole could not be debenzylated even by sodium and liquid ammonia. Obviously, the use of benzyl blocking groups is precluded for compounds containing functional groups vulnerable to hydrogenation, *e.g.*, 5-iodo-2′-deoxyuridine.



I

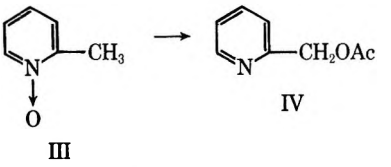


II

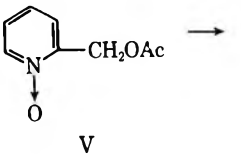
In addition to the benzyl group, a number of protecting groups, *viz.*, propenyl,[5] pivaloyloxymethyl,[6] and cyanoethyl,[7] have been used to block heterocyclic nitrogen and direct the entering group. None of these, however, are stable enough both to acid and base.

There is an urgent need for a blocking group whose removal and stability are compatible with the base lability and vulnerability to reduction of pyrimidine nucleosides and the acid lability of purine nucleosides. Such a protecting group will be especially useful for the synthesis of oligonucleotides containing both purine and pyrimidine nucleosides.

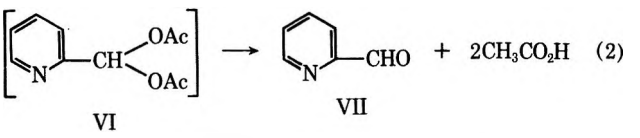
Kobayashi[8] has shown that 2-picoline 1-oxide (III) was converted in acetic anhydride to 2-pyridylmethyl acetate (VI, eq 1). Boekelheide[9] reported a similar type of rearrangement with 2-pyridylmethyl acetate 1-oxide (V, eq 2) which was converted to the aldehyde



III IV (1)



V



VI VII (2)

VII by way of the diacetate VI. Compound V may be viewed as a derivative of acetic acid whose hydroxyl function is protected by the 1-oxy-2-picolyl group, which can be removed by treatment with acetic anhydride and subsequent mild hydrolysis. These qualities suggest that the 1-oxy-2-picolyl (OP) group may be useful as an easily removable blocking group for amino or imino functions. Model studies were carried out therefore with uracil (VIII) and hypoxanthine to prepare 3-benzyluracil (XII)[10] and 7-benzylhypoxanthine (XIX).[14] The benzyl derivatives were not obtainable by the direct alkylation of their respective parent heterocycles.[11]

Alkylation of the tetraethylammonium salt of uracil (VIII) with 1 equiv of 1-oxy-2-picolyl chloride (IX)[17]

(1) Presented in part at the 2nd National Meeting of Heterocyclic Chemistry at Nagasaki, held in November of 1969.

(2) J. F. W. McOmie, "Advances in Organic Chemistry, Methods and Results," Vol. 3, R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience Publishers, New York, N. Y., 1963, p 191.

(3) (a) J. A. Montgomery and H. J. Thomas, *J. Org. Chem.*, **28**, 2304 (1963); (b) *J. Amer. Chem. Soc.*, **87**, 5442 (1965); (c) *J. Org. Chem.*, **31**, 1413 (1966); (d) M. Rasmussen and N. J. Leonard, *J. Amer. Chem. Soc.*, **84**, 5439 (1967).

(4) H. J. Anderson and S. J. Grifinths, *Can. J. Chem.*, **45**, 2227 (1967).

(5) J. A. Montgomery and H. J. Thomas, *J. Org. Chem.*, **30**, 3235 (1965).

(6) M. Rasmussen and N. J. Leonard, *J. Amer. Chem. Soc.*, **89**, 5439 (1967).

(7) E. P. Lira, *J. Heterocycl. Chem.*, **5**, 863 (1968).

(8) G. Kobayashi and S. Furukawa, *Chem. Pharm. Bull.*, **1**, 454 (1953).

(9) V. Boekelheide and W. J. Linn, *J. Amer. Chem. Soc.*, **76**, 1286 (1954).

(10) Alkylation of uracil may afford mainly 1-substituted uracil. Benzylation is no exception.[11] With excess alkylating agent, 1 substitution may be accompanied by formation of 1,3-disubstituted uracil.[12] Although relative amounts of 1- and 1,3-disubstituted uracil formed may depend on the reaction conditions, in any conditions appreciable amount of 3-substituted uracil was not formed on direct alkylation.[12] 3-Benzyluracil has been prepared by an indirect method.[13]

(11) (a) B. R. Baker and G. B. Chleda, *J. Pharm. Sci.*, **54**, 25 (1965); (b) B. R. Baker and T. J. Schwan, *J. Med. Chem.*, **9**, 73 (1966).

(12) A. R. Martinez and W. W. Lee, *J. Org. Chem.*, **30**, 317 (1965).

(13) J. B. Johnson and J. H. Derby, *Amer. Chem. J.*, **40**, 444 (1909).

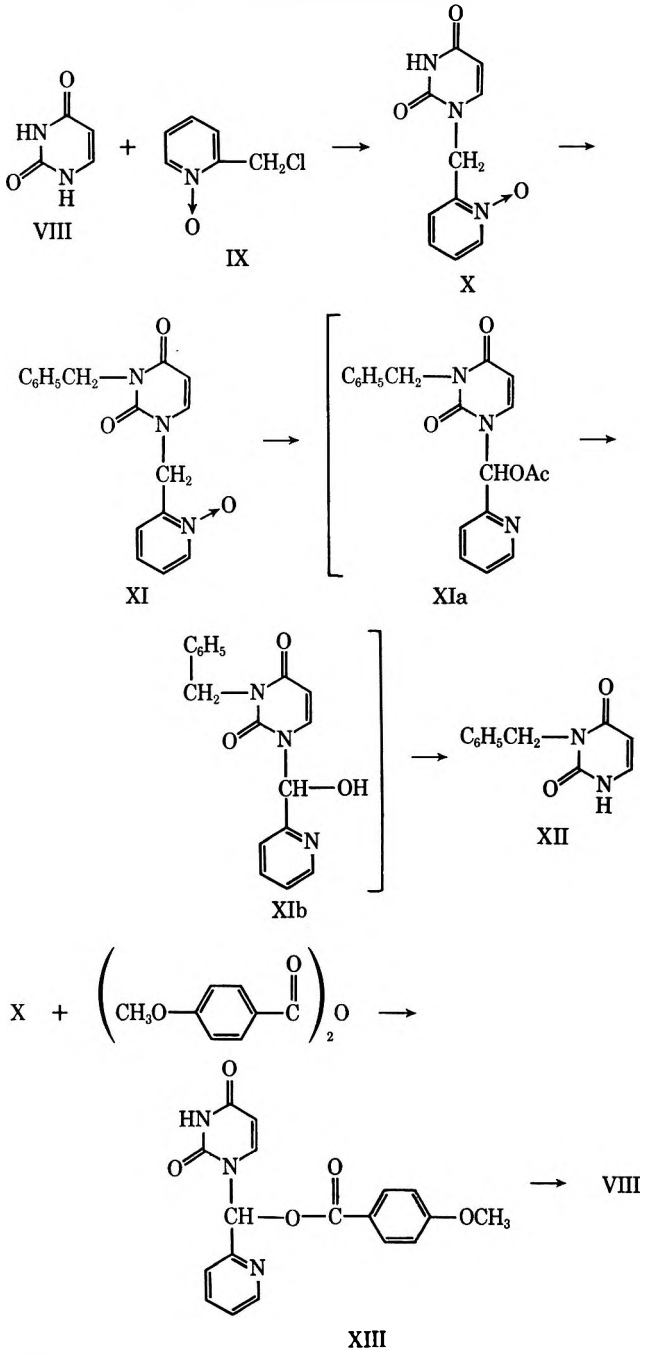
(14) (a) R. K. Robins in "Heterocyclic Compounds," Vol. 8, R. C. Elderfield, Ed., Wiley, New York, N. Y., 1967, p 372. (b) 7-Benzylhypoxanthine has been prepared by two independent (indirect) methods.[15,16]

(15) J. A. Montgomery and K. Hewson, *J. Org. Chem.*, **26**, 4469 (1961).

(16) J. A. Montgomery and C. Temple, Jr., *J. Amer. Chem. Soc.*, **83**, 630 (1961).

(17) P. T. Sullivan, M. Kester, and S. J. Norton, *J. Med. Chem.*, **11**, 1171 (1968).

in DMF afforded a 69% yield of 1-(1-oxy-2-picolyl)-uracil (X). Alkylation of the sodium salt of X with benzyl chloride gave the 1,3-disubstituted uracil XI in fair yield. The structure of X and XI was based upon elemental analysis and spectral properties. The condi-



tions required for complete rearrangement of XI in acetic or anisic anhydride are listed in Table I. As shown, XI was completely rearranged in acetic anhydride under mild conditions (36°, 44 hr) to the corresponding acetate XIa, which in turn was easily hydrolyzed to 3-benzyluracil (XXII) in mild alkaline solution. When X was treated with anisic anhydride, the rearranged product XIII was isolated and characterized. The latter, as expected, was converted into uracil by mild alkaline treatment.

Alkylation of adenine with 1-oxy-2-picolyl chloride (IX)[17] afforded a 40% yield of 3-(1-oxy-2-picolyl)adenine (XV) along with 20–25% of the 9-substituted isomer.[14] Deamination of XV with nitrosyl chloride gave

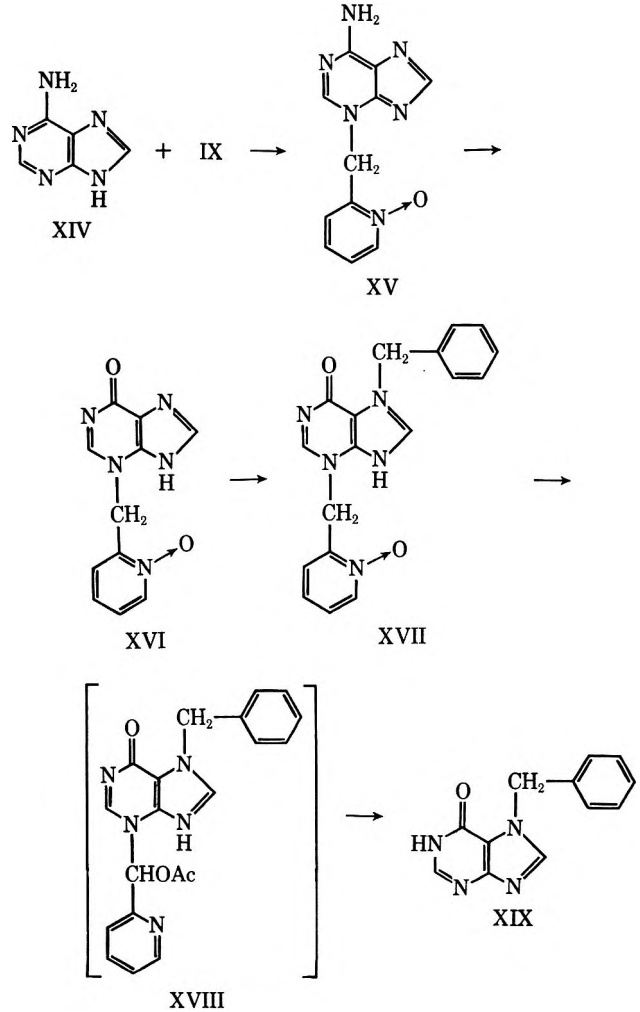
TABLE I

CONDITIONS REQUIRED FOR COMPLETE REARRANGEMENT OF 3-BENZYL-1(1-OXY-2-PICOLYL)URACIL (XI) WITH ANHYDRIDES

Anhydrides[a]	Temp, °C	Time[b]
$(p\text{-}CH_3OC_6H_4CO)_2O$	99 (fusion)	5 min
$(CH_3CO)_2O$	140 (reflux)	5 min
$(CH_3CO)_2O$	60	6.5 hr
$(CH_3CO)_2O$	36	44.0 hr

[a] Uracil derivative (XI) and anhydride employed were 2 and 8.4 mmol, respectively. [b] Time required for disappearance of the starting material on tlc (silica gel, solvent system $CHCl_3$–EtOH 35:5).

an almost quantitative yield of the hypoxanthine derivative XVI. Alkylation of the latter with benzyl chloride gave the 3,7-disubstituted derivative XVII. Treatment of XVII with acetic anhydride at room temperature for 13 hr afforded the rearranged intermediate XVIII, which was not isolated but was treated with aqueous acetic acid to give 7-benzylhypoxanthine (XIX) in 76% yield.

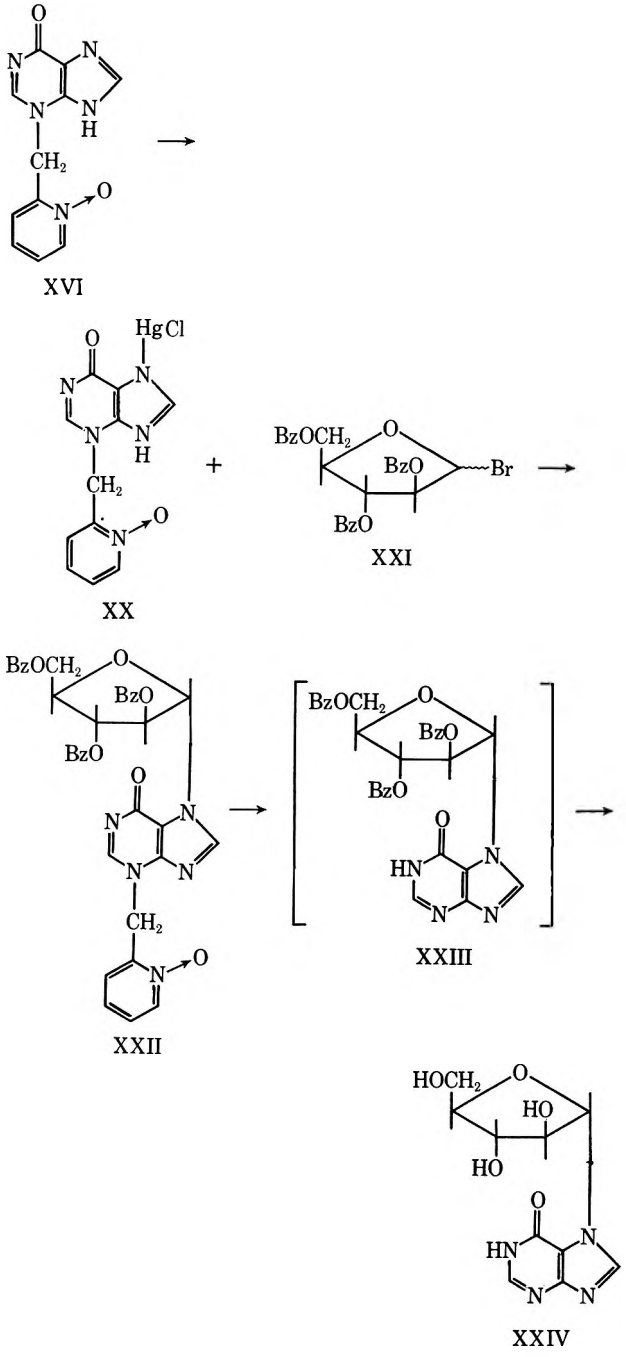


Synthesis of 7-α-D-arabinofuranosylhypoxanthine (XXIV), a nucleoside closely related to 7-α-D-ribofuranosyladenine (XXV) (a degradation product of pseudovitamin B_{12}),[18] has been recently achieved.[3c] This method, however, could not conveniently provide the large quantities of XXIV needed for our future project:

(18) J. A. Montgomery and H. J. Thomas, *J. Amer. Chem. Soc.*, **85**, 2672 (1963).

a conversion of XXIV into XXV by way of the corresponding 2′,6-anhydro derivative.

In view of the successful synthesis of XIX using the OP protecting group, we tried the method in the synthesis of XXIV.



The chloromercuri derivative XX of XVI was prepared and treated with with 2,3,5-tri-*O*-benzoyl-D-arabinofuranosyl bromide (XXI) to give 3-(1-oxy-2-picolyl)-7-(2,3,5-tri-*O*-benzoyl-D-arabinofuranosyl)hypoxanthine (XXII) in 70% yield. After purification by preparative tlc, the blocked nucleoside was treated with acetic anhydride at room temperature for 40 hr to afford the tribenzoate XXIII, which was dissolved in methanolic sodium methoxide to give a 50% overall yield (based on XX) of crystalline 7-α-D-arabinofuranosylhypoxanthine (XXIV) which showed properties (melting point, mixture melting point, uv, nmr, and tlc) identical with those of an authentic sample prepared according to Thomas and Montgomery.[3c]

Experimental Section

General.—The infrared spectra were determined using Nihonbunko 137B spectrophotometer. Ultraviolet spectra were determined using a Hitachi YM 11-26 spectrophotometer, and nuclear magnetic resonance spectra were determined with a Varian Model A-60 spectrometer in deuteriochloroform. The chemical shifts are reported in parts per million downfield from tetramethylsilane as an internal standard. Paper chromatography was carried out by ascending technique. Unless otherwise stated, solvents were removed in a rotary evaporator by a water aspirator (*ca.* 12 mm).

1-(1-Oxy-2-picolyl)uracil (X).—Uracil (VIII, 2.91 g, 26 mmol) was dissolved in 300 ml of water containing tetraethylammonium hydroxide prepared from 5.5 g (26 mmol) of tetraethylammonium bromide by passing the salt through a column (Dowex-1, OH^- form). The solution was concentrated to dryness and the residue was dried completely *in vacuo*. To a solution of the tetraethylammonium salt of VIII in 100 ml of DMF was added with stirring 1-oxy-2-picolyl chloride[17] (IX, 3.71 g, 26 mmol) dissolved in 50 ml of DMF. Stirring was continued overnight at room temperature. The solution was concentrated to dryness and crystallized from 80% aqueous ethanol to give 3.91 g (69%) of X: mp 242° dec; R_f in BuOH–H_2O (84:16) 0.54; uv $\lambda_{max}^{pH\ 2}$ 260, $\lambda_{max}^{pH\ 11}$ 257, $\lambda_{min}^{pH\ 2}$ 230, $\lambda_{min}^{pH\ 11}$ 237 mμ. The uv spectral behavior was characteristic for a 1-substituted uracil.

Anal. Calcd for $C_{10}H_9N_3O_3$: C, 54.80; H, 4.11; N, 19.18. Found: C, 54.84; H, 4.16; N, 19.23.

3-Benzyl(1-oxy-2-picolyl)uracil (XI).—1-(1-Oxy-2-picolyl)-uracil (X) (1.4 g, 6.4 mmol) was dissolved in 30 ml of absolute methanol containing 0.32 mg (14 mg-atoms) of sodium metal. To the solution was added 1.77 g of benzyl chloride dissolved in 30 ml of absolute methanol. The solution was heated with stirring at 55–60° for 10 hr. The solution was filtered and the filtrate was concentrated to dryness. The residue was triturated with *n*-hexane to remove benzyl chloride and collected by filtration. Crystallization from ethanol afforded an analytical sample: mp 141°; yield 711 mg (36%); uv $\lambda_{max}^{pH\ 2}$ 260, $\lambda_{min}^{pH\ 2}$ 233, $\lambda_{max}^{pH\ 11}$ 236 mμ; R_f in BuOH–H_2O (84:16).

Anal. Calcd for $C_{17}H_{15}N_3O_3$: C, 66.00; H, 4.89; N, 13.57. Found: C, 65.63; H, 4.83; N, 13.62.

3-Benzyluracil.—3-Benzyl-1-(1-oxy-2-picolyl)uracil (XI) (200 mg) was dissolved in acetic anhydride (3 ml). The solution was heated under reflux for *ca.* 5 min and, after cooling, the solvent was removed *in vacuo*. The residue was dissolved in 5 ml of methanol containing 16 mg of sodium and the solution was kept overnight at room temperature. The solution was neutralized with a resin IRC (H^+) and filtered. The filtrate was concentrated to dryness and the residue was crystallized from water, yield 52 mg (40%), mp 175–176°. A mixture melting point with 1-benzyluracil[19] was depressed about 10°.

An experiment on the same scale was carried out at room temperature for 40 hr. The ir spectrum of the residue obtained by removal of excess acetic anhydride showed the presence of acetyl group (1770 cm^{-1}) and the absence of the absorption due to *N*-oxide: nmr δ 2.17 (s, 3, $COCH_3$), 3.44 (s, 1, NCHO).

The residue was dissolved in water and the water was removed *in vacuo*. During this process hydrolysis of XIa took place to give 3-benzyluracil (XII),[13] which was crystallized from water, 100 mg (80%), mp 175–176°.

Isolation of the Rearranged Product XIII.—A mixture of 438 mg (2 mmol) of 1-(1-oxy-2-picolyl)uracil (X) and 2.4 g of anisic anhydride was heated at 100° for 5 min. After cooling, the mixture was dissolved in chloroform. The product was isolated over a silica gel column (eluting system $CHCl_3$–EtOH 38:2). The eluate containing XIII was collected and concentrated *in vacuo* to dryness. Crystallization from ethanol afforded an analytical sample (236 mg, 33%): R_f in water (adjusted to pH 10) 0.62; ir 1730 cm^{-1} (CO of *p*-methoxybenzoate); mp 173–174°.

Anal. Calcd for $C_{18}H_{15}N_3O_4$: C, 61.19; H, 4.25; N, 11.90. Found: C, 61.16; H, 4.47; N, 11.86.

Preparation of Uracil from XIII.—Compound XIII (100 mg) was dissolved in 5 ml of 2.0 *N* methanolic sodium methoxide. The solution was kept at room temperature overnight and then neutralized with a resin (IRC, H^+ form). The solution was filtered and the filtrate was concentrated to dryness. The residue was crystallized from water to give uracil in quantitative yield. Structural confirmation rests upon uv spectral properties.

(19) H. J. Wheeler and J. B. Johnson, *Amer. Chem. J.*, **42**, 30 (1909).

3-(1-Oxy-2-picolyl)adenine Hydrochloride.—To a solution of 9.5 g of adenine (XIV) in 520 ml of dimethylacetamide (DMA) was added 9.5 g of 2-picolyl chloride 1-oxide (IX). The solution was kept at 65° for 2 days and then at 75° for 2 days. The solution was concentrated to dryness and the residue was triturated with 70 ml of water. A solid deposited which was collected by filtration and recrystallized from aqueous ethanol to afford an analytical sample: yield 40%; mp 245–246°; uv $\lambda_{max}^{pH\ 1}$ 263, 275 mμ (sh).

Anal. Calcd for $C_{11}H_{10}N_6O \cdot HCl$: C, 47.23; H, 3.96; N, 30.05; Cl, 12.76. Found: C, 47.34; H, 3.95; N, 29.91; Cl, 12.57.

3-(1-Oxy-2-picolyl)adenine (XV).—The above hydrochloride (3.7 g) was dissolved in 250 ml of water. The solution was adjusted to pH 8 with ammonia upon which a solid deposited which was collected by filtration and recrystallized from aqueous ethanol: yield 3.0 g (95%); mp 285–288°; uv $\lambda_{max}^{pH\ 2}$ 276, $\lambda_{max}^{pH\ 12}$ 262 mμ.

Anal. Calcd for $C_{11}H_{10}N_6O$: C, 54.54; H, 4.16; N, 34.70. Found: C, 54.62; H, 4.00; N, 34.73.

3-(1-Oxy-2-picolyl)hypoxanthine (XVI).—To a suspension of 1 g of XV in 20 ml of DMF was added with stirring 1 ml of nitrosyl chloride[20] at −5 to −10°. After 30 min, another 1 ml of nitrosyl chloride was added at the same temperature. The solid dissolved gradually with evolution of nitrogen. After 1 hr, complete solution resulted. The reaction mixture was then kept at room temperature. During this time a solid deposited which was collected by filtration. The filtrate was concentrated to deposit a further crop. The combined crops were washed with a small volume of cold ethanol and dried: yield 1.04 g (97%); R_f in BuOH–H_2O (84:14) 0.11; uv $\lambda_{max}^{pH\ 1}$ 256, $\lambda_{max}^{pH\ 12}$ 259 mμ.

To a suspension of 1.79 g (6.4 mmol) of the hydrochloride of XVI in 25 ml of methanol was added 6.4 ml of 1 *N* methanolic sodium methoxide at 0°. A solid deposited and was collected by filtration. Crystallization from aqueous ethanol afforded an analytical sample: yield 1.02 g (66%); mp 271–273°; uv $\lambda_{max}^{H_2O}$ 258, $\lambda_{max}^{pH\ 2}$ 256, $\lambda_{max}^{pH\ 12}$ 259 mμ.

Anal. Calcd for $C_{11}H_9N_5O_2$: C, 54.32; H, 3.73; N, 28.80. Found: C, 54.30; H, 3.371; N, 28.60.

3-(1-Oxy-2-picolyl)-7-benzylhypoxanthine (XVII).—3-(1-Oxy-2-picolyl)hypoxanthine hydrochloride (364.8 mg, 1.5 mmol) was treated with 379.5 mg (3 mmol) of benzyl chloride in 6 ml of dimethylacetamide in the presence of 414 mg (3 mmol) of potassium carbonate. The mixture was kept at 85° for 21 hr. After completion of the reaction (R_f value of product in BuOH–H_2O 86:14, 0.60), inorganic material was removed by filtration. The filtrate was concentrated to dryness *in vacuo* and the residue was triturated with ether and then crystallized from a mixture of ethanol and acetone. Prism-like crystals were obtained: yield 262 mg (52.4%); mp 215°; uv λ_{max}^{EtOH} 266, $\lambda_{max}^{pH\ 2}$ 261, $\lambda_{max}^{pH\ 11}$ 259 mμ.

Anal. Calcd for $C_{18}H_{15}N_5O_2$: C, 64.85; H, 4.54; N, 21.01. Found: C, 65.13; H, 4.46; N, 20.83.

7-Benzylhypoxanthine (XIX).—3-(1-Oxy-2-picolyl)-7-benzylhypoxanthine (100 mg) was dissolved in 7 ml of acetic anhydride. The solution was kept at 23° (room temperature) with stirring for 13 hr. The solvent was removed at 45° (bath temperature) *in vacuo* to afford crude product, which was crystallized from aqueous ethanol: 52 mg (76.7%); mp 277–279°; uv $\lambda_{max}^{pH\ 2}$ 255, $\lambda_{max}^{pH\ 11}$ 265, λ_{max}^{EtOH} 258 mμ.

Anal. Calcd for $C_{12}H_{10}N_4O$: C, 63.70; H, 4.46; N, 24.77. Found: C, 63.57; H, 4.21; N, 24.91.

Chloromercuri-3-(1-oxy-2-picolyl)hypoxanthine (XX).—To a suspension of 572 mg (2.35 mmol) of 3-(1-oxy-2-picolyl)hypoxanthine (XVI) in 60 ml of water was added 2.35 ml of 1 *N* sodium hydroxide solution. To the solution was added with stirring a solution of 638 mg (2.35 mmol) of mercuric chloride in 40 ml of water to give a precipitate which was collected by filtration, washed successively with water, ethanol, and ether, and dried, yield 904 mg (85%).

3-(1-Oxy-2-picolyl)-7-(2,3,5-tri-*O*-benzoyl-α-D-arabinofuranosylhypoxanthine (XXII).—A mixture of 884 mg of chloromercuri-3-(1-oxy-2-picolyl)hypoxanthine and 884 mg of Celite in 70 ml of dry xylene was azeotropically dried by distilling 30 ml of the solvent. To the mixture was added with stirring at reflux temperature a solution of 960 mg of 2,3,5-tri-*O*-benzoyl-D-arabinosyl bromide (XXI)[21] in 13 ml of dry xylene. Stirring was continued for 70 min. After cooling the gray mixture was filtered and the insoluble material was washed with three 15-ml portions of chloroform. Xylene was removed *in vacuo* to leave a gummy residue which was dissolved in chloroform (20 ml). The chloroform solution was then washed with 80 ml of 30% potassium iodide, then with water, and dried (sodium sulfate). After filtration, the filtrated was concentrated to dryness *in vacuo* and the residue was washed with 20 ml of ether to remove sugar, crude yield 773 mg.

7-α-D-Arabinofuranosylhypoxanthine (XXIV).—Compound XXII (200 mg) was dissolved in 10 ml of acetic anhydride. The solution was kept at room temperature for 18 hr, after which the solvent was removed at 40° *in vacuo*. The residue was purified by tlc (silica gel, 30 g), yield 120 mg (72%). 7-(2,3-5-Tri-*O*-benzoyl-α-D-arabinosyl)hypoxanthine (XXII) was dissolved in 4 ml of methanol containing 0.1 ml of 1 *N* methanolic sodium methoxide solution. The solution was heated for 30 min and then treated with 10 ml of water and neutralized with a resin, Dowex 50W (H^+ form). The resin was filtered and washed with aqueous methanol. The combined washings and filtrate were concentrated to dryness *in vacuo*. The residue was dissolved in 13 ml of water. The aqueous solution was extracted with equal volume of chloroform and the aqueous layer was concentrated to dryness. The residue was crystallized from water, mp 173–175°, and a mixture melting point with an authentic sample showed no depression, $[\alpha]^{22}D$ 28° (c 0.34, H_2O). Literature[3c] R_f values in three different systems were identical with those of an authentic sample.

	R_f	
Solvent system	XXIV	Authentic sample
n-BuOH–H_2O (86:14)	0.10	0.10
n-PrOH–H_2O (3:1)	0.20	0.21
H_2O (pH 10 with NH_4OH)	0.77	0.77

Registry No.—X, 32298-59-2; XI, 32298-60-5; XII, 28734-85-2; XIII, 32298-62-7; XV, 32298-63-8; XV HCl, 32298-64-9; XVI, 32298-65-0; XVII, 32298-66-1; XIX, 6991-06-6; XXIV, 10280-02-1.

Acknowledgments.—The authors are very grateful to Dr. Jack J. Fox of the Sloan Kettering Institute for his help in the preparation of our manuscript. Thanks are also due to Miss A. Maeda and Miss H. Kakizaki for elemental analyses.

(20) H. Siegel and H. Brintzinger, *Helv. Chim. Acta*, **48**, 433 (1965).

(21) R. K. Ness and H. G. Fletcher, *J. Amer. Chem. Soc.*, **80**, 2008 (1958).

Model Studies of the Synthesis of Echitamine and Related Indole Alkaloids[1]

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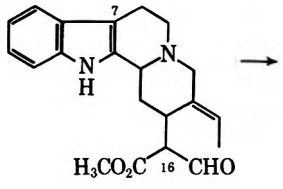
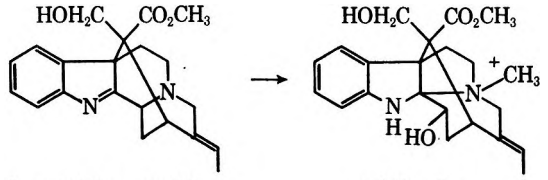
Received June 30, 1971

Cyclizations of 3-(1,2,3,4-tetrahydrocarbazol-1-yl)prop-1-yl tosylate (1) and its *N*-methyl derivative 2 have been examined as model reactions for the synthesis of indole alkaloids bearing a C-16 to C-7 bond. The action of potassium *tert*-butoxide or ethylmagnesium bromide cyclizes tosylate 1 to 6*H*-1,2,3,3a,4,5-hexahydropyrido[3,2,1-*jk*]carbazole (12) resulting from nucleophilic displacement by nitrogen. Formolysis of the *N*-methyl tosylate 2 gives the unstable 7*H*-2,3,3a,4,5-hexahydrocylopenta[*d*]carbazole as the major product. Deuterium-labeling studies show that this reaction proceeds to the extent of about 70% by electrophilic attack at the β position of the indole ring. Formolysis of 2 thus proceeds *via* an intermediate which has four of the five rings common to the skeleton of deacetylakuammiline and related indole alkaloids bearing a C-7 to C-16 bond.

The echitamine structure[2] provided the first example of a group of indole alkaloids bearing a C-16–C-7 bond. A number of these alkaloids are now known[3] and their synthesis has proved to be a very difficult task. These compounds are almost certainly derived in nature by cyclization of a corynantheine derivative.[4]



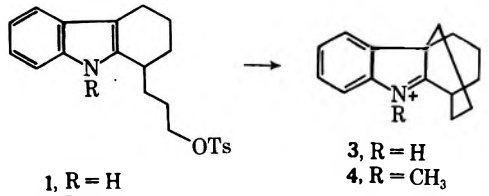
geissoschizine



deacetylakuammiline echitamine

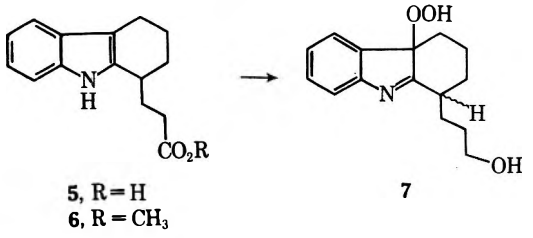
The great susceptibility of indoles to electrophilic attack at the β position suggests a carbonium ion reaction for the formation of another bond at the β position of a 2,3-disubstituted indole. However, a carbonium ion reaction would be an impossible model for the biosynthetic formation of the C-7 to C-16 linkage owing to the difficulty of generating a positive charge on C-16, which is attached to two carbonyl groups. Nevertheless, a carbonium ion reaction might be adapted to the *in vitro* synthesis of this group of compounds.

To test this possibility, we have examined the cyclization of the two tetrahydrocarbazole tosylates 1 and 2 which could lead to tetracyclic materials containing four of the five rings making up the skeleton of deacetylakuammiline-related indole alkaloids.



1, R = H
2, R = CH_3 3, R = H
4, R = CH_3

The synthesis of the alcohol from which tosylate 1 was prepared was attended by some unexpected difficulties. The obvious approach involves reduction of the well-known 3-(1,2,3,4-tetrahydrocarbazol-1-yl)propionic acid[5] (5) or its methyl ester 6. Lithium aluminum hydride reduction of the acid 5 afforded a mixture from which the hydroperoxyindolenine 7 was obtained. Since this reduction did not appear to be a very clean reaction in any case, some other reductions were examined.

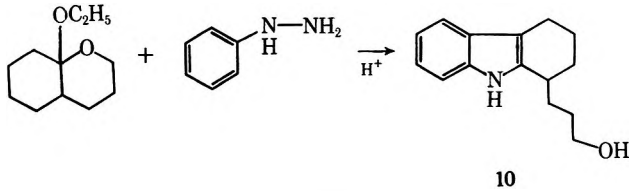


5, R = H
6, R = CH_3 7

Lithium aluminum hydride reduction of the ester 6 gave the cyclic carbinol amine 8 in reasonable yield, whereas reduction of the acid 5 with diborane resulted in cyclization and reduction of the indole double bond to give the known 6*H*-1,2,3,3a,4,5,11b,11c-octahydropyrido[3,2,1-*jk*]carbazole[5] (9) in good yield.

8 9

A thorough study of the reduction of 5 and 6 was not attempted, since another synthetic route appeared quite attractive. The synthesis of the desired 3-(1,2,3,4-tetrahydrocarbazol-1-yl)propan-1-ol (10) was achieved employing 9-ethoxy-1-oxadecalin[6] in a Fischer indole synthesis.



10

(1) The authors gratefully acknowledge financial support from the National Institutes of Health (Grant HE 90521) and a Public Health Service Career Program Award (1-K3-NB-28,105) from the National Institute of Neurological Disease and Blindness.

(2) J. A. Hamilton, T. A. Hamor, J. M. Robertson, and G. A. Sim, *J. Chem. Soc.*, 5061 (1962).

(3) J. E. Saxton, "The Alkaloids," R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1968, p 501.

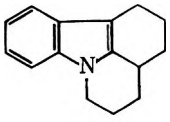
(4) A. I. Scott, *Accounts Chem. Res.*, **3**, 151 (1970).

(5) H. T. Openshaw and R. Robinson, *J. Chem. Soc.*, 941 (1937).

(6) H. Obara, *Nippon Kagaku Zasshi*, **82**, 60 (1961).

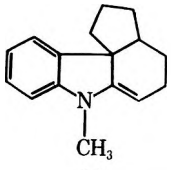
The synthesis of the analogous *N*-methyl compound, 3-(1,2,3,4-tetrahydro-9-methylcarbazol-1-yl)propan-1-ol (**11**), was completed by a lithium aluminum hydride reduction of the corresponding ester. Lithium aluminum hydride reduction proceeded smoothly and the *N*-methyl group obviated the difficulties encountered in the reduction of **5** and **6**. Carbinol **10** and its *N*-methyl derivative were obtained as oils but the corresponding tosylates, obtained by the action of pyridine and *p*-toluenesulfonyl chloride, were nicely crystalline.

Treatment of tosylate **1** with potassium *tert*-butoxide in *tert*-butyl alcohol gave a quantitative yield of the known tetracyclic indole derivative **12** identified from its spectroscopic properties and melting point.[5] The action of ethylmagnesium bromide on **1** afforded the same product **12** in 90% yield.



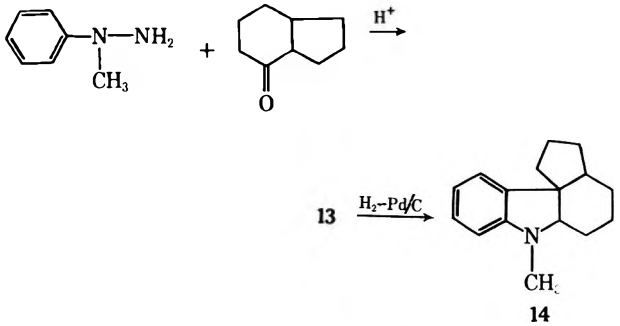
12

Since these reactions showed no sign of reaction at the β position of the indole ring, we turned our attention to the *N*-methyl tosylate **2**. Solvolysis of **2** in formic acid affords as a major product, in up to 65% yield, an unstable base whose ultraviolet spectrum indicates that it is an alkylidene indoline. The pmr spectrum which shows a triplet at δ 4.75 ascribed to a vinyl proton indicates that the material is not related to structure **4** in any event. The spectroscopic evidence and mechanistic considerations lead to structure **13** for the alkylidene indoline.



13

The material was characterized after catalytically reducing the enamine double bond to give the dihydro compound **14**. The structure was secured by independent synthesis involving a Fischer indole condensation employing perhydro-4-indanone and α-methylphenylhydrazine.

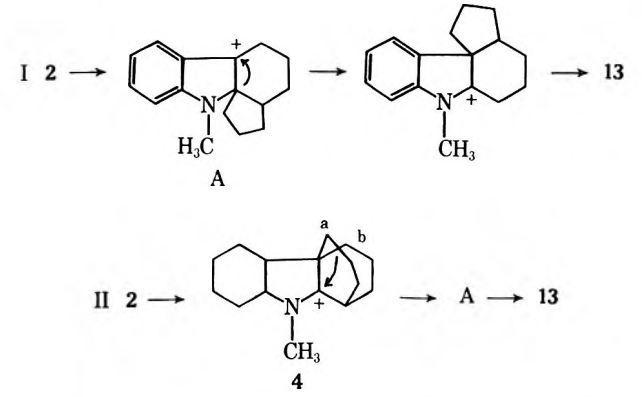


14

The material obtained from the Fischer indole synthesis and reduction was identical with the reduced solvolysis product.

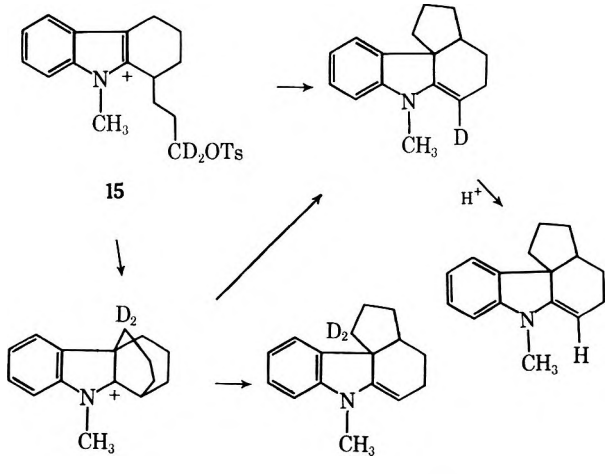
The results of the solvolysis of **2** pose an important mechanistic question. The simplest possible analysis indicates two pathways for the formation of **13** (Scheme I).

SCHEME I



Pathway I, involving initial bond formation at the α position of the indole ring, leads to **13** with only one rearrangement. Pathway II requires two rearrangements after initial bond formation at the β position. Deuterium labeling can be applied to make a straightforward distinction between the two pathways. Considering the possibilities using tosylate **2** labeled with deuterium at the carbinol carbon atom, pathway I would surely result in the loss of at least one deuterium and possibly show loss of both deuteriums by a subsequent exchange.

However, pathway II would involve the formation of **4** as an intermediate, redrawn above to emphasize its symmetry. In fact, carbons a and b are equivalent in structure **4** and assuming equal probability for migration, **13** would be formed as an equimolar mixture of doubly and singly deuterated species which would lead to undeuterated material by exchange. If pathway II was the only mechanism operative, then the product should contain 50% of doubly deuterated material with the remaining material consisting of singly deuterated and undeuterated material.



Solvolysis of the deuterated tosylate did give a mixture of doubly and singly deuterated material along with undeuterated material. For the purposes of the analysis, it was assumed that the deuterated tosylate **15** contained exactly two deuteriums. The material was not conveniently analyzed by mass spectrometry, but the pmr spectrum showed no signal for carbinol protons. Two solvolysis experiments were carried out. In one experiment the crude solvolysis product

was hydrogenated and separated by preparative tlc to give labeled **14**. To guard against any peculiar deuterium exchange associated with catalytic reduction, the crude solvolysis product from the second experiment was reduced with sodium borohydride and then separated as before. The reduced solvolysis products were analyzed by mass spectrometry. Labeled **14** from the first experiment showed 55% undeuterated material, 8% monodeuterated species, and 37% of dideuterated material. The second experiment gave material which was 51% undeuterated, 15% monodeuterated, and 34% dideuterated. The fact that different amounts of undeuterated and monodeuterated material were obtained in the two experiments is not surprising, since the undeuterated material is formed by an exchange reaction and the extent of deuterium loss would be affected by a number of variables. Importantly, the fraction of dideuterated material was very nearly the same in both experiments.

Within the simplified mechanistic scheme, the labeling results indicate that about 70% of the reaction leads to **13** through the symmetrical indolenine intermediate **4**. It may be that more of the reaction proceeds by initial attack at the β position to give an unsymmetrical intermediate related to **4**. However, the simplest explanation is that the remainder of the reaction takes place by initial attack at the α position of the indole ring. That the predominant course of the reaction involves electrophilic attack at the β position of the indole ring is completely consistent with the studies of Jackson and his colleagues on electrophilic substitution of substituted indoles.[7] The results indicate that a carbonium ion reaction may be applied to assembling indole alkaloids bearing a C-16–C-7 bond. Further studies in this direction are in progress.

Experimental Section[8]

3-(1,2,3,4-Tetrahydro-4a-hydroperoxycarbazolinin-1-yl)propan-1-ol.—To a suspension of lithium aluminum hydride (12.16 g, 0.32 mol) in dry tetrahydrofuran (500 ml) was added 38.8 g (0.16 mol) of 3-(1,2,3,4-tetrahydrocarbazol-1-yl)propionic acid, prepared as previously described.[6] The mixture was heated under reflux for 3 hr, after which the cooled reaction mixture was treated with water and sodium hydroxide.[9] The alumina was separated and the solvent was evaporated to yield a brownish oil (36 g). The oil was chromatographed on silica gel (500 g). Elution with 50% benzene–chloroform (1000 ml) afforded 21.6 g of material which deposited 3.5 g of crystalline material from benzene solution. Recrystallization from ethyl acetate gave pure hydroperoxyindolenine **7**: mp 134.5–135°; ir ν_{max}^{KBr} 1580 cm^{-1}; pmr (CD_3SOCD_3) δ 0.80–3.70 (complex multiplets, 13 H); 4.10–4.60 (complex multiplet, 1 H), 6.80–7.20 (complex multiplets, 4 H), 11.6 (s, 1 H); uv λ_{max} 255 nm (ϵ 5070); $\lambda_{max}^{EtOH-HCl}$ 284 nm (ϵ 7160); mass spectrum intense peak at m/e 245 (M − O·).

Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 68.98; H, 7.02; N, 5.28.

6*H*-1,2,3,3a,4,5-Hexahydropyrido[3,2,1-*jk*]carbazol-6-ol (8).—A mixture of methyl 3-(1,2,3,4-tetrahydrocarbazol-1-yl)propionate (3.00 g, 0.012 mol) prepared by Fischer–Spier esterification of the acid, lithium aluminum hydride (1.9 g, 0.05 mol), and dry ether (50 ml) was heated under reflux for 10 hr. The usual work-up afforded 2.6 g of pale yellow oil which was recrystallized from benzene–petroleum ether (bp 30–60°) to give the pure tetracyclic alcohol **8** (1.5 g, 56%): mp 134–136°; ir $\nu_{max}^{CHCl_3}$ 3500, 1600 cm^{-1}; pmr ($CDCl_3$) δ 0.8–3.0 (complex multiplets, 12 H), 5.0–5.6 (m, 1 H), 7.0–7.7 (m, 4 H); uv λ_{max} 222 nm (ϵ 29,035), 235 (18,300), 283 (8610); mass spectrum molecular ion at m/e 227.

Anal. Calcd for $C_{15}H_{17}NO$: C, 79.26; H, 7.54; N, 6.16. Found: C, 79.54; H, 7.42; N, 6.25.

6*H*-1,2,3,3a,4,5,11b,11c-Octahydropyrido[3,2,1-*jk*]carbazole (9).—A solution of 3-(1,2,3,4-tetrahydrocarbazol-1-yl)propionic acid (2.43 g, 0.01 mol) and diborane (0.83 g, 0.03 mol) in dry tetrahydrofuran (100 ml) was stirred at room temperature overnight. The reaction mixture was hydrolyzed with methanolic hydrochloric acid and processed to give the title compound (1.28 g, 59%); mp 75–77° after crystallization from petroleum ether (lit.[5] mp 81–82°); uv λ_{max} 255 nm (ϵ 10,550), 296 (2700); mass spectrum molecular ion at m/e 213.

Anal. Calcd for $C_{15}H_{19}N$: C, 84.46; H, 8.98; N, 6.57. Found: C, 84.69; H, 8.98; N, 6.60.

3-(1,2,3,4-Tetrahydrocarbazol-1-yl)propan-1-ol.—A solution of 9-ethoxy-1-oxadecalin (11.2 g, 0.065 mol), prepared by the procedure of Obara,[6] and phenylhydrazine (7.0 g, 0.065 mol) was heated at 100–120° for 2 hr. The reaction mixture was treated with 20% sulfuric acid (250 ml) and heated slowly to 80° and then at 100° for 10 min. The reaction mixture was diluted with water and extracted with chloroform to give a dark red oil (8.4 g) which was chromatographed on Florisil (600 g). Elution with 44% benzene–chloroform (2000 ml) afforded 5.7 g of the title compound as a pale yellow oil: ir $\nu_{max}^{CHCl_3}$ 3700–3200 cm^{-1}; uv λ_{max} 225 nm (ϵ 20,500), 283 (4900); pmr ($CDCl_3$) δ 0.8–2.2 (m, 8 H), 2.3–2.9 (broad, 3 H), 3.25 (s, 1 H), 3.45–3.7 (m, 2 H), 6.8–7.5 (m, 4 H), 8.35 (s, 1 H); mass spectrum molecular ion m/e 229. The material was used in the next step without further characterization.

3-(1,2,3,4-Tetrahydrocarbazol-1-yl)prop-1-yl Tosylate (1).—A solution of *p*-toluenesulfonyl chloride (1.9 g, 0.01 mol) in dry pyridine (10 ml) was added dropwise at 0° to a solution of the alcohol **10** (2.3 g, 0.01 mol) obtained above in pyridine (5 ml). The reaction mixture was refrigerated overnight and processed in the usual manner to afford the crude tosylate (3.0 g) as a light oil. The oil was chromatographed on Florisil (200 g); elution with 850 ml of 8% benzene–chloroform yielded 1.6 g (42%) of pure tosylate 1: mp 84–86° from petroleum ether–benzene; ir $\nu_{max}^{CHCl_3}$ 3450, 1600, 1360, and 1175 cm^{-1}; pmr ($CDCl_3$) δ 1.20–2.2 (m, 8 H), 2.40 (s, 3 H), 2.50–3.00 (m, 3 H), 3.90–4.25 (undefined triplet, 2 H), 7.0–8.0 (m, 9 H); uv λ_{max} 226 nm (ϵ 43,170), 282 (6800).

Anal. Calcd for $C_{22}H_{25}NSO_3$: C, 68.91; H, 6.57; N, 3.65; S, 8.34. Found: C, 68.81; H, 6.45; N, 3.56; S, 8.52.

Ethyl 3-(1,2,3,4-Tetrahydro-9-methylcarbazol-1-yl)propionate.—A solution of ethyl 3-(2-oxocyclohexyl)propionate (5.0 g, 0.025 mol) and α-methylphenylhydrazine (3.05 g, 0.035 mol) was dissolved in 10 g of polyphosphoric acid. The mixture was gently warmed on the steam bath until the temperature began to rise rapidly. The mixture was cooled with cold water and then diluted with 100 g of ice–water. Extraction with methylene chloride afforded 5.25 g of crude product which was chromatographed on Florisil (600 g). Elution with 4 l. of petroleum ether gave 3.4 g (48%) of the ester **11** as an oil; pmr ($CDCl_3$) δ 1.17 (t, J = 7 Hz, 3 H), 1.5–3.0 (m, 11 H), 3.5 (s, 3 H), 4.1 (q, J = 7 Hz, 2 H), 7.2 (m, 4 H); uv, typical indole absorption.

3-(1,2,3,4-Tetrahydro-9-methylcarbazol-1-yl)propan-1-ol.—The ester (4.85 g, 0.017 mol) was heated under reflux for 2 hr with lithium aluminum hydride (0.76 g, 0.02 mol) in anhydrous ether. The usual isolation afforded 3.7 g (90%) of the crude alcohol as an oil which was used directly in the next step.

3-(1,2,3,4-Tetrahydro-9-methylcarbazol-1-yl)prop-1-yl Tosylate (2).—A sample (3.7 g) of the crude alcohol **11**, obtained above, was converted to the tosylate as described for tosylate 1. The crude tosylate (4.5 g) was chromatographed on 500 g of Florisil. Elution with benzene (1800 ml) gave 2.33 g of the desired tosylate, which crystallized from benzene–hexane after 2 weeks in the refrigerator. Recrystallization from absolute ethanol gave pure 2 as white crystals: mp 63–65°; pmr ($CDCl_3$) δ 1.3–2.0 (com-

(7) A. H. Jackson and B. Naidoo, *Tetrahedron*, **25**, 4843 (1969), and previous papers in the series.

(8) All melting points and boiling points are uncorrected. Reactions involving strong bases or organometallic reagents were carried out under nitrogen. Infrared spectra were determined with a Beckman IR-5a infrared spectrophotometer. Ultraviolet spectra were determined in 95% ethanol with a Cary Model 15 spectrophotometer. Proton magnetic resonance spectra were determined at 60 MHz with a Varian Model A-60 spectrometer. The chemical shifts are recorded in δ values (parts per million) relative to tetramethylsilane internal standard. The mass spectra were obtained with a CEC Model 21-110 mass spectrometer equipped with a direct inlet system at an ionizing potential of 70 eV.

(9) L. J. Amundsen and L. S. Nelson, *J. Amer. Chem. Soc.*, **73**, 242 (1951).

plex multiplets, 8 H), 2.33 (s, 3 H), 2.5–3.0 (broad, 3 H), 3.52 (s, 3 H), 4.05 (t, J = 6 Hz, 2 H), 7.1–7.9 (m, 8 H); uv λ_{max} 226 nm (ϵ 44,643), 283 (6420).

Anal. Calcd for $C_{23}H_{27}NSO_3$: C, 69.50; H, 6.85; N, 3.52; S, 8.05. Found: C, 69.61; H, 7.07; N, 3.39; S, 8.22.

The deuterated material, 3-(1,2,3,4-tetrahydro-9-methylcarbazol-1-yl)propyl tosylate-*1,1-d*$_2$, was prepared as just described using lithium aluminum deuteride for the reduction of ethyl 3-(1,2,3,4-tetrahydro-9-methylcarbazol-1-yl)propionate.

6*H*-1,2,3,3a,4,5-Hexahydropyrido[3,2,1-*jk*]carbazole (12).—A solution of **1** (0.192 g) in 10 ml of 0.5 *M* potassium *tert*-butoxide in *tert*-butyl alcohol was heated under reflux for 10 hr. The alcohol was evaporated under reduced pressure and the residue was treated with dilute hydrochloric acid and extracted with ether. Evaporation of the ether afforded 0.106 g (100%) of the carbazole derivative **12**: mp 82–84° after crystallization from hexane (lit.[5] mp 87–88°); pmr δ 0.8–4.5 (complex multiplets, 13 H), 7.0–7.65 (m, 4 H); mass spectrum molecular ion at m/e 211.

Anal. Calcd for $C_{15}H_{17}N$: C, 85.26; H, 3.11; N, 6.63. Found: C, 84.93; H, 8.25; N, 6.43.

A similar result obtained upon treatment of tosylate with ethylmagnesium iodide in ether solution.

Formolysis of 3-(1,2,3,4-Tetrahydro-9-methylcarbazol-1-yl)-prop-1-yl Tosylate (2).—Tosylate **2** (0.200 g, 0.005 mol), 88% formic acid (10 ml), and benzene (3 ml) were heated under reflux overnight. The cooled reaction mixture was diluted with 10 ml of 10% hydrochloric acid and washed with ether. The aqueous portion was basified with 20% sodium hydroxide solution and extracted with ether to give 0.090 g of a yellow oil which was subjected to preparative tlc on silica gel with benzene. The compounds were observed; the major product, with an intermediate R_f, was collected (0.046 g, 41%) as a colorless oil which quickly changed to cherry red on exposure to air; ir $\bar{\nu}_{max}$ 1670, 1600 cm^{-1}; pmr δ 0.8–3.4 (comlex multiplets, 11 H), 2.92 (s, 3 H), 4.75 (t, J = 5 Hz, 1 H), 6.3–7.30 (m, 4 H); uv λ_{max} 248 nm (ϵ 60,200), 287 (2350); mass spectrum molecular ion m/e 225.

A sample of the product **13** (0.217 g, 0.964 mmol) obtained as just described was hydrogenated in ethanol (100 ml) over 10% palladium on carbon at atmospheric pressure. After hydrogen uptake ceased, the catalyst was filtered and the solvent was evaporated to yield 0.195 g of oil which was crystallized from ethanol to give pure **14**: mp 27–29°; ir $\bar{\nu}_{max}$ 1600 cm^{-1}; pmr δ 1.15–2.5 (complex multiplets, 13 H), 2.68 (s, 3 H), 3.0 (t, J = 2.5 Hz, 1 H), 6.4–7.3 (m, 4 H); uv λ_{max} 255 nm (ϵ 7700), 262 (8880), 267 (7100); mass spectrum molecular ion at m/e 227.

Anal. Calcd for $C_{16}H_{19}N$: C, 84.53; H, 9.31; N, 6.16. Found: C, 84.76; H, 9.21; N, 6.12.

The methiodide of **14**, mp 203–204° dec, from ethanol, was obtained by treating **14** with methyl iodide in benzene solution.

Anal. Calcd for $C_{17}H_{24}NI$: C, 55.28; H, 6.50; N, 3.80; I, 34.42. Found: C, 54.97; H, 6.68; N, 3.54; I, 34.46.

Perhydro-4-indanone.—Commercially available 4-indanol (20 g, 0.149 mol) in ethanol (200 ml) was hydrogenated over 5% Rh/C (1.5 g) at 60 psi for 15 hr. The catalyst was filtered and the solvent was evaporated to give 19.5 g of crude perhydro-4-indanol: pmr (CCl_4) δ 1.8–2.4 (complex multiplets, 14 H), 3.3–4.2 (m, 2 H).

The crude perhydro-4-indanol (19.5 g) was dissolved in acetone (200 ml) and stirred with 8 *N* chromic acid (50 ml) for 1 hr at 0°. The usual isolation and distillation afforded 14.0 g (68% based on 4-indanol) of perhydro-4-indanone, bp 100–104° (12 mm), ir $\nu_{max}^{CCl_4}$ 1710 cm^{-1}.

7*H*-2,3,3a,4,5,6,6a-Octahydrocyclopenta[*d*]carbazole (14).—A solution of perhydro-4-indanone (1.38 g, 0.01 mol) and α-methylphenylhydrazine (1.22 g, 0.01 mol) was heated at 120–125° for 2 hr. The crude phenylhydrazone was dissolved in acetic acid (3.0 g) and heated at 90° for 2 hr. The reaction mixture was diluted with water and washed with ether. The aqueous phase was then basified and extracted with ether to give 1.15 g (51%) of crude **13** as a red oil. The spectral properties of this material were virtually identical with those obtained from the solvolysis of **2**. The crude material was hydrogenated over Pd/C as previously described. The hydrogenation product was purified by preparative tlc on silica gel using benzene as eluent. The major product (0.596 g, 53%) was identical with the sample previously obtained.

Solvolysis of 3-(1,2,3,4-Tetrahydro-9-methylcarbazol-1-yl)propyl Tosylate-*1,1-d*$_2$.—Two samples of deuterated tosylate were solvolyzed in benzene–formic acid as previously described. In one experiment the crude product was hydrogenated over 10% Pd/C and separated by preparative tlc (silica gel–benzene). In the other experiment, the crude product was reduced with excess sodium borohydride in ethanol. The deuterated products were obtained in 40 and 65% yields, respectively, from the two experiments. The distributions of labeled material were computed from the 70 eV mass spectra. Under these conditions, the m − 1 peak for the parent compound was 9% of the parent peak. The calculations were carried out as described by Biemann.[10]

Registry No.—**1**, 32251-92-6; **2**, 32251-93-7; **7**, 32251-94-8; **8**, 32251-95-9; **9**, 32251-96-0; **10**, 32251-97-1; **11**, 32251-98-2; **12**, 32251-99-3; **13**, 32252-00-9; **14** methiodide, 32252-01-0; echitamine, 23106-72-1.

(10) K. Biemann, "Mass Spectrometry, Organic Chemical Applications, McGraw-Hill, New York, N. Y., 1962, p 204.

Reduction of 6β-Methoxy-3α,5-cyclo-5α Steroids with Mixed Hydrides

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Received June 21, 1971

The reduction of 6β-methoxy-3α,5-cyclo-5α steroids with lithium aluminum hydride–aluminum chloride mixtures gives 3α,5-cyclo-5α steroids as the major product. The mechanism of the reaction is discussed. The reduction of cholesteryl tosylate with lithium aluminum hydride and mixed lithium aluminum hydride–aluminum chloride is also considered.

In the past few years considerable attention has been paid to the use of lithium aluminum hydride–aluminum chloride[1] as a reagent capable of reducing a large number of functions insensitive to lithium aluminum hydride; a well-known example is the reduction with mixed hydride of allylic and benzylic alcohols.[2]

In view of the unique electronic structure and the unusual properties of the cyclopropane ring, we decided to investigate the reactivity of several cyclopropylcarbinyl derivatives toward lithium aluminum hydride–aluminum chloride.

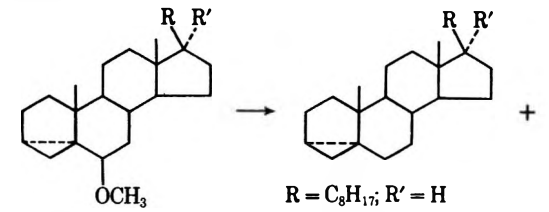
Preliminary work on 3α,5-cyelo-5α-cholestan-6β-ol showed that the reduction with mixed hydride gave 3α,5-cyclo-5α-cholestane, with a yield of 71%. This result seemed to support the similar behavior of the allylic alcohols and the 6β-hydroxy-3α,5-cyclo-5α

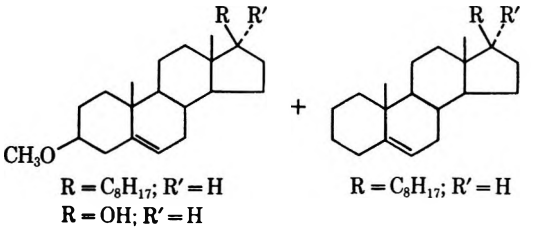
(1) E. L. Eliel, *Rec. Chem. Progr.*, **22** (3), 129 (1961); M. N. Rerick in Augustine's "Reduction," Vol. 2, Marcel Dekker, New York, N. Y., 1968.

(2) J. Broome, B. R. Brown, A. Roberts, and A. M. S. Whithe, *J. Chem. Soc.*, 1406 (1960); R. F. Nystrom and C. R. A. Berger, *J. Amer. Chem. Soc.*, **80**, 2896 (1958).

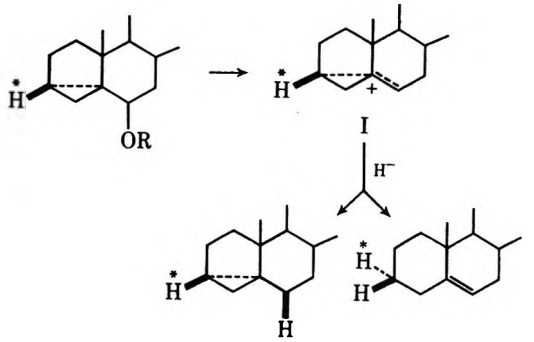
steroids with respect to the reduction with mixed hydride, and encouraged us to extend the investigation to other 3α,5-cyclo-5α steroids, containing a methoxyl group on C-6.

The formation of 3α,5-cyclo-5α steroids with yields ranging from 70 to 75% was observed in the androstane and pregnane series, as illustrated in the following scheme.





The most likely mechanism for this process seems to involve an intermediate mesomeric carbonium ion, usually represented by the nonclassical structure I, the intervention of which would account for the formation of both the 3α,5-cyclo-5α steroids and Δ^5 steroids.



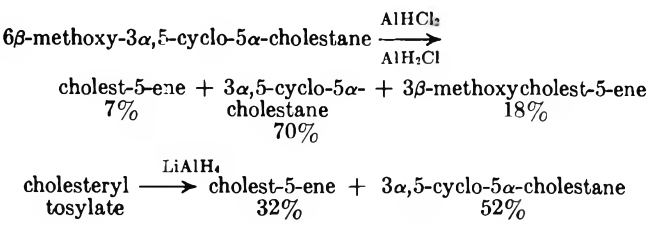
The formation of I was also suggested by Corey,[3] in order to account for the formation of 3α,5-cyclo-5α steroids and Δ^5 steroids in the reduction of the tosylates of 3β-hydroxy-Δ^5 steroids with $LiAlH_4$. Using ir spectroscopy, Corey observed the formation of 3β-deuteriocholest-5-ene and 6β-deuterio-3α,5-cyclo-5α-cholestane from the reduction of cholesteryl tosylate with lithium aluminum deuteride.

However, the ratio of the yields of 3α,5-cyclo-5α-cholestane and cholest-5-ene from the reduction of 6β-methoxy-3α,5-cyclo-5α-cholestane with mixed hydrides is considerably different, showing a noticeable discrepancy between two reactions which should involve the same intermediate (Scheme I).

The formation of 3β-methoxycholest-5-ene cannot clearly justify the large differences encountered using the two reagents. In our opinion, the most likely

(3) E. J. Corey, M. G. Howell, A. Boston, R. L. Young, and R. A. Sneen, *J. Amer. Chem. Soc.*, **78**, 5036 (1956).

Scheme I

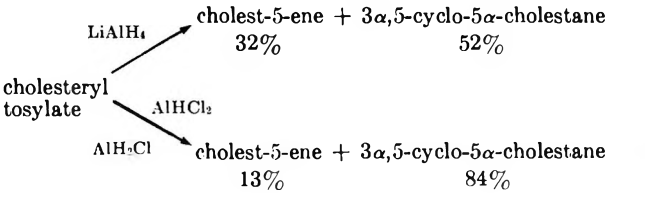


hypothesis is based on the assumption that the reaction of tosylate with $LiAlH_4$ does not involve exclusively the formation of the mesomeric ion I (the precursor of both cholest-5-ene and 3α,5-cyclo-5α-cholestane), but also a normal reduction of the tosylate, which leads exclusively to cholest-5-ene. Such a hypothesis would easily explain the observed increase in the yield of 3α,5-cyclo-5α-cholestane in the reduction of 6β-methoxy-3α,5-cyclo-5α-cholestane with the mixed hydrides.

This hypothesis does not agree with the observation of Corey, that in the reduction of cholesteryl tosylate with lithium aluminum deuteride the isolated cholest-5-ene contained only one 3β-deuterio atom. According to our hypothesis, the product must be a mixture of 3β-deuteriocholest-5-ene and 3α-deuteriocholest-5-ene; the former derives from the hybrid ion, while the normal reduction of the tosylate, in agreement with the usual steric course of such reductions, must lead to an inverted configuration, with the formation of 3α-deuteriocholest-5-ene.

Eliel[4] stated that β-phenylethyl tosylate is not easily reduced by the mixed reagent, which probably involves a normal reduction mechanism. We therefore studied the reductions of cholesteryl tosylate with lithium aluminum hydride–aluminum chloride. The results are given in Scheme II. It should be noted

Scheme II



that in Scheme II the product ratio for $AlHCl_2 \cdot AlH_2Cl$ reduction is very similar to that found with 6β-methoxy-3α,5-cyclo-5α-cholestane (first scheme) assuming that only two compounds are formed in this case.

These results agree with our hypothesis that, in the reduction of cholesteryl tosylate with $LiAlH_4$, the cholest-5-ene must be formed from both the mesomeric ion and a normal reduction mechanism of the tosylates.

To confirm this we prepared the 3α-deuteriocholestane and the 3β-deuteriocholestane following the method of Corey[3] and then studied their ir spectra and those of mixtures of various composition. This preliminary survey showed that mixtures of the two compounds may be distinguished by studying the relative intensity of the two bands in the region between 2190 and 2110 cm^{-1}.

(4) E. L. Eliel, personal communication.

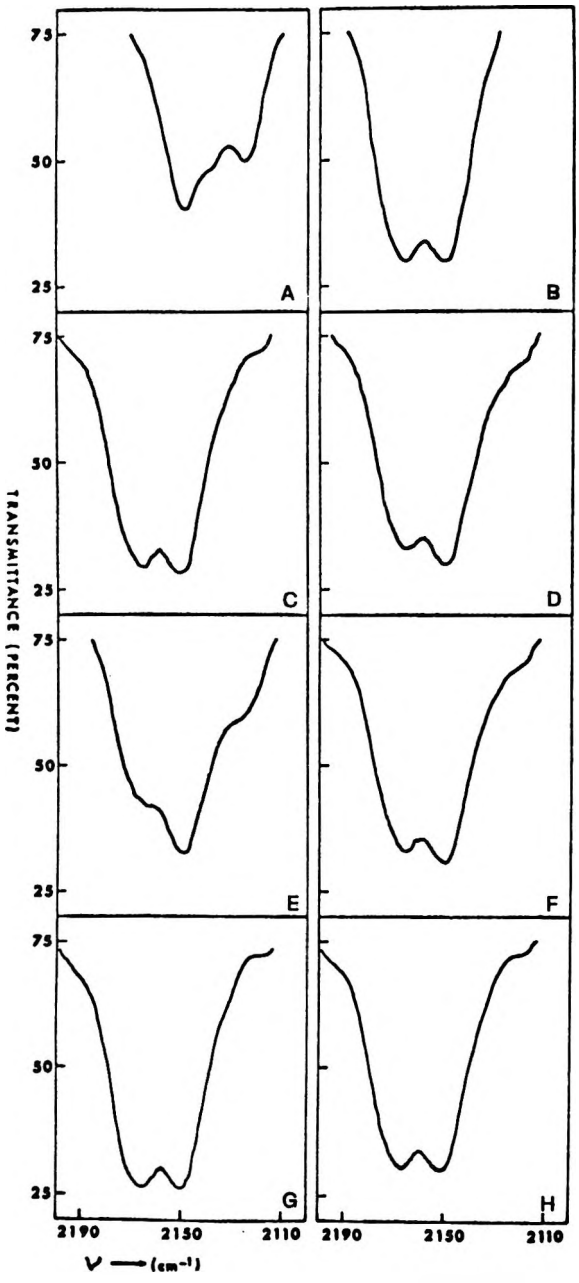


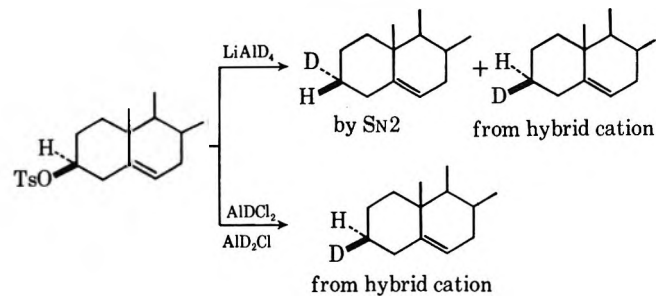
Figure 1.—C–D stretching bands of cholestanes-3-*d*, CCl_4 solution (10%) at 25°: A, cholestane-3α-*d*; B, cholestane-3β-*d*; C, 10% 3α, 90% 3β; D, 20% 3α, 80% 3β; E, 50% 3α, 50% 3β; F, G, H, cholestanes-3-*d* obtained by catalytic hydrogenation of Δ^5-cholestanes-3-*d* (synthesized from F, cholesteryl tosylate–$LiAlD_4$; G, 6β-methoxy-3α,5-cyclocholestane–$LiAlD_4$ and $AlCl_3$; H, cholesteryl tosylate–$LiAlD_4$ and $AlCl_3$).

Lithium aluminum deuteride–aluminum chloride reduction of 6β-methoxy-3α,5-cyclo-5α-cholestane gave 6β-deuterio-3α,5-cyclo-5α-cholestane, together with 3-deuteriocholest-5-ene which, when catalytically hydrogenated,[3] gave a deuteriocholestane (see Figure 1, spectrum G) which proved to correspond to the 3β-deuterio derivative.

Cholesteryl tosylate was then treated with lithium aluminum deuteride;[3] cholest-5-ene, deuterated at C-3, was isolated and catalytically hydrogenated to form the C-3 deuterated cholestane. We followed a similar scheme using lithium aluminum deuteride–aluminum chloride.

The ir spectra in the previously observed region (see Figure 1, spectra F, H) suggest that reduction of cholesteryl tosylate with lithium aluminum deuteride gives a mixture of 3α- and 3β-deuteriocholest-5-ene, while in the case of lithium aluminum deuteride–aluminum chloride only 3β-deuteriocholest-5-ene is formed.

These results confirm our hypothesis of the mechanism of the reduction.



Experimental Section

Melting points were taken on a Culatti capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 521 infrared spectrophotometer; all measurements were made in carbon tetrachloride. Optical rotations were measured with a Schmidt Haensch polarimeter and were obtained on 1% solutions in a 1-dm cell. Vpc analyses were taken on a Perkin-Elmer F 20 gas chromatograph. Analyses of the reaction mixture were made by vpc using a 6-ft column packed with nitrile silicone gum X E 60 on Anacrom "As" 90–100 mesh; separation conditions: column temperature 200°, injection port temperature 200–250°; N_2 flow rate 40 cc/min. Woelm alumina was used for column chromatography.

General Procedure for Mixed Hydride Reductions.—The mixed hydride reagents were prepared by slowly adding measured amounts of an ethereal solution of $AlCl_3$ to a stirred solution of known amounts of $LiAlH_4$ in dry diethyl ether. A solution of the steroid compound in diethyl ether was added dropwise to this reagent. The resulting mixture was allowed to stand and then carefully hydrolyzed with a small amount of water.

The ethereal solutions were separated by filtration and the solid residues were washed with ether. The ethereal solution was washed with water, dried, and evaporated.

Reduction of 6β-Methoxy-3α,5-cyclo-5α-cholestane.—To 0.54 g of $LiAlH_4$ in 20 ml of ether was added 1.9 g of $AlCl_3$ in 20 ml of ether, at room temperature. 6β-Methoxy-3α,5-cyclo-5α-cholestane (2.7 g) in 20 ml of ether was added.

The reaction was carried out as described above. The resulting residue (2.6 g) was chromatographed on a column packed with 78 g of basic alumina (Brockmann I). The eluents used were 60 ml of hexane and 210 ml of benzene, and 30-ml fractions were collected. Fractions 1 and 2 gave 2.1 g of a mixture of 3α,5-cyclo-5α-cholestane (90.5%) and cholest-5-ene (9.5%) (analyzed by vpc); fractions 5–9 gave 0.49 g of a solid which was recrystallized from acetone, mp 82°, $[\alpha]_D$ −42° ($CHCl_3$), and was identified as 3β-methoxycholest-5-ene [lit.[5] mp 82–83°, $[\alpha]_D$ −45.6° ($CHCl_3$)].

The mixture (2.1 g) of 3α,5-cyclo-5α-cholestane and cholest-5-ene was chromatographed on a column packed with 250 g of basic alumina (Brockmann I). The eluent used was petroleum ether (bp 30–50°). The first fractions gave 3α,5-cyclo-5α-cholestane, mp 76–78° from ether–ethanol mixture, $[\alpha]_D$ +78° ($CHCl_3$) [lit.[6] mp 77–78°, $[\alpha]_D$ +80° ($CHCl_3$)]; the later fractions gave cholest-5-ene, mp 90–91° (from acetone), $[\alpha]_D$ −50° ($CHCl_3$) [lit.[7] mp 92–93°, $[\alpha]_D$ −53° ($CHCl_3$)]. $LiAlD_4$–$AlCl_3$ was used to prepare the 3-deuteriocholestene following the previously described scheme.

Reduction of 6β-Hydroxy-3α,5-cyclo-5α-cholestane.—To 0.20 g of $LiAlH_4$ in 10 ml of ether was added 0.70 g of $AlCl_3$ in 10 ml of ether, at room temperature. 6β-Hydroxy-3α,5-cyclo-5α-cholestane (0.68 g) in 10 ml of ether was added.

(5) A. Romeo and R. Villotti, *Ann. Chim. (Rome)*, **47**, 618 (1957).
(6) C. W. Shoppee and G. H. R. Summers, *J. Chem. Soc.*, 3361 (1952).
(7) R. E. Ireland, T. I. Wrigley, and W. G. Young, *J. Amer. Chem. Soc.* **80**, 4604 (1958).

The reaction was carried out as described before. The resulting residue (0.660 g) was chromatographed on a column packed with 66 g of basic alumina (Brockmann II).

The eluent used was 225 ml of petroleum ether, and 25-ml fractions were collected. Fractions 1–5 gave 0.54 g of a mixture of 3α,5-cyclo-5α-cholestane (88.5%) and cholest-5-ene (11.5%) (analyzed by vpc).

The mixture (0.53 g) of 3α,5-cyclo-5α-cholestane and cholest-5-ene was chromatographed as described previously (reduction of 6β-methoxy-3α,5-cyclo-5α-cholestane) to give 3α,5-cyclo-5α-cholestane and cholest-5-ene.

Reduction of 6β-Methoxy-3α,5-cyclo-5α-androstan-17-one.—The reaction was carried out as described for 6β-methoxy-3α,5-cyclo-5α-cholestane, using 1.14 g of $LiAlH_4$, 4 g of $AlCl_3$, and 3.04 g of 6β-methoxy-3α,5-cyclo-5α-androstan-17-one.

The resulting residue (2.84 g) was chromatographed on a column packed with 85 g of alumina (Brockmann III). The eluents used were 420 ml of petroleum ether–benzene (1:1), 180 ml of benzene, and 90 ml of ether; 30-ml fractions were collected. After crystallization (from methanol–water mixture), fractions 1–15 gave 2.0 g of 17β-hydroxy-3α,5-cyclo-5α-androstan, mp 120–121°, $[\alpha]D$ +76° ($CHCl_3$) [lit.[8] mp 122–124°, $[\alpha]D$ +77° ($CHCl_3$)]; fractions 20–23 gave 0.3 g of 3β-methoxy-17β-hydroxyandrostan-5-ene, mp 139–141°, $[\alpha]D$ −53° (ethanol 95%) [lit.[9] mp 142.5–143°, $[\alpha]D$ −51° (ethanol 95%)].

Reduction of 6β-Methoxy-3α,5-cyclo-5α-pregnan-20-one.—The reaction was carried out as described for 6β-methoxy-3α,5-cyclo-5α-cholestane using 1.14 g of $LiAlH_4$, 4 g of $AlCl_3$, and 3.4 g of 6β-methoxy-3α,5-cyclopregnan-20-one. The resulting residue (3.11 g), containing a mixture of epimeric 20-ols, was oxidized in acetic acid (46 ml) by chromium trioxide (0.92 g) in water (5 ml). After 12 hr ice was added and the mixture was made alkaline with ammonia, the precipitated product was extracted with ether, and the ethereal solution was washed with water, dried, and evaporated. The resulting residue (3.06 g) was chromatographed on a column packed with 95 g of alumina (Brockmann III). The eluents used were 600 ml of petroleum ether and 300 ml of benzene; 100-ml fractions were collected. Fractions 1–6 gave after crystallization (from methanol) 2.19 g of 3α,5-cyclo-5α-pregnan-20-one, mp 107–109°, $[\alpha]D$ +173° ($CHCl_3$) [lit.[8] mp 109–111°, $[\alpha]D$ +179° ($CHCl_3$)].

Reduction of 3β-Tosyloxycholest-5-ene.—To 0.35 g of $LiAlH_4$ in 16 ml of ether was added 1.25 g of $AlCl_3$ in 16 ml of ether, at room temperature. 3β-Tosyloxycholest-5-ene (4 g) in 20 ml of benzene was added.

The reaction was carried out as described before. The resulting residue (2.9 g) was chromatographed on a column packed with 580 g of basic alumina (Brockmann II). The eluent used was 350 ml of petroleum ether, 50-ml fractions being collected. Fractions 1–5 gave 2.7 g of a mixture of 3α,5-cyclo-5α-cholestane (86%) and cholest-5-ene (14%) (analyzed by vpc).

The mixture (2.7 g) of 3α,5-cyclo-5α-cholestane and cholest-5-ene was chromatographed as described previously (reduction of 6β-methoxy-3α,5-cyclo-5α-cholestane) to give 3α,5-cyclo-5α-cholestane and cholest-5-ene.

$LiAlD_4$–$AlCl_3$ was used to isolate the 3-deuteriocholest-5-ene following the preparation scheme previously described.

Registry No.—6β-Methoxy-3α,5-cyclo-5α-cholestane, 2867-93-8; 6β-hydroxy-3α,5-cyclo-5α-cholestane, 465-54-3; 6β-methoxy-3α,5-cyclo-5α-androstan-17-one, 14425-92-4; 6β-methoxy-3α,5-cyclo-5α-pregnan-20-one, 32249-55-1; 3β-tosyloxycholest-5-ene, 1182-65-6; lithium aluminum hydride, 16853-85-3; aluminum chloride, 7446-70-0.

(8) A. Kasal, V. Cerny, and F. F. Sorm, *Collect. Czech. Chem. Commun.*, **30** (2), 472 (1965).

(9) M. N. Huffmann and J. W. Sadler, *J. Org. Chem.*, **18**, 919 (1953).

The Structure of Lycorenine and the 7-Hydroxy Alkaloids Derived from the [2]Benzopyrano[3,4-g]indole Nucleus[1]

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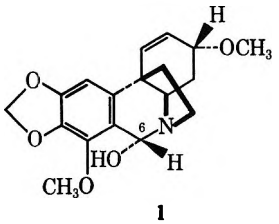
Received June 25, 1971

An X-ray crystallographic study of lycorenine methiodide has established the configuration of the C_7 hydroxyl group in the alkaloid to be that shown in **3**. A comparison of specific and molecular rotations of analogous alkaloids and their 7-oxo derivatives indicates that all alkaloids with the general structure **4** have an α-C_7 hydroxyl group. These data provide complete structures for oduline, nerinine, krigeine, unsevine, and krigenamine.

Amaryllidaceae alkaloids containing a benzylic hydroxyl group (as in **1**, **2**, and **4**) provide a number of



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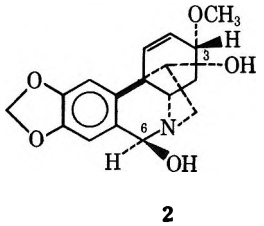
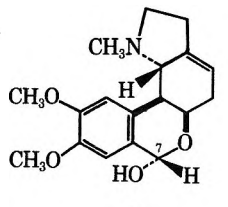


2

reactive compounds of chemical, biosynthetic, and spectroscopic interest.[2] Although the structures for many of these bases frequently have been assigned to the extent of the absolute configuration, the configuration of the benzylic hydroxyl group has been ignored in most representations. The structures of 6-hydroxybuphanidrine (**1**)[3] and 6-hydroxycrinamine (**2**)[4] have been determined by X-ray crystallographic techniques. No chemical methods exist for the assignment of con-



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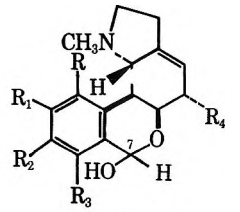

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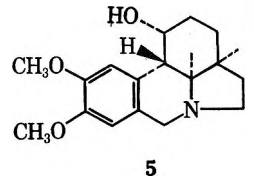

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(1) Supported by a research grant (HE-7503) from the National Institutes of Health, U. S. Public Health Service, and the Ames Laboratory of the U. S. Atomic Energy Commission, Contribution No. 3017.

(2) For a summary of the chemistry of these alkaloids see W. C. Wildman, *Alkaloids*, **11**, 307 (1968).

(3) J. Clardy, F. M. Hauser, D. Dahm, R. A. Jacobson, and W. C. Wildman, *J. Amer. Chem. Soc.*, **92**, 6337 (1970).

(4) J. Karle, J. A. Estlin, and I. L. Karle, *ibid.*, **89**, 6510 (1967).

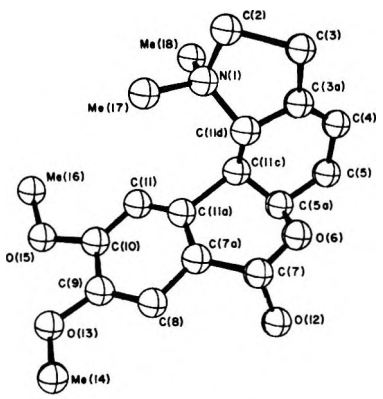

Figure 1.

figuration either at C_6 in **1** or **2**, or at C_7 in the "lycorenine type" alkaloids (**4**). Stereochemical assignment to the benzylic hydroxyl group frequently is complicated because **2** and haemanthidine (the C_3 epimer of **2**) exist *in solution* as an equilibrating mixture of C_6 epimers.[5]

There is no report that hemiacetal-type alkaloids (**3** and **4**) epimerize in solution at C_7 and it was of interest to determine the configuration of the hydroxyl group at this position in a representative alkaloid of this ring system. Lycorenine was chosen for study.

Experimental Section

Lycorenine methiodide was prepared by adding 1 ml of methyl iodide to a solution of 70 mg of lycorenine (mp 194–196°) in 4 ml of acetone. The reaction mixture was allowed to stand for 1 hr at room temperature. The product was filtered, washed with acetone, and recrystallized several times from ethanol to give colorless needles, mp 265° dec. Preliminary Weissenberg and precession photographs showed the $2/m\ 2/m\ 2/m$ Laue symmetry appropriate for the orthorhombic crystal class. A least-squares analysis of diffractometer-measured θ values gave a = 16.49 (1) Å, b = 8.25 (1) Å, c = 14.05 (1) Å. The systematic absences for $h00$ ($h = 2n + 1$), $0k0$ ($k = 2n + 1$), and $00l$ ($l = 2n + 1$) uniquely indicate the common space group $P2_12_12_1$ (D_2^4). Measured and calculated densities indicated four molecules per unit cell or one per asymmetric unit. A cubic crystal fragment of approximate dimensions 0.1 mm was selected for intensity work. The unique reflections ($2\theta \leq 70°$) were collected on a fully automated Hilger–Watts four-circle diffractometer using Zr-filtered Mo Kα (0.7107 Å) radiation. Of the 2425 reflections measured, 1890 were judged observed after background, Lorentz, and polarization corrections. No absorption corrections were made.

The iodine position was determined from the three-dimensional Patterson synthesis, and the 24 nonhydrogen atom positions were revealed in the subsequent iodine-phase electron density synthesis.[6] Full-matrix least-squares refinements in which all atomic positions and anisotropic thermal parameters were varied reduced the discrepancy index to its present minimum of 0.088 for the observed reflections.[7,8] The estimated standard deviations as given by the variance-covariance matrix from least-squares refinements are ±0.01 Å for bond lengths and ±2.0° for bond angles.[9] A computer-generated drawing (less the iodine atom) is given in Figure 1.[10] Table I lists the final atomic fractional coordinates. All bond distances and angles agree well within generally accepted values. No abnormally short intermolecular contacts were found. As can be seen from the final X-ray model the benzylic hydroxyl lies below the plane of the aromatic and dihydropyran rings. The absolute configuration depicted is derived from the chemical conversion of lycorenine to α-dihydropluviine (**5**), the absolute configuration of which is known.[11,12]

TABLE I

FINAL ATOMIC COORDINATES[a]

Atom	x/a	y/b	z/c
1	0.3432 (1)	−0.1512 (1)	0.5310 (1)
2	0.3996 (1)	−0.1228 (2)	0.6312 (1)
3	0.4151 (1)	0.0634 (2)	0.6162 (1)
3a	0.3907 (1)	0.1176 (2)	0.5153 (1)
4	0.3794 (1)	0.2745 (2)	0.4871 (1)
5	0.3515 (1)	0.3090 (2)	0.3878 (1)
5a	0.3496 (1)	0.1638 (2)	0.3247 (1)
6	0.4340 (1)	0.1292 (1)	0.2972 (1)
7	0.4433 (1)	0.0000 (2)	0.2269 (1)
7a	0.3743 (1)	−0.1229 (2)	0.2285 (1)
8	0.3830 (1)	−0.2457 (2)	0.1570 (1)
9	0.3228 (1)	−0.3695 (2)	0.1551 (1)
10	0.2551 (1)	−0.3569 (2)	0.2190 (1)
11	0.2538 (1)	−0.2385 (2)	0.2877 (1)
11a	0.3204 (1)	−0.1245 (1)	0.2936 (1)
11c	0.3162 (1)	0.1240 (2)	0.3734 (1)
11d	0.3707 (1)	−0.0246 (2)	0.4577 (1)
Me(16)	0.1333 (1)	−0.4853 (3)	0.2720 (1)
O(15)	0.2007 (1)	−0.4764 (1)	0.2058 (1)
Me(14)	0.3966 (1)	−0.5243 (3)	0.0366 (1)
O(13)	0.3212 (1)	−0.4884 (1)	0.0904 (1)
Me(17)	0.2549 (1)	−0.1183 (2)	0.5607 (1)
Me(18)	0.3471 (1)	−0.3276 (2)	0.5002 (1)
O(12)	0.4450 (1)	0.09842 (2)	0.1376 (1)

[a] The error in the least significant digit, as estimated by the inverse least-squares matrix, is given in parentheses.

Discussion

The X-ray study confirms the structure assigned to lycorenine by chemical means and specifically locates the benzylic hydroxyl group. Optical rotations at 589 nm for lycorenine (**3**), homolycorine (**3**, >C=O at C_7), and deoxylycorenine (**3**, $>CH_2$ at C_7) provide a basis for the assignment of the benzylic hydroxyl group in oduline, nerinine, krigeine, krigenamine, and unsevine.[2] Homolycorine and deoxylycorenine show comparable rotations at 589 nm. Introduction of the α-C_7 hydroxyl group (as in **3**) increases the specific rotation in a positive direction by almost 70°. Comparable dextrorotatory shifts are found in all other alkaloids possessing this ring system. From these

(5) R. W. King, C. F. Murphy, and W. C. Wildman, *J. Amer. Chem. Soc.*, **87**, 4912 (1965). This phenomenon has been observed in synthetic intermediates: J. B. Hendrickson, T. L. Bogard, and M. E. Fisch, *ibid.*, **92**, 5538 (1970).

(6) J. Rodgers and R. A. Jacobson, "ALF: A General Fourier Program in PL 1 for Triclinic, Monoclinic, and Orthorhombic Space Groups," USAEC Research and Development Report, Ames Laboratory, Iowa State University, Ames, Iowa 50010.

(7) W. R. Busing, K. O. Martin, and H. A. Levy, "ORFLS: Fortran Least-Squares Program," Oak Ridge National Laboratory, USAEC, 1962.

(8) Listings of structure factors will appear immediately following this article in the microfilm edition of this volume of the journal. Single copies may be obtained from the Reprint Department, ACS Publications, 1155 Sixteenth Street, N.W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit check or money order for $3.00 for photocopy or $2.00 for microfilm.

(9) W. R. Busing, K. O. Martin, and H. A. Levy, "ORFFE, A Fortran Crystallographic Function and Error Program," Oak Ridge National Laboratory, USAEC, 1964.

(10) C. K. Johnson, "ORTEP: A Fortran Thermal-Ellipsoid Plot Program for Crystal Structure Illustrations," Oak Ridge National Laboratory, USAEC, 1965.

(11) S. Mizukami, *Tetrahedron*, **11**, 89 (1960).

(12) M. Shiro, T. Sato, and H. Koyama, *Chem. Ind. (London)*, 1129 (1966).

TABLE II
SPECIFIC AND MOLECULAR ROTATIONS OF LYCORENINE, HOMOLYCORINE, AND ANALOGOUS ALKALOIDS

Compd	No.	Registry no.	Structure R	R1	R2	R3	R4	C7	[α]D (solvent), deg	Δα[D], deg	MD, deg	Δ[M]D, deg
Deoxylycorenine	3	13255-14-6						CH_2	+95 (EtOH)	57	+288	282
Lycorenine[a]	3	477-19-0						CHOH	+152 (EtOH)		+570	
Homolycorine	3	477-20-3						C=O	+85 (EtOH)	67	+368	202
Deoxykrigenamine	4	32247-13-5	CH_3O	O_2CH_2		H	H	CH_2	+123 (EtOH)	87	+385	315
Krigenamine	4	1165-00-0	CH_3O	O_2CH_2		H	H	CHOH	+210 ($CHCl_3$)	103	+695	325
Oxokrigenamine	4	1165-01-0	CH_3O	O_2CH_2		H	H	C=O	+117 ($CHCl_3$)		+370	
Oduline	4	477-18-9	H	O_2CH_2		H	H	CHOH	+239 ($CHCl_3$)	99	+720	300
Masonine	4	568-40-1	H	O_2CH_2		H	H	C=O	+140 ($CHCl_3$)		+420	
Krigeine	4	905-37-3	CH_3O	O_2CH_2		H	OH	CHOH	+234 ($CHCl_3$)	72	+813	254
Neronine	4	1167-58-4	CH_3O	O_2CH_2		H	OH	C=O	+162 ($CHCl_3$)		+559	
Nerinine	4	481-44-7	H	OCH_3	OCH_3	OCH_3	H	CHOH	+155 ($CHCl_3$)	83	+538	293
Albomaculine	4	668-63-3	H	OCH_3	OCH_3	OCH_3	H	C=O	+72 ($CHCl_3$)		+225	
Unsevine	4	4838-99-7	H	O_2CH_2		H	OCH_3	CHOH	+170 ($CHCl_3$)	69	+564	231
Nivaline	4	568-40-1	H	O_2CH_2		H	OCH_3	C=O	+101 ($CHCl_3$)		+333	

[a] Registry number for methiodide, 32367-48-9.

comparisons (see Table II) it is most probable that the C_7 hydroxyl groups of oduline, nerinine, krigeine, unsevine, and krigenamine have α configurations as well.

A Synthesis of 4-Azaoxindole

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Received May 28, 1971

The condensation product of ethyl cyanoacetate and 2-chloro-3-nitropyridine (**1**) was converted by reduction, cyclization, and acid hydrolysis into 4-azaoxindole (**4**). A study of the dibenzyl-4-azaoxindole derivatives **5**, **9**, and **13** was made to evaluate the type and extent of the tautomerism possible with this system. Rapid autoxidation of the 3-benzyl-4-azaoxindole (**11**) to the dioxindole **14** was observed. The presence of virtual coupling in the nmr spectrum of **4** was noted.

Azaindoles have attracted considerable interest in view of their potential relationship to pharmacologically important indoles, *e.g.*, serotonin, and a review of azaindoles has recently appeared.[1]

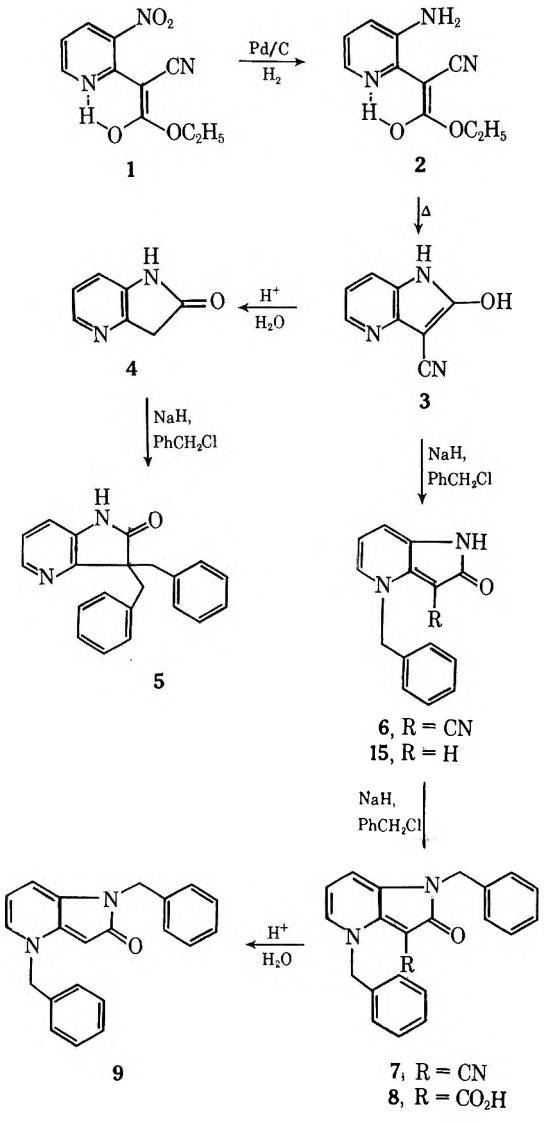
Azaoxindoles, on the other hand, are virtually unknown, with only the preparation of 7-azaoxindole[2,3] and 3,3-dimethyl-7-azaoxindole[4] and unsuccessful attempts at 5-azaoxindole[5] and 4-azaoxindole[6] preparation being described.

Our earlier interest in azaindole chemistry[7] and our current interest in arylations with 2-chloro-3-nitropyridine motivated us to make a contribution to this area. We describe now the synthesis of the previously undescribed 4-azaoxindole and some of its chemistry.

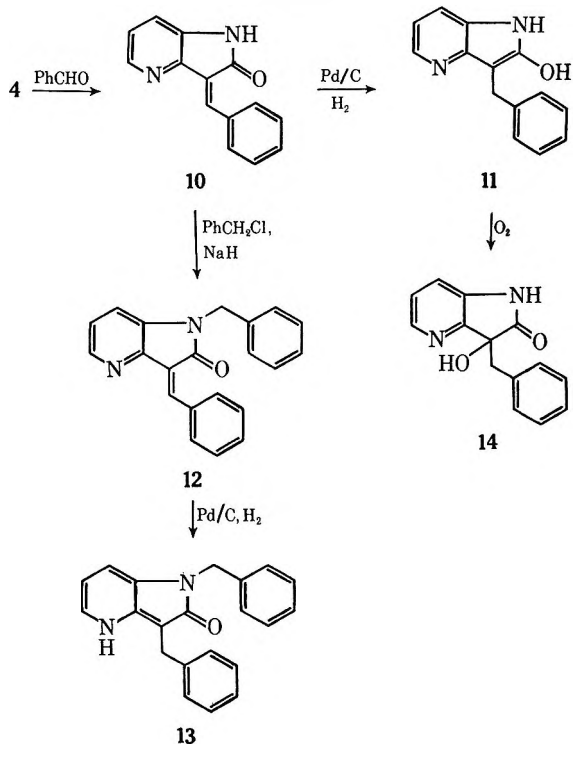
The arylation of ethyl cyanoacetate by 2-chloro-3-nitropyridine was described by Willette.[6] The resulting product, for which we favor the tautomeric structure **1** on the basis of infrared evidence (a very strong CN stretching and the ester C=O at 1628 cm^{-1}), could be reduced in our hands in excellent yield by hydrogenation in ethanol over 10% palladium on carbon at 50 psi and room temperature. Reflux of the product **2** in xylene effected ring closure to the 3-cyano-4-azaoxindole **3**. Some of the interesting chemistry of this new system was evident with this first member, for it is amphoteric. In fact, **3** is best purified by precipitation, from a solution of aqueous sodium hydroxide, with a stream of carbon dioxide. Reflux of **3** in concentrated hydrochloric acid converted it to the unsubstituted 4-azaoxindole **4** (Scheme I), which is shown in the principle tautomeric form **4a** based on the nmr evidence (2-proton singlet at δ 3.6). This is a very easily enolizable compound and uv evidence suggests the presence of the tautomer **4b** in protic solvents [λ max 359 mμ (ε 2070)]. In order to explore this interesting tautomerism we decided to prepare and obtain the physical data on alkyl derivatives of assignable structure, where the alkylation had blocked or restricted the tautomeric possibilities. Benzyl was chosen as the alkyl group for the study and as **4** has three acidic protons, we attempted the synthesis of as many dibenzyl compounds as possible. Reaction of **4** (see Scheme I) with 2 equiv of sodium hydride and benzyl chloride in dimethylformamide yielded a dibenzyl compound **5**. From the nmr spectrum of **5** (4-proton singlet at δ 3.30, a low-field exchangeable proton) it seemed that both benzyl groups were bound to carbon. Thus the only tautomerism available to **5** is normal amide enolization. There was no spectral evidence of this and therefore the spectral data for **5** can be taken as being representative of the pure oxindole tautomer **4a**. Benzylation of the 3-cyano-4-azaoxindole **3** yielded a monobenzyl compound **6**, whose nmr spectrum showed that the benzyl group was attached to a heteroatom, not to carbon (2-proton singlet at δ 5.72). Reaction of **6** under benzylating conditions yielded a dibenzyl-3-cyano-4-azaoxindole **7**, which no longer had an exchangeable proton in its nmr spectrum and where both benzyl groups were attached to heteroatoms (2-proton singlets at δ 5.72 and 5.09).

(1) R. E. Willette, *Advan. Heterocycl. Chem.*, **9**, 27 (1968).
(2) H. Kagi, *Helv. Chim. Acta*, **24**, 141E (1941).
(3) S. Okuda and M. M. Robison, *J. Amer. Chem. Soc.*, **81**, 740 (1959).
(4) G. E. Ficken and J. D. Kendall, *J. Chem. Soc.*, 747 (1961).
(5) S. Okuda and M. M. Robison, *J. Org. Chem.*, **24**, 1008 (1959).
(6) R. E. Willette, *J. Chem. Soc.*, 5874 (1965).
(7) M. M. Robison and B. L. Robison, *J. Amer. Chem. Soc.*, **77**, 457 (1955).

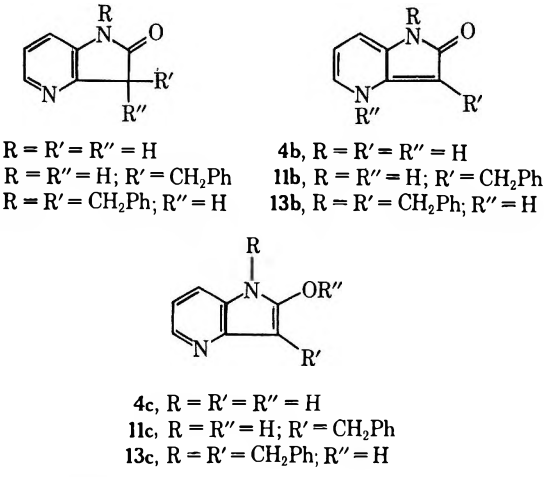
SCHEME I



SCHEME II

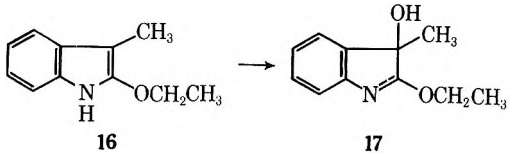


Reflux of **7** in acid proceeded *via* the acid **8** to the dibenzyl-4-azaoxindole **9**. As both the benzyl groups were retained during the acid reflux, we may assume that they are attached to nitrogen. This particular dibenzyl compound **9** cannot tautomerize and therefore its spectral data can be taken as being representative of the **4b** tautomer of 4-azaoxindole. A third dibenzyl compound **13** was prepared as outlined in Scheme II. Reaction of 4-azaoxindole with benzaldehyde gave the benzylidene derivative **10**. This is blocked to enolization, except of the amide type, and as the infrared spectrum showed a strong carbonyl absorption, this type of tautomerism could be discounted. Benzylation of **10** gave a monobenzyl derivative **12**. The benzyl group of **12** was attached to the oxindole nitrogen, rather than oxygen, as the carbonyl band in the infrared spectrum of **10** was still present in that of **12**. Catalytic reduction of **12** yielded the dibenzyl-4-azaoxindole **13**, which lacked major absorption in the infrared above 1600 cm^{-1}. This is in contrast to the dibenzyl azaoxindole **9**, which has a strong band at 1620 cm^{-1}. Thus in the solid state **13** prefers the 2-hydroxy-4-azaindole form **13c**, which means that each of the dibenzyl-4-azaoxindoles prepared, **5**, **9**, and **13**, was representative of one of the three most reasonable tautomers possible for the parent substance, *i.e.*, **4a**, **4b**, and **4c**. This situation, alas, did not appertain in solution.



The nmr spectrum in dimethyl sulfoxide of **13** showed that three tautomers were present in the approximate ratio of 4:1:1 (three different NCH_2Ph and three different CCH_2Ph signals). In view of the similarity of the uv spectrum of **13** in methanol with that of **9**, it is assumed that the principal form in solution is **13b**, with minor contributions from **13a** and **13c**. Hydrogenation of the benzylidene derivative **10** before benzylation yielded a monobenzyl-4-azaoxindole **11**. This compound **11** also lacked a carbonyl group in the infrared spectrum suggesting the solid form was **11c**. Analogously to **13**, the nmr spectrum of **11** in dimethyl sulfoxide showed it to be a mixture of tautomers, although in this case only two were evident, in the approximate ratio of 4:1, based on the CCH_2Ph signal. As the spectrum of the principal tautomer of **11** resembled that of the principal tautomer of **13**, it was assigned structure **11b**; the minor isomer could be assigned structure **11a** based on the multiplicity of the benzyl signal.

The uv spectrum of **11** in methanol was in general agreement, although quantitatively it would seem that more of isomers **11a** and/or **11c** were present in this protic solvent. Support for this view came when **11** was recrystallized from ethanol; the unsolvated material obtained by drying in high vacuum showed a carbonyl band in its infrared spectrum (1720 cm^{-1}). Interestingly, though, the ethanol solvate obtained by simple air drying lacked a carbonyl band entirely. The presence of this tautomer **11c** could be inferred, in some aprotic solvents, by a rapid autoxidation of **11**. For example, on attempted recrystallization from acetonitrile, **11** was converted into the 4-azadioxindole **14**. The carbonyl band present in the infrared spectrum of **14**, 1742 cm^{-1}, is somewhat higher than that of the analogous benzo compound (1730 cm^{-1}),[8] but generally dioxindoles do absorb at higher frequency than the corresponding oxindoles. The ultraviolet spectrum also supports the structural assignment of **14** and there are several analogies for this transformation. The most pertinent is perhaps the extremely rapid autoxidation of **16** to **17**, on its liberation from the fluoroborate salt.[9]



16 **17**

The mechanism of this process has recently been discussed in detail.[10]

One interesting physical property of 4-azaoxindole **4**, unrelated to our study, is the presence of virtual coupling[11] in the nmr spectrum, in which the C_6 and C_7 protons are fortuitously chemically equivalent. This explains the simplicity of the aromatic pattern of **4**, *i.e.*, a 2-proton doublet at δ 7.16 ($J_{5,6} + J_{5,7}$ = 6 Hz) and a 1-proton triplet at δ 8.10 (J = 3 Hz).[12] That this in fact was the case was supported by the observation that running the nmr spectrum in D_2O–DCl one obtains an ABX type of multiplicity for the pyridine protons.

In conclusion, it is evident from our preliminary study that free-energy differences between the principal tautomers of 4-azaoxindoles are small and that relatively minor changes of substitution or solvent can have major effects on the position of equilibrium. It is, therefore, unwise to make predictions with regard to the outcome for alkylations with other reagents or even benzylation under other experimental conditions. Nevertheless, with the spectral data and assignments made in this study, it should be possible to readily determine what in fact does occur in a specific case during further studies.

Experimental Section[13]

Ethyl α-Cyano-3-nitro-2-pyridine Acetate (1).—To a stirred solution of 172.2 g (1.6 mol) of potassium *tert*-butoxide in 2 l. of *tert*-butyl alcohol was added 181.2 g (1.6 mol) of ethyl cyanoacetate. To the resultant suspension was added a hot solution of 126.1 g (0.8 mol) of 2-chloro-3-nitropyridine in 2 l. of *tert*-butyl alcohol. The mixture was refluxed for 6 hr. Evaporation of the *tert*-butyl alcohol yielded a red residue which was treated with 800 ml of 1 *N* hydrochloric acid. The insoluble solid was collected, washed with water, and recrystallized from methanol to yield 148 g (79%) of product. One recrystallization from methanol gave an analytical sample: mp 139–141° (lit.[6] 136–137°); ν_{max}^{Nujol} 2850, 2190, 1625, 1560, 1250 cm^{-1}; nmr ($CDCl_3$) δ 1.20 (t, 3, J = 7 Hz), 4.25 (q, 2, J = 7 Hz), 6.7 (m, 2), 8.4 (m, 2); mass spectrum (70 eV) m/e 235 (parent peak).

Anal. Calcd for $C_{10}H_9N_3O_4$: C, 51.06; H, 3.86; N, 17.87. Found: C, 50.91; H, 4.06; N, 17.59.

Ethyl 3-Amino-α-cyano-2-pyridine Acetate (2).—A solution of 146 g (0.62 mol) of ethyl α-cyano-3-nitro-2-pyridine acetate (1) in 3 l. of 95% ethanol was hydrogenated at 50 psi in the presence of 14.6 g of 10% palladium on carbon. After the catalyst had been removed by filtration, the ethanol was evaporated to yield 123 g of product 2 (100%). An analytical sample was prepared by recrystallization from methanol: mp 115–117°; $\lambda_{max}^{methanol}$ 222 mμ (ε 18,070), 292 (9810), 387 (15,580); ν_{max}^{Nujol} 3480, 3350, 2170, 1640, 1450, 1280 cm^{-1}; nmr ($CDCl_3$) δ 1.32 (t, 3, J = 7 Hz), 4.23 (q, 2, J = 7 Hz), 4.95 (m, 2), 6.78 (m, 2), 7.25 (m, 1).

Anal. Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.45. Found: C, 58.79; H, 5.80; N, 20.27.

3-Cyano-4-azaoxindole (3).—A stirred solution of 110 g (0.530 mol) of ethyl 3-amino-α-cyano-2-pyridine acetate (2) in 7 l. of xylene was refluxed for 20 hr. The reaction mixture was cooled to 0° and the resulting tan solid was collected by filtration. The product was purified by dissolving it in 2 l. of 3% sodium hydroxide solution, filtering the solution through activated charcoal, and reprecipitating the product by bubbling carbon dioxide into the solution. This procedure yielded 42.6 g of purified product **3** (50%): mp >325°; $\lambda_{max}^{methanol}$ 215 mμ (ε 28,290), 252 (10,510), 353 (12,120); ν_{max}^{Nujol} 3080, 2200, 1660, 1620, 1340 cm^{-1}; nmr (DMSO-d_6) δ 7.08 (t, 1, J = 8 Hz), 7.41 (d, 1, J = 8 Hz), 7.83 (d, 1, J = 8 Hz), 10.16 (m, 1); mass spectrum (70 eV) m/e 159 (parent peak).

Anal. Calcd for $C_8H_5N_3O$: C, 60.37; H, 3.17; N, 26.41. Found: C, 60.10; H, 3.41; N, 26.05.

Hydrolysis of 3 to 4-Azaoxindole (4).—A stirred solution of 50 g (0.314 mol) of 3-cyano-4-azaoxindole (**3**) in 5 l. of concentrated hydrochloric acid was refluxed for 22 hr. After cooling, the hydrochloric acid solution was evaporated to dryness. The residue was dissolved in a minimal amount of water. The aqueous solution was made basic with solid sodium bicarbonate and evaporated to dryness. The dry residue was extracted six times with 300-ml portions of boiling chloroform. Evaporation of the chloroform extracts yielded 24 g of product 4 (56%). An analytical sample was prepared by recrystallization from toluene: mp 205–207°; $\lambda_{max}^{methanol}$ 220 mμ (ε 5150), 246 (11,720), 289 (3420), 359 (2070); ν_{max}^{Nujol} 3200, 1700, 1610, 1430 cm^{-1}; nmr (DMSO-d_6) δ 3.62 (s, 2), 7.17 (d, 2), 8.10 (t, 1), 10.4 (s, 1, exchanges); mass spectrum (70 eV) m/e 134 (parent peak).

Anal. Calcd for $C_7H_6N_2O$: C, 62.68; H, 4.51; N, 20.89. Found: C, 62.72; H, 4.60; N, 20.77.

Benzylation of 4 to 3,3-Dibenzyl-4-azaoxindole (5).—To a stirred solution of 0.5 g (3.73 mmol) of 4-azaoxindole (4) in 50 ml of dry dimethylformamide was added 0.314 g (7.44 mmol) of sodium hydride (57% in oil) under a nitrogen atmosphere. After 20 min, 0.94 g (7.44 mmol) of benzyl chloride was added all at once. The solution was heated to 50° and stirred for 18 hr. The dimethylformamide was taken off under reduced pressure. To the residue was added 50 ml of 1 *N* hydrochloric acid. This solution was washed with petroleum ether and then made basic with solid potassium carbonate. The basic solution was extracted three times with methylene chloride. The methylene chloride was dried and evaporated. The residue was recrystallized from acetonitrile to yield 0.5 g (38%) of product 5: mp 281–283°; $\lambda_{max}^{methanol}$ 252 mμ (ε 8310), 291 (3602); ν_{max}^{Nujol} 1710, 1610, 1580 cm^{-1}; nmr (DMSO-d_6) δ 3.3 (s, 4), 6.82 (m, 2), 7.0 (m, 10), 8.28 (d, 1, J = 6 Hz), 10.02 (s, 1).

Anal. Calcd for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.91. Found: C, 80.01; H, 5.91; N, 9.10.

Benzylation of 3 to 4-Benzyl-3-cyano-4-azaoxindole (6).—A 0.54-g (0.0132 mol) sample of 57% sodium hydride–mineral oil was added to a stirred solution of 2.0 g (0.0126 mol) of 3-cyano-4-azaoxindole (**3**) in 30 ml of DMF under a nitrogen atmosphere. After 0.5 hr 1.58 g (0.0126 mol) of benzyl chloride was added all at once. The mixture was heated to 50° and allowed to stir for

(8) H. E. Baumgarten and P. L. Creger, *J. Amer. Chem. Soc.*, **82**, 4634 (1960).

(9) T. Hino, M. Nakagawa, and S. Akaboshi, *Chem. Commun.*, 656 (1967).

(10) M. Nakagawa, H. Yamaguchi, and T. Hino, *Tetrahedron Lett.*, 4035 (1970).

(11) J. I. Musher and E. J. Corey, *Tetrahedron*, **18**, 791 (1962).

(12) We are indebted to Professor Peter Yates for this explanation.

(13) Melting points were obtained in a Thomas-Hoover melting point apparatus and are uncorrected. Nmr spectra were obtained on a Varian A-60 instrument. Mass spectra were obtained on a MS-9 instrument.

16 hr. The DMF was removed under reduced pressure. The residue was washed with 50 ml of 1 *N* hydrochloric acid and then recrystallized from ethanol–dimethylformamide to yield 1.7 g of product **6** (54%): mp 308–310°; nmr (DMSO-d_6) δ 5.72 (s, 2), 6.88 (t, 1, J = 8 Hz), 7.15 (d, 1, J = 8 Hz), 7.38 (s, 5), 7.78 (d, 1, J = 8 Hz), 11.30 (m, 1); $\lambda_{max}^{methanol}$ 210 mμ (ϵ 29,260), 258 (9660), 362 (12,910); ν_{max}^{Nujol} 2200, 1630, 1580, 1450, 1370 cm^{-1}.

Anal. Calcd for $C_{15}H_{11}N_3O$: C, 72.27; H, 4.45; N, 16.86. Found: C, 72.41; H, 4.77; N, 16.57.

Benzylation of 6 to 1,4-Dibenzyl-3-cyano-4-azaoxindole (7).—To a stirred solution of 5.0 g (20.1 mmol) of 4-benzyl-3-cyano-4-azaoxindole (**6**) in 150 ml of dimethylformamide was added 0.93 g of sodium hydride (57% in oil) under a nitrogen atmosphere. After 20 min 2.8 g (22 mmol) of benzyl chloride was added all at once. The solution was heated to 60° and allowed to stir for 18 hr. The dimethylformamide was removed under reduced pressure. The residue was washed with 20 ml of petroleum ether and then 50 ml of water. The washed residue was recrystallized from methyl alcohol to yield 5.3 g (76%) of product **7**: mp 198–200°; $\lambda_{max}^{methanol}$ 210 mμ (50,280), 263 (14,360), 363 (17,640); γ_{max}^{Nujol} 2205, 1670, 1645, 1600 cm^{-1}; nmr (DMSO-d_6) δ 5.09 (s, 2), 5.76 (s, 2), 6.94 (t, 1), 7.34 (m, 11), 7.9 (d, 1).

Anal. Calcd for $C_{22}H_{17}N_3O$: C, 77.85; H, 5.05; N, 12.38. Found: C, 77.46; H, 5.30; N, 12.44.

Hydrolysis of 7 to 1,4-Dibenzyl-4-azaoxindole (9).—A solution of 1.0 g (2.97 mmol) of 1,4-dibenzyl-3-cyano-4-azaoxindole (**7**) in 100 ml of concentrated hydrochloric acid was refluxed for 72 hr. The hydrochloric acid was evaporated. A minimal amount of water was added to the residue. The solution was then made basic with solid sodium bicarbonate and extracted three times with 75-ml portions of methylene chloride. The methylene chloride was dried and evaporated. Recrystallization of the residue from acetonitrile yielded 0.5 g (56%) of product **9**: mp 175–177°; $\lambda_{max}^{methanol}$ 233 mμ (ϵ 12,580), 262 (6610), 286 (1710), 362 (6240); ν_{max}^{Nujol} 1638, 1570, 1590, 1370 cm^{-1}; nmr (DMSO-d_6) δ 5.02 (s, 2), 5.26 (s, 2), 5.17 (s, 1), 6.4 (t, 1, J = 8 Hz), 6.81 (d, 1, J = 8 Hz), 7.32 (m, 10), 7.56 (d, 1, J = 8 Hz).

Anal. Calcd for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.91. Found: C, 80.55; H, 5.97; N, 9.10.

Hydrolysis of 6 to 4-Benzyl-4-azaoxindole (15).—A stirred solution of 1.2 g (4.82 mmol) of 4-benzyl-3-cyano-4-azaoxindole (**6**) in 150 ml of concentrated hydrochloric acid was refluxed for 65 hr. The hydrochloric acid solution was evaporated to dryness. The residue was dissolved in a minimal amount of water. The solution was saturated with solid sodium bicarbonate and then extracted six times with 50-ml portions of methylene chloride. The methylene chloride was dried over anhydrous sodium sulfate and evaporated. Two recrystallizations of the residue from ethanol–acetonitrile 4:1 yielded 0.6 g (55%) of pure product: mp 257–258°; $\lambda_{max}^{methanol}$ 216 mμ (ϵ 25,350), 256 (12,360), 276 (3770), 360 (12,110); ν_{max}^{Nujol} 2850, 1620, 1580, 1450 cm^{-1}; nmr (DMSO-d_6) δ 4.9 (s, 1), 5.13 (s, 2), 6.30 (t, 1, J = 8 Hz), 6.63 (d, 1, J = 7 Hz), 7.25 (s, 5), 7.41 (d, 1, J = 7 Hz), 10.13 (m, 1).

Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.99; H, 5.38; N, 12.35. Found: C, 74.65; H, 5.48; N, 12.35.

Benzylidene Derivative of 4-Azaoxindole (10).—A solution of 3.02 g (0.022 mol) of 4-azaoxindole (**4**), 2.39 g (0.022 mol) of benzaldehyde, and 1 ml of piperidine in 700 ml of toluene was refluxed for 4 hr. After the toluene was evaporated, the residue was recrystallized from ethanol–benzene to yield 3.75 g of product **10** (75%): mp 206–208°; $\lambda_{max}^{methanol}$ 253 mμ (ϵ 9270), 290 (12,860), 316 (17,140), 391 (6,110); ν_{max}^{Nujol} 3130, 1700, 1600, 1370, 1200 cm^{-1}; nmr (DMSO-d_6) δ 7.20 (d, 2, J = 4 Hz), 7.45 (m, 3), 7.65 (s, 1), 8.23 (t, 1, J = 4 Hz), 8.75 (m, 2), 10.07 (m, 1).

Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.65; H, 4.54; N, 12.61. Found: C, 75.65; H, 4.77; N, 12.38.

Benzylation of 10 to 12.—To a stirred solution of 1.0 g (5.0 mmol) of 3-benzylidene-4-azaoxindole (**10**) in 50 ml of dry dimethylformamide was added 0.24 g (5.5 mmol) of sodium hydride (57% in oil) under a nitrogen atmosphere. After 20 min 0.699 ml (5.0 mmol) of benzyl chloride was added all at once. The solution was heated to 50° and allowed to stir for 18 hr. The dimethylformamide was removed under reduced pressure. The residue was washed with 20 ml of petroleum ether and then 40 ml of 1 *N* hydrochloric acid was added. The solution was then made basic with solid potassium carbonate at 0° and extracted with methylene chloride. The methylene chloride was dried and evaporated. The residue was recrystallized from benzene–hexane to yield 0.7 g (47%) of product **12**: mp 122–125°; $\lambda_{max}^{methanol}$ 232 mμ (ϵ 10,140), 320 (22,340), 394 (4830); ν_{max}^{Nujol} 1713, 1630, 1600 cm^{-1}; nmr ($CDCl_3$) δ 4.98 (s, 1), 6.99 (m, 2), 7.29 (m, 5), 7.50 (m, 3), 8.02 (s, 1), 8.29 (q, 1), 8.79 (m, 2).

Anal. Calcd for $C_{21}H_{16}N_2O$: C, 80.75; H, 5.16; N, 8.97. Found: C, 81.25; H, 5.31; N, 9.03.

1,3-Dibenzyl-4-azaoxindole (13).—A solution of 0.5 g (1.6 mmol) of 1-benzyl-3-benzylidene-4-azaoxindole (**12**) in 50 ml of 95% ethanol was hydrogenated at 1 atm in the presence of 50 mg of 10% palladium on carbon. After the catalyst had been removed by filtration, the ethanol was evaporated. The residue was recrystallized from methanol to yield 0.3 g (66%) of product **13**: mp 158–160°; uv $\lambda_{max}^{methanol}$ 260 mμ (ϵ 10,280), 288 (3720), 364 (3910); ν_{max}^{Nujol} 1610 (w) 1560 cm^{-1}; nmr (DMSO-d_6) δ 3.86 (s, 2), 5.07 (s, 2), 6.27 (t, 1, J = 8 Hz), 6.75 (d, 1, J = 7 Hz), 7.0 (m, 10), 8.25 (d, 1, J = 6 Hz).

Anal. Calcd for $C_{21}H_{18}N_2O$: C, 80.23; H, 5.77; N, 8.91. Found: C, 80.22; H, 5.97; N, 9.02.

Hydrogenation of 10 to 3-Benzyl-4-azaoxindole (11).—A solution of 2.5 g (0.011 mol) of 4-azaoxindole benzal **10** in 150 ml of ethanol was hydrogenated at 1 atm in the presence of 0.25 g of 10% palladium on carbon. The catalyst was removed by filtration through filter cell and the ethanol evaporated. The yellow solid which remained was recrystallized from ethanol to yield 2.3 g of product **11** (92%): mp 188–190°; $\lambda_{max}^{methanol}$ 257 mμ (ϵ 12,280), 284 (4040), 372 (5580); ν_{max}^{Nujol} 1602, 1590, 1575 cm^{-1}; nmr (DMSO-d_6) δ 1.06 (t, 3), 3.70 (s, <2), 7.18 (m, 7); mass spectrum (70 eV) m/e 224 (parent peak) <5% of 240.

Anal. Calcd for $C_{14}H_{12}N_2O \cdot C_2H_5OH$: C, 71.20; H, 6.65; N, 10.30. Found: C, 70.92; H, 6.84; N, 9.91.

A portion of the solvate was recrystallized from ethanol with rapid cooling and scratching. The crystals were collected and dried for 18 hr in high vacuum at 100°: ν_{max}^{Nujol} 1720, 1586, 1570 cm^{-1}; nmr (DMSO-d_6) δ 3.24 (m, ~0.4 H), 3.70 (s, ~1.6 H), 7.18 (m, 7).

Anal. Calcd for $C_{14}H_{12}N_2O$: C, 74.99; H, 5.38; N, 12.49. Found: C, 74.82; H, 4.92; N, 12.90.

3-Benzyl-4-azadioxindole (14). A.—Three recrystallizations of 3-benzyl-4-azaoxindole (**11**) from acetonitrile yielded **14** in 50% yield: mp 278–280°; $\lambda_{max}^{methanol}$ 245 mμ (10,060), 292 (2670); ν_{max}^{Nujol} 3196, 1745, 1626, 1604 cm^{-1}; nmr (DMSO-d_6) δ 3.20 (s, 2), 6.90 (m, 8); mass spectrum m/e 240 (M^+).

Anal. Calcd for $C_{14}H_{12}N_2O_2$: C, 70.00; H, 5.00; N, 11.68. Found: C, 70.32; H, 5.14; N, 11.90.

B.—**11** (0.3 g, 1.25 mmol) was dissolved in acetic acid (30 ml). Hydrogen peroxide (0.155 g, 1.37 mmol) was added with stirring. The solution was heated (70°) for 2 hr. The acetic acid was removed under reduced pressure. The residue (0.30 g, 98% yield) was crystalline, mp 276–278°, and was identical (mmp and ir) with the material from A.

Registry No.—**1**, 32501-02-3; **2**, 32501-03-4; **3**, 32501-04-5; **4a**, 32501-05-6; **4b**, 32501-06-7; **4c**, 32501-07-8; **5**, 32501-08-9; **6**, 32544-48-2; **7**, 32501-09-0; **9**, 32605-76-8; **10**, 32500-77-9; **11a**, 32500-78-0; **11b**, 32500-79-1; **11c**, 32500-80-4; **12**, 32500-81-5; **13a**, 32500-82-6; **13b**, 32500-83-7; **13c**, 32500-84-8; **14**, 32500-85-9.

Acknowledgment.—We wish to acknowledge the support and encouragement of Dr. George deStevens and helpful discussions of the spectral data with Mr. L. Dorfman, whose staff we thank for the microanalyses and spectra.

The Reaction of Pyridine N-Oxide with Acetic Anhydride in Anisole and in Benzonitrile[1a,b]

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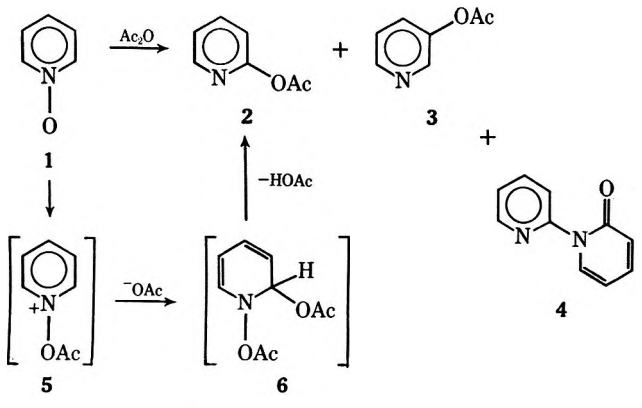
Received May 17, 1971

The reaction of pyridine N-oxide and acetic anhydride in anisole provided 22% of a mixture of 2-(o-, m-, and p-methoxyphenyl)pyridine in relative yields of 50.7:15.5:33.9, respectively. The same reaction in benzonitrile yielded 8.5% of N-2-pyridylacetamide and trace quantities of N-2-pyridylbenzamide and 2-(m- and p-cyanophenyl)pyridine (relative yields of the latter, 71:29). Under the reaction conditions, N-2-pyridylbenzamide is converted to N-2-pyridylacetamide. The products are thought to arise by attack of solvent on an intermediate with an electrophilic site at the 2 position of the pyridine ring.

The reaction of pyridine N-oxide (**1**) with acetic anhydride yields mainly 2-acetoxypyridine (**2**),[2,3] but several side products, including 3-acetoxypyridine (**3**) and N-(2′-pyridyl)-2-pyridone (**4**), are also formed.[4]

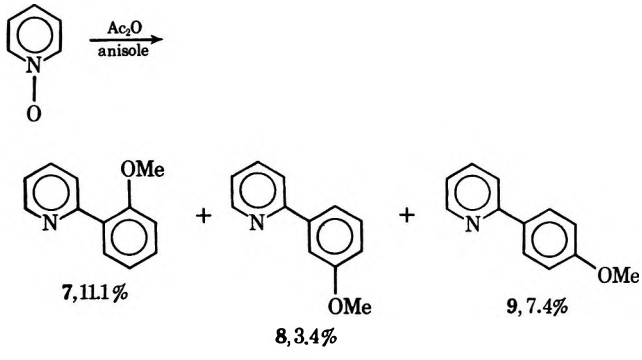


Mechanistic studies[3,5] indicate that the 2-acetoxypyridine is probably produced by way of acetate ion attack on the N-acetoxypyridinium ion **5** to yield the dihydropyridine **6**, which loses acetic acid to give **2**. The detailed mode of loss of acetic acid is unknown as are the mechanisms of formation of the minor products.

In the hope of being able to trap intermediates in the acetic anhydride–pyridine N-oxide reaction, the latter was performed in anisole and in benzonitrile. These solvents have recently been found useful in trapping picolyl cations produced in the reaction of acetic anhydride with 2- and 4-picoline N-oxide.[6] Cations substitute into anisole very predominantly at the ortho and para positions,[6,7] whereas radical attack on the ring yields more meta- than para-substituted product.[8] Organic cations attack benzonitrile at the nitrogen atom[6,9] and any electrophilic attack that does occur on the ring leads mainly to meta-substituted products; radical attack occurs readily at the ortho and para positions of the ring.[8]

Results

Anisole.—The reaction of pyridine N-oxide with acetic anhydride in refluxing anisole for 6 hr yielded, in addition to 2-acetoxypyridine, a three-component mixture of 2-(methoxyphenyl)pyridines. The product was analyzed by combined gas chromatography–mass spectrometry. The mass spectra of the three isomers are consistent with the assignment as methoxyphenylpyridines. A sample of the major component, which had the shortest glpc retention time, was shown by nmr spectroscopy to possess one α proton on the pyridine ring, thus indicating that the methoxyphenyl group is attached to the 2 position. This isomer was shown to be 2-(o-methoxyphenyl)pyridine (**7**) by glpc and mass spectrometric comparison with an authentic sample prepared by the reaction of pyridine with o-methoxyphenyllithium followed by air oxidation.[10] The component present in second greatest amount and having the longest retention time was similarly identified as 2-(p-methoxyphenyl)pyridine (**9**). The minor component was assigned the structure 2-(m-methoxyphenyl)pyridine (**8**) on the basis of the similarity of its mass spectrum to the other two, its retention time (between those of the other two; typical behavior for a meta isomer), and the expectation that the meta isomer would accompany the ortho and para isomers. The yields, as indicated by gas chromatography, are listed below. No other solvent-derived products could be detected.



(1) (a) We wish to thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this work. (b) Taken from the Ph.D. Thesis of G. L. D., University of Pittsburgh, Pittsburgh, Pa., 1969. (c) NASA Predoctoral Fellow.

(2) M. Katada, *J. Pharm. Soc. Jap.*, **67**, 51 (1947).

(3) V. J. Traynelis in "Mechanisms of Molecular Migrations," Vol. II, B. S. Thyagarajan, Ed., Interscience, New York, N. Y., 1969, p 1.

(4) D. M. Pretorius and P. A. de Villiers, *J. S. Afr. Chem. Inst.*, **28**, 48 (1965); A. Klaebe and A. Lattes, *J. Chromatogr.*, **27**, 502 (1967).

(5) E. Ochiai and T. Okamoto, *J. Pharm. Soc. Jap.*, **68**, 88 (1948); *Chem. Abstr.*, **47**, 8073e (1953); J. H. Markgraf, H. B. Brown, Jr., S. C. Mohr, and R. G. Peterson, *J. Amer. Chem. Soc.*, **85**, 958 (1963); S. Oae and S. Kozuka, *Tetrahedron*, **20**, 2691 (1964); S. Oae and S. Kozuka, *ibid.*, **21**, 1971 (1965).

(6) T. Cohen and G. L. Deets, *J. Amer. Chem. Soc.*, **89**, 3939 (1967); T. Cohen and G. L. Deets, *ibid.*, in press.

(7) A. T. Jurewicz, J. H. Bayless, and L. Friedman, *ibid.*, **87**, 5788 (1965); P. Kovacic and J. J. Hiller, Jr., *J. Org. Chem.*, **30**, 1581 (1965).

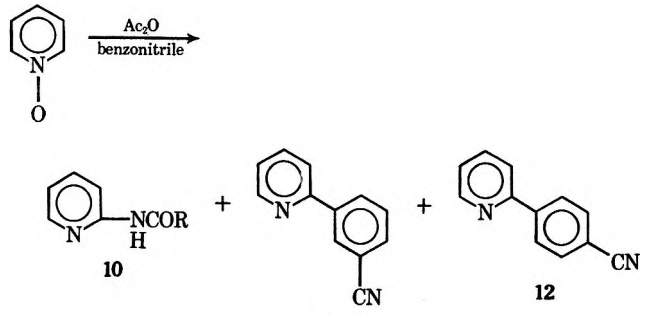
(8) J. R. Shelton and C. W. Uzelmeier, *J. Amer. Chem. Soc.*, **88**, 5222 (1966).

(9) R. M. Lusskin and J. J. Ritter, *ibid.*, **72**, 5577 (1950); R. F. Borch, *J. Org. Chem.*, **34**, 627 (1969).

(10) H. Gilman and J. T. Edwards, *Can. J. Chem.*, **31**, 457 (1953).

In attempts to improve the yield of anisylpyridines, pyridine *N*-oxide was treated with *p*-toluenesulfonyl chloride in refluxing anisole in the presence and absence of 2,6-lutidine (a potential proton acceptor), and *N*-acetoxypyridinium perchlorate[11] was heated in refluxing anisole in the presence and absence of 2,6-lutidine. None of these reactions produced detectable quantities of anisylpyridines.

Benzonitrile.—When the reaction of pyridine *N*-oxide with acetic anhydride was performed in benzonitrile at 160°, four products which appeared to have resulted from reaction with solvent were detected by combined glpc–mass spectrometry. Two of these had the fragmentation patterns expected of *N*-2-pyridylbenzamide (**10**, R = phenyl) and *N*-2-pyridylacetamide (**10**, R = methyl), and these identifications were confirmed by comparison with authentic samples prepared by treatment of 2-aminopyridine with the appropriate acid chloride. The two remaining products had the fragmentation patterns expected of 2-(cyanophenyl)pyridines. They were identified as 2-(*m*-cyanophenyl)-pyridine (**11**) and 2-(*p*-cyanophenyl)pyridine (**12**) by comparison with samples prepared by decomposition in pyridine of the diazonium ion derived from the appropriate aminobenzonitrile.[12] The yield of *N*-2-pyridylacetamide was 8.5%. That of *N*-2-pyridylbenzamide was less than 1%. The 2-(cyanophenyl)pyridine mixture was also formed in less than 1% yield and the composition was 71% meta and 29% para.



10 **11** **12**

It was also shown that *N*-2-pyridylbenzamide (**10**, R = phenyl) is converted to *N*-2-pyridylacetamide (**10**, R = methyl) under the conditions employed in the reaction of pyridine *N*-oxide with acetic anhydride in benzonitrile.

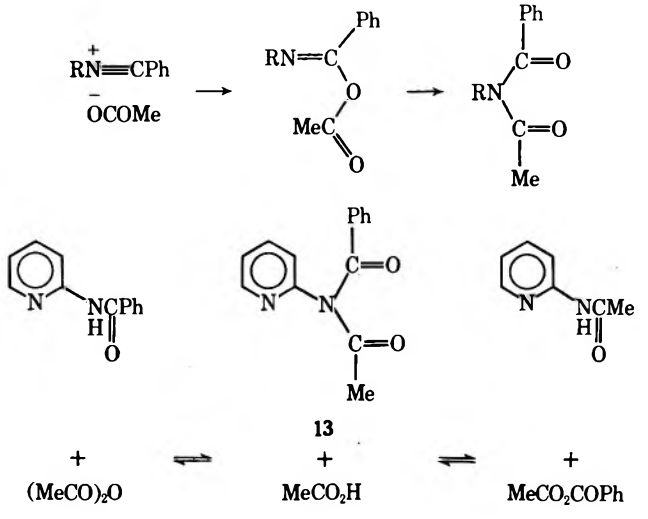
Discussion

The nature of the products is consistent with the attack on the solvents of some intermediate with an electrophilic site at the 2 position of the pyridine ring. The attack on anisole occurs with ortho/para and meta/para ratios of 1.5 and 0.46, respectively. These values are similar to those (up to 1.9 and 0.37, respectively) which have been found for several electrophilic substitutions in the literature[7] and very different from those (5.3–13.5 and 1.4–5.6, respectively) for some reported examples of radical attack on anisole.[8] However, this evidence by itself does not demand that the attack on anisole be electrophilic rather than radical in nature, since the rate-determining step could occur subsequent to the attack on solvent.

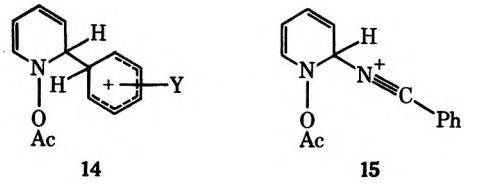
(11) C. W. Muth and R. S. Darlak, *J. Org. Chem.*, **30**, 1909 (1965).
(12) J. W. Haworth, I. M. Heilbron, and D. H. Hey, *J. Chem. Soc.*, 349 (1940).

The attack on benzonitrile occurs predominantly at the nitrogen atom (*vide infra*) and the very small quantity of ring-substituted benzonitrile arises mainly from meta attack. As noted above, this pattern is characteristic of cationic attack on benzonitrile.

According to the results of our experiments on the trapping of picolyl cations by benzonitrile,[6] one might expect *N*-acetyl-*N*-(2-pyridyl)benzamide (**13**) to result from attack of the type of electrophile discussed above on the nitrogen atom of benzonitrile. Its expected mode of formation is shown below (R represents the 2-pyridyl group or its precursor). However, the expected imide **13** must be readily deacylated, as shown, under the reaction conditions. This follows from our finding that *N*-(2-pyridyl)benzamide is converted to *N*-(2-pyridyl)acetamide under the reaction conditions; this exchange presumably proceeds through the intermediate formation of **13**. Thus, the production of *N*-(2-pyridyl)acetamide in 8.5% yield indicates that benzonitrile has reacted with an electrophilic site at the 2 position of the pyridine nucleus.



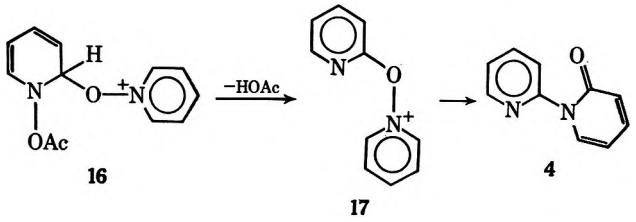
The simplest hypothesis is that these products arise by attack of the *N*-acetoxypyridinium ion on the nucleophilic solvents to produce species such as **14** (Y = OMe or CN) and **15**. In the case of **14**, rearomatization of the pyridine ring by the loss of acetic acid and of the



14 **15**

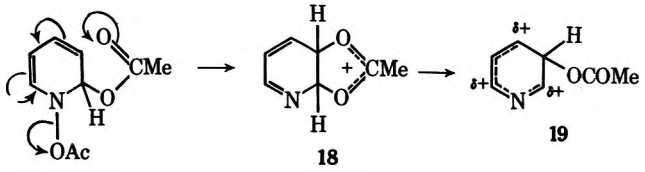
substituted ring by proton loss would yield the 2-arylpyridine products. Loss of acetic acid from **15** and subsequent reactions of the resulting nitrilium ion as outlined above would lead to the amide products. One attractive feature of this scheme is that it is consistent with the presently accepted mechanism for the production of 2-acetoxypyridine, in which acetate ion is the nucleophile which attacks the 2 position. Another is that if pyridine *N*-oxide is the nucleophile which attacks **5** then the known product, *N*-(2′-pyridyl)-2-pyridone (**4**), would result *via* intermediates **16** and **17**. The latter is almost certainly an intermediate in the

known reaction of 2-bromopyridine with pyridine N-oxide to produce **4**.[13]



16 **17** **4**

If solvent attack is indeed occurring on the N-acetoxypyridinium ion **5**, then the acetate counterion appears to be an important competitor. However, when this ion was replaced by the much less nucleophilic perchlorate ion in anisole, no solvent-derived products were obtained even when 2,6-lutidine was present as a potential proton acceptor. The failure of this reaction and of the reaction of pyridine N-oxide with *p*-toluenesulfonyl chloride in anisole to produce solvent-derived products suggests that a step following nucleophilic attack on the 2 position of a pyridinium cation may be rate determining in these cases. Another possibility is that acetate ion plays an important role in the formation of some other intermediate which is responsible for the solvent capture in the reaction of pyridine N-oxide with acetic anhydride. A possible candidate is **19** which could be produced from the intermediate **6** by the sequence shown (the conversion of **6** to **18** could be stepwise or concerted) and which may also be converted to the minor product 3-acetoxypyridine (**3**) by a proton loss.



6 **18** **19**

Experimental Section

General.—Melting points were determined in a Kofler block utilizing a stage calibrated thermometer and are thus corrected. Boiling points are uncorrected. Infrared spectra were determined on a Beckman IR-8 spectrophotometer. Proton magnetic resonance spectra are for deuteriochloroform solutions and were determined on a Varian A-60 instrument; chemical shifts are reported on the τ scale relative to internal tetramethylsilane. Analytical gas chromatography was performed on F & M 1609 or Varian 1520 A instruments equipped with flame ionization detectors and Disc Integrators. The glpc results are reported as follows: peak no., compound name (retention time in minutes). For determining yields, the flame responses of authentic samples were calibrated against those of suitable standards. Isomers were assumed to have identical flame responses; this was shown to be true in several cases. Mass spectra were determined at 70 eV on a LKB-9000 combined gas chromatograph–mass spectrometer. The *m/e* values are reported for major peaks followed in parentheses by the per cent of the base peak.

Reaction of Pyridine N-Oxide with Acetic Anhydride in Anisole.—A solution of 12.3 g (120 mmol) of acetic anhydride and 7.8 g (83 mmol) of pyridine N-oxide in 50 ml of anisole was heated at reflux for 6 hr. A portion of the cooled reaction mixture was extracted with 10% hydrochloric acid (one 25-ml and three 15-ml portions). This acidic extract was extracted with ether (three 5-ml portions), made basic with sodium carbonate, and extracted with ether (two 25-ml portions) and chloroform (three 25-ml portions). The combined organic extract was dried over magnesium sulfate, concentrated, and examined by glpc on a 10 ft × 0.125 in. 3% OV-17 column at an initial temperature of 100° with a programmed rise of 4°/min: 1, 2-acetoxypyridine (12.2); 2, 2-(*o*-methoxyphenyl)pyridine (19.9); 3, 2-(*m*-methoxyphenyl)pyridine (21.1); 4, 2-(*p*-methoxyphenyl)-pyridine (21.8). The identification of 2-acetoxypyridine is based on its mass spectrometric fragmentation pattern which exhibited major peaks at *m/e* 137, 95, 67, and 43. The mass spectra of the other peaks are: peak 2, *m/e* 185 (100), 184 (93), 156 (55), 155 (81), 154 (92), 153 (11), 142 (16), 128 (51), 127 (15), 115 (18), 89 (16), 80 (96), 79 (18), 78 (24), 77 (28), 64 (10), 63 (23), 62 (14), 52 (14), 51 (29), 50 (15), 39 (32); peak 3, *m/e* 185 (92), 184 (100), 156 (33), 155 (59), 154 (55), 143 (10), 142 (12), 115 (12), 95 (14), 89 (11), 78 (17), 77 (12), 63 (12), 52 (11), 51 (19), 50 (11), 39 (21); peak 4, *m/e* 185 (100), 184 (9), 154 (8), 143 (39), 142 (20), 115 (8), 63 (9), 51 (10), 39 (11). These spectra are consistent with those expected for methoxyphenylpyridines. The nmr spectrum of a sample of peak 2 isolated by preparative glpc shows τ 1.70 (q, single 2-pyridyl proton), 2.47–3.50 (m, 7 aromatic protons), 6.43 (s, 3 methyl protons). The 2-*o*- and 2-*p*-methoxyphenylpyridine were found to be identical by glpc and mass spectrometric comparison with authentic samples. The relative yields of ortho:meta:para were found to be 50.7:15.5:33.9. In another run using 4.16 g (43.7 mmol) of pyridine N-oxide and 8.34 g (81.7 mmol) of acetic anhydride in 25 ml of anisole, the yield of 2-(methoxyphenyl)pyridines was found to be 22%. No extractions were used in this run and triphenylmethane was used as the glpc standard. The analysis was performed at 200°.

Reaction of Pyridine N-Oxide with Acetic Anhydride in Benzonitrile.—A solution of 4.4 g (46 mmol) of pyridine N-oxide and 6.6 g (65 mmol) of acetic anhydride in 50 ml of benzonitrile was heated for 6 hr at a bath temperature of 160°. A portion of the reaction mixture was worked up by the same extraction techniques described above for the same reaction in anisole. The glpc analysis was also performed in the same way: 1, N-2-pyridylacetamide (11.9); 2, probable structure N-(2′-pyridyl)-2-pyridone (19.8); 3, 2-(*m*-cyanophenyl)pyridine (20.8); 4, 2-(*p*-cyanophenyl)pyridine (21.1); 5, N-2-pyridylbenzamide (22.3). The material constituting the first peak had the same retention time and mass spectrum as those of an authentic sample: mass spectrum *m/e* 136 (23), 94 (100), 78 (10), 67 (81), 43 (42), 39 (16). The probable structure for the material in the second peak is derived from its mass spectrum and the fact that this substance has been noted previously as a product of this reaction:[4] mass spectrum *m/e* 172 (100), 171 (16), 144 (20), 118 (60), 117 (12), 79 (60), 78 (48), 52 (26), 51 (40), 50 (12), 40 (36), 39 (20). The materials constituting peaks 3–5 had identical glpc behavior and mass spectra with those of authentic samples. The mass spectra follow: peak 3, *m/e* 180 (100), 179 (47), 153 (9), 152 (8), 52 (7), 51 (14), 50 (8), 39 (8); peak 4, *m/e* 180 (100), 179 (52), 153 (11), 152 (10), 52 (11), 51 (17), 50 (11), 39 (25); peak 5, *m/e* 198 (10), 197 (7), 170 (16), 169 (37), 106 (9), 105 (100), 78 (12), 77 (78), 51 (25), 39 (12). The relative yields of 2-(*m*-cyanophenyl)- and 2-(*p*-cyanophenyl)pyridine were determined by glpc to be 71 and 29%, respectively. In another run using 33.2 mmol of pyridine N-oxide and 52.1 mmol of acetic anhydride, by direct analysis of the product (no extractions) utilizing 2-methoxynaphthalene as a standard and a 5 ft × 0.125 in. 15% Carbowax column at 200°, the yield of N-2-pyridylacetamide was found to be 8.5% and those of N-2-pyridylbenzamide and the 2-(cyanophenyl)pyridines were shown to be less than 1% each.

2-(*o*-Methoxyphenyl)pyridine (7) and 2-(*p*-Methoxyphenyl)-pyridine (9).—These compounds were prepared according to the method of Gilman and Edwards.[10] The picrate of the liquid ortho isomer had mp 155–156° (lit.[10] mp 152–155°; lit.[14] mp 155–156°). The para isomer had mp 47–49° (lit.[10] mp 47–50°; lit.[14] mp 50–51°).

2-(*p*-Cyanophenyl)pyridine.—It has been shown[12] that aryl diazonium ions react with pyridine to give arylation very predominantly in the α position. To a solution of 25 g (0.21 mol) of *p*-aminobenzonitrile (Eastman) in 75 ml of concentrated hydrochloric acid and 700 ml of water was added dropwise a solution of 15 g (0.22 mol) of sodium nitrite in 75 ml of water at 5–10°. The diazonium solution was then added dropwise over a period of 1 hr to 250 ml of pyridine and the mixture was stirred for 24

(13) F. Ramirez and P. W. von Ostwalden, *J. Amer. Chem. Soc.*, **81**, 156 (1959).

(14) J. W. Haworth, I. M. Heilbron, and D. H. Hey, *J. Chem. Soc.*, 358 (1940).

hr at room temperature. The solution was made basic with concentrated ammonium hydroxide and extracted with chloroform (five 100-ml portions). Chloroform and pyridine were removed from the dried extract by evaporation and the resulting solid was dissolved in 150 ml of hot ethanol and treated with 45 g of picric acid in 300 ml of hot ethanol. A crude picrate (20 g, 25%) was obtained by cooling the ethanolic solution in Dry Ice and recrystallizing the precipitate once from acetone. Several additional recrystallizations yielded 7.0 g of picrate, mp 172–173°. The free base was liberated by treatment of this picrate with 10% ammonium hydroxide and was recrystallized from acetone–petroleum ether yielding 2.2 g of pure 2-(*p*-cyanophenyl)-pyridine: mp 98–99° (lit.[15] mp 97–98°); nmr τ 1.25 (q, one 2-pyridyl proton), 2.65–3.50 (m, 7 remaining aromatic protons).

***m*-Aminobenzonitrile.**—A solution of 26 g (0.68 mol) of sodium borohydride in 350 ml of water was added to a slurry of 200 mg of 10% palladium on charcoal in 100 ml of water.[16] A solution of 46 g (0.31 mol) of *m*-nitrobenzonitrile in 800 ml of methanol was added dropwise with ice cooling over a period of 50 min while nitrogen was passed through the mixture. Caution must be exercised in the above procedure as the order of addition is critical and an explosion could ensue if the order were reversed. The reaction mixture was stirred for an additional 15 min, filtered, acidified with 10% hydrochloric acid, made basic with 10% ammonium hydroxide, and extracted with ether (nine 100-ml portions). The dried ether extract was evaporated and the residue recrystallized from ether yielding 24.2 g (67%) of *m*-aminobenzonitrile, mp 53–54° (lit.[17] mp 52°).

2-(*m*-Cyanophenyl)pyridine.—To a solution of 24 g (0.20 mol) of *m*-aminobenzonitrile in 700 ml of water and 75 ml of concentrated hydrochloric acid was added dropwise a solution of 14 g (0.20 mol) of sodium nitrite at 5°. The diazonium solution was then added to 250 ml of pyridine and the resulting solution was stirred for 24 hr at room temperature. The solution was made basic with concentrated ammonium hydroxide and extracted with chloroform (five 100-ml portions). Chloroform and pyridine were removed from the extract by evaporation.

The residue was dissolved in hot ethanol and treated with 46 g of picric acid in hot ethanol. The resulting picrate was crystallized from the ethanol with Dry Ice cooling and the crude picrate was recrystallized several times from acetone, treated with Norite, recrystallized from ether, and mixed with 10% aqueous sodium hydroxide; the resulting solid was filtered and recrystallized from pentane–carbon tetrachloride to yield 0.028 g of product which contained approximately 70% (glpc) of a compound which had a retention time and mass spectrum which were identical with those of the compound assigned the structure 2-(*m*-cyanophenyl)pyridine. Since *m*-aminobenzonitrile was used in this preparation, the cyano group in the product is surely at the meta position. Since this arylation reaction results in very predominantly 2-substituted pyridine[12] and since the pyridine–acetic anhydride reaction produced this material along with 2-*p*-cyanophenylpyridine, the likelihood is extremely high that the *m*-cyanophenyl group is also substituted into the pyridine nucleus at the 2 position of the latter.

***N*-2-Pyridylbenzamide (10, R = Phenyl).**—To a solution of 9.5 g (0.100 mol) of 2-aminopyridine (Aldrich) in 20 ml of dry pyridine was added dropwise with ice cooling 14.2 g (0.100 mol) of benzoyl chloride. The reaction mixture was stirred for 90 min at room temperature, 100 ml of water was added, and the aqueous solution was extracted with chloroform (one 50-ml and two 20-ml portions). The dried chloroform extract was evaporated and the resulting oil was crystallized from benzene–hexane, yielding 13.9 g (70%) of *N*-2-pyridylbenzamide, mp 81–82° (lit.[18] mp 82–83°). The product also exhibited an infrared spectrum identical with that reported (Sadtler No. 3632).

***N*-2-Pyridylacetamide (10, R = Methyl).**—To a solution of 9.8 g (0.104 mol) of 2-aminopyridine in 20 ml of pyridine was added dropwise with ice cooling 8.3 g (0.110 mol) of acetyl chloride. The reaction mixture was stirred for an additional 90 min at room temperature, 100 ml of water was added, and the reaction mixture was worked up as in the previous experiment to yield 8.2 g (60%) of *N*-2-pyridylacetamide, mp 68.0–68.5° (lit.[19] mp 71°; lit.[20] mp 66–67°). The product exhibited an infrared spectrum identical with that reported (Sadtler No. 19556).

Conversion of *N*-2-Pyridylbenzamide to *N*-2-Pyridylacetamide.—A solution of 2 g of *N*-2-pyridylbenzamide, 6 g of acetic anhydride, and 6 g of acetic acid in 50 ml of benzonitrile was heated for 6 hr at a bath temperature of 160°. The benzamide was shown by glpc to be completely converted to *N*-2-pyridylacetamide. The product identification was based upon glpc comparison with an authentic sample.

Registry No.—**1**, 694-59-7; **2**, 3847-19-6; **7**, 5957-89-1; **8**, 4373-58-4; **9**, 5957-90-4; **10** (R = Ph), 4589-12-2; **11**, 4350-51-0; **12**, 32111-34-5; acetic anhydride, 108-24-7; anisole, 100-66-3; benzonitrile, 100-47-0; *N*-(2′-pyridyl)-2-pyridone, 3480-65-7.

Acknowledgments.—We wish to thank the National Institutes of Health for providing the LKB 9000 combined gas chromatograph–mass spectrometer (Grant RR 00273) and Dr. C. C. Sweeley and Mr. John Naworal for recording the mass spectra.

(15) E. C. Butterworth, I. M. Heilbron, and D. H. Hey, *J. Chem. Soc.*, 355 (1940).

(16) This method of reduction of nitro compounds is that of A. J. Nunn and K. Schofield, *ibid.*, 583 (1952).

(17) E. A. Braude, R. P. Linstead, and K. R. H. Woolridge, *ibid.*, 3586 (1954); M. M. Fickling, A. Fischer, B. R. Mann, J. Packer, and J. Vaughan, *J. Amer. Chem. Soc.*, **81**, 4226 (1959).

(18) S. I. Lur'e, *Zh. Obshch. Khim.*, **20**, 195 (1950); *Chem. Abstr.*, **44**, 5880*g* (1950).

(19) A. Buzas, F. Canac, C. E. Gnell, and P. Freon, *C.R. Acad. Sci., Ser. C*, **262**, 658 (1966).

(20) A. L. Mndzhoyan and V. G. Afrikyan, *Izv. Akad. Nauk Armyan. SSR, Ser. Khim. Nauk*, **10**, 143 (1957); *Chem. Abstr.*, **52**, 4641*a* (1958).

1-(*p*-Chlorophenyl)-3,4-dimethylenepyrrolidine, a New Pyrrole Isomer

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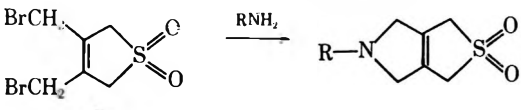
Received June 22, 1971

1-(*p*-Chlorophenyl)-3,4-dimethylenepyrrolidine, isomeric with the corresponding pyrrole, was prepared. The key step involves the SO_2 extrusion of a bicyclic sulfolene under reduced pressure. The structure of the diene was confirmed by its spectral data as well as by conversion to a dimer and two Diels–Alder adducts.

The synthesis and characteristics of the reactive double bond isomer of *o*-xylene, 4,5-dimethylenecyclohexene, have been reported.[1] Among the corresponding isomers of the five-membered oxygen, sulfur, and nitrogen heterocycles, only 3,4-dimethylenetetrahydrofuran has been accessible to date.[2] The present article describes the preparation and characteristics of 1-(*p*-chlorophenyl)-3,4-dimethylenepyrrolidine, a new double bond isomer of 3,4-dimethylpyrrole.

A rather effective way of masking a diene is its cycloaddition to sulfur dioxide. This cheletropic,[3] reversible reaction has found great synthetic utility not only for the preparation of sulfones[4] but in particular for stereospecific syntheses and protection of dienes and polyenes.[5–8]

3,4-Bis(bromomethyl)-2,5-dihydrothiophene 1,1-dioxide (1), which is easily obtained by brominating the cycloaddition product of 2,3-dimethyl-1,3-butadiene and sulfur dioxide,[9] seemed to be an attractive precursor for a masked 3,4-dimethylenepyrrolidine (2).



1 2

However, reaction of the dibromide **1** with various primary amines under very mild conditions in either protic or nonprotic solvents produced only intractable mixtures. A possible explanation for these results would be that the strongly acidic character of the sulfolene protons toward the amines strongly favors proton abstraction and thus virtually suppresses the nucleophilicity of the amines.

A 1,4-HBr elimination from **1** would then yield rather reactive dienes, prone to undergo secondary reactions. By reacting **1** with a weakly basic amine, such as *p*-chloroaniline (pK_a 3.97), in either a protic or a nonprotic solvent, the bicyclic sulfolene **2a** (R = *p*-Cl-C_6H_4) was obtained in moderate yield. Its nmr spectrum with singlets at δ 4.03 and 4.16 ppm, respectively, each accounting for 4 protons, leaves no doubt about the symmetry of the structure. In trifluoroacetic acid, the signals of the hydrogens adjacent to the now-protonated N shift to lower field (4.97 ppm). A low-temperature mass spectrum (100°) exhibits the molecular ion at 269 as well as *m/e* 205, the reaction product of the sulfur dioxide extrusion. Catalytic reduction of **2a** produces a nicely crystalline dihydro derivative **3**. **2a** is stable in its crystalline state at room temperature over extended periods of time. In solution, however, it is slowly oxidized to the pyrrole **4**, a reaction which preparatively and reproducibly can be achieved (60%) by stirring a solution of **2a** in CH_2Cl_2 with an excess of an ethanolic solution of $(NH_4)_2Ce(NO_3)_6$ for a short period of time. The assignment of the pyrrole structure **4** as opposed to the possible alternative (thiophene 1,1-dioxide) is corroborated as follows. (a) The uv [λ_{max} 263 mμ (ϵ 20,400)] and ir spectra[10] are compatible with 1-*p*-chlorophenyl pyrrole. (b) The pyrrole protons in the nmr shift from δ 6.95 ($CDCl_3$) to 11.4 ppm (2 H) in CF_3COOH, whereas the sulfolene hydrogens remain virtually in the same area (4.20 and 4.42 ppm, respectively). (c) The properties of **4** would not be compatible with the reported[11,12] instability of thiophene 1,1-dioxides.

Thermolysis of **2a** leads to rapid and clean SO_2 extrusion. Upon heating **2a** beyond its decomposition point (148–155°), the material resolidifies. An nmr spectrum of this crude and rather insoluble material (CF_3COOD) agrees quite well with the Diels–Alder adduct **6** of the initially formed diene **5**. At δ 2.1–2.8 there are the signals (broad) for two allylic CH_2 groups: at 4.1 the peak of the nonallylic CH_2 adjacent to the N, at 4.6–4.9 the absorption for 3 allylic CH_2's adjacent to N, at 5.5 the geminal vinyl protons, and finally at 7.6 ppm the 8 aromatic hydrogens. A mass spectrum of this material at 205° clearly reveals it to be a dimer (M^+ 410). The next major fragment is *m/e* 204, *i.e.*, one mass unit short of the monomer **5** and thus probably not a molecular ion. Further confirmation of structure **6** is obtained by observing a spectrum at 300°; it still reveals M^+ 410 (dimer **6**) as well as some trimeric material (M^+ 615) and now a relatively strong M^+ at 205, attributable to the thermal retro-Diels–Alder reaction.[13]

Practical preparation of the diene **5** is brought about simply by subliming the bicyclic sulfolene **2** at 135–138° (0.1 mm); the crystalline diene can be collected in 79% yield. The residue again is dimeric and trimeric material. **5** is a relatively stable compound and

(1) W. J. Bailey and J. Rosenberg, *J. Amer. Chem. Soc.*, **77**, 73 (1955).

(2) (a) W. J. Bailey and S. S. Miller, *J. Org. Chem.*, **28**, 802 (1963); (b) E. J. Fetter, *Diss. Abstr.*, **22**, 2985 (1962) [*Chem. Abstr.*, **57**, 758e (1963)]; only indirect evidence is presented for the formation (3–5%) of 3,4-dimethylenethiophane by pyrolysis of 3,4-bis(acetoxymethyl)thiophane.

(3) R. B. Woodward and R. Hoffmann, *Angew. Chem.*, **81**, 797 (1969).

(4) (a) S. D. Turk and R. L. Cobb in "1,4-Cycloaddition Reactions," J. Hamer, Ed., Academic Press, New York and London, 1967, pp 13–45; (b) W. L. Mock, *J. Amer. Chem. Soc.*, **89**, 1281 (1967); (c) O. Grummit and A. L. Endrey, *ibid.*, **82**, 3614 (1960).

(5) (a) W. L. Mock, *ibid.*, **88**, 2857 (1966); (b) *ibid.*, **91**, 5682 (1969); (c) *ibid.*, **92**, 3807 (1970); (d) *ibid.*, **92**, 6918 (1970).

(6) S. D. McGregor and D. M. Lemal, *ibid.*, **88**, 2858 (1966).

(7) E. J. Corey, N. H. Anderson, R. M. Carlson, E. Vedejs, J. Paust, I. Vlattas, and R. E. K. Winter, *ibid.*, **90**, 3245 (1968).

(8) P. Dowd, *ibid.*, **92**, 1066 (1970).

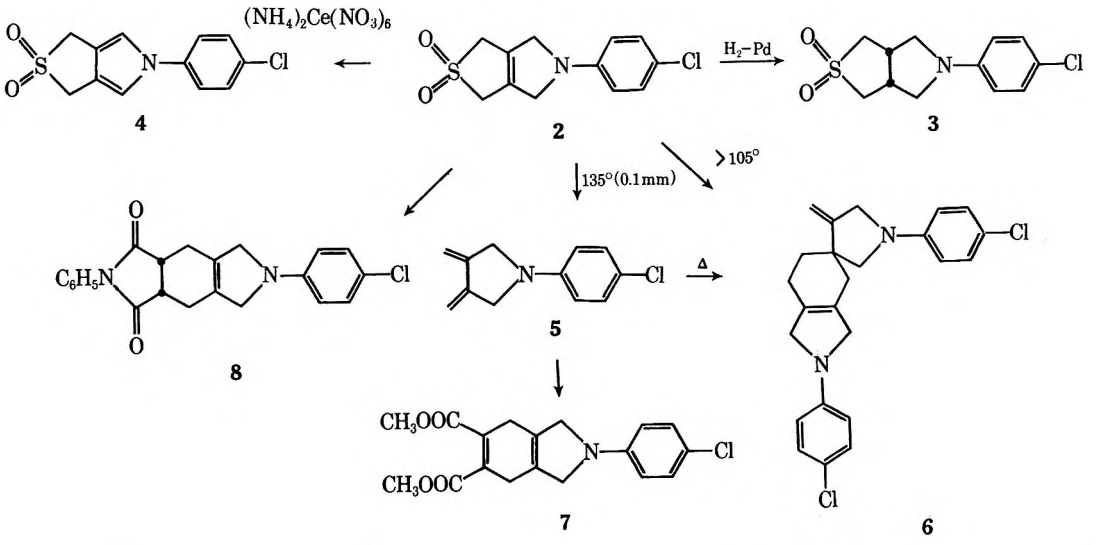
(9) G. B. Butler and R. M. Ottenbrite, *Tetrahedron Lett.*, 4873 (1967).

(10) (a) Ir of 1-(*p*-chlorophenyl)-3,4-dimethylpyrrole [R. A. Jones, *Aust. J. Chem.*, **19**, 289 (1966)]; (b) uv of 1-phenylpyrrole [253 mμ (log ϵ 4.3)] [J. Davoll, *J. Chem. Soc.*, 3802 (1953)].

(11) (a) W. L. Mock, *J. Amer. Chem. Soc.*, **92**, 7610 (1970); (b) L. A. Carpino, L. V. McAdams, R. H. Rynbrandt, and J. W. Spiewak, *ibid.*, **93**, 476 (1971).

(12) (a) W. J. Bailey and E. W. Cummins; *ibid.*, **76**, 1932 (1954); (b) J. L. Melles and H. J. Backer, *Recl. Trav. Chim. Pays-Bas*, **72**, 314 (1953).

(13) H. Kwart and K. King, *Chem. Rev.*, **68**, 415 (1968).



can be stored in its crystalline state. By warming a solution of the diene, polymeric material is formed quite readily. The most evident proof for structure **5** is obtained by its nmr spectrum. The methylene hydrogens adjacent to the N appear as an apparent triplet at 4.05 ppm with an allylic coupling of $J \cong 2$ Hz. Each pair of equivalent vinyl protons exhibits a triplet (J = 2 Hz) at 5.05 (exo proton) and at 5.52 ppm (J = 2 Hz) (endo proton). Finally, the aromatic hydrogens show the expected AB system, centered at δ 6.5 and 7.55 ppm, respectively (J = 9 Hz). The spectrum of **5** is thus in good agreement with the one reported for tetrahydro-3,4-dimethylenefuran.[2]

The isomerization of the diene **5** into the aromatic pyrrole has not been observed, either thermally (only oligomeric products formed) or by acid catalysis. The stability of **5** toward acids is demonstrated by observing its nmr spectrum in CF_3COOD: except for a downfield shift of the aliphatic and vinyl protons, the very characteristic pattern remains unchanged. The ir spectrum of the diene **5** has a strong band at 890 cm^{-1} (out of plane deformation frequency) and at 810 cm^{-1}. The ultraviolet spectrum of **5** reflects the superimposed absorptions of the diene and *p*-chloroaniline chromophores with a λ_{max} at 253 mμ (ϵ 25,800) and 306 (4400). By subtracting the spectrum of *p*-chloro-*N*,*N*-dimethylaniline[14] one obtains a λ_{max} in the area of 240–260 mμ with an extinction coefficient of 9000, a result which is compatible with the λ_{max} 244 mμ (ϵ 9820) reported[2] for tetrahydro-3,4-dimethylenefuran. The mass spectrum of the diene once again reveals its thermal reactions: at 265° the most intense molecular ion is at 410 (dimer), whereas M^+ 205 is only a minor peak. Again, *m/e* 204 is attributed to a fragmentation of the dimer, rather than to a M − 1 loss of the monomeric diene **5**. At 50° the spectrum shows no dimer and the "normal" fragmentation pattern of **5** can be observed with peaks at M^+ 205 and *m/e* 190, 154, 138, 111.

Some chemical evidence was gained by forming the Diels–Alder adduct **7** of the diene with dimethyl acetylenedicarboxylate. The Diels–Alder reaction can be carried out directly on the masked diene **2** as has been shown by heating equimolar amounts of **2** and *N*-phenylmaleimide in refluxing xylene. The adduct **8** was obtained in a considerably higher yield than by the stepwise procedure **2a** → **5** → **7**. This is an appealing preparative aspect in the reaction of dienophiles with rather unstable 1,3-dienes, as had been demonstrated by other investigators.[15,16]

(14) *p*-Chloro-*N*,*N*-dimethylaniline, λ_{max} 260 mμ (ϵ 15,900): P. r Gammaticakis, *Bull. Soc. Chim. Fr.*, 534 (1951).

Experimental Section[17]

5-(*p*-Chlorophenyl)-1,3,4,6-tetrahydrothieno[3,4-*c*]pyrrole 2,2-Dioxide (2a).—The dibromo sulfone 1 (12 g, 40 mmol) and 5.1 g (40 mmol) of *p*-chloroaniline were stirred in 250 ml of CH_2Cl_2 with 8.45 g of anhydrous Na_2CO_3 for 3 days at room temperature. After filtration from the inorganic solid, the solvent was removed *in vacuo*. The crude residue (15.45 g) was boiled in ethanol, and after cooling two crops of the bicyclic product 2a (4.2 and 0.9 g, dec pt 147–149°) were obtained (47%). From the mother liquors 1.85 g of the unreacted dibromo sulfone 1 (12%) could be recovered. An analytical sample was obtained by washing the bicyclic sulfone with hot ethanol or by recrystallizing it from CH_2Cl_2: both operations raised the decomposition point to 153°; ν_{max}^{Nujol} 1600, 1500, 1370, 1290, 1187, 1110, 1085, 770 cm^{-1}; nmr (CF_3COOD) δ 4.22 (s, 4 H), 4.97 (s, 4 H), 7.62 ppm (s, 4 H); nmr (DMFA-d_6) 4.03 (s, 4 H), 4.16 (s, 4 H), 6.55 and 7.22 ppm (AB, J = 9 Hz, 4 H); mass spectrum (100°) M^+ 269, *m/e* 205, 138, 111.

Anal. Calcd for $C_{12}H_{12}ClNO_2S$: C, 53.44; H, 4.49; N, 5.19. Found: C, 53.13; H, 4.59; N, 4.91.

5-(*p*-Chlorophenyl)-1,3,3a,4,6,6a-hexahydrothieno[3,4-*c*]-pyrrole 2,2-Dioxide (3).—A solution of 4 g (16 mmol) of bicyclic sulfone in 200 ml of ethanol was hydrogenated over 800 mg of 10% Pd/C at 30 lb of hydrogen pressure for 2 hr. After filtration and removal of some ethanol, the product crystallized: 2.6 g (65%); mp 174–175°; ν_{max}^{Nujol} 1600, 1500, 1375, 1310, 1305, 1130, 1110, 800 cm^{-1}; nmr ($CDCl_3$) δ 2.9–3.7 (m, 10 H), 6.53 and 7.2 ppm (AB, J = 9 Hz, 4 H).

Anal. Calcd for $C_{12}H_{14}ClNO_2S$: C, 53.08; H, 5.20; N, 5.16. Found: C, 52.80; H, 5.24; N, 5.05.

5-(*p*-Chlorophenyl)-1,3-dihydrothieno[3,4-*c*]pyrrole 2,2-Dioxide (4).—To a solution of 600 mg (2.23 mmol) of bicyclic sulfone 2a in 30 ml of CH_2Cl_2 was added a freshly prepared solution of 2.5 g of $(NH_4)_2Ce(NO_3)_6$ in 60 ml of ethanol. After the mixture was stirred for 30 min at room temperature the solvent was removed, and the residue was taken up in CH_2Cl_2 and washed with water. After drying over Na_2SO_4 and removal of the solvent, the residue was filtered through a column of 24 g of silica gel, using $CHCl_3$. The first fraction of 150 ml was evaporated and its residue (400 mg) crystallized from CH_2Cl_2–ether to yield 360 mg of product (60%), mp 176–177°, as white crystals: ν_{max}^{Nujol} 1520, 1500, 1310, 1200, 1130, 825, 790 cm^{-1}; $\lambda_{max}^{CH_3OH}$ 263 mμ (ϵ 20,400); nmr ($CDCl_3$) δ 4.20 (s, 4 H), 6.95 (s, 2 H), 7.35 ppm (AB, J = 9 Hz,

(15) I. L. Klundt, *Chem. Rev.*, **70**, 471 (1970).

(16) L. F. Hatch and D. Peter, *Chem. Commun.*, 1499 (1968).

(17) Melting points were obtained in a Thomas-Hoover melting point apparatus and are uncorrected. Nmr spectra were recorded on a Varian A-60 instrument, ir spectra on a Perkin-Elmer 521, and uv curves on a Cary Model 14. The mass spectra were recorded on an AEI MS 902 by direct insertion.

4 H); nmr (CF_3COOD) 4.42 (s, 4 H), 7.35 (AB, J = 9 Hz, 4 H), 11.4 ppm (s, 2 H).

Anal. Calcd for $C_{12}H_{10}ClNO_2S$: C, 53.84; H, 3.76; N, 5.23. Found: C, 53.52; H, 3.97; N, 5.25.

1-(*p*-Chlorophenyl)-3,4-dimethylenepyrrolidine (5).—The sulfone **2a** (500 mg) was left under vacuum (0.1 mm) and 135–138° overnight. The diene sublimed and was collected (300 mg, 79%). The crystalline residue (dimer) amounted to 80 mg (21%). The sublimed diene was virtually pure, the only impurities being traces of dimeric and polymeric material. The 300 mg were recrystallized from ether–hexane (without excessive heating) to give a first crop of 110 mg (melting point not detectable due to dimerization upon heating): ν_{max}^{Nujol} 1600, 1500, 1100, 900, 890, 810 cm^{-1}; $\lambda_{max}^{CH_3OH}$ 253 mμ (ε 25,780), 306 (4420); nmr ($CDCl_3$) δ 4.05 (~t, J = 2 Hz, 4 H), 5.05 (~t, J = 2 Hz, 2 H), 5.52 (t, J = 2 Hz, 2 H), 6.5 and 7.18 (AB, J = 9 Hz, 4 H); nmr (CF_3COOD) 4.7 (m, broad, 4 H), 5.43 (m, broad, 2 H), 5.93 (m, broad, 2 H), 7.55 ppm (s, 4 H); mass spectrum (50°) M^+ 205, *m/e* 190, 168, 154, 138, 111.

Anal. Calcd for $C_{12}H_{12}ClN$: C, 70.08; H, 5.88; N, 6.81. Found: C, 70.18; H, 5.94; N, 6.57.

Dimer of 1-(*p*-Chlorophenyl)-3,4-dimethylenepyrrolidine 6.—The dimer of **5** was obtained as a side product in the preparation of **5** (see above). By heating the sulfolene **2a** for 5 min in an oil bath of 170°, a complete conversion into crude **6** is observed (dec 220°). Owing to very poor solubility, purification of the dimer **6** was not feasible: nmr (CF_3COOD) δ 2–2.8 (m, 6 H), 4.1 (m, 2 H), 4.6–4.9 (m, 6 H), 5.5 (m, 2 H), 7.6 (m, 8 H); mass spectrum (205°) M^+ 410, *m/e* 204, 140, 138, 111; mass spectrum (300°) M^+ 613, 410, 205, *m/e* 270, 242, 218, 204, 190, 140, 138, 125, 111.

Diels–Alder Adduct with Dimethyl Acetylenedicarboxylate (7).—A solution of 860 mg (4.2 mmol) sublimed diene **5** and 1.5 ml (12 mmol) of dimethyl acetylenedicarboxylate in 10 ml of dry toluene was refluxed for 20 hr. After evaporation of the solvent the residue is crystallized from ether to give 720 mg of diester (mp 189–191°) (50%). Recrystallization of 500 mg thereof from CH_2Cl_2–ether gave 350 mg (mp 189–191°): ν_{max}^{Nujol} 1740, 1720, 1705, 1650, 1500, 1280, 1060, 810 cm^{-1}; $\lambda_{max}^{CH_3OH}$ 260 mμ (ε 24,890), 315 (2490); nmr ($CDCl_3$) δ 3.05 (s, 4 H), 3.76 (s, 6 H), 3.94 (s, 4 H), 6.35 and 7.13 (AB, J = 9 Hz, 4 H).

Anal. Calcd for $C_{18}H_{16}ClNO_4$: C, 62.21; H, 5.22; N, 4.04. Found: C, 62.54; H, 5.35; N, 4.08.

Diels–Alder Adduct with *N*-Phenylmaleimide (8).—A solution of 269 mg (1 mmol) of sulfone **2a** and 173 mg (1 mmol) of *N*-phenylmaleimide in 2.5 ml of xylene was refluxed under nitrogen for 3 hr. The mixture was then cooled and diluted with some benzene, and the product crystallized out: 250 mg; mp 204–206° (66%); ν_{max}^{Nujol} 1708, 1390, 795 cm^{-1}; nmr ($CDCl_3$) δ 2.7 (broad s, 4 H), 3.4 (m, 2 H), 4.04 (s, 4 H), 6.4 and 7.2 (AB, J = 9 Hz, 4 H), 7.4 (m, 5 H); mass spectrum 378 (M^+), 230, 204, 190, 138, 111.

Anal. Calcd for $C_{22}H_{19}ClN_2O_2$: C, 69.76; H, 5.05; N, 7.34. Found: C, 70.10; H, 5.13; N, 7.29.

Registry No.—**2a**, 32515-66-5; **3**, 32515-67-6; **4**, 32515-68-7; **5**, 32515-69-8; **6**, 32515-70-1; **7**, 32515-71-2; **8**, 32515-72-3.

Acknowledgment.—The authors would like to thank Dr. N. Finch for his support and encouragement and Mr. Dorman and his staff for recording and discussing the analytical and spectral data.

Allenes from Fragmentation of Tosylhydrazones

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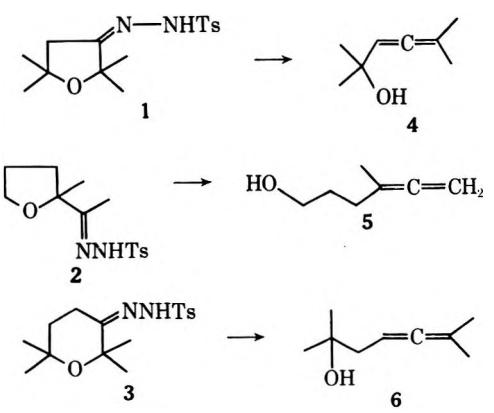
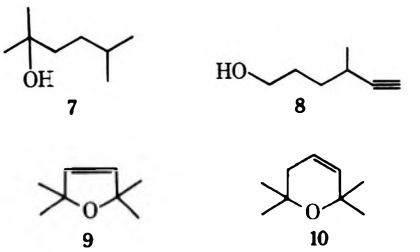
Received June 25, 1971

Tosylhydrazones **1**, **2**, and **3** undergo fragmentation on treatment with 2 equiv of butyllithium to form allenic alcohols **4**, **5**, and **6**. Mechanistic pathways and structural restrictions on the reaction are discussed.

We describe here the fragmentation of three α-alkoxytosylhydrazones to form the related allenes. In each case the tosylhydrazone reacted with 2 equiv of butyllithium in ether–hexane to give an allenic alcohol in 48–58% yield, **1**, **2**, and **3** leading to **4**, **5**, and **6** as indicated. These products were characterized by ir



and nmr spectroscopy; in addition, **4** was reduced over platinum to the saturated alcohol **7**, which was identical with an authentic sample.[2] Excess base favored partial isomerization of **5** to the terminal acetylene **8**, and both **1** and **3** yielded a small amount of olefinic ether (**9** and **10**, respectively) in addition to allenes.



Closely related transformations suggest two possible pathways for these fragmentations. A mechanism considered[3] for the base-catalyzed decomposition of α,β-epoxytosylhydrazones is reproduced in eq 1 and involves carbon–oxygen bond cleavage in the first step. The reaction of simple tosylhydrazones with butyl-

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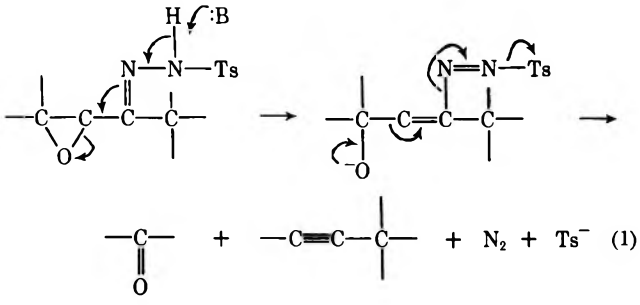
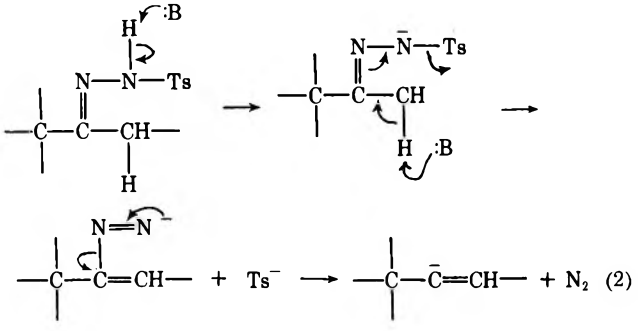
(2) Authentic **7** was prepared by reaction of isopentylmagnesium bromide with acetone: L. E. C. Barclay and J. W. Hilchie, *J. Org. Chem.*, **22**, 633 (1957).

(3) A. Eschenmoser, D. Felix, and G. Ohloff, *Helv. Chim. Acta*, **50**, 708 (1967); M. Tanabe, D. F. Crowe, R. L. Dehn, and G. Detre, *Tetrahedron Lett.*, 3739 (1967).



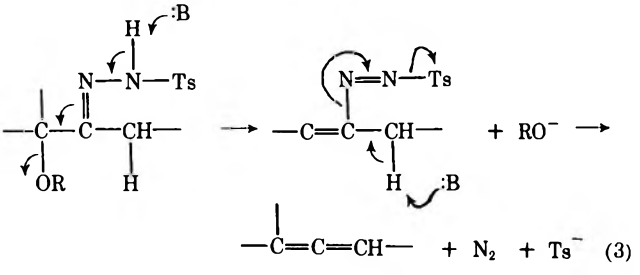
(1)

lithium, however, requires 2 equiv of base, as shown in eq 2, and leads to a vinyl anion which is subsequently

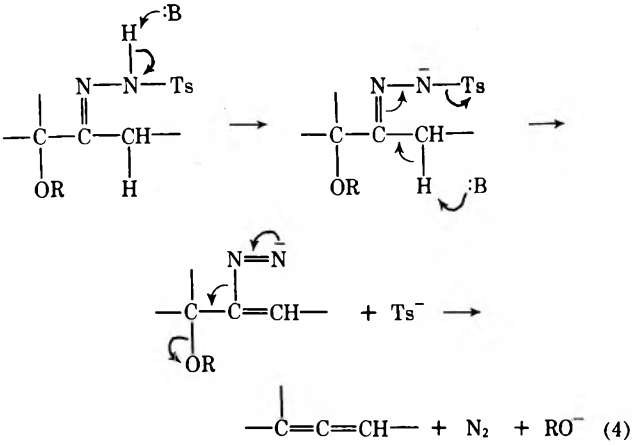


(2)

protonated to furnish the product olefin.[4] The two analogous sequences for formation of allenes are given in eq 3 and 4; the key difference is scission of the carbon–oxygen bond upon reaction of 1 (eq 3) or 2 (eq 4)



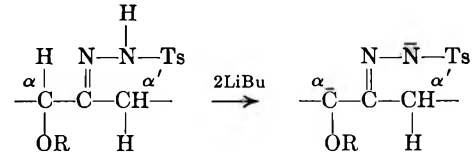
(3)



(4)

equiv of butyllithium. Since treatment of **1** with a single equivalent of base and subsequent work-up leads only to recovered starting material, it is clear that 2 equiv of base are needed for ether cleavage and that the pathway of eq 3 is not operative here. Without the ring strain of an epoxide there is insufficient driving force for immediate elimination of alkoxide ion, and these α-alkoxy derivatives apparently react according to eq 4.

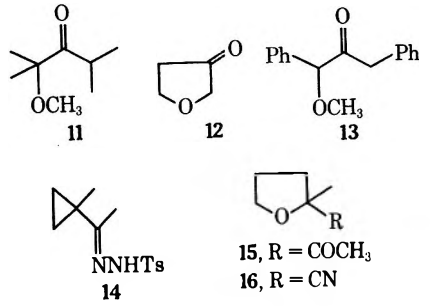
It is known[4,5] that simple tosylhydrazones fragment according to eq 2 only when the second mole of base can attack the hydrogen of a methyl or methylene group. The same restriction appears applicable here, for the tosylhydrazone of α-methoxydiisopropyl ketone (**11**) gave no allene upon exposure to butyllithium. A further structural restriction is that there can be no hydrogen on the carbon bearing the α-alkoxy group; the tosylhydrazones of dihydro-3(2*H*)-furanone (**12**) and α-methoxydibenzyl ketone (**13**), for example, did not yield allenes. This behavior probably results from preferential removal of the more acidic α proton on the carbon bearing oxygen (eq 5)[6] rather than the less



(5)

acidic α' proton necessary for allene formation. Within these restrictions this fragmentation reaction should provide a convenient route to allenes structurally related to **4**, **5**, and **6**.

An attempt to generate an allene through ring opening of a cyclopropyl ketone derivative failed. Fragmentation of **14** gave only 1-methyl-1-vinylcyclopropane, the product expected from a simple tosylhydrazone.



11 **12** **13**

14 **15**, R = $COCH_3$; **16**, R = CN

The ketones used in this work were all previously known with the exception of **15**, which was prepared by addition of methylmagnesium bromide to 2-methyltetrahydro-2-furonitrile (**16**)[7] and subsequent hydrolysis. We assume that the tosylhydrazones derived from these ketones are mixtures of syn and anti isomers, since they melted over rather wide ranges even when analytically pure.

Experimental Section

Materials and Equipment.—Unless otherwise noted, both ir and nmr spectra were obtained for carbon tetrachloride solutions, the former on a Perkin-Elmer 237B spectrophotometer and the latter on a Varian A-60 (60 MHz) nmr spectrometer. Vpc was carried out using a Varian Aerograph Model 700 Autoprep equipped with a 10 ft × 0.375 in. aluminum column packed with 30% SE-30 on Chromosorb W and operated at 110–135° with a helium carrier gas flow rate of 120 ml/min. Melting points are corrected.

(4) R. H. Shapiro and M. J. Heath, *J. Amer. Chem. Soc.*, **89**, 5734 (1967); G. Kaufman, F. Cook, H. Shechter, J. Bayless, and L. Friedman, *ibid.*, **89**, 5736 (1967).

(5) W. G. Dauben, M. E. Lorber, N. D. Vietmeyer, R. H. Shapiro, J. H. Duncan, and K. Tomer, *ibid.*, **90**, 4762 (1968).

(6) For an investigation of such systems, see J. H. Robson and H. Shechter, *ibid.*, **89**, 7112 (1967).

(7) R. Justoni and M. Terruzzi, *Gazz. Chim. Ital.*, **80**, 259 (1950).

Preparation of Tosylhydrazones. A. General Procedure.—A solution containing equimolar quantities of ketone and *p*-toluenesulfonyl hydrazine in anhydrous methanol or ethanol was heated at reflux for 1–2 hr. The corresponding tosylhydrazone, which crystallized from solution on cooling, was isolated by filtration, dried *in vacuo*, and used in the next step without further purification. An analytical sample was prepared by recrystallization from methanol or ethanol. These derivatives all showed ir absorption ($CHCl_3$) at approximately 3200, 1600, and 1160 cm^{-1}.

B. 2,2,5,5-Tetramethyltetrahydrofuran-3-one Tosylhydrazone (1).—2,2,5,5-Tetramethyltetrahydrofuran-3-one[8] gave a 94% yield of **1**: mp 169–171°; nmr ($CDCl_3$) δ 1.23 (s), 1.25 (s) (12 H), 2.44 (s, 5 H), 7.30 (d, J = 8 Hz, 2 H), 7.5 (br, 1 H), 7.83 (d, J = 8 Hz, 2 H).

Anal. Calcd for $C_{15}H_{22}N_2O_3S$: C, 58.03; H, 7.15; N, 9.03. Found: C, 58.14; H, 7.18; N, 9.10.

C. Methyl 2-(2-Methyltetrahydrofuryl) Ketone Tosylhydrazone (2).—Methyl 2-(2-methyltetrahydrofuryl) ketone (**15**) gave 70% of **2**: mp 128–130°; nmr ($CDCl_3$) δ 1.25 (s), 1.78 (s), 1.4–2.2 (m), 2.43 (s), 3.8 (m), 7.41 (d, J = 8 Hz), 7.6 (br, 1 H), 7.86 (d, J = 8 Hz).

Anal. Calcd for $C_{14}H_{20}N_2O_3S$: C, 56.73; H, 6.80; N, 9.45. Found: C, 56.78; H, 6.80; N, 9.54.

D. Dihydro-2,2,6,6-tetramethyl-2*H*-pyran-3(4*H*)-one Tosylhydrazone (3).—Dihydro-2,2,6,6-tetramethyl-2*H*-pyran-3(4*H*)-one[9] gave 82% of **3**: mp 151–154°; nmr ($CDCl_3$) δ 1.13 (s, 6 H), 1.27 (s, 6 H), 1.6–2.4 (m, 4 H), 2.44 (s, 3 H), 7.28 (d, J = 8 Hz, 2 H), 7.6 (br, 1 H), 7.83 (d, J = 8 Hz, 2 H).

Anal. Calcd for $C_{16}H_{24}N_2O_3S$: C, 59.24; H, 7.46; N, 8.64. Found: C, 59.38; H, 7.52; N, 8.52.

E. Tosylhydrazone of α-Methoxydiisopropyl Ketone (11).—This derivative was obtained from **11**[10] in 83% yield, mp 111–124°.

Anal. Calcd for $C_{15}H_{24}N_2O_3S$: C, 57.66; H, 7.74; N, 8.97. Found: C, 57.75; H, 7.66; N, 9.14.

F. Tosylhydrazone of Dihydro-3(2*H*)-furanone (12).—This derivative was obtained from **12**[11] in 88% yield, mp 139–147° dec.

Anal. Calcd for $C_{11}H_{14}N_2O_3S$: C, 51.95; H, 5.55; N, 11.02. Found: C, 52.01; H, 5.55; N, 11.13.

G. Tosylhydrazone of α-Methoxydibenzyl Ketone (13).—This derivative was prepared from **13**,[12] mp 100–104°.

Anal. Calcd for $C_{23}H_{24}N_2O_3S$: C, 67.63; H, 5.92; N, 6.86. Found: C, 67.63; H, 5.90; N, 6.88.

H. Methyl 1-(1-Methylcyclopropyl) Ketone Tosylhydrazone (14).—This derivative was obtained from the commercially available ketone in 76% yield, mp 138–141°.

Anal. Calcd for $C_{13}H_{18}N_2O_2S$: C, 58.62; H, 6.81; N, 10.52. Found: C, 58.88; H, 6.80; N, 10.54.

Reaction of Tosylhydrazones with *n*-Butyllithium. A. General Procedure.—A slurry of tosylhydrazone in ether (10 ml/g) was stirred at 25° under nitrogen and 2.5–3.0 equiv of a 2.55 *M* solution of *n*-butyllithium in hexane was added dropwise during a period of 30 min. After an additional 10 min water was added and the mixture was extracted with ether. The resulting ethereal solution was dried (Na_2SO_4) and concentrated, and the residue was distilled at reduced pressure. When more than one product was present the ratio of components was determined from their relative vpc peak areas. Analytical samples were obtained by preparative vpc.

B. Reaction of 2,2,5,5-Tetramethyltetrahydrofuran-3-one Tosylhydrazone (1) with *n*-Butyllithium.—Tosylhydrazone **1** gave a 58% yield of 2,5-dimethyl-3,4-hexadien-2-ol (**4**): bp 57° (12 Torr); ir 3600, 3500–3100, 1950 cm^{-1}; nmr δ 1.27 (s, 6 H), 1.71 (d, J = 3 Hz, 6 H), 2.2 (br, 1 H), 5.10 (m, 1 H). The spectral data for **1** are in agreement with published[13] values.

The distillation forerun contained a 3% yield of 2,2,5,5-tetramethyl-2,5-dihydrofuran (**9**):[14] ir 3050 cm^{-1}; nmr δ 1.23 (s, 12 H), 5.55 (s, 2 H).

C. Reaction of Methyl 2-(2-Methyltetrahydrofuryl) Ketone Tosylhydrazone (2) with *n*-Butyllithium.—Tosylhydrazone **2** gave a 53% yield of distillate (bp 45°, 1.0 Torr) containing two components in a 9:1 ratio. The major component was identified as 4-methyl-4,5-hexadien-1-ol (**5**): ir 3625, 3500–3100, 3020, 1940 cm^{-1}; nmr δ 1.68 (t, J = 3 Hz), 1.2–2.3 (m) (7 H), 3.26 (s, 1 H, exchanges with D_2O), 3.54 (t, J = 7 Hz, 2 H), 4.54 (m, 2 H).

Anal. Calcd for $C_7H_{12}O$: C, 74.95; H, 10.78. Found: C, 74.84; H, 10.84.

The minor component was identified as 4-methyl-5-hexyn-1-ol (**8**): ir 3625, 3500–3100, 3300, 2085 cm^{-1}; nmr δ 1.17 (d, J = 7 Hz, 3 H), 1.4–1.8 (m, 4 H), 1.92 (d, J = 2.5 Hz, 1 H), 2.38 (m, 1 H), 3.06 (br s, 1 H, exchanges with D_2O), 3.55 (t, J = 6 Hz, 2 H).

Anal. Calcd for $C_7H_{12}O$: C, 74.95; H, 10.78. Found: C, 75.10; H, 10.94.

D. Reaction of Dihydro-2,2,6,6-tetramethyl-2*H*-pyran-3(4*H*)-one Tosylhydrazone (3) with *n*-Butyllithium.—Tosylhydrazone **3** gave a 74% yield of distillate containing two components in a 2:1 ratio. The major component was identified as 2,6-dimethyl-4,5-heptadien-2-ol (**6**): ir 3600, 3560, 3500–3100, 1950 cm^{-1}; nmr 1.15 (s, 6 H), 1.34 (s, 1 H, exchanges with D_2O), 1.68 (d, J = 3 Hz, 6 H), 2.04 (d, J = 8 Hz, 2 H), 4.86 (m, 1 H).

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.03; H, 11.47.

The minor component was identified as 2,2,6,6-tetramethyl-2,3-dihydropyran (**10**): ir 3025, 700 cm^{-1}; nmr δ 1.16 (s, 12 H), 1.87 (m, 2 H), 5.59 (br s, 2 H).

Anal. Calcd for $C_9H_{16}O$: C, 77.09; H, 11.50. Found: C, 77.06; H, 11.55.

E. Reaction of Methyl 1-(1-Methylcyclopropyl) Ketone Tosylhydrazone (14) with *n*-Butyllithium.—Tosylhydrazone **14** gave 1-methyl-1-vinylcyclopropane[15] which was isolated by vpc: ir 3065, 890 cm^{-1}, nmr 0.53 (s, 4 H), 1.16 (s, 3 H), 4.6–5.5 (m, 3 H). There was no evidence of formation of 3-methyl-1,2-pentadiene.

Methyl 2-(2-Methyltetrahydrofuryl) Ketone (15).—To 8.5 ml of *ca.* 3 *M* methylmagnesium bromide (*ca.* 1.4 equiv) in ether was added dropwise 2.0 g of nitrile **16**[7] in 20 ml of ether. The resulting mixture was heated at reflux for 1 hr and then treated with 2 *M* aqueous hydrochloric acid until acidic. After being stirred at room temperature for 15 min, the reaction mixture was worked up with ether and water to give 1.95 g (84%) of yellow oil. This showed a single peak on vpc analysis. A sample was purified by vpc: ir 2960 (m), 2750 (m), 1720 (s), 1350 (m), 1105 (m), 1038 cm^{-1} (m); nmr δ 1.23 (s, 3 H), 1.4–2.4 (m), 2.10 (s) (7 H), 3.85 (m, 2 H).

Anal. Calcd for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.45; H, 9.54.

Catalytic Hydrogenation of 2,5-Dimethyl-3,4-hexadien-2-ol (4).—A solution of 0.257 g of **4** in 2.0 ml of methanol was hydrogenated at 1 atm over 20 mg of platinum oxide. A hydrogen uptake of approximately 2 mol was observed, after which the solution was filtered and concentrated, and the residue was collected by preparative vpc. The major component, amounting to 60% of the volatile material was identified as 2,5-dimethyl-2-hexanol (**7**) by comparison of its ir and nmr spectra with those obtained from an authentic sample:[2] ir 3600, 3500–3100 cm^{-1}; nmr δ 0.88 (d, J = 5 Hz, 6 H), 1.13 (s, 6 H), 1.2–1.7 (m, 5 H), 2.47 (s, 1 H, exchanges with D_2O).

Registry No.—**1**, 32319-67-8; **2**, 32319-68-9; **3**, 32319-69-0; **4**, 2424-45-5; **5**, 32319-71-4; **6**, 32319-72-5; **7**, 3730-60-7; **8**, 32319-74-7; **9**, 32319-75-8; **10**, 32319-76-9; **11** tosylhydrazone, 32319-77-0; **12** tosylhydrazone, 1708-19-6; **13** tosylhydrazone, 32380-91-9; **14**, 22301-72-0; **15**, 32318-87-9; 1-methyl-1-vinylcyclopropane, 16906-27-7.

Acknowledgment.—We are grateful to the National Science Foundation for support of this investigation through Grant No. GP-17319.

(8) H. Richet, *Ann. Chim. (Paris)*, **3**, 317 (1948).

(9) I. K. Korobitsyna and K. K. Pivnitskii, *Zh. Obshch. Khim.*, **30**, 4016 (1960); *J. Gen. Chem. USSR*, **30**, 3975 (1960).

(10) A. A. Sacks and J. G. Astor, *J. Amer. Chem. Soc.*, **73**, 3902 (1951).

(11) J. H. S. Weiland, H. Dijkstra, and A. B. Pik, *Recl. Trav. Chim. Pays-Bas*, **82**, 651 (1963).

(12) A. W. Fort, *J. Amer. Chem. Soc.*, **84**, 2620 (1962).

(13) M. Bertrand and R. Maurin, *Bull. Soc. Chim. Fr.*, 2779 (1967).

(14) N. Lozac'h, *ibid.*, 286 (1949); A. S. Zanina, S. I. Shergina, and I. L. Kotlyarevskii, *Zh. Prikl. Khim. (Leningrad)*, **36**, 203 (1963).

(15) L. A. Nakhapetyan, I. L. Safonova, and B. A. Kazanskii, *Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 840 (1962); R. J. Ellis and H. M. Frey, *J. Chem. Soc.*, 959 (1964).

Characterization of the Dimethyl-1,2-dimethylenecyclobutanes from the Methylallene Thermal Dimerization

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Received April 21, 1971

Thermal dimerization of methylallene has been investigated in a static system at 170° for various lengths of time. On the basis of spectral data and chemical evidence, the structures of all seven dimethyl-1,2-dimethylenecyclobutanes possible from the dimerization are assigned, namely *trans*- and *cis*-3,4-dimethyl-1,2-dimethylenecyclobutane (**1** and **2**), 3-methyl-2-methylene-*syn*-ethylidenecyclobutane (**3**), 3-methyl-2-methylene-*anti*-ethylidenecyclobutane (**4**), *syn,syn*-1,2-diethylidenecyclobutane (**5**), *anti,syn*-1,2-diethylidenecyclobutane (**6**), and *anti,anti*-1,2-diethylidenecyclobutane (**7**). The relative amounts of compounds **1**–**7** produced at low conversion are 25:4:37:18:13:3:0.5. As the reaction proceeds, however, the relative amounts of **1**, **2**, **3**, and **4** decrease.

Allene has long been known to give two dimeric products, 1,2- and 1,3-dimethylenecyclobutane, in a ratio of 85:15 along with various oligomers upon heating.[1] However, none of the latter type of dimer (head to tail) has been reported as being formed in the cases of dimerization of substituted allenes. On the basis of these observations, it has been postulated that combination of two molecules of allene occurs initially between two central carbon atoms to form a relatively stable bisallyl diradical which then collapses to the products.[2] Although the stereochemistry of the substituted allene dimers had long been unknown, recent work on dimerizations of tribromoallene,[3,4] trichloroallene,[5] methylallene,[6] chloroallene,[7] and 1,3-dimethylallene[8] revealed that the major products are those with substituents trans on the cyclobutane ring and syn on the exocyclic double bonds. Interest has also focused on the stereochemistry of dimer products from optically active and racemic chiral allenes.[8,9]

In view of the close relationship of allene dimerization to the degenerate thermal rearrangement of 1,2-dimethylenecyclobutanes,[6,10,11] dimerization of methylallene was studied in hopes of providing additional information on the thermal rearrangements of *trans*- and *cis*-3,4-dimethyl-1,2-dimethylenecyclobutane[6] (**1** and **2**). In this work, the characterization of the seven possible nongeminal dimethyl-1,2-dimethylenecyclobutanes and their distribution from the thermal dimerization of methylallene are recorded.

Dimerization of Methylallene.—Thermal dimerization of methylallene in a flow system has been reported,[12] but no compounds were separated or identified; only the molecular weight, 105.9 (Victor Meyer method), of a fraction boiling from 75 to 135° (760 Torr) was obtained. The results of dimerization of methylallene in a static system at 170° for various lengths of time are given in Table I. Preparative vpc on dibutyl tetrachlorophthalate (DBTCP) allowed isolation of each peak except **4**, which was obtained as a mixture with **3**. Large quantities of pure **4** could be obtained from pyrolysis of **1**.[6]

TABLE I

PERCENTAGES OF DIMER PRODUCTS FROM METHYLALLENE (AT 170°) IN ORDER OF INCREASING RETENTION TIME ON DBTCP CAPILLARY VPC COLUMN

Reaction time, hr	1	2	3	4	5	6	7
1	25	4	37	18	13	3	~0.5
13[a]	10	2	32	14	29	11	2
20	4	0.6	25	7	46	15	2.5

[a] Recovered methylallene, 32% (minimum); dimer, 29%; less volatile material, 8%; nonvolatile material, 31%.

Structural and Stereochemical Assignments. Spectroscopic Studies.—From the uv of each material, it was clear that all were cisoid, conjugated dienes, and the nmr spectral data (Table II) allowed assignment of the stereochemistry in every case.[13] Thus, ring proton resonances in **1** are at higher field than those of **2** indicating that **1** had trans dimethyls while **2** had the cis stereochemistry. Secondly, methyl groups syn on the double bonds would be expected to be deshielded by the adjacent double bond and therefore at lower field than the anti methyl groups. The nmr spectra and vpc retention times of both **6** and **7** were identical with those of the two 1,2-diethylidenecyclobutanes obtained from the base-catalyzed isomerization of *cis*-1,2-divinylcyclobutane.[14]

Chemical Studies.—Chemical evidence for the assignments was also obtained. Thus, to distinguish between the 3,4-dimethyl compounds, **2** was synthesized by an unambiguous route shown in Scheme I.

Thus compound **2** was synthesized from the sensitized, 2 + 2 photocycloadduct of maleic anhydride and 2-butyne,[15] namely **8**, by reduction first with lithium aluminum hydride and then with hydrogen gas in methanol over a platinum catalyst giving, mostly, *cis*-

(1) (a) S. V. Lebedev, *J. Russ. Phys. Chem. Soc.*, **45**, 1249 (1913); *Chem. Abstr.*, **8**, 320 (1914); (b) J. K. Williams and W. H. Sharkey, *J. Amer. Chem. Soc.*, **81**, 4269 (1959).

(2) (a) J. D. Roberts and C. M. Sharts, *Org. React.*, **12**, 1 (1962); (b) D. R. Taylor, *Chem. Rev.*, **67**, 317 (1967).

(3) A. Roedig and N. Detzer, *Justus Liebigs Ann. Chem.*, **710**, 1 (1967).

(4) A. Roedig, N. Detzer, and H. J. Friedrich, *Angew. Chem., Int. Ed. Engl.*, **3**, 382 (1964).

(5) A. Roedig and N. Detzer, *ibid.*, **7**, 471 (1968).

(6) See J. J. Gajewski and C. N. Shih, *J. Amer. Chem. Soc.*, **91**, 5900 (1969), for a preliminary communication of part of this work.

(7) T. L. Jacobs, J. R. McClenon, and O. J. Muscio, Jr., *ibid.*, **91**, 6038 (1969).

(8) J. J. Gajewski and W. A. Black, *Tetrahedron Lett.*, 899 (1970).

(9) W. R. Moore, R. D. Bach, and T. M. Ozretich, *J. Amer. Chem. Soc.*, **91**, 5918 (1969).

(10) J. J. Gajewski and C. N. Shih, *ibid.*, **89**, 4532 (1967).

(11) W. von E. Doering and W. R. Dolbier, Jr., *ibid.*, **89**, 4534 (1967).

(12) C. D. Hurd and R. N. Meinert, *ibid.*, **53**, 289 (1931).

(13) For background in interpretation of the relative chemical shifts in these systems, see N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 47, 88, 89.

(14) (a) P. Heimbach and R. Schimpf, *Angew. Chem., Int. Ed. Engl.*, **8**, 206 (1969); (b) P. Heimbach, private communication; (c) the authors thank Dr. Heimbach for a generous sample of this mixture.

(15) R. Criegee, U. Zirngibl, H. Furrer, D. Seebach, and G. Freund, *Chem. Ber.*, **97**, 2942 (1964).

SCHEME I

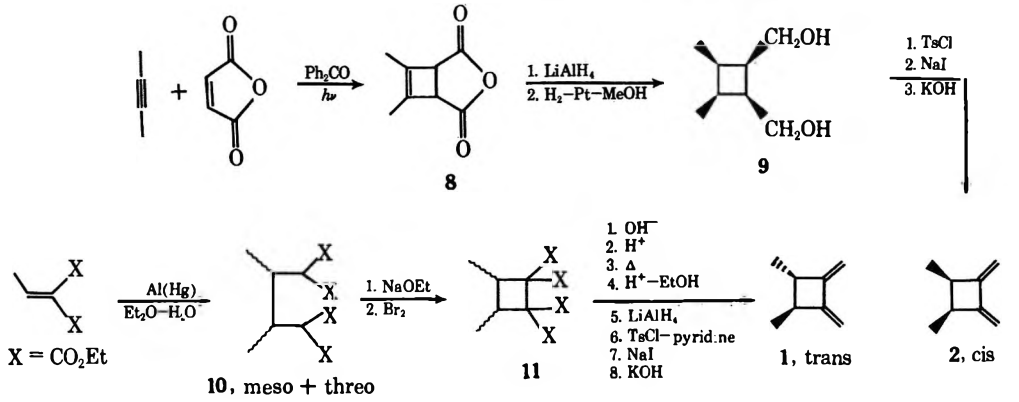


TABLE II

UV[a] AND NMR[b] DATA FOR ALL C_8H_{12} HYDROCARBONS REPORTED HEREIN

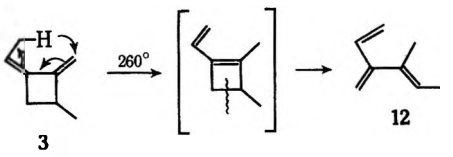
Compd	Uv max	Ir					
		Vinyl H's	*exo*-Methylene H's	Ring tertiary H's	Ring secondary H's	Vinyl Me H's	Ring Me H's
1	244		5.03 s, 4.64 s	2.38 m			1.18 d
2	245		5.03 s, 4.65 s	2.97 m			1.06 d
3	248	5.2 q	4.98 s, 4.75 s	2.7 m	2.7 m, 2.1 m	1.78 d	1.2 d
4	248	5.64 m	5.0 s, 4.6 s	2.8 m	2.8 m, 2.12 m	1.62 d	1.2 d
5	247	4.98 q			2.40 s	1.77 d	
6	249	5.47 q, 5.0 q			2.45 br s	1.6, 1.7 (2 d's)	
7	252	5.33 q			2.48 s	1.55 d	
12	216	6.32 (dd) 1 H; 5.49 (q) 1 H; 4.7–5.3 (m) 4 H; 1.77 (s) 3 H 1.70 (d) 3 H					
13	216	6.33 (dd) 1 H; 5.0 (m) 6 H; 2.23 (q) 2 H; 1.05 (t) 3 H					

[a] In isooctane, reported in nanometers. [b] At 100 MHz in carbon tetrachloride reported in parts per million downfield from TMS.

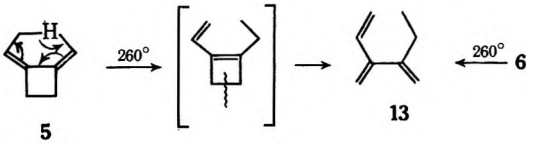
1,2-bis(hydroxymethyl)-*cis*-3,4-dimethylcyclobutane[15] (**9**), which was treated with excess tosyl chloride in pyridine, doubly displaced with iodide ion in acetone, and doubly dehydroiodinated with molten potassium hydroxide, according to the method of Dorko.[16] The volatile material was a 1:9 mixture of two compounds identical with the first and second vpc peaks, respectively, from the methylallene dimerization. It was also found that hydrogenation with 10% palladium on carbon as catalyst gave the same mixture.

Large quantities of both **1** and **2** were available by reductive dimerization of diethyl ethylidenemalonate to give *meso*- and *threo*-1,1,4,4-tetracarbethoxy-2,3-dimethylbutane[17] (**10**) (1:1 mixture), which could be cyclized to 1,1,2,2-tetracarbethoxy-3,4-dimethylcyclobutane (**11**) and decarboxylated to a mixture of 3,4-dimethylcyclobutane-1,2-dicarboxylic acids,[17] which, after esterification, were reduced with lithium aluminum hydride and then converted to a nearly 1:1 mixture of **1** and **2** by the elimination sequence described above. Compounds **1** and **2** were identical with the first and second vpc peaks from the methylallene dimerization, respectively.

To distinguish between the two 2-ethylidene-4-methyl compounds, **3** was subjected to vapor phase pyrolysis at 260°[6] and gave nearly quantitatively (90%) a triene, 3-methylene-4-methyl-*trans*-1,4-hexadiene (**12**). The trans stereochemistry was assigned in analogy to Gil-Av's finding that 3-methylcyclobutene gave *trans*-1,3-pentadiene upon pyrolysis[18a] and Frey's results with the thermolysis of 1,2,3,4-tetramethyl- and 1,4-dimethylcyclobutene.[18b,c] The triene **12** could only arise from **3** by a 1,5-hydrogen shift[19] to give 1-vinyl-2,3-dimethylcyclobutene, which would be expected[18,20] to ring open to **12**. On the other hand, the anti material **4** underwent substantially slower conversion to **12** under these conditions.[6]



Lastly, to distinguish between **5**, **6**, and **7**, the first two were individually subjected to vapor phase pyrolysis at 260° and each gave clearly a new triene, 2-ethyl-3-methylene-1,4-pentadiene (**13**), also *via* the 1,5-hydrogen shift; **7** was relatively inert under the reaction conditions.[6]



(16) E. A. Dorko, *J. Amer. Chem. Soc.*, **87**, 5518 (1965). The authors thank Professor R. Cargill for the details of this procedure.

(17) I. Vogel, *J. Chem. Soc.*, 594, 1985 (1927).

(18) (a) E. Gil-Av and J. Shabtai, *J. Org. Chem.*, **29**, 257 (1964); (b) H. M. Frey, D. C. Marshall, and R. F. Skinner, *Trans. Faraday Soc.*, **61**, 861 (1965); (c) G. R. Branton, H. M. Frey, and R. F. Skinner, *ibid.*, **62**, 1546 (1966).

(19) R. B. Woodward and R. Hoffmann, *J. Amer. Chem. Soc.*, **87**, 2511 (1965).

(20) See (a) E. F. Kiefer and J. Y. Fukunaga, *Tetrahedron Lett.*, 933 (1969); (b) E. F. Kiefer and C. H. Tanna, *J. Amer. Chem. Soc.*, **91**, 4478 (1969), for analogous reactions.

Discussion

Dimer Distributions.—The data of Table I reveal that some chemical fractionation of the dimers occurred during the first 65% of reaction. Thus, as the reaction proceeded, the percentages of **1** and **2** decreased relative to the other materials, as did those of **3** and **4**, albeit somewhat less. Nevertheless, there had been relatively little fractionation thus allowing the conclusion that the dimer distribution after 1 hr of reaction reflects the relative energetics of pathways leading to the dimers. After extended reaction periods, chemical fractionation is very possible owing to the difference in reactivity of the various products undergoing secondary reactions in the mixture. It is known that tetramethyl-1,2-dimethylenecyclobutane undergoes polymerization much faster than 1,2-diisopropylidenecyclobutane and 1-isopropylidene-2-methylene-3,3-dimethylcyclobutane in the dimerization of 1,1-dimethylallene.[20b,21]

A second conclusion is that the dimer distribution reflects the relative thermodynamic stabilities of the various compounds within the first family, namely, **1** and **2**, but not in the other two, **3** and **4**, or **5**, **6**, and **7**. Inspection of models reveals that nonbonded interactions would render **3** less stable than **4**, and **5** should be less stable than **6**, which in turn would be less stable than **7**. Unfortunately, there is presently no experimental verification of these expectations. Nonetheless, it does appear that the transition states for formation of dimeric product reflect the stability of products only at the developing doubly allylic cyclobutane bond and not at the residual unsaturated linkages. It is not obvious what is responsible for the dimer distribution obtained in the methylallene dimerization, but it is possible that as a result of various twisting motions associated with a concerted, or effectively so,[9] cycloaddition, the sterically most favored orientation of addends at the transition state is drawn inexorably into the highest potential energy well on the energy surface responsible for formation of two of the three families of dimeric products.

Experimental Section

General.—Nuclear magnetic resonance spectra were recorded on Varian A-60 and HA-100 spectrometers. Carbon tetrachloride was used as a solvent with TMS (or chloroform) as an internal lock in frequency sweep mode; chemical shifts are reported as δ values in parts per million downfield from TMS. Infrared spectra were obtained with Perkin-Elmer Model 137 and 137G spectrophotometers in the indicated phase. Vapor phase chromatography was performed on Varian Aerograph A90P-3 and Series 1220-2 (capillary) instruments using dibutyl tetrachlorophthalate (DBTCP) as liquid phase. For separation and purification, a 15 ft × 0.25 in. column with 30% DBTCP on 60–80 Chromosorb W was used and operated at 130°, 40 psi, and 60 ml/min of helium. A 200-ft DBTCP capillary column operated at 90° and 30 psi was used for analysis. Mass spectra were taken on an AEI MS-9 mass spectrometer operating at 70 eV. Melting points were measured with a Thomas–Hoover capillary melting point apparatus without correction.

Dimerization of Methylallene.—Heavy wall 5-ml tubes, which were washed with dilute ammonium hydroxide solution and dried, each containing 450 μl of methylallene (99+% by vpc), were evacuated and sealed at liquid nitrogen temperature. Four such tubes were placed in a 150-ml stainless steel bomb, which contained about 10 ml of benzene for balancing the vapor pressure of methylallene at reaction temperature, and heated at 170° in an oven for the desired lengths of time. The compositions of the dimers were determined by analyses of the samples taken from several individual tubes on a 200-ft DBTCP capillary column. Retention times were compared with those of authentic samples. The average percentage compositions of the dimers obtained from pyrolyses for 1, 13, and 20 hr are shown in Table I.

The reaction mixture from a 13-hr reaction (5.78 g) was fractionated bulb to bulb, giving 1.83 g (31.6%) of unchanged methylallene, from 760 to 135 Torr at room temperature, 1.66 g (28.8%) of a dimer fraction from 10 to 0.5 Torr at room temperature, 0.5 g (8.65%) of a liquid at 0.5 Torr at 95°, and 1.79 g (31%) of a residue. After passage of 1.5 g of the distilled dimer mixture through a preparative DBTCP column, the following compounds, 1–7, in the order of increasing retention time were obtained.

trans-**3,4-Dimethyl-1,2-dimethylenecyclobutane** (**1**).—Nmr and ir spectra were superimposable in all respects on those of the pure compound obtained by independent synthesis (see below).

cis-**3,4-Dimethyl-1,2-dimethylenecyclobutane** (**2**).—Nmr and ir spectra were superimposable in all respects on those of the pure compound obtained by independent synthesis (see below).

3-Methyl-2-methylene-*syn*-ethylidenecyclobutane (**3**).—3-Methyl-2-methylene-*syn*-ethylidenecyclobutane (**3**) was obtained pure by passage three times through the DBTCP preparative column: nmr (CCl_4, 100 MHz) δ 1.2 (d, J = 6 Hz, 3 H), 1.78 (d with fine structure, J = 6 Hz, 3 H), 2.1 (m, 1 H), 2.7 (m, 2 H), 4.75 (s, 1 H), 4.98 (s, 1 H), 5.2 (q with fine structure, 1 H); ir (CCl_4) 3.24 (w), 3.3 (sh), 3.38 (s), 3.42 (s), 3.48 (m), 6.0 (m), 6.14 (m), 6.92 (m), 7.31 (m), 11.43 μ (s); uv (isooctane) 239, 248 (λ_{max}), 258 nm; m/e 108.0946 (calcd for C_8H_{12}, 108.0939).

3-Methyl-2-methylene-*anti*-ethylidenecyclobutane (**4**).—3-Methyl-2-methylene-*anti*-ethylidenecyclobutane (**4**) was not obtained pure from the dimer mixture, since even with repeated injections through the column it was still contaminated by **3**. However, it could be isolated from the pyrolysate of the stereospecific thermal rearrangement of **1** (see below).

syn,syn-**1,2-Diethylidenecyclobutane** (**5**): nmr (CCl_4, 100 MHz) δ 1.77 (d, J = 7 Hz, 6 H), 2.4 (s with fine structure, 4 H), 4.98 (q, J = 7 Hz, 2 H); ir (CCl_4) 3.3 (sh), 3.37 (s), 3.42 (s), 3.49 (m), 4.28 (w), 6.94 (m), 6.99 (m), 7.26 (sh), 7.32 (m), 9.54 (w), 9.77 (w), 10.73 μ (m); uv (isooctane) λ_{max} 247 nm; m/e 108.0946.

anti,syn-**1,2-Diethylidenecyclobutane** (**6**): nmr (CCl_4, 100 MHz) δ 1.6, 1.7 (2 overlapped d's, J = 7 Hz, 6 H), 2.45 (broad s, 4 H), 5.0 (q with fine structure, J = 7 Hz, 1 H), 5.47 (q with fine structure, J = 7 Hz, 1 H); ir (CCl_4) 3.3 (m), 3.38 (s), 3.4 (s), 3.49 (m), 3.52 (sh), 4.28 (w), 6.06 (w), 6.98 (m), 7.08 (sh), 7.3 (m), 10.35 (w), 10.7 (w), 12.08 μ (s); uv (isooctane) 241, 249 (λ_{max}), 250 nm; m/e 108.0946.

anti,anti-**1,2-Diethylidenecyclobutane** (**7**).—This compound was isolated after repeated injections: nmr (CCl_4, 100 MHz) δ 1.55 (d, J = 7 Hz, 6 H), 2.48 (s, 4 H), 5.33 (q with fine structure, J = 7 Hz, 2 H); ir (CCl_4) 3.3 (w), 3.37 (m), 3.4 (m), 3.42 (m), 3.5 (w), 6.04 (w), 6.94 (m), 7.3 μ (w); uv (isooctane) 243, 252 (λ_{max}), 262 nm; m/e 108.0937.

cis-**3,4-Dimethyl-1,2-dimethylenecyclobutane** (**2**).—To a cold solution of 8 g (42 mmol) of recrystallized *p*-toluenesulfonyl chloride in 20 ml of pyridine was added a cold solution of 2 g (13.9 mmol) of crude *cis*-1,2-bis(hydroxymethyl)-*cis*-3,4-dimethylcyclobutane[16] (**9**) in 10 ml of pyridine and the solution was stirred for 3 hr at 0°. Then to the reaction mixture was added a small volume of ice water. After the mixture was stirred for 20 min, it was poured into ice water. The solid precipitate was filtered from the mixture and dissolved in ether. This ether solution was dried over anhydrous magnesium sulfate and evaporated *in vacuo*, giving 4.4 g (70% yield) of white crystals. Recrystallization from ether–pentane gave *cis*-3,4-dimethyl-*cis*-1,2-bis(tosyloxymethyl)cyclobutane: mp 102–103°; nmr ($CDCl_3$, 60 MHz) δ 0.9 (m, width at half-height 8 Hz, 6 H), 1.9–2.8 (complex m, 4 H), 2.43 (s, 6 H), 4.05 (m, width at half-height 8 Hz, 4 H), 7.54 (A_2B_2, J = 8 Hz, 8 H); ir (CS_2) 3.36 (sh), 3.46 (m), 7.32 (s), 8.4 (sh), 8.5 μ (s).

To a boiling solution of 6.2 g (41.3 mmol) of sodium iodide in 50 ml of acetone was added a solution of 4.4 g (9.75 mmol) of the ditosylate in 45 ml of acetone. After the reaction mixture was refluxed for 33 hr, it was evaporated to dryness, and the residue was dissolved in ether. The yellow ether layer was then washed with a saturated aqueous sodium sulfite solution until the organic

(21) S. V. Lebedev, *J. Russ. Phys. Chem. Soc.*, **43**, 1735 (1911); *Chem. Abstr.*, **6**, 1373 (1912).

layer was colorless. After having been washed with water and dried over anhydrous sodium sulfate, the solvent was evaporated, giving 3.38 g (95% yield) of a pale yellow viscous liquid, *cis*-3,4-dimethyl-*cis*-1,2-bis(iodomethyl)cyclobutane: nmr ($CDCl_3$, 60 MHz) δ 1.02 (m, width at half-height 8 Hz, 6 H), 1.68–2.83 (complex m, 4 H), 3.25 (complex m, 4 H).

The diiodide was added to molten potassium hydroxide under the reaction conditions described by Dorko.[16] A liquid pyrolysate was obtained in 40% yield which was analyzed on a DBTCP capillary column indicating a major peak greater than 90%. The major component was isolated in the pure form by passage of the crude pyrolysate through a preparative DBTCP column: nmr of **2** (CCl_4, 100 MHz) δ 1.06 (d, J = 7 Hz, 6 H), 2.97 (complex m, width at half-height 14 Hz, 2 H), 4.65 (s, 2 H), 5.03 (s, with fine structure, 2 H); ir (CCl_4) 3.32 (m), 3.45 (s), 3.5 (sh), 5.67 (m), 6.07 (m), 6.9 (m), 11.35 μ (vs); uv (isooctane) 238 (sh), 245 (λ_{max}), 255 nm (sh); m/e 108.0932 (calcd for C_8H_{12}, 108.0939).

meso- and *threo*-**1,1,4,4-Tetracarbethoxy-2,3-dimethylbutane** (**10**).—A modification of Vogel's method[17] for preparation of *meso*- and *threo*-1,1,4,4-tetracarbethoxy-2,3-dimethylbutane (**10**) was employed. In a 5-l. flask, 40 g of household thin aluminum foil (Kaiser Aluminum and Chemical Corp., Oakland, Calif.) in strips about 1 × 3 in., which were loosely folded, was placed and covered with a 5% aqueous solution of sodium hydroxide for exactly 2.5 min. After decantation of the solution, the foil was washed with water and then with absolute ethanol. Immediately a sufficient quantity of a 2% aqueous solution of mercuric chloride was added to cover the foil completely. After having been allowed to stand for exactly 3 min, the aqueous solution was poured off and the metal was washed with water, then with absolute ethanol, then with moist ether (USP, and a trace of water added), and finally covered with 3 l. of ether in the presence of an additional 25 ml of water. Immediately to this amalgam was added slowly with stirring 120 g of diethyl ethylidenemalonate.[22] A vigorous reaction took place and continued for 1.5–2 hr. The reaction mixture was stirred further at room temperature overnight and then filtered to remove the aluminum residue and mercury. Evaporation of the ethereal solution gave 114 g (95% yield) of **10** as a viscous liquid: bp 155–160° (0.5 mm); $n^{17.0}$D 1.4480 (lit.[17] 1.44873); nmr (CCl_4, 60 MHz) δ 0.85 (d, J = 7 Hz, 3 H), 1.0 (d, J = 7 Hz, 3 H), 1.26 (t with fine structure, J = 7 Hz, 12 H), 2.25 (m, 2 H), 3.25 (unsymmetrical t, 2 H), 4.14 (q with fine structure, J = 7 Hz, 8 H); ir (neat) 3.42 (m), 5.78 μ (s).

1,1,2,2-Tetracarbethoxy-3,4-dimethylcyclobutane (**11**).—For preparation of 1,1,2,2-tetracarbethoxy-3,4-dimethylcyclobutane (**11**), Vogel's method was followed.[17] Distillation of the crude liquid product at 170–180° (0.5 mm) gave a pure colorless oil: $n^{16.7}$D 1.4590 (lit.[17] 1.45573, impure); nmr (CCl_4, 60 MHz) δ 1.0 (d with fine structure, J = 7 Hz, 6 H), 1.25 (t with fine structure, J = 7 Hz, 12 H), 2.82 (m, 2 H), 4.15 (m, 8 H); ir (neat) 3.44 (m), 5.78 μ (s).

1,2-Dicarbethoxy-3,4-dimethylcyclobutane (**14**).—Saponification of 100 g (0.269 mol) of crude **11** in 215 ml of absolute ethanol with 100 g (1.78 mol) of potassium hydroxide in 180 ml of water, followed by acidification with dilute sulfuric acid according to Vogel's method,[17] gave 53 g (76% yield) of the corresponding crude tetraacid: ir (neat) 3.18 (broad, m), 3.4 (m), 5.77 μ (s). This tetraacid was then decarboxylated under nitrogen to yield 35 g of a gummy residue which was immediately esterified with 900 ml of absolute ethanol in the presence of 10 ml of concentrated sulfuric acid to give 38 g of a dark brown liquid. On fractionation, 34 g (55.5% yield, overall) of pale yellow liquid 1,2-dicarbethoxy-3,4-dimethylcyclobutane (**14**) was collected at 90–115° (0.5 mm): nmr (CCl_4, 60 MHz) δ 0.83–1.42 (complex m, 12 H), 1.82–2.75 (complex m, 4 H), 3.9–4.35 (complex m, 4 H); ir (neat) 3.44 (m), 5.78 μ (s).

3,4-Dimethyl-1,2-bis(hydroxymethyl)cyclobutane (**15**).—To a stirred suspension of 9.8 g (0.258 mol) of lithium aluminum hydride in 400 ml of anhydrous ether at 0° was added, dropwise, a solution of 34 g (0.149 mol) of **14** in 400 ml of anhydrous ether. The reaction mixture was stirred for 9 hr at room temperature, then hydrolyzed with a freshly prepared saturated aqueous solution of anhydrous sodium sulfate, and filtered. The white cake was washed thoroughly with tetrahydrofuran. The washings and the original filtrate were combined and dried over anhydrous sodium sulfate. Evaporation of the solvents *in vacuo* to 50° gave 20.5 g (95.5% yield) of 3,4-dimethyl-1,2-bis(hydroxymethyl)cyclobutane (**15**) as a viscous liquid: nmr ($CDCl_3$, 60 MHz) δ 0.94 (m, 6 H), 1.25–3.0 (complex m, 4 H), 3.62 (m, 4 H), 4.5 (broad s, 2 H, concentration-dependent); ir (neat) 3.08 (broad, s), 3.48 (s), 6.89 (m), 7.27 (m), 9.65 μ (broad, s).

trans-**3,4-Dimethyl-1,2-dimethylenecyclobutane** (**1**).—The mixture of diols **15** was converted to the ditosylates, displaced with iodide ion in acetone, and dehydroiodinated in the same manner as described for the preparation of **2** from **9**.

Analysis on a 200-ft DBTCP capillary column indicated that the crude reaction product consisted of two major components which accounted for 96% of the mixture, in a ratio of 47 to 53 in the order of increasing retention time. The mixture was separated by passage through a preparative DBTCP column into two pure compounds, which were pure by capillary vpc. The compound with longer retention time (on both capillary and preparative columns) had superimposable nmr, ir, uv, and vpc with those of **2** prepared by the sequence described above. The compound with the shorter retention time was assigned as *trans*-3,4-dimethyl-1,2-dimethylenecyclobutane (**1**): nmr (CCl_4, 100 MHz) δ 1.18 (d, J = 6 Hz, 6 H), 2.38 (complex m, width at half-height 14 Hz, 2 H), 4.64 (s, 2 H), 5.03 (s with fine structure, 2 H); ir (CCl_4) 3.33 (m), 3.46 (s), 3.52 (sh), 5.69 (m), 6.03 (sh), 6.1 (m), 6.92 (m), 11.35 μ (vs); uv (isooctane) 238 (sh), 244 (λ_{max}), 255 nm (sh); m/e 108.0943 (calcd for C_8H_{12}, 108.0939).

Pyrolysis of 1 to 3-Methyl-2-methylene-*anti*-ethylidenecyclobutane (**4**).—A well-conditioned 5-l. flask containing 100 μl of **1** was sealed at 0.5 mm at liquid nitrogen temperature and heated at 260° for 4 hr. After having been condensed in a liquid nitrogen trap, 85 μl of a pyrolysate was obtained. Analysis on a 200-ft capillary DBTCP column indicated the following composition: 35.4% of unchanged **1**, 22.2% of **12**, 3.32% of **3**, 33.2% of 3-methyl-2-methylene-*anti*-ethylidenecyclobutane (**4**), and other possible isomers, except **5**, in small amounts. Pure **4** was isolated from the pyrolysate by passage through a preparative DBTCP column: nmr (CCl_4, 100 MHz) δ 1.2 (d, J = 7 Hz, 3 H), 1.62 (d with fine structure, J = 8 Hz, 3 H), 2.12 (complex m, 1 H), 2.8 (complex m, 2 H), 4.6 (s, 1 H), 5.0 (s, 1 H), 5.64 (complex m, 1 H); ir (CCl_4) 3.24 (w), 3.38 (s), 3.42 (s), 3.48 (m), 5.98 (m), 6.11 (m), 6.92 (m), 7.12 (w), 7.29 (m), 10.45 (m), 11.05 (m), 11.55 μ (s); uv (isooctane) 240 (sh), 248 (λ_{max}), 257 nm (sh); m/e 108.0942.

3-Methylene-4-methyl-*trans*-1,4-hexadiene (**12**).—Pyrolysis of 40 μl of **3** at 260° for 2 hr in a 5-l. bulb, which had been evacuated at 0.5 Torr, gave 30 μl of a pyrolysate. Analysis by capillary vpc indicated only one product. After purification on a DBTCP column, the product was assigned as 3-methylene-4-methyl-*trans*-1,4-hexadiene (**12**) from the spectral data and the analogous precedents:[18,20] nmr (CCl_4, 100 MHz) δ 1.7 (d, J = 7 Hz, 3 H), 1.77 (s, 3 H), 4.91 (overlapped d with fine structure, J = 8 Hz, 3 H), 5.16 (d of d, J = 18, 2 Hz, 1 H), 5.49 (q, J = 7 Hz, 1 H), 6.32 (d of d, J = 18, 10 Hz, 1 H); ir (CCl_4) 3.23 (m), 3.32 (sh), 3.35 (m), 3.42 (s), 3.48 (m), 6.18 (sh), 6.32 (m), 6.35 (m), 6.96 (m), 7.06 (m), 7.28 (m), 10.07 (vs), 10.9 (vs), 11.2 μ (vs); uv (isooctane) 216 (λ_{max}), 230 nm (sh); m/e 108.0940.

2-Ethyl-3-methylene-1,4-pentadiene (**13**).—Similarly, pyrolysis of 120 μl of pure **5** at 260° for 2 hr gave 100 μl of a liquid pyrolysate which showed complete disappearance of the starting material and three products in the ratio 2:1:1 on analytical vpc. Upon separation and purification by preparative vpc, the latter two were identified as **6** and **7**, respectively, and the major product was identified as 2-ethyl-3-methylene-1,4-pentadiene (**13**) by its spectra: nmr (CCl_4, 100 MHz) δ 1.05 (t, J = 7 Hz, 3 H), 2.23 (q, J = 7 Hz, 2 H), 4.97 (m with fine splitting, 5 H), 5.21 (d, J = 18 Hz, 1 H), 6.33 (d of d, J = 18, 10 Hz, 1 H); ir (CCl_4) 3.25 (m), 3.37 (m), 3.46 (sh), 6.1 (sh), 6.3 (m), 6.9 (m), 7.29 (m), 10.12 (m), 10.95 (s), 11.12 μ (vs); uv (isooctane) 215.9 (λ_{max}), 223 nm; m/e 108.0941.

Registry No.—**1**, 26198-76-5; **2**, 26198-75-4; **3**, 26198-77-6; **4**, 26198-78-7; **5**, 32414-36-1; **6**, 22467-63-6; **7**, 22467-62-5; *meso*-**10**, 32414-37-2; *threo*-**10**, 32414-38-3; **11**, 32388-86-6; **12**, 26198-74-3; **13**, 26111-15-9; **14**, 32388-88-8; **15**, 32388-89-9; methylallene,

(22) W. S. Fones, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 293.

590-19-2; *cis*-3,4-dimethyl-*cis*-1,2-bis(tosyloxymethyl)-cyclobutane, 32388-90-2; *cis*-3,4-dimethyl-*cis*-1,2-bis-(iodomethyl)cyclobutane, 32388-91-3.

Acknowledgment.—We thank the donors of the Petroleum Research Fund for partial support (2754 A1,4) of this work.

Dehydration of 3,4-Dimethyl-3,4-hexanediol to the Six Possible C_8H_{14} Dienes and Proof of Structure of the Substituted Butadienes[1]

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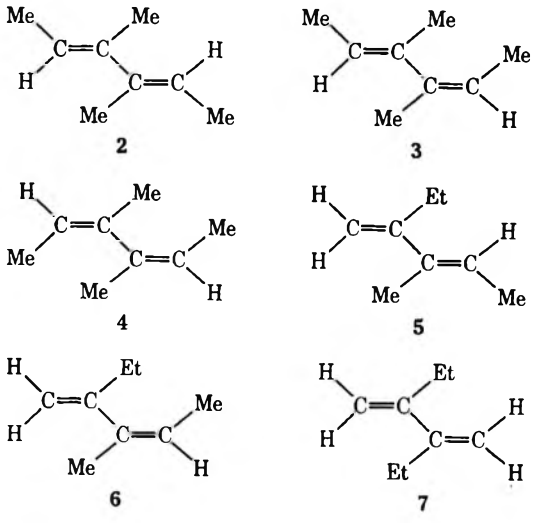
Received May 5, 1971

3,4-Dimethyl-3,4-hexanediol (1) has been dehydrated, using a variety of reagents, to mixtures of the six isomeric C_8H_{14} dienes. The use of acidic reagents, or iodine in propionic anhydride, favors the formation of *cis,cis*-3,4-dimethyl-2,4-hexadiene (2) and *cis,trans*-3,4-dimethyl-2,4-hexadiene (3), the dehydration following the Saytzeff pathway. An initial cis double bond is favored over an initial trans configuration because the conformations of the diol leading to a cis double bond exhibit less steric crowding. Phenyl isocyanate as a dehydrating agent is unusual in that double bond formation predominately follows the Hofmann pathway; even 2,3-diethylbutadiene can be prepared in this manner. The structures of the dienes follow from their spectral data. Models show that only the cis,cis isomer of the 3,4-dimethyl-2,4-hexadienes can exist in a conformation with the double bonds coplanar, and only this isomer absorbs strongly in the uv. Infrared and nmr spectra follow a consistent pattern to support the structural assignments. The boiling points of the six isomers range from 104 to 134° (760 mm).

Dehydration of a mixture of meso and *dl* pinacol **1**, 3,4-dimethyl-3,4-hexanediol, prepared from ethyl methyl ketone can give rise to six substituted isomeric butadienes of the formula C_8H_{14}. The purpose of this work was to prepare and characterize these dienes. Previously, two of the dienes (**2** and **3**) have been satisfactorily characterized by Criegee;[2a] the other four are new compounds. Recently, **4** has been reported to be formed in the thermal decomposition of 2-butenylsilver. No yield was given.[2b] The synthesis of **7**[3,4] and of a mixture of **5** and **6**[4] has been claimed by earlier workers but Criegee[2] has shown the assignments of Gostunskaya, *et al.*, to be in error, and the later synthesis of **7**,[3] based on an abnormal Grignard reaction, appears to be doubtful. The isolation was by distillation, the boiling point does not agree with ours, and neither glpc nor nmr spectra were used to characterize the fraction obtained.



Dehydration of 3,4-Dimethyl-3,4-hexanediol.—The dehydration of pinacol, 2,3-dimethyl-2,3-butanediol, has been studied over the past hundred years with a variety of reagents. With pinacol, only two products are possible, 2,3-dimethylbutadiene and pinacolone. It has been observed that pinacolone formation is favored by the use of less strong acids such as phosphoric or oxalic acids, whereas the use of hot strong acids such as hydrobromic acid causes dehydration to the diene to predominate. Iodine[5] and phenyl isocyanate[6] are known to be effective reagents for dehydrating pinacol to butadiene with little pinacolone formation. With 3,4-dimethyl-3,4-hexanediol, dehydration can lead to the two isomeric pinacolones or any of the six isomeric dienes.

We have studied the dehydration of a *dl*–meso mixture of the 3,4-dimethyl-3,4-hexanediols with a variety of reagents and the results are tabulated in Table I. The pinacol was obtained by the reduction of ethyl methyl ketone with magnesium and was an approximately 1:1 mixture of the *dl* and meso isomers.

The data in Table I show that iodine in propionic anhydride is the reagent of choice for the preparation of a diene mixture consisting mostly of the cis–cis (**2**) and cis–trans (**3**) isomers. The use of iodine alone is somewhat less desirable. Of the six possible isomers, these two are the ones preferentially formed in most of the dehydration reactions. The third most easily formed isomer is **5**; this is the major product when phenyl isocyanate is used as the dehydrating agent. This latter reagent is unique in that it preferentially forms a methylene rather than an ethylidene bond. Thus, **7** is also a major product using phenyl isocyanate whereas it is only a minor product in all of the other dehydration reactions. Sulfuric acid and hydrogen bromide also cause isomers **2**, **3**, and **5** to predominate, and with the latter reagent only small amounts of the pinacolones are formed. The use of potassium acid

(1) Taken in part from the doctoral thesis of D. M. Reichel, University of Maryland, 1970.

(2) (a) R. Criegee and K. Noll, *Justus Liebigs Ann. Chem.*, **627**, 1 (1959); (b) G. M. Whitesides, C. P. Casey, and J. K. Krieger, *J. Amer. Chem. Soc.*, **93**, 1388 (1971).

(3) G. M. Mkryan, S. M. Gasparyan, E. A. Avetisyan, and Sh. L. Mndzhoyan, *Zh. Org. Khim.*, **3**, 808 (1967); *Chem. Abstr.*, **67**, 43326 (1967).

(4) I. V. Gostunskaya, E. A. Krasnyanskaya, and B. A. Kazanskii, *J. Gen. Chem. USSR*, **25**, 1393 (1955).

(5) H. Hibbert, *J. Amer. Chem. Soc.*, **37**, 1748 (1915).

(6) D. A. McKenzie, Ph.D. Dissertation, University of Maryland, 1962.

TABLE I

DEHYDRATION OF PINACOL (1) WITH VARIOUS REAGENTS[a]

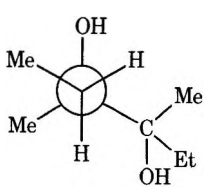
Reagent	% yield of diene fraction	Composition of diene fraction, %[b]							
		2	3	4	5	6	7	EtCOAm[c]	MeCOHx[d]
Iodine with propionic anhydride	74	35	38	1	13	3	3	Tr[e]	Tr
Iodine	63	34	39	2	8	3	3	1	2
PhNCO	26	16	6	Tr	41	3	28	Tr	Tr
$KHSO_4$	52	41	18	Tr	18	1	7	3	5
H_2SO_4	30	38	5	0	10	0	2	13	29
HBr	47	44	28	0	10	3	6	2	2
Potassium alum	53	37	4	0	28	0	5	7	14
P_2O_5	24	32	11	1	19	3	7	8	10
H_3PO_4	33	14	41	Tr	5	Tr	2	11	24
Polyphosphoric acid	27	11	11	0	2	Tr	1	23	51
Al_2O_3	40	9	8	3	6	5	4	19	43

[a] All dehydrations were carried out in the liquid phase at 120–140° except with alumina which dehydration was in the vapor phase at 250°. [b] Data are glpc percentages. [c] 4,4-Dimethyl-3-hexanone. [d] 3-Ethyl-3-methyl-2-pentanone. [e] Tr = trace.

sulfate causes the same three isomers to predominate, whereas potassium alum favors **2** and **5**. Vapor phase dehydration over alumina gives an indiscriminate mixture of all isomers. It was the method used to prepare the trans–trans isomer **4**; while the yield of this is only about 1%, most of the other procedures give even less.

Two facts stand out from the above. The formation of a cis double bond occurs preferentially to a trans, and the double bond formation occurs according to the Saytzeff rule, except with phenyl isocyanate. While this reagent has been used to dehydrate pinacol itself,[6] it has not been used with higher members of the pinacol series. One might expect on statistical grounds a three to two ratio of the Hofmann to Saytzeff pathways, assuming steric effects are not a factor. From the phenyl isocyanate data in Table I, it can be calculated that 53% of the double bonds formed are *via* the Hofmann pathway, whereas with iodine or the acidic reagents only 13–19% of the double bonds are formed by this pathway. Earlier investigators studying the use of this reagent have speculated that the dehydration mechanism is analogous to that of acetate pyrolysis at 500°.[6]

The reason for the preferential cis double bond formation becomes apparent after an examination of the possible conformations leading to a reaction. The hydrogens of the number two methylene group can exist in four such conformations with the hydroxyl group



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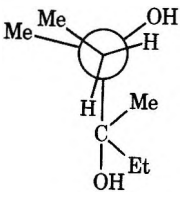

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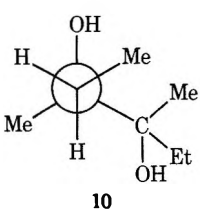

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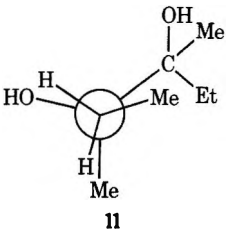

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on carbon number three. Fisher–Taylor–Hirschfelder models show that neither of the two conformations [one staggered (**8**), one eclipsed (**9**)] which might lead to an initial cis double bond exhibit severe steric crowding; much more severe steric interactions do occur with the two conformations (**10, 11**) leading to the trans double bond, particularly with the meso isomer of the pinacol. Furthermore, in a stepwise conversion of the pinacol to the dienes with the first double bond being trans, the intermediate, *trans*-3,4-dimethyl-4-hexen-3-ol, has much more severe steric interactions than does its cis isomer; this factor alone would strongly favor the formation of the initial double bond with a cis configuration. Once the first double bond is formed, the molecular geometry changes so that the steric effects discussed above have less influence on the conformations leading to the cis or trans second double bond.

The results of the dehydration of the high-melting form[7] of the 3,4-dimethyl-3,4-hexanediol were contrasted with that of the approximately 1:1 mixture of the *dl* and meso isomers to see if the use of the meso pinacol did lead to less trans double bond formation as the study of the models suggested. The dehydrations were carried out using the iodine in propionic anhydride reagent. The diene fraction obtained from the high-melting form of the pinacol contained 63% of the cis–cis isomer **2** and 4% of the cis–trans isomer **3**. The approximately 1:1 mixture of the meso and *dl* forms of the pinacol gave 39 and 33%, respectively (see Table I). The percentages of isomers **4, 5, 6,** and **7** from the meso pinacol were 0, 24, 0, and 2%, respectively. It is apparent that the diastereoisomers do behave differently, and the form presumed to be the meso isomer gives rise to less trans double bond formation as predicted.

Proof of Structure of the 3,4-Dimethyl-2,4-hexadienes.—The three geometrical isomers **2, 3,** and **4** could be distinguished from the remaining three isomers by their similar nmr spectra, which showed four methyl groups and two vinyl hydrogens, and their almost identical mass spectra. Isomers **2** and **3** have been characterized previously by Criegee,[2] but the proof of structure given here is independent of his work. A study of Fisher–Taylor–Hirschfelder models of the three isomers showed that only the cis–cis isomer **2**

(7) This form is assumed to be the meso isomer by analogy with the two 4,5-octanediols where the stereochemistry has been definitely established: S. Veibel, *Biochem. Z.*, **239**, 456 (1931) [*Brit. Chem. Abstr.*, **A**, 1332 (1931)]; W. G. Young, L. Levanas, and Z. Jasaitis, *J. Amer. Chem. Soc.*, **58**, 2274 (1936).

TABLE II
SPECTRAL DATA ON ISOMERS

Configuration	Uv max (ϵ)	Olefinic absorption, cm^{-1}	Nmr, δ units	
			$C=CHCH_3$	$C=CHCH_3$
Cis–cis (**2**)	237 (17,000)	1625 (str)	1.70	5.6
Cis–trans (**3**)	210 (3,600)	1650 (intermediate)	1.68, 1.58	5.22
Trans–trans (**4**)	205 (2,000)	1650 (weak) 1620 (weak)	1.47	5.3
Cis (**5**)		1640 (med) 1620 (str)	1.68	5.63
Trans (**6**)		1630 (str)	1.60	5.32

could easily exist in a conformation with the double bonds coplanar, either cisoid or transoid. This must correspond to the isomer with the uv maximum at 237 mμ (ϵ 17,000). A model of the trans–trans isomer **4** cannot exist in a coplanar form, and consequently **4** exhibits the lowest uv maximum and lowest extinction coefficient as shown by the data in Table II. The isomer with the intermediate uv spectra is assigned the cis–trans structure **3** since a model of this is intermediate between the other two isomers in the ease of forcing the double bonds into coplanarity. These structural assignments are supported by the ir spectra, by the consistent changes observed in the chemical shifts of the methyl and olefinic protons in the nmr spectra as one proceeds through the series, and by the ease of sulfone formation. The boiling points of the isomers also change in a consistent manner.

The infrared spectra of the trans–trans isomer of 3,4-dimethyl-2,4-hexadiene would be expected to have the least absorption in the 1630-cm^{-1} region because of the relatively symmetrical arrangement around each of the double bonds. As shown in Table II this was found to be the case. The isomer assigned the cis–cis structure on the basis of its uv maximum at 237 mμ absorbed strongly, and the third geometrical isomer exhibited an absorption band of intermediate strength.

In the nmr spectra, the chemical shifts of the terminal methyl groups change in a consistent manner as one proceeds from the cis–cis to the trans–trans structures, and these shifts were used to assign the cis and trans configurations to the 2-ethyl-3-methyl-1,3-pentadienes.

The reaction of the mixture of the dienes with sulfur dioxide provided chemical evidence for the assignment of the trans–trans structure to the isomer of uv max 205 mμ. Butadiene and one of the piperylenes react with sulfur dioxide to form cyclic sulfones.[8] The diene must be in the cisoid form for this reaction to occur, and it is known that the reaction with sulfur dioxide can be slowed down or prevented by a terminal methyl group in the position where the sulfur dioxide must approach.[8] Accordingly, it would be expected that the trans–trans **4**, with two methyl groups blocking the approach of the sulfur dioxide, would not react. This was found to be the case; most of the isomer assigned the trans–trans structure was still present unreacted after standing for 10 days with sulfur dioxide at $-17°$. In constrast, the isomer assigned the cis–cis structure had completely reacted as had all but small amounts of the isomer assigned the cis–trans structure.

Microboiling points were determined on the three isomers after purification by glpc and found to be 134, 114, and 104° (760 mm) for the cis–cis, cis–trans, and trans–trans isomers, respectively. This rather wide range, and the higher boiling point of the cis–cis isomer, are probably related to the ability of the cis–cis molecule to exist in a linear form with coplanar double bonds, whereas the trans–trans isomer for steric reasons is in a nonlinear, more compact form.

Finally, our structural assignments for the cis–cis and the cis–trans isomers are in agreement with those made by Criegee[2] as is shown by comparing the melting point data on the maleic anhydride adducts.

Proof of Structure of the 2-Ethyl-3-methyl-1,3-pentadienes.—Two of the dienes formed in the dehydration of the pinacol are clearly the isomeric 2-ethyl-3-methyl-1,3-pentadienes since they have nearly identical mass spectra and their nmr spectra show an ethyl group, two methyl groups, and three vinyl protons. As shown in Table II, the methyl doublet and the vinyl proton quartet of one have chemical shifts nearly identical with those of the *cis,cis*-3,4-dimethyl-2,4-dimethyl-2,4-hexadiene (**2**); it is accordingly the *cis*-2-ethyl-3-methyl-1,3-pentadiene (**5**). The other isomer has chemical shifts of these groups upfield from the cis isomer and nearly identical with those of *trans,-trans*-3,4-dimethyl-2,4-hexadiene (**4**) and is accordingly the *trans*-2-ethyl-3-methyl-1,3-pentadiene (**6**). These structural assignments were consistent with the ir spectra of the two isomers. The cis isomer has two absorption bands of strong and medium intensity at 1620 and 1640 cm^{-1}; the trans isomer has a single strong peak at 1630 cm^{-1}. Both exhibited strong absorption at 880–890 cm^{-1} due to the methylene group. The relative ease of formation of the sulfone derivatives adds further supporting evidence. The cis isomer **5** reacts completely whereas the trans isomer **6** reacts to a much lesser degree. The cis isomer is again observed to have a higher boiling point (127°) than the trans isomer (108°).

Proof of Structure of 2,3-Diethylbutadiene.—The structure of this isomer (**7**) is established by its nmr spectrum which clearly shows the two ethyl groups and the four terminal vinyl protons.

Experimental Section

Melting points and boiling points are corrected. The infrared spectra were determined with a Perkin-Elmer Model 337 on the neat liquid using a 0.025-mm sodium chloride cell; the ultraviolet spectra with a Cary Model 14; the mass spectra with a Varian M-66; and the nmr spectra with a Varian Model A-60A. Chemical shift values are expressed as δ values (parts per million) downfield from tetramethylsilane internal standard. Elemental microanalyses were performed by Dr. F. J. Kasler.

Dehydration with Iodine in Propionic Anhydride.—A 250-ml three-necked flask was charged with 64 ml of propionic anhydride,

(8) D. Craig, *J. Amer. Chem. Soc.*, **65**, 1006 (1943).

130 mg of iodine, and 60 g of the *dl*–meso mixture of the 3,4-dimethyl-3,4-hexandiols, bp 108–114° (32 mm), obtained by the reduction of ethyl methyl ketone with amalgamated magnesium.[9] The mixture was stirred with a magnetic stirrer and heated for 2 hr at 125°. A stream of carbon dioxide was passed through the reaction flask to sweep the volatile products through a water-cooled condenser into a receiving flask immersed in an ice–salt mixture. The propionic anhydride that distilled along with the diene fraction was removed by shaking with saturated sodium bicarbonate solution. The diene mixture was 44 ml (74% of theory). Its composition is given in Table I.

Dehydration with Other Reagents.—All of the dehydrations in the liquid phase were carried out in the same way as the example above but without solvent and on a smaller scale. After the initial heating at 120°, the temperature was slowly raised over a 2-hr period to 130–140°. The data are in Table III.

TABLE III

EXPERIMENTAL DATA ON THE PINACOL (1) DEHYDRATIONS

1, g	Reagent	Final temp, °C	Reaction time, hr	Yield,[a] ml
3.4	20 mg of iodine	140	2	2
29	108 ml of PhNCO, 0.6 g of *N*-phenyl-β-naphthylamine, 0.2 g of lithium slices	150	2	7
9.6	2.5 g of $KHSO_4$	140	2	5.5
4.3	5 drops of concentrated H_2SO_4	140	2	1.2
4.8	0.2 ml of 48% HBr	140	2	2.5
4.3	1 g of potassium alum	140	2	2.5
6.7	0.1 g of P_2O_5	140	2	1.5
4.8	1 ml of 85% H_3PO_4	140	4	1.5
4.8	1 ml of poly H_3PO_4	140	2	1.5

[a] Composition given in Table I.

Dehydration over Alumina.—This was patterned after the procedure for dehydrating pinacol.[10] The mixture (40 ml) of the meso and *dl* isomers of the 3,4-dimethyl-3,4-hexanediol was added dropwise at about 1 ml/min to a 40-cm column of 8–14 mesh Fisher alumina electrically heated to about 250°, and the products were caught in a series of traps cooled in ice and finally Dry Ice. The product consisted of 20 g of an organic layer which gave 12 g of the diene fraction on distillation. Composition data are in Table I.

Analysis of Diene Fraction.—This was done by glpc using an F & M Model 300 vapor phase chromatograph. Of the various columns used, the best was a 2-m long, 6.3-mm o.d. copper tube packed with 10% Carbowax-1000 on 80-100 mesh silanized diatomaceous earth (Anakrom P). The glpc percentages in Table I were shown to approximate weight percentages by analyzing a mixture consisting of 71.5 mg of **3** (79.3 mg of 90% pure **3** isolated by distillation) and 25.7 mg of **2** (28.7 mg of 89% pure **2** isolated by distillation). The weight ratio of **3** to **2** was 2.78; the ratio of the areas obtained by glpc was 2.8. The retention times in minutes (at 50° with a helium flow of approximately 50 ml/min) for the compounds are as follows: **4**, 4.7; **6**, 5.3; **3**, 6.3; **7**, 7.2; **5**, 10.3; rearranged product, 13; **2**, 17; 4,4-dimethyl-3-hexanone, 39; and 3-ethyl-3-methyl-2-pentanone, 51.

cis,cis-**3,4-Dimethyl-2,4-hexadiene** (**2**) was best prepared by the procedure using iodine in propionic anhydride. The following data are on material separated by glpc: bp 134° (760 mm)[11] [lit.[2] bp 134–135° (760 mm)]; uv max (cyclopentane) 237 mμ (ε 17,000) [lit.[2] uv max (solvent unspecified) 230 mμ (ε 13,000)]; ir (neat) 3055, 3000–2900, 2865, 1625, 1450, 1385, 1055, 995, 890 (w), 815, and 795 cm^{-1}; nmr ($DCCl_3$) δ 5.60 (quartet, 2, J = 6.5 Hz, C=C**H**CH_3), 1.77 (s, 6, =C(CH_3)C), 1.70 (d, 6, J = 6.5 Hz, C=CHCH_3); mass spectrum (70 eV) m/e (rel intensity) 110 (58), 95 (100), 81 (15), 79 (10), 77 (12), 67 (46).

Anal. Calcd for C_8H_{14}: C, 87.20; H, 12.80. Found: C, 87.27; H, 12.72.

cis,trans-**3,4-Dimethyl-2,4-hexadiene** (**3**) was best prepared by the procedure using iodine in propionic anhydride. The following data are on material separated by glpc: bp 113.5° (760 mm)[11] [lit.[2] bp 113–115° (760 mm)]; uv max (cyclopentane) 210 mμ (ε 3600) (lit.[2] reported no max); ir (neat) 3015, 2970–2900, 2850, 1650 (w), 1445, 1370, 1230, 1090, 1050–1030, 1005, 840, and 810 cm^{-1}; nmr ($DCCl_3$) δ 5.22 (quartet, 2, J = 6 Hz, C=C**H**CH_3), 1.70 (s, 6, =C(CH_3)C), 1.68 (d, 3, J = 6 Hz, cis C=CHCH_3), 1.58 (d, 3, J = 6 Hz, trans C=CHCH_3); mass spectrum (70 eV) m/e (rel intensity) 110 (77), 95 (100), 81 (23), 79 (11), 77 (16), 67 (66).

Anal. Calcd for C_8H_{14}: C, 87.20; H, 12.80. Found: C, 87.33; H, 12.67.

trans,trans-**3,4-Dimethyl-2,4 hexadiene** (**4**) was prepared by dehydration of the pinacol (*dl*–meso mixture) over aluminum oxide at 250°. The following data are on material separated by glpc: bp 104° (760 mm);[11] uv max (cyclopentane) 205 mμ (ε 2000); ir (neat) 3040, 2980–2900, 2850, 1650 (w), 1620 (w), 1440, 1360, 1310, 1080, 1030, 890 (m), and 830–810 cm^{-1}; nmr ($DCCl_3$) δ 5.28 (quartet, 2, J = 6.5 Hz, C=C**H**CH_3), 1.72 (s, 6, =C(CH_3)C), 1.47 (d, 6, J = 6.5 Hz, C=CHCH_3); mass spectrum (70 eV) m/e (rel intensity) 110 (100), 95 (100), 81 (14), 79 (11), 77 (13), 67 (51).

Anal. Calcd for C_8H_{14}: C, 87.20; H, 12.80. Found: C, 87.40; H, 12.78.

cis-**2-Ethyl-3-methyl-1,3-pentadiene** (**5**) was best prepared by procedure using phenyl isocyanate. The following data are on material separated by glpc: bp 127° (760 mm);[11] ir (neat) 3090, 2970–2900, 2880, 1640 (m), 1620 (s), 1470, 1390, 1080, 1010, 880 (s), 830, 800, 730, and 695 cm^{-1}; nmr ($DCCl_3$) δ 5.63 (quartet, 1, J = 7 Hz, C=C**H**CH_3), 4.90 (s, 1, =CH_2), 4.78 (s, 1, =CH_2), 2.25 (quartet, 2, J = 7 Hz, CH_2CH_3), 1.75 (s, 3, =C(CH_3)C), 1.68 (d, 3, J = 7 Hz, C=CHCH_3), 1.03 (t, 3, J = 7 Hz, CH_2CH_3); mass spectrum (70 eV) m/e (rel intensity) 110 (57), 95 (100), 81 (41), 79 (17), 77 (17), 68 (14), 67 (46), 65 (10).

Anal. Calcd for C_8H_{14}: C, 87.20; H, 12.80. Found: C, 87.32; H, 12.60.

trans-**2-Ethyl-3-methyl-1,3-pentadiene** (**6**) was prepared by the procedure using iodine in propionic anhydride. The following data are on materials separated by glpc: bp 108° (760 mm);[11] ir (neat) 3075, 2970-2900, 2860, 1630 (s), 1445, 1360, 1080, 1030, 890 (s), 865, and 820 cm^{-1}; nmr ($DCCl_3$) δ 5.32 (quartet, 1, J = 7 Hz, C=C**H**CH_3), 4.95 (s, 1, =CH_2), 4.68 (s, 1, =CH_2), 2.13 (quartet, 2, J = 8 Hz, CH_2CH_3), 1.75 (s, 3, =C(CH_3)C), 1.60 (d, 3, J = 7 Hz, C=CHCH_3), 0.98 (t, 3, J = 8 Hz, CH_2CH_3); mass spectrum (70 eV) m/e (rel intensity) 110 (63), 95 (100), 81 (32), 79 (17), 77 (10), 68 (15), 67 (56), 65 (9).

Anal. Calcd for C_8H_{14}: C, 87.20; H, 12.80. Found: C, 87.23, H, 12.78.

2,3-Diethyl-1,3-butadiene (**7**) was best prepared by the procedure using phenyl isocyanate. The following data are on material separated by glpc: bp 119° (760 mm);[11] ir (neat) 3080, 2980–2900, 2870, 1790 (w), 1630 (w), 1600 (s), 1460, 1390, 1365, 1070, and 890 cm^{-1} (s); nmr ($CHCl_3$) δ 5.07 (s, 2, =CH_2), 4.93 (s, 2, =CH_2), 2.28 (quartet, 4, J = 7 Hz, CH_2CH_3), 1.07 (t, 6, J = 7 Hz, CH_2CH_3).

Anal. Calcd for C_8H_{14}: C, 87.20; H, 12.80. Found: C, 87.39; H, 12.57.

Maleic anhydride adducts were prepared by Criegee's method.[2] The diene (0.5 g), 0.44 g of maleic anhydride (purified by recrystallization from chloroform), and 0.5 or 2 ml (for **2** and **3**, respectively) of benzene were heated in a sealed tube in a steam bath for 8 or 17 hr (for **2** and **3**, respectively). **2** had mp 111–112° (lit.[2] 113–114°); **3** had mp 70–71° (lit.[2] 68–69°).

Sulfones.—The diene mixture (10 ml), bp 104–135°, which had been prepared by the iodine in the propionic anhydride procedure was cooled in Dry Ice and mixed with 10 ml of liquid sulfur dioxide. The mixture was stored in a cold room at −17° and samples were analyzed periodically by glpc. The glpc data were obtained using a Carbowax-1000 column at 50° with the injection port at 105°. After 10 days, the reaction appeared to have proceeded as far as it was going to go; after 30 days the results were essentially the same. The amounts of the diene that reacted

(9) W. Reeve and M. Karickhoff, *J. Amer. Chem. Soc.*, **78**, 6053 (1956).

(10) L. W. Newton and E. R. Coburn in "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 313.

(11) Microboiling point by Siwoloboff's method in F. Schneider, "Qualitative Organic Microanalysis," Wiley, New York, N. Y., 1946, p 93.

follow (compound, per cent in original mixture, per cent unreacted hydrocarbon in final hydrocarbon mixture): **2**, 35, 0; **3**, 38, 5; **4**, 1, 80; **5**, 13, 0; **6**, 3, 15; **7**, 3, 0.

Registry No.—*meso*-**1**, 32388-93-5; *dl*-**1**, 32388-94-6; **2**, 18265-39-9; **3**, 2417-88-1; **4**, 21293-01-6; **5**, 32388-98-0; **6**, 32388-99-1; **7**, 16356-05-1.

Reaction of Ethynyl Compounds with Lactones

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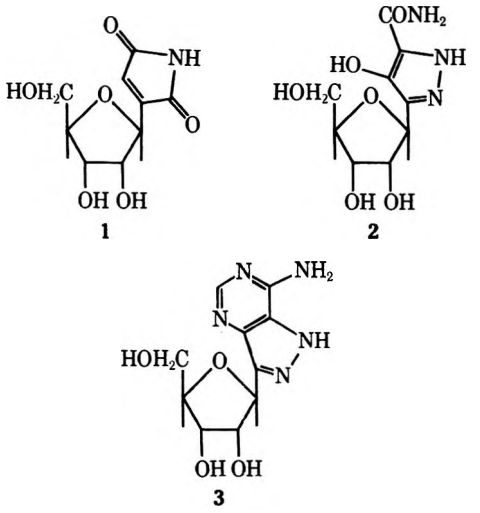
Received May 20, 1971

Acetylenic lactols, 3-butyl-3,3′-dihydroxy-1,5-diphenylpenta-1,4-diyne, 6-hydroxy-1-phenylheptan-3-one, 1-(2-substituted ethynyl)-β-L-gulofuranose, and 1-(2-substituted ethynyl)-α-D-ribofuranose, were synthesized *via* the lithium derivative of ethynyl compounds. The reaction mechanism involving the lactone carbonyl is similar to the reaction of aldehyde or ketone with the ethynyllithium compound.

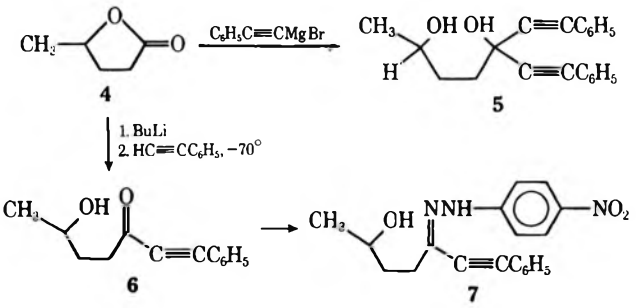
The nucleoside antibiotics, showdomycin[1] (**1**), pyrazomycin[2] (**2**), and formycin[3,4] (**3**), are carbon-linked nucleosides. The carbon-linked nucleosides are interesting compounds with potent biological activity, and the synthetic studies on these compounds have been reported by Šorm, *et al.*,[5] and by Goodman, *et al.*[6]



Tronchet and Perret[7] reported the synthesis of an analog of pyrazomycin (**2**), 3-β-D-erythrofuranosyl-1-*p*-nitrophenylpyrazole. On the other hand, Asbun and Binkley[8] synthesized 5-substituted pyrimidine nucleosides from the reaction of diisopropylidene aldehydopentose with 2,4-dibenzyloxy-5-lithiopyrimidine.

The present paper concerns attempted reaction of ethynyl compounds with lactones and sugar lactones, which was expected as a model experiment for the preparation of the carbon-linked nucleoside.[9] γ-Valerolactone (**4**) (Scheme I) was treated with the

SCHEME I



Grignard compound of phenylacetylene to obtain 3-butyl-3,3′-dihydroxy-1,5-diphenylpenta-1,4-diyne (**5**). This is similar to the reaction of γ-butyrolactone and phenylmagnesium bromide.[10] Butyllithium was used in place of the Grignard compound of γ-butyrolactone (**4**) to form 6-hydroxy-1-phenylhepta-1-yn-3-one (**6**), which was confirmed as its *p*-nitrophenylhydrazone (**7**) through examination of ir, nmr, and mass spectra.

By application of this method to sugar lactones, it has been possible to obtain acetylenic lactols. Treatment of 5-*O*-(tetrahydropyran-2-yl)-2,3-*O*-isopropylidene-D-ribonolactone (**9**) with butyllithium and phenylacetylene in ether failed to afford phenylacetylenic lactol. On the other hand, reaction of 2,3-*O*-isopropylidene-D-ribonolactone (**8**) or 2,3-*O*-isopropylidene-5-*O*-acetyl-D-ribonolactone (**10**) with lithium acetylenic compounds gave 1-(2-substituted ethynyl)-2,3-*O*-isopropylidene-D-ribofuranose (**11a,b**) in 30% yield (Scheme II). The ir spectra of these compounds (**11a,b**) show hydroxyl bands at 3380 and 3280 cm^{-1} and acetylenic band at 2180–2190 cm^{-1}, and no lactonic band at around 1780 cm^{-1}.

In case of L-gulonolactone, 2,3:5,6-di-*O*-isopropylidene derivative (**12**) was treated with various lithium acetylenic compounds to obtain 1-substituted 2,3:5,6-di-*O*-isopropylidene-L-gulofuranose (**13a–g**) in a reasonable yield (40–50%) (Scheme III). The ir spectra of these compounds (**13a–g**) showed a hydroxyl band at around 3300–3400 cm^{-1} and an acetylenic band at 2160–2180 cm^{-1}, and the mass spectra of these compounds showed molecular ion (M^+) peaks.

The nmr spectra of these compounds (**13a–g**) showed a broad singlet due to C_1-hydroxyl group at around δ

(1) K. R. Darnall, L. B. Townsend, and R. K. Robins, *Proc. Nat. Acad. Sci. U. S.*, **57**, 548 (1967).

(2) R. H. Williams, K. Gerzon, M. Hoehn, M. Gorman, and D. C. Delong, Abstract of Papers, No. MICR 38, 158th National Meeting of the American Chemical Society, New York, N. Y., Sep 1969.

(3) R. K. Robins, L. B. Townsend, F. C. Cassidy, J. F. Gerster, A. F. Lewis, and R. L. Miller, *J. Heterocycl. Chem.*, **3**, 110 (1966).

(4) C. Koyama, K. Maeda, H. Umezawa, and Y. Iitaka, *Tetrahedron Lett.*, 597 (1966).

(5) M. Sprinzl, J. Farkas, and F. Šorm, *ibid.*, 289 (1969); L. Kalvoda, J. Farkas, and F. Šorm, *ibid.*, 2297 (1970); M. Bobek, J. Farkas, and F. Šorm, *ibid.*, 4611 (1970).

(6) E. M. Acton, K. J. Ryan, and L. Goodman, *Chem. Commun.*, 313 (1970).

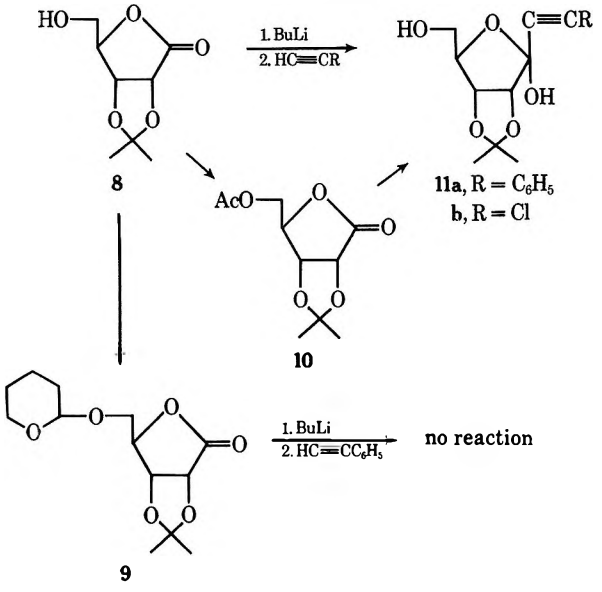
(7) J. M. J. Tronchet and M. F. Perret, *Helv. Chim. Acta*, **53**, 648 (1970).

(8) W. Asbun and S. B. Binkley, *J. Org. Chem.*, **31**, 2215 (1966).

(9) H. Ogura and H. Takahashi, unpublished work.

(10) M. S. Kharash and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, Englewood Cliffs, N. J., 1954, p 574, and references cited therein.

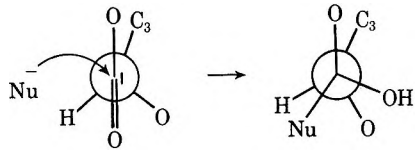
SCHEME II



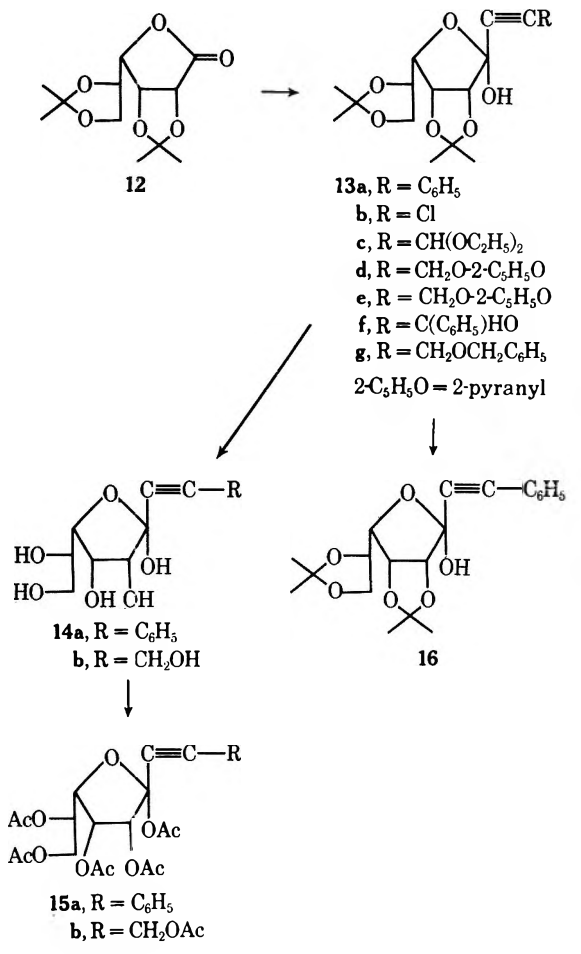
3.20–3.50 ppm, and four singlets at around δ 1.20–1.55 ppm due to the isopropylidene group. Therefore, the structure of these compounds (**13a–g**) was firmly established.

Hydrolysis of both 1-(3-phenylethynyl)-2,3:5,6-di-*O*-isopropylidene-L-gulofuranose (**13a**) and 1-(3-tetrahydropyranyloxypropynyl)-2,3:5,6-di-*O*-isopropylidene-L-gulofuranose (**13e**) by treatment with 70% acetic acid[11] yielded 1-(3-phenylethynyl)-L-gulofuranose (**14a**) and 1-(3-hydroxypropynyl)-L-gulofuranose (**14b**), respectively. Further acetylation of these compounds in acetic anhydride in the presence of pyridine afforded 1,2,3,5,6-penta-*O*-acetyl derivatives (**15a,b**). This result was confirmed by ir spectra, by the absence of a hydroxyl band at around 3000–3500 cm^{-1} and the presence of a molecular peak in the mass spectra. Easy acetylation of the anomer hydroxyl group may be explained by small steric hindrance. This was confirmed by the acetylation of **13a** under the same condition to yield 1-acetoxy-1-phenylethynyl-2,3:5,6-di-*O*-isopropylidene-L-gulofuranose (**16**). For a similar reason, acetylation of a tertiary hydroxyl group occurred in steroid[12] and in pikromycin (amaromycin), a macrolide antibiotic, under the same conditions.[13]

The ethynyl group in these acetylenic lactols is assumed to have the configuration depicted in the structural formulae because the nucleophilic addition reaction would probably take place from the least hindered side of the molecule, namely opposite to the 2,3-*O*-isopropylidene ring. The reaction proceeds stereospecifically and the isomeric lactols were not detected by tlc or gas chromatography.



SCHEME III



Experimental Section

All melting points were obtained on a Mettler FP-1 melting point apparatus and are corrected. Gas chromatography was performed with a JGC-810 gas chromatograph and a OV-1 column was used at 180°. Optical rotations were measured in chloroform solution, in a 0.1-dm tube with a JASCO automatic polarimeter DIP-SL, unless otherwise noted. Nmr spectra were recorded in deuteriochloroform at 60 MHz with a Varian Associates C-60 spectrometer and tetramethylsilane was used as an internal reference. Mass spectra were taken with a Japan Electron Optics JMS-01S high-resolution spectrometer with a direct inlet system.

3-Butyl-3,3′-dihydroxy-1,5-diphenylpenta-1,4-diyne (5).—To a solution of isopropylmagnesium bromide prepared from magnesium (1.4 g, 0.06 mol) and isopropyl bromide (6.5 g, 0.05 mol) in ether (50 ml), 5.1 g (0.05 mol) of phenylacetylene was added dropwise, with stirring under introduction of dry nitrogen. After stirring for 0.5 hr, the solution was refluxed for 1.5 hr and γ-valerolactone (5.7 g, 0.06 mol) was added to the hot solution, which was stirred for 2 hr and allowed to stand overnight at room temperature. The reaction solution was treated with saturated NH_4Cl solution and extracted with ether. The ether solution was washed with $NaHCO_3$ solution and dried over $MgSO_4$. The solvent was removed under reduced pressure to give **5** (3.0 g, 20%) as colorless prisms: mp 102.2° [recrystallized from ether–petroleum ether (bp 30–60°)]; ir λ_{max}^{KBr} 3360 (OH), 2180 (C≡C), 1600 and 1570 cm^{-1} (phenyl); nmr δ 7.24–7.64 (10 H, m, aromatic proton), 3.82–5.90 (1 H, m), and 1.26 (3 H, d, CH_3); mass spectrum *m/e* 304 (M^+).

6-Hydroxy-1-phenylhepta-1-yn-3-one (6).—To a solution of lithium (0.39 g, 0.06 mol) in anhydrous ether (50 ml), butyl bromide was added dropwise under introduction of dry nitrogen at room temperature. When the solution became turbid, the solution was cooled to −10° and the remaining butyl bromide (total amount, 3.4 g, 0.03 mol) was added during 30 min. After stirring for 1.5 hr at 0–2°, phenylacetylene (2.5 g, 0.03 mol) in ether (5 ml) was added dropwise at −70°. To the reaction solution γ-valerolactone (2.5 g, 0.03 mol) was added dropwise at −60 to −70° during 30 min. After stirring for 3 hr, the reaction

(11) D. Shapiro, Y. Rabinsohn, A. J. Acher, and A. Diver-Haber, *J. Org. Chem.*, **35**, 1464 (1970).

(12) D. B. Cowell and D. W. Mathieson, *J. Pharm. Pharmacol.*, **9**, 549 (1957).

(13) H. Ogura, K. Furuhata, and K. Kikuchi, Abstracts of Papers, 89th Annual Meeting of the Pharmaceutical Society of Japan, 1969, p 334.

mixture was worked up as described for the preparation of **5** to give an orange oil: ir λ_{max}^{film} 3380 (OH) and 1665 cm^{-1} (unsaturated ketone). *Anal.* Calcd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.25; H, 7.03.

p-**Nitrophenylhydrazone** (**7**) was prepared from **6** (0.5 g, 0.02 mol) and *p*-nitrophenylhydrazine (0.37 g, 0.02 mol) in glacial acetic acid (3 ml). The reaction mixture was poured into water (200 ml) and extracted with ether. The ether solution was washed with $NaHCO_3$ solution and water, dried, and ether was evaporated to leave yellow crystals. This was recrystallized from ethanol to **7** as yellow needles: mp 108.3°; ir λ_{max}^{KBr} 3290 (NH), 3380 and 1115 (OH), and 1600 cm^{-1} (phenyl); nmr δ 1.30 (3 H, d, CH_3), 1.60 (1 H, s, OH), 3.95 (1 H, m, CH), and 7.50 (5 H, m, phenyl), 7.10 and 8.15 (2 H, d, proton of hydrazine); mass pectrum *m/e* 337 (M^+). *Anal.* Calcd for $C_{19}H_{19}O_3N_3$: mol wt 337.143. Found: mol wt 337.144.

3-(2-Tetrahydropyranyloxy)-1-propyne.—This compound was prepared by the procedure of Crombie,[14] in 80% yield: bp 45–50° (3–4 mm) (reported[15] bp 63–65° (9 mm); ir λ_{max}^{film} 2100 cm^{-1} (C≡C); tlc R_f 0.78 (benzene–acetone, 4:1).

3-Phenyl-3-(2-tetrahydropyranyloxy)-1-propyne.—To a stirred solution of α-phenylpropargyl alcohol (25.4 g, 0.5 mol) in ether (20 ml), 2,3-dihydropyran (16.8 g, 0.2 mol) and a catalytic amount of *p*-toluenesulfonic acid were added under ice cooling.[16] After stirring for 2 hr at room temperature, the reaction mixture was treated by the general method as described above in the preparation of **5** to give a colorless liquid: bp 100–103° (1 mm); ir λ_{max}^{film} 2100 (C≡C) and 1600 cm^{-1} (phenyl); tlc R_f 0.68 (benzene–acetone, 4:1).

2,3-*O*-Isopropylidene-D-ribonolactone (**8**).[17]—To a solution of D-ribonolactone[18] (25 g, 0.13 mol) in acetone (500 ml), concentrated H_2SO_4 (10 ml) was added dropwise under ice cooling, and then the whole was stirred continuously for 5 hr at room temperature. After the reaction, ammonia gas was passed through into the reaction solution under ice cooling. The filtrate was evaporated under reduced pressure and the resulted crystalline residue was recrystallized from benzene to 26.6 g (80%) of **8** as colorless needles: mp 138.0–139.0°; $[\alpha]^{26}D$ −84.17° (*c* 0.9); ir λ_{max}^{KBr} 3420, 1080 (OH), 1780 (lactone), 1390, and 1380 cm^{-1} (*gem*-CH_3); nmr δ 1.49 and 1.42 (6, H, s, isopropylidene), 3.28 (1 H, s, OH), 3.90 (2 H, d, C_5H_2), and 4.64 (1 H, t, C_4H); mass spectrum *m/e* 188 (M^+). *Anal.* Calcd for $C_8H_{12}O_6$: C, 51.06; H, 6.43. Found: C, 50.88; H, 6.52.

5-*O*-(Tetrahydropyran-2-yl)-2,3-*O*-isopropylidene-D-ribonolactone (**9**).—A solution of 2,3-*O*-isopropylidene-D-ribonolactone (**8**, 3.76 g, 0.02 mol) in dimethylformamide (30 ml) was treated with 2,3-dihydropyrane (1.68 g, 0.02 mol) in the presence of *p*-toluenesulfonic acid at room temperature. After standing at room temperature for 2 days, ether was added and the reaction mixture was worked up to give **9** as colorless needles (from water) (4.0 g, 74%): mp 105–107°; $[\alpha]^{26}D$ −69.78° (*c* 0.9); mass spectrum *m/e* 272 (M^+). *Anal.* Calcd for $C_{13}H_{20}O_6$: C, 57.34; H, 7.40. Found: C, 57.28; H, 7.45.

5-*O*-Acetyl-2,3-*O*-isopropylidene-D-ribonolactone (**10**).—A solution of 2,3-*O*-isopropylidene-D-ribonolactone (**8**, 11.7 g, 0.06 mol) in acetic anhydride (15 ml) and pyridine (15 ml) was stirred for 30 hr at room temperature. The slightly brownish solution was concentrated, poured into ice–water (500 ml), and extracted with $CHCl_3$ (300 ml). The organic layer was washed with $NaHCO_3$ solution (100 ml) and dried over $MgSO_4$, and the solvent removed to give 13 g (90%) of **10** as colorless needles: mp 47.5°; ir λ_{max}^{KBr} 1790 (lactone), 1760 (acetate), 1390 and 1380 cm^{-1} (*gem*-CH_3); nmr δ 1.36, 1.48 (6 H, s, isopropylidene) and 2.12 (3 H, s, $OCOCH_3$); mass spectrum *m/e* 230 (M^+). *Anal.* Calcd for $C_{10}H_{14}O_6$: C, 52.17; H, 6.13. Found: C, 52.28; H, 6.18.

1-Phenylethynyl-2,3-*O*-isopropylidene-α-D-ribofuranose (**11a**). **A.**—A solution of 2,3-*O*-isopropylidene-D-ribonolactone (**8**, 1.0 g, 0.005 mol) was treated with phenylacetylene (1.02 g, 0.01 mol) in the same manner as described for **6**, and **11a** was obtained (0.5 g, 30%) as colorless needles: mp 152.3°; ir λ_{max}^{KBr} 3380 (OH), 2180 (C≡C), 1600 and 700 cm^{-1} (phenyl); nmr δ 1.45, 1.64 (6 H, s, isopropylidene), 3.75, 3.95 (2 H, dd, C_5H_2), and 7.40 (5 H, m,

TABLE I

1-(2-SUBSTITUTED ETHYNYL)-2,3:5,6-DI-*O*-ISOPROPYLIDENE-β-L-GULOFURANOSE (**13**)

Compd	R	Yield, %	Mp, °C	Ir, λ_{max}^{KBr}, cm^{-1}	Formula	Calcd, % C	Calcd, % H	Found, % C	Found, % H	$[\alpha]D$ (temp, °C)	Calcd	Found	Nmr (CDCl$_3$), δ
13a	C_6H_5	50	145.0–147.0[a]	3320, 2180 1600, 695	$C_{20}H_{24}O_6$	66.65	6.75	66.62	6.72	+13.31° (21) (*c* 1.0)	360.157	360.162	1.35, 1.42, 1.50, 1.58 (12 H, s, isopropylidene), 3.20 (1 H, s, OH), 7.40 (5 H, m, phenyl)
13b	Cl	45	172.6[b]	3380, 2180 1385, 1375	$C_{14}H_{19}O_6Cl$	52.75	6.01	52.56	6.11	+39.25° (21) (*c* 1.0)	318	318	1.35, 1.40, 1.48, 1.54 (12 H, s, isopropylidene), 3.50 (1 H, s, OH)
13c	$CH(OC_2H_5)_2$	45	87.3[a]	3380, 1385 1375	$C_{19}H_{30}O_8$	59.05	7.83	58.88	7.93	−35.82° (26) (*c* 1.2)	386.194	386.188	1.34, 1.38, 1.48, 1.53 (12 H, s, isopropylidene), 3.65 (4 H, q, OCH_2CH_3), 5.32 (1 H, s, $CH(OC_2H_5)_2$)
13d	CHOO C_6H_5	40	85.0–86.0[a]	3360, 1385 1375	$C_{26}H_{34}O_8$	65.81	7.22	65.72	7.20	−10.56° (25) (*c* 1.0)	474	474	1.20, 1.32, 1.40, 1.45 (12 H, s, isopropylidene), 1.68 (6 H, m, tetrahydropyran), 7.40 (1 H, s, phenyl)
13e	CH_2OO	40	124.9[b]	3260, 1380 1365 (KBr)	$C_{20}H_{30}O_8$	60.29	7.59	60.04	7.68	+25.87° (24) (*c* 0.9)	398.194	398.194	1.35, 1.38, 1.44, 1.45 (12 H, s, isopropylidene), 1.68 (6 H, m, tetrahydropyran), 3.40 (1 H, s, OH)
13f	CHOH C_6H_5	5	87.6[a]	3400, 2180 1385, 1375 700	$C_{21}H_{26}O_7$						390.168	390.167	
13g	$CH_2OCH_2C_6H_5$	17	88.3[a]	3300, 1600 700 (KBr) 2180 ($CHCl_3$)	$C_{22}H_{28}O_7$	65.33	6.98	65.18	7.05	+18.67° (20) (*c* 1.0)	404.184	404.180	1.25, 1.27, 1.40, 1.48 (12 H, s, isopropylidene), 3.20 (1 H, s, OH), 7.35 (5 H, m, phenyl)

[a] Colorless needles. [b] Colorless fine needles.

(14) L. Crombie and A. G. Jocklin, *Chem. Ind. (London)*, 1197 (1954); L. Crombie, *J. Chem. Soc.*, 1007 (1955).

(15) R. G. Jones and M. J. Mann, *J. Amer. Chem. Soc.*, **75**, 4048 (1953).

(16) D. N. Robertson, *J. Org. Chem.*, **25**, 931 (1960).

(17) L. Hough, J. K. N. Jones, and D. L. Mitchell, *Can. J. Chem.*, **36**, 1720 (1958).

(18) Available from SIGMA Chemical Co., St. Louis, Mo.

phenyl). *Anal.* Calcd for $C_{16}H_{18}O_5$: C, 66.20; H, 6.25. Found: C, 66.36; H, 6.25.

B.—A solution of 5-*O*-acetyl derivative (**10**, 2.3 g, 0.01 mol) was treated with phenylacetylene (1.0 g, 0.01 mol) in the same manner as described for A; **11a** (0.5 g, 20%), mp 153.0°, was obtained. This was identical in all respects with a sample prepared by A.

1-(2-Chloroethynyl)-2,3-*O*-isopropylidene-α-D-ribofuranose (11b).—This compound was prepared by the procedure similar to that described for the preparation of **13b**. **11b** was obtained (0.7 g, 30%) as colorless needles: mp 130.5°; $[\alpha]^{27}D$ −71.45° (*c* 0.9); ir λ_{max}^{KBr} 3380 (OH), 2190 (C≡C), 1390 and 1380 cm^{-1} (gem-CH_3); nmr δ 1.38, 1.60 (6 H, s, isopropylidene), and 3.67, 3.84 (2 H, dd, C_5H_2); mass spectrum *m/e* 248 (M^+). *Anal.* Calcd for $C_{10}H_{13}O_5Cl$: C, 48.30; H, 5.27. Found: C, 48.24; H, 5.31.

2,3:5,6-Di-*O*-isopropylidene-L-gulonolactone (12).—To a suspension of L-gulonolactone[19] (20 g, 0.11 mol) in acetone (400 ml), concentrated H_2SO_4 (8 ml) was added slowly and the mixture was stirred at room temperature for 7 hr. After reaction, ammonia gas was passed through the reaction solution under ice cooling and the reaction mixture was treated by the similar method as described for the preparation of **6**. **12** (12 g, 55%) was obtained as colorless needles: mp 153–154°; $[\alpha]^{24}D$ +91.48° (*c* 1.0); nmr δ 1.40, 1.49 (12 H, s, isopropylidene); mass spectrum *m/e* 258 (M^+). *Anal.* Calcd for $C_{12}H_{18}O_6$: C, 55.81; H, 7.03. Found: C, 55.66; H, 7.05.

1-Phenylethynyl-2,3:5,6-di-*O*-isopropylidene-β-L-gulofuranose (13a). General Procedure for 13c–g (Table I).—By a similar procedure to that described for the preparation of **6**, a solution of phenylethynyllithium (prepared from 1.2 g, 0.01 mol of phenylacetylene) was obtained. To this reaction solution 2,3:5,6-di-*O*-isopropylidene-L-gulonolactone (2.58 g, 0.01 mol) in tetrahydrofuran (10 ml) was added dropwise at −70° during 30 min, stirring was continued for 3 hr at the same temperature, and the mixture was left overnight at room temperature. The brownish solution was treated as mentioned above for the preparation of **5** to give 1.8 g (50%) of **13a** as colorless needles, mp 145–147°. Recrystallization from ether–petroleum ether gave a product of mp 151.1°: uv λ_{max}^{EtOH} 240.0 nm (log ε 4.2), 251.0 (3.5), and 282.5 (3.3).

1-Chloroethynyl-2,3:5,6-di-*O*-isopropylidene-β-L-gulofuranose (13b).—To a mixture of lithium (1.3 g, 0.02 mol) in anhydrous ether (50 ml), butyl bromide (3 g, 0.02 mol) in ether (5 ml) was added under a current of dry nitrogen and under stirring at −10 to 0° during 30 min and the reaction mixture was stirred for 1.5 hr at −5 to 0°. To this reaction solution, *cis*-1,2-dichloroethylene (1 g, 0.01 mol) in ether was added dropwise at −2 to 0° during 20 min. After stirring for 1.5 hr at 5–15°, the solution wash chilled to −60°, 2,3:5,6-di-*O*-isopropylidene-L-gulonolactone (2.58 g, 0.01 mol) in tetrahydrofuran (10 ml) was added to the cooled reaction at −60° during 30 min, and stirring was continued for 3 hr. This reaction solution was treated as above in the preparation of **6** and gave 1.4 g (45%) of **13b**.

1,2,3,5,6-Penta-*O*-acetyl-1-phenylethynyl-β-L-gulofuranose (15a).—A solution of **13a** (1 g, 0.003 mol) in 70% acetic acid (10 ml) was warmed at 50° for 2.5 hr. The solvent was completely removed by distillation under a reduced pressure. Remaining liquid was dissolved in ether which was washed with a minimum amount of $NaHCO_3$ solution, and then dried and evaporated. There was obtained 1-phenylethynyl-L-gulofuranose (**14a**) as a white powder: $[\alpha]^{22}D$ +19.53° (*c* 1.1, MeOH); ir λ_{max}^{film} 3360 (OH), 2180 (C≡C), 1600 and 695 cm^{-1} (phenyl).

This compound (**14a**), without further purification, was acetylated with acetic anhydride (5 ml) in the presence of pyridine (5 ml). After the reaction solution was stirred for 24 hr at room temperature, this was worked up to obtain **15a** as a brownish liquid. Thin layer chromatography showed a spot at R_f 0.58 in benzene–acetone (3:2): $[\alpha]^{25}D$ +5.45° (*c* 1.0); ir λ_{max}^{film} 2220 (C≡C), 1750 (acetyl), and 762 cm^{-1} (phenyl); mass spectrum *m/e* 490 (M^+). *Anal.* Calcd for $C_{24}H_{26}O_{11}$: mol wt, 490.148. Found: mol wt, 490.147.

1,2,3,5,6-Penta-*O*-acetyl-1-(3-acetyloxypropyn-1-yl)-β-L-gulofuranose (15b).—1-(3-Tetrahydropyranyloxypropynyl)-2,3:5,6-di-*O*-isopropylidene-L-gulofuranose (**13e**, 1 g, 3 mmol) was hydrolyzed by the same procedure as that of **15a** to obtain 1-(3-hydroxypropyn-1-yl)-L-gulofuranose (**14b**) as a brownish liquid: $[\alpha]^{22}D$ +47.11° (*c* 0.8, MeOH); ir λ_{max}^{film} 3280 (OH) and 2160 cm^{-1} (C≡C).

This compound (**14b**) was acetylated in the same way as described for the preparation of **15a** to yield **15b** as a pale brown liquid (0.6 g, 39%): $[\alpha]^{25}D$ +13.87° (*c* 1.0, MeOH); ir λ_{max}^{film} 2250 (C≡C) and 1750 cm^{-1} (acetyl); mass spectrum *m/e* 486 (M^+).

1-*O*-Acetyl-1-(2-phenylethynyl)-2,3:5,6-di-*O*-isopropylidene-β-L-gulofuranose (16).—1-(2-Phenylethynyl)-2,3:5,6-di-*O*-isopropylidene-β-L-gulofuranose (**13a**, 0.13 g, 0.3 mmol) was acetylated in the same way as described for the preparation of **15a** to yield **16** as colorless needles (0.08 g, 54%): mp 112.5°; $[\alpha]^{22}D$ +32.83° (*c* 0.5); ir λ_{max}^{KBr} 2190 (C≡C), 1745 (acetyl), 1385 and 1375 (gem-CH_3), 760 and 693 cm^{-1} (phenyl); uv λ_{max}^{EtOH} 240.2 nm (log ε 4.32) and 250.3 (4.25); mass spectrum *m/e* 402 (M^+). *Anal.* Calcd for $C_{22}H_{26}O_7$: C, 65.66; H, 6.51; mol wt, 402.168. Found: C, 65.59; H, 6.55; mol wt, 402.168.

Registry No.—**5**, 32257-12-8; **6**, 32257-13-9; **7**, 32257-14-0; **8**, 30725-00-9; **9**, 31858-77-2; **10**, 32257-17-3; **11a**, 32257-18-4; **11b**, 32257-19-5; **12**, 7306-64-1; **13a**, 32257-21-9; **13b**, 32257-22-0; **13c**, 32257-23-1; **13d**, 32257-24-2; **13e**, 32257-25-3; **13f**, 32257-26-4; **13g**, 32257-27-5; **14a**, 32257-28-6; **14b**, 32257-29-7; **15a**, 32304-30-6; **15b**, 32304-31-7; **16**, 32257-30-0; 3-phenyl-3-(2-tetrahydropyranyloxy)-1-propyne, 32257-31-1.

Acknowledgment.—We wish to acknowledge our indebtedness to Dr. H. Kuwano, Central Research Laboratories, Sankyo Co., Ltd., for the nmr measurements and to Dr. K. Takagi and Mrs. A. Hatano for the mass spectral measurements.

(19) M. Matsui, M. Okada, and M. Ishidate, *Yakugaku Zasshi*, **86**, 110 (1966).

Reduction with Trichlorosilane. III. Cyclic Ether from Lactone

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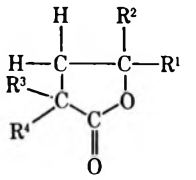
Received June 1, 1971

The reduction of γ, δ, and ϵ lactones to the corresponding cyclic ethers by means of trichlorosilane is described. The reaction was initiated by γ and uv irradiations and photoinduced decomposition of *tert*-butyl peroxide. This method yielded cyclic ethers in comparatively high yields except for the β lactone which was found to suffer ring opening.

Recently we reported that aliphatic esters were reduced to dialkyl ethers by trichlorosilane under free-radical conditions.[1] The present paper reports the extension of this reduction to lactones, which are expected to give the corresponding cyclic ethers. Although reductions of lactones are well known to give diols, some literature reports of successful hydrogenation of lactones to cyclic ethers have been made. Pettit, *et al.*,[2] reported that boron trifluoride–lithium aluminum hydride or boron trifluoride–sodium borohydride can reduce some lactones occurring in natural products to cyclic ethers, but reduce lactones prepared from primary alcohols to glycols. Edward and Ferland,[3] found that Adams catalyst in acetic acid can



1, $R^1 = CH_3$; $R^2 = R^3 = R^4 = H$
2, $R^1 = C_2H_5$; $R^2 = R^3 = R^4 = H$
3, $R^1 = R^2 = CH_3$; $R^3 = R^4 = H$
4, $R^1 = R^2 = R^3 = H$; $R^4 = CH_3$
5, $R^1 = R^2 = H$; $R^3 = R^4 = CH_3$

reduce δ lactones to the corresponding cyclic ethers, but cannot reduce γ and ϵ lactones to ethers. From the viewpoints mentioned above, β, γ, δ, and ϵ lactones and several γ lactones such as **1**–**5** were subjected to the reduction with trichlorosilane. Since the reduction to cyclic ethers succeeded in all lactones except β lactone, this method will provide a new synthetic route to cyclic ethers.

The reduction with trichlorosilane was initiated by three methods, γ and uv irradiation and photoinduced decomposition of di-*tert*-butyl peroxide. A degassed mixture of γ-butyrolactone and trichlorosilane was irradiated with γ rays in a glass tube, and with uv rays in a quartz tube. The same mixture in the absence or presence of di-*tert*-butyl peroxide in a Pyrex tube was also irradiated similarly with uv. Comparison of run 4 with 3, and further comparison of run 4 with 5 and 6 in Table I allow us to realize that photoinduced decomposition of the peroxide can initiate the reaction as γ and uv irradiations can. The *G* value (number of molecules formed per 100 eV of energy absorbed) calculated from run 1 is about 600. These results clearly indicate a free-radical chain mechanism for this reduction.

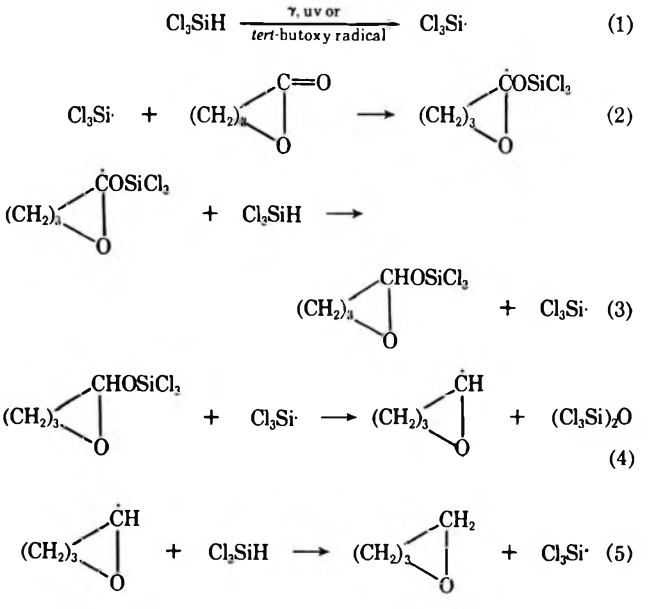
TABLE I

REDUCTION OF γ-BUTYROLACTONE TO TETRAHYDROFURAN WITH TRICHLOROSILANE

Run	Starting molar ratio: Silane/lactone	Starting molar ratio: Peroxide/lactone	Irradiation time, hr: γ[a]	Irradiation time, hr: Uv	Yield, %, based on lactone
1	2		8		33
2	2		40		81
3	4			1 (quartz)	37
4	4	0		2 (Pyrex)	0
5[b]	4	0.02		2 (Pyrex)	66
6[b]	4	0.05		2 (Pyrex)	94

[a] Dose rate = 0.185 Mrad/hr. [b] Initiated by photoinduced decomposition of the peroxide, because run 4 shows that in the absence of the peroxide the reduction does not proceed by light filtered by Pyrex.

The high yield (81%) of run 2 (2:1 molar ratio of silane/lactone) supports that a 2 *M* amount of trichlorosilane is sufficient to reduce the lactone as in our previous communication.[1] Our detailed kinetic study on the reduction of methyl acetate to ethyl methyl ether[4] revealed that the reduction proceeds *via* a free-radical chain mechanism, *i.e.*, addition of trichlorosilane to the carbonyl group of methyl acetate followed by further attack of the silane to the resulting acetal-type intermediate. By the analogy with the reduction of methyl acetate, we can write the sequence of the present reaction as eq 1–5.



(1) J. Tsurugi, R. Nakao, and T. Fukumoto, *J. Amer. Chem. Soc.*, **91**, 4587 (1969).

(2) (a) G. R. Pettit, B. Green, T. R. Kasturi, and U. R. Ghatak, *Tetrahedron*, **18**, 953 (1962); (b) G. R. Pettit, U. R. Ghatak, B. Green, T. R. Kasturi, and D. M. Piatak, *J. Org. Chem.*, **26**, 1685 (1961).

(3) J. T. Edward and J. M. Ferland, *Chem. Ind. (London)*, 975 (1964).

(4) Y. Nagata, T. Dohmaru, and J. Tsurugi, submitted for publication. This paper also reports that benzene acts as a scavenger of trichlorosilyl radical. Therefore, carboxylic esters containing a benzene ring could not be reduced by this method. In the present paper lactones containing no benzene ring were used as starting materials, and di-*tert*-butyl peroxide was utilized as an initiator.

TABLE II

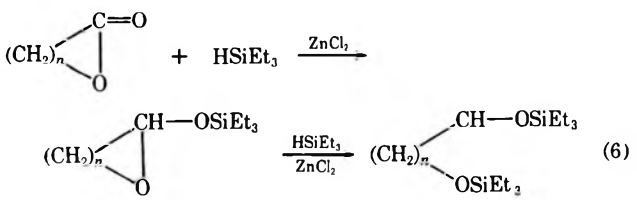
SCOPE OF THE REDUCTION OF LACTONES TO CYCLIC ETHERS (LACTONE/SILANE = 1:4)

Lactone	Registry no.	Product	Registry no.	Yield, % γ[a]	Yield, % Photoinduced decompn of peroxide[b]
β-Propio-	57-57-8	Trimethylene oxide		0	0
γ-Butyro-	96-48-0	Tetrahydrofuran		82	94
δ-Valero-	542-28-9	Tetrahydropyran		68	93
ϵ-Capro-	502-44-3	Hexamethylene oxide		86	96
γ-Valero- (1)	108-29-2	2-Methyltetrahydrofuran		62	88
γ-Capro- (2)	695-06-7	2-Ethyltetrahydrofuran		89	37
γ-Isocapro- (3)	3125-97-5	2,2-Dimethyltetrahydrofuran	1003-17-4	~100[c]	~80[d]
α-Methyl-γ-Butyro- (4)	1679-47-6	3-Methyltetrahydrofuran	13423-15-9	~80[c]	~70[d]
α,α-Dimethyl-γ-Butyro- (5)	3709-08-8	3,3-Dimethyltetrahydrofuran	15833-75-7	~90[c]	~70[d]

[a] Dose rate = 0.3 Mrad/hr, total dose = 7.2 Mrad. [b] Peroxide/lactone = 0.05, uv irradiation time = 2 hr. [c] Identified and estimated by nmr. (See Experimental Section.) [d] Estimated by glpc using the corresponding ether which was identified by footnote c as the standard.

For synthetic purposes, the scope of this reduction is summarized in Table II, where only γ irradiation and photoinduced decomposition are utilized for the initiation. Table II indicates that the reaction product of β-propiolactone was not trimethylene oxide, but a complex mixture, judging from the glpc chart. This may be ascribed to ring opening, probably because of the greater strain of the four-membered ring. Shostakovskii and Lavrov reported that ethylene oxide[5] and propylene oxide[6] underwent ring opening by simple mixing or mild warming with alkylchlorosilane. Here we attempted to mix trimethylchlorosilane with trimethylene oxide, which was the expected product from β-propiolactone. The product was identified as 3-chloropropoxytrimethylsilane, $ClCH_2CH_2CH_2OSiMe_3$, by glpc. Nmr study suggests that trichlorosilane reacts similarly with trimethylene oxide to give 3-chloropropoxydichlorosilane, $ClCH_2CH_2CH_2OSiCl_2H$. Therefore, even if trimethylene oxide would be produced, it would undergo ring opening with trichlorosilane. The complexity of the glpc chart of the product from β-propiolactone suggests that ring opening really occurs.

Calas, *et al.*,[7] reported that γ-butyro-, γ-valero- and δ-valerolactones, when heated at 120–130° with triethylsilane in the presence of a catalytic amount of zinc chloride, gave disiloxy derivatives *via* intermediates similar to the one assumed in eq 3 and 4. In contrast to Calas' results, higher yields of cyclic ethers shown in Table II support that C–O bond fission of the –C(O)O– group did not occur in the free-radical reduction with trichlorosilane.



(6)

The results in Table II indicate that this reduction is applicable to γ, δ, and ϵ lactones and several alkyl-substituted γ lactones to yield the corresponding cyclic ethers in comparatively high yields, and may be presumed to be applicable also to alkyl-substituted δ and ϵ lactones. In this respect, this method has the advantage over other methods using lithium aluminum hydride and Adams catalyst, and will provide a new synthetic route to cyclic ethers from lactones.

Experimental Section

All boiling points are uncorrected. Ir spectra were taken with a Perkin-Elmer Model 221, and nmr spectra on a JNM 3H-60 with tetramethylsilane as an external standard. Gas chromatography was performed with a Yanagimoto GCG-5DH using a 2.5-m column containing 25% Silicone DC-200 on Celite 545.

Lactones.—δ-Valerolactone was prepared from 1,5-pentanediol in the presence of copper chromite as a catalyst similar to the literature[8] for β-methyl-δ-valerolactone: bp 112–113° (13 mm) [lit.[9] bp 113–114° (13–14 mm)]; ir 1735 cm^{-1} (δ-lactone C=O). γ-Isocaprolactone (**3**) was synthesized by the method of Stevens and Tarbell[10] *via* diethyl β-methylallylmalonate starting from diethyl malonate and β-methylallyl chloride: bp 68–70° (4 mm); $n^{25}D$ 1.4320 [lit.[10] bp 74–76° (5–6 mm); $n^{25}D$ 1.4315]; ir 1770 cm^{-1} (γ-lactone C=O); nmr (neat) δ 1.57 [s, 6, $C(CH_3)_2$], 2.25 (m, 2, $-CH_2C(O)-$), 2.75 (m, 2, CCH_2C). The $CCH_2CH_2C(O)$ group constitutes an A_2B_2 system ($\Delta\nu_{AB}$ = *ca.* 30 Hz, J_{AB} = *ca.* 10 Hz). α-Methyl-γ-butyrolactone (**4**) was prepared from diethyl methyl-β-hydroxyethylmalonate by the method of Meincke and McElvain[11] for α-ethyl-γ-butyrolactone. Diethyl methyl-β-hydroxyethylmalonate was prepared from diethyl methylmalonate and ethylene chlorohydrin by the conventional method: bp 77° (10 mm) [lit.[12] bp 81° (11 mm)]; ir 1770 cm^{-1} (γ-lactone C=O); nmr (neat) δ 1.42 (d, 3, CH_3), 1.90–3.2 (m, 3, $>CHCH_2-$C), 4.45 (m, 2, CCH_2O). α,α-Dimethyl-γ-butyrolactone (**5**) was prepared by the method of Baas, *et al.*,[13] from γ-butyrolactone and methyl iodide using sodium hydride: bp 69° (10 mm)

(5) M. F. Shostakovskii and S. P. Lavrov, *Dokl. Akad. Nauk SSSR*, **114**, 128 (1957); *Chem. Abstr.*, **52**, 1056*h* (1958).

(6) M. F. Shostakovskii, M. S. Malinovskii, M. K. Romantsevich, and D. A. Kochkin, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 632 (1956); *Chem. Abstr.*, **51**, 1026*i* (1957).

(7) E. Frainnet, R. Calas, and A. Berthault, *C. R. Acad. Sci.*, **258**, 613 (1964). Yields of disiloxy derivatives were 76, 51, and 47% for γ-butyro-, γ-valero-, and δ-valerolactones, respectively. Yields of cyclic ethers could be read as a trace in all cases. When disiloxy derivatives were heated with 7 mol % of zinc chloride at 200°, they gave the corresponding cyclic ethers in *ca.* 80% yields.

(8) R. I. Longley, Jr., and W. S. Emerson, *Org. Syn.*, **35**, 87 (1955).

(9) Beilstein's "Handbuch der Organischen Chemie," Vol. 17, 1933, p 235.

(10) C. M. Stevens and D. S. Tarbell, *J. Org. Chem.* **19**, 1996 (1954).

(11) E. R. Meincke and S. M. McElvain, *J. Amer. Chem. Soc.*, **57**, 1444 (1935).

(12) G. Jones and J. Wood, *Tetrahedron*, **21**, 2961 (1965).

(13) J. L. Baas, A. Davies-Fidder, and H. O. Huisman, *Tetrahedron*, **22**, 285 (1966).

[lit.[13] bp 74° (10 mm)]; ir 1765 cm^{-1} (γ-lactone C=O); nmr (neat) δ 1.43 [s, 6, $(CH_3)_2$], 2.37 (t, 2, CCH_2C), 4.48 (t, 2, CCH_2O).

Other lactones, commercial materials, were distilled and each stored in an ampoule.

Procedure for Irradiation.—A given amount of lactone or mixture with di-*tert*-butyl peroxide was degassed by three thawings and freezings at −190° in a glass tube or nmr sample tube, to which degassed trichlorosilane was transferred by a vacuum line. The tube, after being fused, was irradiated by γ rays from a ^{60}Co source or uv rays from a medium-pressure mercury lamp at room temperature.

Identification and estimation of cyclic ethers was performed by glpc, except for those described in footnote *c* in Table II. Commercial cyclic ethers purified by the conventional method were used as the standards, with the exception of 2-ethyl tetrahydrofuran and hexamethylene oxide. These were prepared by γ-induced reduction of 25 g of γ- and ϵ-caprolactones with trichlorosilane, respectively. To the irradiated mixture was added water for decomposition of chlorosilanes and siloxanes. After neutralization with aqueous sodium hydroxide solution, the cyclic ethers produced were extracted with diethyl ether. Two distillations gave 2-ethyltetrahydrofuran and hexamethylene oxide, respectively, which were identified by the coincidence of physical constants cited in the literatures: 2-ethyltetrahydrofuran, bp 106–108° (lit.[14] bp 108.5°), $n^{20}D$ 1.4159 (lit.[15] 1.4170); hexamethylene oxide, bp 117–118° [lit.[16] bp 121° (741 mm)], $n^{20}D$ 1.4369 [lit.[17] 1.4361].

Identification and Estimation of Cyclic Ether by Nmr.—The cyclic ethers which were footnoted by *c* in Table II were identified by nmr. The nmr spectrum of α,α-dimethyl-γ-butyrolactone (**5**) in trichlorosilane follows: δ 1.54 [s, 6, $(CH_3)_2$], 2.42 (t, 2, $>CCH_2C$), 4.53 (t, 2, CCH_2O). The γ irradiation of the mixture in the same nmr tube as used for nmr determination of **5** in trichlorosilane gave the following spectrum: δ 1.45 [s, 6, $(CH_3)_2$], 1.57 (s, 0.7), 2.01 (t, 2, $>CCH_2C$), 3.72 (s, 2, $>CCH_2O$), 4.17 (t, 2, CH_2CH_2O). Among these, the singlet at δ 1.57 was regarded as the methyl signal of the unchanged lactone, and the others were assigned to protons of 3,3-dimethyltetrahydrofuran produced. The amount of the ether produced was estimated by comparison of the intensity of the methyl signal which appeared newly at δ 3.72 with the sum of methyl absorptions of unchanged lactone (at δ 1.57) and the ether (at δ 1.45). The same procedure was applied for 2,2-dimethyl- and 3-methyltetrahydrofurans. In the case of 2,2-dimethyltetrahydrofuran, methyl absorption (δ 1.72) of the starting γ-isocaprolactone (**3**) was not observed among the absorptions of the irradiated mixture: δ 1.58 [s, 6, $(CH_3)_2$], 2.11 (m, 4, CCH_2CH_2C), 4.15 (t, 2, CCH_2O). Nmr spectrum of the irradiated mixture of α-methyl-γ-butyrolactone (**4**) with trichlorosilane was δ 1.43 (d, 3, CH_3), 1.62 (d, 0.7), 1.70–3.00 (m, 3, CCH_2C and >CH), 3.60 (m, 1, one proton of $>CHCH_2O$), 4.12 (m, 3, CH_2CH_2O and one proton of $>CHCH_2O$), where the doublet at δ 1.62 is regarded as the methyl signal of the unchanged **4**. The $>CHCH_2O$ group constitutes an ABX system; the multiplet at δ 3.60 is the B part; and the A and X parts may be contained in multiplets at δ 4.12 and 1.70–3.00, respectively. 3-Methyltetrahydrofuran produced was estimated by comparing the intensity of the methylene signal which appeared newly at δ 3.60 with the sum of methyl absorptions at δ 1.43 (ether) and 1.62 (**4**).

3-Chloropropoxytrimethylsilane.—The titled compound as standard was prepared by the procedure of Speier[18] using pyridine as an acceptor for hydrogen chloride.

3-Chloropropoxydichlorosilane.—Degassed trichlorosilane was transferred by a vacuum line into a nmr tube, which in advance contained degassed trimethylene oxide. Nmr spectrum of the mixture after γ irradiation: δ 2.45 (m, 2, CCH_2C), 4.02 (t, 2, $ClCH_2C$ or CCH_2O), 4.51 (t, 2, CCH_2O or $ClCH_2C$), 6.00 (s, 1, SiH).

Registry No.—Trichlorosilane, 10025-78-2.

Acknowledgment.—The authors wish to thank Dr. S. Kawamura for assistance in the interpretation of nmr spectra.

(14) O. Riobe, *Ann. Chim. (Rome)*, **4**, 593 (1949); *Chem. Abstr.*, **44**, 2984*b* (1950).

(15) Yu. K. Yur'ev and I. P. Gragerov, *Zh. Obshch. Khim.*, **19**, 724 (1949); *Chem. Abstr.*, **44**, 1092*f* (1950).

(16) E. E. Schweizer and W. E. Parham, *J. Amer. Chem. Soc.*, **82**, 4085 (1960).

(17) J. Meinwald and H. Nozaki, *ibid.*, **80**, 3132 (1958).

(18) J. L. Speier, *ibid.*, **74**, 1003 (1952).

Acid-Catalyzed Rearrangements and Additions of β,γ-Unsaturated Ketones[1]

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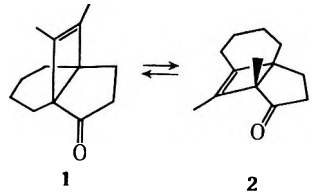
Received June 9, 1971

The acid-catalyzed isomerization of 10,11-dimethyltricyclo[4.3.2.$0^{1,6}$]undec-10-en-7-one (**1**) to 7,8-dimethyltricyclo[5.2.2.$0^{1,6}$]undec-5-en-9-one (**3**) and 1,11-dimethyltricyclo[6.2.1.$0^{3,8}$]undec-3-en-2-one (**4**) is described. Chemical and X-ray diffraction analyses provided evidence for structures **3** and **4**. The mechanism of the isomerization is discussed and a new interpretation of the addition of hydrogen halide to 7-ketonorbornene is presented.

We have previously described acid-catalyzed addition and isomerization reactions of β,γ-unsaturated ketones in which the double bond is contained in a four-membered ring.[2,3] Similar studies have also been reported from other laboratories.[3] We report here our study of the acid-catalyzed isomerizations of tricyclic ketones **1** and **2**.

Ketones **1** and **2** have already been shown to undergo light-induced as well as acid-catalyzed interconversion.[4]



1 **2**

The equilibrium concentrations of **1** and **2** indicate that **1** is the more stable isomer by *ca.* 1.5 kcal/mol.[4] In our investigation of the acid-catalyzed equilibration of **1** and **2** we found that vigorous or prolonged treatment of either **1** or **2** with *p*-toluenesulfonic acid in benzene led to disappearance of both **1** and **2** and formation of two new ketones which are assigned structures **3** and

(1) We thank the National Science Foundation for generous support of this research.

(2) R. L. Cargill and J. W. Crawford, *J. Org. Chem.*, **35**, 356 (1970).

(3) R. L. Cargill, D. M. Pond, and S. O. LeGrand, *ibid.*, **35**, 359 (1970), and references cited therein.

(4) R. L. Cargill, M. E. Beckham, A. E. Siebert, and J. Dorn, *ibid.*, **30**, 3647 (1965).

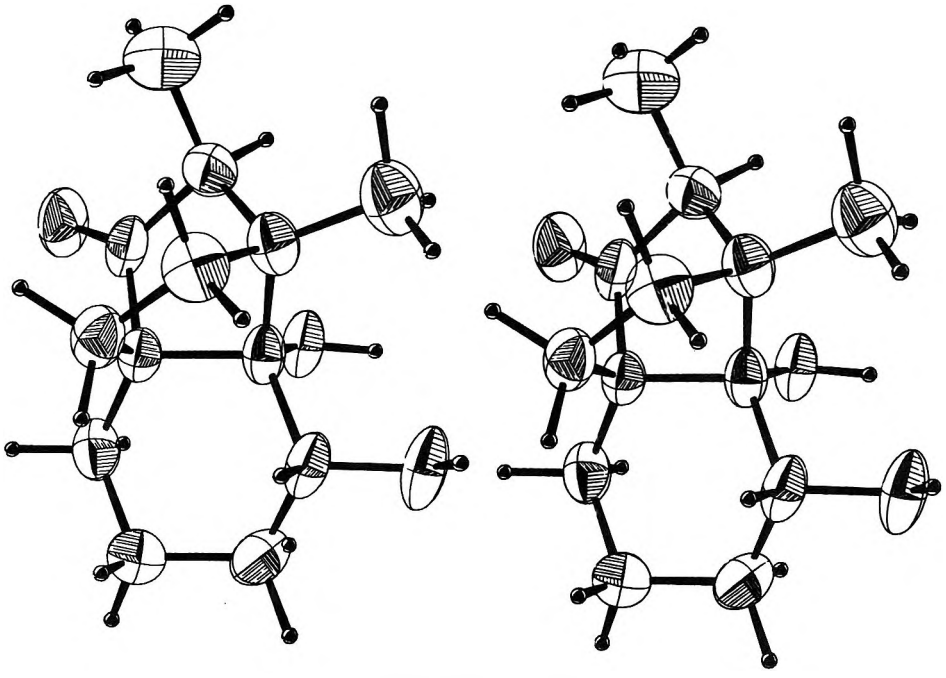
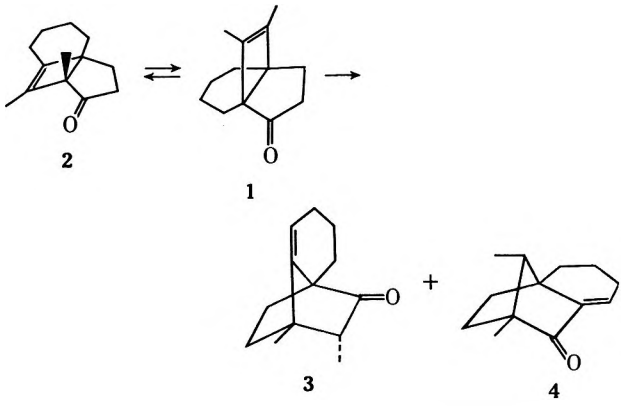


Figure 1.—Stereoplot of compound 5.

4. These two new ketones are formed in approximately equal amounts and account for *ca.* 80% of the product mixture. The remainder is composed of two minor products[5] which were not further investigated. Each of the new ketones, 3 and 4, was recovered unchanged from boiling toluene containing *p*-toluenesulfonic acid, indicating that each is formed irreversibly from 1 or 2.



Structures 3 and 4 for the two new ketones were first proposed on the basis of spectroscopic and mechanistic considerations. Subsequent chemical degradation and X-ray crystallographic analysis have confirmed these structures. We shall first discuss the evidence for the structural assignments, then we shall turn to the mechanisms of the isomerizations leading to ketones 3 and 4.[6]

Ketone 3 exhibits spectral characteristics[7] typical of a cyclopentanone, a strained double bond, a β,γ-unsaturated ketone, a methyl on tertiary carbon, a methyl on quaternary carbon, and a single vinyl hydrogen. Ketone 3 undergoes base-catalyzed hydrogen–deuterium exchange, whereupon the methyl doublet at δ 1.02 collapses to a singlet, with no further change in the nmr spectrum, indicating that the corresponding methyl is attached to the carbon α to the carbonyl, and further that the configuration at this α carbon is the thermodynamically favored one. Oxidation of 3 with osmium tetroxide gave the crystalline diol 5 in high yield. This diol was converted into 4-(3,4-dimethylphenyl)butyric acid (6) by the sequence outlined in Scheme I, with only spectroscopic characterization[7] of the indicated intermediates.

Cleavage of the glycol 5 with lead tetraacetate gave an oily aldehyde in which the β-dicarbonyl function evidently remains intact. Conversion of the aldehyde function into the corresponding carboxylic acid with bromine–water was apparently accompanied by some, but not complete, hydrolysis of the β-dicarbonyl system. Complete hydrolysis was effected with methanolic potassium hydroxide. Reduction of the remaining ketone with sodium borohydride followed by eliminative decarboxylation and dehydrogenation gave 4-(3,4-dimethylphenyl)butyric acid (6).[8] These data indicate structure 3 for one of the new ketones.

Unambiguous confirmation of structure 3 was obtained by single-crystal X-ray diffraction analysis of glycol 5. (See Figure 1.)

Spectroscopic analysis[7] of ketone 4 indicated the presence of a cisoid α,β-unsaturated ketone bearing a β-vinyl proton, a methyl on quaternary carbon, and a methyl on tertiary carbon. Catalytic hydrogenation of 4 gave a cyclopentanone 7. Periodate–permanganate oxidation of 4 gave a triacid 8a without loss of carbon. Heating the triacid at 120° for 20 min gave an anhydride (1860, 1765 cm^{-1}) presumably 9. The

(5) Neither of these minor products is ketone 20 as evidenced by their separation from authentic 20 by glpc.

(6) (a) W. Parker, R. A. Raphael, and J. S. Roberts, *Tetrahedron Lett.*, 2313 (1965); T. F. W. McKillop, J. Martin, R. A. Raphael, and J. S. Roberts, *Chem. Commun.*, 162 (1967); (b) J. R. Prahlad, R. Ranganathan, U. R. Nayak, T. S. Santhanakrishnan, and S. Dev, *Tetrahedron Lett.*, 417 (1964); (c) W. G. Dauben and E. I. Aoyagi, Abstracts, 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March 1971, No. ORGN 74; (d) G. Brieger, *J. Amer. Chem. Soc.*, **85**, 3783 (1963); see also E. J. Corey and R. S. Glass, *ibid.*, **89**, 2600 (1967).

(7) Spectroscopic data are presented in the Experimental Section.

(8) E. Barnett and F. G. Sanders, *J. Chem. Soc.*, 434 (1933).

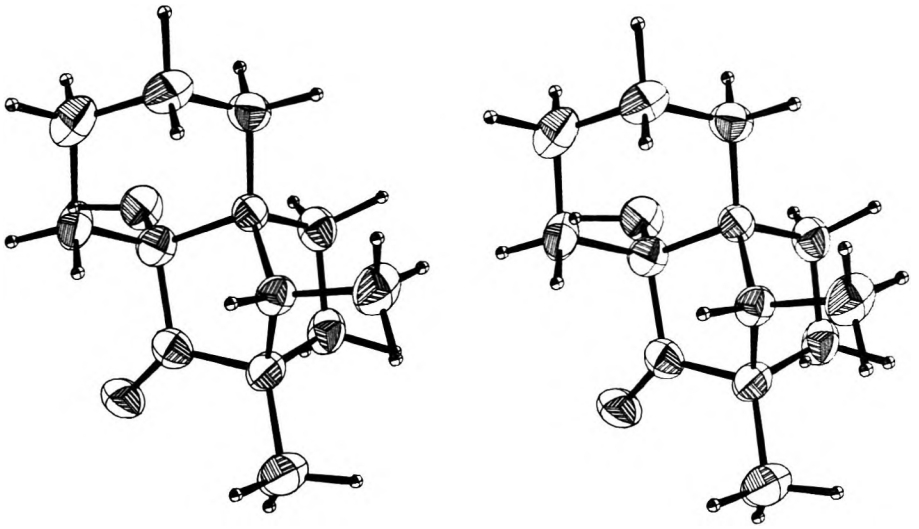
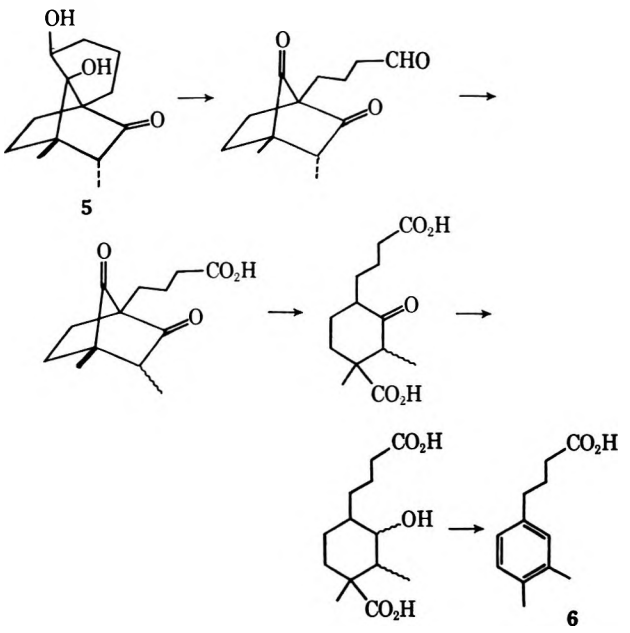
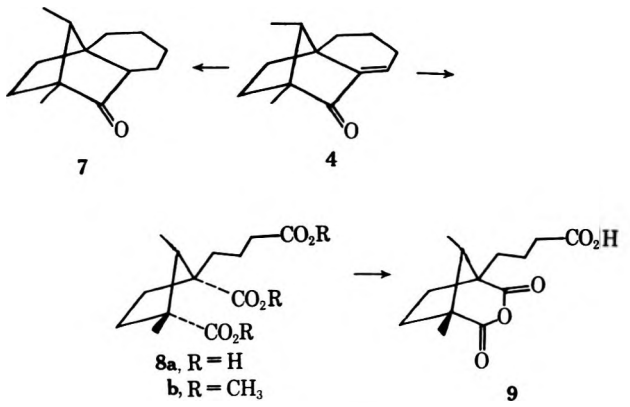


Figure 2.—Stereoplot of compound 13.

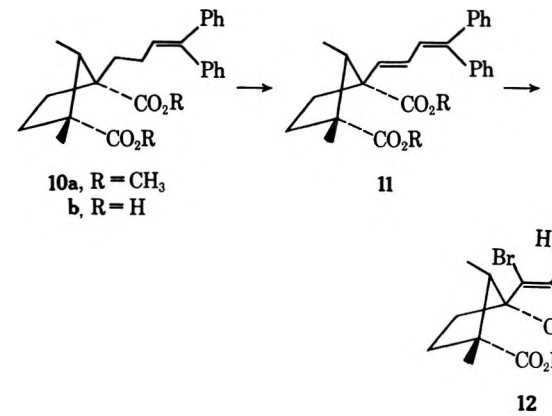
SCHEME I



mass spectrum of triester **8b** is easily interpreted in terms of the assigned structure.[7]



Removal of the butyric acid side chain of **8** by Barbier–Wieland degradation to provide santenic acid would establish completely the structure and stereochemistry of ketone **4**. Reaction of **8b** with phenylmagnesium bromide followed by dehydration of the crude alcohol gave diphenyl diester **10a**. Attempts to introduce the required second double bond by allylic bromination–dehydrobromination were frustrated in that invariably a mixture of products apparently containing the geometrical isomers of bromodiene thought to be **12** (ratio *ca.* 2:1) was obtained. The structure of the bromodiene **12a** is assigned on the basis of the mass spectrum (M^+ 496, 498) and the 100-MHz nmr spectrum (AB quartet δ 6.62, Δ_{AB} = 51.0 Hz, J_{AB} = 10 Hz) (AB quartet δ 6.35, Δ_{AB} = 58.7 Hz, J_{AB} = 9 Hz).[9] This product probably arises from the desired **11** *via* an addition–elimination sequence.[10]

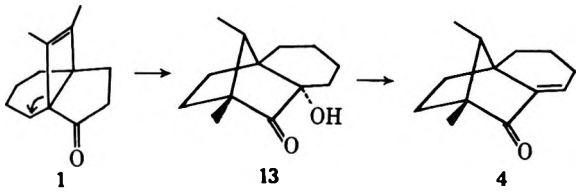


When a mixture of **1** and **2** was stirred with 6 *N* hydrochloric acid a new crystalline hydroxy ketone was obtained in 54% yield. On the basis of spectroscopic evidence and our previous experience[3] with this reaction we proposed structure **13** for the hydration product. Conversion of **13** into ketone **4** by dehydration with thionyl chloride in pyridine confirmed the relation of ketones **4** and **13**. Final proof of the structure of **13**, and therefore of **4**, was obtained by single-crystal X-ray diffraction analysis (see Figure 2).

We now turn to the mechanism by which the new ketones **3** and **4** are formed. Although either **1** or **2** could serve as the immediate precursor of the new

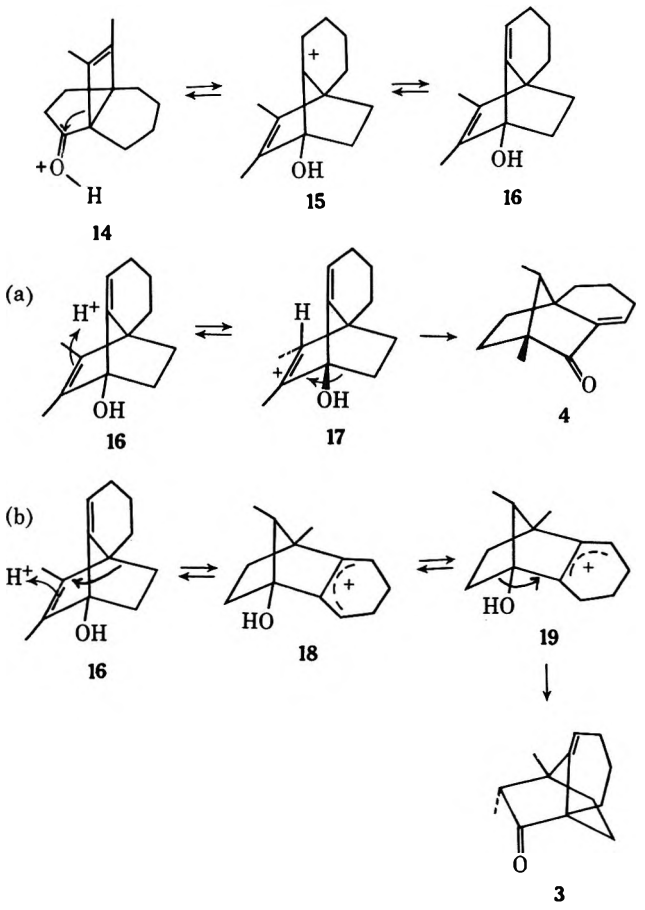
(9) We thank Dr. P. D. Ellis for this nmr spectrum and the National Science Foundation for a Department Development Grant which provided funds for the purchase of the Varian XL-100-15 nmr spectrometer.

(10) J. H. Incremona and J. C. Martin, *J. Amer. Chem. Soc.*, **92**, 627 (1970).



isomers, both **3** and **4** must arise from **1**, as will be seen. Net migration of the etheno bridge in the protonated ketone leads to ion **15** with relief of considerable strain. Loss of a proton provides the undetected alcohol **16**. Protonation of the tetrasubstituted double bond in **16** from the top side (path a) followed by a Wagner–Meerwein shift leads directly to ketone **4**. The santenone-type stereochemistry of **4** is determined by the exo protonation of **16**[3] (Scheme II).

SCHEME II

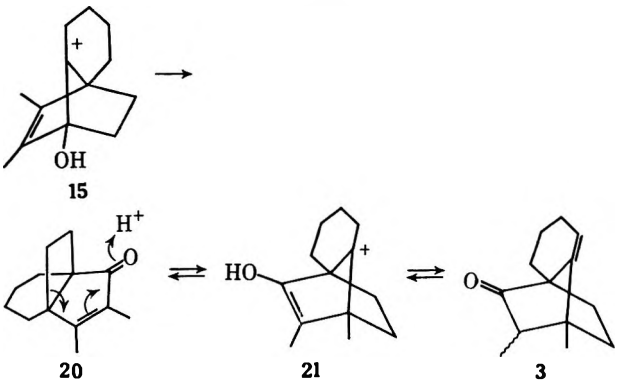


Ketone **3** is considered to arise from alcohol **16** *via* protonation (path b) and Wagner–Meerwein shift giving **18**. Isomerization of ion **18** to **19** followed by a second carbon shift provides **3**.

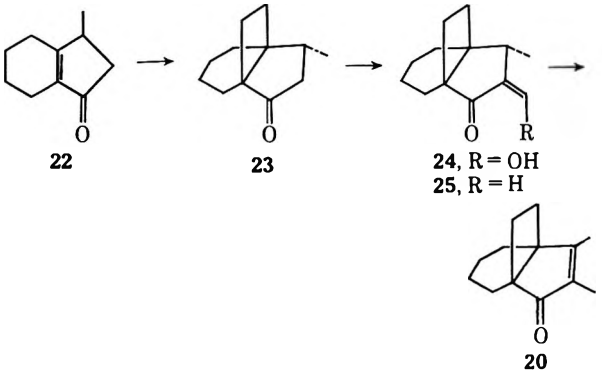
An alternate path for production of **3** from **1** is shown in Scheme III. In order to test this hypothesis we synthesized the supposed intermediate ketone **20** and subjected it to treatment with *p*-toluenesulfonic acid in boiling benzene and in boiling *o*-dichlorobenzene. In each case only unchanged **20** was recovered.[11]

The synthesis of ketone **20** is of some interest. Condensation of cyclohexene and crotonic acid with polyphosphoric acid gave the bicyclic enone **22**.[12] Conversion of **22** into **23** was accomplished by methods already described[13] in 53% yield. Condensation of **23** with ethyl formate gave the hydroxymethylene compound **24** which was then converted into the methylene ketone **25**.[14] Although **25** was recovered unchanged from attempted acid-catalyzed isomerization,[15] the desired **20** was obtained in 83% yield when an ethanolic solution of **25** was refluxed with a trace of palladium on charcoal (Scheme IV).[16]

SCHEME III



SCHEME IV



Alternatively, hydrogenolysis of the benzoate of **24** provided **20** as a minor product along with the corresponding saturated ketone.[17]

At this point a brief discussion of the addition of hydrogen halides to the β,γ-unsaturated ketone, 7-ketonorbornene (**26**), is appropriate. Caple[18] has shown that addition of deuterium bromide to **26** yields **27** and **28**. The suggested mechanisms for the formation of these products involves exo,cis addition of DBr to yield **27** and exo protonation, rearrangement to an α-keto carbonium ion, and trapping of the latter from the exo side by bromide ion to yield **28**. Initial interaction of acid with the carbonyl group is discounted. We suggest that **27** and **28** more likely arise

(11) The corresponding unsubstituted tricyclic enone was likewise recovered from treatment with acid.

(12) S. Dev, *J. Indian Chem. Soc.*, **33**, 703 (1956); **34**, 169 (1957). See also J.-M. Conia and M.-L. Leriverend, *Tetrahedron Lett.*, 2101 (1968); *Bull. Soc. Chim. Fr.*, 2981, 2991 (1970).

(13) (a) R. L. Cargill, A. C. Miller, D. M. Pond, P. de Mayo, M. F. Tchir, K. R. Neuberger, and J. Saltiel, *Mol. Photochem.*, **1**, 301 (1969); (b) R. L. Cargill, W. A. Bundy, D. M. Pond, A. B. Sears, J. Saltiel, and J. Winterle, *ibid.*, in press.

(14) A. J. Manson and D. Wood, *J. Org. Chem.*, **32**, 3434 (1967).

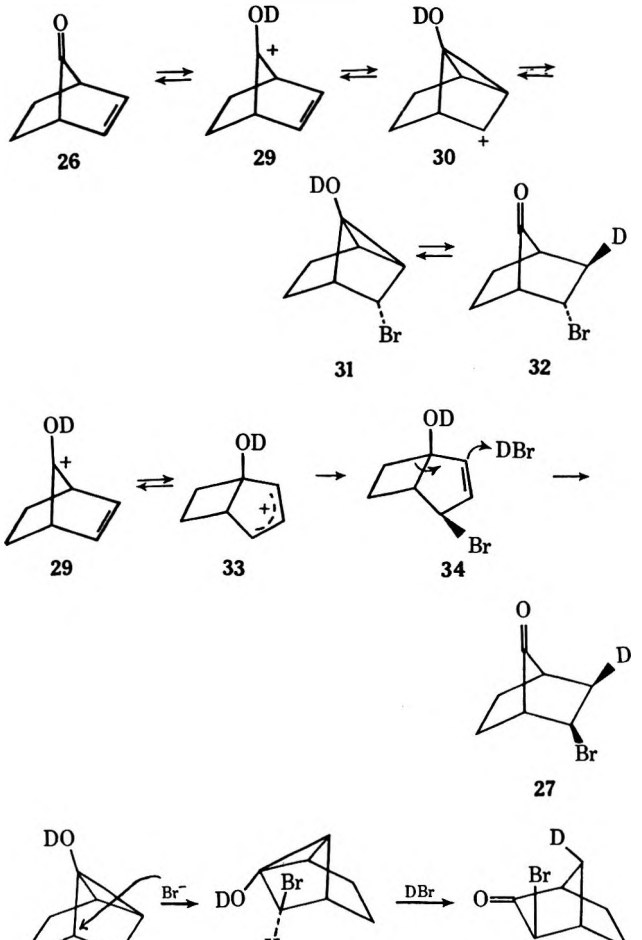
(15) J.-M. Conia and P. Anice, *Bull. Soc. Chim. Fr.*, 2972 (1970).

(16) The synthesis of **20** is described in detail in ref 13b.

(17) B. D. Astill and V. Boekelheide, *J. Amer. Chem. Soc.*, **77**, 4079 (1955).

(18) R. Caple, H. W. Tan, and F. M. Hsu, *J. Org. Chem.*, **33**, 1542 (1968).

SCHEME V



via the more complex series of changes in Scheme V.[19]

The absence of the endo bromo ketones **31** and **32** in the reaction mixture is more likely the result of their reversion to the precursors **29** and **30** (a stereoelectronically favorable process) than their not being formed.[20] The depicted mechanism by which **27** and **28** may arise is consistent with a great body of known carbonium ion chemistry[21] and has the advantages that the first step is protonation of **26** at its most basic site, the carbonyl oxygen, and the acid-catalyzed opening of the cyclopropanol systems is consistent with the findings of DePuy[22] and Nickon.[23,23a]

Experimental Section

All boiling and melting points are uncorrected. Microanalyses were performed by Bernhardt Microanalytisches Laboratorium, Elbach uber Engelskirchen, West Germany. Analytical gas chromatograms were obtained using a Aerograph Model 1200 Hi-Fi employing either a 3% SE-30, 8 ft × 0.125 in. or 3% diethylene glycol succinate (DEGS), 8 ft × 0.125 in. column. For preparative gc an Aerograph Model A-90-P3 was employed.

Acid-Catalyzed Rearrangement of 10,11-Dimethyltricyclo[4.3.2.0^{1,6}]undec-10-en-7-one (1) and 7,8-Dimethyltricyclo[6.3.-0.0^{1,6}]undec-6-en-9-one (2).—To a solution of 4.43 g (23.2 mmol) of a mixture of **1** and **2**[4] in benzene was added 1.5 g of *p*-toluenesulfonic acid and the mixture was refluxed for 5 hr. The solution was washed with 5% sodium hydroxide, then with water, dried ($MgSO_4$), and concentrated to yield 4.18 g of crude product. Distillation (bath temperature 100°, 0.5 Torr) gave 3.42 g (77.4%) of a colorless liquid containing four new compounds, two of which, ketones **3** and **4**, constituted *ca.* 80% and were present in approximately equal amounts (glpc). Pure samples of **3** and **4** were obtained by preparative glpc (20% DEGS).

7,8-Dimethyltricyclo[5.2.2.0^{1,6}]undec-5-en-9-one (3) gave uv max (95% ethanol) 298 nm (ϵ 221); uv max (isooctane) 305 nm (ϵ 200); ir (CCl_4) 3010, 1745, 1700, and 955 cm^{-1}; nmr (CCl_4) δ 1.02 (d, 3, J = 7.0 Hz), 1.20 (s, 3), and 5.47 (m, 1).

Anal. Calcd for $C_{13}H_{18}O$ (190.25): C, 82.06; H, 9.54. Found: C, 81.91; H, 9.73.

1,11-Dimethyltricyclo[6.2.1.0^{3,5}]undec-3-en-2-one (4) gave uv max (95% ethanol) 332 (ϵ 55) and 238 nm (ϵ 13,000); uv max (isooctane) 340 (ϵ 46) and 238 nm (ϵ, 14,000); ir (CCl_4) 3015, 1730, 1670, and 865 cm^{-1}; nmr (CCl_4) δ 0.87 (d, 3, J = 7.0 Hz), 0.98 (s, 3), and 6.33 (t, 1, J = 3.0 Hz).

Anal. Calcd for $C_{13}H_{18}O$ (190.25): C, 82.06; H, 9.54. Found: C, 81.87; H, 9.73.

The semicarbazone had mp 186–188°, from ethanol.

Anal. Calcd for $C_{14}H_{21}N_3O$(259.28): C, 67.98; H, 8.56; N, 16.99. Found: C, 67.87; H, 8.29; N. 17.03.

The 2,4-dinitrophenylhydrazone had mp 170–171°, from ethanol.

Anal. Calcd for $C_{19}H_{22}N_4O_4$ (370.40): C, 61.61; H, 5.99; N, 15.12. Found: C, 61.75; H, 6.20; N, 15.20.

Hydrogenation of **4** in ethanol over platinum oxide provided the dihydro derivative **7**: mass spectrum (70 eV) *m/e* (molecular ion) 192; ir (CCl_4) 1740 cm^{-1}; nmr (CCl_4) δ (d, 3, J = 6.5 Hz) and 0.97 (s, 3).

5,6-Dihydroxy-7,8-dimethyltricyclo[5.2.2.0^{1,6}]undecan-9-one (5).—A solution of 358 mg (1.88 mmol) of **3**, 511 mg (2.02 mmol) of osmium tetroxide, and 15 ml of pyridine was stirred in the dark at room temperature for 26 hr. To this solution was added a mixture of 1.80 g of sodium bisulfite, 30 ml of water, and 200 ml of pyridine. The resulting solution was stirred for 6 hr (until it became orange) and extracted with chloroform (four 50-ml portions). The organic phase was washed with several portions of water, dried (K_2CO_3), and concentrated *in vacuo* to yield 407 mg (96.5%) of light brown solid. Recrystallization from benzene gave white plates: mp 183.5–184.5°; ir (CCl_4) 3610, 3560, and 1745 cm^{-1}.

Anal. Calcd for $C_{13}H_{20}O_3$ (224.29): C, 69.61; H, 8.99. Found: C, 69.51; H, 8.77.

Degradation of 5. 4-(3,4-Dimethylphenyl)butyric Acid (6).—To a rapidly stirred solution of 110 mg (0.49 mmol) of **5** in 10 ml of benzene was added 270 mg (0.56 mmol) of lead tetraacetate in 10 ml of benzene. The solution was stirred for 1 hr, filtered, dried (K_2CO_3), and concentrated at reduced pressure to yield a milky oil. Chromatography over 10 g of Merck acid-washed alumina gave 90 mg of an oily aldehyde: ir (CCl_4) 2715, 1790, and 1740 cm^{-1}; nmr (CCl_4) δ 1.10 (s, 3), 1.19 (d, 3, J = 7.0 Hz), and 9.7 (t, 1, J = 1.5 Hz).

To 300 mg (1.35 mmol) of the above aldehyde was added saturated bromine water until the rapid uptake of bromine ceased (3.0 ml). Water (20 ml) and 3 ml of saturated sodium bisulfite were added and the mixture was extracted with ether (two 50-ml portions). The organic phase was dried (Na_2SO_4) and concentrated to yield 260 mg of an oily keto acid, ir (CCl_4) 3450 (broad), 1770, and 1740 cm^{-1}.

A solution of 260 mg (1.05 mmol) of the keto acid, 520 mg of potassium hydroxide, and 10 ml of methanol was refluxed for 3 hr. The resulting solution was acidified with 20% sulfuric acid and continuously extracted for 12 hr. The ether extract was dried (Na_2SO_4) and concentrated to yield 240 mg of a keto diacid, ir (CCl_4) 3500 (broad) and 1710 cm^{-1}.

A mixture containing 240 mg (0.93 mmol) of the keto diacid, 48 mg of sodium borohydride, and 20 ml of methanol was stirred at room temperature for 3 hr. The resulting mixture was acidi-

(19) For clarity, ions are drawn as equilibrating classical ions.

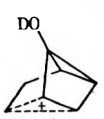
(20) J. J. Tufariello and R. J. Lorence, *J. Amer. Chem. Soc.*, **91**, 1546 (1969); J. Lhomme, A. Diaz, and S. Winstein, *ibid.*, **91**, 1548 (1969).

(21) (a) P. D. Bartlett, Ed., "Nonclassical Ions: Reprints and Commentary," (b) J. A. Berson in "Molecular Rearrangements," Part 1, P. de Mayo, Ed., Interscience, New York, N. Y., 1963, p 111.

(22) C. H. DePuy, *Accounts Chem. Res.*, **1**, 33 (1968).

(23) A. Nickon, J. L. Lambert, S. J., R. O. Williams, and N. H. Werstuick, *J. Amer. Chem. Soc.*, **88**, 3354 (1966).

(23a) NOTE ADDED IN PROOF.—Dr. T. E. Jackson of this laboratory has pointed out that products **27** and **28** are those expected from the addition of bromide ion to ion i, which is the nonclassical equivalent of **30**.



i

fied with 20% sulfuric acid and continuously extracted for 12 hr. The ether extract was dried (Na_2SO_4) and concentrated to yield 210 mg of a hydroxy diacid. A solution of 200 mg of *o*-chloranil, 100 mg of *p*-toluenesulfonic acid, 136 mg (0.53 mmol) of the hydroxy diacid, and 25 ml of xylene was refluxed for 4 hr. The resulting mixture was filtered, washed with water, and extracted with 10% sodium bicarbonate. The basic extract was acidified and continuously extracted with pentane for 24 hr. The organic extract was dried (Na_2SO_4) and concentrated to yield 22 mg of a milky oil. The organic extract was dried (Na_2SO_4) and concentrated to yield 22 mg of a milky oil. Crystallization from pentane gave a white solid, mp 48–51°, which showed no melting point depression upon admixture with an authentic sample of 4-(3,4-dimethylphenyl)butyric acid (6).[8]

4-(1,3-Dicarboxy-2,3-dimethylcyclopentyl)butyric Acid (8a).—A solution containing 1.24 g (6.51 mmol) of **4**, 2.5 g of potassium carbonate, 12 g of sodium metaperiodate, and 0.05 g of potassium permanganate in 1500 ml of water was stirred for 72 hr. A small amount of sodium metaperiodate was added after 24 hr to restore the original color of the mixture. The solution was made basic with *ca.* 1 g of potassium hydroxide and the neutral material was extracted with pentane (200 ml). The aqueous solution was acidified, saturated with sodium chloride, and extracted with ether (three 500-ml portions). The combined organic layers were dried (Na_2SO_4) and concentrated to yield a white solid. Subsequent recrystallization from ether yielded 1.63 g (91.8%) of white solid **8a**: mp 199–200° dec; ir (KBr) 3410 and 1720 cm^{-1}.

Anal. Calcd for $C_{13}H_{20}O_6$ (272.29): C, 57.34; H, 7.40. Found: C, 57.26; H, 7.32.

When the melt was cooled, the infrared spectrum of the resulting material exhibited absorptions of 1820 and 1765 cm^{-1}.

Dimethyl 1-(4,4-Diphenylbut-3-enyl)-2,3-dimethylcyclopentan-1,3-dicarboxylate (10a).—A solution of phenylmagnesium bromide, prepared from 1.25 ml of bromobenzene and 290 mg (12.1 mg-atoms) of magnesium turnings, in 10 ml of anhydrous ether was added dropwise to a stirred solution of 1.25 g (4.0 mmol) of triester **8b** in 100 ml of anhydrous ether in a dry nitrogen atmosphere. After 6 hr ice was added, followed by saturated aqueous ammonium chloride solution until the ether layer was clarified. The layers were separated, and the aqueous layer was extracted with ether (three 50-ml portions). The combined organic phase was concentrated, the residue was dissolved in 100 ml of glacial acetic acid and 10 ml of water, and the resulting solution was refluxed for 4 hr. The acetic acid was removed at aspirator pressure and the residue was dissolved in ether. The ethereal solution was washed with aqueous sodium bicarbonate, water, and brine, dried ($MgSO_4$), and concentrated to yield **10a** as a crude oil: ir (CCl_4) 3070, 3050, 3015, 1720, 1200, and 1115 cm^{-1}; nmr (CCl_4) δ 0.95 (d, 3, J = 7.0 Hz), 1.08 (s, 3), 3.48 (s, 3), 3.57 (s, 3), 5.94 (t, 1, J = 7.0 Hz), and 7.18 (m, 10).

The crude diester **10a** was added to a solution of 1 g of potassium hydroxide in 100 ml of water containing 1 ml of methanol and refluxed for 48 hr. The reaction mixture was cooled, extracted with pentane (100 ml), acidified (3 *M* HCl), and extracted with ether (3 100-ml portions). The ethereal solution was dried ($MgSO_4$) and concentrated. Crystallization of the residue from ether yielded 810 mg (51.6%) of white solid **10b**: mp 131–132°; uv max (95% ethanol) 252 nm (ε 15,800); ir (KBr) 3400, 3075, 3050, 3010, 1710, 765, and 700 cm^{-1}; nmr (CCl_4) δ 5.97 (m, 1), 7.08 (m, 10), and 12.38 (s broad, 1); mass spectrum (70 eV) *m/e* 392 (M^+).

Anal. Calcd for $C_{25}H_{28}O_4$ (392.47): C, 76.50; H, 7.19. Found: C, 76.22; H, 7.06.

Attempted Synthesis of Dimethyl 1-(4,4-Diphenylbuta-1,3-dienyl)-2,3-dimethylcyclopentan-1,3-dicarboxylate (11).—A solution of 390 mg (0.099 mmol) of **10a**[24] and 200 mg of *N*-bromosuccinimide in 25 ml of carbon tetrachloride was refluxed under irradiation from a sunlamp for 30 min. The solution was cooled, filtered, and the carbon tetrachloride removed by distillation with 8 ml of s-collidine as a cosolvent. The residual solution was diluted with 50 ml of 5% s-collidine in xylene and refluxed for 4 hr. The solution was cooled and washed successively with 3 *M* hydrochloric acid (two 75-ml portions), water (two 75-ml portions), and sodium bicarbonate solution (two 75-ml portions). The organic phase was dried ($MgSO_4$) and concentrated to yield 434 mg of crude material. Chromatography over 10 g of Woelm neutral alumina gave 216 mg of an oily mixture of geometric isomers of **12** (ratio 2:1): uv max (95% ethanol) 307 nm (ε 26,000); ir (neat) 3070, 3050, 3020, 1750, 1670, 1220, and 700 cm^{-1}; nmr (100 MHz) (CCl_4), major isomer, δ 0.94 (d, 3, J = 8.0 Hz), 1.12 (s, 3), 3.60 (s, 3), 3.64 (s, 3), 6.62 (AB q, 2, Δ_{AB} = 51.0 Hz, J_{AB} = 10.0 Hz), and 7.30 (m, 10); minor isomer, 1.02 (d, 3, J = 7.0 Hz), 1.10 (s, 3), 3.60 (s, 3), 3.56 (s, 3), 6.35 (AB q, 2, Δ_{AB} = 58.7 Hz, J_{AB} = 9.0 Hz), and 7.30 (m, 10); mass spectrum (70 eV) *m/e* 496, 498 (M^+).

1,11-Dimethyl-*endo*-3-hydroxytricyclo[6.2.1.$0^{3,8}$]undecan-2-one (13).—A solution containing 842 mg (4.42 mmol) of a mixture of **1** and **2** (ratio *ca.* 3:7)[4] in 50 ml of ether was stirred with 20 ml of 6 *M* hydrochloric acid for 75 hr. The reaction mixture was poured into 100 ml of water and extracted with ether (three 100-ml portions). The combined extracts were dried ($MgSO_4$) and concentrated to give a thick brown oil which crystallized upon standing. The crystalline mass was dissolved in 5 ml of ether and passed through activated charcoal. Removal of the ether gave white crystals which were dried (25–30°) at reduced pressure (0.4 Torr) for 24 hr to yield 500 mg (54.3%) of **13**: mp 96–97°; ir (CCl_4) 3560, 3445, and 1745 cm^{-1}; nmr (CCl_4) δ 0.84 (d, 3, J = 6.5 Hz), 0.98 (s, 3), 2.67 (s, 1), and 1.55 (m, 13); nmr (DMSO) δ 5.10 (s, 1).

Anal. Calcd for $C_{13}H_{20}O_2$ (208.30): C, 74.96; H, 9.68. Found: C, 74.75; H, 9.64.

Dehydration of 1,11-Dimethyl-*endo*-3-hydroxytricyclo[6.2.1.$0^{3,8}$]tricycloundecan-2-one (13).—To a stirred solution of 137 mg (0.63 mmol) of **13** in 25 ml of pyridine maintained at 0° was added 2 ml of thionyl chloride. The solution was allowed to warm to room temperature and was stirred for 10 hr at 25°. The solution was poured onto ice and extracted with pentane (three 75-ml portions). The combined organic phase was washed several times with 3 *M* hydrochloric acid to remove pyridine, dried ($MgSO_4$), and concentrated to yield 90 mg (65%) of **4**, which was identified by comparison of glpc retention time (coinjection), ir spectra, and nmr spectra with those of **4** obtained as described above.

Attempted Rearrangement of 8,9-Dimethyltricyclo[4.3.2.$0^{1,6}$]undec-8-en-7-one (20).—A mixture of 23 mg (0.012 mmol) of **20**, 40 mg of *p*-toluenesulfonic acid, and 15 ml of benzene was refluxed for 4 days. Analysis by glpc showed that the only change was slight decomposition of **20**. A similar experiment using *o*-dichlorobenzene as solvent gave the same result. Attempts to rearrange tricyclo[4.3.2.$0^{1,6}$]undec-8-en-7-one in the manner also led only to recovered starting material.

X-Ray Analysis of 5 and 13.—The crystal structure of compounds **5** and **13** were concluded in a routine manner. Since both analyses were similar, they will be reported together. Suitable crystals of both compounds were grown from suitable solvents (see Table I) by slow evaporation. The resulting platelike crystals were cut to a suitable size and surveyed on a precession camera. Both the survey and data collection were performed at ambient room temperature. Compound **13** was observed to slowly sublime at room temperature and was therefore enclosed in a 0.3-mm capillary tube. Compound **5** was stable at room

TABLE I
DETAILS OF CRYSTAL SURVEYS

Compound	5	13
Crystallization media	Benzene	Pentane
Crystal size, mm	0.3 × 0.4 × 0.3	0.2 × 0.3 × 0.4
Cell dimensions, Å	a = 8.45 ± 0.01	a = 9.56 ± 0.01
	b = 9.89 ± 0.01	b = 11.91 ± 0.01
	c = 15.17 ± 0.01	c = 13.89 ± 0.01
	β = 103.32 ± 0.03°	β = 132.13 ± 0.04°
Space group	$P2_1/c$	$P2_1/c$
Molecules/unit cell	4	4
Density observed, g/cm³	1.19	1.17
Density calculated, g/cm³	1.208	1.179
Number of reflections	1263	1215
Nonzero reflections	1136	1119

(24) Prepared from a pure sample of **10b** with ethereal diazomethane.

temperature. Final cell dimensions were obtained on the Syntex P_1 diffractometer using a least-squares fit of six high angle ($2\theta > 55°$) axial reflections (the three positive and the three negative directions). Both surveys are summarized in Table I. A 1-Å data set (maximum $2\theta = 100.0°$) was collected on a Syntex P_1 diffractometer using copper radiation which had been passed through a graphite monochromator. A θ-2θ scan technique was employed, the scan rate was 2°/min, and the background was counted for half the scan time at each end of the scan. A single check reflection was monitored every 30 reflections; this reflection indicated no crystal damage and was reproducible well within counting statistics.

The diffractometer output was processed using subprograms of the CRYM crystallographic computer system.[25] The processing included corrections for background and for Lorentz and polarization effects. The effect of the graphite monochromator was included in these corrections. No correction for absorption was made. The data processing also included calculation of the F^2 value and its standard deviation for each reflection (reflections with observed intensities less than or equal to zero were assigned a value of zero intensity). The standard deviations were assigned on the basis of the following equation

$$\sigma^2(I) = S + (B_1 + B_2)\alpha^2 + (dS)^2$$

where S is the scan count, B_1 and B_2 are the background counts, d is an empirical constant equal to 0.02, and $\alpha = n/2mt$ where n = scan range, m = scanning speed, and t = time for background count in seconds. Finally, the data set was placed on an absolute scale by means of Wilson statistics.[26]

Determination of Structure and Refinement.—A trial set of phases was obtained through the reiterative application of Sayre's equation.[27,28] In both compounds, a trial structure was obtained with the first E map and refined smoothly to an acceptable R index. The refinement procedure included a full matrix least-squares treatment of coordinates, anisotropic temperature factors, and scale factor. Hydrogen positions were located by difference Fourier techniques and were added to the structure factor calculation in the latter stages of refinement. Hydrogen parameters were not refined. The quantity minimized by the least-squares procedure is $\Sigma w(F_o^2 - F_c^2)^2$, where $w = 1/\sigma^2(F_o^2)$.

(25) D. J. Duchamp, Annual Meeting of the American Association of Crystallographers, Bozeman, Mont., 1964, Abstracts, Paper B-14, p 29.

(26) A. J. C. Wilson, *Nature*, **150**, 152 (1942).

(27) D. Sayre, *Acta Crystallogr.*, **5**, 60 (1952).

(28) The phasing process was facilitated by the use of a computer program written by R. E. Long, U.C.L.A. Of the 16 possible solutions generated by the program, in each case, the solution which converged in the fewest cycles and had the highest internal consistency index proved to be the correct solution. Compound **5** converged in 7 cycles and has a consistency index of 0.74805. Compound **13** converged in 7 cycles and had a consistency index of 0.83394.

TABLE II

DATA FIT AND DEVIATIONS

Compound	5	13
Final R index ($\Sigma\|\|F_o - F_c\|\|/\Sigma\|F_o\|$)	0.064	0.091
Std deviations[a] of coordinates, Å		
C	0.005	0.008
O	0.003	0.006
Uncertainties in C, O bond lengths, Å	0.007	0.01
Uncertainties in C, O bond angles, deg	0.4	0.8
Range in C–C single bond lengths, Å	1.51–1.56	1.52–1.56

[a] Standard deviations in the coordinates were derived from the residuals and the diagonalized elements of the inverse matrix of the final least-squares cycle.

The final R values are given in Table II. A final difference Fourier revealed no missing or misplaced atoms.

Results of the X-Ray Analyses.—The structures obtained in this were stereographically plotted (Figures 1 and 2) using the ORTEP computer program of Johnson.[29] An estimate of errors in positional parameters, bond lengths, and bond angles is summarized in Table II. The data fit for compound **5** is slightly superior to that of compound **13**. This is to be expected, since data for compound **13** was collected on a crystal enclosed in a capillary. Bond distances and angles for both compounds were as expected. Therefore, due to limitations in space they will not be reported here. Full crystallographic data may be obtained by writing the author.[30]

Registry No.—**3**, 32298-47-8; **4**, 32298-48-9; **4** semicarbazone, 32298-49-0; **4** DNPH, 32298-50-3; **5**, 32298-51-4; **6**, 5465-18-9; **7**, 32298-53-6; **8a**, 32298-54-7; **10a**, 32298-55-8; **10b**, 32367-55-8; **12** (one isomer), 32298-56-9; **12** (second isomer), 32298-57-0; **13**, 32298-58-1.

Acknowledgment.—It is a pleasure to thank Professor G. Büchi for his interest in and his stimulating discussions of this work. It was he who first brought structures **3** and **4** to our attention.

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(30) J. Bordner.

Mechanism of the Decarboxylation of Monoethyl Oxalacetate

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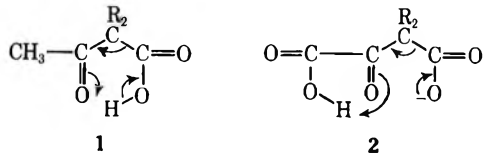
Received March 18, 1971

The monoethyl ester of oxalacetic acid was synthesized and its rate of decarboxylation studied. While the rate of decarboxylation of un-ionized monoethyl oxalacetate is not affected by a change in the solvent polarity, the rate of decarboxylation of its anion is facilitated by a lowering of the polarity of solvents. In contrast to the decarboxylation of the un-ionized monoester which exhibits the kinetic deuterium isotope effect, the decarboxylation of its anion is insensitive to the deuterium isotope. Reaction mechanisms consistent with experimental results are proposed for the decarboxylation of the un-ionized and anionic oxalacetates.

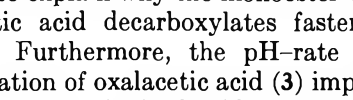
A great number of organic reaction mechanisms have been studied with a view that they may serve as chemical models for enzymic reactions.[1] One such system is the decarboxylation of β-keto acids.[2-5] Acetoacetic acid and α,α-dimethyl acetoacetic acid decarboxylate as free acids[6,7] by way of **1**, whereas oxalacetic acid and its α,α-dimethyl derivative decarboxylate mainly as their monoanions[2,8] by way of **2**. However, the intermediate **2** fails to explain why the monoester of α,α-dimethyl oxalacetic acid decarboxylates faster than its parent acid.[2] Furthermore, the pH–rate profile for the decarboxylation of oxalacetic acid (**3**) implicates the contribution of the un-ionized acid and its dianion to the rate.[8] In an attempt to resolve some of these uncertainties, the present work was undertaken to investigate the decarboxylation of monoethyl oxalacetate (**4**).



1 **2**

R = H or CH_3

Although a study of the decarboxylation of the monoethyl ester of α,α-dimethyloxalacetic acid has appeared,[2] a detailed kinetic study of the decarboxylation of **4**, which is the ester of the natural substrate of several enzymes,[9-11] may present a better model than its α,α-dimethyl derivative. The monoester **4** tautomerizes between keto and enol forms of which the keto tautomer is the active substrate for decarboxylase[9] and dehydrogenase[12] while the enol tautomer is responsible for the inhibitory effect of oxalacetate ion in an enzymic system.[13] The consideration of the keto–enol tautomerization in the decarboxylation study should lead to better understanding of the role of oxalacetates in enzymic reactions.



3, R = H
4, R = C_2H_5

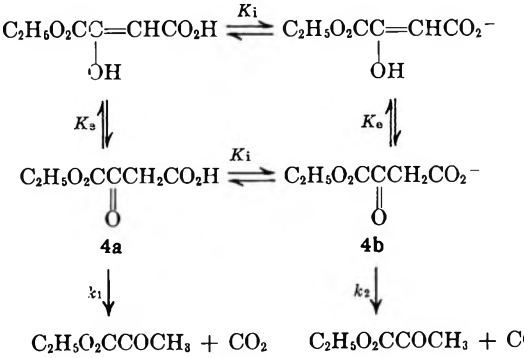
Results and Discussion

To assess the structural requirement of carboxyl groups in decarboxylation, reactivities of oxalacetic acid and its esters to decarboxylate were examined. Within the pH range studied, oxalacetic acid (**3**) and 1-ethyl oxalacetate (**4**) decarboxylate in solutions. 4-Ethyl oxalacetate and diethyl oxalacetate, which are esterified at the 4-carboxyl group, do not undergo decarboxylation. The result is in agreement with the C_3–C_4 cleavage for the decarboxylation.[14,15] Although the decarboxylation of **3** has been studied in some detail,[8] a similar study of **4** is lacking. In discussing their results, Steinberger and Westheimer[2] assumed that the anion of the monoethyl ester of α,α-dimethyloxalacetic acid was the only species active in the decarboxylation. However, the sigmoidal pH–rate profile for the decarboxylation of **4** as shown in Figure 1 reveals that both un-ionized (**4a**) and anionic (**4b**) monoethyl oxalacetates decarboxylate.

At a given pH, **4** exists as **4a** and **4b**, which tautomerize between the enol and keto form. If keto tautomers are active in the decarboxylations,[2] according to Scheme I, the observed rate constant (k_{obsd}) can be expressed by

$$k_{obsd} = \frac{k_1[H^+] + k_2K_i}{(1 + K_e)([H^+] + K_i)}$$

SCHEME I



(1) T. C. Bruice and S. Benkovic, "Bioorganic Mechanisms," Vol. 1 and 2, W. A. Benjamin, New York, N. Y., 1966.
(2) R. Steinberger and F. H. Westheimer, *J. Amer. Chem. Soc.*, **73**, 429 (1951).
(3) J. V. Rund and R. A. Plane, *ibid.*, **86**, 367 (1964).
(4) B. R. Brown, *Quart. Rev., Chem. Soc.*, **5**, 131 (1951).
(5) F. H. Westheimer, *Proc. Chem. Soc. (London)*, 253 (1963).
(6) K. Pedersen, *J. Amer. Chem. Soc.*, **51**, 2098 (1929).
(7) F. H. Westheimer and W. A. Jones, *ibid.*, **63**, 3283 (1941).
(8) C. S. Tsai, *Can. J. Chem.*, **45**, 873 (1967).
(9) G. W. Kosicki and F. H. Westheimer, *Biochemistry*, **7**, 4303 (1968).
(10) R. Y. Hsu, H. A. Lardy, and W. W. Cleland, *J. Biol. Chem.*, **242**, 5315 (1967).
(11) D. D. Davies and E. Kun, *Biochem. J.*, **66**, 307 (1957).
(12) F. A. Loewus, T. T. Chen, and B. Vennesland, *J. Biol. Chem.*, **212**, 787 (1955).
(13) L. Hellerman, O. K. Reiss, S. S. Parmar, J. Wein, and N. L. Lesser, *ibid.*, **235**, 2468 (1960).
(14) S. Seltzer, G. A. Hamilton, and F. H. Westheimer, *J. Amer. Chem. Soc.*, **81**, 4018 (1959).
(15) A. Wood, *Trans. Faraday Soc.*, **62**, 1231 (1966).

TABLE I

KINETIC (30°, μ = 0.08 M) AND THERMODYNAMIC CONSTANTS OF OXALACETATES

Oxalacetate	$10^2 k_1$, min^{-1}	$10^2 k_2$, min^{-1}	K_e	K_i
$HO_2CCOCH_2CO_2H$		0.6[a]	0.09[b]	(3.16×10^{-3} and 4.27×10^{-5})[c]
$C_2H_5O_2CCOCH_2CO_2H$	0.4	4.5	0.19 ± 0.08	1.9×10^{-4}
$HO_2CCOCH_2CO_2C_2H_5$			0.32 ± 0.10	(1.8×10^{-3})[d]

[a] Reference 8. [b] Reference 17. [c] K. J. Pedersen, *Acta Chem. Scand.*, 6, 243 (1952). [d] E. Gelles and R. W. Hay, *J. Chem. Soc.*, 3673 (1958).

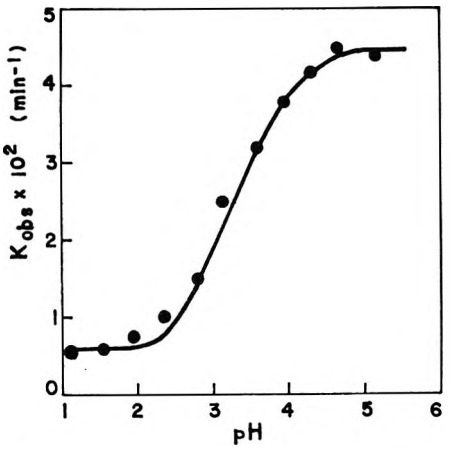


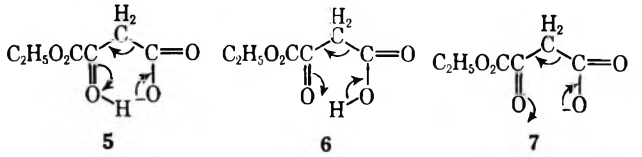
Figure 1.—pH-rate profile for the decarboxylation of 1-ethyl oxalacetate at 30°. KCl was added to maintain constant ionic strength at μ = 0.16 M.

where k_1 and k_2 are rate constants. K_i and K_e are the ionization constant and the enolization constant, respectively.[16] If $[H^+] \gg K_i$, and $k_1 \gg k_2K_i/[H^+]$,[17a] then $k_1 = k_{obsd}(1 + K_e)$, whereas if $[H^+] \ll K_i$[17b] and $k_2 \gg k_1[H^+]/K_i$, then $k_2 = k_{obsd}(1 + K_e)$. K_e is calculated from the percentage of keto tautomer by nmr spectrometry[18] and K_i is estimated from the pH–rate profile.[19] Results are summarized in Table I.

The faster rate of decarboxylation of **4** than that of **3** was attributed to a difference in ionization constants of the two carboxyl groups.[2] Indeed, the acidity of 1-carboxyl group is experimentally greater than that of the 4-carboxyl group by one pK unit. Thus, the monoanion of **3** is the mixture of monoanions, $^-O_2CCOCH_2COOH$ (**3a**) and $HO_2CCOCH_2COO^-$ (**3b**), consisting largely of the inert anion **3a**, whereas **4** can only exist in the active anion **4b**.

Table I shows that the per cent of enol tautomer in monoethyl esters of **3** is considerably higher (16 and 24% for 1- and 4-ethyl esters, respectively) than in the parent acid (8%). This result agrees with the previous report[18] that the esterification of carboxylic groups favors the enol tautomer.

Although the rate constant for the decarboxylation of un-ionized **4a** is only one-tenth that of monoanionic **4b**, both are active in the decarboxylation. While **4b** decarboxylates by way of **7**, the decarboxylation of **4a** may proceed by way of **5** or **6**, analogous to mechanisms proposed for acetoacetic acid.[7,20]



5 6 7

According to the theory of Hughes and Ingold,[21] the rate of decarboxylation of **4b** *via* **7** is enhanced by solvents of low polarity, whereas that of **4a** *via* **6** is virtually unaffected by a change in the solvent polarity. The solvent effect on the decarboxylation of **4a** *via* **5** is less conclusive because the formation of **5** is favored by polar solvents but its decomposition is facilitated by nonpolar solvents. Table II shows that the rate of the decarboxylation of **4b** is facilitated by a decrease in the polarity of solvents as expected, whereas that of **4a** is unaffected by the polarity of solvents.

TABLE II

SOLVENT EFFECT ON DECARBOXYLATION OF MONOETHYL OXALACETATE AT 30° AND μ (ACETATE ANION) = 0.08 M

Vol % ethanol	$10^2 k_{obsd}$, min^{-1} [a] pH 2.0[b]	pH 5.6[b]
0	0.40 ± 0.1	3.7 ± 0.5
16	0.34 ± 0.1	5.8 ± 0.8
36	0.42 ± 0.1	7.2 ± 0.4
50	0.40 ± 0.1	8.9 ± 0.8

[a] The observed rate constant (k_{obsd}) approximates k_1 and k_2 at pH 2.0 and pH 5.6, respectively. However, ethanol may also effect K_i (by suppressing the ionization) and K_e (by increasing the enol tautomer). Increased k_{obsd} values at pH 5.6 represent the lower limit as affected by ethanol; therefore, the conclusion that ethanol facilitates the rate of decarboxylation remains valid. [b] pH values quoted are direct meter readings.

The insensitivity of the decarboxylation of **4b** to the deuterium isotope (Table III) further substantiates

TABLE III

DEUTERIUM ISOTOPE EFFECT ON THE DECARBOXYLATION OF MONOETHYL OXALACETATE AT 30° AND μ (ACETATE ANION) = 0.08 M

	$10^2 k_1$, min^{-1}	$10^2 k_2$, min^{-1}
4 in H_2O[a]	0.46	4.0
Deuterated 4 in D_2O	0.15	3.9
k_H/k_D	3.07	1.03

[a] Monoethyl oxalacetate (**4**) used in this experiment has been treated by an identical procedure as deuterated **4**.

(16) Ionization constants for the enol and keto tautomers are assumed to be identical because **4** decarboxylates too rapidly to permit an experimental determination of an average K_i value. Enolization constants at pH 2.0 and 6.0 are identical within the experimental error (±5%).

(17) (a) This relationship holds only if $[H^+] \gg 1.14 \times 10^{-3}$. (b) This relationship is true as long as $[H^+] \ll K_i$.

(18) W. D. Kumler, E. Kun, and J. N. Shoolery, *J. Org. Chem.*, **27**, 1165 (1962).

(19) (a) The ionization constant obtained from the pH–rate profile corresponds to that of the keto tautomer. (b) If the average K_i[18] can be determined potentiometrically, the ionization constant for the enol tautomer can be calculated.

(20) K. R. Brower, B. Gray, and T. L. Konkol, *J. Amer. Chem. Soc.*, **88**, 1681 (1966).

(21) E. D. Hughes and C. K. Ingold, *J. Chem. Soc.*, 244 (1935).

the intermediary formation of **7** in the decarboxylation of the anionic oxalacetate. The existence of a kinetic deuterium isotope effect (k_H/k_D = 3.1) implicates a proton transfer process leading to the decarboxylation of **4a**. However, the present experiment does not distinguish between the two mechanisms, namely **4a** → **6** → products and **4a** → **6** ⇌ **5** → products.

Experimental Section

Melting points were determined on a Fisher–Johns hot-stage apparatus. Infrared spectra were taken with a Perkin-Elmer Model 225 spectrophotometer. Ultraviolet spectra were taken with a Cary 14 spectrophotometer using 1.0-cm matched quartz cells. Nuclear magnetic resonance spectra were taken on JEOLCO JNM-C-60 and Varian Associates T-60 instruments. Chemical shifts are reported on the δ scale, parts per million downfield from tetramethylsilane or sodium 3-(trimethylsilyl)-1-propanesulfonate as internal standard. Elementary analyses were performed by Organic Microanalyses, Montreal, Quebec, and Chemalytics, Inc., Tempe, Ariz. pH measurements were made with a Radiometer TTTlc. Trifluoroacetate (pH 1.5–3.0), acetate (pH 3.0–5.0), and phosphate (pH 5.0–6.5) buffers were prepared according to Gomori.[22] Ethanol was refluxed with magnesium turnings prior to the distillation.

Purification of Oxalacetic Acid (3) and Its Esters.—Oxalacetic acid and 4-ethyl oxalacetate were products of Nutritional Biochemical Corp. **3** was recrystallized twice from hexane as white crystals: mp 165–166°; uv (acetate buffer, pH 5.0) λ_{max} 260 nm (shoulder) (ϵ 1.3 × 10^3); nmr (CD_3COCD_3) δ 3.85 (s) and 5.95 (s). 4-Ethyl oxalacetate was recrystallized once each from chloroform and benzene as white crystals: mp 102–103°; uv (acetate buffer, pH 5.0) λ_{max} 260 nm (shoulder) (ϵ 0.6 × 10^3); ir (KBr) in the carbonyl stretching region, 1805, 1755, 1730, 1710, and 1664 cm^{-1}; nmr (CD_3COCD_3) δ 1.35 (t), 4.33 (q), 3.85 (s), and 6.00 (s). Diethyl oxalacetate was obtained from K & K Laboratories and purified by vacuum distillation: uv (acetate buffer, pH 5.0) λ_{max} 297 nm (ϵ 22.3 × 10^3); nmr (CD_3Cl) δ 1.25 (t), 1.36 (t), 4.08–4.50 (m), 3.80 (s), and 5.95 (s).

Synthesis of 1-Ethyl Oxalacetate (4).—Although the hydrolysis of the sodium enolate of diethyl oxalacetate was reported to yield **4**,[13] attempts by us and others[2] to prepare **4** or its α,α-dimethyl derivative by this procedure were unsuccessful. It gave white crystals, presumably 4-ethyl oxalacetate and a minor decarboxylating component. The following procedure was eventually employed to synthesize **4**. *tert*-Butyl acetate was prepared from *tert*-butyl alcohol and acetyl chloride in the presence of dimethylaniline.[23] The condensation of *tert*-butyl acetate with ethyl oxalate by means of isopropylmagnesium chloride[24] yielded 1-ethyl 4-*tert*-butyloxalacetate. The hydrolysis of 1-ethyl 4-*tert*-butyloxalacetate with HBr in glacial acetic acid[2] gave **4**, which was crystallized from hexane. Recrystallization of **4** from hexane twice gave white needles: mp 53–54°; uv (acetate buffer, pH 5.0) λ_{max} 262 nm (ϵ 1.4 × 10^3); ir (KBr) in the carbonyl stretching region, 1810, 1755, 1740, 1710, and 1640 cm^{-1}; nmr (CD_3COCD_3) δ 1.40 (t), 4.42 (q), 3.95 (s), and 6.13 (s).

Anal. Calcd for $C_6H_8O_6$: C, 45.00; H, 5.04. Found: C, 45.53; H, 5.27.

Preparation of Deuterated Compounds.—Deuterated trifluoroacetic acid was prepared by adding trifluoroacetic anhydride dropwise to D_2O. The distillation gave an azeotropic mixture (bp 91–92°). CH_3COOD was prepared by treating acetyl chloride with D_2O.[25] NaOD was obtained by dissolving sodium metal in D_2O. Deuterated **4** was prepared by an exchange reaction in D_2O followed by an immediate lyophilization. Deuterated buffers were prepared from CF_3COOD, CH_3COOD, and NaOD in D_2O. pH readings were corrected for pD values.[26]

Measurement of Enolization Constants.—Nuclear magnetic resonance spectra of freshly prepared solutions (in 0.1 *M* trifloroacetate buffer, pH 2.0 or phosphate buffer, pH 6.0) of monoethyl oxalacetates were taken. The ratio of ketonic CH_2 and esteric CH_3 (adjusted for the number of protons) was used to estimate the per cent of keto tautomer which was converted into enolization constant.

Rates of Decarboxylation.—The reactant–product relationship was established first by nmr spectrometry. A freshly prepared solution of **4** exhibits a triplet centered at δ 1.30 ppm (esteric CH_3) and a singlet at δ 3.20 ppm (ketonic CH_2). The esteric CH_2 was not detectable in H_2O. As the decarboxylation proceeded, the intensity of the ketonic CH_2 decreased with a concurrent appearance and a subsequent increase in the intensity of a singlet at δ 1.60 ppm corresponding to the CH_3 of ethyl pyruvate. For kinetic studies, rates of decarboxylation were determined manometrically in a Gilson differential respirometer as described previously.[8] The reaction mixture (2.5 ml) contained 200 μmol (based on the anionic species) buffer and 15 μmol of oxalacetate. The reaction was normally followed until 25% completion.

Registry No.—**3**, 328-42-7; **3** ethyl ester, 2401-96-9; **4**, 7597-72-0.

Acknowledgment.—The financial support of the National Research Council of Canada is gratefully acknowledged. The authors thank Dr. P. M. Laughton for reading the manuscript and valuable suggestions.

(22) S. Gomori in "Methods in Enzymology," Vol. 1, S. P. Colowick and N. O. Kaplan, Ed., Academic Press, New York, N. Y., 1955, p 138.

(23) C. R. Hauser, D. E. Hudson, B. Abramovich, and J. C. Shiver in "Organic Syntheses," Collect. Vol. III, E. C. Horning, Ed., Wiley, New York, N. Y., 1955, p 142.

(24) J.-E. Dubois, F. Hennequin, and M. Durand, *Bull. Soc. Chim. Fr.*, 791 (1963).

(25) A. Murry, III, and D. L. Williams, "Organic Synthesis with Isotopes," Vol. III, Interscience, New York, N. Y., 1958, p 1260.

(26) T. H. Fife and T. C. Bruice, *J. Phys. Chem.*, **65**, 1079 (1961).

Thallium in Organic Synthesis. XXV. Electrophilic Aromatic Bromination Using Bromine and Thallium(III) Acetate[1-3]

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Received December 21, 1970

A mixture of thallium(III) acetate and bromine is shown to be a mild and efficient reagent for electrophilic aromatic bromination. The reaction is applicable to the preparation of a wide range of isomerically pure monobromo aromatic compounds but is successful only when the substrate is activated toward electrophilic substitution. Several possible mechanisms are considered and explanations suggested for the role of thallium(III) acetate.

Thallium(III) acetate was first described in 1903 by Meyer and Goldschmidt,[4] but it is only in the last few years that the versatility and synthetic utility of this reagent in organic chemistry have deen demonstrated. The scope[5,6] and status[7] of thallium(III) acetate as an oxidant have been reviewed, and among recent applications to organic synthesis are reports describing its use in the oxidative cleavage of cyclopropanes,[5] the preparation of α-acetoxy ketones from ketones[8] and enamines,[9] the synthesis of 4,5-dihydrofurans from β-dicarbonyl compounds,[10] the direct conversion of chalcones into isoflavones,[11,12] and the hydration of acetylenes.[13] In all of these reactions thallium(III) acetate has been shown to function as a moderately reactive yet highly selective[5,6,11,12] electrophile. As far as we are aware, however, there are no reports on the Friedel–Crafts catalytic activity of the salt with respect to electrophilic aromatic substitution. Studies on the use of the thallium(III) halides as Friedel–Crafts catalysts have established that alkylation,[14,15] acylation,[14,15] chlorination,[16-18] and bromination[19] of aromatic compounds proceed normally but in low yields. The inefficiency of the thallium(III) halides in these reactions is almost certainly due primarily to the thermal instability of these compounds.[20] By contrast, thallium(III) acetate is a readily accessible, stable, crystalline solid which can be stored indefinitely without decomposition.

We have investigated the utility of thallium(III) acetate as a Friedel–Crafts catalyst and describe in this paper a general procedure for electrophilic bromination of activated aromatic compounds.

Results

A mixture of thallium(III) acetate and bromine is an effective and highly selective reagent for electrophilic aromatic bromination. Addition of a solution of bromine in carbon tetrachloride to a suspension of thallium(III) acetate in carbon tetrachloride containing an aromatic substrate results in the instantaneous discharge of the red color of the bromine. Thallium(III) acetate is rapidly converted to thallium(III) bromide, with simultaneous formation of the brominated aromatic compound. In the majority of examples studied the reaction proceeded rapidly at room temperature.

The scope of the reaction can be seen by examination of the data in Table I, in which typical conversions are summarized, and by consideration of the following general observations. Bromination occurs readily only with substrates activated toward electrophilic substitution. Even mildly deactivated compounds such as the halobenzenes were recovered unchanged when carbon tetrachloride was employed as solvent. These compounds underwent bromination smoothly, however, when excess of the aromatic substrate was employed as solvent, and the reaction was conducted at 80–90°. All other electron-withdrawing groups completely inhibited bromination in monosubstituted benzenes. A number of substituent groups were efficiently oxidized by thallium(III) acetate and bromine in carbon tetrachloride and nuclear substitution was not observed with such monosubstituted benzenes. Thus, benzaldehyde and benzyl alcohol, both of which could be recovered unchanged after being heated with thallium(III) acetate in carbon tetrachloride, were converted to benzoic acid (58%) and benzaldehyde (62%), respectively, when bromine was added to the reaction mixture. In polysubstituted benzenoid compounds, however, oxidation of these substituents was suppressed in favor of substitution when powerfully electron-donating groups were present. Thus 4-methoxybenzaldehyde was smoothly converted into 3-bromo-4-methoxy-

(1) Part XXIV: E. C. Taylor, H. W. Altland, G. McGillivray, and A. McKillop, *Tetrahedron Lett.*, 5285 (1970).

(2) We gratefully acknowledge partial financial support of the initial phase of this work by Smith Kline & French Laboratories, Philadelphia, Pa., and later support by the Lilly Research Laboratories, Indianapolis, Ind., and the Ciba Pharmaceutical Co., Summit, N. J.

(3) Certain aspects of this work were reported in preliminary form: A. McKillop, D. Bromley, and E. C. Taylor, *Tetrahedron Lett.*, 1623 (1969).

(4) R. J. Meyer and E. Goldschmidt, *Chem. Ber.*, **36**, 238 (1903).

(5) A. South, Jr., and R. J. Ouellette, *J. Amer. Chem. Soc.*, **90**, 7064 (1968).

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

(7) P. M. Henry, *Advan. Chem. Ser.*, **70**, 126 (1968).

(8) S. Uemura, T. Nakano, and K. Ichikawa, *J. Chem. Soc. Jap.*, **88**, 1111 (1967).

(9) M. E. Kuehne and T. J. Giacobbe, *J. Org. Chem.*, **33**, 3359 (1968).

(10) K. Ichikawa, S. Uemura, and T. Sugita, *Tetrahedron*, **22**, 407 (1966).

(11) W. D. Ollis, K. L. Ormand, and I. O. Sutherland, *J. Chem. Soc. C*, 119 (1970).

(12) W. D. Ollis, K. L. Ormand, B. J. Redman, and I. O. Sutherland, *ibid.*, 125 (1970).

(13) S. Uemura, R. Kitoh, K. Fujita, and K. Ichikawa, *Bull. Chem. Soc. Jap.*, **40**, 1499 (1967).

(14) L. I. Kashtanov, *J. Gen. Chem. USSR*, **2**, 515 (1932).

(15) G. A. Olah, Ed., "Friedel-Crafts and Related Reactions," Vol. 1, Interscience, New York, N. Y., 1963, p 255.

(16) V. Thomas, *C. R. Acad. Sci.*, **144**, 32 (1907).

(17) A. G. Page, *Justus Liebigs Ann. Chem.*, **225**, 196 (1884).

(18) C. Willgerodt, *J. Prakt. Chem.*, **34**, 264 (1886).

(19) L. Bruner, *Bull. Acad. Sci. Cracow*, 22 (1901).

(20) F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry," Interscience, New York, N. Y., 1965, p 337.

TABLE I
SYNTHESIS OF AROMATIC BROMIDES USING $Tl(OOCCH_3)_3/Br_2$

	Starting material		Product		
					
No.	R	R′	R	R′	Yield, %[a]
1	H	H	H	H	83
2	CH_3	H	4-CH_3	H	60[b,c]
3	C_2H_5	H	4-C_2H_5	H	60[b]
4	C_6H_5	H	4-C_6H_5	H	93
5	CH_3O	H	4-CH_3O	H	91
6	CH_3NH	H	4-CH_3NH	H	62
7	$(CH_3)_2N$	H	4-$(CH_3)_2N$	H	75
8	CH_3CONH	H	4-CH_3CONH	H	95
9	CH_3S	H	4-CH_3S	H	73
10	F	H	4-F	H	70[d]
11	Cl	H	4-Cl	H	70[d]
12	Br	H	4-Br	H	73[d]
13	I	H	4-I	H	69[d]
14	CH_3	2-CH_3	3-CH_3	4-CH_3	85
15	CH_3	3-CH_3	2-CH_3	4-CH_3	88
16	CH_3	4-CH_3	2-CH_3	5-CH_3	76
17	CH_3O	2-CH_3O	3-CH_3O	4-CH_3O	85
18	CH_3O	3-CH_3O	2-CH_3O	4-CH_3O	87
19	NO_2	2-CH_3O	3-NO_2	4-CH_3O	90
20	NO_2	2-C_6H_5	4-(2′-$NO_2C_6H_4$)	H	70
21	CHO	4-CH_3O	5-CHO	2-CH_3O	66
22	$COOCH_3$	3-CH_3O	2-$COOCH_3$	4-CH_3O	93
23	$COOCH_3$	4-CH_3O	5-$COOCH_3$	2-CH_3O	90
24	Thiophene		2-Bromothiophene		82[e]
25	2-Methylthiophene		2-Bromo-5-methylthiophene		75
26	3-Methylthiophene		2-Bromo-3-methylthiophene		72
27	Naphthalene		1-Bromonaphthalene		71
28	1-Methylnaphthalene		4-Bromo-1-methylnaphthalene		84
29	1-Methoxynaphthalene		4-Bromo-1-methoxynaphthalene		70
30	2-Methoxynaphthalene		1-Bromo-2-methoxynaphthalene		68
31	1-Nitronaphthalene		5-Bromo-1-nitronaphthalene		75
32	Anthracene		9-Bromoanthracene		89
33	Biphenylene		2-Bromobiphenylene		88
34	Fluorene		2-Bromofluorene		80
35	Phenanthrene		9-Bromophenanthrene		78
36	*p*-Terphenyl		4-Bromo-*p*-terphenyl		79[f]

[a] Calculated on pure recrystallized or redistilled material. [b] Reaction conducted at 0° throughout. [c] Accompanied by 8% *o*-bromotoluene. [d] Excess of the aromatic substrate was used as solvent; reaction conducted at 80–90°. [e] Accompanied by 8% of 2,5-dibromothiophene. [f] Accompanied by 2–4% of 4,4′-dibromo-*p*-terphenyl.

benzaldehyde in 66% yield on treatment with thallium(III) acetate and bromine in carbon tetrachloride.

The rate of addition of the bromine solution in these reactions is critical; the presence of free bromine in the reaction mixture leads to mixtures of isomers and should be avoided. For example, addition of the bromine solution all at once to a mixture of ethylbenzene and thallium(III) acetate in carbon tetrachloride resulted in formation of both 2- and 4-bromoethylbenzene (15:85).

From the above results and the data in Table I, it is evident that the thallium(III) acetate/bromine reaction involves a species of low electrophilicity. This conclusion is compatible with the two most outstanding features of the reaction: (1) monobromination was observed in almost all of the aromatic substrates studied and (2) exclusive para bromination was observed with almost all of the monosubstituted benzenes. The latter feature, which distinguishes the present method from the majority of electrophilic aromatic bromination reactions, is indicative of an electrophile of low reactivity but high steric requirement.[21]

Bromination of phenol, aniline, thiophene, 1,4-dimethoxybenzene, and *p*-terphenyl with thallium(III) acetate and bromine gave mixtures of mono- and dibrominated products. The yield of dibromo compounds was low with thiophene (8%) and *p*-terphenyl (2–4%) but considerably higher with phenol, aniline, and 1,4-dimethoxybenzene (10–25%). We interpret these results as reflecting the relative rates with which these compounds and their monobromo derivatives undergo electrophilic bromination. Thus competitive substitution by molecular bromine and by the thallium(III) acetate/bromine reagent would be expected with phenol, aniline, thiophene, and 1,4-dimethoxybenzene provided that the relative electrophilicities of the reagents were comparable. In 4-bromo-*p*-terphenyl, the initial substitution product of *p*-terphenyl, deactivation of the 4′ position by the bromine substituent should be considerably reduced relative to the 4′ position in bromobenzene, and a small amount of dibromination is predictable.

Discussion

Many procedures have been described for the direct introduction of bromine into an aromatic nucleus. The majority of these can be classified into one of three categories depending on the nature of the bromine source which is employed, namely (a) molecular bromine, as such, or generated *in situ*, (b) molecular bromine activated by a catalyst, or (c) a positive bromine species.[22] The general trend of increasing electrophilicity in this series is a < b < c. With respect to this classification, and in view of the unusually high selectivity of substitution encountered with thallium(III) acetate/bromine, we have examined a number of possible mechanisms for this reaction. Our objective in this work was to elucidate two interrelated aspects of the reaction, namely the nature of the bromine electrophile involved and the specific role of the thallium(III) acetate.

There are three obvious pathways for electrophilic aromatic bromination using thallium(III) acetate and bromine: (1) formation of acetyl hypobromite as the active bromine reagent; (2) generation of an arylthallium diacetate by electrophilic thallation and subsequent reaction of this intermediate with bromine; (3) bromination by molecular bromine catalyzed either by thallium(III) bromide or by thallium(III) acetate. The results summarized below clearly eliminate the first two of these possibilities and are in general agreement with the third.

(1) **Acetyl Hypobromite Formation.**—Preparation of acyl hypohalites by treatment of metal carboxylates with molecular halogen is a well-documented process[23] which has been used to generate "positive" halogen

(21) R. O. C. Norman and R. Taylor, "Electrophilic Substitution in Benzenoid Compounds," Elsevier, New York, N. Y., 1965.
(22) Reference 21, pp 119–155.
(23) M. Anbar and D. Ginsburg, *Chem. Rev.*, **54**, 925 (1954).

(by decomposition of the acyl hypohalite[24,25]). Evidence that an analogous pathway (eq 1 and 2) is not

$$3Br_2 + Tl(OOCCH_3)_3 \longrightarrow 3CH_3COOBr + TlBr_3 \quad (1)$$

$$3CH_3COOBr + 3ArH \longrightarrow 3CH_3COOH + 3ArBr \quad (2)$$

involved in the thallium(III) acetate/bromine reaction was obtained as follows. Thalluim(III) acetate was shaken with a solution of bromine in carbon tetrachloride, aliquots were withdrawn periodically, and the uv spectra were recorded. The characteristic absorption maximum at 265 nm due to acetyl hypobromite[26] was not observed; a solution of genuine acetyl hypobromite[26] in carbon tetrachloride was used as reference standard. Identical results were obtained using acetonitrile as solvent [in which thallium(III) acetate is soluble]. Aliquots were also withdrawn from reaction mixtures consisting of thallium(III) acetate, bromine, and an aromatic substrate, both in carbon tetrachloride and acetonitrile. Again, examination of the uv spectra showed that acetyl hypobromite was not formed in these reactions.

(2) **Electrophilic Thallation.**—The reactions shown in eq 3 and 4 constitute a plausible explanation for the

$$ArH + Tl(OOCCH_3)_3 \longrightarrow ArTl(OOCCH_3)_2 + CH_3COOH \quad (3)$$

$$ArTl(OOCCH_3)_2 + 2Br_2 \longrightarrow ArBr + TlBr + CH_3COOBr \quad (4)$$

bromination of aromatic compounds with thallium(III) acetate and bromine. Electrophilic aromatic thallation with thallium(III) trifluoroacetate[27] and isobutyrate[28,29] has been described; arylthallium dicarboxylates (eq 3) are known to undergo C–Tl bond cleavage on treatment with molecular halogen to give aromatic halides.[30] As discussed above, acetyl hypobromite is not produced in the thallium(III) acetate/bromine reaction (*cf.* eq 4). Acyl hypobromites have been shown to react with thallium(I) bromide, however, to give the unstable sesquihalide Tl_2Br_4, which readily decomposes to a mixture of thallium(I) and thallium(III) bromides.[31] Consequently, failure to detect the presence of acetyl hypobromite in the reaction mixture does not necessarily negate the feasibility of bromination as shown in eq 3 and 4.

Equation 3 was shown to be untenable as follows. Attempted thallation of a variety of aromatic substrates by heating with thallium(III) acetate in carbon tetrachloride was totally unsuccessful, and the reactants were recovered unchanged. Under more forcing conditions (absence of solvent, 100–150°), extensive decomposition resulted and led to intractable tars. In an alternative approach designed to test the validity of eq 4, phenylthallium and 4-*o*-xylylthallium diacetates were prepared independently (see Experimental Section) and treated with solutions of bromine in carbon tetrachloride. In both cases, extensive decomposition of the organothallium derivatives was observed, and complex reaction mixtures were obtained. The major constituents of these mixtures were *p*-dibromobenzene and 4,5-dibromo-*o*-xylene, respectively.

(3) **Molecular Bromine as Electrophile.**—The stoichiometry of the thallium(III) acetate/bromine reaction is shown in eq 5. Thallium(III) bromide is insoluble

$$Tl(OOCCH_3)_3 + 3ArH + 3Br_2 \longrightarrow 3ArBr + 3CH_3COOH + TlBr_3 \quad (5)$$

in carbon tetrachloride, the solvent used in preparative scale operations, and separated during reaction. It is, however, soluble in acetonitrile and its formation during reactions conducted in this solvent was confirmed by observation of its characteristic uv absorption maxima at 275 and 300 nm. Solutions of freshly prepared thallium(III) bromide in acetonitrile (see Experimental Section) were used as reference standards.

As mentioned above, the thallium(III) halides are mild but inefficient Lewis acid catalysts in electrophilic aromatic halogenation reactions. Their thermal instability severely limits their application to synthesis; the bromide, for example, disproportionates at temperatures in excess of 40° (eq 6). Nevertheless, we

$$TlBr_3 \underset{<40°}{\overset{>40°}{\rightleftharpoons}} TlBr + Br_2 \quad (6)$$

considered that some portion of the product formed in the thallium(III) acetate/bromine substitution of aromatic compounds might be derived by processes involving catalysis of substitution by molecular bromine either by thallium(I) or thallium(III) bromide. The following control experiments were undertaken to test these possibilities. Anisole was added to a freshly prepared solution of thallium(III) bromide in acetonitrile and the reaction mixture was monitored by uv spectroscopy during the course of several days. No diminution was observed in the absorption maxima due to thallium(III) bromide. On a preparative scale, a mixture of equimolar amounts of anisole and thallium(III) bromide in acetonitrile was stirred at room temperature for 7 days; anisole was recovered unchanged. Thallium(III) bromide itself is not therefore the active reagent in the bromination reaction.

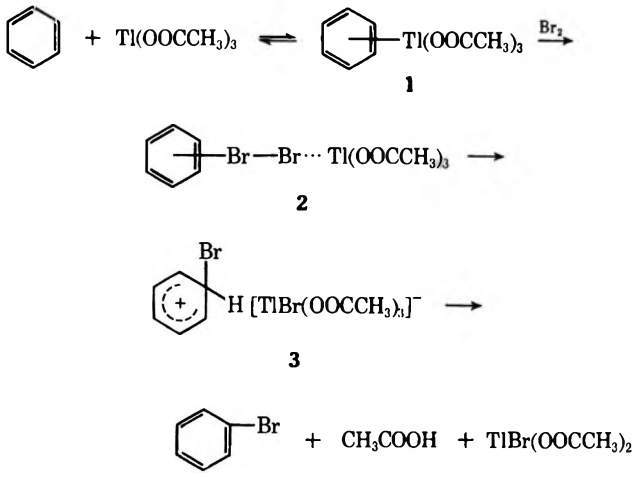
The rate of bromination of toluene by bromine in acetonitrile was then studied, both in the presence and absence of thallium(III) bromide. The concentration of thallium(III) bromide was varied from 0.1 to 1.0 *M* with respect to the aromatic substrate. There was no evidence of rate enhancement in reactions conducted in the presence of thallium(III) bromide. This latter result, though indicative, does not however conclusively eliminate the possibility that in acetonitrile solution part of the product may be formed by bromination of the aromatic substrate by a mixture of thallium(III) bromide and bromine. Acetonitrile is a relatively strong base which may effectively quench the catalytic activity of Lewis acids. Thus, Stock and Himoe have observed that the second-order rate constants for the chlorination of toluene in acetonitrile are little changed by the addition of aluminum chloride.[32]

It proved impossible to assess the extent (if any) to which thallium(III) bromide might function as a catalyst in reactions in which carbon tetrachloride was

(24) R. N. Haszeldine, *J. Chem. Soc.*, 584 (1951).
(25) R. N. Haszeldine and A. G. Sharpe, *ibid.*, 993 (1952).
(26) M. Anbar and I. Dostrovsky, *ibid.*, 1105 (1954).
(27) A. McKillop, J. S. Fowler, M. J. Zelesko, J. D. Hunt, E. C. Taylor, and G. McGillivray, *Tetrahedron Lett.*, 2423 (1969).
(28) V. P. Glushkova and K. A. Kocheshkov, *Izv. Akad. Nauk USSR, Otd. Khim. Nauk*, 1186 (1957).
(29) V. P. Glushkova and K. A. Kocheshkov, *Zh. Obshch. Khim.*, **36**, 1690 (1966).
(30) A. N. Nesmeyanov and R. A. Sokolik, "Methods of Elemento-Organic Chemistry. Vol. 1. The Organic Compounds of Boron, Aluminium, Gallium, Indium and Thallium," North Holland Publishing Co., Amsterdam, 1967, p 587.
(31) A. McKillop, D. Bromley, and E. C. Taylor, *J. Org. Chem.*, **34**, 1172 (1969).
(32) L. M. Stock and A. Himoe, personal communication.

employed as solvent. These reaction mixtures were heterogeneous, and attempts to obtain satisfactory kinetic data both by spectroscopic and quenching techniques were unsuccessful. Thallium(III) halides are known to be ineffective Friedel–Crafts catalysts,[14–19] however, and the yields of products obtained in thallium(III) halide-catalyzed halogenations of aromatic compounds are much inferior to those realized when thallium(III) acetate is employed. Consequently, we believe that the reaction pathway involving molecular bromine activated by thallium(III) acetate is the more important and that the mechanism is best represented as shown in Scheme I. Decomposition of the

SCHEME I



ion pair **3** into product and bromothallium diacetate is presumably followed by similar reaction sequences involving bromothallium diacetate and dibromothallium acetate as catalysts. The high degree of positional selectivity observed in substitution can then be attributed primarily to the steric bulk of the electrophile, species such as **2** and **3** representing highly ordered arrays.

Experimental Section

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. Where appropriate, identity of compounds was confirmed by comparison of ir spectra determined by the normal Nujol mull or liquid film techniques on a Perkin-Elmer Model 237 grating infrared spectrophotometer. Analytical gas–liquid chromatograms were carried out using Perkin-Elmer Model PE 452 and F 11 gas chromatographs. Standard columns comprising 1-m and 2-m Apiezon and 2-m silicon oil packing were used throughout with the PE 452; a 50-m PPG capillary column was employed with the F 11 instrument. Quantitative analyses of chromatograms were performed using a Vitatron UR 400 digital readout integrator. Ultraviolet spectra were recorded on a Perkin-Elmer Model 137 uv spectrophotometer and on a Unicam SP 500 Series 2 ultraviolet and visible spectrophotometer.

Starting Materials.—Compounds **1–21**, **24–32**, and **34–36** were commercial samples and were purified prior to use. Methyl 3-methoxybenzoate[33] and methyl 4-methoxybenzoate[34] were prepared by literature procedures; compound **33** was kindly donated by Dr. J. F. W. McOmie of the University of Bristol.

Purification of Solvents.—Carbon tetrachloride was dried by stirring over phosphorus pentoxide for at least 24 hr, followed by distillation on to molecular sieves which had been previously heated under vacuum at 80° for 10 hr. Acetonitrile was distilled off phosphorus pentoxide, the fraction bp 81° being collected. Acetic acid was purified by the procedure of Orton and Bradfield,[35] and bromine was dried over phosphorus pentoxide for 24 hr prior to use.

Reaction of Aromatic Compounds with Thallium(III) Acetate and Bromine in Carbon Tetrachloride. Standard Procedure.—To 0.01 mol of the aromatic substrate was added 0.03 mol of thallium(III) acetate. The mixture was stirred in 100 ml of carbon tetrachloride under an atmosphere of dry nitrogen in a flask fitted with a dropping funnel and reflux condenser, both of which were protected by silica gel drying tubes. Maintaining a vigorous rate of stirring, a solution of 0.01 mol of bromine in 50 ml of carbon tetrachloride was added dropwise, the concentration of free bromine being maintained at a minimum throughout reaction. Addition of bromine was generally complete within 15–20 min. The mixture was then heated under reflux for 30 min. The cooled reaction mixture was filtered through a sintered glass funnel and then washed with approximately 150-ml quantities of aqueous sodium metabisulfite, aqueous sodium bicarbonate, and finally water. The organic layer was dried over anhydrous sodium sulfate and the solvent was removed to give the crude product. To remove traces of thallium, this material was filtered down a short alumina column using chloroform as eluent. Distillation or recrystallization then gave the pure product.

Procedure for the Bromination of Halobenzenes with Thallium(III) Acetate and Bromine.—To 20 ml of the halobenzene was added 0.01 mol of thallium(III) acetate. The mixture was stirred under an atmosphere of dry nitrogen and heated to 80–90°. A solution of 0.03 mol of bromine in 10 ml of the halobenzene was added slowly. The mixture was stirred at 80–90° for 1 hr and allowed to cool. The mixture was then worked up as in the above procedure.

Preparation of Phenylthallium Diacetate.—To a solution of 5 g (0.06 mol) of sodium acetate in 20 ml of acetic acid was added 2.5 g (0.005 mol) of phenylthallium ditrifluoroacetate.[27] The mixture was stirred for 48 hr and filtered, and the colorless product was dried under high vacuum. This gave 2.0 g (50%) of phenylthallium diacetate as a colorless solid, mp 205–209° (lit.[36] mp 193–195°).

The general method of Glushkova and Kocheshkov[37] was also employed to prepare this compound, yield 43%, mp 204–208°.

Preparation of 4-*o*-Xylylthallium Diacetate.—The procedure used was the same as for phenylthallium diacetate, using as starting material 4-*o*-xylylthallium ditrifluoroacetate,[27] yield 52%, mp 201–206°. Satisfactory analytical data could not be obtained for this compound because of the ease with which it underwent symmetrization to the diarylthallium acetate.[38,39] The identity of the compound was, however, easily confirmed by examination of its ir and nmr spectra.[40]

Reaction of Phenylthallium Diacetate with Bromine in Carbon Tetrachloride.—To a stirred suspension of 4 g (0.01 mol) of phenylthallium diacetate in 30 ml of carbon tetrachloride was added, from a graduated dropping funnel, a solution of 4.8 g (0.03 mol) of bromine in 10 ml of carbon tetrachloride. After one-third of the solution had been added the mixture was stirred for 5 min; the color of the bromine did not discharge at a detectable rate. The mixture was thus heated to reflux and the rest of the bromine solution was added. Total decolorization of the bromine required heating under reflux for 12 hr. The mixture was worked up as described above in the general procedure to give 0.5 g of a thick, yellow oil; distillation gave 0.3 g of a pale yellow oil, bp 200–220° (1 mm), glc analysis of which showed it to be a mixture of four products. One of these components was identified as *p*-dibromobenzene by comparison of its retention time with that of an authentic sample.

Reaction of 4-*o*-Xylylthallium Diacetate with Bromine in Carbon Tetrachloride.—To a stirred suspension of 4.3 g (0.01 mol) of 4-*o*-xylylthallium diacetate in 30 ml of carbon tetrachloride was added a solution of 1.66 g (0.01 mol) of bromine in 10 ml of carbon tetrachloride. The bromine was decolorized after 5 hr. The work-up used was similar to that described above and gave 0.1 g of a yellow oil which could not be identified.

(33) K. Kindler, *Justus Liebigs Ann. Chem.*, **452**, 90 (1927).
(34) E. Votecek and J. Matejka, *Chem. Ber.*, **46**, 1755 (1913).
(35) K. J. P. Orton and A. E. Bradfield, *J. Chem. Soc.*, **130**, 983 (1927).
(36) H.-J. Kabbe, *Justus Liebigs Ann. Chem.*, **656**, 204 (1962).
(37) V. P. Glushkova and K. A. Kocheshkov, *Dokl. Akad. Nauk USSR*, **116**, 233 (1957).
(38) K. Yasuda and R. Okawara, *Organometal. Chem. Rev.*, **2**, 255 (1968).
(39) Reference 30, pp 581, 582.
(40) A. McKillop, J. D. Hunt, and E. C. Taylor, *J. Organometal. Chem.*, **24**, 77 (1970).

The above experiment was repeated using 4.8 g (0.03 mol) of bromine in 20 ml of carbon tetrachloride. Work-up gave 0.4 g of a brown gum which, after filtration through an alumina column, using chloroform as eluent, gave 0.3 g of a yellow oil which had the same retention time on glc analysis as 4,5-dibromo-*o*-xylene. Its ir spectrum was superimposable on that of authentic 4,5-dibromo-*o*-xylene.

Reaction of Thallium(I) Bromide with Bromine in Acetonitrile. Preparation of Thallium(III) Bromide.—A suspension of 0.28 g (0.001 mol) of thallium(I) bromide in 20 ml of acetonitrile was stirred vigorously while 0.16 g (0.001 mol) of bromine in 10 ml of acetonitrile was added. The bromine was decolorized, and the solid dissolved to give a solution of thallium(III) bromide. Dilution of an aliquot of this solution (0.1 ml made up to 10 ml) gave a solution whose uv spectrum showed an intense absorption band at 275 nm, with a shoulder at 300 nm.

Registry No.—Bromine, 7726-95-6; thallium(III) acetate, 2570-63-0; phenylthallium diacetate, 20425-82-5; 4-*o*-xylylthallium diacetate, 31947-39-4; thallium(III) bromide, 13701-90-1.

Structure–Activity Relationship in the Chymotrypsin Hydrolysis of *p*-Nitrophenyl Esters[1]

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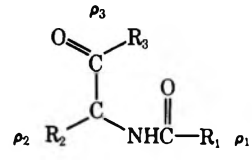
Received February 26, 1971

The structure–activity relationship in chymotrypsin substrates is examined using the substituent constants σ^*, E_s, and π for the evaluation of electronic, steric, and hydrophobic effects on the relative rates of reaction. It is found that hydrophobic forces (defined by π) play a positive role in the deacylation step.

We have been interested in studying substituent effects (hydrophobic, electronic, and steric) on enzyme substrate interactions.[2] The present paper analyzes substituent effects on chymotrypsin hydrolysis from the work of Dupaix, Béchet, and Roucous[3] and compares this with earlier studies. The structure–activity problem with chymotrypsin has been approached from many points of view.[4,5] In this report our primary purpose is to consider the role of hydrophobic forces in the hydrolysis step *via* extrathermodynamic correlations. There appears to be a role for these forces independent of specific steric and electronic effects of substituents.

In a recent study[6] of chymotrypsin substrates and inhibitors, the Hein–Niemann[7,8] model of the active site was employed in an analysis of the structure–activity relationship. This model pictures four sections in space into which the four substituents attached to the α carbon of an amino acid moiety of a protein or peptide would fit. This is depicted as in I. In I the hydrogen



I

atom on the α carbon is not shown. It is in the space below the plane of the page. The ρ_H region into which the hydrogen fits is assumed to be occupied only by solvent. The ρ_1, ρ_2, and ρ_3 regions have quite different binding characteristics for substrates and inhibitors. We[6] have attempted a characterization of these areas using linear modeling techniques[9] employing four types of physicochemical parameters: hydrophobic ($\log P$, π), electronic (σ), steric (E_s), and polarizability (P_E). Our general model[10] is formulated in eq 1. In eq 1, k may

$$\log k = k_1\pi + k_2\sigma + k_3E_s + k_4 \quad (1)$$

be a rate or equilibrium constant and the disposable parameters, k_1–k_4, are evaluated *via* the method of least squares.[9] The parameter π is obtained from octanol–water partition coefficients[11,12] and is an operationally defined "hydrophobic bonding" constant analogous to the familiar Hammett constant.[13] E_s is Taft's steric parameter.[13] Atomic refractivities[14] have been used as a measure of polarizability.[15]

In a review of the chymotrypsin literature it was found[6] that, for eight sets of substrates and inhibitors with hydrophobic groups attached to an α carbon, the coefficient with the hydrophobic term (π or $\log P$) in eq 1 or its simpler forms had a mean value with standard deviation of 1.21 ± 0.23. The dependent variable in these correlations was either $\log 1/K_m$, $\log K_i$, or $\log 1/C$. K_i is an inhibition constant and C is the molar concentration causing 50% inhibition. There was no apparent difference in the coefficients for substrates or inhibitors. This high coefficient (1.21) was suggested to be a ρ_2 area characteristic. For four sets of congeners with groups fitting the ρ_3 area, the mean coefficient with the apolar term was 0.29 ± 0.1. Binding in the ρ_3 area was found to be quite different; the ρ_3 area does not behave by our operationally defined hydrophobic

(1) This work was supported by Grant CA 11110 from the National Institutes of Health.

(2) (a) C. Hansch, E. W. Deutsch, and R. N. Smith, *J. Amer. Chem. Soc.*, **87**, 2738 (1965); (b) C. Hansch, *Accounts Chem. Res.*, **2**, 232 (1969).

(3) A. Dupaix, J. J. Béchet, and C. Roucous, *Biochem. Biophys. Res. Commun.*, **41**, 464 (1970).

(4) M. L. Bender and F. J. Kézdy, *Annu. Rev. Biochem.*, **34**, 49 (1965).

(5) T. C. Bruice and S. Benkovic, "Bioorganic Mechanisms," Vol. I, W. A. Benjamin, New York, N. Y., 1966, p 212.

(6) C. Hansch and E. Coats, *J. Pharm. Sci.*, **59**, 731 (1970).

(7) G. E. Hein and C. Niemann, *J. Amer. Chem. Soc.*, **84**, 4487, 4495 (1962).

(8) C. L. Hamilton, C. Niemann, and G. Hammond, *Proc. Nat. Acad. Sci. U. S.*, **55**, 664 (1966).

(9) N. R. Draper and H. Smith, "Applied Regression Analysis," Wiley, New York, N. Y., 1966.

(10) C. Hansch and T. Fujita, *J. Amer. Chem. Soc.*, **86**, 1616 (1964).

(11) T. Fujita, J. Iwasa, and C. Hansch, *ibid.*, **86**, 5175 (1964).

(12) C. Hansch and S. M. Anderson, *J. Org. Chem.*, **32**, 2583 (1967).

(13) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963.

(14) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1964.

(15) D. Agin, L. Hersh, and P. Holtzman, *Proc. Nat. Acad. Sci., U. S.*, **53**, 952 (1965).

TABLE I

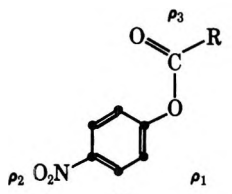
DATA EMPLOYED IN FORMULATION OF EQ 2–4

		$O_2NC_6H_4OCOR$				Log k_3		pK_1''	
No.	R	π[a]	σ^*[b]	E_s[b]	P_E[c]	Obsd[b]	Calcd[d]	Obsd[b]	Calcd[e]
1	$ClCH_2$	0.89	1.05	−0.24	10.58	0.42	0.33	6.90	6.96
2	H	0.00	0.49	1.24	1.10	0.18	0.27	7.60	7.62
3	ICH_2	1.50	0.85	−0.37	18.50	−0.24	−0.01	6.95	7.00
4	CH_3OCH_2	0.03	0.64	−0.19	11.86	−0.47	−0.84	7.16	7.14
5	$ClCH_2CH_2$	1.39	0.38	−0.90	15.20	−1.68	−1.62	7.13	7.04
6	$C_6H_5CH_2$	2.63	0.21	−0.38	29.83	−1.73	−1.01	7.41	7.26
7	CH_3	0.50	0.00	0.00	5.72	−2.00	−1.88	7.40	7.46
8	$(CH_3)_2CH$	1.30	−0.19	−0.47	14.92	−2.47	−2.48	7.34	7.40
9	$(CH_3)_3C$	1.68	−0.30	−1.54	19.58	−3.74	−3.66	7.04	7.13
10	$Cl(CH_2)_3$	1.89	0.14	−0.40	19.82	−1.29	−1.46	7.33	7.29
11	$Cl(CH_2)_4$	2.39	0.05	−0.40	24.40	−1.35	−1.47	7.41	7.32
12	$C_6H_5CH_2CH_2$	3.13	0.08	−0.38	34.45	−0.75	−1.11	7.26	7.32
13	$C_6H_5(CH_2)_3$	3.63	0.02	−0.45	39.07	−0.92	−1.12	7.33	7.32
14	$C_6H_5(CH_2)_4$	4.13	0.02	−0.45	43.69	−1.73[f]	−0.93	7.73[f]	7.32
15	H_2NCH_2	0.00	0.49	1.24		−0.46	−0.31[g]	7.01	7.00[h]
16	L-CH_3CHNH_2	0.50	0.00	0.00		0.28	0.04[g]	7.21	7.23[h]
17	L-$(CH_3)_2CHCHNH_2$	1.80	−0.13	−0.93		0.83	0.95[g]	7.59	7.57[h]
18	L-$C_6H_5CH_2CHNH_2$	2.63	0.22	−0.38		1.57	1.53[g]	7.53	7.55[h]

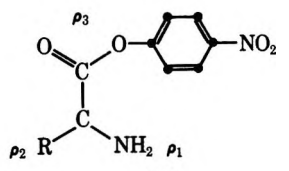
[a] From ref 11 and 12. [b] From ref 3. [c] From ref 14. [d] Calculated using eq 4. [e] Calculated using eq 14. [f] These values not used in deriving eq 4 and 14. [g] Calculated using eq 12. [h] Calculated using eq 16.

standard as other enzymic systems we have studied.[16] Substituents binding in the ρ_1 area are not well correlated by π but do correlate well with polarizability (6).

Dupaix, *et al.*,[3] employing a well-designed set of substrates (II and III), analyzed the structure–activity



II

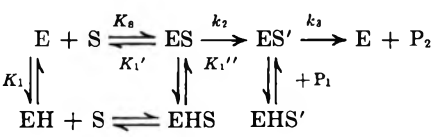


III

relationship in chymotrypsin hydrolysis in terms of electronic (σ^*) and steric (E_s) parameters but did not attempt to include hydrophobic terms in their linear free energy relationship. In II, one set of congeners has been cast in the Hein–Niemann model as we have previously done with structures of this type.[6] A second set of congeners derived from L-amino acids is formulated in III which previous work[6] indicates to be most likely.

Dupaix, *et al.*,[3] schematically represent their study in Scheme I, where S is the substrate, E and EH are the

SCHEME I



active and inactive forms of the enzyme, ES and EHS are the corresponding enzyme substrate complexes, ES′ and EHS′ the corresponding forms of the acyl–enzyme intermediate, and P_1 and P_2 are the hydrolysis products *p*-nitrophenol and carboxylic acid, respectively. Dupaix, *et al.*,[3] reported values of k_3 and pK_1'' values for the 18 compounds listed in Table I.

(16) H. F. Schaeffer, R. N. Johnson, E. Oldin, and C. Hansch, *J. Med. Chem.*, **13**, 452 (1970).

Results and Discussion

First, considering the larger set of congeners (compounds 1–14), we have derived, *via* the method of least squares, eq 2–4. Of the four independent variables of

$$\log k_3 = 2.349(\pm 1.06)\sigma^* - 1.852(\pm 0.49) \quad (2)$$
$$n = 13;\ r = 0.827;\ s = 0.668$$

$$\log k_3 = 1.890(\pm 0.87)\sigma^* + 0.792(\pm 0.58)E_s - 1.458(\pm 0.47) \quad (3)$$
$$n = 13;\ r = 0.915;\ s = 0.503$$

$$\log k_3 = 2.201(\pm 0.60)\sigma^* + 1.012(\pm 0.40)E_s + 0.374(\pm 0.22)\pi - 2.067(\pm 0.48) \quad (4)$$
$$n = 13;\ r = 0.969;\ s = 0.327$$

Table I, σ^* gave the highest correlation with log k_3 (eq 2). The best two-variable equation is eq 3, which is statistically a significant improvement over eq 2 ($F_{1,10} = 9.4$). Adding a term in π or P_E to eq 3 gives the same result because of the large amount of cocorrelation between these two parameters ($r^2 = 0.935$). Equation 4 with a π term represents a statistically significant reduction in the variance when compared with eq 3 ($F_{1,9} = 14.6$). The overall significance of eq 4 is high ($F_{3,9} = 136$; $F_{3,9\ \alpha.005} = 8.7$). The positive coefficient with σ^* means that k_3 is increased by electron-withdrawing substituents, while the positive coefficients with E_s mean that large groups slow down the reaction. The positive slope of the π term means that reaction is favored by hydrophobic bonding. This is surprising for the hydrolysis step. In a previous study[2a] of k_3 in a hydrolysis by emulsin, it was found that the coefficient with the hydrophobic term was negative, as one might expect. In the emulsin work, k_3 refers to the overall hydrolysis so that the meaning is somewhat different than in Scheme I. The value of the coefficient with π in eq 4 is about what we have found for binding in the ρ_3 area as characterized by $1/K_m$ or K_i correlations. It seems likely that the value of the π coefficient in eq 4 being near that found in equations correlating binding is coincidental. However, the positive coefficient is most interesting in that it indicates that some kind of apolar interaction promotes deacylation. Exactly how

TABLE II

DEACYLATION OF CHYMOTRYPSIN. DATA USED IN DERIVATION OF EQUATIONS

No.	R	E_s[a]	π[b]	σ^*[a]	Log k_3 Obsd[c]	Log k_3 Calcd[d]	Log k_3' Obsd[c]	Log k_3' Calcd[e]
1	CH_3	0.00	0.50	0.00			−2.46	−2.51
2	CH_3CH_2	−0.07	1.00	−0.10	−2.10	−2.16	−2.21	−2.25
3	$CH_3CH_2CH_2$	−0.36	1.50	−0.12	−2.22	−2.21	−2.36	−2.32
4	$CH_3(CH_2)_4$	−0.40	2.50	−0.13	−1.44	−1.48	−1.60	−1.66
5	$(CH_3)_2CH$	−0.47	1.30	−0.19	−2.61	−2.54	−2.74	−2.63
6	$(CH_3)_2CHCH_2$	−0.93	1.80	−0.13	−2.90	−2.85	−3.03	−2.95
7	$(CH_3)_3C$	−1.54	1.68	−0.30	−3.80	−3.88	−3.85	−3.93
8	$(CH_3)_3CCH_2$	−1.74	2.18	−0.17	−3.82	−3.79	−3.87	−3.87

[a] From ref 13. [b] From ref 11 and 12. [c] From ref 17. [d] Calculated using eq 6. [e] Calculated using eq 9.

apolar interactions aid deacylation is not clear. It could be that a conformational change in the enzyme is produced so that the histidine moiety is more favorably positioned to displace the acyl function, or binding the acyl function in a hydrophobic cleft could aid in breaking the acyl linkage by a kind of mechanical stretching action. Still another possibility is simply that of better orienting of substrate so that deacylation is sterically favored.

The above work of Dupaix, *et al.*,[3] can be compared with that of Fife and Milstein.[17] From their data on deacylation in Table II, eq 5 and 6 have been derived.

$$\log k_3 = 1.259(\pm 0.66)E_s - 1.707(\pm 0.65) \quad n = 7;\ r = 0.909;\ s = 0.404 \tag{5}$$

$$\log k_3 = 0.793(\pm 0.18)\pi + 1.539(\pm 0.14)E_s - 2.842(\pm 0.28) \quad n = 7;\ r = 0.998;\ s = 0.072 \tag{6}$$

Equation 6 is quite a significant improvement over eq 5 ($F_{1,4} = 155.5$). All possible combinations of π, E_s, and σ^* did not yield an equation with a lower standard deviation than eq 6. Omitting molecule 3 of Table II, Fife and Milstein[17] plotted log k_3 against E_s to obtain a rather good correlation ($r = 0.988$). Thus it occurred to us that possibly molecule 3 was behaving in a different manner from the others in Table II. Omitting this datum point, eq 7 and 8 are obtained. Not only

$$\log k_3 = 1.106(\pm 0.24)E_s - 1.967(\pm 0.26) \quad n = 6;\ r = 0.988;\ s = 0.133 \tag{7}$$

$$\log k_3 = 0.572(\pm 0.43)\pi + 1.413(\pm 0.26)E_s - 2.607(\pm 0.49) \quad n = 6;\ r = 0.998;\ s = 0.058 \tag{8}$$

does eq 8 have essentially the same shape as eq 6, the additional term in eq 8 over eq 7 is very significant statistically ($F_{1,3} = 18.5$; $F_{1,3\ \alpha.025} = 17.4$) even though only three degrees of freedom remain. The evidence that apolar forces are involved in k_3 is quite compelling.

Using Fife and Milstein's data for k_3' measured at pH 7.7 gives a set of points including one more value (Table II). From these data, eq 9 and 10 have been formulated.

$$\log k_3' = 1.065(\pm 0.58)E_s - 2.032(\pm 0.53) \quad n = 8;\ r = 0.878;\ s = 0.410 \tag{9}$$

$$\log k_3' = 0.718(\pm 0.16)\pi + 1.472(\pm 0.15)E_s - 2.869(\pm 0.22) \quad n = 8;\ r = 0.996;\ s = 0.085 \tag{10}$$

Equation 10 is an excellent correlation, quite comparable to eq 6. However, including the additional molecule makes even more apparent the importance of apolar forces in k_3. The additional term in eq 10 is quite significant compared to eq 9 ($F_{1,5} = 135$) ($F_{2,5} = 302$).

Milstein and Fife[18] have measured the parameter k_2/K_m in the acylation of chymotrypsin. Equation 11

$$\log k_2/K_m = 1.51(\pm 0.42)E_s + 0.63(\pm 0.39)\pi + 2.98(\pm 0.51) \quad n = 8;\ r = 0.976;\ s = 0.198 \tag{11}$$

results from our earlier analysis of these data.[6] Here, as in the other work by Fife and Milstein, no role can be seen for σ^*. No doubt this is because sufficient variation in this parameter was not present in the derivatives. The forces involved in the k_2 step are quite similar to those of the k_3 step (compare eq 10 and 11). The coefficients with the E_s and π terms are quite similar. That the weighting factors are the same with E_s is not unexpected. Again it is surprising that apolar forces play a role in this step. Unfortunately, the confidence intervals on the π term in eq 11 are not so tight as in eq 10. It is possible that apolar effects are not so important in k_2 as in k_3.

Compounds 15–18 in Table I are structurally so different from 1–14 that they have been treated separately, as shown in eq 12. Equation 12 is significant ($F_{1,2} = 44$; $F_{1,2\ \alpha.025} = 38.5$). The correlations with E_s ($r = 0.801$) and σ^* ($r = 0.443$) were very much poorer. Adding a second variable is rather meaningless for so few data points; however, doing so did not in any case give an equation with a lower standard deviation than eq 12. The coefficient with the π term in eq 12 is in agreement with that found in eq 4, 6, 8, 10, and 11. Even though little data are available, this group appears to behave mechanistically different than compounds 1–14. However, more sterically hindering functions might establish the need for an E_s term.

$$\log k_3 = 0.70(\pm 0.45)\pi - 0.31(\pm 0.73) \quad n = 4;\ r = 0.978;\ s = 0.219 \tag{12}$$

Two types of initial binding have been depicted in structures II and III corresponding to our earlier work.[6] The coefficients with the π term would suggest that different apolar forces are involved with k_2 and k_3 than with K_i and K_m.

The substituent effects on K_1'' are quite different from those on k_3, as seen from eq 13 and 14. The

$$pK_1'' = 0.190(\pm 0.18)E_s + 7.316(\pm 0.12) \quad n = 13;\ r = 0.568;\ s = 0.175 \tag{13}$$

$$pK_1'' = 0.292(\pm 0.09)E_s - 0.407(\pm 0.14)\sigma^* + 7.458(\pm 0.08) \quad n = 13;\ r = 0.932;\ s = 0.081 \tag{14}$$

(17) T. H. Fife and J. B. Milstein, *Biochemistry*, **6**, 2901 (1967).

(18) J. B. Milstein and T. H. Fife, *ibid.*, **8**, 623 (1969).

"best" single-variable equation is that in eq 13. The "best" two-variable equation is eq 14, which is quite significantly better than eq 13 ($F_{1,10} = 41$). The overall significance of eq 14 is high ($F_{2,10} = 33$; $F_{2,10\ \alpha.005} = 9.4$). It is interesting and logical that apolar forces have no influence on pK_1''. Adding terms in π or P_E to eq 14 does not result in improved correlation. The steric effect of the substituent on pK_1'' is qualitatively the same as for k_3, only much smaller in magnitude. The electronic effect is in the opposite direction.

As with k_3, a different story results from the analysis of molecules 15–18 of Table I. This is summarized in eq 15 and 16. Although a good correlation in terms of

$$pK_1'' = -0.28(\pm 0.29)E_s + 7.33(\pm 0.23) \quad (15)$$
$$n = 4;\ r = 0.945;\ s = 0.109$$

$$pK_1'' = -0.45(\pm 0.65)E_s + 0.65(\pm 2.2)\sigma^* + 7.23(\pm 0.41) \quad (16)$$
$$n = 4;\ r = 0.996;\ s = 0.002$$

r, eq 15 is not statistically significant ($F_{1,2} = 2.1$; $F_{1,2\ \alpha.1} = 8.5$). However, eq 16 is significant ($F_{2,1} = 69.6$; $F_{2,1\ \alpha.1} = 49.5$). Even though shown to be significant by the F test, very little confidence can be placed in eq 16 because of the few data points. It is simply of interest to note that it is quite different from eq 4.

Compound 14 was not included in deriving any of the above equations. The values predicted by eq 4 and 14 are wide of the mark. This is to be expected, since there are at least seven known examples[6] where a break in the structure–activity relationship of chymotrypsin substrates and inhibitors occurs when π for the side chain is 3.50 or greater. Compound 14 is yet another such example.

The type of derivatives selected by Dupaix, *et al.*,[3] in Table I constitute by far the best set yet studied from the point of view of the physical organic chemist trying to separate substituent effects. Their work, when taken with that of Fife and Milstein, clearly shows that apolar forces are important in the k_3 step.

Acknowledgment.—I wish to thank Professor Neal Cornell for suggesting the present study and for helpful discussions. I also thank Professor T. H. Fife for an enlightening discussion.

Clarification of the Acid-Catalyzed Reaction of Glyoxal with Carbamate Esters

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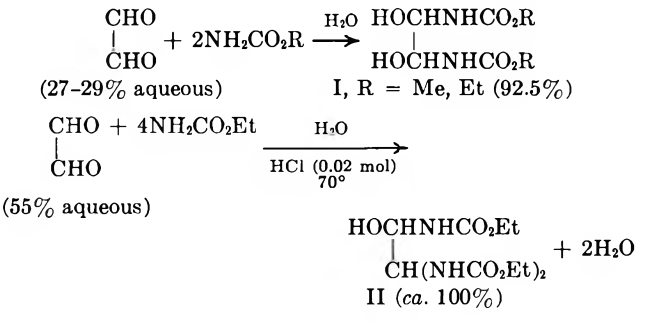
Received May 21, 1971

The reaction of glyoxal with ethyl carbamate in the presence of concentrated hydrochloric acid gives 1,1,2,2-tetra(carbethoxyamino)ethane (VI), in contrast with the reports of Pauly and Sauter and Gaylord who claimed that the reaction product was glyoxal bis(carbethoxyimide) (III). The mechanism of formation of the tetracarbamate (VI) is discussed, and it is shown that certain parallels exist between the reactions of glyoxal with carbamate esters and with primary amines.

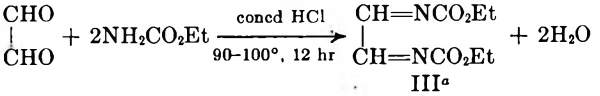
The reaction of glyoxal with carbamate esters yields a variety of products depending on the acidity or basicity of the reaction medium. For example,[1] treatment of neutralized glyoxal with carbamate esters (1:2 molar ratio) is reported to give 1,2-di(carbalkoxyamino)-ethane-1,2-diol (I), whereas in the presence of dilute acid the reaction with ethyl carbamate gives 1,2,2-tri-(carbethoxyamino)ethanol (II) (Scheme I, % yields in parentheses).

SCHEME I



There is some doubt, however, as to the structure of the product formed in stronger acid solution. The reaction of glyoxal with ethyl carbamate in the presence of concentrated hydrochloric acid was investigated first by Pauly and Sauter[2] who reported that the product was an insoluble, microcrystalline powder; the structure assigned was that of glyoxal bis(carbethoxyimide) (III) (Scheme II). No melting point was reported for the

SCHEME II



III[a]

[a] *Anal.* Calcd for $C_8H_{12}N_2O_4$: C, 47.99; H, 6.04; N, 13.99. Found: C, 47.74; H, 6.4; N, 14.07.

product, but the microanalysis was correct for the assigned structure.

A similar result was reported by Gleim[3] who examined the reaction of glyoxal with allyl carbamate in the presence of concentrated hydrochloric acid. The reaction product was claimed to be glyoxal bis(carballyloxyimide) (IV); however, the microanalysis was not in good agreement with this structure (Scheme III).

For some obscure reason, the abstract literature[4] subsequently referred to compound III as "carbamic acid, *N,N'* acetylene bis-, diethyl ester," $EtO_2CNHC{\equiv}CNHCO_2Et$ (V), and this prompted Gaylord[5] to re-

(1) British Patent 801,991 (B.A.S.F.); *Chem. Abstr.*, **53**, 7019*a* (1959).

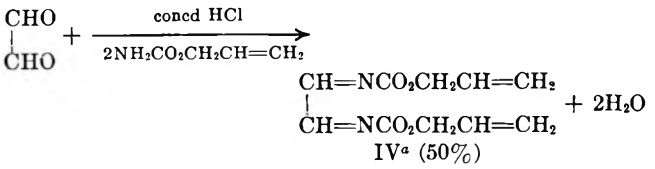
(2) H. Pauly and H. Sauter, *Chem. Ber.*, **63**, 2063 (1930).

(3) C. E. Gleim, *J. Amer. Chem. Soc.*, **76**, 107 (1954).

(4) Subject Index, *Chem. Abstr.*, 3rd Decennial Index, 1927–1936.

(5) N. G. Gaylord, *J. Org. Chem.*, **20**, 547 (1955).

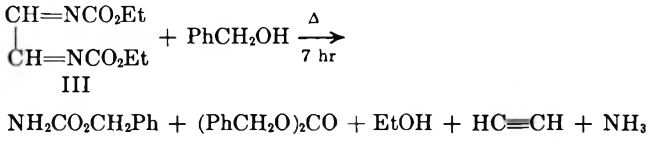
SCHEME III



[a] *Anal.* Calcd for $C_{10}H_{12}N_2O_4$: N, 12.50. Found: N, 10.92.

examine the work of Pauly and Sauter. The reaction of 30% aqueous glyoxal (1 mol), ethyl carbamate (2 mol), and concentrated hydrochloric acid (1.5 mol) at 90–100° for 12 hr was found to give a white solid, mp 286–287°, in 49% yield.[6] The product was insoluble in water, ethanol, ethyl acetate, dioxane, and hexane. The structure of the white solid was concluded to be III, apparently confirming the earlier findings of Pauly and Sauter, on the basis of the ir spectrum which indicated the absence of an acetylenic linkage, the nitrogen analysis (Found: N, 14.26.), and the products obtained on treatment of III with benzyl alcohol (Scheme IV).

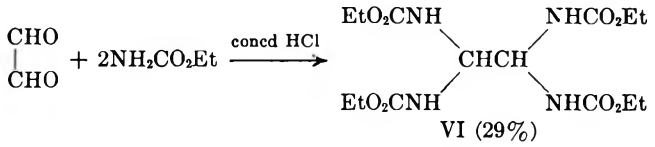
SCHEME IV



$$NH_2CO_2CH_2Ph + (PhCH_2O)_2CO + EtOH + HC{\equiv}CH + NH_3$$

We have repeated the preparation of the white solid according to the method of Gaylord, and we have ascertained that the structure assigned both by Pauly and Sauter and by Gaylord is incorrect. The identity of the white solid, deduced primarily from the mass spectrum, is 1,1,2,2-tetra(carbethoxyamino)ethane (VI) (Scheme V, % yield in parentheses).

SCHEME V



The tetracarbamate VI, mp 286–287° dec (from nitromethane), is insoluble in a wide range of solvents, in accord with Gaylord's observations. The ir spectrum has ν max 3292 (NH stretch) and 1698 cm^{-1} (C=O stretch), which supports the assignment of structure VI but does not uniquely define it. It should be noted that in symmetrical disubstituted acetylenes, the C≡C absorption is often too weak to be detectable[7] and thus the absence of an absorption band in the 2190–2260-cm^{-1} region cannot be cited as evidence against structure V. The nmr spectrum (in DMSO-d_6 at 90°) is in agreement with structure VI, and our microanalysis is in accord also (*Anal.* Calcd for $C_{14}H_{26}N_4O_8$: C, 44.44; H, 6.93; N, 14.80. Found: C, 44.68; H, 6.88; N, 14.94.). Structure III requires N, 13.99%, and it is apparent that the microanalysis reported by Gaylord[5] is inadequate for characterization since a nitrogen analysis of, say, 14.4% could be considered more or less acceptable for either III or VI; clearly a C, H, and N analysis is a minimal requirement in this case.

The key evidence we employed in the elucidation of the structure was derived from the chemical ionization and electron impact mass spectra. The significant features of the mass spectra are shown in Scheme VI (ra = relative abundance; the molecular formula of each fragment was established by exact mass measurement).

The chemical ionization (CI) spectrum with methane shows a quasimolecular ion, QM (M + 1), at *m/e* 379. This is consistent with structure VI and conclusively eliminates structures III and V since the latter two would be expected to show a quasimolecular ion at a much lower *m/e* value. The electron impact spectrum confirms the structure as the tetracarbamate VI; loss of $NHCO_2Et\cdot$ from the molecular ion gives the fragment at *m/e* 290 which then eliminates ethanol affording the ion at *m/e* 244. The major fragmentation pathway is cleavage at the central C–C bond to yield the ion at *m/e* 189 (base peak); the subsequent loss of ethanol and of ($CO_2 + C_2H_4$) is diagnostic of the carbamate function.[8] The spectrum of the tetracarbamate VI below *m/e* 189 bears a striking resemblance to the spectrum of the structurally related 1,1-di(carbethoxyamino)ethane[9] (VII) (Scheme VII).

The tetracarbamate VI is soluble in hot dimethylformamide and hot DMSO. Attempted tlc, glc, and molecular weight determination (Rast method) were unsuccessful. An independent synthesis of the tetracarbamate VI has been reported by Curtius[10] *via* a rearrangement of ethanetetracarboxylic acid tetrahydrazide (Scheme VIII, % yield in parentheses). However, the product isolated has mp 268° and was soluble in ethanol and in ether, in contrast with our own observations.

The reactions of monoaldehydes with carbamate esters are similar in some respects to the reactions of glyoxal.[11] For example, formaldehyde and ethyl carbamate in the presence of a trace amount of base give ethyl *N*-(hydroxymethyl)carbamate,[12] while in acid solution dicarbamates are formed (Scheme IX, % yields in parentheses).

In contrast, when the aldehyde contains an electron-withdrawing group α to the carbonyl function, the reaction with carbamate esters in the presence of a trace of concentrated sulfuric acid gives *N*-(1-hydroxyalkyl)carbamates[13] (VIII) (Scheme X).

There are two possible pathways which can be envisaged for the acid-catalyzed reaction of aldehydes with carbamate esters (Scheme XI). The first step of the reaction is protonation of the carbonyl group followed by nucleophilic attack of the carbamate ester to give the secondary alcohol VIII; this is the typical acid-catalyzed nucleophilic addition reaction of an aldehyde. In pathway A, protonation of the alcohol followed by loss of water yields the intermediate

(6) The reported yield of 49% was calculated on the basis of the incorrect structure III, although from the figures reported we calculate the yield to be 58%; on the basis of structure VI the yield is 61%.

(7) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Wiley, New York, N. Y., 1966, Chapter 4.

(8) H. Budzikiewicz, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967.

(9) W. M. Kraft and R. M. Herbst, *J. Org. Chem.*, **10**, 483 (1945).

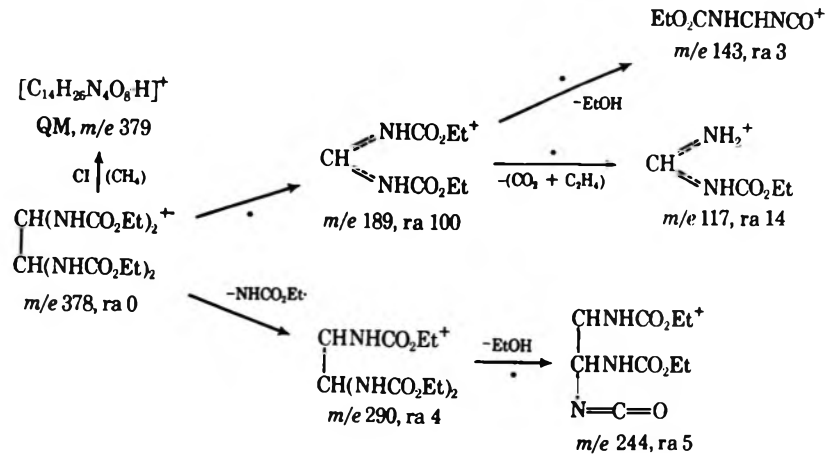
(10) Th. Curtius, *J. Prakt. Chem.*, **94**, 367 (1916).

(11) P. Adams and F. A. Baron, *Chem. Rev.*, **65**, 567 (1967).

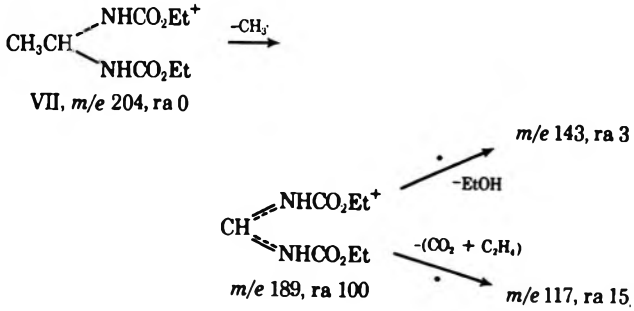
(12) A. Einhorn, *Justus Liebigs Ann. Chem.*, **361**, 113 (1908).

(13) G. Vasilev, *Farmatsiya (Sofia)*, **13**, 40 (1963); *Chem. Abstr.*, **60**, 5378*b* (1964).

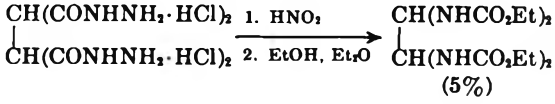
SCHEME VI



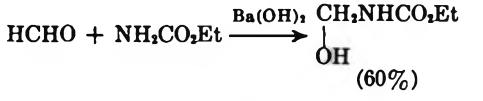
SCHEME VII

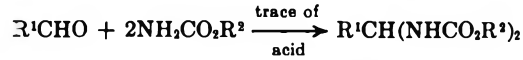


SCHEME VIII



SCHEME IX

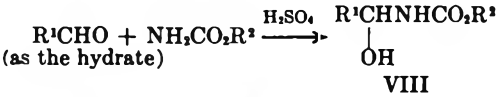




R^1 = H; R^2 = Et (80%)[a]
R^1 = Me; R^2 = *n*-Pr (86%)[a]

[a] M. Conrad and H. Hock, *Chem. Ber.*, **36**, 2206 (1903).

SCHEME X



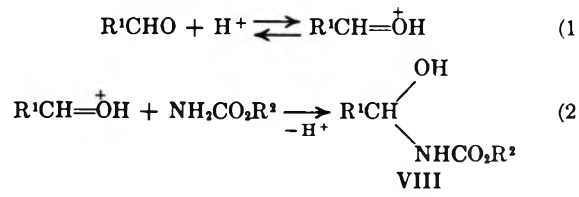
R^1 = Br_3C; R^2 = Me, *n*-Pr, *n*-Bu
R^1 = Cl_3C; R^2 = *i*-Pr, *n*-Bu, *tert*-Bu
R^1 = MeCHClCCl$_2$; R^2 = Me, *n*-Pr, *n*-Bu

carbonium ion, which undergoes nucleophilic attack by the carbamate ester to give the dicarbamate (SN1 process). In pathway B, loss of water from the secondary alcohol VIII gives the imine, which then participates in a Michael-type addition reaction with the carbamate ester to yield the dicarbamate. The formation of the intermediate imine is analogous to the preparation of hydrazone derivatives of aldehydes.

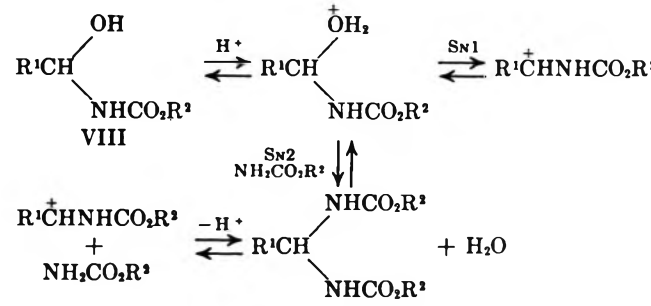
When R^1 contains electron-withdrawing groups, such as Cl_3C– and Br_3C–, the reaction leads to the formation of the secondary alcohol VIII in the presence of trace amounts of acid (Scheme X). It seems likely that further reaction to the dicarbamate is inhibited because the electron-withdrawing effect of the R^1 group destabilizes the transition state leading to the intermediate carbonium ion (Scheme XI, pathway A, SN1 process). However, in the presence of larger amounts of concentrated acid, formation of the dicarbamate could occur *via* an SN2 process directly from protonated VIII.

In the case of glyoxal (Scheme XI, R^1 = CHO), the reaction with carbamate esters in the presence of traces of acid gives the tricarbamate (Scheme I), and, as we have shown, in stronger acid solution the tetracarbamate is formed (Scheme V). It is clear that formation of the tetracarbamate requires more vigorous reaction conditions, and this may be rationalized by considering

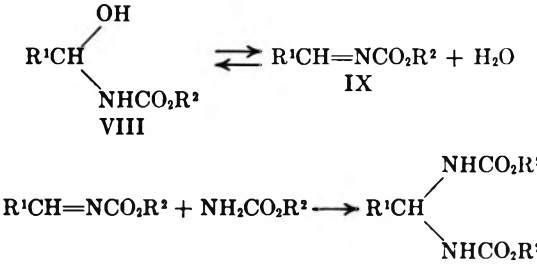
SCHEME XI



Pathway A

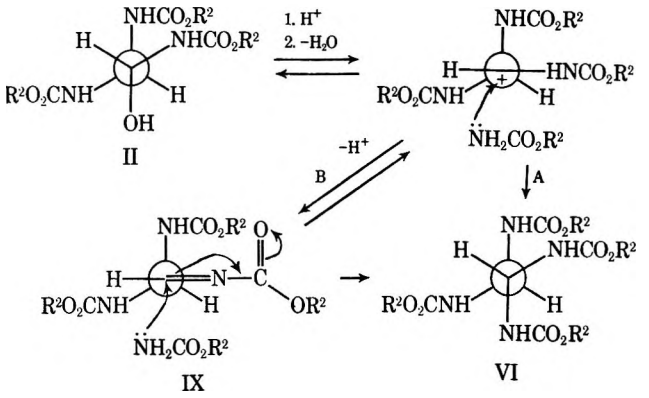


Pathway B, acid-catalyzed dehydration and Michael-type addition



the intermediates involved in either pathway A or pathway B (Scheme XII). In the case of acid-catalyzed glyoxal reactions, steric factors appear to be more important than electronic factors in determining the final outcome of the reaction. The tricarbamate II, formed by an analogous sequence of steps to that in Scheme XI has two gauche interactions in its most stable conformation. Protonation of the alcohol function followed by loss of water results in a slight decrease of steric compression in the molecule due to the planarity of the intermediate carbonium ion. If subsequent reaction proceeds *via* pathway B, proton loss affords the intermediate imine IX which then undergoes Michael addition of carbamate ester to give the tetracarbamate VI. If reaction proceeds *via* pathway A, nucleophilic attack of the carbamate ester on the carbonium ion occurs from the less hindered side (as shown) to give VI. VI is a less stable molecule than the starting alcohol II since (a) the steric compression in the tetracarbamate is higher and (b) the stabilization due to intramolecular hydrogen bonding is smaller. Accordingly, the conversion of the tricarbamate II into the tetracarbamate VI *via* pathway A or B will involve a significant energy of activation.

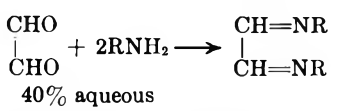
SCHEME XII



The reaction of glyoxal with aliphatic primary amines in the absence of added acid or base gives conjugated diimines[14] (Scheme XIII, % yields in parentheses), while with aromatic primary amines a variety of products are formed[15] (Scheme XIV). In the latter case, the molar ratios and the nature and position of the ring substituents appear to be the main factors in determining the structure of the product. The tentative reaction pathway put forward (Scheme XV) is similar in some respects to the rationalization proposed by us for the acid-catalyzed reactions.

SCHEME XIII

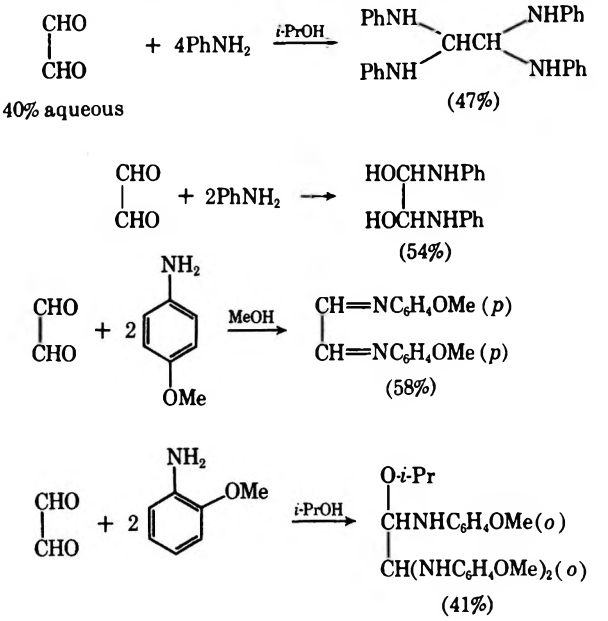
REACTION OF GLYOXAL WITH ALIPHATIC PRIMARY AMINES[14]



R = cyclohexyl (95%), *i*-Pr (77%), *n*-Bu (18%), *i*-Bu (26%), *tert*-Bu (63%)

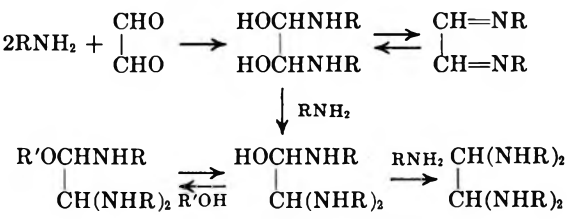
SCHEME XIV

REACTION OF GLYOXAL WITH AROMATIC PRIMARY AMINES[15]



SCHEME XV

TENTATIVE REACTION PATHWAY[15]



Experimental Section

Ir spectra were obtained with a Perkin-Elmer 225 grating infrared spectrophotometer, and nmr spectra were taken using a 100-MHZ JEOL spectrometer. Chemical ionization mass spectra were measured using a quadrupole mass spectrometer, and electron impact spectra were obtained with an AEI MS-902 instrument (source temperature 200°, ionizing voltage 70 eV). Melting points are uncorrected.

The mass spectral data are presented in the following format: *m/e* value (relative abundance), origin of the fragment, molecular formula (difference in parts per million (ppm) between the calculated and observed mass). Metastable peaks, $M_1 \rightarrow M_2$ (observed position of metastable peak).

Preparation of 1,1,2,2-Tetra(carbethoxyamino)ethane (VI).—A mixture of ethyl carbamate (17.8 g, 0.20 mol, mp 48–50°), 30% w/w aqueous glyoxal (19.3 g, 0.10 mol), and concentrated hydrochloric acid (16.1 g, 0.05 mol, sp gr 1.19) was heated on a steam bath for 12 hr. The solid product was collected by filtration, washed with water (six 50-ml portions), triturated with acetone (two 150-ml portions), and dried *in vacuo* to give the crude tetracarbamate (5.62 g, mp 274–276° dec, 30%) a portion of which (0.665 g) was crystallized from hot nitromethane to yield pure VI (0.628 g, mp 286–287° dec, overall yield 29%), a white solid.

The crystallized product was insoluble in water, acetone, hexane, ethanol, ether, chloroform, triethyl phosphate, and hexamethylphosphoramide, slightly soluble in hot nitromethane, and moderately soluble in hot dimethylformamide and hot DMSO.

Variations in Preparative Method.—When 40% aqueous glyoxal was used (molar ratios as above) the yield of VI was significantly higher (crude yield 64%, recrystallized 58%). When the reaction mixture was stirred, considerable frothing and charring was observed, and the yield was considerably lower (crude yield 28%, using 40% aqueous glyoxal).

The spectroscopic characteristics of the recrystallized tetracarbamate are as follows.

(14) J. M. Kliegman and R. K. Barnes, *Tetrahedron*, **26**, 2555 (1970).
(15) J. M. Kliegman and R. K. Barnes, *J. Org. Chem.*, **35**, 3140 (1970).

Ir spectrum (KBr disk): ν max 3292 (s) (NH stretching vibration due to $RNHCO_2R'$), 2975 (m) (CH stretching vibration), 1698 (s) (C=O stretch in $RNHCO_2R'$), 1549, 1524 (s) (NH bend, amide II band), 1478 (m) (CH asymmetrical deformation), 1370 (m) (CH symmetrical deformation), 1332 (m), 1295 (s) (unassigned), 1241, 1030 (s) (CO stretching vibration), 881 (w), 783 (w) (unassigned), 674 cm^{-1} (m) (NH o.o.p. deformation). The spectrum was identical with that reported[16] for "acetylenedicarbamic acid, diethyl ester."

Nmr spectrum (DMSO-d_6 at 90°): δ 6.64 (d*, 2.8, J = 7 Hz, NH), 5.20 (t*, 1.9, J = 7.5 Hz, $CH(NHCO_2Et)_2$), 3.99 (q, 7.8, J = 7.5 Hz, $NHCO_2CH_2CH_3$), 1.15 (t, 12.0, J = 7.5 Hz, $NHCO_2CH_2CH_3$). (Asterisk indicates broad signals with further splitting present.)

Electron impact mass spectrum (direct insertion at 200°): molecular ion absent; m/e 290 (4), M − $NHCO_2Et$, $C_{11}H_{20}N_2O_6$ (4.6 ppm); 244 (5), m/e 290 − EtOH, $C_9H_{14}N_2O_5$ (3.4 ppm); 202 (0.4), m/e 290 − $NHCO_2Et$, $C_8H_{14}N_2O_4$ (1.9 ppm); 201 (0.9), m/e 244 − NHCO, $C_8H_{13}N_2O_4$ (1.9 ppm); 198 (0.3), m/e 244 − EtOH, $C_7H_8N_2O_4$ (0.4 ppm); 189 (100), M − $CH(NHCO_2Et)_2$, $C_7H_{13}N_2O_4$ (3.6 ppm); 172 (1), m/e 244 − (CO_2 + C_2H_4), $C_6H_{10}N_2O_3$ (2.0 ppm); 161 (1.5), m/e 189 − C_2H_4, $C_5H_9N_2O_4$ (10.9 ppm); 143 (3), m/e 189 − EtOH, $C_5H_7N_2O_3$ (5.3 ppm); 117 (14), m/e 189 − (CO_2 + C_2H_4), $C_4H_9N_2O_2$ (11.6 ppm); 102 (4), m/e 117 − NH, $C_4H_8NO_2$ (5.0 ppm); 90 (1), m/e 117 − HCN, $C_3H_8NO_2$ (11.3 ppm); 89 (9), m/e 117 − C_2H_4, $C_2H_5N_2O_2$ (7.0 ppm); 62 (3), m/e 90 − C_2H_4, CH_4NO_2 (101 ppm). Metastable peaks: 378 → 189 (94.5); 290 → 244 (205.3); 290 → 172 (102.1); 244 → 198 (160.8); 244 → 172 (121.2); 189 → 161 (137.1); 189 → 143 (108.1); 189 → 117 (72.5); 117 → 89 (67.75).

Anal. Calcd for $C_{14}H_{26}N_4O_8$: C, 44.44; H, 6.93; N, 14.80. Found: C, 44.68; H, 6.88; N, 14.94.

1,1-Di(carbethoxyamino)ethane.[9]—The relevant portion of the electron impact mass spectrum is given below (direct insertion at 100°): molecular ion absent; m/e 203 (0.5), M − H, $C_8H_{15}N_2O_4$ (4.9 ppm); 189 (100), M − CH_2, $C_7H_{13}N_2O_4$ (3.8 ppm); 143 (3), m/e 189 − EtOH, $C_5H_7N_2O_3$ (6.5 ppm); 117 (15), m/e 189 − (CO_2 + C_2H_4), $C_4H_9N_2O_2$ (26.5 ppm); 90 (4), m/e 117 − HCN, $C_3H_8NO_2$ (3.0 ppm); 89 (10), m/e 117 − C_2H_4, $C_2H_5N_2O_2$ (1.3 ppm); 62 (13), m/e 90 − C_2H_4, CH_4NO_2 (35.8 ppm).

(16) "Sadtler Standard Spectra," No. 13888, Sadtler Research Laboratories Inc., Philadelphia, Pa., 1962.

Registry No.—VI, 17350-57-1; glyoxal, 107-22-2; ethyl carbamate, 51-79-6; 1,1-di(carbethoxyamino)-ethane, 539-71-9.

Acknowledgment.—The authors thank Dr. Rodger Foltz (Battelle Memorial Institute) for running the mass spectra. This work was supported in part by the U. S. Public Health Service under Grants CA-07803, CA-07174, and CA-10439 of the National Cancer Institute.

The Chemistry of Sulfonyl Isocyanates. VIII. Kinetics of the Reaction with Hindered Phenols

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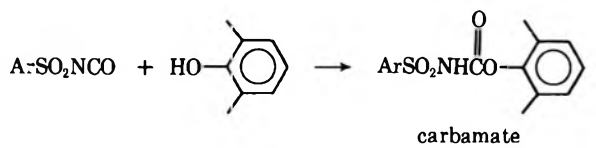
Received January 5, 1971

4-Chlorobenzenesulfonyl isocyanate (I) and 4-toluenesulfonyl isocyanate (II) reacted with 2,6-disubstituted and 2,4,6-trisubstituted phenols. The products were highly crystalline carbamates. Kinetic studies showed the reactions to be second order, first order in isocyanate and first order in phenol. The relative rates of reaction of the phenols were 2,6-diisopropyl- > 2,6-dimethyl- > 2,6-dibromo- > 2,4,6-tri-*tert*-butyl- > 2,6-di-*tert*-butyl- > 2,4,6-tribromo-. Isocyanate I was found to be somewhat more reactive than II.

Billeter first showed that benzenesulfonyl isocyanate reacts with phenol and reported the product to be carbamate.[2] It was shown in this laboratory that benzenesulfonyl isocyanate also reacts with 2,6-disubstituted, as well as other substituted, phenols to give crystalline solid derivatives.[3] The products were shown to be carbamates rather than para-substituted amides of phenols.



carbamate

More recently the kinetics of the reactions of hindered triarylcarbinols with sulfonyl isocyanates have been explored.[4-7] These reactions were found to be first order in alcohol and first order in isocyanate. Although the reaction products were in most cases not carbamates such intermediates could not be ruled out.[7]

This paper shows the kinetic results obtained from the reactions of 4-chlorobenzenesulfonyl isocyanate (I) and 4-toluenesulfonyl isocyanate (II) with 2,6-disubstituted phenols.

Experimental Section

Reagents.—4-Chlorobenzenesulfonyl isocyanate (I) and 4-toluenesulfonyl isocyanate (II) were obtained from the Upjohn Co., Carwin Organic Chemicals, and used without further purification. The phenols were commercial products which were redistilled or recrystallized before use. Toluene solvent was reagent grade and dried over sodium metal or molecular sieves. The di-*n*-butylamine was Eastman White Label grade reagent.

Kinetics.—The method used for measuring the concentration of isocyanate in the reaction mixture at various times was that already reported.[7] Second-order kinetics were followed with each of the phenols used from 4:1 to 1:4 isocyanate–phenol ratios. When 1:1 ratios of isocyanate–phenol were employed, plots of $1/(C - C_\infty)$ *vs.* time gave straight lines over at least 2 half-lives. For reactions in which initial isocyanate–phenol ratios were not unity, plots of log $[b(a - x)/a(b - x)]$ *vs.* time were linear.

Isolation of Products.—The products were removed from the reaction mixture (toluene solvent) by cooling to about 25° and adding 1 vol of petroleum ether (bp 60–70°). In most cases this procedure effected quantitative precipitation of the carbamate. When quantitative separation was not realized, the toluene–

(1) Taken in part from the M.A. thesis of S. P. G., DePauw University, 1969.

(2) O. C. Billeter, *Ber.*, **37**, 690 (1904).

(3) J. W. McFarland and J. B. Howard, *J. Org. Chem.*, **30**, 957 (1965).

(4) J. W. McFarland, D. E. Lenz, and D. J. Grosse, *ibid.*, **31**, 3798 (1966).

(5) J. W. McFarland, D. E. Lenz, and D. J. Grosse, *ibid.*, **33**, 3514 (1968).

(6) J. W. McFarland, D. Green, and W. Hubble, *ibid.*, **35** 702 (1970).

(7) J. W. McFarland and D. J. Thoennes, *ibid.*, **35**, 704 (1970).

petroleum ether solvent mixture was removed under vacuum and the residue recrystallized from petroleum ether.

As a typical example, I and 2,6-dimethylphenol gave 2,6-dimethylphenyl *N*-(4-chlorobenzenesulfonyl)carbamate (III), yield 95%, mp 156–157°.

Anal. Calcd for $C_{15}H_{14}NO_4SCl$: C, 53.20; H, 4.15; N, 4.12; S, 9.44; Cl, 10.43. Found: C, 53.01; H, 4.11; N, 4.34; S, 9.29; Cl, 10.54.

Results

4-Chlorobenzenesulfonyl isocyanate (I) reacted with all of the substituted phenols studied, including alkylated and brominated phenols at 85 and 100° (Table I).

Table I

Reaction of 4-Chlorobenzenesulfonyl Isocyanate (I) with Phenols

Phenol	Registry no.	Temp, °C	k, l. mol^{-1} min^{-1}
2,6-Diisopropyl	2078-54-8	85	2.25 ± 0.10
		100	3.70 ± 0.10
2,6-Dimethyl	576-26-1	85	1.03 ± 0.03
		100	2.32 ± 0.09
2,6-Dibromo	608-33-3	85	0.27 ± 0.03
		100	0.41 ± 0.03
2,4,6-Tri-*tert*-butyl	732-26-3	85	0.17 ± 0.02
		100	0.35 ± 0.02
2,6-Di-*tert*-butyl	128-39-2	85	0.08 ± 0.01
		100	0.19 ± 0.02
2,4,6-Tribromo	118-79-6	85	0.08 ± 0.01
		100	0.09 ± 0.01

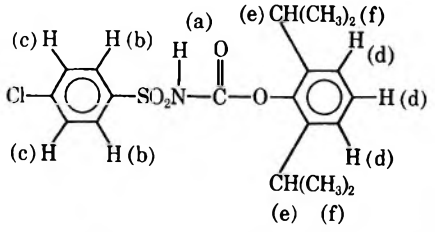
Likewise, 4-toluenesulfonyl isocyanate (II) reacted with the alkylated phenols at 100° (Table II). In all

Table II

Reaction of 4-Toluenesulfonyl Isocyanate (II) with Phenols at 100°

Phenol	k, l. mol^{-1} min^{-1}
2,6-Diisopropyl	1.44 ± 0.05
2,6-Dimethyl	1.29 ± 0.04
2,4,6-Tri-*tert*-butyl	0.019 ± 0.001
2,6-Di-*tert*-butyl	0.017 ± 0.001

cases the products were the carbamates and not the phenolic amides. Evidence for the carbamate structure came largely from nmr. The product from I and 2,6-diisopropylphenol was assigned structure IV on the basis of the nmr absorption peaks. Alternative struc-

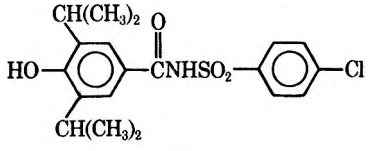


2,6-diisopropylphenyl *N*-(4-chlorobenzenesulfonyl)-carbamate (IV)

(a) singlet at τ 1.40, 1 H
(b) doublet at τ 1.86, 2 H
(c) doublet at τ 2.38, 2 H
(d) singlet (unresolved) at τ 2.80, 3 H
(e) septet at τ 7.26, 2 H
(f) doublet at τ 8.85, 12 H

ture V would give a very different spectrum. Studies with many 2,6-disubstituted phenols indicate that the phenolic hydrogen absorbs in the τ 4–6 range.

All of the reactions of sulfonyl isocyanates with the hindered phenols followed second-order kinetics, first



V

order in isocyanate and first order in phenol. The rate constants, k, were sensitive to the nature of the phenolic substituents. The alkylated phenols showed the following order of reactivity toward each of the sulfonyl isocyanates: 2,6-diisopropyl > 2,6-dimethyl > 2,4,6-tri-*tert*-butyl $\gtrless$ 2,6-di-*tert*-butyl. The 2,6-dibromophenol was slightly more reactive than 2,6-di-*tert*-butylphenol. On the other hand, 2,4,6-tribromophenol was less reactive than 2,4,6-tri-*tert*-butylphenol (see Discussion).

The yields of carbamates were almost quantitative. The products were highly crystalline and were usually purified by recrystallizing from petroleum ether (Table III).

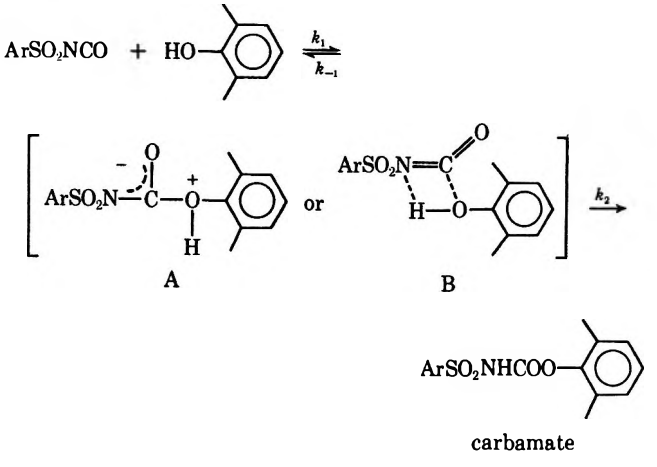
Table III

Products from Sulfonyl Isocyanates and Phenols

Sulfonyl isocyanate	Phenol	Mp of product, °C	Registry no.
4-Chlorobenzene	2,6-Dimethyl	156–157	
	2,6-Diisopropyl	129–131	
	2,6-Di-*tert*-butyl	149–150.5	31662-23-4
	2,6-Dibromo	127–128	31662-24-5
	2,4,6-Tri-*tert*-butyl	151–152	31593-67-6
	2,4,6-Tribromo	131–132	31662-25-6
4-Toluene	2,6-Dimethyl	160–162	31662-26-7
	2,6-Diisopropyl	162–163	31593-68-7
	2,6-Di-*tert*-butyl	95–107 (crude)	31593-69-8
	2,4,6-Tri-*tert*-butyl	110–115 (crude)	31953-70-1

Discussion

The first step in the reaction of sulfonyl isocyanate with phenol is most likely the formation of some sort of a complex[8] (which may be the transition state). A similar type of complex was postulated in the reaction of sulfonyl isocyanate with triarylcarbinols.[7] Different



from the triarylcarbinols, the phenols give carbamate products. This is understandable in view of the fact

(8) J. W. Baker and J. Gaunt, *J. Chem. Soc.*, **151**, 19 (1949).

that no stable arbonium ion can be obtained from the phenol such as can be from triarylcarbinols.

The relative rates of the reactions of the different phenols are consistent with the above postulated mechanism. Two factors must be considered in connection with the different substituents—the electronic and the steric factors. Any substituent in the ortho position would predictably hinder the approach of isocyanate to form the transition state. Phenol itself reacted very rapidly with the sulfonyl isocyanates, too fast in fact to obtain good kinetic data under the conditions of the reactions.

From the steric effects alone, it would be expected that the 2,6-dimethylphenol would be fastest reacting, followed by 2,6-diisopropyl-, and finally 2,6-di-*tert*-butylphenol.[9] Indeed, the di-*tert*-butylphenol is extremely slow. 2,6-Diisopropylphenol, however, consistently reacted at a faster rate than did 2,6-dimethylphenol under comparable conditions. The polar contributions of the ortho alkyl groups to the basicities of the phenols are, however, in the reverse order: *tert*-butyl > isopropyl > methyl.[10]

The most logical explanation for the results obtained, then, is that the polar effect of the isopropyl group is considerably stronger than that of the methyl group and more than compensates for any steric differences. In the case of the *o*-*tert*-butyl groups, however, the steric effect predominates.

That electronic effects are important is shown by the fact that 2,4,6-tri-*tert*-butylphenol is slightly more reactive toward each of the isocyanates than is 2,6-di-*tert*-butylphenol. The effect of the *p*-*tert*-butyl group is also shown by the fact that 2,4,6-tri-*tert*-butylphenol (pK_a = 12.19) is a weaker acid than 2,6-di-*tert*-butylphenol (pK_a = 11.70).[11] Placing a *tert*-butyl group in the para position should not produce additional steric effect. The electron-donating ability of the *tert*-butyl group does, however, help to stabilize the partial positive charge on phenol oxygen in the transition state.

Noteworthy is the slow reaction of either 2,6-dibromophenol or 2,4,6-tribromophenol. Since bromine has approximately the steric effect of a methyl group,[9] the electronic effect is very significant. Bromine is inductively electron withdrawing and should thereby destabilize the transition state. The presence of a bromine atom in the 4 position, where steric effects are negligible, lowers the reactivity even further. Our results are consistent with the finding that 4-bromo-2,6-dimethylphenol is a stronger acid than 2,6-dimethylphenol.[12]

An effort was made to separate the electronic and steric effects of the ortho substituents by using a Brønsted-type plot of literature[11-13] pK_a values of the phenols against the log of their rate constants (Figure 1). 2,6-Dimethylphenol and the 2,6-dibromophenols were plotted together since the steric effects are similar. The straight line through the points representing the 2,6-di-*tert*-butylphenols was parallel to that representing 2,6-dimethyl- and the bromophenols (Brønsted β = 0.546). Making the assumption that all groups with similar steric effects would fall on one straight line, the relative electronic and steric effects of the *o*-*tert*-butyl groups with respect to the *o*-methyl groups could be determined. The *tert*-butyl groups increased the electronic portion of the rate by 3.9 times but decreased the steric portion by 47.5 times.

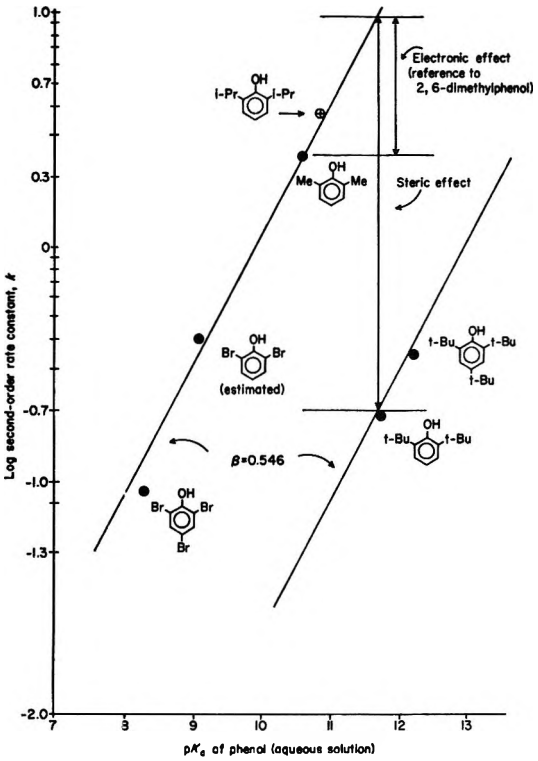


Figure 1.—Reaction of 4-chlorobenzenesulfonyl isocyanate with phenols at 100° in toluene.

Unfortunately, pK_a values for a series of 2,6-diisopropylphenols have not been reported in the literature. A value of approximately 11.0 for the pK_a of 2,6-diisopropylphenol itself was reported, although the value was determined in 20% aqueous ethanol,[14] whereas other pK_a values used herein were from aqueous solutions. The extent to which the value is reliable indicates that 2,6-diisopropylphenol falls roughly on the same line as 2,6-dimethylphenol and that the differences in their rates are mostly due to electronic effects. Models indicate that it is possible for the two methyl groups in the isopropyl group to rotate out of the way of an approaching isocyanate molecule. Further data are obviously desirable before conculsions may be drawn relative to the steric effect of the isopropyl group.

A comparison of the reactions of 4-chlorobenzenesulfonyl isocyanate (I) and 4-toluenesulfonyl isocyanate (II) with phenols shows that I is more reactive than II (Tables I and II). It was found before that II is slightly less reactive than is benzenesulfonyl isocyanate toward triarylcarbinols.[7] Apparently for both reactions there is a partial negative charge on nitrogen or carbon of the isocyanate in the transition state. A methyl group on the ring of the isocyanate destabilizes the negative charge while electron-withdrawing chlorine stabilizes it. These facts plus the substituent effects in the phenols

(9) R. W. Taft in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 601.

(10) Reference 9, p 591.

(11) L. A. Cohen and W. M. Jones, *J. Amer. Chem. Soc.*, **85**, 3397 (1963).

(12) A. Fischer, G. J. Leary, R. D. Topson, and J. Vaughan, *J. Chem. Soc. B*, 782 (1966).

(13) J. Pless, *Peptides, Proc. Eur. Symp., 5th, Oxford*, 69 (1962); *Chem. Abstr.*, **62**, 627*g* (1962).

(14) P. Demerseman, J. P. Lechartier, R. Reynard, A. Cheutin, R. Royer, and P. Rumpf, *Bull. Soc. Chim. Fr.*, 2559 (1963).

give evidence that transition state A is more probable than B.

Registry No.—I, 5769-15-3; II, 4083-64-1; III, 31593-65-4; IV, 31593-66-5.

Acknowledgment.—One of us (J. W. M.) was partially supported by the Petroleum Research Fund Grant 2571, administered by the American Chemical Society. For such support we are deeply grateful.

Asymmetric Synthesis of Diastereomeric Hydroxy Sulfides, Sulfoxides, and Sulfones by Condensation and Oxidation Reactions

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Received August 24, 1970

The oxidation of diastereomeric 2-thiophenoxy-1,2-diphenyl-1-ethanols to the corresponding sulfoxide–alcohols is shown to be dependent upon the configuration of the carbon bearing the hydroxyl group. Condensations of the lithium salts of phenyl benzyl sulfide, sulfoxide, and sulfone with benzaldehyde give predominately threo products. Crossover products and other evidence for epimerization were found in the sulfoxide condensation. Reduction of 2-phenylsulfinyl-1,2-diphenylethanone gives just one erythro sulfoxide. Evidence for configuration of sulfur and the pseudocontact shifts of the isomeric sulfoxides are briefly discussed.

Sulfoxide chemistry is characterized by a considerable number of relatively highly stereospecific reactions.[1-5] The present work is an inquiry into the stereospecificity of reactions which form the isomeric 2-phenylsulfinyl-1,2-diphenyl-1-ethanols (**4**–**7**), compared to reactions which form the corresponding sulfides **2** and **3** and the sulfones **8** and **9**. The compounds in question are shown in Scheme I in their preferred conformation at carbon.[6]

Condensation of phenyl benzyl sulfide (**10**) with benzaldehyde (**13**) gave a *ca.* 55% overall yield of the 2-thiophenoxy-1,2-diphenyl-1-ethanols of which 40% was the erythro isomer **3** and 60% was the threo isomer **2**.[7-9] This ratio of isomers was insensitive to reaction time. Isomer **2** could also be prepared by reaction of thiophenoxide with cis-stilbene oxide, which proved its threo configuration. Similarly, **3** was formed by reaction of thiophenoxide with *trans*-stilbene oxide.

Condensation of phenyl benzyl sulfoxide (**11**) with **13** gave a mixture of the four sulfoxide–alcohols in *ca.* 40% overall yield. When the reaction was worked up immediately, the following relative yields were observed: 41% **4**, 19% **5**, 8% **6**, and 32% **7**. Reactions using several other aldehydes were similar, showing low yields of the isomers analogous to **5** and **6**. When the reaction was allowed to stir for *ca.* 10 hr before work-up, the isolated products were observed to be significantly richer in the threo isomer **5**: 34% **4**, 29% **5**, 6% **6**, and 31% **7**. A crossover experiment was attempted in which *p*-chlorobenzaldehyde was added to the final reaction mixture of **11** and **13**. Two crossover products (the *p*-chlorophenyl analogs of **4** and **7**) were isolated, which suggests that the mechanism of the epimerization may be a decondensation–recondensation sequence, similar to that found for the Darzens condensation.[10]

The initial product ratio was somewhat richer in the two sulfoxide–alcohols, **4** and **7**, which exhibit substantial intramolecular hydrogen bonding through a six-membered ring. The transition state for the formation of **4** and **7** also very likely involves a six-membered ring, in which a lithium cation is chelated by two oxygen groups (Figure 1). Similar transition states involving highly coordinating cations have been postulated for the Ivanov reaction[7b] and certain carboxylation reactions.[11,12]

Reaction of phenyl benzyl sulfone (**12**) and **13** was the least successful of the condensations, as frequent failure of the reaction occurred. In most successful runs, a *ca.* 59% overall yield was observed, of which 77% was the threo product, **8**, and 23% was the erythro product, **9**.[13] Thus, each condensation gave more of the threo isomer(s), which probably reflects the stability of this isomer,[7c] and the semiequilibrating nature of the reaction.

Oxidation of the cyclic sulfide, penicillin to its sulfoxide has been reported to give predominately one

(1) This field has been reviewed by C. R. Johnson and J. C. Sharp, *Quart. Rev. Sulfur Chem.*, **4**, 4 (1969).

(2) T. Durst, *J. Amer. Chem. Soc.*, **91**, 1034 (1969).

(3) (a) D. J. Abbott, S. Colonna, C. Stirling, *Chem. Commun.*, 471, 472 (1971); (b) J. Coxon, M. Hartshorn, G. Little, and S. Maister, *ibid.*, 271 (1971).

(4) E. V. Bell and G. M. Bennett, *J. Chem. Soc.*, 86 (1928).

(5) C. R. Johnson and D. McCants, Jr., *J. Amer. Chem. Soc.*, **87**, 1109 (1965).

(6) A previous paper has covered the conformational studies: C. Kingsbury and R. Auerbach, *J. Org. Chem.*, **36**, 1737 (1971).

(7) The stereochemistry of various condensation reactions has been investigated in older work: (a) H. E. Zimmerman and L. Ahramjian, *J. Amer. Chem. Soc.*, **81**, 2086 (1959); (b) H. E. Zimmerman and M. D. Traxler, *ibid.*, **79**, 1920 (1957); (c) H. E. Zimmerman, L. Singer, and B. Thyagaryan, *ibid.*, **81**, 108 (1959); (d) M. Stiles. R. Winkler, Y. Chang, and L. Traynor, *ibid.*, **86**, 3337 (1964); (e) A. T. Nielsen, *J. Org. Chem.*, **30**, 3650 (1965); (f) A. Wettstein, K. Hensler, H. Ueberwasser, and P. Wieland, *Helv. Chim. Acta*, **40**, 323 (1957); (g) P. Rabe, *Justus Liebigs Ann. Chem.*, **313**, 129 (1900), and related papers; (h) O. Widman, *Chem. Ber.*, **51**, 533 (1918); (i) E. P. Kohler and C. Allen, *J. Amer. Chem. Soc.*, **46**, 1522 (1924), and many related papers; (j) R. A. Abramovitch and J. Muchowski, *Can. J. Chem.*, **38**, 554 (1960); (k) I. Iwai and J. Ide, *Chem. Pharm. Bull.*, **13**, 663 (1965); (l) W. S. Fones, *J. Org. Chem.*, **17**, 1534 (1952).

(8) The earliest example of this type of reaction is (a) E. Fromm and E. Erfurt, *Chem. Ber.*, **42**, 3823 (1909); **41**, 3397 (1909).

(9) For other work on condensations involving sulfinyl anions, see (a) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **86**, 1639 (1964); (b) *ibid.*, **87**, 1345 (1965); (c) G. A. Russell and G. J. Mikol, *ibid.*, **88**, 5498 (1966); (d) G. A. Russell, E. T. Sabourin, and G. J. Mikol, *J. Org. Chem.*, **31**, 2854 (1966); G. A. Russell and H.-D. Becker, *J. Amer. Chem. Soc.*, **85**, 3406 (1963); (e) T. J. Wallace, H. Pobiner, J. Hoffman, and A. Schriesheim, *Proc. Chem. Soc.*, 137 (1963); L. Field, *J. Amer. Chem. Soc.*, **74**, 3919 (1952); (f) W. E. Truce and K. R. Buser, *ibid.*, **76**, 3577 (1954).

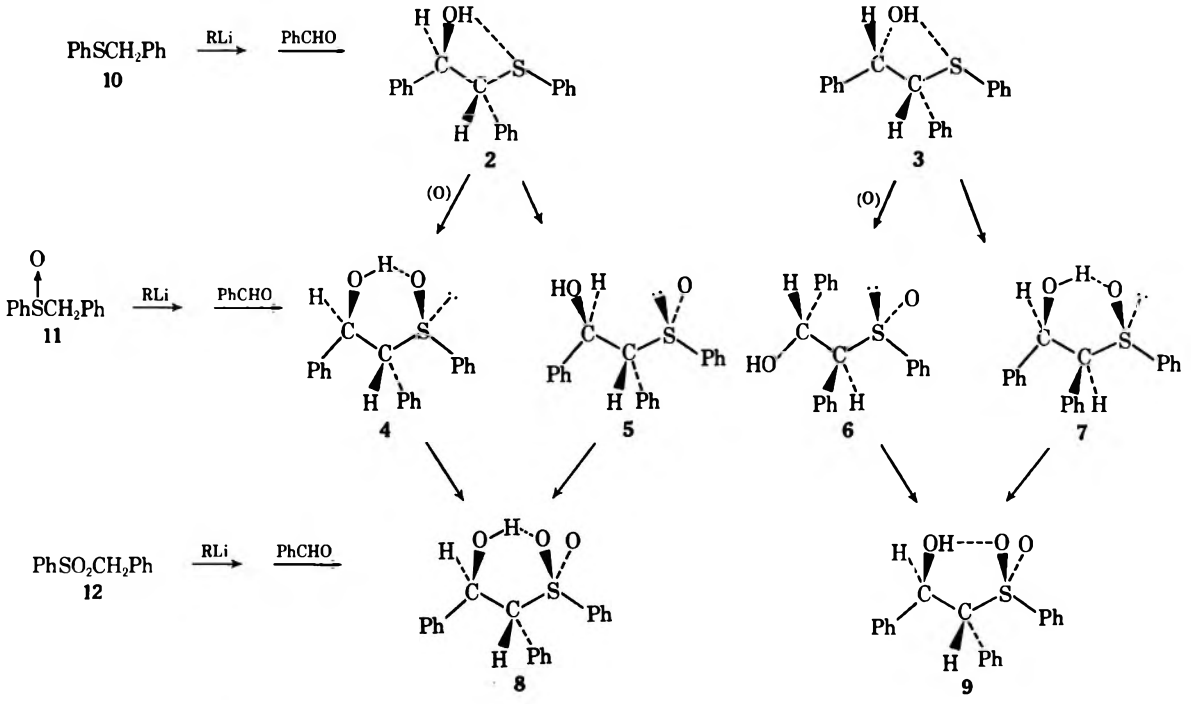
(10) H. E. Zimmerman and L. Ahramjian, *ibid.*, **82**, 5459 (1960). See also A. J. Speziale and D. Bissing, *ibid.*, **85**, 1888, 3878 (1963); M. Schlosser and K. Christmann, *Angew. Chem., Int. Ed. Engl.*, **4**, 689 (1965); E. J. Corey and H. Yamamoto, *J. Amer. Chem. Soc.*, **92**, 226 (1970).

(11) M. Stiles, *ibid.*, **81**, 2598 (1959); M. Stiles and H. Finkbeiner, *ibid.*, **81**, 505 (1959).

(12) See also (a) R. Steinberger and F. H. Westheimer, *ibid.*, **73**, 429 (1951); (b) M. Bender, *Advan. Chem. Ser.*, No. 37, 19 (1963); (c) T. C. Bruice and S. Benkovic, "Bio-organic Mechanisms," Vol. I, W. A. Benjamin, New York, N. Y., 1966, pp 110–118.

(13) A crossover experiment was again successful for the condensation of **12** and **13**.

SCHEME I



diastereomer.[14] The results were interpreted in terms of a hydrogen bond between the amide group and the oxidant, which leads the oxidant to attack one side of the molecule. It was of interest to see if the hydroxyl group of **2** and **3** would exert a similar directive effect in these conformationally mobile molecules.[15] Two different oxidants were used, sodium metaperiodate (**14**) and *m*-chloroperoxybenzoic acid (**15**). These oxidants gave widely varying isomer ratios in the oxidation of a non-hydrogen-bonding system, the 4-substituted thianes.[16] In general, oxidation of **2** and **3** gave predominately the most highly hydrogen bonded sulfoxide. Thus, oxidation of **2** with **14** produced 76% **4** and 24% **5**. Similar oxidation of **2** with **15** formed *ca.* 95% **4** and 5% **5**. Oxidation of the erythro sulfide with **14** formed 89% **7** and 11% **6**. With the peracid **15**, 85% **7** and 15% **6** were observed. These results are completely consistent with a *de facto* directive effect by hydroxyl.

The above synthesis, at best, produced only small yields of the erythro sulfoxide–alcohol **6**. The most convenient synthesis of **6** was the reduction of 2-phenylsulfinyl-1,2-diphenylethanone (**16**). This ketone was formed by condensation of **11** and methyl benzoate.[9c] Two isomeric ketones, **16** and **17**, resulted from the reaction in approximately equal ratios, as observed by nmr, but only **16** could be isolated in a pure state. The isomer **17** was inexplicably labile, although equilibration in *dry* deuteriochloroform catalyzed by piperidine showed 50 ± 5% **16** and 50% **17**. $LiAlH_4$ reduction of **16** in cold tetrahydrofuran gave >95% **6** (>30% overall yield). Other hydrides gave similar results.

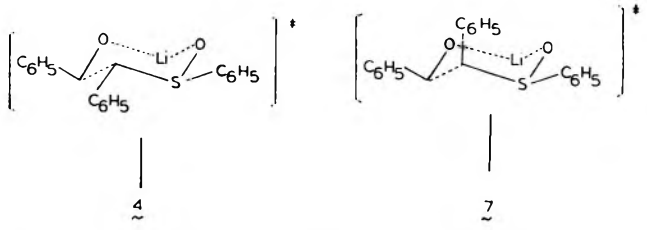
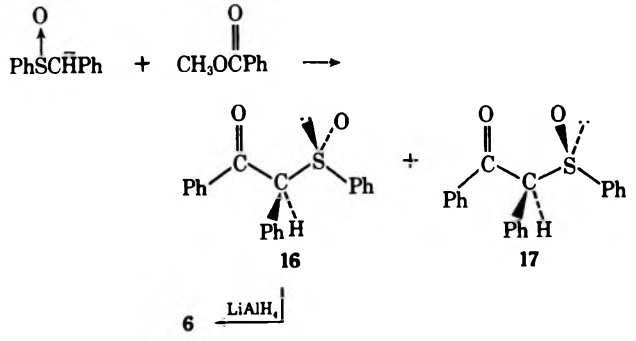


Figure 1.—Condensation transition states leading to isomers **4** and **7**.

The steric course of the reduction is consistent with Cram's rule if the phenyl group is considered larger than the phenylsulfinyl group. The *de facto* larger size of phenyl than phenylsulfinyl is not obvious from molecular models, but it is consistent with cyclohexane conformational free energies.[17]



Configuration at Sulfur. Pseudocontact Shifts.—The configurations at sulfur have been given in Scheme I, and in a previous paper without proof, although these configurations were consistent with hydrogen-bonding studies[6] and with oxidation product ratios. Additional evidence for configuration was sought from rela-

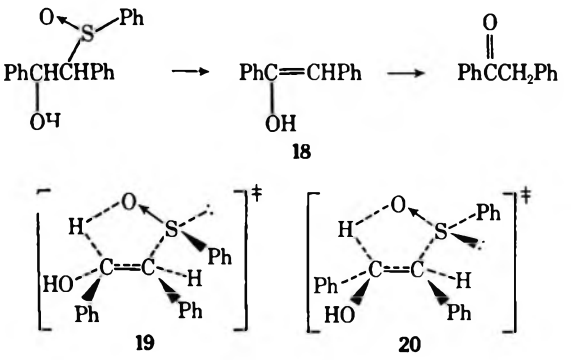
(14) (a) R. A. Archer and P. V. DeMarco, *J. Amer. Chem. Soc.*, **91**, 1530 (1969); (b) R. Cooper, P. V. DeMarco, J. Cheng, and N. Jones, *ibid.*, **91**, 1408 (1969); (c) see, however, D. H. R. Barton, F. Comer, and P. Sammes, *ibid.*, **91**, 1529 (1969).

(15) Similar directive effects by hydroxyl have been noted in other reactions: (a) H. E. Henbest and R. Wilson, *J. Chem. Soc.*, 1958 (1957); (b) M. Mousseron-Canet, B. Labeeuw, and V.-C. Lanet, *Bull. Soc. Chim. Fr.*, 2125, 4165, 4171 (1968); (c) J. Chan and B. Rickborn, *J. Amer. Chem. Soc.*, **90**, 6406 (1968); (d) S. Yamada and K. Koga, *Tetrahedron Lett.*, 1711 (1967).

(16) C. R. Johnson and D. McCants, Jr., *ibid.*, **87**, 1109 (1965).

(17) (a) E. Eliel, N. Allinger, S. Angyal, and G. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, p 438; (b) D. J. Cram and F. A. Abd Elhafez, *J. Amer. Chem. Soc.*, **74**, 5828 (1952); (c) see also T. Leitereq and D. J. Cram, *ibid.*, **90**, 4011 (1968).

tive rates of pyrolysis of **4**–**7**.[18] The order of reactivity is **6** > **7** > **4** > **5**, by rough factors of 40:7:2:1. The erythro sulfoxides, **6** and **7**, which initially form the trans enol **18**, were the more reactive. By use of Stuart–Briegleb models, **5** was assigned the structure that gave the most sterically hindered transition state, *i.e.*, **19**, in which two sets of phenyl groups are eclipsed.[19] Conversely, **6** was assigned the structure that gave the least hindered transition state *i.e.*, **20**. Although the pyrolysis data should best be considered as an indication rather than a proof of configuration, the assignments are completely consistent with hydrogen-bonding studies and oxidation product ratios.



18

19 **20**

Pseudocontact shifts were studied in hopes of obtaining more evidence about configuration and conformation at sulfur.[20,21] Although **2**, **3**, **8**, and **9** and their respective benzoates gave well-resolved nmr spectra in the presence of $Eu(dpm)_3$ or $Pr(dpm)_3$, the sulfoxides **4**–**7** and their benzoates gave very broad nmr absorptions at both 60 and 100 MHz. The spectra tended to sharpen at higher temperature, but the peak position moved back to near the peak position in the absence of $Eu(dpm)_3$. The chelating character of these bifunctional compounds with Eu^{III} is presently thought to have an adverse effect upon relaxation times.

Experimental Section

Preparation of Starting Materials.—Phenyl benzyl sulfide (**10**) was prepared by literature methods, mp 39.5–40.5° (lit.[22] 44°). Oxidation by *m*-chloroperoxybenzoic acid (**15**) gave phenyl benzyl sulfoxide (**11**), mp 122.5–124.5° (lit.[22] 125°). Phenyl benzyl sulfone (**12**) was prepared by stirring 35 g (0.176 mol) of sodium benzenefulfinate with an excess of benzyl chloride in an ethanol–water solution for 24 hr. The product was filtered, washed thoroughly with water, and triturated with ethanol–methylene chloride, yielding 28 g of colorless needles, mp 147–149° (lit.[22] 144°).

Preparation of *threo*-2-Thiophenoxy-1,2-diphenyl-1-ethanol (2) and 2 Benzoate.—This material was prepared by addition of sodium thiophenoxide to *cis*-stilbene oxide, by essentially the method used by Pasto, Cumbo, and Fraser.[23] The product was difficult to crystallize. After repeated chromatographies on silica gel, a solid was obtained, mp 70–72° (lit.[23] 77–78°).

A 1.1-g portion of *threo*-**2** was treated with excess benzoyl chloride in 50 ml of ether containing 1 ml of pyridine. After standing overnight, the mixture was poured into dilute HCl and extracted twice with water. The combined aqueous extracts were extracted with ether. The combined ether layers were extracted with dilute HCl, water, and then dilute sodium carbonate solution. After drying ($MgSO_4$) and evaporation of the solvent, **2** benzoate crystallized upon long standing. This material was recrystallized from ether–pentane, giving 0.3 g (20% yield) of product, mp 70–72°. The main side product was an oily material whose nmr spectrum showed only aromatic protons.

Preparation of *erythro*-2-Thiophenoxy-1,2-diphenyl-1-ethanol (3) and 3 Benzoate.—The literature procedure[23] was again used. The product, **3**, was recrystallized three times from ether–hexane, mp 98–99.5° (43% yield).

A portion of *erythro*-**3** was benzoylated as above, yielding a solid which was recrystallized three times from ether–hexane, mp 111.0–111.3°.

Condensation of Phenyl Benzyl Sulfide[10] and Benzaldehyde (13).—To 0.44 g (0.062 g-atom) of lithium stirred under nitrogen in 30 ml of ether was added dropwise 4.7 g (0.03 mol) of bromobenzene. The reaction was started by grinding a piece of lithium in ether with bromobenzene and adding this to the above mixture. The final mixture was refluxed for 0.25 hr, after which **10** was added (5.0 g, 0.025 mol). The resulting orange solution was refluxed for 10 min, and **13** was added dropwise until the color was discharged (3.0 g, 0.028 mol). The colorless final solution was stirred overnight, then added to ice–dilute HCl. The mixture was extracted twice with ether and then with water and dried ($MgSO_4$), and the solvent was evaporated. Crystallization could not be induced; so the mixture was chromatographed on silica gel using increasing amounts of benzene in hexane and ether in benzene, as eluents. The first product obtained was benzhydrol, 3.0 g, then the mixed sulfides **2** and **3** (4.3 g, 56% yield), and finally an unidentified solid, mp 79.2–80.5° (0.2 g). The mixture of sulfides showed 60% of the threo isomer (**2**) and 40% of the erythro isomer (**3**) by nmr. These could be separated only as their benzoate esters.

In another run, the reagents were mixed as before, and aliquots of the final reaction mixture were withdrawn over a 10-hr period, worked up as above, and assayed by nmr. No variation in the ratio of **2** (59%) and **3** (41%) was noted within experimental error.

In another run, *p*-chlorobenzaldehyde (4.6 g) was added to the final reaction mixture formed from 0.01 mol of each reagent. Work-up as before yielded no identifiable *p*-chlorophenyl analogs of **2** or **3**. The nmr spectrum of the sulfide chromatography fraction, however, was exceedingly complex, and suggestive of a mixture of phenyl and *p*-chlorophenyl sulfides.

Preparation of *threo*-2-Phenylsulfinyl-1,2-diphenyl-1-ethanols (4 and 5).—To 3.7 g (0.012 mol) of *threo*-**2** in 20 ml of methanol was added 2.74 g (0.013 mol) of sodium metaperiodate (**14**) in about 30 ml of water.[24] Methanol was added to the resulting mixture until the cloudy solution became clear. Even though the inorganic product precipitated rapidly, the mixture was stirred for 6–8 hr. The precipitate was collected and treated twice with hot chloroform, then it was discarded. The remaining methanol solution was added to much water and extracted twice with warm chloroform. The combined chloroform solutions were extracted with water, dried ($MgSO_4$), and evaporated, and the residue was recrystallized by the triangle scheme, yielding 0.65 g of **5** (16% yield), mp 194.0–194.5°, and 1.8 g of **4** (47% yield), mp 126–126.7°.

Anal. Calcd for $C_{20}H_{18}O_2S$ (**5**): C, 74.52; H, 5.63. Found: C, 74.18, H, 5.60. Calcd for $C_{20}H_{18}O_2S$ (**4**): C, 74.52; H, 5.63. Found: C, 74.43; H, 5.30.

Oxidation of the benzoate of **2** with **15** in warm chloroform gave a mixture of *threo*-sulfoxide benzoates in the ratio of 1.75:1, in addition to a trace of **8** benzoate and unreacted starting material. Nmr of the major isomer (probably **4** benzoate) ($CDCl_3$): δ 4.69 (d, 1, J = 9.6 Hz, CHSOPh), 6.7 (d, 1, CHOBz), *ca.* 7.2 (m, Ph), and *ca.* 8.1 (m, 2, *o*-Bz). Nmr of the minor isomer (probably **5** benzoate) ($CDCl_3$): δ 4.09 (d, 1, J = 10.6 Hz, CHOSOPh), *ca.* 6.7 (d, 1, CHOBz) *ca.* 7.2 (m, Ph), and

(18) (a) C. Walling and L. Bollyky, *J. Org. Chem.*, **29**, 2699 (1964). (b) I. D. Entwhistle and R. A. W. Jchnstone, *Chem. Commun.*, 29 (1965); see also *J. Chem. Soc.*, 502 (1967). (c) D. G. Bannard-Smith and J. F. Ford, *Chem. Commun.*, 120 (1965). (d) D. W. Emerson, A. P. Craig, and I. W. Potts, Jr., *J. Org. Chem.*, **32**, 102 (1967). (e) S. I. Goldberg and M. Sahli, *Tetrahedron Lett.*, 4441 (1965).

(19) An earlier paper gives a more complete account of eclipsing effects: C. Kingsbury and D. J. Cram, *J. Amer. Chem. Soc.*, **82**, 1810 (1960).

(20) R. Fraser and Y. Wigfield, *Chem. Commun.*, 1471 (1970), and references cited therein.

(21) K. K. Andersen, P. Card, and J. J. Uebel. Abstracts, 161st National Meeting of the Amerian Chemical Society, Los Angeles, Calif., 1971, No. ORGN 143.

(22) H. W. Clapham and H. Hepworth, *J. Chem. Soc.*, **119**, 1189 (1921).

(23) D. J. Pasto, C. Cumbo, and J. Fraser. *J. Amer. Chem. Soc.*, **88**, 2194 (1966).

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

ca. 8.1 (m, *o*-Bz). On a preparative scale, the two benzoates, mp 143–147°, defied separation.

Preparation of *erythro*-2-Phenylsulfinyl-1,2-diphenyl-1-ethanols (6 and 7) and Benzoate Derivatives.—By essentially the procedure of Leonard and Johnson[24] (see above), *erythro*-**3** (5.0 g, 0.016 mol) was oxidized with **14** (3.75 g, 0.018 mol) yielding **7**, 4.1 g (71% yield), mp 190–193°, recrystallized from pyridine, mp 204.2–205.4°, and **6**, 0.5 g (9% yield), mp 140–143°, recrystallized from methylene chloride–ether, mp 154.5–155.2°.

Anal. Calcd for $C_{20}H_{18}O_2S$ (**7**): C, 74.52; H, 5.63. Found: C, 75.03; H, 5.80. Calcd. for $C_{20}H_{18}O_2S$ (**6**): C, 74.52; H, 5.63. Found: C, 74.22; H, 5.48.

erythro-**3** was oxidized with **15** and the product ratio was determined by nmr integration (average of several traces) over the characteristic resonances[6] of **6** and **7**. The relative product yields were 85% **7** and 15% **6**. In a large-scale run beginning with 0.9 g (0.00294 mol) of **3**, 0.7 g (74% yield) of **7** was isolated, mp 195–196°. The minor isomer was difficult to isolate in this case. Esterification of the alcohols was complicated by other reactions. The esters were prepared by placing *erythro*-**3** benzoate (3.0 g, 0.007 mol) into 40 ml of cold chloroform, and adding **15** (1.2 g, 0.0073 mol) in 20 ml of cold chloroform in increments. The final mixture was heated for *ca.* 5 min, cooled, extracted twice with dilute Na_2CO_3 and once with water, dried ($MgSO_4$), and evaporated, and the residue was recrystallized by the triangle scheme yielding 0.65 g of **6** benzoate (20% yield), mp 180–181°, and 0.85 g of **7** benzoate (27% yield), mp 169.8–171.2°. An unknown material, 0.45 g, mp 134–136°, whose nmr spectrum showed no alkyl protons, and starting material, 0.4 g, were also isolated. *erythro*-**3** benzoate could not be oxidized with $NaIO_4$ in our hands. The high-melting sulfoxide–benzoate formed **6**, and the low-melting benzoate formed **7**, when treated with potassium hydroxide in ethanol, with the usual work-up.

Anal. Calcd for $C_{27}H_{22}O_3S$ (**7** benzoate): C, 76.03; H, 5.20. Found: C, 75.98; H, 5.23. Calcd for $C_{27}H_{22}O_3S$ (**6** benzoate): C, 76.03; H, 5.20. Found: C, 76.23; H, 5.13.

Condensation of Phenyl Benzyl Sulfoxide (11) with Benzaldehyde.—The calculated quantity of commercial *n*-butyllithium (in this case 12 ml) was added to a slurry of 6.0 g (0.027 mol) of **11**, stirred under nitrogen in 105 ml of dry ether. The mixture was gently heated for 0.5 hr in an attempt to dissolve all of the **11** (in later runs tetrahydrofuran was used with better success). To the orange solution, benzaldehyde (2.2 g, 0.021 mol) was added dropwise, and the mixture was stirred for *ca.* 10 hr. The mixture was poured into ice–dilute HCl. The solid which formed (**5** and **7**) was filtered, washed with water, and air dried. The ether layer was washed with water, dried ($MgSO_4$), and evaporated, yielding 4.7 g of an oil. The nmr spectrum of the oil showed a complex mixture of **11**, benzaldehyde, butyl-containing materials, and **4**. Crystallization was induced with some difficulty. The precipitates were separated by the triangle scheme of recrystallization, yielding 1.1 g (17% yield) of **7**, mp 202–203°, 1.05 g (17% yield) of **5**, mp 193–194°, 0.6 g (9.3% yield) of **4**, mp 124–125°, and 1.3 g of a substance, mp *ca.* 90°, whose nmr spectrum showed it to be a mixture of **4**, **6**, and starting material. From this was isolated 0.05 g of **6**, mp 146–147°, and 0.055 g of **4**, plus 0.7 g of a material whose nmr showed it to contain 78% **4** and 22% **6**.

In another run, 5.0 g (0.023 mol) of **11** was treated with phenyllithium and then benzaldehyde, and the reaction mixture was worked up immediately. The initial precipitate, 1.23 g, was almost pure **7**. The ether solution was worked up as before, and yielded 0.74 g of a material (mp *ca.* 170°) whose nmr spectrum was similar to **5**. Recrystallization from hot chloroform gave pure **5**, mp 193–194°. The remainder was chromatographed on Florisil. With 50% benzene in hexane, the intramolecularly hydrogen bonded isomer **4** and benzhydrol were eluted. Using benzene with a trace of ether as eluent, **4** and **6** were eluted, and these were separated by crystallization. With ether as eluent, a mixture of **5** (0.10 g), **7** (0.03 g), and **4** (0.68 g) were eluted. The latter mixture was separated by recrystallization. A total of 1.26 g (17% yield) of **7**, 0.72 g (9.7% yield) of **5**, 0.34 g (4.6% yield) of **6**, and 1.56 g (21% yield) of **4** were obtained from all sources. In another run, relative yields of 40% **4**, 10% **5**, 15% **6**, and 35% **7** were observed by nmr analysis.

The *p*-chlorophenyl analogs of **4** and **7** (termed **4′** and **7′**) were prepared by condensing the lithium salt of **11** (0.046 mol) with *p*-chlorobenzaldehyde (6.0 g, 0.043 mol). The reaction was worked up as before and the crude product was recrystallized by the triangle scheme. The first material to be isolated, 1.4 g, mp 238–240°, was *p*-chlorobenzoic acid, then 0.8 g of **7′**, mp 185–187°, and finally 1.4 g of the mixed isomers analogous to **16** and **17**, mp 144–149°. The remainder was chromatographed on Florisil, yielding 0.2 g of *p*-chlorobenzyl alcohol, mp 68.5–69.5°, 0.8 g of **4′**, mp 145–146°, and 0.4 g of mixed sulfoxides, mp >173°. The latter, upon recrystallization, yielded some **7′** and small amounts of a third sulfoxide (probably **5′**) which could not be completely separated from **7′**. The fourth sulfoxide (**6′**) was not observed. The sulfoxides **7′** and **4′** were recrystallized to purity, mp 198.5–199.0° and 148.0–149.0°, from chloroform and from methylene chloride–ether, respectively.

Anal. Calcd for $C_{20}H_{17}ClO_2S$ (**7′**): C, 67.31; H, 4.80. Found: C, 67.19; H, 4.63. Calcd for $C_{20}H_{17}ClO_2S$ (**4′**): C 67.31; H, 4.80. Found: C, 67.05; H, 4.70.

Crossover Run.—To a mixture of lithium metal (0.39 g, 0.056 g-atom) stirred under nitrogen in ether, 3.6 g of bromobenzene (0.023 mol) was added and the reaction was induced to begin by crushing a piece of lithium in the mixture. To the phenyllithium solution, **11** (5.0 g, 0.023 mol) was added with a long period of stirring to dissolve as much **11** as possible. To the orange solution, benzaldehyde (about 1.1 g) was added until the solution became colorless. An aliquot of this solution showed no apparent reaction with water. To this mixture 3.2 g of *p*-chlorobenzaldehyde (0.023 mol) was added and the mixture was stirred for 10 hr. The usual work-up was followed. The organic precipitate, *ca.* 1 g, mp >140°, was a mixture of sulfoxides which defied separation. The combined organic materials were chromatographed on Florisil. The first material isolated was **4**, 0.3 g (4% yield), mp 122–123°, then **4′**, 0.1 g (1% yield), mp 145°, mmp with authentic **4′**, 148–149°. Later fractions gave a solid, mp 182°, whose nmr spectrum suggested the presence of **7′**. After repeated recrystallizations, a small amount of **7′** was isolated, *ca.* 0.05 g, mp 199°. Later fractions gave *p*-chlorobenzyl alcohol, 0.8 g, and an inseparable mixture of sulfoxides.

Preparation of 2-Phenylsulfinyl-1,2-diphenylethanone (16).—Commercial *n*-butyllithium (12.1 ml, *ca.* 0.029 mol) was added by syringe to **11** (6.0 g, 0.0271 mol) in 30 ml of ether. The resulting milky orange solution was stirred for 15 min, then methyl benzoate (4.1 g, 0.028 mol) was added dropwise. The resulting mixture was poured onto dilute HCl–ice, extracted twice with water, dried ($MgSO_4$), and evaporated. Recrystallization afforded 1.5 g (20% yield) of **16**, mp 150–151°. The second isomer, **17**, was unaccountably very difficult to purify, although eventually 0.2 g, mp 137–139°, was obtained (somewhat contaminated with **16**). Chromatography of the remaining oil yielded starting materials and an unknown solid material, mp 188–190°.

Anal. Calcd for $C_{20}H_{16}O_2S$ (**16**): C, 74.97; H, 5.03. Found: C, 74.98; H, 5.07.

The above ketone **16** (0.40 g) was dissolved in the minimum tetrahydrofuran (*ca.* 40 ml) and *ca.* 0.2 g of $LiAlH_4$ was added with stirring. Saturated aqueous sodium sulfate solution was added to decompose excess hydride; very dilute HCl was then added and the organic layer was taken up in methylene chloride, dried ($MgSO_4$), and evaporated. The nmr spectrum of the residue showed **6** to be the only observable sulfoxide. Isolation yielded 0.135 g (30% yield) of **6** and a noncrystallisable oil smelling of thiophenol. It runs at lower temperature, the reaction was much cleaner with only **6** and occasionally a trace of **5** being isolated. Control experiments showed that **4**–**7** were about equally unstable to the reaction conditions.

Preparation of 2-Phenylsulfonyl-1,2-diphenyl-1-ethanols (8 and 9).—The condensation was run in a manner analogous to the sulfide and sulfoxide condensations. In several runs the red color of the anion faded before **15** could be added and no product resulted. The lack of solubility of phenyl benzyl sulfone (**13**) was also troublesome. In a run beginning with 5.0 g (0.0216 mol) of **13**, the nmr spectrum showed 35% starting material, 50% threo product, **8**, and 15% erythro product, **9**. The erythro product cocrystallized with **13** and was difficult to isolate, but 4.3 g of **8** was easily obtained (58% yield), mp 118.2–118.7°.

Anal. Calcd for $C_{20}H_{18}O_3S$ (**8**): C, 70.98; H, 5.36. Found: C, 70.94; H, 5.39.

The threo sulfone benzoate was formed by oxidation of **2** benzoate with 2 equiv of **15**, mp 197–198°.

Anal. Calcd for $C_{27}H_{22}O_4S$ (**8** benzoate): C, 73.30; H, 5.02. Found: C, 73.31; H, 5.13.

The erythro sulfide benzoate resisted oxidation to the sulfone. The sulfide–alcohol **3** could be oxidized with **15** at 65° to yield *erythro*-**9**, mp 129.5–131.0°.

Anal. Calcd for $C_{20}H_{18}O_3S$: C, 70.88; H, 5.36. Found: C, 70.93; H, 5.34.

In a crossover run, the anion of **13** was prepared as before (22 mmol). To this material benzaldehyde was added until no color remained. To this mixture, *p*-chlorobenzaldehyde (2.0 g) was added and the mixture was stirred for 3 hr. Chromatography on Florisil gave **16**, 1 (0.4 g), and several fractions of mixed **8′** and **13**. With pure benzene as eluent, **8′**, 0.15 g, mp 151–152° was isolated, which was identical with authentic material prepared separately.

Procedure for the Pyrolyses.—Equal quantities (*ca.* 0.050 g) of two of the four sulfoxides, **4–7**, were dissolved in *ca.* 1 ml of DMSO in an nmr tube and placed in an oil bath at 119 ± 3°. A trace of pyridine was added to absorb any acid formed. The nmr tube was withdrawn at invervals and the diminishment of the characteristic nmr signals[6] of **4–7** was followed by nmr integration (the average of 3–5 traces in each of eight points was taken). As **4–7** diminished, the spectrum of deoxybenzoin appeared, identical with that of authentic material.

Registry No.—**2** benzoate, 32120-62-0; **3**, 10277-57-3; **3** benzoate, 32120-64-2; **4**, 28455-74-5; **4′**, 32120-77-7; **5**, 28455-94-9; **6**, 28455-75-6; **6** benzoate, 32120-68-6; **7**, 32120-69-7; **7** benzoate, 32120-70-0; **7′**, 28455-78-9; **8**, 28520-74-3; **8** benzoate, 32120-73-3; **8′**, 32120-74-4; **9**, 28520-75-4; **16**, 32120-75-5; **17**, 32120-76-6.

Substituent Effects on the Half-Wave Potentials of Chalcones in Dimethylformamide

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Received March 12, 1971

The reduction half-wave potentials of two series of substituted *trans*-chalcones (I) have been determined in dimethylformamide. One series contains substituents in ring A, included in this series are five ortho-substituted compounds, and the other contains substituents in ring B. The first polarographic reduction wave was studied and it was shown to be a one-electron, diffusion-controlled process. Polarographic data and preliminary cyclic voltametric data indicate that the electrochemical reduction involves rapid chemical reaction of the one-electron transfer product. A very good linear free-energy relationship for substituents in ring A, excluding the ortho substituents, was obtained between $E_{1/2}$ and σ (r = 0.997). The linear free-energy relationship for substituents in ring B obtained between $E_{1/2}$ and σ was virtually as good (r = 0.985). The $E_{1/2}$ values for the ortho substituents in ring A were positively displaced by about 35 mV from their para isomers. The ortho isomers show a good linear relationship when $E_{1/2}$ is plotted against σ_p (r = 0.982). The $E_{1/2}$ data were also treated with the Swain–Lupton expression and generally poorer correlations were obtained with it than those obtained with the Hammett expression. Comparisons of these linear free-energy relationships with others previously reported for the chalcone system are made.

A number of linear free-energy relationships have been established for several α,β-unsaturated ketone systems,[3] including the chalcones. The effect of substituents on ultraviolet spectra,[4] basicities,[5] carbonyl stretching frequencies of chalcones,[6] and dipole moments[7] of chalcone types have been reported. The results of a wide variety of investigations on the effect of substituents on the polarographic half-wave potentials for the reduction of carbonyl compounds have been reported for numerous systems.[8a] Furthermore, there are many examples of correlation of their half-wave potentials with Hammett substituent constants.[8a] For example, good correlations of reduction half-wave potentials with Hammett σ constants were observed for acetophenones[9] and benzophenones.[10]

The effect of substituents on the reduction half-wave potentials of chalcones and chalcone analogs in aqueous media has been reported.[11] The electrochemical reduction mechanism of chalcone in aqueous alcohol mixtures has been studied extensively and is well summarized in a recent publication.[12] The reduction process involves several chemical reactions, is dependent upon hydrogen ion activity, and is further complicated by the formation of organomercury compounds. Electrochemical studies in nonaqueous solvents on chalcone also have been reported;[13] however, a systematic study of substituent effects in a nonaqueous medium has not been carried out. In acetonitrile and in dimethylformamide, chalcone is reduced to a carbanion radical which undergoes rapid polymerization.[13] No evidence is reported for the other reactions which were observed in aqueous solvents. The absence of the more complicated chemical reactions in nonaqueous media should lead to more reliable relationships between half-wave potentials and structure. The elucidation of the structure–reactivity–potential relationship of this relatively simple α,β-unsaturated ketone system will enhance the understanding of the reduction of this system and provide a model for other similar but more complex systems, some

(1) This work represents a partial fulfillment of the requirements for the B.S. degree with honor by M. L. A.

(2) Author to whom inquiries should be addressed.

(3) (a) J. R. Dimmock, P. L. Carter, and P. D. Ralph, *J. Chem. Soc. B*, 698 (1968); (b) S. Toma and A. Perjessy, *Chem. Zvesti*, **23**, 343 (1969); (c) R. W. Woodard and D. W. Boykin, Jr., *Chem. Commun.*, 628 (1970).

(4) (a) W. B. Black and R. E. Lutz, *J. Amer. Chem. Soc.*, **77**, 5134 (1955); (b) H. H. Szmant and A. J. Basso, *ibid.*, **74**, 4397 (1952).

(5) D. S. Noyce and M. J. Jorgenson, *ibid.*, **84**, 4312 (1962).

(6) (a) A. Perjessy, *Chem. Zvesti*, **23**, 905 (1969); (b) N. L. Silver and D. W. Boykin, Jr., *J. Org. Chem.*, **35**, 759 (1970).

(7) S. V. Tsukerman, V. P. Izvekov, and V. F. Lavrushin, *Zh. Fiz. Khim.*, **42**, 2159 (1968).

(8) P. Zuman, "Substituent Effects in Organic Polarography," Plenum Press, New York, N. Y., 1967: (a) Chapter 3; (b) p 74; (c) p 40; (d) p 75 ff.

(9) D. M. Coulson, W. R. Crowell, and S. K. Tendrick, *J. Amer. Chem. Soc.*, **79**, 1354 (1957).

(10) N. Fuson, M. L. Josien, and E. M. Shelton, *ibid.*, **76**, 2526 (1954).

(11) (a) V. F. Lavrushin, V. D. Bezuglyi, and G. G. Belous, *Zh. Obshch. Khim.*, **33**, 1711 (1963); (b) V. D. Bezuglyi, V. F. Lavrushin, and G. G. Belous, *ibid.*, **35**, 606 (1965); (c) S. Stankoviansky, A. Beno, S. Toma, and E. Gono, *Chem. Zvesti*, **24**, 19 (1970).

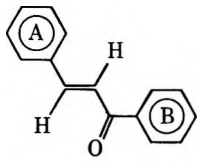
(12) A. R. Kyharova and P. Zuman, *J. Electroanal. Chem.*, **21**, 197 (1969).

(13) (a) S. Wawzonek and Z. Gunderson, *J. Electrochem. Soc.*, **111**, 324 (1964); (b) J. P. Zimmer, J. A. Richards, J. C. Turner, and D. Evans, *Anal. Chem.*, **43**, 1000 (1971).

of which may be related to those involved in biological processes.[14]

An interesting pattern of behavior is beginning to appear for the effects of substituents in both ring A and ring B of substituted *trans*-chalcones (I) and of other chalcone types. For example, pK data[5] and half-wave potential data[11] in aqueous media give about equally good correlations with substituents in both ring A and ring B; however, infrared data[6] and dipole moment data[7] for chalcones show a better correlation for substituents in ring A than in ring B. An ortho effect was observed on the pK for chalcones substituted in ring A; however, in contradistinction no such effect was detected on the carbonyl stretching frequency in the same series.

In order to further assess the relative effect of substituents in ring A and ring B on the properties of the *trans*-chalcone system, we have determined the polarographic half-wave potentials in dimethylformamide of two series of *trans*-chacones (I) one with substituents in ring A and the other with substituents in ring B. In addition, several chalcones with substituents in the ortho positions of ring A have been studied.



I

Polarography.—The reduction of all the chalcones in DMF at the dropping mercury electrode exhibited two well-defined waves. Since the first wave is of interest in this study, the following discussion will pertain only to it. The polarograms recorded for all compounds reported herein were similar except as noted.

The current varies linearly with the square root of mercury height on the limiting plateau, indicating that the process is diffusion controlled. The limiting current divided by concentration is constant over a concentration range of from 1.3×10^{-4} to 1.0×10^{-3} M. The diffusion current constant ($i_d/m^{2/3}t^{1/6}C$) for a representative compound, **17**, is 2.92. This is similar to a literature value for a confirmed one-electron process in the same solvent.[15] These observations indicate that the reduction is a one-electron diffusion controlled process uncomplicated by chemical reactions antecedent to the potential determining step.

Additional information on the overall mechanism was obtained from the preliminary cyclic voltammetric investigation of the parent chalcone **8**. At slow scan rates, 0.04 V/sec, a reduction wave is observed (Figure 1A). When the direction of scan is reversed, no corresponding oxidation process is observed but an oxidation wave is seen at a more positive potential (−0.2 V). At a scan rate of 4.0 V/sec, an oxidation wave attributable to the oxidation of the radical is observed (Figure 1B). As the scan rate is increased, the height of this wave increases with concomitant decrease in the height of the oxidation wave at −0.2 V. At 40.0 V/sec (Figure 1C), only the one oxidation wave is present. The various

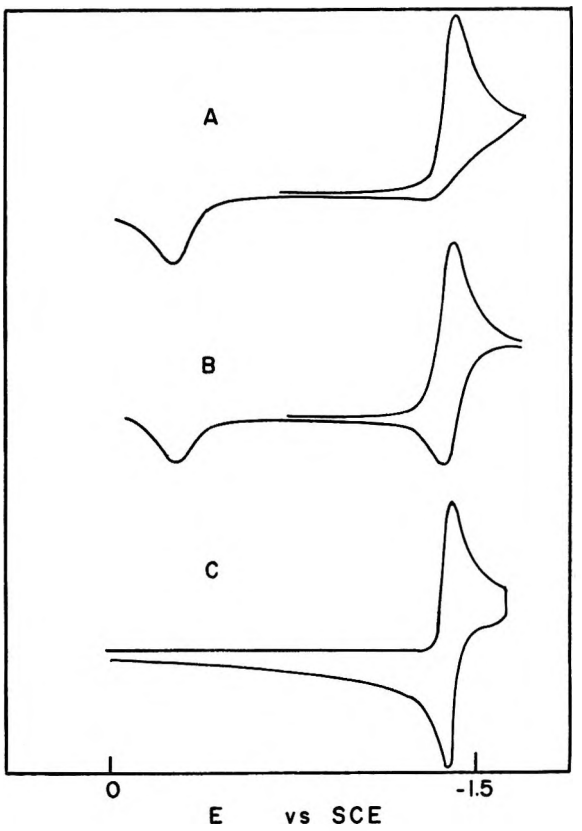


Figure 1.—Cyclic voltammograms of chalcone in DMF.

parameters of this wave meet the diagnostic criteria of Nicholson and Shain for a reversible one-electron wave with no chemical or adsorption complications.[16] If the reduction of the substituted chalcones proceed by the same general mechanism, the only direct effect of the chemical kinetics on the linear free energy studies will be a shift in the polarographic $E_{1/2}$ from the reversible value.

These combined results indicate that the electrochemical reduction of chalcone in DMF is to the anion radical which undergoes chemical reaction, one product of which is a more easily oxidizable species. Recently reported coulometric studies indicate that the final products of reduction of chalcone and other analogous α,β-unsaturated ketones are polymers consisting of from two to possibly four monomer units.[13b]

Preliminary chronoamperometric studies indicate that the overall follow-up chemical reaction is relatively fast and that it is at least second order with respect to chalcone. Complete results of these investigations will appear at a later date.

The Effect of Meta and Para Substituents in Ring A.—The $E_{1/2}$ data for compounds substituted in the meta and para positions of ring A (3- and 4-substituted chalcones) are shown in Table I. The influence of substituents on the reduction half-wave potential is that expected; the *p*-dimethylamino substituted chalcone (**1**) exhibits the most positive value whereas the 3,4-dichloro substituted compound exhibits the most negative one. The difference in $E_{1/2}$'s from the dimethylamino substituted compound to the 3,4-dichloro one is about 300 mV. The values of $E_{1/2}$ are correlated well with Hammett σ constants which were taken from

(14) *Cf.* (a) F. L. O'Brien and J. W. Olver, *Anal. Chem.*, **41**, 1810 (1969); (b) W. B. Geiger and J. E. Conn, *J. Amer. Chem. Soc.*, **67**, 112 (1945); (c) F. M. Menger and J. H. Smith, *ibid.*, **91**, 4211 (1969).

(15) J. L. Sadler and A. J. Bard, *J. Electrochem. Soc.*, **115**, 343 (1968).

(16) R. S. Nicholson and I. Shain, *Anal. Chem.*, **36**, 706 (1964).

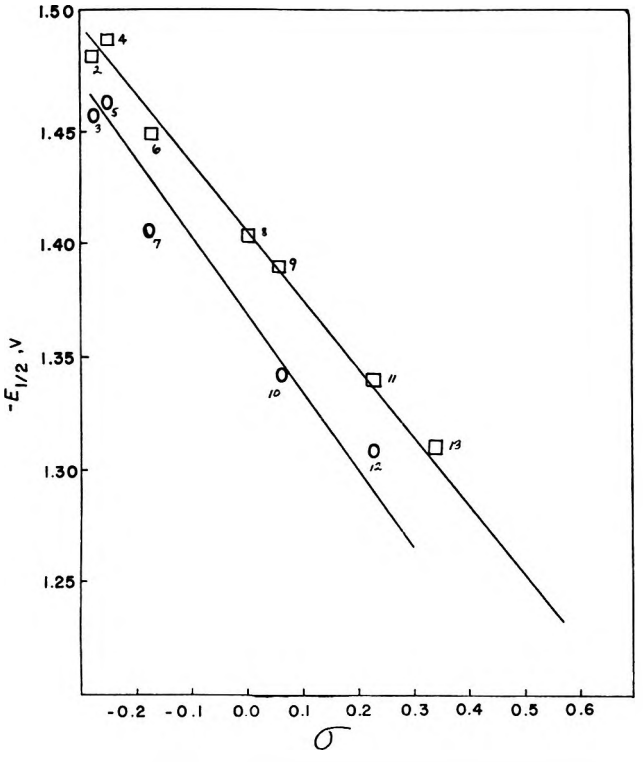


Figure 2.—Plots of $-E_{1/2}$ (V) *vs.* σ for ring A substituent: □, meta- and para-substituted compounds; ○, ortho-substituted compound.

TABLE I

HALF-WAVE POTENTIALS OF CHALCONES SUBSTITUTED IN RING A

Compd	Substituent	$-E_{1/2}$, V	Slope[a]
1	4-$(CH_3)_2N$	1.569	0.062
2	4-CH_3O	1.482	0.060
3	2-CH_3O	1.456	0.070
4	4-C_2H_5O	1.488	0.059
5	2-C_2H_5O	1.462	0.072
6	4-CH_3	1.450	0.062
7	2-CH_3	1.408	0.071
8	4-H	1.404	0.060
9	4-F	1.389	0.055
10	2-F	1.342	0.061
11	4-Cl	1.340	0.065
12	2-Cl	1.311	0.070
13	3-F	1.313	0.056
14	3,4-DiCl	1.268	0.075

[a] The slope of the plot of $-E$ (V) *vs.* $\log [i/(i_d - i)]$.

the tabulation by Ritchie and Sager.[17] Least-squares and statistical treatment of the data were carried out as previously described and are given in Table II.[6b,18] The pertinent data are presented in graphical form in Figure 2.

The two points which correspond to compounds **1** and **14** deviate markedly from the least-squares line. The deviation of the amino group and its derivatives from electrochemical linear-free energy relationships is now well documented, although not well understood.[8b,19] The deviation in the system reported here is in the same direction as previously observed in other systems.[19] As has been pointed out, this deviation indicates a

(17) C. D. Ritchie and W. F. Sager in "Progress in Physical Organic Chemistry," Vol. 2, Interscience, New York, N. Y., 1964.

(18) H. H. Jaffe, *Chem. Rev.*, **53**, 191 (1953).

(19) P. Zuman, O. Exner, R. F. Rekker, and W. Th. Nauta, *Collect. Czech. Chem. Commun.*, **33**, 3213 (1968).

TABLE II

RESULTS OF STATISTICAL TREATMENT USING σ CONSTANTS[a]

Series	n	r	s	ρ	i
Meta and para substituents in ring A	7[b]	0.997	0.0054	0.286	−1.407
Ortho substituents in ring A (σ_o^*)	5	0.974	0.0176	0.220	−1.380
Ortho substituents in ring A (σ_p)	5	0.982	0.0148	0.305	−1.371
Ortho, meta, and para substituents in ring A	12[b]	0.953	0.0206	0.279	−1.393
Meta and para substituents in ring B	9	0.985	0.0138	0.289	−1.408

[a] n = number of points; r = correlation coefficient; s = standard deviation; ρ = slope of line; i = intercept. Unless otherwise noted Hammett σ constants were used in the calculations. [b] Compounds 1 and 14 were excluded in this calculation.

diminution of the mesomeric electron donor function of the group for the electrode reaction in comparison to homogeneous reactions. Speculations about the origin of the deviation have been presented by others and will not be repeated here.[8b,19]

Zuman[8c] suggests that, when the errors of measurement of $E_{1/2}$'s have a range of ±5 mV, as is the case here, only deviations of greater than 20 mV should be considered significant. The deviation of the dimethylamino compound **1** from the least-squares line is about 35 mV; for this reason and because of the documented atypical electrochemical behavior of amino functions the value for it has been excluded from the statistical treatments. Although the deviation of the 3,4-dichloro compound **14** is only 18 mV, it has been excluded from the statistical treatments because the value of its current–potential slope (see Table I) suggests that its reduction mechanism probably differs from the other members of the series.

The value obtained for ρ in this work is of similar magnitude to that obtained by polarography on other carbonyl systems, although the previous work cited[9-11] was carried out in aqueous media. Meaningful assessment of the carbon–carbon double bond as a transmitting link during the electrode reaction cannot be made at present because of the apparent absence of $E_{1/2}$ data in DMF on systems such as acetophenones and benzaldehydes.[6b]

The new linear free energy relationship proposed by Swain and Lupton[20] provides a method by which an estimate of the contribution of resonance and field effects to the correlation may be made. Table III contains the results of correlations of $E_{1/2}$ data with the Swain F and R constants. The correlation obtained with the two-parameter approach (r = 0.915) is significantly poorer than the one obtained with the Hammett expression (r = 0.997). Because the Swain–Lupton report does not include treatment of $E_{1/2}$ data with their expression, previously reported $E_{1/2}$ data for acetophenones[9] and benzophenones[10] are included in Table III for comparison. In the four cases treated here, the Swain–Lupton treatment does not success-

(20) C. G. Swain and E. C. Lupton, Jr., *J. Amer. Chem. Soc.*, **90**, 4328 (1968).

TABLE III

RESULTS OF STATISTICAL TREATMENT USING F AND R CONSTANTS[a]

Series	n	f	r	i	E	c	%R
Meta and para substituents in ring A	7[b]	0.201 ± 0.047	0.315 ± 0.086	−1.404	0.331	0.917	50 ± 9
Ortho, meta, and para substituents in ring A	12[b]	0.185 ± 0.029	0.307 ± 0.054	−1.390	0.278	0.921	50 ± 6
Ortho substituents in ring A	5	0.160 ± 0.027	0.337 ± 0.051	−1.360	0.165	0.985	56 ± 6
Meta and para substituents in ring B	9	0.170 ± 0.033	0.227 ± 0.050	−1.403	0.315	0.934	44 ± 7
Acetophenones	10[c]	0.140 ± 0.035	0.251 ± 0.055	−0.977	0.337	0.899	54 ± 8
Benzophenones	6[d]	0.167 ± 0.038	0.253 ± 0.084	−1.132	0.297	0.939	34 ± 9

[a] Swain–Lupton field and resonance parameters; see ref 20. [b] Compounds 1 and 14 were not used in this correlation. [c] The $E_{1/2}$ values were taken from ref 9. The substituents were 4-H, 3-CH_3, 4-CH_3, 4-OH, 3-CH_3O, 4-CH_3O, 3-Cl, 4-Cl, 3-Br, 4-Br. The results of the least-squares treatment with σ: s = 0.0139; r = 0.981; i = −0.997; ρ = 0.252; n = 10. [d] The $E_{1/2}$ values were taken from ref 10. The substituents were 4-CH_3O, 4-CH_3, 4-H, 4-Cl, 4-Br, 3-Br. The results of the least-squares treatment with σ: s = 0.0169; r = 0.974; i = −1.128; ρ = 0.254; n = 6. n = number of points, f = regression coefficient for field parameter; r = regression coefficient for resonance parameter; i = intercept; E = standard error of estimate; c = multiple correlation coefficient; %R = per cent resonance contribution. These were calculated as indicated in ref 20; ϕ and ψ were calculated internally based upon the number of points used in the correlation.

fully treat the data as well as the simple Hammett approach. A similar finding was noted for treatment of carbonyl stretching frequency data.[6b] The contribution to the correlation by resonance as estimated by the Swain–Lupton approach for the chalcone system is 47%. The values for %R for the acetophenone (54%) and benzophenone (34%) correlation are not distinctly different from chalcone, suggesting, as has been previously noted,[6b] that the double bond transmits resonance effects efficiently.

The Effect of Ortho Substituents in Ring A.—Polarographic ortho effects may be attributed to changes in stability of the highest occupied molecular orbital and/or the lowest unoccupied molecular orbital which accepts the electron(s). Such alterations have been attributed[8d] to direct polar and steric effects; others[21] attribute them to an increase in the inductive and polar contribution of the substituent concomitantly with a decrease in resonance interaction.

The application of the Taft two-parameter expression[22] to electrochemical ortho-effect studies to assess steric factors has been questioned.[8d] More recently, Charton[23a] has shown that $E_s°$ constants do not represent steric influences and essentially represent only electrical factors. Further, Charton observes that σ_o* constants do not represent an intrinsic general ortho electrical effect[23b] and that generation of a single set of generally applicable ortho-substituent constants is unlikely.[23c] We have tested the data for the five ortho-substituted (2′-substituted) chalcones shown in Table I with the Taft expression and indeed no correlation is observed (r = 0.672). Treatment of the data with σ_o* alone gives a good correlation (r = 0.974) and treatment of the same five points with σ_p gives a better correlation (r = 0.982).

It is interesting that the ρ value (ρ_o = 0.305) for treatment of the five ortho compounds using σ_p is essentially the same as the slope for the line arising from the five corresponding para compounds (ρ_p = 0.292). The two lines differ only in displacement on the $E_{1/2}$ axis. The similarity of the Hammett slopes implies that the ortho and para substituents exhibit essentially the same electrical response during the electrochemical process. The positive displacement of $E_{1/2}$ for the ortho substituent with respect to the para isomers can be interpreted in terms of increased energy of the ground state for the ortho isomers. The positive displacement could be attributed to a decrease in coplanarity of the styryl moiety which would allow the inductive effect of the substituted styryl groups to come into play and decrease electron density at the reaction site (raise the energy of the highest occupied molecular orbital) and thus result in easier reduction. Although the slopes of the Hammett plots for the ortho and para lines are the same, it is possible that the positive shift of the $E_{1/2}$ value for the ortho isomer may reflect a change in the electrochemical mechanism in view of the consistently (except for 10) high values for the current function–potential slopes.

It is interesting to note that an ortho effect in the chalcone system has been noted previously on pK's;[5] however, no effect was observed on the carbonyl stretching frequencies.[6b] The two studies in which ortho effects were detected involve the effect of substituents in cases in which reactive intermediates are being generated, carbonium ions in one case and anion-radicals in the other. That the carbonyl stretching frequency study did not reveal a detectable ortho effect reflects the relative insensitivity of the stretching vibration to substituents which are well removed from the reaction site and demonstrates that ortho effects are more readily detected in α,β-unsaturated ketone systems when electronic demands are intensified by charged intermediates.

Effects of Meta and Para Substituents in Ring B.—The effects of substituents in ring B (3′ and 4′ substitution) on the reduction half-wave potentials of the compounds shown in Table II were studied. The $E_{1/2}$'s for these compounds are correlated well with Hammett σ constants (r = 0.985) (see Table III and Figure 3). This correlation is essentially as good as, although slightly poorer than, the one obtained for the values in ring A (0.997). A similar relationship of ring

(21) W. W. Hussey and A. J. Diefenderfer, *J. Amer. Chem. Soc.*, **89**, 5359 (1967).

(22) R. W. Taft, Jr., "Steric Effects in Organic Chemistry," M. S. Newman, Ed., Wiley, New York, N. Y., 1956, p 565.

(23) (a) M. Charton, *J. Amer. Chem. Soc.*, **91**, 615 (1969); (b) *ibid.*, **91**, 624 (1969); (c) M. Charton and B. I. Charton, *J. Org. Chem.*, **36**, 260 (1971).

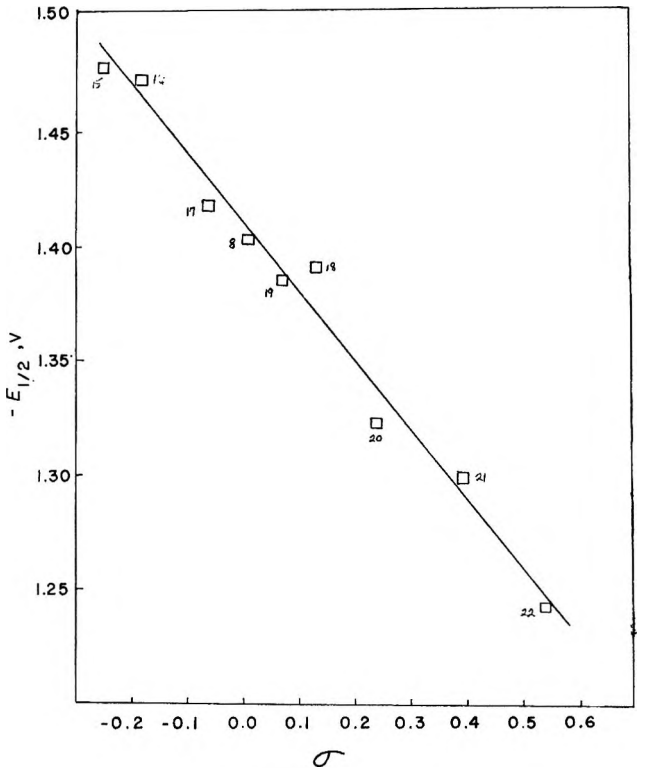


Figure 3.—Plot of $-E_{1/2}$ (V) *vs.* σ for ring B substituted compounds.

A values, correlating only slightly better than those of ring B, was observed for the reduction of chalcones in aqueous media (Table IV).[11]

TABLE IV
HALF-WAVE POTENTIALS OF CHALCONES SUBSTITUTED IN RING B

Compd	Substituent	$-E_{1/2}$, V	Slope[a]
15	4′-CH_3O	1.477	0.061
16	4′-CH_3	1.474	0.065
17	3′-CH_3	1.419	0.056
18	3′-CH_3O	1.396	0.057
19	4′-F	1.385	0.057
20	4′-Cl	1.328	0.060
21	3′-Br	1.305	0.050
22	4′-CF_3	1.247	0.066

[a] The slope of $-E$ (V) *vs.* log $[i/(i_d - i)]$.

Treatment of this data by the two-parameter approach of Swain and Lupton again results in a poorer correlation (r = 0.934) than was obtained with the simple Hammett expression. However, the pattern of behavior of substituents in the chalcone system is further complicated in this case since the correlation of ring B data is better than that of the ring A data using the Swain–Lupton approach (*cf.* ref 6b).

Conclusions

The Hammett expression correlates the chalcone polarographic data very well, whereas the Swain–Lupton approach is not so successful. In spite of the overall good description of a variety of chalcone linear free energy relationship data by the Hammett expression, the relationship of ring A to B continues to exhibit interesting vagaries which do not appear, as yet, to fall into a discernible pattern. These differing results probably arise from conformational effects which may be a function of the physical phenomenon or chemical reaction used as a probe, or from the solvent system employed and perhaps they may also be a function of the expression with which the data are correlated. It would be premature to discuss the relative significance of these factors until the results of other investigations are available. Additional studies of similar α,β-unsaturated ketones including systems in which conformational changes are restricted are under way.

Experimental Section

Chalcones.—The melting points were obtained with a Thomas–Hoover Uni-melt and are uncorrected. The analyses were performed by Atlantic Microlab, Inc., Atlanta, Ga. All chalcones were made following the procedure of Kohler.[24] The physical properties of all the chalcones shown in Tables I and II were described previously by us[6b] except **4**, **5**, and **22**. Compound **4** has been reported by Kostanecki and Schinder,[25] observed mp 61.5–62° (lit. mp 63°). Compounds **5** and **22** appear to be new. **5**: bp 179° (0.075 mm); λ_{max} 253 nm (ϵ 11,000), 300 (11,500), 350 (10,400). *Anal.* Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 80.79; H, 6.50. **22**: mp 117.5–118.5°; λ_{max} 233 nm (ϵ 10,300), 318 (19,700). *Anal.* Calcd for $C_{16}H_{11}F_3O$: C, 69.59; H, 3.98. Found: C, 69.36; H, 4.17. The chalcones were purified and dried as previously reported.[6b]

Electrochemistry.—The dimethylformamide was purified by shaking over several portions of molecular sieves (Linde size 4A) followed by vacuum distillation. The middle 60% was collected and used on the day of the distillation. Tetraethylammonium perchlorate, used as the supporting electrolyte, was prepared according to the method of Kolthoff[26] and stored in an oven at 80° until used. Airco prepurified nitrogen was used for solution deaeration.

The polarograph consisted of a three-electrode potentiostat and ramp generator of conventional design.[14a] All polarograms were recorded on a Hewlett-Packard 7005-B x–y recorder. The polarographic scan rate was 0.06 V/min. For the cyclic experiments a fast-rise time potentiostat similar to one discussed in the literature[27] and a model 564 Techtronic scope were employed.

The polarographic cell consisted of a 100-ml Brezelius beaker fitted with a Teflon top into which the electrodes and gas dispersion tube were inserted. The reference electrode, an aqueous sce, was separated from the test solution by a bridge filled with DMF and TEAP. A platinum button was used as the auxiliary electrode. The open circuit capillary constant, $m^{2/3}t^{1/2}$, was 1.625. A Metrohm EA-410 microburet and EA-874 and EA-876-5 cells were used for the cyclic voltammetry experiments.

All glassware was carefully cleaned, then dried at 100–120° for several hours immediately prior to each experiment to ensure dryness.

The reported half-wave potentials are the average of at least nine polarograms taken on three separate days. The maximum range was 5 mV. The $E_{1/2}$ value of a given polarogram was the zero intercept of a plot of log $(i/i_d - i)$ *vs.* E. This intercept was determined by the least squares analysis of ten maximum currents taken from each side of a graphically approximated $E_{1/2}$.

Registry No.—**1**, 22965-98-6; **2**, 22252-15-9; **3**, 22965-99-7; **4**, 32111-71-0; **5**, 32111-72-1; **6**, 22252-14-8; **7**, 22966-01-4; **8**, 614-47-1; **9**, 22966-07-0; **10**, 22966-06-9; **11**, 22252-16-0; **12**, 22966-11-6; **13**, 22966-12-7; **14**, 22966-16-1; **15**, 22966-19-4; **16**, 14802-30-3; **17**, 13565-44-1; **18**, 22966-24-1; **19**, 22966-25-2; **20**, 22966-22-9; **21**, 22966-26-3; **22**, 32120-33-5; dimethylformamide, 68-12-2.

(24) E. P. Kohler and H. M. Chadwell, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1932, p 78.
(25) St. V. Kostanecki and M. Schinder, *Ber.*, **29**, 1891 (1896).
(26) I. M. Kolthoff and J. F. Coetzee, *J. Amer. Chem. Soc.*, **86**, 3403 (1964).
(27) E. R. Brown and D. E. Smith, *Anal. Chem.*, **40**, 1411 (1968).

Correlation of Proton Shifts of Pyrazines with Substituent Constants

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Received June 9, 1971

A study of the ^1H nuclear magnetic resonance spectra of monosubstituted pyrazines in dimethyl sulfoxide revealed that the assigned peak values of the ortho, meta, and para protons correlated quite well with substituent constants. A substituent-ring "second-order" mesomeric interaction is proposed to explain the correlation of the proton meta to electron-donating substituents.

The hope that nuclear magnetic resonance would provide a direct, clear-cut method for measuring the variously hypothesized interactions between the substituent and the ring of substituted benzenes (or other aromatic systems) has never quite materialized.

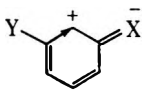
The reason for this is that the significance of chemical shifts in regard to ring-substituent interactions is obscured by the simultaneous action of several mutually opposite effects which determine chemical shifts. In addition to the sometimes overwhelming task of interpreting the complex spectrum of multiproton system (such as substituted benzenes), the difficulty and oftentimes futility in correlating proton nuclear magnetic resonance data with various other data is well documented.

Ring-substituent interactions as described by the Hammett σ constants are generally thought of as the additive effects of mesomeric and inductive interactions.[2] Taft and coworkers have attempted to quantitatively describe the contribution of inductive and mesomeric effects of a substituent to a particular ring position (σ_I is the inductive parameter and σ_R^0 is the resonance parameter).[3]

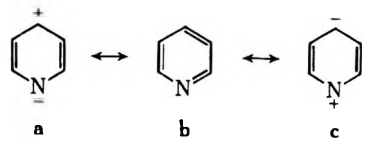
$$\sigma_m^0 = \sigma_I + {}^1/_2\sigma_R^0$$

$$\sigma_p^0 = \sigma_I + \sigma_R^0$$

The mixing of both inductive and resonance effects at the meta position may be schematically illustrated by the arrow in the following valence bond resonance form (X-meta substituent, Y-reaction center). The resonance interaction between the meta substituent (X) and the reaction center is called a "second-order" mesomeric effect.



In their analysis of Hammett substituent constants as applied to nitrogen heterocycles, Jaffé and Jones[3b] point out that, while resonance structures a, b, and c all contribute to the ground state of the molecule, structure c may not be too important due to the energy requirements of such a resonance form.



a b c

Another proposed series of substituent constants, designated as σ^+, have been applied to reactions in which strong electrophilic resonance interactions occur between the substituent and the reaction site.[4]

Chemical shifts, as affected by substituents, are postulated to be derived from changes in electron densities, magnetic anisotropy, localized van der Waals forces, and field effects induced by the substituent dipole moments.[5]

In spite of the theoretical and practical difficulties involved in interpreting chemical shifts, empirical attempts to correlate chemical shifts with parameters of electronic interaction have not been entirely unsuccessful. The para ^{13}C and para ^1H shielding of substituted benzenes were found to correlate with Hammett constants. The ^{13}C shifts of several monosubstituted benzenes and para-disubstituted fluorobenzenes were found to correlate with Taft's resonance parameters (σ_R^0).[6]

In a recent series of studies to determine the nature of a possible ortho effect,[7] Charton concluded that significant ortho correlations are obtained using an extended Hammett (Taft–Lewis) equation on a variety of phenomena, including chemical shifts.[7b] The results indicated that in general, no steric effects are exerted by ortho substituents. There was an apparent wide variance in the σ_I and σ_R contributions, evidently precluding the definition of a single set of valid ortho substituent constants.

Previous work on correlating a variety of physical measurements of a family of heterocyclic compounds to Hammett substituent constants[8] has been the subject of a review article by Jaffé and Jones.[2b] In it, they point out that a heteroatom ortho to a substituent might presumably change the substituent's electronic structure, and hence its σ value. They also point out that the heteroatom may affect the transmission of the electronic characteristics of the substituent to the various ring positions.

(1) (a) Taken in part from the doctoral dissertation of G. S. Marx presented to the Graduate Faculty of the Polytechnic Institute of Brooklyn, 1967. (b) To whom inquiries should be sent: Department of Organic Chemistry, Hebrew University, Jerusalem, Israel.

(2) (a) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953); (b) H. H. Jaffé and H. L. Jones, *Advan. Heterocycl. Chem.*, **3**, 209 (1964).

(3) (a) R. W. Taft, Jr., and I. C. Lewis, *J. Amer. Chem. Soc.*, **82**, 5846 (1960); (b) R. W. Taft, Jr., *J. Phys. Chem.*, **64**, 1805 (1960); (c) R. W. Taft, Jr., E. Price, I. R. Fox, I. C. Lewis, K. K. Anderson, and G. T. Davis, *J. Amer. Chem. Soc.*, **85**, 709 (1963); (d) R. W. Taft, Jr., E. Price, I. R. Fox, I. C. Lewis, K. K. Anderson, and G. T. Davis, *ibid.*, **85**, 3146 (1963).

(4) L. M. Stock and H. C. Brown, *Advan. Phys. Org. Chem.*, **1**, 35 (1963).

(5) (a) H. Spiesecke and W. H. Schneider, *J. Chem. Phys.*, **35**, 731 (1961); (b) J. S. Martin and B. P. Dailey, *ibid.*, **39**, 1722 (1963); (c) T. Schaefer, W. P. Reynolds, and T. Yamamoto, *Can. J. Chem.*, **41**, 2969 (1963); (d) A. D. Buchingham, *ibid.*, **38**, 300 (1960); (e) M. J. S. Dewar and Y. Takeuchi, *J. Amer. Chem. Soc.*, **87**, 390 (1969); (f) W. B. Smith and J. L. Roark, *ibid.*, **87**, 5018 (1969).

(6) G. E. Maciel and J. J. Natterstad, *J. Chem. Phys.*, **42**, 2427 (1965).

(7) (a) M. Charton, *J. Org. Chem.*, **36**, 882 (1971), and references cited therein; (b) M. Charton, *ibid.*, **36**, 266 (1971).

(8) B. M. Lynch, B. C. MacDonald, and J. G. K. Welb, *Tetrahedron*, **24**, 3595 (1968).

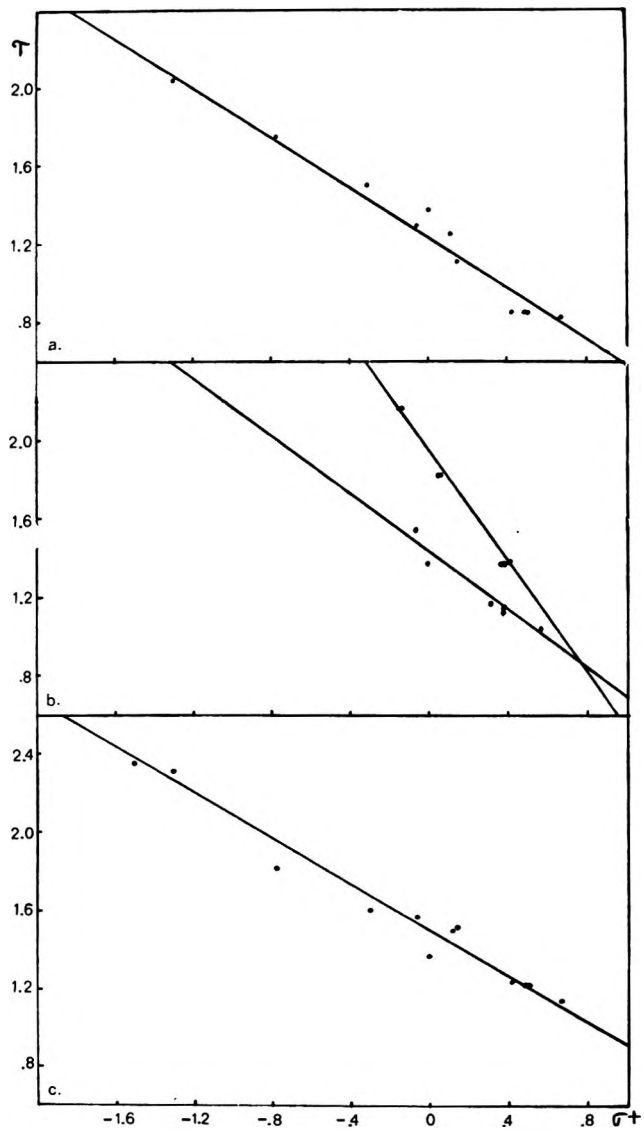
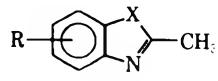


Figure 1.—Least-squares plot of substituent constants σ^+ *vs.* (a) ortho, (b) meta, and (c) para ring proton shifts of monosubstituted pyrazines.

Nevertheless, in a study of substituted benzazoles (1), a good correlation was obtained between the chemical shift of the 2-methyl group and the Hammett substituent constants.[9] The correlation of σ constants



1

X = Se, S, O

to the chemical shift of the methyl group was found to be parallel when X was Se, S, and O. It was concluded that the predominant transmission of electronic effects was through the nitrogen atom in all three series. While the heteroatom X plays an important role in establishing the shielding of the 2-methyl protons, it did not seem to influence the transmission of electronic effects.

Dailey, *et al.*, derived a simple additivity relationship of proton chemical shifts for benzene systems. However, attempts to adapt this method to heterocyclic systems were not successful.[10]

(9) G. DiModica, E. Barni, and A. Gasio, *J. Heterocycl. Chem.*, **2**, 457 (1965).

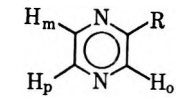
Results and Discussion

In this study, the nuclear magnetic resonance spectra of 13 monosubstituted pyrazines in dimethyl sulfoxide were observed.

The pyrazine system is convenient in that the spectra are not overly complex and are subject to analysis using simple splitting rules. The data are shown in Table I. For the most part, the spectra were found to be quite characteristic for this group of compounds.

TABLE I

CHEMICAL SHIFTS OF SUBSTITUTED PYRAZINES IN DIMETHYL SULFOXIDE[a]



R	Registry no.	H_o	H_m	H_p
CN	19847-12-2	0.82	1.03	1.14
CO_2Et	6924-68-1	0.85	1.14	1.22
CO_2Me	6164-79-0	0.85	1.15	1.22
CO_2H	98-97-5	0.85	1.17	1.24
CHO	5780-66-5	0.97	1.12	1.18
$CONH_2$	98-96-4	0.84	1.19	1.31
I	32111-21-0	1.10	1.36	1.52
Cl	14508-49-7	1.25	1.36	1.50
F	4949-13-7	1.29	1.36	1.57
H	290-37-9	1.37	1.37	1.37
Me	109-08-0	1.50	1.54	1.60
OMe	3149-28-8	1.75	1.82[b]	1.82[b]
NH_2	5049-61-6	2.05	2.14	2.31
NHMe	32111-28-7	2.06[b]	2.06[b]	2.35[b]

[a] Precision ±0.05. [b] Unresolved peak.

The spectra exhibited two doublets and one quartet, the quartet lying upfield. The lowest lying doublet (J = 1.25 cps) was assigned to the ortho proton and the other doublet (J' = 2.50 cps) was assigned to the meta proton. The quartet (J = 1.25 and J' = 2.50 cps) was assigned to the para proton. The assignment of these peaks corresponded to that of substituted benzenes.[2a] The downfield position of the ortho proton, and a larger coupling between the meta and the para proton than between the ortho and the para proton, could be expected.

In three cases, the spectra were not quite so straightforward. The methoxypyrazine showed two unresolved peaks with a relative area of 1:2 (τ_A 1.75, τ_B 1.82). Aminopyrazine showed three doublets (τ_A 2.05, τ_B 2.14, τ_C 2.31; $\Delta\delta_A$ 1.6, $\Delta\delta_B$ 1.6, and $\Delta\delta_C$ 2.1 cps). Methylaminopyrazine exhibited two groups of peaks in a ratio of 2:1 (τ_A 2.06, τ_B 2.35). The downfield peak could not be resolved and the other was a doublet with a coupling constant of $\Delta\delta_B$ 2.50 cps. On the basis of the coupling constants of the peaks and of the expectation that the meta proton does not exhibit greater resonance interaction with the substituent than does the para proton, the highest field peak has been partially assigned to the para proton. While

(10) (a) T. K. Wu and B. P. Dailey, *J. Chem. Phys.*, **41**, 2796 (1964); (b) *ibid.*, **41**, 3307 (1964); (c) A. H. Gawer and B. P. Dailey, *ibid.*, **42**, 2658 (1965).

some lack of accuracy might result from the inability to definitely assign the peaks, the error is not greater than $\tau \pm 0.04$.

Using eq 1, the data were analyzed in terms of a least-squares correlation with the three sets of substituent constants forwarded by Hammett (σ), Brown (σ^+), and Taft (σ^0), the latter being calculated from Taft's σ_I and σ_R^0 values in DMSO (Table II). The

$$\tau = a\sigma + b \quad (1)$$

TABLE II
META AND PARA SUBSTITUENT CONSTANTS COMPILED BY JAFFE,[2] TAFT,[3] AND BROWN[4]

R	Hammett		Taft		Brown	
	σ_m	σ_p	σ_m^0	σ_p^0	σ_m^+	σ_p^+
CN	0.56	0.66	0.58	0.70	0.56	0.66
CO_2Et			0.26	0.34	0.37	0.48
CO_2Me	0.32	0.39			0.37	0.49
CO_2H	0.35	0.41			0.32	0.42
CHO	0.25	0.38	0.39	0.53		
$CONH_2$			0.15	0.21		
I	0.35	0.28	0.38	0.27	0.36	0.14
Cl	0.36	0.25	0.38	0.29	0.40	0.11
F	0.34	0.06	0.37	0.22	0.35	−0.07
H	0	0	0	0	0	0
Me	−0.07	−0.17	−0.13	−0.20	−0.07	−0.31
OMe	−0.12	−0.27	−0.03	−0.18	−0.05	−0.78
NH_2	−0.16	−0.66	−0.24	−0.47	−0.16	−1.3
NHMe	−0.18	−0.84	−0.22[a]	−0.46[a]		−1.5

[a] These values are obtained by averaging the amino and the dimethylamino substituent constants.

results indicate that a high degree of linearity exists between the ortho proton shifts and the three sets of (para) substituent constants (see Table III) and compare quite favorably with the results summarized by Charton.[7b]

TABLE III
PARAMETERS IN CORRELATION OF ORTHO PROTON SHIFTS WITH SUBSTITUENT[a]

	a	b	r	s	n
Hammett	−0.96	1.36	0.980	0.085	12
Brown	−0.64	1.23	0.985	0.075	12
Taft	−1.11	1.44	0.926	0.161	12

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

The correlation of para proton shifts with substituent constants is also high (see Table IV). While the use of Taft's substituent constants gives the poorest results in both the above cases, the same trends are quite apparent. It is noteworthy that the slopes (a) for both the ortho and the para correlations have a similar value for each set of substituent constants. This may imply that the nitrogen atom does not appreciably differ from carbon in its ability to transmit the electronic characteristics of substituents.[9]

TABLE IV
PARAMETERS IN CORRELATION OF PARA PROTON SHIFTS WITH SUBSTITUENT CONSTANTS[a]

	a	b	r	s	n
Hammett	−0.86	1.60	0.957	0.115	12
Brown	−0.57	1.50	0.984	0.070	12
Taft	−0.98	1.68	0.897	0.171	12

[a] As applied to eq 1, with correlation coefficient (r), root-mean-square deviation (s), and the number of points (n).

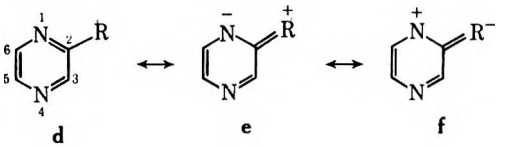
Attempts to correlate the meta shifts with the three sets of substituent constants gave very poor results. However, further analysis indicated that quite good results could be obtained by separately correlating those pyrazines having substituents capable of electron-donating resonance (−R) interaction with the ring. This procedure allowed the substituent constants of both classes of substituents (−R and +R) to correlate very well with the chemical shift data of the meta protons (see Table V).

TABLE V
PARAMETERS IN CORRELATION OF META PROTON SHIFTS WITH SUBSTITUENT CONSTANTS[a]

	a	b	r	s	n
Hammett	−1.25	1.66	0.867	0.174	12
Hammett (+R)	−0.76	1.41	0.941	0.058	6
Hammett (−R)	−1.30	1.81	0.973	0.078	6
Brown	−1.14	1.66	0.847	0.166	11
Brown (+R)	−0.75	1.43	0.976	0.037	6
Brown (−R)	−1.34	1.85	0.984	0.058	5
Taft	−1.12	1.65	0.841	0.189	12
Taft (+R)	−0.69	1.38	0.946	0.056	6
Taft (−R)	−1.21	1.81	0.998	0.021	6

[a] As applied to eq 1, with correlation coefficient (r), root-mean-square deviation (s), and the number of points (n).

In attempting to rationalize these results, it can be pointed out that the resonance structure **f** is expected to make a negligible contribution.[2b] Electron-donating substituents (−R) can interact with the ring system as shown in **e**, whereas electron-attracting substituents (+R) would have little recourse to the type of interaction described by **f**.



d **e** **f**

Adapting the concept of "second-order" mesomeric effect[3,4] to this case, one can see that resonance interaction between the substituent and the nitrogen on position 4 would affect the electronic characteristics on position 6. Depending on the substituent, this takes the form of variably greater electron density on position 6 as reflected by the chemical shift of the proton on that position.

The nmr spectra of two pyrazines were run in a number of solvents. The spectrum of chloropyrazine did not show any changes in going from DMSO to CCl_4. However, methylpyrazine did show some variation with solvent changes but with the overall effect being a convergence of the ring protons. The chemical shift of the methyl group did not exhibit any large solvent dependence (see Table VI).

In conclusion, it appears that the linear correlations of the ortho and para protons of substituted pyrazines with substituent constants indicate that changes in the

TABLE VI
SOLVENT EFFECT ON PROTON SHIFTS OF SUBSTITUTED PYRAZINES

Substituent	H_o	H_m	H_p	H_{CH_3}	Solvent
CH_3	1.52	1.52	1.60	7.47	Neat
CH_3	1.63	1.65	1.68	7.50	CCl_4
CH_3	1.60	1.58	1.62	7.49	$HCCl_3$
CH_3	1.71	1.73	1.75	7.53	CS_2
CH_3	1.50	1.54	1.60	7.50	DMSO
CH_3	1.50	1.54	1.60	7.44	MeOH
Cl	1.25	1.37	1.50		CCl_4
Cl	1.25	1.36	1.50		DMSO

chemical shift of the ring protons of pyrazines parallel changes in substituents. The double linearity of the meta correlation seems to reinforce the view that selective "second-order" mesomeric interaction between some substituents and the meta position is operative.

Experimental Section

2-Pyrazinamide was commercially obtained (Eastman), mp 189–90°.

2-Pyrazinecarboxylic acid was prepared by a basic hydrolysis of 2-pyrazinamide, mp 222–223° dec.

Methyl pyrazinoate[11] was prepared by a sulfuric acid–absolute methanol esterification of 2-pyrazinecarboxylic acid (67% crude) yield). Sublimation at 85° (2.5 mm) gave pure product, mp 57–58°.

2-Hydroxypyrazine was prepared by the method of Yafuso,[12] mp 187–188°.

2-Chloropyrazine[13] was obtained from J. Moshera.

Pyrazinaldehyde was prepared by the method of Rutner and Spoerri,[14] bp 57° (6 mm).

2-Cyanopyrazine,[15] bp 87° (6 mm), was obtained from J. Moshera.

2-Methoxypyrazine, bp 68° (28 mm), was prepared by the method of Albert and Phillips.[13]

2-Fluoropyrazine,[16] bp 107–108°, was obtained from H. Rutner.

2-Iodopyrazine,[17] bp 109–110° (34 mm), was obtained from H. Hertz.

2-Methylpyrazine was commercially obtained (K and K).

Physical Measurements.—All pyrazine nuclear magnetic resonance spectra were run at 37° on a Varian A-60 spectrometer operating at 60 MHz. The peak areas were integrated. Spinning of the samples was always employed. The samples were run five times, once relative to tetramethylsilane as the internal standard, in dimethyl sulfoxide at a rate of 500 cps, and four times relative to benzene as the internal standard in dimethyl sulfoxide, scanning the sample both upfield and downfield.

The least-squares correlations were obtained on a IBM 7040 computer using a program obtained from the Brooklyn Polytechnic Computer Center, and repeated at the computer facility of the Hebrew University.

Acknowledgment.—The authors wish to thank Mr. H. Talz, who ran the nmr spectra, and Mr. J. Moshera for some of the syntheses. Thanks are also due to Dr. A. Meyer for his help in obtaining the use of the computer facility at the Hebrew University.

(11) W. F. Newell, private communication, 1965.
(12) M. Yafuso, B. S. Thesis, Polytechnic Institute of Brooklyn, June 1964.
(13) A. Albert and J. N. Philips, *J. Chem. Soc.*, 1294 (1956).
(14) H. Rutner and P. E. Spoerri, *J. Org. Chem.*, **28**, 1898 (1963).
(15) M. Robba, *Ann. Chim (Paris)*, **5**, 351 (1960).
(16) H. Rutner and P. E. Spoerri, *J. Heterocycl. Chem.*, **2**, 492 (1965).
(17) A. Hirshberg and P. E. Spoerri, *J. Org. Chem.*, **26**, 1907 (1961).

An Evaluation of Base–Solvent Systems Using Olefin Isomerization as a Probe

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Received June 16, 1971

The base-catalyzed olefin isomerization reaction has been used to probe the efficacy of a wide variety of base–solvent systems. Changes in base type have produced changes in reaction rate that range over eleven powers of ten. The metal alkylamides in hexamethylphosphoramide are the most active. With a given type of anion, both its ligands and the metal cation have pronounced effects. Solvent variation produced a smaller range of reactivity (10^3). Dielectric constant and solvent proticity also play critical roles.

During the past 10 years the use of dipolar aprotic solvents has provided numerous advantages for the organic chemist.[1–3] Perhaps the most significant of these is the discovery of homogeneous base–solvent systems that promote anionic reactions of very weak organic acids under mild conditions. Although the role of the base and solvent are critical to the reaction, a comprehensive study of the relative effectiveness of various combinations is not available. The present work was initiated to provide both practical and theoretical information.

The base-catalyzed olefin isomerization reaction was selected as the probe for this study for several reasons. First, considerable information about the reaction has been obtained and many of the mechanistic details have been elucidated.[4–8] Second, the reaction is experimentally simple since it is homogeneous in both olefin and base. Third, preliminary experiments indicated that the reaction is exceedingly sensitive to variations in the efficacy of the base–solvent system. Fourth, a wide variety of olefin structures are available and, by appropriate selection, olefins of widely varying isomerization capability are obtained easily. Finally, and most important, base-catalyzed olefin isomerization involves the activation of the very weak carbon–hydrogen bond. Accordingly, a broad study of the

(1) For a comprehensive review see D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965.
(2) A. J. Parker, *Chem. Rev.*, **69**, 1 (1969).
(3) H. Normant, *Russ. Chem. Rev.*, **39**, 457 (1970).
(4) S. Bank, C. A. Rowe, Jr., A. Schriesheim, and L. A. Naslund, *J. Org. Chem.*, **33**, 221 (1968).
(5) S. Bank, C. A. Rowe, Jr., A. Schriesheim, and L. A. Naslund, *J. Amer. Chem. Soc.*, **89**, 6897 (1967), and references cited therein.
(6) L. A. Yanovskaya and Kh. Shakhidayatov, *Russ. Chem. Rev.*, **39**, 859 (1970).
(7) H. J. Hubert and H. Reimlinger, *Synthesis*, **1**, 97 (1969).
(8) H. Kloosterziel and J. A. A. van Drunen, *Recl. Trav. Chim. Pays-Bas*, **89**, 37 (1970), and references cited therein.

effect of base and solvent upon the relative rates of isomerization of select olefins was undertaken.

Results and Discussion

Effect of Base.—Attention was focused on several aspects of base variation. Initially, representative classes of bases were selected for study. Table I records

TABLE I
RELATIVE RATES OF BASE-CATALYZED OLEFIN ISOMERIZATION AS A FUNCTION OF BASE TYPE

Class	Example	Solvent	Olefin[a]	$k_{rel\ isom}$
M	K	HMPA	1	10^3
MOH	KOH	DMSO	1	10^{-2}–10^{-3}
MOR	KO-*tert*-Bu	DMSO	1	1.0
MH	NaH			
MMH_x	$NaBH_4$	HMPA	2	10^{-7}
MR	LiBu			
	$NaCH_2SOCH_3$	HMPA	1	10^1–10^2
	$MgPh_2$	HMPA	1	10^{-1}
MNH_2	$NaNH_2$			
MNR_2	$LiNMe_2$	HMPA	3	10^5–10^6

[a] 1, 2-Methyl-1-pentene; 2, allylbenzene; 3, 2,4,4-trimethyl-1-pentene.

the general classes with examples and a suitable solvent for those bases that were screened. Of the three groups, the alkoxides and hydroxides were studied in dimethyl sulfoxide (DMSO). The metals, organomagnesium reagents, metal amides, and borohydrides required the more weakly acidic solvent hexamethylphosphoramide (HMPA). No suitable solvent was obtained for the group including hydrides and metal alkyls.

Direct comparison of the relative reactivities of the bases in the first two groups was precluded by necessary changes in solvent, cation, temperature, and olefin structure. Nevertheless, a sufficient number of direct comparisons were made such that corrections for the variations achieved approximate relative reactivities. The relative rate constants were obtained from the observed rate constants (tabulated in the Experimental Section) with the following corrections. Data obtained in HMPA was correlated with data in DMSO since the same reaction is known to be 5.8 times faster in DMSO (*vide infra*). Data for the several olefins were compared since the order of activity of the olefins with a single base–solvent system has been shown to be[9] 2,4,4-trimethyl-1-pentene:2-methyl-1-pentene:allylbenzene, $9.1 \times 10^{-3}:1:7.8 \times 10.^5$ Data at various temperatures were correlated by the known activation energies and in all cases normalized to 55°. Finally, corrections for cation variation were applied from studies with a single anion (*vide infra*).

The most dramatic effect revealed by Table I is the enormous range, $\sim 10^{11}$, of relative reactivities. This suggests that by suitable selection of the base type, one could design anionic reaction conditions to be very facile or very selective. Table I reveals both expected and unexpected behavior. Not surprisingly, the metal itself provides a very active system, and the trends found for hydroxides, alkoxides, and borohydrides follow the expected order. However, the enhanced reactivity of nitrogen anions relative to carbon

(9) A. Schreisheim, C. A. Rowe, Jr., and L. A. Naslund, *J. Amer. Chem. Soc.*, **85**, 2112 (1963).

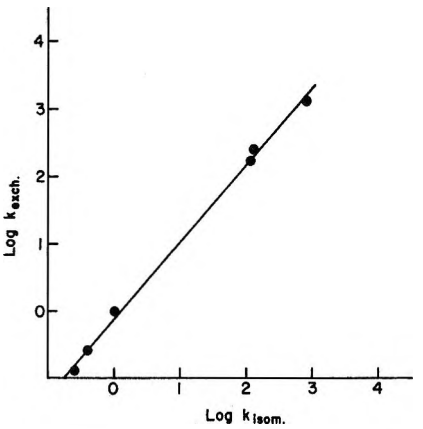

Figure 1.—Relationship between base-catalyzed tritium exchange and base-catalyzed olefin isomerization (data taken from Table II).

anions, and the metal itself for that matter, is unusual. Equally perplexing is the very low reactivity of the organomagnesium reagent. These data reinforce the view that the state of aggregation of the base in the solvent is of critical importance and may take precedence over the order expected from simple electronegativities.[10–12] Finally, these data demonstrate the need for experimental determination of relative reactivities.

Bases having cation and anion variations on a given central atom were studied to allow a more detailed investigation of the important factors in base strength. The metal alkoxides were used with a single olefin and a single solvent.

Table II records data for the isomerization reaction and the related base-catalyzed isotopic exchange of

TABLE II
BASE-CATALYZED REACTIVITIES OF ALKALI METAL ALKOXIDES

Base	Olefin isom, 10^3K, sec^{-1}[a]	k_{rel}	Exchange, k_{rel}[c]
LiO-*tert*-Bu	0.0013[b]	0.0011	0.00077
NaO-*tert*-Bu	0.0106	0.0091	0.006
KO-*tert*-Bu	1.16	1.00	1.0
RbO-*tert*-Bu	2.84	2.5	3.9
CsO-*tert*-Bu	4.47	3.9	7.8
KOMe	0.0092[b]	0.008	0.004
KO-*i*-Pr			0.67

[a] For isomerization of 1-butene at 55° in DMSO solution. [b] Rate constant estimated from measured rate constant for isomerization of 1-pentene and factor derived for difference between 1-butene and 1-pentene at 55° using KO-*tert*-Bu (ref 9). [c] For reaction $PhC^3H_3 + CH_3SOCH_3 \rightarrow PhCH_3 + CH_3SOC^3H_3$ [J. E. Hofmann, R. J. Muller, and A. Schriesheim, *J. Amer. Chem. Soc.*, **85**, 3000 (1963)].

tritiated toluene with solvent.[13] Figure 1 illustrates the close parallel between the two base-catalyzed reactions, and supports the view that data obtained for olefin isomerization can be validly extrapolated to other base-catalyzed reactions.

The reactivity for base-catalyzed reactions was found to be strongly dependent on both the cation and anion. For example, Li^+ and Cs^+ *tert*-butoxides gave the rate

(10) T. E. Hogen-Esch and J. Smid, *ibid.*, **88**, 307 (1966).
(11) S. Bank and B. Bockrath, *ibid.*, **93**, 430 (1971).
(12) J. I. Brauman, N. J. Nelson, and D. C. Kohl, *ibid.*, **90**, 490 (1968).
(13) J. E. Hofmann, unpublished data.

difference of 10^4. The anion variation from methoxide to *tert*-butoxide gave a similar 10^4 increase in rate. In principle, then, a table of bases ranging in reactivity of more than 10^8 could be constructed from the series LiOMe to CsO-*tert*-Bu.

Base catalytic activity was found to increase with increasing cation atomic weight. Interestingly, the largest difference was found between sodium and potassium, which finds analogy in some alkali metal compounds.[14] A reasonable explanation is the decreasing electronegativity of the cation with increasing atomic number. Since the ionic character of the metal–oxygen bond depends in part upon the electronegativity difference between the metal and oxygen, CsO-*tert*-Bu is expected to be the most ionic. One could argue that the greater the ionic character of the metal oxygen bond, the greater the reactivity of oxygen anion for proton activation. While this may be true in part, solvation terms are probably very important as well, and unfortunately these factors are inseparable here.

Anion variations followed the expected order of solution basicity, namely *tert*-$BuO^- > i$-$PrO^- > MeO^-$. This is the reverse order of gas-phase reactivities,[15] and amplifies the view that solvation terms are critical, that is, *tert*-butoxide is a stronger base than methoxide because it is not solvated as well. What is surprising, is that the difference should be so great in a so-called "aprotic" solvent where solvation of anions is not expected to be a large factor, therefore, minimizing differences between anions. Indeed the gas-phase order might have been expected insofar as thermodynamic basicities and kinetic basicities can be related. Of the several interpretations of this anomaly, the one favored is that the solvent is not truly aprotic. Recent work by Brauman has shown that KO-*tert*-Bu in DMSO is in actual fact a mixture of the dimsyl and the *tert*-butoxide anions,[16] and, therefore, alcohol is present and solvates the anion. This point of view leads to two interesting facets. First, a so-called aprotic solvent may be just that for some anions but need not be that for all. Second, if indeed the gas-phase basicities may be related to reactivities, then in a truly aprotic solvent media methoxide would be a stronger base than *tert*-butoxide.

The final aspect of base variation concerned structural changes in the organic moiety. The bases chosen for this series were the highly active lithium organoamides in HMPA using the very unreactive olefin 2,4,4-trimethyl-1-pentene. Solutions of the lithium amides in HMPA are not stable indefinitely, and it was found that the observed rate constant slowly decreased as a function of the period of time the lithium amide HMPA solutions were stored. However, there was no noticeable change in the observed rate constant until a period of 5–15 hr had elapsed. Accordingly, all rate studies were performed with freshly prepared solutions.

The data in Table III can be accounted for on the basis of steric and electronic factors. The suggestion that reactivity difference between lithium dimethylamide and lithium diisopropylamide is largely steric is borne out by the relative rate increase in going to the piperidine amide. Clearly, the electronic factors of the isopropyl compound and the piperidine compound are similar whereas the acyclic isopropyl compound has a significantly greater steric effect. As expected based on thermodynamic basicity, the aromatic amide lithium anilide is considerably less reactive than lithium cyclohexylamide. Finally, note is made of the enormous reactivity difference ($\sim 10^5$) between these bases and what is often thought to be a strong base, potassium *tert*-butoxide. This could have synthetic applications for a variety of anionic reactions.

TABLE III

RATES OF BASE-CATALYZED ISOMERIZATION OF 2,4,4-TRIMETHYL-1-PENTENE AT 20° FOR SELECT LITHIUM METAL AMIDES

Amide	k_{isom},[a] $sec^{-1} \times 10^4$	k_{rel}
$LiNMe_2$	40	7×10^5
LiN-*i*-Pr_2	1.8	3×10^4
Li piperidide	9.8	1.7×10^5
LiNH-*c*-C_6H_{10}	1.4	2.3×10^4
LiNH-C_6H_5	0.00013	2.5
KO-*tert*-Bu	0.00006[b]	1.0

[a] Using 0.7 *M* base in HMPA. [b] Estimated from conversion factors for 2,4,4-trimethyl-1-pentene and 2-methyl-1-pentene.

Effect of Solvent.—The base potassium *tert*-butoxide dissolves in diglyme and gives solutions that are stable at 55°. With the introduction of the terminal olefin 2-methyl-1-pentene, there is a very slow conversion to the internal isomer ($t_{1/2}$ ~80 days). In striking contrast, using the same base, olefin, and temperature but substituting DMSO for diglyme brings about a rapid conversion to the internal isomer ($t_{1/2}$ ~2 hr). Clearly, that solvent has a dramatic effect upon the rate of base-catalyzed olefin isomerization requires no additional support. Our detailed investigation sought to probe for the factors which contribute significantly to the effect.

The isomerization of representative olefins with a single base was studied in solvents of varying dielectric constant. Table IV summarizes the results and Figure 2 depicts the relationship between the rates and the dielectric constants. Overall the rate variation was $\sim 10^3$ and the relative rates increased with increasing dielectric constant. Figure 2 reveals, except for diglyme, a linear relationship for the plot of the log k against the recipricals of the dielectric constant. Such a

TABLE IV

EFFECT OF SOLVENT ON THE BASE-CATALYZED OLEFIN ISOMERIZATION REACTION

Solvent	10^4k, sec^{-1}[a]	k_{rel}	Dielectric constant
DMSO, 100%	1.22[b]	1580	48.8
DMSO, 95%–THF, 5%[c]	1.05[b]	1370	45.5[d]
DMSO, 90%–THF, 10%[c]	0.68[b]	525	42.3[d]
DMSO, 75%–THF, 25%[c]	0.48[b]	370	34.0[d]
HMPA	0.60[b]	465	30.2
TMU[e]	0.021[b]	16.4	24.5
NMP[f]	0.405[g]	311	33.1
Diglyme	0.0013[b]	1	7.7

[a] Using 0.7 *M* KO-*tert*-Bu at 55°. [b] For 2-methyl-1-pentene. [c] By volume. [d] Measured by a Sargent oscillometer calibrated from known standards. [e] Tetramethylurea. [f] *N*-Methyl-2-pyrrolidone. [g] Estimated from observed rate using 1-butene and conversion factor from ref 9.

(14) O. L. Brady and J. Jakobovits, *J. Chem. Soc.*, 767 (1950).
(15) J. I. Brauman and L. K. Blair, *J. Amer. Chem. Soc.*, **92**, 5896 (1970).
(16) J. I. Brauman, J. A. Bryson, D. C. Kohl, and N. J. Nelson, *ibid.*, **92**, 6679 (1970).

relationship is expected for a reaction in which charge is developed in the transition state. This relationship holds reasonably well for solvents of higher dielectric constant, but the assumptions that necessarily go into the simple treatment are no longer valid for the very low dielectric constant solvent, diglyme. The behavior of diglyme is a function of specific solvation rather than of bulk dielectric properties.[10]

Other important solvent properties include solubility of reactants and lack of reactive hydrogens. Previous work has shown that the addition of the hydroxylic species *tert*-butyl alcohol to the system potassium *tert*-butoxide–dimethyl sulfoxide brings about a marked decrease in rate with increasing concentration of *tert*-butyl alcohol.[17] As expected, the hydrogen-bonded base is weaker. The acidity of the solvent protons affects the rate since they produce hydrogen-bonded bases. The several dipolar solvents studied had varying acidities and the term aprotic is not very revealing. In large measure whether the solvent is protic or aprotic is a function of the reference base. In actual fact all of the solvents had some acidity and an estimation of the relative acidity was obtained from the relative rates of base-catalyzed proton exchange with tritiated toluene.[13] For some solvents, side reactions rendered kinetic interpretation impossible; however, in general, it was possible to correlate relative acidities on the basis of the time elapsed for 10% exchange. Using this technique, the following order of solvent acidities was found: DMSO > NMP > TMU > HMPA.

Experimental Section

Materials.—All the alkali metal *tert*-butoxides as well as potassium methoxide and isopropoxide were purchased from Mine Safety Appliances. They were the alcohol-free, sublimed powders and were used without further purification. Sodium hydride and sodium borohydride were purchased from Ventron, Inc. Butyllithium was obtained from the Lithium Corporation of America. Diphenylmagnesium was prepared by dioxane precipitation of phenylmagnesium bromide obtained from Araphoe Chemical Co. Sodium amide was obtained from Matheson Coleman and Bell. The several lithium alkylamides were prepared by addition of the appropriate amine to butyllithium in the drybox. The resulting solids were washed with *n*-heptane and stored in the drybox.

Dimethyl sulfoxide (Matheson Coleman and Bell) was dried and distilled over Linde 13X molecular sieves. Diglyme (Matheson Coleman and Bell) was distilled under reduced pressures from lithium aluminum hydride. Hexamethylphosphoramide (Eastman) was dried and distilled under reduced pressures over Linde 13X molecular sieves. Tetramethylurea (OTT Chemical Co.) was distilled under vacuum from barium oxide. *N*-Methyl-2-pyrrolidone (Matheson Coleman and Bell) was obtained as the Spectroquality material and used without further purification.

The olefins 2-methyl-1-pentene, 1-butene, 2,4,4-trimethyl-1-pentene, and allylbenzene were API samples. Gas chromatographic analysis indicated a purity greater than 99.6%.

Kinetic Procedures.—A typical experiment was carried out as follows: A 0.60 *M* stock solution was prepared in a nitrogen-blanketed drybox from 6.74 g (0.060 mol) of potassium *tert*-butoxide and sufficient dimethyl sulfoxide to give 100.0 ml of solution. The solution was stirred magnetically for 12 hr before use. A 7.0-ml aliquot of this solution was placed in a 10-ml vial that was then capped with a self-sealing neoprene septum. The vial was removed from the drybox and placed in a thermostated bath at 55.2°.

A mixture of 5.86 g (0.069 mol) of 2-methyl-1-pentene and 1.38 g (0.016 mol) of the internal standard 2,3-dimethylbutane was placed in another 10-ml vial sealed with a rubber septum. The vial was placed in the thermostated bath and a sample removed (~2 μl) by hypodermic syringe for gas chromatographic analysis. The analyses were performed on a Model 500 F & M gas chromatograph equipped with a 21-ft column containing 20% DC 200 on Chromosorb P, 60–80 mesh. Complete separation of the internal standard (2,3-dimethylbutane), the starting olefin (2-methyl-1-pentene), and the product olefin (2-methyl-2-pentene) was obtained at 50° with 10 psig of helium pressure.

After thermal equilibration (~0.5 hr) a 0.50-ml (0.34-g) aliquot of the hydrocarbon solution containing 280 mg (3.3 mmol) of 2-methyl-1-pentene and 65 mg (0.77 mmol) of 2,3-dimethylbutane was injected into the vial containing the potassium *tert*-butoxide solution. The reaction mixture was agitated by hand (~5 sec) and returned to the bath. The first sample was taken at 1 min.

Samples (0.50 ml) were taken by inserting a hypodermic syringe through the self-sealing neoprene septum. These samples were quenched in 5.0 ml of ice water containing 0.5 ml of cyclohexane. Nine samples covering more than three half-lives ($t_{1/2}$ ~40 min) of the isomerization reaction were taken at various intervals. The aqueous dimethyl sulfoxide layer was frozen and the supernatant cyclohexane extract was analyzed by gas chromatography.

The analyses revealed a monotonic decrease in the concentration of 2-methyl-1-pentene with time and a corresponding increase in the concentration of 2-methyl-2-pentene. There was no loss of total olefin relative to the internal standard. First-order rate constants were obtained from plots of the logarithm of the concentration remaining *vs.* time (obtained by a least-squares computer program) for conversions up to about 70%. For higher conversions, deviations from linearity in this plot were obtained since the isomerization reaction is an equilibration. For longer reaction times adequately linear lines were obtained from the plot of the logarithm of the concentration remaining minus concentration at equilibrium *vs.* time. The desired rate constant for the forward reaction (k_f) was obtained from the slope of this

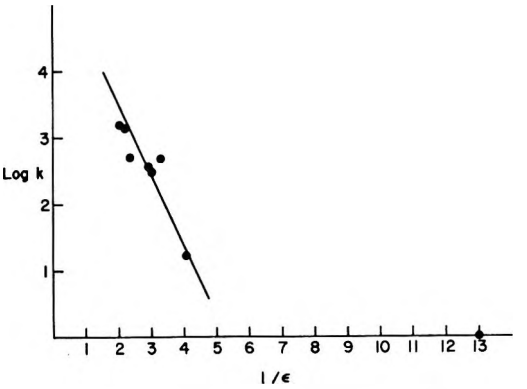

Figure 2.—Relationship between the rate constants for base-catalyzed olefin isomerization and the solvent dielectric constant.

Table V
Rate of Base-Catalyzed Olefin Isomerization of Various Bases

Base	Base concn	Temp, °C	k, sec^{-1}
K	0.43[a,b]	33	2.33×10^{-2}
KOH	0.43[a,c]	55	1.23×10^{-6}
KO-*tert*-Bu	0.56[a,c]	55	1.22×10^{-4}
NaH	0.40[a,b]	55	*e*
$NaBH_4$	0.40[b,d]	55	2×10^{-7}
LiBu	0.40[f]	25	*f*
$Na^+\bar{C}H_2SOCH_3$	0.70[a,c]	40	1.48×10^{-5}
$MgPh_2$	0.70[a,b]	55	1.2×10^{-5}
$NaNH_2$	0.70[a,b]	55	*e*
$LiNMe_2$	0.70[g,b]	20	4.0×10^{-3}

[a] Using 2-methyl-1-pentene, 0.45 *M*. [b] HMPA. [c] DMSO. [d] Using allylbenzene, 0.40 *M*. [e] After 100 hr at 55° there was no measurable 2-methyl-2-pentene as determined by gc. It should be noted that the amide and hydride are insoluble in HMPA and studies in DMSO are precluded due to reaction. [f] Rate studies were precluded by the fact that in all solvents butyllithium decomposed as measured by conversion to butane. [g] 2,4,4-Trimethyl-1-pentene, 0.40 *M*.

(17) A. Schriesheim and C. A. Rowe, Jr., *J. Amer. Chem. Soc.*, **84**, 3160 (1962).

line (obtained by a least-squares computer program) which is $k_f + k_r$ and the equilibrium constant, k_f/k_r.[18] The rate constants obtained by the two methods agreed within ±5%.

Analogous procedures were used for the isomerization of the other olefins (Table V). The gas chromatographic analyses for 2,4,4-trimethyl-1-pentene were performed on 21 ft of 20% DC 200 on Chromosorb P 60–80 mesh. The 1-butene analyses were performed on a 10-ft sqalene on acid-treated Chromosorb 40–60 mesh. The allylbenzene isomerizations were analyzed on 21 ft of Carbowax 20 M.

(18) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1961, p 186.

Registry No. **1**, 763-29-1; **2**, 300-57-2; **3**, 107-39-1; K, 7440-09-7; KOH, 1310-58-3; KO-*tert*-Bu, 865-47-4; NaH, 7646-69-7; $NaBH_4$, 16940-66-2; LiBu, 109-72-8; $NaCH_2SOCH_3$, 32249-19-7; $MgPh_2$, 555-54-4; $NaNH_2$, 7782-92-5; $LiNMe_2$, 26480-00-2;; LiO-*tert*-Bu, 1907-33-1; NaO-*tert*-Bu, 865-48-5; RbO-*tert*-Bu, 3934-10-9; CsO-*tert*-Bu, 3934-09-6; KOMe, 865-33-8; KO-*i*-Pr, 6831-82-9; LiN-*i*-Pr_2, 26396-97-4; Li piperidino, 24316-38-9; Li cyclohexylamine, 26372-63-4; Li aniline, 32249-32-4.

A Novel Intramolecular Free-Radical Cyclization in the Vapor-Phase Arylation of Methyl Benzoate

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Received May 20, 1971

Nitrobenzene reacts with methyl benzoate at 500–600° to give phthalide, methyl biphenylcarboxylate, dimethyl biphenyldicarboxylate, and benzene as major products. Methyl *p*-nitrobenzoate with methyl benzoate at 600° gives the same products. Experiments with labeled reagents show that the products arise by hydrogen abstraction, cyclization, and decomposition of the carbomethoxy group of methyl benzoate. Arylation in the liquid phase gives no phthalide; the free-radical cyclization occurs only in the gas phase. Meta substitution predominates in the gas phase, whereas ortho substitution is favored in the liquid phase; apparently thermodynamic factors operating in the intermediate σ complex control the isomer distribution in the gas phase.

Earlier work from this laboratory on high-temperature arylations dealt with the arylation of benzene, aromatic fluorine derivatives, toluene, pyridine, and thiophene.[1] Those reactions involved the thermal decomposition of nitrobenzene above 500° to a phenyl radical and NO_2 in the presence of an excess of the aromatic substrate, and yielded biphenyl and substituted biphenyls as the major products. We have extended the scope of these arylations to include the reactions of methyl benzoate with nitrobenzene and methyl *p*-nitrobenzoate, compared the liquid- and vapor-phase arylations of methyl benzoate, and discovered a novel intramolecular free-radical cyclization.

Experimental Section

Reactions were run in a Vycor tube filled with Vycor chips in an electric furnace under pure dry nitrogen with contact times of 10–18 sec. Solutions of reactants were fed by a syringe whose needle fitted through a rubber septum in a glass adaptor connected to the Vycor tube. The syringe was pumped by an infusion pump (Harvard Apparatus Co., Dover, Mass., compact infusion pump, Model 974) at a rate to give the required contact time. During the reaction a sample of the noncondensable gases was taken for mass spectrometric analysis. The vapors from the reaction were condensed at −60°, the condensate was distilled to recover unreacted material, and the distillates and residues were analyzed by gas chromatography and mass spectrometry.

In a typical experiment, a solution of 6.2 g (0.05 mol) of nitrobenzene and 68 g (0.5 mol) of methyl benzoate was passed through a Vycor tube filled with Vycor chips at 600° under a nitrogen flow of 20 cc/min; contact time was 18 sec. The vapors were condensed in a flask at −60°; the condensate was distilled to give 2.9 g of low-boiling products (40–55° at 200 mm), 40.0 g of methyl benzoate, and 9.3 g of residue whose analysis is shown in Table I.

TABLE I

REACTION OF NITROBENZENE AND METHYL *p*-NITROBENZOATE WITH METHYL BENZOATE

Conditions			
Temp, °C	600	600	600
Nitrobenzene, mol	0.05		
Methyl *p*-nitrobenzoate, mol		0.05	0.05
Methyl benzoate, mol	0.50	0.25	0.50
Contact time, sec	18	13	11
Per cent conversion of nitro aromatic	94	72	72
Products[a]	—Yield, mol %[b,c]—		
Methyl biphenylcarboxylates	25	15	27
Dimethyl biphenyldicarboxylates	4	12	19
Phthalide	17	17	28
Biphenyl	9	3	6

[a] Other products included carbon monoxide, carbon dioxide, formaldehyde, methanol, methane, and methyl terphenylcarboxylates, as well as benzene and methyl benzoate. [b] Calculated on the basis of 0.05 mol of nitrobenzene and methyl *p*-nitrobenzoate giving a theoretical yield of 0.05 mol of each product. [c] Determined by gas chromatography.

Preparation of Aniline-d_5.—A mixture of 10 g of nitrobenzene-d_5, 150 ml of ethanol, 35 ml of 65% hydrazine, and 0.5–0.8 g of wet Raney nickel was refluxed for 1 hr. The filtered reaction mixture was distilled to obtain 5.4 g of deuterated aniline, bp 42° (0.2 mm); isotopic composition 0.1% d_3, 3.7% d_4, 95.2% d_5, 1.0% d_6.

Reaction of Diazotized Aniline-d_5 with Methyl Benzoate.—A solution of 3 g of aniline-d_5, 41 g of methyl benzoate, and 5 g of amyl nitrite was stirred for 5 hr at 120°. The reaction mixture was distilled at 200 mm to give 2.2 g of low-boiling products, 30 g of methyl benzoate, and 11 g of residue. Mass spectrometric analysis showed that the lower boiling products consisted of 96% benzene-d_5 and 4% benzene-d_4; the residue was methyl biphenylcarboxylates-d_5 with small amounts of methyl terphenylcarboxylates-d_9 and -d_{10}.

Analyses.—Mass spectra were measured on a modified Consolidated Model 21-103 instrument with the inlet system at 140°. Isotopic compositions were derived from low-ionizing voltage measurements in which possible isotope effects on sensitivity were ignored. Gas chromatographic separations were run on a column of 10% OV17 on Chromosorb W.

(1) (a) E. K. Fields and S. Meyerson, *Intra-Science Chem. Rept.*, **3**, 219 (1969); (b) *J. Amer. Chem. Soc.*, **88**, 21 (1966); (c) *J. Org. Chem.*, **35**, 62, 67 (1970); (d) A. I. Feinstein, E. K. Fields, and S. Meyerson, *ibid.*, **35**, 303 (1970).

Results and Discussion

The products from the reaction of nitrobenzene and methyl *p*-nitrobenzoate with methyl benzoate are listed in Table I. The major higher boiling products were methyl biphenylcarboxylates, dimethyl biphenyldicarboxylates, and phthalide. Methyl benzoate alone under the same conditions was recovered in 95% yield. The thermal stability of methyl benzoate suggested that the products formed by a radical-induced decomposition of the carbomethoxy group. To learn more about the mechanism, nitrobenzene-d_5 was allowed to react with methyl benzoate. The isotopic distribution of the products is listed in Table II. The high percentages of

TABLE II

REACTION OF NITROBENZENE-d_5 WITH METHYL BENZOATE[a] (ISOTOPIC DISTRIBUTION OF PRODUCTS)[b]

D atoms	Benzene	Biphenyl	Methyl biphenyl-carboxylate	Methyl terphenyl-carboxylate
0	62	51	55[c]	43
1	2		2	14
2				
3	1		1	
4	7	12	10	14
5	28	32	32	29
6		2		
7				
8				
9		2		
10		1		

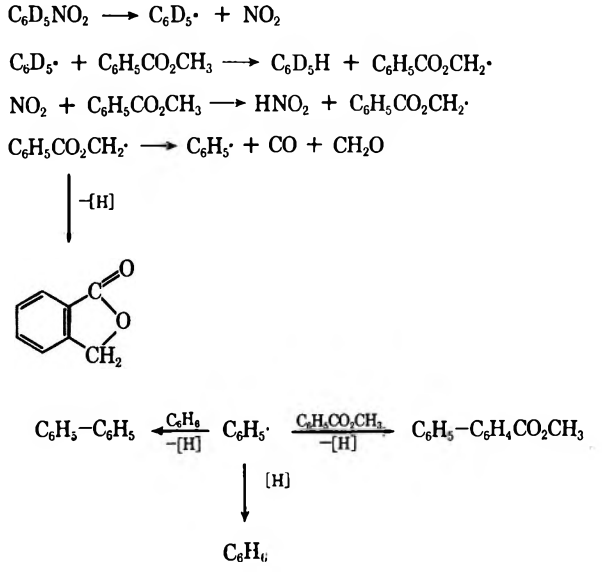
[a] At 600°, contact time 17.9 sec; mole ratio nitrobenzene-d_5: methyl benzoate = 1:10; isotopic composition of nitrobenzene-d_5: 3.3% d_4, 96.7% d_5. [b] Estimated from the low ionizing voltage (7.5 V, uncorrected) mass spectrum. [c] Dimethyl biphenyldicarboxylate, 100; phthalide, 100.

undeuterated benzene, methyl biphenylcarboxylates, and methyl terphenylcarboxylates indicate that the major reaction is the radical-induced loss of the carbomethoxy group of methyl benzoate. The aromatic rings of these undeuterated components and the dimethyl biphenyldicarboxylates, and phthalide were derived solely from methyl benzoate. The yield of unlabeled benzene was 87%, based on 1 mol of nitrobenzene-d_5 giving 1 mol of benzene. This high yield suggests the participation of NO_2 as well as the phenyl-d_5 radical in the decarbomethoxylation of methyl benzoate (Scheme I).

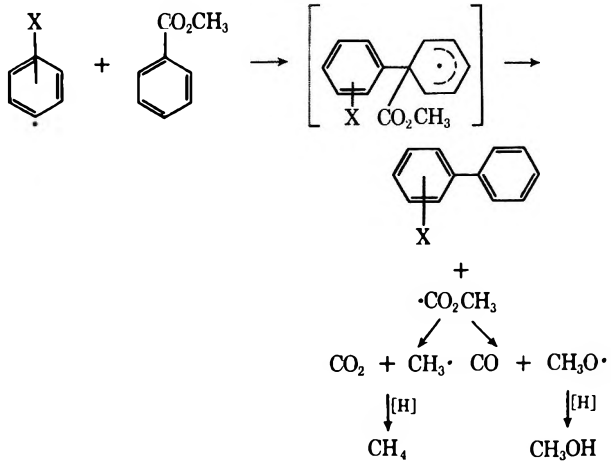
The phenyl-d_5 radical and NO_2 derived from nitrobenzene-d_5 abstract hydrogen from the methyl group of methyl benzoate to give a methyl benzoate radical with the radical site located α to the carboxy group. This intermediate can then decompose to phenyl radical, carbon monoxide, and formaldehyde, as well as undergo an intramolecular cyclization to give phthalide. The formation of phthalide by an intramolecular cyclization of this type has not been described until now.

The phenyl radical derived from methyl benzoate gives benzene by hydrogen abstraction; phenylation of methyl benzoate and benzene yields methyl biphenylcarboxylates and biphenyl, respectively. The formation of carbon dioxide, methanol, and methane in these reactions suggests that methyl biphenylcarboxylates and biphenyl could also result from a reaction in-

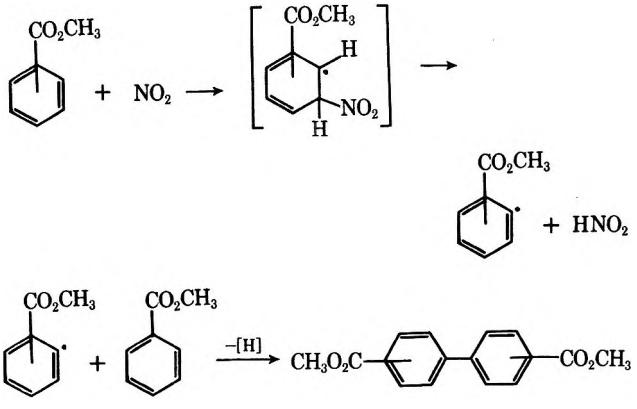
SCHEME I



volving the displacement and subsequent decomposition of a carbomethoxy group (X = H or CO_2CH_3).

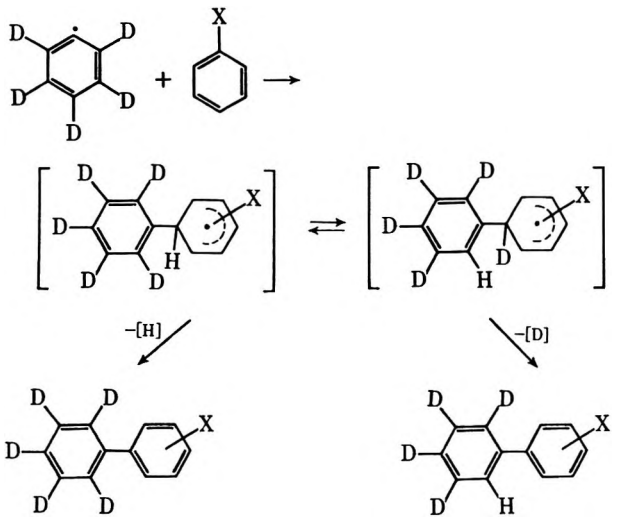


Dimethyl biphenyldicarboxylates form by arylation of methyl benzoate by the methyl benzoate radical. Abstraction of hydrogen from methyl benzoate to give methyl benzoate radicals is probably by addition of NO_2 to methyl benzoate followed by loss of HNO_2.



Arylation of benzene and methyl benzoate by the phenyl-d_5 radical gives biphenyl and the methyl biphenylcarboxylate-d_4 and -d_5. The d_4 species could arise from protium–deuterium exchange in the inter-

mediate cyclohexadienyl radical (X = H or CO_2CH_3). This phenomenon has been observed in the pyrolysis of benzene-*d*.[1b]



Methyl terphenylcarboxylate had a deuterium distribution similar to that of methyl biphenylcarboxylate, and was evidently derived by arylation of the latter.

The reaction of methyl *p*-nitrobenzoate with methyl benzoate gave the same products as the nitrobenzene reaction (Table I). Although higher yields of dimethyl biphenyldicarboxylates were obtained from the former reaction, significant amounts of methyl biphenylcarboxylates were formed. Increasing the mole ratio of methyl *p*-nitrobenzoate to methyl benzoate from 1:5 to 1:10 did not have an appreciable effect on the yield of the dimethyl biphenyldicarboxylates.[2] The reactions which lead to the formation of phthalide and methyl biphenylcarboxylates (Scheme I) compete with the direct arylation of methyl benzoate and result in low yields of dimethyl biphenyldicarboxylates.

Comparison of Liquid- and Vapor-Phase Arylation of Methyl Benzoate.—Homolytic arylation of methyl benozate hitherto has been studied exclusively in the liquid phase.[3,4] Low reactivity toward phenyl radical of the C–H bond of the methyl group of methyl benzoate has been observed at 60°.[5] In other studies phenyl radicals were produced by thermal decomposition of benzoyl peroxide[3] and aprotic diazotization of aniline;[4] the only products reported were methyl biphenylcarboxylates. To determine whether decarbomethoxylation occurs in the liquid phase, we examined the reaction of the phenyl-d_5 radical made by the aprotic diazotization of aniline-d_5, with methyl benzoate at 120°. The major products were methyl biphenylcarboxylate-d_5 and benzene-d_5, along with small amounts of biphenyl-d_{10} and methyl terphenylcarboxylate-d_9 and -d_{10}. Phthalide and biphenyl-d_5 were not formed; evidently abstraction of methyl hydrogens α to the carboxyl group with subsequent loss of the carbomethoxy group does not occur in the liquid phase. The preferred arylation of methyl benzoate in the liquid phase suggests a high $\Delta H^{\pm}$ for the hydrogen abstraction reaction.

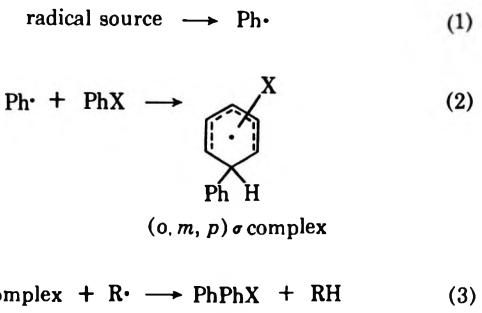
Another difference between the liquid- and vapor-phase arylations of methyl benzoate was the isomer distribution of the methyl biphenylcarboxylates, shown in Table III.

TABLE III
PHENYLATION OF METHYL BENZOATE

Source of phenyl radical	Isomer distribution of PhPhCO₂CH₃, % Ortho	Meta	Para
Benzoyl peroxide at 80° [a]	58	17	25
Aprotic diazotization of aniline at 120°	45	24	31
Nitrobenzene at 600°	9	52	39

[a] Reference 3.

Ortho substitution predominates in the liquid phase, whereas meta substitution is favored in the vapor phase. Meta substitution was also favored in the vapor-phase phenylation of chlorobenzene in which azobenzene was employed as the source of phenyl radicals.[6] The following mechanism has been generally accepted[7,8] for the liquid-phase homolytic arylation of arenes.



Isomer distributions are determined by step 2. However, if we assume that this step is reversible and neglect small differences in the relative rates of step 3, then the high meta percentage observed in the vapor phase can be rationalized on the basis of thermodynamic factors such as steric hindrance.[6] This rationalization is supported by the high meta percentages observed in the thermodynamic equilibria of PhPhCl[9] and PhPhCH₃,[10] which at 160 and 60°, respectively, are ortho, 3, 2.7%; meta, 64, 64.3%; para, 33, 33%. Thermal isomerization does not occur at 600° as evidenced by the recovery of unchanged dimethyl 4,4′-biphenyldicarboxylate from a separate experiment in which this isomer was submitted to the reaction conditions given in Table I alone.

The isomer distributions of the products from the reaction of methyl *p*-nitrobenzoate with methyl benzoate are listed in Table IV. The dimethyl biphenyldicarboxylate isomers show a high meta percentage and are consistent with the data from the other vapor-phase

(2) Decreasing the mole ratios of nitrobenzene:benzene and nitrobenzene:pyridine resulted in increased yields of biphenyl and phenylpyridines, respectively.[1c]

(3) D. H. Hey, F. C. Saunders, and G. H. Williams, *J. Chem. Soc.*, 3409 (1964).

(4) L. Friedman and J. F. Chlebowski, *J. Org. Chem.*, **33**, 1633 (1968).

(5) G. A. Russell and R. Bridger, *J. Amer. Chem. Soc.*, **85**, 3754 (1963).

(6) R. Louw and J. W. Rothuizen, *Tetrahedron Lett.*, 3807 (1967).

(7) D. R. Augood and G. H. Williams, *Chem. Rev.*, **47**, 123 (1957).

(8) G. H. Williams, "Homolytic Aromatic Substitution," Pergamon Press, London, 1960, Chapter 4.

(9) H. Weingarten, *J. Org. Chem.*, **27**, 2024 (1962).

(10) R. M. Koca, private communication.

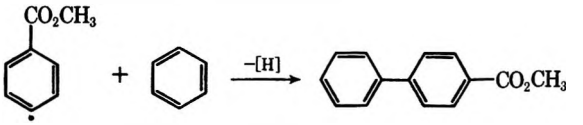
TABLE IV

ISOMER DISTRIBUTIONS FROM REACTION OF METHYL *p*-NITROBENZOATE WITH METHYL BENZOATE[a] AT 600°

Methyl biphenylcarboxylate isomer	1:5[b]	1:10
2	6	7
3	36	40
4	58	53
Dimethyl biphenyldicarboxylate isomer		
2,4′	9	12
3,4′	56	64
4,4′	35	24

[a] Conditions given in Table I. [b] Mole ratio methyl *p*-nitrobenzoate:methyl benzoate.

arylations. Isomer distributions of the methyl biphenylcarboxylates are difficult to interpret, as they may arise either from the reaction of a phenyl radical with methyl benzoate or from the interaction of a methyl benzoate radical ($CH_3O_2CPh\cdot$) with benzene. The high para percentage suggests the latter.



Differences in isomer distribution of arylation products, as well as differences in the nature of the products formed, provide a sharp contrast between free-radical attack on methyl benzoate in the gas phase *vs.* the liquid phase. Formation of phthalide from methyl benzoate by reaction with radicals in the gas phase represents a new type of intramolecular alkylation. This reaction is being studied further to extend its synthetic utility.

Registry No.—Methyl benzoate, 93-58-3; nitrobenzene, 98-95-3; methyl *p*-nitrobenzoate, 619-50-1.

Acknowledgment.—We acknowledge with thanks the assistance of D. K. Albert and S. Meyerson of the American Oil Company for gas chromatographic and mass spectrometric analyses.

A Novel Route to Bicyclo[2.2.2]octenetetracarboxylic Acid Dianhydrides

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Acetoxy-1,3-dienes, generated *in situ* from mesityl oxide, 2-cyclopentylidenecyclopentanone, 2-cyclohexenylcyclohexanone, and pulegone, undergo the Diels–Alder reaction with 2 equiv of maleic anhydride to yield bicyclo[2.2.2]oct-7-ene-2,3,5,6-tetracarboxylic acid dianhydride derivatives. Hydrolysis of dianhydrides **7** and **8** derived from 2-cyclopentylidenecyclopentanone and pulegone yields tetracarboxylic acids, whereas hydrolysis of dianhydrides **4** and **6** derived from mesityl oxide and 2-cyclohexenylcyclohexanone affords triacid lactone derivatives. Ozonolysis of tetramethyl ester **13** derived from **7** results in exclusive allylic oxidation yielding the unsaturated keto tetramethyl ester **15**, and lead tetraacetate oxidation of the corresponding tetraacid **12** occurs with participation of the carbon–carbon double bond affording a mixture of dilactones **16** and **17**.

Cyclic acetoxy 1,3-dienes, generated *in situ* from cyclic 1,2-, 1,3-, and 1,4-diketones, and from α,β-unsaturated ketones, react with maleic anhydride,[2] *p*-benzoquinone,[3] and dimethyl acetylenedicarboxylate[4] to yield oxygenated bicyclo[2.2.2]alkene derivatives. We have now extended this study to acyclic and exocyclic α,β-unsaturated ketones and find that reaction takes place with 2 equiv, rather than 1 of maleic anhydride to afford, instead of the expected acetoxy cyclohexenedicarboxylic anhydride,[5,6] bicyclo[2.2.2]-oct-7-enetetracarboxylic acid dianhydride derivatives.

Heating mesityl oxide in isopropenyl acetate containing a catalytic amount of *p*-toluenesulfonic acid with 2.3 equiv of maleic anhydride affords 1,8-dimethylbicyclo[2.2.2]oct-7-ene-2,3,5,6-tetracarboxylic acid dianhydride (**4**). Dianhydride **4** was identified by spectral analysis and by comparison with an authentic sample of **4** prepared by the reaction of 4,6-dimethyl-2-pyrone with maleic anhydride.[7]

The bridgehead methyl group of adduct **4** exhibits a unique nmr resonance signal at δ 1.98 ppm which is at lower field than the vinyl methyl group which resonates at 1.78 ppm. Examination of molecular models indicates that the methyl group is in the deshielding cone of two rigidly held anhydride carbonyls. Hydrolysis of adduct **4** with sodium bicarbonate solution, followed by acidification with hydrochloric acid and esterification with diazomethane, gives trimethyl ester lactone **5**[8] in which the bridgehead methyl group is found at 1.0 ppm, a chemical shift which is normal for methyl attached to a saturated carbon atom. We attribute this change to the free rotation permitted for the carbonyl groups of the carbomethoxy groups and subsequent removal of the deshielding effect displayed by the dianhydride.

A plausible pathway for the formation of dianhydride **4** in the condensation of mesityl oxide with maleic anhydride is shown in Scheme I. 1,2 or 1,4 elimination of acetic acid from the initially formed monoadduct[9] would yield dienes **2** or **3**. Under the conditions of the reaction, dienes **2** and **3** might be inter-

(1) David Ross Research Fellow, 1968–1969.

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

(3) J. Wolinsky and R. B. Login, *J. Org. Chem.*, **35**, 1987 (1970).

(4) J. Wolinsky and R. B. Login, *ibid.*, **35**, 3205 (1970).

(5) H. J. Hagemeyer and D. C. Hull, *Ind. Eng. Chem.*, **41**, 2920 (1949).

(6) W. Flaig, *Justus Liebigs Ann. Chem.*, **568**, 1 (1950).

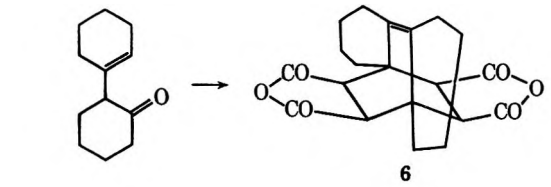
(7) O. Diels and K. Alder, *ibid.*, **490**, 259 (1931).

(8) Diels and Alder[7] reported the hydrolysis and esterification of **4** by this procedure and assigned the product, mp 155°, as a tetramethyl ester. The product we have isolated shows mp 153–154° and on the basis of its ir, nmr, and mass spectra is clearly trimethyl ester lactone **5**.

(9) P. Blanc, *Helv. Chim. Acta*, **44**, 1 (1961).

converted by a 1,5-hydrogen shift.[10] Diene **2** would be expected to react selectively[11] with maleic anhydride in the next Diels–Alder step to give adduct **4**.

2-Cyclohexenylcyclohexanone, 2-cyclopentylidenecyclopentanone, and pulegone also react with 2 equiv of maleic anhydride to form bicycloalkenedicarboxylic dianhydride derivatives **6**, **7**, and **8**, respectively.



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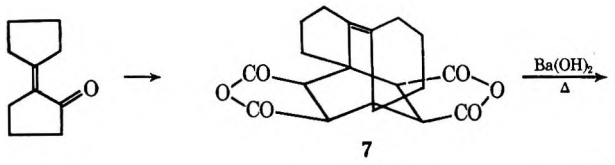

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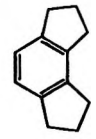

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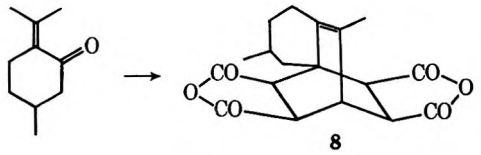
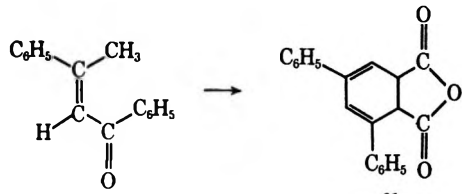


8

Adducts **6** and **7** display nmr singlets at 3.78 and 3.45 ppm, respectively, assigned to 4 HCCO protons; consequently, highly symmetrical structures are demanded for these adducts. This would not be the case if the adducts had been derived from a cyclohexadiene intermediate of structure related to diene **3**. Additional confirmation for the structure of adduct **7** was provided by its conversion on heating with barium hydroxide to hydrocarbon **9**. This latter transformation must involve a reverse Diels–Alder reaction followed by decarboxylation and aromatization.[12]

Dypnone (**10**) gave only a 1:1 adduct **11** with maleic anhydride. It is possible that the lower reactivity of **11** associated with the presence of two electron-withdrawing phenyl groups permits its isolation from the reaction mixture.



10 **11**

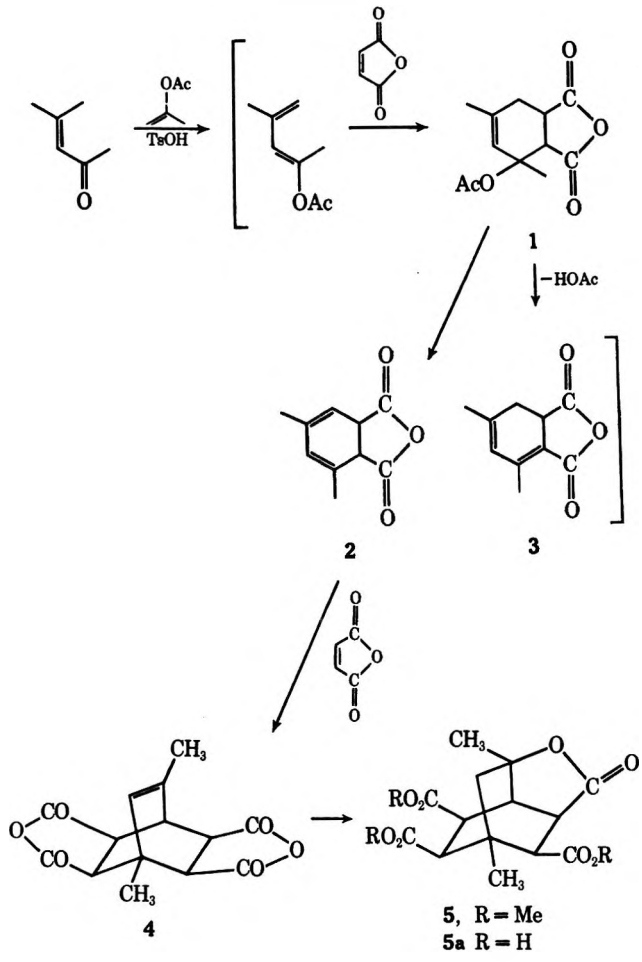
We turn next to a description of some chemical transformations of adduct **7**. Hydrolysis of **7** with aqueous sodium bicarbonate, followed by acidification with hydrochloric acid, affords tetraacid **12** which, in

(10) J. Wolinsky, B. Chollar, and M. Baird, *J. Amer. Chem. Soc.*, **84**, 2775 (1962).

(11) M. J. Goldstein, *ibid.*, **87**, 1925 (1965).

(12) See C. F. H. Allen and J. Van Allen, *J. Amer. Chem. Soc.*, **64**, 1260 (1942), for related transformations.

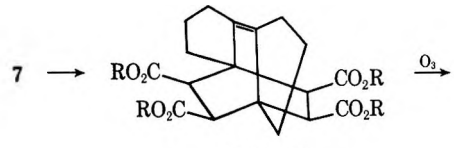
SCHEME I



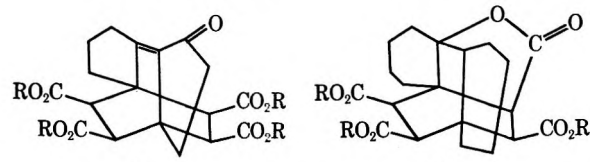
1 **2** **3** **4**

5, R = Me
5a R = H

turn, is converted into tetramethyl ester **13** by treatment with diazomethane. This behavior is similar to that observed with adduct **8**, but contrasts with the behavior of adducts **4** and **6** which are converted into trimethyl ester lactones **5** and **14** under similar conditions. Heating tetraacid **12** in acetic acid containing 5% sulfuric acid regenerated dianhydride **7**.



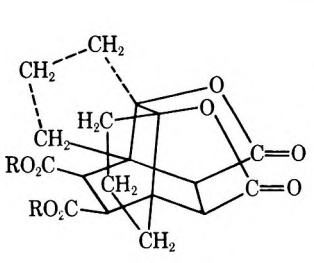
12, R = H
13, R = CH_3



15 **14**

The carbon–carbon double bonds in all the dianhydrides are extremely hindered and do not decolorize bromine or reduce easily with hydrogen. Ozonolysis of **7** could not be performed because of its insolubility in common solvents; however, ozonolysis of tetramethyl ester **13** gave the conjugated keto tetramethyl ester **15**, providing dramatic illustration of the hindered nature of the double bond.

Oxidation of tetraacid **12** with lead tetraacetate[2] gave dilactones **16** and **17** which were isolated as their methyl esters following treatment with diazomethane. Participation of the double bond during lead tetraacetate oxidation[2] offers chemical evidence for the syn stereochemical assignment of the carboxyl groups relative to the carbon–carbon double bond.



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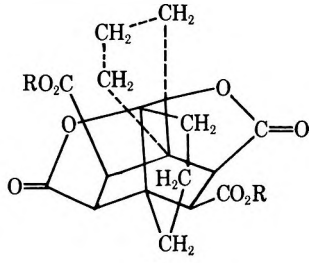

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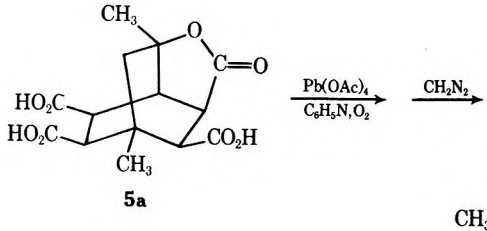
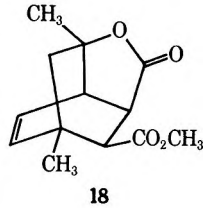
The action of lead tetraacetate on triacid lactone **5a** gave a complicated mixture which was separated into neutral and acidic fractions. The acid fraction was esterified with diazomethane and subjected to column chromatography. Unsaturated ester lactone **18** was isolated in pure form and identified on the basis of spectral considerations (see Experimental Section).



5a



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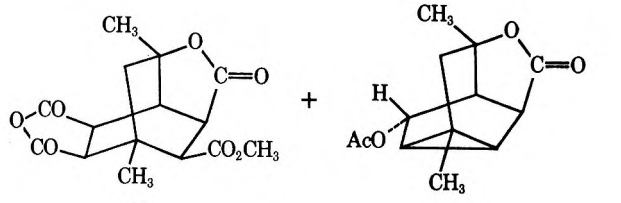
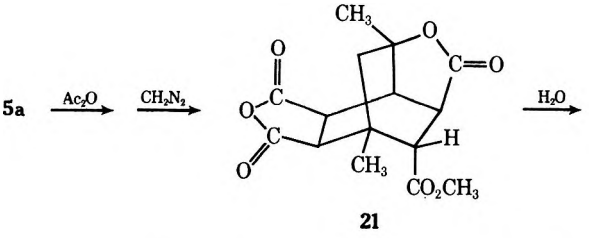


19 **20**



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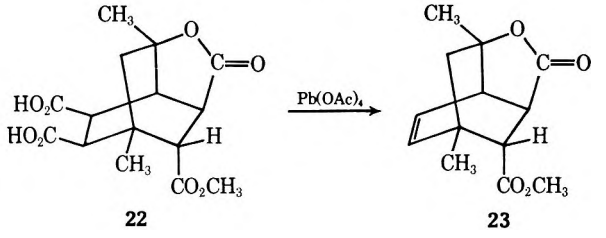

22 **23**

Another amorphous fraction showed a molecular ion at *m/e* 308 and on the basis of its nmr and ir spectra was assigned structure **19**.

The neutral fraction contained at least three major components, only one of which was isolated in pure form and was assigned structure **20** on the basis of (1) elemental analysis and the appearance of a molecular ion at *m/e* 236; (2) an infrared spectrum which showed carbonyl absorption at 5.6 and 5.72 μ; and (3) a fit of the nmr spectrum with the proposed structure, including confirmation of the presence of an acetate group by the appearance of a signal at 2.08 ppm and the indication of two methyl groups by singlets at 1.06 and 1.41 ppm. The endo configuration of the acetate group was assigned on the basis of a singlet for the CHOAc proton at 5.04 ppm. Examination of molecular models indicates an approximate 90° dihedral angle between this proton and the adjacent bridgehead proton, requiring a very small spin–spin coupling constant, whereas appreciable spin coupling would have been anticipated if the acetate group were exo.

Heating triacid lactone **5a** with acetic anhydride, followed by esterification with diazomethane, gave the anhydride methyl ester **21**, whose nmr spectrum indicates that the carbomethoxy group is endo, epimerization apparently takes place during heating with acetic anhydride. Hydrolysis of anhydride **21** with water gave diacid methyl ester **22**, which was bisdecarboxylated in good yield to unsaturated ester lactone **23**. Treatment of unsaturated ester lactone **18** with sodium methoxide produced lactone **23**, establishing the configurational relationship between these two isomers.

From the array of products produced from triacid lactone **5a** and from the single product isolated from diacid methyl ester lactone **22** it is obvious that all three carboxyl groups are involved in the reaction of **5a** with lead tetraacetate. It seems reasonable to suggest that bisdecarboxylation of **5a** to acid **18a** is followed by a rapid reaction of lead tetraacetate to give acetate lactone **20**.[13]

Experimental Section[14]

1,8-Dimethylbicyclo[2.2.2]oct-7-ene-2,3,5,6-tetracarboxylic Acid Dianhydride (4).—A stirred solution of 100 g of mesityl oxide and 230 g of maleic anhydride in 175 ml of isopropenyl acetate containing *ca.* 50 mg of *p*-toluenesulfonic acid was refluxed for 17 hr.[15] After cooling, part of the solvent was removed under diminished pressure, and cooling to −20° gave 144 g (52%) of crude adduct **4**, which was purified by recrystallization from acetonitrile: mp 270–272°; ir (KBr) 5.35 and 5.57 μ; nmr (C_6H_5CN) 1.78 (d, 3, J = 1 Hz, $CH_3C{=}C$), 1.98 (s, 3, CH_3C), 2.0–2.4 (broad m, impurity), 3.42 and 3.85 (distorted AB type quartet, 5), and 5.71 ppm (HC=C); mass spectrum (70 ev) *m/e* (rel intensity) 276 (28), 178 (73), 150 (56), 107 (23), 106 (59), 105 (32), 91 (100), 77 (25), 65 (25), 57 (23), 43 (28). No depression in melting point was observed when this sample was mixed with an authentic sample of dianhydride **4**, mp 272–274°.[7] The ir and nmr spectra were also identical with those of the authentic sample.

(13) See N. A. LeBel and J. E. Huber, *J. Amer. Chem. Soc.*, **85**, 3193 (1963), for a related transformation.

(14) All melting points are uncorrected. Infrared spectra were determined with a Perkin-Elmer Infracord spectrometer. Nmr spectra were measured with a Varian Associates A-60 spectrometer. The mass spectra were determined by the Purdue University Spectral Service Department employing a Hitachi RMU-6A mass spectrometer. Microanalyses were performed by Dr. C. S. Yeh and associates.

(15) *Caution:* Reactions run on this scale may require cooling if the reflux rate becomes too vigorous.

Trimethyl Ester Lactone 5.—A mixture of 2 g of dianhydride **4** and 20 ml of sodium bicarbonate solution was heated at reflux until the adduct dissolved (2–3 hr). The solution was cooled and concentrated hydrochloric acid was added resulting in the precipitation of 2.1 g of a white solid. The acid was dried *in vacuo*, dissolved in methanol, and treated with ethereal diazomethane. The solvents were evaporated to leave 2.3 g of crude ester lactone **5**. An analytical sample of **5** was prepared by recrystallization from ethanol: mp 153–154°; ir (Nujol) 5.65 and 5.75 μ; nmr ($CDCl_3$) 1.03 (s, 3, CCH_3), 1.68 (s, 3, CCH_3), 2.1 and 2.3 (m, 2), 3.06 (m, 5), 3.75 and 3.81 ppm (2s, 9, $-OCH_3$); mass spectrum (70 ev) *m/e* (rel intensity) 354 (3), 322 (13), 290 (6), 262 (5), 190 (8), 164 (14), 145 (30), 144 (100), 132 (13), 130 (10), 112 (77), 90 (33), and 58 (50).

Anal. Calcd for $C_{17}H_{22}O_8$: C, 57.62; H, 6.26. Found: C, 57.87; H, 6.42.

The same product (**5**) was obtained when adduct **4** was hydrolyzed by heating with water and the resulting acid esterified with diazomethane.

Dianhydride 6.—From 18.4 g of 2-cyclohexenylcyclohexanone[16] and 19.6 g of maleic anhydride in 60 ml of isopropenyl acetate there was obtained 10 g (26%) of crude adduct **6**. An analytical sample was obtained by recrystallization from acetonitrile: mp 308–310° (sealed tube); ir (Nujol) 5.4 and 5.6 μ; nmr (pyridine) 1.71 (m, 8), 2.16 (t, 4, $-CH_2C{=}C-$), 2.89 (t, 4), 3.78 ppm (s, 4, CHC=O); mass spectrum (70 ev) *m/e* (rel intensity) 356 (7), 328 (39), 300 (14), 230 (14), 229 (21), 186 (26), 185 (100), 158 (15), 143 (27), 129 (22), 128 (28), and 115 (22).

Anal. Calcd for $C_{20}H_{20}O_6$: C, 67.40; H, 5.66. Found: C, 67.67; H, 5.75.

Hydrolysis of 1 g of adduct **6** with 10 ml of aqueous sodium bicarbonate solution, followed by acidification and esterification with diazomethane, gave 1.07 g (85%) of trimethyl ester lactone **14**. An analytical sample of **14** was obtained by recrystallization from benzene–hexane: mp 236–239°; ir ($CHCl_3$) 5.6–5.8 μ (broad); nmr ($CDCl_3$) 1.63 (m, 16), 2.5 (m, 2), 2.71 and 3.34 (AB q, 2, J = 13 Hz), 3.6 and 3.73 ppm (2s, 9, OCH_3).

Anal. Calcd for $C_{23}H_{30}O_8$: C, 63.58; H, 6.96. Found: 63.43; H, 7.06.

Dianhydride 8.—From 100 g of pulegone and 150 g of maleic anhydride there was obtained 118 g (54%) of crude adduct **8**. A pure sample of **8** was obtained by recrystallization from acetonitrile: mp 327–328° (sealed tube); ir (Nujol) 5.4 and 5.6 μ; nmr [$(CD_3)_2SO$] 0.98 (d, 3, J = 6 Hz, $-CHCH_3$), 1.63 (s, 3, $C{=}CCH_3$), 2.32 (m, 4, $-CH_2-$), and 3.40 ppm (m, 5); mass spectrum (70 ev) *m/e* (rel intensity) 330 (43), 312 (4), 302 (15), 256 (8), 232 (13), 228 (15), 204 (69), 160 (31), 150 (100), 145 (20), 129 (13), 128 (13), 118 (20), 115 (13), 105 (13), and 91 (12).

Hydrolysis of dianhydride **8** with aqueous sodium bicarbonate, followed by acidification with hydrochloric acid and then esterification with diazomethane, afforded a tetramethyl ester which was recrystallized from benzene–hexane: mp 131–133°; ir (Nujol) 5.7 and 5.8 μ; nmr ($CDCl_3$) 0.88 (d, 3, CH_3), 1.0–1.8 (m, 5), 2.0 (s, 3, $C{=}CCH_3$), 2.4 (m, 2, $-CH_2C{=}C$), 2.89 and 2.99 (2s, 4, $-CHCO_2$), 3.22 (s, 1), and 3.56 (s, 12–OCH_3).

Anal. Calcd for $C_{22}H_{30}O_8$: C, 62.54; H, 7.16. Found: C, 62.40; H, 7.30.

Dianhydride 7.—From 10 g of 2-cyclopentylidenecyclopentanone[17] and 16.1 g of maleic anhydride there was obtained 13.5 g (62%) of dianhydride **7**. A pure sample of **7** was obtained by recrystallization from acetic anhydride: mp 317–318° (sealed tube); ir (Nujol) 5.4 and 5.6 μ; nmr [$(CD_3)_2SO$] 1.71 and 2.07 (m, 4, $C{=}CCH_2CH_2$), 2.58 (t, 4, $-CH_2-$), and 3.45 (s, 4, $-CHCO$) mass spectrum (70 eV) *m/e* (rel intensity) 328 (11), 298 (28), 270 (11), 229 (21), 202 (29), 201 (33), 158 (42), 157 (100), 129 (36), and 115 (24).

Anal. Calcd for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91. Found: C, 65.91; H, 5.07.

Tetraacid 12.—A 2.0-g sample of dianhydride **7** was refluxed with 30 ml of aqueous sodium bicarbonate solution until solution occurred (2–3 hr). The solution was cooled and acidified with concentrated hydrochloric acid to give 1.8 g of tetraacid **12**, which was generally used without further purification.

A portion of tetraacid **12** was esterified with diazomethane to yield tetramethyl ester **13**. A pure sample of **13** was obtained by recrystallization from methanol: mp 223–224°; ir (Nujol) 5.72 μ; nmr ($CDCl_3$) 1.90 (broad s, 8, $-CH_2CH_2-$), 2.62 (broad s, 4, $-CH_2C{=}C$), 3.13 (s, 4, $-CHCO_2$), and 3.61 ppm (s, 12, $-OCH_3$).

Anal. Calcd for $C_{22}H_{28}O_8$: C, 62.85; H, 6.71. Found: C 63.00; H 6.92.

3,5-Diphenyl-1,2-dihydrophthalic Anhydride (11).—The reaction of 46.6 g of dypnone (**10**) and 50 g of maleic anhydride afforded an oil which was dissolved in a minimum amount of ethyl acetate, treated with Norit, filtered, and treated with hexane until some of the "tar" had precipitated. Upon cooling, 25 g (40%) of a yellow solid was isolated. Further recrystallization from ethyl acetate–hexane gave a pure sample of **11**: mp 158–159°; ir (Nujol) 5.42 and 5.62 μ; nmr ($CDCl_3$) 3.5 (m, 2) and 7.7 ppm (m, 12); mass spectrum (70 ev) *m/e* (rel intensity) 302 (4), 301 (18), 300 (78), 256 (61), 228 (70), 226 (41), 128 (100), and 44 (83).

Anal. Calcd for $C_{20}H_{14}O_3$: C, 79.46; H, 4.67. Found: C, 79.62; H, 4.76.

1,2,3,6,7,8-Hexahydro-*as*-indacene (9).—A mixture of 3 g of dianhydride **7** and 12 g of dry barium hydroxide[12] in a short path distilling apparatus was heated over a flame and after a few minutes 550 mg of material distilled (180–220°). This product was sublimed to give 520 mg (36%) of **9**: mp 38–38.5° (lit.[18] mp 40–42°); nmr ($CDCl_3$) 2.02 (m, 4), 2.75 (q, 8), and 7.0 ppm (s, 2).

Ozonolysis of Tetramethyl Ester 13.—A solution of 1.87 g of ester **13** in 30 ml of methylene chloride and 40 ml of acetic anhydride was ozonized at −78° for 30 min. The solution was added to 100 ml of water and 1 g of zinc dust and the mixture was stirred for 1 hr, filtered, and extracted with methylene chloride. The methylene chloride was washed with dilute sodium hydroxide solution, dried ($MgSO_4$), and evaporated to give 1.41 g (73%) of conjugated keto tetramethyl ester **15**. Recrystallization from acetone–hexane gave a pure sample of **15**: mp 201–202°; ir (Nujol) 5.71 and 6.01 μ; λ_{max}^{EtOH} 257 nm (ϵ 8000); nmr (pyridine) 1.82–3.5 (m's, 12), 3.50 and 3.51 ppm (2s, 12); mass spectrum (70 ev) *m/e* (rel intensity) 434 (21), 402 (6), 305 (8), 290 (13), 257 (19), 256 (11), 230 (24), 229 (36), 171 (26), 145 (13), 128 (9), 113 (100), and 59 (14).

Anal. Calcd for $C_{22}H_{26}O_8$: C, 60.82; H, 6.03. Found: C, 60.81; H, 5.99.

Lead Tetraacetate and Tetraacid 12.—Oxygen was bubbled for 15 min through a solution of 7.46 g of tetraacid **12** in 75 ml of pyridine and then 50 g of lead tetraacetate was added at one time. The mixture was heated to 60°, turned light orange and after several minutes boiled violently, turning dark brown. Stirring was continued for 1 hr, at which time the mixture was cooled, poured into dilute nitric acid, and extracted with ether. The ether extracts were washed with brine solution, dried ($MgSO_4$) and evaporated, leaving an oil which was triturated with ether to give 1.2 g of solid. This solid was treated with ethereal diazomethane to give dimethyl ester dilactone **16**, which was recrystallized from chloroform–hexane: mp 233–235°; ir 5.6 and 5.75 μ; nmr ($CDCl_3$) 2.0 (m, 12), 2.81 and 3.29 (AB q, 4, J = 9 Hz, CHCO), 3.75 ppm (s, 6, $-OCH_3$); mass spectrum (70 ev) *m/e* (rel intensity) 390 (42), 358 (47), 314 (61), 260 (36), 216 (49), 215 (80), 157 (100), 155 (57), 131 (37), 129 (40), 115 (36), 113 (34), 91 (33), 59 (42), and 55 (39).

Anal. Calcd for $C_{20}H_{22}O_8$: C, 61.54; H, 5.68. Found: C, 61.65; H, 5.54.

Evaporation of the ether solution obtained by trituration of the crude reaction product left 2.3 g of oil. A 1.0-g portion of this material was treated with ethereal diazomethane and the resulting oil was chromatographed on silica gel. Elution with hexane–ethyl acetate gave several fractions, the second of which solidified when triturated with ether to give 400 mg of solid dilactone **17**, which was recrystallized from chloroform–hexane: mp 201–202°; ir (Nujol) 5.6 and 5.8 μ; nmr ($CDCl_3$) 2.0 (m, 12), 2.84 (broad s, 3, $-CHCO$), 3.03 (s, 1, $-CHCO$), 3.65 and 3.71 ppm (2s, 6, $-OCH_3$); mass spectrum (70 ev) *m/e* (rel intensity) 390 (9), 359 (28), 358 (100), 314 (9), 286 (7), 258 (9), 215 (10), 210 (14), 157 (20), 131 (10), 129 (13), 115 (12), 91 (12), 59 (16) and 55 (14).

Anal. Calcd for $C_{20}H_{22}O_8$: C, 61.54; H, 5.68. Found: C, 61.24, H, 5.75.

Lead Tetraacetate and Trimethyl Ester Lactone 5a.—Oxygen was bubbled through a stirred solution of 5.0 g of trimethyl

(16) J. Reese, *Chem. Ber.*, **76**, 384 (1942).
(17) R. Meyer, *ibid.*, **89**, 1443 (1956).
(18) H. Rapoport and G. Smolinsky, *J. Amer. Chem. Soc.*, **82**, 1171 (1960).

ester lactone **5a** in pyridine and then 16 g of lead tetraacetate was added at once. The mixture was heated to 65° and, after a 2–3-min induction period, carbon dioxide evolution began and became quite vigorous. After carbon dioxide evolution ceased (3 min), stirring was continued for 5 min, and the mixture was cooled and then poured into dilute nitric acid. The resulting mixture was extracted with ether. The ether extracts were washed with brine solution, concentrated to 100 ml, and then extracted with saturated sodium bicarbonate solution. The neutral ether solution was washed with brine solution and dried ($MgSO_4$), and the ether was evaporated to leave 620 mg of oil. Thick layer chromatography on silica gel employing hexane–ether–ethyl acetate (10:1:3) gave 400 mg of oil as the fastest moving component. The oil was rechromatographed on silica gel using hexane–ethyl acetate (1:1) to develop the plate and afforded 310 mg in the fastest moving fraction. Recrystallization from benzene–hexane gave 240 mg of acetate lactone **20**: mp 95.5–97.5°; ir ($CHCl_3$) 5.6 and 5.72 μ; nmr ($CDCl_3$) 1.06 and 1.41 (2s, 6, $-CH_3$), 1.63 (m, 2), 1.92 (s, 2, $-CH_2$), 2.08 (s, 3, $-OCOCH_3$), 2.62 (d, 1, J = 6 Hz C_4 H), 3.03 and 3.12 (d of d, 1 J = 6 and 4 Hz, C_5 H), and 5.04 ppm (s, 1, C_3 H); mass spectrum (70 ev) m/e (rel intensity) 236 (6), 194 (3), 176 (3), 150 (4), 133 (7), 132 (8), 106 (9), 91 (7), 87 (10), 85 (66), 83 (100), 43 (15).

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 66.29; H, 6.86.

The sodium bicarbonate solution obtained above was neutralized with hydrochloric acid and extracted with ether. The ether extracts were washed with brine solution, dried ($MgSO_4$), and evaporated to afford an oil which was esterified with diazomethane to yield 0.92 g of a viscous oil. A 278-mg sample of this oil was subjected to thick layer chromatography using silica gel and 1:1 hexane–ethyl acetate as a developer. The fastest moving component, 35 mg, proved to be unsaturated ester lactone **18** and was purified by recrystallization from benzene–hexane: mp 72–73°; ir ($CHCl_3$) 5.6 and 5.75 μ; nmr ($CDCl_3$) 1.0 and 1.23 (d of d, 1, J = 2 and 15 Hz, C_7 H), 1.20 and 1.38 (2s, 6, CH_3), 2.23 and 2.42 (d of d, 1, J = 1.5 and 10 Hz, C_5 H), 2.68 (d, 1, J = 15 Hz, C_7 H), 2.65 (broad s, 1, C_6 H), 3.18 (m, 1 C_4 H) 3.71 (s, 3, $-OCH_3$), and 6.20 ppm (m, 2, CH=CH); mass spectrum m/e (rel intensity) 236 (71), 208 (95), 205 (15), 176 (20), 161 (31), 151 (84), 149 (77), 148 (20), 133 (20), 119 (16), 107 (96), 106 (41), 105 (52), 92 (30), 91 (100), 79 (19), 77 (21), 65 (18), 59 (26), and 43 (82).

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: 66.30; H, 6.83.

The next fastest moving component isolated from tlc, 117 mg, proved to be a mixture and could not be separated by additional thin layer chromatography. The mixture showed four $-OCH_3$ singlets at 3.70, 3.73, 3.78, and 3.80 ppm and a molecular ion in its mass spectrum at m/e 294 (20) and important ions at m/e 266 (20), 175 (28), 165 (21), 133 (38), 106 (23), 105 (32), 91 (28), 85 (65), 83 (100). This mixture was not characterized further.

The slowest moving component, 70 mg, proved to be **19** as indicated by ir bands at 5.62 and 5.75 μ and a molecular ion at m/e 308.

Lead Tetraacetate and Diacid Lactone 22.—Diacid lactone **22** was obtained by heating 4.5 g of triacid lactone **5a** with 40 ml of acetic anhydride for 1–2 hr. The excess anhydride was removed under diminished pressure and the resulting solid, mp 280–285°, was treated with excess diazomethane in ether. Evaporation of the ether gave 4.2 g of an oil which was heated with 30 ml of water until solution occurred (2 hr). The ether was evaporated under diminished pressure to leave 4 g of **22** as a viscous oil, which was used directly in the next step.

The crude **22** was dissolved in pyridine and oxygen was bubbled through the solution for 15 min. Lead tetraacetate (12 g) was added at once and the mixture was immediately placed in an oil bath maintained at 70°. After 2–3 min carbon dioxide evolution began. When bubbling ceased the mixture was cooled and worked up in the usual fashion to give 1.03 g of neutral oil. Column chromatography of 0.8 g of this oil on silica gel and elution with hexane–ethyl acetate gave 70 mg of unidentified oil and 600 mg of unsaturated ester lactone **23**. The analytical sample was secured by recrystallization from pentane: mp 53–55°; ir ($CHCl_3$) 5.62 and 5.75 μ; nmr ($CDCl_3$) 1.23 and 1.80 (AB q, 2, J = 14 Hz, C_7 H), 1.34 (s, 6, $-CH_3$), 2.6 (d, 1, J = 1.5 Hz, $-CHCO_2$), 2.77 and 2.86 (d of d, 1, J = 9 and 1.5 Hz, C_5 H), 3.18 (q, 1, J = 4 Hz, C_4 H), 3.68 (s, 3, $-OCH_3$), and 6.18 (d, 2, CH=CH).

Anal. Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: 66.23; H, 6.82.

The acid fraction isolated in the work-up of the above reaction gave 1.1 g of oil. Chromatography of 800 mg of this material on silica gel and elution with hexane–ethyl acetate gave 150 mg of anhydride **21**, while later fractions (0.6 g) when heated with acetic anhydride gave an additional 350 mg of anhydride **21**: mp 179–180.5°; ir ($CHCl_3$) 5.39, 5.6, and 5.79 μ; nmr ($CDCl_3$) 1.38 and 1.44 (2s, 6, $-CH_3$), 1.73 (s, 1, C_7 H), 1.83 (d, 1, J = 2 Hz, C_7 H), 2.66 (s, 1, C_8 H), 2.99 (broad, s, 2), 3.00 and 3.19 (m, 1), 3.77 ppm (s, 3, $-OCH_3$); mass spectrum (70 eV) m/e (rel intensity) 308 (20), 290 (7), 277 (7), 264 (17), 236 (6), 205 (7), 192 (13), 177 (12), 165 (100), 151 (20), 133 (49), 121 (16), 119 (15), 107 (15), 91 (27), and 43 (36).

Anal. Calcd for $C_{15}H_{16}O_7$: C, 58.44; H, 5.23. Found: C, 58.61; H, 5.18.

Epimerization of Unsaturated Ester Lactone 18.—A solution of 60 mg of **18** in methanol containing *ca.* 40 mg of sodium methoxide was kept at ambient temperature for 12 hr. Water and hydrochloric acid were added and the mixture was extracted with ether. Work-up of the ether solution gave an oil which was recrystallized from pentane to give a solid, mp 47–50°, whose spectral properties were identical with those of unsaturated ester lactone **23**.

Registry No.—**4**, 32251-35-7; **5**, 32251-36-8; **6**, 32251-37-9; **7**, 32304-26-0; **8**, 32251-38-0; **9**, 1076-17-1; **11**, 25278-11-9; **13**, 32251-41-5; **14**, 32251-42-6; **15**, 32251-43-7; **16**, 32237-59-5; **17**, 32237-60-8; **18**, 32304-27-1; **20**, 32251-44-8; **21**, 32251-45-9; **23**, 32251-46-0; tetramethyl ester, mp 131–132°, 32251-47-1.

Reactions of Vicinal Dianions. The Alkylation of the Benzophenone Anil Dianion

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Received June 28, 1971

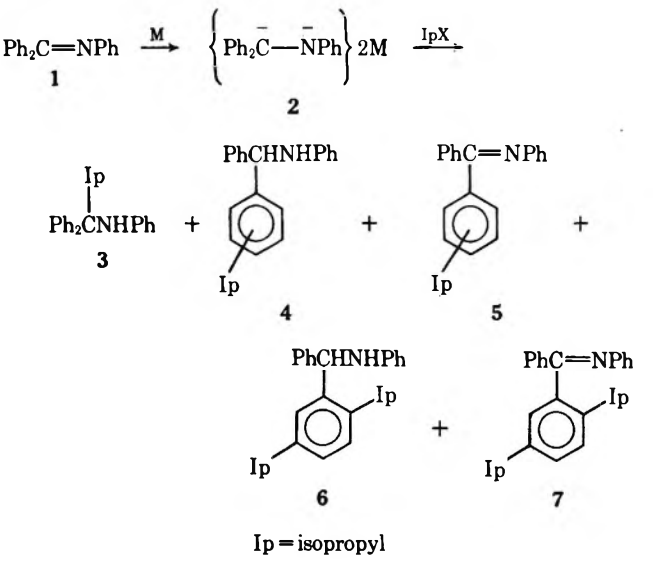
Reduction of benzophenone anil (**1**) with alkali metals produces a vicinal dianion **2**. The alkylation of this dianion with isopropyl halides is studied as a function of alkali metal (Li, Na, K), solvent (THF, DEE), and amount (1 and 2 equiv) and kind of isopropyl halide (Cl, Br, I). The alkylation product consists of a mixture of 2-methyl-*N*,1,1-triphenylpropylamine (**3**), *N*-(*o*- and *p*-isopropylbenzhydryl)aniline (**4**), *o*- and *p*-isopropylbenzophenone anil (**5**), *N*-(2,5-diisopropylbenzhydryl)aniline (**6**), and 2,5-diisopropylbenzophenone anil (**7**). The exact composition varies over a wide range depending on the reaction conditions. The most reactive halide, isopropyl iodide, produces the largest amount of alkylation in the aromatic ring and, if 2 equiv are present, also produces the largest amount of dialkylation. The cation associated with **2** also exerts a marked influence; while large amounts of ortho alkylation occur with lithium as cation, essentially only alkylation at the benzylic carbon is observed when the cation is potassium. These effects are discussed.

Benzophenone anil (**1**) on reduction by alkali metals[1,2] in aprotic solvents produces a dianion **2** which has the complex and intriguing possibility of reaction at either or both of the two vicinal anionic centers. In addition to this, reaction at sites on the aromatic rings of the diphenylmethyl moiety might be anticipated by analogy with the observed behavior of other benzyl organometallic reagents.[3]

Our earlier preliminary studies[2] of the alkylation of the dianion **2** have provided examples of each of these reactions. We wish to report a detailed study of this alkylation with isopropyl halides. This study was initiated in order to determine the factors controlling the alkylation, in order to provide some understanding of the mechanism involved in the alkylation, and in order to gain some control over the synthetic utility of the reaction. The parameters selected for study were alkali metal (Li, Na, K), solvent [tetrahydrofuran (THF) and diethyl ether (DEE)], and the leaving group of the isopropyl halide (Cl, Br, I).

SCHEME I

PRODUCTS FROM THE ALKYLATION REACTION



Results

A variety of alkylation products were observed, the exact product composition depending on all the parameters studied. The reaction mixtures were analyzed by vapor phase chromatography (vpc) and the individual components were identified by isolation, by vpc retention time, and/or by conversion to and identification of a derivative. Scheme I summarizes the products observed.

In addition to the compounds shown in Scheme I, two others were detected by vpc. One of these, unknown C, had the largest retention time of any compound observed and probably contains two isopropyl groups. Since it was formed in small amounts and only when DEE solutions of the dianion **2** were used, no attempt was made to characterize it. The other compound, unknown A, was generally formed together with compound **7**. Several attempts to isolate this compound were unsuccessful. Since it was observed that unknown A was completely converted to **7** on brief contact with aqueous acid and also was converted to **6** by reduction, this compound is considered to be the less stable of the syn–anti pair of compounds **7**, formed under the nonequilibrating alkaline (or neutral) conditions of the alkylation reaction.

One additional compound was detected which is not shown in Scheme I, *m*-isopropylbenzophenone anil (**5**, *m*-Ip). Originally, the dialkylated products were thought to be the *m*-isopropyl analogs of **4** and **5** and authentic samples were prepared.[4] This synthesis was not entirely in vain, since a very minor product proved to have an identical retention time as **5** (*m*-Ip) and from the hydrolysis products *m*-isopropylbenzophenone was isolated by preparative vpc. However, the quantities of this material are so minor (*ca.* 1%) that it has been omitted from the discussion (see ref 15).

While nitrogen alkylation has been effected by methyl iodide,[2a] no *N*-isopropylbenzhydrylaniline was detected among the reaction products. The absence of any "C,N-diisopropylated" product was indicated[2] by the absence of any *N*-isopropylaniline among the compounds formed on heating the reaction mixtures with aqueous HCl. Finally, protonation of the dianion **2** with 1

(1) (a) W. Schlenk and E. Bergmann, *Justus Liebigs Ann. Chem.*, **463**, 281 (1928); (b) B. M. Mikhailov and K. N. Kurdyumova, *J. Gen. Chem. USSR*, **26**, 899 (1956).

(2) (a) J. G. Smith and C. D. Veach, *Can. J. Chem.*, **44**, 2245 (1966); (b) J. G. Smith, *ibid.*, **46**, 2271 (1968); (c) R. Turle and J. G. Smith, *Tetrahedron Lett.*, 2227 (1969).

(3) (a) M. S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, New York, N. Y., 1954, p 1134; (b) R. A. Benkeser and T. E. Johnston, *J. Amer. Chem. Soc.*, **88**, 2220 (1966); (c) R. A. Benkeser and W. De Talvo, *ibid.*, **89**, 2141 (1967); (d) R. A. Benkeser, T. E. Johnston, and W.-H. Tong, *J. Org. Chem.*, **33**, 2203 (1968); (e) G. A. Russell, *J. Amer. Chem. Soc.*, **81**, 2017 (1959).

(4) We are indebted to Mr. R. Pearce who synthesized this series of compounds as part of an undergraduate research project.

TABLE I

SUBSTITUTION PATTERN IN THE ALKYLATION OF THE BENZOPHENONE ANIL DIANION (2)

			Position of entering isopropyl group										
			% 3 (benzylic)			% 4 + 5 (*o*-Ip)			% 4 + 5 (*p*-Ip)			% 6 + 7 (di-Ip)	
Solvent	Metal	IpX, equiv	X = Cl	Br	I	Cl	Br	I	Cl	Br	I	Cl	Br	I
THF	Li	1	46	25	22	45	57	48	9	18	30			
THF	Na	1	61	51	38	39	45	49		4	13			
THF	K	1	98	90	63	0	9	17	2	1	20			
THF	Li	2	34	25	26	57	57	11	9	18	35			25
THF	Na	2	61	64	41	39	21	9		13	18		2	32
THF	K	2	92	93	68	8	6	0		1	19			13
DEE	Na	1	60	68	52	16	14	9	12	12	39	12	6	
DEE	Na	2	60	60	46	18	14	8	12	23	45	9	3	1

equiv of *tert*-butyl alcohol followed by several attempts to alkylate the resulting anion failed; the only product isolated was *N*-benzhydrylaniline. In the case of secondary halides, dehydrohalogenation was the only observed reaction.[5]

The complete analytical data is presented in the Experimental Section (Table II) but a simpler presentation showing only the substitution patterns is given in Table I. Results obtained with the dianion 2 (M = Li) in DEE are omitted here since the solution was not homogeneous. As Kornblum[6] has shown, homogeneity can be a major variable in the alkylation of bidentate anions. A potassium dianion 2 (M = K) could not be formed in DEE.

A comparison of the products generated by 1 mol of isopropyl halide with those formed by 2 mol shows that the extent of benzylic and para alkylation is the same. When differences do occur, they do so chiefly in the formation of dialkylated products at the expense of the ortho alkylated ones. It should be noted that such a deviation occurs when the alkylating agent is isopropyl iodide or (less often) isopropyl bromide. Furthermore, this effect of the amount of alkylating agent is seen in THF but not in DEE.

The substitution pattern observed in THF with 1 mol of isopropyl halide is influenced both by the cation and by the halogen. As the cation changes, Li → Na → K, the amount of benzylic alkylation increases at the expense of all other modes of alkylation. As the halogen changes Cl → Br → I, ring alkylation (especially para) increases at the expense of benzylic alkylation (ortho alkylation remains approximately constant). In the less basic solvent, DEE, this same trend can be seen but the increase in para alkylation is accompanied by a decrease of both benzylic and ortho alkylation.

Discussion

The influence of the halogen atom upon the course of the reaction prompted consideration of an exchange reaction operating with the more reactive halides. Conceivably, the dianion 2 might react[7] with isopropyl

$$\underset{2}{\{Ph_2\bar{C}-\bar{N}Ph\}}2M^+ + IpI \longrightarrow MI + IpM + \underset{1}{Ph_2C{=}NPh}$$

iodide (or bromide) in the manner shown. The organometallic compound (IpM) might then react with the regenerated benzophenone anil (1) to form the products observed.

This possibility was examined by treating 1 with isopropyllithium both with and without the subsequent addition of 1 mol of isopropyl halide; the former conditions simulated those experiments in which alkylation of 2 was effected with 2 mol of isopropyl halide. The observed alkylation pattern differs substantially from that obtained in the alkylation of dianion 2. First, no dialkylation products were observed in the isopropyllithium experiments while they are quite prevalent in the alkylation of 2 (M = Li) and isopropyl iodide (the most likely system to undergo an exchange reaction). Second, the substitution pattern itself differs. With isopropyllithium, approximately equal amounts of benzylic, ortho, and para alkylation occur while, with 2 (M = Li) and isopropyl iodide, the product composition is heavily biased toward ortho alkylation.

It is concluded that an exchange reaction does not play a significant role in the alkylation of dianion 2.

If this alkylation is considered to be a nucleophilic substitution of the isopropyl halide by the dianion 2, the trends observed in this study become understandable. Delocalization of the anionic charge from the benzylic carbon into the aromatic rings[8] permits alkylation to occur at several points within the diphenylmethyl unit. Russell[3e] has reported that ring substitution in a benzylic anion became observable only when the second reagent was a reactive (and hence a nondiscriminating) one. The extent of ring alkylation, especially in the para position, increases as the reactivity of the isopropyl halide increases.

Other factors appear to control the extent of alkylation at the ortho position. By analogy with the "abnormal" reactions of Grignard reagents,[3a] one may consider a cyclic six-center transition state[9] as being responsible for this mode of attack. However, the argument of Kornblum[10] seems more appropriate. Alkylation of the benzylic position requires a moderately large separation between the metal cation and the developing halide ion. On the other hand, alkylation at the ortho position permits the metal cation and the developing halide ion to be spatially proximate. In solvents of low dielectric constant such as THF, the latter mode of reaction is favored.

(5) Color changes indicated that a reaction was indeed occurring.

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

(7) R. G. Jones and H. Gilman, *Org. React.*, **6**, 339 (1951). (b) A related effect of halogens has been observed; see W. G. Kofron and C. R. Hauser, *J. Amer. Chem. Soc.*, **90**, 4126 (1968).

(8) Charge delocalization in the diphenylmethyl carbanion has been reported: (a) V. R Sandel and H. H. Freedman, *ibid.*, **85**, 2328 (1963); (b) R. Waack, L. D. McKeever, and M. A. Doran, *Chem. Commun.*, 117 (1969).

(9) (a) J. J. Eisch, "The Chemistry of Organometallic Compounds," Macmillan, New York, N. Y., 1967, pp 54, 88; (b) H. D. Zook and J. A. Miller, *J. Org. Chem.*, **36**, 1112 (1971).

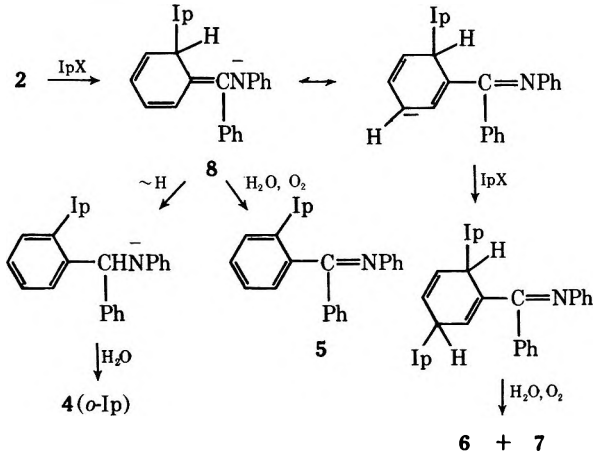
(10) N. Kornblum, R. Seltzer, and P. Haberfield, *J. Amer. Chem. Soc.*, **85**, 1148 (1963).

As Kornblum suggests, this electrostatic constraint on the direction of alkylation will be dependent on the cation. The effect will be large with small cations forming tight ion pairs (*i.e.*, Li^+) but less effective as the cation becomes larger, the positive charge more diffuse and the ion pairs looser.

The primary product from alkylation at the ortho (or para) position is a triene such as **8** and evidence for such intermediates has been adduced by Benkeser[3c] and others.[11] Two means are available for rearomatization of these derivatives, a proton shift to form a substituted benzhydrylaniline and oxidation during isolation to form a substituted benzophenone anil (see Scheme II).

SCHEME II

RING ALKYLATION OF THE BENZOPHENONE ANIL DIANION



The former seems favored by the ortho-substituted product while the latter is favored by the para-substituted product.

In the presence of a second equivalent of isopropyl iodide, further alkylation may occur. The triene **8** is now an ambident anion and the anionic charge is delocalized over an extended conjugated system as is shown (in part) in Scheme II. A second alkylation producing disubstituted derivatives is thus a possibility.

Only with the more reactive halides (iodide) do significant amounts of dialkylation occur. With the less reactive chloride, the second alkyl group is not introduced but dehydrohalogenation predominates with the most noticeable consequence being that the para-substituted product appears now as the *N*-substituted aniline rather than the anil.

This dialkylation is confined to the ortho-substituted primary product **8**. Probably the controlling factor is steric. Analogous reasoning with the primary para product would predict the formation of 3,4-diisopropyl derivatives and the introduction of a second isopropyl group adjacent to the first would be energetically unfavorable.

Indeed, it is probably essential[12] that the dialkylated products **6** and **7** be derived from the intermediate **8**. Alternative routes involving nucleophilic substitution of **5** (*o*-Ip) or alkylation of the dianion of **5** (*o*-Ip) (formed by electron transfer from **2**) should not produce the 2,5-diisopropyl derivatives **6** and **7** but instead 2,4-, 2,6-, and compounds with the alkyl groups in different aromatic rings.

Recently, considerable attention has focused on radical intermediates in the reactions of organometallic compounds with alkyl halides.[13] Unfortunately, these mechanistic studies are directed toward aliphatic organometallic compounds or toward those that are clearly radical anions. The possibility that radical anions are intermediates in the alkylations studied here cannot be completely excluded particularly in view of a recent suggestion that electron transfer may well be the first step in nucleophilic substitution.[13i]

The presently available data on the reaction of resonance stabilized organometallic compounds with optically active alkyl halides supports a nucleophilic substitution mechanism[14] and for this reason the discussion has centered around such a mechanism. We are presently comparing the reactions of the radical anion[15] of **1** and the dianion of **1** (*i.e.*, **2**) with a number of different reagents to see what differences there may be.

Experimental Section

Melting points were determined in an open capillary using a Mel-Temp melting point apparatus and are uncorrected. Infrared spectra were recorded on a Beckman IR-10 spectrophotometer and nmr spectra on a Varian T-60 spectrometer. Chemical shifts are reported in parts per million downfield from internal TMS (δ units). Vapor phase chromatography (vpc) was carried out on a Varian-Aerograph Model 1520 instrument equipped with flame ionization detectors (for analytical results) and thermal conductivity detectors (for preparative work). Silica gel (0.05-0.20 mm) from E. Merck AG was used for column chromatography and Eastman Chromagram 6060 (silica gel) sheets were used for thin layer chromatography (tlc). Analytical results were obtained from A. B. Gygli, Toronto, Ontario, and M-H-W Laboratories, Garden City, Mich.

Preparation and Reactions of Benzophenone Anil Dianion (2).—The preparation and handling of the dianion **2** has been described[2] elsewhere. The normal experiment utilized 0.01 mol of **2** in 70 ± 10 g of solvent (distilled from $LiAlH_4$). This solution was cooled to −50° and the isopropyl halide was injected through a septum into the stirred solution. After stirring at −50° for 30 min, the solution was allowed to warm to room temperature and stand for 12 hr. Water was then added and the reaction products were isolated by ether extraction.

Analysis.—No column could be found which resolved **3** and **4** (*o*-Ip). Consequently, each reaction mixture was subjected to two analyses. In the first, the reaction mixture was analyzed on a 10 ft by $^1/_8$ in. column of 3% SE-52 on 100–120 HP Chromosorb W with injection port at 150° and the oven temperature programmed as follows: 6 min at 145°, heated 9 min at 4°/min, heated 18 min at 2°/min (final temperature 220°), held at 220° for 20 min.

An 0.2–0.3-g sample of the reaction mixture was heated on a steam bath for 1.5 hr with 20 ml of 20% aqueous HCl and the organic layer was extracted with ether, neutralized, dried, and analyzed under the same conditions. The peak areas of 1,1-

(11) (a) R. A. Sulzbach, *J. Organometal. Chem.*, **24**, 307 (1970); (b) A. J. Birch, E. G. Hutchinson, and G. S. Rao, *J. Chem. Soc. C*, 637 (1971).

(12) We are grateful to a referee for calling this to our attention.

(13) (a) D. Bryce-Smith, *J. Chem. Soc.*, 1603 (1956); (b) G. A. Russell, E. G. Janzen, and E. T. Strom, *J. Amer. Chem. Soc.*, **86**, 1807 (1964); (c) G. A. Russell and D. W. Lamson, *ibid.*, **91**, 3967 (1969); (d) S. Bank and J. F. Bank, *Tetrahedron Lett.*, 4533 (1969); (e) J. F. Garst, J. T. Barbas, and F. E. Barton, *J. Amer. Chem. Soc.*, **90**, 7159 (1968); (f) G. D. Sargent and G. A. Lux, *ibid.*, **90**, 7160 (1968); (g) J. F. Garst and J. T. Barbas, *Tetrahedron Lett.*, 3125 (1969); (h) J. F. Garst and F. E. Barton, *ibid.*, 587 (1969); (i) K. A. Bilevitch, N. N. Pubnov, and O. Yu. Okhlobystin, *ibid.*, 3465 (1968).

(14) H. F. Ebel and A. Luttringhaus, "Methoden der Organischen Chemie," Houben-Weyl, Ed., Georg Thieme Verlag, Stuttgart, 1970, p 498, and references cited therein.

(15) (a) A. G. Evans and J. C. Evans, *J. Chem. Soc. B*, 271 (1966). (b) As a referee has pointed out, the presence of meta-substituted products raises the possibility that a radical or radical–anion mechanism is contributing to product formation in those reactions involving alkyl iodides. We hope to gain further information on this question from the study mentioned here.

TABLE II

ANALYSIS OF THE ALKYLATION PRODUCTS FROM 2 AND ISOPROPYL HALIDES

Solvent	Alkali metal	X	IpX, mol	% rel peak area of: o-Ip 4	o-Ip 5	3	p-Ip 4	p-Ip 5	di-Ip A	di-Ip 7	di-Ip C
THF	Li	Cl	1	42	3	46	0	9			
THF	Li	Br	1	55	2	25	0	18			
THF	Li	I	1	46	2	22	2	28			
THF	Na	Cl	1	36	3	61	0	0			
THF	Na	Br	1	35	10	51	0	4			
THF	Na	I	1	48	1	38	2	11			
THF	K	Cl	1	0	0	98	2	0			
THF	K	Br	1	8	1	90	<1	0			
THF	K	I	1	15	2	63	18	2			
DEE	Na	Cl	1	4	12	60	4	8	2		10
DEE	Na	Br	1	3	11	68	2	10	1		5
DEE	Na	I	1	1	8	52	14	25			
THF	Li	Cl	2	57	0	34	1	8			
THF	Li	Br	2	56	1	25	15	3			
THF	Li	I	2	10	1	26	32	3	22	3	
THF	Na	Cl	2	36	3	61	0	0			
THF	Na	Br	2	20	1	64	9	4	2		
THF	Na	I	2	3	3	41	14	4	23	9	
THF	K	Cl	2	8	0	92	0				
THF	K	Br	2	6	0	93	1				
THF	K	I	2	0	0	68	19		11	2	
DEE	Li	Cl	2	23	1	46	0	30			
DEE	Li	Br	2	13	13	35	11	25	2		1
DEE	Li	I	2	8	0	41	18	28	4		1
DEE	Na	Cl	2	4	14	60	2	10	1		9
DEE	Na	Br	2	1	13	60	10	13			3
DEE	Na	I	2	1	7	46	3	42			1

diphenyl-2,2-dimethylethylene (from **3**) and **4** (*o*-Ip) were used to subdivide the appropriate peak in the first analysis into the relative areas due to **3** and **4** (*o*-Ip).

This analytical procedure was checked using known mixtures of **3**, **4** (*o*-Ip), and **4** (*p*-Ip). Results were found to be within the reproducibility of separate alkylation runs under identical reaction conditions. The peak areas quoted are reliable to ±10% for those products amounting to more than 10% of the reaction products.

Table II summarizes the analytical results obtained in the alkylation experiments. Small amounts of 1 (1–2%) and $Ph_2CHNHPh$ (2–8%) occurred in each experiment and these have been omitted from the analyses and the peak areas normalized.

Identification of Reaction Products.—Isolation and identification of **3** and **4** (*o*-Ip) have been reported.[2] The remaining compounds were initially identified by their vpc retention times and by "spiking" the reaction mixtures with reference compounds. Isolation of several products is reported below. The anils **5** (*o*-Ip), **5** (*p*-Ip), and **7** were further identified by acid hydrolysis of those reaction mixtures containing them and identification of the corresponding benzophenones by their vpc retention times. Reduction of the reaction mixtures with $LiAlH_4$ coupled with the observed increase in peak area of the corresponding substituted aniline provided further identification.

N-(*p*-**Isopropylbenzhydryl)aniline** (**4**, *p*-**Ip**).—The crude reaction product (5.3 g) from a Li–THF–2IpI experiment (32% **4**, *p*-Ip) was heated on a steam bath for 2 hr with 35 ml of 20% HCl. The gummy solid which formed was filtered off and washed with ether to give a white solid, 0.78 g, mp 146–148°. A portion (0.28 g) was recrystallized from methanol–diethyl ether to give 0.11 g: mp 156–160°; ir (Nujol) identical with that of an authentic sample of the hydrochloride of **4** (*p*-Ip).

The remaining salt (0.50 g) was converted to the free amine with methanolic sodium hydroxide. Isolation of the amine by ether extraction gave 0.44 g of an oil whose ir spectrum (film) was identical with that of **4** (*p*-Ip).

p-**Isopropylbenzophenone Anil** (**5**, *p*-**Ip**).—The reaction product from a Li–DEE–2IpBr reaction (25% **5**, *p*-Ip) was separated by preparative gas chromatography using a 20 ft by $^3/_8$ in. column containing 15% SE-30 on Chromosorb W operated at 275° with a flow rate of 150 ml/min of helium. The peak tentatively identified as **5** (*p*-Ip) was collected and found to have an ir (film) identical with that of an authentic sample.

Attempts to isolate the anil **5** (*p*-Ip) by column chromatography using CCl_4 as eluting agent resulted in partial hydrolysis. Only mixtures of **5** (*p*-Ip) and *p*-isopropylbenzophenone were isolated although the latter compound was obtained pure and identified by its ir.

N-(**2,5-Diisopropylbenzhydryl)aniline** (**6**).—The crude reaction product (13.6 g) from a Li–THF–2IpI reaction (25% dialkylation) was dissolved in ether and the solution saturated with HCl. After filtering off the gummy solid which formed, the filtrate was washed with aqueous Na_2CO_3, dried, and evaporated. The residue (3.00 g) was chromatographed on 80 g of silica gel and eluted with CCl_4. The first material to elute (0.29 g) crystallized. Recrystallization from 80–100 petroleum ether gave 0.11 g: mp and mmp (with authentic **6**) 117–119°; nmr and ir (CCl_4) identical with those of **6**.

2,5-Diisopropylbenzophenone. Hydrolysis Product of 7.—The crude reaction product (2.8 g) from a Na–THF–2IpI experiment (32% dialkylation) was decomposed by heating with 20% aqueous HCl and the products were isolated by an ether extraction. After removal of the ether, the residue was dissolved in pentane and saturated with HCl. The solution was decanted from the gummy solid (0.23 g), washed with dilute Na_2CO_3 solution and water, dried, and evaporated (residue 2.02 g).

This residue was separated by preparative gas chromatography on a 10 ft by $^3/_8$ in. column packed with 3% SE-30 on 100–120 mesh Chromosorb W and operated at 190° with a He flow rate of 100 ml/min. Only the two largest peaks (of 6) were collected. The first peak proved to be 1,1-diphenyl-2-methylpropene on the basis of its ir and nmr spectrum. The second peak was contaminated with two minor impurities and was rechromatographed on a 20 ft by $^3/_8$ in. column containing 30% SE-30 on Chromosorb W using the same operating conditions. The main component was established as 2,5-diisopropylbenzophenone by comparison of its ir and nmr with reference spectra. One of the minor impurities proved to be *m*-isopropylbenzophenone on the basis of its ir spectrum.

Reaction of Benzophenone Anil with Isopropyllithium.—Isopropyllithium was prepared from isopropyl chloride in pentane and its concentration determined, as described by Applequist[16] (0.181 *M*).

(16) D. E. Applequist and A. H. Peterson, *J. Amer. Chem. Soc.*, **83**, 862 (1961).

A solution of 0.514 g (0.002 mol) of benzophenone anil in 30 ± 5 g of THF was cooled to −50° and treated with 11.0 ml (0.002 mol) of the prepared isopropyllithium. The solution immediately became deep orange red. After 15 min at −50°, the solution was allowed to warm to room temperature and stand overnight. The reaction product was isolated by dilution with water and extraction with ether.

In addition to the above experiment, three additional experiments were performed in which 0.002 mol of isopropyl chloride, bromide, and iodide were added to the benzophenone anil–isopropyl lithium reaction product as soon as it had warmed to room temperature. No color changes different from those described above were noted. The analysis of the products showed 15–20% of the benzophenone anil unreacted. The composition of the alkylation products was essentially constant in these four experiments and the average composition was 40 ± 4% of **3**, 23 ± 3% of **4** (*o*-Ip), 2 ± 1% of **5** (*o*-Ip), <1% of **4** (*p*-Ip), and 34 ± 1% of **5** (*p*-Ip).

Attempted Alkylation at the Nitrogen Anionic Center.—Following the procedure described earlier,[2a] the dianion **2** was treated with 1 equiv of *tert*-butyl alcohol and the resulting monoanion reacted with 2 equiv of isopropyl halide. Both isopropyl chloride and iodide were used with **2** (M = Li, Na, or *K*) in THF. The color changes observed and the absence of residual alkalinity in the final reaction mixture indicated that reaction had occurred. The crude products were examined by nmr for the presence of isopropyl groups but none were observed. Recrystallization of the product provided only *N*-benzhydrylaniline.

Reference Compounds.—*N*-Benzhydryl-*N*-isopropylaniline was prepared by stirring a solution of benzhydryl bromide (4.9 g, 0.02 mol) and *N*-isopropylaniline (5.9 g, 0.044 mol) in 15 ml of benzene and the solution stirred for 32 hr at 25°. After neutralizing, the mixture was distilled [bp 208–216° (15 mm)] and the distillate crystallized from 35–60° petroleum ether to give 3.3 g (55% yield) of solid: mp 91–92.5°; nmr (CCl_4) 0.95 and 1.17 (double d, J = 7 Hz, 6, CH_3), 3.60 (septet, 1, CH), 5.66 (s, 1, Ph_2CH), 6.2–7.5 (m, 15, aromatics).

Anal. Calcd for $C_{22}H_{23}N$: C, 87.65; H, 7.69; N, 4.69. Found: C, 87.47; H, 7.69; N, 4.68.

m-Bromoisopropylbenzene was prepared by refluxing a mixture of red phosphorus (62 g, 2 mol), 47% hydriodic acid (94 ml, 1 mol), and *m*-(bromophenyl)dimethylcarbinol[17] (71 g, 0.33 mol) with stirring for 40 hr. The mixture was cooled and filtered and the solid was washed with ether and water. From the combined filtrates, the ether phase was separated and washed with water, sodium bisulfite, and again with water. After drying and evaporating, the residue was distilled to give 54 g (84% yield) of *m*-bromoisopropylbenzene: bp 73° (2.5 mm); nmr (CCl_4) δ 1.15 (d, J = 7 Hz, 6, CH_3), 2.85 (septet, 1, CH), 7.0–7.4 (m, 4, aromatics).

m-Isopropylbenzoic acid was prepared by siphoning the Grignard reagent prepared from magnesium (6.04 g, 0.25 mol), *m*-bromoisopropylbenzene (50 g, 0.25 mol), and 300 ml of ether onto Dry Ice. After the slurry warmed to 25°, the mixture was acidified with aqueous HCl and the ether layer separated. The ether layer was extracted with aqueous NaOH and the aqueous extract was acidified with aqueous HCl. The yellow oil which separated crystallized giving 24.8 g (60% yield) of product: mp 42–45°; nmr (CCl_4) δ 1.34 (d, J = 7 Hz, 6, CH_3), 3.00 (septet, 1, CH), 7.3–8.1 (m, 4, aromatics).

This acid was converted to its acid chloride with thionyl chloride and the product distilled, bp 57–58° (0.3 mm).

Substituted Benzophenones.—The various substituted benzophenones were prepared by the procedure described by Friedman and Koca[18] using the appropriate aromatic hydrocarbon and acid chloride.

p-Isopropylbenzophenone (excess cumene + benzoyl chloride): 59% yield; bp 136–140° (0.5 mm) [lit.[19] 116–118° (0.04 mm); ir 1640 (C=O), 1390 and 1370 cm^{-1} ($C(CH_3)_2$); nmr ($CDCl_3$) δ 1.29 (d, J = 7 Hz, 6, CH_3), 3.00 (septet, 1, CH), 7.0–8.0 (m, 9, aromatics); oxime mp 135–138° (lit.[20] 132°). The crude 2,4-dinitrophenylhydrazone (mp 160–182°) was chromatographed on alumina and the eluted derivative recrystallized from 1:7 ethyl acetate–ethanol, mp 194–196°.

Anal. Calcd for $C_{22}H_{20}N_4O_4$: C, 65.33; H, 4.99; N, 13.86. Found: C, 65.32; H, 5.17; N, 13.87.

The filtrate from the original preparation on evaporation gave material,[21] mp 125–131°. Recrystallization from ethyl acetate–ethanol gave an analytical sample, mp 136–139°.

Anal. Calcd for $C_{22}H_{20}N_4O_4$: C, 65.33; H, 4.99; N, 13.86. Found: C, 65.59; H, 5.11; N, 13.81.

m-Isopropylbenzophenone (excess benzene + *m*-isopropylbenzoyl chloride): 85% yield; bp 123–125° (0.5 mm); ir (film) 1655 (C=O), 1379 and 1358 cm^{-1} ($C(CH_3)_2$); nmr (CCl_4) δ 1.20 (d, J = 6 Hz, 6, CH_3), 2.90 (septet, 1, CH), 7.0–7.5 (m, 9, aromatics); 2,4-dinitrophenylhydrazone mp 168–169.5.°

Anal. Calcd for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found: C, 85.81; H, 7.19.

2,5-Diisopropylbenzophenone (excess *p*-diisopropylbenzene + benzoyl chloride): 50% yield; bp 146–150° (1 mm); ir (film), 1670 (C=O), 1380 and 1360 cm^{-1} ($C(CH_3)_2$); nmr (CCl_4) δ 1.12 and 1.24 (double d, J = 3 Hz, 12, CH_3), 2.96 (m, 2, CH), 6.8–8.0 (m, 8, aromatics).

Substituted Benzophenone Anils.—The various substituted benzophenone anils were prepared from their corresponding substituted benzophenones and aniline by the procedure of Reddelien.[22]

p-Isopropylbenzophenone anil: 90% yield; bp 170–180° (1 mm); viscous yellow oil which crystallized. Recrystallization from 35–60° petroleum ether gave a 78% yield: mp 54–55°; ir (CCl_4) 1620 (C=N), 1390 and 1370 cm^{-1} ($C(CH_3)_2$); nmr (CCl_4) δ 1.15 and 1.28 (double d, J = 3 Hz, 6, CH_3), 2.85 (septet, 1, CH), 6.7–8.0 (m, 14, aromatics).

Anal. Calcd for $C_{22}H_{21}N$: C, 88.23; H, 7.07; N, 4.68. Found: C, 88.34; H, 7.21; N, 4.65.

m-Isopropylbenzophenone anil: 89% yield; viscous liquid; bp 167–169° (0.5 mm); ir (film) 1655 (C=N), 1378 and 1355 cm^{-1} ($C(CH_3)_2$); nmr (CCl_4) δ 1.08 and 1.30 (double d, J = 6 Hz, 6, CH_3), 2.78 (septet, 1, CH), 6.4–8.0 (m, 14, aromatics).

Anal. Calcd for $C_{22}H_{21}N$: C, 88.23; H, 7.07; N, 4.68. Found: C, 88.00; H, 7.20; N, 4.79.

2,5-Diisopropylbenzophenone anil: 65% yield; bp 162–175° (0.3 mm), a very viscous orange liquid containing 5–10% unreacted ketone; ir (film) 1615 (C=N), 1380 and 1360 cm^{-1} ($C(CH_3)_2$); nmr (CCl_4) δ 0.82 and 0.92 (double d, J = 6 Hz, 6, CH_3 of 2-Ip), 1.13 (d, J = 8 Hz, 6, CH_3 of 5-Ip), 2.67 (septet, 2, CH), 6.4–8.0 (m, 13, aromatics).

Substituted *N*-Benzhydrylanilines.—The various substituted *N*-benzhydrylanilines were prepared by a lithium aluminum hydride reduction of the corresponding substituted anils using the procedure previously described.[2b]

N-(*p*-isopropylbenzhydryl)aniline: 77% yield; viscous oil; bp 192–208° (0.6 mm) (hydrochloride mp 158–159°); ir (film) 3410 (NH), 1390 and 1370 cm^{-1} ($C(CH_3)_2$); nmr (CCl_4) 1.18 (d, 6, J = 8 Hz, CH_3), 2.70 (septet, 1), 3.90 (broad s, 1, NH), 5.31 (s, 1, CH), 6.1–7.2 (m, 14, aromatics).

Anal. Calcd for $C_{22}H_{23}N$: C, 87.64; H, 7.69; N, 4.65. Found: C, 87.46; H, 7.89; N, 4.39.

The α-naphthylurea derivative had mp 130–130.5°.

N-(*m*-isopropylbenzhydryl)aniline: 81% yield; viscous yellow oil; bp 198° (2 mm); ir (film) 3410 (NH), 1397 and 1359 cm^{-1} ($C(CH_3)_2$); nmr (CCl_4) δ 1.20 (d, J = 6 Hz, 6, CH_3), 2.85 (septet, 1, $(CH_3)_2CH$), 3.90 (broad s, 1, NH), 5.40 (s, 1, CH), 6.3–7.4 (m, 14, aromatics).

Anal. Calcd for $C_{22}H_{23}N$: C, 87.64; H, 7.69; N, 4.65. Found: C, 87.97; H, 7.84; N, 4.69.

N-(2,5-Diisopropylbenzhydryl)aniline: 55% yield; mp 111–114°. Three recrystallizations from 80–100° petroleum ether provided an analytical sample: mp 119–120.5°; ir (CCl_4) 3450 (NH), 1385 and 1365 cm^{-1} ($C(CH_3)_2$); nmr ($CDCl_3$) δ 1.0–1.4 (m, 12, CH_3), 2.6–3.4 (m, 2, CH), 4.10 (broad s, 1, NH), 5.80 (s, 1, CH), 6.4–7.5 (m, 13, aromatics).

Anal. Calcd for $C_{25}H_{29}N$: C, 87.42; H, 8.51; N, 4.08. Found: C, 87.38; H, 8.82; N, 4.21.

Registry No.—**1**, 574-45-8; **2**, 32388-60-6; **4** (*p*-Ip), 23431-27-8; **4** (*p*-Ip) α-naphthylurea derivative, 32388-77-5; **4** (*p*-Ip) HCl, 32388-79-7; **5** (*p*-Ip),

(17) M. Stiles and A. Sisti, *J. Org. Chem.*, **25**, 1691 (1960); 84% yield, bp 100° (3 mm).

(18) L. Friedman and R. Koca, *ibid.*, **33**, 1255 (1968).

(19) W. E. Bachmann, E. Carlson, and J. C. Moran, *ibid.*, **13**, 916 (1968).

(20) A. W. Smith, *Chem. Ber.*, **24**, 4025 (1891).

(21) Syn–anti isomers from substituted benzophenones have been observed: see, for example, P. A. S. Smith and E. P. Antoniades, *Tetrahedron*, **9**, 210 (1960).

(22) G. Reddelien, *Chem. Ber.*, **46**, 2718 (1913).

18864-77-2; **5** (*o*-Ip), 19103-10-7; **6**, 32414-35-0; **7**, 32388-64-0; Li, 7439-93-2; Na, 7440-23-5; K, 7440-09-7; isopropyl chloride, 75-29-6; isopropyl bromide, 75-26-3; isopropyl iodide, 75-30-9; *N*-benzhydryl-*N*-isopropylaniline, 32388-68-4; *m*-bromoisopropylbenzene, 5433-01-2; *m*-isopropylbenzoic acid, 5651-47-8; *p*-isopropylbenzophenone, 18864-76-1, 32388-72-0 (2,4-DNPH); *m*-isopropylbenzophenone, 32388-73-1; 2,5-diisopropylbenzophenone, 2887-73-2; *m*-isopropylbenzophenone anil, 32388-75-3; 2,5-diisopropylbenzophenone anil, 32388-64-0; *N*-(*m*-isopropylbenzhydryl)-aniline, 32388-78-6.

Acknowledgment.—This work was financially supported by the National Research Council of Canada. We gratefully acknowledge the assistance of Mr. R. Pearce and Mr. R. E. Needham in various portions of this study.

Notes

Reactions of Some Dithiazolium Cations with Potassium Cyanate

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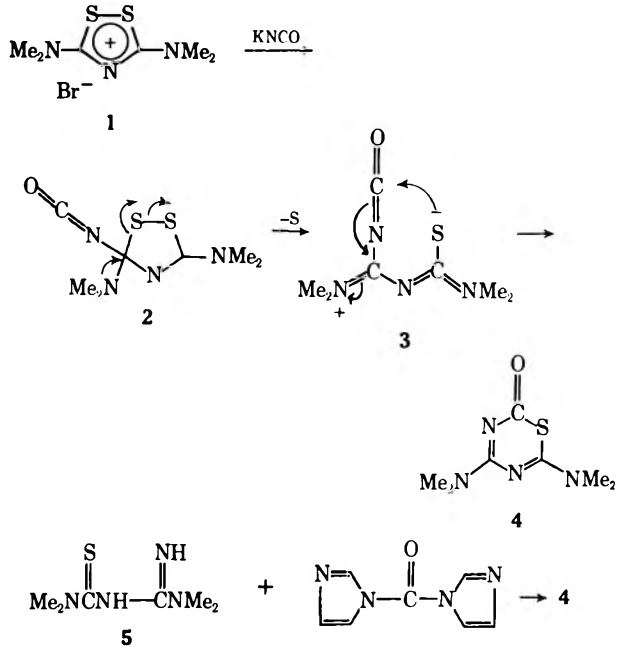
Received June 29, 1971

In the course of our studies of 3,5-disubstituted 1,2,4-dithiazolium salts as insect chemosterilants,[1] we recently found that 3,5-bis(dimethylamino)-1,2,4-dithiazolium bromide (**1**) and several related dithiazolium salts react with sodium azide in DMF or DMSO to provide 3,5-disubstituted 1,2,4-thiadiazoles.[2] Cyanate ion, like azide, is a nucleophile that contains a potential electrophilic center, and we felt that, if ring opening of **1** could be initiated by KNCO, a reaction similiar to the NaN_3 addition should occur except that in this case a six-membered ring would result. Indeed, when **1** and KNCO were allowed to react in refluxing DMF, a neutral compound was obtained (71%) that has been identified by its elemental analysis, ir, nmr, and mass spectra as 4,6-bis(dimethylamino)-2*H*-1,3,5-thiadiazin-2-one (**4**). Final confirmation of structure came from an alternate synthesis achieved by condensing 3-(*N*,*N*-dimethylamidino)-1,1-dimethyl-2-thiourea[1,2] (**5**) with carbonyldiimidazole in refluxing toluene (Scheme I).

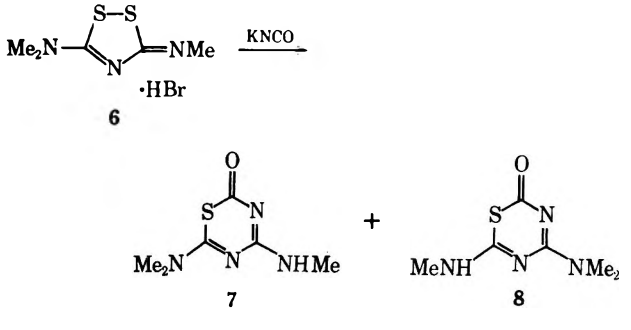
The nmr signals of the methyl hydrogens of dimethylamides and related compounds are frequently observed as doublets because of restricted rotation around the N–C bonds.[3] Both of the dimethylamino signals of **7** appear as doublets at room temperature (coalescence temperatures in chlorobenzene *ca.* 45 and 87°). This constitutes an interesting extension of the dialkylamide phenomenon, as in this case the carbonyl group is in a heterocyclic ring. We assume, without evidence, that the 4-dimethylamino group has the larger rotation barrier.

SCHEME I



3,5-Dipiperidino- and 3,5-bis(1-pyrrolidinyl)-1,2,4-dithiazolium bromides reacted analogously with KNCO to give 4,6-dipiperidino- and 4,6-bis(1-pyrrolidinyl)-2*H*-1,3,5-thiadiazin-2-ones in 40–88% yield (few attempts were made to optimize conditions or yields). Thus it appears that this constitutes a general synthesis of 4,6-bis(dialkylamino)-1,3,5-thiadiazin-2-ones, a previously unreported class of compounds.

5-(Dimethylamino)-3-(methylimino)-3*H*-1,2,4-dithiazole hydrobromide (**6**) reacted with NaN_3 to give 5-

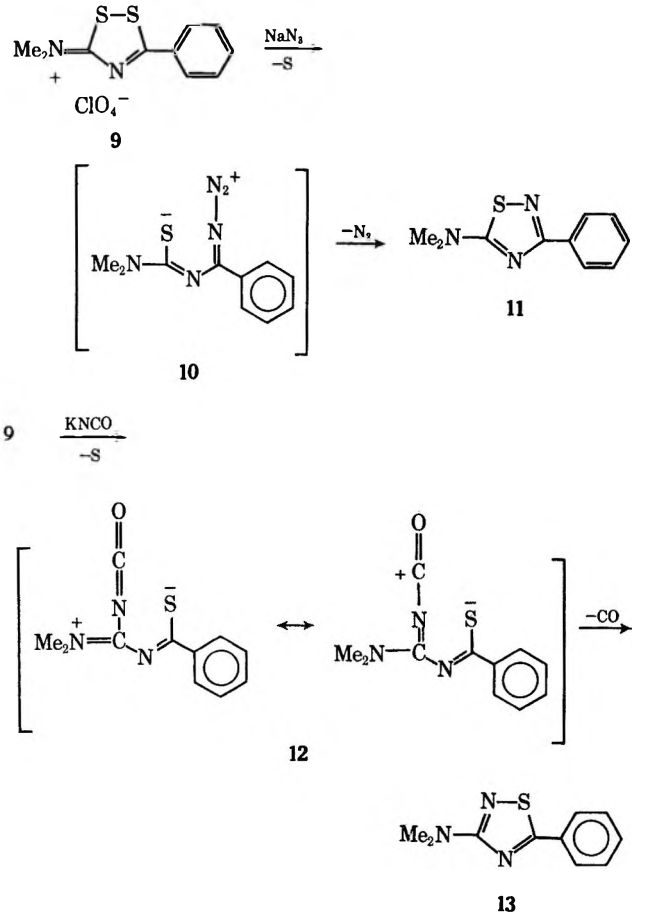


(1) J. E. Oliver, S. C. Chang, R. T. Brown, J. B. Stokes, and A. B. Borkovec, *J. Med. Chem.*, in press.
(2) J. E. Oliver, *J. Org. Chem.*, **36**, 3465 (1971).
(3) W. E. Stewart and T. H. Siddall, III, *Chem. Rev.*, **70**, 517 (1970).

(dimethylamino)-3-(methylamino)-1,2,4-thiadiazole.[2] The reaction of **6** with KNCO was more complex, and both **7** and **8** were obtained along with an unidentified material. The two isomers were obtained pure only with considerable difficulty (column chromatography followed by repeated fractional recrystallization), and the exact ratio of the two isomers in the reaction mixture is unknown. Their high-resolution mass spectra allowed us to assign structures **7** and **8** to the major and minor isomers, respectively. Thus the major product corresponds to attack by cyanate at C-3 of **6**, as was the case in the NaN_3 reaction, where the only observed product also resulted from attack at C-3.

An interesting but unexplained contrast between the NaN_3 and KNCO additions was provided by the reactions of these reagents with 3-(dimethylamino)-5-phenyl-1,2,4-dithiazolium perchlorate (**9**). 5-(Dimethylamino)-3-phenyl-1,2,4-thiadiazole (**11**) was the only isolated product from **9** and NaN_3.[2] When **9** was treated with KNCO in DMF or DMSO, the product was not a 1,3,5-thiadiazin-2-one, but instead was 3-(dimethylamino)-5-phenyl-1,2,4-thiadiazole (**13**, 76–83% yield). This unexpected product is best explained by assuming that carbon monoxide was eliminated from **12** in the same manner that nitrogen was lost from **10** (Scheme II). Thiadiazole **13** is a result of

SCHEME II



cyanate addition to the 3 position of **9**, whereas thiadiazole **11** resulted from azide addition to the 5 position of **9**. Thus, although it appears that similar mechanisms can explain the reactions of cyanate and azide anions with dithiazolium cations, the two reagents do not necessarily add to the same positions. Whether potassium *vs.* sodium counterions influenced this difference has not been investigated, but, if, as seems likely, ion exchange (*e.g.*, formation of a dithiazolium cyanate salt) precedes the nucleophilic attack, the presence of sodium or potassium bromide or perchlorate would not be expected to have much effect.

Potassium thiocyanate could not be made to undergo an analogous reaction with **1**; the only product that could be identified was the thiocyanate salt of cation **1**.[4] This thiocyanate salt was remarkably stable; indeed, it was recovered unchanged after 45 min in a sealed tube at 215°, and, upon attempted pyrolysis in a sublimation apparatus (250°, 0.05 mm), an oily sublimate was collected whose infrared spectrum was essentially identical with that of the starting thiocyanate salt.

As was the case with the NaN_3 reaction, deeply colored reaction mixtures often resulted when a dithiazolium salt and KNCO were heated together in DMF or DMSO, but again there were a few instances in which shades deeper than yellow did not develop. Since a variety of sulfur compounds produce colors with NaN_3 in DMF,[2] we feel that the colors observed here were probably not directly associated with these specific reactions.

Experimental Section[5]

Melting points are uncorrected. Nuclear magnetic resonance spectra were recorded on a Varian Model T-60 spectrometer except for the variable temperature spectra which were recorded on a Varian A-60 spectrometer. Mass spectra were recorded on a Finnigan Model 1015 Quadrupole mass spectrometer or on a Consolidated Electrodynamics Corp. Model 21-110B high resolution mass spectrometer. Infrared spectra were obtained on a Perkin-Elmer Model 137 sodium chloride prism spectrophotometer. Magnesium sulfate was employed as a drying agent. DMSO and DMF were stored over molecular sieves but were not otherwise purified. A high-vacuum rotary evaporator with a CO_2 trap was employed to remove DMF. The preparation of the dithiazolium salts has been reported.[1,2,4] Microanalyses were preformed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Reactions of 3,5-Bis(dialkylamino)-1,2,4-dithiazolium Bromides with Potassium Cyanate. 4,6-Bis(dimethylamino)-2*H*-1,3,5-thiadiazin-2-one (4).—A mixture of 3,5-bis(dimethylamino)-1,2,4-dithiazolium bromide (**1**, 8.10 g) and KNCO (2.52 g) in DMF (50 ml) was refluxed under N_2 for 40 min, then was stirred overnight at room temperature. The mixture was filtered and the filtrate was stripped *in vacuo*. The residue was extracted with hot MeOH (to remove sulfur), the MeOH solution was filtered and evaporated, and the residue was extracted with several portions of hot CCl_4 (total 150 ml). The filtered CCl_4 solution was chilled and **4** separated as a white solid (4.25 g, 71%, mp 132–133°). The analytical sample (CCl_4) had mp 135.5–136°; ir ($CHCl_3$) 1160, 1550, 1400, 1375, cm^{-1}; nmr (C_6H_5Cl) δ 2.70 and 2.80 (poorly resolved at 37°, coalesce to a singlet at *ca.* 45°), 2.88 and 3.04 (sharp singlets at 37°, coalesce to a single peak at *ca.* 87°); mass spectrum (70 eV) *m/e* (rel intensity) 200 (30, parent ion), 172 (44, M − CO), 156 (72, M − Me_2N), 88 (32, $Me_2NC{=}S^+$), 70 (100, Me_2NCN^+).

Anal. Calcd for $C_7H_{12}N_4OS$: C, 41.97; H, 6.04; N, 27.98; S, 16.01. Found: C, 41.76; H, 6.02; N, 27.85; S, 16.19.

4,6-Dipiperidino-2*H*-1,3,5-thiadiazin-2-one was obtained by heating 3.50 g of 3,5-dipiperidino-1,2,4-dithiazolium bromide with 0.81 g of KNCO in DMSO (25 ml) at 115–120° for 1 hr. The mixture was cooled and poured into cold water. A solid separated that was collected and taken up in 1:1 MeOH–EtOH. The solution was filtered and evaporated, and the residue was re-

(4) W. R. Diveley, U. S. Patent 3,166,564 (Jan 19, 1965); *Chem. Abstr.*, **62**, 9145*g* (1965).

(5) Mention of a proprietary product or company does not necessarily imply endorsement by the U. S. Department of Agriculture.

crystallized from isooctane–EtOAc to give 2.47 g (88%) of 4,6-dipiperidino-2*H*-1,3,5-thiadiazin-2-one, mp 133–138°. Recrystallization from EtOH–H_2O and then heptane–EtOAc gave the pure material: mp 141–142°; ir ($CHCl_3$) 1650, 1523, 1440, 1410 cm^{-1}.

Anal. Calcd for $C_{13}H_{20}N_4OS$: C, 55.68; H, 7.19; N, 19.98; S, 11.44. Found: C, 56.01; H, 7.15; N, 20.17; S, 11.20.

4,6-Bis(1-pyrrolidinyl)-2*H*-1,3,5-thiadiazin-2-one was prepared by refluxing 3,5-bis(1-pyrrolidinyl)-1,2,4-dithiazolium bromide (3.23 g) and KNCO (0.86 g) in DMF (25 ml) for 1 hr. The DMF was stripped and the residue was extracted into MeOH. The MeOH extract was filtered and evaporated and the residue was extracted with hot EtOAc. Dilution of the EtOAc solution with hexane and chilling precipitated the product as a light tan solid (1.19 g, 40%, mp 133–137°). Recrystallization from EtOAc gave 0.80 g, mp 140–141°; ir ($CHCl_3$) 1650, 1530, 1410 cm^{-1}.

Anal. Calcd for $C_{11}H_{16}N_4OS$: C, 52.35; H, 6.39; N, 22.20. Found: C, 52.45; H, 6.21; N, 22.21.

Synthesis of 4 from 3-[*N*,*N*-(Dimethylamidino)]-1,1-dimethyl-2-thiourea[1] (5) and Carbonyldiimidazole.—A solution of **5** (258 mg) and 1,1-carbonyldiimidazole (240 mg) in toluene (12 ml) was refluxed for 4 hr, cooled, washed with H_2O, dried, and evaporated. The residue (40 mg, mp 124–129°) was recrystallized from CCl_4 to give pure **4**, mp 135–136°, shown by its infrared spectrum and by mixture melting point to be identical with that prepared from **1** and KNCO.

Reaction of 5-(Dimethylamino)-3-(methylimino)-3*H*-1,2,4-dithiazole Hydrobromide (6) with Potassium Cyanate.—A mixture of **6** (5.00 g) and KNCO (1.74 g) in DMF (50 ml) was refluxed under N_2 for 1 hr. After cooling to room temperature the mixture was filtered and the filtrate was stripped. The residue (in CH_2Cl_2) was added to a silica gel column. Elution with C_6H_6 gave 1 g of an unidentified yellow solid, mp 140–177°, that moved with the solvent front. The column was then eluted with $CHCl_3$–C_6H_6 and finally with $CHCl_3$. 6-(Dimethylamino)-4-(methylamino)-2*H*-1,3,5-thiadiazin-2-one (**7**) and 4-(dimethylamino)-6-(methylamino)-2*H*-1,3,5-thiadiazin-2-one (**18**) were eluted together over a series of fractions (as judged by nearly identical ir spectra of early and late fractions). The evaporated fractions were combined in hot CH_3CN; chilling the solution gave 0.80 g (22%) of a whilte solid, mp 185–195°. Several recrystallizations from EtOH and then CH_3CN gave pure **7**, mp 188–189°; ir (KBr) 1695, 1620, 1560, 1515, 1480, 985 cm^{-1}; nmr (DMSO-d_6) δ 3.11 (s, 6 H), 3.50 (s, 3 H); mass spectrum (70 eV) *m/e* (rel intensity) 186 (100, molecular ion), 158 (22, M − CO), 113 (28), 88 (10), 84 (21), 83 (30). High-resolution analysis of the *m/e* 88 area showed two peaks with exact molecular weights 88.0100 and 88.0223 (calcd for $C_2H_4N_2S$ and C_3H_6NS, respectively, 88.0095 and 88.0221). The latter peak, absent in the spectrum of **8**, corresponds to $Me_2NC{=}S^+$ which could only have been derived from structure **7**.

Anal. Calcd for $C_6H_{10}N_4OS$: C, 38.69; H, 5.41; N, 30.08; S, 17.22. Found: C, 38.56; H, 5.29; N, 29.87; S, 17.42.

Crude **8** was obtained from the mother liquors of **7**; the analytical sample was obtained by repeated recrystallizations (three from EtOH, then two from CH_3CN), mp 218–220°; ir (KBr) 1665, 1610, 1510, 1430, 1260, 1110, 1020, 863 cm^{-1}; nmr (DMSO-d_6) δ 3.11 (s, 6 H) and 3.52 (s, 3 H); mass spectrum (70 eV) *m/e* (rel intensity) 186 (100, molecular ion), 113 (34), 98 (14), 83 (11), 71 (10).

Anal. Calcd for $C_6H_{10}N_4OS$: C, 38.69; H, 5.41; N, 30.08; S, 17.22. Found: C, 38.92; H, 5.44; N, 30.33; S, 17.25.

Reaction of 3-(Dimethylamino)-5-phenyl-1,2,4-dithiazolium Perchlorate (9)[2] and KNCO.—A mixture of **9** (5.00 g) and KNCO (1.47 g) was heated for 0.5 hr in refluxing DMF (100 ml). The solution was cooled to room temperature, filtered, and stripped, and the residue was chromatographed on silica gel. 5-(Dimethylamino)-3-phenyl-1,2,4-thiadiazole (**13**) was quickly eluted with petroleum ether (bp 30–60°) and was obtained as a clear oil that solidified on standing (2.62 g, 83%). A portion was sublimed *in vacuo* and then recrystallized from MeOH–H_2O, mp 46°; ir ($CHCl_3$) 1540, 1410, 1340, 975, 885 cm^{-1}; nmr ($CDCl_3$) δ 3.25 (s, 6, Me_2N) 7.33–7.60 (m, 3, Ph), 7.84–8.17 (m, 2, Ph); mass spectrum (70 eV) *m/e* 205 (100, parent ion), 121 (12, $PhC{=}S^+$). The isomeric 3-(dimethylamino)-5-phenyl-1,2,4-thiadiazole has mp 89°.[2,6]

The same product was obtained by reacting **9** and KNCO in DMSO (100°, 45 min); the reaction mixture was partitioned between C_6H_6 and H_2O and **13** was obtained in 76% yield upon evaporation of the C_6H_6 solution.

Anal. Calcd for $C_{10}H_{11}N_3S$: C, 58.51; H, 5.40; N, 20.47. Found: C, 58.30; H, 5.35; N, 20.31.

Registry No.—**4**, 32251-48-2; **7**, 32251-49-3; **8**, 32304-28-2; **13**, 32251-50-6; 4,6-dipiperidino-2*H*-1,3,5-thiadiazin-2-one, 32251-51-7; 4,6-bis(1-pyrrolidinyl)-2*H*-1,3,5-thiadiazin-2-one, 32251-52-8.

Acknowledgment.—We thank Professor C. Storm of Howard University for the variable-temperature nmr spectra.

(6) J. Goerdeler and K. H. Heller, *Chem. Ber.*, **97**, 225 (1964).

Nuclear Magnetic Resonance Spectroscopy. Effect of *N,N,N′,N′*-Tetramethylethylenediamine on the Schlenk Equilibrium of Ethylmagnesium Bromide[1]

J. A. MAGNUSON[2] AND JOHN D. ROBERTS*

Contribution No. 4191 from the Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California 91109

Received April 7, 1971

The composition of Grignard reagents has been studied extensively by nuclear magnetic resonance spectroscopy and other physical techniques.[3] Recently Parris and Ashby,[4] using nmr spectroscopy, observed both dialkyl- and alkylmagnesium species in Grignard solutions from methyl and *tert*-butyl halides. Earlier Evans and coworkers[5] had observed diarylmagnesium and arylmagnesium halides by both fluorine and proton magnetic resonance. We wish to report the observation of diethylmagnesium and ethylmagnesium bromide in tetrahydrofuran solutions containing *N,N,N′,N′*-tetramethylethylenediamine.

The proton magnetic resonance spectrum of the Grignard reagent prepared from ethyl bromide and magnesium is a typical A_2X_3 type spectrum. The resonances of both the methyl, 1.11 ppm downfield from external tetramethylsilane, and methylene protons, 0.78 ppm upfield, are easily distinguished from those of the solvent. A small quantity of ethane is usually formed from trace amounts of moisture. Spectra obtained at temperatures down to −70° exhibited no change other than slight loss in resolution. Variable-temperature spectra of the methylene protons of 0.33 *M* ethylmagnesium bromide in tetrahydrofuran, which is 0.18 *M* in *N,N,N′,N′*-tetramethylethylenediamine, are shown in Figure 1. Broadening of the resonance occurs when lowering the temperature and, at −50°, the methylene proton resonances appear as overlapping

(1) Taken from the Ph.D. Dissertation of J. A. Magnuson, 1968. Supported by the National Science Foundation.

(2) National Defense Education Act Fellow, 1965–1967.

(3) For recent review articles, see the following and other volumes in series: (a) J. P. Oliver, *Advan. Organometal. Chem.*, **8**, 167 (1970); (b) D. Seyferth, *Organometal. Chem. Rev., Sect. B*, **3**, 37 (1967); (c) B. J. Wakefield, *Organometal. Chem. Rev.*, **1**, 131 (1966); (d) E. C. Ashby, *ibid.*, **5**, 225 (1969).

(4) G. E. Parris and E. C. Ashby, *J. Amer. Chem. Soc.*, **93**, 1206 (1971).

(5) (a) D. F. Evans and M. S. Kahn, *J. Chem. Soc. A*, 1643 (1967); (b) D. F. Evans and M. S. Kahn, *ibid.*, 1648 (1967); (c) D. F. Evans and V. Fazakerly, *Chem. Commun.*, 974 (1968).

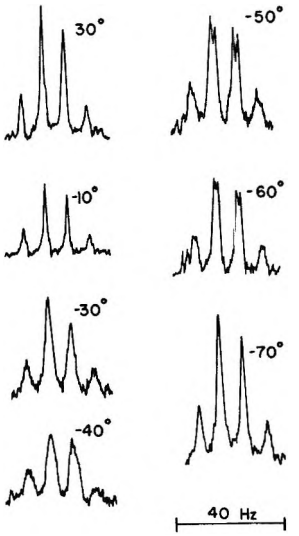


Figure 1.—The nmr spectra (60 MHz) of the $-CH_2Mg-$ protons in ethylmagnesium bromide in tetrahydrofuran and *N,N,N′,N′*-tetramethylethylenediamine.

quartets. The $^3J_{HH}$ coupling constants of the species present, as indicated from the four central lines, are equal. The outer lines are unresolved because of lower intensity and resulting difficulty in obtaining good spectra. At still lower temperatures (down to $-70°$), the lines move closer together and coincide, presumably because of a differential chemical shift change with temperature.

No changes in the nmr spectra were found at low temperature for diethylmagnesium prepared from diethylmercury and magnesium in tetrahydrofuran when the diamine is present. Addition of magnesium bromide, prepared *in situ* from ethylene bromide and magnesium, did lead to a solution whose nmr spectra at low temperature consisted of two quartets. Dioxane precipitation of magnesium bromide from the Grignard reagent gave a solution which exhibited only one methylene quartet at low temperature in the presence of diamine.

Variable-temperature spectra taken of a sample to which diamine and then dioxane had been added were obtained within several hours of dioxane addition. Two clearly resolved quartets were obtained at $-40°$ for the methylene protons. After sitting for several months, presumably after all magnesium bromide had precipitated, only one quartet was observed. That the diamine reduces the rate of the dioxane precipitation was confirmed by measuring bromide concentration as a function of time by standard gravimetric silver precipitation.

In general, the equilibrium mixture of alkylmagnesium species can be obtained rapidly by several methods employing different starting materials. Figure 2 shows the 100-MHz spectrum ($-50°$) for the methylene protons for a mixture containing diamine, diethylmagnesium from diethylmercury, magnesium bromide from ethylene bromide and magnesium, and Grignard reagent from ethyl bromide and magnesium. All lines of both quartets are easily distinguished.

The quartets observed near $-50°$ are best attributed to methylene resonances of diethylmagnesium and ethylmagnesium bromide and support the existence of

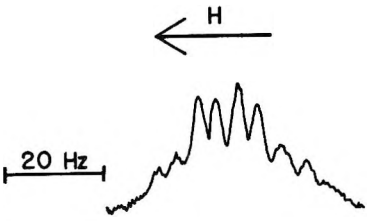
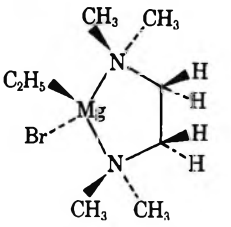


Figure 2.—The nmr spectrum (100 MHz) at $-50°$ of the $-CH_2Mg-$ protons in a sample of ethylmagnesium bromide, diethylmagnesium, and magnesium bromide in tetrahydrofuran and *N,N,N′,N′*-tetramethylethylenediamine.

the Schlenk equilibrium[6] $(C_2H_5)_2Mg + MgBr_2 \rightleftharpoons 2\ C_2H_5MgBr$. House and coworkers[7] have demonstrated that *N,N,N′,N′*-tetramethylethylenediamine can markedly affect rates of alkyl exchange of alkylarylmagnesium species. Fraenkel and coworkers[8] have found similar results for the diamine sparteine. Presumably exchange between alkylmagnesium species is slowed by the presence of complexes like **1**. A four-



1

fold change in ratio of diamine to ethyl group from 0.5 to 2.0 has no apparent effect on the position of the equilibrium, as one might expect if one of the magnesium species were preferentially solvated. From the spectra obtained, the number of ethyl groups in both species is approximately equal, giving an equilibrium constant at $-50°$ of 4 for the Schlenk equilibrium as written above. This is similar to the 5.09 reported by Smith and Becker[9] from thermometric studies.

All magnesium species may be solvated by the diamine in Grignard reagent solutions. The diamine appears to confer solubility on all species, unlike the result reported for Grignard reagents of 3-chloronortricyclene.[10] In particular, the solubility of magnesium bromide in tetrahydrofuran is increased markedly by the diamine. The nmr spectrum of the diamine changes with temperature in the presence of alkylmagnesium species or magnesium halide. The changes vary with Grignard reagent and concentration. Interpretation is not simple since spectra of several species, including very complicated spectra from species such as **1**, may contribute. The nmr spectra do indicate that tight solvent complexes exist, and these are reducing the rate of alkyl exchange allowing observation of the different species of the Schlenk equilibrium.

(6) Careful studies by others have shown this Grignard reagent to be monomeric in tetrahydrofuran: (a) E. C. Ashby and F. Walker, *J. Organometal. Chem.*, **7**, 17 (1967); (b) E. C. Ashby and W. E. Becker, *J. Amer. Chem. Soc.*, **85**, 118 (1963); F. W. Walker and E. C. Ashby, *ibid.*, **91**, 3845 (1969).

(7) H. O. House, R. A. Latham, and G. M. Whitesides, *J. Org. Chem.*, **32**, 2481 (1967).

(8) G. Fraenkel, C. Cottrell, J. Ray, and J. Russell, *Chem. Commun.*, 273 (1971).

(9) M. B. Smith and W. E. Becker, *Tetrahedron*, **23**, 4215 (1969).

(10) D. O. Cowan, G. Krieghoff, J. E. Nordlander, and J. D. Roberts, *J. Org. Chem.*, **32**, 2639 (1967).

Experimental Section

Proton magnetic resonance spectra were obtained with a Varian HA-100 nmr spectrometer or with a Varian A-56/60A spectrometer equipped with a Varian C-1024 time-averaging computer. The probe on the A-56/60A spectrometer carried a dewar-jacketed probe insert which could maintain stable temperatures as low as $-100°$, so that low-temperature, time-averaged spectra could be obtained with no great difficulties.

The starting halides were commercial products and used as received. Tetrahydrofuran (Matheson Coleman and Bell) was distilled from lithium aluminum hydride and stored over Linde 13X molecular sieves. Solvent was never stored for more than 3 days. *N,N,N′,N′*-tetramethylethylenediamine (Matheson Coleman and Bell) was dried over potassium hydroxide and then distilled from sodium immediately before adding to Grignard reagents. Magnesium was in the form of shavings ground from blocks of triply sublimed magnesium.[11] Dioxane (Eastman) was distilled from lithium aluminum hydride before use.

The various alkylmagnesium reagents were prepared directly in sealed nmr tubes. After centrifugation of solids to one end, careful decantation of the liquid to the other end of the tube provided a clear sample suitable for nmr spectroscopy.

Registry No.—*N,N,N′,N′*-Tetramethylethylenediamine, 110-18-9; ethylmagnesium bromide, 925-90-6; diethylmagnesium, 557-18-6; magnesium bromide, 7789-48-2.

(11) We thank Dow Chemical Co. for the gift of magnesium.

A Convenient Route to Aromatic α Diketimines and α Diketones

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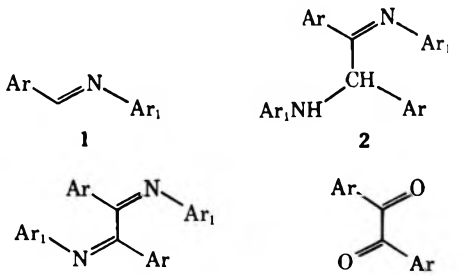
Received June 1, 1971

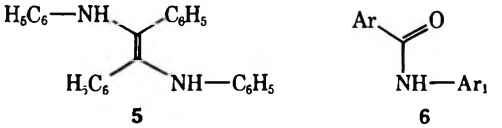
In a preliminary report[1] we have described a simple cyanide ion catalyzed oxidative dimerization of some aromatic aldimines **1** to α diketimines **3**.[2] This paper



gives details of these experiments and additional examples delineating to some extent the scope and limitations of this method. Further, the smooth acid hydrolysis of α diketimines **3** constitutes a convenient route to α diketones **4**. Since the appearance of our communication another report of the cyanide ion catalyzed dimerization of aromatic Schiff bases has appeared.[3]

Although the benzoin condensation[4] is usually carried out in alcoholic solvents, we decided to investigate the reaction of aromatic aldimines **1** with cyanide ion in dimethyl sulfoxide (DMSO) in the hope that the initially formed anilinoimines **2**, a formal benzoin type condensation product of **1**, would suffer *in situ* oxidation by DMSO to yield directly diketimines **3**. We were gratified to find that the reaction of a 0.66 *M* solution of *N*-benzylideneaniline (**1a**) in dry DMSO with an equivalent amount of sodium cyanide at 20° afforded benzildianil (**3a**) in 65% yield. A recent note[3] describes the formation of dianilinostilbene (**5**) in dimethylformamide (DMF) when the reaction is run under nitrogen. Apparently under our conditions the initial product (**5** or **2a**) undergoes aerial oxidation to diketimine **3a**. We also find that the oxidative dimerization of **1** to **3** proceeds as well or better in DMF. The role of DMSO in this reaction is therefore only as a solvent (and not additionally as an oxidizing agent).

The data for the reaction carried out with 0.6–0.7 *M* solutions of **1** is presented in Table I. A small amount of anilide **6** was usually a by-product of reactions run in DMSO. The ratio of α diketimines **3** to anilide **6** was sensitive to both concentrations of azomethine **1** and to temperature (see Table I). The best results were obtained by running the reaction in dilute solution using DMF as solvent.



That the cyanide ion acts as a specific catalyst in the oxidative dimerization **1** to **3** is shown by the observations that transformation of **1a** to **3a** proceeds to completion with as little as 0.1 molar equiv of cyanide ion, and **1a** in DMSO or DMF was unchanged either alone or in the presence of sodium hydroxide. The possibility of the reaction proceeding *via* prior hydrolytic cleavage of **1a** to benzaldehyde and aniline is dismissed, since the reaction of benzaldehyde, aniline, and cyanide ion in DMSO gives only benzoin.

Inspection of Table I shows that this method for the synthesis of α diketimines **3** is fairly general and the substituents in Ar and Ar_1 can vary considerably. The reaction is apparently limited to aromatic aldimines. However, diketimines were not obtained from *p*-dimethylaminobenzylideneaniline (**1m**), *p*-hydroxybenzylideneaniline (**1n**), *p*-nitrobenzylideneaniline (**1p**), *o*-methoxybenzylideneaniline (**1q**), or benzylidenecyclohexylamine (**1r**); the benzoin condensation also fails with the aromatic aldehydes of **1m**, **1n**, or **1p**.

The mechanism of this reaction appears to resemble that of the benzoin condensation;[5] a possible route is presented in Scheme I.

Experimental Section

General.—Melting points were taken on a Thomas–Hoover melting point apparatus and are uncorrected. Analyses were

(1) J. S. Walia, J. Singh, M. S. Chattha, and M. Satyanarayana, *Tetrahedron Lett.*, 195 (1969).

(2) For synthesis of ketimines, see (a) R. W. Layer, *Chem. Rev.*, **63**, 489 (1963); (b) H. Weingarten, J. P. Chupp, and W. A. White, *J. Org. Chem.*, **32**, 3246 (1967); (c) J. S. Walia, L. Heindl, H. Lader, and P. S. Walia, *Chem. Ind. (London)*, 155 (1968); (d) R. Patarcity and B. R. Franko-Filipasic, *ibid.*, 1704 (1969); (e) S. Dayagi and Y. Degani in "The Chemistry of Carbon–Nitrogen Double Bond," S. Patai. Ed., Interscience, New York, N. Y., 1970, Chapter 2.

(3) H.-D. Becker, *J. Org. Chem.*, **35**, 2099 (1970).

(4) W. S. Ide and J. S. Buck in "Organic Reactions," Vol. IV, R. Adams, Ed., Wiley, New York, N. Y., 1948, p 269.

(5) R. L. Schowen, J. P. Kuebrich, M.-S. Wang, and M. E. Lupes, *J. Amer. Chem. Soc.*, **93**, 1214 (1971).

TABLE I

YIELDS OF α DIKETIMINES, ANILIDES, AND α DIKETONES

Run	Ar	Ar$_1$	Solvent	Yield, % diketimine **3**	anilide **6**	diketone **4**
a	Phenyl	Phenyl	DMSO	65	6	92
	Phenyl	Phenyl	DMF	77		
	Phenyl	Phenyl	DMSO[a]	48	41	
	Phenyl	Phenyl	DMSO[b]	75		
b	*p*-Chlorophenyl	Phenyl	DMSO	58	11	90
	p-Chlorophenyl	Phenyl	DMSO[a]	41	29	
	p-Chlorophenyl	Phenyl	DMSO[b]	65	6	
c	*p*-Methoxyphenyl	Phenyl	DMSO	59	4	98
	p-Methoxyphenyl	Phenyl	DMSO[a]	60	14	
	p-Methoxyphenyl	Phenyl	DMSO[b]	72	1	
d	*p*-Methylphenyl	Phenyl	DMSO	72		92
e	*o*-Chlorophenyl	Phenyl	DMSO	83		96
f	Phenyl	*p*-Methoxyphenyl	DMSO	50	1–2	90
g	Phenyl	*p*-Methylphenyl	DMF	60		91
h	Phenyl	*m*-Methoxyphenyl	DMF	54		95
i	Phenyl	*p*-Chlorophenyl	DMSO	73	10	87
j	3,4,5-Trimethoxyphenyl	Phenyl	DMF	65		93
k	3,4-Methylenedioxyphenyl	Phenyl	DMF	28		92
l	Phenyl	3,4-Dimethyl-5-isoxazyl	DMF	36		86

[a] At 59–60°. [b] Using 0.13 *M* solution.

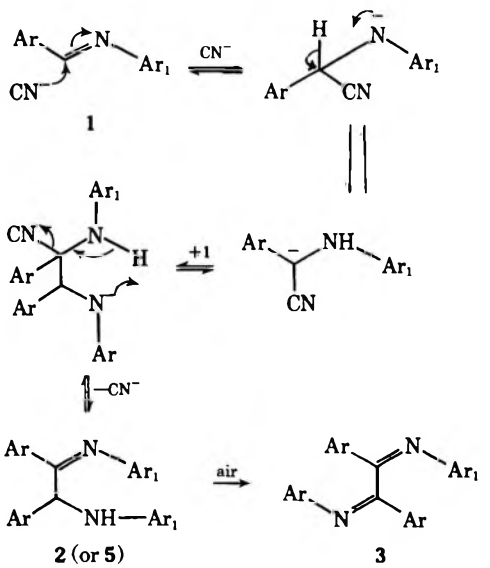
TABLE II

MELTING POINTS AND CHARACTERIZATIONS OF DIKETIMINES, DIKETONES, AND ANILIDES

	Diketimine **3**							Diketone **4**		Anilide **6**	
		Calcd, %			Found, %						
Run	Mp, °C	C	H	N	C	H	N	Mp, °C	Lit. mp, °C	Mp, °C	Lit. mp, °C
a	144–145[a]	86.66	5.55	7.73	86.31	5.72	7.84	94–95	94–95[b]	160–161	162[c]
b	155–156	72.73	4.20	6.52	72.47	4.36	6.22	198–200	200[d]	194–196	194[c]
c	150–151	80.00	5.71	6.67	79.58	5.56	6.49	131–133	131–132[f]	170–171	168–169[g]
d	147–148	86.56	6.23	7.21	86.30	6.35	7.39	104–105	104–105[h]	*i*	
e	216–217	72.73	4.20	6.52	72.88	4.43	6.75	133–134	133–134[j]	*i*	
f	162–163	80.00	5.71	6.67	80.11	5.70		94–95	94–95[b]	153–154	156[k]
g	157–158	86.56	6.23	7.21	86.23	6.15		94–95	94–95[b]	*i*	
h	134–135	80.00	5.71	6.67	79.81	5.80		94–95	94–95[b]	*i*	
i	172–173	72.73	4.20	6.52	72.63	4.27	6.53	94–95	94–95[b]	192–194	192–193[l]
j	120–121	71.06	5.97	5.18	70.52	6.29		191–192	192–193[m]	*i*	
k	125–127	74.96	4.49	6.25	74.81	4.33		170–171	170–171[n]	*i*	
l	223–224	72.34	5.32	14.05	72.41	5.57		94–95	94–95[b]	*i*	

[a] Lit. mp 141–142: G. Reddelien, *Chem. Ber.*, **46**, 2723 (1913). [b] I. A. Pearl and W. M. Dehn, *J. Amer. Chem. Soc.*, **60**, 57 (1938). [c] H. Franzen, *Chem. Ber.*, **42**, 2466 (1909). [d] A. Hantzsch and W. H. Glower, *ibid.*, **40**, 1519 (1907). [e] A. Hantzsch, *ibid.*, **24**, 56 (1891). [f] C. Deliwala and S. Rajgopalan, *Proc. Indian Acad. Sci.*, **31A**, 107 (1950). [g] R. Haller, *C. R. Acad. Sci.*, **121**, 190 (1895). [h] D. Vorlander, *Chem. Ber.*, **46**, 2455 (1911). [i] Not obtained. [j] Reference *f*. [k] F. Reverdin, *Chem. Ber.*, **42**, 1523 (1909). [l] R. von Walther, *J. Prakt. Chem.*, [2] **67**, 453 (1903). [m] I. A. Pearl, *J. Org. Chem.*, **22**, 1229 (1957). [n] C. D. Shacklett and H. A. Smith, *J. Amer. Chem. Soc.*, **75**, 2654 (1953).

SCHEME I



performed by Drs. Weiler and Strauss, Microanalytical Laboratories, Oxford, England. DMSO and DMF were distilled over CaH_2 *in vacuo* and stored over molecular sieves.

Starting Material.—*N*-Benzylideneaniline (**1a**) was commercially available and was used without further purification. The *N*-benzylideneaniline derivatives **1b**–**1i** were prepared by standard procedures, mostly following the method of Law.[6]

***N*-3,4,5-Trimethoxybenzylideneaniline (1j).**—Faint yellow crystals were recrystallized from benzene–petroleum ether (bp 30–60°), mp 84–85°.

Anal. Calcd for $C_{16}H_{17}NO_3$: C, 70.83; H, 6.32. Found: C, 70.56; H, 6.13.

***N*-3,4-Methylenedioxybenzylideneaniline (1k).**—Light, pale crystals were recrystallized from benzene–petroleum ether, mp 63–64°.

Anal. Calcd for $C_{14}H_{11}NO_2$: C, 74.65; H, 4.92. Found: C, 74.44; H, 4.89.

***N*-Benzylidene-3,4-dimethylisoxazylamine (11).**—Colorless crystals were recrystallized from petroleum ether–benzene, mp 90–91°.

Anal. Calcd for $C_{12}H_{12}N_2O$: C, 71.98; H, 6.04. Found: C, 72.10; H, 5.81.

(6) H. D. Law, *J. Chem. Soc.*, **101**, 154 (1912).

Benzildianil (3a).—In a 50-ml erlenmeyer flask was placed 3.62 g (0.02 mol) of *N*-benzylideneaniline (**1a**) in 30 ml of dry DMSO. To this solution was added 0.98 g (0.02 mol) of powdered sodium cyanide, and the flask was stoppered and magnetically stirred for a period of 72 hr at room temperature (20°). The reaction mixture was poured slowly, with stirring into an ice-water mixture and the precipitated product was filtered. The crude yield was 3.6 g, mp 107–130°. This was taken up in 20 ml of boiling benzene, diluted with 5 ml of petroleum ether, and allowed to cool. A little benzanilide separated and was filtered; the filtrate was evaporated to half its volume and 5 ml of boiling ethanol was then added. On cooling, 2.45 g of dianil **3a** separated out as light yellow plates, mp 142–143°. Further evaporation of filtrate and cooling afforded an additional 0.7 g of dianil **3a**, mp 139–141°. A very pure sample of dianil **3a**, mp 144–145°, was obtained by recrystallization from petroleum ether: uv λ_{max} (ethanol) 264 nm (ϵ 37,350); ir 1620 cm^{-1} (C=N) ($CHCl_3$).

The above reaction when run in DMF gave no benzanilide; dianil **3a** was isolated in 77% yield.

In general, the reaction of aldimines **1** with cyanide ion in DMSO or DMF was carried out at room temperature for a period of 72 hr. No care was taken to exclude air from the reaction. The reaction mixture was poured in ice-water and the crude product was crystallized to afford α diketimines **3b–3l**. Their melting points and analytical data are summarized in Table II.

Benzil (4a).—A mixture of 1 g of dianil **3a** and 10 ml of concentrated hydrochloric acid was magnetically stirred for 14 hr. The precipitated diketone **4a** was filtered, mp 94–95° (0.63 g, 92%).

Diketones **4b–4l** were prepared in the same fashion as described for **4a**. Their melting point data are recorded in Table II.

Registry No.—**1j**, 32349-41-0; **1k**, 27738-39-2; **1l**, 32349-43-2; **3a**, 7510-33-0; **3b**, 21854-87-5; **3c**, 21854-89-7; **3d**, 21854-88-6; **3e**, 21913-95-1; **3f**, 32349-49-8; **3g**, 24099-56-7; **3h**, 32349-50-1; **3i**, 32382-35-7; **3j**, 32349-51-2; **3k**, 24099-55-6; **3l**, 32349-53-4.

Acknowledgments.—We thank the Research Corporation (New York) and the Academic Grant Fund of Loyola University, New Orleans, for support and Mr. Chris Christensen for valuable assistance.

Preparation of *N,N*-Dialkyl Aromatic Amines *via* Benzyne Reaction[1a]

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Received June 1, 1971

This paper reports on the investigation of the reaction of haloaromatic compounds with sodamide in secondary aliphatic amine solvents. Two factors prompted this study. First, Bunnett and Brotherton[2] proposed a distinct steric interaction in the preparation of certain *N,N*-dialkylanilines *via* the reaction of bromobenzene and sodamide in refluxing secondary amine solvent. Thus, *N,N*-diethylaniline was prepared in only a 53% yield after 2 hr of heating. Heating for 16 hr increased the yield to only 64%. In contrast, we[3] have shown that *N*-alkylanilines are readily obtained by the action of bromobenzene and sodamide in primary aliphatic amine solvent at room temperature. Steric factors were of minor importance in this system since good yields of amines containing bulky groups such as *tert*-butyl (72%) are achieved. Higher yields of *N*-alkylanilines were precluded by further addition of *N*-alkylaniline ion to benzyne forming *N*-alkyl-*N*-phenylanilines. This indicated that the extent of those steric effects proposed by Bunnett in the addition of secondary amines to benzyne might be in error. In support of this conclusion, Caubere and Derozier[4] observed that good yields of *N,N*-dialkylanilines were obtained if bromobenzene and the appropriate dialkylamine were allowed to react in the presence of sodamide and sodium *tert*-butoxide in tetrahydrofuran. Thus, it was clear that a reinvestigation of the reaction of bromobenzene and sodamide in secondary aliphatic amine solvents was in order.

Secondly, it is well established that certain substituted haloaromatic compounds are in part reductively dehalogenated by treatment with certain alkali dialkylamides.[5] For example, Benkeser[6] has noted that the reaction of lithium dimethylamide with *o*-bromoanisole afforded anisole (17%) in addition to the expected benzyne product, *N,N*-dimethyl-*m*-anisidine (35%). Interestingly, we[7] have shown that competition reactions between acetonitrile anion and dimethylamine for various arynes (including 3-methoxybenzyne) generated by the action of sodamide on the corresponding haloaromatic compound produced no reduced dehalogenated compounds. In addition, high yields of several meta derivatives of *N*-alkylanilines were obtained by the reaction of sodamide and various primary aliphatic amines with ortho-substituted haloaromatic compounds possessing strong −I groups [OCH_3, Cl, and $N(CH_3)_2$].[8] No reductive dehalogenated products were observed in any case. Therefore, it was of interest to see if high yields of meta derivatives of *N,N*-dialkylanilines could also be obtained using sodamide. Also, more insight into the nature of the reduction mechanism would be obtained.

Experimental Section

Glpc analyses were performed on a MicroTek instrument Model GC 1600 using helium as the carrier gas at a flow rate of 45 ml/min, inlet and detector temperatures at 250°, and a 10 ft × 0.125 in. i.d. column packed with 5% Carbowax, 20M (polyethylene oxide) on Chromosorb W, acid-washed, 60–80 mesh. Microanalytical analyses were performed by Chemalytics, Tempe, Ariz.

Starting Materials.—Reagent grade sodium was obtained from J. T. Baker. Amine solvents, obtained from Aldrich Co., were dried over anhydrous calcium hydride for 24 hr and then distilled directly into a thoroughly dried reaction flask. Bromobenzene and *o*-bromoanisole, which were obtained from Eastman Kodak, were dried over calcium chloride and distilled before use. *o*-Chloro-*N,N*-dimethylaniline was prepared by the method of Huenig.[9]

General Procedure.—The reactions were carried out in a manner similar to that previously described[8] with the exception that sodamide was prepared *in situ* by the addition of sodium to liquid ammonia in the presence of ferric nitrate. In addition, the mole ratio of 0.3:0.1 sodamide to haloaromatic in 100 ml of amine

(1) (a) Supported in part by Grant N-118 from the Robert A. Welch Foundation, Houston, Tex. (b) Robert A. Welch Predoctoral Fellow.

(2) J. F. Bunnett and T. K. Brotherton, *J. Org. Chem.*, **22**, 832 (1957).

(3) E. R. Biehl, S. M. Smith, and P. C. Reeves, *ibid.*, **36**, 1841 (1971).

(4) P. Caubere and N. Derozier, *Bull. Soc. Chim. Fr.*, 1737 (1969).

(5) For a comprehensive listing see R. W. Hoffmann, "Dehydrobenzene and Cycloalkynes," Academic Press, New York, N. Y., 1967, pp 101–105.

(6) R. A. Benkeser and C. E. DeBoer, *J. Org. Chem.*, **21**, 365 (1956).

(7) E. R. Biehl, E. Nieh, and K. C. Hsu, *ibid.*, **34**, 3595 (1969).

(8) E. R. Biehl, R. Patrizi, and P. C. Reeves, *ibid.*, **36**, 3252 (1971).

(9) S. Huenig, *Chem. Ber.*, **85**, 1056 (1952).

TABLE I

PREPARATION OF *N,N*-DIALKYLANILINES, G-$C_6H_4NR_2$

G	R	Registry no.	Yield, %	Bp, °C (mm)	Formula		C, %	H, %	N, %
H	C_2H_5		93	77 (7)[a]					
	i-C_3H_7		22[b]	87 (9)[c]					
	n-C_3H_7		88	118 (5)[d]					
	n-C_4H_9		74	89 (0.8)[e]					
	i-C_4H_9		81	107 (4)[f]					
m-OCH_3	C_2H_5		95	100–102 (1.2)[g]					
	i-C_3H_7	7000-87-5	72	101–103 (1.2)	$C_{13}H_{21}NO$	Calcd	75.32	10.21	6.76
						Found	75.45	10.36	7.05
	n-C_4H_9		78	134–135 (1.0)[h]					
	i-C_4H_9	32319-29-2	65	118–120 (1.1)	$C_{14}H_{23}NO$	Calcd	76.58	10.71	5.95
						Found	76.43	10.65	6.04
m-$N(CH_3)_2$	C_2H_5		95	125–128 (1.9)[i]					
	i-C_3H_7	32319-30-5	38	105–107 (1.1)	$C_{14}H_{24}N_2$	Calcd	76.63	10.98	12.71
						Found	76.82	10.80	12.53
	n-C_4H_9	32319-31-6	87	138–140 (1.3)	$C_{15}H_{26}N_2$	Calcd	77.36	11.36	11.28
						Found	78.42	11.41	11.46
	i-C_4H_9	32319-32-7	82	124–126 (1.0)		Found	77.32	11.54	11.27

[a] Lit.[2] bp 62–66° (3 mm). [b] Yield was increased to 38% by using reaction time of 6 hr. [c] Lit.[2] bp 95.5° (12 mm). [d] Lit.[10] bp 110–115° (10 mm). [e] Lit.[2] bp 103.5–106° (3.5 mm). [f] Lit.[11] bp 146° (21 mm). [g] Lit.[12] bp 87–89° (0.5 mm). [h] Lit.[12] bp 136.5–138.5° (1.9 mm). [i] Lit.[13] bp 100–102° (0.5 mm).

solvent, and a reaction time of 3 hr (after color change) was utilized. Products were obtained by vacuum distillation. Vpc analysis revealed that the small amounts (less than 5%) of ortho isomers were readily removed from the desired meta-substituted *N,N*-alkylaniline by one distillation. Pertinent data are listed in Table I.

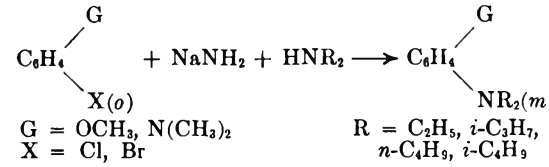
Results and Discussion

Table I[2,10–13] reveals that in general good to excellent yields of *N,N*-dialkylanilines are obtained when bromobenzene is allowed to react with sodamide in various secondary amine solvents. Improved yields in the

$$C_6H_5Br + NaNH_2 + R_2NH \longrightarrow C_6H_5NR_2$$
$$R = C_2H_5,\ i\text{-}C_3H_7,\ n\text{-}C_5H_7,\ n\text{-}C_4H_9,\ i\text{-}C_4H_9$$

case of *N,N*-diethylaniline (93% *vs.* 53%[2]) is most likely attributable to our use of an improved amine drying procedure (drying over CaH_2 for 24 hr *vs.* azeotropic benzene distillation.) It should be pointed out that diethylamine is very difficult to dry. The high yield of *N,N*-diethylaniline reported in this study was obtained only when an extensive drying period was utilized. The low yield (22%) of *N,N*-diisopropylaniline observed in this study, however, is the same as that obtained by Bunnett[2] indicating that at least in this system steric effects are important. Huisgen[14] has observed a similar effect in the nucleophilic addition to 1-naphthyne. In that study steric effects only became important when the attacking secondary amine possessed a carbon atom (α to the nitrogen atom) substituted with at least two alkyl groups. The yields obtained in this study compare very favorably with those obtained by Caubere and Derozier,[4] indicating that no synthetic advantage is obtained by employing both sodium amide and sodium *tert*-butoxide.

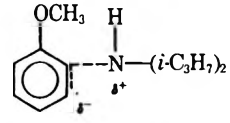
Table I also indicates that, in general, good to excellent yields of *N,N*-dialkyl-*m*-anisidines (95–65%) and *N,N*-dialkyl-*N'*,*N'*-dimethylphenylenediamines (95–38%) are produced by the reaction of the corresponding ortho-substituted haloaromatic compounds with sodamide in various secondary amine solvents. Only in the case of the reaction between diisopropylamine and *o*-chloro-*N,N*-dimethylaniline were low yields (38%) achieved.



The generally good to high yields are due in part to the fact that no reductive dehalogenated products (anisole and *N,N*-dimethylanilines) are formed. Although there is still controversy[15,16] over the reduction mechanism, it is generally agreed that alkali dialkylamides possessing α-hydrogen atoms are the hydride ion donors. Experimentally, no liberation of ammonia was observed until the addition of the haloaromatic compound. Consequently, no appreciable amount of the dialkylamine was converted to the corresponding sodium dialkylamide. Thus, the reduction pathway was circumvented.

$$R_2NH + NaNH_2 \longrightarrow R_2NNa + NH_3$$

Interestingly, the steric effects operating on the addition of diisopropyl amine to 3-methoxybenzyne are considerably less than those observed in the addition of the same amine to 3-(*N,N*-dimethylamino)benzyne. It is known that 3-methoxy groups destabilize arynes.[7] Hence, the low steric requirements in the diisopropylamine addition to 3-methoxybenzyne simply reflects the longer carbon–nitrogen bond-making length in the transition state for this particular nucleophilic addition.



(10) H. Bock and K. L. Kompa, *Chem. Ber.*, **99**, 1361 (1966).
(11) A. Stüder, *Justus Liebigs Ann. Chem.*, **211**, 236 (1882).
(12) H. Gilman and R. H. Kyle, *J. Amer. Chem. Soc.*, **74**, 3028 (1952).
(13) H. Gilman, R. H. Kyle, and R. A. Benkeser, *ibid.*, **68**, 143 (1946).
(14) R. Huisgen and L. Zirngible, *Chem. Ber.*, **91**, 2375 (1959).
(15) R. A. Benkeser and C. E. DeBoer, *J. Org. Chem.*, **21**, 281 (1956).
(16) G. Wittig, H. J. Schmidt, and H. Renner, *Chem. Ber.*, **95**, 2377 (1962).

Preparation of 2-Alkoxyimino Aldehydes and Ketones by the Oxidation of Alkoxyiminoalkanes with Selenium Dioxide[1]

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Received June 25, 1971

Two 2-alkoxyiminoaldehydes have been prepared in low yield by reduction of the corresponding 2-alkoxyiminoacyl halides with lithium tri-*tert*-butoxyaluminohydride.[3] 2-Alkoxyimino ketones have not been reported, however.

Imine nitrogens in heteroaromatic systems like carbonyls cause adjacent methylenes to become oxidized to aldehydes or ketones by SeO_2. In these systems, however, the corresponding acid derivatives have a great propensity to form.[4,5]

In an effort to develop a general procedure for introducing a carbonyl adjacent to an alkoxyimino function, *O*-alkyl oximes were treated with SeO_2. Ethers (methyl and ethyl) of acetophenone oxime were oxidized to the desired aldehydes in good yield. The corresponding free oximes produced tar. The *O*-ethyl ether of butyraldoxime was readily oxidized to 2-oxobutyraldoxime *O*-ethyl ether. The compounds prepared are shown in Table I with pertinent physical and analytical data.

When the *O*-ethyl ethers of purely aliphatic compounds like acetone and 3-methyl butanone were treated with SeO_2 in ethanol they yielded mainly ethyl esters of the corresponding 2-alkoxyimino acids. Spectral and chemical evidence confirmed the presence of the esters (see Experimental Section). Ester formation apparently results from an acid-catalyzed condensation between the carboxylic acids generated and the solvent (ethanol).

In the case of acetone oxime *O*-ethyl ether, running the reaction without solvent or in a mixture of dioxane and water produced no aldehyde.

Experimental Section

General Procedure.—The optimum conditions varied from compound to compound, but the general procedure involved heating equimolar quantities of selenium dioxide and the oxime ether in a solution of *p*-dioxane and water (8:1) at reflux for 4.5 hr. Filtration of the reaction mixture to remove selenium was followed by removal of solvent and distillation of the residue.

Characterization of Esters.—When acetone oxime *O*-ethyl ether was treated with selenium dioxide in alcohol–water at reflux the product, bp 70–72° (15 Torr), $n^{25}D$ 1.4540, showed no aldehydic proton in the nmr. It did show a weak carbonyl bond at 1735 cm^{-1} (film) in the ir and a parent ion at m/e 159 in the mass spectrum. Basic hydrolysis of the product yielded a white solid which was identified as 2-ethoxyiminopropionic acid, mp 68–70° (lit.[6] 68–70°).

TABLE I

COMPOUNDS PREPARED BY THE SeO_2 OXIDATION OF ALKOXYIMINOALKANES

$$R_1—\underset{\underset{NOR_2}{\|}}{C}—X$$

Registry no.	R_1	R_2	X	Bp, °C (Torr)	Refractive index	Yield, %	Composition	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
32349-36-3	Ph	Me	CHO	63–65 (0.035)	$n^{26}D$ 1.5455	49	$C_9H_9NO_2$[a]	54.09	5.41	24.54	54.32	5.33	24.92
32349-37-4	Ph	Et	CHO	59–61 (0.002)	$n^{24}D$ 1.5380	60	$C_{10}H_{11}NO_2$[b]	56.41	5.98	23.93	56.65	5.68	23.85
32349-39-6	EtCO	Et	H	132–134	$n^{24}D$ 1.4318	33	$C_6H_{11}NO_2$	55.81	8.53	10.85	55.54	8.72	10.65

[a] Analyzed as semicarbazone ($C_{10}H_{12}N_4O_2$), mp 195°, registry no. 32382-33-5. [b] Analyzed as semicarbazone ($C_{11}H_{14}N_4O_2$), mp 175°, registry no. 32349-38-5.

In like manner ethyl 2-ethoxyimino-3-methylbutanoate, bp 64–66° (13 Torr), $n^{25}D$ 1.4339, was obtained from 2-ethoxyimino-3-methylbutanone. No aldehydic proton was observed in the nmr, but there was a weak carbonyl at 1730 cm^{-1} (film) in the ir and a parent ion at m/e 187 in the mass spectrum.

Registry No.—SeO_2, 7446-08-4.

(1) Abstracted in part from the Ph.D. dissertation of L. A. S., University of Illinois, 1971.

(2) Department of Medicinal Chemistry, University of Kansas, Lawrence, Kans.

(3) D. A. Coviello and W. H. Hartung, *J. Org. Chem.*, **24**, 1611 (1959).

(4) A. Burger and L. R. Modlin, *J. Amer. Chem. Soc.*, **62**, 1079 (1940).

(5) W. Henze, *Ber.*, **67**, 750 (1934).

(6) A. F. Ferris *J. Org. Chem.*, **24**, 1726 (1959).

Hückel Molecular Orbital Calculations of the Index of Aromatic Stabilization of Polycyclic Conjugated Molecules[1,2]

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Received April 20, 1971

In recent years there have been various attempts[3-7] to improve the predictive power of the HMO method originated by Hückel[8] in 1931. Here we would like

(1) Presented in part at the Meeting of Croatian Chemists, Zagreb, Croatia, Yugoslavia, Feb 1971.

(2) This note was based upon B.S. theses submitted by M. Milun and Ž. Sobotka in partial fulfillment of the requirements for the B.S. degree at the Croatian University, Zagreb, 1971.

(3) H. P. Figeys and P. Dedieu, *Theor. Chim. Acta*, **9**, 82 (1967).

(4) H. P. Figeys, *Tetrahedron*, **26**, 4615, 5225 (1970).

(5) J. Kruszewski and T. M. Krygowski, *Tetrahedron Lett.*, 319 (1970).

(6) T. M. Krygowski, *ibid.*, 1311 (1970).

(7) J. Kuthan and T. M. Krygowski, *ibid.*, 4109 (1970).

(8) E. Hückel, *Z. Phys.*, **70**, 204 (1931); **72**, 310 (1931); **76**, 628 (1932).

to report a different and more realistic criterion for aromaticity. Namely, one of the long-standing problems is concerned with Hückel delocalization energies (DE), which estimated in the standard manner[9] are not always a reliable guide of aromaticity. For example, pentalene, a very unstable molecule showing no aromatic properties,[10,11] has a greater value of DE (2.46 β) than benzene (2.00 β). There are a number of other examples: heptalene, fulvene, fulvalene, heptafulvene, etc., which were all predicted to be aromatic on the grounds of their DE values being large, thus having a significant resonance stabilization. Such a prediction has been largely disproved by efforts to synthesize these compounds: heptalene has not been prepared[12] as yet, while fulvene, fulvalene, and heptafulvene were prepared,[13,14] but they undergo polymerization readily.

Therefore, we present here a new and simple criterion for aromaticity: the HMO index of aromatic stabilization (A_s). We define the index of aromatic stabilization as the difference between the HMO energy of a given conjugated molecule and the HMO energy of a corresponding classical structure. The HMO energy of the classical structure is equal to the sum of the "polyene" double bond energies and "polyene" single bond energies. "Polyene" bond energies can be obtained by considering linear conjugated polyenes. The general formula for a linear conjugated polyene is

$$\underset{\text{A}}{CH_2{=}CH(-CH{=}CH)_nH}$$

Dewar presented evidence in several works[15-17] that bonds in classical polyenes[18] can be regarded as localized. Accepting this conclusion[19] one can write the total HMO energy for polyene A as

$$E_{\text{total}} = n(E_{C=C} + E_{C-C}) + E_{C-C}$$

where $E_{C=C}$ and E_{C-C} are "polyene" double and single bond energies, respectively. A plot of E_{total} *vs.* n should then be a straight line of slope $(E_{C=C} + E_{C-C})$ and intercept $E_{C=C}$. We have calculated HMO energies for polyenes from $n = 1$ to $n = 9$ and have found a linear relationship which led to the following "polyene" bond energies: $E_{C=C} = 2.00\ \beta$ and $E_{C-C} = 0.52\ \beta$.

Using these values we calculated the HMO index of aromatic stabilization for various conjugated hydrocarbons. These results are listed in Table I, which also contains, for comparison, the HMO delocalization energies and "resonance energies" (DRE) determined in the manner described by Dewar and coworkers[20-22] using a variant[23] of the SCF π-molecular orbital method.[24]

TABLE I

DELOCALIZATION ENERGIES (DE), INDICES OF AROMATIC STABILIZATION (A_s), AND DEWAR'S RESONANCE ENERGIES (DRE)

Compd	DE (in units β)[a]	A_s (in units β)	DRE, kcal/mol[b]
Benzene (1)	2.000	0.440	20.0
Naphthalene (2)	3.683	0.563	30.5
Anthracene (3)	5.314	0.634	36.9
Phenanthrene (4)	5.448	0.768	44.6
Chrysene (5)	7.192	0.952	57.3
Triphenylene (6)	7.274	1.034	61.2
Perylene (7)	8.245	0.965	60.4
Coronene (8)	10.572	1.212	81.3
Pyrene (9)	6.505	0.785	48.4
Styrene (10)	2.424	0.344	19.8
Biphenyl (11)	4.383	0.743	39.2
Azulene (12)	3.364	0.244	4.2
Pentalene (13)	2.456	−0.144	−6.5
Heptalene (14)	3.618	−0.022	−2.1
Fulvene (15)	1.466	−0.094	1.1
Heptafulvene (16)	1.994	−0.086	0.5
Fulvalene (17)	2.799	−0.321	2.5
Heptafulvalene (18)	4.004	−0.155	2.3
Cyclcobutadiene (19)	0.000	−1.040	−18.0[c]
Cyclooctatetraene (20) (planar)	1.657	−0.420	−2.6

[a] C. A. Coulson and A. Streitwieser, Jr., "Dictionary of π-Electron Calculations," Pergamon Press, Oxford, 1965. [b] M. J. S. Dewar and C. de Llano, *J. Amer. Chem. Soc.*, **91**, 789 (1969); C. de Llano, Ph.D. Thesis, University of Texas, Austin, 1968. [c] M. J. S. Dewar, M. C. Kohn, and N. Trinajstić, *J. Amer. Chem. Soc*, **93**, 3437 (1971).

As seen from Table I, compounds **1–11** are predicted to be aromatic, all having large values of the A_s index. This is in agreement with their observed properties.[25] A number of nonbenzenoid hydrocarbons investigated in the present work are predicted to be nonaromatic, polyolefinic compounds, having negative A_s indices. This prediction agrees with their high degree of instability.[10-14]

The HMO delocalization energies, as it is clearly seen from Table I, do not differ between typically aromatic and nonaromatic molecules; the DE values, with the exception of cyclobutadiene (**19**), are very much alike for both classes of hydrocarbons. On the other hand, our results follow closely Dewar's resonance. energies, the only discrepancy being azulene (**12**). Dewar's RE (4.2 kcal/mol) is perhaps too low for azulene, which has a stability and chemical behavior more similar to benzene than to cyclic polyolefinic compounds.[26] We agree rather nicely for cyclobutadiene predicting it to be a very unstable molecule. This is in agreement with experimental evidence: cyclobutadiene was prepared[27] a few years ago only as a

(9) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1961, p 239.
(10) E. D. Bergman in "Non-Benzenoid Aromatic Compounds," D. Ginsburg, Ed., Interscience, New York, N. Y., 1959, p 141.
(11) G. M. Badger, "Aromatic Character and Aromaticity," Cambridge University Press, New York, N. Y., 1969.
(12) Reference 10, p 155.
(13) J. Thiec and J. Wiemann, *Bull. Soc. Chim. Fr.*, 177 (1956); *ibid.*, 1066 (1960).
(14) W. von E. Doering, "Theoretical Organic Chemistry," Kekulé Symposium, 1958, p 35.
(15) M. J. S. Dewar and H. N. Schmeising, *Tetrahedron*, **5**, 166 (1959); *ibid.*, **11**, 96 (1960).
(16) M. J. S. Dewar, *Chem. Ind. News*, **43**, 86 Jan 11, (1965).
(17) M. J. S. Dewar, *Tetrahedron, Suppl.*, **8**, 75 (1966).
(18) A classical polyene is a polyene for which only a single classical structure (unexcited resonance structure) can be written.
(19) M. J. S. Dewar, "The Molecular Orbital Theory of Organic Chemistry," McGraw-Hill, New York, N. Y., 1969, p 173.
(20) M. J. S. Dewar and G. J. Gleicher, *J. Amer. Chem. Soc.*, **87**, 685 (1965).
(21) M. J. S. Dewar and C. de Llano, *ibid.*, **91**, 789 (1969).
(22) M. J. S. Dewar and A. J. Harget, *Proc. Roy. Soc., Ser. A*, **315**, 443 (1970).
(23) Reference 19, Chapter V.
(24) J. A. Pople, *Trans. Faraday Soc.*, **49**, 1375 (1953).
(25) E. Clar, "Polycyclic Hydrocarbons," Academic Press, London, 1964.
(26) E. Heilbronner in ref 10, p 171.
(27) L. Watts, J. D. Fitzpatrick, and R. Pettit, *J. Amer. Chem. Soc.*, **87**, 3253 (1965).

highly reactive intermediate of its iron tricarbonyl complex, which cannot be isolated.[28]

Registry No.—**1**, 71-43-2; **2**, 91-20-3; **3**, 120-12-7; **4**, 85-01-8; **5**, 218-01-9; **6**, 217-59-4; **7**, 198-55-0; **8**, 191-07-1; **9**, 129-00-0; **10**, 100-42-5; **11**, 92-52-4; **12**, 275-51-4; **13**, 250-25-9; **14**, 257-24-9; **15**, 497-20-1; **16**, 539-79-7; **17**, 91-12-3; **18**, 531-45-3; **19**, 1120-53-2; **20**, 629-20-9.

Acknowledgments.—We would like to thank Professor Michael J. S. Dewar (Austin) and Professor Jaroslav Koutecký (New York) for helpful discussions. We would also like to thank Dr. Tomislav Cvitaš (Zagreb) for help in the presentation of this paper.

(28) NOTE ADDED IN PROOF.—After this note was submitted for publication, we noticed two important papers by B. A. Hess and L. J. Shaad [*ibid.*, **93**, 305, 2413 (1971)] describing a similar approach. We found general agreement between our results and theirs. A discussion about these two approaches is given in our paper on monocyclic conjugated molecules, submitted for publication in *Croat. Chem. Acta.*

The Photolysis of 1-Phenylcyclohexene in Methanol[1]

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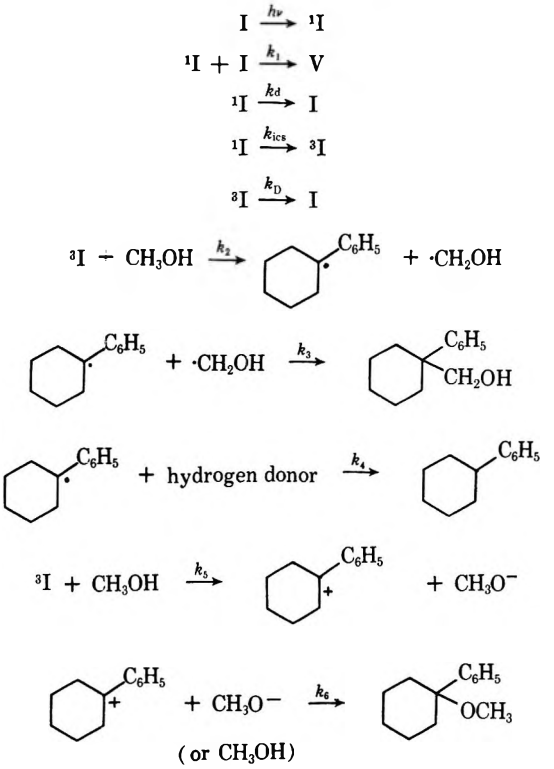
The photolysis of 1-phenylcyclohexene in methanol, with or without triplet sensitizer, yields the ionic addition product, 1-methoxy-1-phenylcyclohexane.[2] This reaction was found to be susceptible to acid catalysis.[2] No other adducts or reduction products have previously been reported for this reaction. Recent reports of hydrogen atom abstraction reactions for electronically excited olefins[3] prompted us to reexamine the photolysis of 1-phenylcyclohexene in methanol.

The photolysis of degassed solutions of 1-phenylcyclohexene (I) (0.2 *M*) in methanol for 96 hr at 2537 or 3000 Å afforded four major products: phenylcyclohexane (II), 13%, 1-methoxy-1-phenylcyclohexane (III), 26%, 1-hydroxymethyl-1-phenylcyclohexane (IV), 7%, and a dimer of 1-phenylcyclohexene of undetermined structure (V), 46%. Yields are based on reacted 1-phenylcyclohexene. Quantum yield for disappearance of I at 3000 Å was 0.12. The reaction products were separated by column chromatography (Al_2O_3) and the characterized products gave ir spectra which were identical with those of authentic samples. It is noted that in previous studies[2a,b] the radiation exposures were considerably less than in the present study and that irradiation of a methanol solution of 1-phenylcyclohexene (E_T = 62 kcal/mol[4]) containing 3-methoxyacetophenone (E_T = 72.5 kcal/mol[5]) at 3500 Å gave the first three products (II, III, IV) in the above ratios and only trace amounts of dimer. 1-Phenylcyclohexene was unreactive at 3500 Å in the absence of sensitizer. A solution of 3-methoxyacetophenone in methanol and a similar solution containing 1-phenylcyclohexene were photolyzed simultaneously at 3500 Å. The quantum yield for disappearance of 3-methoxyacetophenone in the first solution was significantly lower than the quantum yield for disappearance of 1-phenylcyclohexene, thereby indicating the occurrence of triplet energy transfer rather than hydrogen atom transfer "chemical sensitization." 1,3-Cyclohexadiene (E_T = 52.5 kcal/mol[6]) quenched the photochemical formation of II, III, and IV, but not V, on irradiation at 3000 Å. These data are consistent with the following mechanism.



In the above mechanism we have assumed that phenylcyclohexane is formed *via* a hydrogen abstraction process, although there is evidence for photoreduction of some olefins.[7] We have also treated the formation of products from free radical and carbonium ion as irreversible. Although we have represented hydrogen abstraction and protonation as involving ^{3}I directly, we do not preclude prior decay of the triplet to ground state trans molecule.

Stern–Volmer quenching studies of 1-phenylcyclohexene were performed in degassed acetonitrile solu-

(1) H. M. Rosenberg and M. P. Servé, presented in part at the 161st National Meeting of the American Chemical Society, Los Angeles, Calif., March–April 1971.

(2) (a) P. J. Kropp, *J. Amer. Chem. Soc.*, **91**, 5783 (1969); (b) M. Tada and H. Shinozaki, *Bull. Chem. Soc. Jap.*, **43**, 1270 (1970).

(3) (a) J. Nasielski, M. Jauquet, E. Vander Donckt, and A. Van Sinov, *Tetrahedron Lett.*, 4859 (1969); (b) M. P. Servé, H. M. Rosenberg, and R. Rondeau, *Can. J. Chem.*, **47**, 4295 (1969); (c) H. M. Rosenberg and M. P. Servé, *J. Amer. Chem. Soc.*, **92**, 4746 (1970); (d) T. S. Cantrell, *Chem. Commun.*, 1633 (1970).

(4) D. F. Evans, *J. Chem. Soc.*, 1351 (1957).

(5) N. C. Yang, D. S. McClure, S. L. Murov, J. J. Houser, and R. Dusenberry, *J. Amer. Chem. Soc.*, **89**, 5466 (1967).

(6) R. E. Kellogg and W. T. Simpson, *ibid.*, **87**, 4230 (1965).

(7) J. A. Marshall and A. R. Hochstetler, *Chem. Commun.*, 296 (1968).

tions containing varying concentrations of methanol and 1,3-cyclohexadiene. Relative quantum yields for formation for products II, III, and IV were determined by glpc. Stern–Volmer plots (eq 1) were

$$\Phi_0/\Phi = 1 + k_q\tau[Q] \quad (1)$$

linear. k_q and τ represent quenching rate constant and triplet lifetime, respectively. Values for $k_q\tau$ and τ are given in Table I, in which k_q is assumed to be 1.1×10^{10} sec^{-1}.[8]

TABLE I

QUENCHING OF THE REACTION OF 1-PHENYLCYCLOHEXENE WITH METHANOL BY 1,3-CYCLOHEXADIENE IN ACETONITRILE

[Methanol], 10^{-2} M	$k_q\tau$, M^{-1}	τ, 10^{-8} sec
8.3	655	5.95
12.5	484	4.40
16.7	394	3.58
20.8	329	2.99

Rate constants for unimolecular triplet decay (k_D) and the sum of bimolecular rate constants for hydrogen atom and proton abstraction ($k_2 + k_5$) were obtained from the plot of $1/\tau$ *vs.* [methanol] according to eq 2

$$1/\tau = k_D + (k_2 + k_5)[\text{methanol}] \quad (2)$$

and were found to be 0.60×10^7 and 1.31×10^8 M^{-1} sec^{-1}, respectively. From the product ratios, $k_2 = 1.07 \times 10^8$ M^{-1} sec^{-1} and $k_5 = 0.23 \times 10^8$ M^{-1} sec^{-1}. These values are subject to the assumptions previously stated.

Experimental Section

Materials.—1-Phenylcyclohexene, phenylcyclohexane, and 3-methoxyacetophenone were purchased from the Aldrich Chemical Co. Cyclohexadiene was obtained from Matheson Coleman and Bell. 1-Hydroxymethyl-1-phenylcyclohexane was prepared according to the method of Wilt and Roberts.[9] 1-Methoxy-1-phenylcyclohexane was prepared as follows: A solution of 1-phenylcyclohexanol (8.6 g, 0.05 mol) and concentrated sulfuric acid (3 drops) in 50 ml of methanol was stirred at room temperature for 15 hr. The solution was then poured into a separatory funnel containing 150 ml of ether and 100 ml of a saturated sodium chloride solution. The ether layer was separated, washed with a 5% sodium bicarbonate solution, and dried over anhydrous sodium sulfate. Removal of the ether yielded a liquid which upon distillation gave 1-methoxy-1-phenylcyclohexane (7.5 g, 82%), bp 91–92° (0.6 mm). *Anal.* Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 82.15; H, 9.67.

Photolysis of 1-Phenylcyclohexene.—A degassed solution of 3 g of 1-phenylcyclohexene in 100 ml of methanol in a quartz vessel was irradiated for 96 hr in a Rayonet photochemical reactor containing lamps having peak emission at 3500 Å. Four major products were isolated by column chromatography (Al_2O_3): phenylcyclohexane (13%), 1-methoxy-1-phenylcyclohexane (26%), 1-hydroxymethyl-1-phenylcyclohexane (7%), and the dimer of 1-phenylcyclohexene (46%). The first three products were identified by comparison of ir spectra with those of authentic samples. The fourth product exhibited a mass spectral parent peak of 316 corresponding to a dimer of 1-phenylcyclohexene. It had the following spectral properties: ir (thin film) 3020, 2900, 1450, 920, 735, 700 cm^{-1}; nmr (60 MH_2, CCl_4) τ 8.5 (m, 16 H), 7.15 (m, 2 H), 2.75 (m, 10 H).

Kinetic Study.—All quantitative measurements were made on a rotating assembly with a central light source (internal water-cooled mercury arc lamp, Hanovia Type L-450-W). Samples in 12-mm Pyrex vessels were placed in holders approximately 6 cm from the immersion well. The light was filtered by a 1-mm Corex jacket fitted over the light source. Samples in 12-mm Pyrex test tubes were degassed to 10^{-3} mm in three freeze–thaw sequences. After the last thawing, an atmosphere of helium was placed over the solutions. The solutions were irradiated to about 15% completion at a constant temperature of 25.7°. Excess solvent was removed under reduced pressure. The extent of reaction was measured by glpc, 3% SE-30 column, using 1-dodecane as an internal reference. Both the loss of 1-phenylcyclohexene and the production of products was measured, the first method being easier to monitor.

In a typical run, 1 ml of 0.05 M 1-phenylcyclohexene in acetonitrile was added to each of the reaction vessels. To each vessel was also added 1 ml of a 0.5 M methanol in acetonitrile solution and a variable amount of a 0.3 M 1,3-cyclohexadiene in acetonitrile solution. Reaction vessels were then brought to equal volume by the addition of the appropriate amount of acetonitrile.

Attempted Sensitization of the Reaction of 1-Phenylcyclohexene in Methanol.—A solution of 1-phenylcyclohexene (0.80 g, 0.005 mol) in methanol (50 ml) was divided into two portions. To one portion was added 3-methoxy acetophenone (1.5 g, 0.01 mol). Both solutions were degassed, placed under a helium atmosphere, and irradiated at 3500 Å. After 96 hr, the sensitized solution had reacted to about 30% completion while the unsensitized solution had failed to react.

Registry No.—I, 771-98-2; I dimer, 32239-45-5; III, 32249-58-4; methanol, 67-56-1.

(8) P. J. Wagner and I. Kochvar, *J. Amer. Chem. Soc.*, **88**, 3665 (1966).
(9) J. W. Wilt and D. D. Roberts, *J. Org. Chem.*, **27**, 3434 (1962).

The Clemmensen Reduction of 2-Acetonaphthone

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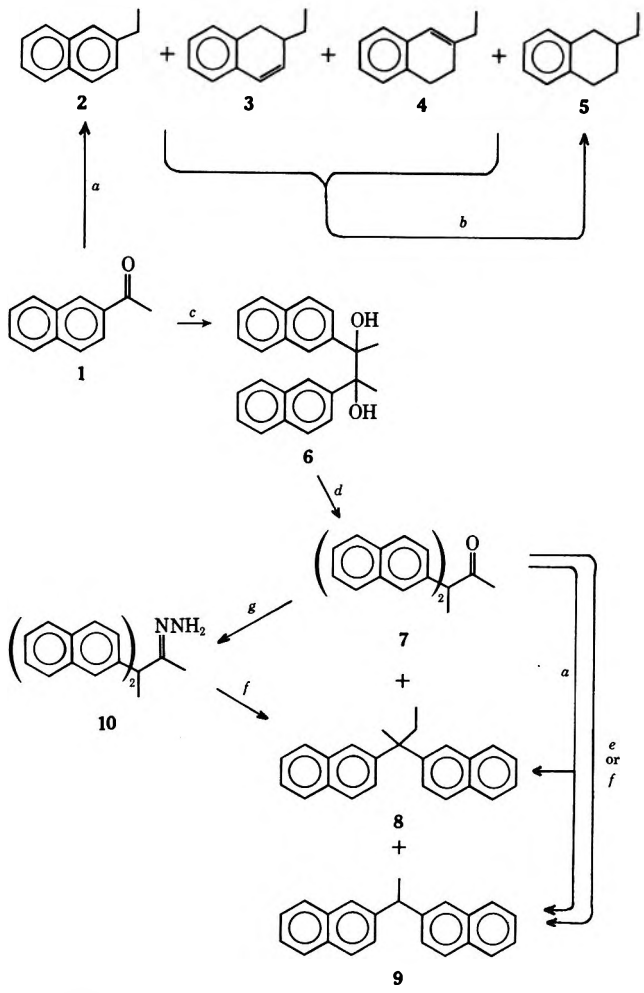
Received May 24, 1971

The Clemmensen reduction of ketones has been reviewed[2] and mechanisms[2b,c,3] accounting for major products have been proposed. We have used the Clemmensen reaction to reduce the carbonyl group of 2-acetonaphthone (1) and have observed the hydrocarbon products **3**, **4**, and **5**, formation of which requires reduction of the naphthalene nucleus (Scheme I). The maximum combined yield (16%) of these hydrocarbons was realized when boiling toluene and mossy zinc amalgam were used (Table I). Other combinations of reagents studied and the yields of the resulting volatile hydrocarbons as well as nonsteam-volatile products are reported in Table I.

The conventional Clemmensen reduction[2a] (procedures D and E) of **1** gave low yields (30–40%) of **2** and mainly condensation products which include **7**, **8**, and **9**. In addition, since distillation of the condensation products resulted in some pot residue, polymerization products may be present.

(1) (a) National Science Foundation, Science Faculty Fellowship, 1970–1972, Grant 60052; (b) Undergraduate Research Assistant, 1970.
(2) (a) E. L. Martin, *Org. React.*, **1**, 155 (1942); (b) D. Staschewski, *Angew. Chem.*, **71**, 726 (1959); (c) J. G. St. C. Buchanan and P. D. Woodgate, *Quart. Rev., Chem. Soc.*, **23**, 522 (1969).
(3) (a) J. H. Brewster, *J. Amer. Chem. Soc.*, **76**, 6361, 6364, 6368 (1954); (b) T. Nakabayashi, *ibid.*, **82**, 3900, 3906, 3909 (1960); (c) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, 1965, p 58.

SCHEME I



[a] Zn(Hg), HCl, toluene—procedure A. [b] Pd/C, H_2. [c] Zn-(Hg), HCl, toluene—procedure C. [d] H^+, Δ. [e] NH_2NH_2, OH^-, DEG, Δ. [f] OH^-, DEG, Δ. [g] $NH_2NH_2 \cdot 2HCl$.

TABLE I

CLEMMENSEN REDUCTION OF 2-ACETONAPHTHONE

Procedure	Yield[a] of steam-volatile hydrocarbon products, % 2	3	4	5	Yield[b] of nonsteam-volatile products, % 7	8	9
A	61	14	1	1	2	2	1
B	54	<1	<1	<1	21	15	7
C	42[c]	0	0	0	3[d]	34	12
D	40	<1	<1	<1	12	31	12
E	30	<1	<1	<1	17	15	6

[a] Yields based on combined weight of steam-distilled products and their glc[7a] peak ratios. [b] Yields based on weight of distilled products and their glc[7b] peak ratios. [c] A trace of **12** and 1% of **13** were observed through glc.[7a] [d] In addition, 5% of the diol from the pinacol condensation of **1** was isolated from the nonsteam-volatile fraction.

Despite the numerous reports[4a,b] of the Clemmensen reduction of **1**, the formation of **3**, **4**, and **5** has gone unreported. Perhaps this is a result of the frequent use of picric acid in the purification[4b,c] of **2**. However, it should be noted that loss of a methoxy group and hydrogenation of the aromatic nucleus was observed in the Clemmensen reduction of β-(1,5-dimethoxy-4-naphthoyl)propionic acid.[4d]

These results should be considered in selecting a reduction procedure for aromatic ketones, since unwanted side products may be obtained in the Clemmensen reduction. It must be assumed that other examples of this behavior have gone unnoticed.

Our combined instrumental data (glc, ir, nmr, mass, and uv spectra) appeared to exclude those isomers of **3**, **4**, and **5** that could arise by reduction[5] of the aromatic ring *not adjacent* to the carbonyl group. To establish this point rigorously, the hydrocarbon mixture containing **3**, **4**, and **5** was hydrogenated until only **5** remained (Scheme I) and the glc of the latter was compared with that of its isomer, 6-ethyl-1,2,3,4-tetrahydronaphthalene (**11**), prepared by independent Friedel–Crafts synthesis from tetralin.[6] Since the glc[7a] retention times are different, **11** must be absent, and its absence shows that it is not produced by the Clemmensen reduction of **1**; hence isomers of **3** and **4** must also be absent. The stability of **2** to Clemmensen reduction is evidence against its being a precursor to **3**, **4**, or **5**.[8]

Since alcohols and olefins have been shown to be intermediates in reduction at benzylic or allylic positions,[3a,9] we prepared 1-(2-naphthyl)ethanol (**12**) and 2-vinylnaphthalene (**13**) and subjected them to Clemmensen reduction (procedure A). The alcohol **12** was reduced to **2**:**3**:**4**:**5**:**13** (300:13:1:2:69), whereas **13** yielded **2**:**3**:**4**:**5**:**13** (103:5:1:2:85).

As shown in Table I, in the absence of toluene[2a] (procedures D and E) or stirring (procedures B, C, D, and E), the formation of dimeric products is favored. At room temperature in toluene with stirring (procedure C), the pinacol **6** could be isolated. Under conditions of procedure A, the pinacol **6** was readily converted to the expected products **7** and **8** and the unexpected cleavage product **9** in the ratio 45:1:1 as determined by glc analysis.[7b] It is of interest that application of procedure A to **6** yields a lower ratio of **8**:**9** (1:1) than its application to **7**, which gives the **8**:**9** ratio as 15:1.

These findings caused us to use the Wolff–Kishner reduction for the preparation[10a] of **2** in 82–91% yield. However, conventional Wolff–Kishner conditions were unsuited to the reduction of **7** to **8** since base-promoted cleavage[10b] to **9** is a strongly competing side reaction. This side reaction may be minimized by treatment of **7** with hydrazine dihydrochloride and then alkali.[11]

(4) (a) E. Clemmensen, *Ber.*, **46**, 1837 (1913); (b) see J. E. Faraday and A. S. Freeborn, "Encyclopedia of Hydrocarbon Compounds," Chemical Publishing Co., New York, N. Y., 1964, pp 84–88, for six references; (c) for a convenient procedure for the separation, purification, and cleavage of the picrates of **1** and **15**, see A. I. Vogel, "Practical Organic Chemistry," 3rd ed, Wiley, New York, N. Y., 1966, p 767; (d) L. F. Fieser and E. B Hershberg, *J. Amer. Chem. Soc.*, **58**, 2382 (1936).

(5) Our data do not exclude exchange of protons in the aromatic ring of **3**, **4**, or **5**.

(6) C. M. Staveley and J. C. Smith, *J. Inst. Petrol., London*, **42**, 55 (1956).

(7) (a) A 0.25 in. (o.d.) × 12 ft copper column containing 80–100 mesh, acid-washed Chromosorb W coated with 25% Carbowax 20M was used in a Beckman GC-2A instrument operating at 220°. (b) A 0.125 in. (o.d.) × 8 ft stainless steel column containing 80–100 mesh, acid-washed, DMCS-treated Chromosorb W coated with 5% of UC W-98 silicone rubber was used in a Hewlett–Packard 5750 instrument operating at 280°. (c) Glc preparative separations were made with an F & M Model 700 chromatograph using a 0.375 in. (o.d.) × 10 ft column containing 80–100 mesh, acid-washed Chromosorb W coated with 25% Carbowax 20M and heated at 150°.

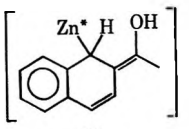
(8) 2-Ethylnaphthalene was recovered unchanged after exposure to the reduction conditions of procedure A for 4 days.

(9) M. Poutsma and E. Wolthus, *J. Org. Chem.*, **24**, 875 (1959).

(10) (a) E. J. Eisenbraun and H. Hall, *Chem. Ind. (London)*, 1535 (1970); (b) B. C. L. Weedon in "Techniques of Organic Chemistry," Vol. XI, Part II, A. Weissberger, Ed., Interscience, New York, N. Y., 1963, p 664.

(11) W. Nagata and H. Itazaki, *Chem. Ind. (London)*, 1194 (1964).

An extension of the mechanisms proposed by Brewster[3a] for the reduction of saturated and α,β-unsaturated ketones accounts for the above mentioned products. The selectivity of reduction in the substituted ring of **1** suggests attachment of zinc as shown in structure **14**.



14

* Zn denotes electron-rich metal surface

Acid-catalyzed isomerization and disproportionation of a mixture of **2**, **3**, **4**, and **5** show that **3** is most affected by the conditions of procedure A[12] and hence is a likely intermediate.

We established by glc analysis[7a] that the ethyl group does not migrate in the Clemmensen reduction (procedure A) of **1** or 1-acetonaphthone (**15**).[13] However, in addition to 1-ethylnaphthalene, three partially reduced hydrocarbons were observed in a combined yield of 5% in the reduction of **15** (procedure A) as compared to 16% total yield of **3**, **4**, and **5** from **1**. The glc retention times[7a] of these unidentified hydrocarbons were similar to those of **3**, **4**, and **5**.

Experimental Section[14]

Zinc Amalgams.—Zinc amalgams were prepared as follows. The desired weight of zinc [Fisher, certified reagent, mossy, or Baker and Adamson, technical (90%) dust] was placed in a flask and covered with an equal weight of distilled water. A volume of 37% hydrochloric acid equal to 5% of that of the water was added with vigorous swirling. After 1 min, the calculated amount of mercuric chloride (Fisher, certified reagent) to give a 3.5% amalgam was added and the resulting mixture was then shaken vigorously for 15 min. The amalgam was washed twice with distilled water and used at once.

General Procedures.—The Clemmensen reductions were carrired out using one of the following procedures.

Procedure A.—To 220 g of mossy zinc amalgam was added 85 g (0.50 mol) of 2-acetonaphthone in 250 ml of toluene, 133 ml of distilled water, and 311 ml of concentrated hydrochloric acid. The reaction mixture was refluxed vigorously for 96 hr or until no ketone was present as determined by glc analysis.[7b] Concentrated hydrochloric acid (50 ml) was added about every 8 hr during the reaction period.

Procedure B.—To 22 g of zinc dust amalgam was added 8.5 g (0.05 mol) of 2-acetonapthone in 25 ml of toluene, 13 ml of distilled water, and 31 ml of concentrated hydrochloric acid. The refluxing reaction mixture was vigorously stirred with a mechanical stirrer (Teflon paddle) until no ketone was present.[7b] Concentrated hydrochloric acid (6 ml) was added every 2 hr during the reaction period.

Procedure C.—Same as B, excepting that a Vibro stirrer, Model No. E-1, was used to stir the reaction mixture and the reaction was carried out at 15–25°.

Procedure D.—Same as B, excepting that toluene was not used.

Procedure E.—Same as D, excepting that mossy zinc was used to prepare the amalgam.

At the end of the heating period for any of the above procedures, the reaction mixture was cooled and decanted from the amalgam residue. The residue was washed thoroughly with ether, and the washings were combined with the reaction mixture and extracted with ether. The extracts were combined, washed with water and saturated sodium bicarbonate solution, dried (Na_2SO_4), and concentrated to give a yellow, viscous residue. This residue was steam distilled to separate the more volatile products. The steam distillate was extracted with ether, dried (Na_2SO_4), concentrated, and analyzed by glc.[7a] The residue from the steam distillation was extracted with ether, dried (Na_2SO_4), concentrated, distilled at *ca.* 160° (0.2 mm), and analyzed by glc.[7b] Separation of components was achieved by preparative glc[7c] and by column chromatography on neutral alumina. Final purification was realized by distillation and crystallization. Products were identified by spectral and elemental analysis. Data on products follow.

1,2-Dihydro-2-ethylnaphthalene (3).—Bp 232–234°;[15] ir (neat) 3.30, 3.40, 3.48, 3.53, 6.72, 6.88, 7.01, 7.24, 7.77, 8.37, 8.94, 9.64, 11.05, and 11.58 μ; mass spectrum (70 eV) *m/e* (rel intensity) 158 (16), 130 (11), 129 (100), 128 (33) 127 (12), and 27 (7); nmr (CCl_4) δ 8.16–7.77 (m, 4, ArH), 7.44–7.27 (2d, 1, vinylic adjacent to ring), 6.94–6.75 (2d, 1, vinylic), 2.97–2.08 (m, 3, $-CH_2$–benzylic and –CH–allylic), 1.72–1.21 (m, 2, $-CH_2$–nonbenzylic), 0.94 (t, 3, $-CH_3$); uv max (95% EtOH) 212 nm (log ϵ 4.60), 217.5 (4.63), 224 (4.47) and 261 (4.23).

Anal. Calcd for $C_{12}H_{14}$: C, 91.08; H, 8.92. Found: C, 91.26; H, 8.94.

3,4-Dihydro-2-ethylnaphthalene (4).[16]—Mass spectrum (70 eV) *m/e* (rel intensity) 158 (41), 143 (29), 129 (100), 128 (43), 127 (13), and 115 (19); nmr (CCl_4) δ 6.98–6.81 (m, 4, ArH), 6.06 (broad s, 1, vinylic), 2.92–2.02 (m, 6, $-CH_2$–benzylic and $-CH_2$–allylic), 1.09 (t, 3, $-CH_3$).

1,2,3,4-Tetrahydro-2-ethylnaphthalene (5).—Mass spectrum (70 eV) *m/e* (rel intensity) 160 (54), 131 (63), 115 (23), 105 (20), 104 (100) and 91 (33); nmr (CCl_4) δ 7.02–6.82 (m, 4, ArH), 3.03–2.13 (broad m, 4, $-CH_2$–benzylic), 1.83–0.81 (broad m, 8, $-CH_2$–nonbenzylic, –CH and $-CH_3$); boiling point, ir, and uv agree with reported values.[6]

3,3-Di(2-naphthyl)-2-butanone (7).—Mp 144–145°;[17a] ir ($CHCl_3$) 5.86, 6.12, 6.25, 7.37, 7.83, 8.83, 10.37, and 10.51 μ; mass spectrum (70 eV) *m/e* (rel intensity) 324 (1), 282 (25), 281 (100), 266 (21), 265 (29), and 153 (13); nmr (CCl_4) δ 7.89–7.03 (m, 14, ArH), 2.13 (s, 3, $-COCH_3$), 2.00 (s, 3, $-CCH_3$);[17b] uv max (95% EtOH) 219 nm (log ϵ 5.01), 222 (5.06), 268 (4.10), and 276 (4.10).

Anal. Calcd for $C_{24}H_{20}O$: C, 88.85; N, 6.21. Found: C, 88.66; H, 6.37.

2,2-Di(2-naphthyl)butane (8).—Mp 90–92°; ir (Nujol) 6.15, 6.27, 7.72, 7.87, 8.38, 8.87, 10.56, 11.69 and 12.22 μ; mass spectrum (70 eV) *m/e* (rel intensity) 310 (21), 282 (24), 281 (100), 266 (16), 265 (22), and 153 (15); nmr (CCl_4) δ 7.82–6.82 (m, 14, ArH), 2.28 (quartet, 2, $-CCH_2CH_3$), 1.69 (s, 3, $-CCH_3$), 0.73 (t, 3, $-CH_2CH_3$); uv max (95% EtOH) 217 nm (log ϵ 4.99), 231 (5.05), 235 (5.08), 266.5 (4.11), and 275.5 (4.10).

Anal. Calcd for $C_{24}H_{22}$: C, 92.86; H, 7.14. Found: C, 92.73; H, 7.24.

1,1-Di(2-naphthyl)ethane (9).—Mp 95–96° (lit.[18] 95°); ir (Nujol) 6.13, 6.24, 8.86, 10.37, 10.51, 11.13, 11.58, and 12.10 μ; mass spectrum (70 eV) *m/e* (rel intensity) 282 (51), 268 (23), 267 (100), 266 (15), 265 (31), 252 (15); nmr (CCl_4) δ 7.92–7.11 (m, 14, ArH), 4.35 (quartet, 1, Ar_2CH), 1.76 (d, 3, $ArCHCH_3$); uv max (95% EtOH) 217 nm (log ϵ 5.00), 231.5 (5.08), 267 (4.08), and 276 (4.07).

Catalytic Hydrogenation of a Mixture of 3, 4, and 5.—To 100 mg of 10% Pd/C was added a solution of 1 g of a mixture of **3**,

(12) Exposure of a mixture of **2**, **3**, **4**, and **5** (6.0:4.6:1.7:1) under the conditions of procedure A for 3 days resulted in the new ratio 5.8:3.4:1.7:1.

(13) MMe. Elphimoff-Felkin and P. Sarda, *Tetrahedron Lett.*, 3045 (1969).

(14) Nmr spectra were obtained with a Varian HR-100 or A-60 spectrometer. Peak positions are reported in terms of parts per million downfield from internal TMS standard in CCl_4 or $CDCl_3$ solvent. Mass spectra were obtained with a CEC Model 21-103C mass spectrometer. Ir and uv spectra were obtained on Beckman IR-5A and Cary 14 spectrophotometers, respectively. Melting points were taken with a Thomas–Hoover capillary melting point apparatus and are corrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. The petroleum ether, bp 60–68°, was distilled before use.

(15) For Emich's method, see A. I. Vogel, "Practical Organic Chemistry," 3rd ed, Wiley, New York, N. Y., 1956, p 86.

(16) The boiling point, ir, and uv agree with those reported by H. Christol, R. Jacquier, and M. Mousseron, *Bull. Soc. Chim. Fr.*, 248 (1958).

(17) (a) M. P. Balfe, J. Kenyon, and C. E. Searle, *J. Chem. Soc.*, 380 (1951). These authors report the formation of a compound, mp 144–145°, by the treatment of 1,2-dimethyl-1,2-di(2-naphthyl)-1,2-ethanediol, mp 184°, with acetic anhydride for 1.5 hr at reflux. They reported that the compound was probably a mixture of the two possible rearrangement products. However, our data indicate that **7** is formed exclusively when procedure C is used. (b) The distinction between the $-COCH_3$ and $-CH_2CH_3$ was made by nmr analysis of **7** which had been subjected to acid-catalyzed enolization in D_2O.

(18) R. Quelet, C. Borgel, and R. Durand, *C. R. Acad. Sci.*, **240**, 1900 (1955).

4, and 5 (28:2:1)[7a] in 150 ml of ethanol. This stirred mixture was hydrogenated at 25° and 1 atm for 5 hr. After filtration through Dicalite and evaporation of the solvent, glc[7a] analysis indicated the presence of only 5.

Wolff–Kishner Reduction of 7 to a Mixture of 8 and 9.—The apparatus and procedure used has been described[10a] except that the product was isolated by ether extraction. From 16.2 g (0.05 mol) of 7 was isolated 14.5 g of crude crystalline reaction products. These products were taken up in petroleum ether[14] and subjected to column chromatography using acidic and basic alumina with petroleum ether[14] as the eluent. Concentration of the eluate gave white crystals (12.9 g) which were shown by glc[7b] to be a mixture of 8:9 (3:7).

Base-Catalyzed Cleavage of 7.—The reaction vessel was a 25-ml, one-necked, flat-bottomed, stainless steel flask equipped with a Dean–Stark trap. A ball joint on the trap fitted with a Teflon O-ring provided a seal with the flask. The top of the trap directly above the reaction flask was threaded and fitted with a screw cap containing a glass tube which constituted a helium inlet. The tube was sealed to the screw with silicone rubber. The glass joint above the stopcock of the trap was fitted with a straight-bore glass condenser which acted as the helium outlet. A 0.25-g (0.77 mmol) sample of 7, 0.3 g of KOH pellets, 0.3 g of NaOH pellets, and 10 ml of diethylene glycol were added to the flask and the assembled system was purged for several minutes with a fast stream of helium. The flow was lessened to maintain a slight positive pressure and the flask was lowered into a preheated (250°) Wood's metal bath. After 3 hr of heating, the reaction mixture was allowed to cool under a helium atmosphere. The resulting brown reaction mixture was extracted with ether. The ethereal extracts were combined, washed with water, dried (Na_2SO_4), and concentrated, giving a dark brown oil. The oil was taken up in petroleum ether[14] and subjected to column chromatography using a silica gel, neutral alumina column, and petroleum ether as the eluent. Concentration of the eluate gave a faint yellow oil which crystallized on trituration with petroleum ether.[14] Recrystallization from 95% ethanol gave 150 mg (70%) of 9 as white crystals: mp 95–96° (lit.[18] mp 95°).

Clemmensen Reduction of 7.—Two grams (6.2 mmol) of 7 was reduced using the conditions of procedure A. After 4 days, less than 10% of 7 had reacted to give 8:9 (15:1) as determined by glc analyses.[7b] However, addition of powdered zinc amalgam resulted in 95% reduction in an additional 24 hr to give 1.1 g (54% combined yield) of a mixture of 8:9 (15:1).[7b]

Wolff–Kishner Reduction of 7 to 8.—By use of procedure A,[11] 0.65 g (2 mmol) of 7 gave 0.55 g (88%) of 8.

Isolation and Reduction of 6.—Steam distillation of the products from the reduction of 25 g (0.15 mol) of 1, using procedure C, gave 12 g of nonvolatile residue. This residue was triturated with hot petroleum ether[14] and the liquid was decanted leaving crude 6. Recrystallization from 1:1 chloroform–ethanol gave 1.1 g (4.5%) of white, crystalline 6: mp 182–184° (lit.[17a,19] mp 184°); ir ($CHCl_3$) 2.80, 6.25, and 8.88 μ; mass spectrum (70 eV) *m/e* (rel intensity) 281 (9), 172 (25), 171 (31), 155 (10) 127 (13), and 43 (100); nmr ($CDCl_3$) δ 7.96–7.13 (m, 14, ArH), 2.30 (s, 2, –OH), 1.65 (s, 6, $-CH_3$); nmr (CD_3COCD_3) δ 8.03–7.23 (m, 14, ArH), 2.04 (broad s, 2, –OH), 1.63 (s, 6, $-CH_3$); uv max (95% EtOH) 219 nm (log ϵ 5.42), 232 (5.43), 269 (4.09), and 277 (4.01).

Anal. Calcd for $C_{24}H_{22}O_2$: C, 84.17; H, 6.47. Found: C, 83.94; H, 6.36.

The reduction of 0.24 g (0.7 mmol) of 6 using procedure A gave 7:8:9 (5:1:1) as shown by glc analysis.[7b]

Reduction of 1-Acetonaphthone (15).—The reduction of 8.5 g (0.05 mol) of 15 using procedure A gave 1-ethylnaphthalene in 82% yield as shown by glc analysis.[7a] Three other volatile hydrocarbons were also observed by glc analysis (combined yield 5%); they had retention times like those of 3, 4, and 5. The nonvolatile fraction showed three major components in a ratio of 1:1.25:1.50, which were similar in retention times to 7, 8, and 9.

6-Ethyl-1,2,3,4-tetrahydronaphthalene (11).—This compound was prepared as outlined previously[6] except that nitroethane was used as solvent: mass spectrum (70 eV) *m/e* (rel intensity) 160 (41), 145 (35), 132 (27), 131 (100), 117 (21), and 115 (20); nmr (CCl_4) δ 6.91–6.59 (m, 3, ArH), 2.99–2.27 (broad m, 6, $ArCH_2-$), 2.01–1.52 (broad m, 4, $-CH_2-$nonbenzylic), 1.17 (t, 3, $-CH_3$). The boiling point, ir, and uv agreed with reported values.[6]

1-(2-Naphthyl)ethanol (12).—A 75.6-g (0.44 mol) sample of 1 was reduced with diisobutylaluminum hydride[20] to give 69.6 g (95%) of crude 12 which, when recrystallized twice from petroleum ether,[14] gave 67.1 g (88%) of pure 12, mp 70–72° (lit.[21] mp 71–72°).

2-Vinylnaphthalene (13).—A sample of 13 was prepared from 12 in 41% yield as described.[22] Conversion of the crude product to picrate and its recrystallization from methanol gave yellow needles, mp 90–92° (lit.[22] mp 91–92°). Chromatographic regeneration gave 2.5 g (35%) of 13, mp 64–66° (lit.[21,22] mp 65–66°). Glc analysis indicated the purity of 13 to be 98%.[7a]

Registry No.—1, 93-08-3; 3, 31861-77-5; 4, 31861-78-6; 5, 32367-54-7; 6, 32298-43-4; 7, 32298-44-5; 8, 32298-45-6; 9, 32298-46-7.

Acknowledgments.—We are grateful to the National Science Foundation and the American Petroleum Institute for partial support. We thank Dr. O. C. Dermer for reading the manuscript.

(19) (a) M. S. Newman, *J. Org. Chem.*, **26**, 582 (1961); (b) R. S. Davidson, P. F. Lambeth, and F. H. Younis, *J. Chem. Soc. C*, 2203 (1969). These authors report melting points of 158–171° and 165–171°, respectively, for mixtures of *meso*- and (±)-6.

(20) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 260.

(21) S. Yura, Y. Yamamoto, H. Hara, and R. Oda, *J. Soc. Chem. Ind. Jap.*, **45**, 575 (1942).

(22) L. H. Klemm, J. W. Sprague, and H. Ziffer, *J. Org. Chem.*, **20**, 182 (1955).

Cholesterol 26-Hydroperoxide[1]

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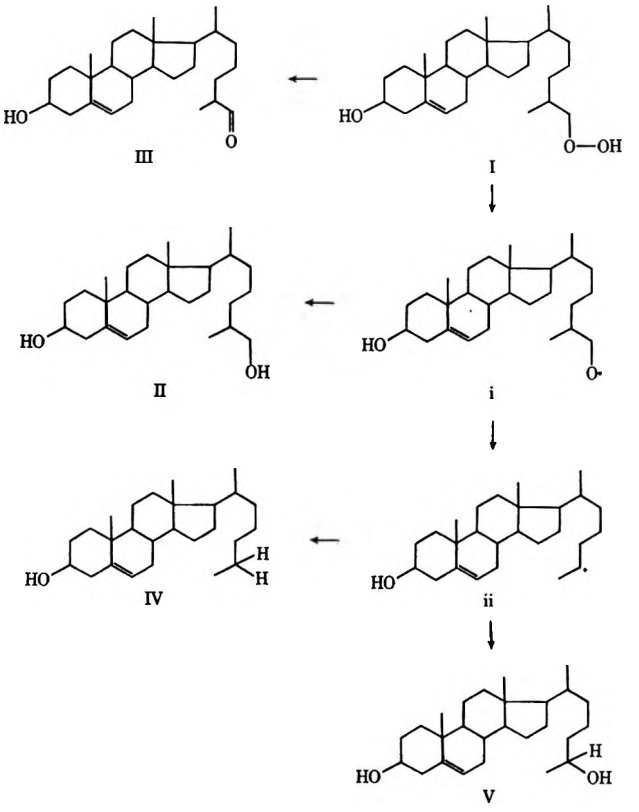
Received June 1, 1971

Recent investigations have shown that the autoxidation of cholesterol proceeds *via* hydroperoxide formation at the tertiary 20α and 25 positions as well as the secondary 24 position of the side chain.[2] The present communication reports the isolation of another cholesterol hydroperoxide identified as 3β-hydroxy-5-cholestene 26-hydroperoxide (I). Upon sodium borohydride reduction of the hydroperoxide I, a single diol was obtained which was identified as 5-cholestene-3β,26-diol (II) by comparison of its chromatographic and physical properties with those of an authentic sample. Further proof of the structure of compound I was obtained from its infrared absorption at 3610 and 3540 cm^{-1}, characteristic of the OH stretching of the hydroxyl and hydroperoxyl groups, respectively; from its proton magnetic resonance spectra which shows the C_{27}-methyl protons as a three-proton doublet at δ 0.94 and the C_{26}-methyl protons as a two-proton multiplet at δ 3.92, deshielded 2.05 ppm by the 26-hydroperoxyl group; and from its high-resolution mass spectral analysis. The four major thermal decomposition products of the compound I were identified by their chromatographic and spectral properties as 5-cholestene-3β,26-diol (II), 3β-hydroxy-5-cholesten-26-al (III),

(1) (a) Supported by the Medical Research Council of Canada (Grant MA-4051) and the Conseil de la Recherche Médicale du Québec. (b) Presented at the 14th Annual Meeting of the Canadian Federation of Biological Societies, Toronto, June 1971, Abstract 367.

(2) (a) J. E. van Lier and L. L. Smith, *J. Org. Chem.*, **35**, 2726 (1970); (b) *ibid.*, **36**, 1007 (1971); (c) *Steroids*, **15**, 4 (1970).

27-nor-5-cholesten-3β-ol (IV), and 27-nor-5-cholestene-3β,25ξ-diol (V). The decomposition followed a similar pattern as observed for the 20α-, 24-, and 25-hydroperoxy derivatives of cholesterol[2] and may be viewed as to proceed *via* homolysis of the peroxide oxygen–oxygen bond to produce the 26-alkoxy radical i or *via* dehydration of the 26-hydroperoxy group to afford the 26-aldehyde III.[3]



The recombination of i with a hydrogen radical afforded the 26-alcohol II while β scission of the C_{25}–C_{26} bond in the 26-alkoxy radical i yielded the norcholestene 25-alkyl radical ii, which upon recombination with a hydrogen radical led to the formation of compound IV, and which upon recombination with a hydroxy radical led to the formation of compound V. Because of their scarce availability and the lack of authentic samples, the absolute configurations at the 25 positions in both compounds II and V will await future experimentation. Products II, III, IV, and V as well as the putative intermediate radicals i and ii were revealed in the mass spectrum of the 26-hydroperoxide I by *m/e* 402 (36), 400 (12), 372 (59), 388 (25), 401 (36), and 371 (19), respectively. The low intensity of the molecular ion *m/e* 418 (2.5) reflects the instability of the 26-hydroperoxide I at elevated temperatures.[5] Since thermal decomposition or prolonged storage of the 26-hydroperoxide I gave the 26-alcohol II as a major product, the presence of II in commercial cholesterol samples[6] must be regarded as a result of air oxidation and not of animal origin. Our present finding also does not support the earlier proposed enzymic origin of the 26-hydroxycholesterol isolated from lipid deposits of the human atherosclerotic aorta.[7]

(3) The formation of an aldehyde from a primary hydroperoxide may not involve a radical mechanism. The thermal decomposition of organic hydroperoxides has recently been reviewed.[4]

(4) D. Swern, "Organic Peroxides," Vol. I, Wiley-Interscience, New York, N. Y., 1970.

(5) In the mass spectra of the 20α-, 24-, and 25-hydroperoxy derivatives of cholesterol[2c] only the 24- and 25-hydroperoxides revealed a molecular ion.

(6) J. E. van Lier and L. L. Smith, *Lipids*, **6**, 2 (1971).

Experimental Section[8]

3β-Hydroxy-5-cholestene 26-Hydroperoxide (I).—One kilogram of cholesterol was kept for a total period of 3 months at 70° in the dark and was recrystallized in ethanol every 4 weeks. The pooled mother liquor was stored at −20° while pending for chromatographic separation. Finally, column chromatography of the mother liquor on silica gel in toluene–ethyl ether (20:1, v/v) gave five major fractions (A–E).[8] Most sterol hydroperoxides of our interest were located in fraction C, including the major cholesterol 25-hydroperoxide, together with small amounts of the 24-, 20α-, and the new 26-hydroxyperoxy derivatives of cholesterol. Fraction C was chromatographed on a column of Sephadex LH-20 (60 × 2.5 cm) developed in methylene chloride–ethanol (100:1, v/v). Fractions of 950 drops (15 ml) were collected and analyzed by tlc. Traces of cholesterol were located in fractions 10–13, which was followed by some unidentified minor hydroperoxides (fractions 26–30). The major constituent of fraction C, the cholesterol 25-hydroperoxide, was obtained in fractions 30–39 and the 26-hydroperoxide I in fractions 43–50. Some unidentified compounds were also detected in fractions 51–62. The cholesterol 26-hydroperoxide I was finally recrystallized from toluene–hexane (1:1, v/v) to give 140 mg of white needles: mp 153–155°; ir (CCl_4) 3610 (OH), 3540 cm^{-1} (OOH); pmr ($CDCl_3$) δ 0.68 (s, 3 H, C_{18} protons), 0.94 (d, 3 H, J = 6 Hz, C_{27} protons), 0.96 (d, 3 H, J = 6 Hz, C_{21} protons), 1.01 (s, 3 H, C_{19} protons), 3.56 (m, 1 H, $W_{1/2}$ = 16 Hz, 3α proton), 3.92 (m, 2 H, C_{26} protons), and 5.42 (d, 1 H, J = 4 Hz, C_6 vinyl proton); mass spectrum (70 eV) *m/e* (rel intensity) 418 (2.5), 403 (42), 402 (38), 401 (36), 400 (22), 398 (24), 388 (25), 387 (45), 384 (100), etc. By gas chromatographic analysis the thermal decomposition of this compound gave the following products: 27-nor-5-cholesten-3β-ol (IV, 19%), 27-nor-5-cholestene-3β,25-diol (V, 11%), 3β-hydroxy-5-cholesten-26-al (III, 27%), and 5-cholestene-3β,26-diol (II, 24%). Prolonged storage of the 26-hydroperoxide I in solution resulted also in its partial decomposition to give 26-hydroxycholesterol II as the major product as shown by tlc.

Anal. Calcd for $C_{27}H_{46}O_3$: mol wt, 418.3446. Found: mol wt, 418.3473.

(7) (a) G. Steel, C. J. W. Brooks, and W. A. Harland, *Biochem. J.*, **99**, 51P (1966); (b) *Biochem. Biophys. Acta*, **125**, 620 (1966); (c) J. E. van Lier and L. L. Smith, *Biochemistry*, **6**, 3269 (1967).

(8) Cholesterol was purchased from Sigma Chemical Co., St. Louis, Mo., and purified *via* several crystallizations from chloroform–methanol. Purified cholesterol was kept for periods of 4 weeks at 70° in the dark, followed by crystallization from ethanol in order to harvest the autoxidation products. Isolation of oxidized sterols from the accumulated mother liquors was conducted using the slight modification of previously described procedures.[2a] Thus, mild acid and alkaline extractions were avoided and instead the mother liquor was chromatographed directly on silica gel columns (Baker analytical grade, 60–200 mesh) developed in toluene containing 0–5% ethyl ether. Eluents were pooled upon thin layer and gas chromatographic analyses, such as to give five major fractions: (A) compounds more mobile than cholesterol; (B) cholesterol and sterols of similar polarity; (C) sterols less mobile than cholesterol, but more mobile than 25-hydroxycholesterol; (D) 25-hydroxycholesterol and sterols of similar polarity; (E) polar sterols, possibly sterol triols and sterol acids. Selected fractions were further separated *via* chromatography on Sephadex LH-20 (Pharmacia, Uppsala, Sweden) developed in methylene chloride containing 1% ethanol, as previously described.[9a] Thin layer chromatography (tlc) and preparative gas chromatography (gc) were performed in the same manner as previously described.[2a,c,9a] Steroid mobilities R_c (tlc) and r_T (gc) are given in terms of cholesterol as unity.

Infrared absorption (ir) spectra were recorded with a Perkin-Elmer Model 357 spectrophotometer equipped with a beam condensor. Steroids were either incorporated in KBr pellets 1.5 mm in diameter or dissolved in carbon tetrachloride or deuteriochloroform in a 1.0-mm path cell. Proton magnetic resonance (pmr) spectra were obtained with a Varian T-60 spectrometer in deuteriochloroform solution using tetramethylsilane as internal standard. High-resolution mass spectral measurements were obtained with an AEI MS-9 mass spectrometer, and medium-resolution mass spectra were recorded on a Hitachi Perkin-Elmer RMU-6E instrument (70 eV). Melting points were determined on a calibrated Kofler block and are corrected.

(9) (a) J. E. van Lier and L. L. Smith, *J. Chromatogr.*, **41**, 37 (1969); (b) *ibid.*, **36**, 7 (1968).

5-Cholestene-3β,26-diol (II). A. From Sodium Borohydride Reduction of Cholesterol 26-Hydroperoxide (I).—Compound I (10 mg) in 5 ml of methanol was cooled to 0° and sodium borohydride (50 mg) was added. After 5 min the excess sodium borohydride was destroyed by the addition of a few drops of acetic acid. The mixture was stirred with 10 ml of water and the product was extracted with methylene chloride. The methylene chloride extract was dried ($MgSO_4$) and concentrated to afford 4.0 mg of 5-cholestene-3β,26-diol (II): mp 169–170° [*cf.* mp 168–173° for (25*RS*)-26-hydroxycholesterol,[10] mp 169–171°[6]]; ir (KBr) 3300 cm^{-1} (OH); R_c 0.47 (magenta); r_T 3.18 and 2.27 on 3% QF-1 and 3% OV-1, respectively, identical with the r_T of an authentic sample of (25*RS*)-26-hydroxycholesterol.[6]

B. From Thermolysis of I.—Samples of 100–200 μg of the 26-hydroperoxide I in 10 μl of ethanol were injected into the flash heater zone (270°) of the gas chromatograph (6 mm i.d., 3% OV-1). The decomposition products were collected in glass capillaries by methods described earlier.[9b] After five successive collections sufficient materials were accumulated for further chromatographic and spectral identification purposes. Thus the least mobile sterol with R_c 0.47 (magenta), r_T 3.18 and 2.27 on 3% QF-1 and 3% OV-1, respectively, was identified as 5-cholestene-3β,26-diol (II) by comparison of its chromatographic data with those of an authentic sample. The structure was further confirmed by mass spectral analysis, which gave the correct molecular ion at *m/e* 402 (10).

3β-Hydroxy-5-cholesten-26-al (III).—Preparative gas chromatography of cholesterol 26-hydroperoxide gave in addition to 26-hydroxycholesterol II a comparatively more mobile component, R_c 0.87 (orange-red), r_T 3.83 and 1.88 on 3% QF-1 and 3% OV-1, respectively. The reverse mobile behavior of this compound on the selective 3% QF-1 column suggested the presence of a carbonyl group. By analogy with the thermal decomposition of cholesterol 24-hydroperoxide which afforded the 24-keto sterol as the major product[2b] this component was tentatively assigned as 3β-hydroxy-5-cholesten-26-al (III). This structural assignment was further supported by its mass spectral data which gave the expected molecular ion at *m/e* 400 (70), and by ir spectroscopy (KBr) 1720 cm^{-1} (CHO).

27-Nor-5-cholestene-3β,25ξ-diol (V). A. From Thermolysis of I.—A third major thermal decomposition product of the 26-hydroperoxide I, obtained from preparative gas chromatography, was identified as 27-nor-5-cholestene-3β,25ξ-diol (V) by comparison of its chromatographic data with those of an authentic sample: R_c 0.47 (magenta); r_T 2.30 and 1.53 on 3% QF-1 and 3% OV-1, respectively. Its mass spectrum showed the molecular ion at *m/e* 388 (8).

B. From 27-Nor-3β-hydroxy-5-cholesten-25-one.—Nor-25-ketocholesterol (4.0 mg) dissolved in 0.5 ml of methanol was treated with an excess of sodium borohydride (25 mg). The course of the reduction was followed by tlc. After all the starting material had disappeared a few drops of acetic acid was added followed by 10 ml of water. The product was extracted with methylene chloride, dried ($MgSO_4$), and concentrated to give a colorless product. Recrystallization of the product from hexane–ethyl ether gave 1.8 mg of 27-nor-5-cholestene-3β,25-diol (V): mp 159–169° (*cf.* lit.[11] mp 158–168°); R_c 0.47 (magenta); r_T 2.30 and 1.53 on 3% QF-1 and 3% OV-1, respectively; ir (KBr) 3300 cm^{-1} (OH).

27-Nor-5-cholesten-3β-ol (IV). A. From Thermolysis of I.—The most mobile thermal decomposition product of the 26-hydroperoxide I, isolated *via* preparative gas chromatography, was identified as 27-nor-5-cholesten-3β-ol (IV) by comparison of its spectral and chromatographic properties with those of an authentic sample: R_c 0.97 (magenta); r_T 0.86 and 0.84 on 3% QF-1 and 3% OV-1, respectively. Mass spectral analysis gave a molecular ion at *m/e* 372 (100).

B. From 27-Nor-5-cholestene-3β,25-diol (V).—Nor-5-cholestene-3β,25-diol (3.0 mg) was selectively converted to the 25-monotosylate upon treatment with 20 mg of *p*-toluenesulfonyl chloride in 0.5 ml of dry pyridine. The reaction was monitored by tlc and when most of the starting material had disappeared, anhydrous ether (3 ml) was added followed by lithium aluminum hydride (200 mg). The mixture was refluxed for 5 hr, followed by the addition of 10 ml of water. The product was extracted with methylene chloride. Gas chromatographic analysis of the methylene chloride extract revealed the presence of two major components, 27-norcholesterol (IV, 50%) and 27-nor-5-cholestene-3β,25-diol (V, 30%), together with a small amount of norcholestene.[12] The product mixture was separated by preparative tlc and recrystallization from hexane–ethyl ether to afford 1.2 mg of 27-nor-5-cholesten-3β-ol (V): mp 127–131° (*cf.* lit.[11] mp 132°); R_c 0.97 (magenta); r_T 0.86 and 0.84 on 3% QF-1 and 3% OV-1 respectively; ir (KBr) 3300 cm^{-1} (OH).

Registry No.—I, 23652-97-3; II, 13095-61-9; III, 32557-11-2; IV, 4420-91-1; V, 7548-79-0.

Acknowledgment.—The authors are grateful to Dr. J. W. A. Meijer, Gaubius Institute, Leyden, for a sample of nor-25-ketocholesterol, and to Miss Helen Buttemer and Mrs. Pauline van Lier for technical assistance.

(10) P. D. G. Dean and M. W. Whitehouse, *Biochem. J.*, **98**, 410 (1966).

(11) J. Jacques, H. Kagan, and G. Ourisson, "Tables of Constants of Numerical Data," Vol. 14, S. Allard, Ed., Pergamon Press, Oxford, 1965.

(12) H. Schmid and P. Karrer, *Helv. Chim. Acta*, **32**, 1371 (1949).

Poly-α,α,2,3,5,6-hexafluoro-*p*-xylylene

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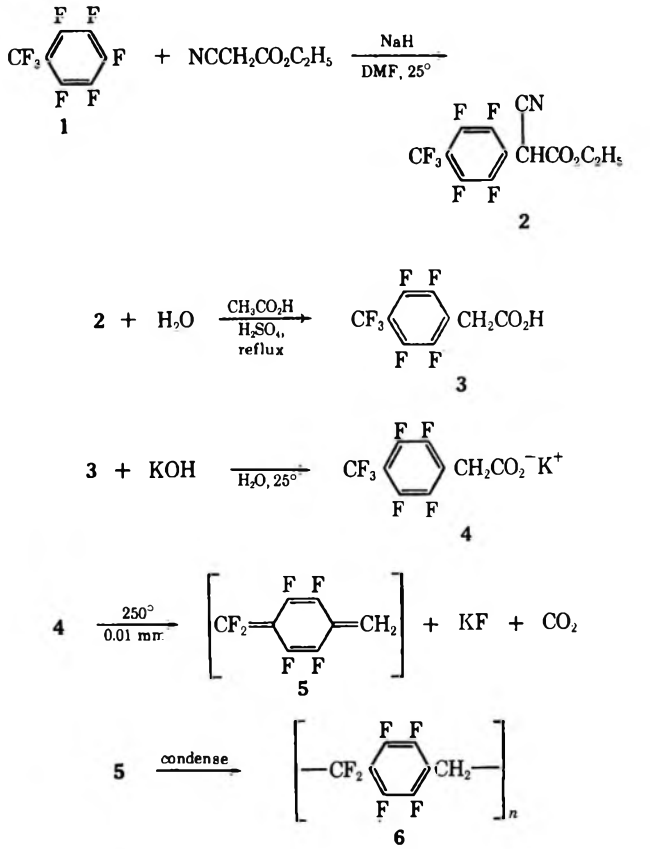
Received June 9, 1971

Poly-α,α,2,3,5,6-hexafluoro-*p*-xylylene (**6**) is formed by pyrolyzing potassium (4-trifluoromethyl-2,3,5,6-tetrafluorophenyl)acetate (**4**) under vacuum. The highly reactive intermediate, α,α,2,3,5,6-hexafluoro-*p*-xylylene (**5**), is transported, in the gas phase, to a cool surface where it condenses and immediately polymerizes.[1] The polymer was obtained as a clear



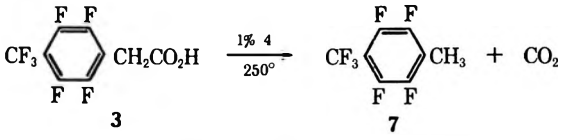
(1) Poly-*p*-xylylenes are commonly prepared by generating the monomeric *p*-xylylenes in the gas phase and condensing them to give polymers: L. A. Errede and M. Szwarc, *Quart. Rev., Chem. Soc.*, **12**, 301 (1959); W. F. Gorham, *J. Polym. Sci.*, **4**, 3027 (1966).

film on the inside of the condenser. It was swollen slightly with acetone but did not dissolve. An X-ray diffraction pattern shows well-defined lines indicating a high degree of crystallinity which is common with poly-*p*-xylylenes.[1] Whether the polymer units were joined head to tail or head to head and tail to tail was not determined. The polymer begins absorbing strongly in the ultraviolet at 300 nm.

Sodio ethyl cyanoacetate reacts readily with **1** to give ethyl (4-trifluoromethyl-2,3,5,6-tetrafluorophenyl)cyanoacetate (**2**).[2] Only one isomer was isolated, presumably the para isomer. Toward nucleophilic substitution on an aromatic system, trifluoromethyl is strongly, perhaps exclusively, para directing.[3] The trifluoromethyl group also increases the rate of aromatic nucleophilic substitution relative to fluorine, 10^3 times,[4] which accounts for the ease with which **2** is prepared. Acidic hydrolysis of **2** to **3** was used instead of basic hydrolysis because of the sensitivity of the highly fluorinated nucleus to nucleophilic attack.

Pyrolysis of alkali salts of fluorinated aliphatic acids leads to olefins. For instance, pyrolysis of sodium heptafluorobutyrate gives hexafluoropropene in high yield.[5] In the present instance the reaction has been extended from a 1,2 elimination to a 1,6 elimination.

The free acid, **3**, was thermally stable to its boiling point at 250°. Addition of a small amount of **4** to the



boiling **3** caused loss of CO_2 to give **7**. Heating **4** in dimethylacetamide at 120° resulted in the formation of **7** also. The source of protons necessary to form **7** from **4** in the latter case was not investigated.

Experimental Section

Ethyl (4-Trifluoromethyl-2,3,5,6-tetrafluorophenyl)cyanoacetate (2).—Ethyl cyanoacetate (22.6 g, 0.20 mol) was added to 5.0 g (0.21 mol) of sodium hydride suspended in 75 ml of dimethylformamide keeping the reaction temperature at 25 ± 5°. When hydrogen evolution ceased, 23.6 g (0.10 mol) of octafluorotoluene (**1**) was added, maintaining the temperature at 25 ± 5°. The solution was stirred for 15 min after adding **1**. The reaction mixture was poured into 300 ml of ice water and extracted with 100 ml of ether. The ether phase was discarded; 30 ml of concentrated hydrochloric acid was added to the aqueous phase and extraction was performed with three 50-ml portions of ether. Evaporation of ether and distillation of residue gave 28 g (85% yield) of **2**, bp 107–113° (1.5 mm), mp 48–51°.

Anal. Calcd for $C_{12}H_6F_7NO_2$: C, 43.78; H, 1.84; F, 40.40; N, 4.26. Found: C, 44.08; H, 2.08; F, 39.86; N, 4.67.

(4-Trifluoromethyl-2,3,5,6-tetrafluorophenyl)acetic Acid (3).—Ethyl (4-trifluoromethyl-2,3,5,6-tetrafluorophenyl)cyanoacetate (28 g, 0.085 mol) was added to 50 ml of water, 50 ml of acetic acid, and 80 ml sulfuric acid and the mixture was heated at reflux for 5 hr. The mixture was poured into 500 ml of water and cooled to 5° overnight. The solid was filtered off to give 20 g (85% yield) of product, mp 60–70°. Recrystallization from *n*-hexane gave 18 g of **3**, mp 77–80°.

Anal. Calcd for $C_9H_3F_7O_2$: C, 39.15; H, 1.09; F, 48.17. Found: C, 39.04; H, 1.22; F, 49.52.

Methyl (4-Trifluoromethyl-2,3,5,6-tetrafluorophenyl)acetate.—To a mixture of 35 ml of methanol, 20 ml of benzene, and 1 ml of concentrated H_2SO_4 was added 9.8 g (0.034 mol) of **3**. The mixture was heated to reflux and the water was collected in a Dean–Stark trap. When the reaction was finished the reaction mixture was cooled and extracted with water. The organic phase was dried over Drierite and distilled to give 6.0 g (0.021 mol, 60% yield) of methyl (4-trifluoromethyl-2,3,5,6-tetrafluorophenyl)acetate, bp 90–100° (10 mm).

Anal. Calcd for $C_{10}H_5F_7O_2$: C, 41.39; H, 1.74; F, 45.84. Found: C, 41.37; H, 1.89; F, 45.74.

Potassium (4-Trifluoromethyl-2,3,5,6-tetrafluorophenyl)acetate (4).—(4-Trifluoromethyl-2,3,5,6-tetrafluorophenyl)acetic acid, 4.7 g (0.017 mol), was suspended in 25 ml of water, two drops of phenolphthalein indicator solution was added, and then 50% KOH solution was added to give a faint pink end point. The water was removed under reduced pressure at 25°. The dry residue was dissolved in 15 ml of acetone, filtered, and heated to boiling. Ethylene dichloride was added to the cloud point. Cooling gave 5.0 g (93%) of white needles, mp 222° dec. The salt was heated at 100° for 5 hr at 0.001 mm pressure and then analyzed.

Anal. Calcd for $C_9H_2F_7O_2K$: C, 34.40; H, 0.64; F, 42.33; K, 12.44. Found: C, 34.20; H, 0.57; F, 42.37; K, 12.48.

Poly-α,α,2,3,5,6-hexafluoro-*p*-xylylene (6).—Two grams of **4**, evacuated to a pressure of 0.01 mm, was heated in a 250° bath. The gases were led through a condenser cooled with Dry Ice. A thin film of polymer (0.1 g) formed on the inside of the condenser tube. The film was removed by wetting with acetone. It was 0.04 mm thick, clear, and pliable. An X-ray diffraction pattern on the film dried at 100° (0.001 mm) shows definite lines indicating crystallinity. Differential thermal analysis under nitrogen shows a small endothermic process starting at 421°. The sample showed no weight loss after 20 min at 400°. At 500° for 20 min it showed a 17% weight loss.

Anal. Calcd for $(C_8H_2F_6)_n$: C, 45.30; H, 0.95; F, 53.75. Found: C, 45.17; H, 0.83; F, 53.71.

α,α,α,2,3,5,6-Heptafluoro-*p*-xylene (7).—Ten grams (0.036 mol) of **3** was heated to 250° with no noticeable decomposition. It was allowed to cool and 0.10 g of **4** was added and then reheated to 250°. Seven grams of material distilled over at 135°. Redistillation gave 5.1 g (60%), bp 135–136° (705 mm), of **7**. The mass spectrum had a strong parent ion peak at *m/e* 232 and a base peak at *m/e* 163 (parent ion minus CF_3).

Anal. Calcd for $C_8H_3F_7$: C, 41.39; H, 1.31; F, 57.30. Found: C, 41.15; H, 1.39; F, 57.25.

One-half gram of **4** was heated to 120° in *N*,*N*-dimethylacetamide. Gas was evolved which gave a precipitate with barium hydroxide solution. After gas evolution ceased the mixture was poured into water and a dark liquid settled to the bottom. Vpc analysis (Dowfax 9N9 on Chromosorb W, 100°) showed only one volatile component, **7**. The mass spectrum was identical with that of **7** prepared in the previous experiment.

Registry No.—**2**, 32251-53-9; **3**, 32304-29-3; **3** methyl ester, 32251-56-2; **4**, 32251-54-0; **6**, 32218-15-8; **7**, 778-35-8.

(2) Ethyl (pentafluorophenyl)cyanoacetate has been prepared similarly from hexafluorobenzene but under much more vigorous conditions: German Patent 1,146,890 (April 11, 1963); *Chem. Abstr.*, **59**, 11331e (1963).

(3) D. J. Alsop, J. Burdon, and J. C. Tatlow, *J. Chem. Soc.*, 1801 (1962); J. Burdon, *Tetrahedron*, **21**, 3373 (1965).

(4) J. Burdon, W. B. Hollyhead, C. R. Patrick, and K. V. Wilson, *J. Chem. Soc.*, 6375 (1965).

(5) R. N. Haszeldine, *J. Chem. Soc.*, 4259 (1952).

The Configuration of D-Alanyl-D-cycloserine Confirmed

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Received July 6, 1971

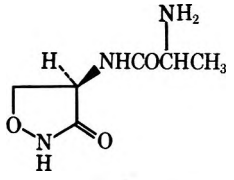
In an earlier report,[3] we described the synthesis of the dipeptide, D-alanyl-D-cycloserine (**1**), but the basis

(1) Abstracted from the M.S. thesis presented to the University of Georgia Graduate School by Mr. C. S. Levine.

(2) To whom inquiries should be directed.

(3) R. A. Payne and C. H. Stammer, *J. Org. Chem.*, **33**, 2421 (1968).

for the configurational assignment rested upon the exact position of the methyl resonance in the nmr spectrum of **1** and the melting point and optical rotation of



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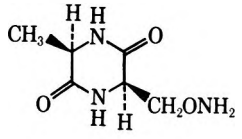

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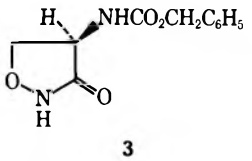
the piperazinedione, **2**, into which **1** is converted upon neutralization. The steric ambiguity of the earlier synthesis resulted from the fact that the blocked dipeptide from which **1** was obtained was one of a pair of diastereomers resulting from the coupling of *N*-carbobenzyloxy-DL-alanine with 2-trityl-DL-cycloserine. Racemic amino acids were used in this work because we had found no way to synthesize optically active cycloserine derivatives having the ring blocked. This report describes the synthesis of 2-carbobenzyloxy-D-cycloserine, which allows the unambiguous synthesis of **1**.

In our investigations of the carbobenzyloxylation of D-cycloserine, it was found that at high pH only the amine acylated product[4] (**3**) was obtained, while at a pH of ~8 both active sites reacted giving *N*,2-dicarbobenzyloxy-D-cycloserine (**4**), $[\alpha]^{25}D$ 32.8°. This compound was presumed to be optically pure since all its physical characteristics indicated it to be a single entity. This is the second[4] optically active ring-substituted cycloserine derivative to be prepared, but is the first to be useful in the synthesis of optically active peptides of cycloserine. Its usefulness derives from the fact that the amino group of **4** could be deblocked in 0.5 *N* HBr–acetic acid while the 2-carbobenzyloxy protecting group was retained *without* loss of optical activity.[5] Thus, the ring-protected derivative **5** became readily available for conversion to optically active cycloserine derivatives. Comparison of the nmr spectra of **3**, **4**, and **5** gave strong confirmation of the



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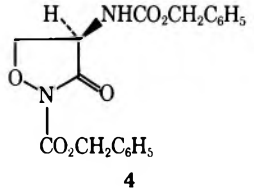

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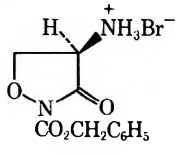

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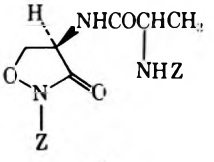
assigned structures. The carbobenzyloxy methylene groups of **4** appeared as singlets at δ 5.01 and 5.23 ppm while **3** and **5** showed singlets at δ 5.02 and 5.30 ppm, respectively. Consistent with these assignments was the infrared spectra and the fact that **3** is nitroprusside[6] positive and ninhydrin negative while **5** showed the opposite reactions with these reagents. The utility of **5** was confirmed when it was found that both **4** and **5** could be completely deblocked in liquid hydrogen fluoride according to the method of Sakakibara,[7] giving the parent cycloserine. The availability of **5** makes it possible to synthesize new cycloserine peptides and to check our earlier steric assignments.

The coupling of *N*-carbobenzyloxy-D-alanine with **5** was accomplished by the mixed anhydride procedure[8] and the dipeptide **6** was obtained in 65% yield. The required neutralization of the hydrobromide salt **5** with *N*-methylmorpholine prior to coupling was done at − 78° because it was found that the free amine rapidly dimerized, forming the biscarbobenzyloxy-2,5-piperazinedione (**7**). The structure of **7** was confirmed by carbobenzyloxylation of cycloserine dimer[9] in neutral to acidic aqueous solution.

The blocked dipeptide **6** was treated with anhydrous hydrogen fluoride, giving the ninhydrin-positive dipeptide as an extremely hygroscopic solid which gave a single spot on paper chromatography. Attempts to convert this product to the more tractable 2,5-piperazinedione **2** using a weakly basic ion exchange resin as was previously done[3] were unsuccessful. It was found alcoholic ammonia accomplished the neutral-



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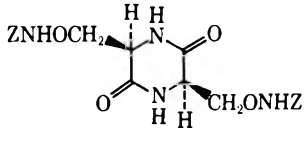

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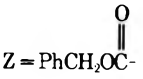

ization without destruction[10] of **2**. Warming of the free base in aqueous solution then afforded **2** in 62% yield. The physical properties of this product were essentially[11] identical with those previously[3] reported. A *p*-nitrobenzylidene derivative of **2** was prepared and found to be identical with that formed from the previously prepared material. This constitutes a proof of the configuration of a dipeptide previously synthesized and confirms the correctness of a configurational assignment based primarily on the chemical shift positions of the alanine methyl groups.[12]

Experimental Section

All melting points were measured on a Nagle–Kopfler micro hot stage. All infrared spectra were recorded on a Perkin-Elmer

(4) C. H. Stammer, C. C. Kartha, N. C. Chaturvedi, and J. D. McKinney, *J. Med. Chem.*, **13**, 1013 (1970).

(5) In ref 4, an optically active 2-trityl-D-cycloserine Schiff base was described. Hydrolysis of the Schiff base gave the ring-protected 2-trityl-cycloserine, but complete racemization occurred during the reaction. Thus, **5** is the only *useful* blocked cycloserine prepared so far.

(6) A specific color test for the N-*un*substituted isoxazolidone ring system: *cf.* L. R. Jones, *Anal. Chem.*, **28**, 39 (1956).

(7) S. Sakakibara, Y. Shimonishi, M. Okada, and Y. Kishida in "Proceedings of the Eighth European Peptide Symposium," H. C. Beyerman, Ed., Wiley, New York, N. Y., 1967, pp 44–49.

(8) N. Izumiya and J. P. Greenstein, *Arch. Biochem. Biophys.*, **52**, 203 (1954); G. W. Anderson, J. E. Zimmerman, and F. M. Callahan, *J. Amer. Chem. Soc.*, **89**, 5012 (1967).

(9) C. H. Stammer and J. D. McKinney, *J. Org. Chem.*, **30**, 3436 (1965).

(10) These aminoxymethyl-2,5-piperazinediones are very sensitive to base; *cf.* J. C. Miller, F. C. Neuhaus, F. O. Lassen, and C. H. Stammer, *J. Org. Chem.*, **33**, 3908 (1968).

(11) Reference 3 reports $[\alpha]^{29}D$ +21.3° (H_2O); the present work affords a purer material, $[\alpha]^{30}D$ +23.2° (H_2O).

(12) B. Halpern, L. F. Chew, and B. Weinstein, *J. Amer. Chem. Soc.*, **89**, 5051 (1967); B. Halpern, D. E. Nitecki, and B. Weinstein, *Tetrahedron Lett.*, 3075 (1967).

Infracord Model 257; the nmr spectra were recorded on an Hatachi HA 100 and optical rotations were determined on a Rudolph Model 80 polarimeter.

N,2-Dicarbobenzyloxy-D-cycloserine (4). A. From D-Cycloserine.—To a solution of 10.2 g (100 mmol) of D-cycloserine in 250 ml of 1 *N* $NaHCO_3$ (250 mmol) in a three-necked flask equipped with a mechanical stirrer and a delivery funnel and cooled in an ice bath, 42 g (240 mmol) of benzyl chloroformate was added dropwise over a period of 25 min. The ice bath was removed and the reaction mixture was stirred for 2 hr at room temperature. The mixture was filtered and the white solid was washed with 25 ml of ether and dried *in vacuo* overnight to yield 15.0 g of *N*,2-dicarbobenzyloxy-D-cycloserine. To the filtrate 5.0 g (15 mmol) of benzyl chloroformate was added and shaken vigorously by hand for 20 min. Filtration gave a solid which was washed with 25 ml of ether to give another 8.9 g of product. The total yield was 23.9 g (64.5%); mp 125–128°. Recrystallization from ethyl acetate afforded 20.5 g of *N*,2-dicarbobenzyloxyl-D-cycloserine: mp 127–128°; ir (KBr) 3350 (NH), 1800 (C=O), 1700 (C=O), 1760 cm^{-1} (C=O); nmr (DMSO-d_6) δ 4.3 (m, 3 H, $-CH_2CH-$), 5.01 (s, 2 H, $-CH_2C_6H_5$), 5.22 (s, 2 H, $-CH_2C_6H_5$), 7.28 (s, 5 H, 501 (s, 2 H, $-CH_2C_6H_5$), 5.33 (s, 2 H, $-CH_2C_6H_5$), 7.28 (s, 5 H, $-C_6H_5$), 7.33 ppm (s, 5 H, $-C_6H_5$); $[\alpha]^{25}D$ 36.9° (*c* 2, H_2O).

Anal. Calcd for $C_{19}H_{18}N_2O_6$: C, 61.60; H, 4.90; N, 7.56. Found: C, 61.35; H, 4.94; N, 7.54.

B. From 2-Carbobenzyloxy-D-cycloserine Hydrobromide.—To a mixture of 413 ml (2.43 mmol) of benzyl chloroformate and 50 ml of distilled water in a 250-ml round-bottomed flask equipped with a ground glass stopper, 632 mg (2 mmol) of 2-carbobenzyloxy-D-cycloserine hydrobromide was added. After shaking the flask vigorously for 5 min, 2 ml of 1 *N* $NaHCO_3$ (2 mmol) was added and shaking was continued. After 10 min, the reaction mixture was treated with 1 ml of 1 *N* $NaHCO_3$ (1 mmol) and after 10 min 336 mg of a white solid was collected on a filter. The filtrate was treated with ten drops of benzyl chloroformate and 1 ml of 1 *N* $NaHCO_3$ (1 mmol), shaken vigorously for 10 min, and extracted with 100 ml of hot ethyl acetate. The ethyl acetate solution was dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to give a brown oil, which when triturated with anhydrous ether gave 117 mg of a white solid. The two amide products were combined to give 453 mg (61%) of **4**: mp 124–127°; $[\alpha]^{25}D$ +32.8° (*c* 2, H_2O); ir identical with that of an authentic sample.

2-Carbobenzyloxy-D-cycloserine Hydrobromide (5).—A solution of 4.4 g (12 mmol) of *N*,2-dicarbobenzyloxy-D-cycloserine (4) and 50 ml of glacial acetic acid in a 250-ml round-bottomed flask equipped with a magnetic stirrer and a drying tube was treated with 50 ml of 1 *N* HBr in acetic acid. The reaction solution was stirred for 5 hr at room temperature and was slowly poured into 500 ml of anhydrous ether and stirred magnetically for 10 min to yield 3.56 g (94%) of 2-carbobenzyloxy-D-cycloserine hydrobromide after filtration and drying *in vacuo*: mp 128–131° dec; ir (KBr) 2800 ($-NH_3^+Br$), 1770 (C=O), 1760 cm^{-1} (C=O); nmr (DMSO-d_6) δ 4.3 (m, 3 H, $-CH_2CH-$) 5.30 (s, 2 H, $-CH_2C_6H_5$), 7.28 ppm (s, 5 H, $-C_6H_5$). An analytical sample was prepared by recrystallization from methanol and ether, mp 131–133°.

Anal. Calcd for $C_{11}H_{13}N_2O_4Br$ (316): C, 41.65; H, 4.10; N, 8.33. Found: C, 40.71; H, 4.16; N, 8.74.

N-Carbobenzyloxy-D-alanyl-2-carbobenzyloxy-D-cycloserine (6).—A solution of 3.35 g (15 mmol) of *N*-carbobenzyloxy-D-alanine[13] and 1.65 ml (15 mmol) of *N*-methylmorpholine in 75 ml of tetrahydrofuran (dried over CaH_2) in a 200 ml round-bottomed flask equipped with a thermometer and magnetic stirrer, and cooled in a Dry Ice–acetone bath, was treated with 15 mmol of isobutyl chloroformate. After stirring for 30 sec, a cold solution of 4.74 g (15 mmol) of 2-carbobenzyloxy-D-cycloserine hydrobromide and 1.65 ml (15 mmol) of *N*-methylmorpholine in 35 ml of tetrahydrofuran was added. The Dry Ice–acetone bath was removed, the reaction mixture was stirred for 15 min and filtered, and the filtrate was evaporated *in vacuo* at 36° to give a brown oil. It was dissolved in 100 ml of ethyl acetate and the solution was washed with 100 ml of H_2O, 100 ml of 1 *N* HCl, 100 ml of H_2O, and 100 ml of 1 *N* $NaHCO_3$, and dried over anhydrous Na_2SO_4. The solution was evaporated *in vacuo* at 40° to yield 5.93 g of crude 6: mp 137–146°; $[\alpha]^{30}D$ +19.3° (*c* 2, THF). Recrystallization from absolute ethanol afforded 4.33 g (65%) of 6: mp 149–151°; ir (KBr) 3310, 3280 (NH), 1770 (C=O), 1695. (C=O), 1665 cm^{-1} (C=O);

Anal. Calcd for $C_{22}N_{23}N_3O_7$ (441.4): C, 59.86; H, 5.25; N, 9.52. Found: C, 59.63; H, 5.17; N, 9.59.

DD-*cis*-3-Aminoxymethyl-6-methyl-2,5-piperazinedione (2).—A mixture of 2.23 g (5 mmol) of *N*-carbobenzyloxy-D-alanyl-2-carbobenzyloxy-D-cycloserine (6) and 1.10 g (10 mmol) of anisole in a 50-ml Nalgene erlenmeyer flask equipped with a magnetic stirrer and cooled in an ice bath was treated with 10 ml of anhydrous hydrogen fluoride. The reaction mixture was stirred for 30 min at 0° and was evaporated in a stream of dry nitrogen gas. The remaining gum was washed with several 10-ml portions of anhydrous ether and dried *in vacuo* for 4 days to yield 893 mg (92%) of the hygroscopic D-alanyl-D-cycloserine hydrofluoride. A mixture of this solid and 10 ml of absolute ethanol was treated with ammonia gas for 10 min, evaporated in a stream of dry nitrogen, and dried overnight *in vacuo*. The remaining solid was dissolved in 5 ml of hot H_2O, 20 ml of ethanol, and 5 ml of 2-propanol. After cooling, the solution was filtered and evaporated *in vacuo* at 53° leaving 534 mg of crude **2**, mp >200°. Recrystallization from methanol and water gave 450 mg of **2**: mp >360; ir (KBr) 3310 (NH), 1670 (C=O), 1340 cm^{-1} (CO); $[\alpha]^{25}D$ +23.9° (*c* 2, H_2O); identical with previous sample.[3]

cis-3-[*N*-(4-Nitrobenzylidene)aminoxymethyl]-6-methyl-2,5-piperazinedione.—A suspension of 17.3 mg (0.1 mmol) of **2** and 15.2 mg (0.1 mmol) of *p*-nitrobenzaldehyde in 0.2 ml of H_2O and 5 ml of methanol was stirred magnetically in a 10-ml round-bottomed flask for 1 hr at room temperature. After the solution was evaporated *in vacuo* the residue was dissolved in 3 ml of hot DMF and the mixture was centrifuged. The supernatant liquid was treated with 10 ml of H_2O. The precipitated solid was recrystallized from DMF–H_2O and washed with ethanol to give 25 mg of *cis*-3-[*N*-(4-nitrobenzylidene)aminoxymethyl]-6-methyl-2,5-piperazinedione: mp 244–246°; ir (Nujol) 3198 (NH), 1675 cm^{-1} (C=O); identical with previously prepared sample.[3]

D-Cycloserine Hydrofluoride. A. From *N*,2-Dicarbobenzyloxy-D-cycloserine (4).—A mixture of 370 mg (1 mmol) of *N*,2-dicarbobenzyloxy-D-cycloserine and 216 mg (2 mmol) of anisole in a 15-ml Nalgene centrifuge tube was treated with 5 ml of anhydrous hydrogen fluoride. The mixture was stirred with a nagalene stirring rod for 25 min in an ice bath 0° and evaporated in a stream of dry nitrogen. The remaining pink oil was washed with three 5-ml portions of anhydrous ether and the white, gummy residue was dried *in vacuo* for 2 days resulting in 132 mg of D-cycloserine hydrofluoride (95%): ir (KBr) 3400 ($-N^+H_3F^-$) and 1750 cm^{-1} (C=O). This product was identical with a sample prepared from D-cycloserine by treatment with anhydrous hydrogen fluoride.

Registry No.—**1**, 32296-73-4; **2**, 16562-03-1; **4**, 32296-75-6; **5** (HBr), 32296-76-7; **6**, 32296-77-8; *cis*-3-[*N*-(4-nitrobenzylidene)aminoxymethyl]-6-methyl-2,5-piperazinedione, 32296-78-9; D-cycloserine hydrofluoride, 32367-42-3.

(13) Prepared in 71% yield, mp 86–87°, $[\alpha]^{25}D$ +15.6°, by the procedure of M. Bergmann and L. Zervas, *Ber.*, **65**, 1192 (1932).

Nuclear Bromination of Thiopyrans and Pyrans by *N*-Bromosuccinimide

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Received February 23, 1971

N-Bromosuccinimide is a reagent which selectively brominates allylic and benzylic positions.[1] However, a number of exceptions have been reported[2–6] where

(1) L. Horner and E. H. Winkelmann in "Newer Methods of Preparative Organic Chemistry," Vol. 3, W. Foerst, Ed., Academic Press, New York, N. Y., 1964, p 151.

(2) N. B. Chapman and J. F. A. Williams, *J. Chem. Soc.*, 5044 (1952).

(3) H. Pines, A. Alul, and M. Kolobielski, *J. Org. Chem.*, **22**, 1113 (1957).

(4) K. Dittmer, R. P. Martin, W. Herz, and S. J. Cristol, *J. Amer. Chem. Soc.*, **71**, 1201 (1949).

(5) W. J. Bailey and J. Bello, *J. Org. Chem.*, **20**, 525 (1955).

(6) M. F. Grundon and K. J. James, *Chem. Commun.*, 1427 (1970).

N-bromosuccinimide was shown to brominate nuclear rather than benzylic positions. Chapman and Williams[2] showed that bromination of 2-methylnaphthalene gave 1-bromo-2-methylnaphthalene unless the *N*-bromosuccinimide was carefully purified; in the latter case, bromination took place in the side chain.

We were interested in the synthesis of benzylic bromides in the thiopyran and pyran series. The starting material, 2-benzyl-2,4,6-triphenyl-2*H*-thiopyran (**1a**), was prepared[7] by the action of benzylmagnesium chloride on triphenylthiopyrylium perchlorate and separation of the resulting mixture of isomers by Soxhlet extraction with ethanol. Under the same conditions triphenylthiopyrylium iodide[8] gave exclusively the 4*H*-thiopyran **2a**. The nmr spectra given are in Table I. Assignment of the signals for the protons at

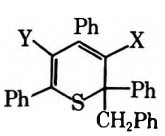
TABLE I

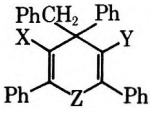
NMR SPECTRA OF SUBSTITUTED PYRANS AND THIOPYRANS[a]

Compd	H-3	H-5	Benzylic protons
1a	3.18 (s)	3.90 (s)	6.45 (s)
2a	4.04 (s)	4.04 (s)	6.67 (s)
1b		4.16 (s)	6.21, 6.48 (dd, J = 13.5 Hz)
1c			6.29, 6.41 (dd, J = 13.5 Hz)
2b	4.49 (s)	4.49 (s)	6.72 (s)
2c	4.77 (s)		6.24, 6.94 (dd, J = 13 Hz)

[a] In $CDCl_3$; chemical shifts in τ.

C-3 and C-5 in **1a** were made by means of the nuclear Overhauser effect (NOE); irradiation of the benzylic protons resulted in an enhancement of the signal at τ 3.18. Long-range coupling (J = 0.15 Hz) between the protons at C-3 and C-5 was confirmed by double resonance.





1a, X = Y = H
b, X = Br; Y = H
c, X = Y = Br
d, X = Cl; Y = H

2a, X = Y = H; Z = S
b, X = Y = H; Z = O
c, X = Br; Y = H; Z = O
d, X = Y = Br; Z = O

Treatment of **1a** with 1 molar equiv of *N*-bromosuccinimide in the presence of benzoyl peroxide gave a colorless solid, $C_{30}H_{23}BrS$, the nmr spectrum of which (see Table I) showed it to be the 3-bromo derivative **1b**. The benzylic protons in **1b**, unlike those in **1a**, are nonequivalent.

When the experiment was repeated with purified reagents according to the method of Chapman and Williams[2] the same compound **1b** was obtained.

When the thiopyran **1a** was treated with 3 equiv of *N*-bromosuccinimide a dibromo derivative, $C_{30}H_{22}Br_2S$, was obtained. The nmr spectrum (Table I) clearly showed it to have structure **1c**; the benzylic protons were again nonequivalent. The dibromo derivative **1c** was recovered unchanged on treatment with 2 molar equiv of *N*-bromosuccinimide.

4-Benzyl-2,4,6-triphenyl-4*H*-pyran **2b** (for nmr see Table I) on treatment with 1 molar equiv of *N*-bromosuccinimide under various conditions yielded a solid, $C_{30}H_{23}BrO$. The nmr spectrum (Table I) showed that again substitution of bromine had taken place in the ring with the formation of **2c**.

The action of 2, 3, or more equiv of *N*-bromosuccinimide on **2b** produced mixtures from which the monobromo derivative **2c** could be isolated. The nmr of the residue, which showed a singlet at τ 6.4 as well as the signals corresponding to **2c**, indicated the formation of the dibromo derivative **2d**.

Attempted benzylic chlorination of **1a** with *N*-chlorosuccinimide or with trichloromethanesulfonyl chloride led to complex mixtures, the nmr of which suggested the presence of the monochloro derivative **1d**.

Experimental Section

Melting points were determined on a Thomas–Hoover capillary melting point apparatus. Nmr spectra were recorded on a Varian A-60 instrument.

2,4,6-Triphenylthiopyrylium Iodide.—2,4,6-Triphenylpyrylium perchlorate[9] (15.4 g) in acetone (500 ml) was treated with sodium sulfide (20 g) in water (200 ml), stirred for 5 min, treated with 26% hydriodic acid (200 ml), and stirred for 30 min. The reaction mixture was diluted with water (500 ml) and extracted with chloroform (two 200-ml portions). The chloroform extract was concentrated and treated with ether (500 ml) to precipitate the iodide (10.8 g), which had mp 204–205° (lit.[8] mp 205–206°).

Preparation of 2-Benzyl-2,4,6-triphenyl-2*H*-thiopyran (1a) and 4-Benzyl-2,4,6-triphenyl-4*H*-thiopyran (2a). A. From 2,4,6-Triphenylthiopyrylium Perchlorate.—The method of Dimroth, *et al.*,[7] was used. The crude mixture of thiopyrans (6.3 g), mp 132–140°, was separated by Soxhlet extraction with ethanol. The residual 2-benzyl-2,4,6-triphenyl-2*H*-thiopyran (**1a**, 2.40 g) had mp 158–159°, raised to 159–160° on crystallization from ethyl acetate (lit.[5] mp 160°).

The above procedure was repeated and the extract was evaporated to dryness. The residual 4-benzyl-2,4,6-triphenyl-4*H*-thiopyran (**2a**) had mp 116–117° after one crystallization from ethanol (lit.[7] mp 117°).

B. From 2,4,6-Triphenylthiopyrylium Iodide.—The method of Dimroth, *et al.*,[7] was followed using the iodide (8.2 g) and benzylmagnesium chloride [from benzyl chloride (9 g) and magnesium (1.35 g)]. The crude solid (6.25 g), mp 93–95°, was shown by nmr to consist mainly of the 4H isomer **2a**.

2-Benzyl-3-bromo-2,4,6-triphenyl-2*H*-thiopyran (1b).—2-Benzyl-2,4,6-triphenyl-2*H*-thiopyran (0.16 g) was treated with *N*-bromosuccinimide (0.067 g, 1 molar equiv) and benzoyl peroxide (1 mg) in dry carbon tetrachloride (10 ml). The reaction mixture was warmed to initiate the reaction and stirred for 15 min, keeping the solution warm. It was cooled and filtered. The filtrate was evaporated and the residue was chromatographed on a silica gel column using 40% benzene in petroleum ether (bp 30–60°) as the eluent. This afforded 2-benzyl-3-bromo-2,4,6-triphenyl-2*H*-thiopyran (**1b**), which had mp 163–164° after crystallization from *n*-hexane.

Anal. Calcd for $C_{30}H_{23}BrS$: C, 72.73; H, 4.65. Found: C, 72.33; H, 4.88.

The experiment was repeated using *N*-bromosuccinimide which had been kept at 0.05 mm for 16 hr.[2] The nmr of the crude product was identical with that of **1b**. After crystallization from benzene–petroleum ether, **1b**, mp 160–162°, was isolated in 70% yield.

2-Benzyl-3,5-dibromo-2,4,6-triphenyl-2*H*-thiopyran (1c).—The 2*H*-thiopyran (**1a**, 1 g) was treated with *N*-bromosuccinimide (1.42 g, ~3 mol equiv) and benzoyl peroxide (14 mg) in the usual manner. The 3,5-dibromo-2,4,6-triphenyl-2*H*-thiopyran (**1c**) which separated was crystallized from cyclohexane–petroleum ether and had mp 199–200°.

Anal. Calcd for $C_{30}H_{22}Br_2S$: C, 62.72; H, 3.83; Br, 27.87. Found: C, 62.63; H, 4.08; Br, 27.62.

The dibromo derivative **1c** was treated with 2 molar equiv of *N*-bromosuccinimide and refluxed in carbon tetrachloride for several hours, when it was recovered unchanged.

4-Benzyl-2,4,6-triphenyl-4*H*-pyran (2b) was prepared by the

(7) K. Dimroth, K. Wolf, and H. Kroke, *Justus Liebigs Ann. Chem.*, **678**, 183 (1964).

(8) K. Kanai, M. Umehara, H. Kitano, and K. Fukui, *Nippon Kagaku Zasshi*, **84**, 432 (1963); *Chem. Abstr.*, **59**, 13934*f* (1963).

(9) R. Wizinger, S. Losinger, and P. Ulrich, *Helv. Chim. Acta*, **39**, 5 (1956).

method of Dimroth, *et al.*,[7] and had mp 143–144° after crystallization from ethanol (lit.[7] mp 143°).

Bromination of 4-Benzyl-2,4,6-triphenyl-4*H*-pyran (2b). A. With 1 Molar Equiv of *N*-Bromosuccinimide.—(i) 4-Benzyl-2,4,-6-triphenyl-4*H*-pyran (2b, 0.5 g) and *N*-bromosuccinimide (0.25 g, ~10% excess) in carbon tetrachloride (20 ml) were refluxed for 2 hr and the reaction mixture was filtered. On evaporation of the filtrate an oil (0.535 g) was obtained. The oil was warmed with *n*-hexane, and the undissolved solid was filtered and identified as succinimide by mixture melting point with an authentic sample. On cooling the filtrate 4-benzyl-3-bromo-2,4,6-triphenyl-4*H*-pyran (2c), mp 120–122°, separated; after repeated crystallization from *n*-hexane it had mp 136–137°.

Anal. Calcd for $C_{30}H_{23}BrO$: C, 75.16; H, 4.80; Br, 16.70. Found C, 74.89; H, 4.90; Br, 16.60.

(ii) The above experiment was repeated but the mixture was refluxed for only 15 min. The 3-bromopyran 2c, mp 136–137°, was again obtained. (iii) The 4*H*-pyran (2b, 0.214 g), *N*-bromosuccinimide (0.090 g), and benzoyl peroxide (3 mg) were stirred in carbon tetrachloride (10 ml) for 25 min, keeping the solution warm. The same product 2c was obtained.

B. With 2 Molar Equiv of *N*-Bromosuccinimide.—The 4*H*-pyran (2b, 0.209 g), *N*-bromosuccinimide (0.186 g), and benzoyl peroxide (3 mg) in carbon tetrachloride (10 ml) were stirred for 45 min, keeping the solution warm. The nmr of the product (0.345 g) showed it to be a mixture, containing 4-benzyl-3-bromo-2,4,6-triphenyl-4*H*-pyran (2c) and a product which gave a singlet at τ 6.4.

C. With 3 Molar Equiv of *N*-Bromosuccinimide.—The 4*H*-pyran (2b, 1.32 g), *N*-bromosuccinimide (1.78 g), and benzoyl peroxide (18 mg) in dry carbon tetrachloride (50 ml) were warmed to initiate the reaction. The reaction mixture was kept warm and stirred for 1 hr. It was cooled and filtered and the filtrate was evaporated. The residual oil was dissolved in hot *n*-hexane. On cooling, crystals (0.2 g) separated which had mp 128–130°; mmp with 2c, 134–135°. The mother liquors were evaporated. The nmr of the residue (1.15 g) showed the peaks for 2c along with a singlet at τ 6.4.

The above residue was treated with *N*-bromosuccinimide (0.52 g) in carbon tetrachloride and the solution was refluxed for 2.5 hr. It was cooled and filtered. On evaporation of the filtrate an oil (1.32 g) was obtained. The nmr of the oil showed it to be a mixture containing 2c and the compound, presumably 2d, giving a singlet at τ 6.4, the latter being the major constituent.

Registry No.—1a, 1177-70-4; 1b, 32247-00-0; 1c, 32247-01-1; 2a, 1177-68-0; 2b, 1255-14-7; 2c, 32247-04-4.

Acknowledgment.—We are indebted to Professor L. M. Jackman, Penn State University, for helpful discussions and to Mr. E. Sokoloski, NHLI, National Institutes of Health, for measuring the NOE.

Synthesis of Fluorodinitromethyl Epoxides

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Received April 16, 1971

General methods for the preparation of fluorodinitromethyl compounds have recently been described.[1] The synthesis of two fluorodinitromethyl epoxides, 1-fluoro-1,1-dinitro-3,4-epoxybutane (VI) and 2-fluoro-2,2-dinitroethyl glycidyl ether (IX), is described in this paper.

1-Fluoro-1,1-dinitro-3,4-epoxybutane (VI) was prepared by the sequence of reactions shown below. The

$$CH_2{=}CHCH_2CH_2OH \xrightarrow{PBr_3} CH_2{=}CHCH_2CH_2Br \xrightarrow{AgNO_2}$$
I II

$$CH_2{=}CHCH_2CH_2NO_2 \xrightarrow[AgNO_2]{NaNO_2} CH_2{=}CHCH_2C(NO_2)_2H \xrightarrow{FClO_3}$$
III IV

$$CH_2{=}CHCH_2C(NO_2)_2F \xrightarrow[Na_2HPO_4]{CF_3CO_3H} CH_2{-}CHCH_2C(NO_2)_2F$$
V VI

initial reaction involved the conversion of 3-buten-1-ol (I) to 1-bromo-3-butene (II). 1-Nitro-3-butene (III) was prepared from II and silver nitrite. At least one fume-off was encountered during the distillation of III, illustrating the inherent instability of this type of compound. One of the by-products of this reaction has been tentatively identified from its infrared spectrum as 1-nitrito-3-butene. The conversion of III to 1,1-dinitro-3-butene (IV) involved the Shechter–Kaplan oxidative nitration reaction.[2] A fume-off was also encountered with the distillation of this compound. Initially it was thought that aqueous fluorination of IV to V would be the method of choice because of a shorter reaction time and easier work-up. However, aqueous fluorinations of both the sodium and potassium salts of IV resulted also in fluorination of the double bond. The desired reaction was accomplished by fluorinating with perchloryl fluoride, following the procedure of Kamlet and Adolph.[1] The conversion of V to 1-fluoro-1,1-dinitro-3,4-epoxybutane (VI) proved to be a clean high-yield reaction. It involves epoxidation with peroxytrifluoroacetic acid in the presence of the buffer disodium hydrogen phosphate.[3]

The approach to the synthesis of 2-fluoro-2,2-dinitroethyl glycidyl ether (IX)[4] utilized the dinitroethylation reaction.[5] This reaction consists of the 1,4 addition of active hydrogen compounds, such as aci-nitro compounds or alcohols, to 1,1-dinitroethylene. The 1,1-dinitroethylene is a reactive intermediate, which

$$[CH_2{=}C(NO_2)_2] + RH \longrightarrow RCH_2C(NO_2)_2H$$

has never been isolated but is generated *in situ* from 2-bromo-2,2-dinitroethyl acetate,[5–7] 1,2-dichloro-1,1-dinitroethane,[8] or 1,1,1-trinitroethane.[9]

2,2-Dinitroethyl allyl ether (VII) was prepared by the addition of allyl alcohol to 1,1-dinitroethylene, which was generated from 1,2-dichloro-1,1-dinitroethane and potassium iodide.[8] Fluorination of the sodium salt of VII with perchloryl fluoride gave 2-fluoro-2,2-dinitroethyl allyl ether (VIII), which was

(1) M. J. Kamlet and H. G. Adolph, *J. Org. Chem.*, **33**, 3073 (1968).

(2) R. B. Kaplan and H. Shechter, *J. Amer. Chem. Soc.*, **83**, 3535 (1961).

(3) W. D. Emmons and A. S. Pagans, *ibid.*, **77**, 89 (1955).

(4) The preparation of this compound by the alkylation of 2-fluoro-2,2-dinitroethanol has recently been reported: V. Grakauskas, *J. Org. Chem.*, **35**, 3030 (1970).

(5) M. B. Frankel, *ibid.*, **23**, 813 (1958).

(6) H. Feuer, G. Leston, R. Miller, and A. T. Nielsen, *ibid.*, **28**, 339 (1963).

(7) L. J. Winters and W. E. McEwen, *Tetrahedron*, **19** (1), 49 (1963).

(8) H. E. Ungnade and L. W. Kissinger, *J. Org. Chem.*, **31**, 369 (1966).

(9) L. Zelden and H. Shechter, *J. Amer. Chem. Soc.*, **79**, 4708 (1957).

epoxidized to 2-fluoro-2,2-dinitroethyl glycidyl ether (IX).

$$ClCH_2C(NO_2)_2Cl + 2KI \longrightarrow [CH_2{=}C(NO_2)_2] + 2KCl + I_2$$

$$[CH_2{=}C(NO_2)_2] + HOCH_2CH{=}CH_2 \longrightarrow CH_2{=}CHCH_2OCH_2C(NO_2)_2H$$

VII

$$VII \xrightarrow[NaOH]{FClO_3} CH_2{=}CHCH_2OCH_2C(NO_2)_2F \xrightarrow[Na_2HPO_4]{CF_3CO_3H}$$

VIII

$$CH_2\text{—}CHCH_2OCH_2C(NO_2)F$$

$$\diagdown\ \diagup$$

$$O$$

IX

A by-product was isolated in the distillation of VIII as a volatile forerun. It was identified as 2-fluoro-2,2-dinitroethyl methyl ether (X) by its infrared spectrum and elemental analysis. Compound X was probably formed by cleavage of the ether linkage of VIII with subsequent formation of the methyl ether by reactions with the methanol solvent.

$$CH_2{=}CHCH_2OCH_2C(NO_2)_2F + FClO_3 \xrightarrow[CH_3OH]{H_2O}$$

VIII

$$CH_3OCH_2C(NO_2)_2F$$

X

As was mentioned previously, the reactive intermediate, 1,1-dinitroethylene, can also be generated from 1,1,1-trinitroethane.[9] It was found that 1,1,1-trinitroethane could be prepared in 71% yield from potassium nitroform and methyl iodide. This obviates the necessity of using the hazardous and expensive silver salt of nitroform.[10] Treatment of 1,1,1-trinitroethane with a solution of potassium hydroxide in allyl alcohol gave the potassium salt of allyl 2,2-dinitroethyl allyl ether, which was then subsequently acidified, fluorinated, and epoxidized to the desired monomer IX in the manner described previously.

Experimental Section

General (Caution).—Most of the products described in this paper are explosives of moderate to considerable sensitivity to initiation by impact, shock, fraction or heat. They should therefore be *handled with care*. All distillations should be well shielded. Furthermore, many dinitrofluoromethyl compounds show varying degrees of toxicity. Precautions for fluorinating with perchloryl fluoride are previously described.[1]

Elemental analyses have been reviewed and are in accord with theory. Melting and boiling points are uncorrected.

1-Bromo-3-butene (II).—Phosphorus tribromide, 360 g (1.33 mol), was cooled to −5° and a solution of 257 g (3.56 mol) of 3-buten-1-ol in 120 g (1.52 mol) of pyridine was added dropwise in 1.5 hr with good mechanical stirring. The addition was exothermic and a white solid precipitated. The mixture was stirred for another hour at −5° and allowed to warm to ambient temperature. The reaction flask was connected to a receiver which was immersed in a Dry Ice–acetone bath and the product was stripped off under a vacuum of 2 mm. The product was dissolved in methylene chloride, washed with 5% $NaHCO_3$ and water, dried, and fractionated through a spinning band column. The yield of 1-bromo-3-butene was 261.9 g (54.5%), bp 97.5°, $n^{28}D$ 1.4589.

1-Nitro-3-butene (III).—To a well-stirred mixture of 377 g (2.44 mol) of silver nitrite in 500 ml of dry methylene chloride was added dropwise 288.3 g (2.13 mol) of 1-bromo-3-butene while maintaining the temperature at approximately 15° (this reaction was carried out in the dark to its completion). After the addition was complete (30 min), the reaction mixture was allowed to warm to room temperature and stirring was continued until the supernatant liquid showed a negative test for bromide. This required approximately 4 days. The gray solid was removed by filtration and washed well with methylene chloride. The solvent was removed under vacuum and the orange liquid residue was fractionated through a small Vigreux column to yield 25 g of low-boiling material, $n^{25}D$ 1.4275, presumably the 1-nitroso-3-butene, and 126.3 g (62% yield) of 1-nitro-3-butene, bp 55° (19 mm), $n^{25}D$ 1.4308.

1,1-Dinitro-3-butene (IV).—To 25.2 g (0.63 mol) of sodium hydroxide dissolved in 225 ml of water was added 62.1 g (0.615 mol) of 1-nitro-3-butene dropwise while maintaining the temperature at 3°. After the addition was complete, 42.5 g (0.615 mol) of sodium nitrite was added and the reaction mixture was stirred for approximately 30 min while warming to room temperature.

This freshly prepared solution was then added quickly with good stirring to a solution of 209 g (1.23 mol) of silver nitrate, 450 ml of water, and 450 ml of ether at 3°. (Just prior to this addition a few drops of sodium hydroxide were added to the silver nitrate solution until the appearance of silver oxide was noted.) A heavy cream-colored solid was formed immediately and the temperature rose to 15°. The solid decomposed rapidly with blackening. The cooling bath was then removed and the mixture was stirred for 1 hr. The silver was filtered and washed well with ether. The ether layer was separated and the aqueous layer was extracted several times with ether. The combined ether portions were dried over magnesium sulfate and the excess solvent was removed at reduced pressure. The resulting orange liquid residue was fractionated through a small Vigreux column yielding 38 g (43% yield) of 1,1-dinitro-3-butene, bp 63.5–65° (1.5 mm), $n^{25}D$ 1.4504.

1-Fluoro-1,1-dinitro-3-butene (V).—Into a 250-ml round-bottom flask equipped with a Dry Ice condenser, thermometer, and gas inlet was placed 2 g of sodium hydroxide in 15 ml of water, 7.3 g (0.05 mol) of 1,1-dinitro-3-butene, and 35 ml of methanol. This mixture was stirred at room temperature for 1 hour. After purging the system with nitrogen, perchloryl fluoride was admitted slowly above the liquid until refluxing began; this required approximately 40 min. The rate of perchloryl fluoride admission was then set so that the reaction temperature remained approximately at 20° (cooling was regulated by the reflux rate). After a reaction time of approximately 2 hr, 50 ml of water was added; the hazy solution became clear. The solution was extracted with three 50-ml portions of methylene chloride and the combined methylene chloride extracts were then washed with three 50-ml portions of water. After drying the methylene chloride solution over magnesium sulfate, solvent was removed under reduced pressure and the residual yellow liquid was fractionated through a small Vigreux column to yield 4.1 g (50% yield) of 1-fluoro-1,1-dinitro-3-butene, bp 47° (9 mm), $n^{25}D$ 1.4210.

1-Fluoro-1,1-dinitro-3,4-epoxybutane (VI).—A solution of peroxytrifluoroacetic acid was prepared from 1.72 ml (0.0615 mol) of 90% hydrogen peroxide, 10.4 ml (0.074 mol) of trifluoroacetic anhydride, and 15 ml of methylene chloride. This reagent was added over a 20-min period to a well-stirred, boiling mixture of 8.1 g (0.049 mol) of 1-fluoro-1,1-dinitro-3-butene, 50 ml of methylene chloride, and 28 g (0.197 mol) of disodium phosphate (predried under vacuum oven overnight at 50°). After this mild exothermic reaction had subsided, the solution was heated under reflux for 2.5 hr. The resulting mixture was stirred with 100 ml of water until all of the inorganic salts had dissolved. The organic layer was separated and the aqueous layer was extracted with two 20-ml portions of methylene chloride. The combined methylene chloride extracts were washed with 25 ml of 10% sodium bicarbonate solution and dried over magnesium sulfate. The solvent was removed at reduced pressure and the residual liquid was fractionated through a small Vigreux column to yield 1.77 g of unreacted 1-fluoro-1,1-dinitro-3-butene and 5.79 g (83% yield) of 1-fluoro-1,1-dinitro-3,4-epoxybutane, bp 55° (0.45 mm), $n^{25}D$ 1.4365.

2,2-Dinitroethyl Allyl Ether (VII). From 1,2-Dichloro-1,1-dinitroethane.—To a mixture of 219 g (1.32 mol) of potassium iodide, 85.5 g (1.48 mol) of allyl alcohol, and 200 ml of methylene chloride was added dropwise 50 g (0.264 mol) of 1,2-dichloro-1,1-dinitroethane[8] over a period of 15 min. The reaction mixture, which became deep red in color, was stirred overnight at room temperature. Water (200 ml) was then added to dissolve the inorganic salts and the layers were separated. The water layer was extracted with methylene chloride and the combined methylene chloride portions were washed thoroughly with 10% sodium thio-

(10) G. S. Hammond, *et al.*, *Tetrahedron Suppl.*, **1**, 177 (1963).

sulfate solution followed by a water wash. The methylene chloride solution was dried over magnesium sulfate. Excess solvent was removed under reduced pressure yielding a mixture of white solid and red oil. The white solid (48.4 g) was removed by recrystallization from carbon tetrachloride and identified as 1,2-diiodo-3-hydroxypropane (mp 47°). The red oil (54 g) was contained in the carbon tetrachloride and subsequently isolated by removal of the solvent under vacuum. It was identified by its infrared spectrum as crude allyl 2,2-dinitroethyl ether. An initial attempt to purify the product by distillation resulted in an explosion.

The crude allyl 2,2-dinitroethyl ether was purified by conversion to the potassium salt and subsequent acidification. To a solution of 46.6 g (0.264 mol) of crude allyl 2,2-dinitroethyl ether dissolved in 60 ml of ether was added 14.8 g (0.264 mol) of potassium hydroxide in 50 ml of methanol. A heavy yellow solid formed immediately; the temperature rose slightly but was easily controlled at 20° with an ice bath. The reaction mixture was cooled to 0° and filtered, yielding 40 g of potassium 2,2-dinitroethyl allyl ether, mp 130–133.5°. A recrystallization from methanol yielded potassium 2,2-dinitroethyl allyl ether as yellow needles in 67% yield, mp 140–141°. The potassium 2,2-dinitroethyl allyl ether was dissolved in water and acidified to pH 1 with dilute hydrochloric acid. The resulting insoluble yellow oil was extracted with methylene chloride and the methylene chloride extracts were washed with water. After drying over magnesium sulfate, the methylene chloride was removed under reduced pressure yielding 2,2-dinitroethyl allyl ether in 96% yield as a pale yellow oil, $n^{27.5}$D 1.4527, d^{25} 1.3). The overall yield from 1,2-dichloro-1,1-dinitroethane was 36%.

From 1,1,1-Trinitroethane.—To a solution of 98.3 g (85%, 1.49 mol) of potassium hydroxide in 183 ml of water and 426 ml of ethanol was added dropwise 720 g (1.43 mol) of 30 wt % aqueous nitroform while maintaining the temperature at 15–20°. After the addition was complete (1 hr), the resulting solid potassium nitroform was filtered and washed well with cold water and then cold ethanol. The moist salt was then refluxed for 10 hr with 217.2 g (1.53 mol) of methyl iodide in 1300 ml of acetone. The resulting yellow solid was removed by filtration and washed with acetone. The filtrate and washes were combined and solvent was removed under reduced pressure. The red residue was taken up in 350 ml of methylene chloride and washed with aqueous sodium thiosulfate until the red color was removed. The methylene chloride portion was dried over magnesium sulfate and then concentrated until solid began to come out of solution. Hexane was added and the solid was allowed to crystallize, yielding 166 g (71%) of 1,1,1-trinitroethane, mp 52.5–54°.

To a solution of 32.7 g (85%, 0.5 mol) of potassium hydroxide in 400 ml of allyl alcohol was added dropwise 41.3 g (0.25 mol) of 1,1,1-trinitroethane in 100 ml of allyl alcohol over a 1-hr period while maintaining the temperature at 15–20°. Orange solid appeared immediately. The reaction mixture was stirred for an additional hour at room temperature after the addition was completed. The solid was filtered and washed with cold methanol, yielding 67.5 g of potassium 2,2-dinitroethyl allyl ether. A recrystallization from methanol yielded 35.8 g (67% yield) of potassium 2,2-dinitroethyl allyl ether as fine yellow needles, mp 137–138°. The preparation of allyl 2,2-dinitroethyl ether from the potassium salt was exactly the same as described previously in the 1,2-dichloro-1,1-dinitroethane experiment.

2-Fluoro-2,2-dinitroethyl Allyl Ether (VIII).—The sodium salt was formed *in situ* from 4.11 g (0.023 mol) of 2,2-dinitroethyl allyl ether and 0.94 g (0.023 mol) of sodium hydroxide. The solvent consisted of 15 ml of water and 35 ml of methanol. Perchloryl fluoride was added above the surface of the orange reaction mixture at such a rate that the temperature was maintained at approximately 20°. Total reaction time was approximately 4 hr. Water (50 ml) was then added and the reaction mixture was extracted with three 60-ml portions of methylene chloride. The combined methylene chloride extracts were then washed with three 30-ml portions of 3% sodium hydroxide and finally with water. After drying over magnesium sulfate, the solvent was removed under reduced pressure. The remaining liquid residue was distilled through a small Vigreux column to yield 0.62 g (16%) of 1,1-dinitro-1-fluoro-2-methoxyethane, bp 60–61.5° (12 mm), n^{28}D 1.4030, and 2.4 g (53%) of 2,2-dinitro-2-fluoroethyl allyl ether, bp 41° (1 mm), n^{25}D 1.4245.

2-Fluoro-2,2-dinitroethyl Glycidyl Ether (IX).—A solution of peroxytrifluoroacetic acid was prepared at 0° from 1 ml (0.036 mol) of 90% hydrogen peroxide, 6 ml (0.043 mol) of trifluoroacetic anhydride, and 10 ml of methylene chloride. This reagent was added over a 35-min period to a well-stirred boiling mixture of 4.06 g (0.021 mol) of 2,2-dinitro-2-fluoroethyl allyl ether, 25 ml of methylene chloride, and 15.7 g (0.111 mol) of disodium hydrogen phosphate (predried in vacuum oven overnight at 50°). After the mild exothermic reaction had subsided, the solution was heated under reflux for 2 additional hr. The resulting mixture was stirred with 75 ml of water until all of the inorganic salts had dissolved. The organic layer was separated and the aqueous layer was extracted with three 40-ml portions of methylene chloride. The combined methylene chloride portion was washed with 50 ml of 10% sodium bicarbonate solution and dried over magnesium sulfate. The solvent was removed at reduced pressure and the residual liquid was fractionated through a small Vigreux column to yield 0.27 g of unreacted 2-fluoro-2,2-dinitroethyl allyl ether and 3.92 g (95% yield) of 2-fluoro-2,2-dinitroethyl glycidyl ether, bp 70° (0.4 mm), n^{25}D 1.4362, d^{25} 1.45.

Registry No.—II, 5162-44-7; III, 32349-29-4; IV, 10229-09-1; V, 19273-49-5; VI, 32349-32-9; VII, 32349-33-0; VIII, 25171-99-7; IX, 25184-14-9.

Acknowledgment.—The sponsor of this work was Air Force Armament Laboratory, RTD, Weapons Division, Advanced Technology Branch (ATWR), Eglin AFB, Fla. 32542.

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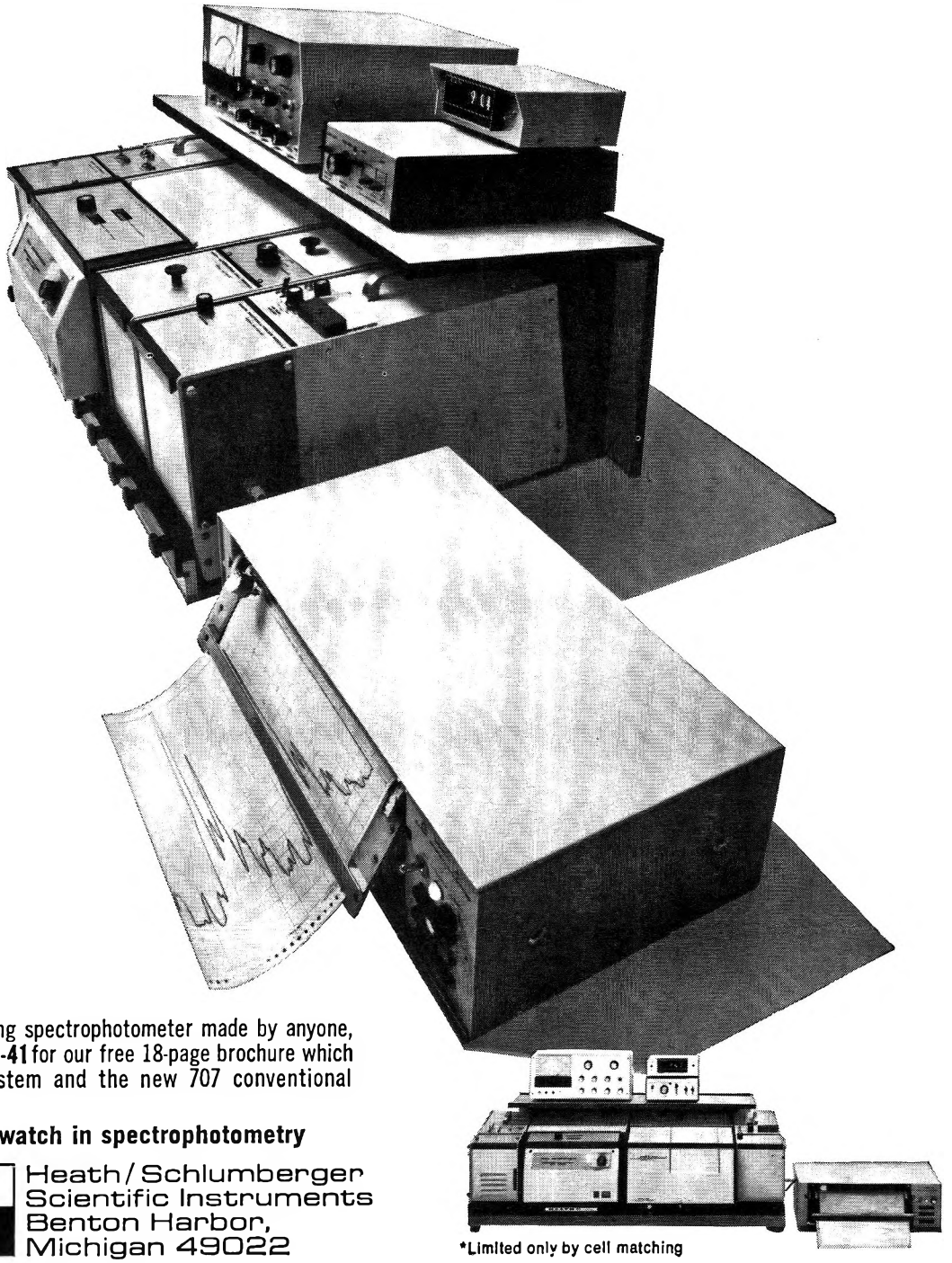

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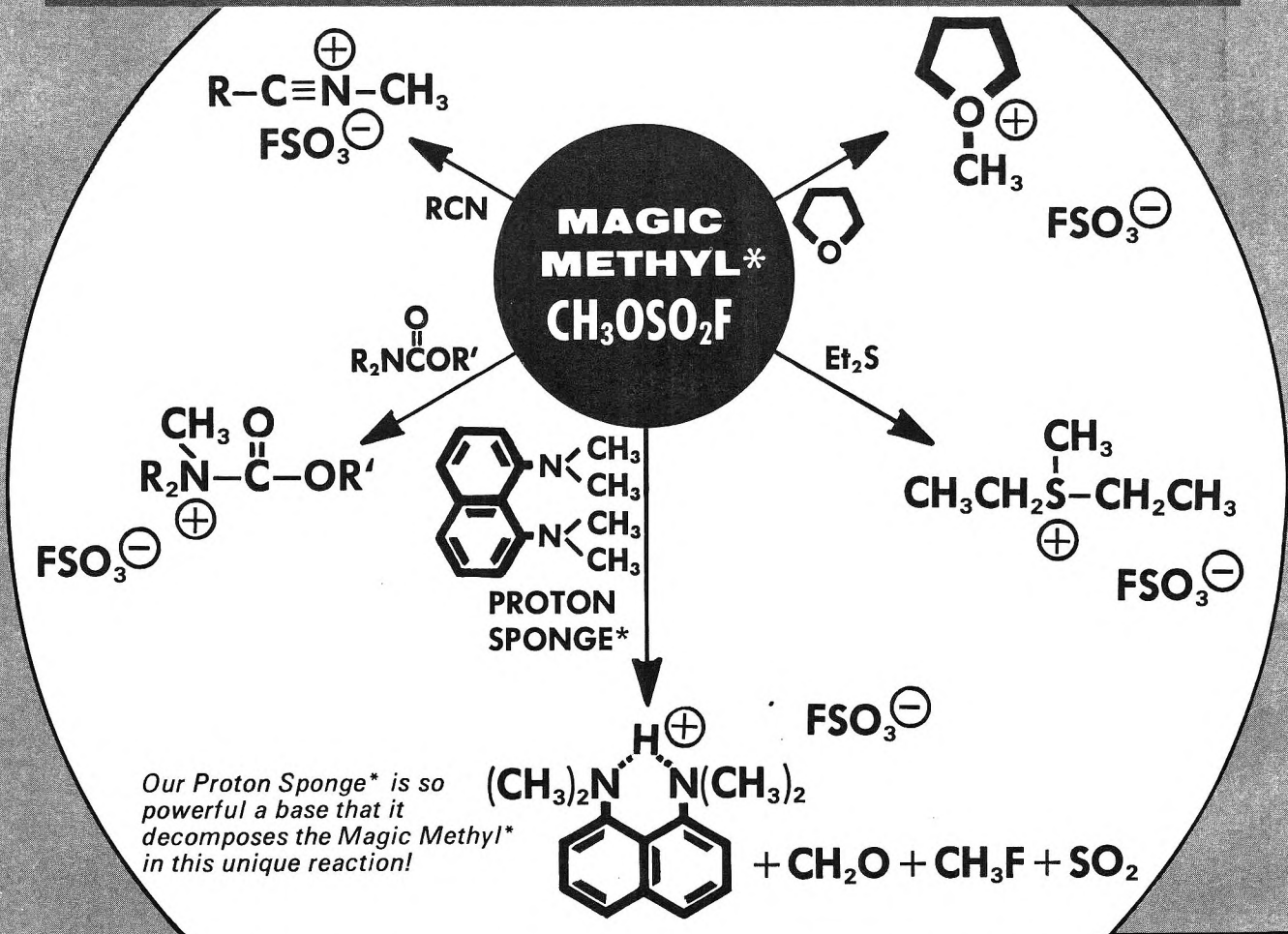

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1. M. G. Ahmed, R. W. Alder, G. H. James, M. L. Sinnott and M. C. Whiting, Chem. Comm., *1968*, 1533.
2. M. G. Ahmed and R. W. Alder, Chem. Comm., *1969*, 1389.
3. R. F. Borch, Chem. Comm., *1968*, 442.
4. R. W. Alder, private communication.
5. R. H. Mitchell and V. Boekelheide, Tetrahedron Letters, *1970*, 1197.

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