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THE JOURNAL OF Organic Chemistry®

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APRIL 21, 1972

Syntheses of Trispirocyclopropanes *via* Triple Photodecarbonylations of Polymethyleneketene Trimers[1]

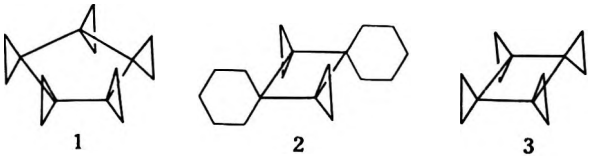
A. PAUL KRAPCHO* AND FRANCIS J. WALLER[2,3]

Department of Chemistry, University of Vermont, Burlington, Vermont 05401

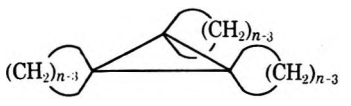
Received August 23, 1971

Trispiro[4.1.4.1.4.1]octadecane-6,12,18-trione (**5**, n = 5), trispiro[5.1.5.1.5.1]heneicosane-7,14,21-trione (**5**, n = 6), and trispiro[6.1.6.1.6.1]tetracosane-8,16,24-trione (**5**, n = 7) undergo triple photodecarbonylation when exposed to ultraviolet irradiation of wavelength greater than 258 nm. The resulting solid hydrocarbons trispiro-[4.0.4.0.4.0]pentadecane (**4**, n = 5), trispiro[5.0.5.0.5.0]octadecane (**4**, n = 6), and trispiro[6.0.6.0.6.0]heneicosane (**4**, n = 7) were isolated in 14.1, 4.2, and 1.6% yields, respectively. Trispiro[5.0.5.0.5.0]octadecane could also be obtained *via* acetone photosensitization of trimer **5** (n = 6). The monodecarbonylated cyclopentane-1,3-diones **7**, **8**, **10**, and **13** and the trispiro cyclobutanones **9** and **12** have been isolated and characterized. In the case of trispiro[3.1.3.1.3.1]pentadecane-5,10,15-trione (**5**, n = 4), irradiation in pentane yielded the δ lactone **6** (30%) and trispiro[3.1.3.1.3.0]tetradecane-5,10-dione (**7**) (11.4%). The effect of ring size in leading to the observed photolysis products is briefly discussed.

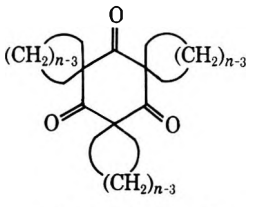
The synthesis of pentaspiro[2.0.2.0.2.0.2.0.2.0]pentadecane (**1**) has been described by Ripoll and Conia.[4] This was the first report of this type of polyspiro system and the general name "rotane" was suggested because of the paddlewheel-like arrangement of the outer cyclopropane rings. The syntheses of tetraspiro-[5.0.2.0.5.0.2.0]octadecane (**2**)[5] and trispiro[2.0.2.0.2.0.-2.0]dodecane (**3**)[6] were subsequently reported. As part of a program in the synthesis of paddlewheel systems with a central three-membered ring **4** (n = 4, 5, 6, 7), the photochemical behavior of polymethyleneketene trimers was studied. The choice of trimers **5** (n = 4, 5, 6, 7) was founded on the expectation that a stepwise triple photodecarbonylation[7] would occur to give the trispiro cyclopropanes. These expectations were partially realized.



1 **2** **3**



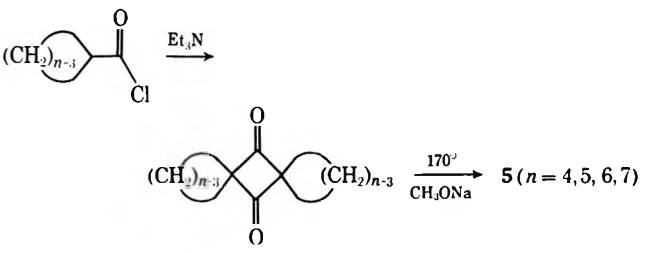
4 (n = 4,5,6, or 7)



5 (n = 4,5,6, or 7)

The trimers **5** (n = 4, 5, 6, 7) have been prepared previously from the appropriately substituted 1,3-cyclobutanediones[9,10] by a base-catalyzed process. The 1,3-cyclobutanediones are readily obtained from the dehydrohalogenation of the corresponding cycloalkanecarbonyl chlorides with triethylamine. The syntheses of trimers **5** (n = 4, 5, 6, 7) are represented in Scheme I.

SCHEME I



All irradiations were conducted in dilute pentane or acetone solutions using a 450-W Hanovia high-pressure broad-spectrum mercury-vapor lamp. A Pyrex (ab-

(1) Part of this material was reported in preliminary form: see A. P. Krapcho and F. J. Waller, *Tetrahedron, Lett.*, 3521 (1970).

(2) Abstracted in part from the Ph.D. Thesis submitted to the University of Ver mont, 1970.

(3) National Aeronautics and Space Administration Trainee, 1968–1970.

(4) (a) J. L. Ripoll and J. M. Conia, *Tetrahedron Lett.*, 979 (1969); (b) J. L. Ripoll, J. C. Limasset, and J. M. Conia, *Tetrahedron*, **27**, 2431 (1971).

(5) A. P. Krapcho and D. E. Horn, *Tetrahedron Lett.*, 4537 (1969).

(6) (a) J. M. Conia and J. M. Denis, *ibid.*, 3545 (1969); (b) P. Le Perchec and J. M. Conia, *ibid.*, 1587 (1970).

(7) A small yield of hexamethylcyclopropane has been reported by Hostettler in the photolysis of hexamethylcyclohexane-1,3,5-trione.[8]

(8) H. U. Hostettler, *Tetrahedron Lett.*, 1941 (1965).

(9) J. L. Erickson, F. E. Collins, Jr., and B. L. Owen, *J. Org. Chem.*, **31**, 480 (1966).

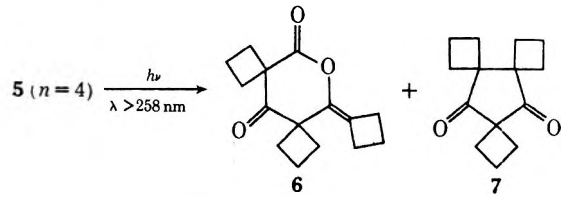
(10) M. Regitz and J. Ruter, *Chem. Ber.*, **102**, 3877 (1969).

solute cutoff at 280 nm) or Corex filter (absolute cutoff at 258 nm) was employed to assure that the initial excitation was restricted to the n–π^* band of the chromophore. The photolyses were followed by withdrawal of small aliquots at periodic intervals and analyzing for the disappearance of the characteristic trimer carbonyl band (see Experimental Section) by infrared spectroscopy.

Results

Trispiro[3.1.3.1.3.1]pentadecane-5,10,15-trione (5, n = 4).—Irradiation of a 0.016 M pentane solution of **5** (n = 4) using Corex optics for 1 hr led to two new products besides an insoluble solid and a small amount of starting material. The two new products, **6** (30.0%) and **7** (11.4%), were isolated by preparative scale vpc. The elemental analysis of **6** indicated that it was isomeric with **5** (n = 4). Pertinent infrared bands at 1715 (C=O) and 1765 cm^{-1} [C–C(=O)–O–C] and two strong bands at 1280 and 1085 cm^{-1} (CO) were characteristic of **6**. In addition, the δ lactone was rearranged by base catalysis[11] to trimer **5** (n = 4) in 59.2% yield. This spectroscopic and chemical data is consistent with the δ lactone assignment. The isomeric δ lactone upon further irradiation under identical conditions for **5** (n = 4) led to an uncharacterized solid.

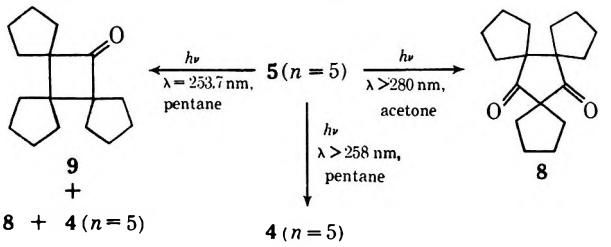
The second photoproduct **7** analyzed for $C_{14}H_{18}O_2$, indicating that a molecule of carbon monoxide had been lost. On the basis of infrared carbonyl absorptions[13] at 1715 (C=O) and 1755 cm^{-1} (C=O) and its nmr spectrum displaying a pattern consistent with the cyclobutyl rings being intact, the photoproduct was assigned the structure trispiro[3.1.3.1.3.0]tetradecane-5,10-dione (**7**). No substituted cyclobutanone or



hydrocarbon could be detected under the above experimental conditions.

Trispiro[4.1.4.1.4.1]octadecane-6,12,18-trione (5, n = 5).—When irradiated with ultraviolet light of wavelength above 258 nm for 3 hr, a 0.01 M pentane solution of trione **5** (n = 5) underwent triple photodecarbonylation. The solid hydrocarbon, $C_{15}H_{24}$, was isolated in 10% yield and exhibited infrared bands at 2955, 2865, and 1455 cm^{-1} and a molecular weight of 204 (mass spectrum). The nmr spectrum indicated that bond ruptures of the cyclopentyl rings did not occur. These spectroscopic data are consistent with the structure trispiro[4.0.4.0.4.0]pentadecane (**4**, n = 5).

Utilizing ultraviolet irradiation at 253.7 nm,[14] a 0.014 M pentane solution of **5** (n = 5) after 65 hr yielded two photolabile intermediates, **8** (7%) and **9** (8%). Compound **8** gave an elemental analysis

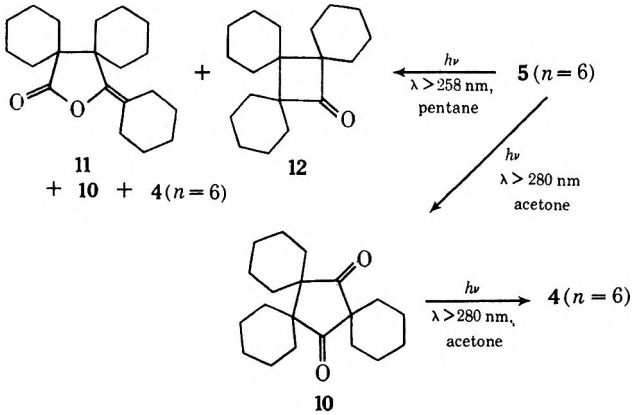


for $C_{17}H_{24}O_2$ and exhibited pertinent carbonyl infrared absorptions[13] at 1715 and 1750 cm^{-1}, while compound **9** possessed a ketone infrared band at 1755 cm^{-1} and analyzed for $C_{16}H_{24}O$. Again nmr spectra for **8** and **9** were in accord with noncyclopentyl ring rupture. The above information is consistent for trispiro[4.1.4.1.4.0]-heptadecane-6,12-dione and trispiro[4.1.4.0.4.0]hexadecan-6-one, respectively. A longer irradiation time, 79.5 hr, gave a 14.1% yield of hydrocarbon **4** (n = 5) isolated by preparative vpc.

Employing acetone[15] as photosensitizer (E_T = 79 kcal/mol, Φ = 1)[16] and Pyrex-filtered light, a 32.6% yield of **8** was obtained after 12.5 hr of irradiation.

Trispiro[5.1.5.1.5.1]heneicosane-7,14,21-trione (5, n = 6).—Photolysis of a 2.1 × 10^{-3} M pentane solution of **5** (n = 6) for 12 hr using a Pyrex filter led to a 51.0% isolation of a solid. The solid, with carbon–hydrogen analysis for $C_{20}H_{30}O_2$, showed infrared bands[13] at 1705 and 1745 cm^{-1}. Likewise, the nmr spectrum did not show any evidence of cyclohexyl ring rupture. This evidence supports the trispiro[5.1.5.1.5.0]eicosane-7,14-dione (**10**) structure. Using acetone[15] as a photosensitizer and a Pyrex filter, a 66% yield of **10** could be isolated after 12 hr of irradiation.

However, when a Corex filtering system was utilized, a 0.015 M pentane solution when photolyzed for 89.5 hr afforded 15.2% of **10** in addition to two new photoproducts **11** (3.2%) and **12** (1.2%) and hydrocarbon



4 (n = 6). Photoproduct **11** was isomeric with **10** and showed infrared bands at 1780 (C=O) and 1680 cm^{-1} (C=C) and a nmr spectrum which displayed a broad four-proton envelope centered at δ 2.30. From these characteristics, the structure was assigned as lactone **11**. The other photoproduct possessed an infrared

(11) Clark[12] has reported the formation of hexamethylcyclohexane-1,3,5-trione from the sodium methoxide catalyzed thermal rearrangement of 5-hydroxy-2,2,4,4,6-pentamethyl-3-oxo-5-heptenoic δ-lactone.

(12) R. D. Clark, *J. Org. Chem.*, **32**, 399 (1967).

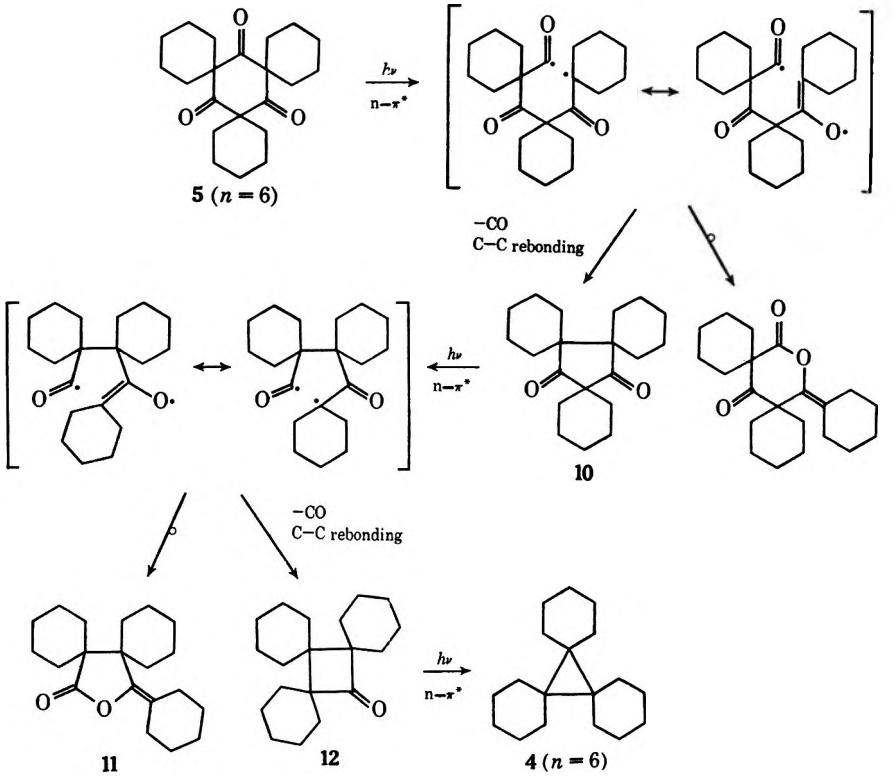
(13) The two absorption bands in the carbonyl region are apparently characteristic of 2,2-substituted 1,3-cyclopentanedione systems. The carbonyl band at higher frequency is more intense than the band at lower frequency. For discussion of two ir bands in the region around 1700 cm^{-1} see O. H. Mattsson and C. A. Wachtmeister, *Acta Chem. Scand.*, **22**, 79 (1968).

(14) A Rayonet RPR-100 chamber reactor fitted with 16 RPR-253.7 nm lamps was used as a light source.

(15) The acetone absorbed >99% of the light.

(16) N. J. Turro, J. C. Dalton, and D. S. Weiss in "Organic Photochemistry," Vol. II, O. L. Chapman, Ed., Marcel Dekker, New York, N. Y., 1969, pp 8–13.

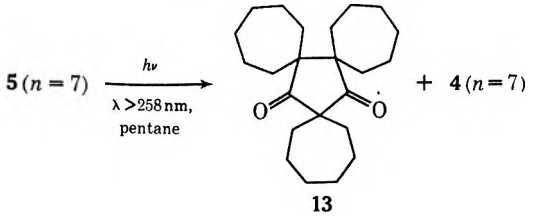
SCHEME II



absorption at 1750 cm^{-1} and was assigned as trispiro-[5.1.5.0.5.0]nonadecan-7-one (12).

The solid hydrocarbon, $C_{18}H_{30}$, gave a simple infrared spectrum with bands at 2980, 2925, 2855, and 1445 cm^{-1}. The nmr spectrum displayed a broad singlet at 1.47 ppm. This hydrocarbon, trispiro[5.0.5.0.5.0]-octadecane (**4**, $n = 6$), was obtained in ~1% yield.[17] The same yield of **4** ($n = 6$) was obtained in the acetone photosensitization of trispiro[5.1.5.1.5.0]eicosane-7,14-dione (**10**).[15]

Trispiro[6.1.6.1.6.1]tetracosane-8,16,24-trione (**5**, $n = 7$).—Similarly, when a 0.022 *M* pentane solution of **5** ($n = 7$) was irradiated with light of wavelength greater than 258 nm for 6 hr, two products, **13** (19.0%)



and **4** ($n = 7$) (1.6%), were isolated. Photoproduct **13** gave analysis consistent for the loss of 1 mol of carbon monoxide, $C_{23}H_{36}O_2$, and pertinent infrared bands[13] at 1715 and 1750 cm^{-1}. The nmr spectrum showed a broad envelope centered at 1.63 ppm. Compound **4** ($n = 7$) was a solid hydrocarbon, $C_{21}H_{36}$, with characteristic infrared bands at 2910, 2855, and 1460 cm^{-1} and a broad singlet at 1.57 ppm in the nmr spectrum.

Hexamethylcyclohexane-1,3,5-trione.—In order to compare our results with those of Hostettler,[8] a 0.014 *M* pentane solution of hexamethylcyclohexane-1,3,5-trione was irradiated for 4 hr with ultraviolet light of wavelength greater than 280 nm. Examination of the photolysate by infrared showed the trione still present and hexamethylcyclopentane-1,3-dione as the major product. The major product was isolated by preparative vpc in 48.0% yield and had identical physical properties with those described by Hostettler.[8] Sensitization by acetone[15] led to unchanged hexamethylcyclohexane-1,3,5-trione.

Discussion

The above experimental results clearly show that the photochemical behavior of the polymethyleneketene trimers is synthetically useful in the preparation of rotanes with a central three-membered ring.

The hexamethylcyclohexane-1,3,5-trione and triones **5** ($n = 5, 6, 7$) behave differently from trione **5** ($n = 4$). However, all have in common the same structural feature, a cyclic nonenolizable 1,3,5-triketone moiety. The mechanism which best describes the photochemical transformation of triones **5** ($n = 4, 5, 6, 7$) is depicted by **5** ($n = 6$) in Scheme II.[8] The photoexcitation of the carbonyl (n–π^*) results in the fission of the C–C bond (α cleavage giving a C,C diradical). In the case of trione **5** ($n = 4$), the major photoproduct is the δ lactone resulting *via* a mesomeric C,O diradical. This is in line with the fact that cycloalkyl radicals[18] are stable in the sequence $C_7 > C_5 > C_6 \gg C_4$.[19] Furthermore, trispiro[5.1.5.-1.5.0]eicosane-7,14-dione also afforded an isomeric lactone which reflects the cyclohexyl radical instability and subsequent rearrangement *via* a mesomeric C,O

(17) An uninterrupted irradiation of trione **5** ($n = 6$) for 90.5 hr afforded 4.2% of **4** ($n = 6$). The effect of oxygen on the overall yield of **4** ($n = 6$) was not investigated.

(18) A formal analogy of photochemical reaction processes to free radical reactions initiated by other sources exists. H. Brown and coworkers predicted, based on I-strain hypothesis, that homolysis to form a free radical on a ring position follows the order 5 > 7 > 6 > 4. See H. C. Brown, R. S. Fletcher, and R. B. Johannesen, *J. Amer. Chem. Soc.*, **73**, 212 (1951).

(19) C. G. Overberger, H. Biletch, A. B. Finestone, J. Lilker, and J. Herbert, *ibid.*, **75**, 2078 (1953).

TABLE I

PROPERTIES AND SPECTRAL DATA FOR THE TRISPIROCYCLOHEXANE-1,3,5-TRIONES

5, n	Mp or bp, °C (mm)	Uv (CH_3OH), nm (ε)	Nmr ($CDCl_3$), δ
4	108–110 (0.07)[a]	244 (218)	2.3–3.0 (12 H, m)
		303 (162)	1.7–2.3 (6 H, m)
5	112–114[b]	224 (535)	1.5–2.45 (m)
		291 (135)	
6	144–146[c]	230 (467)	1.78, 1.68, and
		295 (128)	1.55 (broad envelopes)
7	127–128[d]	235 (281)	1.95 (12 H, broad envelope)
		300 (85)	1.60 (24 H, broad envelope)

[a] Reference 9, bp 139–140° (2.0 mm). [b] Reference 9, mp 112.5–113.5°. [c] Reference 9, mp 147°. [d] Reference 10, mp 127°.

TABLE II

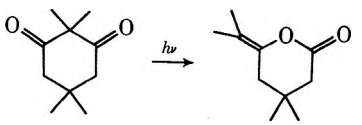
IRRADIATIONS OF THE TRISPIROCYCLOHEXANE-1,3,5-TRIONES

5, n	Solvent (M)	Time, hr	Products (% yield)
4	Pentane (0.016)[a]	1	5, n = 4 (4), 6 (30), 7 (11.4)[b]
5	Pentane (0.015)[c]	80	4, n = 5 (14.1)[d]
5	Pentane (0.014)[c]	65	4, n = 5 (1),[e] 8(7),[f] 9 (8)[g]
5	Pentane (0.01)[a]	3	4, n = 5 (10.0)[e]
5	Acetone (0.01)[h]	12.5	8 (33)[f]
6	Pentane (0.015)[a]	89.5	4, n = 6 (1),[e] 10 (15.2),[i] 11 (3.2),[j] 12 (1.2)[g]
6	Pentane (0.03)[a]	90.5	4, n = 6 (4.2)[e]
6	Pentane (0.002)[h]	12	10 (51)[k]
6	Acetone (0.002)[h]	12	10 (66)[k]
7	Pentane (0.022)[a]	6	4, n = 7 (1.6),[e] 13 (19)[f]

[a] Corex filter. [b] Products isolated by vpc separation. [c] Rayonet RPR-100 chamber reactor with 16 253.7-nm lamps. [d] Eluted with hexane on neutral alumina followed by passing through a silver nitrate impregnated alumina column followed by vpc purification on a silicone column (160°). [e] Eluted with hexane and purified on a silver nitrate impregnated alumina column. [f] Eluted with a 1:1 hexane–benzene mixture. [g] Eluted with ether. [h] Pyrex optics. [i] Eluted with 4:1 hexane–benzene. [j] Eluted with benzene. [k] Crude reaction mixture crystallized from ether.

diradical. The observation that no isomeric δ lactone in the photolysis of trione **5** ($n = 6$) was seen could be due to the long irradiation times and possible destruction under the photochemical conditions employed. The δ lactone isomeric with trione **5** ($n = 4$) is unstable to ultraviolet irradiation.

Other diradical type mechanisms have been proposed in analogous reactions. Nozaki and coworkers[20] have reported the isolation of an exocyclic enol δ lactone as the major component in the photolysis of 2,2,5,5-tetramethyl-1,3-cyclohexanedione (**14**). The exocyclic enol



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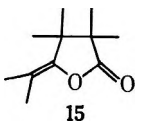
lactone arises *via* a mesomeric C,O diradical. Also, Hostettler[8] has rationalized the formation of 4-hydroxy-2,2,3,3,5-pentamethyl-4-hexenoic acid λ-lactone (**15**)



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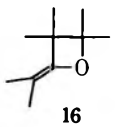

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(20) H. Nozaki, Z. Yamaguti, T. Okada, R. Noyori, and M. Kawanisi, *Tetrahedron*, **23**, 3993 (1967).

TABLE III

PHYSICAL PROPERTIES AND SPECTRAL DATA FOR THE PHOTOLYSIS PRODUCTS

Structure	Mp, °C	Ir (CCl_4), cm^{-1}	Nmr ($CDCl_3$), δ
4, n = 5[a]	34–35	2955, 2865, 1455	1.13–1.87 (m)
4, n = 6[b]	119–120	2980, 2925, 1445	1.47 (broad s)
4, n = 7[c]	61–63	2910, 2855, 1460	1.57 (broad s)
6[d]	e	1715, 1765	2.85–3.23 (4 H, m)
			1.78–2.85 (12 H, m)
7[f]	e	1715, 1755	2.19–2.44 (6 H, m)
			1.59–2.19 (12 H, m)
8[g]	62–64	1715, 1750	1.85 (broad s)
			1.67 (broad envelope)
9[h]	44–45	1755	1.70 (broad s)
			1.64 (broad s)
10[i]	93–94	1705, 1745	1.61 (broad)
11[j]	150–151	1680, 1780	2.30 (4 H, broad envelope)
			1.60 (26 H, broad envelope)
12[k]	126–128	1750	1.60 (broad envelope)
13[l]	103–105	1715, 1750	1.63 (broad envelope)

[a] *Anal.* Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.3[illegible]; H, 12.00. [b] *Anal.* Calcd for $C_{18}H_{30}$: C, 87.73; H, 12.27. Found: C, 87.80; H, 12.05. [c] *Anal.* Calcd for $C_{21}H_{36}$: C, 87.42; H, 12.58. Found: C, 87.13; H, 12.42. [d] *Anal.* Calcd for $C_{15}H_{18}O_3$: C, 73.14; H, 7.37. Found: C, 72.99; H, 7.27. [e] Isolated by vpc collection from a Silicone GE-SS-96 on Firebrick column. [f] *Anal.* Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 77.03; H, 8.58. [g] *Anal.* Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29. Found: C, 78.49; H, 9.43. [h] *Anal.* Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.67; H, 10.31. [i] *Anal.* Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.06; H, 9.68. [j] *Anal.* Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.62; H, 9.89. [k] Insufficient material for analysis. [l] *Anal.* Calcd for $C_{23}H_{36}O_2$: C, 80.18; H, 10.53. Found: C, 80.22; H, 10.80.

and 2,2,3,3-tetramethyl-4-isopropylideneoxetane (**16**) from hexamethylcyclopentane-1,3-dione and hexamethylcyclobutanone, respectively, *via* mesomeric C,O diradicals formed from the initial C,C diradical.

The multiplicity of the excited state involved in the transformation of trione **5** ($n = 6$) to hydrocarbon **4** ($n = 6$) apparently cannot be established by the preparative experiments reported here. It might be noted that benzophenone did not sensitize the monodecarbonylation of hexamethylcyclohexane-1,3,5-trione, and it has been suggested that this photoreaction occurs from the n–π* singlet.[8] Photolysis of this trione in acetone as solvent (and presumably sensitizer) led mainly to unchanged trione. Trimers **5** ($n = 5$ or 6) on irradiation in acetone solution led to **8** (32.6%) and **10** (66%), respectively. The photolysis of dione **10** in acetone solution led to a poor yield of **4** ($n = 6$) (1%). The acetone sensitizations are suggestive of a n–π* triplet as the chemically reactive species in the latter three cases.[21]

Experimental Section

All melting points and boiling points are uncorrected. Infrared spectra were determined on a Perkin-Elmer Model 237-B grating infrared spectrophotometer. Ultraviolet spectra above 215 nm

(21) The multiplicity of the excited state(s) has (have) certainly not been clearly established. See J. M. Beard and R. H. Eastman, *Tetrahedron Lett.*, 3029 (1970), and N. C. Yang, M. H. Hui, and S. A. Bellard, *J. Amer. Chem. Soc.*, **93**, 4056 (1971), and references cited therein.

were taken using a Perkin-Elmer 202 ultraviolet–visible spectrophotometer. Nmr spectra were obtained on a Varian Associates A-60 spectrophotometer, and are reported as parts per million relative to internal TMS. Mass spectra were taken on a JMS-01SG Mattauck-Herzog type double focusing mass spectrometer by Jeolco, Inc., Medford, Mass. Gas chromatography was performed on an Aerograph Model A-90-P instrument. Microanalyses were done by Robertson Laboratory, Florham Park, N. J.

Materials.—Pentane (Eastman Organic Chemicals), purified by oleum and permanganate, was used as received. Acetone (Fisher Scientific, Certified A. C. S.) was used as received. *n*-Hexane used for column chromatography was purified by shaking with concentrated sulfuric acid, washing with water, drying with calcium chloride, and distilling from phosphorus pentoxide. Benzene used for column chromatography was distilled from sodium. Silver nitrate–alumina was prepared by the procedure of Murray and coworkers.[22]

Hexasubstituted Cyclohexane-1,3,5-triones.—Hexamethylcyclohexane-1,3,5-trione was prepared by the procedure described by Erickson and Kitchens.[23] This trione exhibited infrared absorption (CCl_4) at 1698 cm^{-1}, exhibited a singlet at δ 1.38 ppm ($CDCl_3$) in the nmr, and showed uv absorption maxima (CH_3OH) at 226 (ϵ 340) and 297 nm (ϵ 85). The properties and spectral data for the trispirocyclohexane-1,3,5-triones **5** (n = 4, 5, 6, or 7) are tabulated in Table I.

General Irradiation Procedure.—The solvent employed was degassed by slowly bubbling nitrogen through the solution for 5 min. A degassed solution of the compound in pentane or acetone (generally 1.7–2.7 mmol of compound in 170 ml of solvent) was irradiated with a 450-W Hanovia mercury-vapor lamp, No. 6-79A-36, in a quartz immersion well apparatus fitted with a Pyrex or Corex filter. The reaction progress was monitored periodically by infrared analysis. Upon termination of the irradiation, the solution was filtered in those cases where insoluble material formed. The solution was concentrated and the residue was subjected to purification by column chromatography on neutral alumina or vpc separation or the residual material was crystallized.

Typical Irradiation. Photolysis of Hexamethylcyclohexane-1,3,5-trione.—A degassed solution of 422 mg (2.0 mmol) of the trione in 170 ml of pentane was irradiated using a Pyrex filter for 4 hr. After removal of the solvent, hexamethylcyclopentane-1,3-dione was isolated by vpc (6 ft 20% GE-SS-96 on Firebrick; column operated at 196° with an He flow rate of 75 ml/min). There was obtained 174.3 mg (48.0%) of the dione, mp 49.5–51.5° (lit.[8] mp 51°).

A degassed solution of 535 mg (2.54 mmol) of hexamethylcyclohexane-1,3,5-trione in 700 ml of acetone was irradiated for 4 hr using a Pyrex filter. After removal of the acetone, crystallization from ether yielded 349 mg (65.4%) of starting trione.

The pertinent experimental conditions and results for the irradiations of the trispirocyclohexane-1,3,5-triones are summarized in Table II.

Irradiation of 10.—A degassed solution of **10** (468 mg, 1.55 mmol) in 170 ml of acetone was irradiated for 73 hr using Pyrex optics. After solvent removal, the residue was dissolved in hexane and chromatographed on neutral alumina. A hydrocarbon fraction was collected which was rechromatographed on a silver nitrate impregnated alumina column to yield 2.3 mg (1%) of **4** (n = 6). Elution with ether yielded starting material (30% recovery).

The physical properties and the spectral data for the photolysis products are tabulated in Table III.

Base-Catalyzed Thermal Rearrangement of 6 to 5 (n = 4).—A solution of 135 mg (0.55 mmol) of **6** in 2.0 ml of dry benzene was heated to reflux. Upon adding 40 mg of $NaOCH_3$ an exothermic reaction occurred. Following 15 min of additional heating, the orange-colored solution was cooled and neutralized with a few drops of glacial acetic acid. The mixture was extracted with ether and the organic phase was dried over K_2CO_3. After solvent removal, 80.0 mg (59.2%) of an oil was obtained. Vpc analysis (6 ft 20% Silicone GE-SS-96 on Firebrick, column operated at 185°) yielded 34.5 mg of a component that had ir and vpc retention time identical with those of **5** (n = 4).

Registry No.—**4** (n = 5), 29150-89-8; **4** (n = 6), 33780-60-8; **4** (n = 7), 33777-05-8; **6**, 33777-06-9; **7**, 33777-07-0; **8**, 29798-98-9; **9**, 29798-99-0; **10**, 33777-10-5; **11**, 33777-11-6; **12**, 33777-12-7; **13**, 33777-13-8.

Acknowledgment.—Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research (PRF 3437-A1, 4).

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(23) J. L. Erickson and G. C. Kitchens, *J. Org. Chem.*, **27**, 460 (1962).

A Model Iron-Catalyzed Biomimetic Cyclization of a Cyclic Tryptamine *N*-Oxide

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The tryptamine *N*-oxide **5** is cleanly converted to the tetracyclic amine **6** with hydrated ferrous sulfate in methanolic acetic acid. The biosynthetic significance, synthetic potential, and mechanistic implications of the reaction are considered.

The iminium ion **1**, derived from stemmadenine,[2] appears to be a key intermediate in the biogenetic relationship between preakuammicine **2** and precondylocarpine **3**, and thus occupies a central position in the later stages of indole alkaloid biogenesis. The elegant cyclization reactions of Kutney,[3] Schmid,[4] and their coworkers clearly illustrate the potential of synthetically generated iminium ions for realizing analogous conversions. We now report that an iminium species, generated under very mild conditions from an *N*-oxide function, can undergo clean internal cyclization to give a β-carboline which may serve as a model in indole alkaloid biogenesis; in addition, we record some findings which relate to the mechanisms of analogous reactions *in vitro* and *in vivo*.

The dealkylation of tertiary amine oxides with aqueous Fe^{2+} has been extensively investigated, and the following mechanism has been proposed[5] for trimethylamine *N*-oxide.

$$Me_3N^+\text{-}OH + Fe^{2+} + H^+ \longrightarrow Me_2N^{\cdot+} + H_2O + Fe^{3+}$$

$$Me_3N^{\cdot+} + Fe^{3+} \longrightarrow Me_2\overset{+}{N}{=}CH_2 + H^+ + Fe^{2+}$$

$$Me_2\overset{+}{N}{=}CH_2 \xrightarrow{H_2O} Me_2\overset{+}{N}H_2 + HCHO$$

$$Me_3N^{\cdot+} + Fe^{2+} + H^+ \longrightarrow Me_3\overset{+}{N}H + Fe^{3+}$$

(1) To whom inquiries should be addressed.
(2) A. I. Scott, *Accounts Chem. Res.*, **3**, 151 (1970).
(3) J. P. Kutney, R. T. Brown, and E. Piers, *J. Amer. Chem. Soc.*, **86**, 2286 (1964).
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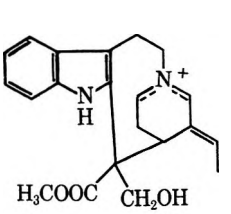

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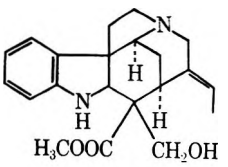

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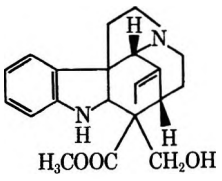

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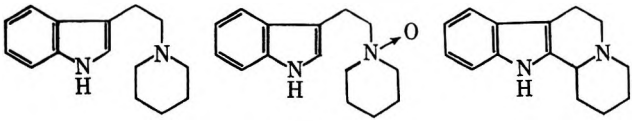
In accord with this mechanism, Ghosal and Mukherjee found[6] that *N*,*N*-dimethyltryptamine *N*-oxide with aqueous ferrous sulfate gave formaldehyde, *N*-methyltryptamine, and indole-3-acetaldehyde, and that 5-methoxy-*N*,*N*-dimethyltryptamine gave 6-methoxy-2-methyl-1,2,3,4-tetrahydrocarboline in *ca.* 12% yield. This carboline could have arisen either by cyclization of an iminium species or by condensation between a dealkylated amine and formaldehyde formed by hydrolysis. Norman and his coworkers[7] found that 3,4-dimethoxy-*N*,*N*-dimethyl-β-phenethylamine *N*-oxide under similar conditions gave dealkylated amine and some 1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline. Deuterium labeling implicated formaldehyde in the cyclizations, and increases in Fe^{3+} concentration led to increases (up to 20%) of isoquinoline. These observations also support the mechanism of Ferris and coworkers.[5]

We have investigated the cyclization of the amine oxide **5** as a model for more complex polycyclic indole alkaloid systems. The amine **4**[8] on treatment with 30% H_2O_2 gave the *N*-oxide **5**, in 95% yield.



4 5 6

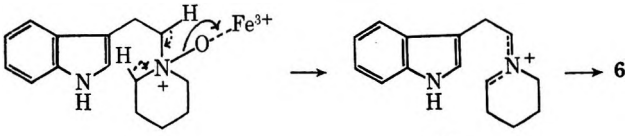
This compound was treated with $FeSO_4 \cdot 7H_2O$ in refluxing methanol–acetic acid, followed by removal of iron salts with H_2S and work-up *via* $NaBH_4$ reduction (compare ref 9). Only three products were obtained; sulfur from the work-up, the uncyclized amine **4**, and the cyclized amine **6**, in approximately 30% yield. These yields have not yet been maximized, but the exceptionally mild conditions and complete absence of side products suggest a considerable synthetic potential for the method.

The yields of cyclized amine **6** were not improved when Fe^{3+} salts were added to the Fe^{2+} salt already present. Attempted cyclizations of the *N*-oxide **5** with $FeSO_4 \cdot 7H_2O$ in the presence of cyclohexanol gave only minute traces of cyclized product, strongly supporting the intermediacy of radical cations in the cyclization, as advocated by Ferris and coworkers.[5] Under strictly anhydrous conditions in the presence of acetic anhydride no cyclization was observed. This suggests that some water is necessary for the reaction, although no hydrolysis products were observed either chromatographically or on work-up. Tlc studies showed that both the uncyclized amine **4** and the cyclized amine **6** were strongly chelated by ferrous and ferric salts; moreover, the separation of iron from the amines using H_2S at the end of the reaction was often slow.

Reaction of the *N*-oxide **5** with hydrated $Fe_2(SO_4)_3$ containing <0.01% Fe^{2+} in methanol–acetic acid gave a trace of the cyclized amine **6**. This suggests that the ionic reaction below may take place to a small extent; however, it is clearly not the major pathway in the Fe^{2+} reactions (Scheme I).

SCHEME I

POSSIBLE FERRIC ION INDUCED CYCLIZATION OF *N*-OXIDE **5**



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The strong similarity between this reaction and the mercuric acetate cyclization[8,9] of amines such as **4** suggests the intermediacy of iminium ions **7**, which arise in our work from *N*-oxides by the mechanism of Ferris and his coworkers.[5] Under these conditions only the desired product and starting material are obtained. These results strongly support the suggestion, adumbrated previously,[6] that tryptamine *N*-oxides may be involved in biogenetic cyclizations, and describe a potentially useful biomimetic synthetic method. Strong added support for such an involvement is offered by studies of enzyme-catalyzed dealkylation of *N*-oxides,[10] and by the natural occurrence of *N*-oxides both of simple[11] and more complex[12] indole alkaloids. Further experiments to test the selectivity of this reaction for diastereomeric *N*-oxides of chiral substrates are underway in our laboratory.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer 237 spectrophotometer and mass spectra on an A. E. I. MS-902 instrument.

Preparation of Amines 4 and 6.—The tricyclic amine **4** was prepared from 3-indolylglyoxalic acid piperidide[13] by reduction with lithium aluminum hydride.[14] It was crystallized conveniently from absolute ethanol, mp 150–151.5° (lit.[13] mp 150–152°). The amine **6** was prepared by mercuric acetate cyclization of **4** in methanol–acetic acid by the methods of Wenkert,[8] Kutney[9] and coworkers, mp 149–150° (lit.[8] mp 153–155°).

Preparation of 3-(β-Piperidinoethyl)indole *N*-Oxide 5.[15]—To a solution of the amine **4** (2.5 g, 11 mmol) in absolute ethanol (85 ml), hydrogen peroxide (30 ml of 30%) was added and the solution was allowed to stir at room temperature for 24 hr. The excess hydrogen peroxide was destroyed by adding a small amount

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of manganese dioxide and stirring in an ice bath until the evolution of bubbles ceased. The solution was then filtered through Celite and the ethanol was evaporated under vacuum. The oily residue crystallized on standing to furnish a quantitative yield of the *N*-oxide **5**. Tlc (silica gel with 10% methanol–chloroform) was used to show the presence of only one compound (R_f 0.14) which was different from starting material (R_f 0.44): mp 162–163; ir (KBr) 3450 (NH), 3000–2200 (quaternary N-salt absorption), 1620 (indole absorption), 740 (ortho-disubstituted phenyl absorption), and 960 cm^{-1} (characteristic band due to *N*-oxide not present in the starting material). The picrate salt formed yellow needles, mp 168–171°. *Anal.* Calcd for $C_{21}H_{23}N_5O_8$: C, 53.28; H, 4.9; N, 14.79. Found: C, 53.84; H, 5 01; N, 14.80.

General Procedure for the Small Scale *N*-Oxide Cyclization.[6]—Several scrapings of the pure *N*-oxide **5** (4–5 mg) were dissolved in methanol (8 ml), and acetic acid (1.5 ml) was added slowly. The iron salt was then added and the solution was refluxed. After refluxing the reaction was cooled and filtered through Celite. Hydrogen sulfide was passed through the solution for about 5 min and sodium borohydride (excess) was added slowly with cooling. The reaction mixture was let stand for 30 min and then filtered through Celite.

The yellow solution was evaporated to a yellow slurry under vacuum, dissolved in water, and extracted several times with benzene. The benzene layer was dried (K_2CO_3) and evaporated under vacuum, leaving a small amount of brown oil. The oil was analyzed by tlc (silica gel plates with ethyl acetate as the eluent). Three products were found: R_f 0.72, 0.35, 0.18. The furthest moving component corresponded to sulfur (R_f 0.72), mp 119°. The spot of lowest R_f corresponded to 3-(β-piperidinoethyl)indole (**4**) (R_f 0.18), while the compound with R_f 0.35 was identical with the cyclized tetracyclic amine **6** (R_f 0.35). No *N*-oxide **5** was found at any time after work-up.

The reaction was run under the conditions that follow.

Ferrous and Ferric Ions. Experiment I.—To a solution of the *N*-oxide **5** (5 mg) in methanol (5 ml) and acetic acid (1 ml), $FeSO_4 \cdot 7H_2O$ (0.2 g) was added, and, after refluxing for 30 min, $Fe_2(SO_4)_3 \cdot xH_2O$ (0.15 g) was also added. Tlc showed the presence of the uncyclized 3-(β-piperidinoethyl)indole (**4**) in the highest yield, a small amount of sulfur, and only a very small amount of the cyclized product.

Ferric Ion under Anhydrous Conditions. Experiment II.—The reaction was carried out using anhydrous ferric chloride (50 mg) under anhydrous conditions (8 drops of acetic anhydride were added to the solvents before the reaction was started) and refluxed for 1.5 hr. Tlc showed spots for the uncyclized amine **4** and sulfur, but no cyclized amine was observed.

Ferrous Ion. Experiment III.—The solution was allowed to react as in experiment I except that $FeSO_4 \cdot 7H_2O$ (0.1 g) was used and the reaction was refluxed for 2 hr. No ferric sulfate was used. Tlc showed sulfur and uncyclized amine, while the cyelized amine appeared to be present in higher yield than in experiment I.

Ferrous Ion. Experiment IV.—The mixture was allowed to react as in experiment III except that $FeSO_4 \cdot 7H_2O$ (0.2 g) was employed and the reaction was refluxed for 20 hr. Again sulfur and the uncyclized amine **4** were shown to be present by tlc. However, the cyclized product **6** was the strongest spot on the tlc plate and was present in much higher concentration than in experiments I and III.

Ferric and Ferrous Ions under Anhydrous Conditions. Experiment V.—To a solution of the *N*-oxide **5** in methanol, anhydrous ferric chloride (50 mg) was added under anhydrous conditions. The solution was refluxed for 1.5 hr. Tlc showed presence of uncyclized amine **4** and sulfur. No cyclized amine **6** was present.

Ferric Ion. Experiment VI.—To a solution of the *N*-oxide **5** (0.5 g) in methanol, $Fe_2(SO_4)_3 \cdot xH_2O$ (0.5 g) was added and the solution was refluxed for 20 hr. After work-up tlc showed the absence of the cyclized amine; however, after chromatography of the crude oil on Woelm activity III alumina, a trace of the cyelized material **6** was evident in one of the fractions.

Ferrous Ion and Cyclohexanol. Experiment VII.—The solution was allowed to react as in experiment III except that cyclohexanol (2 ml) was added and the solution was refluxed for 4 hr. Tlc showed the presence of uncyclized amine **4**, sulfur, and only a trace of the cyclized amine **6**.

Preparation of the Cyclized Tetracyclic Amine 6 on a Large Scale.—To a solution of the *N*-oxide **5** (2.5 g, 10 mmol) in methanol (400 ml), acetic acid (75 ml) was added slowly. Then $FeSO_4 \cdot 7H_2O$ (10.0 g) was added and the solution was allowed to reflux for 18 hr. The reaction turned a dark orange-brown color. After cooling, hydrogen sulfide was bubbled through the reaction mixture and the characteristic black precipitate of FeS began to form. Sodium borohydride (30.0 g) was added in small portions and a vigorous reaction took place. The reaction was cooled in an ice bath during the borohydride reduction. Again hydrogen sulfide was passed through the solution and the precipitate was allowed to settle for 30 min. The reaction was then filtered through Celite and the filtrate was evaporated under vacuum to leave a yellow slurry. Water (200 ml) was added and the solution was made basic with 25% sodium hydroxide. The alkaline solution was extracted four times with benzene and filtered to break up an emulsion. The benzene extracts were washed with water and dried over anhydrous potassium carbonate. Evaporation of the benzene left a viscous oil which was chromatographed on Woelm activity III neutral alumina packed with cyclohexane. The column was eluted with cyclohexane (eight fractions of 150 ml). The sulfur was eluted in the first three fractions. The solvent polarity was increased to 10:1 cyclohexane–benzene and gradually increased to 1:1 cyclohexane–benzene; 24 fractions were taken. Fractions 8–18 (75 ml each) were combined to yield the cyclized amine **6** (520 mg, R_f 0.35) in a 22.5% yield. Fractions 18–20 contained both the cyclized product **6** and the uncyclized amine **4** (total 300 mg) while fractions 21–24 (including the chloroform washing of the column) contained 3-(β-piperidinoethyl)indole (**4**) (900 mg) of R_f 0.18.

Registry No.—**5**, 33777-27-4; **5** picrate, 33777-28-5; **6**, 4802-79-3; Fe^{3+}, 20074-52-6; Fe^{2+}, 15438-31-0.

Acknowledgments.—We thank Dr. J. R. Wiseman for useful discussions and The National Institutes of Health for a predoctoral fellowship (to J. M. C.). We thank Professor James V. Neel, Department of Human Genetics, University of Michigan, for his encouragement, and the Atomic Energy Commission, Contract AT(11-1)-1552, for partial support for C. A. D. The mass spectrometer was purchased with funds provided by the National Science Foundation.

Base-Catalyzed Intermolecular Condensation of α,β-Unsaturated Ketones. Dimerization of 2,4-Diarylidenecyclobutanones to 2-Spiro(2-oxocyclobutyl)bicyclo[3.2.0]heptan-6-one Derivatives[1]

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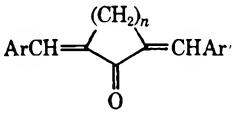
The self-condensation of 2,4-dibenzylidenecyclobutanone (**2a**) in aqueous ethanolic sodium hydroxide produces a crystalline dimer, 7-benzylidene-3,4-diphenyl-2-spiro(2-oxo-3-benzylidenecyclobutyl)bicyclo[3.2.0]-heptan-6-one (**5a**) in 20–30% yield. Its structure has been established from chemical and spectral evidence, including nmr spectra of **5a** and its d_1, d_{20}, d_{24}, and d_{25} deuterio derivatives (**5b–e**), prepared by dimerization of **2a**, **2a**-d_{10}, and **2a**-d_{12} in aqueous ethanol or deuterium oxide–ethanol-*O*-*d*. Other 2,4-diarylidenecyclobutanones (4-methylbenzylidene and 3,4-dimethoxybenzylidene) form crystalline dimers (**5f,g**). The base-catalyzed dimerization reactions proceed through the unique 2,4-diarylidenecyclobutanone anion intermediate and involve an intermolecular Michael addition followed by intramolecular Michael cyclization. The stereochemistry of dimer **5a** is discussed.

Many α,α′-diarylidenecycloalkanones (**1**, n = 2–7) have been prepared in good yields by base-catalyzed



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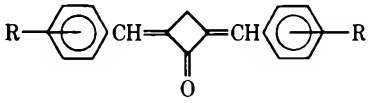
condensation of aromatic aldehydes (2 molar equiv) with cycloalkanones.[2-5] The α,β-unsaturated ketones obtained from cyclopentanone and larger ring cycloalkanones are stable in basic media and undergo no known self-condensation reactions under normal reaction conditions. By contrast, 2,4-diarylidenecyclobutanones (**1**, n = 1) are sensitive to base and difficult to purify.

Pure 2,4-diarylidenecyclobutanones (**2a–d**) were first reported only recently by Thieme.[6] A substance previously described as **2a** by Demjanov[7] is believed to be a dimer. In the present work a modified procedure has produced **2b** in improved yield and new ketones **2e,f**.



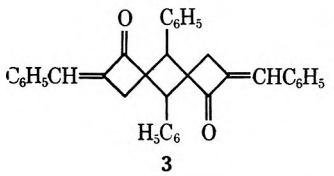
2a, R = H
b, R = 4-CH_3
c, R = 4-CH_3O
d, R = 4-Cl
e, R = 3,4-$(CH_3O)_2$
f, R = 4-$(CH_3)_2N$

The only other aldehydes reported to undergo aldol condensation with cyclobutanone are formaldehyde and acetaldehyde. These produced 2,2,4,4-tetramethylolcyclobutanone and epimeric 2-(1-hydroxyethyl)-cyclobutanones, respectively.[8,9]

2,4-Dibenzylidenecyclobutanone (**2a**, mp 190–191°) in basic media reacts rapidly to form dimers of unknown structure, $C_{36}H_{28}O_2$. Three such dimers have been isolated in crystalline form, including a new one described in the present work. By condensing benzaldehyde (2 molar equiv) with cyclobutanone in 60% ethanolic potassium hydroxide at ambient temperature, Demjanov[7] obtained a crystalline product (large yellow leaflets from chloroform, mp 170–171°) which he described as monomer **2a**. It is now believed to be a dimer of **2a**. Conia,[8] in carrying out the same reaction under similar conditions, obtained a dimeric product, $C_{36}H_{28}O_2$, mp 168–170°. Both workers experienced great difficulty in securing a crystalline sample and satisfactory elemental analyses. Yields were not stated. Conia's sample was amorphous and contained some ketol impurity.

Thieme,[6] by treating pure 2,4-dibenzylidenecyclobutanone (**2a**) with 95% ethanolic sodium hydroxide (*ca.* 0.075 *M*) at 50°, obtained a crystalline dimer in 20% yield (yellow cubes from acetonitrile, mp 223–225°). In our hands his procedure gave amorphous products. However, employing a lower concentration of sodium hydroxide (0.01–0.035 *M*) in 85–95% aqueous ethanol at 25–45°, we obtained a new dimer in 20–30% yield (mp 191–193°, yellow spear-shaped prisms from acetonitrile). Heating a sample of our dimer in refluxing ethanolic sodium hydroxide converted it into an amorphous product from which no crystalline material could be isolated. Thieme determined the nmr and infrared spectra of his dimer but did not speculate on its structure.

Conia, principally on the basis of ultraviolet and infrared spectra, suggested structures **3** or **4** for his



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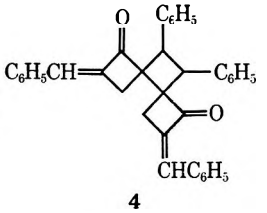


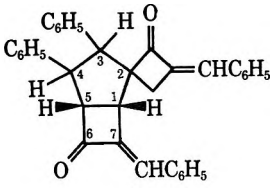
4

dimer.[8] He noted that dimers of benzylidene α,β-unsaturated ketones formed by irradiation, or in alkaline media, may have a cyclobutane structure. However, we have demonstrated that such structures are incorrect for dimers produced in alkali-catalyzed re-

(1) A preliminary account of this work has appeared: A. T. Nielsen, R. C. Weiss, and D. W. Moore, *Chem. Commun.*, 1281 (1969).
(2) A. T. Nielsen and W. J. Houlihan, *Org. React.*, **16**, 38, 238 (1968).
(3) E. A. Braude and B. F. Gofton, *J. Chem. Soc.*, 4720 (1957).
(4) (a) F. Mattu, *Rend. Semin. Fac. Sci. Univ. Cagliari*, **32**, 230 (1962); *Chem. Abstr.*, **63**, 17935 (1965); (b) F. Mattu and M. R. Manca-Mura, *Rend. Semin. Fac. Sci. Univ. Cagliari*, **34**, 286 (1964); *Chem. Abstr.*, **63**, 13126 (1965).
(5) S. V. Tsukerman, L. A. Kutulya, and V. F. Lavrushin, *Zh. Obshch. Khim.*, **34**, 3597 (1964).
(6) P. Thieme, *Chem. Ber.*, **101**, 378 (1968).
(7) N. J. Demjanov and M. Dojarenko, *ibid.*, **55**, 2737 (1922).
(8) J.-M. Conia and J.-P. Sandré, *Bull. Soc. Chim. Fr.*, 744 (1963).
(9) J.-E. Dubois and M. Dubois, *ibid.*, 3120 (1969).

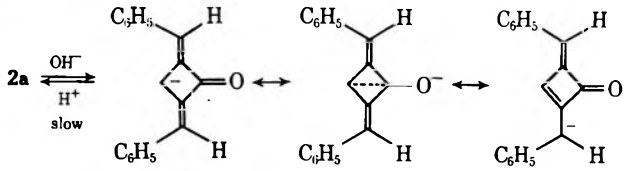
actions.[10] Styryl alkyl ketones dimerize to 3,5-diaryl-4-alkanoylcyclohexanones or 5-aryl-3-styryl-2-cyclohexen-1-ones in aqueous ethanolic sodium hydroxide.[11-13] Thieme demonstrated that **2a** dimer is not produced photochemically or thermally.[6]

We have established the structure of 2,4-dibenzylidenecyclobutanone dimer prepared in the present work as 7-benzylidene-3,4-diphenyl-2-spiro(2-oxo-3-benzylidenecyclobutyl)bicyclo[3.2.0]heptan-6-one (**5a**) on the basis of chemical evidence, spectral data, and deuterium-labeling experiments. The complete configuration of **5a** is unknown. It appears likely that dimers of **2a** described by Thieme[6] and Conia[8] are epimers of **5a**.



5a

The 2,4-dibenzylidenecyclobutanone anion **6** has been postulated as an intermediate in the base-catalyzed dimerization leading to **5a**.[1] α,α'-Diarylidenecycloalkanones other than **1** ($n = 1$) cannot form such an anion. Anion **6** is unique in that, unlike other α,β-

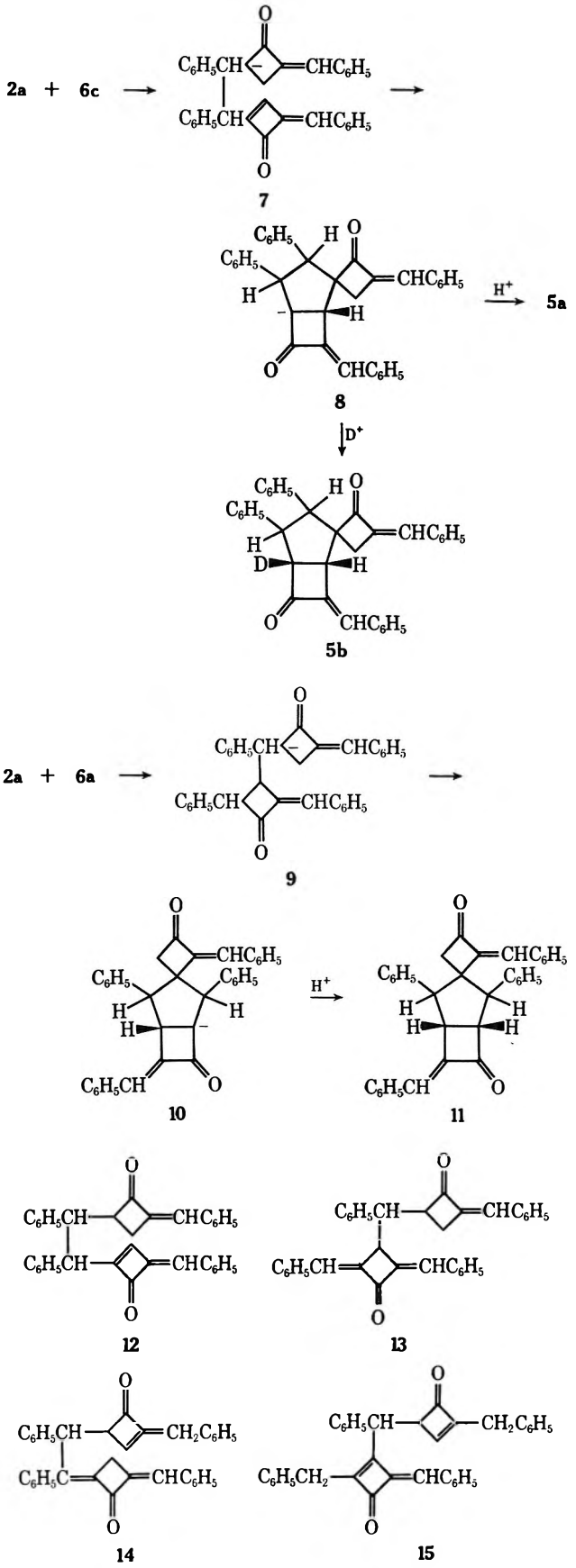


6a **6b** **6c**

unsaturated ketone derived anions, it cannot participate in classical enolate anion resonance. Charge delocalization on oxygen (**6b**) is believed to contribute to its stabilization, however. It was observed that the anion does not undergo rapid deuterium exchange under the reaction conditions, since in ethanol-*O*-*d* the dimer product is found to have but one deuterium.

The mechanism of the base-catalyzed formation of **2a** dimer is believed to follow that of other base-catalyzed α,β-unsaturated ketone dimerizations.[10-13] The initial step is a Michael addition leading to anion **7**, a step faster than reprotonation of **6a** to regenerate **2a**. A second, intramolecular Michael addition would produce anion **8**, and protonation of **8** would lead to dimer **5a**. The ring closure **7** → **8** is probably more rapid than retrogression to **2a** or protonation of **7**, since in ethanol-*O*-*d* only one deuterium is incorporated in product **5b**.

Other structures may be considered for **2a** dimer. An alternate Michael addition path involving C-3 of anion **6** would produce a different bicyclo[3.2.0]heptanone (**11**) *via* anion intermediates **9** and **10**. C-Protonation of anions **7** and **9** would produce acyclic diketones **12** and **13**, respectively. Double-bond isomers of these compounds might arise by prototropic rearrangement, *e.g.*, **14** and **15**; in ethanol-*O*-*d* such products would be expected to incorporate at least two deuterium atoms, however.



7 **8** **5b** **9** **10** **11** **12** **13** **14** **15**

Spectral data support **5a** over alternate structures. The infrared and ultraviolet spectra of 2-benzylidenecyclobutanone (**16**) were determined by Conia,[8] who first prepared this compound. When these data are

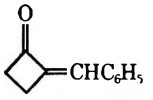
(10) A. T. Nielsen and H. J. Dubin, *J. Org. Chem.*, **28**, 2120 (1963).
(11) A. T. Nielsen and S. Haseltine, *ibid.*, **33**, 3264 (1968).
(12) A. T. Nielsen and D. W. Moore, *ibid.*, **34**, 444 (1969).
(13) A. T. Nielsen, H. Dubin, and K. Hise, *ibid.*, **32**, 3407 (1967).

TABLE I

INFRARED AND ULTRAVIOLET SPECTRA OF 2,4-DIBENZYLIDENECYCLOBUTANONE AND DERIVED COMPOUNDS

Compd	ν, cm⁻¹ (KBr) C=O	C=C	λmax (EtOH), nm (εmax)
16	1735[a]	1645	223 (10,000)[a]
			229.5 (11,500)
			299 (27,500)
2a	1720[b,c]	1670	236 (18,300)[b]
		1635	349 (36,500)
5a (mp 191–193°)	1746[b,d,e]	1638	227 (20,500)[b]
	1734		233 (21,400)
			318 (50,500)
Conia's dimer (mp 168–170°)	1740[a,f]	1645	310 (24,000)[a,f]
Thieme's dimer (mp 223–225°)	1746[g]	1643	
5a 2,4-DNP[h]	1735[b,e]	1640	

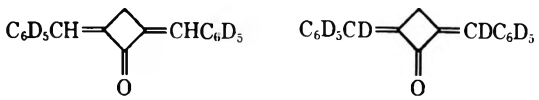
[a] Data of Conia, ref 8. [b] This work. [c] Thieme (ref 6) reports 1721 (C=O), 1669, 1636 cm⁻¹ (C=C) for **2a**. [d] In chloroform solution a single carbonyl band is observed at 1739 cm⁻¹; C=C at 1638 cm⁻¹. [e] Measurement with Perkin-Elmer 620 grating instrument. [f] A moderately intense band at 1770 cm⁻¹ and a weak band at 3400 cm⁻¹ (OH) are also present suggesting the presence of ketol (ref 8). [g] Data of Thieme, ref 6. [h] Mono-2,4-dinitrophenylhydrazone of **5a**, mp 279–280°.



16

compared with the spectra of dibenzylidene derivative **2a** and dimer **5a** (Table I) it is clear, as Conia concluded,[8] that the dimer contains two 2-benzylidenecyclobutanone ring units and that the 2,4-dibenzylidenecyclobutanone structure is absent (**13**, **14**, and **15** are excluded). Benzaldehyde is produced by osmium tetroxide–sodium periodate oxidation of **5a**. That both oxygens in **5a** are carbonyl groups was established by preparing the mono-2,4-dinitrophenylhydrazone derivative (reaction with excess 2,4-dinitrophenylhydrazine). It retained one carbonyl group absorbing at 1735 cm⁻¹, suggesting that reaction had occurred at the bicycloheptanone carbonyl while the spirocyclobutanone carbonyl group did not react. The dimer is stable in acidic medium under the conditions of hydrazone formation.

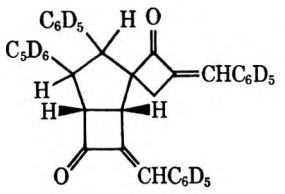
Deuterium-labeled dimers were prepared and their nmr spectra were determined to distinguish structure **5a** from others. Monomers **2g** and **2h** were prepared from cyclobutanone and benzaldehyde-*2,3,4,5,6-d*$_5$ and benzaldehyde-*d*$_6$, respectively. Dimerizations of **2a,g,h**



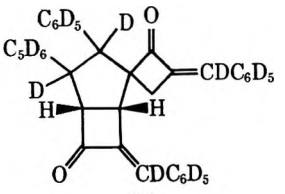
2g **2h**

were conducted in aqueous ethanolic sodium hydroxide or ethanol-*O-d*–deuterium oxide–NaOD to prepare deuterio dimers **5b–e**. The nmr spectra of monomers **2a,g,h** and dimers **5a–e** are summarized in Table II.

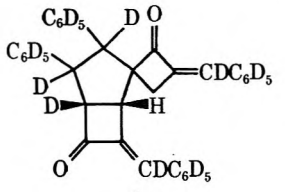
Dimer **5b** was prepared from **2a** in ethanol-*O-d*–D_2O. The four ring protons which appear in **5a** as a complex multiplet at δ 4.0–4.4 are reduced to three: the two benzylic protons at C-3 and C-4 now appear as an AB



5c



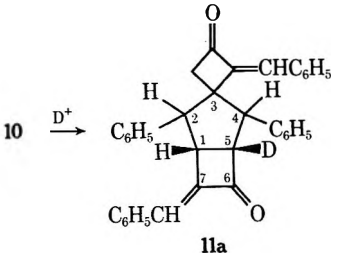
5d



5e

quartet at δ 4.20 and 4.08 (J = 7 Hz) and the C-1 proton as a doublet at δ 4.14 (J = 1 Hz) due to weak coupling to the C-7 benzylidene vinyl proton. The phenyl protons appear as three sharp peaks at δ 7.25, 7.18, and 7.12. The methylene group protons of the spirocyclobutanone ring are structurally nonequivalent and appear as a poorly resolved ABX multiplet at δ 2.80 owing to a strong geminal spin coupling as well as the 2.5-Hz coupling to the adjacent benzylidene vinyl proton. In the monomer **2a** the methylene protons are equivalent and appear as a simple 2.5-Hz triplet, since each methylene proton is spin-coupled to two equivalent benzylidene protons.

Structure **11a** produced by deuteration of anion **10** is not possible, since in it the C-2 and C-4 benzylic proton



11a

signals would not be coupled to each other. Also, in **11a** the C-1 proton signal would be complex since it is coupled to two protons; furthermore, the C-4 benzyl proton signal should appear in **11a** as a singlet.

Dimer **5c** (d_{20}) was prepared from monomer **2g** (d_{10}) in aqueous ethanol. Its nmr spectrum revealed two vinyl proton signals. The one on the C-7 benzylidene group appears as a doublet at δ 7.21 (J = 1 Hz) due to coupling with the C-1 proton. This signal is hidden under the phenyl proton signal in **5a** and **5b**. The benzylidene vinyl proton signal in the spirocyclobutanone ring appears as a triplet at δ 6.64 (J = 2.5 Hz). The bicycloheptane ring protons appear as a multiplet as in **5a**. The appearance of only two vinyl proton signals in **5c** rules out dimeric structures such as **12** and **13**. Also, since only one of the vinyl proton signals is a 2.5-Hz split triplet, there is only one benzylidene group having an adjacent methylene group; thus structures **3**, **4**, and **15** are eliminated.

Dimer **5d** (d_{24}) was prepared from monomer **2h** (d_{12}) in aqueous ethanol. In deuteriochloroform its nmr spectrum revealed the AB quartet of the C_1–C_5 protons as two strong inner lines (δ 4.27, 4.22); the spirocyclo-

TABLE II

NMR SPECTRA OF 2,4-DIBENZYLIDENECYCLOBUTANONE AND ITS DIMERS, δ VALUES IN $CDCl_3$ (TETRAMETHYLSILANE INTERNAL STANDARD)

		Cyclobutanone and spirocyclobutanone protons		Bicyclo[3.2.0]heptane ring protons				
Compd	Phenyl protons CH	=CH (exocyclic)	CH_2	C_7=CH (exocyclic)	C-1 CH	C-5 CH	C-3 CH	C-4 CH
2a[a]	7.28 m	7.05 t (J = 2.5 Hz)	3.75 t (J = 2.5 Hz)					
2g (d_{10})		7.11 t (J = 2.5 Hz)	3.77 t (J = 2.5 Hz)					
2h (d_{12})			3.78 s					
5a	7.25, 7.18, 7.12[b]	6.63 t (J = 2.5 Hz)	2.88 m[c]	Not visible	[4.0–4.4 m]			
5b (d_1)	7.25, 7.18, 7.12[b]	6.52 t (J = 2.5 Hz)	2.80 m[c]	Not visible	4.14 d (J = 1 Hz)		[4.20, 4.08 q] (J = 7 Hz)	
5c (d_{20})		6.64 t (J = 2.5 Hz)	2.83 m[c]	7.21 d (J = 1 Hz)	[4.0–4.4 m]			
5d (d_{24})			2.79, 2.77 q,[d] 2.68 s[e,f]		[4.27, 4.22 q[d]] [4.07, 3.88 q[e]] (J = 9 Hz)			
5e (d_{25})			2.85, 2.83 q,[d]		4.27 s			

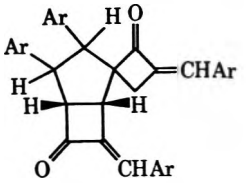
[a] Thieme (ref 6) reports δ 7.4 m, 7.2 t (J = 2.5 Hz), 3.8 t (J = 2.5 Hz) in $CDCl_3$. [b] Signal appears as three principal peaks of nearly equal intensity. [c] Unresolved ABX multiplet. [d] The outer lines of the AB quartet are not visible. [e] Solvent is 1:1 toluene-d_8–$CDCl_3$. [f] Apparent singlet.

butanone methylene protons produced a similar signal (δ 2.79, 2.77). However, in 1:1 toluene–deuteriochloroform the C_1–C_5 protons appear as an AB quartet with weak outer lines (δ 4.07, 3.88, J = 9 Hz).

Dimer **5e** (d_{25}), prepared from monomer **2h** (d_{12}) in ethanol-*O*-*d*–D_2O, has but one proton in the bicycloheptane ring (at C-1) which appears as a singlet at δ 4.27. The spirocyclobutanone ring methylene signal remains as an unresolved multiplet at δ 2.84.

The stereochemistry of dimer **5a** cannot be completely deduced from its nmr spectrum alone, even though coupling constants have been obtained for the C_1–C_5 and C_3–C_4 protons in deuterio derivatives **5b** and **5d**, respectively. The ring juncture in the bicycloheptane ring is necessarily cis and the coupling constant observed for the protons at this ring juncture in **5d** (C_1–C_5 J = 9 Hz) agrees with reported values for cyclobutane systems; J_{cis} = 8–12 Hz and J_{trans} = 8–10 Hz.[14] The coupling constant for the C_3–C_4 proton coupling observed in **5b** (J = 7 Hz) is within the range of either a cis or trans configuration (2–8 Hz).[15] In studies of Michael addition stereochemistry the initially formed carbon–carbon bond is observed to have trans stereochemistry when produced under conditions of kinetic or thermodynamic control.[12,15,17] In product **5a** there is no possibility of subsequent base-catalyzed epimerization at C_3 or C_4, exclusive of retro-Michael reaction. Assuming trans stereochemistry at C_3–C_4, eight diastereoisomers of **5a** are possible. The dimers of **2a** reported by Conia[8] and Thieme[6] are probably epimers of **5a**; the method of their synthesis and the observed similarity in their spectra (Table I) favors this assumption. (The three known styryl isobutyl ketone dimers formed in ethanolic sodium hydroxide are epimers.[12]) Although not shown in **5a**, the exocyclic benzylidene groups are presumed to have the favored trans stereochemistry; structure **6a** illustrates the preferred configuration.[18,19]

The base-catalyzed dimerization reaction has been extended to other 2,4-diarylidenecyclobutanones. 2,4-(4-Methylbenzylidene)cyclobutanone (**2b**) forms a crystalline dimer (assigned structure **5f**) in 32% yield in



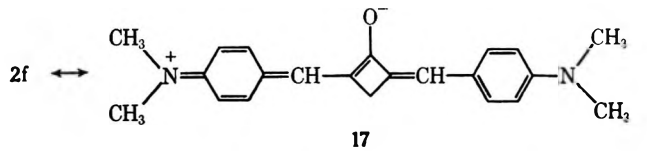
5f, Ar = 4-$CH_3C_6H_4$
g, Ar = 3,4-$(CH_3O)_2C_6H_3$
h, Ar = 4-$CH_3OC_6H_4$

aqueous ethanolic sodium hydroxide at 50–68°, mp 215–218°. Its nmr and infrared spectra are very similar to those of **5a**. 2,4-Bis(3,4-dimethoxybenzylidene)-cyclobutanone (**2e**) by reaction under the same conditions as employed with **2b** gave crystalline dimer **5g** by fractional crystallization from acetonitrile, mp 232–235° (1% yield). 2,4-Bis(4-methoxybenzylidene)cyclobutanone (**2c**) under similar conditions gave a trace of product (mp 240–260°), believed to be principally dimer **5h**. 2,4-Bis(4-chlorobenzylidene)cyclobutanone (**2d**) gave an amorphous product from which no crystalline product could be isolated; its infrared spectrum resembles that of dimers **5a–h**, except for the presence of bands at 3500 and 1770 cm^{-1} which suggest ketol impurity. The effect of aryl substituents on the dimerization of 2,4-diarylidenecyclobutanones parallels results for dimerization of styryl alkyl ketones to 3,5-diaryl-4-alkanoylcyclohexanones (13–22% yield);[10] electron-releasing groups such as alkyl and alkoxy

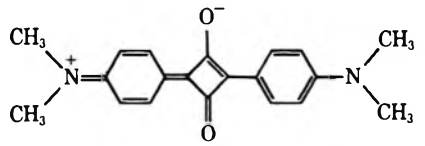
(14) W. A. Thomas in "Annual Review of NMR Spectroscopy," Vol. 1, E. F. Mooney, Ed., Academic Press, New York, N. Y., 1968, pp 74–77.
(15) A. A. Bothner-By in "Advances in Magnetic Resonance," Vol. 1, J. S. Waugh, Ed., Academic Press, New York, N. Y., 1965, pp 239–243.
(16) L. Gorrichon-Guigon, Y. Maroni-Barnaud, and P. Maroni, *Bull. Soc. Chim. Fr.*, 128 (1970).
(17) A.-M. Baradel, J. Dreux, and R. Longeray, *ibid.*, 3543 (1966).
(18) D. N. Kevill, E. D. Weiler, and N. H. Cromwell, *J. Org. Chem.*, **29**, 1276 (1964).
(19) M. Brink, *Tetrahedron*, **25**, 995 (1969).

favor these reactions, which involve a Michael cyclization in an acyclic dimer intermediate.

The preparation of 2,4-bis(4-dimethylaminobenzylidene)cyclobutanone (**2f**) deserves comment. Under conditions used for preparing **2a–e** (43–69% yield) this compound is formed much more slowly and in lower yield (14%). It is isolated as deep-red prisms having a relatively high melting point (274–275°) and, unlike **2a–e**, is very insoluble in most organic solvents. α,α'-Bis(4-dimethylaminobenzylidene)cycloalkanones prepared from cyclopentanone, cyclohexanone, and cycloheptanone are orange, high-melting substances, but are more soluble in organic solvents than is **2f**.[2] The carbonyl stretching frequency of **2f** (1680 cm^{-1}) is relatively low compared to that of **2a** (1720 cm^{-1}), characteristic of charge delocalization in β-amino ketones. The delocalized structure of **2f** (**17**) and its physical properties resemble somewhat the highly colored, high-melting cyclobutendiylium dyes (*e.g.*, **18**, deep blue, mp 276°).[20]

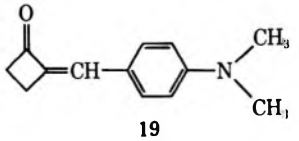


17



18

The principal product of condensation of 4-dimethylaminobenzaldehyde (2 molar equiv) with cyclobutanone at 25° is the 2-benzylidene derivative **19** (scarlet prisms from acetone, mp 181–183°, 38% yield). Only



19

one monoarylidenecyclobutanone other than **19** is known, *i.e.*, 2-benzylidenecyclobutanone (**16**). The latter was prepared in a pure state with some difficulty by condensing benzaldehyde with excess cyclobutanone.[8]

Experimental Section[21]

Materials.—Cyclobutanone (99.7%) from Columbia Chemicals Co., $n^{25}D$ 1.4198, was assayed by vpc. Aldehydes were commercial samples, distilled immediately before use if liquid; melting points of solid samples were checked before use.

Benzaldehyde-d_6 was prepared from toluene-d_8 by chlorination to benzal dichloride-d_6 followed by alkaline hydrolysis;[22] assay by mass spectrum 96% d_6 (112), 4% d_5 (111).

Benzaldehyde-2,3,4,5,6-d_5.—Benzyl alcohol-2,3,4,5,6-d_5 (2.49 g), prepared by lithium aluminum hydride reduction of benzoic acid-2,3,4,5,6-d_5,[23] was dissolved in 200 ml of ether and shaken with 15 g of activated manganese dioxide (catalyst B)[24] at ambient temperature for 118 hr. The solution was filtered and the filtrate was distilled to yield 1.81 g (75%) of benzaldehyde-2,3,4,5,6-d_5, bp 179–180°, assay by mass spectrum 96% d_5 (111), 4% d_4 (110).

2,4-Dibenzylidenecyclobutanone (2a) was prepared by the procedure of Thieme[6] as flat yellow prisms from acetone, 47% yield, mp 191–193° (lit.[6] mp 191–192°, 47% yield).

2,4-Di(benzylidene-2,3,4,5,6-d_5)cyclobutanone (2g).—A solution of cyclobutanone (0.57 g, 0.00815 mol) and benzaldehyde-2,3,4,5,6-d_5 (1.81 g, 0.0163 mol, 96% assay d_5) in 10 ml of 95% ethanol was added dropwise during 2 hr to 40 ml of aqueous ethanol (75% ethanol) containing 4 ml of 1% aqueous sodium hydroxide solution (temperature 20°). After standing for 4 hr at 20° the mixture was chilled in an ice bath for 20 min and filtered to yield 0.30 g of crystals, mp 185–192°; standing at 25° for an additional 17 hr deposited 0.54 g of additional crystalline product, mp 170–185° (46% total yield); recrystallization from acetone gave **2g** as prisms, mp 193–195°, 99% pure by nmr assay.

2,4-Di(benzylidene-α,2,3,4,5,6-d_6)cyclobutanone (2h).—A solution of cyclobutanone (0.78 g, 0.011 mol) and benzaldehyde-d_6 (2.77 g, 0.022 mol, 96% assay) in 15 ml of 95% ethanol gave, by the procedure used for preparation of **2g**, 1.15 g (42%) of crude **2h**, mp 175–185°; recrystallization from acetone gave prisms, mp 191–194°; 98% pure by nmr assay.

7-Benzylidene-3,4-diphenyl-2-spiro(2-oxo-3-benzylidenecyclobutyl)bicyclo[3.2.0]heptan-6-one (5a).—2,4-Dibenzylidenecyclobutanone (1.0 g, 0.0046 mol) was pulverized in a mortar and dissolved in 25 ml of absolute ethanol at 45°; 4.0 ml of 1% aqueous sodium hydroxide solution was added and the solution was heated at 45° for 10 min. The solution after cooling to 25° was shaken in a mechanical shaker for 50 min. The mixture was filtered to yield 0.27 g of dimer **5a**, mp 190–191°. The filtrate was acidified with 20 ml of 2 *N* sulfuric acid, diluted with 50 ml of water, and allowed to stand overnight to deposit 0.70 g of a solid which was crystallized from acetonitrile to yield 0.13 g of additional product, mp 170–185° (0.40 g total); recrystallization from acetonitrile gave 0.30 g (30%) of small, yellow, spear-shaped crystals, mp 191–193°; when mixed with 2,4-dibenzylidenecyclobutanone (mp 191–192°) the melting point was depressed to 155–160°. In a parallel run (2.0 g of monomer, sodium hydroxide 0.011 *M* in 95% ethanol) **5a** was obtained in 23% yield, mp 188–192°.

Anal. Calcd for $C_{36}H_{28}O_2$: C, 87.77; H, 5.73; mol wt 492.6. Found: C, 87.55; H, 5.65; mol wt 492 (mass spectrum).

Reaction of **2a** by the procedure of Thieme[6] gave an amorphous product, mp 108–118°, from which no crystalline product could be isolated by crystallization from various solvents, including acetonitrile. The infrared spectrum [ν KBr 1745 s (C=O), 1770 m (C=O), 1640 s (C=C), 3500 w cm^{-1} (OH)] suggested the presence of ketol in the crude product.

A 10-mg sample of dimer **5a** in 5 ml of 95% ethanol containing 2 drops of concentrated hydrochloric acid was heated under reflux for 1 hr. Removal of the solvent gave recovered dimer, 10 mg, mp 192–194°.

A 10-mg sample of dimer **5a** in a solution of 10 ml of absolute ethanolic sodium methoxide (prepared from 10 mg of sodium) was warmed on the steam bath for 10 min; 1 ml of water was added and the solution was heated for an additional 15 min. Cooling, followed by addition of 10 ml of water and 10 ml of 2 *N* sulfuric acid, gave 10 mg of amorphous solid, mp 75–80°, from which no crystalline material could be isolated by crystallization from acetonitrile.

A 30-mg sample of dimer **5a** in a solution of 1 ml of acetonitrile and 1 ml of 1% sodium hydroxide in 70% ethanol was heated on the steam bath for 15 min. After standing at 25° for 15 min there precipitated 20 mg of recovered **5a**, mp 184–189°.

Mono-2,4-dinitrophenylhydrazone of Dimer 5a.—A 100-mg (0.0204 mmol) sample of dimer **5a** and 150 mg (0.076 mmol) of 2,4-dinitrophenylhydrazine were dissolved in 50 ml of hot 95%

(20) H.-E. Sprenger and W. Ziegenbein, *Angew. Chem., Int. Ed. Engl.*, **7**, 530 (1968).

(21) Melting points were determined on a Kofler block and are corrected. Ultraviolet spectra were determined on a Cary Model 11 spectrophotometer (95% ethanol solvent); infrared spectra were determined on a Perkin-Elmer Model 137 spectrophotometer unless otherwise stated; nmr spectra were determined on a Varian A-60 spectrometer (10–20% solutions) in $CDCl_3$ unless otherwise stated. Mass spectra were determined on a Hitachi Model RMU-6E. Magnesium sulfate was employed as drying agent. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee.

(22) J. Ronayne, D. H. Williams, and J. H. Bowie, *J. Amer. Chem. Soc.*, **88**, 4980 (1966).

(23) J. C. Evans, *Spectrochim. Acta*, **17**, 129 (1961).

(24) M. Harfenist, A. Bavley, and W. A. Lazier, *J. Org. Chem.*, **19**, 1608 (1954).

ethanol. Concentrated hydrochloric acid (10 drops) was added and the mixture was heated on the steam bath for 1 hr. After standing at 25° for 14 hr there was obtained 130 mg (95%) of **5a** mono-2,4-dinitrophenylhydrazone, mp 271–273°; recrystallization from ethylene dichloride gave small orange prisms, mp 279–280°.

Anal. Calcd for $C_{42}H_{32}N_4O_5$: C, 74.98; H, 4.79; N, 8.33. Found: C, 74.72; H, 4.91; N, 8.25.

Sodium Periodate–Osmium Tetroxide Oxidation of Dimer 5a.[25]—To dimer **5a** (0.40 g, 0.08 mmol) in 15 ml of acetonitrile was added 7 ml of water and, with stirring, 25 mg (1.0 mmol) of osmic acid (nitrogen atmosphere maintained). The brown solution was treated with sodium periodate (0.67 g, 3.3 mmol), added in small portions at frequent intervals with stirring during 30 min, causing the color to change to yellow. After stirring for an additional 90 min, the solution was diluted with 100 ml of water and steam-distilled; 150 ml of distillate was collected, diluted with water, and extracted several times with ether. The dried ether extracts were distilled, leaving 0.10 g of crude benzaldehyde which was isolated as its 2,4-dinitrophenylhydrazone, 0.185 (40%), mp 225–236°; recrystallization from ethyl acetate gave orange prisms, mp 240–242°; when mixed with an authentic sample (mp 242–243°) the melting point was not depressed (lit.[25] mp 241–242.5°). In the flask remaining after steam distillation was 0.17 g of amorphous material, from which no crystalline product could be isolated, mp 185–195°, having an infrared spectrum characterized by broad bands, ν (KBr) 1720 cm^{-1} (C=O).

7-Benzylidene-3,4-diphenyl-2-spiro(2-oxo-3-benzylidenecyclobutyl)bicyclo[3.2.0]heptan-*5-d*-6-one (**5b**).—2,4-Dibenzylidenecyclobutanone (0.50 g, 2.03 mmol) was dissolved in an alkaline solution, prepared by dissolving 20 mg of sodium in 30 ml of absolute ethanol-*O-d* and 2 ml of D_2O, and the solution was kept at 45° for 10 min. The clear solution was then shaken mechanically for 50 min while allowing it to cool to 25°. Deuterium oxide (10 ml) and *N*-deuteriosulfuric acid in D_2O (10 ml) were added and the mixture, now containing a yellow precipitate, was allowed to stand at 25° for 16 hr. Filtration gave 0.47 g of product, mp 130–180°; crystallization from acetonitrile gave 0.10 g (20%) of crystalline dimer **5b**, mp 180–190°; recrystallization gave 0.05 g, mp 188–190°.

7-(Benzylidene-*2,3,4,5,6-d*$_5$)-3,4-di(phenyl-*2,3,4,5,6-d*$_5$)-2-spiro[2-oxo-3-(benzylidene-*2,3,4,5,6-d*$_5$)cyclobutyl]bicyclo[3.2.0]heptan-6-one (**5c**).—A solution of 2,4-di(benzylidene-*2,2,4,5,6-d*$_5$)cyclobutanone (**2g**, 0.40 g, 1.56 mmol) in 25 ml of absolute ethanol and 2.5 ml of 1% aqueous sodium hydroxide was kept at 45° for 10 min. After shaking at 45–25° (self-cooling) for 50 min the mixture was diluted with 10 ml of 2 *N* aqueous sulfuric acid and 100 ml of water. Standing at 25° for 16 hr deposited 0.3 g of product, mp 92–100°, which was crystallized from acetonitrile to give 0.09 g (23%) of dimer **5c** as small prisms, mp 190–193°.

7-(Benzylidene-*α,2,3,4,5,6-d*$_6$)-3,4-di(phenyl-*2,3,4,5,6-d*$_5$)-2-spiro[2-oxo-3-(benzylidene-*α,2,3,4,5,6-d*$_6$)cyclobutyl]bicyclo[3.2.0]heptan-*3,4-d*$_2$-6-one (**5d**).—2,4-Di(benzylidene-*α,2,3,4,5,6-d*$_6$)cyclobutanone (**2h**, 220 mg) was dissolved in 12 ml of absolute ethanol and 1.2 ml of 1% aqueous sodium hydroxide at 45°; after keeping at 45° for 15 min and shaking for 45 min while cooling to 25°, water (25 ml) and 2 *N* sulfuric acid (5 ml) were added and the mixture was stored at 25° overnight. Filtration gave 0.20 g of product, mp 98–103°, which was recrystallized from acetonitrile to yield 31 mg (14%) of crude dimer **5d** as spear-shaped crystals, mp 168–188°. This sample was not purified further; assay 90% dimer **5d** and 10% monomer **2h** by nmr.

7-(Benzylidene-*α,2,3,4,5,6-d*$_6$)-3,4-di(phenyl-*2,3,4,5,6-d*$_5$)-2-spiro[2-oxo-3-(benzylidene-*α,2,3,4,5,6-d*$_6$]cyclobutyl)bicyclo[3.2.0]heptan-*3,4,5-d*$_3$-6-one (**5e**).—2,4-Di(benzylidene-*α,2,3,4,-5,6-d*$_6$)cyclobutanone (**2h**, 0.50 g, 1.94 mmol) was dissolved in a solution prepared by dissolving 20 mg of sodium in 30 ml of ethanol-*O-d* and 2 ml of D_2O and the solution was kept at 45° for 10 min. The clear orange solution was allowed to cool to 25° during 50 min; D_2O (10 ml) and *N*-deuteriosulfuric acid in D_2O (10 ml) were added and the mixture was allowed to stand overnight. Filtration gave 0.45 g of solid, mp 122–130°, which was crystallized from acetonitrile to yield 80 mg (16%) of dimer **5e**, mp 191–192°, as clusters of pale-yellow spear-shaped crystals.

2,4-Bis(4-methylbenzylidene)cyclobutanone (**2b**).—A solution of cyclobutanone (1.0 g, 0.0143 mol) and *p*-tolualdehyde (3.5 g, 0.029 mol) in 16 ml of 95% ethanol was added dropwise, with stirring, to 80 ml of 0.1% sodium hydroxide in 70% ethanol during 4 hr, keeping the temperature at 18–20°; stirring was continued at 20° for an additional 4 hr. The mixture was filtered and washed with 70% ethanol to yield 3.19 g of ketone **2b**, mp 191–201°; recrystallization from acetone gave long yellow needles, 1.95 g (61%), mp 205–207° (lit.[6] mp 200–202°) (43%); ν (KBr) 1720 (C=O), 1670, 1635 cm^{-1} (C=C); nmr ($CDCl_3$) δ 7.37, 7.17 (q, J = 8.0 Hz, 8, aryl), 7.12 (t, J = 2.5 Hz, 2, =CH), 3.71 (t, J = 2.5 Hz, 2, CH_2), 2.37 (s, 6, CH_3).

7-(4-Methylbenzylidene)-3,4-di(4-methylphenyl)-2-spiro[2-oxo-3-(4-methylbenzylidene)]bicyclo[3.2.0]heptan-6-one (**5f**).—3,4-Di(4-methylbenzylidene)cyclobutanone (**2b**, 0.50 g, 1.82 mmol) was dissolved in 50 ml of absolute ethanol and heated to 45°. Aqueous sodium hydroxide solution (4 ml of 1% solution) was added and the solution was kept at 50° for 30 min and at 68° for 20 min. The clear orange solution was allowed to cool to 25° during 1 hr; it was then treated with 20 ml of 2 *N* sulfuric acid and diluted with water. The following day the solid was filtered, 0.48 g, mp 98–100°. Recrystallization from acetonitrile gave 0.23 g of crude crystalline dimer **5f**, mp 204–207°; one recrystallization gave small prisms, 0.16 g (32%), mp 213–217°. Further recrystallization from acetonitrile raised the melting point to 215–218°: ν (KBr) 1740 (C=O), 1635 cm^{-1} (C=C); nmr ($CDCl_3$) δ 7.0–7.4 (m, 17, aryl and =CH), 6.67 (m, 1, =CH), 4.0–4.3 (m, 4, ring CH), 2.78 (m, 2, CH_2), 2.30 (s, 6, CH_3), 2.22 (s, 6, CH_3).

Anal. Calcd for $C_{40}H_{36}O_2$: C, 87.56; H, 6.61; mol wt 548.7. Found: C, 87.52; H, 6.62; mol wt 548 (mass spectrum).

The above procedure applied to 2,4-bis(4-methoxybenzylidene)-cyclobutanone[6] (**2c**, 0.5 g) gave recovered reactant (10%) and an amorphous product, mp 105–108°. Fractional crystallization of the product from acetonitrile ultimately gave 2 mg of amorphous product which forms tiny crystals near the melting point, 240–260° [ν (KBr) 1725 cm^{-1} (s, C=O), 1635 (s, C=C)]. With 2,4-bis(4-chlorobenzylidene)cyclobutanone (**2d**)[6] the procedure gave an amorphous product, mp 125–138° [ν (KBr) 3500 (w, OH), 1770 (m), 1740 (s, C=O), 1640 cm^{-1} (C=C)]; no crystalline material could be isolated from this product.

2,4-Bis(3,4-dimethoxybenzylidene)cyclobutanone (**2e**).—Cyclobutanone (1.0 g, 0.0143 mol) and 3,4-dimethoxybenzaldehyde (4.82 g, 0.029 mol) were condensed employing the procedure used in preparation of **2b**; crude crystalline product, 3.38 g, mp 174–178°, was obtained. Recrystallization from acetone gave 2.23 g (52%) of **2e**, mp 182–186°; two more recrystallizations gave long yellow needles, mp 191–193°; ν (KBr) 1710 (C=O), 1650, 1620 cm^{-1} (C=C); nmr ($CDCl_3$) δ 6.3–7.8 (m, 8, aryl and =CH), 3.90 (s, 12, CH_3O), 3.75 (t, J = 2.5 Hz, 2, CH_2).

Anal. Calcd for $C_{22}H_{22}O_5$: C, 72.11; H, 6.05; mol wt 366.4. Found: C, 71.91; H, 6.10; mol wt 370 (osmometry).

Dimerization of **2e** (0.50 g) employing the procedure used in the preparation of dimer **5f** gave an amorphous product, mp 109–120°, from which 5 mg (1%) of dimer **5g** was isolated by fractional crystallization from acetonitrile, small prisms, mp 232–235°; ν (KBr) 1740 (C=O), 1635 cm^{-1} (C=C).

Anal. Calcd for $C_{44}H_{44}O_{10}$: C, 72.11; H, 6.05; mol wt 732.8. Found: C, 71.98; H, 5.95; mol wt 741 (osmometry).

2,4-Bis(4-dimethylaminobenzylidene)cyclobutanone (**2f**).—A solution of cyclobutanone (1.0 g, 0.0143 mol) and 4-dimethylaminobenzaldehyde (4.32 g, 0.029 mol) in 16 ml of 95% ethanol was added dropwise, with stirring, during 2 hr to 80 ml of 0.1% sodium hydroxide in 70% ethanol, keeping the temperature below 20°; stirring was continued at 20° for 5 hr. After standing at 25° for 10 days there was obtained in several crops a total of 2.50 g of scarlet needles, mp 171–180°. The filtrate on standing at 25° for 4 weeks deposited 0.07 g of **2f**, mp 271–273°. Crystallization of the first crop from 250 ml of boiling acetone gave 0.60 g of **2f**, mp 270–275°; total yield, 0.67 g (14%). Recrystallization from dimethylformamide gave flat, dark-red prisms, mp 274–275°; ν (KBr) 1680 (C=O), 1640 cm^{-1} (C=C). The material is only very slightly soluble in most organic solvents (hot), including acetone, acetonitrile, dimethyl sulfoxide, ethylene dichloride, pyridine, chloroform and nitromethane; nmr (CF_3CO_2H) δ 7.85, 8.02 (m, 8, aryl), 7.68 (t, poorly resolved, 2, J = 2.5 Hz, =CH), 4.22 (m, 2, CH_2), 3.60 (s, 12, CH_3).

Anal. Calcd for $C_{22}H_{24}N_2O$: C, 79.48; H, 7.28; N, 8.43; mol wt 332.4. Found: C, 79.32; H, 7.27; N, 8.30; mol wt 332 (mass spectrum), 342 (vapor osmometry in dimethylformamide).

2-(4-Dimethylaminobenzylidene)cyclobutanone (**19**).—The filtrate (acetone solvent) remaining from crystallization of **2f** above was concentrated to *ca.* 60 ml and filtered hot to remove additional **2f** (0.05 g, mp 269–270°). Chilling the filtrate to 0° de-

(25) Procedure of R. Pappo D. S. Allen, Jr., R. U. Lemieux, and W. S. Johnson, *J. Amer. Chem. Soc.*, **21**, 478 (1956).

posited 1.11 g (38%) of 19 as scarlet prisms, mp 178–182°; recrystallization from acetone gave long scarlet needles, mp 181–183°; ν (Nujol) 1715 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_{15}NO$: C, 77.58; H, 7.51; N, 6.96; mol wt 201.3. Found: C, 77.86; H, 7.53; N, 6.96; mol wt 170 (vapor osmometry in dimethylformamide).

Registry No.—**2e**, 33777-57-0; **2f**, 33777-56-9; **2g**, 33872-68-3; **2h**, 33777-52-5; **5a**, 27109-24-6; **5a** mono-2,4-DNP, 31451-10-2; **5b**, 33777-54-7; **5c**, 33872-66-1; **5d**, 33777-55-8; **5e**, 33886-25-8; **5f**, 33777-30-9; **5g**, 33872-67-2; **19**, 33777-31-0.

The Synthesis of 2-Keto-4a-phenyloctahydro-Δ^8-naphthyridine and 2-Keto-8-methyl-7-oxa-Δ^5-1-azabicyclo[4.3.0]nonane[1]

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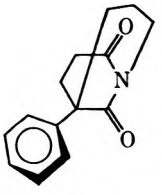
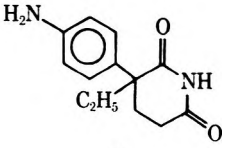
The synthesis of 2-keto-4a-phenyloctahydro-Δ^8-naphthyridine (10) and 2-keto-8-methyl-7-oxa-Δ^5-1-azabicyclo[4.3.0]nonane (16) is presented. A number of new 2,2-dialkylphenylacetonitrile and *N*-alkylglutarimide derivatives were synthesized as intermediates in the formation of 10 and 16.

The synthesis of 5-phenyl-2,9-diketo-1-azabicyclo-[3.3.1]nonane (1) was proposed as part of a continuing study of the steric aspects of the antiepileptic action of drugs having the ureide or imide function. The major anticonvulsant drugs all contain this function and it was desired to prepare a bridged analog of the toxic but efficacious drug aminoglutethimide (2).

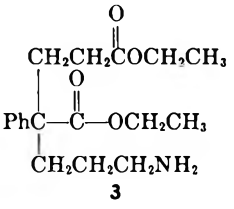


1



2

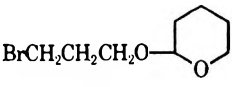
The initial approach to the desired bicyclic glutarimide ring system involved the attempted synthesis of compound 3. It was predicted that a base-catalyzed



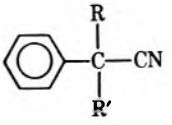
3

intramolecular attack by the amino group on the ester functions would produce 1.

Phenylacetonitrile was allowed to react with 2-(3-bromopropoxy)tetrahydropyran (4) to yield 2-[3-(2-tetrahydropyranyloxy)propyl]phenylacetonitrile (5). The latter compound (5) was converted to 2-cyanoethyl-2-[3-(2-tetrahydropyranyloxy)propyl]phenylacetonitrile (6) *via* cyanoethylation. The protecting group (pyranyl ether) was removed under acidic conditions to give 2-cyanoethyl-2-(3-hydroxypropyl)phenylacetonitrile (7). The alcohol 7 was converted to the *p*-toluenesulfonate 8 and the tosylate function was displaced by ammonia to yield 2-(3-aminopropyl)-2-cyanoethylphenylacetonitrile (9). Treatment of 9 with ethanolic hydrogen chloride did not convert the



4



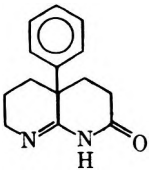
5, R = H; R′ = $CH_2CH_2CH_2O$–

6, R = CH_2CH_2CN; R′ = $CH_2CH_2CH_2O$–

7, R = CH_2CH_2CN; R′ = $CH_2CH_2CH_2OH$

8, R = CH_2CH_2CN; R′ = $CH_2CH_2CH_2OTs$

9, R = CH_2CH_2CN; R′ = $CH_2CH_2CH_2NH_2$



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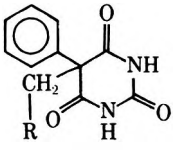
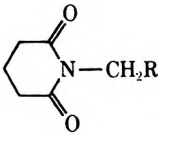


11, R = CH = CH_2

12, R = CH_2CH_2Br



13, R = CH = CH_2

14, R = CH_2CH_2Br

15, R = $CHBrCH_3$

dinitrile to the diester 3 as expected but to a product which was assigned the structure 10 on the basis of spectral and elemental analysis. The treatment of 9 with base afforded the same product. When the reaction was performed in the presence of aqueous hydrogen chloride no identifiable products were obtained.

The failure of 9 to yield 3 can be rationalized by the apparent facility of the intramolecular attack by the primary amine function to yield 10 as compared to the less facile intermolecular attack by ethanol.

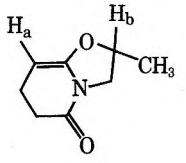
A previous publication[2] reported the light-catalyzed addition of hydrogen bromide to 5-phenyl-5-allylbarbituric acid (11) to produce the primary bromo compound 12. In a similar manner, the treatment of *N*-allylglutarimide (13) was found to yield *N*-(3-bromo-

(1) Taken in part from the dissertation presented by J. W. Ayres, Aug 1970, to the Graduate School of the University of Kansas in partial fulfillment of the requirements for the Doctor of Philosophy Degree.

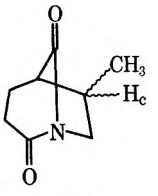
(2) E. E. Smissman, R. A. Robinson, and A. J. B. Matuszak, *J. Org. Chem.*, **35**, 3823 (1970).

propyl)glutarimide (**14**). If a small amount of acetic acid was included in this reaction, the product was found to be *N*-(2-bromopropyl)glutarimide (**15**).

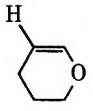
In an effort to secure a general synthetic route to the carbon-bridged bicyclic glutarimides at attempt was made to cyclize **15** to the desired compound. However, compound **15** was converted to 2-keto-8-methyl-7-oxa-Δ^5-1-azabicyclo[4.3.0]nonane (**16**) by treatment with



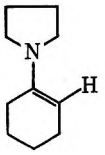
16



17



18



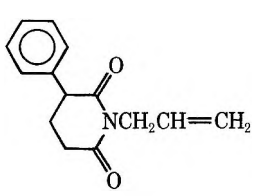
19

sodium hydride in dioxane. The ir spectrum (neat) showed a broad absorption from 1630 to 1750 cm^{-1} and in carbon tetrachloride a sharper peak at 1685 cm^{-1} with slight shoulders at 1665 and 1700 cm^{-1}. The nmr spectrum showed a three-proton doublet at δ 1.35 (methyl), a four-proton multiplet at δ 2.35, and one proton each at δ 3.3, 3.9, 4.15, and 4.5. Decoupling studies indicated that the proton at δ 4.5 was coupled with the methyl protons. Structure **17** was eliminated as a possibility on the basis of these spectral data and the chemical reactivity of the compound. The proton H_c (**17**) would not be predicted to appear as far downfield as δ 4.5 but this is a reasonable absorption for H_b (**16**). H_a (**16**) appears as a triplet at δ 4.15 and a similar proton in dihydropyran (**18**) at δ 4.65,[3] while the analogous proton in compound **19** absorbs at δ 4.21.[4]

Compound **16** was unstable in air and it is likely that it was undergoing hydrolysis to produce a secondary alcohol.

Compound **14** was recovered unchanged after treatment with sodium hydride in dioxane. When dimethylformamide was utilized as the solvent, a crude oil was obtained but it could not be purified.

α-Phenylglutaric anhydride was converted to *N*-allyl-α-phenylglutarimide (**20**). Irradiation of **20** in



20

the presence of hydrogen bromide afforded an oil whose nmr spectrum was consistent with the desired compound, but it could not be purified.

(3) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "High Resolution NMR Spectra Catalog," Analytical Instrument Division of Varian, 1962, National Press, Spectrum No. 111.

(4) H. O. House and M. Schellenbaum, *J. Org. Chem.*, **28**, 34 (1963).

Experimental Section[5]

2-(3-Bromopropoxy)tetrahydropyran (**4**).—The method utilized was essentially that of Robinson.[6] 2-Bromo-1-propanol (100.0 g, 0.720 mol) and 2,3-dihydropyran (67.5 g, 0.804 mol) yielded 124.6 g (80%) of a clear liquid, bp 86° (0.5 mm).

2[3-(2-Tetrahydropyranyloxy)propyl]phenylacetonitrile (**5**).—Sodium hydride (12.0 g, 0.268 mol), 53.5% in mineral oil, was stirred for 20 min in 100 ml of dry C_6H_6 in a N_2 atmosphere to wash away the mineral oil, and to this suspension was added 100 ml of dry DMF. A solution of phenylacetonitrile (30.0 g, 0.256 mol) in 30 ml of DMF was added dropwise. After H_2 evolution ceased the mixture was transferred to a dropping funnel and added dropwise to a stirring, heated (80°) solution of 2-(3-bromopropoxy)tetrahydropyran (**4**) (54.0 g, 0.242 mol) in 50 ml of DMF. The mixture was stirred and maintained at 80° for 2 hr, poured into 400 g of crushed ice, and extracted with Et_2O. The organic layer was dried ($MgSO_4$) and distilled to yield **5** (16.6 g, 25.6%), bp 142–148° (0.3 mm). The spectral data are consistent with the assigned structure.

2-Cyanoethyl-2-(3-hydroxypropyl)phenylacetonitrile (**7**).—A solution of 2[3-(2-tetrahydropyranyloxy)propyl]phenylacetonitrile (**5**) (3.9 g, 0.02 mol) in 6 ml of *tert*-BuOH was added dropwise to a stirred solution of acrylonitrile (1.6 g, 0.03 mol) in 4 ml of *tert*-BuOH. After the first 10 drops were added, 5 drops of 30% KOH–MeOH were added. After addition was complete the reaction mixture was heated at 60° for 1 hr, poured into 25 ml of H_2O, and extracted with Et_2O. The organic layer was dried (K_2CO_3) and the Et_2O was removed *in vacuo* to yield 2-cyanoethyl-2-[3-(2-tetrahydropyranyloxy)propyl]phenylacetonitrile (**6**). Compound **6** was refluxed in 20 ml of Me_2CO and 10 ml of 10% HCl overnight and the solution was extracted with Et_2O. The organic layer was dried ($MgSO_4$) and distilled to yield **7** (1.0 g, 29.4%), bp 190° (0.25 mm).

Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06; N, 12.27. Found: C, 73.75; H, 7.33; N, 12.16.

2-Cyanoethyl-2-(3-hydroxypropyl)phenylacetonitrile *p*-Toluenesulfonate (**8**).—*p*-Toluenesulfonyl chloride (9.5 g, 0.05 mol) was added to a stirred solution of 2-cyanoethyl-2-(3-hydroxypropyl)-phenylacetonitrile (**7**) (5.0 g, 0.02 mol) and 1,4-diazabicyclo-[3.3.3]octane (11 g, 0.10 mol) in 130 ml of C_6H_6 which was cooled in an ice bath. The mixture was placed in the refrigerator overnight, allowed to melt, and washed with 10% HCl. The organic layer was dried ($MgSO_4$) and evaporated *in vacuo* to yield **8** as a crude oil (6.6 g, 78%). The spectral data are consistent with the assigned structure.

2-(3-Aminopropyl)-2-cyanoethylphenylacetonitrile (**9**).—Liquid NH_3 (90 g, 5.3 mol) was added to 2-cyanoethyl-2-(3-hydroxypropyl)phenylacetonitrile *p*-toluenesulfonate (**8**) (14 g, 0.04 mol) in a stainless steel reaction vessel with a glass liner and allowed to react at 25° overnight. The vessel was cooled to −50° and opened, and the NH_3 allowed to evaporate. The residue was washed with $CHCl_3$, the solid was filtered, and the filtrate was evaporated *in vacuo* to yield **9** as a crude oil (6.3 g, 72.5%).

2-Keto-4a-phenyloctahydro-Δ^8-naphthyridine (**10**).—Hydrogen chloride was bubbled through a stirred solution of 2-(3-aminopropyl)-2-cyanoethylphenylacetonitrile (**9**) (5.0 g, 0.02 mol) in 90 ml of absolute EtOH for 1 hr. The solution was stirred overnight, added to 90 ml of H_2O, made basic (10% NaOH), and extracted with $CHCl_3$. The organic layer was dried ($MgSO_4$) and removed *in vacuo* to yield an oil. Addition of a small volume of acetone yielded a solid **10**, which was collected on a filter and purified by sublimation at 130° (0.2 mm) (400 mg, 8.8%): mp 236° dec; ir ($CHCl_3$) 3380 (NH), 1670 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.9 (m, 8 H, CH_2), 3.8 (m, 2 H, CH_2N), 7.3 (s, 5 H, aromatic).

Anal. Calcd for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06; N, 12.27. Found: C, 73.19; H, 7.08; N, 12.13.

***N*-Allylglutarimide** (**13**).—Allylamine (7.53 g, 0.132 mol) was added dropwise to a stirred solution of glutaric anhydride (15.0 g, 0.132 mol) in 25 ml of C_5H_5N. After the reaction cooled, 125 ml of Ac_2O was added and the reaction was maintained at reflux for 2 hr. The excess solvent was removed by distillation and the

(5) Melting points were obtained on a calibrated Thomas-Hoover Unimelt and are corrected. Ir data were recorded on a Beckman IR10 spectrophotometer and nmr data on Varian Associates A-60, A-60A, and HA-100 spectrometers (TMS). Microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind., and on an F and M 185 C, H, N Analyzer, University of Kansas.

(6) R. A. Robinson, Ph.D. Thesis, University of Kansas, 1969.

residue was distilled *in vacuo* to yield **13** (14.1 g, 71%), bp 76° (0.2 mm).

Anal. Calcd for $C_8H_{11}NO_2$: C, 62.72; H, 7.23; N, 9.14. Found: C, 62.98; H, 7.54; N, 8.97.

N-(**3-Bromopropyl**)**glutarimide** (**14**).—A solution of *N*-allylglutarimide (**13**) (50.0 g, 0.326 mol) stirred in 1600 ml of toluene was irradiated (G. E. Sunlamp-275W-100-125V) overnight. During the irradiation HBr was bubbled through the solution. The reaction was cooled, the toluene was removed *in vacuo*, and the residue was distilled to yield **14** (33.8 g, 44.5%), bp 132° (0.2 mm).

N-(**2-Bromopropyl**)**glutarimide** (**15**).—A stirred solution of *N*-allylglutarimide (**13**) (230 g, 1.50 mol) which still contained some HOAc in 4000 ml of toluene was irradiated (G. E. Sunlamp-275W-110-125V) overnight. During the irradiation HBr was bubbled through the solution. The toluene was removed *in vacuo* and the solid residue was dissolved in boiling EtOH and immediately cooled in an ice bath. Compound **15** (28.4 g, 8.5%), mp 58–60° (petroleum ether, bp 60–70°), was collected by filtration.

Anal. Calcd for $C_8H_{12}BrNO_2$: C, 41.09; H, 5.16. Found: C, 40.73; H, 5.36.

The EtOH was removed from the filtrate to yield an oil (70.0 g) which was identified as the ethyl ester of the ring-opened imide from its nmr spectrum.

2-Keto-8-methyl-7-oxa-Δ^5-1-azabicyclo[4.3.0]nonane (**16**).—A solution of *N*-(2-bromopropyl)glutarimide (**15**) (15.0 g, 0.06 mol) in 15 ml of ethylene glycol dimethyl ether was added to a stirred suspension of NaH (2.64 g of 57% in mineral oil, 0.063 mol) and refluxed for 3 days. The solid was removed by filtration and the filtrate was concentrated *in vacuo* to leave an oil which was distilled to yield **16** (7.10 g, 73.5%): bp 57° (0.2 mm); ir ($CHCl_3$) 1660 (C=O), 1710 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.40 (d, 3 H, CH_3), 2.35 (m, 4 H, CH_2CH_2), 3.3 (d, 1 H, HCH–), 3.9 (d, 1 H, HCH), 4.15 (m, 1 H, C=CH), 4.5 (m, 1 H, OCH).

Anal. Calcd for $C_8H_{11}NO_2$: C, 62.72; H, 7.23; N, 9.14. Found: C, 62.42; H, 7.28; N, 8.75.

N-**Allyl-α-phenylglutarimide** (**20**).—Allylamine (6.0 g, 0.10 mol) was added dropwise to a stirred solution of α-phenylglutaric anhydride (20 g, 0.10 mol) in 40 ml of C_5H_5N. The exothermic reaction was allowed to cool to 25° and then 200 ml of Ac_2O was added and the solution was refluxed for 3 hr. The solution was concentrated by distillation and the residue was distilled *in vacuo* to yield **20** (19.7 g, 82%), bp 148–152° (0.2 mm).

Anal. Calcd for $C_{14}H_{15}NO_2$: C, 73.34; H, 6.59. Found: C, 73.06; H, 6.56.

Registry No.—**4**, 33821-94-2; **5**, 33821-95-3; **7**, 33821-96-4; **10**, 33821-97-5; **13**, 3880-20-4; **14**, 33821-99-7; **15**, 33822-00-3; **16**, 33822-01-4; **20**, 33822-02-5.

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Characteristics of Various Reactions of Bromine with Arylcyclopropanes[1]

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The reaction of bromine with *cis*- and *trans*-diphenylcyclopropane gives 1,3-addition products only while phenylcyclopropane gives 1,3-addition products and/or aromatic substitution. The rate of reaction and product composition for all arylcyclopropanes is highly sensitive to light, temperature, and change in solvent but insensitive to the presence of nitrobenzene and trinitrobenzene.

There is ample evidence for the ionic addition of halogen to an array of cyclopropanes taking place under diverse conditions. Cyclopropanes undergo C–C fission with halogen in the presence of Lewis acids to give mixtures of rearranged and unrearranged dihalides.[2] More highly strained cyclopropanes, such as those incorporated into polycyclic systems,[3] and cyclopropanols[4] undergo ionic C–C fission without catalysts.

Contrasting with the generality of ionic additions, free-radical addition to cyclopropanes is less frequent and when it does occur is often competing with free-radical substitution. The free-radical addition of chlorine to bicyclo[2.1.0]pentane has been reported[5] as has the peroxide-catalyzed addition of bromine to 1-alkyl-2-phenylcyclopropanes.[6] Spiropentane gives a mixture of nearly equal amounts of ring-opened and ring-substituted products on photochemical chlorination.[7] Thermal, photochemical, or peroxide-catalyzed chlorination of cyclopropane gives minor amounts of addition product,[8] and arylcyclopropanes are inert to *N*-bromosuccinimide addition of bromine in the presence of free-radical initiators.[9] Consistent with the last mentioned lack of reactivity are the reports that some cyclopropanes also are inert, or are nearly so, to free-radical chain polymerization[10] and halomethane and mercaptan additions.[11]

Our interest in the various modes by which halogens add to cyclopropanes and the conditions which promote one mode of addition as opposed to the other arose during an initial stage of study of bromine addition to *cis*- and *trans*-1,2-diphenylcyclopropane. We observed that the reaction of bromine with these two cyclopropanes in carbon tetrachloride solution was strongly influenced by light and consequently we suspected at first the involvement of a free-radical

(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation for their support of this work.

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(8) (a) J. D. Roberts and P. H. Dirstine, *ibid.*, **67**, 1281 (1945); (b) P. G. Stevens, *ibid.*, **68**, 620 (1946).

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TABLE I

BROMINATION OF *cis*- AND *trans*-1,2-DIPHENYLCYCLOPROPANE

Expt	Diphenylcyclopropane	Conditions[a]	Time, hr	Product compn, % Cycloprop[b]	Product compn, % 1,3-DiBr-1,3-diphenyl[c]
1	Trans	Dark, O_2[d]	44	67	33, *dl*/*meso* = 52/48 ± 2
2	Trans	Light[e]	44[f]		100, *dl*/*meso* = 48/52 ± 2
3	Cis	Dark, O_2[d]	18	63	37, *dl*/*meso* = 17/83 ± 3
4	Cis	Light[e]	18[f]		100, *dl*/*meso* = 43/57 ± 2

[a] All solutions were in CCl_4 and were 0.25 *M* in diphenylcyclopropane and 0.25 *M* in bromine. Reactions were carried out in Pyrex at −20°. [b] Unconverted 1,2-diphenylcyclopropane. [c] Deviations are the maximum based on three nmr integrations of the product mixture from each experiment. [d] Reactions carried out under a slight positive pressure of oxygen. [e] Room light. [f] Minimum time for complete visual disappearance of the bromine color.

TABLE II

BROMINATIONS OF PHENYLCYCLOPROPANE IN THE DARK AND LIGHT

Expt	Conditions[a,b]	Solvent	*T*, °C	Time,[c] hr	Product compn, % Cycloprop	1,3-DiBr	*p*-Br
1–6	Dark	CCl_4	−20	52	18 ± 2		82 ± 2
7–9	Dark	CCl_4	25	7		100	
10	Dark	$CHCl_3$[e]	−20	53	13	30	30[g]
11	Dark, O_2[d]	$CHCl_3$[e]	−20	53		18	82
12	Dark	EtAc	25	2	11	50	39
13	Dark	*n*-Hex	−20	53	10		90
14–15	Light[f]	CCl_4	−20	1.5–2.5		100	
16–19	Light[g]	CCl_4	−20	3.5		100	
20–22	Light, O_2[d,f]	CCl_4	−20	2.5–4.5	20 ± 6	30 ± 6	50 ± 6
23–26	Light	CCl_4	25	~5 min		100	
27	Light	CCl_4, MeOH[h]	25	1	20	80	Trace
28	Light	$CHCl_3$[e]	−20	~15		100	
29	Light	EtAc	25	2	16	60	24
30	Light	*n*-Hex	−20	5 min		100	

[a] All solutions were 0.25 *M* in cyclopropane and 0.25 *M* in bromine. Reactions were carried out in Pyrex unless indicated otherwise. [b] Room light unless indicated otherwise. [c] Except in those cases where unconverted phenylcyclopropane is listed as a component of the product mixture, the reaction time is the minimum time for complete visual disappearance of the bromine color. [d] Reactions carried out under a positive pressure of oxygen. [e] Alcohol-free chloroform. [f] Experiments were carried out on different days. [g] Irradiated with a 40-W incandescent bulb. [h] MeOH–phenylcyclopropane, 1:1 molar. [i] 23% unidentified product.

process. The initial observation of light dependency led us to turn our attention to the simpler phenylcyclopropane and explore the effect of light, temperature, solvent, and the presence of inhibitors on its reactivity. The results of these studies are presented in this paper.

Results

The first bromination of *cis*-1,2-diphenylcyclopropane was carried out in room light at 25° in carbon tetrachloride solution in a Pyrex container. A 2:1 molar ratio of bromine to diphenylcyclopropane was used. The reaction was exothermic. The product consisted of 8.5% *meso*- and 6.5% *dl*-1,2,3-tribromo-1,3-diphenylpropane and 85% 1,3-dibromo-1,3-diphenylpropane made up of a 1:1 ratio of *dl* and *meso* isomers. Evidence for the structure assignment of products and product composition is given in other sections of this paper. The second experiment involved *cis*-diphenylcyclopropane treated with bromine (1:1 molar ratio) in the dark at −20° for 14 hr. Some bromine color persisted. The product, obtained in 95% yield, consisted of a 15:85 mixture of *dl*- and *meso*-1,3-dibromo-1,3-diphenylpropane. The chief differences induced by lowering the temperature, reducing the concentration of bromine, and excluding light were the steric outcome and the diminished rate of bromination. On the basis of these first two experiments, we suspected that the bromine addition in the light was a free-radical chain process. Consequently in the series of reactions carried out thereafter, dark brominations of diphenylcyclopropanes were also run under a slight positive pressure of oxygen in order to help suppress any radical chain process. Results of treating *cis*- and *trans*-diphenylcyclopropanes with bromine in the light and dark at −20° in carbon tetrachloride solution are given in Table I. The results can be summarized as follows. *cis*-Diphenylcyclopropane reacts with bromine more rapidly than the trans isomer in both the light and the dark. Light has an accelerating effect on both cis and trans isomer reactivity. Only the cis isomer reacting with bromine in the dark shows any significant stereoselectivity and this is predominantly cis addition. In ancillary experiments carried out to check for kinetic or thermodynamic control of the dibromide product mixtures, we observed no change in the *dl*:*meso* ratios on treating mixtures of two different compositions (*dl*:*meso* 2.3 and 1.2) with bromine in carbon tetrachloride at −20 or 25° for 60 hr.

The influence of reaction conditions was studied more extensively in the case of phenylcyclopropane. Results are given in Table II.

Light and Temperature Effect.—A comparison of results for dark (Table II, expt 1–6) and light brominations (expt 14–15) carried out at −20° in carbon tetrachloride reveals two significant differences. The light reaction is more than 20 times faster than the dark reaction. Also, the light reaction gives only 1,3-addition product whereas the dark reaction affords only aromatic substitution, presumably electrophilic aromatic substitution. This latter result is consistent with

work of Levina[9a,12] who observed aromatic substitution of phenylcyclopropane taking place at −75°. Unfortunately, Levina did not report whether the reaction was carried out in the light or dark. Our experiments (16–19) show that artificial light also accelerates the reaction with bromine. At 25° the light reaction (expt 23–26) is again faster, by about 85 times, than the dark reaction. Changing the reaction vessel from Pyrex to quartz has no apparent effect on the light reaction in carbon tetrachloride at −20°. However, a light reaction carried out in chloroform at −20° is four times faster in quartz than in Pyrex, all other conditions being precisely the same. Light has very little effect on the reaction carried out in ethyl acetate (expt 12 and 29).

A comparison of results for the reaction carried out at −20° (Table II, expt 1–6) with those carried out at 25° (expt 7–9) shows that a 45° rise in temperature increases the rate and changes the mode of bromine reaction with phenylcyclopropane. Therefore light is a sufficient but not a necessary ingredient for 1,3-bromine addition. In contrast, the diphenylcyclopropanes give only addition products, the diasteromeric ratios of which are the same when formed from the *trans* isomer but differ when formed from the cis isomer in dark and light reactions.

Solvent Effect.—As can be seen from the data of Table II, solvent change has a pronounced effect on the rate and a smaller effect on the product composition of the light reaction. A reaction carried out in *n*-hexane (expt 30) is the most rapid. Use of chloroform as solvent (expt 28) diminishes the rate as does ethyl acetate (expt 29). Moreover, the light reaction in ethyl acetate also affords *p*-bromophenylcyclopropane. In contrast, the consumption of bromine in the dark reaction in ethyl acetate (expt 12) is faster than in carbon tetrachloride (expt 7–9). Similarly, the consumption of bromine in alcohol-free, degassed chloroform is 23 times faster in the dark at 25° than in carbon tetrachloride under the same conditions. These last-mentioned results were obtained by conducting dark reactions in cuvettes and following the decrease of the 415-nm bromine absorption maximum.

The addition of a small amount of methanol (2.2 mmol in 8 ml) to carbon tetrachloride has a large retarding effect on the light reaction (expt 27). The presence of ethanol in chloroform also strongly retards the light bromination and for this reason when chloroform is used as the solvent, the ethanol is first removed.

The presence of oxygen (expt 20–22) diminishes slightly the rate of bromine consumption in carbon tetrachloride in the light but more noticeable is the significant electrophilic aromatic bromination which results. Thus, in the aspect of product composition, the presence of oxygen tends to convert a light bromination at −20° to a dark bromination. The use of ethyl acetate as solvent (expt 29) tends toward the same result which is also suggested in the trace amount of *p*-bromophenylcyclopropane produced when methanol is added to carbon tetrachloride (expt 27).

Inhibitors and Attempted Radical Additions.—When a light bromination in carbon tetrachloride solution was carried out at 25 or −20° in the presence of nitrobenzene, the rate of bromine consumption was only two to three times slower than when no inhibitor was used. A light bromination carried out at 25° in carbon tetrachloride saturated with trinitrobenzene was not visibly retarded. At the same time, such a trinitrobenzene solution retarded the free-radical bromination of hexane by at least a factor of 6.

The absence of the usual inhibitory effect of the nitrobenzenes led us to search for other possible free-radical chain additions of phenylcyclopropane in order to ascertain whether or not phenylcyclopropane would show any reactivity whatsoever in the free-radical mode. Under conditions which promote free-radical chain addition of thiolacetic acid to 1-methylcyclohexene and 2-methylstyrene, phenylcyclopropane was unreactive. Bromotrichloromethane reacted when irradiated 48 hr in the presence of benzoyl peroxide but the product was 1,3-dibromo-1-phenylpropane, the product resulting from the addition of bromine afforded by the disproportionation of bromotrichloromethane. None of the product resulting from the simple addition of bromotrichloromethane could be detected. Levina[9b] reported that both 1,2-diphenylcyclopropane and phenylcyclopropane were stable to free-radical bromination. The conditions included NBS in carbon tetrachloride at 80° with ultraviolet irradiation and addition of benzoyl peroxide or azobisisobutyronitrile. We repeated Levina's experiments and obtained the same result.

Bromine–Phenylcyclopropane Complexes.—The changes produced by the presence of alcohols prompted us to seek evidence for their mode of interaction. We report in this section the results of some exploratory experiments.

Bromine and phenylcyclopropane are found to give rise to new absorption bands at 296 nm in carbon tetrachloride and 299 nm in *n*-hexane. These bands disappear in time as the bromine color is discharged. By comparison, the well-known bromine–benzene charge-transfer complex[13] shows a band at 292 nm in benzene solution. In carbon tetrachloride solution, we find the bromine–benzene band at 287 nm. The corresponding absorption maximum for bromine–phenylcyclopropane in chloroform could not be observed with certainty because of the fast dark reaction in this solvent. Reasonably the presence of the new bands which occur in *n*-hexane and carbon tetrachloride solution can be attributed to charge-transfer complexes similar to those which are well known for simple aromatic hydrocarbons and halogens.

When methanol is added to bromine in carbon tetrachloride, the 296-nm band disappears and only strong end absorption, reasonably from the methanol–bromine complex, is observed. This observation can be attributed to an expected greater stability and lower λ_{max} of the bromine–methanol complex compared to the bromine–phenylcyclopropane complex. Supporting this explanation is the known greater stability and lower λ_{max} of iodine–alcohol complexes relative to iodine–aromatic hydrocarbon complexes.[14] Also supporting the explanation is the observation that the

(12) R. Ya. Levina, P. A. Gembitskii, and E. G. Treschchova, *Zh. Obshch. Khim.*, **33**, 371 (1963).

(13) R. M. Keefer and L. J. Andrews, *J. Amer. Chem. Soc.*, **72**, 4677 (1950).

(14) (a) R. S. Mulliken, *ibid.*, **72**, 600 (1950); (b) R. S. Mulliken and W. S. Person, "Molecular Complexes," Wiley, New York, N. Y., 1969, p 154.

bromine–phenylcyclopropane complex in hexane is observed at 299 nm while the bromine–methanol complex in the same solvent occurs at 269 nm. The exact position of the bromine–methanol complex in carbon tetrachloride could not be measured because of the interference of the solvent.

Structure Determination.—The relative position of bromine atoms in the dibromide product was shown by conversion of a *dl,meso* dibromide mixture (1:1) with zinc dust in methanol to a hydrocarbon mixture consisting of 33% *cis*-, 64% *trans*-1,2-diphenylcyclopropane, and 3% 1,3-diphenylpropane. Also the diastereomeric dibromides were hydrolyzed with aqueous silver nitrate to a mixture of *dl*- and *meso*-1,3-diphenyl-1,3-propanediol which was separated into the pure diastereomeric diols through borate ester formation.[15]

The nmr of the 1,3-dibromide (*dl*:*meso* = 1) included two low field triplets and a high field triplet imposed on a more complex multiplet. Full spectral data is given in the Experimental Section. The combination of the high field triplet with one of the two low field triplets was recognized as an A_2X_2 resonance pattern stemming from the four methylene and methine protons of *dl*-1,3-dibromo-1,3-diphenylpropane. The high field complex multiplet in conjunction with the remaining low field triplet constituted the ABX_2 pattern which originated from four methylene and methine protons of *meso*-1,3-dibromo-1,3-diphenylpropane. The distinction as to which of the two low field triplets represented X_2 of A_2X_2 and which represented X_2 of ABX_2 was made by examining the nmr of a second sample of the 1,3-dibromide. This sample was prepared by aluminum isopropoxide reduction of benzalacetophenone followed by treating the resulting 1,3-diphenyl-2-propen-1-ol with hydrogen bromide, first at 0° to obtain the allylic bromide, and than at 60° to obtain the dibromide. In the nmr of this dibromide sample, the highest field triplet matched the intensity of the lowest field triplet. Therefore lowest and highest field triplets were assigned to the *dl* diastereomer. The lowest and intermediate field triplets were observed in a ratio of 2.3:1 meaning that the ratio of *dl*:*meso* diastereomers was also 2.3. The ratio of the two low field triplet intensities was used routinely to ascertain the *dl* to *meso* ratio.

The two minor solid tribromides (8.5 and 6.5%) isolated when the light bromination of *cis*-1,2-diphenylcyclopropane was carried out at a high bromine concentration were studied by nmr also. The 6.5% diastereomer was assigned the *dl* configuration on the basis of nmr properties consistent with an AMX proton system representing the diastereomeric protons at C_1 (A or M) and C_3 (M or A) and the remaining proton at C_2 (X). Close inspection of the eight-line multiplet displayed by the 8.5% diastereomer revealed a striking similarity to known A_2B[16] proton systems. The 8.5% diastereomer was believed to possess one of two possible *meso* configurations since protons at C_1 and C_3 (A_2) have an enantiomeric relationship.

The two tribromides were prepared by adding bromine to 3-bromo-1,3-diphenyl-2-propene, an intermediate utilized in the synthesis of *dl*- and *meso*-1,3-dibromo-1,3-diphenylpropanes. The pure tribromides were identical in every respect with those obtained in the bromination of *cis*-1,2-diphenylcyclopropane. Reasonably the two tribromides obtained in the exothermic addition of bromine to *cis*-1,2-diphenylcyclopropanes were formed by hydrogen bromide elimination from 1,3-dibromo-1,3-diphenylpropane and then bromine addition to the resulting olefin.

Discussion

The results disclosed in the previous section reveal that the reactivity of bromine with the arylcyclopropanes studied is complex, responding in rate and product composition to changes, some quite small, in light, temperature, and solvent. In the following discussion we give our preferred explanations, when there is some basis for doing so, and point out the unsolved problems raised by our work.

The formation of *p*-bromophenylcyclopropane in the dark in carbon tetrachloride would appear to be an electrophilic substitution reaction. In the more polar chloroform at −20°, 1,3-addition begins to appear. Reasonably this dark addition could be the usual electrophilic addition type since it becomes more competitive as the polarity of the solvent increases.

Should 1,3-electrophilic addition be accepted as one pathway then there must be a second route to 1,3-addition products since the light effect is clearly evident and simple electrophilic addition reactions are not known to be promoted by light. Yet the observed insensitivity toward inhibitors and the large response to change in solvent are characteristics inconsistent with a radical chain mechanism for the light promoted 1,3-addition. Also, the observed lack of reactivity of phenylcyclopropane with reagents which readily react with olefins in the radical chain mode tends to support the evidence obtained from solvent change and inhibition experiments. Whatever the path for the fast light-promoted addition also might be the path for the dark addition which occurs at 25° in carbon tetrachloride. Alternatively this 25° dark reaction might be a temperature-enhanced 1,3-electrophilic addition. At present we prefer the two path explanation for formation of 1,3-addition products. One of these pathways is a slow 1,3-electrophilic addition occurring in the dark at −20° and the other a light-induced process of unspecified nature which is favored in nonpolar solvents.

The above explanation also is consistent with the diphenylcyclopropane results. That the cis isomer reacts more rapidly in both dark and light reactions than the trans isomer may be attributed to the extra ground state destabilization of the cis as opposed to the trans isomer. Based on heat of combustion data, the cis isomer is destabilized by 13 kcal/mol relative to the trans isomer.[17] Release of strain also may explain why addition of bromine to both isomers predominates completely over aromatic ring substitution. Only in the dark reaction of the more highly strained cis isomer is the addition stereoselective. This reactivity characteristic observed only for the dark re-

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(16) J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, N. Y., 1959, p 128.

(17) M. P. Kozina, M. Yu Lukina, N. D. Zubareva, I. L. Safonova, S. M. Skuratov, and B. A. Kazanskii, *Dokl. Akad. Nauk SSSR*, **138**, 843 (1961); *Chem. Abstr.*, **55**, 20596 (1961).

action, along with light catalysis of the bromine addition to both isomers, again would implicate more than one route to 1,3-addition products but the reason for stereoselectivity in the case of the cis isomer and not the trans is not clear.

Another point worthy of attention is the circumstantial evidence which associates bromine–arylcyclopropane complex formation with the rate of the 1,3-light addition. This association follows from the observation that methanol addition simultaneously reduces both the rate of addition and the concentration of the bromine–phenylcyclopropane complex in carbon tetrachloride solution. One can only speculate at present on the particular role of this complex in the light reaction and its importance in general to bromine–arylcyclopropane reactivity.

The studies reported here help establish the reaction condition limits for a given type of bromine arylcyclopropane reaction. Consequently, the results are proving to be a useful guide in isolating various reaction types for further detailed study.

Experimental Section

Spectra were obtained as follows: nmr in CCl_4 solution (unless otherwise indicated) 1% TMS (τ 10.00), Varian A-60A, symbols s, d, t, q, and m refer to singlet, doublet, triplet, quartet, and multiplet, respectively; ir in CCl_4 solution (unless otherwise indicated) Perkin-Elmer 137, 0.05-mm sample and reference cells, symbols s, m, b, w, sh, and br refer to strong, medium, weak, sharp, and broad, respectively; mass spectrum at 70 eV and 160–165° with an all glass heated inlet, Hitachi Perkin-Elmer RMU 6E; uv in solution as indicated, Cary 15.

Melting points were determined on a Köfler micro hot stage and are uncorrected. Glc was performed on a Varian-Aerograph Model 200 using conditions as indicated. The elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Evaporation of solvent or concentration of solution was done at the rotary evaporator at reduced pressure.

Arylcyclopropanes.—1,2-Diphenylcyclopropane was prepared from benzylideneacetophenone in 84% yield by a reported method.[18] Isomers were separated on a spinning band distillation column to obtain cis [bp 116° (0.2 mm)] and trans [125° (0.2 mm)]. Phenylcyclopropane was prepared by a known method.[19]

Uv of Bromine–Arene Complexes.—The spectra of the bromine–phenylcyclopropane complex in CCl_4 and $CHCl_3$ solution was determined in 1-cm cells by a method similar to that employed by Benesi and Hildebrand.[20] A 4-ml, 9.0×10^{-4} M solution of bromine was added in the dark to a solution of 0.05 ml of phenylcyclopropane in 5 ml of the appropriate solvent. Solvent was added to bring the volume to 10 ml and the spectrum of this solution immediately was determined between 280 and 350 nm. The reference beam was balanced with the same phenylcyclopropane solvent pair. The procedure for determining the bromine–benzene complex was the same except benzene replaced phenylcyclopropane.

The effect of added methanol on the bromine–benzene complex was determined in the following manner. The spectrum of a 4.5×10^{-5} M solution of bromine in benzene was determined with benzene as the reference. The λ_{max} at 292 nm diminished 2% in 10 min. Addition of 0.1 ml of methanol to both reference and sample cells resulted in a reduction in the optical density (A) from 1.66 to 1.32 and a shift in λ_{max} from 292 to 283 nm. Only 5 min elapsed between determining the first and the second spectrum.

Bromination Procedures.—In performing brominations in the dark at 25°, substrate and bromine solutions were placed in separated blackened flasks. These were attached to a blackened U tube. This apparatus was inverted to start the reaction. In performing brominations at −20° the apparatus was placed in the constant temperature bath before and after inversion. The reaction was stopped by the addition of aqueous $Na_2S_2O_3$. The CCl_4 layer was separated, washed with water, and dried ($CaCl_2$). Evaporation of the solvent gave a residue which was analyzed for percentage composition as follows. The relative amounts of unconverted phenylcyclopropane and bromine containing products were determined through comparison of integration values for cyclopropyl protons in the region τ 7.8–9.7 and noncyclopropyl, nonaromatic protons in the region τ 4.6–7.7. The relative amounts of unconverted phenylcyclopropane and *p*-bromophenylcyclopropane were then determined by glc which utilized an 0.25 in. × 5 ft 10% Q F-1 on Chromosorb W column at 130°. Nmr and glc properties of 1,3-dibromo-1-phenylpropane[18] and *p*-bromophenylcyclopropane[12] were used as comparison standards.

For reactions carried out under oxygen, the apparatus consisted of a three-neck flask equipped with an efficient overhead stirrer and a gas inlet tube for the introduction of oxygen. The entire apparatus was blackened for dark reactions. The work-up and analysis procedures were the same as those described above for dark reactions carried out in the U-tube apparatus.

Reactions were also carried out in the dark at 25° using degassed CCl_4 and $CHCl_3$. A solution 0.25 M in phenylcyclopropane and bromine was introduced into a 1-mm cuvette containing a 0.9-mm spacer. The cuvette was placed in the spectrometer and the rate of disappearance of bromine was determined by following the optical density (A) at 415 nm. Values of (1/A) and the corresponding time (hr) for reactions no. 1 and 2 in CCl_4 solution were: 1.05, 1.0 (0); 1.15, 1.10 (1); 1.25 (3); 1.35, 1.30 (4); 1.45, 1.35 (5); 1.55, 1.45 (6); 1.60, 1.50 (7). For the reaction run in $CHCl_3$ the values were: 1.30 (0), 4.70 (1), 5.30 (1.25), 5.90 (1.5), 6.60 (1.95), 7.40 (2.25), 8.70 (3.0 hr).

Reactions carried out in the presence of nitrobenzene (20 wt % of phenylcyclopropane) or trinitrobenzene (TNB) (saturated) were performed in Pyrex flasks at 25 and −20° in room light in CCl_4. These reactions were compared with those carried out at the same time but containing no inhibitor. Reaction solutions contained 0.620 g of phenylcyclopropane to which 10 ml of a 0.09 g/ml solution of bromine in CCl_4 was added.

The bromine addition in *n*-hexane was carried out in the following manner. To a solution of 0.126 g of phenylcyclopropane in 2 ml of *n*-hexane at −20° in a Pyrex test tube was added 2 ml of a freshly prepared bromine in *n*-hexane solution (0.09 g/ml) also at −20°. The color discharged in 5 min at −20° in room light. The solvent was evaporated to obtain a yellow oil (0.276 g) which when analyzed by nmr showed the presence of 90% 1,3-dibromo-1-phenylcyclopropane and 10% phenylcyclopropane. In the dark reaction, an aqueous $Na_2S_2O_3$ solution was added to remove any unconsumed bromine.

The inhibitory effect of a solution of CCl_4 saturated with TNB was determined in the following manner. To a solution containing 1 ml of *n*-hexane, 3 ml of CCl_4, and 225 mg of azobisisobutyronitrile at 60° was added 2 ml of a 0.09 g/ml solution of bromine in CCl_4. The bromine color was discharged in 10 min. A second solution containing precisely the same quantities of reactants and solvent, except that the solvent was saturated with TNB, decolorized after 1 hr at 60°.

Bromine Addition to 1,2-Diphenylcyclopropane.—In a typical light-induced addition, 0.194 g of *cis*-1,2-diphenylcyclopropane (1.0 mmol) was dissolved in 2 ml of CCl_4 in a Pyrex flask. A 2-ml solution of bromine in CCl_4 (0.090 g/ml) then was added in one portion and the resulting solution was kept at 25° in room light until the color disappeared (<5 min). The solvent was evaporated to give 1,3-dibromo-1,3-diphenylpropane (*meso*/*dl* = 1): brown oil; nmr τ 2.75 (s, 10 H, Ar H), 4.88 (t, J = 7 Hz, 1/2 H, *dl*-ArCHBr), 5.20 (t, J = 7 Hz, 1/2 H, *meso*-ArCHBr), 7.19 (t, J = 7 Hz, *dl*-CH_2), 6.6–7.5 (m, *meso*-CH_2); ir 1500 (m, sh), 1460 (m, sh), 1225 (m), 690 cm^{-1} (s, br); mass spectrum *m/e* 356, 354, 352 ($M^+ + 4$, $M^+ + 2$, M^+), 375 and 373 ($C_{15}H_{14}Br^+$), 194 ($C_{15}H_{14}^+$). Parent ions at *m/e* 312, 310, 308, corresponding to $C_{15}H_{14}BrCl$, or fragment ions at *m/e* 231, 229, corresponding to $C_{15}H_{14}Cl^+$, were not detected.

Anal. Calcd for $C_{15}H_{14}Br_2$: C, 50.88; H, 3.98; Br, 45.14. Found: C, 51.00; H, 3.96; Br, 45.27.

1,3-Dibromides isolated in the above-described manner were of sufficient purity to give satisfactory analyses for $C_{15}H_{14}Br_2$. Synthetic mixtures of *dl*- and *meso*-dibromides and unconverted phenylcyclopropane in CCl_4 did not change composition on evaporation of solvent.

(18) S. G. Reech, J. H. Turnbull and W. Wilson, *J. Chem. Soc.*, 4686 (1952).

(19) T. F. Corbin, R. C. Hahn, and H. Shechter, *Org. Syn.*, **44**, 30 (1964).

(20) H. A. Benesi and J. H. Hildebrand, *J. Amer. Chem. Soc.*, **71**, 2703 (1949).

Zinc Debromination of 1,3-Dibromo-1,3-diphenylpropane.—A 4.50-g sample of the dibromide (*dl*/*meso* = 1) in 50 ml of anhydrous methanol was stirred 4 hr at 25° with 2.0 g of zinc dust. The mixture was filtered and the filtrate was concentrated. The residue was dissolved in ether and the solution was washed with water and dried ($MgSO_4$). Evaporation of the solvent produced 2.3 g of residue containing *cis*- (33%), *trans*-1,2-diphenylcyclopropane (64%), and 1,3-diphenylpropane (3%) as determined by glc (0.25 in. × 5 ft, 20% SE-30 on Chromosorb W, 225°). Identification was made by chromatographic comparison. The sample of 1,3-diphenylpropane used for comparison was prepared by hydrogenation of *trans*-1,2-diphenylcyclopropane.[21]

Hydrolysis of 1,3-Dibromo-1,3-diphenylpropane.—A solution of 6.28 g of the dibromide in 370 ml of acetone was treated with a solution of 6.2 g of $AgNO_3$ in 370 ml of water. The silver bromide (calcd 6.65 g; obsd 6.45 g) was removed by filtration and the filtrate was concentrated. The largely aqueous residue was extracted with ether. The ether extract was washed with 5% aqueous $NaHCO_3$ and then water and dried ($MgSO_4$). Evaporation of solvent gave 2.60 g (64%) of a mixture of diastereomeric 1,3-diphenyl-1,3-propanediols, mp 116–118° (benzene).

A 3.0-g sample of diastereomeric diols was separated through a known method[15] utilizing borate ester formation. In this manner was obtained 1.2 g of *dl*-diol, mp 128–129° (benzene). Reduction ($NaBH_4$) of 1,3-diphenyl-1,3-propanedione followed by borate ester formation gave a comparison sample of the *dl*-diol: mp 128–129°; nmr τ 2.70 (s, 10 H, Ar H), 5.09 (t, J = 6 Hz, 2 H, $\geq$CH), 6.85 (s, 2 H, OH), 7.90 (t, J = 6 Hz, 2 H, CH_2); ir 3400, 3350 (d, s), 1400 (m, sh), 1030 (d, br, s), 930 cm^{-1} (m).

Also obtained from the 3.0-g mixture of diastereomeric diols was 0.98 g of *meso*-diol:[15] mp 106–107° (benzene); nmr ($CDCl_3$) τ 2.71 (s, 10 H, Ar H), 4.9–5.3 (m, 2 H, $\geq$CH), 6.08 (s, 1 H, OH), 6.10 (s, 1 H, OH), 7.6–8.4 (m, 2 H, CH_2); ir 3400 (s, br), 1065 (m, sh), 780 cm^{-1} (m, br).

1,3-Dibromo-1,3-diphenylpropane.—According to the method of Lutz and Weiss,[22] a 20.8-g sample of benzylideneacetophenone (0.1 mol) was reduced to the unsaturated alcohol (mp 54–56°) in 76% yield using aluminum isopropoxide. A 9.5-g portion of the alcohol in 200 ml of anhydrous ether at 0° was treated with 3.0 g of dry HBr. The resulting solution was kept at 25° for 1 hr. Removal of excess HBr and solvent by evaporation produced 11.4 g (93%) of crude *trans*-1,3-diphenyl-3-bromo-1-propene, mp 45–48°. The crude allylic bromide was heated at 60° and treated with dry HBr for 15 hr. Thereafter the mixture was dissolved in petroleum ether and the resulting solution was washed successively with water, 5% aqueous $NaHCO_3$, and water and then dried ($CaCl_2$). Evaporation of the solvent gave a quantitative yield of 1,3-dibromo-1,3-diphenylpropane (*dl*/*meso* = 2.3).

Light Addition with Excess Bromine.—Addition in room light of 17 g of bromine (107 mmol) in one portion to 10.33 g of *cis*-1,2-diphenylcyclopropane (53 mmol) in 10 ml of CCl_4 produced a reaction which was exothermic to the extent that the CCl_4 was heated momentarily to reflux. The resulting solution was kept at 25° for 4 days. Evaporation of solvent and excess bromine gave 20.4 g of a yellow semisolid of which 14.3 g was treated with 100 ml of *n*-hexane. The 1.56 g of insoluble material (fraction 1) was filtered off and the filtrate was cooled overnight whereupon an additional 0.65 g of solid (fraction 2) was obtained. The mother liquors were evaporated giving 9.63 g of 1,3-dibromo-1,3-diphenylpropane (*dl*/*meso* = 1.0) which was identified by spectral data.

Fraction 1 was stirred in hot *n*-hexane. The insoluble material, 731 mg (8.5%), was filtered off and recrystallized from benzene giving *meso*-1,2,3-tribromo-1,3-diphenylpropane: mp 178–180°; nmr (CS_2) τ 2.4–2.9 (m, 10 H, Ar H), 4.6–5.2 (8-line m, 3 H, CHBr).

Anal. Calcd for $C_{15}H_{13}Br_3$: C, 41.61; H, 3.03; Br, 55.58. Found: C, 41.51; H, 3.08; Br, 55.37.

Fraction 2 was dissolved in the *n*-hexane mother liquor from which the *meso* tribromide was obtained and the resulting solution was cooled overnight. The resulting solid, 971 mg (6.5%), was collected by filtration and recrystallized from ethanol giving *dl*-1,2,3-tribromo-1,3-diphenylpropane: mp 130–132°; nmr (CCl_4) τ 2.72 (s, 10 H, Ar H), 3.89 (d, J = 2 Hz, 1 H, ArCHBr), 4.70 (d, J = 12 Hz, 1 H, ArCHBr), 5.55 (q, J = 12 and 2 Hz, 1 H, CHBr).

Anal. Calcd for $C_{15}H_{13}Br_3$: C, 41.61; H, 3.03. Found: C, 41.32; H, 3.33.

1,2,3-Tribromo-1,3-diphenylpropane.—To 5.2 g of 1-bromo-1,3-diphenylpropene in 100 ml of CCl_4 was added dropwise 3.2 g of bromine in 20 ml of CCl_4 and the resulting solution was stirred at 30° for 27 hr. Evaporation of solvent left 6.1 g (74%) of solid tribromides which was separated by fractional crystallization giving 2.2 g of *meso*, mp 179–181° (benzene), and 3.6 g of *dl*, mp 132–134°.

Attempted Additions to Phenylcyclopropane. Thiolacetic Acid.—Employing conditions previously described for the free-radical addition of thiolacetic acid[23] to olefins, 760 mg (10 mmol) of freshly distilled thiolacetic acid was added slowly at 25° to 1.18 g (10 mmol) of phenylcyclopropane in 8 ml of CCl_4 under irradiation with a 100-W bulb. No increase in the temperature of the reaction was noted. Benzoyl peroxide (~20 mg) was added and the solution was heated to reflux for 24 hr. An nmr of the crude reaction mixture displayed only signals corresponding to thiolacetic acid and unconverted phenylcyclopropane.

Bromotrichloromethane.—A mixture of 1.18 g of phenylcyclopropane (10 mmol), 2.0 g of bromotrichloromethane (10 mmol), and 10 mg of benzoyl peroxide was degassed and sealed in a Vycor tube which was irradiated at 25° with a low-pressure mercury vapor lamp for 48 hr. A small amount of insoluble, high melting (>300°) material was filtered off. The nmr of the filtrate indicated the presence of 77% phenylcyclopropane and 23% 1,3-dibromo-1-phenylpropane. This material, with additional benzoyl peroxide, was irradiated for 4 days; the nmr indicated the presence of 58% phenylcyclopropane and 42% 1,3-dibromo-1-phenylpropane. The phenylcyclopropane was removed by steam distillation and the residue was taken up in acetone. Aqueous $AgNO_3$ was added and the resulting solution was kept at 25° for 6 days. The solid was filtered off, the filtrate was concentrated, and the resulting largely aqueous residue was extracted with ether. The ether extract was washed with aqueous $NaHCO_3$ and water and then dried ($MgSO_4$). Evaporation of the ether gave 0.644 g of 1-phenyl-1,3-propanediol: nmr ($CDCl_3$) τ 2.7 (d, Ar H), 5.7 (q, J = 6 and 7 Hz), 6.3–7.0 (m), 7.40 (s, OH), 7.5–8.1 (m); glc (15% XF-1, 200°) 5.9 min. These properties were identical with those of a solvolysis product obtained from a sample of 1,3-dibromo-1-phenylpropane.

Registry No.—*cis*-Diphenylcyclopropane, 1138-48-3; *trans*-diphenylcyclopropane, 1138-47-2; phenylcyclopropane, 873-49-4; *meso*-1,3-dibromo-1,3-diphenylpropane, 33686-80-5; *dl*-1,3-dibromo-1,3-diphenylpropane, 33735-98-7; *dl*-1,3-diphenyl-1,3-propanediol, 5355-61-3; *meso*-1,3-diphenyl-1,3-propanediol, 5381-86-2; *trans*-1,3-diphenyl-3-bromo-1-propene, 33686-82-7; *meso*-1,2,3-tribromo-1,3-diphenylpropane, 33686-83-8; *dl*-1,2,3-tribromo-1,3-diphenylpropane, 33686-84-9; 1-phenyl-1,3-propanediol, 4850-49-1.

(21) B. A. Kazanskii, M. Yu. Lukina, and I. L. Safonova, *Dokl. Acad. Nauk SSSR*, **130**, 322 (1960); *Chem. Abstr.*, **54**, 10953*f* (1960).

(22) R. Lutz and J. O. Weiss, *J. Amer. Chem. Soc.*, **77**, 1814 (1955).

(23) F. G. Bordwell and W. A. Hewett, *ibid.*, **79**, 3493 (1957).

Hexachlorofulvene. II. Reactions under Ionic Conditions

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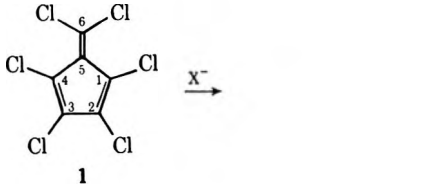
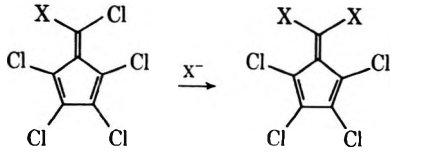
Hexachlorofulvene (1) has been subjected to a number of nucleophiles of varying reactivity. The products resulted from displacement of one or both of the chlorine atoms in the dichloromethylene group. Their structures were assigned by spectral analysis and by analogy with that of **2a**, which was confirmed in three different ways. Fulvene products were also obtained by displacement of the ring chlorines in 1 under Friedel–Crafts conditions. Treatment of 1 with concentrated sulfuric acid gave products arising from initial protonation at the 1 position and subsequent destruction of the fulvene system.

The first paper[3] in this series reported a new method for the preparation of hexachlorofulvene (**1**) and a study of its behavior under Diels–Alder conditions. The reactivity of **1** under ionic conditions is considered in this paper. Thus, we have subjected **1** to a representative set of nucleophiles and to a number of Brønsted and Lewis acids.



1



2a, X = Ph
b, X = *p*-MePh
c, X = Me
d, X = (*c*-C_6H_{11})$_2$NCH=CH
e, X = *p*-NMe_2Ph
f, X = Ph(Me)N

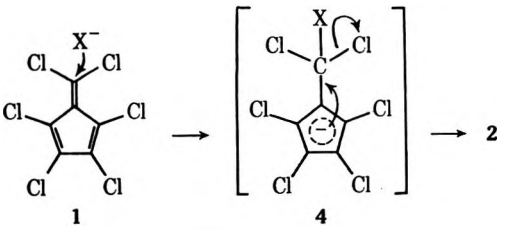
3a, X = *o*-MeOPhNH
b, X = PhO
c, X = *p*-MePhS

Results and Discussion

Reaction of Hexachlorofulvene (1) with Nucleophiles. —Previously, Roedig[4] showed that two of the chlorine atoms in **1** were labile to aromatic amines (aniline, *p*-toluidine, and *o*-phenylenediamine), but the products were not further identified. We have shown that the nucleophilic reagents given in Table I react with **1** to give monosubstituted (**2**) or disubstituted (**3**) products.

Evidence that nucleophilic substitution occurred exclusively at the 6 position is given later. Representative nucleophiles were chosen so that the products obtained had a variety of atoms bonded to the 6 position. The reaction conditions used were relatively mild, and product mixtures were not encountered. In all of the reactions with **1**, the nucleophile was present in excess amounts. Interestingly, those products having a *carbon* linked directly to the 6 position (**2a–e**) were monosubstituted, whereas, except for **2f**, the products with a *heteroatom* attached to the 6 position were disubstituted. Compound **2a** was recovered unchanged after an attempted further reaction with phenylmagnesium bromide, thus indicating the decreased reactivity of the remaining 6-chlorine atom relative to those in **1**.

The exclusive replacement of the 6-chlorine atom by nucleophiles may be attributed to the extra stabilization in intermediate **4** provided by the delocalization of



1 **4**

the electrons into a six-π-electron aromatic system. Hydrocarbon fulvenes also undergo nucleophilic attack at the 6 position. However, because they lack suitable leaving groups, the products[5] are not substituted fulvenes, since the intermediate carbanions analogous to **4** undergo secondary reactions such as autooxidation, hydrolysis, or ferrocene formation.

Elucidation of the structures of **2** and **3** was based on the following arguments. Elemental analysis and mass spectroscopy gave the molecular formulas, which together with (1) the color of the products, (2) ir absorptions in the carbon–carbon double-bond stretching frequency region (6.20–6.47 μ) and at 7.75–8.00 μ,[5,6] and (3) the strong uv absorption at long wavelengths [314–425 nm (log ϵ 4.14–4.36)[7]] provided reliable evidence for fulvene structures. That substitution of the fulvene occurred at the 6 position was established by analogy to the formation of **2a**, whose structure was proven in the following way. First **2a** was prepared by an alternate synthesis. Benzotrichloride and 1,2,3,4,5-pentachlorocyclopentadiene (**5**)[8] formed an addition compound, **6**, which was converted by base to the diene **7**. Dechlorination of **7** with triethylphosphite yielded a deep red solid with an ir spectrum identical with that of **2a** prepared previously from **1**. Secondly, **2a** was treated with morpholine and gave a product, **9**, whose ir and melting point were identical with those of a sample prepared from the sodium salt of 1,2,3,4-tetrachlorocyclopentadiene (**8**)[9,10] and *S*-methylthiobenzoyl-

(1) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

(2) Supported by the Purdue Research Foundation.

(3) E. T. McBee, E. P. Wesseler, D. L. Crain, R. Hurnaus, and T. Hodgins, *J. Org. Chem.*, **37**, 683 (1972).

(4) A. Roedig, *Justus Liebigs Ann. Chem.*, **569**, 161 (1950).

(5) P. Yates, *Advan. Alicycl. Chem.*, **2**, 59 (1968).

(6) J. C. Wood, R. M. Elofson, and D. M. Saunders, *Anal. Chem.*, **30**, 1339 (1958).

(7) Shifts to even longer wavelengths (see Table I) occurred when the 6 substituent had a resonance donor group in conjugation with the fulvene moiety.

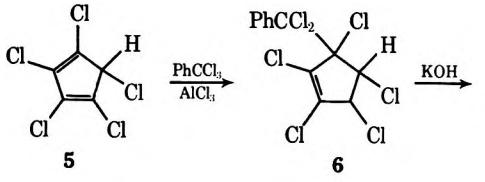
(8) E. T. McBee and D. K. Smith, *J. Amer. Chem. Soc.*, **77**, 389 (1955).

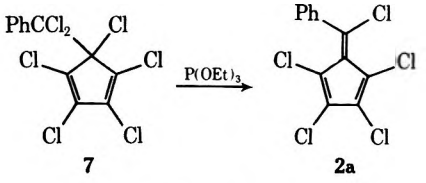
TABLE I

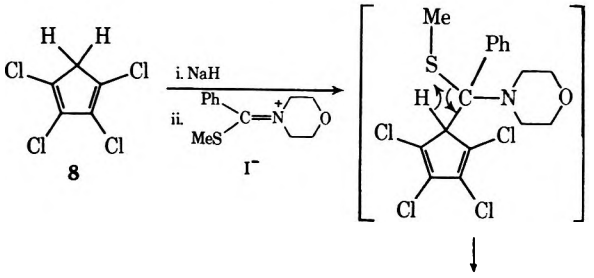
NUCLEOPHILIC REACTIONS OF 1

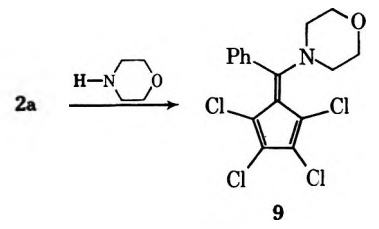
Nucleophilic reagent	Product	% yield	Mp, °C	λ_{max} (C_6H_6), nm (log ε)
PhMgBr	2a	49[a]	75.5–76	334[b] (4.16)
p-MePhMgBr	2b	56	113–115	350.5 (4.2)
MeMgI	2c	73.5[c]	160–162	299[d] (4.14)
$(c\text{-}C_6H_{11})_2NCH{=}CH_2$	2d	83.5	154.5–155.5	467 (4.74)
$PhNMe_2$	2e	78.5	149–150.5	488 (4.45)
PhNHMe	2f	82.5	86–88	393 (4.31)
o-$MeOPhNH_2$	3a	32.5[e]	176.5–177.5 dec	384.5 (4.43)
PhONa	3b	55	133–135	314.5 (4.45)
p-MePhSH[f]	3c	75	172–173	425 (4.34)

[a] Conversion of 1 was 57%. [b] 95% ethanol was used as the solvent. [c] A trace amount of material (possibly 3c) was also formed. [d] Also 416 nm (ε 2.63). [e] Acetylation gave the *N,N'*-diacetyl derivative. [f] Reaction was performed in the presence of triethylamine.





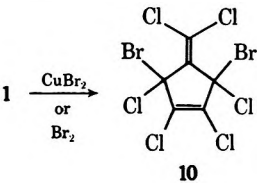




morpholinium iodide.[11] Spectral data for **9** (nmr, ir, and uv) were totally consistent with its structure. The third method, which indicated the accuracy of the structure assigned to **2a**, involved the use of ^{13}C nmr and is discussed later.

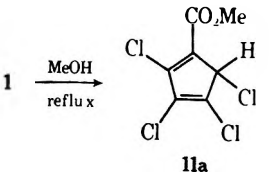
In addition to the nucleophiles listed in Table I, several others were studied. Both sodium bromide and calcium bromide in refluxing acetone were unreactive toward **1**. However, 1,4 addition of bromine to **1** occurred to a limited extent in a reaction with cupric bromide. Adduct **10** was identified by ir comparison with that of a sample prepared by an alternate method.[4]

Sodium cyanide, potassium thiocyanate, sodium methoxide, and metal hydrides ($LiAlH_4$ and $NaBH_4$) were extremely reactive with **1**, yielding dark amorphous solids or intractible tars from which products

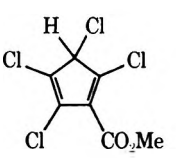


were not isolated. Sodium ethoxide and **1** gave a violet solution which similarly decomposed to a black tar on evaporation of the solvent.

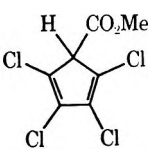
Roedig has reported[4] that **1** also decomposed slowly when heated in alcohol. We have confirmed this fact and find that an ester is formed as the principal product. For example, after refluxing in methanol until the red color disappeared, distillation of the reaction mixture afforded a trace amount of **8** and a 55% yield of **11a**.



The dichloromethylene group of 2-dichloromethylenecyclopentanone has similarly been converted to a carbomethoxy group with sodium methoxide.[12] The structure of **11a** was assigned from spectral data. The mass spectrum of the ester had ions with the predicted isotopic pattern corresponding to the molecular ion (M), M − 59, and 59 (COOMe). The ir spectrum of **11a** had absorptions typical of an ester,[13] and its nmr spectrum had singlets at δ 3.85 (3 H, COOMe) and 5.18 (1 H). The latter resonance distinguishes **11a** from other reasonable isomers since δ 5.18 is low for a vinylic hydrogen.[14] In addition, the proton in **5** absorbs at δ 4.71. Isomer **11b** would be expected to



11b



11c

have a very similar chemical shift, while the proton in **11c** should be more shielded since carbomethoxy substituents deshield α protons less than chlorine sub-

(9) E. T. McBee, R. K. Meyers, and C. F. Baranauckas, *J. Amer. Chem. Soc.*, **77**, 86 (1955).

(10) A. S. Kende, P. T. Izzo, and P. T. MacGregor, *ibid.*, **88**, 3359 (1966).

(11) (a) F. H. McMillan, *ibid.*, **70**, 868 (1948); (b) L. Maier, *Angew. Chem., Int. Ed. Engl.*, **8**, 141 (1969).

(12) J. Wolinsky and R. Kasubick, *J. Org. Chem.*, **35**, 1211 (1970).

(13) R. Silverstein and G. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed, Wiley, New York, N. Y., 1967, p 91.

(14) D. W. Mathieson, "Nuclear Magnetic Resonance for Organic Chemists," Academic Press, New York, N. Y., 1967, p 183.

stituents.[15] Presumably the extended conjugation in **11a** makes it the most thermodynamically stable product. Absolute ethanol also gave an analogous ester. Since **1** was completely unreactive in refluxing glacial acetic acid, the reaction most likely proceeds by nucleophilic attack of alcohol on the 6 position of **1**.

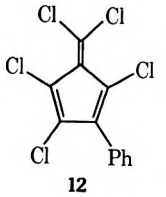
Reaction of Hexachlorofulvene Under Acidic Conditions.—While nucleophilic substitution allows the 6 chlorines of **1** to be replaced with a large number of substituents, Lewis acids allow replacement of the ring chlorines. One example of the latter type was given in an earlier paper,[3] where **1** in the presence of a small amount of aluminum chloride yielded a difulvene. However, when a 1:1 molar ratio of **1** to aluminum chloride (instead of 2:1 or higher) was used, **1** was recovered unchanged after hydrolysis. Apparently a complex is formed which cannot react further to give the difulvene under these circumstances. However, if a substrate such as benzene is present, the electrophilic complex reacts with the subsequent replacement of the ring chlorines. The number and position of the chlorines replaced can be controlled to some degree as shown in Table II. At room temperature, 2-phenylpentachlorofulvene (**12**) was the only product isolated when a 1:1 molar ratio of **1** to benzene reacted in the presence of aluminum chloride. Lowering the reaction temperature to 5° resulted in a mixture (approximately 1:1) of **12** and 1-phenylpentachlorofulvene (**13**). In Table III is listed some of the data of the three possible monophenylated fulvenes. Proof for structure **2a** has already been given. Identification of **12** and **13** is not nearly so rigorous, but all the information suggests that the assigned structures are correct. Both **2a** and **13** have extended conjugated systems while **12** is cross conjugated and would therefore be expected to absorb at slightly shorter wavelength in the uv as was observed. In addition, **12** is the only isomer without any appreciable steric hindrance to planarity. Slight crowding is known to result only in a hypochromic shift[16] which would account for the lower extinction coefficients of **2a** and **13**. This same steric hindrance may explain why these two isomers appeared as singlets in the nmr while **12** was a multiplet.

The final evidence for the structural assignment given was provided by ^{13}C nmr data.[17] Unfortunately, the amount of **13** necessary for ^{13}C nmr could not be isolated. The chemical shifts measured for the other two isomers and **1** are shown in Chart I. The assignments were based on substituent effects. All the values above 70 ppm were assigned to the 2,3 positions of the fulvenes because the same positions of 6,6-dimethylfulvene were found to absorb at 71.9 ppm.[18] The fact that **12** contains only one absorption above 70 ppm immediately suggests that the phenyl group is in the 2 position and is lowering the absorption of this carbon below 70 ppm. In fact, the lowest absorption observed (40.9 ppm) must be assigned to the carbon bearing the phenyl group in **2a**. This is a decrease or α shift of 23.0 ppm from **1**. A similar shift of 21.8 ppm is observed in **12**. The remaining chemical shifts in Chart I are only tentatively assigned owing to the lack of suitable models.

Table II

Reaction of 1 and Benzene in the Presence of Aluminum Chloride under Various Conditions

Temp, °C	Molar ratio of 1:benzene	Position of phenyl substitution	Yield, %
5	1:1 (in CS_2)	1 and 2	46
25	1:1 (in CS_2)	2	45
25	Benzene as solvent	2,3 and 1,2,3	41 and 10
80	Benzene as solvent	1,2,3	46.5



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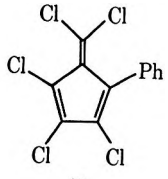


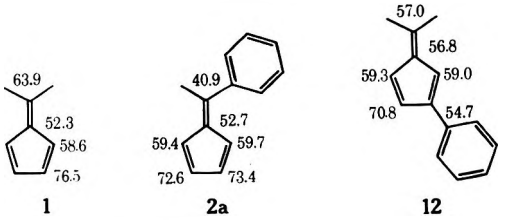
13

Table III

Comparison of the Three Isomeric Phenylpentachlorofulvenes

	2a	12	13
Mp, °C	75.5–76	72–73	94–95
Uv λ_{max} (log ϵ)	334 (4.16)	296 (4.21)	317 (4.11)
Nmr, δ	7.40 (s)	7.30 (m)	7.38 (s)
Color	Very deep red	Orange	Deep red

Chart I[a]



[a] Chemical shifts (given in parts per million upfield from CS_2) were obtained from the ^{13}C nmr spectra of **1**, **2a**, and **12**. For simplicity the chlorine atoms are omitted.

We had previously hydrolyzed several chlorocarbons

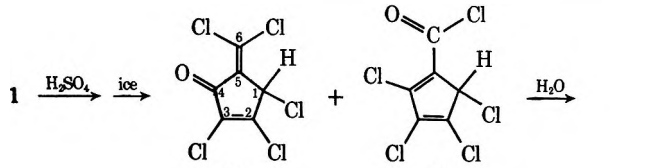
(15) Reference 13, p 137.

(16) H. H. Jaffé and M. Orchin, "Theory and Applications of Ultraviolet Spectroscopy," Wiley, New York, N. Y., 1962, p 384.

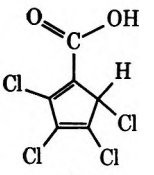
(17) We are indebted to Dr. J. Grutzner for determining the ^{13}C nmr spectra and for his help in analyzing them.

(18) J. B. Grutzner, unpublished results.

with concentrated sulfuric acid,[19] and we were consequently interested in the hydrolysis of 1 with this acid.[20] The reaction was carried out by heating 1 in concentrated sulfuric acid until a green solution resulted. When this solution was poured over ice a tan solid consisting of 14 and 15 precipitated. Two singlets were



14a 15



16

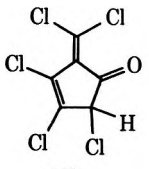
present in the nmr of the crude product at δ 5.43 and 4.88 in a ratio of 6:1. The larger singlet corresponded to the ketone **14a** as shown by the nmr spectrum of a pure sample. The structure of **14a** was determined mainly by the ^{13}C nmr data given in Table IV. The

TABLE IV

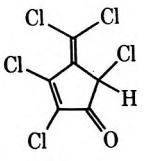
^{13}C NMR DATA FOR COMPOUND 14a

Position	Shift upfield from CS_2, ppm	Coupling, Hz
1	5.5	2.8
2	54.4	3.7
3	29.8	7.1
4	128.5	174.4
5	47.3	4.5
6	49.6	3.2

carbonyl carbon (position 1) was readily assigned the absorption at 5.5 ppm since carbonyl carbons are known to absorb at very low field.[21] The tetrahedral carbon (position 4) is also easily assigned for it is observed at very high field (128.5 ppm) and it has the largest ^{13}C–H coupling constant (174.4 Hz).[22] Since the carbonyl carbon is observed to have the *smallest* ^{13}C–H coupling constant, which generally decreases with increasing number of intervening bonds,[23] the alternative structures (**14b** and **14c**) having the carbonyl and tetrahedral carbons adjacent are not so likely as structure **14a**.



14b



14c

Roeding has reported,[4] and we have confirmed, that **1** is oxidized to 2,3,4-trichloro-5-(dichlormethylene)-cyclopentene-1,4-dione by heating with fuming nitric acid. Under the same conditions **14a** is totally unreactive and consequently does not appear to be an intermediate in the oxidation reaction.

The minor product (**15**), although shown to be present in the crude reaction mixture by nmr and mass spectroscopy, was isolated only as the corresponding carboxylic acid (**16**). The structure of **16** was determined mainly from mass spectroscopy, ir, and nmr data. Mass spectroscopy, as well as elemental analysis, indicated that the molecular formula was $C_6H_2Cl_4O_2$. The ir spectrum of **16** had broad absorption between 3.6 and 4.0 μ characteristic of an acid. In addition, this compound was soluble in sodium bicarbonate, and its nmr spectrum (in acetonitrile) contained two singlets at δ 5.30 and 8.56. The singlet at 5.30 is close to that observed for the analogous ester **11a**, and, by the same reasoning used to deduce the structure of this ester, structure **16** was assigned to the acid. Because of the instability of these compounds, several attempts to interconvert **11a** and **16** were not successful.

Experimental Section

Procedures and Equipment.—Melting points were determined with a Mel-Temp apparatus in sealed tubes and are uncorrected. Proton nmr spectra were obtained on a Varian Associates A-60A spectrometer; carbon tetrachloride was used as a solvent with tetramethylsilane as an internal standard. ^{13}C nmr spectra were determined by J. Grutzner using a Varian XL 100 nmr spectrometer operating at 25.2 MHz. Infrared spectra were determined as KBr pellets using a Perkin-Elmer 221 ir spectrophotometer. Ultraviolet spectra were determined in 95% ethanol on a Bausch and Lomb Spectronic 505 spectrophotometer. Thin layer chromatography (tlc) was carried out on glass plates coated with silica gel HF-254, E. Merck AG. Mass spectra were recorded on a Hitachi Perkin-Elmer HU-6D high resolution mass spectrometer. Elemental analyses were performed by Dr. C. S. Yeh and her staff at Purdue University.

6-Phenylpentachlorofulvene (**2a**).—A Grignard solution was prepared from 10.5 ml (0.10 mol) of bromobenzene and 2.4 g (0.10 g-atom) of magnesium turnings in 400 ml of anhydrous ether. This solution was filtered and allowed to drop slowly into a solution of 14.1 g (0.05 mol) of 1 in 150 ml of THF at 10°. After 5 hr, dilute HCl was added; the organic layer was separated, dried, and evaporated to a dark solid. Column chromatography (silica gel, hexane) gave 6 g of 1 as the first fraction and 4 g (49% yield) of **2a** as the second red fraction. After recrystallization of **2a** from methanol, crystals were obtained which were so deep red that they appeared black unless examined closely: ir (KBr) 6.28 (s), 6.45 (m), 6.90 (w), 7.87 (s), 7.97 (m), 10.27 (w), 10.77 (w), 10.98 (w), 13.14 (s), 14.06 (w), 14.47 (m), 14.79 μ (m).

Anal. Calcd for $C_{12}H_5Cl_5$: C, 44.13; H, 1.54; Cl, 54.33. Found: C, 44.12; H, 1.75; Cl, 54.20.

6-*p*-Tolylpentachlorofulvene (**2b**).—A Grignard solution, prepared from 3.44 g (20 mmol) of *p*-bromotoluene and 0.50 g (20 mg-atoms) of magnesium in 100 ml of dry ether, was added dropwise to a solution of 2.85 g (10 mmol) of 1 in 100 ml of ether. After the mixture was stirred for 60 hr, dilute HCl was added. The organic layer was separated, washed with a $NaHCO_3$ solution, and dried, and the solvent was removed. Recrystallization of the residue from acetonitrile gave deep red crystals of **2b**: ir (KBr) 6.30 (s), 6.44 (s), 7.32 (s), 7.95 (s), 8.43 (m), 9.05 (w), 10.23 (w), 10.84 (w), 12.25 (s), 14.23 μ (s).

Anal. Calcd for $C_{13}H_7Cl_5$: C, 45.86; H, 2.07; Cl, 52.07. Found: C, 46.02; H, 1.94; Cl, 52.06.

6-Methylpentachlorofulvene (**2c**).—A Grignard solution was prepared from 1 g (0.4 g-atom) of magnesium and 6 g (0.4 mol) of methyl iodide in 100 ml of dry ether. Then 3.00 g (0.105 mol)

(19) (a) J. S. Newcomer and E. T. McBee, *J. Amer. Chem. Soc.*, **71**, 946 (1949); (b) D. L. Crain, Ph.D. Thesis, Purdue University, 1956.

(20) After completion of this work the same hydrolysis was reported by V. D. Simonov, R. T. Gazizov, and M. I. Kollegova, *J. Org. Chem. USSR*, **6**, 1613 (1970). We report our study here because these workers did not report a minor product which we found, and also we have further confirmation that the structure of the major product reported is correct.

(21) J. B. Stothers, *Quart. Rev., Chem. Soc.*, **19**, 144 (1965).

(22) F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York, N. Y., 1969, p 235.

(23) The authors are aware that there are a number of exceptions to the simple relationship between the magnitude of the coupling constant and the number of intervening bonds; however, in the alternate structures the carbonyl carbon is not likely to have the *smallest* coupling constant.

of 1 in 100 ml of ether was added dropwise to the stirred ice-cold Grignard solution. After an additional 30-min stirring, the product was isolated as in the previous example and recrystallized from hot acetonitrile to give reddish orange needles of 2c: ir (KBr) 6.23 (m), 6.42 (m), 7.83 (s), 7.95 (w), 8.11 μ (w).

Anal. Calcd for $C_7H_3Cl_5$: C, 31.78; H, 1.14; Cl, 67.07. Found: C, 31.95; H, 1.36; Cl, 67.09.

Synthesis of 6-[2-(*N*,*N*-Dicyclohexylamino)-1-vinyl]pentachlorofulvene (2d).—A mixture of 4.4 g (0.10 mol) of acetaldehyde, 17.5 g (0.096 mol) of *N*,*N*-dicyclohexylamine, and 5 g (0.04 mol) of magnesium sulfate in 70 ml of dry benzene was stirred for 30 min. Then 1.0 g (3.5 mmol) of 1 in benzene (20 ml) was added dropwise, and the reaction was stirred for 3 hr at room temperature. The addition of dilute HCl caused a white precipitate to form which was filtered off and washed with ethyl acetate. The solid residue from evaporation of the filtrate was recrystallized from petroleum ether yielding 1.50 g of 2d as deep red crystals: ir (KBr) 2.90 (w), 3.40 (w), 3.49 (w), 6.27 (s), 6.56 (s), 6.88 (m), 6.95 (m), 7.75–7.90 (s), 8.06 (s), 8.68 (w), 9.02 (w), 9.16 (w), 9.87 (w), 11.31 μ (w).

Anal. Calcd for $C_{20}H_{24}NCl_5$: C, 52.71; H, 5.31; N, 3.07; Cl, 38.90. Found: C, 52.89; H, 5.31; N, 3.03; Cl, 39.19.

Synthesis of 6-(*p*-Dimethylaminophenyl)pentachlorofulvene (2e).—To 1.0 g (3.5 mmol) of 1 in 20 ml of tetrahydrofuran was added 5 ml (40 mmol) of *N*,*N*-dimethylaniline. After the mixture was stirred for 24 hr at room temperature, dilute HCl was added. The product was isolated by extraction with ethyl acetate and evaporation of the solvent. Recrystallization from hot petroleum ether gave greenish blue prisms of 2e: ir (KBr) 6.20 (s), 6.44 (m), 6.59 (s), 6.91 (w), 7.28 (m), 7.81 (s), 8.17 (w), 8.37 (m), 9.19 (m), 12.25 (w), 14.35 μ (w).

Anal. Calcd for $C_{14}H_{10}NCl_5$: C, 45.51; H, 2.73; N, 3.79; Cl, 47.98. Found: C, 45.81; H, 2.90; N, 3.76; Cl, 48.06.

Synthesis of 6-*N*-Methylanilinopentachlorofulvene (2f).—For 2 hr 1.0 g (3.5 mmol) of 1 and 5 ml (46 mmol) of *N*-methylaniline were stirred in an ice bath. The product was then isolated as in the previous example and recrystallized from petroleum ether. Dark red prisms of 2f were obtained: ir (KBr) 6.46 (s), 6.70 (m), 6.84 (m), 6.89 (m), 7.05 (s), 7.20 (m), 7.76 (s), 8.10 (w), 9.04 (s), 9.74 (m), 10.04 (w), 11.06 (m), 12.42 (w), 13.0–13.2 (m), 14.05 (w), 14.47 μ (m).

Anal. Calcd for $C_{13}H_8NCl_5$: C, 43.92; H, 2.27; N, 3.94; Cl, 49.87. Found: C, 43.92; H, 2.28; N, 3.80; Cl, 49.74.

6,6-Di(*o*-anisidino)tetrachlorofulvene (3a).—A solution containing 2.0 g (7 mmol) of 1 in 25 ml of tetrahydrofuran was treated under cooling and stirring with 5.0 ml (45 mmol) of *o*-anisidine. After 30 min the solution was poured onto crushed ice, dilute HCl was added, and the resulting yellow precipitate was sucked off. Chartreuse needles of 3a were obtained after recrystallization from carbon tetrachloride: ir (KBr) 2.95 (w), 6.19 (s), 6.32 (s), 6.60 (m), 6.88 (s), 6.97 (m), 7.62 (s), 8.00 (s), 8.20 (w), 8.30 (w), 8.50 (m), 8.92 (m), 8.97 (m), 9.74 (m), 13.38 μ (s).

Anal. Calcd for $C_{20}H_{16}N_2Cl_4O_2$: C, 52.43; H, 3.52; N, 6.12; Cl, 30.95. Found: C, 52.45; H, 3.40; N, 6.26; Cl, 30.82.

6,6-Di(*N*-acetyl-*o*-anisidino)tetrachlorofulvene (17).—A solution containing 2 g (7 mmol) of 1 in 25 ml of tetrahydrofuran was treated as above with 5 ml of *o*-anisidine. The crude 3a was dried and dissolved in tetrahydrofuran. Then 2.5 ml (35 mmol) of acetyl chloride was added dropwise followed by 8.0 ml (58 mmol) of triethylamine. After the mixture was stirred for 1 hr, ethyl acetate was added followed by dilute HCl and $NaHCO_3$ solutions. The product was then isolated as usual, and, after recrystallization from acetonitrile, 1.51 g (38.5% yield) of 17 as red needles was obtained: mp 202–203° dec; ir (KBr) 2.89 (w), 5.76 (s), 6.24 (m), 6.35 (s), 6.64 (m), 7.67 (m), 7.82 (s), 7.96 (m), 8.18 (w), 8.41 (m), 8.59 (m), 8.94 (m), 9.74 (w), 13.31 μ (w); uv max (benzene) 393.5 nm (log ε 4.36); mass spectrum (75 eV) *m/e* (rel intensity) 540 (54), 498 (40), 425 (19), 390 (13), 333 (100).

Anal. Calcd for $C_{24}H_{20}N_2O_4Cl_4$: C, 53.16; H, 3.72; N, 5.17; Cl, 26.15. Found: C, 52.90; H, 3.75; N, 4.89; Cl, 26.21.

6,6-Diphenoxytetrachlorofulvene (3b).—To 2.85 g (10 mmol) of 1 in 50 ml of acetone was added 3.32 g (20 mmol) of sodium phenoxide. The mixture was stirred in an ice bath for 1 hr, poured over crushed ice, and extracted with ethyl acetate. After evaporation of the solvent, the residue was recrystallized from acetonitrile yielding golden needles of 3b: ir (KBr) 6.06 (s), 6.28 (s), 6.46 (w), 6.72 (s), 7.58 (m), 7.66 (w), 7.78 (s), 8.02 (s), 8.53 (m), 8.67 (s), 9.75 (w), 9.88 (m), 10.03 (m), 11.98 (w), 13.09 (m), 14.33 (w), 14.67 μ (w).

Anal. Calcd for $C_{18}H_{10}O_2Cl_4$: C, 54.05; H, 2.52; Cl, 35.46. Found: C, 53.88; H, 2.41; Cl, 35.70.

6,6-Bis(*p*-thiocresyl)tetrachlorofulvene (3c).—To an ice-cold solution containing 5 g (17.5 mmol) of 1 in 200 ml of dry benzene was added dropwise a solution of 5.0 g (40 mmol) of *p*-thiocresole and 7.5 ml (54 mmol) of triethylamine in 100 ml of benzene. After 4 hr of stirring, the reaction mixture was washed with dilute HCl and a $NaHCO_3$ solution. The solution was then dried and evaporated. The residue after recrystallization from hot petroleum ether yielded deep red needles of 3c: ir (KBr) 6.80 (s), 7.73 (s), 8.09 (w), 8.99 (w), 11.88 (w), 12.42 μ (m).

Anal. Calcd for $C_{20}H_{14}S_2Cl_4$: C, 52.19; H, 3.07; S, 13.93; Cl, 30.81. Found: C, 52.32; H, 3.36; S, 14.04; Cl, 30.93.

1,2,3,4,5,5-Hexachloro-3-phenyldichloromethylcyclopentene (6).—To 23 g (97 mmol) of 5 and 100 ml (0.7 mol) of benzotrichloride was added 2.0 g (15 mmol) of aluminum chloride. The mixture was stirred and heated on a water bath for 3 hr and then stirred overnight at room temperature. Water was added, and the organic layer separated. Unreacted benzotrichloride was removed by vacuum distillation. The residue after recrystallization from hexane yielded 29 g (67% yield) of 6: mp 142–143°; ir (KBr) 6.17 (m), 6.67 (w), 6.88 (m), 7.57 (w), 7.81 (m), 8.04 (w), 8.39 (s), 9.72 (m), 12.13 (m), 12.90 (s), 13.04 (w), 13.91 (m), 14.48 (s), 14.53 μ (m); nmr (CCl_4) δ 7.3–8.0 (m, 5, Ar H), 5.05 (s, 1).[24]

Anal. Calcd for $C_{12}H_6Cl_8$: C, 33.21; H, 1.39; Cl, 65.43. Found: C, 33.29; H, 1.46; Cl, 65.36.

Conversion of 6 to 6-Phenylpentachlorofulvene (2a).—To a solution of 5.0 g (11.6 mmol) of 6 in 100 ml of absolute ethanol was added 0.65 g (11.6 mmol) of KOH. After the mixture was stirred at room temperature for 3.5 hr, water was added and the product was extracted with hexane. The residue after evaporation of the hexane was chromatographed on a silica gel column, and 4.2 g of clear crystals of 7 was obtained: mp 72.5–73°; ir (KBr) 6.23 (s), 6.37 (w), 6.67 (w), 6.88 (m), 8.00 (s), 8.62 (m), 8.94 (m), 12.58 (s), 13.80 (s), 14.20 (s), 14.52 μ (s); mass spectrum (75 eV) *m/e* (rel intensity) 394 (0.8), 324 (3.1), 289 (10), 254 (35), 159 (100).

A solution of 4.2 g (10.5 mmol) of 7 was cooled in an ice bath, and then 0.2 g (12 mmol) of triethylphosphite in 25 ml of hexane was added slowly. The solution gradually turned red and 1 hr after the addition tlc indicated that the dechlorination was proceeding very slowly. After 18 hr the solvent was removed, the residue was chromatographed on a silica gel column, and 0.4 g (13% conversion) of 2a was isolated, as shown by tlc and ir.

Preparation of 6-Phenyl-6-morpholinotetrachlorofulvene (9). Method A.—A solution containing 2.04 g (10.0 mmol) of 8 in 20 ml of diglyme was cooled to −20° and treated carefully with 500 mg (10.4 mmol, 50% in paraffin oil) of sodium hydride. When a clear dark blue solution was obtained, 3.40 g (9.7 mmol) of the salt, prepared from phenylmorpholino thioketone and methyl iodide in acetone, was added in small portions. After the mixture was stirred for 1 hr, ethyl acetate, dilute HCl, and $NaHCO_3$ were successively added. The organic layer was separated, dried, and then evaporated. The residue was recrystallized from methanol and then from cyclohexane from which was obtained 0.5 g (13.4% yield) of orange crystals of 9: mp 199.5–200°; uv max (benzene) 403.5 nm (log ε 4.18); ir (KBr) 6.52 (s), 6.82 (m), 6.97 (m), 7.54 (s), 7.75 (s), 7.96 (m), 8.98 (m), 9.20 (m), 9.78 (m), 13.02 (m), 13.87 (w), 14.4 (w), 14.77 μ (w).

Method B.—An ice bath was used to cool a solution of 0.5 g (1.5 mmol) of 2a in 50 ml of anhydrous ether. Then 0.68 g (3.7 mmol) of morpholine was added all at once. The reaction mixture was stirred for 2.5 hr. From this reaction was obtained 0.56 g (99% yield) of 9 as shown by ir spectroscopy.

Anal. Calcd for $C_{16}H_{13}NOCl_4$: C, 50.96; H, 3.47; N, 3.71; Cl, 37.61. Found: C, 51.05; H, 3.53; N, 3.82; Cl, 37.65.

3,5-Dibromo-1,2,3,5-tetrachloro-4-(dichloromethylene)cyclopentene (10).—After 2.2 g (10 mmol) of cupric bromide and 2.8 g (10 mmol) of 1 were refluxed for 4 hr in acetonitrile, 0.17 g (5% conversion) of a clear crystalline material was found in addition to unreacted 1. This compound decomposed to a red melt between 177 and 187° and had an ir spectrum identical with that

(24) On heating, compound 6 gradually isomerized to an isomer with a singlet at δ 5.27.

of **10** prepared by an alternate route:[4] ir (KBr) 6.11 (s), 6.25 (m), 8.28 (m), 8.60 (s), 10.77 (w), 12.75–12.95 μ (s).

Methyl 2,3,4,5-Tetrachlorocyclopentadiene-1-carboxylate (11a).—A dark solution was obtained after refluxing 8.5 g (30 mmol) of **1** in 75 ml of dry methanol for 24 hr. The methanol was removed, and the dark residue was vacuum distilled [90° (0.08 mm)]. The distillation yielded 4 g (51% yield) of **11a** as a yellow liquid and also a small amount of **8** (identified by mass spectroscopy, nmr, and melting point).[9] The yellow distillate decomposed on attempted purification by gas and column chromatography; however, after about 1 month in a refrigerator, it suddenly crystallized. It was then recrystallized from hexane: mp 59.5–60.5°; ir (KBr) 5.90 (s), 6.25 (w), 6.45 (m), 6.96 (m), 7.49 (m), 7.68 (m), 8.19 (s), 8.41 (m), 8.96 (m), 12.71 (m), 13.57 μ (m); uv max (95% EtOH) 216 nm (log ϵ 4.03), 298 (3.94); mass spectrum (75 eV) *m/e* (rel intensity) 260 (11), 200 (31), 59 (100).

Anal. Calcd for $C_7H_4Cl_4O_2$: C, 32.10; H, 1.54; Cl, 54.11. Found: C, 32.01; H, 1.73; Cl, 54.01.

Aluminum Chloride Catalyzed Reactions of 1 with Benzene. Method A. Monophenylation at 23°.—To a solution containing 5.68 g (20 mmol) of **1** and 1.56 g (20 mmol) of benzene in 75 ml of CS_2 was added 2.66 g (20 mmol) of $AlCl_3$ at room temperature. After the mixture was stirred for 1 hr, dilute HCl was added and the organic material was isolated. Column chromatography (silica gel–hexane) gave 0.7 g of **1** and 2.6 g of **12** (45% yield). Orange–red needles of **12** were obtained from methanol: ir (KBr) 6.38 (s), 6.71 (m), 6.91 (w), 7.96 (s), 8.45 (m), 9.74 (w), 10.33 (m), 10.82 (s), 10.94 (m), 11.26 (w), 13.03 (m), 13.67 (m), 14.38 μ (s); mass spectrum (75 eV) *m/e* (rel intensity) 324 (24.6), 289 (42.6), 254 (100), 184 (27.8).

Anal. Calcd for $C_{12}H_5Cl_5$: C, 44.13; H, 1.55; Cl, 54.32. Found: C, 44.19; H, 1.55; Cl, 53.90.

Method B. Monophenylation at 5°.—A solution containing 5.68 g (20 mmol) of **1** and 1.56 g (20 mmol) of benzene in 50 ml of CS_2 was cooled by means of an ice bath to 5° before 2.66 g (20 mmol) of $AlCl_3$ was added. The reaction mixture was stirred at this temperature for 3 hr, then dilute HCl was added, and the reaction was worked up as in the previous example. About 1.9 g of **1** and 2.0 g (46% yield) of a mixture of **12** and **13** were obtained. A small amount of **13** was isolated as dark red needles by careful recrystallizations from methanol: ir (KBr) 6.37 (s), 6.72 (w), 6.90 (w), 7.71 (m), 8.16 (m), 8.71 (m), 10.52 (w), 10.82 (w), 11.28 (w), 13.07 (m), 13.92 (m), 14.48 (s), 14.93 μ (m); mass spectrum (75 eV) *m/e* (rel intensity) 324 (100), 289 (4.2), 254 (65.5), 184 (31.9). More data on **12** and **13** are given in Table III.

Anal. Calcd for $C_{12}H_5Cl_5$: C, 44.13; H, 1.55; Cl, 54.32. Found: C, 43.89; H, 2.04; Cl, 53.87.

Method C. Diphenylation at 23°.—A solution containing 5.68 g (20 mmol) of **1** in 125 ml of benzene was stirred while 5.33 g (40 mmol) of $AlCl_3$ was added. After 2 hr at room temperature, the reaction was worked up as usual. Column chromatography (silica gel, 10:1 hexane–benzene) gave 3.0 g (41% yield) of diphenyltetrachlorofulvene and 0.8 g (10% yield) of triphenyltrichlorofulvene (see method D). The former product was a red oil and all attempts to crystallize it failed: ir (neat) 6.42 (s), 6.91 (m), 8.72 (w), 10.94 (m), 11.30 (w), 13.60 (m), 14.37 (s), 14.77 μ (m); mass spectrum (75 eV) *m/e* (rel intensity) 366 (42), 331 (86), 296 (100), 260 (45), 224 (41); nmr (CCl_4) δ 7.2 (br m).

Method D. Triphenylation.—A mixture of 1.42 g (5 mmol) of **1**, 3.0 g (22 mmol) of $AlCl_3$, and 50 ml of benzene was refluxed for 6 hr. The organic material was isolated as usual. From column chromatography (silica gel, 8:1 hexane–chloroform) was obtained 1.4 g of brown needles. After recrystallization from methanol, 0.95 g (46.5% yield) of triphenyltrichlorofulvene was obtained: mp 126–128°; ir (KBr) 6.45 (m), 6.71 (w), 6.94 (m), 7.75 μ (w); uv max (benzene) 312 nm, sh at 420 nm (log ϵ 4.20).

Anal. Calcd for $C_{24}H_{15}Cl_3$: C, 70.35; H, 3.69; Cl, 25.96. Found: C, 70.44; H, 3.83; Cl, 26.01.

Hydrolysis of 1 with Concentrated Sulfuric Acid.—A mixture of 2.84 g (10 mmol) of **1** and 40 ml of concentrated H_2SO_4 was stirred and heated on a steam bath for 3 hr. The dark green solution was then cooled and poured over ice. A tan solid formed which was filtered off and washed with water. Recrystallization from ethanol yielded 1.7 g (64% yield) of 2,3,4-trichloro-5-(dichloromethylene)cyclopent-2-en-1-one (**14a**): mp 100–100.5°.

Anal. Calcd for C_6HCl_5O: C, 27.04; H, 0.38; Cl, 66.56. Found: C, 27.10; H, 0.34; Cl, 66.75.

A minor product was also isolated in 8% yield by adding the crude product to a $NaHCO_3$ solution. Insoluble material was filtered off and the filtrate was acidified. The amorphous light tan solid that precipitated was identified as 2,3,4,5-tetrachlorocyclopentadiene-1-carboxylic acid **16**: mp 202–204° dec; ir (Nujol) 3.6–4.0 (m), 5.89 (m), 6.15 (s), 6.48 (s), 6.83 (s), 8.58 (m), 10.83 (m), 13.95 (s), 14.17 μ (s); mass spectrum (75 eV) *m/e* (rel intensity) 246 (63), 211 (100), 183 (65); uv max (CCl_4) 286 nm (log ϵ 3.93).

Anal. Calcd for $C_6H_2Cl_4O_2$: C, 29.06; H, 0.81; Cl, 57.23. Found: C, 29.08; H, 1.07; Cl, 57.51.

Registry No.—**1**, 6317-25-5; **2a**, 33834-97-8; **2b**, 33834-98-9; **2c**, 33834-99-0; **2d**, 33835-00-6; **2e**, 33835-01-7; **2f**, 33835-02-8; **3a**, 33835-03-9; **3b**, 33835-04-0; **3c**, 33835-05-1; **6**, 33835-06-2; **7**, 33835-07-3; **9**, 33835-08-4; **10**, 33835-09-5; **11a**, 33835-10-8; **12**, 33835-11-9; **13**, 33835-12-0; **14a**, 29897-40-3; **16**, 33835-14-2; diphenyltetrachlorofulvene, 33825-85-3; triphenyltrichlorofulvene, 33825-86-4.

Adducts of Fulvene and 6-Acetoxyfulvene with Dimethyl Azodicarboxylate

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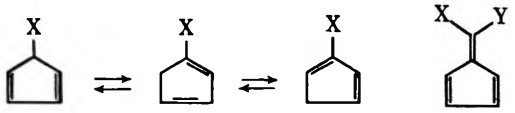
The syntheses of dimethyl 7-methylene- and 7-acetoxymethylene-2,3-diazabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate are described. All efforts to hydrolyze the enol acetate to the corresponding aldehyde were unsuccessful. Catalytic hydrogenation reduced the bridge double bond and then the enol acetate double bond sequentially in a highly stereoselective reaction to produce dimethyl 7-*syn*-acetoxymethyl-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate. Nevertheless, a reversal of double bond reactivity is observed on bromination. Addition of bromine to the enol acetate generates stereoselectively dimethyl 7-*anti*-formyl-7-*syn*-bromo-2,3-diazabicyclo[2.2.1]-hept-5-ene-2,3-dicarboxylate. Rationalization of these stereoselectivities is presented. The adducts of 4-phenyl-1,2,4-triazoline-2,5-dione with the ethyl ketal of cyclopentadienone and the ethylene and dibenzyl ketals of tetrachlorocyclopentadienone are also described.

The preparation of 7-substituted 2,3-diazabicyclo-[2.2.1]hept-5-enes, important compounds both for physical chemical studies and as intermediates in the synthesis of theoretically interesting small rings, may be approached in several ways. Functionalization of 7-keto derivatives provides a direct and versatile approach to such compounds.[3] Alternatively, the utilization of substituted cyclopentadienes avoids such

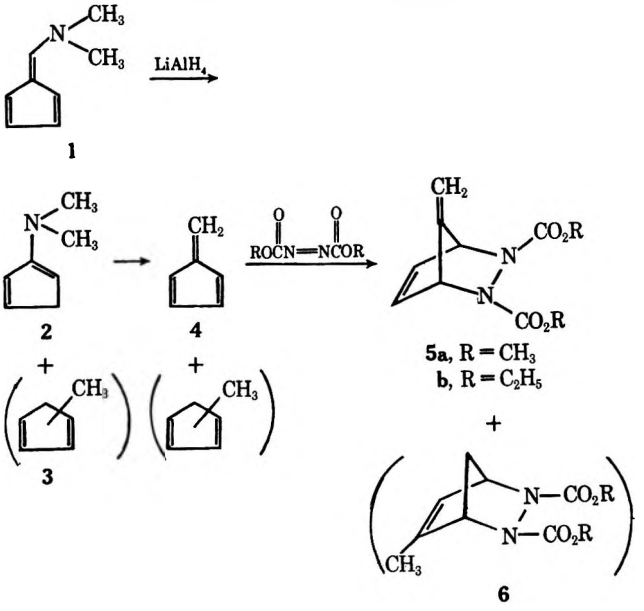


intermediates. Two types of substituted cyclopentadienes may be employed—5-alkylcyclopentadienes[4] or 5-alkylidenecyclopentadienes (fulvenes). Use of the latter class precludes the formation of isomeric adducts arising from the 1,5-hydrogen shift in the 5-alkylcyclopentadienes competing with condensation. Only 6,6-dimethyl- and 6,6-diphenylfulvene have been employed as dienes with azodienophiles.[3c-e,5] Fulvenes substituted with strong electron-releasing substituents (*e.g.*, dimethylamino) in the six position do not participate in normal Diels–Alder reactions;[6] nevertheless, such functionality was of particular interest to us since our goal was the synthesis of a 7-formyl derivative. We, therefore, examined the behavior of fulvene and 7-acetoxyfulvene toward dimethyl azodicarboxylate and the chemistry of the resultant adducts.

Fulvene **4** was prepared by the method of Sturm and Hafner.[7] Full details are included in the Experimental Section since these conditions are not available. Treatment of a solution of fulvene in ether with excess dimethyl or diethyl azodicarboxylate gave a 95% yield of the desired adduct **5** contaminated with a trace of the 2-methylcyclopentadiene adduct **6** (see Scheme I). The formation of methylcyclopentadiene **3** arises as a result of overreduction in the conversion of 6-dimethyl-

SCHEME I

SYNTHESIS OF DIMETHYL 7-METHYLENE-2,3-DIAZABICYCLO[2.2.1]HEPT-5-ENE-2,3-DICARBOXYLATE



aminofulvene **1** into 6-dimethylaminomethylcyclopentadiene **2**. An attempt to convert the 7-methylene into a 7-formyl substituent by epoxidation and rearrangement was made. Epoxidation with *m*-chloroperbenzoic acid led to production of *m*-chlorobenzoic acid; however, nmr examination of the remaining organic material indicated the presence of mostly recovered starting material. A singlet did appear at δ 3.17 which potentially could be assigned to the desired 7-epoxide. The lability of the reaction mixture precluded isolation of any pure compounds.

This investigation subsequently centered upon the adduct derived from 6-acetoxyfulvene since this compound possesses the desired aldehyde masked as its enol acetate. 6-Acetoxyfulvene, readily available by the condensation of cyclopentadiene and ethyl formate followed by acetylation,[8] readily cycloadded in a variety of solvents with dimethyl azodicarboxylate to form a very labile adduct **7** (see Scheme II). A variety of mild reagents, including methanol, converted it into intractable tars. Its characterization by spectral means, however, fully confirms the assigned structure (see Experimental Section).

(1) Camille and Henry Dreyfus Teacher–Scholar Grant Recipient.

(2) National Science Foundation and National Institutes of Health Predoctoral Fellow.

(3) (a) B. M. Trost, R. M. Cory, and P. D. Carpenter, submitted for publication; (b) E. L. Allred and C. Anderson, *J. Org. Chem.*, **32**, 1874 (1967); (c) N. P. Marullo and J. A. Alford, *ibid.*, **33**, 2368 (1968); (d) N. P. Marullo, A. Bodine, J. L. Eggers, and A. Sobti, *Tetrahedron Lett.*, 3939 (1969); (e) J. J. Tufariello and J. J. Spadaro, Jr., *ibid.*, 3935 (1969).

(4) B. M. Trost and R. M. Cory, *J. Amer. Chem. Soc.*, **93**, 5572 (1971).

(5) J. A. Berson, R. J. Bushby, J. M. McBride, and M. Tremelling, *J. Amer. Chem. Soc.*, **93**, 1544 (1971).

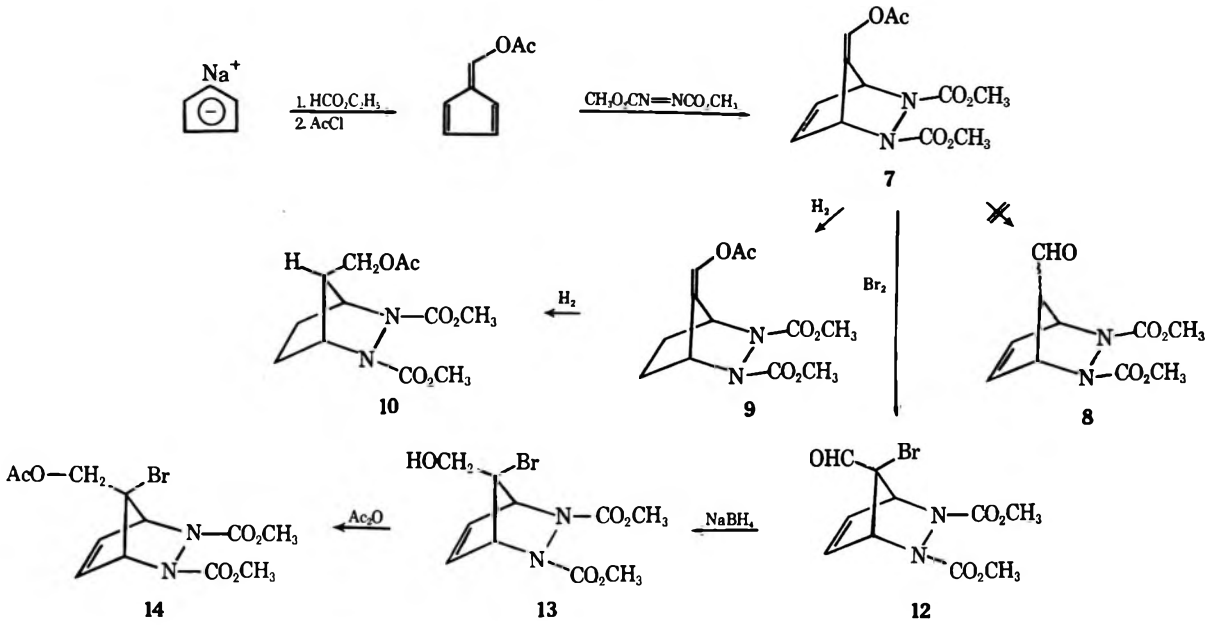
(6) K. Hafner, K. H. Vöpel, G. Ploss, and C. König, *Justus Liebigs Ann. Chem.*, **661**, 67 (1963). See, however, K. Hafner and W. Bauer, *Angew. Chem., Int. Ed. Engl.*, **7**, 297 (1968).

(7) E. Sturm and K. Hafner, *ibid.*, **3**, 749 (1964).

(8) K. Hafner, G. Schultz, and K. Wagner, *Justus Liebigs Ann. Chem.*, **678**, 49 (1964).

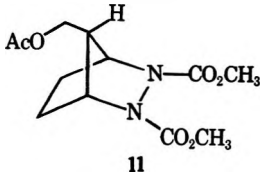
SCHEME II

SYNTHESIS AND CHEMISTRY OF DIMETHYL 7-ACETOXYMETHYLENE-2,3-DIAZABICYCLO[2.2.1]HEPT-5-ENE-2,3-DICARBOXYLATE



All attempts to convert **7** to the aldehyde, **8**, under many different conditions met with failure in that only tars and other intractable materials were produced. Reagents tried included dilute aqueous sulfuric acid in monoglyme, aqueous oxalic acid, aqueous sodium acetate, acidic ion-exchange resin in aqueous monoglyme, aqueous sodium bisulfite in monoglyme, hydrogen bromide in methylene chloride, and methyllithium in tetrahydrofuran. Although peaks were observed in some of the reaction mixtures in the nmr region of δ 9–10, the expected product and the compounds responsible for the peaks could not be isolated.

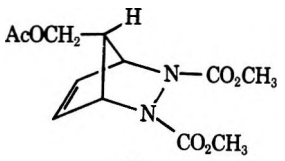
Catalytic hydrogenation of fulvene adducts normally leads to saturation of the 5,6 double bond.[3] The possibility that acetoxy substitution could reverse this selectivity to provide the acetate of the alcohol corresponding to **8** was briefly examined. Catalytic hydrogenation over palladium on carbon led after uptake of 1 equiv of hydrogen to the dihydro derivative **9** exclusively. Prolonged hydrogenation produced the fully saturated derivative **10**. Chromatographic and spectroscopic properties indicated that **10** was a homogeneous substance. None of the *anti*-7-acetoxymethyl compound **11**, available by an alternate sequence,[4] was



11

detectable. The high stereoselectivity observed in this hydrogenation can be attributed to the steric hindrance created by the carbamate groups to approach of the catalyst syn to these groups.

Whereas catalytic hydrogenation followed the traditional reactivity patterns of such fulvene adducts, bromination led to a reversal of the relative double-bond reactivities.[9] Treatment of **7** with 1 equiv of bromine in methylene chloride led directly to a compound $C_{10}H_{11}O_5N_2Br$ (high resolution mass spectroscopy). The ir spectrum indicated the presence of an aldehyde in addition to the carbamate groups (2725, 1754, and 1724 cm^{-1}). The nmr spectrum confirmed the presence of the aldehyde bound to a fully substituted carbon (δ 9.19, 1 H, singlet). The remaining absorptions indicated the presence of the 2,3-diazabicyclo[2.2.1]hept-5-ene system (see Experimental Section). This data requires the gross structure depicted in **12**. The stereochemistry was assigned on a consideration of the solvent-induced shifts of a derivative, **14**, compared to the related shifts for the bromine free compound **15** and the



15

saturated acetoxymethyl compounds **10** and **11**. Dimethyl 7-bromo-7-acetoxymethyl-2,3-diazabicyclo-[2.2.1]hept-5-ene-2,3-dicarboxylate (**14**) was obtained by sodium borohydride reduction of **12** to the hydroxymethyl compound **13** followed by acetylation.

Table I summarizes the solvent-induced shifts observed for **10**, **11**, **14** and **15**. The key differences arise in the magnitude of the ASIS for the 7-CH_2OAc and the 7-CH absorptions in **10** and **11**. Prior investigations of

TABLE I

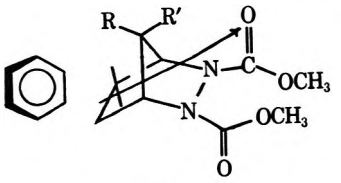
BENZENE-INDUCED SOLVENT SHIFTS[a] (ASIS[b])

Compd	CH_3CO	CH_2OAc	7-CH	CO_2CH_3	5,6-H	Bridgehead H
10	9	1	15	8	13	5
11	12	11	3	7	9	2
14	13	10		8	18	8
15	12	11	7	9	14	7

[a] All shifts are obtained from the equation $\Delta Hz = Hz_{CDCl_3} - Hz_{CDCl_3 + PhH}$. [b] ASIS = aromatic solvent-induced shift.

(9) T. J. Limasova, J. Ronayne, and D. H. Williams, *Zh. Org. Khim.*, **7**, 751 (1971).

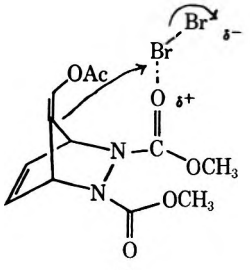
such shifts established that benzene associates with the more positive end of a solute molecular dipole.[10] In any of the compounds under discussion, the predominant influence on the dipole moment is the highly polarized carbamate functions. Thus, the collision complex should mostly resemble **16**. Indeed, the 7-*syn*-acetoxy-



16

methyl compound **10** exhibits a large shift for the 7-methine hydrogen and only a small one for the methylene group of the 7-acetoxymethyl substituent. Exactly the reverse behavior is observed for the 7-*anti*-acetoxymethyl series. The presence of a double bond in the 5,6 position does not alter the magnitude of the shifts (*cf.* **15**). Comparing the ASIS for the protons of the bromo compound **14** to those of the related derivatives shows remarkably close shifts to those of **11** and **15**. This result suggests the 7-anti stereochemistry for **14** and thus for the aldehyde **12**. Attempts to confirm these assignments by cyclizing the bromohydrin failed.[11]

The high stereoselectivity of the bromination contrasts to that of the catalytic hydrogenation—bromine approaches from the more hindered side. Two reasons may be suggested. First, the urethane linkages may facilitate syn approach by complexing molecular bromine and delivering the reagent intramolecularly, *i.e.*, **17**. Second, the 5,6 double bond may stabilize the in-



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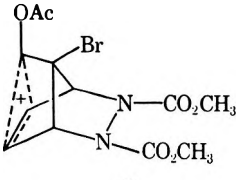
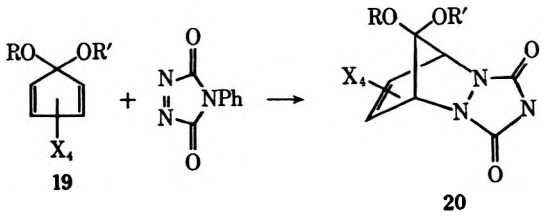


18

termediate cation **18**. This latter possibility, though attractive, appears less likely since it has been shown that, in the case of the bicyclo[2.2.1]hept-2-en-7-ylmethyl cation, the syn isomer is not stabilized relative to the anti isomer.[12] The fact that bromoaldehyde is a direct product of bromination indicates that deacylation of **18** by bromide addition to the carbonyl and elimination of acetyl bromide is the preferred mode of satisfying the positive charge. Such fulvene adducts and especially the bromoaldehyde should prove to be valuable synthetic intermediates.

In an ancillary investigation, obtention of 7-substituted 2,3-diazabicyclo[2.2.1]hept-5-enes from their 7-keto derivatives was examined. Utilizing the Diels–Alder reaction of 4-phenyl-1,2,4-triazoline-3,5-dione with ketals **19a**, **19b**, and **19c** generated the correspond-



19 **20**

a, R, R′ = CH_2CH_2; X = Cl
b, R = R′ = CH_2Ph; X = Cl
c, R = R′ = CH_2CH_3; X = H

ing Diels–Alder adducts **20a**, **20b**, and **20c**. Hydrolysis, hydrogenolysis, or dealkylation procedures failed to convert any of these ketals to their ketones or ketone hydrates.[3]

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus and are corrected. Ir spectra were determined on a Beckman IR-8 spectrophotometer, and uv spectra were recorded on Cary Model 11 and Model 15 spectrophotometers. Nmr spectra were determined on a Varian Associates Model A-60A spectrometer fitted with a variable-temperature probe. Chemical shifts are given in δ units, parts per million relative to TMS as an internal standard. Mass spectra were taken on a CEC 103 C or a MS-902 mass spectrometer at an ionizing current of 40 mA and ionizing voltage of 70 V. Analyses were performed by Spang Microanalytical Laboratory.

All reactions were carried out under nitrogen. Thick layer chromatography (tlc) was performed on 20 × 20 cm × 1.5 mm or 20 × 40 cm × 1.5 mm layers of silica gel PF-254 (E. Merck AG Darmstadt).

N,*N*-**Dimethylaminomethylcyclopentadiene** (**2**).—The following operations were performed with the room lights off. To 10.08 g (83.3 mmol) of 6-(*N*,*N*-dimethylamino)fulvene (**1**),[6] with stirring, was added, by direct distillation from lithium aluminum hydride, sufficient ether (~250 ml) to just dissolve the yellow solid. The resulting yellow solution was transferred to a dropping funnel and added in 15 min to a stirred suspension of 3.12 g (82.3 mmol) of lithium aluminum hydride in 50 ml of ether (dried as above) kept between −5 and 0° by means of a methanol–ice bath. After the mixture had been stirred for another 75 min in that temperature range, it was cooled to −20°, and there were added very slowly with vigorous stirring *via* syringe 3.5 ml of water, 3.5 ml of 15% aqueous sodium hydroxide, and 9.5 ml of water. During these additions the temperature was not allowed to rise above −3°. The suspension was allowed to stir for 15 min thereafter and then filtered by suction. The white cake was washed with ether, and the filtrate was evaporated at −20° until the pressure had fallen to 15 mm. The concentrated solution was filtered through a short column of anhydrous sodium carbonate, which was then washed with ether, and the filtrate was cooled to −20° under nitrogen. The bulk of the remaining ether was distilled at −20° under aspirator pressure into a trap at −70° protected by a drying tower. The residue was shown by nmr, using benzene as internal standard, to contain 75% (8.0 g, 78% yield) amine **2** (mixture of isomers) in ether.

Nmr (CCl_4) showed δ 2.13 (s, 6 H, NCH_3), 2.90 (m, 2 H, divinyl CH_2), 3.12 (m, 2 H, vinyl amino CH_2), 5.95–6.55 (m, 3 H, vinyl H).

Fulvene (**4**).—A 2.7 × 32.7 cm column of 200 g of Woelm alumina (activity II) was prepared in pentane under nitrogen. To this was applied 2.02 g (16.4 mmol) of amine **2** in the crude solution described above. A yellow band was produced immediately and was eluted in ~70 ml of pentane. Using benzene as internal standard, this solution was shown by nmr and vpc to contain 0.40 g of fulvene with minor amounts of two other volatile products. Further fractions from the column, though a yellow coloration on the column could not be discerned, were found to contain almost pure fulvene and were eluted in ~600 ml of pentane. These were analyzed as before and found to contain a total of 0.58 g of fulene, bringing the combined yield to 0.98 g

(10) For a review, see J. Ronayne and D. H. Williams, *Annu. Rev. NMR. Spectrosc.*, **2**, 83 (1969).

(11) See R. K. Bly and R. S. Bly, *J. Org. Chem.*, **28**, 3165 (1963); J. C. J. MacKenzie, A. Rodgman, and G. F. Wright, *ibid.*, **17**, 1666 (1952).

(12) R. K. Bly and R. S. Bly, *ibid.*, **31**, 1577 (1966); J. A. Berson, M. S. Poonian, W. J. Libby, J. J. Gajewsky, and D. S. Donald, *J. Amer. Chem. Soc.*, **91**, 5550, 5567 (1969).

(77%). These dilute fractions were concentrated by flash distillation of the solvent through an efficient fractionating column.

Nmr[13] (pentane) showed δ 5.71 (s, 2 H, CH_2), 6.12 (m, 2 H, ring H), 6.43 (m, 2 H, ring H).

Fulvene Adduct 5 with Dimethyl Azodicarboxylate. Dimethyl 7-Methylene-2,3-diazabicyclo[2.2.1]-5-heptene-2,3-dicarboxylate.—To a solution of 63 mg (0.81 mmol) of the crude fulvene in 13 ml of ether was added 0.394 g (2.70 mmol) of dimethyl azodicarboxylate. The solution was refluxed for 44.5 hr, after which vpc showed that only 60% of the fulvene had reacted. An additional 0.233 g (1.57 mmol) of the azo compound was added bringing the total to 4.27 mmol. After a total of 70 hr of refluxing the mixture was allowed to stand at room temperature for 24 hr. The ether solution was decanted from the brown solids and evaporated to a reddish brown syrup. The excess azo compound was removed by distillation at 0.3 mm; the bath temperature was allowed to rise to 65°. The residue was chromatographed on 15 g of Woelm alumina (activity III), and elution with methylene chloride gave a mixture which was shown by nmr to consist of 0.17 g (95%) of the fulvene adduct, **5**, 0.07 g of the adduct of methylcyclopentadiene with the azo compound (**6**, dimethyl 5-methyl-2,3-diazabicyclo[2.2.1]-5-heptene-2,3-dicarboxylate), and ~0.02 g of an unidentified compound. Further elution with methylene chloride gave 42 mg of dimethyl hydrazodicarboxylate $CH_3O_2CNHNHCO_2CH_3$, mp 128–130° (chloroform).

Although the two adducts were difficult to separate, they could be purified by preparative tlc, eluting with ether or methylene chloride.

Nmr ($CDCl_3$) of the fulvene adduct showed δ 3.77 (s, 6 H, OCH_3), 4.56 (s, 2 H, 7-CH_2), 5.17 (unresolved m, 2 H, bridgehead CH), 6.74 (t, 2 H, J = 2 Hz, bridge vinyl H); ir ($CHCl_3$) 1712 (s, br) cm^{-1}; mass spectrum m/e (%) 59 (80, $^+CO_2CH_3$), 78 (100, fulvene), 106 (3, M − 2 × 59), 165 (2, M − 59), 224 (1.5, M); exact mass determination calcd for $C_{10}H_{12}N_2O_4$, 244.07970; found, 224.07751 ± 0.004.

Nmr[14] (CCl_4) for adduct **6** showed δ 1.65 (m, 2 H, bridge CH_2), 1.90 (d, 3 H, J = 1.5 Hz, vinyl CH_3), 3.68 (s, 6 H, OCH_3), 4.80 (unresolved m, 1 H, bridgehead CH), 4.96 (unresolved m, 1 H, bridgehead CH), 5.97 (unresolved m, 1 H, vinyl H).

Enol Acetate 7. Dimethyl 7-Acetoxymethylene-2,3-diazabicyclo[2.2.1]-5-heptene-2,3-dicarboxylate.—To 99.4 mg (0.73 mmol) of 6-acetoxyfulvene[8] in 0.5 ml of chloroform in an nmr tube was added 104.1 mg (0.71 mmol) of dimethyl azodicarboxylate. The reaction was followed by nmr, and at probe temperature (~40°) a rough plot of [adduct 7]/[azo] *vs.* time gave a second-order rate constant of 5×10^{-3} l. mol^{-1} sec^{-1}. After 45 min the azo compound had been consumed, leaving about 10% of the starting fulvene. The solvent was evaporated to a yellowish gum which could not be purified without decomposition.

Nmr ($CDCl_3$) showed δ 2.14 (s, 3 H, CH_3CO), 3.79 (s, 6 H, OCH_3), 5.33 (unresolved m, 1 H, bridgehead CH), 5.62 (unresolved m, 1 H, bridgehead CH), 6.72 (t, 2 H, J = 2 Hz, bridge vinyl H), 6.86 (s, 1 H, vinyl HCOAc); ir (CCl_4) 1767 (s), 1721 (s) cm^{-1}; mass spectrum m/e (%), 43 (100, CH_3CO^+), 49 (37), 66 (28, 94 − CO, cyclopentadiene), 83 (30), 94 (61, 136-ketene), 136 (29, 94), 240 (0.4, M − ketene), 282 (0.4, M); exact mass determination calcd for $C_{12}H_{14}N_2O_6$, 282.08518; found, 282.08518 ± 0.001.

Saturated *syn*-Acetate 10. Dimethyl 7-*syn*-Acetoxymethyl-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate.—To 24.6 mg of 10% palladium on charcoal in 2 ml of ethyl acetate which had been equilibrated under 1 atm of hydrogen for 10 hr was added 100 mg (0.36 mmol) of the crude enol acetate **7** in 0.8 ml of ethyl acetate. The first equivalent of hydrogen (~10 ml) was taken up in 15 min and the second in 5 hr. After a total of 11 hr, 0.54 mmol of hydrogen had been consumed, and the mixture was filtered. The filtrate was evaporated to a brown gum, which was purified by preparative tlc (ether elution, R_f 0.16) to give 42 mg (>41%) of the completely saturated acetate **10**. Molecular distillation at a bath temperature of 130° (0.02 mm) produced a colorless, gummy liquid.

Nmr (CCl_4) showed δ 1.79 (unresolved m, 4 H, ring CH_2), 2.02 (s, 3 H, CH_3CO), 2.21 (t of unresolved m's, J = 8 Hz, 1 H, 7-CH), 3.72 (s, 6 H, OCH_3), 3.92 (d, 2 H, J = 8 Hz, OCH_2), 4.37 (unresolved m, 2 H, bridgehead CH); ir (CCl_4) 1748 (s), 1715 (s) cm^{-1}; mass spectrum m/e (%) 43 (100, Ac^+), 59 (44, $^+CO_2CH_3$), 81 (34), 95 (82), 139 (53), 227 (12, M − 59), 286 (40, M); exact mass determination calcd for $C_{12}H_{18}N_2O_6$, 286.11648; found, 286.11120 ± 0.005.

Anal. Calcd for $C_{12}H_{18}N_2O_6$: C, 50.35; H, 6.34; N, 9.79. Found: C, 50.26; H, 6.29; N, 9.71.

Dihydro Enol Acetate 9. Dimethyl 7-Acetoxymethylene-2,3-diazabicyclo[2.2.1]heptane-2,3-dicarboxylate.—After 22.2 mg of 10% palladium on charcoal in 2 ml of ethyl acetate had been equilibrated under 1 atm of hydrogen for 6 hr, 0.118 g (<0.42 mmol) of the crude enol acetate **7** in 1 ml of ethyl acetate was added. After 18 min the hydrogen uptake began to slow down, and the hydrogen was replaced by nitrogen. At this point, 8.5 ml (0.30 mmol) of hydrogen had been consumed. The mixture was filtered, and the filtrate was evaporated to a brown gum. Preparative tlc (eluting with ethyl acetate) yielded 19 mg of the completely saturated *syn*-acetate **10** (R_f 0.45) and 63 mg (>53%) of enol acetate **9** (R_f 0.55).

Nmr (CCl_4) showed δ 1.85 (unresolved m, 4 H, ring CH_2), 2.14 (s, 3 H, CH_3CO), 3.70 (s, 6 H, OCH_3), 4.67 (unresolved m, 1 H, bridgehead CH), 4.96 (unresolved m, 1 H, bridgehead CH), 7.09 (s, 1 H, vinyl H); ir (CCl_4), 1767 (s), 1718 (s) cm^{-1}; mass spectrum m/e (%) 43 (99, Ac^+), 59 (29, $^+CO_2CH_3$), 67 (33), 79 (35), 95 (35), 116 (39), 117 (44), 119 (41), 148 (100, M − $MeO_2CNHNHCO_2Me$), 213 (2, 241 − CO), 225 (2, M − 59), 241 (6, M − Ac), 284 (10, M); exact mass determination calcd for $C_{12}H_{16}N_2O_6$, 284.10083; found, 284.09819 ± 0.003.

Bromo Aldehyde 12. Dimethyl 7-*anti*-Formyl-7-bromo-2,3-diazabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate.—To 67.4 mg (<0.24 mmol) of crude enol acetate **7** in 3 ml of methylene chloride at −78° was added 13 μl (0.24 mmol) of bromine in 0.5 ml of methylene chloride. The addition required 10 min. After it had stirred for 15 min at −78°, the mixture was allowed to warm to room temperature. The solvent was evaporated under aspirator pressure, and the resulting brown gum was redissolved in methylene chloride and extracted twice with 5% aqueous sodium bicarbonate, twice with water, and twice with saturated aqueous sodium chloride. The methylene chloride solution was dried over sodium sulfate and evaporated to a brown gum which was purified by preparative tlc, eluting with ethyl acetate. The major band (R_f 0.54) was shown to contain 42 mg (>55%) of the bromo aldehyde **12**.

Nmr ($CDCl_3$) showed δ 3.78 (s, 6 H, OCH_3), 5.23 (unresolved m, 2 H, bridgehead CH), 6.52 (t, 2 H, J = 2 Hz, vinyl H), 9.19 (s, 1 H, CHO); ir ($CHCl_3$) 1754 (s, sh), 1724 (s) cm^{-1}; mass spectrum m/e (%) 59 (100, $^+CO_2CH_3$), 163 (8, 239 − 76), 195 (12, 239 − 44), 239 (43, M − Br), 259 and 261 (1.5, M − 59), 318 and 320 (2, M), metastables at 111.3 (239 → 163), 159.2 (239 → 195), 179.1 (M → 239); exact mass determination calcd for $C_{10}H_{11}O_5N_2Br$, 317.98518; found, 317.98513 ± 0.003.

Bromohydrin 13. Dimethyl 7-*anti*-Hydroxymethyl-7-bromo-2,3-diazabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate.—To 101.5 mg (0.318 mmol) of bromo aldehyde **12** in 3 ml of absolute ethanol at 0° was added 31 mg (0.18 mmol) of the 1:1 complex of sodium borohydride and diglyme in 1.7 ml of ethanol. The addition required 10 min, and the solution was then allowed to warm to room temperature. After it had been stirred for 4.5 hr, the yellowish solution was squirted into 20 ml of water and stirred for 10 min. The mixture was treated with 10 ml of methylene chloride and 6.5 g of sodium chloride. The aqueous layer was washed with three 10-ml portions of methylene chloride, and the combined organic extracts were washed with 20 ml of saturated sodium chloride, dried over sodium sulfate, and evaporated. The resulting brown gum was purified by preparative tlc (ether elution) to give a single band (R_f 0.08) (in addition to diglyme) which contained 76 mg (74%) of the bromohydrin **13**.

Nmr ($CDCl_3$) showed δ 3.16 (position variable, br t, 1 H, J = 6.5 Hz, OH), 3.81 (s, 6 H, OCH_3), 3.98 (br d, 2 H, J = 6.5 Hz, CH_2OH), 5.07 (unresolved m, 2 H, bridgehead CH), 6.52 (t, 2 H, J = 2 Hz, vinyl H); ir ($CHCl_3$) 3584 (w), 3484 (wb), 1748 (s), 1709 (s) cm^{-1}; mass spectrum m/e (%) 39 (35), 41 (30), 42 (31), 49 (57), 59 (100, $^+CO_2CH_3$), 91 [91, $HOC(OCH_3)_2^+$], 92 (63), 241 (86, M − Br), 320 and 322 (5, M); exact mass determination calcd for $C_{10}H_{13}O_5N_2Br$, 320.00083; found, 320.00516 ± 0.005.

Bromo Acetate 14. Dimethyl 7-*anti*-Acetoxymethyl-7-bromo-2,3-diazabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate.—To 87 mg (0.27 mmol) of bromohydrin **13** in 0.3 ml of deuteriochloroform in an nmr tube was added 76 mg (0.75 mmol) of acetic anhydride. After a few milligrams of *p*-toluenesulfonic acid had been added,

(13) H. Schaltegger, M. Neuenschwander, and P. Meuche, *Helv. Chim. Acta*, **48**, 955 (1965).

(14) J. Wagner, W. Wojnarowski, J. E. Anderson, and J. M. Lehn, *Tetrahedron*, **25**, 657 (1969).

the rate of the reaction could be followed easily by nmr and was 75% complete in ~1 hr. The tube was then placed in the refrigerator (0°) for 12 hr, after which nmr showed only a trace of starting material. The mixture was transferred with methylene chloride to a flask containing a small amount of calcium carbonate, filtered, and evaporated to an off-white oil, which was purified by preparative tlc (ether elution) to give 74 mg (75%) of a colorless gum. On long standing, the latter crystallized to a white solid, mp 102–104°.

Nmr ($CDCl_3$) showed δ 2.17 (s, 3 H, CH_3CO), 3.88 (s, 6 H, OCH_3), 4.53 (s, 2 H, OCH_2), 5.11 (unresolved m, 2 H, bridgehead CH), 6.60 (t, 2 H, J = 2 Hz, vinyl H); ir (CCl_4) 1754 (s), 1724 (s) cm^{-1}; mass spectrum m/e (%) 43 (89, Ac^+), 49 (31), 59 (63, $^+CO_2CH_3$), 165 [41, 283 − (2 × 59)], 283 (100, M − Br), 362 and 364 (1, M), metastables at 96.2 (283 → 165) and 205.1; exact mass determination calcd for $C_{12}H_{15}O_6N_2Br$, 362.01140; found, 362.01140 ± 0.005.

1,4,5,6-Tetrachloro-2,3-diazabicyclo[2.2.1]hept-5-en-7-one-2,-3-phenyldicarboximide Ethylene Ketal (19a).—Into a suspension of 7.5 g (0.04 mol) of 4-phenylurazole[15] in 75 ml of reagent grade acetone under nitrogen cooled to −78° was added dropwise over a period of 45 min 4.45 g (0.04 mol) of *tert*-butyl hypochlorite.[16] Subsequent to this addition, a solution of 10.5 g (0.04 mol) of the ethylene ketal of tetrachlorocyclopentadienone in a minimum volume of acetone (~25 ml) was added at a rapid dropwise rate. The cooling bath was removed and stirring continued at room temperature until the red color of the triazoline disappeared (3–5 hr). The suspended solid was removed by filtration and the solvent evaporated *in vacuo* to yield more solid. Combined weight of crude material was 16.1 g (90% yield). Recrystallization from ethyl acetate–cyclohexane generated colorless crystals, mp 223°, weighing 13.4 g (75% yield).

Nmr (DMSO-d_6) showed apparent A_2B_2 with H_A at δ 4.35 and H_B at 4.30 (J_{AB} = 6 Hz), 7.38 (m, 5 H); ir ($CHCl_3$) 1790, 1740, 1590, 1555, 1500 cm^{-1}.

Anal. Calcd for $C_{15}H_9N_3O_4Cl_4$: C, 41.22; H, 2.08; N, 9.61; Cl, 32.45. Found: C, 41.41; H, 2.24; N, 9.89; Cl, 32.47.

1,4,5,6-Tetrachloro-2,3-diazabicyclo[2.2.1]hept-5-en-7-one-2,-3-phenyldicarboximide Dibenzyl Ketal (19b).—To a solution of 1.01 g (5.74 mmol) of 4-phenyl-1,2,4-triazoline-3,5-dione[2b] in 10.0 ml of methylene chloride was added 2.39 g (5.78 mmol) of tetrachlorocyclopentadienone dibenzyl ketal[17] in 10.0 ml of methylene chloride over 10 min. After an additional 15 min of stirring, the red color of the azo compound had been replaced by dark yellow. The solution was stirred for another 3.5 hr and evaporated to a gum which crystallized on standing for a few minutes. The gum was digested with refluxing cyclohexane, the suspension was filtered, and the filtrate was cooled, yielding 2.42 g (71%) of pale yellow crystals in three crops. The first crop was recrystallized from cyclohexane to give an analytical sample, mp 152.5–153.5°.

Nmr ($CDCl_3$) showed δ 7.36 (m, 15 H, Ar H), 5.17 (s, 2 H, OCH_2Ph), 4.95 (s, 2 H, OCH_2Ph); ir ($CHCl_3$) 1792 (w), 1752 (s) cm^{-1}; ir (Nujol mull) 748 (m) cm^{-1}; uv (ethanol) λ_{max} 2.51 nm (log ϵ 3.59), 257 (sh); mass spectrum m/e (%) 497 (8.7, M − CH_2Ph), 119 (25, PhNCO), 91 (100, C_7H_7).

Anal. Calcd for $C_{27}H_{19}Cl_4N_3O_4$ (mol wt, 590.98): C, 54.82; H, 3.25, Cl, 24.00; N, 7.11. Found: C, 54.87; H, 3.28; Cl, 23.93; N, 7.10.

(15) G. Zinner and W. Deucker, *Arch. Pharm. (Weinheim)*, **294**, 370 (1961).

(16) H. M. Teeter and E. W. Bell, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 125.

(17) L. S. Besford, R. L. Cookson, and J. Cooper, *J. Chem. Soc. C*, 1385 (1967).

2,3-Diazabicyclo[2.2.1]hept-5-en-7-one-2,3-phenyldicarboximide Diethyl Ketal.—To a solution of 1.00 g (6.32 mmol) of cyclopentanone diethyl ketal[18] in 16 ml of absolute ethanol at 5° was added, with stirring, 2.02 g (12.63 mmol) of bromine at such a rate that a small concentration of bromine was present at all times. The temperature was maintained below 20° by means of an ice bath. Anhydrous sodium carbonate (3.0 g) was then added, and the mixture was stirred for 10 min. After addition of 15 ml of pentane at 0° the mixture was poured into 8 ml of ice water. The pentane extract was separated, dried over anhydrous magnesium sulfate, and filtered, and the solvent was evaporated at 0°. The remaining colorless oil, crude 2,5-dibromocyclopentanone diethyl ketal, weighed 1.53 g (77%).

The above product was dissolved in 5 ml of dimethyl sulfoxide and added with vigorous stirring to 2.5 g (20.5 mmol) of potassium *tert*-butoxide in 15 ml of dimethyl sulfoxide. During the addition, which required 5 min, the temperature was kept just above 17° by cooling with a Dry Ice–acetone bath. To the resulting dark brown mixture was added 15 ml of cold pentane, and the mixture was poured into ~15 ml of ice, water, and salt. The pentane layer was separated and transferred to a dropping funnel jacketed with Dry Ice. The aqueous layer was extracted with four more 15-ml portions of pentane at 0°, each being combined with the first.

The combined extracts at −70° were added dropwise to 1.18 g (6.75 mmol) of 4-phenyl-1,2,4-triazoline-3,5-dione in 15 ml of methylene chloride at 25–30° during 1.5 hr. The mixture was refluxed for 0.5 hr after the addition was complete and then stirred at room temperature for 65 hr. The light brown solution was decanted and evaporated to a sticky solid. The latter was chromatographed on 100 g of alumina, eluting with methylene chloride. The product was recrystallized from benzene–petroleum ether (bp 60–68°) yielding 0.76 g (36%) of the ketal as white needles. An analytical sample was prepared by one more recrystallization, mp 144–145.5° (turned bright red while melting).

Nmr ($CDCl_3$) showed δ 1.17 (t, 6 H, J = 7.0, CH_2), 3.55 (pseudoquintet—superimposed doublet of quartets, 4 H, J = 6.9, OCH_2), 4.90 (A_2B_2 pattern, 2 H, bridgehead CH), 6.59 (A_2B_2 identical in appearance with that at 4.90, 2 H, vinyl H), 7.45 (m, 5 H, Ar H); ir ($CHCl_3$) 1767 (m), 1706 (s) cm^{-1}; uv (ethanol) λ_{max} 222 nm (log ϵ 4.15); mass spectrum m/e (%) 154 (4, cyclopentadienone diethyl ketal), 119 (100, PhNCO), 91 (58, C_6H_5N), 64 (48).

Anal. Calcd for $C_{17}H_{19}N_3O_4$ (mol wt, 329.33): C, 62.1; H, 5.82; N, 12.77. Found: C, 62.19; H, 5.88; N, 12.79.

Registry No.—**2**, 33608-32-1; **4**, 497-20-1; **5a**, 33527-33-2; **6** (R = CH_3), 22700-75-0; **7**, 33527-35-4; **9**, 33527-36-5; **10**, 33536-28-6; **12**, 33536-29-7; **13**, 33536-30-0; **14**, 33536-31-1; **19a**, 33527-37-6; **19b**, 33527-38-7; dimethyl hydrazodicarboxylate, 17643-54-8; 2,3-diazabicyclo[2.2.1]hept-5-en-7-one-2,3-phenyldicarboximide diethyl ketal, 33527-40-1.

Acknowledgment.—We wish to thank the National Science Foundation for their generous support of our programs. We also thank P. Carpenter for carrying out part of the experimental work.

(18) U. Schmidt and P. Grafen, *Justus Liebigs Ann. Chem.*, **656**, 97 (1962)

Derivatives of Thiacyclobutene (Thiete). VI.[1] Synthesis and Properties of Some Thietes[2-4]

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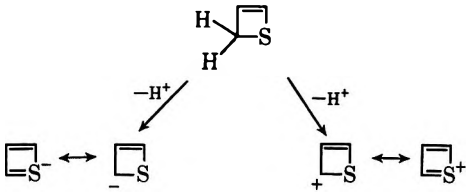
The synthesis and properties of five thiacyclobutenes (thietes) are described. Thietes are of theoretical interest because they have the potential of forming anions and cations isoelectronic with the anion and cation of cyclopentadiene. They are prepared by facile Hofmann eliminations from 3-aminothietane derivatives usually obtained *via* synthetic schemes which start with the addition of sulfene ($CH_2{=}SO_2$) to enamines. Thietes, while relatively stable at low temperatures, show a marked tendency to polymerize or to otherwise decompose over a period of time. Thietes (**4**, **5**), in which the sulfur-containing ring is fused to a six- or seven-membered carbocyclic ring, are less stable than thiete itself or thietes substituted with alkyl groups. Ring opening occurs when thietes are treated with acidified 2,4-dinitrophenylhydrazine to yield 2,4-dinitrophenylhydrazones. Several thietes can be oxidized to cyclic sulfones (thiete sulfones).

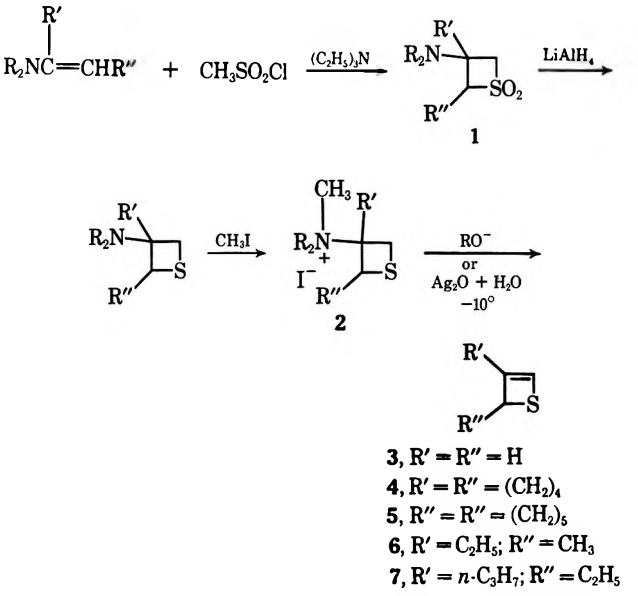
Thietes belong to a relatively new[5] class of compounds and represent, in a formal way, sulfur heterocyclic analogs of cyclopentadienes. Replacement of a formal double bond by a sulfur atom results in no change in the number of π electrons available for possible conjugation, and, since sulfur has approximately the same electronegativity as carbon,[6] this molecular modification may lead to a less drastic change in properties for these sulfur analogs of cyclopentadiene. Thietes are potential precursors of new 6-π-electron conjugated anions and of new 4-π-electron conjugated cations which may be considered as analogs of the anion and cation of cyclopentadiene, respectively.



The first thiete derivatives were sulfones,[6,7] although a relatively stable dithiete, 3,4-bis(trifluoromethyl)-1,2-dithiete, was reported in 1960.[8] The analogous diselenium compound has been reported recently.[9]

A thiete (2,2-dimethyl-3,8-diphenyl-2*H*-naphtho[2,3-*b*]thiete) in which the double bond was part of an aromatic system was prepared by reduction of the sulfone,[10] but thiete itself (**3**) could not be obtained by reduction of thiete sulfone.[6,11] Several oxetes have been reported.[12]

SCHEME I



Synthesis.—The general plan for the synthesis of thietes is given in Scheme I. The quaternary ammonium salt required for the Hofmann elimination in the preparation of **3** may be obtained also by treatment of 3-thietanol with *p*-toluenesulfonyl chloride and trimethylamine (eq 1). The amino sulfone required for the synthesis of **3** may be prepared alternatively by addition of the secondary amine to thiete sulfone (eq 2) or to 3-chlorothietane 1,1-dioxide.[6]

The preparation of the aminosulfones shown in Scheme I follows the procedure of Stork and Borowitz[7a,13] and Opitz and Adolph.[14] The reduction of the sulfone normally proceeds well, but the yield of product is reduced by concomitant elimination of R_2NH.[15] The Hofmann elimination is very facile,

(1) Paper V: D. C. Dittmer, K. Ikura, J. M. Balquist, and N. Takashina, *J. Org. Chem.*, **37**, 225 (1972).

(2) The authors are grateful for support of this research by the National Science Foundation.

(3) Preliminary accounts of some of this research have been given: (a) D. C. Dittmer and F. A. Davis, *J. Amer. Chem. Soc.*, **87**, 2064 (1965); (b) D. C. Dittmer, K. Takahashi, and F. A. Davis, *Tetrahedron Lett.*, 4061 (1967).

(4) Taken in part from P. L.-F. Chang, Ph.D. Thesis, Syracuse University, 1970; F. A. Davis, Ph.D. Thesis, Syracuse University, 1966; and I. Stamos, Ph.D. Thesis, Syracuse University, 1969.

(5) D. W. Cruickshank and B. C. Webster, "Inorganic Sulfur Chemistry," G. Nickless, Ed., Elsevier, Amsterdam, 1968, p 10.

(6) D. C. Dittmer and M. E. Christy, *J. Org. Chem.*, **26**, 1324 (1961); D. C. Dittmer and M. E. Christy, *J. Amer. Chem. Soc.*, **84**, 399 (1962).

(7) (a) W. E. Truce, J. R. Norell, J. E. Richman, and J. P. Walsh, *Tetrahedron Lett.*, 1677 (1963); (b) W. E. Truce and J. R. Norell, *J. Amer. Chem. Soc.*, **85**, 3236 (1963); (c) R. H. Hasek, P. G. Gott, R. H. Meen, and J. C. Martin, *J. Org. Chem.*, **28**, 2496 (1963); (d) G. Optiz and H. Schempp, *Z. Naturforsch., B*, **19**, 78 (1964); (e) D. C. Dittmer and F. A. Davis, *J. Org. Chem.*, **29**, 3131 (1964).

(8) C. G. Krespan, B. C. McKusick, and T. L. Cairns, *J. Amer. Chem. Soc.*, **82**, 1515 (1960); C. G. Krespan, *ibid.*, **83**, 3434 (1961).

(9) A. Davison and E. T. Shawl, *Inorg. Chem.*, **9**, 1820 (1970).

(10) L. A. Paquette, *J. Org. Chem.*, **30**, 629 (1965).

(11) C. L. Schelling, M.S. Thesis, Syracuse University, 1964; R. S. Henion, Ph.D. Thesis, Syracuse University, 1967.

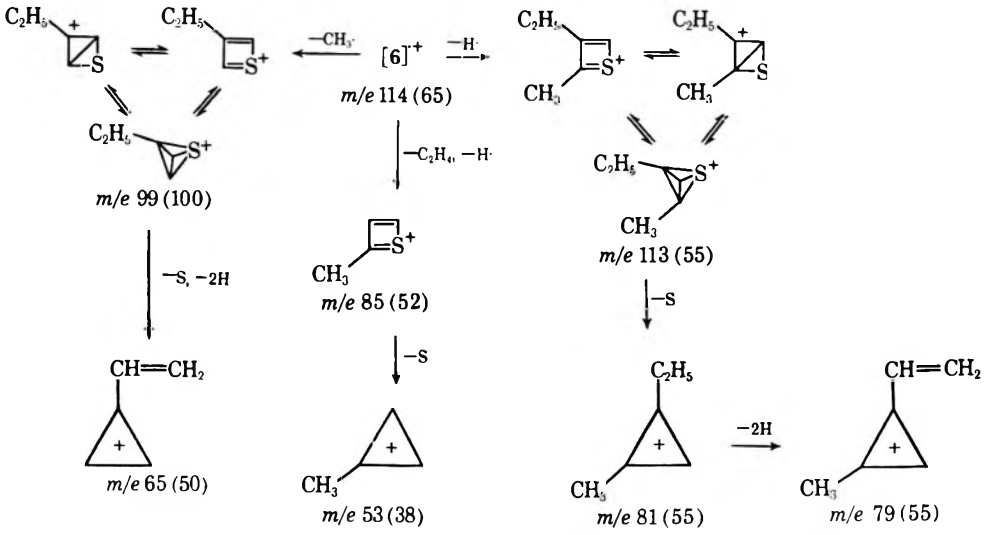
(12) L. E. Friedrich and G. B. Schuster, *J. Amer. Chem. Soc.*, **91**, 7204 (1969); W. J. Middleton, *J. Org. Chem.*, **30**, 1307 (1965); E. Müller, R. Mayer, B. Narr, A. Rieker, and K. Scheffler, *Justus Liebigs Ann. Chem.*, **645**, 25 (1961); J. Hollander and C. Woolf, Belgian Patent 671,439; *Chem. Abstr.*, **65**, 8875 (1966).

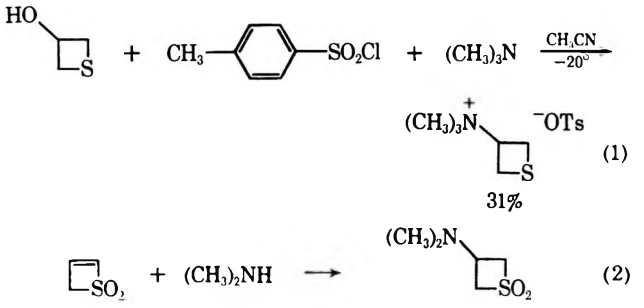
(13) G. Stork and I. J. Borowitz, *J. Amer. Chem. Soc.*, **84**, 313 (1962).

(14) G. Opitz and H. Adolph, *Angew. Chem.*, **74**, 77 (1962).

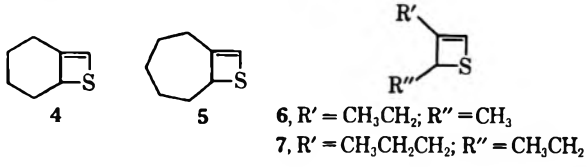
(15) Dr. John McCaskie in our laboratory has detected the amine during work-up of the reduction mixture.

SCHEME II





the only difficulty being the separation of the volatile components of the product mixture. In addition to thiete itself (**3**), thietes **4**–**7** were prepared as outlined in Scheme I. All of these thietes are liquids.



4 **5** **6**, R′ = CH_3CH_2; R″ = CH_3
7, R′ = $CH_3CH_2CH_2$; R″ = CH_3CH_2

Thietes **4**–**7** can be oxidized to the corresponding sulfones, which aids in establishment of the cyclic structures and disposes of alternate tautomeric thioacrolein structures. The sulfones also may be prepared by elimination of amine from the aminosulfones **1**.

The thietes usually have three absorptions in the ultraviolet: 215–228 (ε 1100–2270), 236–248 (ε 2000–3050), and 285–294 (ε 50–567) mμ. The ^1H nmr spectrum of the thietes shows the following absorptions: δ 6.05–6.50 (α-olefinic proton), 5.60 (β-olefinic proton), 3.40–4.10 (protons on C-3).[16] Infrared absorption for the double bond is weak and difficult to assign; thietes **5**, **6**, and **7** have absorption at 1600–1625 cm^{-1}. Thietes **3**, **6**, and **7** show very intense ions in the mass spectrum corresponding to the thiete cation formed by loss of a hydrogen atom or an alkyl group.[17] The bicyclic compounds can yield the thiete cation by ring cleavage. As expected, thietes **4** and **5** have abundant parent ions.

(16) Thiete sulfones show absorption for the olefinic protons in which the magnitude of the shielding is reversed, *i.e.*, the α proton is at higher field than the β proton.

(17) The chemistry of the thiete cation and, in particular, its complexes with transition metals are being investigated and will be described in a subsequent report.

Scheme II illustrates a typical mass spectral fragmentation pattern for a thiete (in this instance, **6**) with structures suggested for the various ions. The intensities of the mass spectral peaks relative to the peak of the most abundant ion at *m/e* 99 are given in per cent in parentheses. The observation of metastable ions in the spectrum of **6** at *m/e* 42.7, 77, and between 63 and 64 supports the proposed transformations *m/e* 99 → 65, 81 → 79, and 114 → 85. The structures of the thiete cations are as yet unknown, but a thiatetrahedrane configuration cannot be excluded.

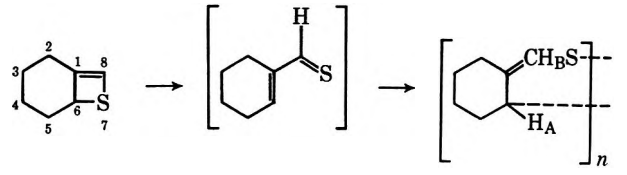
Thermal Stability.—The strain inherent in the unsaturated four-membered ring can be relieved by opening of the ring, which, in the case of thietes, would involve breaking a relatively weak carbon–sulfur bond.

The thietes described in this report are all somewhat thermally unstable. Thiete **4** is least stable; a neat sample has been observed to decompose explosively at room temperature. It is stable for at least 2 weeks at −10° but decomposes in about a week at 5°. A white solid (approximate empirical formula $C_7H_{10}S$) is obtained from the decomposition. Apparently, the material is some oligomer or polymer of the original compound. Attempts to purify the solid were not successful. Ultraviolet spectra of the material indicate the possible presence of an α,β-unsaturated sulfide functionality. Double bond absorption in the infrared appears at 1620 cm^{-1}. Oxidation with 30% hydrogen peroxide yields a sulfone as indicated by infrared absorption at 1320 and 1190 cm^{-1}. The double bond absorption of the sulfone "polymer" is at 1645 cm^{-1}, an increase of 25 cm^{-1} over that in the sulfide. A similar increase of 39 cm^{-1} was observed in the conversion of methyl vinyl sulfide to methyl vinyl sulfone.[18] A smaller increase (5 cm^{-1}) was observed in the oxidation of methyl allyl sulfide to methyl allyl sulfone.[18] Material obtained from the decomposition of neat **4** may be predominantly trimeric (mol wt 371; calcd for trimer, 378). The nmr spectrum of this supposedly trimeric material shows, in addition to absorption for the aliphatic protons of the cyclohexane ring, absorption at δ 3.2 (2 H), 4.5 (1 H), and 5.9–6.0 (3 H). The absorptions at δ 3.2 and 5.9–6.0 are similar to the absorptions of the protons on C-6

(18) C. C. Price and R. G. Gillis, *J. Amer. Chem. Soc.*, **75**, 4750 (1953).

and C-8 of thiete **4** and may correspond to protons H_A and H_B.

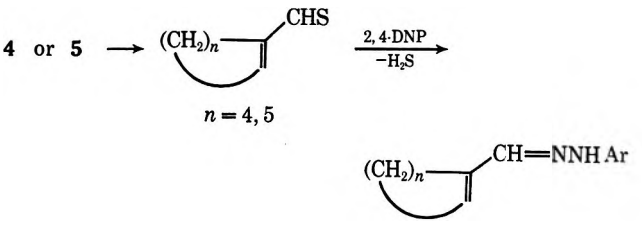
A material of high viscosity (inherent viscosity 0.75) was deposited from a pentane solution of **4** over a 24-hr period.[19] Although evidence is lacking concerning the involvement of 1,4 polymerization in acrolein,[20] the decomposition products of thiete **4**, on the basis of the above data, appear to be derived from a 1,4-addition reaction of a thioacrolein. A cyclic dimer and trimer are possible (although unlikely because of the large ring size) as well as linear oligomers and polymers.



Thiete **5** decomposes to a glassy solid at room temperature. In thietes **4** and **5** the exocyclic double bond creates enough strain so that rupture of the C–S bond occurs more readily than normal.

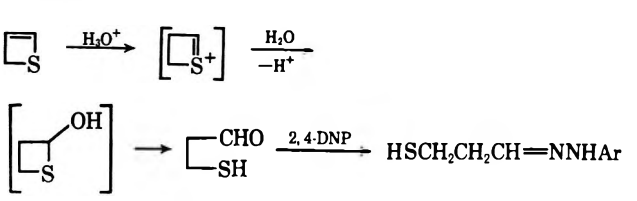
Thiete (**3**) itself is stable at room temperature for up to 1 hr and is much more stable in solution. When it is allowed to stand overnight, a clear, viscous oil if formed from which a white amorphous solid of empirical formula $(C_3H_4S)_n$ is obtained. Infrared absorption at 1600 and 930 cm^{-1} suggests the presence of an α,β-unsaturated sulfide group.

Reactions with 2,4-Dinitrophenylhydrazine.—Thiete **3** reacts quite differently from thietes **4** and **5** with acidic 2,4-dinitrophenylhydrazine (2,4-DNP). From **4** and **5** 2,4-dinitrophenylhydrazones of cyclohexene- and cycloheptenethioaldehyde are obtained, ring opening preceding hydrazone formation. These derivatives are identical with the 2,4-dinitrophenylhydrazones of 1-cyclohexene-1-aldehyde and 1-cycloheptene-1-aldehyde. Thiete **4** also forms the semicarbazone of 1-cyclohexene-1-aldehyde.



Thiete **3** apparently undergoes an acid-catalyzed hydration of the double bond followed by hydrolysis of the thiohemiacetal to β-mercaptopropionaldehyde which yields the 2,4-dinitrophenylhydrazone.[21] The derivative is acetylated with acetic anhydride in pyridine to give a compound identical with the 2,4-dinitrophenylhydrazone prepared from β-acetylthiopropionaldehyde obtained by addition of thiolacetic acid to acrolein. This reaction of **3** is analogous to the acid-catalyzed hydrolysis of alkyl propenyl sulfides to alkanethiols and propionaldehyde reported by Tarbell and Lovett.[22]

The differences in reactivity between **3** and **4** or **5** with acidic 2,4-dinitrophenylhydrazine probably reflect the differences in thermal stability of these thietes. In **4** or **5** the ring strain is such that ring opening to the α,β-unsaturated thioaldehyde occurs faster than the somewhat sterically hindered double bond is protonated. The greater thermal stability of **3** allows protonation of the double bond to be faster than ring opening to thioacrolein.



Experimental Section

Thiete (3).—3-(*N*,*N*-Dimethylamino)thietane[6] (6.1 g, 0.059 mol), prepared by reduction of 3-(*N*,*N*-dimethylamino)thietane 1,1-dioxide,[6,23] in methyl ethyl ketone (250 ml) was treated at 0° with methyl iodide (8.3 g, 0.059 mol). The product precipitated after 12 hr at 5°. Recrystallization from methyl alcohol gave white crystals: mp 209–210° dec (8.5 g, 56%); nmr (D_2O) δ 3.2 (N^+CH_3, 2 cis H), 3.8 (t, 2 trans H), 4.9 (t, >CHN^+<).

Anal. Calcd for $C_6H_{14}INS$: C, 27.80; H, 5.45; N, 5.39. Found: C, 27.50; H, 5.15; N, 5.10.

An alternate preparation of the quaternary salt involves treatment of 3-thietanol[6] (70 g, 0.78 mol) and trimethylamine (350 ml, 4.2 mol, dried over NaOH) in acetonitrile (500 ml) at −5 to −10° with *p*-toluenesulfonyl chloride (224 g, 1.18 mol) in acetonitrile (440 ml) added dropwise during 2 hr. The reaction mixture was allowed to stand in a freezer at −20° for 2 hr and excess amine was removed by an aspirator. The precipitate was collected by filtration and recrystallized twice from ethanol (350 ml) to give 3-thietanyltrimethylammonium tosylate (74 g, 0.44 mol, 31%): mp 240–242°; nmr (D_2O) δ 7.53 (m, 4, C_6H_4), 4.55 (m, 1, CHN^+), 3.69 (t, 2, CH_2S), 3.20 (d, 2, CH_2S), 2.95 (s, 9, NCH_3), 2.35 (s, 3, $C_6H_4CH_3$). The tosylate may be converted to the iodide by an ion exchange resin or by treatment with hydriodic acid.

Anal. Calcd for $C_{13}H_{21}NO_3S_2$: C, 51.48; H, 6.98; N, 4.62; S, 21.20. Found: C, 51.49; H, 7.11; N, 4.47; S, 21.40.

A solution of the methiodide of 3-(*N*,*N*-dimethylamino)thietane (40 g, 0.16 mol) in dimethylformamide (380 ml, −20°) was mixed with a solution of potassium 1-methylcyclohexoxide (46 g, 0.30 mol) in dimethylformamide (270 ml, −20°) and the mixture was stirred at −20° for 30 min. Glacial acetic acid (15 ml) was added, the mixture was warmed to 30°, and volatile materials were removed *in vacuo* (2 mm) and collected in two traps, one at −78° and one at liquid nitrogen temperature. Trimethylamine (9.4 g, 100%) was collected in the liquid nitrogen trap. The contents of the −78° trap were distilled as before, the volatile materials being collected in traps at −20 and −78°. In the −20° trap, about 100 ml of a dilute solution of thiete in dimethylformamide was collected, and in the −78° trap, a more concentrated solution (23 g) of thiete was obtained. Distillation of this concentrated solution at 20 mm and 30° gave thiete (9.1 g, 79%) which was collected in a trap at −78° and dried (Na_2SO_4): $n^{25}D$ 1.5160; d^{25}_{25} 0.997; nmr ($CDCl_3$) δ 6.50 (d, 1, J, = 3 Hz, C=CHS), 5.60 (two triplets, 1, J = 3.2, 1 Hz), 3.80 (d, 2, J = 1 Hz). Other physical and spectral properties were reported previously.[3b]

When **3** was allowed to stand overnight or longer at room temperature, a white, amorphous solid and a colorless oil formed. Tlc of the oil indicated that it was a mixture of at least four components. The solid was insoluble in water, hydrochloric acid,

(19) We are indebted to Professor L. Guy Donaruma of Clarkson College of Technology for the viscosity measurement.

(20) R. C. Schulz, *Angew. Chem., Int. Ed. Engl.*, **3**, 416 (1964).

(21) The hydrazine also may add directly to the sulfonium ion to ultimately yield the hydrazone. Conceivably, the mercaptoaldehyde also could be formed by addition of hydrogen sulfide (derived from hydrolysis of the thiocarbonyl group) to the double bond of the α,β-unsaturated aldehyde or thioaldehyde. However, the nearly quantitative yield of 2,4-dinitrophenylhydrazone would require a very efficient scavenging of the hydrogen sulfide. In fact, hydrogen sulfide is evolved and lost to the atmosphere, as indicated by odor and by lead acetate paper.

(22) D. S. Tarbell and W. E. Lovett, *J. Amer. Chem. Soc.*, **78**, 2259 (1956).

(23) P. L.-F. Chang and D. C. Dittmer, *J. Org. Chem.*, **34**, 2791 (1969).

sodium hydroxide, methanol, acetone, chloroform, dimethylformamide (DMF), and dimethyl sulfoxide (DMSO); ir (KBr) 2980, 2870, 1600 (C=CS), 930 cm^{-1}.

Anal. Calcd for $(C_3H_4S)_n$: C, 49.95; H, 5.59; S, 44.46. Found: C, 48.23; H, 6.40; S, 42.57.

Aminosulfone Derivatives 1.—The aminosulfones were prepared by addition of sulfene obtained from methanesulfonyl chloride and triethylamine to the pyrrolidine enamines of cyclohexanone, cycloheptanone, diethyl ketone, and di-*n*-propyl ketone.[13,14,24] They were recrystallized from ethanol or ethanol–petroleum ether (bp 30–60°). The synthesis of 1-(1-pyrrolidinyl)-7-thiabicyclo[4.2.0]octane 7,7-dioxide was previously reported.[7e]

1-(1-Pyrrolidinyl)-8-thiabicyclo[5.2.0]nonane 8,8-dioxide [1, R′ = R″ = $-(CH_2)_5-$] had mp 80–81°; ir 1310, 1120 cm^{-1}; nmr ($CDCl_3$) δ 4.53 (t, 1, $-CHSO_2-$), 3.42, 4.20 (AB quartet, 2, CH_2SO_2-), 2.5–3.05 (m, 4, CH_2N-), 1.5–2.3 (m, 14).

Anal. Calcd for $C_{12}H_{21}NO_2S$: C, 59.30; H, 8.64; N, 5.77; S, 13.15. Found: C, 58.96; H, 8.92; N, 5.84; S, 13.27.

cis-2-Methyl-3-ethyl-3-(1-pyrrolidinyl)thietane 1,1-dioxide (1, R′ = CH_3CH_2, R″ = CH_3) was an oil: ir 1300, 1120 cm^{-1}; nmr ($CDCl_3$) δ 4.48 (quartet, 1, $CHCH_3$), 3.62, 4.13 (AB quartet, 2, CH_2SO_2), 2.70 (m, 4, CH_2N-), 1.75 (m, 6, CH_2CH_2N, CH_3CH_2-), 1.35 (d, 3, CH_3), 0.90 (t, 3, CH_3CH_2-).

cis-2-Ethyl-3-*n*-propyl-3-(1-pyrrolidinyl)thietane 1,1-dioxide (1, R′ = $CH_3CH_2CH_2$, R″ = CH_3CH_2) had mp 60–61°; ir 1300, 1120 cm^{-1}; nmr ($CDCl_3$) δ 4.32 (quartet, 1, $CHCH_2CH_3$), 3.70, 4.20 (AB quartet, 2, CH_2SO_2), 2.72 (m, 4, CH_2N-), 1.30–2.30 (m, 10, CH_2CH_2N, $CH_3CH_2CH_2$, CH_3CH_2-), 1.10 (t, 6, $CH_3CH_2CH_2$, CH_3CH_2).

Anal. Calcd for $C_{12}H_{23}NO_2S$: C, 58.80; H, 9.38; N, 5.72; S, 13.05. Found: C, 59.07; H, 9.36; N, 5.67; S, 12.92.

Aminothietane Methiodides 2.—The corresponding sulfone (0.1 mol) in dry ether (200 ml) was added dropwise to a solution of lithium aluminum hydride (11.4 g, 0.300 mol) in dry ether (200 ml) cooled in an ice bath. When the addition of the sulfone was completed, the reaction mixture was stirred for 6 hr at the temperature of the ice bath. Excess hydride was destroyed by dropwise addition of ethyl acetate (50 ml), a 20% solution of ammonium chloride (60 ml), and finally a 1:1 mixture of concentrated ammonium hydroxide and ammonium chloride solutions (*ca.* 70 ml, the addition was stopped when a granular precipitate formed). The ether solution was removed from the precipitate and dried ($MgSO_4$). Removal of the ether by means of a water aspirator left the amino sulfide as an oil. Yields varied from 63 to 85%.

Methyl iodide (equimolar with sulfide) was added to a solution of the sulfide in methyl ethyl ketone (1.5–2.0 l. per mol of sulfide) at 5°, and the solution was allowed to stand overnight at room temperature. The precipitated salt was removed by filtration, and more methyl iodide (0.25–0.5 equiv) was added to the filtrate from which additional salt precipitated overnight.[25] The salts were recrystallized from methanol–ether.

1-(1-Methylpyrrolidinium)-7-thiabicyclo[4.2.0]octane iodide [2, R′ = R″ = $-(CH_2)_5-$] (37% yield) had mp 133–135°; nmr (D_2O) δ 4.5 (1, CHS–), 3.8 (m, CH_2N^+, $-CH_{cis}H_{trans}S-$), 3.2 (s, 4, CH_3N^+, $CH_{cis}H_{trans}S-$), 2.2 [m, 12, $CH_2CH_2N^+$, $-(CH_2)_4-$].

Anal. Calcd for $C_{12}H_{22}INS$: C, 42.47; H, 6.53; N, 4.13; S, 9.45. Found: C, 42.61; H, 6.49; N, 3.93; S, 9.47.

1-(1-Methylpyrrolidinium)-8-thiabicyclo[5.2.0]nonane iodide [2, R′ = R″ = $(CH_2)_5-$] (54% yield) had mp 139–140°; nmr (DMSO-d_6) δ 4.6 (s, 1, CHS–), 3.0–4.0 (m, 6, $-CH_2S-$, $-CH_2N^+$), 2.98 (s, 3, N^+CH_3), 1.5–2.3 [m, 14, $CH_2CH_2N^+$, $-(CH_2)_5-$].

Anal. Calcd for $C_{13}H_{24}INS$: C, 44.30; H, 6.81. Found: C, 44.27; H, 6.98.

cis-2-Methyl-3-ethyl-3-(1-methylpyrrolidinium)thietane iodide [2, R′ = C_2H_5-, R″ = CH_3] (45% yield) had mp 117–118°; nmr (DMSO-d_6) δ 4.52 (quartet, 1, CH_3CH), 3.0–4.0 (m, 6, $-CH_2S-$, CH_2N^+), 2.92 (s, 3, CH_3N^+), 2.15 (m, 6, CH_2CH_2N, CH_3CH_2-), 1.40 (d, 3, CH_3CH), 1.35 (t, 3, CH_3CH_2).

Anal. Calcd for $C_{11}H_{22}INS$: C, 40.04; H, 6.90. Found: C, 40.13; H, 6.85.

cis-2-Ethyl-3-*n*-propyl-3-(1-methylpyrrolidinium)thietane iodide (2, R′ = C_3H_7, R″ = C_2H_5) (23% yield) had mp 120–121°; nmr (DMSO-d_6) δ 4.3 (complex d, 1, CH_3CH_2CH), 3.1–4.0 (m, 6, CH_2S-, CH_2N^+), 3.0 (s, 3, CH_3N^+), 1.60–2.40 (broad s, 10, $CH_3CH_2CH_2-$, $CH_2CH_2N^+$, CH_3CH_2), 0.9 (m, 6, CH_3CH_2-, $CH_3CH_2CH_2-$).

Anal. Calcd for $C_{13}H_{26}INS$: C, 44.00; H, 7.32. Found: C, 44.02; H, 7.48.

Thietes 4–7.—Potassium *tert*-butoxide (0.00087 mol/ml) in dry (CaH_2) dimethylformamide (*ca.* 20 ml) was added 1 ml at a time through a syringe cap to a stirred solution of quaternary salt (2) (0.009 mol) in dry dimethylformamide (50 ml)–pentane (50 ml) cooled to −10° in a 300-ml, three-necked round-bottomed flask fitted with a mechanical stirrer, syringe cap, and nitrogen inlet. A few minutes elapsed between additions of base. After 9.5 ml of base had been added, the stirring was continued for 10 min. Then the pentane and dimethylformamide layers were allowed to separate. The pentane layer was removed by a syringe and placed in a flask at −20° (Dry Ice–isopropyl alcohol). Additional pentane (30 ml) was added to the dimethylformamide in the original reaction flask, the mixture was stirred for about 15 min, and the pentane was removed as before and combined with the original pentane layer. This process was continued until about 300 ml of pentane was consumed. The combined pentane solutions at −10° were washed with cold 10% hydrochloric acid and twice with cold water. The pentane solution was dried ($MgSO_4$) at −10° and the pentane was removed at 0° on a rotary evaporator to leave the thiete as a colorless oil.

7-Thiabicyclo[4.2.0]-1(8)-octene (4)[3a] (50–55% yields) had ir[26] (−50°, between KBr plates) 2900 (s), 2850 (s), 1430 (s), 1310 (w), 1120 (m), 950 (w), 780 (s), 740 cm^{-1} (s); uv max ($CHCl_3$, −10°) 247, 260 mμ (sh); nmr ($CDCl_3$, −30°) δ 6.1 (s, 1, C=CH), 3.7 (m, 1, –CHS–), 1.8 [m, 8, $-(CH_2)_4-$]; mass spectrum (70 eV) *m/e* (rel intensity) 128 (5.2), 127 (9.2), 126 (100, parent), 125 (9), 93 (96), 91 (67), 77 (68).

Anal. Calcd for $C_7H_{10}S$: mol wt, 126. Found: mol wt, 127.[27]

If thiete 4 is warmed to room temperature, decomposition occurs with the evolution of heat. The glassy solid obtained was insoluble in ethanol, methanol, ether, ethyl acetate, and pentane but was soluble in chloroform: ir (KBr) 2950, 2940, 1620 (C=CS), 1445, 975, 915, 800 cm^{-1}; nmr ($CDCl_3$) δ 6 (2), 5.9 (1), 4.5 (1), 3.2 (2), 1.2–2.4 (24); mass spectrum (70 eV) *m/e* (rel intensity) 252 (2), 126 (85), 93 (100), 91 (69), 77 (62), 45 (42).

Anal. Calcd for $(C_7H_{10}S)_3$: C, 66.62; H, 7.99; S, 25.41; mol wt, 378. Found: C, 65.01; H, 7.35; S, 27.54; mol wt, 371.

Oxidation of this apparently trimeric material with excess 30% hydrogen peroxide in acetic acid for 12 hr at room temperature and for 1 hr at 70° gave a gummy solid, mp 110–125°, after removal of solvent (water aspirator) and recrystallization (ether): ir (KBr) 2950, 1725, 1645 (C=C), 1320 (SO_2), 1190 (SO_2), 945, 930, 890, 845, 790, 755 cm^{-1}.

Anal. Calcd for $(C_7H_{10}O_2S)_n$: C, 53.15; H, 6.33. Found: C, 51.20; H, 6.80.

8-Thiabicyclo[5.2.0]-1(9)-nonene (5) (76% yield) had ir (film) 3050 (w), 1600 (w), 775 cm^{-1} (s); uv max (pentane) 228 mμ (sh, ε 1100), 248 (2000), 252 (2000), 256 (1715), 294 (567); nmr ($CDCl_3$) δ 6.05 (s, 1, CC=H), 3.40 (doublet of doublets, 1, CHS–), 1.4–2.5 [m, 10, $-(CH_2)_5-$]; mass spectrum (20 eV) *m/e* (rel intensity) 142 (3), 141 (5), 140 (29, parent), 112 (10), 111 (17), 107 (11), 106 (18), 97 (16), 91 (30), 84 (13), 71 (34), 58 (50), 57 (52), 43 (100).

Anal. Calcd for $C_8H_{12}S$: C, 68.60; H, 8.57. Found: C, 68.55; H, 8.85.

3-Ethyl-4-methyl-2-thiacyclobutene (6) (67% yield) had ir (film) 3100 (w), 1625 (w), 810 (s), 755 cm^{-1} (m); uv max (pentane) 225 mμ (ε 1710), 247 (2250), 289 (420); nmr ($CDCl_3$) δ 6.16 (s, 1, C=CH), 4.10 (quartet, 1, CH_3CHS-), 1.97 (quartet, 2, CH_3CH_2-), 1.55 (d, 3, CH_3-), 1.00 (t, 3, CH_3CH_2-); mass spectrum (20 eV) *m/e* (rel intensity) 114 (65, parent), 113 (55), 99 (100), 85 (52), 81 (55), 79 (55), 67 (13), 65 (50), 53 (38), 41 (54).

Anal. Calcd for $C_6H_{10}S$: C, 63.08; H, 8.83; S, 28.09. Found: C, 63.19; H, 8.92; S, 28.14.

(24) G. Stork, A. Brizzolara, H. Landesman, J. Szmuszkovicz, and R. Terrell, *J. Amer. Chem. Soc.*, **85**, 207 (1963); I. J. Borowitz, *ibid.*, **86**, 1146 (1964).

(25) The salt of *cis*-2-ethyl-3-*n*-propyl-3-(1-pyrrolidinyl)thietane was precipitated by addition of petroleum ether (bp 30–60°) or ethyl ether.

(26) The infrared spectrum was obtained by means of a special cell: E. L. Wagner and D. F. Hornig, *J. Chem. Phys.*, **18**, 296 (1950); A. B. Palmer, Ph.D. Thesis, Syracuse University, 1963.

(27) Obtained at −10° by nmr by means of a standard (benzil): S. Barcza, *J. Org. Chem.*, **28**, 1914 (1963). A value of 126 was obtained from the mass spectrum as noted. This thiete was too unstable for elemental analysis.

3-*n*-Propyl-4-ethyl-2-thiacyclobutene (**7**) (85% yield) had ir (film) 3100 (w), 1625 (w), 760 (s); uv max (pentane) 225 mμ (ε 2270), 247 (3050), 291 (345); nmr ($CDCl_3$) δ 6.18 (s, 1, C=CH), 4.0 (quartet, 1, CHS–), 1.20–2.25 (m, 6, $CH_3CH_2CH_2$–, CH_3CH_2–), 1.0 (t, 6, $CH_3CH_2CH_2$–, CH_3CH_2–); mass spectrum (20 eV) *m/e* (rel intensity) 142 (100, parent), 141 (16), 140 (38), 127 (28), 113 (74), 112 (29), 111 (50), 99 (35), 85 (32), 79 (45), 67 (49), 43 (36).

Anal. Calcd for $C_8H_{14}S$: C, 67.60; H, 8.57. Found: C, 67.55; H, 8.85.

Thiete Sulfones.—Peracetic acid (20 ml, 40%) was added dropwise during 30 min to the pyrrolidinyl sulfone [**1**, $R_2 = (CH_2)_4$] (0.044 mol) in a 125-ml erlenmeyer flask cooled in an ice–salt bath. After the addition was completed, the mixture was allowed to remain in the bath for 30 min longer. The reaction mixture was allowed to stand (1) at room temperature for 12 hr and then at 30–32° for 12 hr for the sulfone derived from cycloheptanone, (2) at room temperature for 48 hr for the sulfone derived from methyl ethyl ketone or (3) at room temperature for 12 hr and then at 30–32° for 5 hr for the sulfone derived from di-*n*-propyl ketone. The reaction mixture was cooled, cold water (*ca.* 100 ml) was added, and the mixture was saturated with sodium chloride and extracted with chloroform. The chloroform extracts were washed with 10% hydrochloric acid and dried (Na_2CO_3). Removal of the chloroform left an oil which was chromatographed on Florisil and eluted with ether–petroleum ether.

The product from the pyrrolidinyl sulfone derived from cycloheptanone consisted of an exo and an endo isomer. The mixture was treated with potassium hydroxide in dry methanol, cooled with ice, and neutralized with a cold 10% solution of hydrochloric acid. The solution was diluted with water and saturated with sodium chloride and the organic layer was extracted with chloroform, which was dried ($MgSO_4$) and evaporated to leave the endo sulfone, which was purified by column chromatography on Florisil (ether eluent) and recrystallized from ether. The sulfone of **4** was reported previously.[7e]

8-Thiabicyclo[5.2.0]-1(7)-nonene 8,8-dioxide (66% yield) had mp 65–66°; ir (KBr) 1660 (w), 1290 (s), 1170 (s), 1120 (s), 805 cm^{-1} (s); nmr ($CDCl_3$) δ 4.32 (s, 2, CH_2SO_2–), 2.43 (s, 4, CH_2-C=CCH_2), 1.75 [m, 6, –$(CH_2)_3$–].

Anal. Calcd for $C_8H_{12}O_2S$: C, 55.80; H, 6.99. Found: C, 55.61; H, 7.16.

2-Methyl-3-ethyl-2-thiacyclobutene 1,1-dioxide (67% yield) had mp 46–47°; ir (film) 1650 (w), 1290 (s), 1180 (s), 1120 cm^{-1} (s); nmr ($CDCl_3$) δ 4.31 (s, 2, CH_2SO_2–), 2.42 (quartet, 2, CH_3CH_2–), 1.90 (s, 3, CH_3–), 1.15 (t, 3, CH_3CH_2).

Anal. Calcd for $C_6H_{10}O_2S$: C, 49.25; H, 6.82. Found: C, 49.15; H, 6.73.

2-Ethyl-3-*n*-propyl-2-thiacyclobutene 1,1-dioxide (74% yield) had $n^{25}D$ 1.4775; ir (film) 1650 (w), 1300 (s), 1230 (s), 1180 (s), 1130 (s), 1090 cm^{-1} (s); nmr ($CDCl_3$) δ 4.30 (s, 2, CH_2SO_2–), 2.1–2.6 (m, 4, CH_3CH_2–, $CH_3CH_2CH_2$–), 0.8–1.9 (m, 8, CH_3CH_2–, $CH_3CH_2CH_2$–).

Anal. Calcd for $C_8H_{14}O_2S$: C, 55.20; H, 8.45. Found: C, 55.30; H, 8.29.

Oxidation of Thiacyclobutenes.—An ether solution of monoperphthalic acid (0.017 mol) was added to a solution of the thiete (**4**–**7**) in pentane (50 ml) at −20° in a three-necked flask equipped with a stirrer and nitrogen inlet. After the reaction mixture was stirred for 4 days at −15 to −20°, it was allowed to warm to 0° and was stirred for 1 day more. The precipitated phthalic acid was removed and washed with chloroform or ether and the washings were combined with the mother liquor. The solution was washed with sodium carbonate solution and the solvent was removed by evaporation. The oil which remained was treated with cold potassium hydroxide in absolute methanol. The mixture was cooled in an ice bath, neutralized with cold 10% hydrochloric acid, diluted with water, and saturated with sodium chloride. The organic layer was extracted with chloroform, which was dried ($MgSO_4$) and removed by evaporation to leave the sulfone, which was chromatographed on Florisil and eluted with ether–petroleum ether.

From **4** was obtained 7-thiabicyclo[4.2.0]-1(8)-octene 7,7-dioxide, mp 88–89° (lit.[7e] mp 88–89°), whose ir and nmr spectra were identical with those of an authentic sample.

Thiete **5** yielded 8-thiabicyclo[5.2.0]-1(9)-nonene 8,8-dioxide as an oil [nmr ($CDCl_3$) δ 6.5 (C=CH)]. The oil was treated with potassium hydroxide, which isomerized it to 8-thiabicyclo-[5.2.0]-1(7)-nonene 8,8-dioxide (9% yield), mp 65–66°, whose ir and nmr spectra were identical with those of a sample prepared by the amine oxide elimination described in the preceding section.

Thiete **6** yielded an oily mixture which contained 3-ethyl-4-methyl-2-thiacyclobutene 1,1-dioxide [nmr ($CDCl_3$) δ 6.47]. Isomerization with potassium *tert*-butoxide in *tert*-butyl alcohol gave 2-methyl-3-ethyl-2-thiacyclobutene 1,1-dioxide (7% yield), mp 46–47°, whose ir and nmr spectra were identical with those of an authentic sample prepared by the amine oxide elimination.

Thiete **7** also gave an oily mixture containing 3-*n*-propyl-4-ethyl-2-thiacyclobutene 1,1-dioxide [nmr ($CDCl_3$) δ 6.5]. Isomerization with potassium hydroxide in methanol gave 2-ethyl-3-*n*-propyl-2-thiacyclobutene 1,1-dioxide (12% yield) whose refractive index, ir, and nmr spectra were identical with those of an authentic sample.

Reaction of Thietes with 2,4-Dinitrophenylhydrazine. A. Thiete (3).—Thiete (**3**, 0.072 g, 0.001 mol) was treated with 2,4-dinitrophenylhydrazine (in phosphoric acid–ethanol) to give yellow crystals of the 2,4-dinitrophenylhydrazone of β-mercaptopropionaldehyde (0.250 g, 0.00092 mol, 92%), mp 140–142°. The sample was purified by recrystallization from ethanol.

Anal. Calcd for $C_9H_{10}N_4O_4S$: C, 40.00; H, 3.73; N, 20.74. Found: C, 39.90; H, 3.75; N, 20.60.

The 2,4-dinitrophenylhydrazone (0.250 g, 0.0009 mol) in pyridine (20 ml) was treated with excess acetic anhydride (5 ml) at room temperature. After 15 min, water (50 ml) was added to the reaction mixture. The precipitate was recrystallized from ethanol, mp 127–128° (lit.[28] mp 127.5°), and its infrared spectrum was identical with that of the 2,4-dinitrophenylhydrazone of β-acetylthiopropionaldehyde.

B. Thietes 4 and 5.—Thietes **4** and **5** were treated with 2,4-dinitrophenylhydrazine reagent[29] in a manner similar to the treatment of **3**. The derivatives may require purification by chromatography on neutral alumina and recrystallization. Thiete **4** yielded the 2,4-dinitrophenylhydrazone of 1-cyclohexene aldehyde, mp 218–220° (lit.[30] mp 219–220°). The ir and uv spectra were identical with those of an authentic sample of the derivative. Hydrogen sulfide was detected by lead acetate paper. Treatment of **4** with semicarbazide[29] resulted in evolution of hydrogen sulfide and the formation of the semicarbazone of 1-cyclohexene aldehyde, mp 210–213 (lit.[30] mp 213–214°). The ir and uv spectra were identical with those of an authentic sample.

Likewise **5** yielded the 2,4-dinitrophenylhydrazone of 1-cycloheptene aldehyde, mp 214–215° (lit.[31] mp 210–212°).

Registry No.—**1** [R′,R″ = $-(CH_2)_5-$], 33527-81-0; **1** [R′ = CH_3CH_2; R″ = CH_3], 33527-82-1; **1** [R′ = $CH_3CH_2CH_2$; R″ = CH_3CH_2], 33527-83-2; **2** [R′ = R″ = $-(CH_2)_4-$], 33527-84-3; **2** [R′ = R″ = $-(CH_2)_5-$], 33527-85-4; **2** [R′ = C_2H_5; R″ = CH_3], 33527-86-5; **2** [R′ = C_3H_7; R″ = C_2H_5], 33527-87-6; **2** [R = CH_3; R′ = R″ = H], 33527-47-8; **3**, 503-31-1; **4**, 33527-89-8; **4** (trimer), 33520-74-0; **4** (sulfone polymer), 33520-75-1; **5**, 33608-40-1; **6**, 33527-90-1; **7**, 33527-42-3; 3-thietanyltrimethylammonium tosylate, 33527-43-4; 8-thiabicyclo[5.2.0]-1(7)-nonene 8,8-dioxide, 33527-41-2; 2-methyl-3-ethyl-2-thiacyclobutene 1,1-dioxide, 33527-44-5; 2-ethyl-3-*n*-propyl-2-thiacyclobutene 1,1-dioxide, 33527-45-6; β-mercaptopropionaldehyde (2,4-DNPH derivative), 17515-61-6.

(28) J. R. Catch, A. H. Cook, A. R. Graham, and I. Heilbron, *J. Chem. Soc.*, 1609 (1947).

(29) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 5th ed, Wiley, New York, N. Y., 1964, p 253.

(30) I. Heilbron, E. R. H. Jones, R. W. Richardson, and F. Sondheimer, *J. Chem. Soc.*, 737 (1949).

(31) Z. Eckstein, A. Sacha, T. Urbanski, and H. Wojnowska-Makaruk, *ibid.*, 2941 (1959).

Derivatives of Thiacyclobutene (Thiete). VII.[1] Reaction of Thietes with Bases[2,3]

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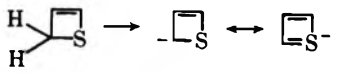
Proton abstraction from thiete (1) by sodium methoxide in CH_3OD and other bases has been observed by nmr spectroscopy, but the thiete could not be recovered on acidification of the alkaline solution. The proton abstraction from thiete appeared faster than the abstraction from allyl sulfide. Wine-red or purple colors are observed when thietes 1 or 2 are treated with strong bases (*e.g.*, lithium piperidide, *n*-butyllithium) at low temperatures. Treatment of 1 with *n*-butyllithium gave a mixture of allyl *n*-butyl sulfide and *n*-butyl propenyl sulfide. With tritylllithium a mixture of *cis*- and *trans*-4,4,4-triphenyl-1-mercapto-2-butene was obtained; whereas with trityl-potassium, 4,4,4-triphenylbutanethial (identified as the 2,4-dinitrophenylhydrazone) was obtained. Potassium dimsylate and 1 yield the thioaldehydes (identified as 2,4-dinitrophenylhydrazones) corresponding to crotonaldehyde and 3-butenal. Treatment of 2 with *tert*-butyllithium gave 1-cyclohexenylmethyl *tert*-butyl sulfide.

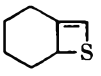
The anion of thiete, which could be formed by proton abstraction from thiete (1), is an analog of the cyclopentadienyl anion in that it contains six π electrons. Simple HMO calculations indicate a delocalization energy of from 1.5 to 1.6 β which is nearly one β unit less than calculated for the anion of cyclopentadiene.[4] Inclusion of the sulfur 3d orbitals does not change the calculated delocalization energy significantly. A rather low energy for the $\pi \rightarrow \pi^*$ transition is predicted (as compared with the calculated energy for the cyclopentadienyl anion) which indicates that the thiete anion may be colored. However, the simple Hückel treatment does not, among other things, properly account for electronic repulsions which would be expected to be of considerable magnitude in such a small molecule. The electronically similar dianion of cyclobutadiene has resisted efforts for its synthesis.[5a] The stability of 3,4-bis(trifluoromethyl)-1,2-dithiete[5b] can be attributed to the two electron-withdrawing trifluoromethyl groups, which decrease the energy of the six π electrons by an inductive effect and possibly by fluorine hyperconjugation. In addition, the two large polarizable sulfur atoms with their d orbitals may help to reduce electronic repulsions. In the absence of such stabilizing factors, the thiete anion might be quite reactive. In all of the reactions with bases to be described, either the anion appears not to be formed at all (other reactions intervene) or, if it is formed, it is unstable and the ring is destroyed. Work is in progress to prepare thietes with electron-withdrawing groups which can stabilize the anion.



1

Reactions with Alkoxides and Lithium Piperidide.—Evidence for removal of a proton from thiete is obtained by examination by means of nmr of a carefully dried solution of thiete, sodium methoxide, and methanol-*d*. Undeuterated methanol (CH_3OH) appears in the reaction mixture and after 8–10 hr at ambient temperature, the thiete proton spectrum has disappeared and the intensity of CH_3OH is at a maximum. A similar experiment with allyl sulfide showed no formation of CH_3OH in 24 hr. This would indicate that the protons of thiete possess considerable kinetic acidity relative to those of allyl sulfide. The proton abstraction by potassium *tert*-butoxide in *tert*-butyl alcohol-*d* is faster and with potassium *tert*-butoxide in dimethyl sulfoxide-d_6 is almost instantaneous. In the latter case, a rapid increase in absorption for dimethyl sulfoxide-d_5 is observed which corresponds to *ca.* 1.6 protons. A similar experiment, in which phenylacetylene was treated with potassium *tert*-butoxide in dimethyl sulfoxide-d_6, showed a rapid increase in the absorption of dimethyl sulfoxide-d_5 corresponding to 0.8 proton. In these reactions with base, the thiete ring system is destroyed and an apparently polymeric material is formed.

When 1 is treated with potassium *tert*-butoxide in dimethylformamide or when 2 is treated with potassium *tert*-butoxide in tetrahydrofuran (THF) and the reaction mixture is quenched with D_2O, no deuterium incorporation into the recovered thiete could be detected. When thiete is treated with potassium 1-methylcyclohexoxide, the nmr absorption of the thiete protons disappears immediately.



2

Treatment of 2 with lithium piperidide in dimethoxyethane (DME) at −20° followed by acidification and treatment with 2,4-dinitrophenylhydrazine gave the 2,4-dinitrophenylhydrazones of 2-mercaptocyclohexane carboxaldehyde (3) and 2-mercaptomethylcyclohexanone (4) in low yield. This contrasts with the reaction of 2 with 2,4-dinitrophenylhydrazine alone, which yields the hydrazone of 1-cyclohexene aldehyde.[1] The products from the reaction of 2 with lithium piperidide may arise from hydrolysis of enamines produced by addition of piperidide ion to the double bond of the thiete followed by elimination of a mercaptide ion. The addition of lithium piperidide to a solution of 2 results in immediate formation of a purple color. Treatment of 2 at −10° with potassium *tert*-butoxide in *n*-pentane or tetrahydrofuran, lithium diethylamide in pentane, so-

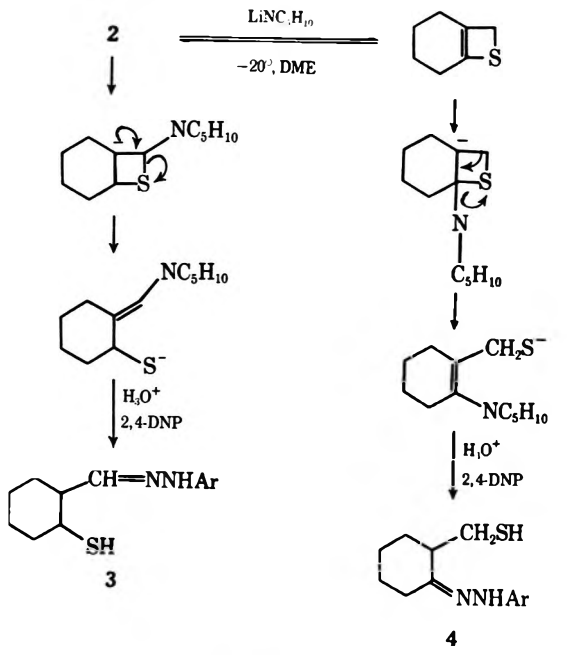
(1) Paper VI: D. C. Dittmer, P. L.-F. Chang, F. A. Davis, M. Iwanami, I. Stamos, and K. Takahashi, *J. Org. Chem.*, **37**, 1111 (1972).

(2) The authors are grateful for support of this research by the National Science Foundation.

(3) Taken in part from P. L.-F. Chang, Ph.D. Thesis, Syracuse University, 1970; F. A. Davis, Ph.D. Thesis, Syracuse University, 1966; and I. Stamos, Ph.D. Thesis, Syracuse University, 1969.

(4) R. Zahradnik and C. Parkanyi, *Collect. Czech. Chem. Commun.*, **30**, 3016 (1965); R. Zahradnik, *Advan. Heterocycl. Chem.*, **5**, 1 (1965). Recent calculations by F. A. Davis in which a different Coulomb integral for sulfur was used ($\alpha_S = \alpha_C + 1.5\beta$) indicate a much larger delocalization energy (2.6β) for thiete anion.

(5) (a) W. Adam, *Tetrahedron Lett.*, 1387 (1963). (b) C. G. Krespan, B. C. McKusick, and T. L. Cairns, *J. Amer. Chem. Soc.*, **82**, 1515 (1960); C. G. Krespan, *ibid.*, **83**, 3434 (1961).

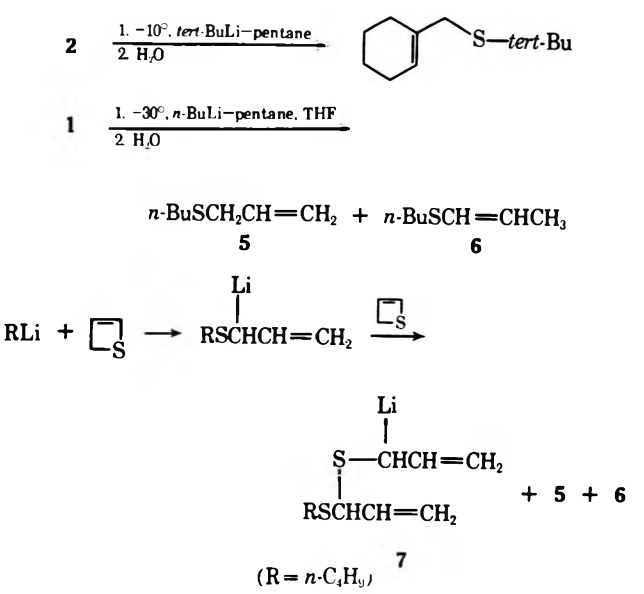


dium methoxide in tetrahydrofuran, lithium aluminum hydride in ether, or potassium hydroxide in tetrahydrofuran gave no purple color and no evidence of isomerization of the thiete, which was recovered in yields of 60–100%. Formation of the mercaptomethylcyclohexanone derivative (**4**) may involve an isomerization by way of the thiete anion,[6] although isomerization can also occur by way of an addition, proton migration, and elimination.[7]

Reactions with Alkyllithium and Alkylpotassium Bases.—When **1** or **2** is treated with alkyllithium reagents, good yields of ring-opened products are obtained in which the alkyl group of the alkyllithium is attached to sulfur.[8] No unchanged thiete is recovered. If wet tetrahydrofuran is added to the reaction mixture of **2** and *tert*-butyllithium in pentane at −78° a wine-red color is obtained instantly. The color is stable at −78° but fades at −50°. Work-up of the reaction mixture gives 1-cyclohexenylmethyl *tert*-butyl sulfide (80–90%). If the reaction of **1** with *n*-butyllithium is done in tetrahydrofuran a wine-red color (λ_{max} 524 mμ) also is observed (unlike the reaction in pentane in which there is no color). The red color is discharged immediately to yellow on addition of water. No thiete could be recovered, only the sulfides **5** and **6**.

Further investigation of the reaction of thiete with *n*-butyllithium in tetrahydrofuran revealed that in addition to **5** and **6**, small amounts of a high-boiling oil and an apparently polymeric material were obtained. These products may result from a secondary ring opening of thiete by a lithium derivative of one of the primary products.

Since the complex of *n*-butyllithium with *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMED) is reported to be more reactive than the alkyllithium alone,[9] thiete was



treated with this complex. The two sulfides **5** and **6** were the only products isolated in pentane, ether, or tetrahydrofuran. The pentane solution was pale yellow, the ether, pale pink, and the tetrahydrofuran, wine red. If the red color is caused by a free anion, the solvent behavior is explicable in terms of an equilibrium between a covalent lithium compound and the free anion. As the ability of the solvent to stabilize the lithium ion increases, more free anion is formed and the color deepens.

The wine-red color may be attributed to the thiete anion. However, an anion of a product also may be red, or the color may be produced by an intermediate thiocarbonyl compound. An esr spectrum of the red solution indicated the absence of any detectable anion-radical. The possibility that the red color from **1** and *n*-butyllithium was caused by anions of the products, **5** and **6**, was investigated, but no red color could be produced from these compounds nor was any red color observed when 1-cyclohexenylmethyl *tert*-butyl sulfide was treated with *tert*-butyllithium.

The possibility that an anion of an intermediate (*e.g.*, **7**) may be responsible for the observed red color was investigated. A solution of *n*-propylthioallyllithium in tetrahydrofuran was prepared from allyl *n*-propyl sulfide and *n*-butyllithium in the presence of TMED. Addition of **1** resulted in formation of a wine-red color (λ_{max} 512 mμ) within 2–3 min which deepened during 10 min. Addition of aqueous acid discharged the color, and work-up of the reaction mixture gave a colorless liquid (A) and a high-boiling yellow oil (B) together with some polymeric material. Although A could not be obtained pure, a mass spectrum showed ions at *m/e* 188 and 113 and intense ions at *m/e* 115 (*n*-PrSC$^+$HCH=CH$_2$), 73 (S$^+$CH$_2$CH=CH$_2$), 43 (C$_3$H$_7^+$), and 41 (C$^+$H$_2$CH=CH$_2$). The ions *m/e* 188 and 113, as well as the others, can be derived from a logical structure, **8** (or a tautomer), resulting from attack of *n*-propylthioallyllithium on thiete. The infrared spectrum of A shows absorption at 1640 and 1620 cm^{-1} ($\nu_{C=CH_2}$, $\nu_{C=CS}$) indicating a mixture of tautomers. Oil B was not investigated but its infrared spectrum indicated that its structure was similar to that of A. Anions derived from **8** could react with thiete to give a higher molecular weight mate-

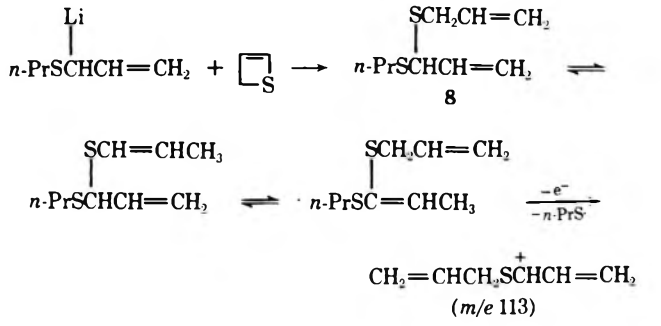
(6) The temptation to assume that the purple color is caused by the anion should be resisted in the absence of definite proof. This point is discussed subsequently.

(7) An addition–elimination mechanism for the isomerization of 2-sulfolene has been disproven: reviewed by C. D. Broaddus, *Accounts Chem. Res.*, **1**, 236 (1968).

(8) Trimethylene sulfide (thietane) yields *n*-butyl *n*-propyl sulfide when treated with *n*-butyllithium: F. G. Bordwell, H. M. Anderson, and B. M. Pitt, *J. Amer. Chem. Soc.*, **76**, 1082 (1954).

(9) G. G. Eberhardt and W. A. Butte, *J. Org. Chem.*, **29**, 2928 (1964).

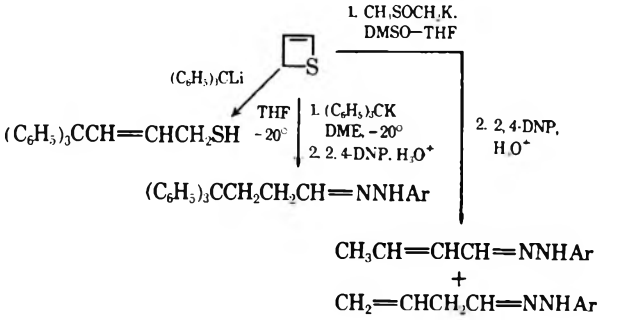
rial. Treatment of A with *n*-butyllithium in tetrahydrofuran gave a violet color (λ_{max} 550 mμ) and similar treatment of B gave a wine-red color (λ_{max} 495 mμ).

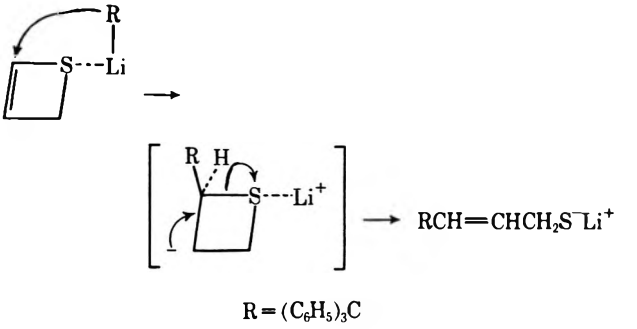


Another possible chromophore is a dianion of a sulfide, *e.g.*, $S(\bar{C}HCH{=}CH_2)_2$. Treatment of allyl sulfide in tetrahydrofuran with TMED and 1 equiv of *n*-butyllithium gave only a pale yellow solution, but addition of a second equivalent gave an orange solution which changed gradually to a wine red (λ_{max} 490 mμ) during 1 hr at room temperature. However, no starting material or isomerized starting material could be recovered from the red solution after addition of water. Therefore, the red color produced when thiete is treated with *n*-butyllithium in tetrahydrofuran may not be caused by the anion of thiete but by an anion or dianion of a small amount of oligomeric product. However, the production of color by the thiete anion is not excluded.[10] The very rapid production of the red color from thiete may militate against the products as the source of color unless they are formed instantly.

Ring opening of **1** also occurs on treatment with tritylithium, tritylpotassium, and potassium dimsylate (CH_3SOCH_2K). There is, however, a difference in the mode of cleavage between the first-named reagent and the last two. Tritylithium yields *cis*- and *trans*-4,4,4-triphenyl-1-mercapto-2-butene (38%) after work-up of the reaction mixture. Tritylpotassium after work-up of the reaction mixture and treatment of it with 2,4-dinitrophenylhydrazine yields the 2,4-dinitrophenylhydrazone of 4,4,4-triphenylbutanal (74%) and potassium dimsylate yields, after a similar work-up, the 2,4-dinitrophenylhydrazones of crotonaldehyde and 3-butenal. Conceivably, the reaction with tritylpotassium also could yield 4,4,4-triphenyl-1-mercapto-2-butene, which, on treatment with the acidic 2,4-dinitrophenylhydrazine reagent, may be isomerized to the enol of 4,4,4-triphenylbutanthial, which subsequently yields the observed hydrazone. This hypothesis was discarded because treatment of the mercaptobutene with 2,4-dinitrophenylhydrazine reagent gave no reaction.

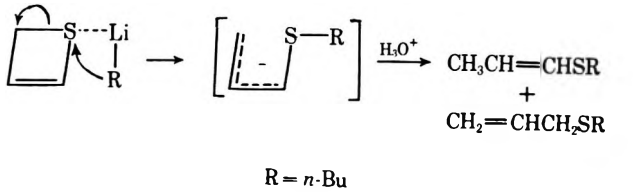
Alkyllithium reagents have considerable covalent character and are associated in solution; they are much less ionic than potassium derivatives.[11] Reaction of thiete with an alkyllithium reagent may be expected to proceed by association of the lithium with the unshared electrons on sulfur.[8] Two extreme orientations of the lithium–alkyl bond with respect to the plane of the thiete ring may be considered. In one, the bond lies in the plane; in the other it lies perpendicular to it. If a displacement reaction on sulfur proceeds by an attack on the back side of the bond being displaced, then the in-plane orientation of R–Li is more suitable. If the R–Li bond is perpendicular to the plane of the ring, the alkyl group is situated well for attack on the π-orbital system of the double bond. Which of the two modes of attack of alkyllithium compounds occurs may well depend on steric factors and perhaps on weak secondary valence interactions, such as an attraction between the double bond and a polarizable group (*e.g.*, phenyl). In the reaction of thiete with tritylithium, the bulky trityl group may cause the in-plane pathway of attack to be of higher energy than the attack on the double bond. Furthermore, there may be an attraction between the phenyl rings and the double bond which favors the perpendicular orientation of R–Li. Thus, one would predict that tritylithium would react *via* an addition–elimination mechanism, which gives the observed product. The more stable olefin would be expected to be formed.





R = $(C_6H_5)_3C$

The in-plane mode of attack of *n*-butyllithium on thiete occurs because of the less bulky nature of the butyl group as compared with the trityl group. Also, the butyl group would have less affinity for association with the double bond. The in-plane attack ordinarily may be preferred over the perpendicular one because of the development of an allylic anion in the former case. This would provide electronic stabilization for the in-plane pathway, and only when steric factors become important does the other mode of attack occur.



R = *n*-Bu

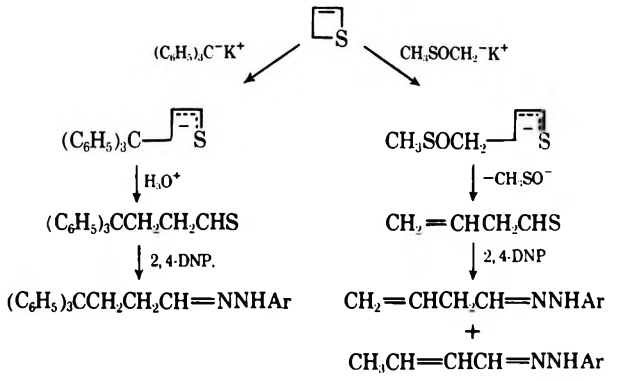
The reaction of *tert*-butyllithium with thiete **2** may seem contradictory to the above discussion, since apparently an in-plane attack on sulfur by the bulky

(10) The 1,3-bis(methylthio)allyl anion is purple: E. J. Corey, B. W. Erickson, and R. Noyori, *J. Amer. Chem. Soc.*, **93**, 1724 (1971).

(11) G. E. Coates, M. L. H. Green, P. Powell, and K. Wade, "Principles of Organometallic Chemistry," Methuen, London, 1968, Chapter 3.

tert-butyl group occurs. Consideration of a model reveals unfavorable steric interactions with the hydrogens of the six-membered ring in the above-the-plane attack on the double bond, and the electronically more favorable pathway is followed.

Since tritylpotassium is more ionic than trityllithium, the trityl ion no longer is necessarily very near the potassium ion. The large potassium ion also has less need for stabilization by solvation by the sulfur atom. The same applies to the dimsyl ion. The relatively free trityl and dimsyl ions can attack the methylene group to displace mercaptide ion. This last mode of attack may be favored over the in-plane attack on sulfur, since making a carbon–carbon bond is favored energetically.



Experimental Section

Thiete 1 and Sodium Methoxide.—Thiete (0.038 g, 0.53 mmol) was treated with a saturated solution (0.3 ml) of sodium methoxide in methanol-d_1 in an atmosphere of nitrogen. The solution was transferred by means of a syringe into a nitrogen-flushed nmr sample tube. The tube was closed by a pressure cap. The sample was examined at ambient temperature by nmr. The absorption of the thiete protons at δ 6.50, 5.60, and 3.80 gradually disappears and a new band appears upfield from the δ 5.60 absorption. Maximum intensity of the new band is reached in 8–10 hr. The rate of decrease of the absorption at δ 3.80 ($-CH_2-$) seems slightly greater than that at δ 6.50 as determined by integration (during a 1.5-hr time period) of the peak areas by means of a planimeter. The new absorption at *ca.* δ 5.50 is observed immediately on addition of water or methanol to the saturated solution of sodium methoxide in methanol-*d*. This supports the assignment of the new peak to the hydroxyl protons of undeuterated methanol.

After 24 hr at room temperature, no change was observed in the nmr spectrum of a solution of diallyl sulfide in a saturated solution of sodium methoxide in methanol-*d*.

Thiete 1 and Potassium *tert*-Butoxide. A.—Deuterium oxide (2 mg, 0.1 mmol) and dry potassium *tert*-butoxide (56 mg, 0.5 mmol) were added to thiete (0.36 g, 0.5 mmol) in dimethylformamide (3 ml). The nmr spectrum of this thiete solution was examined during 30 min. The ratios of the areas of absorption at δ 6.56 ($C_3{=}C_2H$), 5.65 ($C_2{=}C_3H$), and 3.88 (CH_2) were determined at 10-min intervals as follows (time, min; rel ratios): 0, 1, 1, 2.0; 10, 1, 1, 1.8; 20, 1, 1, 1.5; 30, 1, 1, 1.3. At the end of this period the initially colorless solution had become red and viscous. Treatment of this solution with 2,4-dinitrophenylhydrazine reagent gave the 2,4-dinitrophenylhydrazone of β-mercaptopropionaldehyde[1] (0.075 g, 6%) which showed no absorption in the C–D stretching region (2200 cm^{-1}) in the infrared.

B.—The nmr spectrum of a solution of thiete (0.072 g, 1 mmol, dried over $MgSO_4$ or KH) and dry potassium *tert*-butoxide (0.056 g, 0.5 mmol) in dry (4A molecular sieves) dimethyl sulfoxide-d_6 (0.5 ml) was examined. As soon as the base was added, a substantial increase (*ca.* 111%) in the absorption at δ 2.50 for dimethyl sulfoxide-d_5 was observed. The increase in absorption corresponds to *ca.* 1.6 protons (based on the area of the absorption of the nine protons of the *tert*-butyl group). A control experiment with phenylacetylene replacing thiete showed a similar immediate increase in dimethyl sulfoxide-d_5 absorption which corresponded to 0.8 proton.

Thiete 2 and Lithium Piperidide.—*n*-Butyllithium (1.22 ml of a 21% solution in hexane) was added by syringe through a septum to piperidine (0.4 ml, dried over KOH and distilled from sodium) in a dry, three-necked flask equipped with a mechanical stirrer and a nitrogen inlet. The hexane was removed under vacuum and the flask was cooled in a Dry Ice–isopropyl alcohol bath. Thiete 2, prepared from 2 g of the quaternary salt, in cold dimethoxyethane (20 ml, distilled from $LiAlH_4$) was added by syringe through the septum. The mixture became purple at once and after 20 min was yellow-brown. Stirring was continued for 4 hr at bath temperature and 12 hr at −20°. The mixture was acidified to pH 2–3 with hydrochloric acid and treated with 2,4-dinitrophenylhydrazine (1 g, 0.005 mol). The reaction mixture was allowed slowly to come to room temperature, stirred for 2 hr, and heated for a few minutes at 40–50°. Water was added and the mixture was extracted with chloroform. The chloroform was dried ($MgSO_4$) and removed by evaporation on a rotary evaporator. The residue was chromatographed on alumina ($CHCl_3$) and on Florisil ($CHCl_3$) to separate two 2,4-dinitrophenylhydrazones, mp 168–170° and 235–238°. The lower melting compound was considered to be the 2,4-dinitrophenylhydrazone of 2-mercaptomethylcyclohexanone (0.2 g, 0.0006 mol, recrystallized from ethyl acetate) because it lacked absorption in the nmr at *ca.* δ 7.6 for the aldehydic proton:[12] nmr ($CDCl_3$) δ 11.10 (s, 1, NH), 9.00 (s, 1, ArC_3H), 8.25 (d, 1, ArC_5H), 7.90 (d, 1, ArC_6H), 1.2–3.1 (m, 12).

Anal. Calcd for $C_{13}H_{16}N_4O_4S$: C, 48.11; H, 4.94; N, 17.22; S, 9.88. Found: C, 48.10; H, 4.76; N, 16.95; S, 9.80.

The other compound was assigned the structure of the 2,4-dinitrophenylhydrazone of 2-mercaptocyclohexyl-1-carboxaldehyde. Its nmr spectrum could not be obtained because of its insolubility. An isomeric structure, the 2,4-dinitrophenylhydrazone of 2-methylthiocyclohexanone, was eliminated on the basis of the melting point of the derivative, 141°.[13]

Anal. Calcd for $C_{13}H_{16}N_4O_4S$: C, 48.11; H, 4.94; N, 17.22; S, 9.88. Found: C, 47.94; H, 4.75; N, 16.90; S, 9.47.

Thiete 2 and *tert*-Butyllithium (1-Cyclohexenylmethyl *tert*-Butyl Sulfide).—*tert*-Butyllithium in pentane (0.0045 mol, 2.5 ml)[14] was added by syringe to thiete 2 (0.5 g, 0.004 mol) in pentane (100 ml) in a cooled (−10°) 300-ml, three-necked flask equipped with a mechanical stirrer, serum cap, and nitrogen inlet tube. The reaction mixture was stirred for 4 hr, water (10 ml) was added, and stirring was continued for 1 hr. The pentane solution was separated from the water and dried (Na_2SO_4, −10°) and the solvent was removed to give a clear oil (0.8 g, 80%) which was distilled through a 20-cm spinning band column to give 1-cyclohexenylmethyl *tert*-butyl sulfide: bp 36–38° (0.25 mm); ir (neat) 1663 (w, C=C), 940 (w), 910, (w), 790 cm^{-1} (w); uv max (CH_3CN) 255 mμ (ϵ 790); nmr ($CDCl_3$) δ 5.6 (m, 1, C=CH), 3.08 (s, 2, $C{=}CCH_2S$), 2.0 (m, 4, $C{=}CCH_2CH_2$), 1.5 (m, 4, $C{=}CCH_2CH_2$), 1.3 (s, 9, CH_3); mass spectrum (70 eV) *m/e* (rel intensity) 95 (88), 57 (100).

Anal. Calcd for $C_{11}H_{20}S$: C, 71.64; H, 10.94; S, 17.39. Found: C, 71.51; H, 10.69; S, 17.72.

The same reaction was done at −78° in pentane. After 2 hr the pentane solution was pink. Addition of water (0.09 ml)–tetrahydrofuran (10 ml) cooled to −78° caused the reaction mixture to become wine red. Addition of more water or warming the mixture destroyed the color. Only 1-cyclohexenylmethyl *tert*-butyl sulfide was isolated. When a 1:1 pentane–ether solvent was used instead of pentane alone, a red color was obtained on addition of *tert*-butyllithium.

Thiete 1 and *n*-Butyllithium (*n*-Butyl Propenyl Sulfide and *n*-Butyl Allyl Sulfide). A. In Pentane.—*n*-Butyllithium in hexane (2 ml, 20%) was added to a stirred solution of thiete 1 (0.30 g, 0.0042 mol) in pentane (30 ml) at −30° under nitrogen. Water was added after 10 min and the mixture was extracted with pentane. Neither the water nor pentane layer gave a reaction with 2,4-dinitrophenylhydrazine. The pentane was washed (H_2O), dried ($MgSO_4$), and removed by evaporation. The res-

(12) G. J. Karabatsos, B. L. Shapiro, F. M. Vane, J. S. Fleming, and J. S. Ratka, *J. Amer. Chem. Soc.*, **85**, 2784 (1963).

(13) v. F. Asinger, M. Thiel, and H. Kaltwasser, *Justus Liebigs Ann. Chem.*, **606**, 67 (1957).

(14) The solution of *tert*-butyllithium was standardized by the method of H. Gilman and A. H. Haubein, *J. Amer. Chem. Soc.*, **66**, 1515 (1944).

idue was distilled (1 atm) to give a colorless liquid (0.25 g, 0.0019 mol) which was identified as a mixture of *cis*- and *trans*-*n*-butyl propenyl sulfide (**6**) and *n*-butyl allyl sulfide (**5**) by vpc (comparison with authentic samples): ir (film) 3080 (w), 2950 (s), 2880 (s), 1830 (w), 1640 (m, C=CCH$_2$S), 1620 (m, C=CS), 1460 (s), 1425 (s), 1400 (m), 1377 (s), 1330 (m), 1290 (m), 1275 (m), 1225 (s), 988 (s), 935 (m), 915 (s), 787 (w), 750 (m); ir (film, *n*-C$_4$H$_9$SCH$_2$CH=CH$_2$) 3080 (m), 2930 (s), 2875 (s), 1830 (w), 1640 (s), 1455 (s), 1420 (s), 1395 (m), 1377 (m), 1290 (w), 1270 (m), 1220 (s), 988 (s), 915 (s), 787 (w), 750 (m); ir (film, *n*-C$_4$H$_9$SCH=CHCH$_3$) 3020 (m), 2950 (s), 2880 (s), 1620 (m), 1460 (s), 1425 (m), 1377 (m), 1330 (s), 1290 (w), 1275 (m), 1225 (m), 935 (s), 750 (m). The nmr spectrum of the mixture was consistent with the combined spectra of allyl *n*-butyl sulfide and *n*-butyl propenyl sulfide.[15]

An authentic sample of *n*-butyl allyl sulfide was prepared from *n*-butanethiol and allyl chloride.[15,16] Isomerization of *n*-butyl allyl sulfide with potassium *tert*-butoxide gave *n*-butyl propenyl sulfide.[15,17]

The reaction of **1** with the complex of *n*-butyllithium and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMED) in pentane gave a yellow solution and the products **5** and **6**.

B. In Ether with TMED.—*n*-Butyllithium (2 ml, 20% in hexane) was added to a solution of TMED (2 ml) in dry (KH) ether at 0°. This mixture was added to a solution of **1** (0.200 g) in dry (KH) ether (20 ml) at −30°. A faint pink color appeared immediately. After 20 min, the reaction mixture was treated with aqueous tetrahydrofuran and worked up as before to give allyl *n*-butyl sulfide and *n*-butyl propenyl sulfide.

C. In Tetrahydrofuran with TMED.—A solution of **1** (0.350 g) and TMED (2 ml) in anhydrous tetrahydrofuran was dried (KH) at 0°. The supernatant liquid was removed and cooled to −60° under nitrogen. Addition of *n*-butyllithium (3 ml, 20% in hexane) produced a deep wine-red color, λ_{max} 524 mμ. The color was stable up to 1 hr at room temperature. Addition of D$_2$O (2 ml) after 30 min caused the solution to become yellow immediately. The only products were allyl *n*-butyl sulfide (**6**) and *n*-butyl propenyl sulfide (**5**), which contained deuterium as indicated by infrared and nmr spectra.

Thiete 1 and *n*-Propylthioallyllithium.—*n*-Butyllithium (3.3 ml, 20% in hexane) was added to a dry (KH) solution of allyl *n*-propyl sulfide (1.61 g) and TMED (1.6 g) in anhydrous tetrahydrofuran (40 ml) and the resulting mixture was stirred for 2 hr. Thiete (0.500 g) in dry (KH) tetrahydrofuran (10 ml) was added to the pale orange solution of *n*-propylthioallyllithium at −20°. Within 2 or 3 min a wine-red color developed which deepened during 10 min, λ_{max} 512 mμ. Addition of water caused a color change to green, then yellow. The reaction mixture was poured into ice–water, neutralized with hydrochloric acid, and extracted with pentane, which was washed with water and sodium bicarbonate solution and dried (MgSO$_4$). The pentane was removed by evaporation under reduced pressure and the residue was distilled to yield a colorless liquid, bp 28° (5 mm), identified as *n*-propyl propenyl sulfide by its infrared spectrum (1620 cm^{-1}, C=CS; 940 cm^{-1}, trans CH=CH).[18] The residue was separated by chromatography on Florisil into two fractions, A (0.2 g), a colorless oil eluted with pentane, and B (0.5 g), a yellow oil eluted with ether. The mass spectrum and infrared spectrum of A indicated that it might be a mixture of isomers of 3-(propylthio)-4-thia-1,6-heptadiene (**8**) (calcd mol wt 188): ir (film) 3090, 1640 (C=C), 1620 (C=CS–), 990 (CH=CH$_2$), 920 cm^{-1} (CH=CH$_2$); mass spectrum (70 eV) *m*/*e* (rel intensity) 188 (10), 115 (100), 113 (25), 79 (60), 73 (75), 43 (78), 41 (47). Oil B appeared to be similar to A: ir (film) 3090, 1640, 1620, 990, 920 cm^{-1}; nmr (CDCl$_3$) δ 4.8–6.2 (m), 2.5 (m), 1.6 (m), 0.9 (t).

Treatment of A with *n*-butyllithium in tetrahydrofuran gave a violet color (λ_{max} 550 mμ); likewise, B gave a wine-red color (λ_{max} 495 mμ).

Treatment of allyl sulfide (2 g) in dry tetrahydrofuran (50 ml) with TMED (4 g) and *n*-butyllithium (5.6 ml, 20% in hexane) at −30° resulted in no color change. Addition of more *n*-butyllithium (5.6 ml) caused development of a yellow color which gradually changed to orange. Finally, at room temperature after 1 hr a wine-red color appeared (λ_{max} 490 mμ). Neither allyl sulfide nor its isomers could be identified in the reaction mixture after addition of water.

Thiete 1 and Trityllithium (4,4,4-Triphenyl-1-mercapto-2-butene).—Trityllithium was prepared by treatment of a dry (KH) solution of triphenylmethane (2.7 g, 0.011 mol) and TMED (1.3 g) in THF (40 ml) with *n*-butyllithium (2 ml, 20% in hexane) at room temperature. The solution of trityllithium was stirred for 1 hr and cooled to −20°. Thiete 1 (0.40 g, 0.0056 mol) in dry (KH) tetrahydrofuran (10 ml) was added, discharging the red color of the trityllithium. After 30 min the light orange reaction mixture was poured into ice–water and the solution was neutralized with hydrochloric acid. The product was removed by filtration. The filtrate gave no reaction with 2,4-dinitrophenylhydrazine. The product was washed with ether and recrystallized from CCl$_4$ to give white crystals of *cis*- and *trans*-4,4,4-triphenyl-1-mercapto-2-butene (0.66 g, 0.0021 mol, 38%): mp 172°; ir (KBr) 3050, 2580 (–SH); nmr (CDCl$_3$) δ 7.2 (s, 15, C$_6$H$_5$), 5.3–6.2 (m, 2, CH=CH), 3.45 (d, 0.5, C=CCH$_2$), 3.35 (d, 0.5, C=CH$_2$), 2.7 (s, 0.5, SH), 2.55 (s, 0.5, SH).

Anal. Calcd for C$_{22}$H$_{20}$S: C, 83.50; H, 6.37; S, 10.13. Found: C, 83.58; H, 6.41; S 10.34.

Thiete 1 and Tritylpotassium (4,4,4-Triphenylbutanal 2,4-Dinitrophenylhydrazone).—Thiete 1 (0.43 g, 0.059 mol) in dimethoxyethane (5 ml) was added to tritylpotassium (0.5 *M*, prepared from 2.23 g of triphenylmethane)[19] in dimethoxyethane (25 ml) at −20° under nitrogen. The original red solution at first became colorless, then again red. After 1 hr, water and 2,4-dinitrophenylhydrazine reagent were added. The yellow, crystalline precipitate was recrystallized from ethanol to give the 2,4-dinitrophenylhydrazone of 4,4,4-triphenylbutanal (2.8 g, 0.0058 mol, 96%): mp 86–87°; nmr (DMSO-*d*$_6$) δ 11.40 (m, 1, NH), 8.90 (d, 1), 8.00, 8.27 (m, 1), 7.90 (d, 1), 6.20 (m, 1, CH=N), 2.70 (m, 2, CH$_2$CPh$_3$), 2.20 (m, 2, CH$_2$CH$_2$CPh$_3$).

Anal. Calcd for C$_{28}$H$_{24}$N$_4$O$_4$: C, 69.99; H, 5.03. Found: C, 69.71; H, 4.80.

Thiete 1 and Potassium Dimsylate (Crotonaldehyde and 3-Butenal 2,4-Dinitrophenylhydrazones).—Thiete was generated *in situ* by treatment of trimethyl-3-thietanylammonium iodide[1] (1.0 g, 0.0038 mol) in DMSO (7 ml) with potassium *tert*-butoxide (0.8 g, 0.007 mol) in DMSO (3 ml) at 15°. After 10 min the reaction mixture was poured into acidic (2 *N* HCl) 2,4-dinitrophenylhydrazine. The orange crystals (0.45 g, 0.0018 mol) of hydrazone were removed by filtration, washed (H$_2$O), and dried. Tlc (silica gel–benzene) indicated that two products were present. One recrystallization of the mixture (CHCl$_3$–C$_2$H$_5$OH) gave red crystals (0.05 g, 0.002 mol), which after several further recrystallizations gave the 2,4-dinitrophenylhydrazone of crotonaldehyde, mp 192° (lit.[20] mp 190°), whose mixture melting point with an authentic sample showed no depression and whose ir spectrum was identical with that of an authentic sample.

The solution remaining from the recrystallization of the crotonaldehyde derivative was concentrated and washed with cold methanol to give yellow crystals (0.3 g, 0.001 mol) of the 2,4-dinitrophenylhydrazone of 3-butenal, which was purified further by chromatography (Florisil, CCl$_4$) and recrystallization (CH$_3$OH), mp 125–129° (lit.[21] mp 128–129°). The infrared spectrum of an authentic sample[21] was identical with that of the above sample.

In a similar reaction with thiete itself, the same result was obtained. Isomerization occurs under the conditions employed for the formation of the 2,4-dinitrophenylhydrazones: treatment of 3-butenal diethyl acetal with acidic (2 *N* HCl) 2,4-dinitrophenylhydrazine gave a mixture of the 2,4-dinitrophenylhydrazones of 3-butenal and crotonaldehyde.

Registry No.—**1**, 503-31-1; **5**, 5399-19-9; cis-**6**, 33531-82-7; *trans*-**6**, 33531-83-8; **8**, 33527-71-8; sodium methoxide, 124-41-4; potassium *tert*-butoxide, 865-47-4; lithium piperidide, 4442-11-9; 2-mercaptomethylcyclohexanone (2,4-DNPH derivative), 33527-74-1; *tert*-butyllithium, 594-19-4; 1-cyclohexenylmethyl *tert*-butyl sulfide, 33608-38-7; *n*-butyllithium, 109-72-8;

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(18) G. Sosnovsky and H. J. O'Neill, *J. Org. Chem.*, **27**, 3469 (1962).
(19) H. O. House and V. Kramar, *ibid.*, **27**, 4146 (1962).
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(21) R. I. Hoaglin, D. G. Kubler, and A. E. Montagna, *J. Amer. Chem. Soc.*, **80**, 5460 (1958).

n-propylthioallyllithium, 33527-76-3; tritylllithium, 733-90-4; *cis*-4,4,4-triphenyl-1-mercapto-2-butene, 33608-39-8; *trans*-4,4,4-triphenyl-1-mercapto-2-butene, 33531-84-9; tritylpotassium, 1528-27-4; 4,4,4-triphenylbutanal (2,4-DNPH derivative), 33527-79-6; potassium dimsylate, 17609-15-3.

Iminosulfuranes (Sulfilimines). IV.[1a] The Preparation and Properties of *N*-Acetyliminodialkylsulfuranes[1b]

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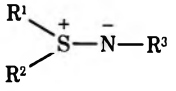
N-Acetyliminodialkylsulfonium bromides, $(R^1R^2S^+NHCOCH_3)Br^-$ [$R^1 = R^2 = CH_3$; $R^1 = CH_3$, $R^2 = C_2H_5$; $R^1 = R^2 = C_2H_5$; $R^1 = R^2 = n\text{-}C_3H_7$; $R^1 = R^2 = i\text{-}C_3H_7$; $R^1, R^2 = -(CH_2)_4-$], were prepared in 38–81% yields by the reaction of *N*-bromoacetamide with alkyl sulfides in a mixture of CCl_4 and acetone. The sulfonium bromides were converted in excellent yields (88–98%) to the *N*-acetyliminodialkylsulfuranes, $R^1R^2S^+N^-COCH_3$, by treatment with triethylamine in methylene chloride. Some *N*-acetyliminodialkylsulfonium chlorides were also prepared. Spectroscopic data show that the iminosulfuranes have extensive charge delocalization over the SNCO system, and the S–N bond is considered to be semipolar. The first detailed mass spectral fragmentation of iminosulfuranes and their salts is reported.

The nature of the N substituent in iminosulfuranes (**1**) has a significant effect on the polarity of the sulfur–



1

nitrogen bond and hence on their reactivity. Iminosulfuranes with alkyl,[2] aryl,[3] halogen,[4] nitrile,[5] carboethoxy,[6] sulfonyl,[7] benzoyl,[8] and halogenated acetyl[9] groups on the nitrogen atom are known.

N-(Haloacetyl)iminosulfuranes have also been prepared by the condensation of di- and trichloroacetylisocyanates with dimethyl sulfoxide,[10] and by the reaction of α-dichloro- and α-dibromoacetamide with sulfides in the presence of sodium hypochlorite.[11]

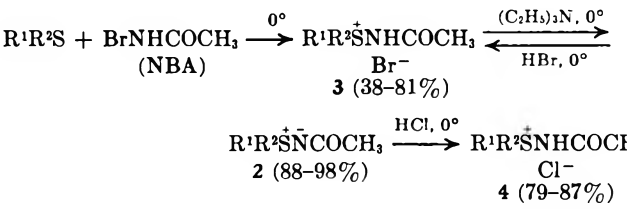
In 1947, Likhosherstov[12] reported that *N*-chloroacetamide reacts with dimethyl sulfide in CCl_4–acetone solution to give *N*-acetyliminodimethylsulfonium chloride, a compound which could not be obtained pure and was highly sensitive to moisture. Treatment of the sulfonium chloride with ammonia was reported to give an oil, suspected to be *N*-acetyliminodimethylsulfurane. The iminosulfurane was not purified nor was its structure established.

We report here (a) the first preparations of pure *N*-acetyliminodialkylsulfuranes by a modification and improvement of Likhosherstov's method and (b) establishment of their structure by ir, nmr, uv, and mass spectrometry. This is the first in a series of papers in which the effects of the substituent on nitrogen on reactivity, nucleophilicity, basicity, and spectral properties of iminosulfuranes are being systematically explored.

Results and Discussion

Preparation of *N*-Acetyliminodialkylsulfuranes and Their Salts.—The synthetic route used is shown in Scheme I (yields in parentheses).

SCHEME I



a, $R^1 = R^2 = CH_3$; **b**, $R^1 = CH_3$, $R^2 = C_2H_5$; **c**, $R^1 = R^2 = C_2H_5$; **d**, $R^1 = R^2 = n\text{-}C_3H_7$; **e**, $R^1 = R^2 = i\text{-}C_3H_7$; **f**, $R^1, R^2 = -(CH_2)_4-$

The yields and melting points of the iminosulfuranes (**2**), sulfonium bromides (**3**), and sulfonium chlorides (**4**) are given in Table I.

N-Bromoacetamide (NBA) is a source of positive bromine and is an oxidizing agent in aqueous media. Consequently, a thoroughly dry and inert solvent system is required for the preparation of the sulfonium bromides (**3**). In carbon tetrachloride, the reaction of NBA with sulfides is slow and in ether the major product is acetamide hydrobromide, $(CH_3CONH_2)_2HBr$. Chloroform and ethyl alcohol are also unsatisfactory solvents because of the predominance of substitution and oxidation reactions. The best solvent system found for the reaction is a mixture of carbon tetrachloride and acetone (4–8:1 by volume); under these conditions the reaction mixture is heterogeneous. The sulfonium bromides (**3**) precipitate at the reaction temperature (0°).

The sulfonium bromides (**3**) are white, crystalline

(1) (a) For part III, see H. Kise, G. F. Whitfield, and D. Swern, *Tetrahedron Lett.*, 1761 (1971). (b) Presented in part at the 161st National Meeting of the American Chemical Society, Los Angeles, Calif., Apr 1971. (c) Postdoctoral Fellow from the University of Tokyo. (d) Postdoctoral Fellow from the University of London.

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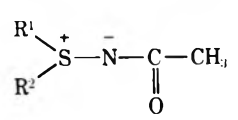
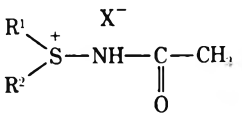
TABLE I

N-ACETYLIMINODIALKYLSULFURANES AND THEIR SALTS[b]



2



3, X = Br
4, X = Cl

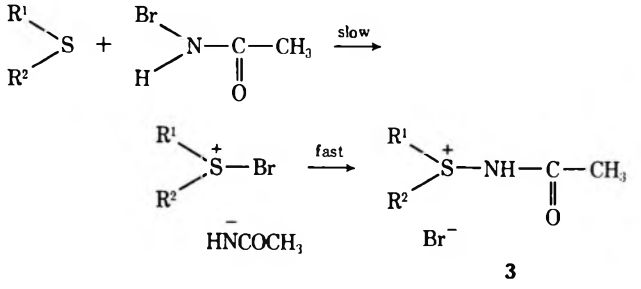
R^1	R^2	Compd	Yield, %	Mp, °C
CH_3	CH_3	**2a**	88	67–68
		3a	81	111–112 dec
		4a	79	132–133 dec[a]
CH_3	C_2H_5	**2b**	94	59–60
		3b	66	109–110
C_2H_5	C_2H_5	**2c**	98	<30
		3c	67	110–111 dec
		4c	87	116–117 dec
n-C_3H_7	n-C_3H_7	**2d**	95	36–38
		3d	38	86–88
i-C_3H_7	i-C_3H_7	**2e**	95	<30
		3e	52	124–125 dec
$-(CH_2)_4-$		**2f**	95	66–68
		3f	72	115–117 dec

[a] Lit.[12] mp 78–90°. [b] Satisfactory analyses (±0.4%) for C, H, N, and S were obtained for all new compounds listed. Ed.

solids that can be recrystallized from alcohol or mixtures of alcohol and ether without decomposition. They are stable in water at room temperature.

A suggested pathway for the reaction of NBA with sulfides is given in Scheme II.

SCHEME II



3

Although the work-up conditions were not exactly the same for all the NBA–sulfide reactions, there is some indication that electron-donating groups on sulfur facilitate the reaction, giving the sulfonium bromides (**3**) in higher yields (Table I). This can be explained by assuming that the rate-determining step is the first one in Scheme II. A similar mechanism was proposed for the reaction of sulfides with chloramine-T to give *N*-tosyliminosulfurancs.[13]

Reaction of NBA with di-*tert*-butyl sulfide failed to yield the sulfonium bromide, presumably due to steric hindrance by the *tert*-butyl groups. Furthermore, we have been unable, to date, to prepare sulfonium bromides (**3**) *via* the reaction of NBA with methyl phenyl sulfide and diphenyl sulfide.

N-Acetyliminodialkylsulfuranes (**2**) were obtained by treatment of the sulfonium bromides (**3**) with triethylamine in methylene chloride at 0°. The purity of **2** was supported by mass spectrometry, nmr, and microanalysis. The iminosulfuranes (**2**) are oils or delinquescent, crystalline solids. They decompose in water at room temperature within a few days to acetamide and the corresponding sulfoxide, except **2e** (R^1 = R^2 = i-C_3H_7), which is stable in water at room temperature for more than 10 days.

Treatment of iminosulfuranes **2a** and **2c** with hydrogen bromide or hydrogen chloride gave the sulfonium bromides (**3a** and **3c**) or chlorides (**4a** and **4c**), respectively. The sulfonium chlorides are stable in water and they can be recrystallized from alcohol without decomposition, contrary to the statement by Likhosherstov[12] who reported that **4a** rapidly decomposes on exposure to moisture.

Spectral Characteristics.[14]—*N*-Acetyliminosulfuranes **2** show some variation in the position of the S–N and C=O stretching bands with change of R^1 and R^2. The greatest differences are found in iminosulfuranes **2e** and **2f**; the former has the highest C=O (1600 cm^{-1}) and the second highest S–N frequencies (802 cm^{-1}), whereas the latter has the lowest (1540 and 788 cm^{-1}). The nmr resonance of the β-methyl protons in **2e** appears as a doublet of doublets, while in the salt **3e** it appears as a doublet. In addition, **2e** is stable in water at room temperature in contrast to **2f**, which decomposes quite rapidly.

The observation of a doublet of doublets for the methyl groups of **2e** in the nmr clearly demonstrates their magnetic nonequivalence. The reason for this is not clear. However, the higher S–N frequency observed in **2e** suggests partial double bond character (S=N) and this, coupled with the greater bulk of the isopropyl groups, could give rise to restricted rotation about the S–N bond, resulting in two sets of nonequivalent methyl groups. The steric effect appears to be more important because in other ylides (**2c**, **2d**) the β protons are identical even though the ir spectra suggest similar S–N double bond character.

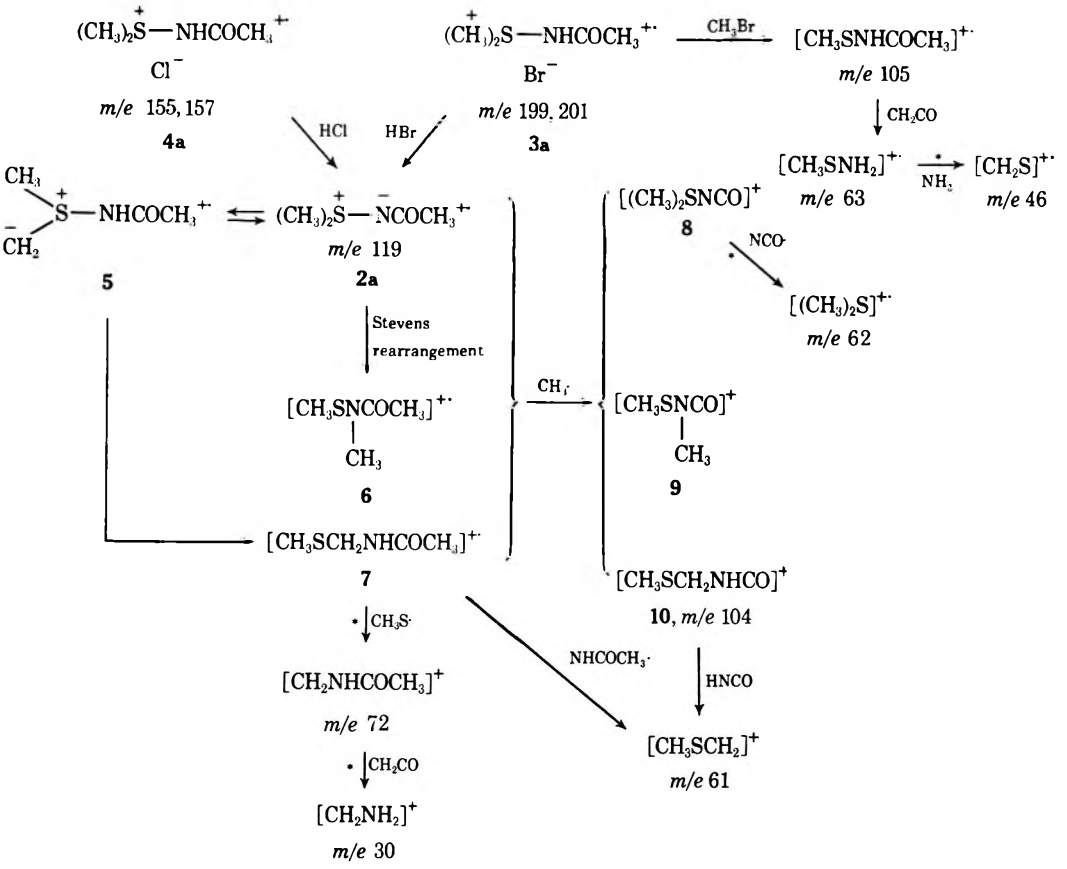
In the uv spectra of iminosulfuranes **2a** and **2c**, large differences were noted between λ_{max} in alcohol and chloroform; these are too large to be accounted for as an ordinary solvent effect. Also, the absorption did not follow the Beer–Lambert law; ϵ decreased with increasing concentration.

Mass Spectrometry.[14]—The literature on mass spectral fragmentations of ylides is sparse; our detailed study of the mass spectra of iminosulfuranes is the first report of their fragmentation pathways. The high-resolution mass spectra of the iminosulfuranes **2a** and **2c** and of their salts (**3a**, **4a**, **3c**, and **4c**) were obtained (see Experimental Section). A condensed "superimposed" version of the spectra of **2a**, **3a**, and **4a** is shown in Scheme III. The mass spectral fragmentations of **2a** and **4a** are quite similar. The primary fragmentation of **4a** is loss of HCl to give **2a**. The sulfonium bromide **3a** also loses HBr to give **2a**, but, in this case, loss of methyl bromide is another primary fragmentation pathway. The subsequent fragmentations of **2a** indicate that some kind of rearrangement

(13) K. Tsujihara, N. Furukawa, K. Oae, and S. Oae, *Bull. Chem. Soc., Jap.*, **42**, 2631 (1969).

(14) Some spectral data on 6 of the 14 compounds described in this paper have been reported in the preliminary communication.[1a] The remaining ir, nmr, and uv data, as well as mass spectral bar graphs for compounds **2a** and **2c** (Table I), will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to code number JOC-72-1121. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche.

SCHEME III



is involved. The formation of the ion at *m/e* 104 can occur in several ways: (1) loss of $CH_3\cdot$ directly from **2a** to give structure **8**; (2) Stevens rearrangement of **2a** to give **6** followed by loss of $CH_3\cdot$ affording **9**; (3) formation of the ylide **5** by a 1,3-prototropic shift, followed by a Stevens rearrangement and loss of $CH_3\cdot$ to give **10**.

The genesis of the fragment at *m/e* 72 involves loss of $CH_3S\cdot$ from the ion at *m/e* 119, and either of the two structures shown (**6** or **7**) appears to be equally feasible. However, the elimination of ketene from *m/e* 72 to give the ion at *m/e* 30 and the formation of the ion at *m/e* 61 (C_2H_5S) suggest that structure **7** is more likely.

Another interesting fragmentation is the loss of methyl bromide from the molecular ion of **3a** to give the fragment at *m/e* 105. This is not observed in the sulfonium chloride **4a** and, accordingly, it appears that the nature of the anion in sulfonium salts has some influence on the primary fragmentation mode.

A condensed version of the spectra of **2c**, **3c**, and **4c** is shown in Scheme IV. As with the analogous dimethyl compounds described above, the primary fragmentation of **4c** is loss of HCl to give **2c**, whereas **3c** loses either HBr or ethyl bromide to afford **2c** or *N*-(ethylthio)acetamide (**15**) (*m/e* 119). Elimination of C_2H_4 from **2c** also gives **15**, which then cleaves in two ways: (a) loss of ketene affords an abundant ion at *m/e* 77, which then loses C_2H_4 giving the fragment at *m/e* 49; and (b) elimination of $CH_3\cdot$ yields the ion at *m/e* 104, which then loses HNCO and CO in two distinct metastable processes to give the fragments at *m/e* 61 and 76, respectively. It seems likely that a 1,3-prototropic shift converts the iminosulfurane (sulfilimine) ion radical (Scheme IV) into the ylide ion radical (**11**), which then undergoes a Stevens type rearrangement affording the fragment of structure **12**. Loss of $C_2H_5S\cdot$ from **12** yields the ion at *m/e* 86 (metastable peak observed); the formation of the ion at *m/e* 89 is additional evidence for structure **12**.

Experimental Section

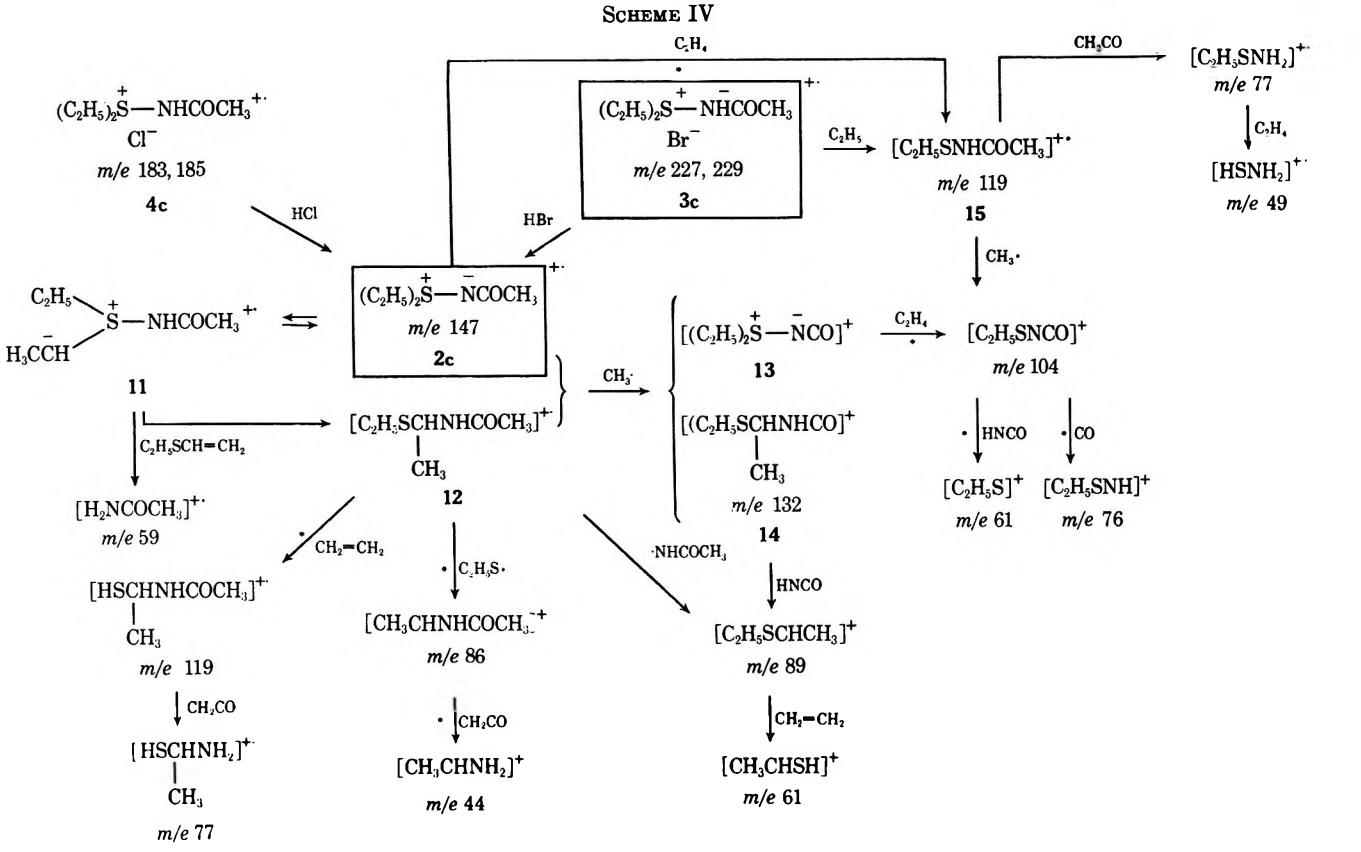
Ir, Nmr, and Uv.—Ir spectra were obtained as KBr discs or liquid films using a Perkin-Elmer Model 225 grating ir spectrophotometer or an Infracord spectrophotometer Model 137B. Nmr spectra of salts and iminosulfuranes were obtained with a Varian A-60A spectrometer, using D_2O as solvent and DSS (sodium 2,2-dimethyl-2-silapentanesulfonate) as internal standard. Nmr spectra of the iminosulfuranes **2** were also taken in $CDCl_3$ using TMS as internal standard. The differences in chemical shift in the two solvents were within 0.1 ppm except for the methine protons in **2e**, in which the difference was 0.18 ppm. When **2** has methylene groups attached to sulfur, they appear as ABX*n* type spectra giving multiplets for **2b**, **2c**, **2d**, and **2f**. Uv spectra were obtained with a Perkin-Elmer spectrometer Model 202.

Preparation of *N*-Acetyliminodimethylsulfonium Bromide (3a).—A solution of dimethyl sulfide (20.3 g, 0.327 mol) in dry CCl_4 (80 ml) was added dropwise with stirring to a supension of *N*-bromoacetamide (32.0 g, 0.232 mol) in a mixture of CCl_4 (160 ml) and dry acetone (60 ml) at 0° over 1 hr. The reaction was exothermic; after 5 hr the precipitate was separated, washed with cold acetone, and dried under vacuum at room temperature. Recrystallization from EtOH gave pure **3a** (37.4 g, 81% yield), mp 111–112° dec.

The other sulfonium bromides (**3b–f**) were prepared similarly using smaller amounts of acetone (30–45 ml) and a longer reaction time for **3d** and **3e** (30 hr). Yields and melting points of **3** are shown in Table I.

Preparation of *N*-Acetyliminodimethylsulfurane (2a).—Freshly distilled triethylamine (17.0 g, 0.168 mol) was added dropwise with stirring to a supension of **3a** (30.7 g, 0.154 mol) in dry CH_2Cl_2 (200 ml) at 0° over 20 min. After 1 hr, the reaction mixture was concentrated to about 100 ml and ether (200 ml) was added at

SCHEME IV



0°. The precipitate ($Et_3N \cdot HBr$) was separated by filtration and washed with cold ether (27.5 g, yield 98%). The solvents were removed from the filtrate at room temperature (rotary evaporator, water pump pressure) and the residue was then dried under vacuum at room temperature for 2 hr. A colorless, crystalline solid was obtained; it was found to be pure **2a** (16.2 g, 88% yield), mp 67–68°. The purity of **2a** was established by microanalysis and nmr and mass spectral measurements.

The other iminosulfuranes (**2b–f**) were prepared similarly. Yields and melting points of **2** are shown in Table I.[14]

The stability of **2** in water was examined by nmr; in the case of **2a**, the formation of dimethyl sulfoxide and acetamide was confirmed.

Preparation of *N*-Acetyliminodimethylsulfonium Chloride (4a).—Aqueous HCl (37%, 0.44 ml, 0.0053 mol HCl) was added dropwise with stirring to a solution of **2a** (0.53 g, 0.0044 mol) in acetone (7 ml) at 0°. After 2 hr, the precipitate was separated, washed with cold acetone, and dried under vacuum. Pure sulfonium chloride **4a** was obtained by recrystallization from EtOH–Et_2O (0.55 g, 79%), mp 132–133° dec.

The analogous diethylsulfonium chloride (**4c**) was obtained by using dry HCl instead of aqueous HCl, and ether instead of acetone. Yields and melting points are shown in Table I.[14]

Mass Spectrometry.—The spectra were run using an A.E.I. MS 902 instrument, at 70 eV, ion source temperature 200°. The sample was introduced (a) *via* direct insertion probe for **3a** (100°), **4a** (100°), **2c** (130°), **3c** (100°), and **4c** (130°); (b) *via* heated inlet for **2a** (200°). The data are presented using the following format: *m/e* value (rel abundance), fragment assignment, molecular formula (difference between the calculated and observed masses). Results with **2a**: *m/e* 119 (29), molecular ion, C_4H_9NOS (4.7 ppm); 104 (100), M − $CH_3\cdot$, C_3H_6NOS (6.0 ppm); 89 (12), *m/e* 104 − $CH_3\cdot$, C_2H_3NOS (11.4 ppm); 72 (23), *m/e* 119 − $CH_3S\cdot$, C_3H_6NO (3.7 ppm); 62 (67), *m/e* 104 − $NCO\cdot$, C_2H_6S (33.7 ppm); 62 (30), *m/e* 104 − ketene, CH_4NS (33.1 ppm); 61 (18), *m/e* 104 − HNCO and *m/e* 119 − $NHCOCH_3\cdot$, C_2H_5S (40.9 ppm); 47 (28), CH_3S (34.8 ppm); 46 (13), *m/e* 62 − CH_4, CH_2S (26.5 ppm); 45 (13), CHS (34.3 ppm); 43 (22), CH_3CO (45.8 ppm); 41 (18), *m/e* 72 − CH_3O, C_2H_3N (41.0 ppm); 30 (5), *m/e* 72 − ketene, CH_4N (18.4 ppm).

Results with **3a**: *m/e* 119 (12), M − HBr, C_4H_9NOS (2.3 ppm); 105 (21), M − CH_3Br, C_3H_7NOS (5.3 ppm); 104 (41), *m/e* 119 − CH_3, C_3H_6NOS (4.3 ppm); 96 (54), $CH_3{}^{81}Br$ (1.9 ppm); 94 (59), $CH_3{}^{79}Br$ (8.7 ppm); 89 (4), *m/e* 104 − CH_3, C_2H_5NOS (2.7 ppm); 82 (16), $H^{81}Br$ (3.0 ppm); 80 (17), $H^{79}Br$ (5.4 ppm); 72 (10), *m/e* 119 − CH_3S, C_3H_6NO (4.1 ppm); 63 (100), *m/e* 105 − ketene, CH_5NS (3.3 ppm); 62 (25), *m/e* 104 − NCO, C_2H_6S (4.8 ppm); 62 (21), *m/e* 104 − ketene, CH_4NS (8.0 ppm); 61 (7), *m/e* 104 − HNCO and *m/e* 119 − $NHCOCH_3$, C_2H_5S (9.9 ppm); 59 (34), *m/e* 105 − CH_2S, C_2H_6NO (4.4 ppm); 47 (23), CH_3S (16.0 ppm); 46 (14), *m/e* 63 − NH_3 and *m/e* 62 − CH_4, CH_2S (27.4 ppm); 45 (16), *m/e* 62 − NH_3, CHS (27.8 ppm); 44 (24), *m/e* 59 − CH_3, CH_2NO (30.6 ppm); 43 (77), $COCH_3$ (35.1 ppm); 41 (11), *m/e* 72 − OCH_3, C_2H_3N (34.5 ppm).

Results with **4a**: *m/e* 119 (40), M − HCl, C_4H_9NOS (0.5 ppm); 104 (100), M − [HCl + $CH_3\cdot$], C_3H_6NOS (23.6 ppm); 89 (12), *m/e* 104 − $CH_3\cdot$, C_2H_3NOS (20.5 ppm); 77 (7), *m/e* 119 − ketene, C_2H_7NS (13.2 ppm); 76 (4), *m/e* 119 − $CH_3CO\cdot$, C_2H_6NS (9.5 ppm); 72 (33), *m/e* 119 − $CH_3S\cdot$, C_3H_6NO (22.4 ppm); 62 (67) *m/e* 104 − $NCO\cdot$, C_2H_6S (61.3 ppm); 62 (35), *m/e* 104 − ketene, CH_4NS (54.9 ppm); 61 (23), *m/e* 104 − HNCO and *m/e* 119 − $NHCOCH_3$, C_2H_5S (18.6 ppm); 60 (5), *m/e* 119 − $C_2H_3S\cdot$, C_2H_6NO (20.4 ppm); 59 (1), C_2H_3S (37.8 ppm); 47 (24), CH_3S (25.3 ppm); 43 (30), CH_3CO (37.9 ppm); 30 (unknown), *m/e* 62 − S, *m/e* 72 − ketene, and *m/e* 77 − $CH_3S\cdot$, CH_4N.

Results with **2c**: *m/e* 147 (16), molecular ion, $C_6H_{13}NOS$ (3.2 ppm); 132 (50), M − CH_3, $C_5H_{10}NOS$ (4.6 ppm); 119 (18), M − C_2H_4, C_4H_9NOS (6.6 ppm); 104 (23), *m/e* 119 − CH_3, C_3H_6NOS (4.9 ppm); 90 (20), *m/e* 132 − NCO, $C_4H_{10}S$ (0.7 ppm); 89 (53), *m/e* 147 − $NHCOCH_3$ and *m/e* 132 − HNCO, C_4H_9S (5.1 ppm); 86 (26), *m/e* 147 − EtS, C_4H_8NO (4.9 ppm); 77 (90), *m/e* 119 − ketene, C_2H_7NS (2.3 ppm); 76 (34), *m/e* 104 − CO, C_2H_6NS (9.5 ppm); 76 (14), *m/e* 104 − C_2H_4, CH_2NOS (4.2 ppm); 75 (24), *m/e* 90 − CH_3, C_3H_7S (1.4 ppm); 62 (20), *m/e* 104 − NCO and *m/e* 90 − C_2H_4, C_2H_6S (10.6 ppm); 62 (18), *m/e* 104 − ketene, CH_4NS (2.9 ppm); 61 (86), *m/e* 104 − HNCO and *m/e* 89 − C_2H_4, C_2H_5S (6.9 ppm); 60 (17), *m/e* 77 − NH_3, C_2H_4S (1.8 ppm); 60 (74), *m/e* 86 − C_2H_2, C_2H_6NO (12.5 ppm); 59 (4), *m/e* 119 − C_2H_4S and *m/e* 147 − C_4H_9S, C_2H_6NO (8.8 ppm); 49 (50), *m/e* 77 − C_2H_4, H_3NS (7.7 ppm); 48 (17), *m/e* 76 − CO and *m/e* 76 − C_2H_4, H_2NS (2.0 ppm); 47 (14), *m/e* 62 − CH_3, CH_3S (5.1 ppm); 45 (10), *m/e* 62 − NH_3 and *m/e* 60 − CH_3, CHS (25.9 ppm); 44 (2), *m/e* 86 − ketene, C_2H_6N (10.1 ppm); 43 (100), *m/e* 119 − EtSNH, CH_3CO (23.7 ppm); 41 (45), C_2H_3N (39.3 ppm); 29 (49), C_2H_5 (26.0 ppm); 28 (85) C_2H_4 (36.2 ppm).

Results with **3c**: *m/e* 147 (3), M − HBr, $C_6H_{13}NOS$ (21.1

ppm); 132 (15), M − [HBr + CH_3·], $C_5H_{10}NOS$ (1.4 ppm); 119 (8), *m/e* 147 − C_2H_4 and M − C_2H_5Br, C_4H_9NOS (4.8 ppm); 110 (42), $C_2H_5{}^{81}Br$ (62.8 ppm); 108 (38), $C_2H_5{}^{79}Br$ (3.4 ppm); 104 (10), *m/e* 119 − CH_3·, C_3H_6NOS (67.3 ppm); 90 (15), *m/e* 132 − NCO·, $C_4H_{10}S$ (32.2 ppm); 89 (18), *m/e* 147 − NHCO-CH_3· and *m/e* 132 − HNCO, C_4H_9S (32.6 ppm); 86 (10), *m/e* 147 − EtS·, C_4H_8NO (40.7 ppm); 82 (28), $H^{81}Br$ (0 ppm); 81 (11), ^{81}Br (11.1 ppm); 80 (32), $H^{79}Br$ (76.4 ppm); 79 (11), ^{79}Br (57.0 ppm); 77 (67), *m/e* 119 − ketene, C_2H_7NS (24.2 ppm); 76 (13), *m/e* 104 − CO, C_3H_6NS (3.1 ppm); 62 (14), *m/e* 104 − NCO· and *m/e* 90 − C_2H_4, C_2H_6S (9.4 ppm); 62 (17), *m/e* 104 − ketene, CH_4NS (13.3 ppm); 61 (44), *m/e* 104 − HNCO and *m/e* 89 − C_2H_4, C_2H_5S (59.0 ppm); 60 (14), *m/e* 77 − NH_3, C_2H_4S (41.6 ppm); 60 (64), *m/e* 86 − C_2H_2, C_2H_6NO (41.6 ppm); 59 (26), *m/e* 119 − C_2H_4S, C_2H_5NO (32.8 ppm); 49 (52), *m/e* 77 − C_2H_4, H_3NS (47.7 ppm); 48 (11), *m/e* 76 − C_2H_4, H_2NS (32.2 ppm); 44 (2), *m/e* 86 − ketene, C_2H_6N (21.3 ppm); 43 (89), CH_3CO (35.5 ppm); 41 (17), C_2H_3N (73.2 ppm); 29 (100), C_2H_5 (65.2 ppm); 28 (53) (doubly ionized), C_4H_8 (22.2 ppm).

Results with **4c**: *m/e* 147 (10), M − HCl, $C_6H_{13}NOS$ (7.4 ppm); 132 (43), *m/e* 147 − CH_3, $C_5H_{10}NOS$ (2.9 ppm); 119 (14), *m/e* 147 − C_2H_4, C_4H_9NOS (5.6 ppm); 104 (25), *m/e* 119 − CH_3, C_3H_6NOS (0.5 ppm); 90 (11), *m/e* 132 − NCO, $C_4H_{10}S$ (10.4 ppm); 89 (34), *m/e* 147 − $NHCOCH_3$ and *m/e* 132 − HNCO, C_4H_9S (9.6 ppm); 86 (17), *m/e* 147 − EtS, C_4H_8NO (0.8 ppm); 77 (81), *m/e* 119 − ketene, C_2H_7NS (5.6 ppm); 76 (31), *m/e* 104 − CO, C_2H_6NS (6.4 ppm); 76 (12), *m/e* 104 − C_2H_4, CH_2NOS (2.4 ppm); 75 (14), *m/e* 90 − CH_3, C_3H_7S (3.6 ppm); 62 (12), *m/e* 104 − NCO and *m/e* 90 − C_2H_4, C_2H_6S (46.8 ppm); 62 (18), *m/e* 104 − ketene, CH_4NS (36.3 ppm); 61 (69), *m/e* 104 − HNCO and *m/e* 89 − C_2H_4, C_2H_5S (27.3 ppm); 60 (11), *m/e* 77 − NH_3, C_2H_4S (28.3 ppm); 60 (57), *m/e* 86 − C_2H_2, C_2H_6NO (28.0 ppm); 59 (3), *m/e* 119 − C_2H_4S and *m/e* 147 − C_4H_8S, C_2H_5NO (28.5 ppm); 49 (51), *m/e* 77 − C_2H_4, H_3NS (13.5 ppm); 48 (20), *m/e* 76 − CO and *m/e* 76 − C_2H_4, H_2SN (8.5 ppm); 47 (12), *m/e* 62 − CH_3, CH_3S (5.1 ppm); 45 (9), *m/e* 62 − NH_3 and *m/e* 60 − CH_3, CHS (16.1 ppm); 44 (2), *m/e* 86 − ketene, C_2H_6N (21.1 ppm); 43 (90), *m/e* 119 − EtSNH, CH_3CO (25.3 ppm); 41 (23), C_2H_3N (49.0 ppm); 38 (24), $H^{37}Cl$ (52.7 ppm); 36 (73), $H^{35}Cl$ (62.3 ppm); 29 (48), C_2H_5 (32.9 ppm); 28 (54), C_2H_4 (39.7 ppm).

Registry No.—**2a**, 32805-43-9; **2b**, 33707-44-7; **2c**, 32805-46-2; **2d**, 33707-46-9; **2e**, 33707-47-0; **2f**, 33707-48-1; **3a**, 32805-42-8; **3b**, 33707-49-2; **3c**, 32805-45-1; **3d**, 33707-50-5; **3e**, 33707-51-6; **3f**, 33707-52-7; **4a**, 32805-44-0; **4c**, 32805-47-3.

Acknowledgment.—This work was supported in part by U. S. P. H. S. Grants CA-07803, 08793, and 07174 of the National Cancer Institute. The mass spectral data were obtained at Battelle's Columbus Laboratories' High Resolution Mass Spectrometry Center supported by the National Institutes of Health, Contract No. NIH-71-2483.

Iminosulfuranes (Sulfilimines). V.[1a] Thermolysis of *N*-Acetyliminodialkylsulfuranes[1b]

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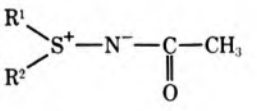
Received July 19, 1971

The thermolysis of *N*-acetyliminodialkylsulfuranes, $R^1R^2S^+N^-COCH_3$ ($R^1 = CH_3$, $R^2 = C_2H_5$; $R^1 = R^2 = C_2H_5$; $R^1 = R^2 = n\text{-}C_3H_7$; $R^1 = R^2 = i\text{-}C_3H_7$), in xylene affords olefin (ethylene or propylene) and *N*-(alkylthio)acetamides, $RSNHCOCH_3$ (R = CH_3, C_2H_5, $n\text{-}C_3H_7$, $i\text{-}C_3H_7$), a series of new compounds. When thermolysis is carried out without solvent, intermolecular reactions also occur. In the case of the dimethyl ylide, thermolysis products include dimethyl sulfide, bis(methylthio)methane, *N*,*N*′-methylenebisacetamide, and *N*,*N*′,*N*″-methylidenetrisacetamide. A mechanism involving a Pummerer type rearrangement is proposed to account for those reaction products.

The thermolysis of *N*-ethoxycarbonyliminodialkylsulfuranes (**1**)[2] and *N*-tosyliminosulfuranes (**2**)[3] with β-hydrogen atoms has been reported. The primary reaction is the elimination of olefin (Scheme I) and it has been rationalized by a mechanism involving a five-center transition state (Scheme I; per cent yields in parentheses).

In this paper, we describe the results of the thermolysis in xylene of *N*-acetyliminodialkylsulfuranes (**3b–e**) containing hydrogen atoms β to the sulfur atom. For purposes of comparison, the thermolysis of the dimethyl ylide, **3a**, which does not have β hydrogens, was also examined both with and without solvents. Possible reaction pathways are also discussed.



3a, $R^1 = R^2 = CH_3$
b, $R^1 = CH_3$; $R^2 = C_2H_5$
c, $R^1 = R^2 = C_2H_5$
d, $R^1 = R^2 = n\text{-}C_3H_7$
e, $R^1 = R^2 = i\text{-}C_3H_7$

Results and Discussion

The iminosulfuranes **3b–e**, prepared as described in the previous paper,[1a] were heated in refluxing xylene for 2.5 hr. The olefin evolved (ethylene or propylene) was trapped in Br_2–CCl_4 solution, and the *N*-(alkylthio)acetamides (**4**) ($R^1SNHCOCH_3$, R^1 = CH_3, C_2H_5, $n\text{-}C_3H_7$, $i\text{-}C_3H_7$) were isolated by distillation of the reaction mixture. The *N*-(alkylthio)acetamides **4** have not been reported previously; their structures were established by ir, nmr, and microanalysis. The results of the thermolysis are summarized in Table I; a typical reaction pathway for thermolysis in refluxing xylene is shown in Scheme II, path a.

In the case of iminosulfurane **3b**, the lower yield of **4** (R^1 = CH_3) may be explained by the presence of fewer β hydrogens. In this case a small amount of *N*,*N*′-methylenebisacetamide, $CH_2(NHCOCH_3)_2$ (yield 3%), is also obtained. This is assumed to be formed by

(1) (a) For the previous paper, see *J. Org. Chem.*, **37**, 1121 (1972). (b) Presented in part at the 161st National Meeting of the American Chemical Society, Los Angeles, Calif., Apr 1971. Preliminary publication: *Tetrahedron Lett.*, 1761 (1971). (c) Postdoctoral Fellow from the University of Tokyo. (d) Postdoctoral Fellow from the University of London.

(2) G. F. Whitfield, H. S. Beilan, D. Saika, and D. Swern, *Tetrahedron Lett.*, 3543 (1970).

(3) S. Oae, K. Tsujihara, and N. Furukawa, *ibid.*, 2663 (1970).

SCHEME I

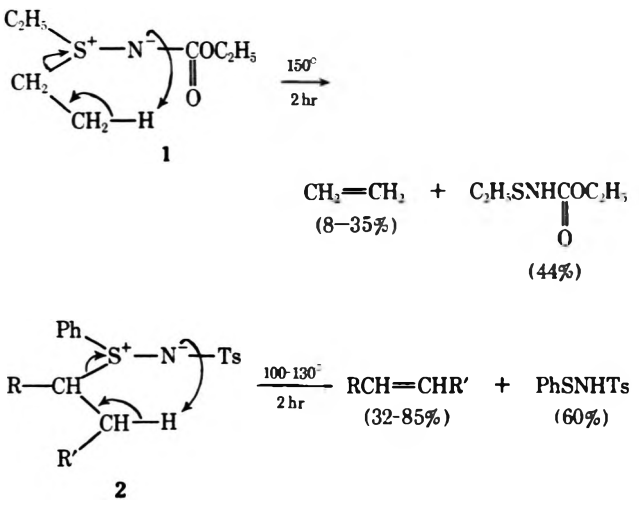


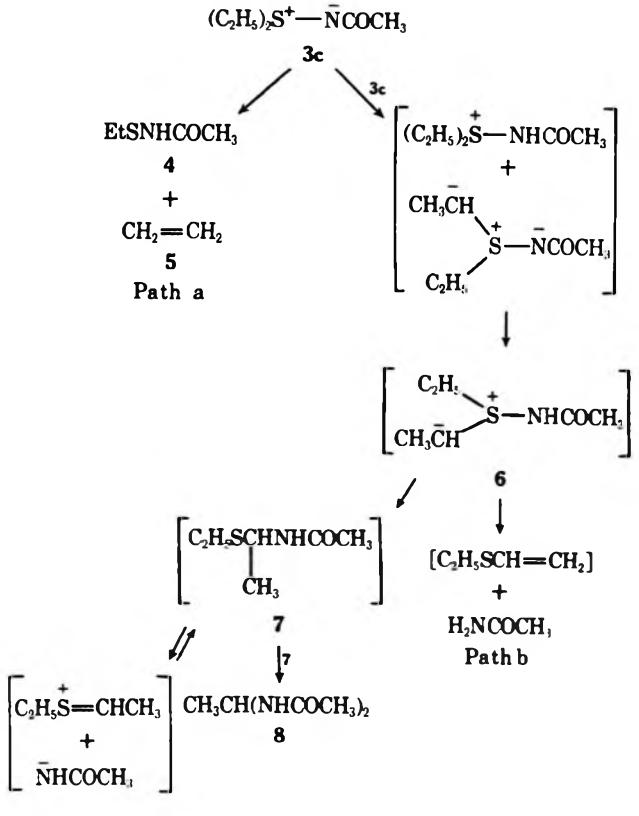
TABLE I

THERMOLYSIS OF *N*-ACETYLIMINODIALKYLSULFURANES, $R^1R^2S^+—N^-COCH_3$, IN REFLUXING XYLENE

	Iminosulfurane[a] R¹	R²	Olefin (yield, %)	R¹SNHCOCH₃ (4) Yield, % Crude	Pure	Bp,[b] °C, at 0.03mm
3b	CH_3	C_2H_5	$CH_2=CH_2$ (44)	50	30	64–65
3c	C_2H_5	C_2H_5	$CH_2=CH_2$ (51)	95	75	72–74
3d	*n*-C_3H_7	*n*-C_3H_7	$CH_3CH=CH_2$ (25)	85	55	77–78
3e	*i*-C_3H_7	*i*-C_3H_7	$CH_3CH=CH_2$ (58)	95	70	83–85

[a] Satisfactory analyses (±0.3%) for C, H, N, and S were obtained for all new compounds listed: Ed. [b] Measured in a capillary.

SCHEME II



a mechanism similar to that proposed for the thermolysis of **3a**, as discussed later.

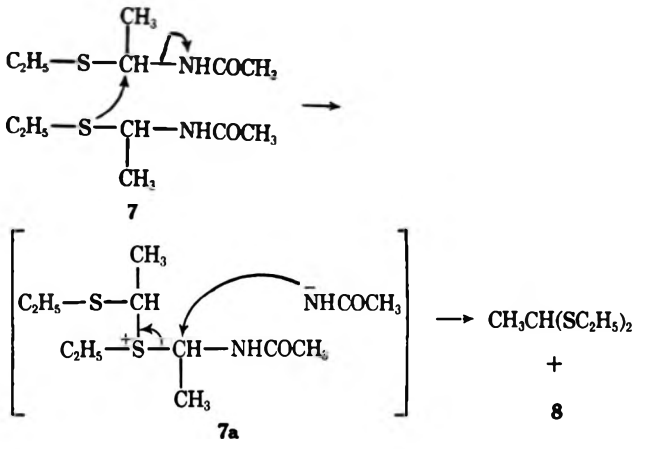
Thermolysis of iminosulfurane **3c** without solvent at 140–145° gives **5** (30%) and **4** ($R^1 = C_2H_5$) (46%) (Scheme II, path a); in addition, acetamide (29%), *N*,*N*′-ethylidenebisacetamide (**8**) (2%), and an unsaturated sulfide suspected to be ethyl vinyl sulfide are also formed (path b). Since pure **4** ($R^1 = C_2H_5$) is stable at the thermolysis temperature [only about 10% of **4** ($R^1 = C_2H_5$) decomposes at 140–145° in 2.5 hr], it is apparent that **4** ($R^1 = C_2H_5$) is not the intermediate for acetamide and unsaturated sulfide.

A possible mechanism for pyrolysis in the absence of solvent is shown in Scheme II, path b; the formation of the ylide **6**, and the subsequent cleavage of the S–N bond by a five-center transition state, is similar to that proposed for the formation of **4** and **5**.

Since acetamide and unsaturated sulfide are not obtained by thermolysis in xylene, it seems likely that path b is an intermolecular process. We assume that the primary step is protonation of the nitrogen atom of the iminosulfurane **3c** by another molecule of **3c**, followed by a second transfer of a proton from a methylene group to give **6**.

The formation of *N*,*N*′-ethylidenebisacetamide (**8**) is especially interesting since in the thermolysis of the analogous dimethyliminosulfurane (**3a**) (Scheme IV), *N*,*N*′-methylenebisacetamide (**10**) is a major product. The formation of **8** may be rationalized by the rearrangement of the ylide **6** to the sulfide **7**, followed by nucleophilic attack of acetamide anion at the methine carbon of **7**. An alternative pathway (Scheme III)

SCHEME III



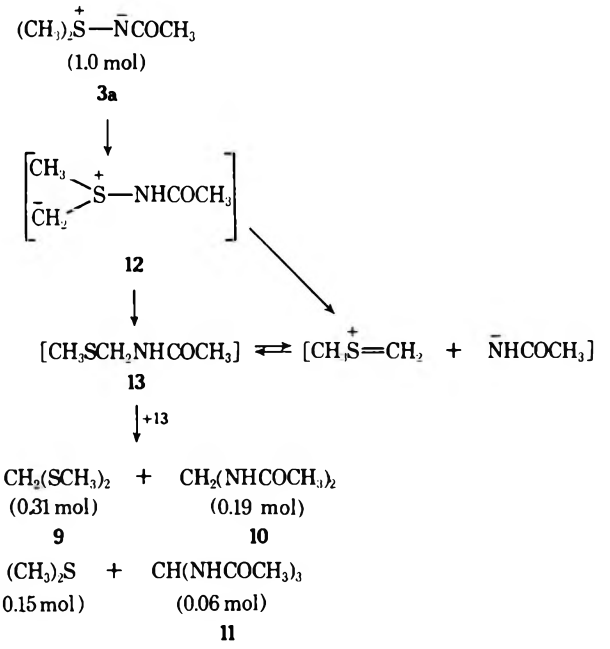
for formation of **8** may involve nucleophilic attack of the sulfur atom of **7** on the methine carbon of another molecule of **7** giving the sulfonium salt **7a**. Subsequent decomposition of **7a** would cause bond cleavage between sulfur and carbon to give **8**. 1,1-Bis(ethylthio)ethane was not isolated; we invoke this compound as the other product on the basis of the isolation of bis(methylthio)methane in the thermolysis of the dimethyl ylide **3a** (Scheme IV).

As shown in our previous paper,[1a] the mass spectrum of the iminosulfurane **3c** shows that the primary fragmentations involve elimination of ethylene to give the radical ion of **4** ($R^1 = C_2H_5$) and rearrangement of **3c** possibly to the sulfide **7**. These processes are very similar to the thermolysis of **3c**, shown in Scheme II.

Similarities between mass spectral fragmentation and thermolysis are also observed with the dimethylsulfurane **3a**.

Thermolysis of the iminosulfurane **3a** without solvent at 120–125° for 24 hr gives bis(methylthio)-methane (**9**), *N*,*N*′-methylenebisacetamide (**10**), dimethyl sulfide, and *N*,*N*′,*N*″-methylidenetrisacetamide (**11**) (Scheme IV, molar yields in parentheses). The material balance was 66%. All the products have been isolated and identified by ir, nmr, and microanalysis and by comparison with authentic samples.

SCHEME IV



A pathway is proposed which involves the rearrangement of **3a** to *N*-(methylthiomethyl)acetamide (**13**) *via* the ylide **12**. The formation of sulfurane **12** may be facilitated by resonance stabilization involving $d\pi$ bonding between sulfur and carbon atoms. Subsequent rearrangement of **12** would give **13**. This process is very similar to the reaction of dimethyl sulfoxide with acetic anhydride (Pummerer rearrangement) to give α-acetoxymethylthiomethane.[4,5]

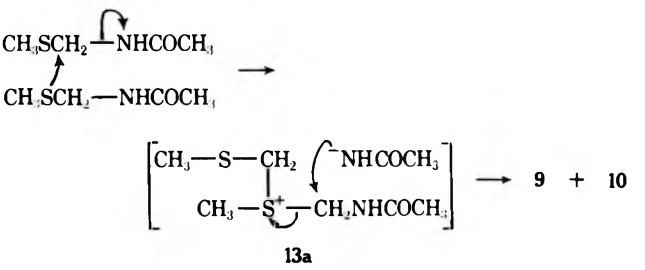
The subsequent partial dissociation of **13** and nucleophilic attack of the acetamide ion on the methylene group of **13** would give **9** and **10**. The pathways for formation of dimethyl sulfide and the minor product (**11**) are not evident; **11** probably comes from **10**.

An alternative pathway for the formation of **9** and **10** would involve nucleophilic attack of the sulfur atom in **13** on the methylene carbon of another molecule of **13**, giving the sulfonium salt **13a** (Scheme V). Subsequent decompsosition of **13a** would cause bond cleavage between sulfur and carbon to give **9** and **10**.

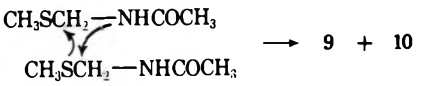
Another pathway (Scheme VI) leading to **9** and **10** from **13** involves a four-center transition state and does not require the discrete existence of the acetamide anion.

As mentioned in our previous paper,[1a] the mass spectral fragmentation of the iminosulfurane **3a** affords the ions at *m/e* 61 (C_2H_5S) and 72 (C_3H_6NO), which

SCHEME V



SCHEME VI

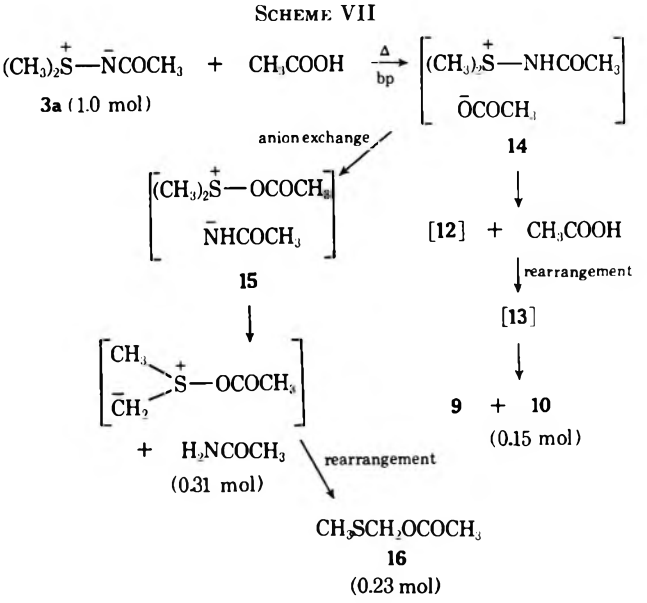


may arise by fragmentation of **13** (formed by rearrangement of **3a**). Thus, there appear to be certain similarities between the thermolysis of **3a** and its behavior on electron impact.

In contrast, when **3a** is heated in refluxing toluene for 24 hr, more than 90% of **3a** is recovered. This suggests that the rearrangement of **3a** to **13** (Scheme IV) is an intermolecular process. The situation is quite similar to the thermolysis of diethylsulfurane **3c** without solvent, as already mentioned (Scheme II, path b). Again, the first step may be a proton transfer from one molecule of **3a** to another molecule of **3a**, followed by a second proton transfer to yield **12**. If this process is correct, it would be expected that a protic acid would catalyze the reaction, thus accelerating rearrangement of **3a** to **13**.

When thermolysis of **3a** is conducted in refluxing acetic acid, the reaction rapidly affords **9** and **10**, along with **16** and acetamide. The reactions have been rationalized in Scheme VII (molar yields in parentheses).

SCHEME VII



In this case, the first step may be the formation of sulfonium salt **14**, which is followed by either proton abstraction by the anion to give the ylide **12** or the exchange of the anion to give another sulfonium salt **15**. Rearrangement of **12** to **13** and the subsequent intermolecular reaction would give the final products

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TABLE II
IR AND NMR OF N-(ALKYLTHIO)ACETAMIDES (4), $R^1SNHCOCH_3$

	Ir, cm^{-1}[a]			Nmr[b]				
R^1	ν_{NH}	ν_{CO}	ν_{CN}	NH	CH_3CO	α-CH	β-CH	γ-CH
CH_3	3250	1660	1240	6.50 (bs)	2.10 (s)	2.38 (s)		
C_2H_5	3240	1660	1240	7.59 (bs)	2.16 (s)	2.77 (q) (J = 8 Hz)	1.26 (t) (J = 7 Hz)	
n-C_3H_7	3250	1670	1245	7.16 (bs)	2.09 (s)	2.67 (t) (J = 7 Hz)	1.61 (se) (J = 8 Hz)	0.97 (t) (J = 7 Hz)
i-C_3H_7	3250	1675	1240	7.43 (bs)	2.10 (s)	3.17 (m)	1.18 (d) (J = 6 Hz)	

[a] Liquid film. [b] Parts per million from TMS in $CDCl_3$ at 37°. Integrations were in accord with the proposed structures; s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, se = sextet, and m = multiplet.

9 and 10. The sulfonium salt 15 could follow a similar process to yield acetamide and 16.

Experimental Section

Ir, Nmr, and Glc.—Ir spectra were obtained as KBr discs or liquid films using a Perkin-Elmer infrared spectrophotometer, Model 137B. Nmr spectra were obtained with a Varian A-60A spectrometer. Gas chromatographic analyses were performed on a Wilkens Aerograph A 90-P3 using a 5 ft × 1/4 in. column packed with 15% Carbowax on Chromosorb W, carrier gas He, column temperature 110°.

Thermolysis of 3c.—Pure **3c** (2.16 g, 0.0147 mol) was dissolved in xylene (40 ml) and the mixture was refluxed for 2.5 hr. Ethylene was trapped in Br_2 (1.5 ml, 0.029 mol/25 ml of CCl_4) solution. The amount of 1,2-dibromoethane was determined by nmr using benzene as an internal standard. Xylene was distilled off under vacuum at room temperature, and a pale yellow oil was obtained as a residue. It was found to be almost pure N-(ethylthio)-acetamide, **4** (R^1 = C_2H_5), by nmr and tlc. Analytically pure **4** (R^1 = C_2H_5) was obtained by fractional distillation under vacuum.

Thermolysis of the other iminosulfuranes (**3b**, **3d**, and **3e**) was carried out in a similar manner. Ir and nmr of **4** are summarized in Table II.

The thermolysis of **3c** without solvent was carried out as follows: **3c** (6.37 g, 0.0432 mol) was placed in a flask equipped with a gas inlet and a condenser which was connected to a cold trap (−78°) and then to a trap containing Br_2 (3.0 ml, 0.058 mol/25 ml of CCl_4). The iminosulfurane **3c** was heated under a dry nitrogen stream at 140–145° for 2.5 hr. After the reaction, the Br_2/CCl_4 trap was removed and the reaction system was evacuated to 0.2–0.3 mm at room temperature for 2 hr. A clear liquid (0.60 g) condensed in the cold trap and a dark-colored pot residue (3.74 g) was obtained. The yield of 1,2-dibromoethane in the Br_2/CCl_4 trap was determined by the method described above.

Examination by glc showed that the cold trap condensate had two major components, one of which had almost the same retention time as did diethyl sulfide, but its nmr indicated that it contained a vinyl group; it was assumed to be ethyl vinyl sulfide. An attempt to separate this component by preparative glc was unsuccessful, probably because of polymerization on the column. Another fraction in the cold trap condensate was separated by preparative glc. It gave an ir spectrum very similar to that of diethyl disulfide, but it was also found by nmr to have a vinyl group. The fraction appears to consist of more than two components, but they could not be separated and identified. The nmr spectrum of the pot residue showed that it consisted mainly of the acetamide **4** (R^1 = C_2H_5) and unreacted **3c**, and their amounts could be estimated by nmr band intensities. Pure acetamide and **4** (R^1 = C_2H_5) were obtained by vacuum distillation. N,N'-Ethylidenebisacetamide (**8**) [0.0678 g, mp 169–170° (lit.[6] 180°)] was obtained by crystallization of the pot residue from $CHCl_3$–Et_2O: ir (KBr disc) 3240 (NH stretch), 1630 (CO stretch), 1560, and 1520 cm^{-1} (NH deformation and CN stretch); nmr (from TMS in DMSO-d_6) 1.23 (d, J = 7 Hz, CH_3CH–), 1.78 (s, CH_3CO–), 5.44 (m, CH_3CH–), 8.09 ppm (d, J = 7 Hz, –NH–).

Thermolysis of 3a.—The iminosulfurane **3a** (2.60 g, 0.0218 mol) was placed in a flask equipped with a gas inlet and a reflux condenser which was connected to a cold trap (−78°). The flask was heated at 120–125° for 24 hr under a dry N_2 stream. Dimethyl sulfide (0.20 g, 0.0032 mol) was obtained in the cold trap. The cold trap was replaced by another one, and the reaction system was evacuated to about 1 mm at room temperature. A clear liquid was then obtained. It was identified as bis(methylthio)methane (**9**) (0.74 g, 0.0068 mol) by comparison with an authentic sample:[7] nmr (from TMS in DMSO-d_6) 2.08 (s, CH_3S–), 3.71 (s, $-CH_2-$). The pot residue was washed with hot acetone; the acetone-insoluble compound was found to be N,N',N''-methylidenetrisacetamide (**11**) (0.26 g, 0.0014 mol): mp 262–264° (lit.[8] 261°); ir (KBr disc) 3250 (NH stretch), 1650 (CO stretch), 1520 (NH deformation and CN stretch).

Anal. Calcd for $C_7H_{13}N_3O_3$: C, 44.90; H, 7.01; N, 22.45. Found: 44.68; H, 7.27; N, 22.50.

An authentic sample of **11** was prepared from acetamide and acetic anhydride.[8] N,N'-Methylenebisacetamide (**10**) was obtained from the acetone-soluble portion of the pot residue by crystallization (0.52 g, 0.0040 mol): mp 200° (lit.[9] 200°); ir (KBr disc) 3200 (NH stretch), 1640 (CO stretch), 1540 cm^{-1} (NH deformation and CN stretch); nmr (from TMS in DMSO-d_6) 1.86 (s, CH_3CO–), 4.46 (t, J = 6 Hz, $-CH_2-$), 8.54 ppm (broad s, –NH–).

Anal. Calcd for $C_5H_{10}N_2O_2$: C, 46.13; H, 7.76; N, 21.53. Found: C, 46.37; H, 7.88; N, 21.49.

A solution of **3a** (3.10 g, 0.0260 mol) in toluene (80 ml) was refluxed for 24 hr. Most of the solvent was distilled off and the residual solution was then cooled to −15°. Unreacted **3a** was recovered as a precipitate (2.85 g, 92% of starting amount).

Reaction of 3a with Acetic Acid.—A preliminary test by nmr showed that when **3a** was heated in acetic acid, almost all of it had reacted within 3.5 hr, giving **9**, **10**, **16**, and presumably acetamide also. The relative amounts of **16**:**9** or **10** was about 3.5. Products were identified by comparison of their spectral properties with those of authentic samples. Preparatively, a solution of **3a** (3.40 g, 0.0285 mol) in acetic acid (80 ml) was refluxed for 3 hr. Most of the acetic acid was then distilled off, and the residue was distilled under vacuum. A mixture of acetic acid and **16** was obtained as a distillate; the amount of **16** was estimated by nmr (0.00664 mol). The pot residue was washed with warm ether and **10** was isolated as a precipitate (0.533 g, 0.00425 mol). The ether was distilled from the filtrate and the residue was recrystallized from $CHCl_3/CCl_4$ to give acetamide (0.54 g, 0.00915 mol). An authentic sample of **16** was prepared by reaction of dimethyl sulfoxide with acetic anhydride.[4]

Registry No.—**4** (R^1 = CH_3), 33707-40-3; **4** (R^1 = C_2H_5), 33815-39-3; **4** (R^1 = n-C_3H_7), 33707-41-4; **4** (R^1 = i-C_3H_7), 33707-42-5; **8**, 5335-91-1; **9**, 1618-26-4; **10**, 2852-14-0; **11**, 29284-49-9.

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Mass Spectra and Pyrolyses of *o*-Phenylene Sulfite and Related Compounds[1a,b]

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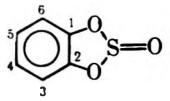
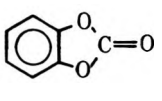
The mass spectra of *o*-phenylene sulfite (**1**) and its 3-methyl (**7**), 4-methyl (**8**), 4-*tert*-butyl (**9**), 3,5-di-*tert*-butyl (**10**), 4,5-dichloro (**11**), and 4-nitro derivatives are discussed. The predominant fragmentation of the molecular ions of **1**, **7**, **8**, and **11** is loss of SO. The molecular ions of **9** and **10** lose $CH_3\cdot$ from the *tert*-butyl substituents; the 4-nitro derivative eliminates NO·. The molecular ions of biphenylylene-2,2′ sulfite (**2**) and its 3,5,3′,5′-tetrachloro derivative and of benzophenone-2,2′ sulfite (**12**) and its 4,4′-dimethoxy derivative lose SO and SO_2 competitively. *o*-Phenylene sulfate and biphenylylene-2,2′ sulfate fragment in the mass spectrometer exclusively *via* initial loss of SO_2. The gas-phase pyrolyses of **1**, **7**, **9**, **10**, and **11** give high yields of the dimers of the corresponding cyclopentadienones, which form upon SO loss. Dibenzofuran, from loss of SO_2, and 1-hydroxydibenzofuran, from loss of SO, form upon pyrolysis of **2**. Dibenzofuran, xanthone, and 3,4-dibenzocoumarin are the major products from the pyrolysis of **12**, arising from initial loss of SO_2. These results from pyrolyses are compared to the fragmentations in the mass spectrometer with the emphasis on using mass spectra to predict pyrolysis products.

In preliminary publications, we have reported the mass spectra and the results of pyrolysis of *o*-phenylene sulfite (**1**)[2,3] and of biphenylylene-2,2′ sulfite (**2**).[3] These data have been compared with the mass spectra and pyrolyses of *o*-phenylene carbonate (**3**),[4] tetra-



1

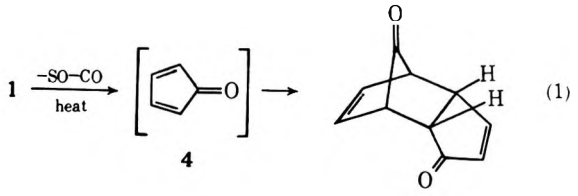


3

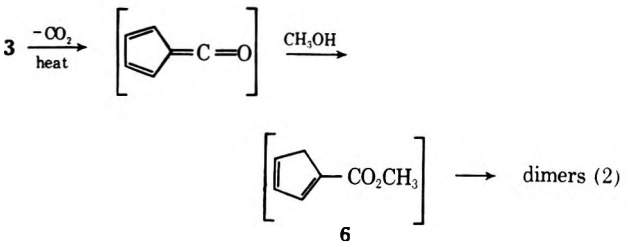
chloro-*o*-phenylene carbonate,[5] and related compounds. Similarities and differences have been noted. For example, in the mass spectrum of **1**, minor loss of SO_2 competes with the major loss of SO from the molecular ions, and in the mass spectrum of **3**, minor loss of CO competes with the major loss of CO_2. As can be seen in Scheme I, the fragment ions are the same with regard to elemental composition from each compound. However, the major path in the 70 eV mass spectrum of **1** is the minor path in the 70 eV mass spectrum of **3**, and vice versa. Relatively intense metastable peaks, indicated by asterisks, are found for the major paths, but not for the minor paths.

The gas-phase pyrolysis of **1**, in a stream of nitrogen, proceeds *via* loss of SO followed by CO, giving cyclopentadienone (**4**), which dimerizes to 1,8-diketo-4,7-methano-3a,4,7,7a-tetrahydroindene (**5**) (eq 1).[2] In contrast, gas-phase pyrolysis of **3**, with methanol in the stream, yields dimers of methyl cyclopentadiene-1-carboxylate (**6**) as the major product (eq 2).[4] Thus, there are similarities between the electron-impact and pyrolytic reactions of **1**; *i.e.*, SO rather than SO_2 is initially lost. The same is true of the corresponding reactions of **3**, *i.e.*, CO_2 rather than CO is initially lost.

The intermediacy of dienone **4** (eq 1) has been proven recently.[6] When **1** was pyrolyzed in a furnace attached to a low-temperature ir cell, **4** was deposited directly on a NaCl plate at −196°, and its ir spectrum



(1)



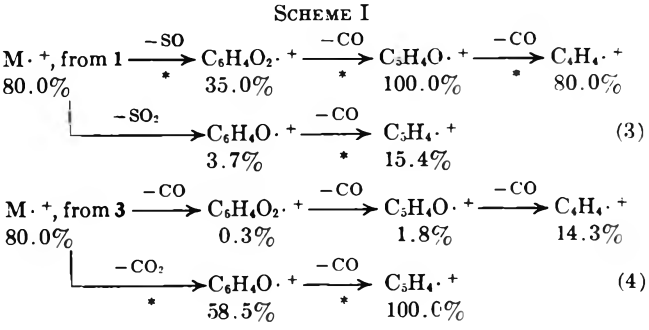
(2)

was obtained. A ketene was obtained from **3**, but it was not identified.

We have been studying the differences between the behavior of cyclic aromatic sulfites and the corresponding carbonates upon electron impact and pyrolysis. In this article we expand our preliminary publications,[2,3] reporting in detail on the mass spectra and pyrolyses of *o*-phenylene sulfite and related compounds.

Mass Spectra.—The mass spectra of a few cyclic aromatic sulfites,[2,3,7] alicyclic sulfites,[8,9] and dialkyl sulfites[10] have been reported. For example, the mass spectra of *meso*- and *dl*-hydrobenzoin cyclic sulfites do not contain molecular ions; the consequence of ioniza-

SCHEME I



(3)

(4)

(1) (a) This investigation was supported in part by the National Institutes of Health. (b) This manuscript was taken in part from the Ph.D. Dissertation of R. Y. Van Fossen, Wayne State University, Detroit, Mich., 1970. (c) Département de Chimie, Université de Montréal.

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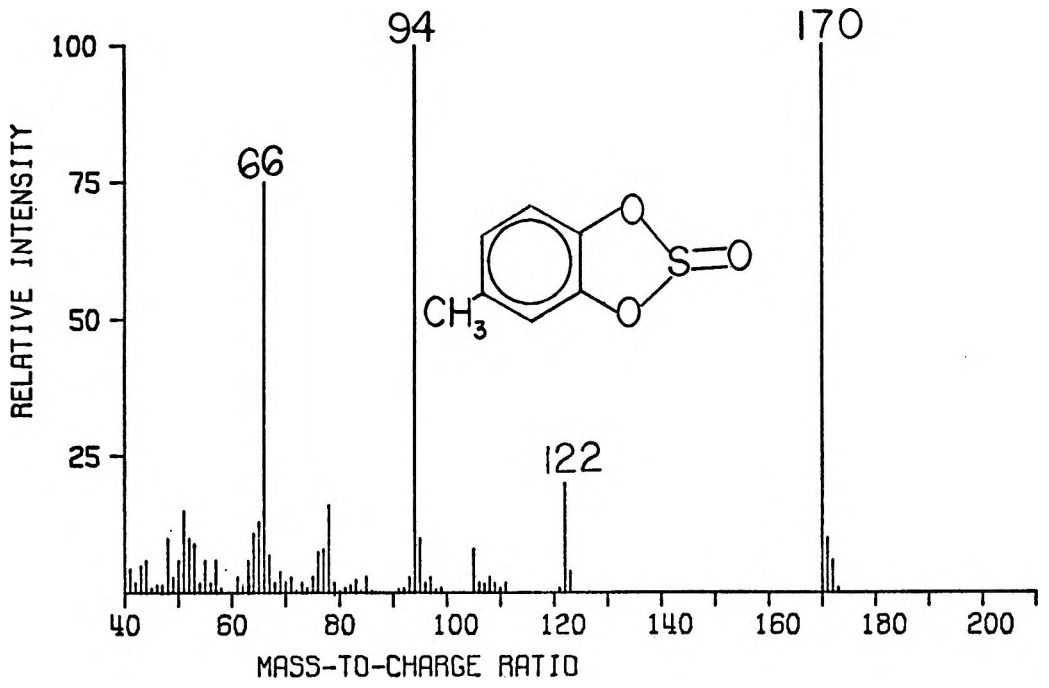


Figure 1.—Mass spectrum (70 eV) of 4-methyl-*o*-phenylene sulfite.

tion is loss of benzaldehyde followed by rearrangement and further fragmentation.[9] On the other hand, the mass spectra of cyclic sulfites of acyclic 1,2-diols show loss of SO_2 from the molecular ions, but this competes with loss of $C_nH_{2n}O$ and HSO_2.[8] In contrast, cyclic aromatic sulfites fragment *via* the major M − SO path illustrated in Scheme I for sulfite **1**.[2,3,7]

The major peaks in the mass spectra of 3-methyl (**7**), 4-methyl (**8**), 4-*tert*-butyl (**9**), 3,5-di-*tert*-butyl (**10**), 4,5-dichloro (**11**), and 4-nitro derivatives of *o*-phenylene sulfite (**1**) are given in the Experimental Section. The mass spectra of **8** and **9** are illustrated in Figures 1 and 2. Mass spectral data from biphenylylene-2,2′ sulfite (**2**) and its 3,5,3′,5′-tetrachloro derivative, from benzophenone-2,2′ sulfite (**12**), and from 4,4′-dimethoxybenzophenone-2,2′ sulfite are also given in the Experimental Section. In addition to data from these sulfites, data from two sulfates, *o*-phenylene sulfate and biphenylylene-2,2′ sulfate, are included.

If the relative intensities at 20 eV of the ions belonging to the M − SO path in the mass spectrum of **1** are added together, and those belonging to the M − SO_2 path are added together, the sum of the former is 14.7 times larger than the sum of the latter. The ratio is 11.3 at 70 eV. This summation of paths, $\Sigma SO/\Sigma SO_2$, can be used to get a rough estimate of the importance of each path. Relatively intense metastable peaks are present for the M − SO path but not for the M − SO_2 path. At 15 eV, the M − SO path remains, but the M − SO_2 path has been eliminated.

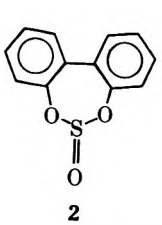
The mass spectra of 3-methyl- and 4-methyl-*o*-phenylene sulfite (**7** and **8**, respectively) are very similar and differ only in relative intensities (see the Experimental Section). In both cases the mode of fragmentation that predominates is the loss of SO. At 70 eV, $\Sigma SO/\Sigma SO_2$ for **7** is 10.8 and for **8** is 6.0. Metastable peaks are found only for the M − SO route. Loss of H· from the methyl substituent to form a benzylic or tropylium ion at M − H is not observed.

In the mass spectra of 4-*tert*-butyl- and 3,5-di-*tert*-butyl-*o*-phenylene sulfite (**9** and **10**, respectively), the molecular ion fragments almost exclusively *via* loss of CH_3·, giving the base peak in the spectra. The resultant ion then decomposes further to a small extent by competitive losses of SO, SO_2, and CO. In the 70 eV mass spectrum of **9**, the peak for the loss of SO is 0.7% and the peak for the loss of SO_2 is 0.8% relative intensity. Below 15 eV, the only fragmentation observed is loss of CH_3· from the molecular ion.

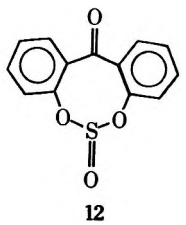
In the 70 eV mass spectrum of 4,5-dichloro-*o*-phenylene sulfite (**11**), the ratio of paths $\Sigma SO/\Sigma SO_2$ = 13.7, with metastable peaks present for the M − SO path only. Fragment ions decompose further by loss of Cl··. The molecular ions of 4-nitro-*o*-phenylene sulfite fragment exclusively by loss of NO· to give an ion which eliminates SO and SO_2 competitively.

Biphenylylene-2,2′ sulfite (**2**) also fragments by competitive losses of SO and SO_2.[3,7] At 70 eV the loss of SO_2 is twice as prominent as the loss of SO ($\Sigma SO/\Sigma SO_2$ = 0.5), whereas at 15 eV they are approaching the same importance.[3] Metastable peaks are found for both paths. The 3,5,3′,5′-tetrachloro derivative gives the same results, except that Cl· is lost from fragment ions.

In the 70 eV mass spectrum of benzophenone-2,2′ sulfite (**12**), the base peak results from loss of SO; this



2



12

ion subsequently eliminates three molecules of CO. The molecular ion also fragments *via* loss of SO_2 followed by losses of 2 CO. The $\Sigma SO/\Sigma SO_2$ ratio is 1.1 at 70 eV and 3.6 at 14 eV. Both paths show corresponding metastable peaks. The mass spectrum of the 4,4′-dimethoxy derivative is similar, although additional fragmentation of the M − SO and M − SO_2

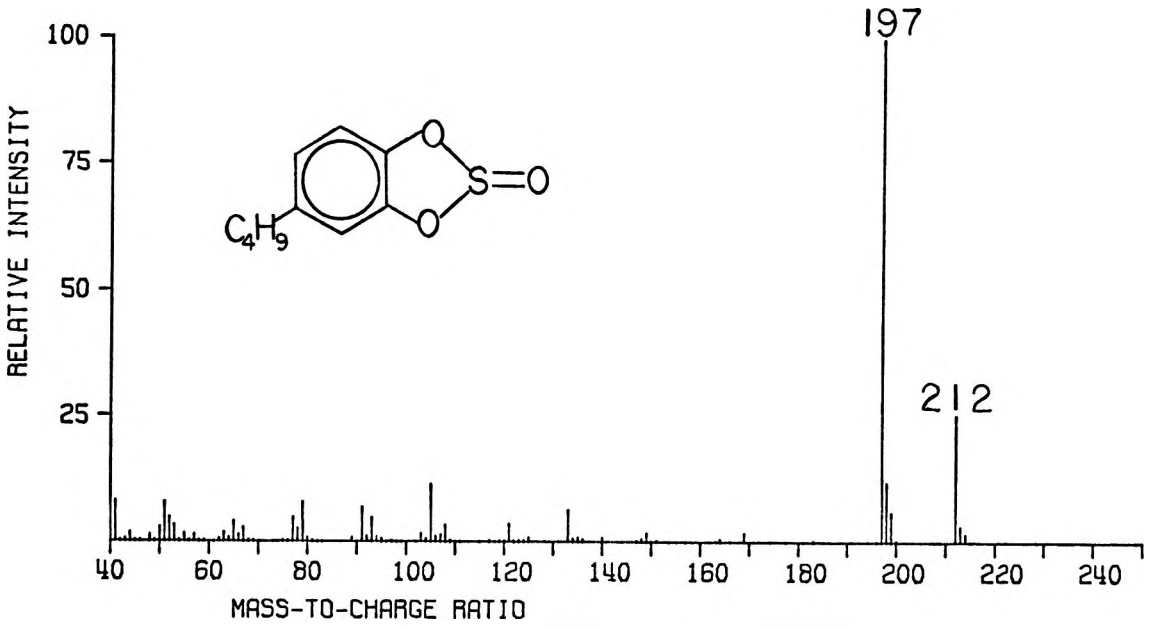
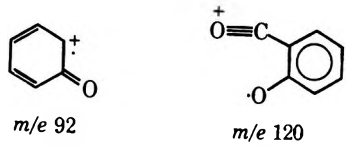


Figure 2.—Mass spectrum (70 eV) of 4-*tert*-butyl-*o*-phenylene sulfite.

ions involves losses of $CH_3O\cdot$ and $CH_3\cdot$ + CO. The M − SO ion from these compounds also fragments to give two ions which formally correspond to *m/e* 92 and 120.



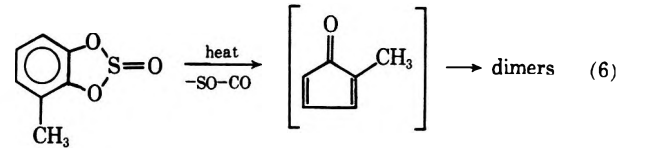
m/e 92 *m/e* 120 (5)

o-Phenylene sulfate and biphenylylene-2,2′ sulfate fragment exclusively by one pathway, the loss of SO_2. This path corresponds to the loss of SO from **1** and **2**; the loss of SO_3, corresponding to loss of SO_2 from the sulfites, is not observed. From comparison of the mass spectra of the sulfites with those of the corresponding sulfates, it is possible to determine exactly which peaks in the mass spectra of **1** and **2** are associated with the M − SO path.

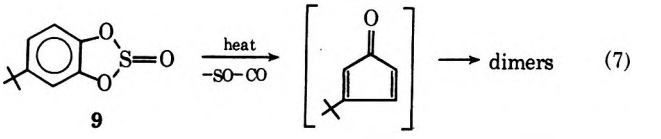
Pyrolyses of *o*-Phenylene Sulfites.—Parallel reactions induced by heat and by electron impact have attracted much interest in the last few years. Two examples relevant to this work are *o*-sulfobenzoic anhydride[11] and dibenzothiophene 5,5-dioxide.[12] In these cases, mass spectra were used to guide exploratory studies of pyrolytic reactions.

The results of the pyrolysis of *o*-phenylene sulfite (**1**) are summarized in the Experimental Section. The major product is the dimer (**5**) of cyclopentadienone and yields range up to 80%, depending on the conditions. Small amounts of 3a,7a-dihydroindenone result from decarbonylation of **5**; a black, polymeric material is also obtained. The optimum conditions for high yields of **5** are pyrolysis over a nichrome wire heated to 500°, a nitrogen flow rate of 0.1 l./min, and a system pressure of 10–15 mm. Four grams or less of starting material was used with our apparatus.[5] Lower temperatures and higher flow rates result in large amounts of recovered starting material. Higher temperatures and lower flow rates give complex mixtures of products.

Pyrolysis of 3-methyl-*o*-phenylene sulfite (**7**) gave 37.1% of a yellow oil which had ir, uv, and mass spectra characteristic of cyclopentadienone dimers. These data indicate that the oil is a mixture of dimers of 2-methylcyclopentadienone (eq 6). Likewise, the pyrolysis of 4-*tert*-butyl-*o*-phenylene sulfite (**9**) gave 39.6% of the dimers of 3-*tert*-butylcyclopentadienone (eq 7). Garbisch and Sprecher have reported that

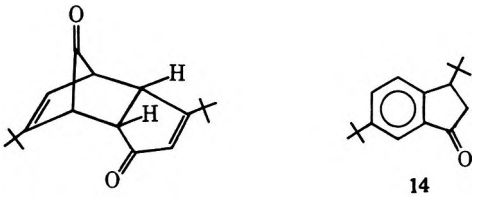


(6)



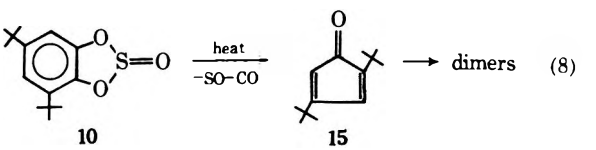
9 (7)

1,8-diketo-3,6-di-*tert*-butyl-4,7-methano-3a,4,7,7a-tetrahydroindene (**13**) is probably the major dimer.[13] A trace amount of 3,6-di-*tert*-butyl-1-indanone (**14**) was also isolated.



13 **14**

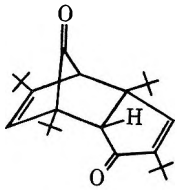
A 16.5% yield of 2,4-di-*tert*-butylcyclopentadienone (**15**) and a 63.8% yield of the dimer were obtained from pyrolyses of 3,5-di-*tert*-butyl-*o*-phenylene sulfite (**10**) (eq 8). Of the dimers of **15** prepared by another route,



10 **15** (8)

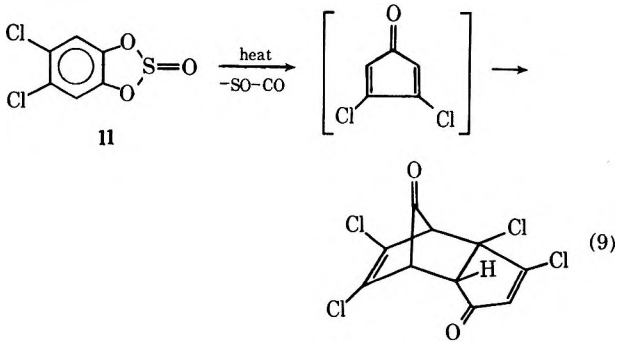
(11) S. Meyerson and E. K. Fields, *Chem. Commun.*, 275 (1966).
(12) E. K. Fields and S. Meyerson, *J. Amer. Chem. Soc.*, **88**, 2836 (1966).
(13) E. W. Garbisch, Jr., and R. F. Sprecher, *J. Amer. Chem. Soc.*, **91**, 6785 (1969).

Garbisch and Sprecher chose **16** as the most likely structure.[13]



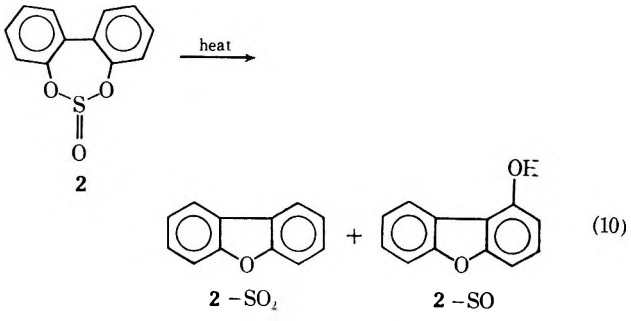
16

The pyrolysis of 4,5-dichloro-*o*-phenylene sulfite (**11**) gave a 14.7% yield of the dimer of 3,4-dichlorocyclopentadienone (eq 9).



11 (9)

In the Experimental Section, the results of pyrolyses of biphenylylene-2,2′ sulfite (**2**) are reported. In a typical run, 980 mg was pyrolyzed over a nichrome wire at 600°, with a nitrogen flow rate of 0.2 l./min and a system pressure of 5 mm. A 21.9% yield of dibenzofuran and a 52.3% yield of 1-hydroxydibenzofuran were obtained (eq 10). The dibenzofuran results from loss

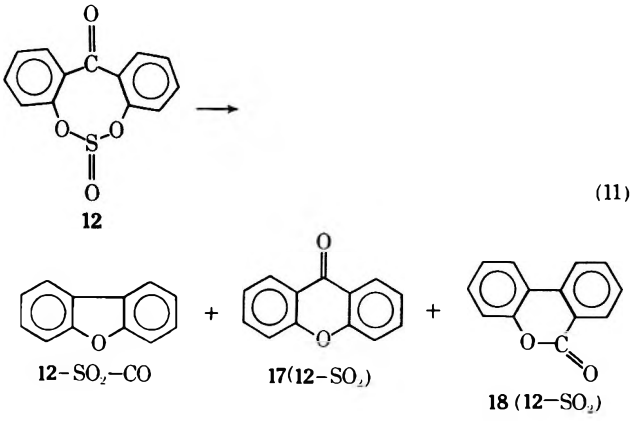


2 **2** − SO_2 **2** − SO (10)

of SO_2 and the 1-hydroxydibenzofuran results from loss of SO. 1-Hydroxydibenzofuran and dibenzofuran do not pyrolyze under these conditions. Pyrolysis of biphenylylene-2,2′ sulfate (**2**, $-OSO_2O-$ instead of $-OSOO-$) under these conditions gave 89% of 1-hydroxydibenzofuran upon loss of SO_2.

Pyrolysis of benzophenone-2,2′ sulfite (**12**) under various conditions gave a mixture of products, arising mainly from the loss of SO_2. The three major products are dibenzofuran (32.2%), xanthone (**17**, 11.6%), and 3,4-benzocoumarin (**18**, 19%) (eq 11). Pyrolyses of dibenzofuran and of xanthone under the conditions used for pyrolyses of **12** resulted in recovered starting material. Pyrolysis of **12** in an eutectic mixture containing 26.5% of biphenyl and 73.5% of diphenyl ether for 20 hr at 258° gave a 40.3% yield of xanthone (**17**) upon loss of SO_2.

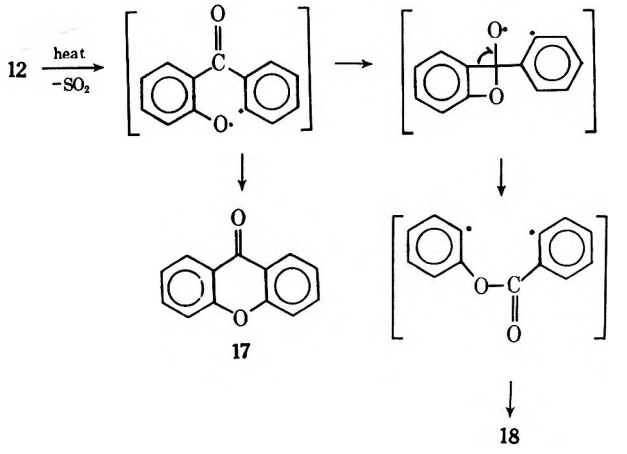
The formation of 3,4-benzocoumarin (**18**) was an interesting and unexpected result. It does not form from **17**. A possible route to **18** is given in Scheme II.



12 (11)

12−SO_2−CO **17**(**12**−SO_2) **18** (**12**−SO_2)

SCHEME II



Discussion

Gas-phase pyrolyses of *o*-phenylene sulfite (**1**), 3-methyl-*o*-phenylene sulfite (**7**), and 4,5-dichloro-*o*-phenylene sulfite (**11**) give rise to products resulting from loss of SO. For these compounds, the pyrolyses are consistent with the fragmentations in the mass spectrometer, which proceed with initial loss of SO from the molecular ions. On the other hand, the 3-*tert*-butyl- (**9**) and 3,5-di-*tert*-butyl- (**10**) substituted *o*-phenylene sulfites fragment differently under electron-impact and pyrolytic conditions. Electron impact leads to loss of a methyl radical from a *tert*-butyl group, presumably forming a very stable tertiary benzylic cation or a ring-expanded analog. The molecules SO and SO_2 are lost at nearly the same extent from these M − CH_3· ions. Upon pyrolyses of **9** and **10**, products resulting from SO loss are observed, similar to the pyrolytic behavior of **1**, **7**, and **11**.

In the *tert*-butyl cases, the reaction centers differ between the two processes owing to the greater importance of stabilization of charge upon electron impact than upon pyrolysis. We have generally observed that there is less similarity between the two processes as the molecules become increasingly aliphatic.

Striking similarity has also been observed in the case of biphenylylene cyclic sulfites. Electron-impact fragmentation of biphenylylene-2,2′ sulfite leads to competitive losses of SO and SO_2. The importance of the loss of SO increases as the electron voltage is lowered, until the two losses are nearly equal in importance. Products related to competitive SO and SO_2 losses in the pyrolysis were isolated in the ratio 2.4:1. On the

other hand, major products from the pyrolysis of benzophenone-2,2′ sulfite are due to the loss of SO_2, whereas SO and SO_2 are lost competitively from the molecular ions with almost the same importance at 70 eV.

On the basis of these data, it seems that the mass spectra of aromatic cyclic sulfites can be used to predict the most probable products of pyrolysis. However, it cannot be used to predict quantitatively the ratio of product formation. As aliphatic substituents are added which can lead to very stable cations, the mass spectra are dominated by cleavage to stable ions, whereas the pyrolysis results resemble those of the unsubstituted analogs.

Experimental Section

Melting points were determined by the open capillary method and are reported uncorrected. Boiling points are also uncorrected. For the ir spectra, 10% solutions in methylene chloride were used in sodium chloride cells. Ultraviolet spectra were recorded in ethanol solutions. The solvents used for obtaining nmr spectra were $CDCl_3$ or CD_3COCD_3; TMS was used as an internal standard. Mass spectra were obtained from an Atlas CH4 (heated inlet, 90–150°) or an AEI MS-902 (direct probe, 100–150°) mass spectrometer.

Pyrolyses were performed on an apparatus described previously.[5] The mixture of pyrolysis products was dissolved in methylene chloride and treated as described below. Silica gel was used for tlc. The gc analyses used a thermal conductivity detector. Analyses were obtained from Midwest Microlabs, Inc., Indianapolis, Ind.

Some of the ions could conceivably arise from pyrolysis in the ion source, followed by ionization. However, metastable ions suggest that this is not happening. Also, the mass spectra are the same from different instruments and at different ion source temperatures.

Except where indicated, the diols used in the syntheses of the sulfites were obtained commercially from Aldrich or from Matheson Coleman and Bell.

o-Phenylene Sulfite.—o-Phenylene sulfite and its ring-substituted analogs were prepared by a procedure based on one described by Green.[14] The modified procedure is given below for preparation of o-phenylene sulfite. The data from the substituted sulfites are given in Table I. Characteristic ir absorptions were observed at 1200–1220 cm^{-1}.

A solution of 30 g of catechol in 150 ml of dry carbon disulfide and 43 ml of pyridine was cooled to 10° by means of an ice–water bath. Thionyl chloride (20.3 ml) in 80 ml of carbon disulfide was then added. The mixture was stirred at room temperature for 1 hr and then heated at reflux for several hours. An additional 2 ml of thionyl chloride was added after cooling to room temperature, followed by stirring for 1 hr. The mixture was filtered to remove the pyridinium hydrochloride. The solution was concentrated and then distilled under reduced pressure in a nitrogen atmosphere. o-Phenylene sulfite had bp 58° (1.5 mm); ir (neat) 1220, 1240, 1460 cm^{-1}; uv (pentane) λ_{max} (absorbance) 273 (0.51), 269 (0.575), 265 nm (sh) (0.450); yield, 72%. o-Phenylene sulfite is a strong lachrymator which hydrolyzes to catechol readily. For this reason, it was distilled before use and checked by glpc.

3,5,3′5′-Tetrachlorobiphenylylene-2,2′ Sulfite.—3,5,3′,5′-Tetrachloro-2,2′-biphenol was prepared from 2,2′-biphenol. To a solution of 2.5 g of sodium in 100 ml of absolute ether was added dropwise a solution of 10 g of 2,2′-biphenol in 100 ml of ether. Stirring was maintained, and the temperature was kept at 0°. Then a solution of 10.8 g of SO_2Cl_2 in 10 ml of ether was added dropwise over a period of 1 hr. The reaction mixture was stirred at 0° for an additional hour and then at room temperature for 3 hr. The ether was distilled and 50 ml of ethyl acetate was added to the residue. The ethyl acetate layer was extracted with water, dried, and evaporated. The oily residue was dissolved in hexane. The tetrachlorobiphenol was obtained from an alumina column and recrystallized from hexane: mp 174–175° (lit.[15] mp 178°); yield 57%; blue $FeCl_3$ test; ir (KBr) 3505 cm^{-1}; ir (CH_2Cl_2) 3080, 3030 cm^{-1}; uv (EtOH) λ_{max} 218, 315 (sh), 350 nm (sh); nmr (CD_3COCD_3, TMS) δ 8.3 (2 H, s), 7.25 (4 H, AB quartet); mass spectrum m/e 322, 324, 326, 328 (molecular ions with relative intensities characteristic of four chlorines).

The corresponding cyclic sulfite was prepared as described above for o-phenylene sulfite: 0.8 g of diol; solvent, C_6H_6; yield 7.2%; mp 220°.

o-Phenylene Sulfate.—The procedure of Denivelle[16] was modified as follows. Catechol (16.5) was dissolved in 25 ml of pyridine in a nitrogen atmosphere and held at 0°. Sulfuryl chloride (12 ml) in 25 ml of petroleum ether (bp 30–60°) was added over a period of 1 hr. Then 5 ml of additional pyridine in 10 ml of petroleum ether was added. The petroleum ether layer was washed with dilute HCl and evaporated. The sulfate was recrystallized from petroleum ether, mp 34–35° (lit.[17] mp 34–35°), yield 4%.

Biphenylylene-2,2′ Sulfate.—To 25 g of 2,2′-biphenol in 75 ml of absolute ether and 13.6 g of triethylamine was added 11 ml of SO_2Cl_2 in 40 ml of absolute ether, dropwise at 0°. Stirring was maintained throughout the addition. The reaction mixture was stirred for 2 hr at room temperature and filtered, and the solvent was evaporated. The sulfate was recrystallized from ethanol: mp 120–121°; yield 30%; ir (CH_2Cl_2) 1410, 1220, 870 cm^{-1}.

Anal. Calcd for $C_{12}H_8O_4S$: C, 58.06; H, 3.23. Found: C, 58.19; H, 3.35.

Mass Spectra.—o-Phenylene sulfite (1): m/e (rel intensity) 156 (80), 108 (35), 92 (4), 80 (100), 64 (15.5), 63 (16), 52 (80), 51 (31), 50 (25), 48 (14), 39 (14.5), and 38 (11.5). Biphenylylene-2,2′ sulfite (2): m/e (rel intensity) 232 (100), 184 (45), 168 (100), 156 (13), 155 (8.0), 140 (6.5), 139 (26.5), 128 (8), 127 (11.5) 102 (12.5), 84 (16.5), 63 (12), 51 (15.5), and 39 (11). 3-Methyl-o-phenylene sulfite (7): m/e (rel intensity) 170 (58), 122 (6), 106 (4), 105 (12), 94 (100), 78(30), 77 (14), 66 (96), 65 (22), 63 (12.5), 52 (16), 51 (24), 50 (11), 48 (12), 40 (24), 39 (54), and 38 (14). 4-Methyl-o-phenylene sulfite (8): m/e (rel intensity) 170 (100), 122 (20), 106 (2), 105 (8), 94 (100), 78 (16), 77 (8), 66 (75), 65 (13), 64 (11), 52 (10), 51 (15), 48 (10), 40 (17), and 39 (37). 4-tert-Butyl-o-phenylene sulfite (9): m/e (rel intensity) 212 (25.5), 197 (100), 169 (2), 149 (2), 133 (6.5), 121 (4), 105 (11.5), 93 (5), 91 (7), 79 (8), 78 (3), 77 (5), 65 (4), 53 (4), 52 (5), 51 (8), 41 (8), and 39 (8.5). 3,5-Di-tert-butyl-o-phenylene sulfite (10): m/e (rel intensity) 268 (26), 253 (100), 189 (6.5), 149 (8), 119 (9), 105 (9), 91 (8), 75 (28), and 41 (17). 4,5-Di-

Table I

Preparation of the Aromatic Cyclic Sulfites

A. Substituted o-Phenylene Sulfites

Compd	Diol, g	Solvent	Yield, %	Bp, °C (mm)
3-Methyl (7)	10.0	C_6H_6	77	61 (0.5)
4-Methyl (8)	0.6	CS_2	85	82 (3.4)
4-tert-Butyl (9)	10.0	C_6H_6	84	75 (0.1)
3,5-Di-tert-butyl (10)	7.6	C_6H_6	78.5	110 (0.5)
4,5-Dichloro (11)	1.8	CS_2	31.5	96 (2.0)
4-Nitro	0.5	C_6H_6	10	

B. Biphenylylene-2,2 Sulfite (2)

Compd	Diol, g	Solvent	Yield, %	Mp, °C	Calcd, % C	Calcd, % H	Found, % C	Found, % H
2	10.0	C_6H_6	95	74–75[a]	62.07	3.45	61.96	3.31

C. Benzophenone-2,2 Sulfite (12)

Compd	Diol, g	Solvent	Yield, %	Mp., °C	Calcd, % C	Calcd, % H	Found, % C	Found, % H
12	10.0	C_6H_6	80	116–117	59.99	3.10	60.07	3.25
4,4′-Di-methoxy	10.0	C_6H_6	70	165–166	56.24	3.78	56.12	3.76

[a] Lit. mp 72.5–74°: P. B. de la Mare, J. G. Tillett, and H. F. van Woerden, *J. Chem. Soc.*, 4888 (1962).

(14) A. Green, *J. Chem. Soc.*, 500 (1927).

(15) W. S. Gump, U. S. Patent 2,487,799 (1950); *Chem. Abstr.*, **44**, 9702b (1950).

(16) L. Denivelle, *C. R. Acad. Sci.*, **203**, 194 (1936).

(17) E. T. Kaiser, I. R. Katz, and T. F. Wulfers, *J. Amer. Chem. Soc.*, **87**, 3781 (1965).

chloro-*o*-phenylene sulfite (11): *m/e* (rel intensity) 224 (100), 176 (14), 148 (91), 132 (7.5), 120 (23), 113 (63), 97 (15), 85 (21), 63 (15), 60 (13.5), 50 (46), 49 (15.5), and 48 (11.5). 4-Nitro-*o*-phenylene sulfite: *m/e* (rel intensity) 201 (100), 171 (3), 123 (2.5), 107 (18), 79 (60), 78 (12), 63 (10), 51 (10), and 50 (17). 3,5,3′,5′-Tetrachlorobiphenylylene-2,2′ sulfite: *m/e* (rel intensity) 368 (53), 320 (22), and 304 (70); the chlorine isotope peak at *m/e* 306 is the base peak. Benzophenone-2,2′ sulfite (12): *m/e* (rel intensity) 260 (76), 259 (9.5), 212 (100), 196 (21.5), 184 (18), 168 (50), 140 (9.5), 139 (32), 128 (11), 120 (26), 92 (52), 84 (10), 76 (18), 64 (19), and 63 (28). 4,4′-Dimethoxybenzophenone-2,2′ sulfite: *m/e* (rel intensity) 320 (100), 319 (49), 272 (81), 257 (13.5), 256 (25), 255 (13), 244 (10), 241 (13), 229 (16), 213 (26), 201 (16.5), 185 (12.5), 170 (11), 151 (22), 150 (50), 122 (68), 114 (14.5), 107 (25), 106 (12.5), and 79 (31). *o*-Phenylene sulfate: *m/e* (rel intensity) 172 (63), 108 (8), 80 (85), 79 (10.5), 64 (29), 52 (100), 51 (29), 50 (21), and 48 (16). Biphenylylene-2,2′ sulfate: *m/e* (rel intensity) 248 (100), 184 (38.5), 156 (69), 155 (14), 128 (45), 127 (15), 102 (21), 78 (14), 64 (21), 63 (16), and 51 (25).

Pyrolyses of o-Phenylene Sulfite (1).—Examples of pyrolyses of 1 under various conditions are given in Table II. The pyrolysate was worked up in one of three ways: preparative tlc with CH_2Cl_2 as solvent; sublimation and recrystallization of the sublimate from hexane; glpc, 10% SE-30 on 60–80 Chromosorb W or 15% Carbowax 20M on 60–80 Chromosorb W, 60–200° at 8°/min, injection port at 170°, detector at 238°. 1,8-Diketo-4,7-methano-3a,4,7,7a-tetrahydroindene (5) was obtained: mp 102–102.5° (lit.[18] mp 101–101.5°); ir 1710, 1780 cm^{-1} (lit.[18] 1710, 1780 cm^{-1}); nmr δ 7.4 (1 H, m), 6.3 (3 H, m), 3.45 (2 H, m), 3.2 (1 H, m), and 2.9 (1 H, t).

Table II

Data from Pyrolyses of *o*-Phenylene Sulfite (1)

Pyrolysis no.	a	b	c	d	e	f
Amount of 1, g	3.9	0.74	0.68	1.7	0.83	3.7
Temp, °C	500	550	450	550	450	500
N_2 flow, l./min	0.2	0.1	0.08	0.8	0.06	0.1
Pressure, mm	27	11	10	25	13	16
Time, min	120	180	60	60	230	200
Recovered 1, g	0.33	0.05	0	1.3	0.28	0
Amount of 5, g	1.03	0.14	0.11	0	0.20	1.50
Yield of 5, %[a]	54.5	38.6	30.7	0	69.2	77.1

[a] Based on unrecovered starting material.

Anal. Calcd for $C_{10}H_8O_2$: C, 74.99; H, 5.03. Found: C, 75.09; H, 5.17.

In pyrolysis e, 88 mg of 1-indanone was isolated. 1-Indanone was identified by comparison of melting point, ir, uv, and mass spectrum with those of an authentic sample.

Pyrolysis of 3-Methyl-*o*-phenylene Sulfite (7).—The pyrolysis of 0.64 g of 7 at 540–550° (17 mm) and a N_2 flow rate of 0.6 l./min for 1 hr gave a crude yellow pyrolysate. The pyrolysate was distilled at 0.1 mm and 0.13 g (37.1%) of material was obtained: ir (CH_2Cl_2) 1815, 1700 cm^{-1}; uv (EtOH) λ_{max} 205, 243, 280 nm. These data indicate the product is a mixture of the dimers of 2-methylcyclopentadienone. The mass spectrum contains major peaks at *m/e* 160 (dimer − CO, 60%), 159 (dimer − HCO, 20%), 132 (dimer − 2 CO, 12.5%), and 145 (dimer − CO − CH_3, 100%). Attempts to separate the mixture of dimers were unsuccessful.

Pyrolysis of 4-*tert*-Butyl-o-phenylene Sulfite (9).—The pyrolysis of 1.16 g of 9 was carried out at 550° (10 mm) and a N_2 flow rate of 0.2 l./min. Crude pyrolysate weighed 0.33 g. The major band from tlc was eluted with benzene and the material in it was recrystallized from hexane. The product was the dimer of 3-*tert*-butylcyclopentadienone: 0.295 g (39.6%); mp 68–70° (lit.[13] mp 70–72°); ir (CH_2Cl_2) 1800, 1710 cm^{-1} (lit.[13] 1790, 1710 cm^{-1}); mass spectrum, *m/e* 244 (dimer − CO).

Another band on tlc contained material which was eluted with methanol and recrystallized from hexane to give 7 mg of product. This product appears to be 3,6-di-*tert*-butyl-1-indanone, formed by loss of CO from the dimer: mp 70–73° (lit.[13] mp 75–77°); ir (CH_2Cl_2) 1710 cm^{-1} (lit.[13] 1705 cm^{-1}); mass spectrum, *m/e* 244 (molecular ion).

Pyrolysis of 3,5-Di-*tert*-butyl-*o*-phenylene Sulfite (10).—In a typical run, 1.20 g of 10 was pyrolyzed at 10 mm, 500°, and a N_2 flow rate of 0.7 l./min. A yellow oil (0.94 g) was obtained. Three fractions were collected from an alumina column eluted with benzene. The first fraction contained 0.14 g (16.5%) of 2,4-di-*tert*-butylcyclopentadienone: ir (CH_2Cl_2) 1710 cm^{-1} (lit.[13] 1708 cm^{-1}); mass spectrum, *m/e* 192 (molecular ion). When allowed to stand overnight, this product dimerized: mp 145–150° dec (lit.[13] mp 151–153°); ir (CH_2Cl_2) 1765, 1700 cm^{-1} (lit.[13] 1765, 1700 cm^{-1}); mass spectrum, *m/e* 356 (dimer − CO).

The second fraction contained 0.55 g (63.8%) of a white solid which was purified by sublimation. This product is the dimers of 2,4-di-*tert*-butylcyclopentadienone: mp 148–151° (lit.[13] mp 151–153°); ir (CH_2Cl_2) 1765, 1700 cm^{-1} (lit.[13] 1765, 1700 cm^{-1}); mass spectrum, *m/e* 356 (dimer − CO).

The third fraction was 30 mg of starting material.

Pyrolysis of 4,5-Dichloro-*o*-phenylene Sulfite (11).—The pyrolysis of 0.72 g of 11 was carried out at 500° (9 mm) and a N_2 flow rate of 0.6 l./min. A colorless solid, 0.07 g (14.7%), recrystallized from hexane, was obtained: mp 134–136° dec; ir (KBr) 1820, 1725 cm^{-1}; uv (EtOH) 205, 222 nm (sh); mass spectrum *m/e* 232, 234, 236, 238 (dimer − CO − HCl and isotopes for 3 Cl). These data are consistent with the formation of the dimer of 3,4-dichlorocyclopentadienone.

Pyrolysis of Biphenylylene-2,2′ Sulfite (2).—The pyrolysis of 2 was carried out under 11 sets of conditions. For example, 0.98 g was pyrolyzed at 600°, a system pressure of 5 mm, and a N_2 flow rate of 0.2 l/min, which took 5 hr. Two fractions were isolated from a silica gel column eluted with benzene. The first fraction, after recrystallization from hexane, contained 21.9% of dibenzofuran, identified by comparison of ir, uv, and mass spectra with those of authentic spectra and by mixture melting point.

The second fraction was recrystallized from hexane. A 52.3% yield of 1-hydroxydibenzofuran was obtained: mp 141–142° (lit.[19] mp 140–140.5°); ir (KBr) 3220, 1440, 1025 cm^{-1}; uv (EtOH) λ_{max} 214, 226, 260, 271, 277, 300 (sh), 310 nm; nmr (CD_3COCD_3) δ 7.0–7.6 (6 H, m), 8.3 (1 H, m), 9.3 (1 H, s); mass spectrum *m/e* 184 (molecular ion). 1-Hydroxydibenzofuran was brominated in acetic acid, mp 180° (lit.[19] mp 178°). Reduction of 1-hydroxydibenzofuran with zinc gave 2,2′-biphenol, identified by comparison with an authentic sample.

Pyrolyses of 0.14 g of 1-hydroxydibenzofuran at 600° (8 mm) and a N_2 flow rate of 0.2 l./min resulted in 97.1% recovery of starting material; no dibenzofuran was isolated. Pyrolysis of 0.90 g of dibenzofuran under the same conditions gave a 98% yield of recovered starting material.

Pyrolysis of Biphenylylene-2,2′ Sulfate.—At 600° (8 mm) and a N_2 flow rate of 0.2 l./min, 0.62 g of biphenylylene-2,2′ sulfate was pyrolyzed. 1-Hydroxydibenzofuran was isolated in 89% yield. Starting material (7.7%) was also recovered.

Pyrolysis of Benzophenone-2,2′ Sulfite (12).—The pyrolysis of 12 was run under five sets of conditions. When 0.56 g was pyrolyzed at 600° (8 mm) and 0.2 l./min N_2 flow rate, crude pyrolysate was obtained, which was eluted through a column of silica gel with hexane–benzene mixtures (10:1, progressing to 1:1 to 0:1), giving three fractions. The first fraction (32.3% yield) was identified as dibenzofuran. The second fraction (11.6% yield) was identical with an authentic sample of 9-xanthenone: mp 174–175° (lit.[20] mp 174°); mixture melting point undepressed. The third fraction was 3,4-benzocoumarin: mp 90–91° (lit.[21] mp 90–91°); ir (CH_2Cl_2) 1740 cm^{-1}; mass spectrum *m/e* 196 (molecular ion); yield, 19.0%.

Several other minor components were present on tlc but could not be obtained in sufficient amount for identification. Pyrolysis of 9-xanthenone at 600° (8 mm) and a N_2 flow rate of 0.2 l./min resulted in 97.5% recovery.

When 0.34 g of 12 was pyrolyzed in refluxing Dowtherm A for 20 hr, 0.10 g (40.3%) of 9-xanthenone was isolated.

Registry No.—**1**, 6255-58-9; **2**, 4425-34-7; **5**, 826-65-3; **7**, 33482-96-1; **8**, 33482-97-2; **9**, 33537-36-9; **10**, 33482-98-3; **11**, 17138-92-0; **12**, 33537-37-0; 3,5,3′,5′-

(18) C. H. DePuy and B. W. Ponder, *J. Amer. Chem. Soc.*, **81**, 4629 (1959).

(19) H. Gilman and P. R. Van Ess, *ibid.*, **61**, 1365 (1939).

(20) "Handbook of Chemistry and Physics," 50th ed, R. C. Weast, Ed., Chemical Rubber Publishing Co., Cleveland, Ohio, 1969, p C-539.

(21) *Beilstein*, 2nd ed, **17**, 360 (1933).

tetrachlorobiphenylene-2,2′ sulfite, 33483-00-0; *o*-phenylene sulfate, 4074-55-9; biphenylylene-2,2′ sulfate, 31268-08-3; 4-nitro-*o*-phenylene sulfite, 33483-03-3; 4,4′-dimethoxybenzophenone-2,2′ sulfite, 33483-04-4; 3,4-dichlorocyclopentadienone dimer, 33483-05-5; 1-hydroxydibenzofuran, 33483-06-6.

A Semiempirical Molecular Orbital Study of *o*-Phenylene Carbonate and *o*-Phenylene Sulfite[1]

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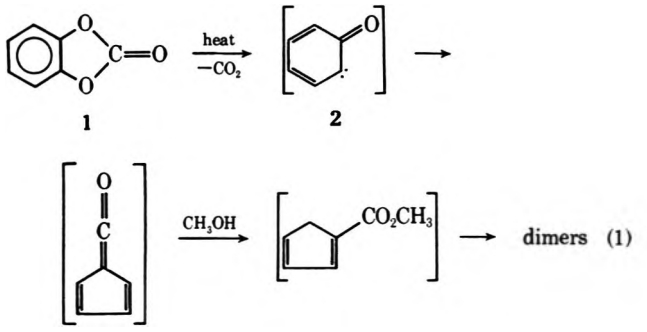
A molecular orbital approach to the rationalization of the preferential loss of CO_2 upon pyrolysis of *o*-phenylene carbonate and from its molecular ions and of the preferential loss of SO from the corresponding species of *o*-phenylene sulfite is reported. Overlap populations obtained from a CNDO/2 program are used as indications of total bond strengths. Also, minimum energies of the species produced by competing fragmentation pathways are compared.

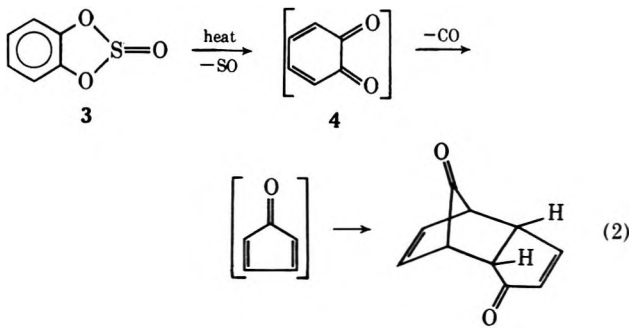
The mass spectrum and gas-phase pyrolysis of *o*-phenylene carbonate (**1**)[3] have been reported. The molecular ion of **1** forms an ion C_6H_4O of major intensity upon loss of CO_2, at *m/e* 92, along with a metastable ion; it also loses CO to a minor extent, forming an ion $C_6H_4O_2$ at *m/e* 108. If **1** is pyrolyzed in a stream of nitrogen with CH_3OH in the stream, the major products are the dimers of methyl cyclopentadiene-1-carboxylate (44%) (eq 1). Thus, CO_2, rather



than CO, is preferentially lost from **1** pyrolytically as well as from the molecular ions.

On the other hand, *o*-phenylene sulfite (**3**)[4,5] and substituted analogs[6] preferentially lose SO rather than SO_2. The major loss from the molecular ion of **3** is SO to form a $C_6H_4O_2$ ion at *m/e* 108 along with the corresponding metastable ion. A minor loss of SO_2 occurs without a metastable ion to form an ion C_6H_4O at *m/e* 92. When **3** is pyrolyzed in a stream of nitrogen, SO, followed by CO, is lost and cyclopentadienone forms, which dimerizes (80%) (eq 2).

In summary, the major path from **1** corresponds to the minor path from **3**, and vice versa. In this article we report a molecular orbital approach toward the rationalization of the preferential loss of CO_2 from **1** and the preferential loss of SO from **3**.



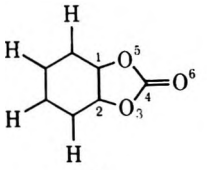
Experimental Section

Mass spectra, pyrolysis results, and syntheses of **1** and **3** have been reported elsewhere.[3-5] Calculations were obtained on an IBM 360/67 computer at the Wayne State University Computing and Data Processing Center.

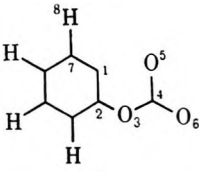
Pople and Beveridge's CNDO/2 program[7] was used to calculate Mulliken overlap populations and total energies.[8] The overlap populations were used as an indication of total bond strengths.[9] There has been a substantial amount of controversy as to whether 3d orbitals should be included to represent third-

TABLE I

OVERLAP POPULATIONS FROM CALCULATIONS MADE ON **1**



1



1a

Structure	Charge	Overlap population for bond 1–5, 2–3	3–4, 4–5	2–3	3–4
1	0	0.817	0.914		
1	+1	0.822	0.941		
1a[a]	0			0.932	0.891
1a[a]	+1			0.922	0.911
1a[b]	0			1.026	0.893
1a[b]	+1			0.994	0.898

[a] A planar benzenoid-type geometry was used for the ring. [b] A carbenoid-type geometry was used for the ring.

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(3) (a) D. C. DeJongh and D. A. Brent, *J. Org. Chem.*, **35**, 4204 (1970). (b) D. C. DeJongh, D. A. Brent, and R. Y. Van Fossen, *ibid.*, **36**, 1469 (1971).

(4) D. C. DeJongh, R. Y. Van Fossen, and C. F. Bourgeois, *Tetrahedron Lett.*, 271 (1967).

(5) D. C. DeJongh, R. Y. Van Fossen, and A. Dekovich, *ibid.*, 5045 (1970).

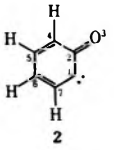
(6) D. C. DeJongh and R. Y. Van Fossen, *J. Org. Chem.*, **37**, 1129 (1972).

(7) J. A. Pople and D. L. Beveridge, "CINDO," Quantum Chemistry Program Exchange, Department of Chemistry, Indiana University, No. 141.

(8) R. S. Mulliken, *J. Chem. Phys.*, **23**, 1841 (1955).

(9) Previously, π-bond orders have been used as indication of bond strengths; see R. C. Dougherty, R. L. Foltz, and L. B. Kier, *Tetrahedron*, **26**, 1989 (1970).

Table II
Minimum Energies

	Energy, kcal	Charge		Energy, kcal	Charge
CO_2	−27,367.8	0	CO	−15,719.2	0
SO_2	−29,849.7[a]	0	SO	−18,270.7[a]	0
 2	−39,876.9	0	 4	−51,503.8	0
	−39,675.8	+1		−51,258.8	+1

[a] From the unmodified program.

row elements.[10,11] We have also used a modified program in which the effect of 3d orbitals was removed by altering the number of $n = 3$ level orbitals from nine to four in the subroutine INTGRL. The removal of these d orbitals has no effect on calculations that concern the first row elements only.

The molecular coordinates were calculated internally from bond angles and bond lengths.[12] The structure of *o*-phenylene sulfate, as determined by X-ray analysis,[13] was used as a starting point for *o*-phenylene sulfite (**3**). Standard bond lengths and angles were used as the starting point for *o*-phenylene carbonate (**1**).[14] The geometries were then systematically varied to achieve a minimum total energy for the system. Overlap populations for bonds at the geometries giving minimum energies are reported in Tables I and IV. Overlap populations for the neutral molecules and for the species with charges of +1 were calculated. Table II contains the minimum energies calculated for the products of the competing pathways, and Table III contains the geometries used to calculate these energies and the overlap populations.

Results and Discussion

***o*-Phenylene carbonate (1).**—In Table I are listed the overlap populations for bonds of the heterocyclic portion of **1** and its +1 charged species. The bond with the lowest overlap population is 1–5; it is therefore the weakest bond in the heterocyclic ring. Table I also contains calculations made on the intermediate **1a** which would be formed by cleavage of bond 1–5. The bond with the lowest overlap population in **1a** is 3–4 when either carbenoid or benzenoid geometry is used for the ring. Thus, the molecular orbital study indicates that the neutral and +1 charged species corresponding to **1** would preferentially eliminate CO_2. This is also the experimental observation, as described in eq 1.

In Table II are the minimum energies calculated for the species which would be produced upon competitive elimination of CO and CO_2 from **1**. The sum of the energies of CO_2 and **2** (uncharged) is 21.7 kcal lower than the sum of the energies of CO and **4** (uncharged). The corresponding value is 65.6 kcal when the energies of the +1 charged species of **2** and **4** are used. Therefore, this comparison also predicts that the loss of CO_2 would be the preferred path in pyrolysis and in the mass spectrometer.

The final geometries of **1**, **1a**, **2**, and **4** which give the lowest energies are given in Table III. The bond lengths and angles can be varied by approximately 5% without changing the relative ordering of the overlap populations.

Table III
Final Geometries Which Give Minimum Energies

A. Bond Lengths

	Bond length, Å					
Compd[a]	1–2	2–3	3–4	4–5	4–6	1–5
1		1.360	1.312	1.312	1.233	1.360
1a (carbenoid)		1.290	1.320	1.260	1.260	
1a (benzenoid)		1.290	1.316	1.260	1.260	
2[b]		1.150				
3[c]		1.400	1.590	1.590	1.390	1.400
3a[c]		1.400	1.590		1.390	1.400
4	1.150		1.150			
CO	1.128[d]					
CO_2	1.160[d]					
SO	1.400[e]					
SO_2	1.432[e]					

B. Bond Angles

	Bond angle, deg					
Compd	512	123	234	345	451	546
1	108	108	105	114	105	123
1a (carbenoid)[b]		120	109.5	120		120
1a (benzenoid)		120	109.5	120		120
2[b]		120				
3[c]	111	112	108.6	97.1	108.6	109.8
3a[c]	128	117			108.6	109.8
4		120				
CO_2	180					
SO_2	120[e]					

C. Dihedral Angles

	Dihedral angle, deg[f]				
Compd	7–3	1–4	2–5	2–6	8–2
1a[b]	220	0	0	180	150
2	220				
3[c]	180	352	1	259	
3a[c]	180	352	1	259	

[a] The benzene ring used was a regular planar hexagon with C–C = 1.394 Å and C–H = 1.084 Å unless noted otherwise. [b] A carbenoid benzene ring was considered. The C=C = 1.336 Å; C–C = 1.54 Å. All angles were 120° except the angle at the carbene center (109.5°). The ring is not planar but has dihedral angles approximately 10–30° above or below the mean plane of the ring. [c] The modified program was used on these structures. [d] Reference 14. [e] L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1960, p 329. [f] Structures not presented in this section were taken as planar compounds.

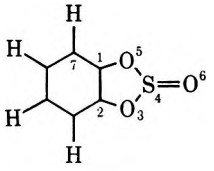
***o*-Phenylene Sulfite (3).**—The sum of the energies in Table II for SO and **4** (uncharged) is 47.9 kcal lower than the sum of the energies of SO_2 and **2** (uncharged). Thus, the comparison of minimum energies predicts that SO would be lost in preference to SO_2, and this is the behavior observed upon pyrolysis. When the

(10) D. P. Santry and G. A. Segal, *J. Chem. Phys.*, **47**, 158 (1967).
(11) A. Rauk, S. Wolfe, and I. G. Csizmadia, *Can. J. Chem.*, **47**, 113 (1969), and references cited therein.
(12) M. J. S. Dewar and N. C. Baird, "Atomic Cartesian Coordinates for Molecules," Program 136, Quantum Chemistry Program Exchange, Department of Chemistry, Indiana University.
(13) F. P. Boer and J. J. Flynn, *J. Amer. Chem. Soc.*, **91**, 6604 (1969).
(14) "Table of Interatomic Distances and Configurations in Molecules and Ions," L. E. Sulton, Ed., Special Publications No. 11 and 18, The Chemical Society, London, 1958 and 1965.

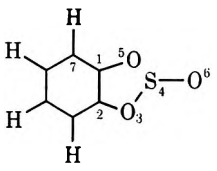
energies of the +1 charged species of **4** and **2** are used, the sum of the energies of SO and **4** (charged) is 4 kcal lower than the sum of the energies of SO_2 and **2** (charged). The preferred loss upon electron impact is SO. Geometries of **2** and **4** are given in Table III.

In Table IV are listed the overlap populations obtained from **3** and **3a** using the geometries given in Table III. The program which was modified to exclude contributions from d orbitals was used. The weakest bond in **3** is the S–O bond of the ring, rather than the C–O bond. For intermediate **3a**, which would form from cleavage of this S–O bond, the calculations show that cleavage of the bond with the lowest overlap population would lead to expulsion of SO from both the charged and the uncharged species. This is the behavior observed experimentally, as described in eq 2. If contributions from d orbitals are included, the overlap populations of the bonds between S and O increase, since the net overlap of all the orbitals on S and O is greater if d orbitals are included.

Table IV
Overlap Populations from Calculations Made on 3



3



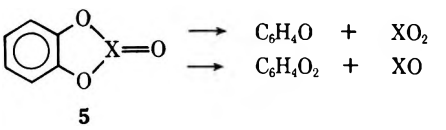
3a

Structure	Charge	Overlap population for bond[a] 1–5, 2–3	3–4, 4–5	2–3	3–4
3	0	0.822	0.620		
3	+1	0.799	0.638		
3a	0			0.813	0.646
3a	+1			0.804	0.642

[a] The program modified to exclude d orbitals was used.

Thus, relating overlap populations to relative bond strengths for bonds involving two different sets of atoms, *i.e.*, C–O and S–O in **3**, might not be so meaningful as in the case of **1** where only C–O bonds are compared. However, the comparison of the sums of the energies of the species produced by the competing losses of SO and SO_2 gives the same qualitative results.

In summary, there are two competing pathways experimentally observed for fragmentation of system **5**



5

upon pyrolysis and electron impact. When X = C, the loss of XO_2 is preferred and when X = S, the loss of XO is preferred. The molecular orbital approach described here rationalizes this behavior both in terms of relative bond strengths and energies of the species produced by the competing paths.

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A Free Electron Molecular Orbital Model of Aromaticity

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Breslow's criterion for aromaticity applied to the simplest FEMO model yields results for single ring molecules in conformity with the literature. In particular, it is shown that incompletely filled shells may produce antiaromaticity in small ring molecules, but underlying closed shells dominate in larger rings so that all annulene and polymethine series eventually become aromatic.

Although the free electron molecular orbital (FEMO) model has shown a degree of success in the interpretation of electronic spectra of conjugated systems,[1] the extension of the approach to chemical properties has given rather limited agreement. In particular, an attempt to use FEMO (in its more refined network model) to calculate resonance energies gave "surprisingly poor" results.[2] However, it is the purpose of this paper to show that FEMO can be used to analyze aromaticity, provided Breslow's recent reformulation of the criterion for aromaticity[3] is employed; *i.e.*, the π energy of a cyclic compound is compared to that of the corresponding iso-π-electronic linear compound, a decrease in π energy upon cyclization indicating aromaticity, an increase indicating antiaromaticity.

The Model.—We shall use in this paper FEMO in its simplest form. The behavior of the π electronic wave functions perpendicular to the carbon skeleton is assumed to be separable from the behavior along the bonds, and to be constant for all π systems considered. Consequently, this component is ignored in all subsequent considerations. For the component along the carbon skeleton the actual periodic potential energy function is replaced by a constant, taken to be zero for convenience; *i.e.*, straight-chain systems are treated as electrons in a linear box while cyclic systems are treated as electrons on circular rings.

The one remaining assumption for each type of molecule is the effective length of the π system. To avoid prejudicing our results, we adopt two assumptions found in the literature. Throughout this paper we will assume all C–C bonds, whether in a straight

(1) A review of the method is given by N. S. Bayliss, *Quart. Rev., Chem. Soc.*, **6**, 319 (1952). A collection of papers has been reprinted: J. R. Platt, *et al.*, "Free-Electron Theory of Conjugated Molecules," Wiley, New York, N. Y., 1964.

(2) C. W. Scherr, *J. Chem. Phys.*, **21**, 1413 (1953).

(3) R. Breslow, *Chem. Eng. News*, **43** (26), 90 (1965); *Chem. Brit.*, **4**, 100 (1968); *Angew. Chem., Int. Ed. Engl.*, **7**, 565 (1968).

chain or a cyclic compound, to have an average length, d. For the linear system, the variable component of the orbital energy is

$$\epsilon_s = \frac{p^2h^2}{8ma^2} \qquad p = 1, 2, 3, \ldots \tag{1}$$

where h is Planck's constant, m is the mass of the electron, and a is the length of the box. Kuhn[4] has obtained quantitative fits to the electronic spectra of cyanine dyes by assuming that the path of π electrons extends one bond length beyond each end of the carbon skeleton, *i.e.*

$$a = (n + 1)d \tag{2}$$

where n is the number of carbon atoms. The corresponding energy contribution for a cyclic system is

$$\epsilon_c = \frac{q^2h^2}{2mL^2} \qquad q = 0, \pm1, \pm2, \ldots \tag{3}$$

where L is the circumference of the ring. We adopt here Platt's perimeter model[5] in which the circumference is taken to be equal to the total bond length of the π system.

$$L = nd \tag{4}$$

Incidentally, Pilar[6] has given a theoretical justification for these assumptions regarding total lengths.

In this paper we will be interested in the signs and relative magnitudes of energy changes. It is thus convenient to express our energies in units of $h^2/8md^2$. In these units (indicated by primes), eq 1–4 become

$$\epsilon_s' = \frac{p^2}{(n + 1)^2} \tag{5}$$

$$\epsilon_c' = \frac{4q^2}{n^2} \tag{6}$$

These two expressions emphasize the two factors that lead to different molecular orbital energy level diagrams for straight chain and for cyclic conjugated systems: (1) the differing structures of the allowed set of quantum numbers (*cf.* eq 1 and 3 for p and q) and (2) the slightly different dependencies of the orbital energies on chain length (through n).

The total π electron energy is a sum over the occupied orbitals.

$$E' = \sum_{\text{occ}} \epsilon' \tag{7}$$

In the present model these sums are easily evaluated through a standard formula since they involve a finite sum over squares of integers. Following Breslow[3] we define a "π stabilization energy" as the difference in total π energy of the cyclic and the corresponding straight chain conjugated molecules.

$$\Delta E' \equiv E_c' - E_s' \tag{8}$$

If this π stabilization energy is less than zero the cyclic compound has the lower π energy and is aromatic; if the stabilization energy is greater than zero the straight chain molecule has the lower energy and the cyclic compound is antiaromatic; and if the difference is zero then the ring compound is termed nonaromatic. Also, paralleling the use of resonance energies, we shall take the magnitude of the π stabilization energy as a measure of the "degree" of aromaticity or antiaromaticity. General expressions for the π stabilization energy of several series of single ring species are given in Table I. An obvious advantage of the simple model developed in this paper is the ability to write and analyze such general formulae.

TABLE I

π STABILIZATION ENERGIES

n	Species	$\Delta E'$
$4r$	Molecule	$\frac{-2r^2 + 4r + 1}{6r(4r + 1)}$
$4r + 1$	Cation	$\frac{r(-16r^2 + 20r + 15)}{6(4r + 1)^2(2r + 1)}$
	Radical	$-\frac{32r^3 + 8r^2 + 3}{12(4r + 1)^2(2r + 1)}$
	Anion	$-\frac{16r^3 + 28r^2 + 15r + 3}{6(4r + 1)^2(2r + 1)}$
$4r + 2$	Molecule	$-\frac{2(r + 1)^2}{3(2r + 1)(4r + 3)}$
$4r + 3$	Cation	$-\frac{(2r + 1)(16r^2 + 44r + 27)}{24(4r + 3)^2(r + 1)}$
	Radical	$\frac{-32r^3 - 56r^2 - 8r + 15}{24(4r + 3)^2(r + 1)}$
	Anion	$\frac{-32r^3 - 8r^2 + 82r + 57}{24(4r + 3)^2(r + 1)}$

Results

The specific results can be presented in terms of four series: the $[4r + 2]$ annulenes, the $[4r]$ annulenes, the cyclic $[4r + 1]$ polymethines, and the cyclic $[4r + 3]$ polymethines.

$n = 4r + 2$.—The π stabilization energy of these molecules is always negative, so that the compounds are predicted to be always aromatic, in complete conformity to the Hückel rule. The *magnitude* of $\Delta E'$ is largest for benzene (0.12698) and slowly decreases (0.10909 for cyclodecapentaene, 0.10159 for cyclotetradecaheptaene) to a value of $^1/_{12} = 0.08333$ for large r.

$n = 4r$.—Here the trend is more involved, the first members of the series being predicted as antiaromatic, but the later members as aromatic. Cyclobutadiene ($\Delta E' = +0.10000$) would be expected to be significantly antiaromatic, cyclooctatetraene ($\Delta E' = +0.00926$) weakly antiaromatic, while cyclododecahexaene ($\Delta E' = -0.02137$) is foreseen to be slightly aromatic. The π stabilization energy decreases steadily for further increases in ring size, approaching the same limit ($-^1/_{12}$) as the $4r + 2$ series for large r.

Qualitatively, this trend agrees with some results of Breslow and Mohacsi.[7] These authors calculated by the Hückel molecular orbital method the change in delocalization energy upon cyclization for a number of hydrocarbon molecules and ions. There is quantitative disagreement, however, in that Breslow and Mohacsi indicate that cyclooctatetraene should be slightly aromatic. A similar result could be obtained with the FEMO model by use of slightly different assumptions regarding the total length of the π systems. On

(4) H. Kuhn, *J. Chem. Phys.*, **16**, 840 (1948); *Helv. Chim. Acta*, **31**, 1411 (1948).

(5) J. R. Platt, *J. Chem. Phys.*, **17**, 484 (1949).

(6) F. L. Pilar, "Elementary Quantum Chemistry," McGraw-Hill, New York, N. Y., 1968, p 654.

(7) R. Breslow and E. Mohacsi, *J. Amer. Chem. Soc.*, **85**, 431 (1963).

the other hand, our prediction of antiaromaticity for cyclooctatetraene is consistent with the same conclusion reached by Figeys[8] through use of his LCAO–BETA method.

$n = 4r + 1$.—The cation series here exhibits a trend similar to the $n = 4r$ molecules. Cyclopentadienyl cation ($\Delta E' = +0.04222$) is expected to be antiaromatic, cyclononatetraenyl cation ($\Delta E' = -0.00741$) weakly aromatic, with the remaining cations increasing in degree of aromaticity. The π stabilization energy is negative for all members of the radical and the anion series, the anions being especially aromatic, *e.g.*, $\Delta E' = -0.13778$ for cyclopentadienyl anion and $\Delta E' = -0.11235$ for cyclononatetraenyl anion. The limit of the π stabilization energy for large r for all three series is again $-1/12$.

$n = 4r + 3$.—In this case the cations are always aromatic with relatively large π stabilization energies ($\Delta E' = -0.12500$ for cyclopropenyl cation, $\Delta E' = -0.11097$ for cycloheptatrienyl cation, $\Delta E' = -0.10273$ for cycloundecahexaenyl cation). Cyclopropenyl radical is antiaromatic ($\Delta E' = +0.06944$) while the remaining radicals are aromatic ($\Delta E' = -0.03444$ for cycloheptatrienyl radical, $\Delta E' = -0.05521$ for cycloundecahexaenyl radical). The first two anions are antiaromatic ($\Delta E' = +0.26389$, a quite high value, for cyclopropenyl anion, and $\Delta E' = +0.04209$ for cycloheptatrienyl anion), the series then becoming aromatic, although the π stabilization energy for cycloundecahexaenyl anion (-0.00769) is quite small. Again, all three series converge to $\Delta E' = -1/12$ for large r.

The conclusions for the cyclopropenyl ions (cation aromatic, anion highly antiaromatic) are, of course, in agreement with the extensive discussions of Breslow.[3] The order of the three cycloheptatrienyl species follows that plotted by Breslow and Mohacsi,[7] although these authors show the anion to be very slightly aromatic while we have predicted it to be slightly antiaromatic.

Dependence of Aromatic Character on Ring Size.—It is obvious from the above cases that ring size is a determinant of aromaticity. We now systematically investigate this dependence. For a *fixed number of electrons* the π stabilization energy has the form

$$\Delta E' = \frac{A}{n^2} - \frac{B}{(n+1)^2} \tag{9}$$

where A and B are positive quantities depending only on the number of electrons. Let us treat for the moment n as a continuous variable and differentiate the π stabilization energy expression to give, after collecting terms,

$$\frac{d\Delta E'}{dn} = -\frac{2}{n}\Delta E' - \frac{2}{n}\frac{B}{(n+1)^3} \tag{10}$$

The last term in eq 10 is of the same order as the preceding one times a factor $1/(n+1)$. Hence *for large n* we get the asymptotic expression

$$\frac{d\Delta E'}{dn} \approx -\frac{2}{n}\Delta E' \tag{11}$$

Thus, in this limit, if n is increased the change in $\Delta E'$ is opposite in sign to $\Delta E'$ itself; *i.e.*, an aromatic compound will get less aromatic and an antiaromatic compound will move towards aromaticity.

(8) H. P. Figeys, *Tetrahedron*, **26**, 5225 (1970).

Table II
The Size Rule

Species	n	$\Delta E'$	Character
Four-Electron Systems ($A = 8$, $B = 10$)			
$C_3H_3^-$	3	+0.26389	Antiaromatic
C_4H_4	4	+0.10000	Antiaromatic
$C_5H_5^+$	5	+0.04222	Antiaromatic
$C_6H_6^{2+}$	6	+0.01814	Antiaromatic
Six-Electron Systems ($A = 16$, $B = 28$)			
$C_4H_4^{2-}$	4	−0.12000	Aromatic
$C_5H_5^-$	5	−0.13778	Aromatic
C_6H_6	6	−0.12698	Aromatic
$C_7H_7^+$	7	−0.11097	Aromatic
$C_8H_8^{2+}$	8	−0.09568	Aromatic
Eight-Electron Systems ($A = 48$, $B = 60$)			
$C_6H_6^{2-}$	6	+0.10884	Antiaromatic
$C_7H_7^-$	7	+0.04209	Antiaromatic
C_8H_8	8	+0.00926	Antiaromatic
$C_9H_9^+$	9	−0.00741	Aromatic
$C_{10}H_{10}^{2+}$	10	−0.01587	Aromatic

To explore behavior away from the asymptotic limit, we note that the last term in eq 10 is always negative. Thus if $\Delta E' > 0$ (the cyclic compound is antiaromatic) the behavior is the same as the asymptotic limit. If $\Delta E' < 0$ (the cyclic compound is aromatic) deviation from the asymptotic behavior may occur if the π energy of the straight chain molecule is sufficiently large relative to the π stabilization energy, and n is relatively small.

The above considerations are summarized as the tentative rule: the aromatic or antiaromatic character of a cyclic compound with specified number of electrons will decrease when the ring size is increased (the number of electrons remaining the same), possible exceptions occurring for aromatic compounds of small size or weak aromaticity.

Calculations of the π stabilization energy for three iso-π-electronic series are presented in Table II. The four-electron antiaromatic series with a 20-fold change in $\Delta E'$ obeys the rule perfectly. There is one exception in the six-electron aromatic series, the smallest ring cyclobutadienyl dianion having a π stabilization energy that is too low, although still strongly aromatic. In the more complicated eight-electron sequence, the change in $\Delta E'$ between the cyclononatetraenyl cation and the cyclodecapentaenyl dication is in the wrong direction, presumably because of the very weak aromatic character of the cyclononatetraenyl cation.

Discussion

Of the several questions that could be raised concerning the theory of the present paper, the first might be why such a simple model should be successful. The computation of the orbital energies depended on assuming the effective potential energy function for the π electrons to be constant so that the FEMO energies are entirely kinetic. As Lichten[9] has shown, FEMO in this form does not satisfy the virial theorem relating average kinetic and potential energies. In addition, the detailed analysis of the bond in the hydrogen molecule–ion by Feinberg, *et al.*,[10] revealed that

(9) W. Lichten, *J. Chem. Phys.*, **22**, 1278 (1954).

(10) M. J. Feinberg, K. Ruedenberg, and E. L. Mehler, *Advan. Quantum Chem.*, **5**, 27 (1970).

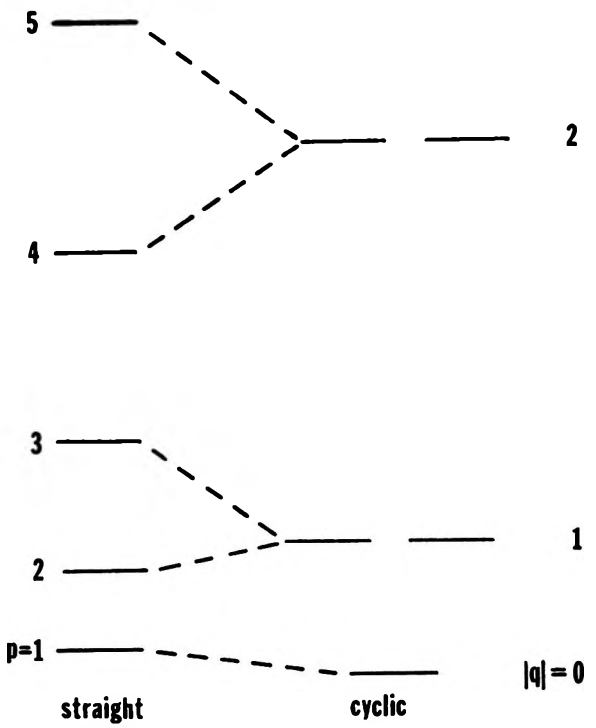

Figure 1.—Correlation of orbital energies (relative values are approximately those for $n = 8$.)

the bond energy was the resultant of a number of competing kinetic and potential energy contributions, chief among them being the lowering of the component of kinetic energy along the bond direction because of the interference density (delocalization of the electron from its atomic density) permitting contraction of the orbitals toward the nuclei with a consequent substantial lowering of potential energy and a concomitant increase in total kinetic energy. However, if we recognize that the energy changes in the FEMO model can be correlated with the kinetic energy contribution of delocalization, and if we are allowed to extrapolate the work of Feinberg, *et al.*, to the present case and thus assume that a contraction of orbitals and lowering of potential energy would occur with the total energy change paralleling the change in kinetic energy of delocalization, then our results should be qualitatively correct. This point is emphasized by the fact that we have dealt in this paper with *changes* in π energy, not with total energies.

Within this context it is interesting to explore why stabilization or destabilization may occur upon cyclization. It is *not* because of further delocalization; in fact in our model the total length of the π system in the cyclic molecule (nd) is less than that in the linear molecule $[(n + 1)d]$. Rather, the effect lies in the pattern of orbital energies. Using the pattern of nodes in the real form of the wave functions, the following correlation can be made between the orbitals of the linear system and those of the cyclic system upon ring closure.

$$p = \begin{cases} 2|q| \\ 2|q| + 1 \end{cases} \longrightarrow |q| \qquad (12)$$

These correlations are illustrated schematically in Figure 1.

The lowest orbital of the ring compound ($q = 0$) correlates with the lowest orbital of the linear compound ($p = 1$) and the change in orbital energy

$$\Delta\epsilon' \equiv \epsilon_c' - \epsilon_s' \qquad (13)$$

is always negative, giving a stabilizing contribution to $\Delta E'$. For $|q| > 0$, the ring orbitals are doubly degenerate and correlate with a pair of nondegenerate linear system orbitals. The contribution to the π stabilization energy of an electron in the lower of these two is

$$\Delta\epsilon' = \frac{4q^2(2n + 1)}{n^2(n + 1)^2} \qquad (14)$$

a quantity that is always greater than zero representing a destabilizing contribution. An electron in the upper orbital of the straight chain pair contributes the amount

$$\Delta\epsilon' = \frac{4q^2(2n + 1) - (4|q| + 1)n^2}{n^2(n + 1)^2} \qquad (15)$$

which is less than zero (stabilizing) for $|q| < n/2$. The total contribution for two electrons in each of these orbitals of the linear molecule can be shown for sufficiently large n to be negative for $|q| < n/4$. Thus completely filled levels of the ring compound give stabilizing contributions to $\Delta E'$, so that closed shell cyclic molecules should be aromatic.

Antiaromaticity may arise if the uppermost pair of ring orbitals is incompletely filled, the determining factor being ring size. Thus for the $[4r + 3]$ polymethine series the model predicts that both the cyclopropenyl radical with one electron in the unfilled level and the anion with two electrons in this level are antiaromatic, while only the anion of the cycloheptatrienyl series is expected to be antiaromatic, and all cycloundecahexaenyl species are forecast as aromatic. Obviously a single electron may determine the character of a small ring compound, but in the larger rings the closed shells exert a dominant influence. For very large rings, the contribution of any given orbital to the π stabilization energy is negligibly small, but since the number of orbitals in the linear molecule goes approximately as $n/2$, the total effect is nonzero. In fact, if we neglect the contributions of the $p = 1$ orbital and any electrons in an unfilled shell, *i.e.*, if we consider only filled pairs of orbitals, the limit for large n of $\Delta E'$ is $-1/12$, precisely the value found in all series discussed in this paper.

The theory and results presented above differ in several aspects from a treatment of the same problem conducted by Dewar using his perturbational molecular orbital (PMO) method.[11] In the present context the PMO theory determines energy changes when the ring is formed by treating the additional π bond formed as a first-order perturbation on the π molecular orbitals of the linear molecule. In practice he uses only the nonbonding molecular orbital of the appropriate odd alternant hydrocarbon. As a consequence he obtains singular predictions for each series, *e.g.*, the $[4r]$ annulenes are always antiaromatic tending toward nonaromaticity for large size, the $[4r + 1]$ polymethine cations and the $[4r + 3]$ polymethine anions are always antiaromatic, while the polymethine radicals are predicted to be nonaromatic. It is clear that the deviation of Dewar's PMO predictions from the results of the present paper is caused by his use of only the

(11) M. J. S. Dewar in "Aromaticity," The Chemical Society Special Publication No. 21, London, 1967, pp 198–210; M. J. S. Dewar, "The Molecular Orbital Theory of Organic Chemistry," McGraw-Hill, New York, N. Y., 1969, Chapter 6, and references cited therein.

uppermost occupied orbital in calculating the energy changes. As our discussion of the various polymethine species has indicated, this uppermost orbital may dominate in small rings, but becomes a minor factor for larger sizes. By putting sole emphasis on the small ring determinant, Dewar misses the crossover from antiaromatic to aromatic character and the limiting degree of aromaticity for all large rings.

On the other hand, our conclusions parallel resonance energies, calculated by the Pople method (including bond alternation),[12] for the first ten annulenes that show negative resonance energies (antiaromaticity) for cyclobutadiene and cyclooctatetraene, but positive values for all the others (including, incidentally, the smallest value for cyclododecahexaene) which seem to quickly converge to a constant value (2.8 kcal/mol) as the ring dimension increases.

In addition to the qualifications on the FEMO model mentioned at the beginning of this section, it should be pointed out that our simple model also neglects any effects arising from the noncircular shape of the cyclic molecules, and perhaps more importantly bond alternation, although it is hoped in the latter case that the effects on the linear and the corresponding ring compounds are approximately the same and cancel in the calculation of the π stabilization energy.

(12) M. J. S. Dewar, "The Molecular Orbital Theory of Organic Chemistry," McGraw-Hill, New York, N. Y., 1969, p 179.

Acknowledgment.—The idea of this paper was stimulated by several conversations with Professor Stephen J. Weininger of Worcester Polytechnic Institute.

A New Synthesis of Substituted 2(1*H*)-Pyridones. Synthesis of a Potential Camptothecin Intermediate

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The acylation of 3-carbalkoxycitraconic esters **1** with amide acetals provides a good method for the synthesis of dimethylaminoalkylidene malonates **3**; these compounds upon treatment with a primary amine cyclize to 2,3-dicarbalkoxy 6-substituted 2(1*H*)-pyridones **4**. Application of this reaction to the acetal or imminium salt from *o*-cyanoarylamides **9a,b** similarly affords the corresponding enamines **3d,e**; hydrogenation of **3** leads directly to the fused pyridones **11** and **13**, a potential camptothecin intermediate.

The acylation of active methylene compounds with acetals of dimethylformamide to give the corresponding dimethylaminomethylene compounds has been reported.[2,3] The analogous condensation between an acetal derived from an alkyl- or arylamide and an alkylidine malonic ester would afford a vinylogous amide which, upon treatment with a primary amine, might undergo enamine exchange and cyclization to a 6-substituted 2(1*H*)-pyridone. Because of the nucleophilic reactivity reported[4] for amide acetals possessing an α hydrogen [arising *via* elimination of alcohol to give the enamine C=C(OEt)NR_2], we chose to restrict our investigation to the hydrogen- and aryl-substituted systems (**2**, R = H or aryl). We describe below the successful completion of this sequence and its application *via* an intramolecular cyclization to the facile synthesis of **13**, a potential intermediate in the synthesis of the antitumor alkaloid camptothecin (**14**).[5]

Initial studies were carried out using ester **1a**, readily prepared from diethyl malonate and ethyl pyruvate.[6] When equimolar quantities of **1a** and the diethyl acetal of dimethylformamide (**2a**) were heated in DMF at 80° for 5 hr, the yellow enamine **3a** was obtained in 87% yield. The enamine double bond in **3a** was assigned as trans on the basis of the vinyl hydrogen coupling constant of 13 Hz in the nmr spectrum. Subsequent reaction of **3a** with benzylamine afforded the *N*-benzylpyridone **4a** in 90% yield.

The feasibility of this approach as a route to camptothecin required the selective transformation of the 3-carbethoxy group into a hydroxymethyl group; the carboxyl group remaining at C_4 would provide the basis for assembly of the α-hydroxy acid moiety. Differentiation of the carbethoxy groups was readily accomplished *via* hydrolysis with 1 equiv of potassium hydroxide to give the acid ester **5a** in 78% yield. Assignment of **5a** as the saponification product was based on the fact that reaction of **5a** with trichloroethanol and *N,N*-dicyclohexylcarbodiimide afforded an ethyl trichloroethyl ester whose nmr spectrum was clearly different from that of the pyridone ester prepared from di(trichloroethyl) malonate and ethyl pyruvate. Extensive efforts to carry out selective reduction of the carbethoxy group proved fruitless. Thus our approach was modified to permit the specific synthesis of the "alternate" acid ester **5b** (Scheme I).

The triester **1b**, prepared from dimethyl malonate,[6] condensed smoothly with **2a** to give the corresponding enamine **3b** in 83% yield; reaction with benzylamine as above led to the crystalline pyridone diester **4b**. When pyridone **4b** was refluxed with anhydrous lithium iodide in pyridine[7] for 1 hr, a single acid ester **5b** was isolated in 86% yield. The nmr spectrum demonstrated unequivocally that the methyl ester had been

(1) Alfred P. Sloan Foundation Fellow.

(2) H. Meerwein, W. Florian, N. Schön, and G. Stopp, *Justus Liebigs Ann. Chem.*, **641**, 1 (1961).

(3) An acylation of this general type has been utilized in the synthesis of the pyrone ring in fulvoplumierin; see G. Büchi and J. A. Carlson, *J. Amer. Chem. Soc.*, **90**, 5336 (1968).

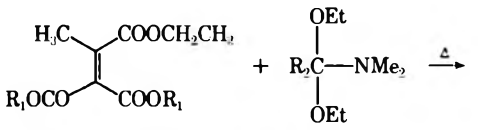
(4) (a) T. Oishi, M. Ochiai, T. Nakayana, and Y. Ban, *Chem. Pharm. Bull.*, **17**, 2314 (1969); (b) for a recent review of amide acetals, see J. Gloede, L. Haase, and H. Gross, *Z. Chem.*, **9**, 201 (1969).

(5) M. E. Wall, M. C. Wani, C. E. Cook, K. H. Palmer, A. T. McPhail, and G. A. Sim, *J. Amer. Chem. Soc.*, **88**, 3888 (1966); A. T. McPhail and G. A. Sim, *J. Chem. Soc. B*, 923 (1968).

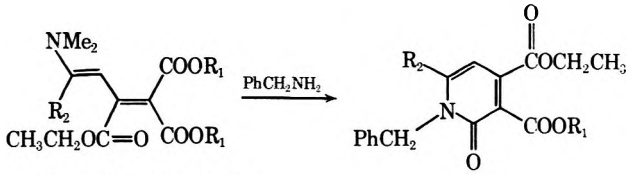
(6) R. Malachowski and W. Czornodola, *Chem. Ber.*, **68B**, 363 (1935).

(7) F. Elsinger, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, **43**, 113 (1961).

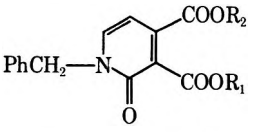
SCHEME I



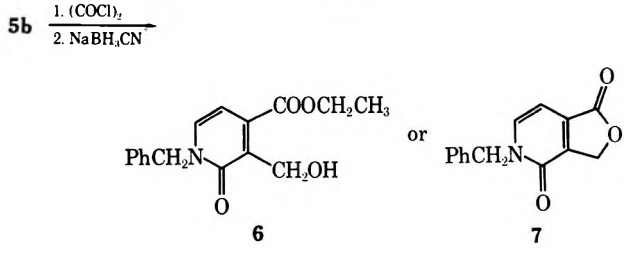
1a, $R_1 = -CH_2CH_3$ 2a, $R_2 = H$
b, $R_1 = -CH_3$ b, R_2 = 3-pyridyl
c, R_2 = 2-cyanophenyl
d, R_2 = 3-cyano-2-quinolyl



3a, $R_1 = -CH_2CH_3$; $R_2 = H$ 4a–c
b, $R_1 = -CH_3$; $R_2 = H$
c, $R_1 = -CH_3$; R_2 = 3-pyridyl
d, $R_1 = -CH_3$; R_2 = 2-cyanophenyl
e, $R_1 = -CH_3$; R_2 = 3-cyano-2-quinolyl



5a, $R_1 = -CH_2CH_3$; $R_2 = -H$
b, $R_1 = -H$; $R_2 = -CH_2CH_3$



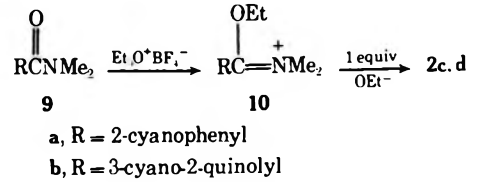
6 7

cleaved selectively; regeneration of **4b** by reaction of **5a** with diazomethane ruled out possible ester interchange.

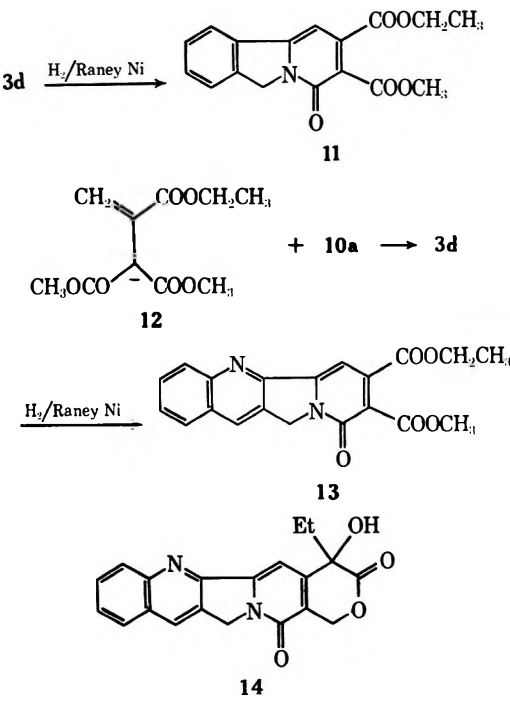
The model sequence was completed by conversion of **5b** to the 3-hydroxymethylpyridone **6**. The acid ester **5a** was converted to the acid chloride by reaction with oxalyl chloride in methylene chloride; reduction with sodium cyanohydridoborate ($NaBH_3CN$)[8] in tetrahydrofuran led to the hydroxy ester **6** or the lactone **7** depending on the work-up conditions.

Having thus demonstrated the feasibility of this sequence for preparing a 2-hydroxymethylpyridone derivative, we turned our attention to the synthesis of the 5-aryl pyridones. We were initially concerned about the preparation of the amide acetals **2b** and **2d** derived from heterocyclic amides, inasmuch as the standard conditions[2] for their preparation require initial treatment with the powerful alkylating agent triethyloxonium fluoroborate. When *N,N*-dimethylnicotinamide was treated with 1 equiv of triethyloxonium fluoroborate, alkylation occurred primarily on the pyridine nitrogen to give the quaternary pyridinium salt as the major product. Another reported method[9] for the synthesis of amide acetals ultimately proved successful in this case. Exposure of *N,N*-dimethylnicotinamide (**8**) to refluxing thionyl chloride, followed by reaction of the chloroimminium intermediate with 2 equiv of sodium ethoxide, afforded a product which contained *ca.* 50% **2b** by nmr analysis. Condensation of this crude product with **1b** gave the oily enamine **3c** in low yield (14% based on amide). The stereochemistry of the trisubstituted double bond in enamine **3c** (and in the other arylenamines **3d** and **3e** reported below) is assigned as shown on the basis of the large shielding effect of the aromatic ring on the $-OCH_2-$ protons of the ethyl ester in the nmr spectrum (see Experimental Section). Conversion of **3c** to **4c** by refluxing with benzylamine in ethanol completed the pyridone synthesis.

SCHEME II



9 10
a, R = 2-cyanophenyl
b, R = 3-cyano-2-quinolyl



11 12 13 14

The application of this method to the synthesis of **13** required the presence of a potential aminomethyl group ortho to the amide on the aromatic ring, thus permitting utilization of an *intramolecular* enamine exchange–cyclization reaction to form the tetracyclic system in one step. *N,N*-dimethyl-*o*-cyanobenzamide (**9a**) was chosen as a model for this conversion. When amide acetal **2c** was heated with triester **1b**, the crystalline enamine **3d** was obtained in 23% yield. Hydrogenation of this enamine with W-2 Raney nickel in ethanol caused reduction of the nitrile with concomitant enamine exchange and cyclization to give a 42% yield of the tricyclic pyridone **11** (Scheme II).

We finally turned our attention to the synthesis of the potential camptothecin intermediate **13**. *N,N*-Dimethyl-3-cyanoquinaldamide (**9b**) was prepared by Friedlander condensation between *o*-aminobenzaldehyde and ethyl 3-cyanopyruvate;[10] the resulting ester

(8) (a) R. F. Borch, M. D. Bernstein, and H. D. Durst, *J. Amer. Chem. Soc.*, **93**, 2897 (1971); (b) R. F. Borch and H. D. Durst, *ibid.*, **91**, 3996 (1969).

(9) H. Eilingsfeld, M. Seefelder, and H. Weidinger, *Angew. Chem.*, **72**, 836 (1960).

(10) A. Rossey and H. Schinz, *Helv. Chim. Acta*, **31**, 473 (1948).

was converted to **9b** by reaction with dimethylamine in ethanol. Using the method successfully applied to the synthesis of **2b**, cyanoamide **9b** was refluxed wth thionyl chloride and the intermediate was subsequently treated with sodium ethoxide. No trace of the desired acetal was observed; instead, a new product was isolated which was isomeric with the starting amide. The infrared spectrum showed no nitrile absorption at 2220 cm^{-1} but showed an intense carbonyl absorption at 1700 cm^{-1}. It was subsequently demonstrated that this product was formed in the thionyl chloride reaction and was unaffected by treatment with sodium ethoxide. Thus it was apparent that the ortho cyano group was participating in the reaction.

The only alternative remaining was to ignore the difficulties inherent in the reaction of amide **9b** with triethyloxonium fluoroborate and attempt the preparation of acetal **2d** by this route. Remarkably, sequential treatment of **9b** with $Et_3O^+BF_4^-$ and sodium ethoxide gave acetal **2d** in 60% yield. Presumably the ring nitrogen is sufficiently hindered in this case to be inert toward alkylation. Having finally prepared the quinoline acetal, we were disappointed to discover that under all conditions investigated **2d** could not be condensed with triester **1b**. We attribute this recalcitrance to the destabilizing effect of the 3-cyano-2-quinolyl group on the presumed reactive intermediate **10b**. This hypothesis was supported by the fact that the alkoxy groups of **2d** could not be exchanged in alcohol; this type of exchange is known to occur readily for amide acetals *via* an imminium intermediate.[2,4b]

Inasmuch as the condensation of amide acetals with **1b** presumably occurs *via* intermediates **10** and **12**, we attempted to prepare and react intermediates of this type directly in the hope of overcoming the lack of reactivity of the acetal itself. Using **9a** as a model, the corresponding imminium salt **10a** was treated with the triester anion **12** to give the corresponding crystalline solid in 32% yield. When this sequence was repeated using imminium salt **10b**, the unstable oily enamine **3e** was obtained in 52% yield. Catalytic hydrogenation of **3e** converted the enamine to the desired tetracyclic pyridone diester **13** in one step.

The conversion of **13** into camptothecin is currently under investigation.

Experimental Section

General.—Melting points were determined on a Kofler hot stage and are uncorrected. Ultraviolet (uv) spectra were determined on a Beckman DK-2A or Cary 11 spectrophotometer. Infrared (ir) spectra were measured on a Perkin-Elmer Model 257 grating spectrometer. Nuclear magnetic resonance (nmr) spectra were measured on Varian Associates T-60 and A-60D instruments and are given in parts per million (δ) downfield from tetramethylsilane as an internal standard. Mass spectra were determined at 70 eV on a Hitachi RMU-6 instrument; the abbreviation M^+ refers to the molecular ion. Elemental analyses were determined by M-H-W Laboratories, Garden City, Mich. Anhydrous magnesium sulfate was employed as a drying agent.

Ethyl 2,3-Dicarbethoxy-*trans*-5-dimethylaminopenta-2,4-dienoate (3a).—To a solution of 3.0 g (11.6 mmol) of **1a** in 3 ml of dry dimethylformamide was added 4.2 g (12.0 mmol) of a 66 mol % solution of dimethylformamide diethyl acetal in dimethylformamide;[11] the resulting solution was heated at 80° for 5 hr. The solution was cooled to room temperature, 60 ml of benzene was added, and the solution was washed with 1 *N* hydrochloric acid and water. The benzene solution was dried and the solvent was removed *in vacuo* to give 3.49 g of orange oil. Trituration with hot petroleum ether (bp 30–60°) gave a solid which was recrystallized from CCl_4–petroleum ether to give 3.17 g (87%) of **3a**: mp 88–89°; ir (Nujol) 1725, 1695, and 1625 cm^{-1}; uv max (95% EtOH) 382 nm (ϵ 38,000); nmr (CCl_4) δ 1.25 (m, 9), 2.94 (s, 6), 4.12 (m, 6), 5.58 (d, 1, J = 13 Hz), and 6.65 (d, 1, J = 13 Hz).

Anal. Calcd for $C_{15}H_{23}NO_6$: C, 57.49; H, 7.40; N, 4.47. Found: C, 57.15; H, 7.51; N, 4.32.

1-Benzyl-3,4-dicarbethoxy-2(1*H*)-pyridone (4a).—To a solution of 1.0 g (3.2 mmol) of enamine **3a** in 5 ml of absolute ethanol was added 367 mg (3.35 mmol) of benzylamine; the resulting solution was refluxed for 5 hr. The cooled solution was evaporated *in vacuo* and the residue was dissolved in 15 ml of ether. The ether solution was washed with 1 *N* hydrochloric acid and water, dried, and evaporated to give 962 mg (90%) of oil which was homogeneous on tlc: ir (liquid) 1740, 1655, and 1610 cm^{-1}; uv max (95% EtOH) 345 nm (ϵ 6200); nmr (CCl_4) δ 1.33 (m, 6), 4.25 (m, 4), 5.01 (s, 2), 6.34 (d, 1), 7.23 (s, 5), and 7.35 (d, 1); mass spectrum m/e 329 (M^+).

1-Benzyl-3-carbethoxy-4-carboxy-2(1*H*)-pyridone (5a).—A solution of 489 mg (1.48 mmol) of the diester **4a** in 16.4 ml (1.48 mmol) of 0.9 *N* ethanolic potassium hydroxide was stirred at room temperature for 4.5 hr. The ethanol was removed *in vacuo*, 4 ml of water was added, and the solution was acidified with 6 *N* hydrochloric acid. The aqueous solution was extracted with chloroform and dried, and the solvent was removed *in vacuo* to give 346 mg (78%) of a thick oil which indicated the presence of a single ethyl group by nmr analysis. The product was crystallized from benzene: mp 126–128°; ir (Nujol) 2900 (broad), 1750, 1730, 1650 cm^{-1}; nmr ($CDCl_3$) δ 1.33 (t, 3), 4.37 (q, 2), 5.18 (s, 2), 6.61 (d, 1), 7.31 (s, 5), 7.37 (d, 1) and 12.5 (s, 1); mass spectrum m/e (rel intensity) 301 (2, M^+), 255 (80), 91 (100).

Anal. Calcd for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65. Found: C, 63.85; H, 5.07; N, 4.57.

Methyl 2-Carbomethoxy-3-carbethoxy-*trans*-5-dimethylaminopenta-2,5-dienoate (3b).—A solution of 10 g (43.5 mmol) of triester **1b**,[6] 7.3 g (45.0 mmol) of a 85 mol % solution of dimethylformamide diethyl acetal in dimethylformamide, and 7 ml of dimethylformamide was heated at 80° for 3 hr. The cooled solution was poured into 100 ml of benzene, washed four times with water, dried, and evaporated *in vacuo* to give 11.25 g of crude product. Crystallization from carbon tetrachloride gave 9.40 g (83%) of **3b**: mp 116.5–118°; ir (Nujol) 1725, 1695, 1620 cm^{-1}; uv max (95% EtOH) 385 nm (ϵ 42,000); nmr ($CDCl_3$) δ 1.34 (t, 3), 2.97 (s, 6), 3.70 (s, 3), 3.80 (s, 3), 4.37 (q, 2), 5.71 (d, 1, J = 13 Hz), and 6.83 (d, 1, J = 13 Hz).

Anal. Calcd for $C_{13}H_{19}NO_6$: C, 54.73; H, 6.71; N, 4.90. Found: C, 54.72; H, 6.61; N, 4.72.

1-Benzyl-3-carbomethoxy-4-carbethoxy-2(1*H*)-pyridone (4b) was prepared according to the procedure described for **3b**. The crude product was recrystallized from carbon tetrachloride to give **4b** in 89% yield: mp 78.5–80.5°; ir (Nujol) 1750, 1730, 1650, 1610 cm^{-1}; uv max (95% EtOH) 343 nm (ϵ 6400); nmr ($CDCl_3$) δ 1.32 (t, 3), 3.91 (s, 3), 4.32 (q, 2), 5.13 (s, 2), 6.55 (d, 1), 7.35 (s, 5), and 7.49 (d, 1); mass spectrum m/e (rel intensity) 3.15 (26, M^+), 283 (58), 91 (100).

Anal. Calcd for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44. Found: C, 65.01; H, 5.51; N, 4.37.

1-Benzyl-3-carboxy-4-carbethoxy-2(1*H*)pyridone (5b).—To a refluxing solution of 6.15 g (46 mmol) of anhydrous lithium iodide in 50 ml of dry pyridine under nitrogen was added a solution of 3.67 g (11.65 mmol) of **4b**. Refluxing was continued for 1 hr. The solution was cooled and the pyridine was removed *in vacuo* (bath temperature 40°). The residue was dissolved in 50 ml of water, acidified with 6 *N* hydrochloric acid, and extracted with chloroform. The extracts were dried and evaporated *in vacuo* to give a residue which was crystallized from absolute ethanol to give 3.02 g (86%) of **5b**: mp 96–100°; ir (Nujol) 1740, 1630, 1450 cm^{-1}; nmr ($CDCl_3$) δ 1.27 (t, 3), 4.34 (q, 2), 5.19 (s, 2), 6.33 (d, 1), 7.30 (s, 5), 7.65 (d, 1) and 12.5 (s, 1); mass spectrum m/e (rel intensity) 301 (4, M^+), 255 (39), 91 (100).

Anal. Calcd for $C_{16}H_{15}NO_5$: C, 63.78; H, 5.02; N, 4.65. Found: C, 63.82; H, 5.12; N, 4.51.

1-Benzyl-3-hydroxymethyl-4-carboxy-2(1*H*)-pyridone Lactone (7).—To a solution of 320 mg (1.06 mmol) of **5b** in 5 ml of methylene chloride was added 1 ml of oxalyl chloride. The resulting solution was stirred for 16 hr at room temperature. The excess oxalyl chloride was removed *in vacuo*, and a solution of 130 mg

(11) Available from Aldrich Chemical Co., Milwaukee, Wis.

(2.1 mmol) of sodium cyanohydridoborate[7,12] in 5 ml of dry tetrahydrofuran was added to the residue. This solution was then stirred for 16 hr at room temperature. Water (10 ml) was added, and the solution was stirred for 15 min, then extracted with benzene. The extracts were dried and evaporated to give a semisolid which was recrystallized from benzene to give 192 mg (75%) of **7**: mp 125–126.5°; ir (Nujol) 1775, 1670 cm^{-1}; uv max (95% EtOH) 328 nm (ϵ 6000); nmr ($CDCl_3$) δ 5.21 (m, 4), 6.57 (d, 1), 7.33 (s, 5), 7.47 (d, 1); mass spectrum *m/e* (rel intensity) 241 (44, M^+), 91 (100), 65 (13).

Anal. Calcd for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.59; N, 5.80. Found: C, 69.23; H, 4.45; N, 5.74.

1-Benzyl-3-hydroxymethyl-4-carbethoxy-2(1*H*)-pyridone (6).—A solution of 215 mg (3.44 mmol) of sodium cyanohydridoborate in 10 ml of dry tetrahydrofuran was added to 510 mg (1.7 mmol) of acid chloride prepared as above. The resulting solution was stirred for 16 hr. After cooling in an ice bath, the solution was added quickly to an ice-cold, rapidly stirred solution of 50 ml of 10% aqueous phosphate buffer at pH 4.9. Stirring was continued for 1 min, and the solution was rapidly extracted with four 50-ml portions of benzene. The combined extracts were washed with cold water, dried, and evaporated *in vacuo* (bath temperature below 20°) to give 490 mg of **6** as a thick oil: ir (liquid) 3430, 1730, 1665, 1600 cm^{-1}; nmr ($CDCl_3$) δ 1.35 (t, 3), 4.37 (q, 2), 4.87 (s, 2), 5.15 (s, 2), 6.49 (d, 1), 7.31 (s, 5), 7.35 (d, 1).

A sample of hydroxy ester **6** was converted quantitatively to the lactone **7**, mp 124–125°, by refluxing for 2 hr with a catalytic amount of *p*-toluenesulfonic acid in tetrahydrofuran.

Methyl 2-Carbomethoxy-3-carbethoxy-5-dimethylamino-5-(3-pyridyl)penta-2,4-dienoate (3c).—A solution of 397 mg (2.65 mmol) of *N,N*-dimethylnicotinamide in 1 ml of thionyl chloride was stirred for 2 hr at 70°. Excess thionyl chloride was removed *in vacuo*, and the residue was dissolved in 1 ml of fresh thionyl chloride. After stirring at 70° for 21 hr, the excess thionyl chloride was again removed *in vacuo*. The residual solid was dissolved in 2 ml of methylene chloride, and to this stirred solution at 0° was added 4.5 ml (11.5 mmol) of 2.56 *N* ethanolic sodium ethoxide. This suspension was stirred for 10 min, diluted with 20 ml of benzene, stirred for an additional 10 min, then filtered through Celite under a dry nitrogen atmosphere. The solvent was evaporated from the filtrate *in vacuo*, and the resulting oil was dissolved in 3 ml of benzene and filtered through Celite under a dry nitrogen atmosphere. The solvent was removed *in vacuo* to give 600 mg of crude product which contained 50 mol % amide acetal[13] **2b** by nmr analysis: nmr ($CDCl_3$) 1.23 (t, 6), 2.12 (s, 6), 3.48 (m, 4), 7.50 (m, 2), and 8.66 (m, 2). This material was used without further purification.

To the crude acetal prepared above was added 450 mg (1.95 mmol) of triester **1b**; the solution was stirred for 20 hr at 88° under a nitrogen atmosphere. The reaction mixture was purified by preparative tlc (five 20 × 20 cm plates, PF_{254} silica gel, eluted with 1:1 ethyl acetate–benzene). The yellow band of R_f 0.2 was removed from the plate and the product was extracted from the silica gel with 4:1 chloroform–methanol to give 127 mg (14%) of enamine **3c** as an unstable yellow oil: ir (liquid) 1735, 1720 cm^{-1}; nmr ($CDCl_3$) δ 1.03 (t, 3), 2.87 (s, 6), 3.37 (q, 2), 3.64 (s, 3), 3.80 (s, 3), 5.97 (s, 1), 7.40 (m, 2) and 8.55 (m, 2); mass spectrum *m/e* 362 (M^+).

1-Benzyl-3-carbomethoxy-4-carbethoxy-6-(3-pyridyl)-2(1*H*)-pyridone (4c).—To a solution of 84 mg (0.23 mmol) of enamine **3c** in 1 ml of absolute ethanol was added 48 mg (0.44 mmol) of benzylamine; the resulting solution was refluxed for 108 hr. The solvent was removed *in vacuo* and the product was purified by preparative tlc (silica gel PF_{254}, eluted with ethyl acetate) to give 24 mg (26%) of colorless oil which crystallized from ethyl acetate–benzene to give **4c**: mp 130–133°; ir (Nujol) 1730, 1710, 1670, 1630 cm^{-1}; nmr ($CDCl_3$) δ 1.35 (t, 3), 3.98 (s, 3), 4.33 (q, 2), 5.18 (s, 2), 6.53 (s, 1), 6.90 (m, 2), 7.23 (m, 5), 8.57 (m, 2); mass spectrum *m/e* 392 (M^+).

Anal. Calcd for $C_{22}H_{20}N_2O_5$: C, 67.36; H, 4.92. Found: C, 67.33; H, 5.14.

***o*-Cyano-*N,N*-dimethylbenzamide (9a).**—To a solution of methyl *o*-cyanobenzoate[11] (2.42 g, 15 mmol) in 15 ml of ethanol was added 21 ml (16 mmol) of 0.75 *N* ethanolic potassium hydroxide. The resulting mixture was stirred for 48 hr, and the potassium salt was collected by filtration of the ethanolic suspension. The white solid was dried at 25° *in vacuo* for 2 hr to give 2.69 g (98%) of potassium *o*-cyanobenzoate. This product was ground to a fine powder and suspended in 50 ml of methylene chloride. Oxalyl chloride (2.0 ml, 20 mmol) was added to the suspension, and then 10 drops of pyridine was *cautiously* added. The resulting suspension was stirred for 3 hr at room temperature and then was transferred to an addition funnel and added dropwise with stirring over 30 min to 50 ml of 25% aqueous dimethylamine at 0°. The mixture was stirred for an additional 15 min at room temperature, the layers were separated, and the aqueous layer was extracted with three 25-ml portions of methylene chloride. Water (20 ml) was added to the combined extracts, and portions of 12 *N* hydrochloric acid were added with intermittent shaking until the aqueous layer remained acidic. The extracts were dried and evaporated to give 2.58 g of impure cyanoamide **9a**. This product was dissolved in 40 ml of 1:1 ether–benzene, and the resulting solution was washed with three 10-ml portions of 0.5 *N* hydrochloric acid. The combined washings were extracted with 10 ml of ether, and the combined extracts were dried and evaporated to give 2.21 g (88%) of gas chromatographically pure amide **9a**: ir (liquid) 2210, 1640 cm^{-1}; nmr (CCl_4) δ 2.86 (s, 3), 3.05 (s, 3), 7.55 (m, 5).

Methyl 2-Carbomethoxy-3-carbethoxy-5-dimethylamino-5-(2-cyanophenyl)penta-2,4-dienoate (3d). Procedure A.—To a solution of 1.33 g (7.0 mmol) of triethyloxonium fluoroborate[14] in 2 ml of methylene chloride was added a solution of 1.13 g (6.5 mmol) of cyanoamide **9a**. The solution was stirred for 23 hr at room temperature and cooled to 0°, and 2.83 ml (7.0 mmol) of 2.47 *N* ethanolic sodium ethoxide was added. The resulting suspension was stirred for 5 min, diluted with 10 ml of petroleum ether, and filtered through Celite under an atmosphere of dry nitrogen. The solvent was removed *in vacuo* to give 1.58 g of an oil which was >95% amide acetal **2c**:[13] nmr ($CDCl_3$) δ 1.27 (t, 6), 2.28 (s, 6), 3.50 (m, 4), 7.58 (m, 4).

To the acetal was added 1.64 g (27.1 mmol) of triester **1b**, and the resulting solution was stirred at 90° for 70 hr under nitrogen. The crude reaction product was dissolved in 1 ml of carbon tetrachloride and transferred to a Morton flask. Petroleum ether (9 ml) was added, and the mixture was stirred vigorously for 15 min. The solution was decanted from the red oil and discarded, and this extraction process was repeated. The red oil (2.2 g) was chromatographed *via* the dry column technique[15] on a 1.5 × 36 in. nylon column packed with Baker silica gel which had been preequilibrated with 1:9 ethyl acetate–benzene. The yellow band was cut from the column, and the product was isolated by extraction from the silica gel to give 800 mg (30% from amide) of **3d** as a dark oil. Crystallization from ethyl acetate–cyclohexane afforded 610 mg (23%) of product, mp 135–138°. Two recrystallizations afforded 360 mg of analytically pure **3d**: mp 138–139°; uv max (95% EtOH) 401 nm (ϵ 27,000); ir (Nujol) 2210, 1740, 1720, 1690 cm^{-1}; nmr ($CDCl_3$) δ 1.06 (t, 3), 2.88 (s, 6), 3.38 (q, 2), 3.62 (s, 3), 3.78 (s, 3), 6.02 (s, 1), 7.50 (m, 4); mass spectrum *m/e* 386 (M^+).

Anal. Calcd for $C_{20}H_{22}N_2O_6$: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.61; H, 5.83; N, 6.95.

Procedure B.—A solution of 1.11 g (6.4 mmol) of amide **9a** and 1.33 g (7.0 mmol) of triethyloxonium fluoroborate[14] in 4 ml of methylene chloride was stirred for 48 hr at 25°. A solution of triester anion was prepared by adding 1.61 g (7.0 mmol) of triester dropwise to a suspension of sodium hydride (340 mg of 50% dispersion, 7.1 mmol) in 4 ml of dimethylformamide at 0°. This solution was then added under nitrogen to the cooled methylene chloride solution in small portions over 3 min. The reaction mixture was allowed to come to room temperature and was stirred under nitrogen for 5 hr. Methylene chloride (25 ml) was added, and the resulting solution was washed with three 25-ml portions of water. The organic layer was dried and evaporated to give 2.48 g of red oil. The product was crystallized from ethyl acetate–cyclohexane to give 790 mg (32%) of **3d**, mp 136–137°.

6-Oxo-7-carbomethoxy-8-carbethoxy-10(*H*)-pyrido[1,2-*a*]isoindole (11).—To a solution of 700 mg (1.75 mmol) of **3d** in 40 ml of ethanol was added 10 ml of W-2 Raney nickel. The resulting suspension was hydrogenated at atmospheric pressure, and the reduction was monitored by observing the decrease in the 401-nm absorption of **3d**. After 17 hr, the catalyst was removed by filtration through Celite, and the ethanol was evaporated. The crude product was purified by dry column[15] chromatography on a

(12) Available from Alfa Inorganics, Beverly, Mass.

(13) The remainder of the material was a mixture of the corresponding ester and dimethylamide.

(14) H. Meerwein, *Org. Syn.*, **46**, 113 (1966).

(15) B. Loev and M. M. Goodman, *Chem. Ind.* (*London*), 2026 (1967).

1 × 25 in. silica gel column, eluting with ethyl acetate. The resulting material (450 mg) was further purified by preparative tlc (silica gel PF_{254}, using 97:3 chloroform–methanol to elute) and the product was recrystallized to give 230 mg (42%) of 11: mp 159–162° (analytical sample mp 161.5–163°); ir (Nujol) 1725, 1710, 1640 cm^{-1}; uv max (95% EtOH) 366 nm (ϵ 14,300); nmr ($CDCl_3$) δ 1.37 (t, 3), 3.95 (s, 3), 4.35 (q, 2), 5.15 (s, 2), 7.10 (s, 1), 7.60 (m, 4); mass spectrum *m/e* 313 (M^+).

Anal. Calcd from $C_{17}H_{15}NO_5$: C, 65.17; H, 4.82; N, 4.47. Found: C, 65.20; H, 4.73; N, 4.29.

***N,N*-Dimethyl-3-cyanoquinaldamide (9b).**—To a suspension of 10.12 g (62.1 mmol) of the sodium enolate of ethyl 3-cyanopyruvate was added 40 ml (86.8 mmol) of 2.17 *N* methanolic hydrochloric acid. The suspension was stirred for 15 min and the solvent was removed *in vacuo*. The resulting mixture was suspended in 80 ml of chloroform and filtered, and the solvent was removed *in vacuo* to give an orange oil. This crude cyano keto ester was dissolved in 200 ml of absolute ethanol containing a catalytic quantity of HCl, and a solution of 10.97 g (91 mmol) of *o*-aminobenzaldehyde in 50 ml of absolute ethanol was added. The reaction mixture was stirred at 25° for 7 days. The solution was made basic with ethanolic sodium ethoxide, and the solvent was removed *in vacuo*. The residue was stirred three times with 250-ml portions of ether, the suspensions being filtered each time. The combined ether extracts were evaporated, and the semisolid residue was crystallized from ether to give 4.40 g (32%) of ethyl 3-cyanoquinaldate: mp 130–132°; ir (Nujol) 2220, 1720 cm^{-1}.

Anal. Calcd for $C_{13}H_{10}N_2O_2$: C, 69.01; H, 4.46; N, 12.38. Found: C, 69.24; H, 4.52; N, 12.60.

A solution of ethyl 3-cyanoquinaldate (967 mg, 4.28 mmol) in 4 ml of dimethylamine was stirred with a Dry Ice–acetone condenser for 1 hr and then diluted with 15 ml of absolute ethanol. The reaction mixture was stirred for 16 hr at 25°. The solvent was removed *in vacuo* and the resulting solid was recrystallized from ethyl acetate to give 645 mg (67%) of 9b: mp 139–141; ir (Nujol) 2220, 1655 cm^{-1}.

Anal. Calcd for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66. Found: C, 69.55; H, 5.04; N, 18.25.

Methyl 2-Carbomethoxy-3-carbethoxy-5-(*N,N*-dimethylamino)-5-(3-cyano-2-quinolyl)penta-2,4-dienoate (3e).—A solution of 555 mg (2.92 mmol) of triethyloxonium fluoroborate and 553 mg (2.38 mmol) of amide 9b in 7 ml of methylene chloride was stirred for 48 hr at 25°. A solution of the triester anion was prepared by adding 876 mg (3.81 mmol) of triester 1b dropwise to a suspension of sodium hydride (213 mg of 50% dispersion, 4.44 mmol) in 2 ml of dimethylformamide at 25° and then stirring for 30 min. This solution was then added at 0° to the methylene chloride solution prepared above. After stirring for 5 min, methylene chloride (*ca.* 25 ml) was added and the solution was washed with four 25-ml portions of water. The organic layer was dried and evaporated to give 1.3 g of crude product. Purification by preparative tlc (silica gel PF_{254}, eluting with 1:1 ethyl acetate–benzene) afforded 539 mg (52%) of 3e as an unstable oil: ir (liquid) 2220, 1730, 1690 cm^{-1}; uv max (95% EtOH) 425 nm (ϵ 27,000); nmr ($CDCl_3$) δ 0.80 (t, 3), 2.88 (q, 2), 2.92 (s, 6), 3.57 (s, 3), 3.78 (s, 3), 6.13 (s, 1), 7.93 (m, 4), 8.67 (s, 1); mass spectrum *m/e* 437 (M^+).

7-Carbethoxy-8-carbomethoxy-9-oxo-11(*H*)-indolizino[1,2-6]-quinoline (13).—To 340 mg (0.78 mmol) of 3a was added 5 ml of ethanolic W-2 Raney nickel, and the suspension was hydrogenated at atmospheric pressure for 15 hr. The reaction mixture was filtered through Celite and the solvent was removed *in vacuo* to give 216 mg of crude material. The product was purified by preparative tlc (silica gel PF_{254}, eluted with ethyl acetate) to give 30 mg (11%) of an insoluble solid: mp 280–284°; ir (Nujol) 1730, 1720, 1660, 1620, 1610 cm^{-1}; uv max (95% EtOH) 372 nm (ϵ 9700).

Anal. Calcd for $C_{20}H_{16}N_2O_5$: mol wt, 364.10592. Found:[16] mol wt, 364.10593.

Registry No.—**3a**, 33707-20-9; **3b**, 33707-21-0; **3c**, 33707-22-1; **3d**, 33703-23-2; **3e**, 33666-43-2; **4a**, 33707-24-3; **4b**, 33707-25-4; **4c**, 33707-26-5; **5a**, 33707-27-6; **5b**, 33707-28-7; **6**, 33707-29-8; **7**, 33707-30-1; **9a**, 26487-08-1; **9b**, 33707-32-3; **11**, 33707-33-4; **13**, 33707-34-5; ethyl 3-cyanoquinaldate, 33707-35-6.

Acknowledgment.—We gratefully acknowledge the generous financial support of the National Institutes of Health in the form of Grant No. CA-10849 and a predoctoral fellowship for C. V. G., 1968–1970.

(16) We thank R. Graham Cooks, Purdue University, for this measurement.

Synthesis of *N*-Alkyl-3-carboxy-4-pyridones

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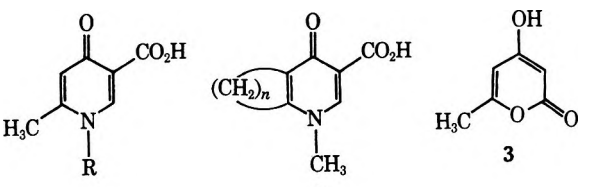
The synthesis of several *N*-alkyl-3-carboxy-4-pyridones is described beginning with substituted 4-hydroxy-2-pyrones. Several of the pyrones are prepared by a new synthesis involving the condensation of a morpholine enamine with carboethoxyacetyl chloride to give a diketo ester. The diketo ester is cyclized with sodium methoxide in dimethylformamide to afford the 4-hydroxy-2-pyrone. The 4-hydroxy-2-pyrones react with the dimethyl acetal of dimethylformamide in a new reaction to introduce a 3-dimethylaminomethylene moiety. Rearrangement of this intermediate with primary amines leads to the title compounds.

In this paper we report the synthesis of several *N*-alkyl-3-carboxy-4-pyridones of types **1** and **2**. A convenient starting material for the preparation of **1** should be **3**. We planned to introduce an aldehyde or related functionality in position **3** after which rearrangement with ammonia or primary amines should yield **1**.

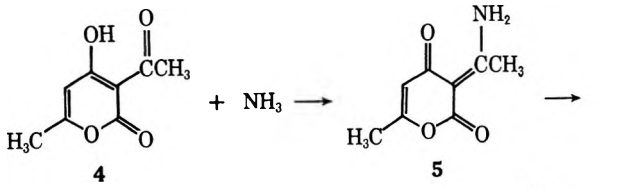
This type of rearrangement has been done with ammonia and dehydroacetic acid (**4** to **6**) when the temperature of the reaction did not exceed 100°.[1] A side product was the decarboxylated pyridone. According to Schut and coworkers[2] only the decarboxylated compound is isolated when dehydroacetic acid is treated with primary amines. In our case the major product was always the pyridonecarboxylic acid.



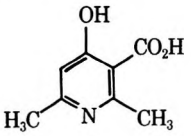
Introduction of the aminomethylene functionality into the 3 position of a 4-hydroxy-2-pyrone was accomplished by using the dimethyl acetal of dimethylformamide, a compound known to react with active methy-

(1) J. N. Collie, *J. Chem. Soc.*, **77**, 971 (1900).

(2) R. N. Schut, W. G. Strycker, and T. M. H. Lin, *J. Org. Chem.*, **28**, 3046 (1963).



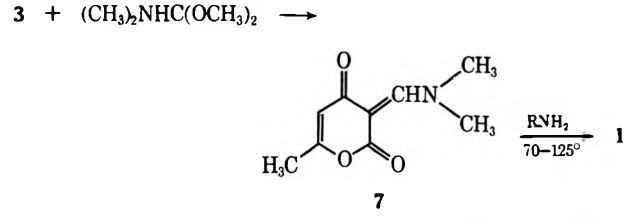
4 5



6

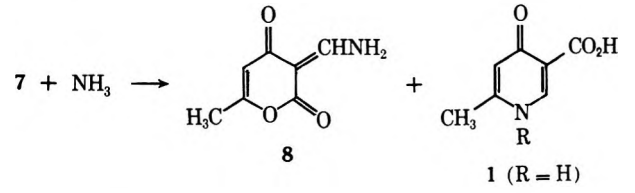
lene groups.[3] This procedure was chosen because of its simplicity, its mild reaction conditions, the ease of work-up, and the high yields obtained. The reaction is conducted at room temperature or below in dioxane and the product crystallizes from solution. This reaction, not previously reported, should prove useful for the placement of various groups in the 3 position of 4-hydroxy-2-pyrones.

Reaction of **3** with dimethylformamide dimethyl acetal yielded **7**, which, when treated with ammonia or primary amines, gave **1** either at temperatures below 100° or at 125° (using boiling Methyl Cellosolve).



7

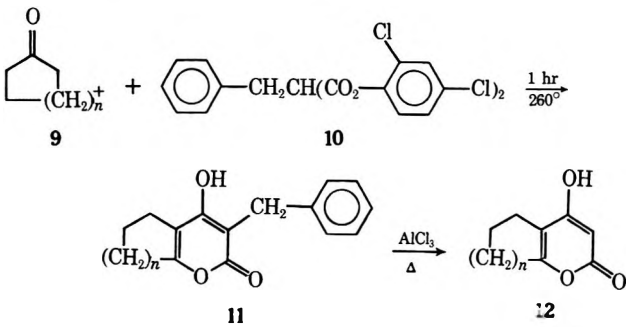
Reaction of **7** with ammonia at room temperature allowed the isolation of an intermediate (**8**) in 73% yield. Work-up of the filtrate yielded 9% of **1** (R = H).



8 1 (R = H)

Support for the structural assignment of **8** rests on the elemental analysis and the strong similarities in the infrared and nmr spectra of **7** and **8**.

Pyridones of type **2** were synthesized by the same procedure. The necessary 4-hydroxy-2-pyrones have been described by Ziegler, *et al.*,[4] who carried out the following reaction sequence.



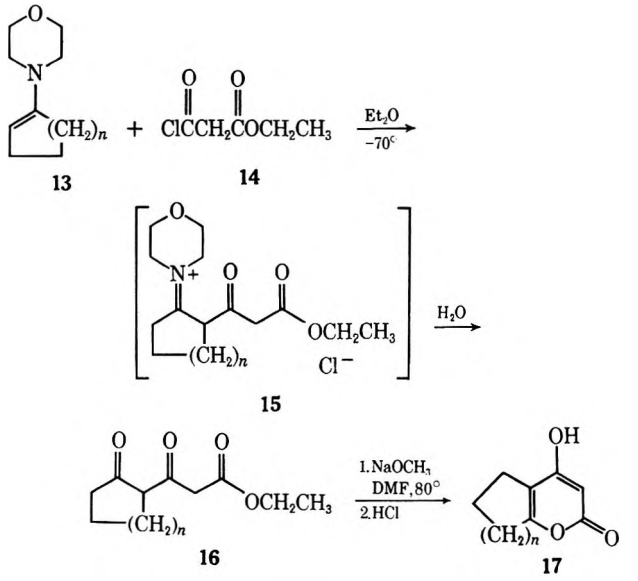
9 10 11 12

$n = 1-4$

(3) L. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. 2, Wiley-Interscience, New York, N. Y., 1969, p 154.

(4) E. Ziegler, H. Junek, and E. Nolken, *Monatsh. Chem.*, **89**, 678 (1958).

While Ziegler's method appeared to be a good one, it was of interest to examine the synthesis of **12** and its homologs by reaction of the morpholine enamine of the appropriate ketone with carboethoxyacetyl chloride followed by base-induced ring closure of the intermediate diketo esters as shown below.



13 14 15 16 17

$n = 1-3$

After many unsuccessful attempts to synthesize **16** ($n = 2$), where solvents such as benzene and chloroform were used, we found that ether was the solvent of choice probably because the intermediate salt **15** precipitates from ether, thereby preventing side reactions. The diketo ester **16** is formed when water is added to the ethereal suspension. Under these conditions, the formation of diketo esters was found to be quite general. These esters were all viscous liquids which resisted crystallization and could not be distilled; so they were used directly in their crude state to prepare the pyrone.

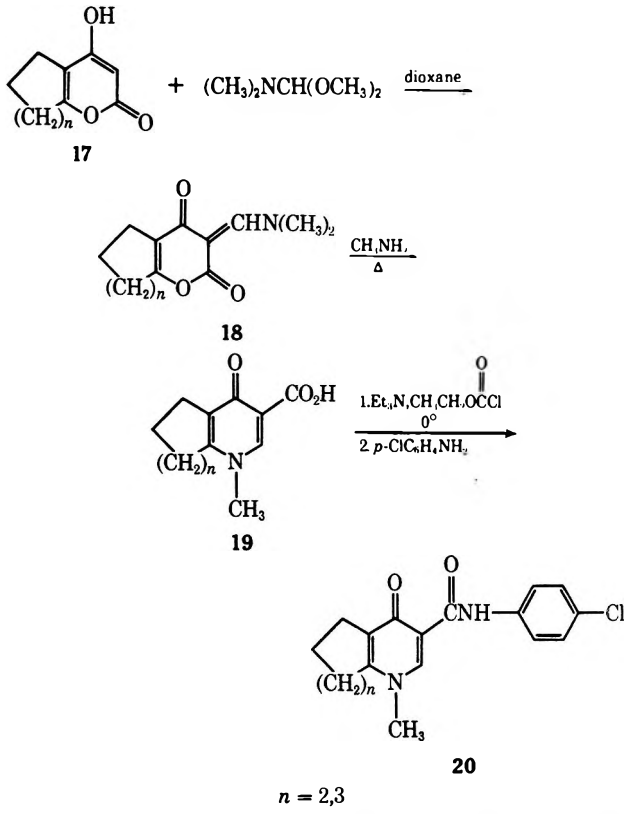
The ring closure of **16** to **17** remained elusive for a time; conditions such as sodium ethoxide in ethanol, cold concentrated sulfuric acid, and acetic anhydride containing a few drops of sulfuric acid all failed; starting material was recovered in all cases. We found that use of sodium methoxide (1 equiv) in dry dimethylformamide at 80–85° caused the desired reaction to take place. The yield of pyrone appears to depend greatly on ring size, although the relationship is only qualitative because of the crude state of the diketo esters; for example, when $n = 1$ only 3% of pyrone was obtained while 37 and 61% yields were obtained where $n = 2$ and $n = 3$, respectively. This constitutes a new method for the preparation of 4-hydroxy-2-pyrones.

These last two pyrones ($n = 2, 3$) were then treated with the dimethyl acetal of dimethylformamide to give the enamines **18**, which were converted to the pyridones **19** and thence to the amides **20**.

Experimental Section

Nmr spectra were determined on a Varian A-60 spectrometer; chemical shifts are reported in τ values in parts per million using tetramethylsilane (TMS) as an internal standard. Infrared spectra were recorded on a Perkin-Elmer grating infrared spectrophotometer. All melting points are uncorrected.

Preparation of Enamines.—The morpholine enamine of cyclo-



heptanone was obtained in 64% yield by use of titanium tetrachloride.[5] All other enamines were prepared by the more usual method.

3-(Dimethylaminomethylene)-4-oxo-6-methyl-2-pyrone (7).—A suspension of 25 g (0.2 mol) of 4-hydroxy-6-methyl-2-pyrone and 44 g (0.37 mol) of *N,N*-dimethylformamide dimethyl acetal in 100 ml of reagent-grade *p*-dioxane was stirred until a brown solution had formed; the solution was left overnight in the refrigerator. The suspension which formed was filtered and the solid was recrystallized from 2-propanol to afford 26 g (72%) of **7**: mp 152–154°, beige crystals; ir (Nujol) 1690, 1660 cm^{-1}; nmr (DMSO) τ 7.83 (s, 3 H, C-methyl), 6.73 (s, 3 H, N-methyl), 6.48 (s, 3 H, N-methyl), 4.33 (s, 1 H, olefinic), and 1.68 (s, 1 H, olefinic).

Anal. Calcd for $C_9H_{11}NO_3$: C, 59.66; H, 6.12; N, 7.73. Found: C, 59.46; H, 6.38; N, 7.53.

3-(Aminomethylene)-4-oxo-6-methyl-2-pyrone (8).—To a solution of pyrone **7** (26 g, 0.144 mol) in 50 ml of water was added 50 ml of concentrated ammonia. The solution was cooled in an ice–water bath; crystallization occurred shortly thereafter. The suspension was quickly filtered and the solid which was isolated was dried to give 16 g (73%) of **8**, mp 211–213° dec, which was analyzed without further purification: ir (Nujol) 3300 (NH_2), 3170 (NH_2), 1720, 1670 cm^{-1}; nmr (DMSO) τ 7.88 (s, 3 H, C-methyl), 4.28 (s, 1 H, olefinic), 1.72 (s, 1 H, olefinic), 1.33 (d, 1 H, NH), and −1.17 (d, 1 H, NH).

Anal. Calcd for $C_7H_7NO_3$: C, 54.90; H, 4.61; N, 9.15. Found: C, 54.90; H, 4.68; N, 9.10.

The filtrate was evaporated *in vacuo* and the residue was dissolved in hot 2-propanol. Crystallization took place upon acidification with acetic acid and cooling to afford 2 g (9%) of 6-methyl-4-pyridone-3-carboxylic acid (**1**, R = H), mp 266–267° dec.

6-Methyl-4-(1*H*)-pyridone-3-carboxylic Acid (1, R = H).—A solution of **7** (14.5 g, 0.08 mol) in 100 ml of Methyl Cellosolve was refluxed for 3 hr while a slow stream of ammonia was bubbled into the solution. The solution was evaporated under reduced pressure and the residue was dissolved in 50 ml of water. Careful acidification with glacial acetic acid gave a suspension which was cooled and filtered to afford 6 g (49%) of **1** (R = H), mp 267–268° dec, ir (Nujol) 1660 cm^{-1}. The compound was analyzed without further purification.

Anal. Calcd for $C_7H_7NO_3$: C, 54.90; H, 4.61; N, 9.15. Found: C, 55.11; H, 4.37; N, 9.04.

(5) H. Weingarten, J. P. Chupp, and W. A. White, *J. Org. Chem.*, **32**, 3246 (1967).

In the same way **1** (R = CH_3) was prepared in 55% yield.

1,6-Dimethyl-4-pyridone-3-carboxylic Acid (1, R = CH_3).—3-(Dimethylaminomethylene)-4-oxo-6-methyl-2-pyrone (111 g, 0.613 mol) was dissolved in 100 ml of water; aqueous methylamine (40%, 300 ml) was added. A precipitate formed immediately and the suspension was heated on a steam bath for 15 min until a solution had formed. After standing for 30 min, the solution was evaporated to about two-thirds of its original volume. The remaining solution was acidified with acetic acid (taking care not to add excess acid for the product will redissolve again), cooled, and filtered. The dried pyridone weighed 77 g (75%), mp 227–228° (231–232° after recrystallization from 95% ethanol), ir (Nujol) 1710, 1670 cm^{-1}.

Anal. Calcd for $C_8H_9NO_3$: C, 57.58; H, 5.43; N, 8.38. Found: C, 57.89; H, 5.36; N, 8.33.

1-(*n*-Butyl)-6-methyl-4-pyridone-3-carboxylic Acid (1, R = *n*-C_4H_9).—Using Methyl Cellosolve as the reaction medium, this analog was prepared in 44% yield, mp 138–139° (recrystallized from water), ir (Nujol) 1715, 1675 cm^{-1}.

Anal. Calcd for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.70. Found: C, 63.28; H, 7.25; N, 6.58.

4-Hydroxycyclohexa[*b*]-2-pyrone (17, *n* = 2).—The morpholine enamine of cyclohexanone (127.5 g, 0.76 mol) was dissolved in 1000 ml of dry ether. The solution was stirred and cooled to −70° (Dry Ice–acetone bath). The enamine may partially crystallize as a white solid. Carboethoxyacetyl chloride (115 g, 0.76 mol) was added dropwise over a 1-hr period while maintaining the temperature in a range of −50 to ~−70°. The mixture was warmed slowly to room temperature and stirred for 16 hr. Water (500 ml) was then added slowly; after stirring for a few minutes the ethereal layer was isolated, dried over anhydrous $MgSO_4$, filtered, and evaporated to afford 145 g of a viscous liquid. Attempts to induce crystallization or to effect purification by distillation were unsuccessful; so the crude liquid was used as such; a broad carbonyl band at 1750–1700 cm^{-1} and sharp band at 1030 cm^{-1} are present in the infrared spectrum (neat) of all the diketo esters.

The viscous liquid (145 g), presumed to be impure ethyl 2-keto-2-(2-ketocyclohexyl)propionate, was dissolved in dry dimethylformamide (500 ml). Sodium methoxide (37.8 g, 0.7 mol) was added all at once to the stirred solution. There was a slight exotherm and a small quantity of solid formed after a few minutes. The mixture was stirred and heated at 80–90° for 4 hr. After cooling, the reaction mixture was poured into 1200 ml of ice water. After extraction with methylene dichloride (three 300-ml portions) the aqueous phase was acidified (concentrated HCl). A white solid soon precipitated and was isolated and dried. The yield of **17** was 42 g (37%), mp 212–217°. Recrystallization from methanol afforded large, rectangular crystals: mp 225–228° (lit.[4] mp 222–223°); ir (Nujol) 3350, 1650, 1610 cm^{-1}; nmr (DMSO) τ 8.27 (m, 4 H, aliphatic), 7.57 (m, 4 H, allylic), −2.8 (1 H, hydroxyl), 4.67 (s, 1 H, olefinic).

3-(Dimethylaminomethylene)-4-ketocyclohexa[*b*]-2-pyrone (18, *n* = 2).—4-Hydroxycyclohexa[*b*]-2-pyrone (8.3 g, 0.05 mol) was suspended in 50 ml of anhydrous 1,4-dioxane. The dimethyl acetal of dimethylformamide (7.5 g, 0.063 mol) was added all at once and the suspension immediately turned yellow. The flask was swirled for a few minutes until a clear yellow solution formed and was placed in the refrigerator. After 3 hr the suspension which had formed was filtered and the solid was washed with 20–30 ml of dry dioxane. The dried solid weighed 9 g (80%) and melted with decomposition at 185–190°. An analytical sample was prepared by recrystallization from 2-propanol, mp 190–193°, as a light yellow solid: ir (Nujol) 1668, 1653 cm^{-1}; nmr ($CDCl_3$) τ 8.3 (m, 4 H, aliphatic), 7.63 (m, 4 H, allylic), 6.63 and 6.55 (s, 6 H, N-methyl), and 1.72 (s, 1 H, olefinic).

Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 65.36; H, 6.77; N, 6.34.

3-Carboxy-*N*-methylcyclohexa[*b*]-4-pyridone (19, *n* = 2).—Reaction of **18** (*n* = 2) with aqueous methylamine, using the same procedure as in the case of **1** (R = CH_3), afforded the product in 60% yield, mp 281–283° dec (recrystallized from methanol), ir (Nujol) 1700 and 1630 cm^{-1}.

Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.63; H, 6.21; N, 6.67.

3-(*p*-Chlorophenylcarbamyl)-*N*-methylcyclohexa[*b*]-4-pyridone (20, *n* = 2).—3-Carboxy-*N*-methylcyclohexa[*b*]-4-pyridone (5 g, 0.024 mol) was slurried in 50 ml of benzene while triethylamine (2.4 g, 0.024 mol) was added. Ethyl chloroformate (2.6 g, 0.024 mol) was slowly added to the cooled suspension. In 5 min, a

solution of *p*-chloroaniline (3.1 g, 0.024 mol) in 40 ml of benzene was added. After stirring for 90 min the suspension was filtered and the solid obtained was washed with water and dried to give 4.5 g (52%) of a white solid, mp 265–267°. An analytical sample was prepared by recrystallization from ethanol, mp 265–267°, ir (Nujol) 1685, 1630 cm^{-1}.

Anal. Calcd for $C_{17}H_{17}ClN_2O_2$: C, 64.45; H, 5.41; N, 8.84. Found: C, 64.31; H, 5.40; N, 8.70.

4-Hydroxycyclopenta[*b*]-2-pyrone (17, *n* = 1).—The diketo ester (19 g), prepared in 49% crude yield from the morpholine enamine of cyclopentanone and carboethoxyacetyl chloride, was dissolved in dry dimethylformamide (100 ml). Sodium methoxide (5.4 g, 0.1 mol) was added to the solution, which was then heated for 20 hr at 75–80°. Work-up gave 0.4 g (3%) of the product: mp 188° dec (lit.[4] mp 191–195° dec); ir (Nujol) 3350, 1650, 1610 cm^{-1}; nmr (DMSO) τ 7.93 (m, 2 H, aliphatic), 7.38 (m, 4 H, allylic), 4.77 (s, 1 H, olefinic), and −1.5 (s, 1 H, hydroxyl).

4-Hydroxycyclohepta[*b*]-2-pyrone (17, *n* = 3).—The morpholine enamine of cycloheptanone (36.2 g, 0.2 mol) was dissolved in 200 ml of ether. After the solution had been cooled to −70° (Dry Ice–acetone bath), carboethoxyacetyl chloride (31 g, 0.2 mol) dissolved in 50 ml of ether was added dropwise. When addition was complete (*ca.* 30 min) the temperature of the mixture, now at −50°, was raised to room temperature. Water (200 ml) was added and the suspension was stirred for 15 min. The ethereal layer was isolated, dried ($MgSO_4$), and evaporated to afford 39 g of a yellow oil.

A solution was prepared of 39 g of the oil in 250 ml of dry dimethylformamide. When sodium methoxide (10.8 g, 0.2 mol) was added, a solid formed immediately and the suspension was heated at 80° for 5 hr. When cooled the suspension was poured into ice water (1000 ml). A light yellow solid (7 g) precipitated and was isolated. The filtrate was extracted with methylene dichloride (300 ml) and then acidified (concentrated HCl). A flocculent precipitate that formed was isolated, washed with water, and dried to give 12 g of a light yellow solid. The infrared spectra of both solids were identical. The combined solids were recrystallized from dioxane to give a white solid: 18 g (59%); mp 183–185° (lit.[4] mp 181–183°); ir (Nujol) 3350, 1650, 1610 cm^{-1}; nmr (DMSO) τ 8.33 (m, 6 H, aliphatic), 7.4 (m, 4 H, allylic), 4.67 (s, 1 H, olefinic), and −3.37 (s, 1 H, hydroxyl).

3-(Dimethylaminomethylene)-4-ketocyclohepta[*b*]-2-pyrone (18, *n* = 3).—Pyrone **17** (*n* = 3, 10.6 g, 0.04 mol) was suspended in 70 ml of anhydrous 1,4-dioxane. Following addition of the dimethyl acetal of dimethylformamide (8.8 g, 0.074 mol), the suspension was swirled until solution was complete. For 3 days the solution was let stand at room temperature. Isolation of the crystalline material and recrystallization from 2-propanol gave 4.2 g (30%) of a white solid, mp 164–166°, ir (Nujol) 1700, 1645 cm^{-1}.

Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.21; N, 5.95. Found: C, 66.23; H, 7.20; N, 5.90.

3-Carboxy-*N*-methylcyclohepta[*b*]-4-pyridone (19, *n* = 3).—Following the same procedure for the synthesis of **19** (*n* = 2), the desired product was prepared in 95% yield, mp 225–230°, as white needles after one recrystallization from methanol, ir (Nujol) 1710, 1645 cm^{-1}.

Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.33; N, 6.8. Found: C, 64.88; H, 6.32; N, 6.77.

3-(*p*-Chlorophenylcarbamoyl)-*N*-methylcyclohepta[*b*]-4-pyridone (20, *n* = 3).—Following the identical procedure for synthesis of **20** (*n* = 2), 3.5 g (0.016 mol) of 3-carboxy-*N*-methyl-1*H*-cyclohepta[*b*] 4-pyridone afforded 2.1 g (40%) of the amide **20**, mp 255–258°, as a white solid. The melting point was unchanged after one recrystallization from ethanol; ir (Nujol) 1690, 1630 cm^{-1}.

Anal. Calcd for $C_{18}H_{19}ClN_2O_2$: C, 65.35; H, 5.80; N, 8.47. Found: C, 64.95; H, 5.73; N, 8.13.

Registry No.—**1** (R = H), 33821-58-8; **1** (R = CH_3), 33821-59-9; **1** (R = *n*-C_4H_9), 33821-60-2; **7**, 33821-61-3; **8**, 33821-62-4; **18** (*n* = 2), 33821-63-5; **18** (*n* = 3), 33821-64-6; **19** (*n* = 2), 33821-65-7; **19** (*n* = 3), 33821-66-8; **20** (*n* = 2), 33821-67-9; **20** (*n* = 3), 33821-68-0.

Acknowledgment.—The authors wish to thank Mrs. Florence Burnley for recording the nmr spectra and Mr. W. David Weir for the synthesis of several intermediates.

The Photochemistry of Substituted 1,5-Hexadien-3-ones

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Received October 8, 1971

The effects of methyl group substitution on the photochemistry of the 1,5-hexadien-3-one system has been examined, with particular emphasis on the intramolecular cycloaddition reaction to form the bicyclo[2.1.1]hexan-2-one system. Monosubstituted compounds **12**, **13**, **15**, **17**, and **18** and disubstituted compounds **14**, **16**, and **19** were studied. These structural changes were found to have profound effects on the photochemical reactions shown by these compounds, but few general trends of reactivity with substitution could be discerned. It appears that each system is unique in its behavior. The results obtained are rationalized on the basis of present knowledge of the mechanisms of photochemical reactions.

In a previous publication we described an approach to the bergamotene sesquiterpenes starting from readily available bicyclo[3.1.1]heptane precursors.[1] Because of the nature of the method used, this synthesis was limited to the formation of representatives of the cis series, *e.g.*, *cis*-β-bergamotene (**1**). The stereospecific nature of the synthesis was useful for the establishment of the absolute stereochemistry of the cis bergamotenes,[1] but could not be used for the synthesis of members of the trans series, *e.g.*, *trans*-α-bergamotene (**2**).[1,2] A method which appeared to have promise for the simultaneous synthesis of both cis and trans material was suggested by the report that direct irradiation of myrcene (**3**) afforded β-pinene (**4**) in low yield.[3] The major product formed in this reaction is the cyclobutene **5**.

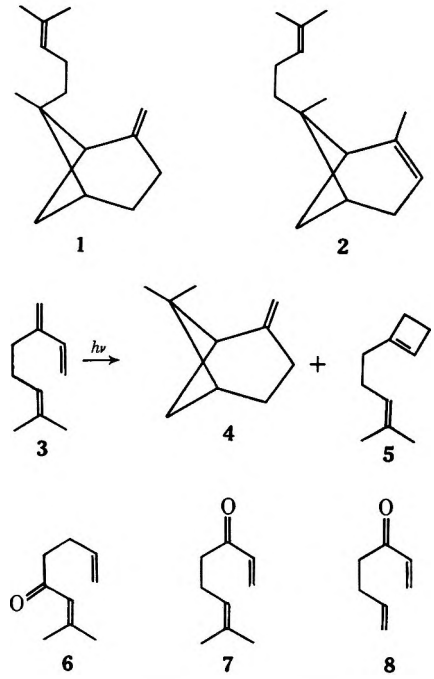
In order to avoid the formation of products such as **5**, we decided to replace the diene chromophore of **3** with the enone system. However, we found the irradiation of the three model compounds **6**, **7**, and **8** to be unsuccessful as a method for the formation of the bicyclo[3.1.1]heptan-2-one system. No evidence could be found for the formation of cyclic products of any type, a result which is substantiated by an independent study of the photochemistry of **7**.[4]

(1) T. W. Gibson and W. F. Erman, *J. Amer. Chem. Soc.*, **91**, 4771 (1969).

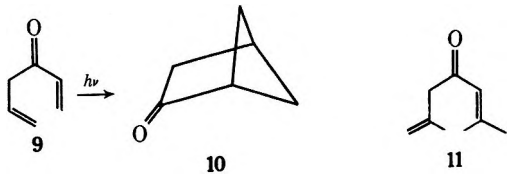
(2) V. Herout, V. Ruzicka, M. Vrany, and F. Sorm, *Collect. Czech. Chem. Commun.*, **15**, 373 (1950).

(3) K. J. Crowley, *Proc. Chem. Soc.*, 245 (1962).

(4) R. A. Schneider, Ph.D. Thesis, Cornell University, 1966, p 133.



An alternate process was suggested by the observation that 1,5-hexadien-3-one (**9**) undergoes relatively efficient photocycloaddition to produce bicyclo[2.1.1]-hexan-2-one (**10**).[5] If this reaction could be accomplished with suitably substituted derivatives of **9**, then a simple ring expansion reaction would provide access to the bicyclo[3.1.1]heptanone system. At the time this work was being contemplated, the photocycloaddition of **9** was the only known example of this reaction, and thus little information was available concerning the effects of structural variation on the course or efficiency of the process. We, and others, had observed the complete absence of cycloaddition products upon irradiation of the dienone **11**.[6,7] We decided,

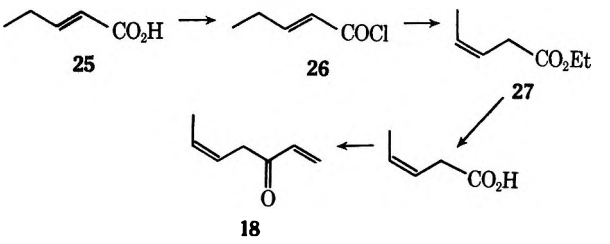


therefore, to begin with a thorough study of the effect of substitution on the cycloaddition process.[8]

Results

Synthesis of Dienones.—Compounds **12–17** were synthesized by the method described for the formation of 1,5-hexadien-3-one,[5] which involves addition of an allylic Grignard reagent to the appropriate aldehyde, followed by Jones oxidation[9] of the resultant alcohol to the dienone. That dienone **12** was uncontaminated with its cis isomer was shown by spectroscopic data.

Compounds **18** and **19** were synthesized by an alternate procedure, since the appropriate Grignard reactions resulted in the exclusive formation of the allylic alcohols leading to **13** and **14**, respectively. The process is exemplified by the following synthesis of **18**. The acid **25**, prepared by the condensation of malonic acid with propanal,[10] was converted to the acid chloride **26** with thionyl chloride. Deconjugation of **26** and conversion to the ester **27** was accomplished in high yield by the use of triethylamine in ethanolic acetone.[11] Hydrolysis of **27** followed by reaction of the resultant acid with vinyllithium resulted in the formation of the cis dienone **18** in good yield. The same process was

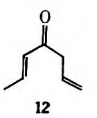
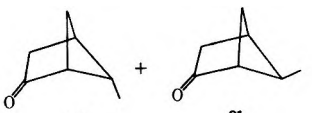
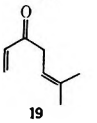
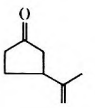


used for the synthesis of **19** starting from isobutyraldehyde.

Irradiation of Dienones.—The results of the irradiation experiments are shown in Table I.[12] Dilute solu-

TABLE I

IRRADIATION OF DIENONES IN PENTANE

Dienone	Product	Yield, %
 12	 20 + 21	3 (2:3)
 13	 22	41
 14	Polymer	
 15	 23	57
 16	No reaction	
 17	Polymer	
 18	20 + 21	56 (2.3:1)
 19	 24	10

(5) F. T. Bond, H. L. Jones, and L. Scerbo, *Tetrahedron Lett.*, 4685 (1965).

(6) P. J. Kropp and T. W. Gibson, *J. Chem. Soc. C*, 143 (1967).

(7) K. J. Crowley, R. A. Schneider, and J. Meinwald, *ibid.*, 571 (1966).

(8) Part of this work has been presented at the 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970.

(9) R. G. Curtis, I. Heilbron, E. R. H. Jones, and G. F. Woods, *J. Chem. Soc.*, 457 (1953).

(10) A. A. Goldberg and R. P. Linstead, *ibid.*, 2343 (1928).

(11) T. Ozeki and M. Kusaka, *Bull. Chem. Soc. Jap.*, **39**, 1995 (1966).

(12) Results essentially identical to those reported in Table I have also been obtained in the laboratory of Professor F. T. Bond, who also studied the trans isomer of **18**. We thank Professor Bond for the communication of his results to us.

tions of the dienones in pentane were irradiated with a 450-W medium-pressure mercury lamp through Vycor or Pyrex glassware until all or most of the starting material had disappeared, as determined by gas–liquid phase chromatography (glpc). Isolation of the highly volatile products was accomplished by removal of solvent by distillation through a spinning band column, followed by distillation of the residual liquids in a microstill. Pure compounds were isolated by preparative glpc and identified by spectroscopic methods. Detailed accounts are included in the Experimental Section.

Bond reported that photocycloaddition of 1,5-hexadien-3-one occurred in 30–60% yield,[5] a result which we have confirmed. However, irradiation of **12**, which possesses a methyl group at the terminal position of the conjugated double bond, leads to very little observable cycloaddition. In fact, no evidence was found for the production of **20** or **21** unless the irradiation was carried out in the presence of excess acetophenone, which presumably serves as a photosensitizer.[13] Under all conditions studied, the initial observed reaction is isomerization of **12** to its cis isomer. In contrast, irradiation of **18**, which possesses a methyl group at the terminus of the nonconjugated double bond, results in the formation of the ketones **20** and **21** in good yield, although in a different ratio.

Irradiation of **15**, which possesses a methyl group at the α position of the conjugated double bond, resulted in cycloaddition to **23** in good yield. Similarly, irradiation of **13**, with a single methyl group at the saturated position, resulted in cycloaddition to **2**. However, with **14**, which possesses two methyl groups at this position, irradiation led only to rapid polymer formation. In one experiment, irradiation of **14** resulted in the isolation of a small amount of a mixture of volatile compounds. The infrared spectrum of the mixture indicated the presence of the bicyclic ketone, but none could be isolated in a pure state. The dienone **16**, which was obtained only in an impure state in low yield, did not appear to undergo any photochemical reaction.

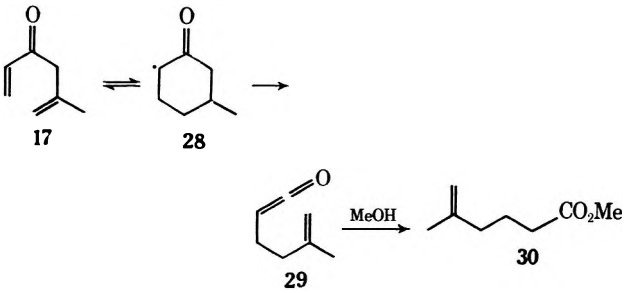
The dienone **17**, with a methyl group at the internal position of the nonconjugated double bond, also proved remarkably stable to light. On extended irradiation, the dienone slowly disappeared with no volatile products being observed.

In view of the photochemical behavior of **18**, the dienone **19** would appear to be ideal for the synthesis of 5,5-dimethylbicyclo[2.1.1]hexan-2-one. However, irradiation of **19** in pentane solution resulted in a mixture of volatile products, from which only 3-isopropenylcyclopentanone (**24**), could be isolated. Again, the infrared spectrum of the crude product indicated the presence of a trace of bicyclohexanone, but none could be isolated *via* glpc.

Discussion

Attempts to rationalize the behavior of the various dienones studied on the basis of results observed in other dienone[14] and triene[15] systems have been largely unsuccessful. In contrast to the photochemically simpler trienes studied by Liu and Hammond,[15b] the dienones examined in this work can react by a variety of processes. In addition to cycloaddition, major pathways should involve types I and II cleavage and hydrogen abstraction. In pentane solution these processes would lead to highly volatile and polymeric products, none of which were characterized. Substitution at the various positions in the system would influence the competition among these processes in different ways, through either ground state or excited state energetics. For example, the decrease in cycloaddition product observed on proceeding from **1** to **13** to **14** is probably due to increased incidence of type I cleavage brought about by increased stability of the allylic radical formed in this process.

In the dienone **17**, the presence of the methyl group at the 5 position may stabilize the six-membered ring diradical intermediate **28** at the expense of the normally preferred five-membered ring.[15] The diradical **28** can fragment either to the starting material or to the ketene **29**. In order to determine whether the ketene was being formed in the reaction, irradiation of **17** was carried out in the presence of methanol, resulting in the formation of ester **30** in 10% yield.



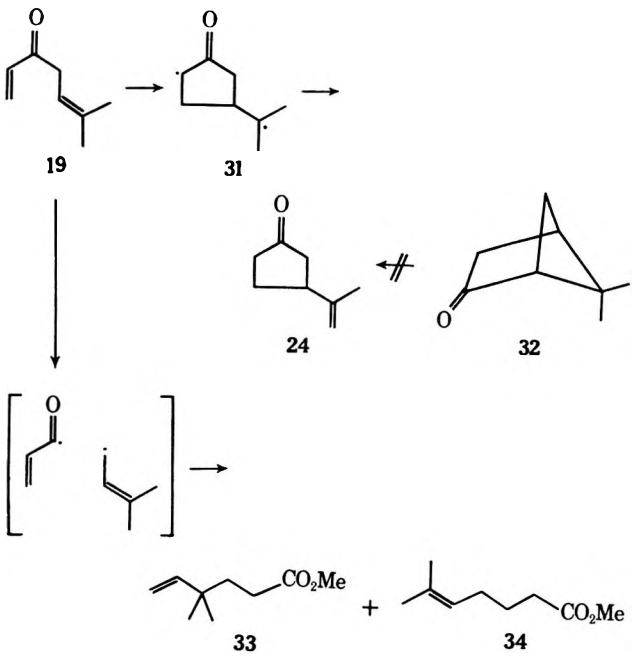
This result prompted us to examine the irradiation of several of the other dienones in methanol solvent. Both **13** and **15**, when irradiated in methanol, afforded only the bicyclic products **22** and **23**, respectively, in about the same yields (and at qualitatively the same rates) as were observed in pentane. Prolonged irradiation led to reaction of the bicyclic ketones to give as yet uncharacterized products.

Irradiation of **19** in methanol led, as before, to formation of **24** in about 14% yield, and also to the esters **33** and **34** in 4 and 13% yields, respectively. Initial cyclization to diradical **31** followed by hydrogen transfer provides a rationalization for the formation of **24**. However, in contrast to **28**, fragmentation of **31** can only result in return to starting material and does not explain ketene formation. The ketenes must, therefore, be formed by initial fragmentation of **19** to give acyl and allyl radicals, which can recombine in two ways to give ketenes. The minor ester **33** results from recombination at the alternate position of the allyl radical. This type of process is probably also responsible for the formation of **30** from **17**.

(13) In contrast to this result, Professor W. R. Roth has obtained a 25% yield of **20** and **21** (ratio 2:3) in the direct irradiation of **12** (private communication).

(14) (a) E. Y. Y. Lam, D. Valentine, and G. S. Hammond, *J. Amer. Chem. Soc.*, **89**, 3482 (1967); (b) P. DeMayo, J. P. Pete, and M. Tchir, *Can. J. Chem.*, **46**, 2535 (1968); (c) E. J. Corey, J. D. Bass, R. LeMahieu, and R. B. Mitra, *J. Amer. Chem. Soc.*, **86**, 5570 (1964); (d) P. D. Bartlett, *Science*, **159**, 833 (1968).

(15) (a) R. Srinivasan and K. L. Carlaugh, *J. Amer. Chem. Soc.*, **89**, 4932 (1967); (b) R. Liu and G. Hammond, *ibid.*, **89**, 4936 (1967).



The lack of ring formation from diradical **31** contrasts strongly with the behavior of its counterpart generated from **18**. This is apparently a result of increased steric hindrance and also to an increased probability of the existence of a favorable conformation for hydrogen transfer. An alternate explanation, that bicyclic product **32** affords **24** *via* a type II photoreaction, does not appear plausible in view of the absence of this type of product in the irradiation of **18**.

It is evident from this study that many complex factors are involved in deciding the course of reaction to be taken by any one of these dienones. However, the investigation has shown that the photocycloaddition reaction is useful synthetically for the formation 1-, 3-, and 5-monosubstituted bicyclo[2.1.1]hexan-2-ones. The method is not applicable, unfortunately, to the 5,5-disubstituted system required for a synthesis of the bergamotenes, or to the 3,3-disubstituted or 4-monosubstituted compounds.[16]

Experimental Section[17]

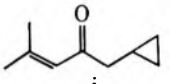
2-Methyl-2,7-octadien-4-one (6).—To 36 g of magnesium metal in 250 ml of ether in a flame-dried flask was added 60.0 g (0.60 mol) of 4-chloro-1-butene in 50 ml of ether. After reaction had started and all the chlorobutene had been added, the mixture was refluxed for 1 hr and stirred overnight under argon. The solution was filtered into a 2-l. Morton flask, and 800 ml of ether and 61 g (0.33 mol) of $CdCl_2$ were added. During the ensuing exothermic reaction, the mixture turned purple and became viscous. After refluxing for 0.5 hr, 72 g (0.61 mol) of 3-methyl-2-butenoyl chloride (prepared in 86% yield from 3-methyl-2-butenoic acid and thionyl chloride) was added, and the mixture was refluxed overnight. After cooling, 170 ml of saturated NH_4Cl solution was added and the aqueous phase was extracted twice with ether. The combined ether extracts were washed four times with saturated $NaHCO_3$, twice with water, and twice with saturated brine, and dried over $MgSO_4$. Distillation gave 43.6 g (52%) of **6**, bp 70–71° (10 mm). Glpc analysis showed the product to be composed of about 82% of one compound and 12 and 6% of two minor products. Purification of the major constituent by glpc gave material with λ_{max} 5.90 and 6.15 μ, λ_{max}^{EtOH} 237.5 mμ (ϵ 11,900), mol wt 154 (mass spectrum), and nmr signals at τ 8.14 (3 H, d, J = 1 Hz), 7.87 (3 H, d, J = 1 Hz), 7.54 (4 H, m), 5.13 (1 H, m), 4.88 (1 H, broad d, J = 5 Hz), 4.2 (1 H, m), and 3.91 (1 H, m).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 77.92; H, 10.05.

The 2,4-dinitrophenylhydrazone derivative had mp 57–57.5°, λ_{max}^{EtOH} 364 mμ (22,000).

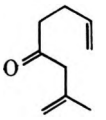
Anal. Calcd for $C_{15}H_{18}N_4O_4$: C, 56.59; H, 5.70; N, 17.60. Found: C, 56.67; H, 5.68; N, 17.62.

The more abundant minor constituent (12%) showed λ_{max} 3.20, 5.90, and 6.14 μ, λ_{max}^{EtOH} 238 mμ (ϵ 11,700), and nmr signals at τ 9.84 (2 H, m), 9.40 (2 H, m), *ca.* 9.0 (1 H, broad), 8.15 (3 H, d, J = 1 Hz), 7.85 (3 H, d, J = 1 Hz), 7.72 (2 H, d, J = 6.4 Hz), and 3.88 (1 H, m). These data suggest structure i for this compound, but this has not been proven unambiguously.



i

Irradiation of 6.—Irradiation of **6** was carried out with a variety of combinations of solvents and light sources. Only with the use of methanol as solvent were any volatile products obtained in more than trace amounts. A solution of 0.70 g of **6** in 400 ml of methanol was irradiated under argon with a 550-W mercury lamp for 12 hr. Distillation gave 0.36 g of colorless oil, bp (bath) 60–80° (25 mm). Glpc analysis on a 5-ft SF-96 column showed two main peaks in a ratio of 1:3.8. Attempted collection by preparative glpc showed the first peak to be unstable, while the major product (*ca.* 40% yield) was obtained in a state of purity sufficient for identification as ii. This ketone, the product of a simple deconjugation of **6**, showed a molecular weight of 138 (mass spectrum), λ_{max} 3.25, 5.80, 6.06, 10.0, 10.95, and 11.2 μ, and nmr signals at τ 8.28 (3 H, s), 7.72 (2 H, m), 7.51 (2 H, d, J = 6 Hz), 6.94 (2 H, s), 5.24 (1 H, s), 5.15 (2 H, s), 5.00 (1 H, d, J = 8 Hz), and 4.28 (1 H, m). Repeated attempts to obtain this compound after the photochemical reaction vessel had been washed with base were unsuccessful, suggesting that the formation of ii was catalyzed by traces of acid.



ii

7-Methyl-1,6-octadien-3-one (7).—This compound was prepared by the same method used by Schneider,[4] except that the vinyllithium was prepared from tetravinyltin and phenyllithium. Our material, purified by glpc, showed essentially the same data as those reported, except for the absence of the band at 11.22 μ in the infrared. This band was probably due to an impurity, since glpc was apparently not used in the purification of **7** by Schneider. In addition, the nmr signals for methyl groups appeared at τ 8.37 (3 H, s) and 8.32 (3 H, d, J = 1 Hz).

Irradiation of 7.—Irradiation of **7** in various solvents with medium pressure mercury lamps led to the formation of only trace amounts of volatile materials, none of which were isolated.

1,6-Heptadien-3-one (8).—To 35.6 g of magnesium shavings under 1 l. of ether was added 50.0 g of 4-bromo-1-butene at a rate sufficient to maintain reflux. A solution of 21.0 g of acrolein in ether was then added at a rate sufficient to maintain reflux, and the mixture was stirred overnight. Hydrolysis was carried out with saturated Na_2SO_4 solution, and the solution was filtered and dried over Na_2SO_4. Distillation gave 21.4 g (52%) of the desired alcohol, bp 58° (23 mm). A solution of 17.8 g of the alcohol in 250 ml of a 1:1 acetone–benzene mixture was oxidized with 46.0 ml of Jones reagent[9] at ice-bath temperature. The resulting mixture was poured into ether, extracted once with water and twice with saturated $NaHCO_3$ solution, and dried over Na_2SO_4. Removal of drying agent and distillation of sol-

(16) A study of some ring expansion reactions of **10**, **20**, **21**, **22**, and **23** will be described soon.

(17) Melting points were determined on a micro hot stage and are corrected; boiling points are uncorrected. Infrared spectra were recorded on Perkin-Elmer 257 or 137 spectrophotometers as neat films or 5% solutions in CCl_4. Nuclear magnetic resonance spectra were obtained on a Varian Associates HA-100 spectrometer using TMS as an internal reference in $CDCl_3$. Nmr data are recorded in this order: chemical shift (integration, multiplicity where s = singlet, d = doublet, t = triplet q = quartet, m = multiplet, and coupling constant in hertz). Mass spectra were determined with an Atlas CH-4 spectrometer, or, where noted, high-resolution spectra were obtained with an Atlas SM-1 spectrometer. Microanalyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich.

vent on a spinning band column left a gelatinous mass, which was distilled *in vacuo* directly into a Dry Ice cooled trap. Redistillation of the trapped material gave 7.65 g (44%) of ketone **8**, bp 35–40° (20 mm), shown to be about 98% pure by glpc. Material collected by preparative glpc showed λ_{max} 3.26, 5.95, 6.08, 6.20, 10.05, 10.35, and 10.95 μ, mol wt 110 (mass spectrum), and nmr signals at τ 7.62 (2 H, m), 7.34 (2 H, m), 5.00 (2 H, m), 4.17 (2 H, m), and 3.77 (2 H, m).

Anal. Calcd for $C_7H_{10}O$: C, 76.32; H, 9.15. Found: C, 75.86; H, 9.06.

Catalytic reduction over PtO_2 gave only 3-heptanone, identified by ir and glpc comparison with an authentic sample.

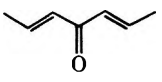
Irradiation of 8.—Irradiation of dilute solutions of **8** in pentane and methanol through Vycor glassware with a 450-W mercury lamp resulted in gradual disappearance of starting material and formation of insoluble polymeric material. Many products were formed in trace amounts in methanol solvent, but no attempt was made to identify these.

Bicyclo[2.1.1]hexan-2-one (10).—The alcohol corresponding to **9** was synthesized in 61% yield using the Grignard reaction between 3-bromo-1-propene and acrolein.[5] Oxidation of 40.0 g of the alcohol with 25% excess Jones reagent[9] in 1:1 benzene–acetone solvent gave good conversion to the ketone **9**, which was irradiated directly in benzene with a 550-W mercury lamp for 9 hr through a Pyrex filter. Distillation gave 7.5 g of 95% pure bicyclohexanone (**10**), bp 55–57° (26 mm). Further purification could be achieved through formation of the crystalline bisulfite adduct followed by regeneration of **10** with base. The low yield (17% from **9**) is probably mainly due to the extreme volatility of both ketones. Spectroscopic data for **10** agreed well with those reported by Bond[5] and those expected for this structure.

1,5-Heptadien-4-one (12).—To 80 g of magnesium shavings in 1 l. of ether was added 100 g of 3-bromo-1-propene at a rate sufficient to maintain reflux. A solution of 50 g of crotonaldehyde in ether was added to the Grignard reagent at a rate as rapid as condensation of refluxing solvent would allow, and the mixture was allowed to stand overnight at room temperature. Hydrolysis was effected with 60 ml of saturated Na_2SO_4 solution, and the resulting mixture was filtered and dried over Na_2SO_4. Distillation gave 72.6 g (91%) of the alcohol, bp 58° (23 mm), $n^{25}D$ 1.4505 [lit.[18] bp 62° (15 mm), $n^{20}D$ 1.4533]. The alcohol, which appeared to be greater than 99% pure by glpc, showed λ_{max} 3.1, 6.12, 10.05, 10.38, and 10.98 μ, indicative of the terminal and trans double bonds as expected for this compound.

A solution of 3.0 g (26.8 mmol) of the alcohol in 100 ml of purified acetone was oxidized with 7.35 ml (80.4 mmol) of Jones reagent.[9] Normal work-up followed by distillation gave 1.32 g (45%) of **12**, bp 42–44° (16 mm). Glpc analysis revealed the presence of one major peak and two minor peaks in the range of 5–10%. Collection of the major constituent *via* preparative glpc gave material with ir λ_{max} 3.25, 5.90, 5.97, 6.12, 10.07, 10.27, and 10.9 μ, uv λ_{max}^{EtOH} 227 mμ (ϵ 10,400) and 320 (56), and nmr signals at τ 8.09 (3 H, dd, J = 6.6 and 1.4 Hz), 6.71 (2 H, dt, J = 6.6 and ~1 Hz), 4.82 (1 H, dd, J = 17 and 1 Hz), 4.80 (1 H, dd, J = 10 and 1 Hz), 4.0 (1 H, m), 3.85 (1 H, dd, J = 16 and 1.4 Hz), and 3.08 (1 H, dq, J = 16 and 6.6 Hz). The major coupling constant, 16 Hz, of the protons of the conjugated double bond and the 10.27-μ infrared band[19] indicate that the conjugated double bond is in the trans configuration. In addition, the intensity of the uv maximum and the relative intensities of the carbonyl bands suggest a preference for the s-trans conformation.[20]

The use of excess oxidant resulted in partial isomerization to the doubly conjugated compound iii, which could be prevented by the use of a benzene–acetone solvent mixture.



iii

Catalytic reduction of **12** over PtO_2 in ethyl acetate gave two saturated ketones in a ratio of 82:18. The major ketone was identified as 4-heptanone by ir and glpc comparison with an authentic sample, while the minor ketone was identified as 2-heptanone by the same method. This apparently is formed by reduction of the ketones resulting from allylic rearrangement of the alcohol during Jones oxidation.

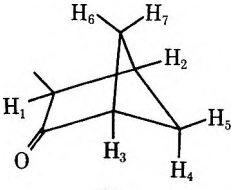
Irradiation of 1,5-heptadien-4-one (12).—A solution of 0.347 g of **12** and 1.9 g of acetophenone in 170 ml of pentane was irradiated under argon for 95 min with a 200-W mercury lamp through Vycor glassware. Distillation gave a liquid consisting mostly of acetophenone and three products in the ratio of 10:35:55. The two major product peaks were isolated *via* glpc and identified by spectroscopic comparison with the products **20** and **21** obtained from the irradiation of **18**. In the present instance, these two compounds were isolated in yields of 1.4 and 2.2%, respectively. Neither product was observed to form during irradiations carried out in the absence of acetophenone. Short-term irradiation allowed the isolation of the cis isomer of **12**, which, purified by glpc, showed ir λ_{max} 5.90, 6.17, 10.1, and 10.9 μ, uv λ_{max}^{EtOH} 227 mμ (ϵ 8600), and nmr signals at τ 7.89 (3 H, d, J = 4.8 Hz), 6.79 (2 H, d, J = 7.0 Hz), 4.82 (1 H, dd, J = 18 and 1.5 Hz), 4.79 (1 H, dd, J = 9.5 and 1.5 Hz), 4.0 (1 H, m), and 3.8 (2 H, m).

4-Methyl-1,5-hexadien-3-one (13).—The alcohol corresponding to **13** was synthesized by the reaction of the Grignard reagent from crotyl bromide with acrolein. Distillation gave a 46% yield of about 90% pure alcohol, bp 53° (18 mm), $n^{25}D$ 1.4483 [lit.[21] bp 55–56° (14 mm), $n^{22}D$ 1.4490].

A solution of 11.5 g of alcohol in 100 ml of 50:50 acetone–benzene was titrated with 30% excess Jones reagent.[9] The resultant solution was diluted with ether, washed with saturated $NaHCO_3$ solution, and dried over Na_2SO_4. Distillation gave 5.36 g (47%) of **13**, bp 54–58° (25 mm), λ_{max} 5.90, 6.09, 6.18, 10.12, 10.35, and 10.85 μ, and nmr signals at τ 8.80 (3 H, d, J = 7 Hz), 6.57 (1 H, quintet, J = 7 Hz), 4.90 (1 H, dd, J = 10 and 1 Hz), 4.88 (1 H, dd, J = 17 and 1 Hz), and 3.4–4.4 (4 H, complex).

Hydrogenation of **13** over PtO_2 gave only 4-methyl-3-hexanone, identified by ir and glpc comparison with an authentic sample.

Irradiation of 13.—A solution of 0.426 g of **13** in 450 ml of pentane was irradiated under argon with a 450-W mercury lamp through Vycor for 45 min, at which time no starting material was detectable by glpc analysis. After filtration to remove the precipitated polymer, the solvent was distilled through a spinning band column, and the residue was distilled in a Hickman flask to give 0.184 g (41%) of **22**, bp 100° (bath) (55 mm), which proved to be 94% pure by glpc analysis. Material purified by preparative glpc showed λ_{max} 5.67 μ, λ_{max}^{EtOH} 278 mμ (ϵ 21), mol wt 110 (mass spectrum), and nmr signals at τ 8.86 (3 H, d, J = 7.0 Hz), 8.43 (H_6, q, J = 9.5 and 7 Hz), 8.23 (H_4, q, J = 9.5 and 7 Hz), 7.8 (H_5, H_7, m), 7.7 (H_1), 7.44 (H_2, m), 7.21 (H_3, d of t, J = 7 and 2.5 Hz). An analysis of this spectrum using spin–spin decoupling allows the following assignment of coupling constants.



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$J_{2,3}$ = 7 Hz, $J_{2,7} = J_{2,5} = J_{3,7} = J_{3,5}$ = 2.5 Hz,
$J_{4,6}$ = 9.5 Hz, $J_{6,7} = J_{4,5}$ = 7 Hz

$J_{1,2}$ could not be determined accurately, but appears to be on the order of 2 Hz.

Anal. Calcd for $C_7H_{10}O$: C, 76.32; H, 9.15. Found: C, 75.65; H, 9.14.

The 2,4-DNP derivative showed mp 165°.

Anal. Calcd for $C_{13}H_{14}N_4O_4$: C, 53.79; H, 4.86; N, 19.30. Found: C, 54.13; H, 4.98; N, 18.91.

4,4-Dimethyl-1,5-hexadien-3-one (14).—The alcohol corresponding to **14** was prepared by the Grignard reaction of 3,3-dimethylallyl bromide with acrolein. The product, bp 61–63° (25 mm), obtained in about 50% yield, was contaminated with the C_{10} hydrocarbon resulting from dimerization of the Grignard reagent. Material purified by glpc showed λ_{max} 2.95, 3.27, 6.16, 10.1, and 10.9 μ, mol wt 126 (mass spectrum), and nmr signals at

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(19) L. J. Bellamy, "The Infra-Red Spectra of Complex Molecules," Methuen, London, 1964, p 45.

(20) R. L. Erskine and E. S. Waight, *J. Chem. Soc.*, 3425 (1960).

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τ 9.01 (6 H, s), 8.34 (1 H, s), 6.26 (1 H, d, J = 6 Hz), 5.92 (4 H, m), and 5.20 (2 H, m).

A solution of 2.88 g of the alcohol in 200 ml of a 50:50 mixture of benzene and acetone was titrated with 5.4 ml of Jones reagent.[9] Normal work-up gave 1.15 g of ketone **14**, bp 62–66° (45 mm), contaminated with some starting material and the C_{10} hydrocarbon. Material collected by glpc showed λ_{max} 3.3, 5.90, 6.14, 6.22, 10.1, and 10.9 μ, and nmr signals at τ 8.75 (6 H, s), 4.88 (1 H, dd, J = 18 and 1.0 Hz), 4.86 (1 H, dd, J = 10 and 1.0 Hz), 4.42 (1 H, dd, J = 10 and 2.5 Hz), 4.10 (1 H, dd, J = 18 and 10 Hz), 3.72 (1 H, dd, J = 17 and 2.5 Hz), and 3.28 (1 H, dd, J = 17 and 10 Hz).

Irradiation of 14.—Irradiation of 0.386 g of a mixture comprised of **14** and the diene impurity in a ratio of 53:47 was carried out in pentane with a 200-W mercury lamp using a Pyrex filter. After 90 min the product was distilled to give 77.3 mg of oil, bp 50–70° (30 mm). Collection of the only new peak observed on chromatography on an SE-30 column gave 7.0 mg of material whose infrared spectrum showed a band at 5.67 μ. Rechromatography on an FFAP column revealed this to be a mixture of three compounds. The bicyclic ketone cannot be present in more than about 1% yield.

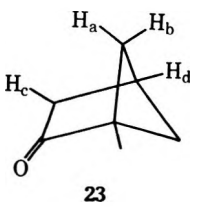
2-Methyl-1,5-hexadien-3-one (15).—Treatment of the Grignard reagent derived from 60 g of allyl bromide and 60 g of Mg in ether with 35 g of methacrolein gave, after normal work-up, 40.3 g (72%) of 2-methyl-1,5-hexadien-3-ol, bp 64–65° (25 mm). Material purified by glpc showed mol wt 112 (mass spectrum), λ_{max} 2.95, 6.07, 10.05, 10.95, and 11.1 μ, and nmr signals at τ 8.39 (3 H, s), 8.02 (1 H, s), 7.70 (2 H, t, J = 6.5 Hz), 5.94 (1 H, t, J = 6.0 Hz), 5.18 (1 H, broad s), 5.07 (1 H, broad s), 4.92 (2 H, m), and 4.14 (1 H, m).

A solution of 5.2 g of the alcohol in 150 ml of acetone was titrated with 17.4 ml of Jones reagent.[9] Normal work-up followed by careful distillation gave 1.87 g (38%) of yellow oil, bp 53–54° (25 mm). Glpc analysis of this material showed it to consist of >95% of a single compound. Material isolated by preparative glpc showed λ_{max}^{EtOH} 217 mμ (ϵ 7200), 320 (52), λ_{max} 3.25, 5.97, 6.14, 10.1, and 10.9 μ, mol wt 110 (mass spectrum), and nmr signals at τ 8.15 (3 H, s), 6.56 (2 H, d, J = 7 Hz), 4.88 (1 H, dd, J = 11 and 1 Hz), 4.90 (1 H, dd, J = 18 and 1 Hz), 4.24 (1 H, s), 4.06 (1 H, s), and *ca* 4.1 (1 H, m).

Hydrogenation over PtO_2 in ethyl acetate gave 2-methyl-3-hexanone, identified by comparison of the infrared spectrum and glpc retention time with those of an authentic sample.

Irradiation of 15.—A solution of 0.614 g of **15** in 150 ml of pentane was irradiated through a Pyrex filter with a 200-W mercury lamp. After 135 min, glpc analysis revealed the presence of only a trace of starting material and one major product peak. Distillation gave 0.347 g (57% of 1-methylbicyclo[2.1.1]hexan-2-one (**23**) in about 95% purity, bp 69–70° (47 mm). Material collected by glpc showed mol wt 110 (mass spectrum), λ_{max}^{EtOH} 277.5 mμ (ϵ 43), ir λ_{max} 5.67 μ, and nmr signals at τ 8.85 (3 H, s), 8.39 (2 H, dd, J = 4.5 and 2 Hz), 8.00 (2 H, m), 7.86 (2 H, m), and 7.32 (1 H, m).

Decoupling experiments showed that both protons H_b and H_c are coupled to proton H_a and to proton H_d, although the coupling constants could not be determined.



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Anal. Calcd for $C_7H_{10}O$: C, 76.32; H, 9.15. Found: C, 76.13; H, 9.22.

The 2,4-DNP derivative had mp 181–182°.

Anal. Calcd for $C_{13}H_{14}N_4O_4$: C, 53.79; H, 4.86; N, 19.30. Found: C, 54.21; H, 4.86; N, 19.03.

6-Methyl-1,5-heptadien-4-one (16).—A Grignard reaction between allyl bromide and 3-methyl-2-butenal (prepared by MnO_2 oxidation of the corresponding alcohol) gave the alcohol 6-methyl-1,5-heptadien-4-ol in 43% yield. Material purified by glpc showed λ_{max} 3.0, 6.10, 10.1, 10.9, and 11.9 μ, and nmr signals at τ 8.32 (3 H, d, J = 1.5 Hz), 8.30 (3 H, d, J = 1.5 Hz), 7.76 (2 H, t, J = 6.5 Hz), 5.65 (1 H, m), 4.96 (2 H, m), 4.83 (1 H, m), and 4.25 (1 H, m). The OH proton signal was apparently obscured by the methyl proton signals at τ 8.3.

Oxidation of 1.37 g of the alcohol with 2.7 ml of Jones reagent[9] afforded a mixture of two compounds in low yield, bp *ca.* 65° (10 mm). The major constituent, isolated by glpc, showed data consistent with dienone **16**, with mol wt 124 (mass spectrum), λ_{max} 5.92, 6.18, 10.05, and 10.9 μ, and nmr signals at τ 8.11 (3 H, s), 7.87 (3 H, s), 6.87 (2 H, d, J = 7.0 Hz), 4.91 (2 H, AB part of normal ABC system), 4.15 (1 H, m), and 3.95 (1 H, s).

Irradiation of the crude distilled product from this reaction in pentane solution with a 450-W lamp produced no noticeable change in glpc or infrared spectrum after 1 hr. No evidence could be found for the formation of the desired bicyclic compound.

5-Methyl-1,5-hexadien-3-one (17).—The Grignard reaction between methallyl chloride and acrolein in ether afforded 5-methyl-1,5-hexadien-3-ol in good purity in 25% yield, bp 59–61° (25 mm). Material purified by glpc showed mol wt 112 (mass spectrum), λ_{max} 2.9, 6.06, 10.05, 10.9, and 11.2 μ, and nmr signals at τ 8.24 (3 H, s), 8.12 (1 H, s), 7.79 (2 H, d, J = 6.5 Hz), 5.78 (1 H, q, J = 6.5 Hz), 5.22 (1 H, s), 5.14 (1 H, s), 4.86 (2 H, m), and 4.14 (1 H, m).

A solution of 4.0 g of the alcohol in 200 ml of 50:50 benzene–acetone was oxidized with 14 ml of Jones reagent.[9] Normal work-up followed by distillation gave 2.2 g (56%) of ketone **17**, bp 66–68° (50 mm). Material collected by glpc showed uv λ_{max}^{EtOH} 209 mμ (ϵ 8400) and 333 (62); ir λ_{max} 3.25, 5.94, 6.05, 6.17, and 11.2 μ; mol wt 110 (mass spectrum), and nmr signals at τ 8.26 (3 H, s), 6.76 (2 H, s), 5.21 (1 H, s), 5.08 (1 H, s), 4.23 (1 H, dd, J = 9 and 2 Hz), and 3.72 (2 H, m).

Irradiation of 17. A. In Pentane.—A solution of 0.603 g of **17** in 180 ml of pentane was irradiated through a Pyrex sleeve with a 200-W mercury lamp. After 90 min, no change could be detected in the glpc analysis of the solution. The irradiation was continued in the absence of the Pyrex filter for 30 min, and some loss of starting material was noted. Acetophenone, 2.0 g, was added, and the irradiation was continued for another 2 hr, at which time no starting material could be detected, and a heavy polymer was observed in the flask. Filtration and distillation gave acetophenone with only minute traces of volatile materials.

B. In the Presence of Methanol.—A solution of 0.336 g of **17** and 1.041 g of methanol in 170 ml of pentane was irradiated through Vycor with a 200-W mercury lamp for 105 min, during which time appreciable polymer appeared and most of the starting material disappeared. Distillation gave 66 mg of colorless oil comprised of 38% of **17** and 62% of the methyl ester **30** (10% yield). Structure **30** for the product was established by spectroscopic investigation of material purified by preparative glpc, which showed λ_{max} 3.25, 5.72, 6.04, and 11.2 μ, mass spectral fragments at m/e 142 (parent ion), 43 (base peak), 111 (P − OMe), and 110 (P − MeOH), and nmr signals at τ 8.31 (3 H, s), 8.19 (2 H, m), 7.96 (2 H, t, J = 6 Hz), 7.72 (2 H, t, J = 7 Hz), 6.39 (3 H, s), and 5.36 (2 H, s).

1,5-Heptadien-3-one (18).—Condensation of 100 g of propanal with 100 g of malonic acid in 160 ml of pyridine and 2 ml of piperidine was carried out at room temperature in the dark for 36 hr.[10] Distillation after work-up gave 65.3 g (68%) of *trans*-2-pentenoic acid, bp 78–80° (1 mm). The trans nature of the conjugated double bond is suggested by an ir band at 10.25 μ,[19] in addition to bands at 3.4, 5.9, and 6.1 μ.

A mixture of 55.0 g of *trans*-2-pentenoic acid and 65.0 g of thionyl chloride was kept overnight at room temperature, then heated to reflux for 2 hr. Distillation gave 53.1 g (82%) of the acid chloride, bp 54–56° (23 mm), ir λ_{max} 5.67 and 6.15 μ.

A mixture of 46.0 g of triethylamine and 24.0 g of ethanol in 250 ml of purified acetone in a 500-ml flask was cooled in an ice bath. To this was added dropwise 53.0 g of the acid chloride at a rate slow enough to keep the temperature below 20°.[11] After 1 hr at room temperature, the mixture was poured into ether, washed twice with water, and dried over $MgSO_4$. Distillation gave 42.1 g (67%) of ethyl *cis*-3-pentenoate, which was >99% pure by glpc analysis. Material collected by glpc showed λ_{max} 5.72 μ and nmr signals at τ 8.73 (3 H, t, J = 7.5 Hz), 8.37 (3 H, d, J = 4 Hz), 6.91 (2 H, d, J = 5 Hz), 5.85 (2 H, q, J = 7.5 Hz), and 4.37 (2 H, m).

Hydrolysis of 41.1 g of ethyl *cis*-3-pentenoate with 16 g of NaOH in water was carried out at room temperature overnight. Distillation of the acidic product gave 28.9 g (88%) of *cis*-3-pentenoic acid, bp 54° (2 mm). The acid was converted to the

lithium salt by treatment with 1 equiv of LiOMe and evaporation of solvent, followed by drying at 100°.

To a solution of 10.0 g of bromobenzene in 100 ml of ether under argon was added 1.10 g of lithium metal. After stirring at room temperature for 4.5 hr, a solution of 4.50 g of tetravinyltin in ether was added.[22] After 0.5 hr the resultant solution was filtered slowly through a sintered glass disk by means of a slight argon pressure into a slurry of 6.0 g of the lithium carboxylate salt in ether, followed by stirring at room temperature for 2 days. The solution was poured into ice water and extracted twice with ether, and the ether solution was dried with $MgSO_4$. Distillation gave 2.76 g (44%) of **18**, bp 58–60° (20 mm), greater than 95% pure by glpc. Material isolated by glpc showed λ_{max} 3.35, 5.95, 6.20, 10.1, and 10.4 μ, mass spectrum signals at *m/e* 110 (P^+) and 55 (base peak), and nmr signals at τ 8.35 (3 H, d, J = 5.6 Hz), 6.67 (2 H, d, J = 6.0 Hz), 4.41 (2 H, m), 4.21 (1 H, dd, J = 8.4 and 3.0 Hz), and 3.72 (2 H, m). The presence of some impurity, possibly the trans isomer, is indicated by the nmr spectrum.

Irradiation of 18.—A solution of ketone **18** (0.308 g) in 130 ml of pentane was irradiated under argon through a Pyrex filter with a 200-W mercury lamp for 3 hr. Distillation gave 0.174 g (58%), bp 60–80° (bath) (15 mm), of colorless oil. Glpc analysis showed this to consist of two peaks in a ratio of 70:30 corresponding in retention times to the products isolated from irradiation of **12**, and a small amount of bromobenzene remaining from the synthesis of **18**. Both compounds were isolated by preparative glpc and identified by spectroscopic means.

Major peak (20) had ir λ_{max} 5.68 μ, mass spectrum signals at *m/e* 110 (P^+) and 67 (C_5H_7, base peak), and nmr signals at τ 9.14 (3 H, d, J = 6.0 Hz), 8.50 (1 H, d, J = 6.6 Hz), 7.97 (3 H, m), 7.50 (1 H, m), and 7.34 (2 H, t, J = 1 Hz).

Minor peak (21) had ir λ_{max} 5.65 μ, mass spectrum signals at *m/e* 110 (P^+) and 68 (C_5H_8), and nmr signals at τ 8.63 (3 H, d, J = 6.4 Hz), 8.37 (1 H, t, J = 7.0 Hz), 7.80 (3 H, m), 7.48 (2 H, m), and 7.26 (1 H, m). The chemical shifts of the methyl doublet signals in these two compounds are in good accord with the assigned structures.[23]

6-Methyl-1,5-heptadien-3-one (19).—Reaction of 100 g of isobutyraldehyde with 100 g of malonic acid in pyridine–piperidine[10] afforded 4-methyl-*trans*-2-pentenoic acid in 82% yield, bp 78° (3 mm). Treatment of 40.0 g of the acid with 55.0 g of thionyl chloride gave 38.9 g (84%) of the acid chloride, bp 61–62° (25 mm), λ_{max} 5.6 and 5.7 μ.

To a solution of 81.5 g of triethylamine and 56.0 g of ethanol in 400 ml of acetone at ice bath temperature was added 97.7 g of the acid chloride to maintain reaction temperature below 20°.[11] Normal work-up followed by distillation gave ethyl 4-methyl-3-pentenoate, bp 66° (17 mm), 85.0 g (80%). Material isolated by glpc showed λ_{max} 5.70 μ and nmr signals at τ 8.72 (3 H, t, J = 7.5 Hz), 8.33 (3 H, broad s), 8.22 (3 H, d, J = 2 Hz), 6.95 (2 H, d, J = 7.5 Hz), 5.81 (2 H, q, J = 7.5 Hz), and 4.83 (1 H, broad t, J = 7.5 and 2 Hz).

Hydrolysis of 68.0 g of the ester with 25.0 g of NaOH in 500 ml of water at room temperature overnight gave 48.0 g (88%) of the acid, bp 65° (2 mm). The acid was converted to the lithium salt with LiOMe in methanol, and dried at 100°.

Treatment of 16.5 g of bromobenzene in ether with 4.0 g of lithium was followed by addition of 7.70 g of tetravinyltin.[22] The resulting solution was filtered under argon pressure into a slurry of 10.0 g of the lithium carboxylate salt in ether and the mixture was stirred for 20 hr. The mixture was cooled in an ice bath and poured into water. Extraction with ether followed by drying over $MgSO_4$ gave material which was flash distilled directly into a Dry Ice trap at 1-mm pressure. This material (5.0 g, 49%) proved to be 90% pure by glpc analysis. Material collected by preparative glpc showed λ_{max} 5.94 and 6.20 μ, mass spectrum signals at 124 (P^+) and 41 (base), and nmr signals at τ 8.36 (3 H, s), 8.25 (3 H, s), 6.80 (2 H, d, J = 6.0 Hz), 4.72 (1 H, broad t, J = 6.0 Hz), 4.27 (1 H, dd, J = 8.4 and 3.4 Hz), and 3.76 (2 H, m).

Irradiation of 19. A. In Pentane.—A solution of 0.292 g of a mixture composed of 85% of ketone **19** and 15% of bromobenzene in 130 ml of pentane was irradiated through Pyrex with a 200-W mercury lamp for 140 min. Distillation gave 63.5 mg of oil, bp 70–90° (15 mm), which showed three peaks on glpc in the ratio of 26:30:44. Collection of these showed the first to be bromobenzene, while the second (a mixture of two unresolved compounds) showed ir absorption at 5.67 μ suggestive of a bicyclohexanone. Further attempts at separation of these compounds were unsuccessful. The last peak was identified by spectroscopic means as 3-isopropenylcyclopentanone (**24**), glpc yield 9.5%. Glpc purified material showed λ_{max} 3.25, 5.71, 6.05, and 11.2 μ, mol wt 124 (mass spectrum), and nmr signals at τ 8.24 (3 H, s), 7.5–8.2 (6 H), 7.27 (1 H, m), and 5.26 (2 H, m).

Hydrogenation of glpc-purified material over PtO_2 gave only 3-isopropylcyclopentanone, identified by ir and glpc comparison with an authentic sample prepared by similar hydrogenation of 3-isopropyl-2-cyclopentenone.[24]

B. In Methanol.—Irradiation of 0.70 g of **19** (~95% pure) in 400 ml of methanol was carried out in Vycor glassware with a 450-W mercury lamp for 30 min. Distillation gave 0.23 g of colorless oil, bp 95–105° (20 mm), which showed three major peaks in the ratio of 12:45:43 on glpc analysis (Reoplex 400 column). The latest peak (43%, 13% yield) was shown to be ketone **24** by ir and glpc comparison. The others were identified as **33** and **34** as follows.

Peak 1 (12%, 4% yield, **33**) had ir λ_{max} 3.25, 5.71, 6.07, 10.0, and 10.95 μ, mol wt 156 (mass spectrum), and nmr signals at τ 9.00 (6 H, s), 8.35 (2 H, t, J = 8 Hz), 7.78 (2 H, t, J = 8 Hz), 6.38 (3 H, s), 5.10 (2 H, AB part of ABC system), and 4.3 (1 H, m).

Peak 2 (45%, 13% yield, **34**) had ir λ_{max} 5.76, 8.05, 8.37, 8.56, and 8.80 μ, mol wt 156 (mass spectrum), and nmr signals at τ 8.45 (3 H, s), 8.36 (3 H, s), 8.2–8.5 (2 H), 8.09 (2 H, m), 7.83 (2 H, t, J = 7 Hz), 6.48 (3 H, s), and 4.98 (1 H, m).

Registry No.—i, 33686-88-3; ii, 33698-56-5; **6**, 33698-57-6; **6** 2,4-DNP, 33698-58-7; **7**, 24903-94-4; **8**, 33698-60-1; **10**, 5164-64-7; *cis*-**12**, 33698-62-3; *trans*-**12**, 33698-63-4; **13**, 33698-64-5; **14**, 33698-65-6; **15**, 33698-66-7; **16**, 33698-67-8; **17**, 998-83-4; **18**, 33698-68-9; **19**, 33698-69-0; **20**, 33698-70-3; **21**, 33698-71-4; **22**, 33698-72-5; **22** 2,4-DNP, 33698-73-6; **23**, 20609-40-9; **23** 2,4-DNP, 33698-75-8; **24**, 33698-76-9; **30**, 32853-30-8; **33**, 33698-78-1; **34**, 33077-53-1; 4,4-dimethyl-1,5-hexadien-3-ol, 33698-80-5; 2-methyl-1,5-hexadien-3-ol, 17123-60-3; 6-methyl-1,5-heptadien-4-ol, 33698-82-7; 5-methyl-1,5-hexadien-3-ol, 17123-61-4; *trans*-2-pentenoic acid, 13991-37-2; *trans*-2-pentenoic acid chloride, 33698-85-0; ethyl *cis*-3-pentenoate, 27829-70-5; *cis*-3-pentenoic acid, 33698-87-2; 4-methyl-*trans*-2-pentenoic acid, 16666-43-6; ethyl 4-methyl-3-pentenoate, 6849-18-9; *trans*-1,5-heptadien-4-ol, 24581-03-1.

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(24) We thank Dr. Wayne Fanta for a sample of this material.

The Acetylation of Butane 2-Diazotate. Mechanism of Decomposition of an Alkyl Diazo Ester[1,2]

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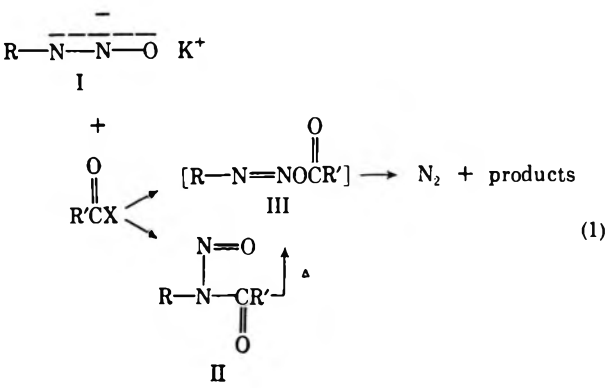
sec-Butyl acetate is formed with 18–25% net retention in the ethereal thermolysis of *N*-nitroso-*N*-*sec*-butylacetamide. In contrast, acetylation of ethereal butane 2-diazotate, with either acetic anhydride or acetyl chloride, leads to the same ester with 17–21% net inversion. The stereochemical responses of both reactions to changes in reaction conditions are examined, and it is concluded that the heterogeneity of the diazotate reaction is responsible for its unique behavior.

Due to the ambident character[4] of alkane diazotate salts I, their acylation affords *N*-alkyl-*N*-nitrosoamides II and the unstable alkyl diazo esters III (eq 1). In-

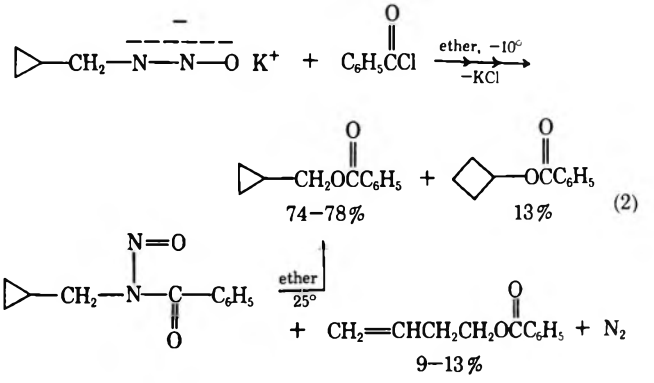


(1)

termediates III are well known in the thermal rearrangements of independently prepared II.[5,6]

Indeed, there are several studies of reaction 1, and these suggest that the partition between products II and III is quite sensitive to the identity of R. When R = CH_3, N-acylation (formation of II) is a major pathway.[4] When R = 2,2-diphenyl-1-cyclopropyl, O-acylation is the sole detected pathway; steric hindrance toward N-acylation by the bulky R group was cited as the probable cause of this path reversal.[7]

Not surprisingly, with a primary substituent in I, R = cyclopropylcarbinyl, we were able to observe both N-acylation (10%) and O-acylation in the reaction of I with benzoyl chloride.[8] More importantly, as summarized in eq 2, the product distribution obtained upon benzoylation of the diazotate was nearly identical with that observed in a separate thermolysis of *N*-cyclopropylcarbinyl-*N*-nitrosobenzamide. It appeared that



(2)

the product-determining steps were the same for both reactions, and (perhaps less cogently) that both reactions involved the identical penultimate precursor, cyclopropylcarbinyl diazobenzoate.[8]

We have now studied the acetylation of butane 2-diazotate and the thermolysis of *N*-nitroso-*N*-*sec*-butylacetamide. The starting materials were optically active, and the stereochemical courses of formation of *sec*-butyl acetate were compared as a test for identity of mechanism.

In contrast to the earlier examples,[8] we find important differences in the present reactions. The results implicate SN2-type reactions of *sec*-butyl diazo acetate, following the acetylation of the diazotate, and they may have meaningful consequences for deamination chemistry[6] and for the chemistry of alkane diazotates.

Results

The Acetylation Reaction.—By an unexceptional sequence of reactions, 2-aminobutane was converted through *N*-2-butylurethan and *N*-nitroso-*N*-2-butylurethan to potassium butane 2-diazotate.[9–11] In the initial acetylation studies, either acetyl chloride (AcCl) or acetic anhydride (Ac_2O) in dry ether was rapidly added to the suspended ethereal diazotate at about −19°. Because 2 equiv of *tert*-butoxide are used in the cleavage of the *N*-nitrosourethan to the diazotate,[9] 2 equiv of acetylating agent were added in the decomposition step, sufficient to acetylate both the excess *tert*-butoxide and the diazotate.

Nitrogen evolution (80–100%) was complete in about 3 min, and an aqueous work-up, followed by gas chromatography (gc), allowed the isolation and identification

(1) Alkyl Diazotates. Part X.

(2) Part IX: R. A. Moss, A. W. Fritz, and E. M. Emery, *J. Org. Chem.*, **36**, 3881 (1971).

(3) Fellow of the Alfred P. Sloan Foundation.

(4) Bond orders of ~1.5 have been established for the N–N and N–O bonds of I, R = CH_3: E. Müller, W. Hoppe, H. Hagenmaier, H. Haiss, R. Huber, W. Rundel, and H. Suhr, *Chem. Ber.*, **96**, 1712 (1963).

(5) (a) E. H. White, *J. Amer. Chem. Soc.*, **76**, 4497 (1954); (b) E. H. White, *ibid.*, **77**, 6008 (1955); (c) **77**, 6011 (1955); (d) **77**, 6014 (1955); (e) R. Huisgen and H. Reimlinger, *Justus Liebigs Ann. Chem.*, **699**, 161 (1956); (f) R. Huisgen and C. Rüchardt, *ibid.*, **601**, 1 (1956), and earlier references in this series.

(6) Recent reviews, which cover various aspects of deamination chemistry, include (a) E. H. White and D. J. Woodcock in "The Chemistry of the Amino Group," S. Patai, Ed., Interscience, New York, N. Y., 1968, pp 440–483; (b) J. T. Keating and P. S. Skell, in "Carbonium Ions," II, G. A. Olah and P. v. R. Schleyer, Ed., Wiley–Interscience, New York, N. Y., 1970, p 573 ff; (c) L. Friedman, *ibid.*, p 655 ff; (d) R. A. Moss, *Chem. Eng. News*, **49** (48), 28 (1971).

(7) T. K. Tandy, Jr., and W. M. Jones, *J. Org. Chem.*, **30**, 4257 (1965).

(8) R. A. Moss and F. C. Shulman, *Tetrahedron*, **24**, 2881 (1968).

(9) R. A. Moss, *J. Org. Chem.*, **31**, 1082 (1966).

(10) R. A. Moss and G. H. Temme, III, *Tetrahedron Lett.*, 3219 (1968).

(11) See the Experimental Section for details.

TABLE I

STEREOCHEMISTRY OF FORMATION OF *sec*-BUTYL ACETATE IN THE ACETYLATION OF BUTANE 2-DIAZOTATE

Run	Diazotate[a]	Decomposing reagent	Mode of addition	N_2 evolved,[b] %	α_D for *sec*-BuOAc,[c] deg	α_D corrected,[d] deg	Stereochemistry, %[e]
1	13.2 mmol in 40 ml of ether[f]	Ac_2O, 26.4 mmol in 25 ml of ether	Direct[g]	90	$\alpha^{23}D$ −0.462[h]	−3.62	16.6 net inv
2	13.8 mmol in 35 ml of ether[f]	Ac_2O, 27.6 mmol in 25 ml of ether	Direct[g]	92	$\alpha^{26}D$ −1.121[i]	−4.26	19.9 net inv
3	17.2 mmol in 47 ml of ether[j]	AcCl, 35 mmol in 13 ml of ether	Direct[g]	100	$\alpha^{22}D$ −0.849[k]	−3.84	17.6 net inv
4	17.2 mmol in 30 ml of ether[j]	AcCl, 35 mmol in 15 ml of ether	Direct[g]	90	$\alpha^{22}D$ −1.889	−4.65	21.2 net inv
5	17.2 mmol in 35 ml of ether[j]	AcCl, 35 mmol in 25 ml of ether	Inverse[l]	*m*	$\alpha^{22}D$ −0.549[n]	−4.76	21.8 net inv
6	17.2 mmol in 55 ml of CH_2Cl_2 +49.2 mmol of dry C_2H_5OH[j]	AcCl, 74 mmol in 250 ml of ether	Inverse[o]	86	$\alpha^{23}D$ +0.223[p]	+1.21	5.53 net ret
7	17.2 mmol in 40 ml of CH_2Cl_2 +51 mmol of dry C_2H_5OH	AcCl, 86 mmol in 500 ml of ether	Inverse[o]	109	$\alpha^{23}D$ −0.017[q]	0.0	Racemization
8	17.2 mmol in 35 ml of HMPA[r]	AcCl, 38.5 mmol in 250 ml of ether	Inverse[s]	89	$\alpha^{20}D$ −1.29[t]	−6.71	30.1 net inv
9	17.2 mmol in 45 ml of HMPA[r] +86 mmol of NaOAc	Ac_2O, 36.8 mmol in 5 ml of HMPA	Direct[u]	*m*	$\alpha^{18}D$ −0.419[v]	−9.53	42.7 net inv

[a] The ether used in all runs was dried over molecular sieves prior to use; 1 equiv of excess $K^+{}^-O$-*tert*-Bu was present. The reaction temperature varied from ~25 to 35°. [b] Nitrogen was determined manometrically; butenes were removed by a sulfuric acid scrubber. [c] All readings were taken in a 0.5-dm cell on neat ester; zero readings were made on racemic ester. A minimum of 10 readings were made for each sample, and the (average) final reading is considered accurate to ±0.02°. This implies a per cent error of ±10% in the stereochemistry of run 6. The per cent error in the other runs is considerably smaller. [d] Corrected for path length, for dilution, and for the optical purity of the initial urethan. [e] Optically pure *d*-*sec*-butyl acetate has $\alpha^{20}D$ +22.30 and $\alpha^{27}D$ +21.38; see ref 17. α_D varies linearly with temperature in this range,[17] and $\alpha^{23.5}D$ +21.84° can be interpolated. In a given run, the most appropriate of these values is used. [f] The *N*-2-butylurethan, from which the diazotate derived, had $\alpha^{23}D$ +15.58° corresponding to an optical purity of 85.6%.[14] [g] The acetylating agent was added to the suspended diazotate. [h] 31.8 mg of product acetate was diluted with 74.9 mg of racemic acetate; *i.e.*, the dilution factor was 1067/318. [i] Dilution factor, 1151/710. [j] The *N*-2-butylurethan precursor had $\alpha^{22}D$ +14.78°, corresponding to an optical purity of 81.2%.[14] [k] Dilution factor, 1223/666. [l] The diazotate slurry was added to the acetylating agent over a period of 30 min. The reaction mixture was mechanically stirred in a Morton flask, and the entire reaction was carried out in a dry-box. [m] Not determined. [n] Dilution factor, 1169/332. [o] The diazotate was in the form of a colloidal suspension. It was stable to small quantities of ethanol (~1 equiv) in CH_2Cl_2.[18] The suspension was added to the rapidly stirred AcCl solution. [p] Dilution factor, 1196/545. [q] This value is within the reading error, and is taken as 0.00. It was determined on *undiluted* product ester. [r] HMPA = hexamethylphosphoric triamide. The diazotate was prepared from *N*-2-butylurethan ($\alpha^{21}D$ +17.37°) of 95.45% optical purity.[14] [s] The diazotate was in the form of a clear purple solution. [t] Dilution factor, 1173/473. [u] The acetylating reagent was added to the diazotate solution, which contained excess (solid) sodium acetate. Not all of the diazotate was in solution. [v] Dilution factor, 975/90.

of *sec*-butyl acetate in yields ranging from 14.5 (AcCl reaction)[12] to 23.4% (Ac_2O reaction).

We also observed substantial olefin yields in these reactions. In the Ac_2O reaction, 45% of a butene mixture (determined gravimetrically as the dibromides) was isolated by low-temperature distillation, and shown by direct gc analysis[11] to consist of 1-butene, *trans*-butene, and *cis*-butene in the distribution 68:21:11. From an AcCl reaction, also at −19°, the same olefins were obtained in a 67:21:12 distribution. (A minor gc component with a retention time intermediate between that of *trans*- and *cis*-butene could have been methylcyclopropane.)

In contrast to our results with the primary diazotate, eq 2,[8] no *N*-*sec*-butyl-*N*-nitrosoacetamide was detected in the product mixture resulting from the acetylation of butane 2-diazotate; the crude product mixtures did not evolve nitrogen on standing.

Qualitative and preparative gc of the crude product mixtures revealed the presence of *tert*-butyl alcohol, *sec*-butyl alcohol, *tert*-butyl acetate, acetic acid, diethyl carbonate, ethyl *tert*-butyl carbonate, ethyl *sec*-butyl carbonate, di-*tert*-butyl carbonate, *sec*-butyl-*tert*-butyl carbonate, and *N*-2-butylurethan. A digression into the probable origins of these mechanistically peripheral products seems in order here.

The diazotate is generated in the presence of excess potassium *tert*-butoxide.[9] Under these conditions, the initial by-product, ethyl *tert*-butyl carbonate, undergoes transesterification reactions leading to diethyl and di-*tert*-butyl carbonates.[9] As demonstrated separately, *sec*-butyl acetate, potassium *tert*-butoxide, and diethyl carbonate, in ether, give rise to carbonates containing the *sec*-butyl moiety. We believe that the traces of such carbonates observed in the diazotate acylation reactions arise during the acetylation step, from product *sec*-butyl acetate.

The small amount of 2-butanol observed (<5%) may have come either from *sec*-butoxide liberated during the transesterifications which accompany the acetylation of the diazotate, or from a minor hydrolysis of *sec*-butyl acetate during the work-up. The trace of *N*-2-butylurethan probably came from butoxide-induced denitrosation of the *N*-nitroso-*N*-2-butylurethan, during the generation of the diazotate. Nmr spectra of starting material showed no evidence of unreacted *N*-

(12) The yields are based on *N*-nitroso-*N*-2-butylurethan. In the AcCl reaction, 6.5% of *sec*-butyl chloride was also formed.

TABLE II

STEREOCHEMISTRY OF FORMATION OF *sec*-BUTYL ACETATE IN THE THERMOLYSIS OF *N*-NITROSO-*N*-*sec*-BUTYLACETAMIDE

Run	Conditions[a]	α_D for *sec*-BuOAc,[b] deg	α_D corrected,[c] deg	Stereochemistry, %[d]
1	10 mmol of nitrosoamide in 45 ml of ether	$\alpha^{25}D$ +0.919[e]	+5.95	27.2 net ret
2	10 mmol of nitrosoamide in 45 ml of ether	$\alpha^{26}D$ +0.770[f]	+3.80	17.8 net ret
3	10 mmol of nitrosoamide in 45 ml of ether	$\alpha^{24}D$ +0.965[g]	+4.26	19.5 net ret
4	10 mmol of nitrosoamide in 52 ml of ether and 50 mmol of HOAc	$\alpha^{24}D$ +1.05[h]	+3.14	14.4 net ret
5	10 mmol of nitrosoamide in 28.7 ml of ether and 6.22 ml of CH_2Cl_2 and 29 mmol of C_2H_5OH	$\alpha^{23}D$ +0.545[i]	+5.29	24.2 net ret[j]

[a] The quantity of *N*-nitrosoamide is based on the amide submitted to the nitrosation reaction, and assumes 100% conversion. This assumption is valid for run 1, in which 6.5 equiv of N_2O_4 were employed in the nitrosation, and 96% of the theoretical N_2 evolution was subsequently observed. In run 3, however, only 1.6 equiv of N_2O_4 were used, and the nitrosation was probably incomplete, as only 47% of the theoretical N_2 evolution was later observed. [b] See Table I, footnote *c*. [c] Corrected for path length, dilution, and for the optical purity of the precursor amide, 95.8% (see above). [d] See Table I, footnote *e*. [e] Dilution factor, 1370/442. [f] Dilution factor, 1237/523. [g] Dilution factor, 1301/616. [h] Dilution factor, 1220/851. [i] Dilution factor, 1183/255. [j] Gc indicated about 4% of minor impurities in the *sec*-butyl acetate used for the polarimetry. Control gc experiments with various *sec*-butyl derivatives (2-butanol, *sec*-butyl ethyl ether) ruled out the possibility that these impurities contained the (chiral) *sec*-butyl moiety.

2-butylurethan, which could have been carried along to the final product mixture.

Stereochemical Studies.—2-Aminobutane was resolved by the procedure of Bruck,[13] and the *d* amine was converted to the corresponding *d* urethane, which served as the basis for the determination of optical purity.[14] The conversion of the optically active urethan to the diazotate and the latter's acetylation were carried out as for the racemic case. *sec*-Butyl acetate was isolated from the reaction mixture by gc, and its purity was established by gc and ir examination. The optical rotation was measured with a Rudolph polarimeter, reading the neat ester (diluted with racemic ester, when necessary) in a 100-μl, 0.5-dm cell.

In a control experiment, *sec*-butyl acetate, $\alpha^{25}D$ $-1.25°$, was treated with Ac_2O, acetic acid, diethyl carbonate, *tert*-butyl acetate, 1-butene, and potassium acetate in dry ether for 1 hr at 25°. An aqueous work-up, followed by gc isolation, returned *sec*-butyl acetate, $\alpha^{24}D$ $-1.31°$. The product of interest appears to be optically stable to simulated experimental conditions.

2-Aminobutane, 2-butanol, and *sec*-butyl acetate of the same rotational sign are known to belong to the same optical series.[15] With this information, the experimentally determined optical purities of initial *N*-2-butylurethan and final *sec*-butyl acetate, and the assumption that no loss of optical activity attends any synthetic procedure through the diazotate formation,[16] the stereochemical consequences of the acetylation of butane 2-diazotate were obtained for several reactions. The data appear in Table I, and represent experiments in which acetylating reagent, solvent, and order of reagent addition were varied.

The *N*-Nitrosoamide Reaction.—For comparative purposes, we also examined the formation of *sec*-butyl acetate by the room temperature thermolysis of *N*-nitroso-*N*-*sec*-butylacetamide. This reaction has been extensively studied by White.[19] We obtained 15.5% of *sec*-butyl acetate, together with a substantial yield of 1-butene, *cis*-butene, and *trans*-butene in the distribution 53:33:14. *sec*-Butyl acetate, formed from the *N*-nitrosoamide in the presence of 5 equiv of DOAc, showed no (<2%) incorporation of deuterium,[20] excluding the substantial intermediacy of 2-diazobutane as an ester precursor. White reached a similar conclusion in a closely related study of the decomposition of *N*-nitroso-*N*-*sec*-butylbenzamide in dioxane.[5d]

Stereochemical Studies.—*d*-2-Aminobutane[13] was converted to *N*-*sec*-butylacetamide with acetic anhydride. The purified amide had $[\alpha]^{24}D$ +15.89° ($CHCl_3$, *c* 6.063 × 10^{-2}) and was 95.8% optically pure based on White's extrapolated value of $[\alpha]^{25}D$ +16.6° in $CHCl_3$.[5d]

The labile *N*-nitrosoamide was prepared by nitrosation of the ethereal amide with N_2O_4 in the presence of suspended NaOAc at -10 to 0°. The temperature was kept below 15° during a rapid aqueous work-up.

Dry *N*-nitroso-*N*-*sec*-butylacetamide was decomposed in a stirred ethereal solution at 28–30° until no further nitrogen evolution was observed (15–18 hr.) The optical purity of the gc-isolated *sec*-butyl acetate was determined as previously described, and the results of several experiments are collected in Table II.

Discussion

The Nitrosoamide Reaction.—An abbreviated version of the general mechanism[6a] is given in eq 3, and can be applied to the data of Table II (R = $CH_3\overset{*}{C}HC_2H_5$).[21] In sufficiently polar solvents, such as dioxane or acetic acid, the collapse of V invariably occurs with net retention.[5d,6a]

That retention is not complete has been explained

(13) P. Bruck, I. N. Denton, and A. H. Lamberton, *J. Chem. Soc.*, 921 (1956).

(14) $\alpha^{21}D$ +18.2° for optically pure *d*-*N*-2-butylurethan.[13] However, see the Experimental Section.

(15) See J. A. Mills and W. Klyne in "Progress in Stereochemistry," Vol. 1, W. Klyne, Ed., Academic Press, New York, N. Y., 1954, p 195.

(16) The only step for which this assumption appears at all questionable is the cleavage of the *N*-nitrosourethan to butane 2-diazotate. The reaction of the latter with phenol affords *o*-*sec*-butylphenol with up to 80% net inversion of the *sec*-butyl moiety.[10] Thus there appears to be little, if any, loss of optical purity in the diazotate formation step.

(17) R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **T105**, 830 (1914); see especially p 889.

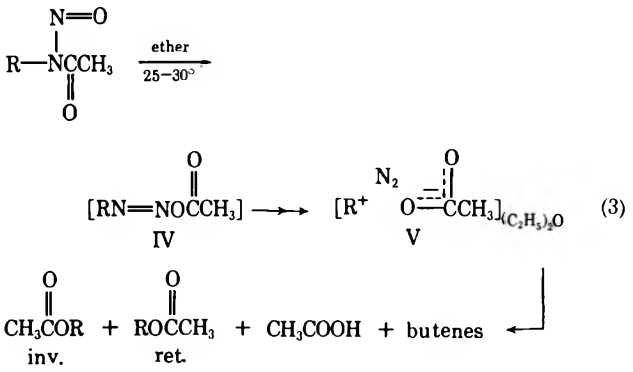
(18) R. A. Moss and M. J. Landon, *J. Amer. Chem. Soc.*, **92**, 5755 (1970).

(19) See especially ref 5d.

(20) Mass spectral analysis employed the ion series *m/e* 86, 87, 88 and 115, 116, 117. See K. Biemann, "Mass Spectrometry: Organic and Chemical Applications," McGraw-Hill, New York, N. Y., 1962, p 225 ff, for a description of the analysis.

(21) It is a matter of some controversy whether a *sec*-carbinyl diazo ester goes to ion pair V with "simultaneous" fission of C–H and N–O bonds, or whether a diazonium carboxylate ion pair ($RN_2^+O^-OCR$,) is an intermediate. Whiting holds the former view[22] and White, the latter.[6a] The problem is not central in the present context, however.

(22) M. C. Whiting, *Chem. Brit.*, **2**, 482 (1966); H. Maskill, R. M. Southam, and M. C. Whiting, *Chem. Commun.*, 496 (1965).



by an "intramolecular inversion" mechanism, that is, by the rotation of R^+ within the ion pair, followed by collapse.[6a,23] Some inverted ester could also arise by back-side solvation of V by acetic acid released in prior molecular events; or (less probably) by the annihilation of cations which escaped the initial ion pair.[24]

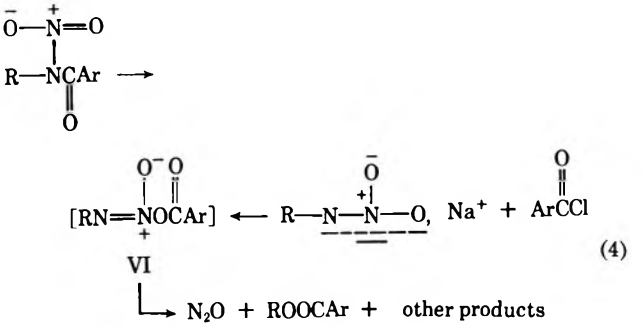
Olefin formation is also a principal fate of V. Not only solvent, but gegenion too acts as a base in the removal of a β proton.[5d,25]

Our ethereal *N*-nitroso-*N*-*sec*-butylacetamide decompositions (Table II) are normal representatives of the general reaction (3). *sec*-Butyl acetate is formed with the anticipated net retention (runs 1–3), and this stereochemical course is only marginally altered in the presence of 5 equiv of acetic acid (run 4), which suggests a limited role for displacement reactions on IV or V. We also observed a 1-butene:*trans*-butene:*cis*-butene distribution of 53:33:14, very similar to that observed by White for a decomposition performed in Na_2CO_3-buffered CCl_4.[5d]

Acetylation of Butane 2-Diazotate.—Formally, this reaction should lead to *sec*-butyl diazoacetate IV, eq 3, the same intermediate involved in the thermolysis of the *N*-nitrosoamide. However, our "calibration" studies of the latter reaction (above), in comparison with the stereochemical data for the acetylation reaction (Table I), prove that there are important mechanistic differences between these reactions.

Differences in mechanism were not expected on the basis of our studies in the cyclopropylcarbinyl system, eq 2.[8] Nor were they anticipated in view of White's related comparative study of the thermal decomposition of (optically active) *N*-nitro-*N*-*sec*-butyl-3,5-dinitrobenzamide and of the reaction of 3,5-dinitrobenzoyl chloride with the sodium salt of *N*-nitro-*sec*-butylamine.[26] *Both* reactions (25°, $CHCl_3$) led to *sec*-butyl 3,5-dinitrobenzoate with about 20% net retention, presumably *via* diazoxy ester VI (eq 4).

We can enumerate the several characteristics which distinguish product formation *via* the acetylation of butane 2-diazotate. (1) *sec*-Butyl acetate is formed with *net inversion* in ethereal decompositions (Table I, runs 1–4). (2) The extent of inversion is independent of the acetylating agent, Ac_2O or AcCl; *i.e.*, the "extra mole" of acetate generated in the Ac_2O reaction is ineffective as SN2 nucleophile (runs 1 and 2 *vs.* 3 and 4). (3) The order of reagent addition can be reversed, and hence the average nucleophile and diazo ester concentrations can be altered, without affecting the stereochemistry (run 5 *vs.* runs 1–4). (4) The stereochemical course of the reaction can be changed from inversion to *retention* by changing the solvent system from ether to methylene chloride–ether containing 4 equiv of ethanol (runs 1–5 *vs.* 6 and 7). This is not a bulk solvent effect, because parallel behavior is not observed in the nitrosoamide decompositions (Table II, runs 1–3 *vs.* 5). (5) Acetylation of butane 2-diazotate solubilized in hexamethylphosphoric triamide (HMPA) affords *sec*-butyl acetate with enhanced inversion (Table I, runs 1–4 *vs.* 8 and 9). (6) Relative to other reactions involving the *sec*-butyl cation, the diazotate acetylation yields the most "Hoffmann-like" olefin distribution (Table III).



The inversion in the ethereal diazotate acetylations must result from displacement processes, for the normal stereochemical course of decomposition of ethereal *sec*-BuN=NOAc is retention. In itself, the occurrence of inverting displacement reactions involving such a species is not new. The decomposition of *sec*-BuN=$NOOCC_6H_5$ in pentane afforded inverted *sec*-butyl benzoate, which was attributed to inverting attack of benzoic acid (liberated in β-elimination reactions of the diazo ester) on the diazo ester or related species.[5d,21] The extent of inversion was sensitive both to substrate concentration and to the addition of nucleophiles,[5d] as expected for such a process.

We believe that the displacement processes which lead to inverted *sec*-butyl acetate in the diazotate acetylation reactions differ from those identified in the *N*-nitrosoamide decomposition, because the former reaction is stereochemically insensitive to the order of reagent addition, and to the presence of additional acetate during the reaction. The opposite behavior would be expected if the inversion in our reaction had the same origin as that in White's examples.[5d]

Moreover, *ethereal sec*-BuN=NOAc, generated from a *N*-nitrosoamide precursor, is only marginally sensitive to the presence of added acetic acid (Table II, run 4). Again we conclude that the stereochemical variance of the diazotate acetylation cannot be simply explained by an altered substrate/nucleophile ratio, *i.e.*, by a different blend of SN2 and SN1 decompositions of IV.

We suggest that the *heterogeneity* of the diazotate reaction system is responsible for its anomalous stereochemistry. Such inverting processes as 5, or the attack of acetate on the diazo ester, could occur either at the surface of the solid diazotate as it reacts with acetylating agent or, thereafter, in nearby local heter-

(23) E. H. White and C. A. Aufdermarsh, Jr., *J. Amer. Chem. Soc.*, **83**, 1179 (1961).

(24) In dioxane (and presumably in ether) it is likely that solvent oxygen plays a configuration-holding role, through relatively strong back-side solvation of the cation.[6a] This enhances the stereochemical retention in the formation of the product ester.

(25) T. Cohen and A. R. Daniewski, *J. Amer. Chem. Soc.*, **91**, 533 (1969).

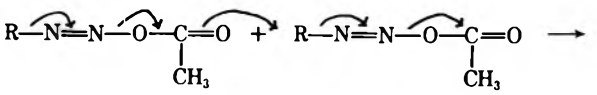
(26) E. H. White and D. W. Grisley, Jr., *ibid.*, **83**, 1191 (1961), and references cited therein.

TABLE III
BUTENE DISTRIBUTIONS IN THE DECOMPOSITION OF *sec*-BUTYL X

Case	X	Registry no.	Reaction conditions	% Distribution 1-Butene	*trans*-Butene	*cis*-Butene	Ref
1	OTs	715-11-7	HOAc, 118°	10	47	43	*a*
2	NH_2	13952-84-6	HNO_2, H_2O, 25°	25	56	19	*b*
3	NO | $NCOC_6H_5$	33124-23-1	HOAc, 25°	45	40	15	*c*
4	NO | $NCOC_6H_5$		Dioxane, 25°	49	39	12	*c*
5	NO | $NCOCH_3$		CCl_4, Na_2CO_3, 25°	54	33	13	*c*
6	NO | $NCOCH_3$		Ether, 28°	53	33	14	*d*
7	$N{=}N{-}O^-K^+$		AcCl, Ether, 25°[e]	70	18	12	*d*

[a] Reference 27. [b] Reference 28. [c] Reference 5d. [d] This work. [e] The distributions at −19°, using either AcCl or Ac_2O, are very similar; see above.

ogeneous regions. Such processes would have to be competitive with the rate at which diazo ester escapes into the solvent.[29]



$$R^+ + 2N_2 + CH_3COOR + {}^-OOCCH_3 \quad (5)$$
$$\hookrightarrow \text{(olefins, ester)}$$

These proposals lead to a consistent, if nevertheless *ad hoc*, interpretation of both present and older data. The inversion and insensitivity to extra acetate and to the order of reagent addition are understandable because, in order to alter the stereochemistry of product formation *via* 5, we would need to change the phase in which the product is formed. Indeed, acetylation of colloidal butane 2-diazotate does produce a marked stereochemical response.[30] (Contrast point 4 with points 1–3, above.) Parity between the diazotate acetylation and the *N*-nitrosoamide thermolysis was not achieved, however, suggesting that some influence of heterogeneity was still operative.

The heterogeneity concept also accommodates recent studies of the $H_2{}^{18}O$ hydrolysis of optically active octane 2-diazotate in ether–water, water, and HMPA–water (solubilized diazotate) systems,[2,31] particularly the observed smooth attenuation of the ^{16}O-conservation–inversion pathway to 2-octanol. It is this pathway which can be most augmented by inverting bimolecular reactions of $RN{=}N^{16}OH$ with itself,[29] and the change in the conservation process stereochemistry, as the solvent system is changed so as to disfavor bimolecular processes (18% net inversion, 22% net retention, and 46% net retention, respectively), is analogous to present results in the *sec*-butyl system.

There are cases in which diazotate decompositions do not exhibit the special characteristics here attributed to heterogeneity effects. Examples include the cylcopropylcarbinyl[8] and *N*-nitro-*sec*-butylamine (sodium salt)[26] systems described above, eq 2 and 4, and the ethanolysis of 1-phenylethane 1-diazotate, which gives 1-phenylethanol (retention) and 1-phenylethyl ethyl ether (inversion).[18] In the latter reaction, the stereochemistries are constant whether ethanol is added to the solid diazotate, or colloidal diazotate (CH_2Cl_2 + 1 equiv of ethanol) or HMPA-solubilized diazotate is added to excess ethanol.

An examination of all the data suggests that poor innate stability of the potential alkyl cation, low solvent polarity, and high gegenion nucleophilicity are experimental factors which accentuate the disparity between the initially heterogeneous diazotate reactions and those homogeneous reactions which formally proceed *via* the same intermediate RN=NX. A more detailed analysis is precluded, in view of the complexities introduced by the heterogeneity.

A final stereochemical point is the enhanced inversion in diazotate acetylation in HMPA (Table I, runs 8 and 9). We believe that SN2 reactions between acetate and *sec*-BuN=NOAc (or related species) are responsible, in these apparently homogeneous, solubilized diazotate reactions.[32] The large nucleophile-potentiating effect of HMPA[33] must enhance the bimolecular component of these decompositions.

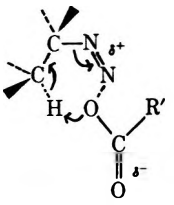
A change of the HMPA acetylation procedure from inverse to direct and the addition of excess acetate bring about increased inversion (run 9 *vs.* run 8), but the effect is not large, owing to the low solubility of sodium and potassium acetate in HMPA. Greater inversion might result if a more soluble added nucleophile were employed, and such experiments are planned.

(27) H. C. Brown and I. Moritani, *J. Amer. Chem. Soc.*, **77**, 3607 (1955).
(28) A. Streitwieser, Jr., and W. D. Schaeffer, *ibid.*, **79**, 2888 (1957).
(29) For simplicity, the reactants in eq 5 are shown as covalent species. They might also be rendered as diazonium or carbonium acetate ion pairs. More than two reactants could be linked in such a surface reaction, and the terminal "R^+" could be involved in a concerted proton loss to acetate ion, or could itself be the substrate for an inverting "trigger" attack by acetate, *tert*-butoxide, or even diazotate ion. The last process would give inverted *sec*-butoxide which could be acetylated to product, or appear as 2-butanol after work-up.
(30) In this experiment, we may be dealing with an alcoholate of the diazotate. This could also be an important cause of the altered stereochemistry. The crucial fact, however, is that the stereochemistry of the diazotate reaction changes at all.
(31) R. A. Moss, D. W. Reger, and E. M. Emery, *J. Amer. Chem. Soc.*, **92**, 1366 (1970); R. A. Moss and S. M. Lane, *ibid.*, **89**, 5655 (1967).
(32) These reactions are probably related to the homogeneous, inverting decompositions described by White.[5d]
(33) For leading references see A. J. Parker, *Chem. Rev.*, **69**, 1 (1969); H. Normant, *Russ. Chem. Rev.*, **39**, 457 (1970); and L. P. Hammett, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1970, Chapter 8.

Indeed, the present results represent an approach to a synthetically useful SN2 chemistry of amines, which we hope to elaborate.

Elimination Reactions.—β elimination from *sec*-BuN=NOOCR gives more 1-alkene (1-/2-alkene = 0.8–1.2) than does β elimination from either *sec*-BuN_2^+ (1-/2-alkene = 0.33) or from the acetolysis of *sec*-BuOTs (1-/2-alkene = 0.1); see Table III, cases 3–6, 2, and 1, respectively.

The transition state for β elimination from *sec*-BuN=NOOCR has been rendered as VII,[5d] and there is independent evidence for the suggested syn elimination in related cases.[25] Now, it is known that the formation of 1-alkene occurs *via* a sterically less demanding transition state than does that of 2-alkene, since, in competitive situations, the former is augmented by increasing the size of the leaving group, the base, and the β-alkyl group.[34] Though most of this work pertains to E2 eliminations, there appears little reason to doubt that related factors would be operative in controlling the orientation of elimination from VII. VII is a sterically demanding transition state, especially in comparison to that for β elimination from hydrated *sec*-BuN_2^+, and it is therefore not surprising that the butenes from *sec*-BuN=NOOCR are richer in 1-butene. Indeed, VII is related to the transition state for *sec*-butyl acetate pyrolysis, and it is noteworthy that this reaction gives an olefin mixture containing 57% of 1-butene.[35]



VII

The olefin mixture from the acetylation of butane 2-diazotate is even richer in 1-butene than is that from the homogeneous *sec*-BuN=NOOCR decompositions (Table III, case 7 *vs.* cases 3–6). As we rationalized the increased inversion in the substitution reactions, which suceeded the acetylation reaction, by the incursion of a "bimolecular" component, so, too, do we suggest a "bimolecular" component in the accompanying elimination reactions. This component, the products of which are perhaps superimposed on those stemming from competing "unimolecular" elimination *via* VII, must, to satisfy the data, afford an olefin mixture richer in 1-butene than that generated from VII alone.

It is difficult to further specify the nature of the transition state for this "bimolecular" elimination component, because, as in the substitution reactions, ill-defined heterogeneous regions and surface reactions are probably involved. However, it is reasonable that steric constraints in the transition state for such a reaction would be severe, the effective base (alkoxide, acetate, and diazotate ions at the solid surface) would be large, and hence the resulting olefins would be very rich in 1-butene.[36]

Experimental Section

N-Nitroso-*N*-*sec*-butylurethan.—*N*-*sec*-Butylurethan was obtained by the reaction of ethyl chloroformate with 2-aminobutane,[37] and had bp 44–47° (0.2 Torr),[38] infrared (film), 5.87 μ (C=O).[40] The nmr spectrum showed, *inter alia*, 4.05 (q, J = 7 Hz, OCH_2), 3.54 (sextet with additional fine structure, J = 7 Hz, CHN), and 1.20 (t, J = 7 Hz, OCH_2CH_3).[41]

The urethan was nitrosated with nitrogen tetroxide in ether in the presence of sodium bicarbonate. The procedure is that of White[5b], as followed by Moss.[9] *N*-Nitroso-*N*-*sec*-butylurethan was obtained as a yellow oil in 98% yield, infrared (film) 5.73 μ. The nmr spectrum showed, *inter alia*, signals corresponding to those of the urethan (cited above) at 4.45 (q, J = 7 Hz), 4.60,[42] and 1.47 (t, J = 7 Hz). The $\Delta\delta$ values (*N*-nitrosourethan–urethan) are characteristic for the *N*-nitrosourethan.[43] When stored at 0°, the *N*-nitrosourethan appeared to be stable for at least several months. Its purity was checked by nmr before each use.

Potassium Butane 2-Diazotate.—The procedure for preparing an ethereal suspension of a diazotate has been described.[9] The direct acetylation of butane 2-diazotate will be described in detail and brief remarks will be made about other procedures.

A solution of 20 mmol of Ac_2O[44] (or AcCl) in 25 ml of dry ether was rapidly injected, through a septum, into a nitrogen-blanketed suspension of 10 mmol of the diazotate at −19°. Nitrogen evolution was rapid, and complete (80–100% of theory) within 2–3 min. Butenes were removed from the evolved nitrogen (which was determined manometrically) by a sulfuric acid scrubber.

The ethereal product solution was washed with 5 ml of water, dried over $MgSO_4$, filtered, and then concentrated to about 25% of its original volume for gc analysis. The following compounds were isolated and characterized by comparison of retention times infrared spectra (and, in some cases, nmr spectra) with those of authentic samples:[45] *tert*-butyl alcohol, *sec*-butyl alcohol (acetic anhydride, acetic acid, *tert*-butyl acetate, eluted as a mixture), *sec*-butyl acetate,[46] diethyl carbonate, ethyl *tert*-butyl carbonate,[9] ethyl *sec*-butyl carbonate,[47] di-*tert*-butyl carbonate,[9] *sec*-butyl *tert*-butyl carbonate,[47] and (impure) *sec*-butylurethan.

The yield of *sec*-butyl acetate was determined by gc,[45] at 70°, of the crude product mixture, to which had been added a 2-hexanol standard. The thermal conductivity detector was calibrated for relative response, and the corrected *sec*-butyl acetate yields were 23–24% for acetylation with Ac_2O at −19°; the yield was lower in the AcCl reaction.[12]

(34) An arbitrary selection of some leading references, not necessarily those which mutually agree over interpretation, includes (a) I. N. Feit and W. H. Saunders, Jr., *J. Amer. Chem. Soc.*, **92**, 1620 (1970); (b) R. A. Bartsch, *J. Org. Chem.*, **35**, 1334 (1970); (c) R. A. Bartsch and J. F. Bunnett, *J. Amer. Chem. Soc.*, **91**, 1376 (1969); (d) **90**, 408 (1968); (e) I. N. Feit and W. H. Saunders, Jr., *Chem. Commun.*, 610 (1967); (f) H. C. Brown and R. L. Klimisch, *J. Amer. Chem. Soc.*, **88**, 1425 (1966).

(35) D. H. Froemsdorf, C. H. Collins, G. S. Hammond, and C. H. Depuy, *ibid.*, **81**, 643 (1959); A. Maccoll, *Advan. Phys. Org. Chem.*, **3**, 91 (1965).

(36) As with the stereochemistry of formation of *sec*-butyl acetate, so too with the positional and geometrical orientation of elimination to butenes, it matters not whether the butane 2-diazotate is acetylated with AcCl or Ac_2O; identical results are obtained.

(37) A. H. Blatt, Ed., "Organic Syntheses," Collect. Vol. II, Wiley, New York, N. Y., 1943, p 278, gives a general procedure. Our yields were generally 80–95%.

(38) Literature bp 83° (16 Torr).[39]

(39) K. Gubbins, S. Cordin, and R. Walker, *J. Gas Chromatogr.*, **3**, 331 (1965).

(40) Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrometer.

(41) Nmr spectra were recorded on either Varian A-60 or T-60 spectrometers as *ca.* 20% solutions in CCl_4. Chemical shift values are reported as parts per million downfield from an internal TMS standard. Signal integrals were consistent with structure.

(42) Only the three low-field lines of the methine proton, $J \sim 7$ Hz, are visible; the three high-field lines fall beneath the quartet at δ 4.46. The center of the methine sextet is estimated to lie at δ 4.60.

(43) R. A. Moss, *Tetrahedron Lett.*, 711 (1966).

(44) Boiling point 139°. Purified in accord with L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Vol. I, Wiley, New York, N. Y., 1967, p 3. The boiling point given here is 139.6°.

(45) A Varian–Aerograph A90-P3 gc was used, fitted with a 5 ft × 0.25 in., 20% SE-30 on 60/80 Gas-Chrom R column. Operating temperatures were injector, 200°; column, 78°; and detector, 200°. The He flow was 60 ml/min. The products are listed in the order of their elution.

(46) This compound was prepared from *sec*-butyl alcohol and acetyl chloride. Its infrared and nmr spectra were fully in accord with expectations.

(47) See the Results section.

When the evolved gases of the reaction were passed through a trap which had been cooled to −70°, volatile products were collected and identified by their gc retention times[48] as 1-butene, *trans*-butene, and *cis*-butene. Ether (5 ml) was distilled from the reaction vessel to the cold trap at the end of the reaction so as to ensure that the olefins had been carried over. Olefin distributions[49] appear above in the Results section and in Table III. The butene yield was determined gravimetrically. Bromination with 10% Br_2/CCl_4 of a freshly obtained butene product mixture provided 1.12 g (5.18 mmol) of a mixture of 1,2-dibromobutane and *meso*- and *dl*-2,3-dibromobutane.[50] Based upon the starting *N*-nitrosourethan, 11.5 mmol, the total butene yield was 45%.

Several variations of the fundamental decomposition procedure were employed in the optically active diazotate studies, which are summarized in Table I. The table lists all reagent quantities and reaction conditions, as well as the amounts of isolated *sec*-butyl acetate.[51] For runs which required solvents other than ether, the latter was removed *in vacuo* and the purified, dried, new solvent was injected through a septum onto the dry diazotate. All manipulations were carried out under nitrogen, and run 5 was performed in a nitrogen-filled drybox.

Optically Active Butane 2-Diazotate.—Optically active (*d*) 2-aminobutane was obtained from the racemate by the method of Bruck,[13] and was converted to the active urethan[14] as described above for the racemic series. Optical purities were determined on the *N*-*sec*-butylurethan, using Bruck's value of $\alpha^{21}D$ 18.2° as 100%. In actuality, the optically pure urethan is probably at least 2% more rotatory.[52-54]

The active urethan was nitrosated and converted to the diazotate as described above for the racemic series. Infrared and nmr spectra of the active compounds agreed with those of the previously examined racemates.

Optical rotations and analyses of *sec*-butyl acetate obtained in the acetylations of optically active butane 2-diazotate appear in Table I.[51]

In a control experiment, 0.19 g of acetic anhydride, 0.14 g of acetic acid, 0.62 g of diethyl carbonate, 0.62 g of *tert*-butyl acetate, 0.14 g of 1-butene, 1.0 g of potassium acetate, and 0.14 g of *sec*-butyl acetate ($\alpha^{25}D$ −1.25°, neat, 0.5 dm) were stirred in 10 ml of ether at 25° for 1 hr. After washing with 2.8 ml of water, we dried, filtered, and concentrated the organic material. Gc isolation at 78° from a 7 ft × 0.25 in., 20% SE-30 on 80/100 Chromosorb P column afforded 0.0592 g of the acetate which, after dilution with 0.0782 g of racemic ester, had $\alpha^{24}D$ −0.565°. The control product thus had (corrected) $\alpha^{24}D$ −1.31°.

(48) A Barber-Colman, Model 5000, flame ionization gc was employed, fitted with a 100-ft SF-96 Golay column. The detector and injector temperatures were 235° and 220°, respectively. The column was immersed in a Dry Ice–acetone bath which was held at −50°.

(49) The flame ionization detector was calibrated using prepared butene mixtures, and the relative responses, 1-butene:*trans*-butene:*cis*-butene were ~0.98:1.00:1.08. The results as given, however, are not corrected.

(50) Gc[48] at 90° showed less than 4% of impurities. Authentic dibromobutanes were obtained by brominating an authentic mixture of butenes.

(51) Full details of all gc procedures and columns used, together with a running commentary on each run, will appear in K. M. Luchter, Ph.D. Thesis, Rutgers University, New Brunswick, N. J., 1972. In general, the product was first isolated from a Carbowax 20M column, and then rechromatographed on a SE-30 column; final purity was established by reinjection and infrared analysis.

(52) Bruck, *et al.*,[14] report $\alpha^{20}D$ +5.47° and $\alpha^{19}D$ −5.56° for *sec*-butylamine and $\alpha^{21}D$ +18.2° for the *d*-urethan. Thomé[53] reports $\alpha^{20}D$ 5.38° for the amine. White has adduced evidence in support of Thomé's value.[5d] In some cases we obtained 2-aminobutane of somewhat *higher* rotation than yet reported (*e.g.*, $\alpha^{27}D$ +5.94°). Yet after conversion to the urethan, rotations lower than 18.2° were obtained. We have no explanation for this behavior. The amine in question was distilled from sodium, and was gc pure. All optical purities above *could*, therefore, be too low by 2–8% of the listed values. This would have no effect on our discussion or conclusions.

(53) L. G. Thomé, *Chem. Ber.*, **36**, 582 (1903).

(54) Optical rotations were measured with a Rudolph polarimeter, using a 100-μl, 0.5-dm cell. Samples were diluted with racemic material when necessary. In several cases, readings were checked, with good agreement, on a Perkin-Elmer spectropolarimeter.

***N*-Nitroso-*N*-*sec*-butylacetamide.**—*N*-*sec*-Butylacetamide was made from 2-aminobutane by the general procedure of White,[5c] and had bp 60–63° (0.15–0.25 Torr) and a C=O absorption (neat) centered at ~6.1 μ in the infrared.[55] The preparation of optically active *N*-*sec*-butylacetamide from the active amine was similarly accomplished. Our sample had $[\alpha]^{24}D$ +15.89° ($CHCl_3$, *c* 6.063 × 10^{-2}) and was 95.8% optically pure.[5d]

The nitrosation of the amide was modeled after the procedure of White.[5b] A three-neck flask was fitted with an inlet tube, low-temperature thermometer, stirring bar, and rubber septum. The flask was charged with 15 ml of ether and 30 mmol of sodium acetate. After cooling the flask (Dry Ice–acetone bath, −60°), nitrogen tetroxide (20–30 mmol) was admitted through the inlet tube. The reaction mixture was warmed to −5°, 10 mmol of *N*-*sec*-butylacetamide in 5 ml of ether was injected through the septum, and then the nitrosation was allowed to proceed, with stirring, for 1 hr at −10 to 0°. Light was excluded.

Work-up was done in the cold room (<15°). The ethereal product mixture was washed twice with saturated sodium bicarbonate solution, then with water, and then dried over molecular sieves. A 10-ml ethereal back-extract of the aqueous washes was combined with the major ether phase.

The dried ethereal *N*-nitroso-*N*-*sec*-butylacetamide[56] was decanted into a three-neck flask containing a stirring bar, a gas outlet tube, and a thermometer. The flask was connected either to a sulfuric acid scrubber, and thence to a gas buret, or to a cold trap (butene isolation). The contents of the flask were stirred in the dark at 28–30° for 15–18 hr, at which time gas evolution was over. The ether solution was washed with saturated aqueous sodium bicarbonate, then with water, and then dried. After filtration and concentration of the reaction product, *sec*-butyl acetate was isolated by gc (see above). The yield of the acetate, determined as before against a 2-hexanol standard, was 13.3–17.9% over two experiments.

The butene products were collected at −70°, in a separate run. The ether reaction solvent was distilled into the trap to ensure that all of the butenes had been purged from the reaction vessel. The 1-butene:*trans*-butene:*cis*-butene distribution was 3.85:2.38:1 as determined at 40° on the 20% SE-30 column described above.

In Table II, there will be found the conditions employed in the several decompositions of the optically active *N*-nitroso-*N*-*sec*-butylacetamide, as well as the optical rotations of the product *sec*-butyl acetate. The pure ester was isolated by iterative gc on the SE-30 column.

There were several unexplained infrared absorptions in the product of run 1 (Table II) at 4.55, 5.55, and 13.2 μ. The high optical rotation for this run's product may therefore be spurious. The *sec*-butyl acetate from runs 2 and 3 still contained an absorption at 13.2 μ which is absent in the racemic product. However, rechromatography of these samples on both SE-30 and Carbowax 20M columns revealed no impurities.

Registry No.—Butane 2-diazotate, 21892-73-9; *sec*-butyl acetate, 105-46-4; *N*-nitroso-*N*-*sec*-butylbenzamide, 33189-79-6; *N*-nitroso-*N*-*sec*-butylurethan, 33124-25-3.

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(55) Literature bp 119° (18 Torr), C=O at 6.06 μ (CCl_4 solution).[5b]

(56) A sample isolated by distillation of the ether at 0° had a C=O absorption in the infrared at 5.8 μ (neat); this is the expected location.[5b]

The Nature of the Carbonium Ion. VIII. Cycloalkyl Cations from Thiocyanate Isomerizations

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Thermal isomerizations of cyclopropylcarbinyl (1), cyclobutyl (2), cyclopentyl (4), and cyclooctyl (5) thiocyanates were effected in sulfolane and, where appropriate, less polar aprotic solvents. In these cases, formation of isomeric isothiocyanates at relative rates which paralleled the relative rate order observed for acetolyses of the corresponding *p*-toluenesulfonate esters indicated the intermediacy of cycloalkyl cations. The cyclobutyl related compounds, 1 and 2, isomerized to similar product mixtures but at vastly different rates. The product ratios observed in these cases did not resemble those from solvolyses of the analogous arylsulfonate esters, thereby suggesting that the partition of the intermediate ion(s) is governed largely by the proximity of the counterion in the intermediate ion pairs. Studies of the isomerizations of 1 with ionic and Lewis acid catalysts supported this notion. The larger cycloalkyl thiocyanates 4 and 5 isomerized only to their corresponding skeletally unrearranged isothiocyanate isomers 9 and 10, respectively. Reaction rates were in keeping with the relative driving forces to ionization for these secondary thiocyanates. Interpretations of the results are presented involving ion pair intermediates in which counterion position is largely influential in determining product compositions.

We have previously utilized the thiocyanate isomerization technique for examination of ion pairs[3] to study cationic intermediates which were generated by π participation and σ participation in bridged bicyclic systems.[4] In this paper we described the application of the technique to monocyclic cations. From the earlier work it was apparent that, among the nonallylic representatives of this category, only a few would be appropriate for study. The reason for the restriction lies primarily in the relative sluggishness of the reaction which only allows isomerizations, at detectable rates, for those primary and secondary thiocyanates which receive appreciable intramolecular assistance in ionization. Since we had established in the previous paper of this series[4e] a fair correlation between the rates of thiocyanate isomerization and the rates of acetolysis of the corresponding *p*-toluenesulfonate esters, we felt that the cyclobutyl (and its related cyclopropylcarbinyl), cyclopentyl, and cyclooctyl thiocyanates should be representative types which would isomerize and provide us with meaningful information. (Cyclohexyl thiocyanate had already been shown by us to be thermally unisomerizable[4c]).

Interest in the cyclobutyl–cyclopropylcarbinyl system stems from a prior examination[5] of the isomerization, in dimethylformamide, of cyclopropylcarbinyl thiocyanate (1). As subsequent work has shown that dimethylformamide induces anomalous results for other thiocyanates,[4b] it was of importance for comparison's sake to thoroughly study the isomerization of 1 in the better ionizing, less nucleophilic solvent, sulfolane. It was also considered likely that cyclobutyl thiocyanate (2), which was inert in dimethylformamide, would isomerize in sulfolane to provide more information on the role of the counterion in the skeletal partition of the intermediate cation(s). Cyclopentyl and cyclooctyl thiocyanates were interesting, in that their driving forces to ionization (if indeed they *did* isomerize) were only torsional and "I" strain—two factors which had not previously been demonstrated as sufficient to cause isomerization.

We therefore prepared these four thiocyanates, as well as allylcarbinyl thiocyanate (3), which is related to the cyclobutyl–cyclopropylcarbinyl series, along with their corresponding isothiocyanates, and subjected them to thermal isomerization conditions.

Results

Cyclopropylcarbinyl thiocyanate (1) was prepared from the corresponding *p*-toluenesulfonate[6] by displacement with potassium thiocyanate in anhydrous acetone. This method afforded material in excess of 98% purity. Further purification was effected by reaction of the isothiocyanate impurities with *n*-butylamine followed by preparative gc separation of the remaining thiocyanates. Pure 1 exhibited the characteristic organic thiocyanate infrared absorption at 2160 cm^{-1} (strong, sharp).

Allylcarbinyl thiocyanate (3) was synthesized by the same procedure used for 1. Allylcarbinyl *p*-toluenesulfonate[7] was treated with potassium thiocyanate in anhydrous acetone. Material prepared in this fashion had a small isothiocyanate impurity (~10% by infrared) which was removed, as before, by treatment with *n*-butylamine.

As no direct displacement route could be found to afford cyclobutyl thiocyanate (2) free of other skeletal isomers,[8] a more elaborate route was employed. Cyclopropylcarbinyl thiocyanate (1) was isomerized for approximately 10 hr at reflux in 0.15 *M* benzene solution containing 2% (w/v) of boron trifluoride etherate.

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(2) From the thesis submitted by R. K. Porter in fulfillment of the requirements for the M.S. degree, Temple University, 1970.

(3) For recent reviews see (a) L. A. Spurlock and T. E. Parks in "Mechanisms of Reactions of Sulfur Compounds," Vol. 3, N. Kharasch, Ed., Intra-Science Research Foundation, Santa Monica, Calif., 1970 p 161; (b) A. Fava in "Organic Sulfur Compounds," Vol. 2, N. Kharasch and C. Y. Meyers, Ed., Permagon Press, Oxford, 1966, p 85. See also (c) A. Fava, *et al.*, *J. Amer. Chem. Soc.*, **87**, 1045 (1965); (d) A. Ceccon, A. Fava, and I. Papa, *Chim. Ind. (Milan)*, **51**, 53 (1969), and references cited therein.

(4) (a) L. A. Spurlock and W. G. Cox, *J. Amer. Chem. Soc.*, **91**, 2961 (1969); (b) L. A. Spurlock and R. G. Fayter, *J. Org. Chem.*, **34**, 4035 (1969); (c) L. A. Spurlock and T. E. Parks, *J. Amer. Chem. Soc.*, **92**, 1279 (1970); (d) L. A. Spurlock and R. J. Schultz, *ibid.*, **92**, 6302 (1970); (e) L. A. Spurlock and W. G. Cox, *ibid.*, **93**, 146 (1971); (f) L. A. Spurlock and Y. Mikuriya, *J. Org. Chem.*, **36**, 1549 (1971).

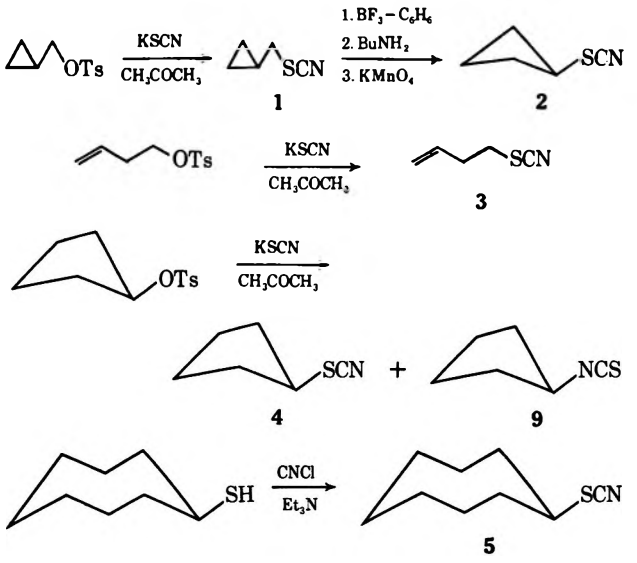
(5) L. A. Spurlock and P. E. Newallis, *Tetrahedron Lett.*, **No. 3**, 303 (1966).

(6) G. G. Bergstrom and S. Siegel, *J. Amer. Chem. Soc.*, **74**, 145 (1952).

(7) K. L. Servis and J. D. Roberts, *ibid.*, **86**, 3773 (1964).

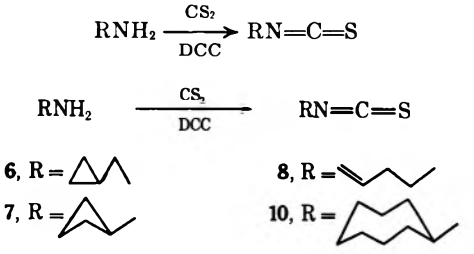
(8) Attempted displacements with thiocyanate ion on cyclobutyl chloride, bromide, or *p*-toluenesulfonate yielded only intractable mixtures.

The extent of isomerization was monitored by gc. When the concentration of **2** in the mixture seemed to be at a maximum, the mixture was worked up and then treated with *n*-butylamine to remove isothiocyanates. The resulting mixture of thiocyanates **2**, **1**, and **3** was then treated with saturated aqueous potassium permanganate at room temperature to remove thiocyanates **1** and **3**. Distillation afforded yet another mixture consisting mainly of **2** with a small amount of **1** remaining. Pure **2** was obtained from this mixture by preparative gc.



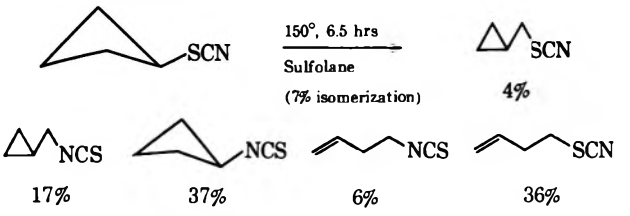
The potassium thiocyanate displacement of cyclopentyl *p*-toluenesulfonate afforded cyclopentyl thiocyanate (**4**) and the corresponding isothiocyanate (**9**). The two compounds were separated by chromatography on silica gel. Cyclooctyl thiocyanate (**5**), being inaccessible by the displacement route (much decomposition of the reactive *p*-bromobenzenesulfonate occurred), was obtained from cyanogen chloride treatment of cyclooctylthiol[9] in ether and triethylamine solution. Thiocyanate obtained in this fashion was utterly free of isothiocyanates.

Allylcarbinyl isothiocyanate (**8**) was obtained by treatment of the corresponding amine[10] with *N*,*N*′-dicyclohexylcarbodiimide[11] and carbon disulfide in ether at 10°. By the same procedure used for **8**, cyclobutyl isothiocyanate (**7**), cyclopropylcarbinyl isothiocyanate (**6**), and cyclooctyl isothiocyanate (**10**) were prepared from cyclobutylamine,[12] cyclopropylcarbinylamine,[10] and cyclooctylamine, respectively. Purifications were accomplished by distillation followed by preparative gc. Isothiocyanates **6**–**10** all exhibited typical organic isothiocyanate infrared absorptions at 2200–2000 cm^{-1} (strong, broad) as characteristic doublets. The *N*-phenylthiourea derivatives used to characterize **6**, **7**, and **8** were all prepared by treating the appropriate isothiocyanate with freshly purified aniline without solvent, followed by recrystallization of the crude material from ether–pentane.



The infrared and nmr spectra for all compounds were in accord with the structural assignments, and minimum purity in excess of 99.5% could be confirmed by gc and elemental analyses. All product and kinetic studies were conducted by gc, with structural assignments being made on the basis of comparison of retention times with those of authentic samples on two different columns.

In the cyclobutyl–cyclopropylcarbinyl series, control experiments confirmed the expectation that isothiocyanates **6**, **7**, and **8** and thiocyanate **3** were stable under the reaction conditions employed.[13] Thiocyanate **2** did, however, exhibit isomerization to the extent of 7% in sulfolane at 150° after 6.5 hr. The following product distribution (in relative per cent) was observed.



The slow isomerization rate and decomposition of some of the products on prolonged heating negated attempts to obtain accurate rate data. It was clear, however, that a large enough difference existed between the isomerization rates of cyclobutyl and cyclopropylcarbinyl thiocyanates that product distributions from the latter would not be markedly affected by secondary isomerizations of **2**.[14]

A more thorough examination of isomerizations of **1** was thus undertaken. Table I summarizes the results of solvent and temperature influences on the relative product ratios and relative isomerization rates of 0.150 *M* solutions of **1**. Values listed are the averages of at least two runs with overall material balances in excess of 90%.

The effects of varying the concentration of **1** were studied over a 100-fold range (0.015 *M* to 1.50 *M*). Results are seen in Table I. The decrease in extent of isomerization with increasing initial concentration of **1** is most readily explained as being caused by a decrease in the ionizing power of the isomerizing medium upon dilution with nonpolar **1**. This observation suggested that any bimolecular route to isomerization was improbable.

(9) (a) R. Frank and P. V. Smith, *J. Amer. Chem. Soc.*, **68**, 2103 (1946); (b) Sandler and Karo, "Organic Functional Group Preparations," Academic Press, New York, N. Y., 1968, p 483.

(10) J. D. Roberts and R. H. Mazur, *J. Amer. Chem. Soc.*, **73**, 2509 (1951).

(11) J. C. Jochims and A. Seeliger, *Angew. Chem., Int. Ed. Engl.*, **6**, 174 (1967).

(12) J. Casanova, Jr., N. D. Werner, and R. E. Schuster, *J. Org. Chem.*, **31**, 3413 (1966).

(13) Cyclopropylcarbinyl isothiocyanate (**6**) could be forced to isomerize to the extent of ~10% after 92 hr in sulfolane at 150°. The product mixture consisted of all thiocyanates and isothiocyanates of this series (**1**–**3**, **7**, and **8**). Because of its slowness, the reaction could have no influence on isomerizations of **1**, and is of interest only in that it is one of the few observed "reverse" thermal isomerizations.

(14) The subsequent observation that product distributions from **2** and **1** were quite similar reinforces this assumption.

TABLE I

ISOMERIZATIONS OF 0.150 *M* SOLUTIONS OF CYCLOPROPYLCARBINYL THIOCYANATE

Solvent	Temp, °C	Time, hr	% isomerization	Relative product, %
CH_3CN	130	12	2.8	6 22 38 11 22
		48	9.6	6 21 37 13 23
	140	6	2.8	5 22 42 10 22
		12	6.2	5 20 39 13 23
		24	11.9	5 20 39 13 23
	150	6	9.1	6 22 38 12 21
		12	14.3	6 21 39 13 21
Sulfolane	130	12	18.8	6 22 36 14 23
		48	55.0	6 22 35 15 22
	140	6	22.4	6 20 36 14 22
		12	40.2	6 20 37 15 22
		24	62.8	6 21 36 16 22
	150	6	46.3	6 21 36 15 20
		6[a]	48	6 22 37 14 21
		6[b]	36	6 20 39 16 20
		12	69.6	6 20 36 16 20
DMA[c]	150	6	23.0	5 10 39 34 11
DMF[d]	150	6	40.0	5 9 34 38 15

[a] 0.015 *M* solution. [b] 1.500 *M* solution. [c] Dimethylacetamide. [d] Dimethylformamide.

TABLE II

CATALYZED ISOMERIZATIONS OF 0.150 *M* SOLUTIONS OF CYCLOPROPYLCARBINYL THIOCYANATE IN SULFOLANE AT 150.0°

Catalyst	Concn, *M*	Time, hr	% isomerization	Relative product, %[a]
$KClO_4$	0.010	6	46.8	7 20 36 16 20
	0.100	6	55.5	7 20 34 18 22
KSCN	0.010	6	54.4	6 18 45 14 18
	0.100	6	79.2	4 10 68 8 10
$BF_3 \cdot Et_2O$[b]	2% (w/v)	2	20.5	5 13 23 18 42
		6	47.3	3 9 17 21 50
		10	68.0	3 8 14 22 54

[a] Values are averages of two runs. [b] In benzene at 80°.

Effects of catalysts were also studied using potassium perchlorate, potassium thiocyanate, and boron trifluoride as the catalytic substances. Table II lists these product distributions.

Isomerization rates were followed by gc. Specific rate constants were determined graphically by measuring the slopes of plots of log [RSCN] *vs.* time. Rate data obtained in this fashion are listed in Table III. Linear plots were obtained for all solvents studied. As expected, the isomerization was found to be more efficient in the more polar solvent, sulfolane, than in acetonitrile. The catalyzed isomerizations were also found to be first-order processes, although rate plots for the 0.100 *M* thiocyanate catalyzed runs began to deviate slightly from linearity. The effect of boron trifluoride catalysis is perhaps the most striking of these results in light of the fact that **1**, in benzene alone, would not isomerize even at 150°.

Cyclopentyl thiocyanate (**4**) and cyclooctyl thiocyanate (**5**) were subjected to product studies analogous to those applied to **1**. In both cases only the skeletally unrearranged isothiocyanate (**9** and **10**, respectively) was obtained. The rate of isomerization for **4**, being quite slow (1.86×10^{-6} sec^{-1}), was measured only in sulfolane at 150°. The cyclooctyl compound, however, isomerized at a comparatively rapid rate, and so rate measurements were conducted in acetonitrile as well as sulfolane and at two temperatures. The rates in these solvents were as follows: sulfolane, 3.0×10^{-5} sec^{-1} ($t_{1/2}$ = 6.5 hr) at 150°; 2.5×10^{-6} sec^{-1} ($t_{1/2}$ = 78 hr) at 130°; and acetonitrile, 3.6×10^{-6} sec^{-1} ($t_{1/2}$ = 54 hr) at 150°.

Discussion

The rate data from **1**, and particularly the strong dependence on solvent ionizing power, indicate a rate-determining step consisting of the unimolecular dissociation of a neutral molecule into ions. As expected for such a process, product ratios were found to be essentially independent of time, temperature, and changes in the concentration of **1** over a wide range. By analogy to other alkyl thiocyanate isomerizations,[3b,4] the ionization is thought to proceed very little past the intimate ion pair stage. Although no experiments were carried out to determine the extent of further dissociation to solvent-separated or "free" ion pairs, it seems reasonable to assume a limit of *ca.* 10–12% for this process.[15] The invariance of product ratios with temperature and time confirms that no significant secondary processes are occurring; thus the products observed may be con-

(15) This is based on a similar limit, determined by isotopic labeling experiments, for isomerizations of *exo*-2-norbornyl thiocyanate.[4c] As the isomerization rates of this compound and **1** are quite close, it is reasonable to assume that they will possess approximately the same dissociative properties.

TABLE III

ISOMERIZATION RATES OF 0.150 *M* SOLUTIONS OF CYCLOPROPYLCARBINYL THIOCYANATE

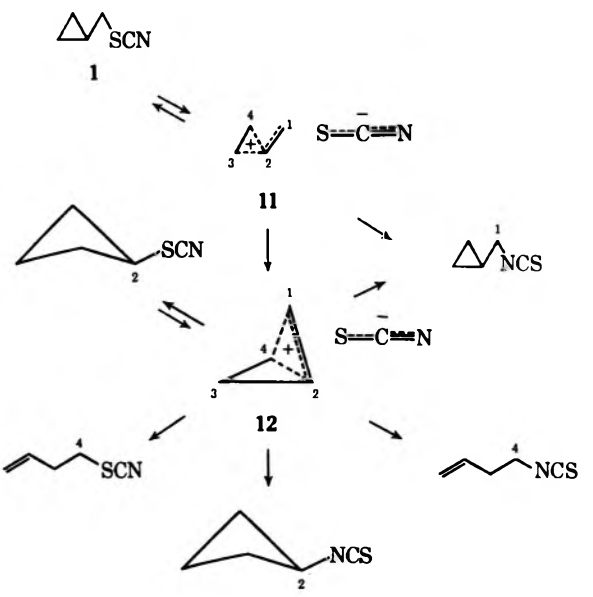
Solvent	Temp, °C	Catalyst	Concn, *M*	$k \times 10^6$ sec^{-1}	$t_{1/2}$, hr
CH_3CN	130			0.578 ± 0.021	333.7
	140			1.46 ± 0.03	131.8
	150			3.66 ± 0.15	52.6
Sulfolane	130			4.49 ± 0.13	43.0
	140			11.2 ± 0.2	17.0
	150			27.0 ± 0.4	7.12
	150	$KClO_4$	0.010	29.4 ± 0.6	6.56
	150	$KClO_4$	0.100	34.9 ± 0.4	5.52
	150	KSCN	0.010	32.2 ± 0.9	5.99
	150	KSCN	0.100	57.7 ± 2.9	3.34
Benzene	80	$BF_3 \cdot Et_2O$	2% (w/v)	30.7 ± 0.3	6.27
CH_3CN: $\Delta H^{\ddagger} = 31$ kcal/mol				$\Delta S^{\ddagger}_{130°} = -10$ eu	
Sulfolane: $\Delta H^{\ddagger} = 30$ kcal/mol				$\Delta S^{\ddagger}_{130°} = -8$ eu	

sidered as mainly the results of the partition of the initial intimate ion pairs.

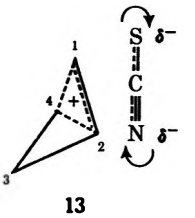
Since the isomerization of **1** proceeds much more rapidly than that of most primary thiocyanates, there is indication that anchimeric assistance to ionization is taking place, as was observed[16] in other carbonium ion reactions of cyclopropylcarbinyl derivatives. This effect is thought to be due to a release of strain in the cyclopropyl ring[16e] and, to a lesser extent, to stabilization of the incipient carbonium ion by delocalization of charge into the ring.[16c] The similarity of the activation parameters calculated for the thiocyanate isomerization with those found by Roberts[17] for homoallylically assisted solvolyses would seem to support the idea of assisted ionization for **1**. If one assumed that the initial carbonium ion formed, **11**, is similar to the cyclopropylcarbinyl ion of the transition state, further rearrangement is necessary to provide the intermediate ion (**12**) from which products of different structure are derived. In the mechanistic picture presented in Scheme I, this second intermediate is represented as the unsymmetrical bicyclobutonium ion (**12**).[18] Alternatively, a set of ions centered about the "symmetrical bicyclobutonium" ion could be postulated.[16b] We have chosen to represent the product-forming ion as **12** mainly for the sake of simplicity, and because our results do not allow us to distinguish between the two types of ions.[19]

For these reactions product formation represents a competition between the S and N ends of the thiocyanate anion for capture of the electrophilic sites of the cations. In carbonium ion reactions, the S end of the thiocyanate anion has been reported to be more nucleophilic than the N end by a factor of about 2–9.[3b,4c] The data outlined in Table I show an average S/N

SCHEME I



ratio of 0.6 for all the products, *i.e.*, (**2**, **3**)/(**6**, **7**, **8**). Isothiocyanate **6** however, can arise by N capture of the first-formed, cyclopropylcarbinyl intermediate, **11** (S capture regenerates starting material), as well as through attack on **12**. The S/N ratio for *all* the products is thus misleading. Comparison of the *rearranged* product ratios reveals S/N ratios of 2.3 for the allylcarbinyl products (**3**/**8**) and 1.0 for cyclobutyl products (**2**/**7**). The latter "abnormally" low S/N ratio shows some unusual preference for N-end attack by the thiocyanate anion on C_2 of the bicyclobutonium ion. Clearly, in the early stages of its formation, ion **12** still retains the majority of positive charge at C_1, which is partially "solvated" by the S end of the leaving group. Attack by the N end of thiocyanate could occur at C_2 *via* a semicyclic mechanism as illustrated in **13**. A similar mechanism could be envisioned as increasing N attack at C_4; however, the longer C_1–C_4 bond length



13

(16) (a) K. B. Wiberg and J. G. Pfeiffer, *J. Amer. Chem. Soc.*, **92**, 553 (1970); (b) K. B. Wiberg and G. Szeimes, *ibid.*, **92**, 571 (1970); (c) P. v. R. Schleyer and G. W. Van Dine, *ibid.*, **88**, 2322 (1968); (d) R. Breslow in "Molecular Rearrangements," Vol. I, P. de Mayo, Ed., Interscience, New York, N. Y., 1963, pp 259–280; (e) S. Winstein and E. M. Kosower, *J. Amer. Chem. Soc.*, **81**, 4397 (1959).

(17) (a) D. D. Roberts, *J. Org. Chem.*, **34**, 285 (1969); (b) D. D. Roberts and T. M. Watson, *ibid.*, **35**, 978 (1970).

(18) A more accurate representation might include an equilibrating set of bicyclobutonium ions; however, only one is used here for the sake of simplicity.

(19) By analysis of the preliminary results reported by Spurlock and Newallis[6] on the isomerization of **1**, Majerski, *et al.* [see *Tetrahedron*, **23**, 661 (1967)] also deduced that the intermediate must be a bicyclobutonium ion. Careful consideration of the factors involved in their arguments leads one to question the certainty of this conclusion. The bicyclobutonium ion was nevertheless adopted as the best representation of the second product-forming intermediate for clarity of presentation.

in the early phase of bicyclobutonium ion formation may preclude this. An alternative explanation might simply reside in different relative electronic requirements for S-end and N-end attacks at C_2 and C_4, since it is conceivable that in the initial stages of the formation of **12** more charge would reside on C_2 than on C_4.

The slight trends in product ratios observed with increasing ionizing strength of the solvent (perchlorate ion catalysis) are best explained in terms of greater ionic mobility. The small decrease in proportion of **6** is probably due to a less efficient capture of the first formed intermediate **11** as solvation of the ion pair is improved. The increases in allylcarbinyl products **3** and **8** may be related to an increased lifetime of the bicyclobutonium ion pair, allowing for more efficient migration by the thiocyanate anion to C_4. The failure of thiocyanate ion catalysis to show similar trends (in that a substantially increased percentage of isothiocyanate **6** was observed) indicates only that a bimolecular displacement process is occurring in competition with unimolecular dissociation.

Catalysis by boron trifluoride ethereate in benzene solution illustrates yet another mode for isomerization. In this case, the effectiveness of the catalyst leads toward an equilibration of the thiocyanate ring skeleta. This is best seen through the time dependence of the product ratios (Table II). Additional experiments at longer reaction times showed a decrease in the relative amount of cyclobutyl thiocyanate (**2**) after reaching a maximum proportion, accompanied by an increase in proportion of the inert allylcarbinyl thiocyanate (**3**). No attempt was made to follow the reaction to completion owing to the slowness of the conversion **2** → **3**, but an analogous situation has been described by Olah and Lin[20] in the aluminum chloride catalyzed isomerizations of cyclopropylcarbinyl chloride, first to cyclobutyl chloride and then to allylcarbinyl chloride. The fact that, in this case, thiocyanate products were formed preferentially to isothiocyanates has been attributed to the ability of the Lewis acid to coordinate with the N end of the thiocyanate moiety, thereby suppressing N-bound product formation. One may therefore suppose that the ultimate composition under these conditions would consist mainly of thiocyanate **3** with small amounts of isothiocyanates **6**, **7**, and **8**.

Isomerizations of **1** in the more nucleophilic solvents, dimethylformamide and dimethylacetamide, also produced a marked enhancement of the relative per cent of thiocyanate **3** in the products. This effect is thought to be due to ionization processes which are assisted by these nucleophilic solvents,[4b] resulting in loosely bound solvent–carbonium ion complexes. If this is the case, the more nucleophilic S end of the thiocyanate moiety might be expected to be more efficient in liberating the carbonium ions from the complexes, leading to increased thiocyanate products.

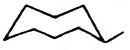
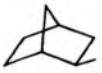
In general, the thermal isomerizations of **1** seem well characterized as anchimerically assisted, unimolecular dissociation processes, in which ion pairs and counterion mobility play important roles in structural partition. In all likelihood the isomerization of cyclobutyl thiocyanate (**2**) may be described in the same fashion.

By contrast, the less complicated isomerizations of cyclopentyl (**4**) and cyclooctyl (**5**) thiocyanates are clearly dissociation–recombination reactions in which structural features allow for no skeletal modifications[21] during the ion pair phase. The unusual feature of these reactions lies in the fact that they are the first observations of uncatalyzed[22] secondary thiocyanate isomerization occurring with no neighboring group assistance. It is usually assumed that torsional strain exerts a driving force to ionization of cyclopentyl and cyclooctyl derivatives, and this would seem to be the reason for the isomerizations of **4** and **5**. The previously mentioned failure of the unstrained cyclohexyl thiocyanate to isomerize adds support to this explanation.

The relationship between rates of thiocyanate isomerizations in sulfolane and rates of acetolysis by the corresponding *p*-toluenesulfonates again essentially holds. (See Table IV and ref 4e.) Based on these facts we now feel secure in the ability to predict the probability of obtaining a thermal thiocyanate–isothiocyanate interconversion, and to suggest likely rates of transformation.

TABLE IV

COMPARISON OF RELATIVE THIOCYANATE ISOMERIZATION RATES IN SULFOLANE WITH *p*-TOLUENESULFONATE ACETOLYSIS RATES

Alkyl group	RSCN rel rate 150°	ROTs rel rate 25°
	1.14	26.7
	0.04	0.20
	0.08	0.19
	1.3	3.4
	1	1

Experimental Section[23]

Cyclopropylcarbinyl Thiocyanate (1).—To a mechanically stirred solution of 33.0 g (0.340 mol) of potassium thiocyanate in 1.3 l. of anhydrous acetone was added rapidly 74.2 g (0.327 mol) of crude cyclopropylcarbinyl *p*-toluenesulfonate[6] in 100 ml of acetone. Precipitation began before the addition was complete (10 min). The resulting mixture was allowed to stir overnight at room temperature. The precipitated salt was removed by filtration and washed well with pentane. The acetone filtrate

(20) G. A. Olah and C.-H. Lin, *J. Amer. Chem. Soc.*, **90**, 6468 (1968).

(21) It is conceivable that some hydride shifts could occur during these isomerizations, thereby changing the carbon of attachment for the functional group. We consider this possibility unlikely, or at best affording a minimal contribution to the reaction, since the ordinarily facile 2,6-hydride shifts of the 2-norbornyl cation were shown[4c] to be completely suppressed during isomerizations of *exo*-2-norbornyl thiocyanate.

(22) sec-Butyl thiocyanate can be isomerized, albeit slowly, when boiled with zinc chloride. See P. A. S. Smith and D. W. Emerson, *J. Amer. Chem. Soc.*, **82**, 3076 (1960).

(23) Melting and boiling points were uncorrected. Infrared spectra were obtained on a Perkin-Elmer Infracord Model 137B using sodium chloride optics. A Perkin-Elmer Model F-11 gas chromatograph was employed for analyses of isomerization mixtures and kinetics, using two columns: a 6 ft × 1/8 in. 30% phenyl diethanolamine succinate (PDEAS) on 60/80 mesh Chromosorb W, and a 6 ft × 1/8 in. 20% diethylene glycol succinate (LAC-728) on 60/80 mesh Chromosorb W. Elemental anslyses were performed by Micro-Analysis, Inc., of Wilmington, Del. Organic solvents were of A. C. S. reagent grade unless otherwise specified. Dioxane was purified by the method described by Fieser. [See "Experiments in Organic Chemistry," third ed.] Sulfolane was distilled from potassium permanganate under vacuum. Dimethylformamide was distilled from calcium hydride. Aniline was purified by distillation from zinc dust.

was divided into two portions, both of which were worked up by addition of 1.0 l. of water and extracted several times with pentane. The combined pentane solutions were washed with water and dried over magnesium sulfate. Evaporation of the solvent and vacuum distillation of the crude product gave 14.7 g (40%) of **1**, bp 73.5–76.5° (10 mm) [lit.[5] bp 76.3–77.2° (14 mm)]. This was shown by gc to be 98% pure. The small isothiocyante impurity was removed by treating the product with 3 ml of *n*-butylamine in the absence of solvent for 0.5 hr. Pentane (50 ml) was added and the solution was washed twice with 10% hydrochloric acid, dried over magnesium sulfate, and concentrated. Distillation gave 10.6 g of pure **1**, bp 75.8–76.0° (10 mm).

A completely homogeneous sample of **1** was also obtained by preparative gc (6 ft × 0.5 in. LAC-728 column) and had ir (film) 3000, 2160, 1425, 1255, 1025, 970, 920, and 835 cm^{-1}; nmr (CCl_4) τ 7.05 (d), 8.60–9.02 (m), 9.02–9.78 (m).

Anal. Calcd for C_6H_7NS: C, 53.06; H, 6.23; N, 12.38. Found: C, 53.36; H, 6.23; N, 12.24.

Cyclobutyl Thiocyanate (2).—To a magnetically stirred solution of 3.52 g (0.0248 mol) of boron trifluoride etherate in 170 ml of benzene being heated at reflux was added in one portion a solution of 3.00 g (0.0265 mol) of **1** in 6 ml of benzene. The course of the reaction was followed by gc. After 10 hr, when the concentration of **2** seemed to be at a maximum, the reaction was quenched by pouring into 100 ml of saturated sodium bicarbonate solution. The organic layer was separated and the aqueous solution was extracted with 50 ml of pentane. The combined organic extracts were washed with water and dried over magnesium sulfate. Removal of the solvent under vacuum left 2.85 g of an orange liquid shown by gc to consist of a complex mixture, 37% of which was the desired **2**. The isothiocyanate impurities were removed by treating the mixture with 3 ml of *n*-butylamine in the absence of solvent for 1 hr. Pentane (50 ml) was added and the solution was washed twice with 10% hydrochloric acid, dried over magnesium sulfate, and concentrated. The yellow residue, amounting to 1.86 g, was then dissolved in 50 ml of pentane and treated with 50 ml of a saturated aqueous potassium permanganate solution. After stirring at room temperature for 0.5 hr, the organic layer was separated and the aqueous layer was extracted twice with 25 ml of pentane. The combined pentane solutions were washed with water and dried over magnesium sulfate. Removal of the solvent under vacuum left 1.17 g of a yellow liquid. This mixture was flash distilled at 10 mm, affording a mixture consisting of 88% of **2**. Pure **2** was collected from the mixture by preparative gc on a 7 ft × 3/8 in. 25% PDEAS column. This material had bp 69.0–70.0° (10 mm); ir (film) 3000, 2950, 2150, 1440, 1280, 1010, 820, and 720 cm^{-1}; nmr ($CDCl_3$) τ 6.20 (quintet), 7.25–8.50 (m).

Anal. Calcd for C_5H_7NS: C, 53.06; H, 6.23; N, 12.38. Found: C, 53.30; H, 6.28; N, 12.46.

Allylcarbinyl Thiocyanate (3).—To a mechanically stirred solution of 5.04 g (0.052 mol) of potassium thiocyanate in 75 ml of anhydrous acetone was added dropwise 11.62 g (0.051 mol) of crude allylcarbinyl *p*-toluenesulfonate[7] in 25 ml of acetone. The mixture was heated at reflux for 66 hr. Upon cooling, the mixture was filtered with suction and the precipitated solid was washed well with acetone. The combined filtrate and washings were concentrated under vacuum to a semisolid residue which was triturated with pentane. Vacuum evaporation of this solvent left 5.62 g (97%) of crude **3**, estimated to have 10% isothiocyanate impurity by infrared analysis. The crude product was purified by treatment with 1.82 g (0.025 mol) of *n*-butylamine in 60 ml of anhydrous dioxane. After stirring for 17 hr at room temperature, the reaction mixture was poured into 350 ml of water and extracted with pentane. The combined extracts were washed with 10% hydrochloric acid followed by saturated sodium bicarbonate solution and dried over magnesium sulfate. Evaporation of the solvent followed by distillation of the residue gave 3.30 g (57%) of pure **3**, bp 65–77° (11.5 mm) [lit.[5] bp 75.5–76.2° (18 mm)]. A completely homogeneous sample of **3** obtained by preparative gc (6 ft × 3/8 in. LAC-728 column) had bp 65.0–67.0° (9.5 mm); ir (film) 2900, 2170, 1650, 1440, 1285, 1000, and 930 cm^{-1}; nmr (CCl_4) τ 3.86–4.58 (m), 4.65–5.08 (m), 7.02 (t), 7.49 (q).

Anal. Calcd for C_5H_7NS: C, 53.06; 6.23; N, 12.38. Found: C, 53.08; H, 6.07; N, 12.63.

Cyclopentyl Thiocyanate (4) and Isothiocyanate (9).—To a mechanically stirred solution of 10.67 g (0.110 mol) of potassium thiocyanate in 500 ml of anhydrous acetone was added in one portion a solution of 23.8 g (0.099 mol) of crude cyclopentyl *p*-toluenesulfonate[24] in 50 ml of acetone. The solution was heated at reflux overnight. The reaction mixture was concentrated under vacuum and the resulting residue was triturated with pentane. The pentane solution was washed with water, dried, and concentrated to yield 11.30 g (90%) of a gold liquid shown by gc to consist of 75% **4** and 25% **9**. Chromatography on silica gel (300 g) gave a complete separation of these materials, with **9** being eluted first by pentane and **4** ultimately eluted with ether.

Thiocyanate **4** was obtained in the amount of 7.24 g after distillation: bp 87.0° (10 mm); ir (film) 2960, 2870, 2150, 1450, 1440, 1320, 1240, 1020, 930, 890, and 805 cm^{-1}; nmr ($CDCl_3$) τ 6.25–6.60 (m), 7.59–8.60 (m); mass spectrum (50 eV) *m/e* 127 (12), 69 (90), 68 (25), 67 (32), 41 (100), and 39 (31).

Isothiocyanate **9** was obtained in the amount of 1.40 g after distillation: bp 80.0° (10 mm); ir (film) 2960, 2870, 2200–2000, 1450, 1440, 1350, 1340, 1315, 1280, 1070, 935, 880, and 800 cm^{-1}; nmr ($CDCl_3$) τ 5.70–6.12 (m), 7.80–8.70 (m); mass spectrum (50 eV) *m/e* 127 (70), 69 (100), 68 (67), 67 (35), 41 (37), and 39 (39).

Cyclooctyl Thiocyanate (5).—A solution of 40.2 g (0.28 mol) of cyclooctylthiol[9] and 34.87 g (0.34 mol) of triethylamine in 100 ml of dry ether was added dropwise to a solution of 17.7 g (0.34 mol) of cyanogen chloride in 200 ml of dry ether. The bath temperature was maintained below −15° during the addition and then allowed to slowly come to room temperature overnight. The white solid which had formed was filtered off and washed several times with ether. The filtrate and washings were combined and washed three times with 100 ml of water, three times with 50 ml of saturated sodium bicarbonate solution, two times with 50 ml of 10% hydrochloric acid, and finally three more times with 100 ml of water. The ether layer was dried and concentrated, affording 51.0 g of a dark brown liquid. The crude material was distilled at 60–64° (0.07 mm) yielding 22.8 g (48.3%) of a colorless liquid. Gc analysis proved this to be an approximately equal mixture of two compounds, one of which could be identified as the desired thiocyanate, **5**. Separation of pure **5** was accomplished by distillation on a 24-in. Teflon spinning band column: bp 61–64° (0.07 mm); mass spectrum (50 eV) *m/e* 169 (1.9), 111 (10.5), 110 (15.2), 82 (40), 81 (37), 69 (41), 68 (44), 67 (48), 57 (100), and 55 (43).

Cyclopropylcarbinyl Isothiocyanate (6).—As in the procedure described for **8**, 2.12 g (0.03 mol) of cyclopropylcarbinyl amine in 1 ml of ether was treated with 6.18 g (0.03 mol) of *N,N*-dicyclohexylcarbodiimide and 18 ml (22.7 g, 0.30 mol) of carbon disulfide in 50 ml of ether to yield, after distillation, 2.20 g (65%) of **6**, bp 81.5–82.5° (21 mm) [lit.[5] bp 78.0–79.0° (20 mm)]. A completely homogeneous sample of **6**, obtained by preparative gc (6 ft × 0.5 in. LAC-728 column), had bp 65° (10 mm); ir (film) 2220, 2000, 1440, 1380, 1320, 1020, 990, 930, and 835 cm^{-1}; nmr ($CDCl_3$) τ 6.58 (d), 8.40–9.02 (m), 9.04–9.88 (m).

Anal. Calcd for C_5H_7NS: C, 53.06; H, 6.23; N, 12.38. Found: C, 53.21; H, 5.98; N, 12.16.

1-Cyclopropylcarbinyl-3-phenylthiourea.—A magnetically stirred mixture of 1.00 g (8.85 mmol) of **6** and 1.00 g (10.8 mmol) of aniline was allowed to stir overnight at room temperature, then cooled to induce crystallization. The resulting solid was pulverized, triturated with pentane, and air dried to yield the crude thiourea in the amount of 1.83 g (100%). Two recrystallizations from 50% ether–pentane gave a sample: mp 94.0–94.6°; ir (Nujol) 3300, 3130, 1590, 1540, 1510, 1310, 1230, 1140, 920, 790, 730, and 680 cm^{-1}; nmr ($CDCl_3$) τ 2.50–3.08 (m), 3.74 (br s), 6.58 (d d), 8.64–9.32 (m), 9.34–9.90 (m).

Anal. Calcd for $C_{11}H_{14}N_2S$: C, 64.04; H, 6.84; N, 13.58. Found: C, 63.80; H, 6.90; N, 13.66.

Cyclobutyl Isothiocyanate (7).—Cyclobutyl isothiocyanate was prepared by the procedure used for **8** with minor changes (the ethereal amine solution was added in one portion and the reaction time was shortened to 18 hr). In this preparation, 5.33 g (0.075 mol) of cyclobutylamine[12] in 20 ml of ether was treated with 15.42 g (0.075 mol) of *N,N'*-dicyclohexylcarbodiimide and 45 ml (57 g, 0.75 mol) of carbon disulfide in 150 ml of ether to yield, after distillation, 7.02 g (82%) of **7**: bp 65.5–66.0° (10.5 mm) [lit.[5] bp 77.4–78.5° (28 mm)]; ir (film) 3000, 2280–2000, 1340, 1140, 1030, 980, 940, 810, and 708 cm^{-1}; nmr (CCl_4) 5.90 (quintet), 7.30–8.50 (m).

Anal. Calcd for C_5H_7NS: C, 53.06; H, 6.23; N, 12.38. Found: C, 53.06; H, 6.43; N, 12.34.

(24) J. D. Roberts and V. C. Chambers, *J. Amer. Chem. Soc.*, **73**, 5034 (1951).

1-Cyclobutyl-3-phenylthiourea.—A mixture of 1.00 g (8.85 mmol) of **7** and 0.830 g (8.93 mmol) of aniline was allowed to stir overnight at room temperature. The solidified reaction mixture was pulverized and recrystallized from ether, yielding 1.66 g (91%) of the desired thiourea as fine needles: mp 100.5–101.5°; ir (Nujol) 3300, 3210, 1585, 1495, 1240, 740, and 685 cm^{-1}; nmr ($CDCl_3$) τ 2.50–3.00 (m), 3.50–3.94 (br d), 5.40 (quintet), 7.38–8.54 (m).

Anal. Calcd for $C_{11}H_{14}N_2S$: C, 64.04; H, 6.84; N, 13.58. Found: C, 64.80; H, 6.82; N, 13.65.

Allylcarbinyl Isothiocyanate (8).—The isothiocyanate was prepared by an adaption of the method of Jochims and Seeliger.[11] To a magnetically stirred solution of 10.30 g (0.05 mol) of *N,N'*-dicyclohexylcarbodiimide and 30 ml (38.0 g, 0.5 mol) of carbon disulfide in 100 ml of ether cooled at −20° was added dropwise 3.55 g (0.05 mol) of allylcarbinyl amine[10] in 5 ml of ether. The cooling bath was removed and the mixture was allowed to stir at room temperature for 47 hr. The precipitated thiourea was removed by filtration and triturated with ether. The combined ethereal solutions were vacuum evaporated to yield, after distillation, 4.35 g (77%) of **8**, bp 69.0–71.5° (16 mm) [lit.[10] bp 77.5° (28 mm)]. A portion of this material, further purified by preparative gc (6 ft × 0.5 in. LAC-728 column), had bp 67° (10 mm); ir (film) 2930, 2200, 2100, 1650, 1460, 1350, 995, and 925 cm^{-1}; nmr ($CDCl_3$) τ 3.76–4.48 (m), 4.58–5.00 (m), 6.41 (t), 7.53 (q).

Anal. Calcd for C_5H_7NS: C, 53.06; H, 6.23; N, 12.38. Found: C, 53.16; H, 6.30; N, 12.38.

1-Allylcarbinyl-3-phenylthiourea.—This derivative was prepared by treating 1.22 g (10.8 mmol) of **8** being stirred magnetically at room temperature with 1.0 g (10.8 mmol) of aniline. The mixture was allowed to stir overnight. The crude thiourea was crystallized from 50% ether–pentane, affording 1.98 g (89%). Three subsequent recrystallizations from 50% ether–pentane gave a sample of pure thiourea having mp 43.8–45.0°; ir (Nujol) 3300, 3175, 1320, 1300, 1240, 1200, 1100, 920, 840, and 780 cm^{-1}.

Cyclooctyl Isothiocyanate[25] (10).—To a magnetically stirred suspension of 20.8 g (0.1 mol) of dicyclohexylcarbodiimide and 100 ml of carbon disulfide in 100 ml of anhydrous ether being cooled in an ice–salt bath at −12°, was added dropwise a solution of 12.7 g (0.1 mol) of cyclooctyl amine in 50 ml of anhydrous ether. After all the amine had been added, the temperature was allowed to rise slowly to room temperature and stirring was continued overnight. The resulting mixture was then combined with 10 g of Celite 545 filter aid and the precipitate was removed by filtration. The filter cake was washed three times with 100-ml portions of ether, and the filtrates were combined and concentrated. This afforded 17.3 g of a light orange liquid. The crude product was distilled at 83–85° (0.8 mm), yielding 16.0 g (94.7%) of a colorless liquid: mass spectrum (50 eV) *m/e* 169 (7.3), 111 (9.4), 69 (41), 55 (21), 44 (61), and 28 (100).

Product Studies.—Solutions 0.150 *M* in pure thiocyanate were prepared using acetonitrile, sulfolane, dimethylacetamide, or dimethylformamide. Aliquots (2 ml) were sealed in ampoules and heated at 130.0° (acetonitrile and sulfolane only), 140° (acetonitrile and sulfolane only), or 150.0° (all) for various times. The ampoules were quenched in ice water and opened, and the contents were poured into 25 ml of water. The resulting mixtures were extracted twice with 5 ml of pentane. The combined pentane extracts were washed with 10 ml of water, dried, and concentrated to yield residues which were anayzed by gc using the following columns and conditions: (A) column, 6 ft × 1/8 in. 30% PDEAS on Chromosorb W 60/80 mesh; temperature, 150°; carrier flow, 20 ml/min [R_t (min) **9**, 5.8; **8**, 6.3; **7**, 7.2; **6**, 8.1; **3**, 9.2; **5**, 9.9; **2**, 10.3; **1**, 14.1] and (B) column, 6 ft × 1/8 in. 20% LAC-278 on Chromosorb W 60/80 mesh; temperature, 110°; carrier flow, 60 ml/min [R_t (min) **8** and **7**, 3.4; **6**, 4.4; **3** and **2**, 5.6; **9**, 6.1; **1**, 8.6; **6**, 12.0].

Kinetic Procedure.—Solutions 0.150 *M* in pure **1**, **4**, or **5** were prepared in acetonitrile and sulfolane and treated as before. Reaction rates were obtained from plots of log [RSCN] *vs.* time by the method of least squares.

Catalyzed Isomerizations and Kinetics in Sulfolane.—Solutions 0.150 *M* in pure **1** were prepared using sulfolane which was either 0.01 or 0.10 *M* in potassium perchlorate or potassium thiocyanate. Aliquots (2 ml) were heated at 150.0° and treated as previously described.

Concentration Variation Studies.—Sulfolane solutions 0.015, 0.150, or 1.500 *M* in **1** were prepared. Aliquots (2 ml) were heated at 150° for 6 hr. The products were analyzed in the usual way.

Catalyzed Isomerizations and Kinetics in Benzene.—A 2% (w/v) solution of boron trifluoride ethereate in benzene was made 0.150 *M* in **1**. At intervals, 2-ml aliquots were withdrawn from the solution at reflux with a hypodermic syringe. The samples were washed with saturated sodium bicarbonate solution, dried, and concentrated to yield residues which were analyzed by gc.

Registry No.—**1**, 6129-85-7; **2**, 6068-88-8; **3**, 6068-89-9; **4**, 5263-57-0; **5**, 5263-56-9; **6**, 6068-90-2; **7**, 6068-91-3; **8**, 3386-97-8; **9**, 33522-03-1; **10**, 33522-04-2; 1-cyclopropylcarbinyl-3-phenylthiourea, 33522-05-3; 1-cyclobutyl-3-phenylthiourea, 33522-06-4; 1-allylcarbinyl-3-phenylthiourea, 33522-07-5.

Acknowledgment.—We wish to express appreciation to the Petroleum Research Fund administered by the American Chemical Society (Grant. No. 2925-A1) for partial support of this research.

(25) O. Billeter, *Ber.*, **8**, 462 (1875).

Stable Carbocations. CXXXI.[1] Intermolecular Fluorine Exchange of the Methylfluorocarbenium and Dimethylfluorocarbenium Ions in $HF-SbF_5-SO_2ClF$ Solution

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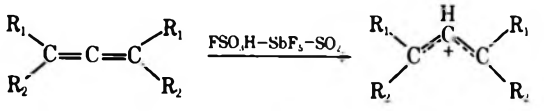
Protonation of allene, methylacetylene, and 2-fluoropropene as well as ionization of 2,2-difluoropropane in $HF-SbF_5-SO_2ClF$ solution all gave the dimethylfluorocarbenium ion which underwent rapid fluorine exchange with the superacid system. The fluorine exchange reaction of the dimethylfluorocarbenium ion as well as that of the methylfluorocarbenium ion was studied by ^1H, ^{19}F, and ^{13}C nmr spectroscopy.

In previous studies, protonation of substituted allenes in $FSO_3H-SbF_5-SO_2$ solution leading to the formation of the corresponding allylic cations was reported.[3]



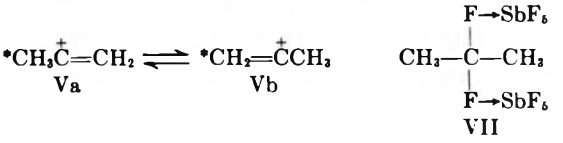
$R_1 = CH_3$; $R_2 = H, CH_3$
$R_1 = R_2 = CH_3$

Protonation of the parent allene in "superacid" media has not been achieved previously. If the protonation were to take place on the sp-hybridized central carbon atom, the allyl cation would be generated. Alternatively, protonation on the terminal carbon atoms would give a vinyl cation. The direct observation of the allyl cation by nmr studies has been reported, although with poor resolution.[4a] The observation of vinyl cations as stable long-lived intermediates has not yet been achieved, although Olah and Pittman studied alkynylcarbenium ions which are mesomeric with allenyl cations.[4b] On the other hand, in a series of solvolytic studies it was concluded that vinyl cations were involved.[5] Presently, we wish to report the results of direct protonation of allene, methylacetylene, and acetylene in $HF-SbF_5-SO_2ClF$ solution resulting in the formation of the dimethylfluorocarbenium and methylfluorocarbenium ion, respectively, which undergo intermolecular fluorine exchange with the solvent system.

The intermolecular fluorine exchange reaction of the acetyl cation with acetyl fluoride was reported by Lunazzi and Brownstein.[6] In our laboratories, methyl and ethyl fluoride were found to exchange intramolecularly with antimony pentafluoride *via* the formation of donor–acceptor complexes, $RF \rightarrow SbF_5$ ($R = CH_3$ and C_2H_5). In the case where alkyl fluorides with antimony pentafluoride form stable ions (*e.g.*, isopropyl and *tert*-butyl cations), the possibility of an intermolecular fluorine exchange reaction (between carbenium ion and excess alkyl fluoride) was studied recently in our laboratories.[7] It was found, however, that only C-alkylated products were formed instead of fluorine exchange. This result is consistent with our unsuccessful attempts to prepare dialkylfluoronium ions. In order to study the possibility of intermolecular fluorine exchange reactions fluorocarbenium ions seem to be the appropriate species.

Results and Discussion

Pmr Spectra.—We carried out protonation of allene (I), methylacetylene (II), and 2-fluoropropene (III) as well as ionization of 2,2-difluoropropane (IV) in $HF-SbF_5-SO_2ClF$ (5/1 mol/mol) solution. Under conditions of stable ion formation, all gave an identical species displaying in the pmr spectra a sharp singlet absorption at δ 3.83. These results gave no indication that either the vinylic propynium ion V or the allyl cation was generated as a long-lived species, and a rapid exchange process Va $\rightleftharpoons$ Vb must be considered. It



Va Vb VII

seems unlikely that V could be generated from IV with $HF-SbF_5-SO_2ClF$. The nmr data can be best interpretated as either the dimethylfluorocarbenium ion VI exhibiting rapid fluorine exchange with the superacid system or as the formation of the antimony pentafluoride complex of 2,2-difluoropropane (VII). The later possibility can be excluded because the proton resonance (δ 3.83) is shifted upfield or downfield upon addition of HF and IV or SbF_5, respectively. Complex VII should have a definite proton shift, as in the methyl fluoride–antimony pentafluoride complex,[8] independent of excess IV or SbF_5.

The dimethylfluorocarbenium ion VI generated from IV in SbF_5-SO_2ClF shows a methyl doublet at δ 4.0 (J_{HF} = 26 Hz).[9] The doublet is shifted and collapsed to a sharp singlet at δ 3.83 when a fivefold amount of HF (relative to SbF_5) was added to the above solution. The singlet absorption shifted further upfield as more HF was added. Finally, the singlet absorption is found at δ 1.88 when a large excess of HF was added to the solution of VI. When this solution was allowed to warm to 25° in a closed system, the only product which could be collected was IV. IV itself was not ionized in

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(2) Postdoctoral research associate, 1969–1971.

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(5) For a review on vinyl cations in solvolysis reactions, see M. Hanack, *Accounts Chem. Res.*, **3**, 209 (1970).

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(7) G. A. Olah and Y. K. Mo, *ibid.*, in press.

(8) G. A. Olah, J. R. DeMember, and R. H. Schlosberg, *ibid.*, **91**, 2122 (1969).

(9) G. A. Olah, R. D. Chambers, and M. B. Comisarow, *ibid.*, **89**, 1268 (1967).

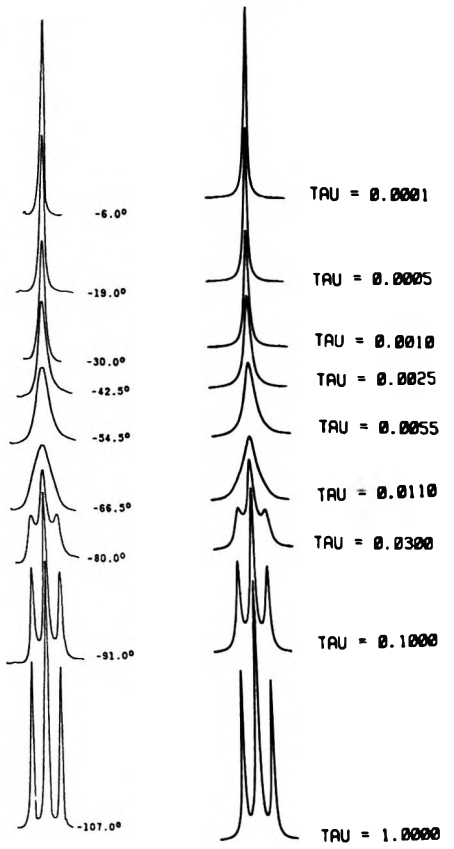

Figure 1.—Temperature-dependent pmr spectra of IV–SbF_5–HF (25:1:1) in SO_2ClF solution (left) and calculated spectra (right).

HF–SO_2ClF solution. Its pmr spectrum, showing a triplet at δ 1.63 (J_{HF} = 18 Hz) remained unchanged from −80 to −20°. However, when this solution was mixed with SbF_5–SO_2ClF (1/20 mol ratio to HF) at −78°, the pmr spectrum showed only one sharp singlet at δ 1.88. This singlet absorption became further deshielded as more SbF_5–SO_2ClF was added.

Further, we found that the singlet absorption observed between δ 1.88 and 3.83 is generally temperature independent between −100 and −20°, indicating that exchange reaction rates of ion IV with the superacid solvent media are more rapid than the nmr time scale. However, when the solution of IV–SbF_5–HF in SO_2ClF has a ratio of 25:1:1 and of 1:1:0.88, variable temperature pmr and fmr spectra could be observed (Figures 1–4, respectively).

Mechanism.—Before discussing the results of kinetic studies of the fluorine exchange reactions, it seems appropriate to discuss the mechanism of the exchange reaction. The nmr data discussed indicate that IV and ion VI as well SbF_5 and HF are involved in the exchange reactions. IV can be ionized to VI when IV is dissolved in SbF_5–SO_2ClF (eq 1). Ion VI itself can react with fluoride ion from HF and regenerate IV (eq 2). HF also interacts with SbF_5 (eq 3). Consequently, the equilibrium of eq 1 is shifted to the left. Finally, IV can fluorine exchange with ion VI (eq 4) but it does not affect the equilibrium of eq 1.

$$\underset{\text{IV}}{CH_3CF_2CH_3} + SbF_5 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{\text{VI}}{CH_3\overset{+}{C}FCH_3} + SbF_6^- \quad (1)$$

$$\underset{\text{VI}}{CH_3\overset{+}{C}FCH_3} + HF \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} \underset{\text{IV}}{CH_3CF_2CH_3} + H^+ \quad (2)$$

$$SbF_5 + HF \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} SbF_6^- + H^+ \quad (3)$$

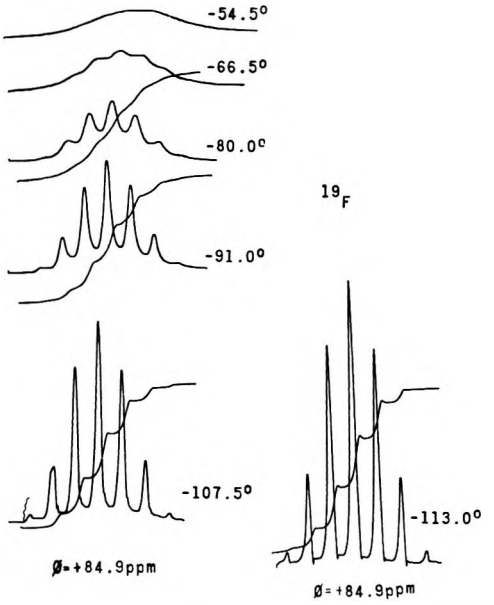

Figure 2.—Temperature-dependent fmr spectra of IV–SbF_5–HF (25:1:1) in SO_2ClF solution.

$$\underset{\text{IV}}{CH_3CF_2CH_3} + \underset{\text{VI}}{CH_3\overset{+}{C}FCH_3} \underset{k_{-4}}{\overset{k_4}{\rightleftharpoons}} \underset{\text{VI}}{CH_3\overset{+}{C}FCH_3} + \underset{\text{IV}}{CH_3CF_2CH_3} \quad (4)$$

The rate of forward and backward reactions 1–4 depend upon the relative concentration of each species. In the absence of HF and excess of SbF_5, IV is completely ionized to ion VI, and the equilibrium is shifted to the right ($k_1 \gg k_{-1}$). However, when HF was added to the above solution, reactions 2 and 3 became important. A fluorine exchange reaction between IV and the superacid medium occurs and washes out the proton–fluorine coupling when the exchange rate is greater than $1/J_{HF}$.[10] Equilibra (1–4) thus can account for the observation of the singlet absorption at δ 3.83 when I, II, and III were protonated or IV was ionized in HF–SbF_5–SO_2ClF (5/1 mol/mol) (eq 5).

$$\left.\begin{array}{l} H_2C{=}CCH_3\ (I) \\ CH_3C{=}CH_2\ (II) \\ CH_3CF{=}CH_2\ (III) \\ CH_3CF_2CH_3\ (IV) \end{array}\right\} \xrightarrow[(5/1\ \text{mol/mol}),\ -78°]{\text{HF–SbF}_5\text{–SO}_2\text{ClF}}$$

$$\underset{\text{VI}}{CH_3\overset{+}{C}FCH_3} + SbF_6^- \rightleftharpoons \underset{\text{IV}}{CH_3CF_2CH_3} + SbF_5 \quad (5)$$

Kinetics.—The relationship between the observed proton chemical shift (δ_{obsd}) and the concentrations of IV (C_{IV}) and VI (C_{VI}) can be expressed by eq 6.[11]

$$\delta_{obsd} = \delta_{VI} - \frac{n_{IV}C_{IV}}{n_{IV}C_{IV} + n_{VI}C_{VI}}(\delta_{VI} - \delta_{IV}) \quad (6)$$

(10) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1969, p 151.

(11) One of the referees pointed out that eq 6, 7, and 8 are only valid if there is no change in chemical shift values with solvent composition. We have shown that change of the solvent composition (SbF_5 and HF) will affect the *average* proton chemical shifts but has negligible effect on proton shift of each individual IV and VI species (δ_{IV} and δ_{VI}). Thus, the pmr shifts themselves have practically no response to the solvent composition which only affects the relative amount of each species.

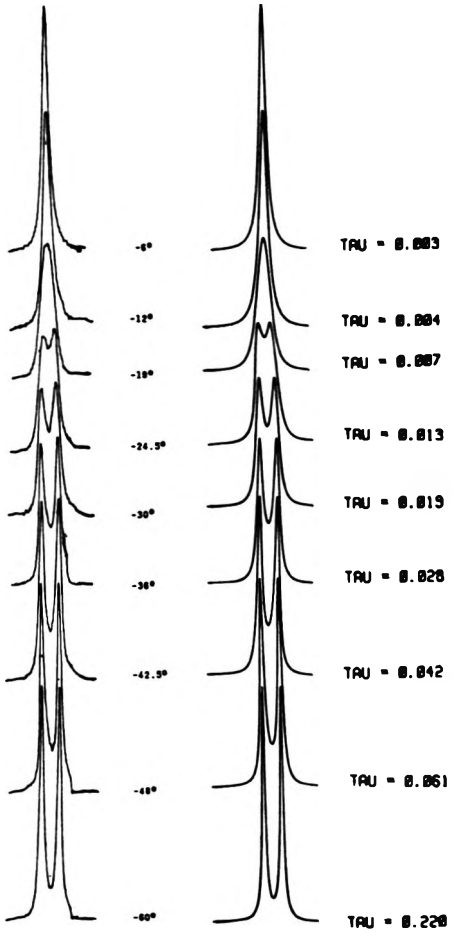

Figure 3.—Temperature-dependent pmr spectra of IV–SbF_5–HF (1:1:0.88) in SO_2ClF solution (left) and calculated spectra (right).

Since the number of labile protons in both IV and VI are equal ($n_{IV} = n_{VI}$) and the chemical shifts of IV and VI in the absence of exchange are known ($\delta_{VI} = 4.01$ and $\delta_{IV} = 1.63$), eq 6 can be simplified to eq 7. Alter-

$$\delta_{obsd} = 4.01 - \frac{C_{IV}}{C_{IV} + C_{VI}}(2.38) \quad (7)$$

natively, it can be expressed in terms of residence times of IV (τ_{IV}) and VI (τ_{VI}) since the $\tau_{IV}/\tau_{VI} = C_{IV}/C_{VI}$ relationship holds.[6] Equation 7 then becomes eq 8 as shown.

$$\delta_{obsd} = \delta\ 4.01 - \frac{\tau_{IV}}{\tau_{IV} + \tau_{VI}}(2.38) \quad (8)$$

In the case of the observed singlet at δ 3.83, the mole fraction $C_{IV}/C_{IV} + C_{VI}$ or the residence time fraction $\tau_{VI}/\tau_{IV} + \tau_{VI}$ is 0.0756. When more HF was added to the above solution, δ_{obsd} becomes smaller and the mole fraction $C_{VI}/C_{VI} + C_{IV}$ is increased. If $C_{VI} = C_{IV}$, $\delta_{obsd} = \delta$ 2.82. For the other singlet observed at δ 1.88 (HF is in large excess), the mole fraction $C_{IV}/C_{VI} + C_{IV}$ is calculated to be 0.90.

In the presence of large excess of HF, reaction 4 is not important. We therefore conclude that the residence times of a species at each site, τ_{IV} and τ_{VI}, and the observed chemical shifts, δ_{obsd}, are totally dependent on the relative amount of HF. Thus, the exchange reaction can be regarded as pseudo first order.

As previously mentioned, when the solution of HF–SbF_5–IV in SO_2ClF has a ratio of 25:1:1, temperature dependent pmr and fmr spectra were observed. Thus

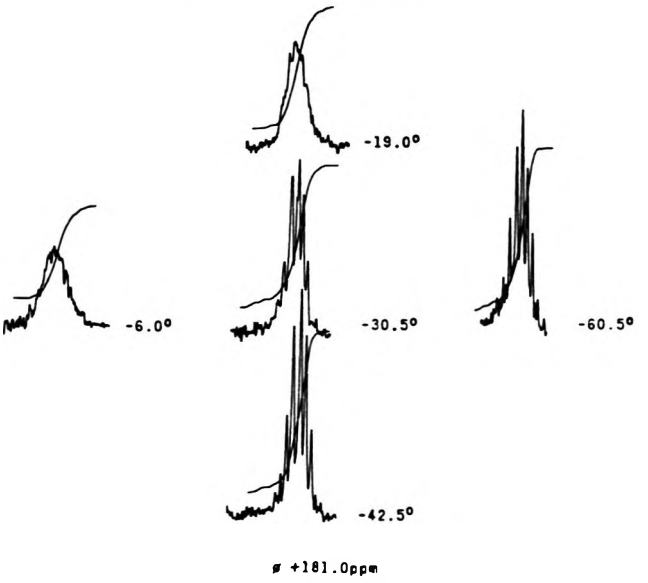

Figure 4.—Temperature-dependent fmr spectra of IV–SbF_5–HF (1:1:0.88) in SO_2ClF solution.

the pmr spectra of a solution containing SbF_5 (3.5 mmol), HF (3.5 mmol), and IV (90.0 mmol) showed the coalescence of a triplet (of IV) to a singlet when the temperature was raised from −107 to −6° (Figure 1). The fluorine exchange reaction can be simplified as an equilibrium of IV and VI (eq 9). The relaxation time

$$IV \underset{1/\tau_{VI}}{\overset{1/\tau_{IV}}{\rightleftharpoons}} VI \quad (9)$$

(τ) of this equilibrium is equal to $1/k$ or $1/k_{IV} + k_{VI}$ since it is a pseudo-first-order reaction.[12] The residence times of each site (IV and VI) are equal to $1/k_{IV}$ and $1/k_{VI}$, respectively (eq 10).

$$\tau_{IV} = 1/k_{IV},\ \tau_{VI} = 1/k_{VI} \quad (10)$$

Further, we also note that concentrations of IV and VI are related to k_{IV} and k_{VI} by eq 11 regardless of the

$$C_{IV}k_{IV} = C_{VI}k_{VI} \quad (11)$$

mechanism of the exchange reaction. Consequently a simple equation (eq 12) can be derived to relate τ and the one directional rate constant, k_{IV}.

$$k = 1/\tau = k_{IV} + k_{VI} = K_{IV} + C_{IV}/C_{VI}k_{IV} = k_{IV}\left(\frac{C_{IV} + C_{VI}}{C_{VI}}\right)$$

$$k_{IV} = \frac{C_{VI}}{C_{IV} + C_{VI}}\frac{1}{\tau} \quad (12)$$

Theoretical spectra were calculated by the multiple sites exchange (MSE) program of Johnson.[13] The mean lifetimes, τ, were obtained by comparison of experimental (pmr) and calculated spectra (Figure 1). It should be noted that the chemical shifts (*ca.* δ 3.90) of experimental pmr spectra were temperature independent throughout the temperature range assessable in this study. Therefore, the mole fraction, $C_{VI}/C_{IV} + C_{VI}$, could be calculated from eq 8 and substituted into eq 12.

$$\frac{C_{VI}}{C_{IV} + C_{VI}} = \frac{4.01 - 3.90}{2.38} = 0.0462$$

(12) F. A. Bovey in "Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York, N. Y., 1969, p 187.

(13) C. S. Johnson, in "Advance in Magnetic Resonance," Vol. 1, J. S. Waugh, Ed., Academic Press, New York, N. Y., 1965, p 33.

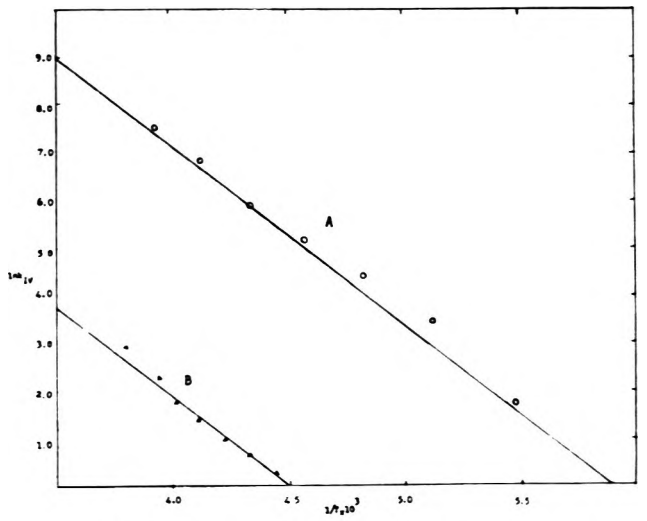

Figure 5.—Arrhenius plot of ln k *vs.* $1/T$.

A simple relation between k_{IV} and τ is shown in eq 13. The values of the Arrhenius activation energy, E_a, and the preexponential factor, A, were determined from the slope and intercepts of ln k_{IV} *vs.* $1/T$ plots (Figure 5, line A). It was found that $E_a = 7.62 \pm 0.9$ kcal/mol and $A = 10^{9.8 \pm 1.1}$.

$$k_{IV} = \frac{0.0462}{\tau} \quad (13)$$

The temperature-dependent pmr spectra of the doublet ($CH_3\overset{+}{C}FCH_3$, VI) were recorded from a SO_2ClF solution containing SbF_5 (31.3 mmol), HF (31.3 mmol), and IV (27.5 mmol). The experimental and calculated spectra are displayed in Figure 3. By a similar approach, the one directional rate constants, k_{IV}, were obtained at different temperatures. A plot of ln k_{IV} *vs.* $1/T$ is shown in Figure 5 (line B). From the slope and the intercepts, the Arrhenius activation energy of 7.35 ± 0.8 kcal/mol and a preexponential factor of $10^{6.5 \pm 1.2}$ were obtained.

Other Systems.—In analogous studies we found that protonation of acetylene (VIII) and vinyl fluoride (IX) as well ionization of 1,1-difluoroethane (X) in excess of HF–SbF_5–SO_2ClF (5/1 mol/mol) at −78° all gave similar species. These solutions displayed identical pmr spectra: a shielded three-proton doublet at δ 1.78 (J_{HH} = 4.2 Hz) and a deshielded one-proton quartet at δ 6.20 (J_{HH} = 4.2 Hz) (Figure 6, bottom trace). Both resonances were deshielded when SbF_5–SO_2ClF was added to the above solutions. These results can be well interpretated as $CH_3\overset{+}{C}HF$ (XI) exchanging fluorine with X (eq 14), a situation similar to the previously observed process.

$$\left.\begin{array}{l} HC{\equiv}CH\ (VIII) \\ H_2C{=}CHF\ (IX) \\ CH_3CHF_2\ (X) \\ CH_3CHCl_2\ (XII) \\ CH_3CHClNO_2\ (XIII) \\ CH_3CHFCl\ (XIV) \end{array}\right\} \xrightarrow[(5/1\ mol/mol),\ -78°]{HF\text{–}SbF_5\text{–}SO_2ClF}$$

$$\underset{XI}{CH_3\overset{+}{C}HF} + SbF_6^- \rightleftharpoons \underset{X}{CH_3CHF_2} + SbF_5 \quad (14)$$

Furthermore, even 1,1-dichloroethane (XII), 1-chloronitroethane (XIII), and 1-chlorofluoroethane (XIV) reacted with HF–SbF_5–SO_2ClF (5/1 mol/mol) at −78° to give the same equilibrium system of X and XI. Obviously, VIII reacted with 1 mol of HF to form IX and then further protonation of IX took place to give XI, but XI is highly reactive and was quenched by fluoride ion from the medium to form X. The equilibrium is then established. Both XII and XIII can be ionized in strong acid medium to give methylchlorocarbenium ion, $CH_3\overset{+}{C}HCl$ (XV). However, XV is not stable and will attack the gegenion (F^-) to give XIV. Further ionization of XIV will generate XI and will then equilibrate (eq 15). Similar halogen–fluorine exchange has been found in dimethylchlorocarbenium ion and dimethylbromocarbenium ion.[9]

$$\left.\begin{array}{l} CH_3CHCl_2\ (XII) \\ CH_3CHClNO_2\ (XIII) \end{array}\right\} \xrightarrow[(5/1\ mol/mol),\ -78°]{HF\text{–}SbF_5\text{–}SO_2ClF} \underset{XV}{CH_3\overset{+}{C}HCl} \xrightarrow{F^-}$$

$$\underset{XIV}{CH_3CHFCl} \xrightarrow{ionized} CH_3\overset{+}{C}HF \underset{SbF_5}{\overset{SbF_6^-}{\rightleftharpoons}} \underset{X}{CH_3CHF_2} \quad (15)$$

The observation of the dependence of chemical shifts upon the relative concentration of SbF_5 and HF, which subsequently control the equilibrium (eq 15), has been discussed previously. No fluorine nmr resonance was detected from these reaction mixtures except those of the solvent, SO_2ClF and SbF_6^- (or $Sb_2F_{11}^-$).

Similarly, when a solution of X (53.0 mmol), SbF_5 (3.2 mmol), and HF (3.2 mmol) in SO_2ClF was prepared at −78°, temperature dependence of the nmr (^1H and ^{19}F) spectra was observed as shown in Figures 6 and 7. Due to the complexity of the spectra and the limits of accuracy of the multiple site exchange program, no attempt was made to calculate the rates of the exchange reaction at various temperatures.

Attempts to prepare methylfluorocarbenium ion XI either by protonation of IX with FSO_3H–SbF_5 or from XIV with SbF_5–SO_2ClF were reported previously to be unsuccessful.[9] Similarly, when we ionized X with excess of SbF_5–SO_2ClF at −80°, the pmr spectrum showed an upfield doublet at δ 4.32 (J_{HH} = 1.8 Hz) and a downfield quartet at δ 10.47 (J_{HH} = 1.8 Hz). These data are not consistent with the formation of ion XI, because both chemical shifts are too shielded for XI and also because of the absence of proton–fluorine coupling. In addition, no fmr resonance was observed except that of the solvent and acid systems. We therefore conclude that the two observed pmr signals are due to the exchange reaction of X and XI, in which the equilibrium was shifted further to the left (eq 15). It should be noted that the proton–proton coupling constant is smaller than that observed previously. When HF was added to this solution, both resonances became more shielded and the coupling constants were also increased. The two signals decreased in intensity as the temperature was increased and disappeared at −20° after 5 min. Apparently, decomposition (to unknown polymers) took place. In the presence of water, protonated acetaldehyde was the sole product observed (eq 16).

$$\underset{X}{CH_3CHF_2} \underset{SbF_6^-}{\overset{SbF_5}{\rightleftharpoons}} \underset{XI}{CH_3\overset{+}{C}HF} \xrightarrow{H_2O} CH_3\overset{+OH_2}{\underset{H}{\underset{|}{\underset{|}{C}}}}F \xrightarrow{-HF} CH_3CH\overset{+}{=}OH \quad (16)$$

In addition, we found that difluoromethane was inert toward SbF_5–SO_2ClF or FSO_3H–SbF_5–SO_2ClF at low temperature. Since the methylfluorocarbenium ion

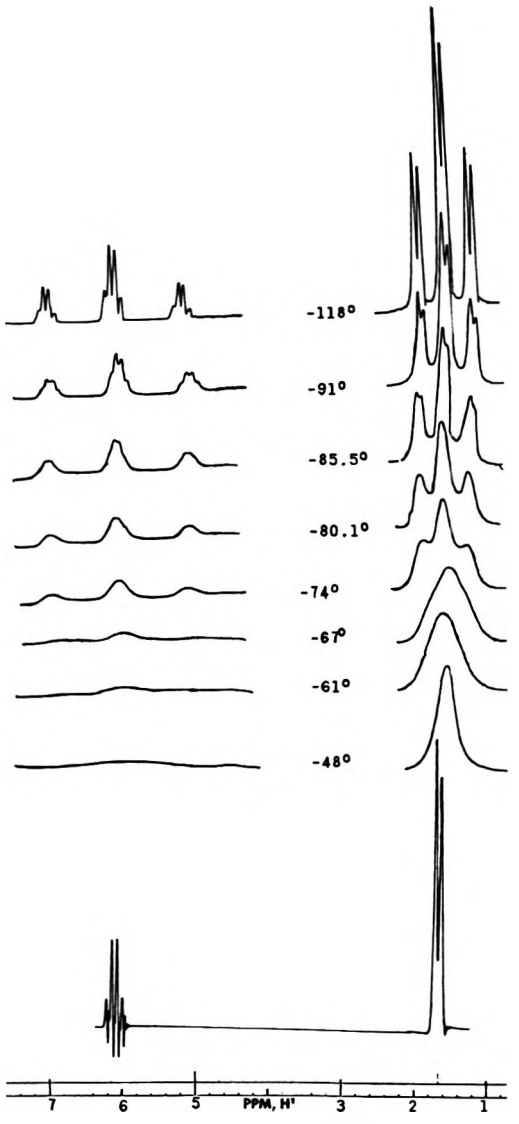

Figure 6.—Temperature-dependent pmr spectra of X–SbF_5–HF (16.5:1:1:) in SO_2ClF solution. (The bottom trace was obtained when a small amount of HF was added to the above solution at −78°.)

XI is not stable under our experimental conditions, CH_2F^+ should be even less stable. On the other hand, phenylmethylfluorocarbenium ion XVI has been directly observed as a stable long-lived species, but it polymerized with added α,α-difluorophenylethane ($C_6H_5CF_2CH_3$, XVII) instead of exchanging fluorine. Obviously, XVI, similarly to the styryl cation ($C_6H_5\overset{+}{C}HCH_3$), could deprotonate to form α-fluorostyrene ($C_6H_5CF{=}CH_2$, XVIII) and then polymerize (eq 17).

$$\underset{\text{XVII}}{C_6H_5CF_2{=}CH_2} \xrightarrow[-78°]{SbF_5\text{–}SO_2ClF} \underset{\text{XVI}}{C_6H_5\overset{+}{C}FCH_3} \xrightarrow{-H^+}$$

$$\underset{\text{XVIII}}{C_6H_5CF{=}CH_2} \xrightarrow{\text{XVI}} C_6H_5CF(CH_3)CH_2\overset{+}{C}FC_6H_5 \longrightarrow \text{etc.} \quad (17)$$

Fluorine-19 and Carbon-13 Nmr Spectra.—The fmr spectra of IV show a heptet (J_{HF} = 19 Hz) at ϕ 81.5 (from $CFCl_3$). Under the same conditions as those used when temperature-dependent pmr spectra were observed, fmr spectra were also recorded at various temperatures. These spectra are shown in Figure 2. It is important to note that the fluorine signals do not

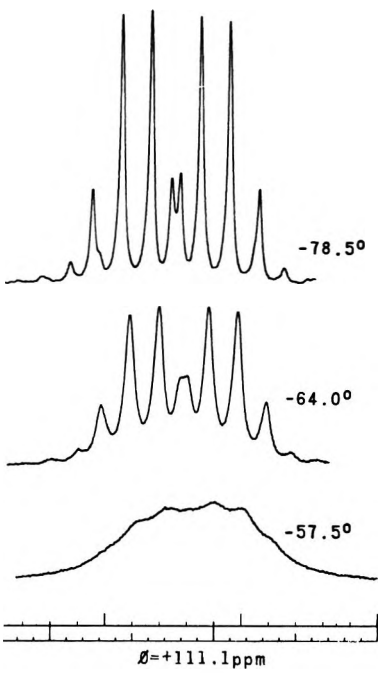

Figure 7.—Temperature-dependent fmr spectra of X–SbF_5–HF (16.5:1:1) in SO_2ClF solution.

coalesce to a singlet, but broaden, reduce intensity, and finally at higher temperature merge into the base line. This is due to the fact that fluorine resonances disappear in the fluoroantimonate region when the exchange rates are more rapid than $1/J_{HF}$. This observation also provides support that the fluorine exchange between IV and VI (eq 4) is less important under these conditions. Hence, the exchange reaction is a pseudo first order with regard to both IV and VI.

Similarly, the fmr heptet (J_{HF} = 26 Hz) of VI also showed temperature dependence (Figure 4). The disappearance of the fluorine signals at higher temperature was also observed. Under conditions where a singlet was observed in the pmr spectrum between δ 1.88 and 3.83, no fmr resonance was observed, except those of solvent SO_2ClF and SbF_6.

Temperature dependent fmr spectra of X in HF–SbF_5–SO_2ClF are shown in Figure 7. Close similarities can be observed in Figures 2, 4, and 7.

The fluorine exchange systems were also studied by carbon-13 nmr spectroscopy. The carbon-13 chemical shifts of each system are tabulated in Table I. It should be noted the carbon shifts of $-CF_2$ and $-CHF_2$ carbon atoms are deshielded substantially as SbF_5 concentration is increased. However, the methyl carbons show only a small change of chemical shifts in the same series.

The C_2 carbon of VI has a cmr shift of δ ^{13}C − 142.0 (from CS_2). For comparison, it is only 6.5 ppm deshielded from the carbenium atom of the *tert*-butyl cation[14] indicating back donation from the fluorine atom to the carbenium center in ion VI.

Experimental Section

Materials.—All the compounds used were commercially available except 2,2-difluoropropane and α,α-fluoroethylbenzene which were prepared by methods described previously.[9]

Nmr Spectra.—The pmr and fmr spectra were obtained on a

(14) G. A. Olah and A. M. White, *J. Amer. Chem. Soc.*, **91**, 5801 (1969).

TABLE I

CARBON-13 NMR SHIFTS OF FLUORINE EXCHANGING FLUOROCARBENIUM ION SYSTEMS[a]

$CH_3CF_2CH_3$ (IV)	$-CF_2$	$-CH_3$	CH_3CHF_2	$-CHF_2$	$-CH_3$
IV in SO_2ClF at $-40°$	+68.2	+167.4	X in SO_2ClF at $-60°$	+77.5	+174.6
IV in HF (excess)–SbF_5–SO_2ClF at $-60°$	+67.7	+168.1	X in HF (excess)–SbF_5–SO_2ClF at $-60°$	+71.8	+145.2
IV in HF–SbF_5–SO_2ClF (5/1 mol/mol) at $-60°$	−91.0	+157.3	X in HF–SbF_5–SO_2ClF (5/1 mol/mol) at $-60°$	−59.1	+140.4
IV in excess SbF_5–SO_2ClF at $-60°$	−142.0	+155.0			

[a] Carbon-13 shifts are in parts per million from external CS_2.

Varian Associates Model A-56-60A spectrometer equipped with variable temperature probes. Probe temperatures were calibrated before use. TMS and $CFCl_3$ in a capillary were used for proton and fluorine references, respectively. Carbon-13 spectra were obtained by the INDOR method described previously.[15]

Preparation of Ions.—Solutions of ions were prepared as described previously in this series, with concentrations and conditions given in text.

Registry No.—IV, 420-45-1; VI, 14665-81-7; X, 75-37-6; XI, 29526-61-2; HF, 7664-39-3; SbF_5, 7783-70-2; SO_2ClF, 13637-84-8.

Acknowledgment.—Support of our work by the National Science Foundation and the Petroleum Research Fund, administered by the American Chemical Society, is gratefully acknowledged. We are also indebted to Dr. Gheorge D. Mateescu and Dr. William E. Heyd for their contribution in calculating the theoretical spectra.

(15) A. M. White and G. A. Olah, *J. Amer. Chem. Soc.*, **91**, 2943 (1969).

Vinylic Cations from Solvolysis. X. SN1 and Nucleophilic Addition–Elimination Routes for 9-(α-Haloarylidene)fluorenes

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The solvolysis of α-anisyl-β,β-diphenylvinyl chloride and bromide (1-Cl and 1-Br) in 80% EtOH in the presence of acetate, hydroxide, benzylthiolate, and *p*-toluenethiolate ions is mechanistically SN1. The solvolysis of 9-(α-haloarylidene)fluorenes (**2** and **4**) in 80% EtOH in the presence of acetate ion also follows the SN1 route. However, **2** and **4** react in the presence of *p*-toluenethiolate and benzylthiolate ions *via* the nucleophilic addition–elimination substitution route. Various criteria (the substituent effect, the solvent effect, the "element effect," the dependency on the nucleophile, and the kinetics) for differentiation between the two routes were investigated and discussed and the behavior of compounds **1** and **2** is compared.

Two of the important mechanisms of nucleophilic vinylic displacement of the leaving group X by the nucleophile Nu^- are the nucleophilic addition–elimination route[1-3] (Ad_N–El, eq 1) and the SN1 route[1,2,4,5]

$$RCX{=}CYR' + Nu^- \xrightarrow{\text{slow}} RCX(Nu)\bar{C}YR' \longrightarrow RC(Nu){=}CYR' + X^- \quad (1)$$

(eq 2). Other mechanisms such as the "elimination–

$$RCX{=}CR'R'' \underset{-X^-}{\xrightarrow{\text{slow}}} R\dot{C}{=}CR'R'' \xrightarrow{Nu^-} RC(Nu){=}CR'R'' \quad (2)$$

addition" routes[1-3] are dependent on the presence of an allylic or a vinylic hydrogen and are less general. The two mechanisms differ by many mechanistic criteria. The rate of the SN1 route is of a first order and is independent of added nucleophiles. This route is activated by electron-donating α substituents R, and it shows an "element effect" of the leaving group X and is accelerated by polar solvents. Both cis and trans isomers give the same product mixture.[6] The Ad_N–El route is of a second order and its rate is strongly nucleophile dependent. The reaction is activated by electron-attracting groups Y from the β position, it shows a small k_{Br}/k_{Cl} element effect, and its stereochemical outcome is retention of configuration.[1-3] No system which reacts by both routes is known. Competition between the powerfully SN1 activating α-*p*-dimethylaminophenyl group and the two Ad_N–El activating β-cyano groups of *p*-$Me_2NC_6H_4C(Cl){=}C(CN)_2$ resulted in the Ad_N–El route alone.[7] Indeed, the SN1 route often competes with the electrophilic addition–elimination route,[8] while the Ad_N–El route often competes with the elimination–addition routes.[1-3]

It was of interest to find a system capable of reacting under different conditions by both the SN1 and the Ad_N–El routes. Since triarylvinyl halides are known

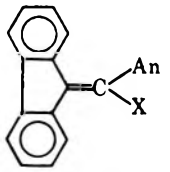
(1) S. Patai and Z. Rappoport in "The Chemistry of Alkenes," S. Patai, Ed., Interscience, London, 1964, p 469.
(2) Z. Rappoport, *Advan. Phys. Org. Chem.*, **7**, 1 (1969).
(3) G. Modena, *Accounts Chem. Res.*, **4**, 73 (1971).
(4) M. Hanack, *ibid.*, **3**, 209 (1970).
(5) G. Modena and U. Tonellato, *Advan. Phys. Org. Chem.*, **9**, 185 (1971). We thank Professor Modena for a preprint of this paper.
(6) (a) Z. Rappoport and Y. Apeloig, *J. Amer. Chem. Soc.*, **91**, 6734 (1969); (b) D. R. Kelsey and R. G. Bergman, *ibid.*, **92**, 228 (1970); **93**, 1941 (1971).
(7) Z. Rappoport and R. Ta-Shma, *J. Chem. Soc. B*, 871, 1461 (1971).
(8) Z. Rappoport, T. Bässler, and M. Hanack, *J. Amer. Chem. Soc.*, **92**, 4985 (1970); Z. Rappoport and J. Kaspi, *Tetrahedron Lett.*, 4039 (1971).

to react *via* the SN1 route,[6a,9-12] a logical starting point is the replacement of the two β-aryl groups by a fluorenyl moiety. This group is much more suitable than the two β-phenyl groups to carry the partial negative charge formed in the transition state of the Ad_N–El route.[13]

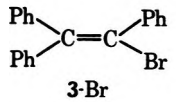
Results

Synthesis.—The triarylhaloethylenes **1**-Cl, **1**-Br, and **3**-Br were prepared by halogenation–dehydrohalogenation of the corresponding ethylenes without isolation of the α,β-dihalides.[9,11,14] The fluorenylidene derivative **4**-Br was prepared similarly from the isolated α,β-dibromide. The dibromide **5**-Br and the corresponding dichloride **5**-Cl were prepared by adding the halogen to 9-anisylidenefluorene, but their analysis and nmr showed that both compounds partially eliminate hydrogen halide rather rapidly.

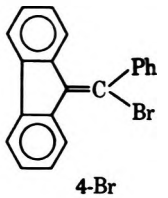
1-Cl, X = Cl
1-Br, X = Br
1-OTs, X = OTs



2-Cl, X = Cl
2-Br, X = Br
2-OTs, X = OTs
2-OAc, X = OAc



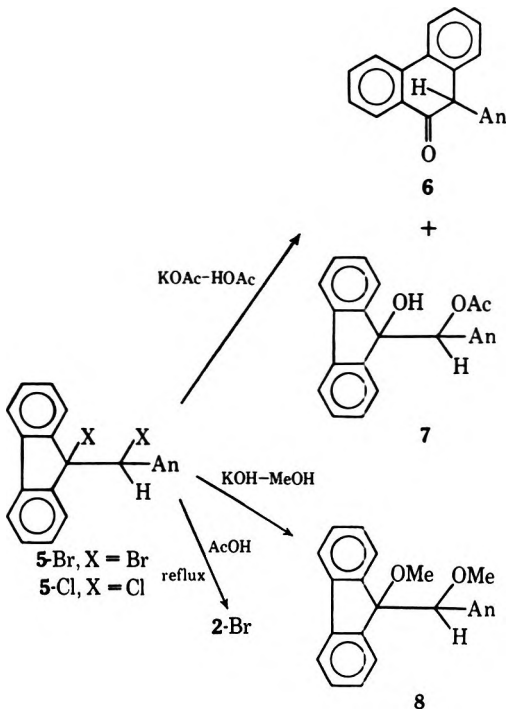
3-Br



4-Br

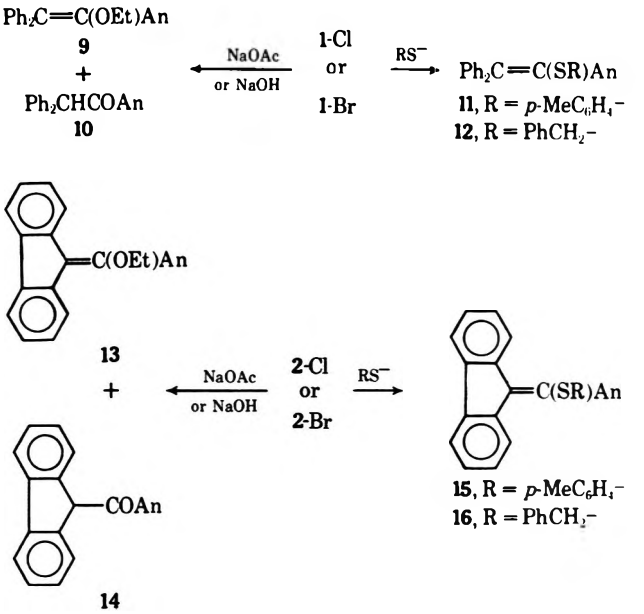
An = *p*-$MeOC_6H_4$–

In attempts to prepare **2**-Br by dehydrobromination of **5**-Br with KOAc in acetic acid, the ring enlargement product, 9-anisyl-9,10-dihydro-10-oxophenanthrene (**6**), was formed and identified by analysis, uv, ir, mass spectrum (base peak at M − HCO), and nmr (H-9 at δ 9.55). A small amount of 9-hydroxy-9-(α-acetoxy-*p*-methoxybenzyl)fluorene (**7**) (or its isomer in which the OH and the OAc groups exchange places) was also formed. The dimethyl ether **8** was formed on attempted dehydrobromination with methanolic KOH. **2**-Br was finally obtained as the main product by reflux of **5**-Br in acetic acid without added base, and **6** was the minor product. Similarly, **2**-Cl was the main product and **6** a minor product in the dehydrochlorination of **5**-Cl in acetic acid.



Formation of **6**, **7**, and **8** is accounted for by the initial formation of the substituted *p*-methoxybenzyl carbonium ion, followed by either capture by the solvent or a Wagner–Meerwein rearrangement followed by solvolysis of the second halogen. **2**-Br is not a precursor to **6** or **7** since it was recovered unchanged after reflux for 2 hr in KOAc–HOAc. Under these conditions, the **5** → **6** + **7** reaction takes place.

Solvolysis Products.—Solvolysis of **1**-Cl and **1**-Br in the presence of 0.18 *M* NaOAc gave the vinyl ether **9** and the ketone **10** (by ketonization of the initially formed enol). In 80% EtOH the **9**:**10** ratios (determined by nmr) are 52:48 from **1**-Br and 50:50 from **1**-Cl, and in 90% EtOH the ratio from **1**-Br is 72:28 at 120°. Similarly, the ether **13** and the ketone **14** are formed from **2**-Br and **2**-Cl. **14** was also prepared independently by the base-catalyzed hydrolysis of the acetate, **2**-OAc, which was obtained in turn by the



(9) Z. Rappoport and A. Gal, *J. Amer. Chem. Soc.*, **91**, 5246 (1969).
(10) Z. Rappoport and A. Gal, *Tetrahedron Lett.*, 3233 (1970); (b) Z. Rappoport and Y. Apeloig, *ibid.*, 1845 (1970); (c) Z. Rappoport and Y. Apeloig, *ibid.*, 1817 (1970).
(11) L. L. Miller and D. A. Kaufman, *J. Amer. Chem. Soc.*, **90**, 7282 (1968).
(12) W. M. Jones and D. D. Maness, *ibid.*, **91**, 4314 (1969); **90**, 5457 (1970).
(13) This is judged by the difference in the pK_a's of fluorene and diphenylmethane: D. J. Cram, "Fundamentals of Carbanion Chemistry," Academic Press, New York, N. Y., 1965, Chapters 1 and 2; K. Bowden, A. F. Cockerill, and J. R. Gilbert, *J. Chem. Soc. B*, 179 (1970).
(14) C. F. Koelsch, *J. Amer. Chem. Soc.*, **54**, 2045 (1932).

TABLE I

SOLVOLYSIS OF 1 AND 2 IN AQUEOUS ETHANOL

Compd	Concn, $M \times 10^2$	Added base	Concn, $M \times 10^2$	Solvent, % EtOH	T, °C	$k_1 \times 10^4$ sec^{-1}	$\Delta H^{\pm}$,[a] kcal/mol	$\Delta S^{\pm}$,[b] eu
1-Br	35	$NaSCH_2Ph$	20	80	120.0	2.02 ± 0.16[c]		
	33–43	$NaSC_6H_4Me$-p	11–20	80	120.3	1.97 ± 0.09[d]		
	43	$NaSC_6H_4Me$-p	13	80	120.3	1.81 ± 0.03		
	35	$NaSC_6H_4Me$-p	20	80	120.7	2.19 ± 0.13		
	29	$NaSC_6H_4Me$-p	8	80	128.2	3.21 ± 0.24	22.0	−20
	57	$NaSC_6H_4Me$-p	8	80	128.2	3.62 ± 0.20		
	29–40	NaOH	30–50	80	120.3	1.92 ± 0.04[d]	22.3[d]	−19[d]
	40	NaOH	44	80	127.8	3.05 ± 0.04		
	20–40	NaOH	29–44	80	127.8	3.48 ± 0.02[d]		
	57	NaOH	27	80	127.8	2.97 ± 0.06		
	40–57	NaOH	29–36	80	139.8	7.75 ± 0.14[d]		
	35	NaOAc	8.6	80	120.3	1.56 ± 0.02	21.6	−22
	35	NaOAc	8.6	80	140.3	6.24 ± 0.07		
	35	NaOAc	11.5	90	140.6	2.70 ± 0.03		
1-Cl	35	NaOAc	18	80	140.2	0.117 ± 0.002	25.5	−21[e]
	35	NaOAc	18	80	155.4	0.368 ± 0.005		
2-Br	35	NaOAc	20	70	140.3	6.03 ± 0.12		
	35	NaOAc	36	70	140.2	6.27 ± 0.10		
	35	NaOAc	8.6	80	120.3	0.63 ± 0.002[f]		
	35	NaOAc	17	80	120.3	0.64 ± 0.01		
	35	NaOAc	50	80	120.3	0.61 ± 0.01		
	35	NaOAc	17	80	140.3	2.94 ± 0.02	24.0	−17
	35	NaOAc	11.5	90	140.6	1.08 ± 0.03		
	35	NaOH	50	80	120.5	2.27 ± 0.10[g]		
	35	NaOH	50	90	120.3	4.6 ± 0.2[h]		
2-Cl	35	NaOAc	18	80	140.2	0.039 ± 0.001		
	35	NaOAc	36	80	140.3	0.039 ± 0.001		
	35	NaOAc	18	80	155.4	0.128 ± 0.003	26.7	−20[e]

[a] Estimated ±1 kcal/mol. [b] Estimated ±3 eu; $\Delta S^{\pm}$ at 120°. [c] The observed infinity of 82% was used. [d] From ref 9. [e] $\Delta S^{\pm}$ at 140°. [f] Extrapolated values: $10^4 k_1$ = 0.047, 0.19, and 9.05 sec^{-1} at 90.2, 105, and 155.5°, respectively. [g] Based on five points at 25–67% reaction. [h] Based only on two points.

AgOAc-catalyzed solvolysis of 2-Br in AcOH. The **13**:**14** ratios from 2-Br in 90, 80, and 70% EtOH are 92:8, 70:30, and 52:48, respectively. A small signal at the δ expected for the acetoxy signal of the acetate 2-OAc was also observed, but thin layer chromatography revealed the presence of only **13** and **14**. 2-Cl gave >85% of **13** (by nmr) in 80% EtOH, and ir showed the formation of **14** in <5%.

While 1-Br was reported to give a 1:1 ratio of **9** to **10** with sodium hydroxide in 80% EtOH at 140°,[9] the solvolysis of 2-Br in 80% EtOH with excess NaOH gave very black reaction mixtures which after several half-lives showed none of **13** and **14** in the nmr. The only signals observed are for methoxyl and aromatic protons in a ratio of 3:16. The reaction mixture from **4** also blackened with NaOH and, in addition to the aromatic signals, several new signals appeared at δ 2.1–2.5 and 4.0–4.7. These reactions were not investigated further.

Reactions of 1-Br in 80% EtOH in the presence of sodium benzylthiolate and sodium p-toluenethiolate gave exclusively the vinyl thiolates **11** and **12** which were isolated in a quantitative yield. **9** and **10** were not formed. Similarly, 2-Cl and 2-Br gave the vinyl thiolates **15** and **16** with the two thiolate anions. Their quantitative formation is verified by the uv of the kinetic runs at infinity, which corresponded to 100% reaction. 4-Br gave quantitatively the analog of **16** in the presence of sodium benzylthiolate.

Kinetics.—Compounds **1**–**4** were solvolyzed in 80% EtOH in the presence of excess NaOAc and occasionally in 70 or 90% EtOH in the presence of NaOH. The formation of the halide ion was followed titrimetrically. In the reaction of 1-Br in the presence of sodium p-toluenethiolate the excess thiolate ion had to be precipitated by $Cu(NO_3)_2$ before titration.[9] As reported earlier,[9] under these conditions the calculated infinity was not achieved and the k_1 values were calculated by using the observed infinity.

In solvolysis of 2-Br in the presence of NaOH the reaction mixtures began to blacken after 10–15% reaction and side reactions took place (see above). Although the titrimetric k_1 was good, only few experiments were conducted. The loss of hydroxide ion by reaction with the glass ampoules under conditions similar to ours was recently reported.[15]

The reaction of 1-Br under solvolytic conditions in the presence of sodium benzylthiolate was followed titrimetrically (see below).

All these reactions were first order in the substrate and zero order in the added base (NaOAc, NaOH, $NaSCH_2Ph$, $NaSC_6H_4Me$-p) with correlation coefficients for the first-order plots over 0.99. The data are summarized in Table I.

One point solvolyses of 0.035 M **3**-Br and **4**-Br in the presence of 0.18 M NaOAc gave $10^7 k_1$ values of 1.7 and 5.7 sec^{-1} at 140 and 155.5° for **3**-Br and 2.9 sec^{-1} at 155.5° for **4**-Br. The last two values are for kinetic points at $\leq$10% reaction, and the values should be considered as upper limits for k_1.

The reaction of 2-Br with excess of an equimolar mixture of p-toluenethiol and NaOH in 80% EtOH

(15) J. MacMillan and R. J. Pryce, *J. Chem. Soc. B*, 337 (1970).

TABLE II

RATE DATA FOR THE REACTIONS OF 2-Cl, 2-Br, AND 4-Br WITH THIOLATE IONS IN AQUEOUS ETHANOL

Compd	RSH, $M \times 10^3$	NaOH, $M \times 10^3$	Solvent, % EtOH	T, °C	$k_1 \times 10^4$ sec^{-1}	$k_2 \times 10^3$ M^{-1} sec^{-1}	$\Delta H^{\pm}$,[a] kcal/mol	$\Delta S^{\pm}$,[b] eu
				RSH = *p*-MeC_6H_4SH				
2-Br[c]	8.0	8.0	80	90.0	4.24	0.53	21	−12
	16.0	16.0	80	90.0	8.88	0.55		
	8.0	8.0	80	105.0	13.6	1.70		
	16.0	16.0	80	105.0	30.0	1.87		
				RSH = $PhCH_2SH$				
2-Br[c]	4.0	4.0	80	90.2	0.86 ± 0.03	6.7 ± 0.3	16	−21
	8.0	8.0	80	90.2	2.38 ± 0.09	7.0 ± 0.3		
	16.0	16.0	80	90.2	6.09 ± 0.08	7.0 ± 0.1		
	8.0	8.0	50	105.0	6.29 ± 0.68	18.6 ± 2.0		
	8.0	8.0	70	105.0	5.67 ± 0.02	16.8 ± 0.1		
	8.0	8.0	80	105.0	5.84 ± 0.32	17.3 ± 0.9		
	16.0	16.0	80	105.0	14.9 ± 0.14	17.2 ± 0.2		
2-Cl[c]	8.0	8.0	80	90.2	1.38 ± 0.02	4.1 ± 0.1	15	−25
	16.0	16.0	80	90.2	3.00 ± 0.30	3.5 ± 0.4		
	8.0	8.0	80	105.0	2.97 ± 0.07	8.8 ± 0.3		
	16.0	16.0	80	105.0	7.62 ± 0.50	8.8 ± 0.6		
4-Br[d]	4.0	4.0	80	90.2	0.96 ± 0.01	7.5 ± 0.1	16	−19
	8.0	8.0	80	90.2	2.45 ± 0.20	7.3 ± 0.6		
	16.0	16.0	80	90.2	6.48 ± 0.22	7.5 ± 0.3		
	8.0	8.0	80	105.3	6.80 ± 0.40	20.0 ± 1.2		
	16.0	16.0	80	105.3	16.4 ± 0.1	19.0 ± 0.1		
	4.0	4.0	80	105.1	2.34 ± 0.10	18.3 ± 0.8		
	4.0	8.0	80	105.1	3.21 ± 0.19	16.5 ± 1.0		
	4.0	16.0	80	105.1	4.44 ± 0.27	16.3 ± 1.0		
	4.0	32.0	80	105.1	5.11 ± 0.27	15.5 ± 0.8		

[a] Estimated ±1 kcal/mol. [b] $\Delta S^{\pm}$ at 105°; estimated ±3 eu. [c] [2] = 2.2×10^{-4} *M*. [d] [4-Br] = 2.52×10^{-4} *M*.

was followed spectrophotometrically at 392 nm, a wavelength where only the product **15** has an appreciable absorption. The reaction is first order in both 2-Br and the thiol and, since the ionization of the latter is practically complete under our conditions, the second-order coefficients k_2 (Table II) are for the reaction of the *p*-toluenethiolate ion with 2-Br.

The reactions of 2-Br, 2-Cl, and 4-Br in the presence of excess α-toluenethiol in aqueous alcohol were followed at both the λ_{max} of the vinyl halide and the vinyl thiolates, and the average rate coefficient from both measurements is given. The isosbestic point at 324 nm remained stable along the reaction and up to >10 half-lives, showing that side reactions are unimportant. The reactions were of first order in the vinyl halide but with an apparent order between one and two for the α-toluenethiol. This is due to incomplete ionization of the thiol as shown by the increase of k_1 with the NaOH concentration in the presence of a constant concentration of α-toluenethiol. The actual concentrations of the benzylthiolate anion were calculated by using the value pK_a = 11.8 for α-toluenethiol in aqueous ethanol.[16] These concentrations were used for calculation of the second-order coefficients for the reaction of the benzylthiolate anion with the vinyl halide (Table II). The slight deviation from the second-order dependency for 4-Br probably reflects the approximations used for the calculation of the anion concentrations.[17]

Discussion

It is clear from Tables I and II that the β,β-diphenyl compounds **1** and **3**-Br react by the same mechanism in the presence of all the nucleophiles studied, while the fluorenyl systems (**2** and **4**-Br) react by the same mechanism in the presence of sodium acetate, but by a different route in the presence of the stronger thio nucleophiles. That this is the first example for the operation of the SN1 and the Ad_N–El routes with the same substrate is best shown by inspecting Table III in which several mechanistic criteria are summarized and compared.

SN1 Mechanism.—The solvolysis of 1-anisyl-2,2-diphenylvinyl halides show the rate-product behavior expected for the formation of an intermediate carbonium ion (eq 3). The k_1 is nucleophile independent with four different nucleophiles (OAc^-, OH^-, $PhCH_2S^-$, and *p*-$MeC_6H_4S^-$) but the products are nucleophile dependent, being the ether and the ketone with the

$$Ph_2C{=}C(An)X \xrightarrow{k_1} Ph_2C{=}\overset{+}{C}An \xrightarrow{Nu^-} Ph_2C{=}C(An)Nu \quad (3)$$

oxygen nucleophiles and the vinyl thiolates with the thio nucleophiles. The $k_{1\text{-Br}}/k_{1\text{-Cl}}$ ratio of 53 (with NaOAc) is similar to those reported for other triarylvinyl halides in 80% EtOH,[9,10b] and their similarity to the ratios reported (32–58) for the solvolyses of

(16) J. Maurin and R. A. Paris, *C. R. Acad. Sci.*, **232**, 2428 (1951), reported the value 11.8 in aqueous ethanol. B. Dmuchovsky, F. B. Zienty, and W. A. Verdenburgh, *J. Org. Chem.*, **31**, 865 (1966), used this value and showed that the pK_a of α-toluenethiol in 3:1 acetone–water (v/v) is 11.8 and that the pK_a values of several thiols are identical in 75% acetone and in 75% ethanol (v/v). We believe that the slight difference in the solvents is balanced by the temperature difference in our experiments and in the pK_a determination. The pK_a's of thiols decrease slightly with the increase in the temperature.

(17) In calculations of $PhCH_2S^-$ concentrations, the autoprotolysis of the EtOH–H_2O solvent was taken as $K = 10^{-14}$. However, except for the reactivity ratio of the two thiolate ions which is slightly dependent on the K and the pK_a ($PhCH_2SH$) values, all the other data of Table III are independent of K and pK_a ($PhCH_2SH$) since comparison of the apparent rate coefficients at a constant [$PhCH_2SH$]/[NaOH] ratio gives the same results.

TABLE III

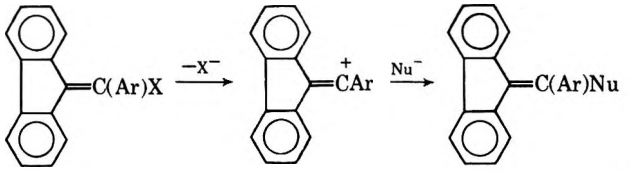
MECHANISTIC CRITERIA FOR THE REACTIONS OF THE β-FLUORENYL AND THE β,β-DIPHENYLVINYL SYSTEMS[a]

System	Order in nucleophile	k_{Br}/k_{Cl}	$k_{\alpha\text{-An}}/k_{\alpha\text{-Ph}}$	m in aq EtOH	$k_{PhCH_2S^-}/k_{p\text{-MeC}_6H_4S^-}$	$\Delta H^{\ddagger}$[b]	$\Delta S^{\ddagger}$[c]
β,β-Diphenyl with NaOAc	0[d]	53	3670	0.49	1	22	−22
β-Fluorenyl with NaOAc	0	75	3100	0.57		24	−17
β-Fluorenyl with $PhCH_2SNa$	1[e]	1.8–1.9	0.93–0.96	~0	12.6	16	−21

[a] The data summarize the behavior of different substrates in different solvents, at different temperatures. [b] In kcal/mol. [c] In eu. [d] Also with NaOH, $NaSCH_2Ph$, and $NaSC_6H_4Me$-*p*. [e] Also with $NaSC_6H_4Me$-*p*.

isopropyl, *tert*-butyl, neophyl, 1-adamantyl, 3-homoadamantyl, 1-bicyclo[3.3.1]nonyl, and 1-bicyclo[3.2.2]nonyl halides in 80% EtOH[18] suggests an SN1 mechanism. The approximate $k_{\alpha\text{-An}}/k_{\alpha\text{-Ph}}$ ratio of 3670 at 120° which amounts to a ρ of −4.6[19] is higher than the ratio for the 1-aryl-2,2-diphenylvinyl iodides in aqueous DMF (880, ρ = −3.6)[11] or for the 1-aryl-2,2-diphenylvinyl tosylates in 70% acetone (830, ρ = −3.8),[20] but is lower than the ratio for α-bromostyrenes in 80% EtOH (8600, ρ = −5.1).[21] The Winstein-Grunwald m value[22] of 0.49 at 120° is similar to those of other triarylvinyl halides and tosylates in aqueous-organic media. Hindrance to back solvation and the high temperature were suggested to be responsible for the low m values.[9-12,20] However, high m values were found for bridged polycyclic compounds[18c,23] in which the approach of solvent from the back is hindered. Our low m values may be due to a combination of the high temperature and the efficient charge dispersion by the α-anisyl group.[9] Indeed, it was suggested that "the sensitivity of the ionization rate to the solvent change tends to be less for the methoxylated than for the parent structures."[24] The activation parameters for our compounds are also similar to those for related systems solvolyzing *via* the SN1 route.[9,11,12]

The similarity of the reaction order in NaOAc, of the effects of the activating and leaving groups, of the m values, and of the activation parameters of lines 1 and 2 of Table III strongly indicates a similar SN1 mechanism for the solvolyses of the β-fluorenyl derivatives **2** and **4**-Br in the presence of NaOAc (eq 4). The slightly higher m value than that for **1**-Br is probably



(4)

connected with the different geometries of both systems.

Additional argument to those brought earlier against the electrophilic addition–elimination mechanism[8-10,12,20] is the constancy of k_1 during a kinetic run, although AcOH is formed by the neutralization of the NaOAc.

The β-fluorenyl systems are 2–3-fold less reactive than the β,β-diphenyl systems in aqueous ethanol, and the reactivity ratio is slightly solvent, activating group, and leaving group dependent. For comparison, the $k_{1\text{-Br}}/k_{2\text{-Br}}$ ratio in acetolysis at 140° is *ca.* 6,[25] and the ratio for the corresponding tosylates $k_{1\text{-OTs}}/k_{2\text{-OTs}}$ in 70% acetone at 75° is 7.5.[26] The available data on the solvolysis of α-anisyl-α-bromoethylenes in 80% EtOH are collected in Table IV which shows that the β-fluorenyl compound is the least reactive of those studied. Table IV also indicates that the inductive effects of alkyl and aryl groups from the β position are relatively small[10c] and that the $k_{1\text{-Br}}/k_{2\text{-Br}}$ ratio can be explained if the β-fluorenyl moiety is slightly more electron attracting than the two β-phenyl groups. However, the large rate differences among pairs of cis–trans isomers were ascribed to a relief of steric strain and to ground state destabilization effects[27,28] These geometrical factors should also be considered for our crowded systems. When the α-anisyl group is twisted from the plane of the double bond, the ground state anisyl double bond conjugation is reduced and the α-anisyl perpendicular cationic orbital interaction in the transition state increases. The rigid fluorenyl moiety of **2** and **4** is more in the plane of the double bond than the β-phenyl groups of **1** and **3** and consequently the α-anisyl group is pushed out of this plane. The dipolar structure **17** contributes electronically to this effect. The appearance of an upfield proton at δ 6.35 in the nmr of **2**-Br (but not in the nmr of **1**-Br) is probably due to the H-1 proton which is cis to the twisted α-anisyl group and in its shielding zone. This is also shown by a model and by analogy to the nmr of 9-benzhydrylidenefluorene.[29] This effect is opposed by the contribution of structure **18**, in which the α-anisyl is buttressed into the double bond plane. In this respect it is noteworthy that the long wavelength λ_{max} and ϵ of **2**-Br are[6a] higher than those for **1**-Br.

While we are unable to dissect the observed $k_{1\text{-Br}}/k_{2\text{-Br}}$ ratio into these contributing factors, its small value argues for the relative unimportance of struc-

(18) (a) K. A. Copper and E. D. Hughes, *J. Chem. Soc.*, 1183 (1937); E. D. Hughes and U. G. Shapiro, *ibid.*, 1177 (1937); A. H. Fairberg and S. Winstein, *J. Amer. Chem. Soc.*, **79**, 1608 (1957); (b) P. v. R. Schleyer and R. D. Nicholas, *ibid.*, **83**, 2700 (1961); (c) R. C. Bingham and P. v. R. Schleyer, *ibid.*, **93**, 3189 (1971).

(19) Using σ^+ values: H. C. Brown and Y. Okamoto, *ibid.*, **80**, 4979 (1958).

(20) Z. Rappoport and Y. Kaspi, *ibid.*, **92**, 3220 (1970). Recalculation of the data with the aid of a computer program which searches and uses the best infinity gave $k_{\alpha\text{-anisyl}}/k_{\alpha\text{-phenyl}}$ = 630, and ρ = −3.66.

(21) C. A. Grob and C. Cseh, *Helv. Chim. Acta*, **47**, 194 (1964).

(22) E. Grunwald and S. Winstein, *J. Amer. Chem. Soc.*, **70**, 846 (1948); S. Winstein, E. Grunwald, and H. W. Jones, *ibid.*, **73**, 2700 (1951).

(23) D. J. Raber, R. C. Bingham, J. M. Harris, J. L. Fry, and P. v. R. Schleyer, *ibid.*, **92**, 5977 (1970).

(24) S. Winstein and R. Heck, *ibid.*, **78**, 4801 (1956).

(25) Z. Rappoport and A. Gal, unpublished results.

(26) Z. Rappoport and J. Kaspi, unpublished results.

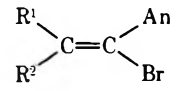
(27) C. A. Grob, *Chimia*, **25**, 87 (1971).

(28) Z. Rappoport and M. Atidia, *Tetrahedron Lett.*, 4085 (1970).

(29) M. Rabinovitz, I. Agranat, and E. D. Bergmann, *J. Chem. Soc. B*, 1281 (1967).

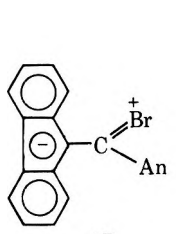
TABLE IV

RELATIVE SOLVOLYSIS RATES IN 80% EtOH AT 120° FOR

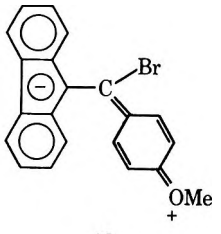


R¹	R²	Rel k_1	Ref	R¹	R²	Rel k_1	Ref
H	H	1.0[a]	21	An	An	1.70[c] (1.48)[b]	9
Me	H	6.43[a,d]	27	An	Ph	1.05[c]	10c
H	Me	0.78[a,d]	27	Ph	An	1.22[c]	10c
Me	Me	3.74[b]	25	Ph	Ph	0.80[c] (0.65)[b]	This work
An	H	13.5[b]	28	Fluorenyl		0.26[b]	This work
H	An	0.29[b]	28				

[a] Base, triethylamine. [b] Base, NaOAc. [c] Base, NaOH. [d] Relative k_1 at 110°.



17



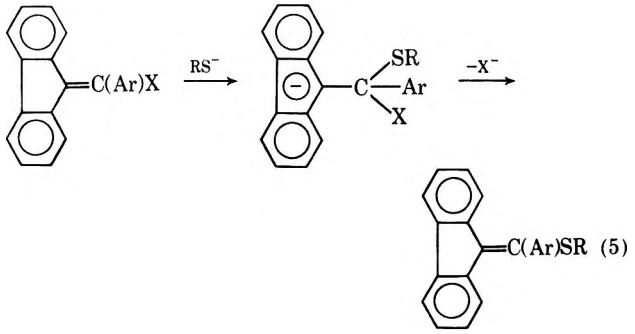
18

tures such as **17** as the main source for the vinylic unreactivity.[9,11,30,31] In view of the enormous differences in the charge-spreading ability of the fluorenyl and the benzhydryl groups,[13] it is highly improbable that an important contribution from **17** would be coincidentally masked by the other factors mentioned above.

Addition–Elimination Route.—The reaction of the β-fluorenyl system with thiolate ions is much faster than with NaOAc. For comparison, the half-lives of **4**-Br are 39 min at 105° in the presence of 0.008 *M* sodium *p*-toluenethiolate and 66 hr at 155.5° in the presence of 0.018 *M* NaOAc. Comparison of lines 2 and 3 of Table III shows that the use of the highly nucleophilic thiolate ions results in their involvement in a rate-determining bond formation. Two possible mechanisms are in-plane SN2 substitution and an Ad_N–El route. The SN2 route which predicts inversion of configuration of the substitution product and k_F/k_{Cl} and k_{Cl}/k_{Br} "element effects" was not yet observed in bimolecular nucleophilic vinylic substitutions, which give retention of configuration and high k_F/k_{Cl} ratios.[2] This route is very unlikely on steric ground since substituents α and β trans to the leaving group prevent approach of the nucleophile to a bonding distance from the α carbon.[2,32] This is especially true in our system where the nucleophile has to attack in-plane a *cis*-stilbene moiety. While we have no stereochemical information, the k_{Br}/k_{Cl} ratio (see below) and analogies with other nucleophilic vinylic reactions[2] suggest the Ad_N–El route.

The reaction is first order in the reactant and in the thiolate nucleophile, provided that the incomplete ionization of α-toluenethiol is taken into account. The $k_{2\text{-Br}}/k_{2\text{-Cl}}$ ratios of 1.8–1.9 are very close to the k_{Br}/k_{Cl} ratios of 2.2–2.6 for the substitution of α-halo-β-arylsulfonylethylenes with thiophenoxide ion,[33] or to the k_{Br}/k_{Cl} ratios in the substitutions *via* Ad_N–El in the $Ph_2C{=}CHX$ system.[34] These small ratios are ascribed to the operation of similar inductive and resonance effects of the two halogens in the rate-determining addition of the nucleophile to the double bond. The 12.6-fold higher reactivity of the benzylthiolate ion compared with the *p*-toluenethiolate ion at 90° is parallel to the reactivity ratio of 15.5 of these two nucleophiles toward α-chloro-β-*p*-toluenesulfonylethylene in methanol.[35]

The $k_{2\text{-Br}}/k_{4\text{-Br}}$ ratios of 0.93–0.96 give Hammett's ρ values (using σ values) of +0.06 to +0.11. While the sign of ρ is positive as found for other nucleophilic vinylic reactions,[36,37] its absolute value is much lower. This cannot be due to a very highly effective charge spreading into the β-fluorenyl moiety, since the ρ's for nucleophilic vinylic reactions of more electrophilic olefins such as arylidenemalononitriles are 1.1–2.0.[36b,c] We ascribe the $k_{\alpha\text{-anisyl}}/k_{\alpha\text{-phenyl}}$ ratio to the intervention of a small contribution from the SN1 route. Extrapolation of the data of Table I gives the half-lives of the SN1 reaction of 2-Br at 90 and 105° as 41 and 10 hr, respectively. Therefore, in our conditions the Ad_N–El route (eq 5) predominates and the SN1 route contributes only 0.5–1% to the overall rate, but this contribution is sufficient to increase the $k_{\alpha\text{-anisyl}}/k_{\alpha\text{-phenyl}}$ ratio. Indeed, in view of the large differences



between such ratios for both routes (*ca.* 3000 for the SN1 route *vs. ca.* 0.5 for the Ad_N–El route) *we suggest that the* $k_{\alpha\text{-anisyl}}/k_{\alpha\text{-phenyl}}$ *ratios are the most sensitive tool for detecting a small contribution of the SN1 route in a pre-*

(30) D. R. Kelsey and R. G. Bergman, *J. Amer. Chem. Soc.*, **93**, 1953 (1971).

(31) E. D. Hughes, *Trans. Faraday Soc.*, **34**, 185 (1938); **37**, 603 (1941).

(32) S. I. Miller and P. K. Yonan, *J. Amer. Chem. Soc.*, **79**, 5931 (1957).

(33) (a) A. Campagni, G. Modena, and P. E. Todesco, *Gazz. Chim. Ital.*, **90**, 694 (1960); (b) L. Maioli, G. Modena, and P. E. Todesco, *Boll. Sci. Fac. Chim. Ind. Bologna*, **18**, 66 (1960); (c) G. Modena, F. Taddei, and P. E. Todesco, *Ric. Sci.*, **30**, 894 (1960).

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(37) The use of a combination of σ and σ^+ values suggested recently for similar reactions (ref 36a) does not change much the ρ value.

dominantly nucleophilic addition–elimination substitution. We predict that these ratios will be nucleophile dependent and higher for the less nucleophilic thiolate ions. Further work on this criterion is now in progress.

A lower rate in the more aqueous solvent is predicted for the reaction of the neutral molecules **2** and **4** with the thiolate ions. This was observed with the benzylthiolate ion, although the effect is rather small. This is probably due to the increased dissociation of the α-toluenethiol in the more aqueous solvents[17] in addition to the small contribution from the SN1 route.

The 3.5-fold faster reaction in the presence of NaOH than with NaOAc may indicate that both routes operate simultaneously.[38] Preliminary experiment showed that the reaction is faster in 90% than in 80% EtOH. Unfortunately, the reaction was not studied further since it is followed by a side reaction which consumes the base.

Experimental Section

Melting points are uncorrected. Nuclear magnetic resonance spectra were recorded with Varian T/60 or HA/100D instruments and are given in δ units downfield from internal tetramethylsilane. Mass spectra were recorded with an Atlas C4 instrument and uv on a Perkin-Elmer 450 or on a Beckman DU spectrometer.

Materials.—α-Toluenethiol (Aldrich), bp 195°, and *p*-toluenethiol (Aldrich), mp 42–43°, bp 195°, were distilled before use. 9-Anisylidenefluorene was prepared according to Thiele[39] and 9-benzylidenefluorene dibromide according to Koelsch.[14] 1-Anisyl-2,2-diphenylvinyl 1-*p*-toluenethiolate was prepared earlier.[9]

Solvents.—The 80% ethanol and the aqueous ethanolic mixtures were prepared according to Grob.[21]

9-Anisylidenefluorene Dichloride (5-Cl).—Into 9-anisylidenefluorene (13.5 g, 48 mmol) in dry carbon tetrachloride (100 ml), chlorine gas (3.5 g, 50 mmol) was bubbled and the solution was shaken for 3 min, washed with water, dilute sodium hydroxide solution, and again with water, and dried, (Na_2SO_4), the solvent was evaporated, and methanol (50 ml) was added. After a few minutes of shaking, 15 g (80%) of white crystals, mp 105–106°, was obtained.

Anal. Calcd for $C_{21}H_{16}Cl_2O$: C, 71.03; H, 4.54. Found: C, 71.10; H, 4.72.

Spectra: nmr ($CDCl_3$) δ 3.66 (3 H, s, MeO), 5.60 (1 H, s, CH), 6.43–8.0 (12 H, m, Ar). If the nmr is taken after 2 hr, it showed the presence of *ca.* 30% of **2-Cl**.

α-Chloro-9-anisylidenefluorene (2-Cl).—9-Anisylidenefluorene dichloride (14.5 g, 40 mmol) in acetic acid (100 ml) was refluxed for 1 hr until the evolution of hydrogen chloride ceased. Water was added to turbidity, and the 10 g of crystals which was separated was recrystallized from 95% ethanol giving 4.1 g (31%) of α-chloro-9-anisylidenefluorene, mp 149–150°.

Anal. Calcd for $C_{21}H_{15}ClO$: C, 79.24; H, 4.72; Cl, 10.80. Found: C, 79.11; H, 4.74; Cl, 11.12.

Spectra: nmr ($CDCl_3$) δ 3.87 (3 H, s, OMe), 6.50 (1 H, unsymmetrical d, H-1), 6.77–7.87 (10 H, m, Ar), 8.60–8.76 (1 H, quart, H-8?); λ_{max} (dioxane) 250 nm (ε 31,100), 259.5 (39,000), 317.5 (14,300).

Additional fractions were mixtures (by nmr) of **2-Cl** and **6**.

9-Anisylidenefluorene Dibromide (5-Br).—To 9-anisylidenefluorene (5.8 g, 20 mmol) in dry carbon tetrachloride (100 ml), bromine (1.1 ml, *ca.* 20 mmol) was added at a rate that its color discharged immediately. With the progress of the reaction the yellow solution turned yellow red. The solution was left for additional 10 min at room temperature, washed with water and with dilute sodium hydroxide solution, and dried (Na_2SO_4), the solvent was evaporated, and the oil was triturated with methanol. White solid, mp 128–129° (with evolution of HBr), 7.6 g (85%), was obtained.

Spectra: nmr (CCl_4) δ 3.66 (3 H, s, MeO), 5.82 (1 H, s, CHBr), 6.77 (4 H, quart with 2 H at 6.58 and 2 H at 6.95, J = 9 cps, An), 6.87–8.23 (8 H, m, Ar).

The compound eliminates HBr easily and analyses gave various results.

Anal. Calcd for $C_{21}H_{26}Br_2O$: C, 56.80; H, 3.61; Br, 35.98. Found: C, 57.82; H, 3.64; Br, 35.10.

The nmr of these samples showed the presence of **2-Br**.

α-Bromo-9-anisylidenefluorene (2-Br).—9-Anisylidenefluorene dibromide (4.5 g, 10 mmol) in glacial acetic acid (50 ml) was refluxed for 30 min. The yellow solution turned brown and an acidic gas was evolved. After cooling, water was added slowly, and the yellow solid precipitated was recrystallized from ethanol giving 2.2 g (60%) of yellow plates, mp 152–154°.

Anal. Calcd for $C_{21}H_{15}BrO$: C, 69.34; H, 4.02; Br, 21.60. Found: C, 69.40; H, 4.16; Br, 22.00.

Spectra: nmr ($CDCl_3$) δ 3.82 (3 H, s, MeO), 6.35 (1 H, half of a quart, H-1), 6.77–7.76 (10 H, m, Ar), 8.80–8.88 (1 H, m, H-8?); λ_{max} (cyclohexane) 243.5 nm sh (ε 29,400), 251 (33,000), 259 (38,200), 281 sh (11,900), 304.5 (12,300), 317 (15,400); mass spectra, parent peak at *m/e* 362, 364 (81%), base peak at 283 (M − Br), and additional peaks at 268 (30%, M − Br − Me) and 252 (30%, M − Br − OMe); ir (KBr) 1580 cm^{-1} (C=C).

1-Anisyl-2,2-diphenylvinyl Chloride (1-Cl).—1-Anisyl-2,2-diphenylethylene[11] was prepared by the dehydration of 2-anisyl-1,1-diphenylethanol[9] by reflux for 2 hr in 20% sulfuric acid. To ethylene (5.72 g, 20 mmol) in carbon tetrachloride (50 ml), chlorine (1.6 g, 22 mmol) in carbon tetrachloride (25 ml) was added. When the addition was finished, air was bubbled into the mixture to remove the excess chlorine and hydrochloric acid formed. The solvent was evaporated and the oil was refluxed in acetic acid (50 ml) for 15 min, and, on cooling and addition of few milliliters of water, white crystals of **1-Cl**, mp 119–120° (4.7 g, 73%), were precipitated.

Anal. Calcd for $C_{21}H_{17}ClO$: C, 78.61; H, 5.34; Cl, 11.05. Found: C, 78.46; H, 5.19; Cl, 10.93.

Spectra: nmr ($CDCl_3$) δ 3.65 (3 H, s, OMe), 6.62–7.28 (14 H, m, Ar).

α-Bromo-9-benzylidenefluorene (4-Br) was prepared according to Koelsch:[40] λ_{max} (cyclohexane) 251.5 nm (ε 32,500), 259.5 (41,300), 283 (12,000), 303 (12,600), 316.5 (15,500).

9-Anisyl-9,10-dihydro-10-oxophenanthrene (6).—9-Anisylidenefluorene dibromide (2 g, 4.5 mmol) and potassium acetate (2 g, 20.2 mmol) in acetic acid (50 ml) were refluxed for 2 hr. KBr was precipitated. The mixture was poured into ice–water (200 ml), and the viscous residue was crystallized from methanol giving 1.22 g (90%) of white crystals of 9-anisyl-9,10-dihydro-10-oxophenanthrene, mp 170° (after recrystallization from acetone–chloroform).

Anal. Calcd for $C_{21}H_{16}O_2$: C, 83.95; H, 5.37. Found: C, 83.63; H, 5.12.

Spectra: nmr ($CDCl_3$) δ 3.70 (3 H, s, MeO), 6.77–7.90 (12 H, m, Ar), 9.55 (1 H, s, CHAn); λ_{max} (cyclohexane) 248 nm (ε 22,500), 256 sh (22,000), 302.5 (5600); ir (KBr) 2800, 2700 (CH), 1715 cm^{-1} (C=O); mass spectra, parent peak at *m/e* 300 (10%), base peak at 271 (M − HCO), other peaks at 257 (4%, M − HCO − Me), 228 (18%), 226 (18%), 135 (9%, AnCO).

9-(α-Acetoxy-*p*-methoxybenzyl)fluoren-9-ol (7).—Addition of water (200 ml) to the aqueous–acetic mother liquor left from the isolation of **6** above precipitated a solid (100 mg), mp 80°, which after recrystallization from carbon tetrachloride–hexane gave 60 mg (4%) of white crystals, mp 153°.

Anal. Calcd for $C_{23}H_{20}O_4$: C, 76.61; H, 5.59. Found: C, 75.81; H, 5.54.

Spectra: nmr ($CDCl_3$) δ 2.08 (3 H, s, MeCO), 3.65 (3 H, s, MeO), 4.65 (1 H, broad s, OH), 6.20 (1 H, s, CH), 6.42–6.88 (4 H, quart centered at 6.73), 7.08–7.67 (8 H, m, Ar); ir (KBr) 3480, 3420 (OH), 1720 cm^{-1} (C=O); mass spectra, parent peak at *m/e* 360 (1%), other peaks at 300 (4%, M − HOAc), 239 (9%), 179 (base peak, $AnCHOAc^+$), 180 (53%, dibenzpyran$^+$, ?).

9-Methoxy-9-(α-*p*-dimethoxybenzyl)fluorene (8).—9-Anisylidenefluorene dibromide (2 g, 4.5 mmol) was kept at room temperature in methanol (50 ml) containing KOMe (2 g, 28 mmol) for 24 hr. The mixture was poured into water and the oil formed was separated by decantation and crystallized from methanol giving 1.25 g (80%) of white solid, mp 110°.

Anal. Calcd for $C_{23}H_{22}O_3$: C, 80.21; H, 6.45; MeO, 27.04. Found: C, 79.96; H, 6.17; MeO, 26.56.

Spectra: nmr ($CDCl_3$) δ 2.85 (3 H, s, OMe), 3.25 (3 H, s,

(38) If the higher reactivity of **2-Br** with NaOH compared with NaOAc is due to the intervention of the Ad_N–E1 route, the second-order rate coefficient for this route is 3.3×10^{-4} l. mol^{-1} sec^{-1}.

(39) J. Thiele and F. Henle, *Justus Liebigs Ann. Chem.*, **347**, 290 (1906).

(40) C. F. Koelsch, *J. Amer. Chem. Soc.*, **54**, 3384 (1932).

OMe), 3.67 (3 H, s, MeO), 4.50 (1 H, s, CH), 6.43–6.85 (4 H, quart centered at 6.58, J = 9 cps, An), 7.18–8.0 (8 H, m, Ar).

α-Acetoxy-9-anisylidenefluorene (2-OAc).—α-Bromo-9-anisylidenefluorene (1.8 g, 5 mmol) and silver acetate (3 g, 12 mmol) in acetic acid (50 ml) were refluxed in the dark for 3 hr. The hot solution was filtered, the solid was washed with hot acetone, and the organic solvents were combined and evaporated. The remaining oil was dissolved in dichloromethane and filtered, the solvent was evaporated, and the residue crystallized fron 95% ethanol giving 1.4 g (82%) of pale yellow crystals of 2-OAc, mp 143–144°.

Anal. Calcd for $C_{23}H_{18}O_3$: C, 80.40; H, 5.22. Found: C, 80.69; H, 5.30.

Spectra: nmr ($CDCl_3$) δ 2.37 (3 H, s, OCOMe), 3.90 (3 H, s, OMe), 6.92–8.05 (12 H, m, Ar); λ_{max} (cyclohexane) 248 nm (ε 26,000), 257 (32,000), 311 (14,000); ir (KBr) 1742 cm^{-1} (C=O).

α-Ethoxy-9-anisylidenefluorene (13).—α-Bromo-9-anisylidenefluorene (128 mg, 0.18 mmol) in 80% ethanol 0.5 N in sodium acetate (10 ml) was kept for 4 days at 140° in an ampoule. On cooling, yellow crystals of **13**, mp 154–156° (50 mg, 41%), were obtained.

Anal. Calcd for $C_{23}H_{20}O_2$: C, 84.67; H, 6.18. Found: C, 84.62; H, 6.22.

Spectra: nmr ($CDCl_3$) δ 1.40 (3 H, t, Me), 3.90 (2 H, quart, CH_2), 3.95 (3 H, s, OMe), 6.33–6.48 (1 H, half of a quart, H-1), 6.80–7.90 (10 H, m, Ar), 8.27–8.40 (1 H, m, H-8?).

9-Anisoylfluorene (14).—α-Acetoxy-9-anisylidenefluorene (0.34 g, 1 mmol) and sodium hydroxide (1 g, 25 mmol) in 80% ethanol (50 ml) were refluxed for 90 min. The mixture was poured into water, extracted with chloroform, washed with water, and dried (Na_2SO_4). White needles of **14**, mp 117–118° (from petroleum ether), were obtained (230 mg, 76%).

Anal. Calcd for $C_{21}H_{16}O_2$: C, 83.95; H, 5.37. Found: C, 83.78; H, 5.08.

Spectra: nmr ($CDCl_3$) δ 3.80 (3 H, s, OMe), 5.50 (1 H, s, CH), 6.73–7.93 (12 H, m, Ar); λ_{max} (cyclohexane) 265 nm (ε 30,000), 301 (6100); ir (KBr) 1653 cm^{-1} (C=O); mass spectra, parent peak at m/e 300 (5%) and peaks at 165 ($C_{13}H_9^+$, 14%), 135 (base peak, $AnCO^+$).

α-p-Toluenethio-9-anisylidenefluorene (15).—An ampoule containing α-bromo-9-anisylidenefluorene (65 mg, 0.18 mmol) and sodium p-toluenethiolate (0.24 M) in 80% ethanol (5 ml) was kept at 140° for 14 hr. On cooling, a yellow solid was separated and on crystallization from 95% ethanol it gave 50 mg (70%) of α-p-toluenethio-9-anisylidenefluorene, mp 150–151°.

Anal. Calcd for $C_{28}H_{22}OS$: C, 82.73; H, 5.46; S, 7.89. Found: C, 82.86; H, 5.29; S, 8.16.

Spectra: nmr ($CDCl_3$) δ 2.22 (3 H, s, Me), 3.77 (3 H, s, MeO), 6.32 (1 H, one-half of a quart, H-1), 6.68–7.90 (14 H, m, Ar), 8.95–9.08 (1 H, m, H-8?); λ_{max} (cyclohexane) 237 nm (ε 50,000), 254 (30,000), 263 (30,000), 348 (17,800).

α-Benzylthio-9-anisylidenefluorene (16).—α-Bromo-9-anisylidenefluorene (0.3 g, 0.82 mmol) and α-toluenethiol (0.5 g, 4 mmol) in 90% dioxane (50 ml) were kept at 75° for 14 hr. The mixture was poured into water and extracted with 1,2-dichloroethane (50 ml), the solvent was evaporated, the remaining viscous oil was triturated with methanol, and the solid was filtered and recrystallized from methanol giving 170 mg (51%) of yellow crystals of **16**, mp 146–147°. Additional fractions contain large percentages of dibenzyl disulfide (mp 63°, mmp 63°).

Anal. Calcd for $C_{28}H_{22}OS$: C, 82.73; H, 5.46; S, 7.89. Found: C, 82.72; H, 5.48; S, 8.01.

Spectra: nmr ($CDCl_3$) δ 3.65 (2 H, s, CH_2), 3.85 (3 H, s, MeO), 6.08–6.20 (1 H, half of a quart, H-1), 6.68–7.75 (15 H, m, Ar), 8.68–8.85 (1 H, m, H-8?); λ_{max} (dioxane) 255 nm sh (ε 21,000), 264.5 (19,600), 350 (17,900).

α-Benzylthio-9-benzylidenefluorene.—A mixture of α-bromobenzylidenefluorene (333 mg, 1 mmol) and α-toluenethiol (620 mg, 5 mmol) in 80% dioxane (50 ml) containing sodium hydroxide (8 mM) was kept at 75° overnight. The mixture was poured into water, extracted (chloroform), washed with water, and dried ($CaCl_2$) and the solvent was evaporated. The remaining oil was crystallized from ethanol giving 200 mg (53%) of yellow crystals, mp 144–145°.

Anal. Calcd for $C_{27}H_{20}S$: C, 86.12; H, 5.35; S, 8.51. Found: C, 86.12; H, 5.34; S, 8.52.

Spectra: nmr ($CDCl_3$) δ 3.66 (2 H, s, CH_2), 6.0–8.9 (18 H, m, Ar); λ_{max} (dioxane) 254 nm (ε 24,000), 264 (22,000), 295 (6400), 305 (6200), 350 (22,000).

Kinetics. A. With Benzylthiolate Ion.—Stock solutions of 2–2.5 × 10^{-4} M of 2-Cl, 2-Br, and 4-Br and of a mixture of α-toluenethiol and sodium hydroxide were prepared, mixed, sealed in ampoules, warmed at 75° for equilibration for 1–2 min, and kept at the reaction temperature. At predetermined times the ampoules were cooled and opened, 5-ml samples were withdrawn and diluted 2–2.5-fold with absolute methanol, and the optical density of the samples were measured in a 1-cm cells at 317 nm (λ_{max} of the vinyl halide) using methanol as a reference. After additional dilution the measurement was repeated at 350 nm (λ_{max} of the product). The isosbestic point at 324 nm remained constant during the reaction. The absorptions of the vinyl halide at the λ_{max} of the product and of the vinyl thiolate at the λ_{max} of the vinyl halide were taken into account. With 1-Br the reaction was followed by titration of the bromide ion after precipitation of the excess thiol with $Cu(NO_3)_2$.[9] Although the calculated infinity was not achieved (the infinities observed are *ca.* 85%), the product was obtained in quantitative yield.

B. With Sodium p-Toluenethiolate.—The reaction with 2-Br was followed essentially as with benzylthiolate above, except that measurements were at 392 nm. The reaction with 1-Br was again followed titrimetrically with the $Cu(NO_3)_2$ variant. The infinities observed were at *ca.* 80%, but the product was obtained quantitatively.

C. With Sodium Acetate.—The solutions were prepared as described previously.[9] The sodium acetate concentration was determined in water by titration with 0.1 N HCl using a combination of 2,4-dinitrophenol and bromophenol blue indicators (color change, blue-violet → yellow). The bromide was titrated with silver nitrate using an eosin indicator, and the chloride (from 1-Cl and 2-Cl) was titrated potentiometrically.

D. With Sodium Hydroxide.—The reactions were conducted as described earlier.[9]

In all cases the first-order rate coefficients were calculated with the aid of a first-order KINDAT program.[41]

Product Analysis.—The product analysis was done usually by nmr in addition to the isolation of the products. The ethers were recognized by their triplet signal for the methyl group and the ketones by the single benzhydrylic proton and by the low-field half-quartet signals for the α-anisyl protons ortho to the carbonyl group. In the case of the vinyl thiolates none of these were observed and the spectra corresponded to that of the vinyl thiolate.

Registry No.—**1** (X = Br), 25354-48-7; **1** (X = Cl), 33686-66-7; **2** (X = Br), 33686-67-8; **2** (X = Cl), 33686-68-9; **2** (X = OAc), 33735-94-3; **4** (X = Br), 33735-95-4; **5** (X = Br), 33686-69-0; **5** (X = Cl), 33686-70-3; **6**, 33686-71-4; **7**, 33735-96-5; **8**, 33686-72-5; **13**, 33686-73-6; **14**, 33735-97-6; **15**, 33686-74-7; **16**, 33686-75-8; acetate, 71-50-1; hydroxide, 14280-30-9; benzylthiolate, 1492-49-5; p-toluenethiolate, 26330-85-8; α-benzylthio-9-benzylidenefluorene, 33686-77-0.

(41) R. C. Williams, *J. Chem. Soc.*, **47**, 129 (1970).

Addition Reactions of *syn*- and *anti*-7-*tert*-Butylnorbornenes[1]

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Cyclic and noncyclic additions to *syn*- and *anti*-7-*tert*-butylnorbornenes have been studied. Reactions of *anti*-7-*tert*-butylnorbornene generally occurred exo,cis independent of the cyclic or noncyclic nature of the transition state. An exception was catalytic hydrogenation which involved 25% endo,cis reduction, a reflection of structural strain in the exocyclic catalyst–olefin complex. Strain factors and nonbonded interactions impacted on all exo additions to the anti olefin as evidenced by retarded rates relative to norbornene. Cyclic additions to *syn*-7-*tert*-butylnorbornene either failed to occur or proceeded slowly to endo product. Noncyclic, or two-stage, additions of thiophenol and mercury(II) to the syn olefin did not occur, a reflection of the steric inhibition presented by the *syn*-7-*tert*-butyl radical.

anti- (1) and *syn*-7-*tert*-butylnorbornenes (2) have recently been synthesized from 7-*tert*-butylnorbornadiene.[2] The availability of these olefins has permitted the study of their reactions with reagents which add to olefins through both cyclic and noncyclic transition states. Comparable additions to *syn*- and *anti*-7-acetoxynorbornenes[3-7] occurred in an exo manner with the syn isomer exhibiting a faster rate due to the stabilization of the transition state through chelation. An exception was catalytic hydrogenation where steric inhibition slowed the reduction of the syn ester relative to the anti and also forced the syn acetate to experience 40% endo hydrogenation.

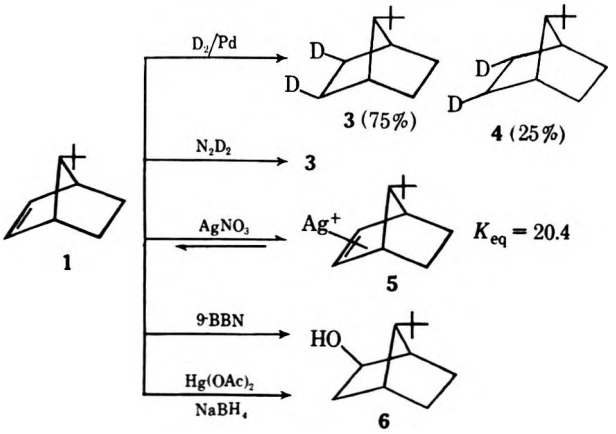
The latter reaction may be viewed as being representative of the types of reactions observed by Brown and coworkers during a study of cyclic and noncyclic additions to 7,7-dimethylnorbornene.[8-14] Brown has found that, in general, reactions involving cyclic transition states, *e.g.*, catalytic hydrogenation, either failed in the presence of the *syn*-7-methyl group or gave endo products. On the other hand, two-stage, or noncyclic additions, were considerably less sensitive to the presence of the 7-methyl group and yielded exo product, albeit the rates were depressed relative to norbornene.[14] It was the purpose of the present study to contrast the behavior of norbornenes bearing a nonpolar, bulky 7 substituent with these previous findings.

Results and Discussion

The reactions of *anti*-7-*tert*-butylnorbornene (1) with various reagents are shown in Scheme I. While the dominance of exo addition indicated that the chemistry of 1 was comparable to that of norbornene and *anti*-7-acetoxynorbornene,[3-7] detailed study of these reactions revealed a sensitivity to the 7-*tert*-butyl group that was not apparent from casual inspection of the structure of this olefin. The influence of this 7 substituent became apparent on the basis of three distinct observations: low reaction rates for *anti*-7-*tert*-butylnorbornene relative to norbornene; endo addition during catalytic hydrogenation of 1; a smaller K_{eq} for silver ion complexation compared to K_{eq} for norbornene.

SCHEME I

ADDITION REACTIONS OF *anti*-7-*tert*-BUTYLNORBORNENE



That reactions of *anti*-7-*tert*-butylnorbornene were slow relative to those of norbornene is illustrated by Table I. Rate retardation was observed independent of the cyclic or noncyclic nature of the reaction. Complexation of the two olefins with silver ion was measured utilizing the gas chromatographic method of Muhs and Weiss.[15] Norbornene gave a K_{eq} of 49.5 while K_{eq} for the silver(I)–*anti*-7-*tert*-butylnorbornene complex was 20.8, representing a reduction in complex stability by a factor of 2.4.[16]

TABLE I

RELATIVE RATES OF REACTION OF NORBORNENE AND *anti*-7-*tert*-BUTYLNORBORNENE

Reagent	$k_{norbornene}/k_{ant}$
N_2H_2	1.55
H_2	3.77
9-BBN	3.73
$Hg(OAc)_2$	5.49
m-$ClC_6H_4CO_3H$	5.16

(1) Presented in part at the 159th National Meeting of the American Chemical Society, Houston, Texas, Feb 1970, PETR 103.

(2) W. C. Baird, Jr., and J. H. Surridge, *J. Org. Chem.*, **37**, 304 (1972).

(3) W. C. Baird, Jr., B. Franzus, and J. H. Surridge, *J. Amer. Chem. Soc.*, **89**, 410 (1967).

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(5) W. C. Baird, Jr., and M. Buza, *ibid.*, **33**, 4105 (1968).

(6) B. Franzus, W. C. Baird, Jr., and J. H. Surridge, *ibid.*, **33**, 1288 (1968).

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(8) H. C. Brown and J. H. Kawakami, *J. Amer. Chem. Soc.*, **92**, 201 (1970).

(9) H. C. Brown, M.-H. Rei, and K.-T. Liu, *ibid.*, **92**, 1760 (1970).

(10) H. C. Brown and J. H. Kawakami, *ibid.*, **92**, 1990 (1970).

(11) H. C. Brown and J. H. Kawakami, *ibid.*, **92**, 3817 (1970).

(12) H. C. Brown, J. H. Kawakami, and S. Ikegami, *ibid.*, **92**, 6914 (1970).

(13) H. C. Brown and K.-T. Liu, *ibid.*, **92**, 3502 (1970).

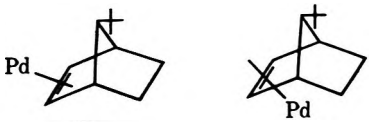
(14) H. C. Brown and K.-T. Liu, *ibid.*, **93**, 7335 (1971).

(15) M. A. Muhs and F. T. Weiss, *ibid.*, **84**, 4697 (1962).

(16) No silver(I)-*anti*-7-*tert*-butylnorbornene complexation was detected with aqueous silver nitrate.[17] This failure has been attributed to the insolubility of the C_{11} olefin in aqueous silver(I) nitrate. Control experiments have confirmed the sensitivity of the aqueous silver nitrate procedure to olefin size and have indicated that C_7–C_8 olefins represent the upper limit for the study of silver(I) complexes in water.

(17) (a) J. G. Traynham and M. F. Sehnert, *J. Amer. Chem. Soc.*, **78**, 4024 (1956); (b) J. G. Traynham and J. R. Olechowski, *ibid.*, **81**, 571 (1959).

Catalytic hydrogenation of *anti*-7-*tert*-butylnorbornene using deuterium as the reducing gas gave 75% exo,cis and 25% endo,cis addition (Scheme I). Comparable endo,cis addition has not been observed with norbornene[18] or the *anti*-7-acetoxy derivative.[7] The formation of the endo,cis dideuterated norbornene (**4**) has indicated that the reduction has involved endocyclic olefin–catalyst coordination (**4a**) as well as the anticipated exocyclic complex (**3a**).

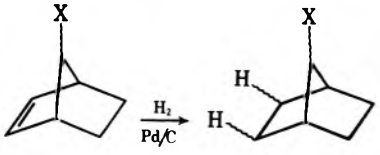


3a

4a

The 7-*tert*-butyl group also produced an unusual effect on the relative rates of hydrogenation of the isomeric 7-*tert*-butylnorbornenes. In Table II are

TABLE II
RELATIVE RATES OF REDUCTION OF 7-SUBSTITUTED NORBORNENES



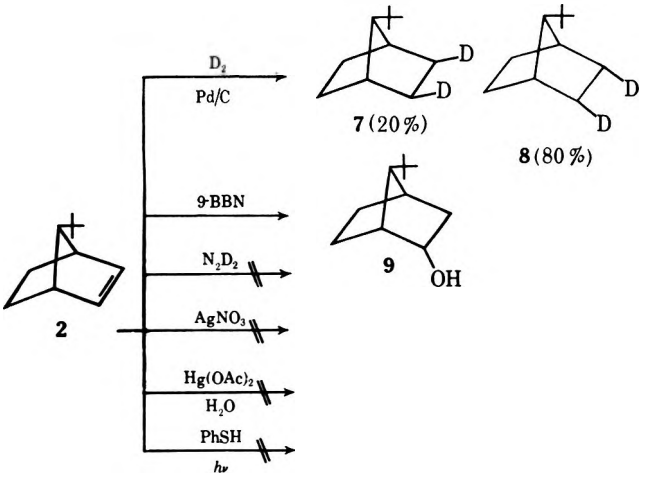
X (anti)	X (syn)	% exo,cis addition	k_{anti}/k_{syn}	Ref
OH		100	0.9	9
	OH	100		
CH_3			2	22
	CH_3			
$OOCCH_3$		100	16.8	9
	$OOCCH_3$	60		
$(CH_3)_3C$		75	9.6	This work
	$(CH_3)_3C$	20		

presented the relative rates of reduction of various syn–anti pairs as a function of the 7 substituent. While small radicals had little or no effect on the relative rates, large groups slowed the reduction of the syn isomer by blocking exo attack.[23] In this sense the data of Table II were inconsistent, for the acetoxy group appeared to exert greater steric influence than the more bulky *tert*-butyl group while simultaneously permitting a higher level of exo reduction of the syn olefin.

The conclusion derived from the consideration of these facts was that the 7-*tert*-butyl group was diminishing the reactivity of the anti double bond even though no direct steric or electronic relationship was evident. Since all the reactions described involved the conversion of the norbornene skeleton to that of norbornane, a common factor that rationalized the behavior of the anti double bond was the development of repulsive interaction between the anti-7-*tert*-butyl group and the exo,cis 5,6 hydrogens in the transition state. Such nonbonded interactions would retard exo electrophilic additions and would encourage endo attack where feasible.[24] The fact that diimide reduction provided the smallest rate differential was a reflection of minimal steric crowding by the cyclic six-membered transition state.[25]

In Scheme II are summarized the reactions of *syn*-7-*tert*-butylnorbornene (**2**) with various reagents. The

SCHEME II
ADDITION REACTIONS OF *syn*-7-*tert*-BUTYLNORBORNENE



results were in accord with those anticipated on the basis of the steric bulk presented by the 7-*tert*-butyl group to reactions of the syn double bond. Reactions that proceeded through cyclic intermediates failed to occur [diimide reduction, silver(I) complexation] or gave endo products (hydrogenation, hydroboration). In these cases the influence of the *tert*-butyl group was comparable to Brown's results with 7,7-dimethylnorbornene.[6-14] The 80% endo,cis hydrogenation of **2** *vs.* 90% for the 7,7-dimethyl compound is ascribed to the different catalysts employed.[18] Both norbornenes failed to complex silver(I); the 7,7-dimethyl derivative, however, experienced 100% exo reduction by diimide, a reagent to which the 7-*tert*-butyl compound was passive. This distinction is attributed to the ability of the diimide transition state to tolerate a *syn*-7-methyl group,[14] but not a *tert*-butyl group.

Noncyclic, or two-stage, additions to 7,7-dimethylnorbornene have been shown to be insensitive to the 7-methyl radical. These reactions have proceeded to yield exo product, presumably because the adding reagent did not approach the double bond symmetrically, but instead attacked the end of the olefinic bond. This direction of approach neutralized the steric influence of the 7-methyl, and the reaction proceeded normally with little or no rate retardation.

(18) Reduction of norbornene over a borohydride reduced platinum catalyst has been reported to give 10% endo reduction.[19] Catalytic hydrogenation in this laboratory has consistently utilized a 10% palladium-on-charcoal catalyst (Matheson Coleman and Bell) over which endo addition to norbornene has not been observed. While this difference may be due to the nature and the activity of the two catalysts, it is true the reductions over platinum are complicated by hydrogen–deuterium exchange and scrambling.[20] The latter reactions are not significant over palladium at room temperature.[6,20,21]

(19) H. M. Bell, Ph.D. Thesis, Purdue University, Lafayette, Ind., 1964.

(20) (a) R. L. Burwell, Jr., *Chem. Rev.*, **57**, 895 (1957); (b) H. C. Volger and H. Hogeveen, *Recl. Trav. Chim. Pays-Bas*, **87**, 1356 (1968).

(21) R. L. Burwell, Jr., B. K. C. Shim, and H. C. Rowlinson, *J. Amer. Chem. Soc.*, **79**, 5142 (1957).

(22) V. A. Mironov, B. D. Polkovnikov, E. P. Mikos, T. M. Fadeeva, and A. A. Akhrem, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 129 (1970).

(23) (a) T. J. Howard and B. Morley, *Chem. Ind. (London)*, 73 (1967); (b) T. J. Howard, *Recl. Trav. Chim. Pays-Bas*, **83**, 992 (1964); (c) S. Mitsui, K. Hebiguchi, and H. Saito, *Chem. Ind. (London)*, 1746 (1967).

(24) The influence of various 7 substituents on the stereochemistry of catalytic reduction of norbornenes has been previously discussed.[2]

(25) E. J. Corey, W. L. Mock, and D. J. Pasto, *J. Amer. Chem. Soc.*, **83**, 2957 (1961). The size of the diimide transition state has permitted exo reduction of 7,7-dimethylnorbornene although steric arguments would have predicted that no reaction would occur.[14]

With the 7-*tert*-butyl compound, this was not the case, and oxymercuration with aqueous mercury(II) acetate and free radical addition of thiophenol failed to occur.[26] The combined bulk of the 7 substituent and the reagents was apparently sufficient to preclude reaction independent of the mode of attack. Endo addition was naturally excluded by the endo 5,6 protons.

Experimental Section

Infrared spectra were recorded on a Beckman IR-5A spectrophotometer. Nmr spectra were measured on Jeol Minimar and Varian Associates A-60 and HA-100 spectrometers using tetramethylsilane as an internal standard. Analytical vapor phase chromatography (vpc) was performed on a Perkin-Elmer 154D fractometer and a Perkin-Elmer Model 226 capillary gas chromatograph. Preparative scale gas chromatography was performed on a Varian Aerograph Model A-700 instrument. Melting points and boiling points are not corrected. All reagents were obtained from commercial sources and were used as received.

Reactions of *anti*-7-*tert*-Butylnorbornene (1). Oxymercuration.[27]—To a suspension of 300 mg (0.95 mmol) of mercury(II) acetate in 2 ml of water and 1 ml of tetrahydrofuran was added a solution of 110 mg (0.73 mmol) of *anti*-7-*tert*-butylnorbornene in 2 ml of tetrahydrofuran. The reaction mixture gradually decolorized. After 5 min the reaction was treated with 3 *M* sodium hydroxide and 0.5 *M* sodium borohydride and worked up in the normal manner. Infrared analysis showed the crude product to be a mixture of an alcohol and an acetate ester. The ester was saponified by refluxing the crude product with 0.1 g of sodium methoxide in 5 ml of methanol. The alcohol was isolated by dilution of the saponification mixture with water and extraction with pentane. Removal of the pentane solvent gave 75 mg (62%) of *exo*-2-hydroxy-*anti*-7-*tert*-butylnorbornane (**6**), mp 84.5–85°, which was shown to be identical with an authentic sample.[2] Vpc analysis (3 ft × 0.25 in., 3% Dowfax column, 100°, 135 ml/min) showed the alcohol to be homogeneous.

Diimide Reduction.—The reduction was performed utilizing 111.9 mg (0.74 mmol) of *anti*-7-*tert*-butylnorbornene, 385.7 mg (2 mmol) of potassium azodicarboxylate in 1 ml of methanol-d_1, and 0.25 ml of acetic acid-d_1 in 0.75 ml of methanol-d_1. The reaction yielded 106 mg (94%) of 2,3-dideuterio-7-*tert*-butylnorbornane (**3**), which was homogeneous by vpc (2 m × 0.25 in. polypropylene glycol column, 175°, 80 ml/min): nmr ($CDCl_3$) δ 2.04 (m, 2, >CH), 1.54–1.85 (m, 2, exo >CHH), 1.24 (m, 1, HC-*tert*-Bu), 0.98–1.20 (m, 4, endo >CHH), 0.90 [s, 9, $(CH_3)_3C$]. Analysis of the exo,endo proton areas showed that the reduction had occurred exclusively exo,cis.

Hydrogenation.—*anti*-7-*tert*-Butylnorbornene (188.2 mg, 1.25 mmol) was reduced with deuterium over 38 mg of 10% palladium on charcoal in 5 ml of methanol in a gas buret apparatus. The product was isolated by dilution with water and extraction with pentane. Removal of the solvent gave 160 mg (85%) of 2,3-dideuterio-7-*tert*-butylnorbornane (**3**, **4**). The nmr spectrum ($CDCl_3$) was identical with that described above except for the relative areas of the exo (2.5) and the endo (3.5) protons, which corresponded to 75% exo,cis and 25% endo,cis reduction.

Silver Nitrate Complexation.—The general procedure has been described.[4] A 0.5 *M* solution of *anti*-7-*tert*-butylnorbornene in carbon tetrachloride and a saturated aqueous solution of silver nitrate were shaken together for 3 hr at room temperature. No measurable complex formation was observed during this interval.

The formation of a silver complex was also investigated by the gas chromatographic method of Muhs and Weiss.[15] Two 6 ft × 0.25 in. vpc columns were employed: 30% ethylene glycol on Chromosorb P (70%) and 30% 0.35 *M* silver nitrate in ethylene glycol in Chromosorb P (70%). The columns were operated at 40° and 480 ml/min helium flow. A control experiment with norbornene gave an equilibrium constant of 49.5 (lit. 62).[16] Under identical conditions *anti*-7-*tert*-butylnorbornene gave a silver ion complexation constant of 20.7. The ratio of the equilibrium constants, $K_{eq_{norbornene}}/K_{eq_{anti}} = 2.4$.[28]

Competitive Reactions of Norbornene and *anti*-7-*tert*-Butylnorbornene.—In the general procedure equimolar amounts of norbornene and *anti*-7-*tert*-butylnorbornene were dissolved in the appropriate reaction solvent, and *n*-decane was added as an internal standard for vpc analysis. The olefin solution was reacted with a limited amount (~50 mol %) of the various reagents. Samples of the reaction were periodically removed, quenched, and analyzed by vpc for olefin content. Relative reaction rates were calculated from the equation

$$k_{norbornene}/k_{anti} = \frac{\log[(norbornene)_0/(norbornene)]}{\log[(anti)_0/(anti)]}$$

The ratios reported represent the average of at least three separate determinations. Pertinent details are summarized in Table III.

TABLE III

Reagent (mmol)	Norbornene, mmol	Anti, mmol	$k_{norbornene}/k_{anti}$	Vpc method	Ref
$Hg(OAc)_2$ (1.01)	1.43	1.05	5.49	*a*	27
H_2 (~1.0)	1.06	1.07	3.77	*b*	7
N_2H_2 (0.42)	0.50	0.47	1.55	*b*	3
9-BBN (0.78)	0.98	0.88	3.73	*b*	29
m-$CO_3HC_6H_4Cl$ (0.36)	0.48	0.55	5.16	*b*	12

[a] 4 m × 0.25 in. 20% polypropylene glycol, 170°, 25 ml/min. [b] 300 ft × 0.01 in. DC-550 silicone, 140°, 30 psig.

Competitive Reduction of *syn*- and *anti*-7-*tert*-Butylnorbornenes.—A mixture of 0.43 mmol of *syn*-7-*tert*-butylnorbornene and 1.44 mmol of *anti*-7-*tert*-butylnorbornene was hydrogenated in a gas buret over 10% palladium on charcoal in 5 ml of methanol. Samples were periodically removed and analyzed by vpc (method b) using *n*-decane as an internal standard. The relative rate, k_{anti}/k_{syn}, was calculated as shown above; the average of eight determinations covering the range 12–80% reduction was 9.6.

Reactions of *syn*-7-*tert*-Butylnorbornene (2). Hydroboration.[29]—To 5 ml of 0.78 *M* 9-BBN in tetrahydrofuran was added 300 mg (2 mmol) of *syn*-7-*tert*-butylnorbornene in 1 ml of tetrahydrofuran. The reaction was stirred under nitrogen at room temperature for 20 hr. To the reaction were added 1 ml of 6 *M* sodium hydroxide and 1 ml of 30% hydrogen peroxide, and the reaction was refluxed for 1 hr. The aqueous phase was saturated with sodium chloride, and the tetrahydrofuran layer was separated and dried over magnesium sulfate. The ether was removed by distillation to give 350 mg of clear oil. Vpc analysis (3 ft × 0.25 in. 3% Dowfax, 100°, 135 ml/min) showed that ~25% of starting olefin remained. The product (retention time 12 min) was separated by vpc to give 136 mg (54% based on olefin consumed) of white needles, mp 85–85.5°. The acetate ester (acetyl chloride–pyridine) gave a single peak, retention time 22.0 min, on a 300 ft × 0.01 in. DC-550 silicone column, 150°, 30 psig. *Anal.* Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.12; H, 11.75. Nmr ($CDCl_3$) δ 4.57 (m, 1, J = 19 Hz, exo HCO), 2.08 (s, 1, OH), 1.93–2.32 (m, 2, >CH), 1.06–1.91 (m, 7, exo,endo $>CH_2$, HC-*tert*-Bu), 0.96 [s, 9, $(CH_3)_3C$]. The nmr spectrum was that anticipated for *endo*-2-hydroxy-*syn*-7-*tert*-butylnorbornane (**9**).

Hydrogenation.—A sample of *syn*-7-*tert*-butylnorbornene (1.87 mg, 1.25 mmol) was reduced with deuterium according to the procedure described for reduction of the anti isomer. The iso-

(26) Less bulky reagents did attack *syn*-7-*tert*-butylnorbornene. Trifluoroacetic acid reacted to give a mixture of products that was not characterized. Mercury(II) trifluoroacetate in tetrahydrofuran and in benzene mercurated the olefin; the resulting adduct was too labile to permit reliable characterization. Nmr experiments, however, suggested that the adduct was not exocyclic.

(27) H. C. Brown and P. Geoghegan, Jr., *J. Amer. Chem. Soc.*, **89**, 1522 (1967).

(28) Control experiments utilizing octene-1 and dodecene-1 as model olefins gave a ratio of constants, $K_{eq_{C_8}}/K_{eq_{C_{12}}} = 1.5$. This value has shown that the K for the *anti*-7-*tert*-butyl olefin is lower than anticipated on the basis of diminished solubility of a C_7 *vs.* C_{11} olefin.

(29) E. F. Knights and H. C. Brown, *J. Amer. Chem. Soc.*, **90**, 5200 (1968).

lated yield of pure norbornane was 132 mg (71%): nmr ($CDCl_3$) δ 2.10 (m, 2, >CH), 1.30–1.76 (m, 3.6, exo >CHH), 1.26 (m, 1, HC-*tert*-Bu), 0.98–1.18 (m, 2.4, endo >CHH), 0.92 (s, 9, $(CH_3)_3C$]. Deuterium addition had occurred 80% endo,cis.

Diimide Reduction.—The reduction of 200 mg (1.35 mmol) of *syn*-7-*tert*-butylnorbornene with diimide was attempted as described above. The olefin was exposed to a fourfold molar excess of diimide generated by two charges of potassium azodicarboxylate over a period of 3 hr. Analysis by vpc (300 ft × 0.01 in. DC-550 silicone column, 115°, 30 psig) showed that the starting olefin was recovered quantitatively.

Silver Nitrate Complexation.—*syn*-7-*tert*-Butylnorbornene failed to complex silver nitrate in aqueous solution. The olefin showed identical retention times on both silver nitrate–ethylene glycol and ethylene glycol vpc columns.

Oxymercuration.—Oxymercuration of the syn olefin was attempted with mercury(II) acetate in aqueous tetrahydrofuran.[27] The reaction was stirred at room temperature for 24 hr; no discharge of the characteristic yellow color of the mercury salt suspension occurred. The reaction was worked up according to the standard procedure to recover unreacted olefin. The absence of product was confirmed by vpc analysis.

Addition of Thiophenol.—A solution of 110 mg (1.0 mmol) of thiophenol and 150 mg (0.84 mmol) of *syn*-7-*tert*-butylnorbornene (84% syn olefin, 16% 7-*tert*-butylnorbornane) in 1 ml of *n*-hexane was stirred at 0° under nitrogen. The solution was irradiated with a Hanovia 100-W quartz ultraviolet lamp. Samples were removed periodically through a rubber septum and were analyzed by vpc for the disappearance of *syn*-7-*tert*-butylnorbornene; 7-*tert*-butylnorbornane was utilized as an internal standard. After 3.5 hr of irradiation the concentration of syn olefin was unchanged. The irradiation was interrupted, and 950 mg (1.0 mmol) of norbornene was injected into the reaction. Irradiation of the reaction mixture was resumed, and after 25 min 75% of the norbornene had reacted; after 50 min only 5% of the norbornene remained. No change in the concentration of the *syn*-7-*tert*-butyl compound was apparent.

Registry No.—**1**, 32640-84-9; **2**, 32640-83-8; **9**, 33905-54-3; **9** anti isomer, 33905-55-4.

Kinetic α-Deuterium Isotope Effects in the Reactions of Benzyl Chlorides with Cyanide Ion and in the Solvolyses of Benzyl Chlorides[1]

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α-Deuterium isotope effects have been determined for the reactions with cyanide ion and the solvolyses of *m*-chlorobenzyl chloride, benzyl chloride, and *p*-methylbenzyl chloride in 55% (by vol) aqueous Methyl Cellosolve. In almost all experiments solvolysis occurs parallel to reaction with CN^-, and it is necessary to apply eq 3 for the calculation of k_2 for the reaction with CN^-. Values of k_1 have been evaluated separately in experiments without CN^- at the same ionic strength. Only the reaction with CN^- and the solvolysis of *m*-chlorobenzyl chloride are examples of practically pure SN2 processes, and the isotope effects are nearly equal to unity. The unusually high result of k_H/k_D = 1.25–1.31 (50°) in the reaction of *p*-methylbenzyl chloride with cyanide ion supplies evidence for a reaction pathway *via* carbonium ions or ion pairs. The rate constants of the reactions of unsubstituted benzyl chloride must contain contributions of the carbonium ion pathway and, consequently, the experimental isotope effects do not refer to pure SN2 processes.

Some work has been done in this laboratory on kinetic deuterium isotope effects in reactions of methyl iodide with various nucleophiles.[3-5] The present study is concerned with α-deuterium isotope effects in SN2 reactions of a halide with a larger primary alkyl group. A suitable choice is benzyl chloride because of its relatively high reactivity. Furthermore, the presence of the aromatic ring provides the opportunity of studying the influence of remote substituents on the isotope effect. A ring substituent may affect reacting bond orders and force constants in the transition state and cause a noticeable change of the isotope effect.[6]

Previous work on deuterium isotope effects in SN2 reactions of benzyl compounds was carried out by Östman[7] and Strecker and Elias,[8] who studied the chloride ion exchange reaction of benzyl chloride. Hill and Fry[9] investigated the influence of substituents on the chlorine isotope effect in reactions of benzyl chloride with various nucleophiles. Variations in the isotope effect were mainly due to changes in the relative contributions of the SN2 and SN1 mechanisms to the overall reaction.

In this work, the α-deuterium isotope effect has been determined for the reactions of benzyl chloride, *m*-chlorobenzyl chloride, and *p*-methylbenzyl chloride with cyanide ion in 55% (by volume) aqueous Methyl Cellosolve. The investigation has been supplemented by measurements of rate constants of solvolysis of the three benzyl chlorides and their α-dideuterated variants at the same ionic strength (addition of $NaClO_4$ instead of KCN). These rate constants are needed for the treatment of the kinetic data of the reaction with cyanide ion, since solvolysis is a competing reaction. A systematic isotope effect study at a series of different temperatures has been carried out for both reactions of the mentioned three benzyl chlorides. Though further work is necessary in order to establish a noticeable substituent effect on the isotope effect of the SN2 reaction, the results are published now as the authors will not have the opportunity to continue the work in the very near future.

The following parallel reactions occur in a solution containing benzyl chloride and cyanide ion.

$$ArCH_2Cl + CN^- \longrightarrow ArCH_2CN + Cl^- \quad (k_2)$$

$$\left.\begin{array}{l} ArCH_2Cl + H_2O + CN^- \longrightarrow ArCH_2OH + Cl^- + HCN \\ ArCH_2Cl + ROH + CN^- \longrightarrow ArCH_2OR + Cl^- + HCN \end{array}\right\} \quad (k_1)$$

(1) Taken in part from the thesis of Mr. Chih-kuo Ho, submitted in partial fulfillment of the requirements for the degree of Master of Science to the College of Pharmaceutical Sciences, Columbia University, 1969.

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(3) A. V. Willi and C. M. Won, *J. Amer. Chem. Soc.*, **90**, 5999 (1968).

(4) A. V. Willi and C. M. Won, *Can. J. Chem.*, **48**, 1452 (1970).

(5) C. M. Won and A. V. Willi, *J. Phys. Chem.*, **76**, 427 (1972).

(6) C. G. Swain and E. R. Thornton, *J. Amer. Chem. Soc.*, **84**, 817 (1962); E. R. Thornton, *ibid.*, **89**, 2915 (1967).

(7) B. Östman, *ibid.*, **87**, 3163 (1965).

(8) H. Strecker and H. Elias, *Radiochim. Acta*, **7**, 22 (1967); *Chem. Ber.*, **102**, 1270 (1969).

(9) J. W. Hill and A. Fry, *J. Amer. Chem. Soc.*, **84**, 2763 (1962).

Strong acid formed in the first-order solvolysis is immediately neutralized by cyanide ion, which is present in excess. Consequently, cyanide ion is consumed in the first-order as well as in the second-order process. This leads to a relatively simple stoichiometric relationship (eq 1 below) (assuming that $[Cl^-]_0 = 0$).

$$[ArCH_2Cl]_0 - [ArCH_2Cl] = [CN^-]_0 - [CN^-] = [Cl^-] \quad (1)$$

In rate eq 2, $[CN^-]$ is substituted with the aid of eq 1, and eq 3 is obtained upon subsequent integration.[10,11]

$$-d[ArCH_2Cl]/dt = k_2[ArCH_2Cl][CN^-] + k_1[ArCH_2Cl] \quad (2)$$

$$Z = \ln \frac{A_0(A + (k_1/k_2) + B_0 - A_0)}{A[(k_1/k_2) + B_0]} = [B_0 - A_0 + (k_1/k_2)]k_2t \quad (3)$$

$$A = [ArCH_2Cl]; \; A_0 = [ArCH_2Cl]_0; \; B_0 = [CN^-]_0.$$

As far as the authors know, systematic kinetic studies of the reactions of benzyl chlorides with CN^- have not been carried out previously, except for the measurements reported by Hill and Fry.[9] Certainly, eq 3 has not been applied to kinetic data for the reaction with CN^- prior to this work, though it has been utilized in kinetic studies of reactions of alkyl halides[10] or sulfonic esters[12] with OH^-. The solvolysis kinetics of benzyl chlorides have been studied thoroughly.[13] However, no data have been reported which refer to the same solvent mixture as applied in this study.

Experimental Section

Materials.—Commercial samples of benzyl chloride [bp 51–52° (4 mm), $n^{23}D$ 1.5374], *m*-chlorobenzyl chloride [bp 71–72° (4 mm), $n^{21}D$ 1.5556], and *p*-methylbenzyl chloride [bp 53–54° (3 mm), $n^{22}D$ 1.5331] were purified by repeated fractional distillations under reduced pressure. The purity was checked with the aid of refractive index measurements and gas–liquid chromatography.

Benzyl-α,α-d_2 chloride was prepared as follows.[14] A solution of 20 g (0.15 mol) of methyl benzoate in 200 ml of ether was added, with continuous stirring, over a period of 2 hr, to 4 g (0.095 mol) of $LiAlD_4$ (99% isotopic purity) in 300 ml of ether. The resulting solution was refluxed for an additional 3 hr. Excessive deuteride then was destroyed by 10% sodium hydroxide solution until the precipitate just coagulated and settled. The ether solution was filtered off from the solid and the latter was dissolved in 50 ml of cold 25% sulfuric acid and extracted with two additional portions of ether. The combined ether solution was washed with 10% sodium bicarbonate solution and water and dried over anhydrous magnesium sulfate, and the ether was distilled off. Repeated distillations of the residue under reduced pressure yielded 14.6 g of benzyl-α,α-d_2 alcohol (91% of theory).

Thionyl chloride (30 ml, 0.4 mol) in 30 ml of ether was mixed slowly with 14.6 g (0.133 mol) of benzyl-α,α-d_2 alcohol in 30 ml of ether.[15] The resulting solution was stirred at room temperature for 12 hr. After evaporation of ether and excess thionyl chloride, two consecutive distillations at reduced pressure yielded 14.1 g (83% of theory) of benzyl-α,α-d_2 chloride, bp 48–49 (3 mm), $n^{21}D$ 1.5372. The purity was checked with the aid of gas–liquid chromatography, and dideuteration in the α position (at least 99%) was confirmed by nmr spectroscopy.

m-Chlorobenzyl-α,α-d_2 chloride [bp 68–70° (3 mm), $n^{19}D$ 1.5552] and *p*-methylbenzyl-α,α-d_2 chloride [bp 53–54° (3 mm), $n^{22}D$ 1.5331) were prepared according to the same method, using correspondingly substituted methyl benzoates as starting materials.

Methyl Cellosolve was purified by twofold distillation under a slow stream of nitrogen. A few pieces of sodium metal were added prior to the first distillation.

Water was freshly distilled, and a stream of nitrogen was passed through every sample in order to remove dissolved oxygen.

Kinetic Procedures.—In a typical experiment, *ca.* 0.002 mol of benzyl chloride was dissolved in 55 ml of Methyl Cellosolve in a 100-ml volumetric flask; 10 ml of freshly prepared *ca.* 0.4 *M* potassium cyanide solution was added; and the flask was filled with water to the mark. (In a solvolysis experiment, sodium perchlorate solution was added instead of potassium cyanide solution.) The solution was immediately filled into ampoules. The sealed ampoules were placed into a thermostated water bath with a temperature constancy of ±0.02°. Experiments with corresponding α,α-h_2 and α,α-d_2 compounds were done simultaneously, in the same thermostat. At suitable time intervals, ampoules were taken out, cooled to 20°, opened, and analyzed.

A 10-ml sample of the kinetic solution was mixed with 5 ml of 20% aqueous formaldehyde in order to remove free cyanide ion.[16] (This would not be necessary in the solvolysis experiments.) Nitric acid (6 *N*, 5 ml) and 150 ml of deionized water were added, and chloride ion was determined quantitatively by potentiometric titration with 0.01 *N* silver nitrate solution at a silver–silver chloride electrode, utilizing a mercurous sulfate reference electrode. The end point was taken from the point of the titration curve with the steepest slope. The end point occurred at about 160 mV in all experiments.

The initial concentrations of benzyl chloride in the kinetic solutions were taken from the Cl^- concentrations in samples in which the reaction had been allowed to go to completion. The CN^- concentration of the stock solution was determined with the aid of the Liebig–Déniges method,[17] by titrating with 0.01 *N* silver nitrate solution in the presence of ammonia and using potassium iodide as an indicator.

First-order rate constants of the solvolysis reactions were calculated from the slopes of the straight lines for log $[ArCH_2Cl]$ as functions of time (eq 4), using a computer with a linear regression program.

$$\log [ArCH_2Cl] = \log [ArCH_2Cl]_0 - k_1t/2.303 \quad (4)$$

A preliminary treatment of the experimental data for the reactions with cyanide ion was carried out with the aid of the integrated second-order rate equation (5).

$$\ln([CN^-]/[ArCH_2Cl]) = \ln([CN^-]_0/[ArCH_2Cl]_0) + ([CN^-]_0 - [ArCH_2Cl]_0)k_2t \quad (5)$$

The preliminary k_2 values were used to compute preliminary values of the ratios k_1/k_2, which then were inserted into eq 3 in order to calculate improved k_2 values from the slopes of the lines for Z as functions of time. Results were utilized to compute improved ratios k_1/k_2 which were inserted again into eq 3. This procedure was repeated several times until the k_2 value changed by less than 0.2% when going through one cycle. These calculations were done in a computer with a suitable iterative program which contained as a subroutine a linear regression program for the calculation of the slope of the line according to eq 3.

Results

The initial concentrations of the benzyl chlorides were *ca.* 0.020 *M* in all experiments. In the experiments with the second-order reaction, the initial concentration of CN^- was 0.0416 *M*. In the solvolysis

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(13) E. Tommila, *Acta Chem. Scand.*, **20**, 923 (1966); J. B. Hyne, *J. Amer. Chem. Soc.*, **82**, 5129 (1960); J. B. Hyne, R. Wills, and R. E. Wonka, *ibid.*, **84**, 2914 (1962); J. B. Hyne and R. Wills, *ibid.*, **85**, 3650 (1963); R. E. Robertson and J. M. W. Scott, *J. Chem. Soc.*, 1596 (1961); B. Bensley and G. Kohnstam, *ibid.*, 4747 (1957), and references cited therein.

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(17) I. M. Kolthoff and V. A. Stenger, "Volumetric Analysis," Vol. 2, 2nd ed, Interscience, New York, N. Y., 1947, p 282.

TABLE I

SECOND-ORDER RATE CONSTANTS AND ISOTOPE EFFECTS OF THE REACTIONS OF BENZYL CHLORIDES (RCl) WITH CYANIDE ION, CORRECTED FOR PARALLEL FIRST-ORDER SOLVOLYSIS, IN 55% (BY VOL) AQUEOUS METHYL CELLOSOLVE

Reactant	Temp, °C	R = $ArCH_2$, $10^4 k_2$, sec^{-1} mol^{-1} l.	R = $ArCD_2$, $10^4 k_2$, sec^{-1} mol^{-1} l.	k_H/k_D
Benzyl chloride	30.0	1.150	1.121	1.0245 (±0.0010)
	40.0	2.933	2.865	1.023 (±0.007)
	50.0	7.044	6.879	1.0235 (±0.0013)
	60.0	16.03	15.77	1.016 (±0.003)
m-Chlorobenzyl chloride	40.0	2.357	2.370	0.995 (±0.002)
	50.0	5.537	5.528	1.001 (±0.004)
	60.0	12.99	13.07	0.994 (±0.010)
	70.0	28.96	28.87	1.0035 (±0.0035)
p-Methylbenzyl chloride	40.0	(5.567)	(4.409)	1.261 (±0.017)
	50.0	(13.22)	(10.63)	1.246 (±0.014)

TABLE II

FIRST-ORDER RATE CONSTANTS AND ISOTOPE EFFECTS OF THE SOLVOLYSES OF BENZYL CHLORIDES IN 55% (BY VOL) AQUEOUS METHYL CELLOSOLVE IN THE PRESENCE OF 0.0416 *M* $NaClO_4$

Reactant	Temp, °C	R = $ArCH_2$, $10^6 k_1$, sec^{-1}	R = $ArCD_2$, $10^6 k_1$, sec^{-1}	k_H/k_D
Benzyl chloride	30.0	1.223	1.199	1.020 (±0.006)
	40.0	3.556	3.456	1.029 (±0.002)
	50.0	9.698	9.430	1.0285 (±0.0060)
	60.0	24.98	24.37	1.025 (±0.002)
m-Chlorobenzyl chloride	50.0	1.836	1.821	1.007 (±0.018)
	60.0	4.498	4.491	1.002 (±0.006)
	70.0	10.99	11.18	0.984 (±0.004)
p-Methylbenzyl chloride	40.0	27.95	26.75	1.045 (±0.020)
	50.0	77.78	72.80	1.068 (±0.020)

TABLE III

ARRHENIUS PARAMETERS

	Reaction with CN^-		Solvolysis	
Reactant	log *A*	E_a, kcal	log *A*	E_a, kcal
$C_6H_5CH_2Cl$	8.766 (±0.002)	17.62 (±0.04)	8.633 (±0.003)	20.18 (±0.07)
$C_6H_5CD_2Cl$	8.793 (±0.003)	17.68 (±0.06)	8.601 (±0.005)	20.15 (±0.11)
m-$ClC_6H_4CH_2Cl$	8.867 (±0.009)	17.92 (±0.19)	7.626 (±0.010)	19.77 (±0.20)
m-$ClC_6H_4CD_2Cl$	8.842 (±0.010)	17.88 (±0.24)	7.798 (±0.010)	20.03 (±0.31)
p-$CH_3C_6H_4CH_2Cl$			9.78 (±0.02)	20.55 (±0.49)

experiments, the solutions contained 0.0416 *M* sodium perchlorate in order to maintain the same ionic strength as in the experiments with the second-order reaction.

Second-order rate constants and α-deuterium isotope effects of the reactions of benzyl chlorides with CN^- are reported in Table I. Each value is the average of three separate determinations. Results of k_2 for the reaction of *p*-methylbenzyl chloride are in parentheses because they probably do not refer to real second-order processes. First-order rate constants and α-deuterium isotope effects of the solvolysis reactions of benzyl chlorides are collected in Table II. Each value is the average of two separate determinations. Standard deviations of the isotope effects are given in both tables.

It is also possible to calculate first-order rate constants for the overall reaction of *p*-methylbenzyl chloride in the presence of CN^-. Their values at 50° are 1.174×10^{-4} sec^{-1} for $CH_3C_6H_4CH_2Cl$ and 1.031×10^{-4} sec^{-1} for $CH_3C_6H_4CD_2Cl$. Subtraction of the corresponding first-order solvolysis rate constants leads to the following value of the α-deuterium isotope effect on the rate increase in the presence of CN^-: $k_H/k_D = 3.96 \times 10^{-5}/3.03 \times 10^{-5} = 1.31$ (±4%) (estimated precision). This result is in approximate agreement with the value based on apparent second-order constants (Table I).

Rate constants are decreased by *m*-Cl and increased by *p*-CH_3 at the ring in the reaction with CN^- as well as in the solvolysis. Both series lead to poor Hammett relationships no matter whether σ or σ^+ is applied.

The α-deuterium isotope effect is equal to unity within experimental error in both reactions of *m*-chlorobenzyl chloride, and it is *ca.* 1.02 in both reactions of benzyl chloride. The value of k_H/k_D is just a little higher in the solvolysis of *p*-methylbenzyl chloride; it is unusually high in the reaction of the *p*-methyl compound with CN^-.

Arrhenius parameters of the rate constants are reported in Table III. The Arrhenius parameters of the α-deuterium isotope effect in the reaction of *m*-chlorobenzyl chloride with CN^- are $A_H/A_D = 1.069$ (±0.006) and $E_{aH} - E_{aD} = 45$ (±48) cal. It has not been possible to obtain reliable Arrhenius parameters for the isotope effect in the solvolysis of *m*-chlorobenzyl chloride because the temperature interval of the data is only 20°. (The experimental Arrhenius parameters of the isotope effects in both reactions of benzyl chloride are irrelevant, as it is likely that neither k_2 nor k_1 is governed by one single mechanism.)

Discussion

The α-deuterium isotope effects in the reactions of benzyl chloride and *m*-chlorobenzyl chloride with cyanide ion and in the solvolyses of all three compounds studied are in the range of values found for SN2 reactions (0.95 to 1.04 per α-D).[3-5,7,8,18-20] These findings indicate that the main reaction pathway in the solvolyses of all three compounds involves nucleophilic participation of solvent.[21]

The α-deuterium isotope effect in the reaction of *p*-methylbenzyl chloride with cyanide ion is much higher. The value based on the increase of the first-order rate constant (k_H/k_D = 1.31) is almost identical with the result obtained by Shiner, *et al.*,[21] for the limiting solvolysis of *p*-methylbenzyl chloride in 70% aqueous trifluoroethanol: k_H/k_D = 1.14 per α-D (or 1.30 per two α-D). Consequently, the reaction of *p*-methylbenzyl chloride with CN^- must pass through a carbonium ion like transition state.[22] Further evidence for rate-determining carbonium ion formation is supplied by the adherence of the overall reaction to the first-order rate law and by Hill and Fry's observation that the first-order rate constants of the reactions of *p*-methylbenzyl chloride with CN^- and $S_2O_3^-$ are nearly equal.[9]

It can be expected that the carbonium ion reacts much faster with the stronger nucleophiles CN^- or $S_2O_3^{2-}$ than with Cl^-. (Reaction with Cl^- is the reversal of the first step in the mechanism.) In such a case, formation of the carbonium ion (or possibly an ion pair) becomes rate-determining. If, on the other hand, no strong nucleophile is present (solvolysis experiments), return from the carbonium ion to *p*-methylbenzyl chloride appears to be more important than reaction with solvent. The rate of reaction *via* the carbonium ion pathway then is decreased, and the parallel one-step SN2 reaction with solvent prevails.

Equation 6 is derived with the aid of the method of

$$k = \frac{k_I(k_{solv} + k_{CN}[CN^-])}{k_{-I}[Cl^-] + k_{solv} + k_{CN}[CN^-]} + k'_{SN2} + k_{SN2}^{CN}[CN^-] \quad (6)$$

the stationary state. k_I is the rate constant of carbonium ion formation from RCl; k_{-I}, k_{solv}, and k_{CN} are the rate constants of the reactions of the carbonium ion intermediate with Cl^-, solvent, and CN^-, respectively. k'_{SN2} is the pseudo-first-order rate constant of the SN2 reaction of RCl with solvent; k_{SN2}^{CN} is the rate constant of the SN2 reaction of RCl with CN^-. (The order of the overall reaction still may be unity within experimental error if k_{SN2}^{CN} is relatively small though not negligible.) A more complicated equation must be applied if ion pair intermediates are to be considered in addition. However, there are not enough data available for a more thorough treatment.

If the CN^- concentration is large enough, eq 6 becomes eq 6b.

$$k_{CN}[CN^-] \gg k_{-I}[Cl^-] + k_{solv}$$
$$k = k_I + k'_{SN2} + k_{SN2}^{CN}[CN^-] \quad (6b)$$

In the solvolysis experiments, on the other hand, $[CN^-] = 0$ and eq 6 reduces to eq 7.

$$k = \frac{k_I}{1 + (k_{-I}/k_{solv})[Cl^-]} + k'_{SN2} \quad (7)$$

It is important to know whether the carbonium ion mechanism contributes to the overall reactions of benzyl chloride and *m*-chlorobenzyl chloride with CN^- or solvent. Estimates of k_I for the unsubstituted and *m*-Cl compounds may be obtained from the k_I value of the *p*-CH_3 compound by application of the Hammett relationship.

The ρ value for the solvolyses of substituted phenyldimethylcarbinyl chlorides in 90% aqueous acetone at 25° is −4.62;[23] ρ values in the range of −4.05 to −4.63 have been found for the solvolyses of substituted benzhydryl chlorides in various solvents.[24] The more polar the solvent, the stronger is the substituent effect. Furthermore, ρ values of −4.41 and −4.39 can be calculated from the data obtained by Hill and Fry[9] in 80% aqueous dioxane for the reactions of *p*-methylbenzyl chloride and *p*-methoxybenzyl chloride with CN^- and $S_2O_3^{2-}$, respectively. Consequently, a good estimate for the ρ value in the carbonium ion formation of substituted benzyl chlorides under the experimental conditions of this work is −4.4.

The overall first-order constant of the reaction of *p*-methylbenzyl chloride in the presence of CN^- includes contributions of SN2 reactions with solvent and CN^-. On the other hand, the contribution of the carbonium ion mechanism still may be a little smaller than k_I. Therefore, k_I is assumed to be approximately equal to the measured overall first-order rate constant, k = 1.17×10^{-4} sec^{-1} at 50°.

According to the observed isotope effect in the solvolysis of *p*-methylbenzyl chloride, approximately one-third (or less) of the measured rate constant corresponds to the carbonium ion mechanism: $7.78 \times 10^{-5}/3 = 2.59 \times 10^{-5}$ sec^{-1}. With the aid of eq 7, the following result is obtained.

$$1 + (k_{-I}/k_{solv})[Cl^-] = 1.17 \times 10^{-4}/2.59 \times 10^{-5} = 4.52.$$

(Since $[Cl^-]$ is variable, this is merely an average value which refers to initial concentrations of RCl near 2×10^{-2} *M*.)

The following estimates of k_I (at 50°) are computed from the Hammett relationship (application of σ^+): 5.55×10^{-6} sec^{-1} for benzyl chloride and 1.30×10^{-7} sec^{-1} for *m*-chlorobenzyl chloride.

If it is assumed that the same value of $1 + (k_{-I}/k_{solv})[Cl^-]$ may be utilized for the three compounds studied, the estimates of the first term in eq 7 (which corresponds to the carbonium ion mechanism) are 1.2×10^{-6} sec^{-1} for the unsubstituted compound and 2.9×10^{-8} sec^{-1} for the *m*-Cl compound. By comparison with the experimental solvolysis rate constants (Table

(18) J. A. Llewellyn, R. E. Robertson, and J. M. W. Scott, *Can. J. Chem.*, **38**, 222 (1960).

(19) K. T. Leffek, *ibid.*, **42**, 851 (1964).

(20) S. Seltzer and A. A. Zavitsas, *ibid.*, **46**, 2023 (1967), and references cited therein.

(21) V. J. Shiner, M. W. Rapp, and H. R. Pinnick, *J. Amer. Chem. Soc.*, **92**, 232 (1970); V. J. Shiner, M. W. Rapp, E. A. Halevi, and M. Wolfsberg, *ibid.*, **90**, 7171 (1968).

(22) It is suggested that the constancy of the value of k_H/k_D per α-D in limiting solvolysis reactions does not necessarily mean that the bond between carbon and leaving group must be completely broken. If the transition states are carbonium ion like with incomplete bond cleavage (as in SN1 reactions), 90% bond cleavage in one individual example and 93% in another would cause only a small difference in the isotope effect. Therefore, a constant isotope effect in different examples with the same leaving group is not incompatible with an SN1 mechanism *via* free carbonium ions.

(23) Y. Okamoto and H. C. Brown, *J. Org. Chem.*, **22**, 485 (1957).

(24) Y. Okamoto, T. Inukai, and H. C. Brown, *J. Amer. Chem. Soc.*, **80**, 4969 (1958).

II), it is concluded that the carbonium ion mechanism may account for *ca.* 12% (high estimate) of the solvolysis rate of benzyl chloride while it is negligible (1.6% or less) in the solvolysis of *m*-chlorobenzyl chloride.[25] It is obvious that there is an appreciable contribution of the carbonium ion mechanism in the solvolysis of *p*-methylbenzyl chloride.

In order to estimate the contributions of the carbonium ion mechanism to the reactions with CN^-, calculated values of k_I are compared with experimental values of $k_2(B_0 - A_0)$. According to these comparisons, the carbonium ion pathway may account for an appreciable fraction of the reaction rate of benzyl chloride with CN^-, but it is negligible (*ca.* 1% or less) in the reaction of *m*-chlorobenzyl chloride with CN^-.

Conclusions

The first goal of this study was the determination of α-deuterium isotope effects in SN2 reactions of a benzyl chloride. The data obtained for the reaction of *m*-chlorobenzyl chloride with CN^- and the solvolysis of *m*-chlorobenzyl chloride refer to practically pure SN2 reactions. Results of k_H/k_D per α-D are a little higher than in the reaction of methyl iodide with CN^- (k_H/k_D = 0.97 per α-D)[3] or in the solvolysis of methyl iodide (k_H/k_D = 0.955 per α-D).[18] This corresponds to findings for other SN2 processes in which isotope effects in reactions of methyl iodide and methyl chloride with the same nucleophile are compared.[20]

It is planned to carry out sample calculations of isotope effects from force constants at a later date. It will be necessary to consider solvation of the entering and leaving groups in the transition state model.[5]

The observed increases of k_H/k_D when going from the *m*-chloro to the unsubstituted compound must be due to an increased contribution of the parallel reaction *via* the carbonium ion pathway. It is very difficult to arrive at reliable quantitative estimates of the contributions of the carbonium ion mechanism. It even may be possible that decreasing electron-withdrawing power of the ring substituent would cause *decreases* of the values of k_H/k_D in the SN2 reactions.

In order to obtain reliable information about the substituent effect on the isotope effects in the SN2 reactions, it will be necessary to study the reactions of benzyl chlorides containing stronger electron-withdrawing substituents, such as *p*-CN, *m*-NO_2, and *p*-NO_2.

An unexpected side result is the occurrence of the carbonium ion mechanism in the reaction of *p*-methylbenzyl chloride with CN^-. It may be worthwhile to carry out a detailed study of this reaction in which $[Cl^-]$ and $[CN^-]$ are varied while the ionic strength is kept constant.

Registry No.—Cyanide ion, 57-12-5; benzyl chloride, 100-44-7; *m*-chlorobenzyl chloride, 620-20-2; *p*-methylbenzyl chloride, 104-82-5; benzyl-α,α-d_2 chloride, 33712-34-4; *m*-chlorobenzyl-α,α-d_2 chloride, 33712-35-5; *p*-methylbenzyl-α,α-d_2 chloride, 33712-36-6.

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(25) A reviewer inquired about the possibility of α elimination as a side reaction.

It may be desirable to confirm experimentally the absence of α-elimination products in the reactions studied in this work. However, evidence for the insignificance of *base-promoted α elimination* was supplied by Bunnett and Reinheimer[26] for the reaction of *o*-chlorobenzyl chloride with LiOMe in MeOH. The present study is concerned with benzyl chlorides carrying groups with comparable or weaker electron-withdrawing power. It can be concluded that base-promoted α elimination is even less likely under the action of a weak base such as CN^-.

Furthermore, it is completely nonessential for the kinetics if some benzyl cyanide (instead of alcohol) is formed also on the SN1 pathway, since it concerns the product-forming rather than the rate-determining step. Determination of the benzyl cyanide product ratio merely would supply a high limit of the relative contribution of the SN2 reaction with CN^-.

(26) J. F. Bunnett and J. D. Reinheimer, *J. Amer. Chem. Soc.*, **84**, 3287 (1962).

Kinetic Study of the Oxidation of *p*-Nitrosophenol by Nitric and Nitrous Acids

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The acid-catalyzed oxidation of *p*-nitrosophenol by nitric and nitrous acid in aqueous sulfuric acid solution has been studied kinetically in the acidity region of $-1 > H_0 > -6$ by means of polarographic and iodometric analysis. The experimental rate law is first order with respect to *p*-nitrosophenol, nitric acid, and nitrous acid. At low initial nitrous acid concentrations, autocatalysis is observed. The acidity profile of the rate constant has a maximum at $H_0 = -4.5$. The uv absorption of *p*-nitrosophenol is acidity dependent, which is in accordance with a protolytic equilibrium between *p*-nitrosophenol and its conjugate acid. The acidity at which half-protonation occurs is $H_0 = -3.7$. A possible reaction mechanism is discussed which assumes a rate-limiting attack of dinitrogen tetroxide on *p*-nitrosophenol in the low acidity region. At high acidities deprotonation of a reaction intermediate may become rate limiting.

The nitric acid oxidation of *p*-nitrosophenol was first studied by Veibel.[1] He reported a pseudo-first-order rate law with respect to *p*-nitrosophenol, the rate constant being strongly enhanced by an increase of the nitric acid concentration. The reaction was found to occur only if a small amount of nitrous acid was initially present. More recently, Ogata and coworkers have investigated the nitric acid oxidation of various aromatic nitroso compounds with aqueous dioxane as a solvent. In the case of nitrosobenzene,

(1) S. Veibel, *Z. Phys. Chem., Abt. B.*, **10**, 22 (1930).

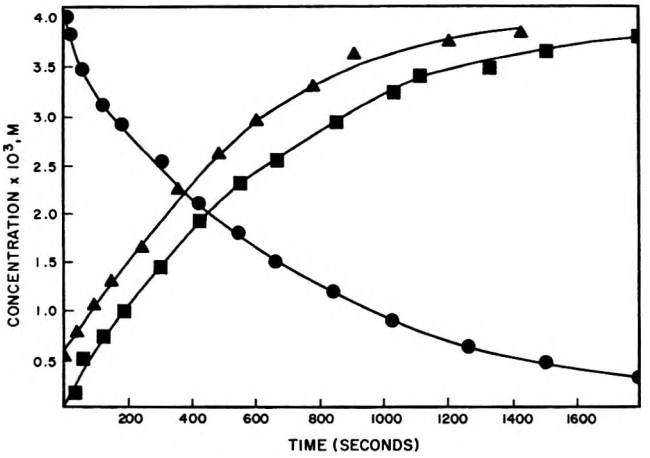

Figure 1.—Concentration-time curves for the oxidation of *p*-nitrosophenol by nitric and nitrous acid: ●, HOC_6H_4NO; ■, $HOC_6H_4NO_2$; ▲, HNO_2. Conditions: $[HOC_6H_4NO]_0 = 4 \times 10^{-3}$ *M*, $[HNO_2]_0 = 7 \times 10^{-4}$ *M*; $[NO_3^-] = 5 \times 10^{-2}$ *M*; $[H_2SO_4] = 5.5$ *M*; $T = 10°$.

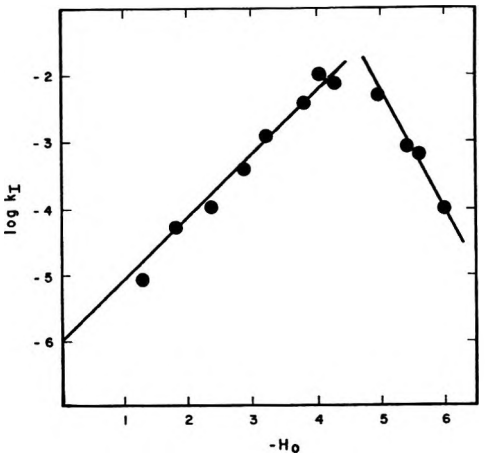

Figure 2.—Plot of the log of the pseudo-first-order rate constant, k_I, *vs.* the acidity function, H_0. Conditions: $[HOC_6H_4NO]_0 = 2 \times 10^{-3}$ *M*; $[HNO_2]_0 = 5 \times 10^{-4}$ *M*; $[NO_3^-] = 2.5 \times 10^{-2}$; $T = +3°$.

the rate law is first order in nitrosobenzene while the order with respect to both nitric and nitrous acids is one-half. The proposed reaction mechanism involves an attack by nitrogen dioxide and its conjugate acid as the rate-limiting step.[2] With identical reaction conditions *p*-nitrosophenol was found to be oxidized much faster than other nitrosobenzenes. Furthermore, in this case, no dependence of the rate on the initial nitrous acid concentration was observed, and the order with respect to nitric acid was unity. The authors account for this fact by assuming that the rate-limiting step is no longer the attack by nitrogen dioxide but rather the decomposition of a reaction intermediate.[3]

We have studied the nitric acid oxidation of *p*-nitrosophenol with aqueous sulfuric acid as a solvent, allowing the reaction to be studied over a wide range of acidities. By selecting suitable reaction conditions it was possible to establish quantitatively the effect of nitrous acid on the reaction. The kinetic data indicate a reaction mechanism which is different from the one that has been suggested by Ogata for the dioxane–water system.

Experimental Section

Materials Used.—Technical *p*-nitrosophenol (American Cyanamid Co.) was purified by recrystallization from ethanol. The pure substance had mp 132–133°. Potassium nitrate (J. T. Baker Chemical Co.), sodium nitrite (Matheson Coleman and Bell), and sulfuric acid (J. T. Baker Chemical Co.) were reagent grade.

Kinetic Procedures.—The kinetic runs were carried out in a thermostat with a temperature constancy of ±0.1°. In a standard run 180 ml of a solution of *p*-nitrosophenol in aqueous sulfuric acid of known acidity were mixed with 20 ml of a solution of sodium nitrite and potassium nitrate in sulfuric acid. To minimize heat effects during mixing, both solutions always had identical acidities. Suitable aliquots (10 ml) of the reaction mixture were quenched in aqueous ammonia (30 ml) at 0°.

Analytical Methods.—The decay of *p*-nitrosophenol concentrations as well as the formation of *p*-nitrophenol was monitored by means of polarographic analysis. The quenched samples had pH 9.8 ± 0.1 and were directly suitable for analysis. Since a sufficiently high concentration of ammonium sulfate was always present, no additional buffer was added. In the concentration range from 5×10^{-3} to 1×10^{-5} *M*, a linear dependence of the wave heights on the concentration was observed. Under our experimental conditions, the half-wave potentials, measured against the saturated calomel electrode were −0.38 ± 0.1 V for *p*-nitrosophenol and −0.73 ± 0.2 V for *p*-nitrophenol. The polarographic measurements were carried out with a Leeds & Northrup Electrochemograph at 25°.

The analysis of nitrous acid could not be achieved by the usual spectrophotometric methods because of the strong optical absorption of the reaction mixture. Therefore, nitrous acid was determined by iodometric titration in which nitrous acid is reduced to nitrogen monoxide. Since reoxidation by air readily occurs, the titration was carried out in an argon atmosphere, but to avoid evaporation of nitrous acid, the solution was initially kept alkaline while the purified argon was passed through. After 5 min the flow rate of argon was reduced. The solution was then acidified with the deoxygenated sulfuric acid and some potassium iodide was added. The titration was carried out with 0.01 *N* sodium thiosulfate solution which had been prepared by diluting a 1 *N* solution with oxygen-free distilled water. With these precautions taken, reproducible results were obtained.

Usually, the reaction was monitored by measuring the decay of *p*-nitrosophenol. However, if initial reaction rates were to be determined, it was more practical to monitor the nitrous acid.

The uv spectra of nitrosophenol and its conjugate acid were measured on a Cary 15 recording spectrophotometer. The ionization ratio was calculated according to a reported method.[4]

Results

Stoichiometry and Empirical Rate Law.—The stoichiometry of the oxidation of *p*-nitrosophenol as given by eq 1 is known from previous work.[1] As in many

$$HOC_6H_4NO + HNO_3 \longrightarrow HOC_6H_4NO_2 + HNO_2 \quad (1)$$

other cases of nitric acid oxidations, the reaction is autocatalyzed by nitrous acid. Consequently, no reaction is observed if a nitrous acid scavenger such as sulfamic acid is added to the reaction mixture. At low initial nitrous acid concentrations an induction period is observed.

To reduce the overall reaction order, all experiments are run with $[H^+] \gg [NO_3^-] \gg [HOC_6H_4NO]$, the acidity being established by sulfuric acid and the nitrate ion being added as potassium nitrate. If a sufficient amount of nitrous acid, added in the form of sodium nitrite, is initially present, the induction period disappears and the reaction obeys pseudo-first-order kinetics with respect to *p*-nitrosophenol.

By simultaneous monitoring of the concentrations of

(2) Y. Ogata and H. Tezuka, *J. Amer. Chem. Soc.*, **89**, 5428 (1967).
(3) Y. Ogata and H. Tezuka, *J. Org. Chem.*, **33**, 3179 (1968).
(4) V. Gold and B. W. V. Hawes, *J. Chem. Soc.*, 2102 (1951).

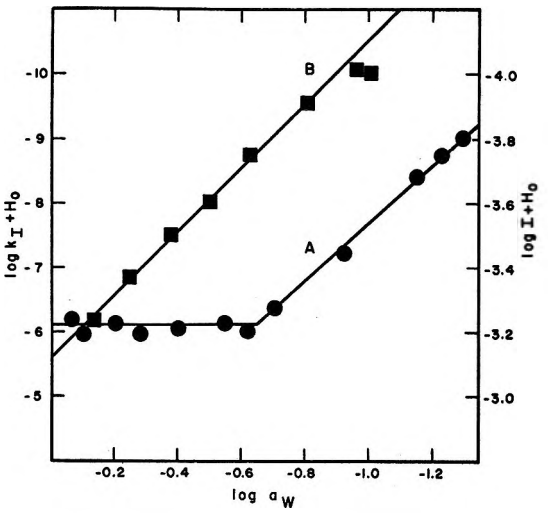

Figure 3.—Bunnett plots: curve A, left scale, data of Figure 2; curve B, right scale, data of Figure 4.

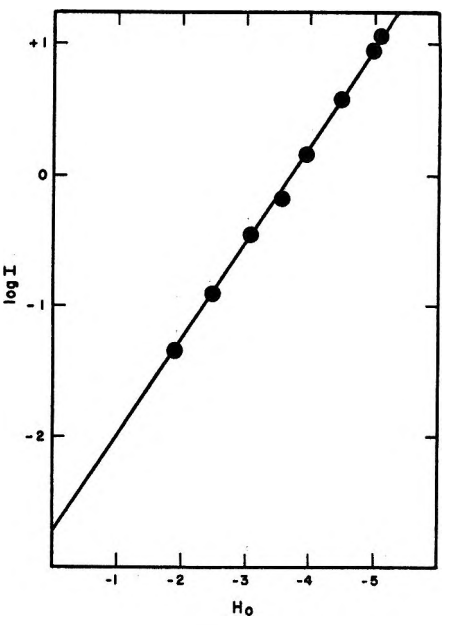

Figure 4.—Logarithmic plot of the ionization ratio, I, *vs.* the acidity function, H_0.

p-nitrosophenol, *p*-nitrophenol, and nitrous acid as shown in Figure 1, the validity of the stoichiometric equation is confirmed. The pseudo-first-order rate coefficient, k_I (Roman numerals indicate experimentally observed rate constants), is constant if $5 \times 10^{-4}\ M < [HOC_6H_4NO] < 5 \times 10^{-3}\ M$, indicating that the dimerization of *p*-nitrosophenol is kinetically unimportant in this concentration range. For $2 \times 10^{-2}\ M < [NO_3^-] < 5 \times 10^{-1}\ M$, the relation $k_{II} = k_I/[NO_3^-]$ was verified. Therefore, provided that the induction period is suppressed and the acidity remains constant, a simple second-order rate law is obtained (eq 2). For $[H_2SO_4] = 4.5\ M$, $[HOC_6H_4NO]_0$, $=$

$$\text{rate} = k_{II}[NO_3^-][HOC_6H_4NO] \quad (2)$$

$4 \times 10^{-3}\ M$, $[NaNO_2]_0$, $= 5 \times 10^{-4}\ M$; and $[KNO_3] = 0.4\ M$, the pseudo-first-order rate constants amount to $k_I = 9.6 \times 10^{-4}$ sec^{-1} (0°), $k_I = 3.2 \times 10^{-3}$ sec^{-1} (10°), $k_I = 8.7 \times 10^{-3}$ sec^{-1} (19.5°), $k_I = 2.4 \times 10^{-2}$ sec^{-1} (30°), where the numbers in parentheses denote the reaction temperatures. Graphical evaluation of the Arrhenius equation leads to the temperature dependence given by eq 3.

$$k_I = 7.2 \times 10^{10} \exp(-17{,}300/RT)\ \text{sec}^{-1} \quad (3)$$

The Effect of Acidity and the Protonation of *p*-Nitrosophenol.—The pseudo-first-order rate constant, k_I, measured with $5 \times 10^{-4}\ M$ nitrous acid initially present, is strongly affected by a variation of sulfuric acid concentration. Figure 2 depicts a plot of log k_I *vs.* the Hammett acidity function, H_0.[5] The resulting acidity profile has a maximum at $H_0 = -4.5$. which is defined by the intersection of two straight lines, the respective slopes being +0.9 and −2. The data also fit a Bunnett plot.[6] Again one obtains two straight lines which intersect at log $a_w = -0.65$. The slopes of the low and high acidity parts are $w \simeq 0$ and $w \simeq +5$, respectively, as shown in Figure 3, curve A.

At even higher acidities the rate constant as monitored by the decay of the *p*-nitrosophenol concentration increases again. However, the reaction now apparently leads to polynitro compounds suggesting that, in this acidity region, nitration by attack of the nitronium ion, NO_2^+, becomes important.

The uv spectrum of *p*-nitrosophenol in neutral aqueous solution shows an absorption maximum at 300 nm with an extinction coefficient of $1.8 \times 10^4\ M^{-1}$ cm^{-1}. If the acidity is increased, the absorption at 300 nm decreases. Simultaneously the appearance of a new absorption with a maximum at longer wavelengths is observed. At an acidity of $H_0 = -5.6$, this maximum is shifted to 390 nm with an extinction coefficient of $1.7 \times 10^4\ M^{-1}$ cm^{-1}. The latter value is probably not very accurate owing to the slow decomposition of *p*-nitrosophenol at high acidity.

The absorption at high acidities may be accounted for in terms of a protolytic equilibrium between *p*-nitrosophenol and its conjugate acid according to eq 4. If

$$HOC_6H_4NO + H^+ \rightleftharpoons HOC_6H_4\overset{+}{N}OH \quad (4)$$

one calculates the ionization ratio, I, from the absorptivities at 300 nm and 390 nm,[4] a plot of log I *vs.* $-H_0$ is linear with a slope of +0.74. The point of half-protonation is at $H_0 = -3.7$ (Figure 4). A Bunnett plot is likewise linear, the slope being $w = 1.0$. Comparison of curves A and B in Figure 3 shows that the acidity function which governs the acidity dependence of the rate constant is definitely different from the one related to the protonation of *p*-nitrosophenol.

The acidity dependence of the ionization ratio also fits a Bunnett–Olson LFER plot[7] which yields a pK_A of −2.85 and a slope of +0.3. The pK obtained from the Bunnett–Olson plot is 0.85 log unit more positive than the H_0 value of half-protonation. This indicates that the H_0 scale differs by this amount from the true acidity function applicable to eq 4.

It should be noted that the neutral form of *p*-nitrosophenol is tautomeric with benzoquinone monoxime, the equilibrium being on the side of the oxime.[8,9] In basic aqueous solution, *p*-nitrosophenol dissociates

(5) C. F. O'Connor, *J. Chem. Educ.*, **46**, 686 (1969).
(6) J. F. Bunnett, *J. Amer. Chem. Soc.*, **83**, 4956, 4968, 4973, 4978 (1961).
(7) J. F. Bunnett and F. P. Olson, *Can. J. Chem.*, **44**, 1899, 1917 (1966).
(8) R. K. Norris and S. Sternhell, *Tetrahedron Lett.*, 97 (1967).
(9) H. Uffmann, *ibid.*, 4631 (1966).

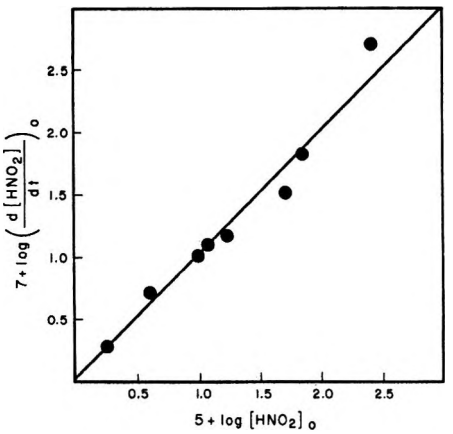

Figure 5.—Dilogarithmic plot of the initial reaction rate *vs.* the initial nitrous acid concentration. Conditions: $[HOC_6H_4NO]_0 = 4 \times 10^{-3}\ M$, $[NO_3]^- = 5 \times 10^{-2}\ M$; $[H_2SO_4] = 5.5\ M$; $T = 10°$.

with formation of a resonance stabilized anion which has an absorption maximum at 397 nm.[10]

The Induction Period and the Influence of Nitrous Acid.—Since nitrous acid is a reaction product and at the same time a reactant, its kinetic order can only be elucidated by determining the variation of the initial rate with the initial nitrous acid concentration, provided that $[HNO_2]_0 \ll [HOC_6H_4NO]_0 \ll [HNO_3]$. Figure 5 depicts a plot of log $(d[HNO_2]/dt)_0$ as determined by the tangent method *vs.* log $[HNO_2]_0$. For $1.5 \times 10^{-5}\ M < [HNO_2]_0 < 2.4 \times 10^{-3}\ M$, a straight line with unity slope is obtained. This implies a first-order dependence on nitrous acid concentration. Consequently, the complete rate law at constant acidity is given by eq 5. The rate constant k_{III} can be evaluated

$$\text{rate} = k_{III}[HNO_2][NO_3^-][HOC_6H_4NO] \quad (5)$$

if the reaction is carried out in the presence of just enough nitrous acid to make the induction period disappear. For a typical experiment depicted in Figure 1, one obtains a half-life of 450 sec and a value of $k_{III} = 4.3 \times 10^1\ M^{-2}\ \text{sec}^{-1}$. The data of Figure 5 are represented by eq 6. The slope obviously represents

$$(d[HNO_2]/dt)_0 = 9 \times 10^{-3}[HNO_2]_0 + 8 \times 10^{-8}\ M\ \text{sec}^{-1} \quad (6)$$

the pseudo-first-order rate constant with respect to nitrous acid. Therefore, one should expect that k_{III} = slope/[nitrosophenol]$_0$ × $[NO_3^-]$. Inserting the concentrations of Figure 5, one obtains $k_{III} = 4.5 \times 10^1\ M^{-2}\ \text{sec}^{-1}$. This agrees with the value observed above for an induction period of zero. Therefore, the validity of the rate law, eq 5, is evidently not confined to the limiting condition of a zero induction period. The small positive intercept in eq 6, which represents the initial rate at $[HNO_2]_0 = 0$ can be accounted for either by spontaneous decomposition of nitric acid with formation of nitrous acid or by trace impurities of nitrite in the potassium nitrate used in our experiments. The direct oxidation by nitric acid alone can be ruled out because of the complete quenching of the reaction by sulfamic acid.

(10) E. Havinga and A. Schors, *Recl. Trav. Chim. Pays-Bas*, **69**, 457 (1950).

Discussion

In an acidic system containing nitrous and nitric acids, various species are present which are known to possess oxidizing properties.[11] Among these, however, only NO_2 and N_2O_4 require the presence of both nitric and nitrous acids for their formation. Since no significant reaction is observed if either of them is absent, the major reaction path has to involve an attack by either NO_2 or N_2O_4. For NO_2 as the oxidizing agent an order of one-half with respect to both nitric acid and nitrous acids has to be expected, provided that the equilibrium of eq 7 is shifted to the right side. A

$$N_2O_4 \rightleftharpoons 2NO_2 \quad (7)$$

kinetic dependence of this type has been found in the case of the oxidation of nitrosobenzene in dioxane–water[2] and also for the oxidation of 2,5-dimethylnitrosobenzene in carbon tetrachloride.[12] Contrary to these results, we have obtained an order of unity for both reactants. No deviation from a first-order dependence has been observed for concentrations of HNO_2 as low as $1.5 \times 10^{-5}\ M$, in spite of the fact that in this range the equilibrium concentration of NO_2 is already significant based on a dissociation constant of $1.53 \times 10^{-5}\ M$.[13] For NO_2 to be the oxidizing entity, this would necessarily require that the order for nitrous acid change from unity to one-half at low concentrations.

Based on these considerations N_2O_4 appears to be the most likely oxidizing species. This gives rise to a "true" rate law as given by eq 8. To obtain an estimate

$$\text{rate} = k_0[N_2O_4][HOC_6H_4NO] \quad (8)$$

of k_0 one has to consider eq 9 for which $K = 3 \times 10^{-3}\ M^{-1}$ has been reported[14] (a_w = activity of water).

$$\frac{[N_2O_4]a_w}{[HNO_2][H^+][NO_3^-]} = K \quad (9)$$

With $[NO_3^-] \gg [HNO_2]$ the N_2O_4 equilibrium concentration is given by eq 10. If one assumes $[H^+]$

$$[N_2O_4] = \frac{K[H^+][NO_3^-][HNO_2]_{anal}}{a_w + K[H^+][NO_3^-]} \quad (10)$$

$= 3.5 \times 10^2\ M$ and $a_w = 0.53$ for the reaction at $[H_2SO_4] = 5.5\ M$ corresponding to Figure 5, the second term of the denominator of eq 10 becomes negligible provided that $[NO_3^-] < 5 \times 10^{-2}\ M$. Therefore, comparing eq 5 and eq 8 one obtains eq 11. This yields an estimated value of $k_0 = 2.4 \times 10^1\ M^{-1}\ \text{sec}^{-1}$.

$$k_0 = \left(\frac{k_{III}a_w}{[H^+]K}\right) M^{-1}\ \text{sec}^{-1} \quad (11)$$

The kinetic results may be explained in terms of a mechanism described by the reaction sequence shown in eq 12a–d. At higher acidities where *p*-nitrosophenol

$$H_3O^+ + NO_3^- \rightleftharpoons HNO_3 + H_2O \quad (12a)$$

$$HNO_3 + HNO_2 \rightleftharpoons N_2O_4 + H_2O \quad (12b)$$

$$N_2O_4 + HOC_6H_4NO \longrightarrow HOC_6H_4NO_2 + N_2O_3 \quad (12c)$$

$$N_2O_3 + H_2O \longrightarrow 2HNO_2 \quad (12d)$$

(11) J. V. L. Longstaff, *J. Chem. Soc.*, 3488 (1957).
(12) T. G. Bonner and R. A. Hancock, *J. Chem. Soc. B*, 519 (1970).
(13) M. Graetzel, A. Henglein, J. Lilie, and G. Beck, *Ber. Bunsenges. Physik. Chem.*, **73**, 646 (1969).
(14) J. V. L. Longstaff and K. Singer, *J. Chem. Soc.*, 2610 (1954).

exists predominantly in its protonated form, a reaction path given by eq 12e and 12f which is parallel to 12c

$$N_2O_4 + HOC_6H_4N^+OH \longrightarrow HOC_6H_4\overset{+}{N}O_2H + N_2O_3 \quad (12e)$$

$$HOC_6H_4\overset{+}{N}O_2H + H_2O \longrightarrow HOC_6H_4NO_2 + H_3O^+ \quad (12f)$$

has to be assumed. The reactions which cause the autocatalysis are 12c and 12e at low and high acidities, respectively. Reaction 12d may be considered to be fast except at very low values of a_w.[15]

The true rate law, eq 8, was derived with the assumption that the preceding steps are fast. This is obviously true for the protolytic equilibrium, 12a. The rate constant for the reverse reaction of eq 12b, determined by pulse radiolytic measurements, is 1×10^3 sec^{-1} $\times a_w$.[13] With this value and the previously mentioned value of the equilibrium constant, the forward rate constant is calculated to be $1.9 \times 10^3 M^{-1}$ sec^{-1}.

Since the initial concentration of *p*-nitrosophenol is of the order of 10^{-3} *M*, the equilibrium approximation appears to be applicable. Consequently, it is justified to assume that eq 12c is the rate-limiting step as long as the relative concentration of protonated *p*-nitrosophenol is not significant. The positive slope of the acidity profile of the rate constant is due to the formation of undissociated nitric acid which is known to increase according to the H_0 acidity function.

(15) M. Graetzel, S. Taniguchi, and A. Henglein, *Ber. Bunsenges. Physik. Chem.*, **74**, 488 (1970).

Since it is reported[16] that the nitrate ion is half-protonated at $H_0 = -2.8$, the rate constant should become acidity independent at $H_0 \simeq -4$. The experimental acidity profile, however, exhibits a maximum at $H_0 = -4.5$ and a decrease of the rate constant at higher acidities. This effect may be connected with a significant heterolytic dissociation of N_2O_4 at high acidity, which would reduce its equilibrium concentration.[17,18] Alternatively, a protonated N_2O_4 species might be formed which could also account for the observed behavior, since its reaction with the equally charged protonated nitrosophenol is expected to be slow.

Most likely, however, a change in the rate-determining step from eq 12c to eq 12f is responsible for the rate decrease. This is supported by the slope of the Bunnett plot, Figure 3A, where the high acidity part with $w = 5$ is typical for a reaction whose rate is limited by a transfer of a proton to the solvent.[19]

Registry No.—*p*-Nitrosophenol, 104-91-6; nitric acid, 7697-37-2; nitrous acid, 7782-77-6.

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(17) T. A. Turney and G. A. Wright, *J. Chem. Soc.*, 2415 (1958).
(18) F. Seel and R. Winkler, *Z. Phys. Chem.*, **25**, 217 (1960).
(19) C. H. Rochester, "Acidity Functions," Academic Press, London, 1970, p 117.

Kinetics and Mechanism of the Hydrolysis of Guanosine and 7-Methylguanosine Nucleosides in Perchloric Acid

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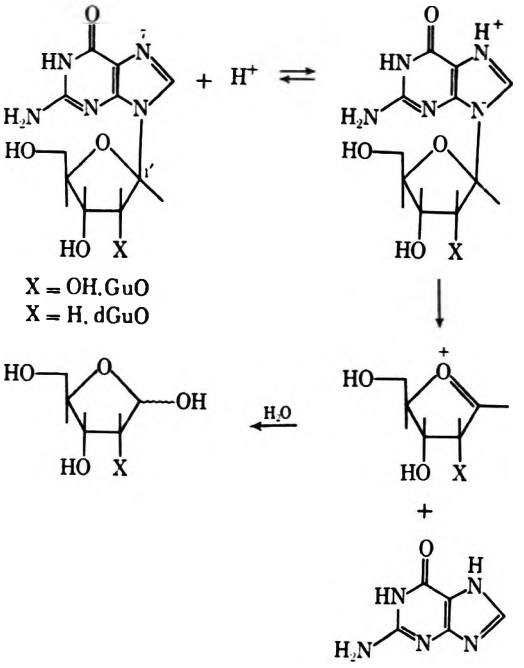
Rates of hydrolysis of guanosine (Guo) and 7-methylguanosine (7-MeGuo) to ribose and guanine or 7-methylguanine were obtained spectrophotometrically and polarimetrically in 1–9 *M* $HClO_4$ at 30.0°. In 1–7 *M* $HClO_4$ the substrates are converted to their diprotonated forms to the extent of about 1–90%. Rate changes in this region are approximated by the expression $k_\psi = kh_0/(h_0 + K_a)$, where h_0 is the Hammett acidity function and k is the first-order rate constant for fragmentation of the nucleoside. For Guo k is $8.8 \pm 0.6 \times 10^{-4}$ sec^{-1} and for 7-MeGuo k is $1.2 \pm 0.1 \times 10^{-3}$ sec^{-1}. "Kinetic" (equilibrium) dissociation constants or pK_a values for Guo and 7-MeGuo are −2.42 (−2.42) and −2.48 (−2.61), respectively. In 7–9 *M* $HClO_4$ rates continue to increase slightly for Guo but decrease slightly for 7-MeGuo. A mechanism involving cleavage of a protonated ribose ring to give a Schiff-base intermediate is ruled out. Instead, a mechanism (A-1) involving reversible protonation of the purine ring to give a dication followed by rate-limiting cleavage of the heterocycle–sugar bond is advanced. This is similar to the mechanism of hydrolysis of the monocationic forms of these substrates in dilute acid.

Nucleosides, fragments of nucleic acids containing a heterocyclic base bonded to a sugar, are model compounds for the study of nucleic acid hydrolysis.[1] We have shown that the acid-catalyzed hydrolysis of some purine nucleosides takes place by the reaction of mono- as well as diprotonated forms.[2] Guanosine (Guo) and deoxyguanosine (dGuo) hydrolyze first by undergoing reversible protonation of the purine ring to give a monocation and then by rate-determining fragmentation to give a purine and a cyclic carboxonium ion form of the sugar. This cation on reaction with water gives the sugar, ribose or deoxyribose (Scheme I). This mechanism of hydrolysis of a monoprotonated species is supported, for example, by the fact that 1,7-dimethylguanosinium ion (1,7-diMeGuO$^+$) reacts at very nearly the same rate as monoprotonated Guo. The dimethyl cation, since it already bears a positive charge, need not protonate in order to react and hence it undergoes ready fragmentation.

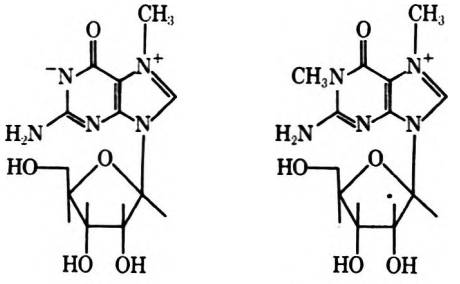
In this paper we consider and eliminate the possibility that mono- and diprotonated purine nucleosides react by different mechanisms. We report the results of the hydrolysis of Guo and 7-methylguanosine (7-MeGuo) in perchloric acid. Our results allow a distinction to be made between two mechanistic possibil-

(1) H. S. Loring in "The Nucleic Acids," E. Chargaff and J. N. Davidson, Ed., Academic Press, New York, N. Y., 1955, Chapter 5.
(2) J. A. Zoltewicz, D. F. Clark, T. W. Sharpless, and G. Grahe, *J. Amer. Chem. Soc.*, **92**, 1741 (1970). Additional references are included in this paper.

SCHEME I



ities. First, the purine ring becomes diprotonated and then leaves in the slow step. This is an extension of the reaction pathway in dilute acid.[2] Second, the ribose ring opens following protonation of the annular oxygen atom. The resultant Schiff base then undergoes hydrolysis. This type of ring-opening pathway has long been considered to be a distinct possibility for the hydrolysis of nucleosides.[2-4]



Experimental Section

Materials.—Guanosine (Guo), guanine, and ribose were obtained from CalBiochem. 7-Methylguanosine (7-MeGuo) was prepared by methylation of Guo.[2,5] Perchloric acid was 70% Baker analyzed or 60 and 70% Mallinckrodt analytical reagent grade. Acid solutions were standarized using Fisher primary "THAM."

Equipment.– Absorbance changes were followed with either a Zeiss PMQ II or a Beckman DU spectrophotometer. The wavelengths employed in kinetic runs were 265 nm for Guo and 285 or 295 nm for 7-MeGuo.

Rotation of polarized light was monitored with a Perkin-Elmer 141 polarimeter. Solutions in a jacketed polarimeter cell were thermostated at 30.0 ± 0.1° by a Haake EDe constant temperature circulator. Changes generally were followed at 546 nm. All temperatures were measured with a National Bureau of Standards certified thermometer.

Stability Studies.—Some kinetic runs employed a sodium hydroxide quench technique. We provided evidence earlier that guanosine, guanine, and 7-methylguanine solutions in ~1 *M* NaOH at room temperature are stable.[2] 7-Methylguanosine under these conditions undergoes a rapid imidazole ring-opening reaction but the resultant hydrolysis product is stable.[2,5]

Guo was exposed to 9.75 *M* $HClO_4$ at room temperature for 345 min and the liberated guanine was recovered following neutralization with sodium hydroxide. The collected solid was reprecipitated from alkaline solution using acetic acid; a 97% yield of guanine, mp >360°, was obtained. Authentic guanine has mp >360°. Recovered material was chromatographically homogeneous.

Ribose degraded during some kinetic runs. Mixtures at the highest acidities employed in the kinetic studies acquired a yellow coloration; acidic samples which stood beyond the period of the run eventually turned black. For example, a 0.1 *M* solution of ribose or guanosine in 9.75 *M* $HClO_4$ acquired a yellow color within 0.5 hr and after about 3 hr at 30° solutions were too black for polarimetric measurements.

Large rotational changes may accompany nucleoside hydrolysis; larger changes result with increasing acid concentration. For example, about a 2.8° change was observed during the hydrolysis of a 0.14 *M* solution of guanosine in 9.75 *M* $HClO_4$. However, small rotational changes are associated with the degradation of ribose. Hence, measured rotational changes are essentially associated with the hydrolysis of the nucleoside. In practice first-order kinetic plots using polarimetry to follow the reaction were linear over at least 3 half-lives. There was no indication of ribose degradation from the kinetic plots themselves. There was no evidence of rotational changes such as those which might occur if anomerization of a sugar preceded hydrolysis.

The presence of guanine seems to have no influence on ribose degradation. Solutions of ribose in 9.75 *M* $HClO_4$ and of ribose and an equivalent of guanine in 9.75 *M* $HClO_4$ show essentially identical rotations.

Ribose degradation was unimportant for hydrolyses carried out at lower acidities. For example, in the hydrolysis of guanosine in 4.68 *M* $HClO_4$ the "infinity" optical rotation (20 hr) was the same as that for ribose in 4.68 *M* $HClO_4$ taken within 10 min after mixing and no color was visible. No attempt was made to establish the acidity and time at which significant ribose degradation occurs.

Kinetics. A. Alkaline Quench Method.—Reactions followed spectrophotometrically employed a sodium hydroxide quenching solution in order to increase the difference in absorbance between reactant and products. Approximately 30–40 mg of guanosine or 7-methylguanosine was weighed into a 100-ml volumetric flask and diluted to volume. Solutions were maintained at 30.0 ± 0.1°; at various intervals 6-ml aliquots were withdrawn and diluted to 50 ml with 2.5 *M* NaOH quenching solution. Pseudo-first-order rate plots using the infinity method were employed.[2] Plots generally were linear over 2–3 half-lives. Results are given in Table I.

B. Polarimetric Method.—Approximately 0.1 g of guanosine or 7-methylguanosine was dissolved in 2 ml of $HClO_4$ and immediately placed in a jacketed polarimeter cell maintained at 30.0 ± 0.1°. Pseudo-first-order rate plots (20–50 points) were constructed in a manner similar to that used for spectrophotometric data. Infinity rotations had finite values, as required for the formation of optically active product. Plots were linear over 3–5 half-lives.

H_0 values for perchloric acid were converted from the original weight per cent scale[6] to molarity using known densities.[7] H_0 values were then obtained from a molarity–h_0 plot.

Results

When Guo and 7-MeGuo are hydrolyzed to guanine and 7-methylguanine in moderately concentrated perchloric acid, their ultraviolet absorption spectra undergo only small changes. This prohibits direct monitoring of the acidic reaction mixture to obtain kinetic data. However, larger absorbance changes result when the acidic mixtures are quenched with concentrated sodium hydroxide and the alkaline reaction

(3) B. Capon, *Chem. Rev.*, **69**, 407 (1969).
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(5) J. W. Jones and R. K. Robins, *J. Amer. Chem. Soc.*, **85**, 193 (1963).
(6) K. Yates and H. Wai, *ibid.*, **86**, 5408 (1964).
(7) A. E. Markham, *ibid.*, **63**, 874 (1941); G. F. Smith and O. E. Goehler, *Ind. Eng. Chem., Anal. Ed.*, **3**, 61 (1931).

solutions are examined as a function of reaction time. This procedure results in imidazole ring opening of 7-MeGuo in alkali but the ring-opened product is stable.[2,5] Simple ionization occurs in the case of Guo, guanine, and 7-methylguanine. Although the liberated ribose may degrade in acid, this side reaction does not interfere with the spectrophotometric study. Good kinetic data were obtained by this spectrophotometric method for Guo and 7-MeGuo for the region 1–9 *M* $HClO_4$ at 30.0°. Results are summarized in Table I.

A few hydrolysis reactions were followed polarimetrically. Kinetic runs were carried out using a jacketed polarimeter tube and rotations of the acid solutions were measured directly. Ribose degraded in the more acidic solutions[8] but was stable over a period of a kinetic run at acidities less than 5 *M* $HClO_4$. Even when ribose degraded, good pseudo-first-order plots were obtained over as much as 5 half-lives. This obtains because rotational changes associated with the hydrolysis reaction are considerably greater than those resulting from ribose degradation. It was possible to obtain essentially constant rotational values after 10 half-lives (infinity) even when ribose degraded. The appearance of a yellow coloration provided visual evidence of ribose degradation; with time these yellow solutions turned black. Studies using polarimetry were carried out at the higher acid concentrations where reactions are fast (Table I).

First-order rate constants obtained spectrophotometrically and polarimetrically agree to within 4% on the average (Table I). This agreement between results obtained by two different physical methods clearly establishes the validity of the rate constants. The spectrophotometric method measures the concentration of the purines while the polarimetric method essentially measures the concentrations of the sugars. Since the concentration of nucleoside is about 150 times larger in the polarimetric than in the spectrophotometric studies and since results from the two approaches agree so well, then it must be concluded that there is no evidence in our results for any kind of molecular aggregation which perturbs chemical reactivity. This is consistent with the knowledge that interactions among purine bases are greatly diminished when the bases are protonated.[9] Moreover, our data show that, in spite of ribose degradation, polarimetry is a valuable method for obtaining solvolysis rates. The method is particularly attractive because of its experimental simplicity.

The data in Table I show that the rates of hydrolysis of Guo and 7-MeGuo increase with increasing acid concentration. Both substrates show very similar rates of hydrolysis in the region 1–7 *M* $HClO_4$. Rates for 7-MeGuo reach a maximum at about 7.2 *M* $HClO_4$ and then decrease slightly as the acidity increases. No rate maximum is observed for the hydrolysis of Guo over the same acidity region but there is a change to a less rapid rate increase at about 7 *M* $HClO_4$. At about 7.5 *M* $HClO_4$ both substrates have identical hydrolysis rates with a half-life of 12 min. Below this acidity Guo is about 10% less reactive than 7-MeGuo but above this acidity the first real differences in reactivity between Guo and MeGuo become apparent. For example, at 9.4 *M* $HClO_4$ Guo is about 70% more reactive than 7-MeGuo.

In the region 1–7 *M* $HClO_4$ it is possible to approximate the rates of hydrolysis of Guo and 7-MeGuo by eq 1 and the observed pseudo-first-order rate constant, k_ψ, by eq 2. Symbols have the following meaning: $[SH]_t$ = concentration of nucleoside in all forms; [SH]

TABLE I

RATE CONSTANTS FOR THE HYDROLYSIS OF GUANOSINE AND 7-METHYLGUANOSINE AT 30.0° IN PERCHLORIC ACID[a]

Guanosine[b]

$[HClO_4]$, *M*	$-H_0$	10^4k_ψ, sec^{-1}	10^4k, sec^{-1}
1.20	0.44	0.0848	8.20
1.40	0.58	0.130	9.15
1.76	0.78	0.196	8.73
2.34	1.06	0.398	9.54
2.40	1.08	0.392	8.98
3.29	1.47	0.869	8.69
3.61	1.61	1.25	9.35
3.64	1.63	1.12	7.18
4.68	2.12	3.61	10.8
4.81	2.21	3.67	9.60
4.86	2.24	2.90	7.45
5.18	2.41	4.13	8.35
5.26	2.46	4.99	9.52
5.65	2.67	5.37	8.40
6.01	2.89	6.17	8.33
6.12	2.96	6.47	8.26
6.59	3.27	7.65	8.72
7.06	3.57	8.31	8.90
7.25	3.69	9.17*	
7.25	3.69	9.00	
7.53	3.83	9.40	
8.00	4.27	10.5	
8.25	4.49	10.9*	
8.47	4.69	11.4	
9.41	5.54	12.9	

7-Methylguanosine[c]

$[HClO_4]$, *M*	$-H_0$	10^4k_ψ, sec^{-1}	10^3k, sec^{-1}
1.00	0.30	0.0847	1.35
2.00	0.89	0.296	1.23
2.50	1.12	0.535	1.33
3.00	1.34	0.929	1.42
4.00	1.79	1.98	1.21
4.00	1.79	1.80*	1.09
4.25	1.90	2.65	1.31
4.75	2.17	4.03	1.29
5.00	2.31	4.66	1.18
5.25	2.45	4.28	0.92
5.68	2.78	6.83	1.13
6.50	3.21	8.90	1.06
6.75	3.36	9.25	1.06
7.00	3.52	9.59	1.05
7.00	3.52	9.59*	1.05
7.25	3.69	9.48	
7.25	3.69	10.8*	
7.50	3.81	9.25	
7.50	3.81	9.51*	
8.00	4.27	8.95	
8.25	4.49	9.00*	
8.50	4.70	8.29	
9.37	5.49	7.95*	
9.41	5.54	7.60	

[a] $k = k_\psi(h_0 + K_a)/h_0$. Rate constants marked with an asterisk were obtained polarimetrically. [b] $K_a = 263$; $k_{avg} = 8.8 \pm 0.6 \times 10^{-4}\ M^{-1}\ sec^{-1}$. [c] $K_a = 315$; $k_{avg} = 1.2 \pm 0.1 \times 10^{-3}\ M^{-1}\ sec^{-1}$.

(8) F. A. H. Rice and L. Fishbein, *J. Amer. Chem. Soc.*, **78**, 1005 (1956); F. A. H. Rice and A. R. Johnson, *J. Org. Chem.*, **23**, 1966 (1958).

(9) S. I. Chan and J. H. Nelson, *J. Amer. Chem. Soc.*, **91**, 168 (1969); P. O. P. Ts'O, N. S. Kondo, R. K. Robins, and A. D. Broom, *ibid.*, **91**, 5625 (1969).

$$\text{rate} = k_\psi[\text{SH}]_t = k_2 h_0[\text{SH}] \quad (1)$$

$$k_\psi = \frac{kh_0}{h_0 + K_a} \quad (2)$$

= concentration of monoprotonated nucleoside; $K_a = h_0[\text{SH}]/[\text{SH}_2]$ = the ionization constant for diprotonated substrate; h_0 is the Hammett acidity function, and $k = k_2K_a$ where k is a first-order rate constant for the hydrolysis of the diprotonated nucleoside. Significant hydrolysis of the monoprotonated species could not be detected.

In Table I are k values of Guo and 7-MeGuo calculated according to eq 2. It may be seen that k values are satisfactorily constant over the region 1–7 M $HClO_4$; $k = 8.8 \pm 0.6 \times 10^{-4}$ sec^{-1} for Guo. The kinetic pK_a value employed for Guo is −2.42. The pK_a value determined in a separate study where hydrolysis is unimportant is −2.42.[2]

When a kinetic pK_a of −2.48 is employed for 7-MeGuo k is $1.2 \pm 0.1 \times 10^{-3}$ sec^{-1}, but when a pK_a of −2.61 is utilized k is $1.4 \pm 0.3 \times 10^{-3}$ sec^{-1}. This latter pK_a value, which is the value found under conditions where hydrolysis is unimportant,[2] gives a k value with a larger (21% *vs.* 8%) uncertainty range. Nevertheless, the agreement between pK_a values determined under hydrolytic and nonhydrolytic conditions is good and the range of k values calculated using the two pK_a values overlap. Hence, rates are adequately described by eq 2 over an acidity range which brings about the conversion of more than 90% of the monoprotonated substrate to its diprotonated form.

Inspection of the data for 7-MeGuo given in Table I indicates, with a few exceptions, that there is a small but systematic decrease in k with increasing acidity. This means that the protonation of 7-MeGuo does not exactly follow the Hammett acidity function. This is not unexpected.[10-12] It is to be remembered that the indicators used in the construction of the Hammett acidity function are primary anilines which undergo monoprotonation. It is not surprising that anilines and monoprotonated purine nucleosides do not respond to changes in medium acidity in identical ways. It is remarkable how well the nucleoside hydrolysis data fit a simple Hammett acidity function.

Rates at >7 M $HClO_4$ are not described by eq 1. It seems that medium effects specific for each substrate may be involved. This is not without ample precedent.[10-14]

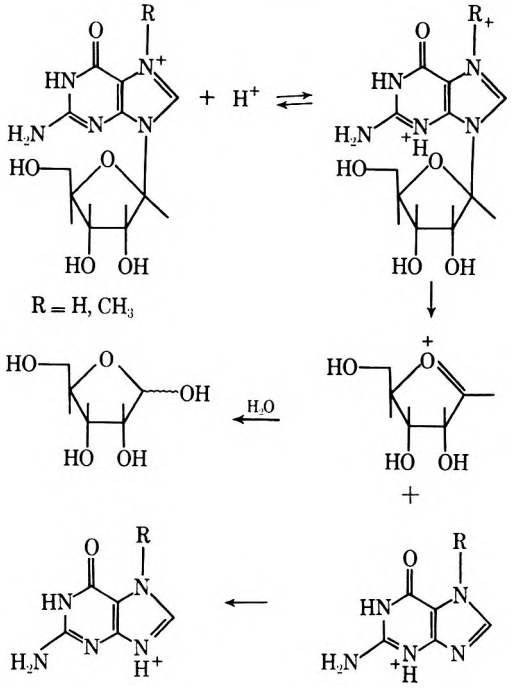
Bunnett plots[10] were constructed for the 1–7 M acid region. Plots of log k (Table I) *vs.* log a_{H_2O} have slopes or "w" values of 0 and 0.2 for Guo and 7-MeGuo, respectively. According to the w value criterion, water is not involved in the reaction of protonated substrate. (Our earlier study[2] of the pK_a values of Guo and 7-MeGuo shows w to be ~0 for equilibrium protonation.)

Discussion

Our kinetic results dealing with the hydrolysis of Guo and 7-MeGuo suggest that these substrates react by a mechanism involving equilibrium protonation which precedes the rate-limiting step. Results supporting this conclusion are the following. (a) Rates of reaction using 1–7 M $HClO_4$ at 30.0° closely follow the Hammett acidity function H_0. (b) Rates of hydrolysis fit eq 1 which assumes a preequilibrium protonation mechanism. The "kinetic" pK_a values used in eq 2 and observed pK_a values are in good agreement. They are, respectively, −2.42 and −2.42 for Guo and −2.48 and −2.61 for 7-MeGuo. (c) Bunnett w values of ~0 for Guo and 7-MeGuo show that water molecules function neither as nucleophiles nor as proton transfer agents (general acids) in the rate-limiting step of the reaction.

These data suggest a mechanism involving protonation of a purine ring to give a heterocyclic dication which then fragments in the rate-determining step to give a monoprotonated guanine and a cyclic carboxonium ion. The second proton has arbitrarily been added to N-3 in Scheme II.[15] Reaction of the carboxonium

SCHEME II



ion and water generates ribose. Hence, mono- and diprotonated purine nucleosides react by the same kind of mechanism, differing in the degree of protonation. The w value suggests that water does not assist the fragmentation step as in an S_N2 reaction; *i.e.*, the hydrolysis mechanism is A-1 and not A-2.

The data are not consistent with a mechanism involving cleavage of a protonated ribose ring to give a Schiff base which then undergoes hydrolysis. The kinetic characteristics of such a mechanism may be discerned by a consideration of the hydrolysis of glycosylamines, compounds similar to nucleosides in that they consist of a nitrogen-containing group bonded to a sugar. Here, too, hydrolysis gives rise to CN bond cleavage products but the mechanism involves ring opening.[3] The hydrolysis of glycosylamines is specific acid–general base (general acid) catalyzed and shows rate maxima which may occur in concentrated acidic

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(14) E. M. Arnett and G. W. Mach, *ibid.*, **88**, 1177 (1966).
(15) R. Wagner and W. V. Philipsborn, *Helv. Chim. Acta*, **53**, 299 (1970); J. P. Shoffner, L. Bauer, and C. T. Bell, *J. Heterocycl. Chem.*, **7**, 487 (1970).

solutions. The rate-determining step in the acidity region where rates increase with increasing acid concentration involves addition of water to the ring-opened cation. Neither of these characteristics is found for the nucleosides considered here. Reactions in which water is acting as a nucleophile have Bunnett w values in the range 1.2–3.3 and those in which water is acting as a proton transfer agent have values >3.3. Clearly these are much larger than the values of approximately 0 observed here. Our results fall into Bunnett's third group (−2.5–0), indicating the lack of the involvement of water in the rate-limiting step of the reaction.

A shallow rate maximum was observed near 7 M $HClO_4$ for the hydrolysis of 7-MeGuo and this would seem to provide support for the ring-opening pathway. However, in the same acidity region where 7-MeGuo shows decreasing hydrolysis rates with increasing acidity, Guo shows just the opposite pattern. A slight increase in rate with increasing acidity results. This is in an acidity region where both substrates are largely converted to their dicationic forms and a region in which kinetic eq 2 predicts small changes in the rate constant k_ψ. Since it is likely that Guo and 7-MeGuo react by the same pathway in this acidity region and since the observed changes are small and in opposite directions, it seems reasonable to conclude that medium effects are influencing reactivity. It is not at all uncommon to find large and nonlinear changes in the reactivity of a substrate in concentrated electrolyte solutions.[10-14] Such changes could, for example, result from variations in solvation of the substrates.

Overall, then, there are no results in our work to support a ring-opening mechanism. Rather, the data suggest a CN bond cleavage mechanism such as that given by Scheme I. A similar conclusion is likely to extend to the hydrolysis of purine deoxyribosides in concentrated acid. Again the hydrolysis is likely to be A-1 rather than A-2 because a more stable carboxonium ion is formed in the case of the deoxyribosides.

Kinetic data now are available to describe the hydrolysis of Guo and 7-MeGuo to ribose and to guanine or 7-methylguanine over a wide acidity range. This varies from pH 3 (Guo) and pH 5 (7-MeGuo)[2] at 100° to 9 M $HClO_4$ at 30°. This variation in acidity covers a factor of about 10,[8-10] neglecting temperature changes. Over this entire acidity region the rate of Guo hydrolysis increases linearly with increasing acid concentration while rates for 7-MeGuo show a similar acid dependence except for pH 3–5 at 100° where rates are independent of acid concentration and except for >7 M $HClO_4$ where rates decreased slightly. It is worth noting that, for example, in 1 M $HClO_4$ at 30° where only about 1% of Guo and 7-MeGuo exist in their diprotonated forms, hydrolysis by way of the monocations is negligible relative to reaction by means of diprotonated structures. This clearly demonstrates that the fragmentation of the dications must be at least 10^3 faster than that for the monocations. Diprotonated purine is a better leaving group than is monoprotonated purine.

The results of kinetic studies such as these on Guo and 7-MeGuo make it possible to select convenient conditions for the hydrolysis of these substrates with the assurance that side reactions such as deamination are unimportant. Thus, if one desires to hydrolyze Guo under conditions where the half-life is, say, 30 min, then pH 1.7 at 100° or 4.8 M $HClO_4$ at 30° may be selected.

Our studies on the hydrolysis of purine nucleosides in dilute and concentrated acids provide the first truly detailed understanding of nucleoside hydrolysis. They are a first step toward an understanding of the factors which influence the rates of cleavage of sugar–heterocycle bonds in nucleic acids. Additional studies are desirable.

Registry No.—Guanosine, 118-00-3; 7-methylguanosine, 33686-50-9.

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Nucleosides. LXXIV. Synthetic Studies on Nucleoside Antibiotics. 8. Syntheses of 1-[4-Deoxy-4-(sarcosyl-D-seryl)amino-β-D-glucopyranosyl]cytosine and Related Analogs of Gougerotin[1]

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The synthesis of 1-[4-deoxy-4-(sarcosyl-D-seryl)amino-β-D-glucopyranosyl]cytosine (**6a**), an analog of gougerotin, is described. Condensation of 1-(4-amino-4-deoxy-β-D-glucopyranosyl)cytosine (**1**) with *N*-Cbz-D-serine in aqueous acetonitrile in the presence of dicyclohexylcarbodiimide gave the 4′-*N*-Cbz-seryl derivative **3a** as the main product. Hydrogenation of **3a** afforded the 4′-seryl nucleoside (**4a**) which was reacted with *N*-Cbz-sarcosine. After removal of the Cbz group by reduction, **6a** was obtained in ~50% overall yield from **1**. Detailed examination of the acid hydrolysate of **6a** showed that little, if any, racemization of the seryl moiety occurred during the synthesis of **6a**. The sarcosyl-D-alanyl (**6b**) and sarcosyl-D-phenylalanyl (**6c**) analogs were also synthesized using the active ester procedure.

Previous reports from this laboratory described the syntheses of 1-(4-amino-4-deoxy-β-D-glucopyranosyluronic acid)cytosine[2] (C-substance) and 1-(4-amino-2,3,4-trideoxy-β-D-*erythro*-hex-2-enopyranosyl)cytosine,[3] derivatives related to the nucleoside moieties of gougerotin and blasticidin S.[4] This paper deals with the synthesis of 1-[4-deoxy-4-(sarcosyl-D-seryl)amino-β-D-glucopyranosyl]cytosine (**6a**) and related derivatives as part of our program designed toward the total synthesis of these antibiotics and/or analogs thereof and their biological evaluation.

The most direct approach to the synthesis of gougerotin analogs (**6**) would be to link a protected sarcosyl-D-serine to the 4′-amino group of the aminoglucosylcytosine (**1**). Both *tert*-butoxycarbonyl (Boc) and benzyloxycarbonyl (Cbz) derivatives of sarcosyl-D-serine[5] and their *O*-acetyl derivatives, however, in our hands failed to condense with nucleoside **1** by use of a number of reported procedures including the dicyclohexylcarbodiimide[7] (DCC), azide,[8] mixed anhydride,[8,9] oxidation–reduction,[10] and other methods. The sarcosyl-D-serine derivatives failed even to form an active ester with *p*-nitrophenol, although *O*-acetyl-*N*-Cbz-serine could be converted to its crystalline *p*-nitrophenyl ester in good yield.[11]

Reaction of **1** with 2 equiv of *N*-Cbz-*O*-acetyl-D-serine *p*-nitrophenyl ester (**7a**) in dimethyl sulfoxide (DMSO) (without base) gave the *N*,*N*′-disubstituted derivative (**2a**) in good yield. Treatment of crude **2a** with Dowex-1 (OH^-) selectively removed the seryl group on cytosine as well as causing de-*O*-acetylation of D-serine. After hydrogenolysis of the Cbz group, the desired D-seryl nucleoside (**4a**) was obtained. It was, however, very difficult to purify **4a**. The nmr of the crude product revealed contamination by alanyl derivatives. Apparently the acetoxy group was eliminated during the Dowex-1 treatment introducing the α–β double bond which was reduced during debenzyloxycarbonylation by hydrogenation. However, application of this active ester procedure to *N*-Cbz-D-alanine and *N*-Cbz-D-phenylalanine gave the corresponding products (**4b** and **4c**) in high yield and in pure state. Reaction of **4b** and **4c** with the *p*-nitrophenyl ester of *N*-Cbz-sarcosine in DMSO followed by Dowex-1 (OH^-) treatment and hydrogenolysis gave the corresponding dipeptidyl nucleosides (**6b** and **6c**) in good yield.

The main difficulty in the synthesis of the seryl nucleoside **3a** is the protection of the hydroxyl group of the amino acid. With an *O*-acyl protecting group some β elimination always occurred. The *O*-benzyl protecting group also failed due to reduction of the 5,6 double bond of cytosine during the subsequent reductive debenzylation step. We found, however, that when *N*-Cbz-D-serine itself was treated with **1** and DCC in aqueous tetrahydrofuran (THF) or aqueous acetonitrile, the *N*-Cbz-D-seryl nucleoside (**3a**) was obtained together with a small amount of **2** (R = OH). Treatment of the mixture of **3a** and **2a** with Dowex-1 (OH^-) followed by hydrogenolysis gave pure D-seryl nucleoside (**4a**) in good yield. Reaction of **4a** with *N*-Cbz-sarcosine and DCC resulted in the formation of *N*-Cbz-sarcosyl-D-seryl nucleoside (**5a**) contaminated with some N^4-acylated material. Treatment of this mixture with Dowex-1 (OH^-) followed by hydrogenolysis afforded 1-[4-deoxy-4-(sarcosyl-D-seryl)-amino-β-D-glucopyranosyl]cytosine (**6a**) as colorless microcrystals in ~50% overall yield from **1**. (Compound **6a** differs structurally from gougerotin only by the presence of a 5′-hydroxymethyl group instead of a 5′-carboxamide function). The uv spectrum of **6a** as a function of pH is similar to that for cytidine, showing that the amino group of the aglycon is unsubstituted. The ir spectrum showed the absence of an ester linkage, thus ruling out the possibility of a linkage of

(1) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant No. CA 08748).

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(3) K. A. Watanabe, I. Wempen, and J. J. Fox, *Chem. Pharm. Bull.*, **18**, 2368 (1970).

(4) For reviews of nucleoside antibiotics, see J. J. Fox, K. A. Watanabe, and A. Bloch, *Progr. Nucl. Acid Res. Mol. Biol.*, **5**, 251 (1966); R. J. Suhadolnik, "Nucleoside Antibiotics," Wiley-Interscience, New York, N. Y., 1970.

(5) Recently Lichtenthaler, *et al.* [*Tetrahedron Lett.*, 2061 (1970)] reported the synthesis of this compound by the same procedure that we reported for the preparation of its racemate.[6]

(6) J. J. Fox, Y. Kuwada, K. A. Watanabe, T. Ueda, and E. B. Whipple, *Antimicrob. Ag. Chemother.*, 518 (1964).

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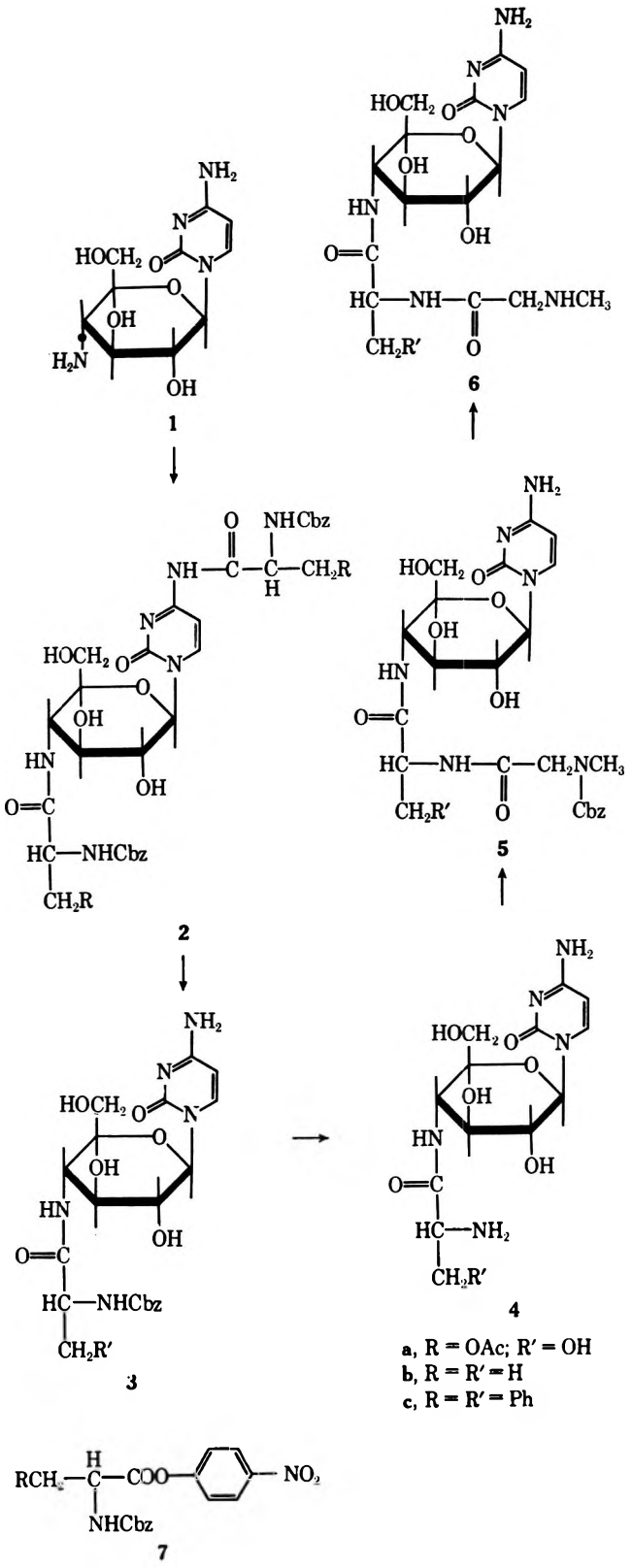

the amino acid to any hydroxyl group. The nmr spectrum was also consistent with structure **6a**. Acid hydrolysis (6 *N* HCl) of compound **6a** according to Iwasaki[12] gave the amino nucleoside **1**, sarcosine, and D-serine. The D-serine was isolated in crystalline form and characterized by paper chromatography, melting point, and optical rotation. The mother liquors from the D-serine crystallizations were combined and subjected to preparative paper chromatography. The optical rotation obtained for the serine was $-13°$ (lit.[12] $-14°$), clearly indicating that very little, if any, racemization of the D-seryl moiety had occurred during the synthesis of **6a**.

Upon completion of these studies, we noted a recent communication by Lichtenthaler, *et al.*,[13] describing the synthesis of **6a** in 40% yield by coupling **1** with *N*-Boc-sarcosyl-D-seryl azide in DMF followed by trifluoroacetic acid treatment. The physical constants given by these authors[13] [decomposition above 155°, $[\alpha]^{23}D$ +5° (*c* 0.6, H_2O)], however, differ appreciably from those obtained in our preparation of **6a** [decomposition at 210–250°, $[\alpha]^{23}D$ +44° (*c* 0.6, H_2O)], suggesting that their D-seryl moiety may be racemized. However, we have also prepared a paper chromatographically homogeneous, solid sarcosyl-DL-seryl nucleoside from racemic serine by the same method used for our synthesis of **6a**. This diastereoisomeric mixture again showed different physical properties [decomposition at 172–189°, $[\alpha]^{23}D$ +11° (c 0.8, H_2O)] from their material. Since they[13] gave no other physical constants or other supporting evidence, it is difficult to rationalize their data with compound **6a**. Indeed, as stated above, in our hands we could not isolate the desired product from the condensation of **1** and *N*-Boc- or *N*-Cbz-sarcosyl-D-seryl azide in various solvents or solvent systems. It should be noted that the azide procedure is known[14] to produce side products.

We have also prepared **6a** by the active ester procedure and purified it by preparative paper chromatography. Nucleoside **6a** thus prepared possessed a smaller optical rotation ($[\alpha]^{23}D$ +33°) than that obtained above by the DCC method ($[\alpha]^{23}D$ +44°), which may indicate some racemization of the D-seryl moiety in this preparation. Acid hydrolysis (6 *N* HCl) of the sarcosyl-D-alanyl derivative (**6b**) prepared by the activated ester process, however, gave D-alanine indicating that little racemization, if any, occurred with this derivative. We assume also that the sarcosyl-D-phenylalanyl analog (**6c**) prepared by the same procedure is essentially optically pure. Apparently, the seryl derivative **6a** shows greater tendency toward racemization than the alanyl derivatives when the activated ester procedure is employed.

Experimental Section

Elemental analyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich., and by Galbraith Laboratories, Inc., Knoxville, Tenn. Melting points are corrected. Nmr spectra were taken on a Varian A-60 spectrometer. Samples for elemental analyses were dried *in vacuo* at 78° for *ca.* 24 hr unless specified otherwise. The presence and quantity of solvent of crystallization (other than water) were determined by nmr. All compounds with analyses described below contained water, as shown by nmr. A quantitative estimate of the amount of water of crystallization was deduced from the elemental analyses.

1-[4-Deoxy-4-(*N*-benzyloxycarbonyl-D-alanyl)amino-β-D-glucopyranosyl]cytosine (3b).—A mixture of **1**[2] (272 mg, 1 mmol) and the *p*-nitrophenyl ester of *N*-benzyloxycarbonyl-D-alanine (**7b**, 688 mg, 2 mmol) in DMSO (2 ml) was stirred for 20 hr at room temperature. Methanol (10 ml) and then ether (200 ml) were added to the mixture, which was stirred for 1 hr. The supernatant was decanted and the gummy residue was washed with ether (three 30-ml portions). The gummy residue (**2b**, λ_{max}^{EtOH}

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(13) F. W. Lichtenthaler, G. Trummlitz, G. Bamback, and I. Rychlik, *Angew. Chem.*, **83**, 331 (1971); *Angew. Chem., Int. Ed. Engl.*, **10**, 334 (1971).

(14) E. Schroder and K. Lubke, "The Peptides," Vol. 1, Academic Press, New York, N. Y., 1965, p 83.

303 and 249 mμ, λ_{min}^{EtOH} 275 and 227 mμ) was stirred with Dowex-1 (OH^-) (4 g) in methanol (150 ml). As soon as uv absorption at 303 mμ disappeared, the resin was removed and washed several times with methanol and water. The combined filtrate and washings were concentrated to dryness to give crude **3b** (322 mg, 67%), which on crystallization from water gave a white powder: mp 190–194° dec; $[\alpha]^{23}D$ +24° (*c* 1.25, 66% ethanol); uv $\lambda_{max}^{pH\ 6.8}$ 267, 237, $\lambda_{min}^{pH\ 6.8}$ 252, 228, $\lambda_{max}^{pH\ 1}$ 277, $\lambda_{min}^{pH\ 1}$ 240 mμ; nmr (D_2O) H-6, δ 7.74 (1 H, d), benzyl 7.44 (5 H, s), H-5, 6.12 (1 H, d), H-1′, 5.75 (1 H, d), benzyl CH_2, 5.17 (2 H, s), alanine CH, 4.22 (1 H, q), alanine CH_3, 1.46 (3 H, d).

Anal. Calcd for $C_{21}H_{27}N_5O_8 \cdot H_2O$: C, 50.91; H, 5.89; N, 14.13. Found: C, 50.44; H, 5.89; N, 14.06.

1-[4-Deoxy-4-(D-alanyl)amino-β-D-glucopyranosyl]cytosine (4b).—A solution of **3b** (1.6 g) in 50% ethanol was hydrogenated over 10% palladium on carbon catalyst (100 mg) for 15 min with an initial pressure of *ca.* 2 atm. Filtration from the catalyst and subsequent concentration of the filtrate gave a white powder, which was purified by reprecipitation from hot ethanol and ethanol (1.03 g, 79%): mp 233–240° dec; $[\alpha]^{23}D$ +22° (*c* 1, H_2O); nmr (D_2O) H-6, δ 7.70 (1 H, d), H-5, 6.07 (1 H, d), H-1′, 5.66 (1 H, m), alanine CH_3, 1.23 (3 H, d).

Anal. Calcd for $C_{13}H_{21}O_6N_5 \cdot {}^1/_2C_2H_5OH \cdot H_2O$: C, 43.74; H, 6.82; N, 18.22. Found: C, 43.46; H, 6.35; N, 18.47.

1-[4-Deoxy-4-(*N*-benzyloxycarbonylsarcosyl-D-alanyl)amino-β-D-glucopyranosyl]cytosine (5b).—The procedure described for **3b** was followed using **4b** (343 mg, 0.89 mmol) and *N*-benzyloxycarbonylsarcosine *p*-nitrophenyl ester[14] (688 mg, 2 mmol) in DMSO (1 ml). After treatment of the crude condensation product with Dowex-1 (OH^-), the colorless powder was crystallized from ethanol (300 mg, 58% dried at 100° for 24 hr *in vacuo*): mp 210–212°; $[\alpha]^{23}D$ +35° (*c* 0.6, 66% ethanol); nmr (pyridine-d_5–D_2O) H-6, δ 7.68 (1 H, d), benzyl, 7.38 (5 H, s), H-1′, 6.40 (1 H, d), H-5, 6.03 (1 H, d), benzyl CH_2, 5.25 (2 H, s), NCH_3, 3.10 (3 H, s), alanine CH_3, 1.66 (3 H, d).

Anal. Calcd for $C_{24}H_{32}O_9N_6 \cdot 2H_2O$: C, 49.31; H, 6.21; N, 14.38. Found: C, 49.17; H, 6.09; N, 14.48.

1-[4-Deoxy-4-(sarcosyl-D-alanyl)amino-β-D-glucopyranosyl]cytosine (6b).—Compound **5b** (300 mg) in 50% ethanol (50 ml) was hydrogenated over 10% palladium on carbon (50 mg) for 5 min at the initial pressure of *ca.* 2 atm. The compound obtained was purified by reprecipitation from hot methanol and ethanol: 200 mg (85%, after drying at 64° *in vacuo* for 24 hr); mp 93–95° dec; $[\alpha]^{23}D$ +33° (*c* 1, H_2O); nmr (D_2O) H-6, δ 7.76 (1 H, d), H-5, 6.08 (1 H, d), H-1′, 5.68 (1 H, m), NCH_3, 2.40 (3 H, s), alanine CH_3, 1.42 (3 H, d); uv $\lambda_{max}^{pH\ 6.8}$ 267, 235, $\lambda_{min}^{pH\ 6.8}$ 253, 225, $\lambda_{max}^{pH\ 1}$ 275, $\lambda_{min}^{pH\ 1}$ 240 mμ.

Anal. Calcd for $C_{16}H_{26}O_7N_6 \cdot {}^1/_2C_2H_5OH \cdot 1{}^1/_2H_2O$: C, 43.96; H, 6.94; N, 18.09. Found: C, 44.08; H, 6.39; N, 17.70.

1-[4-Deoxy-4-(*N*-benzyloxycarbonyl-D-phenylalanyl)amino-β-D-glucopyranosyl]cytosine (3c).—Compound 1 (1.36 g, 5 mmol) and *N*-benzyloxycarbonyl-D-phenylalanine *p*-nitrophenyl ester[15] (4.2 g, 10 mmol) in DMSO (10 ml) were treated in the same manner as **3b**. The product obtained was recrystallized from methanol and dried at 100° for 24 hr *in vacuo* (2.4 g, 82%): mp >300°; $[\alpha]^{23}D$ +20° (*c* 0.6, 66% ethanol); nmr (DMSO) H-6, δ 7.66 (1 H, d), aromatic, 7.28 (10 H, s), H-5, 5.78 (1 H, d), H-1′, 5.56 (1 H, d), benzyl CH_2, 4.96 (2 H, s).

Anal. Calcd for $C_{27}H_{31}O_8N_5 \cdot H_2O$: C, 56.26; H, 5.78; N, 12.28. Found: C, 56.14; H, 5.81; N, 12.25.

1-[4-Deoxy-4-(D-phenylalanyl)amino-β-D-glucopyranosyl]cytosine (4c).—Compound **3c** (1.3 g) was hydrogenated in the usual manner in the presence of 10% palladium on carbon. Compound **5c** (890 mg, 88%) was obtained as a white powder: mp 263–264° (sintered at 183–189°); $[\alpha]^{23}D$ +13° (*c* 1, H_2O); nmr (DMSO) H-6, δ 7.62 (1 H, d), aromatic, 7.25 (5 H, s), H-5, 5.78 (1 H, d), H-1′, 5.55 (1 H, d).

Anal. Calcd for $C_{19}H_{25}O_6N_5 \cdot 1{}^1/_2H_2O$: C, 51.12; H, 6.32; N, 15.69. Found: C, 50.80; H, 6.08; N, 15.58.

1-[4-Deoxy-4-(*N*-benzyloxycarbonylsarcosyl-D-phenylalanyl)amino-β-D-glucopyranosyl]cytosine (5c).—From 418 mg of **4c** and 688 mg of *N*-benzyloxycarbonylsarcosine *p*-nitrophenyl ester, 431 mg of **5c** (70%) was obtained as a white powder: mp 243–247° dec; $[\alpha]D$ +13° (*c* 0.5, 66% ethanol); nmr (DMSO) H-6, δ 7.62 (1 H, d), aromatic 7.33 and 7.23 (total 10 H), H-5, 5.77 (1 H, d), H-1′, 5.52 (1 H, d), benzyl CH_2, 5.03 (2 H, s), NCH_3, 2.72 (3 H, s).

Anal. Calcd for $C_{30}H_{36}O_9N_6 \cdot 1{}^1/_2H_2O$: C, 55.29; H, 6.03; N, 12.89. Found: C, 55.57; H, 5.52; N, 12.97.

1-[4-Deoxy-4-(sarcosyl-D-phenylalanyl)amino-β-D-glucopyranosyl]cytosine (6c).—Hydrogenation of compound **5c** (351 mg) gave 242 mg of **6c** (84%) which was crystallized from 2-propanol–ethanol (1:1). After it had been dried at 100° *in vacuo* for 24 hr, **6c** had mp 221–231° dec (sintered at 116°); $[\alpha]^{23}D$ +19° (*c* 1, H_2O); nmr (DMSO) H-6, δ 7.66 (1 H, d), aromatic 7.28 (5 H, s), H-5, 5.81 (1 H, d), H-1′, 5.55 (1 H, m), NCH_3, 2.25 (3 H, s).

Anal. Calcd for $C_{22}H_{30}O_7N_6 \cdot {}^1/_2C_3H_7OH \cdot H_2O$: C, 52.41; H, 6.73; N, 15.60. Found: C, 52.07; H, 5.95; N, 15.69.

***N*-Benzyloxycarbonyl-D-alanine *p*-Nitrophenyl Ester (7b).**—The compound was prepared from *N*-benzyloxycarbonyl-D-alanine and *p*-nitrophenol in 83% yield by the method of Marchiori, *et al.*,[16] mp 77–78°, $[\alpha]^{23}D$ +54° (*c* 0.8, 66% ethanol). (The L isomer[16] had mp 77–78°, $[\alpha]^{20}D$ −41°.)

1-[4-Deoxy-4-(*N*-benzyloxycarbonyl-D-seryl)amino-β-D-glucopyranosyl]cytosine (3a).—To a mixture of compound 1 (1.36 g, 5 mmol) and *N*-benzyloxycarbonyl-D-serine (2.2 g, 9 mmol) in water (2 ml) was added DCC (2.2 g) in acetonitrile (10 ml) and the solution was stirred for 20 hr at room temperature. Dicyclohexylurea was filtered and washed with 50% aqueous methanol (50 ml). The combined filtrate and washings were stirred with Dowex-1 (OH^-) (20 ml) for 10 min and filtered. The filtrate was stirred with Amberlite IRC-50 (H^+) for 30 min, filtered, and washed with 50% methanol. The combined filtrate and washings were evaporated to *ca.* 75 ml and left overnight at room temperature. The precipitate (probably *N*-Cbz-D-seryl dicyclohexylurea according to nmr and ir) was filtered and the filtrate was evaporated to dryness. The residue was coevaporated several times with ethanol until colorless microcrystals were obtained: 1.78 g (71%); mp 166–170°; $[\alpha]D$ +27° (0.9, 1:2 EtOH–H_2O); nmr (DMSO) H-6, δ 7.70 (1 H, d), aromatic, 7.38 (5 H, s), H-5, 5.95 (1 H, d), H-1′, 5.60 (1 H, d), benzyl CH_2, 5.10 (2 H, s).

Anal. Calcd for $C_{21}H_{27}O_9N_5 \cdot H_2O$: C, 49.31; H, 5.71; N, 13.69. Found: C, 49.58; H, 5.55; N, 14.23.

1-[4-Deoxy-4-(D-seryl)amino-β-D-glucopyranosyl]cytosine (4a).—Compound **3a** (1.41 g) was dissolved in a mixture of water (45 ml) and ethanol (10 ml) and the mixture was shaken for 15 min in a hydrogen atmosphere (initial pressure of about 2 atom) in the presence of *ca.* 250 mg of 10% palladium on carbon. The catalyst was filtered and washed with water. The combined filtrate and washings were evaporated to dryness. The residue was treated with hot ethanol for 10–15 min until microcrystals were obtained; yield 960 mg (96%). The compound did not have a definite melting point but browned at 243° and decomposed at 271–274°: $[\alpha]D$ +29° (0.8, H_2O); nmr (D_2O) H-6, δ 7.73 (1 H, d), H-5, 6.08 (1 H, d), H-1′, 5.68 (1 H, d).

Anal. Calcd for $C_{13}H_{21}O_7N_5 \cdot {}^1/_2H_2O$: C, 42.39; H, 6.02; N, 19.01. Found: C, 42.13; H, 5.79; N, 18.78.

1-[4-Deoxy-4-(*N*-benzyloxycarbonylsarcosyl-D-seryl)amino-β-D-glucopyranosyl]cytosine (5a).—Compound **4a** (720 mg, 2 mmol) was treated with *N*-benzyloxycarbonylsarcosine (890 mg, 4 mmol) and DCC (880 mg) in a mixture of water (1.5 ml) and acetonitrile (6 ml) for 20 hr. Dicyclohexylurea was filtered and washed with 3:7 methanol–water (50 ml). To the filtrate and washings was added acetonitrile (*ca.* 15 ml) until a clear solution was obtained. Dowex-1 (OH^-) (5 ml) was added to the solution and stirred for 5 min and the resin was washed with 3:7 methanol–water (25 ml). The combined filtrate and washings were treated with Amberlite IRC-50 (H^+) (10 ml) for 15 min and filtered. The filtrate was evaporated to dryness and the residue was partitioned between water (70 ml) and chloroform (30 ml). The insoluble solid and chloroform layer were discarded. The aqueous layer was evaporated and the residue was co-evaporated with ethanol until colorless microcrystals were obtained. The yield of the product was 784 mg (71%): mp 163–166° (eff without coloring) and dec 236–239°; $[\alpha]D$ +35° (*c* 1.1, 1:2 EtOH–H_2O); nmr (DMSO) H-6, δ 7.63 (1 H, d), aromatic, 7.35 (5 H, s), H-5, 5.80 (1 H, d), H-1′, 5.57 (1 H, d), benzyl CH_2, 5.07 (2 H, s), NCH_3, 2.88 (3 H, s).

Anal. Calcd for $C_{24}H_{32}O_{10}N_6 \cdot {}^1/_2C_2H_5OH \cdot 1{}^1/_2H_2O$: C, 48.85; H, 6.23; N, 13.67. Found: C, 49.13; H, 6.31; N, 13.91.

1-[4-Deoxy-4-(sarcosyl-D-seryl)amino-β-D-glucopyranosyl]cytosine (6a).—Compound **5a** (400 mg) was dissolved in 1:3

(15) T. Yusupov, A. B. Zegelman, L. Radzhabov, and K. T. Poroshin, *Dokl. Akad. Nauk Tadzh SSR*, **11**, 22 (1968); *Chem. Abstr.*, **70**, 115545u (1969).

ethanol–water (40 ml) and hydrogenated in the presence of *ca.* 200 mg of 10% palladium on carbon catalyst for 15 min with the initial pressure of about 2 atm. The catalyst was filtered and washed with water. The combined filtrate and washings were evaporated to dryness, and then the residue was evaporated several times with ethanol until colorless microcrystals were obtained. After drying overnight at 78° *in vacuo*, 287 mg (92%) of product was obtained: mp 136° (sintered) 210–250° dec; $[\alpha]_D$ +44° (*c* 0.6, H_2O), nmr (D_2O) H-6, δ 7.77 (1 H, d), H-5, 6.03 (1 H, d), H-1′, 5.67 (1 H, d), NCH_3, 2.79 (3 H, s).

Anal. Calcd for $C_{16}H_{26}O_8N_6 \cdot H_2O$: C, 42.86; H, 6.29; N, 18.74. Found: C, 43.13; H, 6.36; N, 18.73.

1-[4-Deoxy-4-(sarcosyl-DL-seryl)amino-β-D-glucopyranosyl]-cytosine [mp 172–189° dec, $[\alpha]^{23}_D$ +11° (*c* 0.8, H_2O)] was synthesized from **1**, *N*-Cbz-DL-serine, and *N*-Cbz-sarcosin by the same procedure used for the preparation of **6a**.

Hydrolysis of Compound 6a and Isolation of D-Serine.—Compound **6a** (980 mg) was dissolved in 6 *N* HCl (50 ml) and refluxed gently for 24 hr. After concentration *in vacuo* the residue was taken up in water (50 ml) and passed through a column of Dowex-1 (OH^-) (2.6 × 9.6 cm). The column was washed with water (2 l.) to remove compound **1**. The amino acids were eluted from the column with 1 *N* HCl (100 ml). The acid eluate was evaporated to dryness and the residue was dissolved in a small amount of water and passed through a column of Amberlite IR-45 (OH^-) (2.6 × 10 cm) to remove hydrogen chloride. The column was washed with water (200 ml) and the effluent was evaporated to dryness. Crude D-serine (106 mg) was crystallized from the residue from methanol (5 ml). One recrystallization of the crude product from water–ethanol gave colorless needles: mp 216–217° dec; $[\alpha]^{23}_D$ +7° (*c* 1, H_2O); $[\alpha]^{23}_D$ −14° (*c* 0.9, 1 *N* HCl). The authentic D-serine, mp 214–215° dec, showed the identical optical rotations under the same conditions.

Both the methanolic and water–ethanol mother liquors of the crystallizations were combined and applied to two sheets of Whatman #1 paper (46 × 57 cm) and developed with 88% phenol. The serine bands were extracted with water and evaporated to dryness. The residue (34.7 mg) showed $[\alpha]^{23}_D$ −13° (*c* 0.9, 1 *N* HCl).

Degradation of Compound 6b and Characterization of D-Alanine.—Compound **6b** (890 mg) was hydrolyzed and D-alanine was obtained after essentially the same processing for the isolation of D-serine from compound **2a**. The crude residue from the Amberlite IR-45 column was taken up in 3 ml of water and applied to two sheets (46 × 57 cm) of Whatman #1 paper, developed with 88% phenol, and the alanine bands were eluted with water and evaporated to dryness. The residue (125 mg) had $[\alpha]_D$ −10° (*c* 1, 6 *N* HCl). One recrystallization of the crude sample gave pure D-alanine (65 mg), $[\alpha]_D$ −12° (*c* 1, 6 *N* HCl).

Registry No.—**3a**, 33780-67-5; **3b**, 33780-68-6; **3c**, 33780-69-7; **4a**, 33780-70-7; **4b**, 33780-71-1; **4c**, 33780-72-2; **5a**, 33780-73-3; **5b**, 33780-74-4; **5c**, 33780-75-5; **6a**, 31883-24-6; **6b**, 33780-77-7; **6c**, 33780-78-8; 1-[4-deoxy-4-(sarcosyl-DL-seryl]amino-β-D-glucopyranosyl]cytosine, 33780-79-9; D-serine, 312-84-5; D-alanine, 338-69-2.

Dioldithiol Analogs of the 1,2,4,5-Cyclohexanetetrols. Chemical and Nuclear Magnetic Resonance Studies[1,2]

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Reaction of 1,4-cyclohexadiene dioxide (cis–trans mixture) with sodium benzylmercaptide gave a mixture from which were isolated three of the four expected isomers of dibenzylmercaptocyclohexanediol. The two possible structures for each product were 4,6-dibenzylmercapto-1,3-cyclohexanediol (**2**) and 2,5-dibenzylmercapto-1,4-cyclohexanediol (**4**). For each structure, one meso and one DL diastereomer (**12** and **8**, or **9** and **10**) would be predicted. For the molecules of either meso isomer, only one (tetraequatorial) chair conformation (**14** or **16**) is predicted. The DL isomer molecules, however, should each be diaxial–diequatorial (**13a** or **15a**) and readily transformed by ring inversion into alternate chair conformations (**13b** or **15b**) indistinguishable from the original. This analysis permitted nmr spectral assignments based on (1) presence of time-averaging effects (DL isomers only); (2) equivalence between corresponding methylene protons at positions 3 and 6 (para isomers only). The assignments are para-DL (14/25), mp 92°; para-meso (15/24), mp 158°; meta-DL (14/36), mp 109°; meta-meso (13/46), unknown. The mp 109° isomer identity was confirmed by chemical correlation with the known *trans*-1,3-cyclohexanediol.

We wish to report nmr configurational proofs for the family of four trans-trans dioldithiols which are analogous to 1,2,4,5-cyclohexanetetrol and derived from 1,3- or 1,4-cyclohexanediol (see formulas **8**, **9**, **10**, and **12**, Scheme I). This family of structural and stereoisomers provides an interesting example of nmr configurational assignments based on conformational analysis and nmr spectroscopy. A similar study on the parent tetrols was previously reported by one of us.[5] Although only the di-*S*-benzyl derivatives were actually examined, the structures and configurations of the parent dioldithiols can now be easily established by simple chemical correlations.[6]

The synthetic and nmr studies here reported are part of a program for preparation of cyclitols and other carbohydrates[7] in which most or all of the oxygen functions will be replaced by sulfur functions (see Acknowledgment).[2b]

(1) Presented to the Division of Organic Chemistry at the 159th National Meeting of the American Chemical Society, Houston, Texas, Feb 1970.

(2) (a) Paper XXXVIII on Alicyclic Carbohydrates; for paper XXXVII, see N. Kurihara, Y. Sanemitsu, M. Nakajima, G. E. McCasland, and L. F. Johnson, *Agr. Biol. Chem.*, **35**, 71 (1971). For paper XXXVI, see G. E. McCasland, M. O. Naumann, and Lois J. Durham, *J. Org. Chem.*, **34**, 1382 (1969). (b) For preceding publication on thio carbohydrates, see G. E. McCasland and A. B. Zanlungo, *Carbohyd. Res.*, **17**, 475 (1971). (c) For preceding paper on (nonalicyclic) carbohydrates, see A. E. Lipska and G. E. McCasland, *J. Appl. Polym. Sci.*, **15**, 419 (1971).

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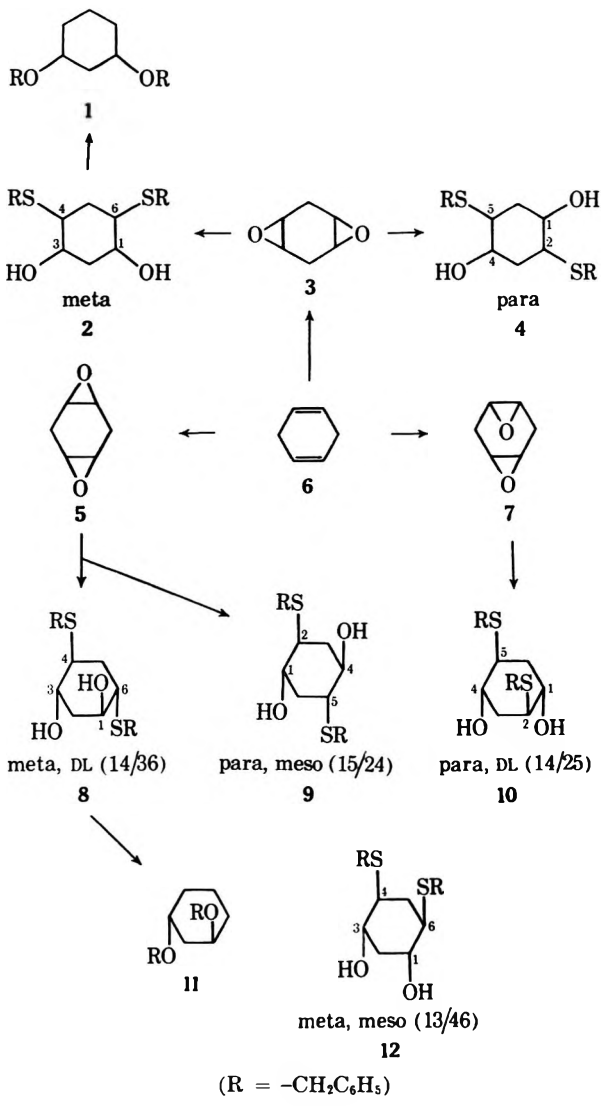
(5) For studies on the 1,2,4,5-cyclohexanetetrols, see G. E. McCasland, S. Furuta, L. F. Johnson, and J. N. Shoolery, *J. Org. Chem.*, **28**, 894 (1963).

(6) A benzylmercaptocyclohexane is easily converted to a mercaptocyclohexane, with retention of configuration, by reaction with sodium in liquid ammonia. See G. E. McCasland, S. Furuta, and A. Furst, *ibid.*, **29**, 724 (1964), for application of this reaction to mercaptodeoxyinositol derivatives.

(7) A report on sulfur analogs of D-iditol and D-mannitol was presented by G. E. McCasland and A. B. Zanlungo to the Division of Carbohydrate Chemistry at the 160th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1970. See also G. E. McCasland and A. B. Zanlungo, *Carbohyd. Res.*, **17**, 475 (1971).

Scheme I



Reaction of 1,4-cyclohexadiene dioxide[8] (**3**) with sodium benzylmercaptide in methanol replaced each epoxy group with the pair of groups, –OH and $-SCH_2-C_6H_5$. The two hydroxyl groups necessarily are meta or para; likewise the two benzylmercapto groups (see formulas **2** and **4**).

Since trans opening of epoxide rings by nucleophiles is assumed, the cis dioxide **7** should produce isomers **10** and **12**; the trans dioxide **5**, isomers **8** and **9**. For convenience, the dioxide[8] actually used was a cis–trans mixture[8] (64% trans). The three products actually isolated have mp 92, 109, and 158°.

The fourth predicted isomer, **12**, has not been obtained. For steric reasons, the yield of **12** may be very small. This diastereomer, once formed, should be quite stable in its all-equatorial conformation **16**. We believe, however, that in the nucleophilic attack on the *second* epoxy group of the dioxide **7** there would be strong steric repulsion between the benzylmercaptide ion attempting to enter at position 6 (formula **12**) and the benzylmercapto group already present at position **4**. In the transition state, these two large groups should have almost a 1,3-diaxial relationship. Similar steric effects have previously been noted by one of us in the formation of tetrol tetrabenzoates from 1,4-cyclohexadiene and silver benzoate (Prevost reaction).[9]

Structures, Configurations, and Conformations.—A large number of structural and stereoisomers are possible for any tetrasubstituted cyclohexane of the general type $C_6H_8A_2B_2$ or $C_6H_8A_2BC$. Since the compounds here reported are derived from 1,4-cyclohexadiene, the substituents are limited to ring positions 1, 2, 4, and 5.[10] Because of the reactions employed, only the "trans–trans" configurations need be considered for the products. In the case of the 1,2,4,5-cyclohexanetetrols[5] or tetrathiols,[11] only two trans–trans configurations are possible, *i.e.*, meso (15/24) and DL (14/25); compare the formulas **9** and **10**. The substitution type for the tetrols and tetrathiols is $C_6H_8A_4$. With four substituents in the substitution type $C_6H_8A_2B_2$, two trans–trans configurations are possible for the meta structure, and two different trans–trans configurations for the para structure (see formulas **12**, **8**, **9**, and **10**).

The isomer meta-meso (13/46), **12**, would be optically inactive, because its molecule in the conformation **16** has a plane of symmetry (see Scheme II). Since it has no axis of symmetry, the point group is C_s. The isomer para-meso (15/24), **9**, is inactive, because in the conformation **14** it has a center of symmetry but no plane or axis of symmetry (point group C_i).

For convenience, the stereoformulas in Schemes I and II depict only one enantiomer of each racemic product. The para (14/25) enantiomer depicted in formula **13a** has a nonsuperposable mirror image (not shown); on ring inversion the molecule is converted to **13b**, which is indistinguishable from the original. The formulas **15a** and **15b** for one of the meta (14/36) enantiomers have a similar relationship.

Nmr Configurational Proofs for the Four Dibenzylmercaptocyclohexanediols.—The spectrum of each isomer was first examined to see if the two protons in one ring methylene were respectively equivalent to those in the other. If so, the para structure **13a,b** or **14** must be present. If not, the meta structure **15a,b** or **16** was indicated. (In the meta isomer **15a,b**, the two protons within each ring methylene are geometrically equivalent only to each other; in the meta isomer **16**, there is no equivalence at all within the set of four methylene protons.)

The spectrum was next examined to see if the four O–C–H and S–C–H protons were strictly axial or a time average of axial and equatorial. This was apparent from the magnitudes of the chemical shifts and coupling constants. The presence of time averaging pointed to the DL configuration **13a,b** or **15a,b**; its absence to the meso configuration **14** or **16**.

These observations provided information necessary and sufficient to classify each isomer as (1) para and meso; (2) para and DL; (3) meta and meso; or (4) meta and DL.

Nmr Spectrum of the Mp 158° Isomer (Para-Meso).—Time averaging due to ring inversion was not observed; the four O–C–H and S–C–H protons were strictly axial (formula **14**).

(8) T. W. Craig, G. R. Harvey, and G. A. Berchtold, *J. Org. Chem.*, **32**, 3745 (1967).

(9) (a) Reference 5, p 897; (b) see also G. E. McCasland and E. C. Horswill, *J. Amer. Chem. Soc.*, **76**, 1654 (1954).

(10) Note that the position numbers for the meta isomers are 1, 3, 4, 6 (*Chemical Abstracts*) not 1, 2, 4, 5.

(11) G. E. McCasland, A. K. M. Anisuzzaman, S. R. Naik, and Lois J. Durham, unpublished results.

The O–C–H signal (3.84 ppm) was a triplet of doublets, due to couplings (large, large, small) with the two axial and one equatorial neighboring protons. The coupling pattern and coupling constant magnitudes of about 10–11 Hz show that the two O–C–H protons are axial and that there is little or no ring inversion.

The two equivalent S–C–H protons (maximum of eight lines expected) appeared actually as a seven-line multiplet centered at 2.92 ppm, due to coincidence of the two center lines. The spacings were 13, 10, and 4 Hz, due to couplings with the two axial and one equatorial neighboring protons. The two equivalent equatorial methylene protons produced a perturbed six-peak pattern (approximately a pair of triplets) centered at 2.64 ppm, with spacings of 4, 4, and 13 Hz. This pattern almost overlapped the S–C–H pattern at 2.92 ppm.

The two equivalent axial methylene protons produced a high-field six-line multiplet at approximately 1.86 ppm, with spacings of 13, 13, and 11 Hz, due to coupling with the one geminal and two neighboring axial protons.

The presence of the four equivalent sets of ring protons points strongly to the centrosymmetric molecule **14**. The coupling patterns are consistent with the para structure **9** and all-equatorial conformation.

Nmr Spectrum of the Mp 92° Isomer (Para-DL).—Time averaging of the signals, due to ring inversion, was observed. The pattern of the two-equivalent O–C–H protons appeared at 3.75 ppm, where it was partly obscured by a large peak at 3.74 ppm assigned to *S*-methylene.

Signals for the two equivalent S–C–H protons appeared as a 1:3:3:1 quartet with 6-Hz spacing at about 2.84 ppm suggesting averaging by ring inversion.

The ring methylene signals in the region 1.9–2.1 ppm consisted apparently of at least two overlapping multiplets. The complexity of these methylene multiplets results from the fact that, even with rapid ring inversion, the geminal protons within each methylene do not become equivalent. The result of averaging is rather to equate H_{3a} in conformation **13a** to H_{6a} in **13b**, and H_{3e} of **13a** to H_{6e} of **13b**, since the relative orientations of the flanking groups also change during ring inversion. For example, in **13a**, H_{3a} is flanked by equatorial OH and axial SR, but after ring inversion to **13b**, it becomes H_{3e}, which is flanked by axial OH and equatorial SR. The spectrum points to the para structure and the DL (14/25) configuration (formula **10** or **13a,b**).

Nmr Spectrum of the Mp 109° Isomer (Meta-DL).—The pattern of the two equivalent O–C–H protons appeared at 3.83 ppm, as a 1:3:3:1 quartet with splitting of 5–6 Hz, broadened by coupling to the OH signals. One quartet line was partly obscured by the *S*-methylene signal at 3.69 ppm.

Signals for the two (equivalent) S–C–H protons were observed at 2.80 ppm (1:3:3:1 quartet, splitting 6 Hz). The O–C–H and S–C–H regions were thus similar to those in the para-DL spectrum. The appearance of both the O–C–H and S–C–H signals as quartets was taken as evidence for averaging of the axial and equatorial protons in these positions by ring inversion.

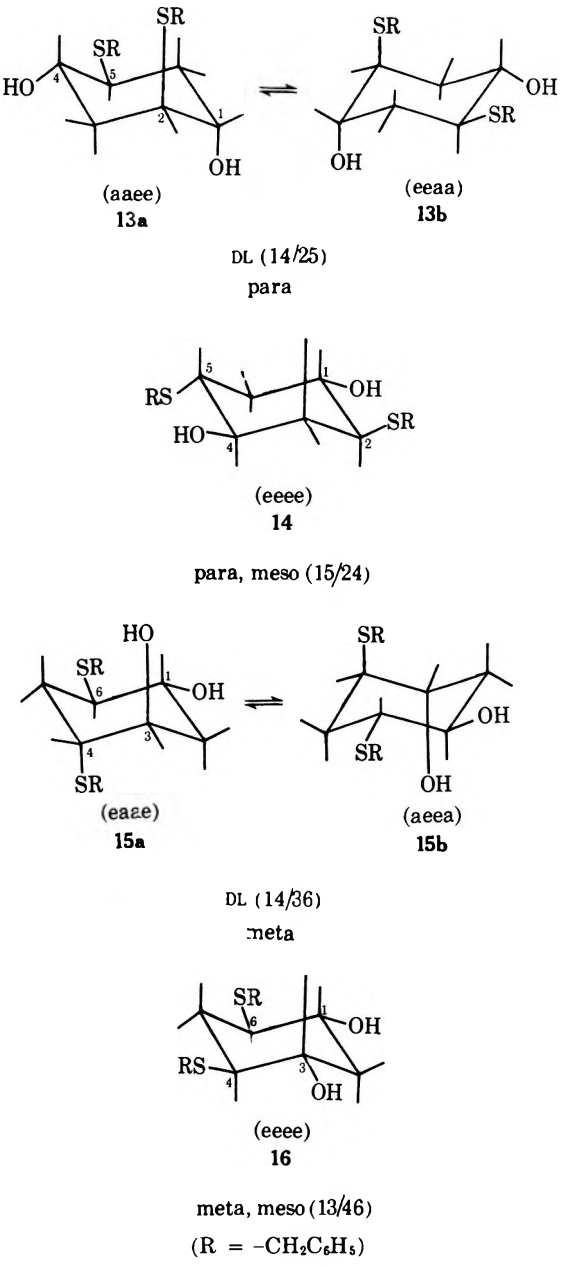
However, the ring methylene region was different from that of the other two isomers. This region consisted of two triplets centered at 1.93 and 2.04 ppm. At 100 MHz one line from each triplet coincided; at 60 MHz, two lines, giving an apparent quartet. The molecule thus must have two nonequivalent ring methylene groups, each of which averages to a triplet upon rapid ring inversion. This agrees with the meta structure, in which one methylene is flanked by axial and equatorial hydroxyl, the other by axial and equatorial –SR. Ring inversion averages the two methylene protons at each position between axial and equatorial, giving an average splitting.

The spectrum points to the meta structure and DL (14/36) configuration, formula **8** or **15a,b**.

Unknown Isomer (Meta-Meso).—By elimination, the remaining isomer obtainable from 1,4-cyclohexadiene dioxide (cis–trans mixture, or pure cis) should have the meta structure and meso (13/46) configuration, formula **12** or **16**.

Confirmation by Chemical Correlation.—The mp 109° isomer of dibenzylmercaptocyclohexanediol on treatment with Raney nickel catalyst in boiling ethanol

SCHEME II



was debenzylated and the sulfur removed, giving the previously known DL-*trans*-1,3-cyclohexanediol, characterized as the dibenzoate[12] **1** or **11** (R = $-COC_6H_5$), mp 124°. This chemical correlation confirms the structure and configuration, meta-DL (14/36), **8** or **15a,b**, based on nmr studies.

Other Features of the Nmr Spectra of the Dibenzylmercaptocyclohexanediols.—Signals from the ten aromatic protons in each compound were found at about 7.3 ppm.

In all three isomers, the two *S*-methylene groups were geometrically equivalent; however, the two protons *within* each *S*-methylene group were not geometrically equivalent. In the mp 158° isomer, the two protons within each *S*-methylene had distinctly different chemical shifts, resulting in an AB pattern, centered at 4.13 ppm (J = 13 Hz). In the mp 92° and mp 109° isomers, however, an apparent singlet was observed for *S*-methylene even at 100 MHz, due to accidental equality of the chemical shifts.

The hydroxyl protons in each isomer produced signals at about 2.15 ppm, using chloroform-*d* as solvent, which collapsed on addition of deuterium oxide (HDO peak appeared at 4.65 ppm). With pyridine, no OH signal was observed, due to exchange.

Experimental Section

All melting points have been corrected and were measured with a Nalge-Axelrod micro hot-stage. Microanalyses were performed by the Micro-Tech Laboratories, Skokie, Ill. The calculated[13] microanalyses, molecular weights, and per cent yields are taken from a computer printout. Found oxygen values are by difference. Infrared spectra were recorded on a Perkin-Elmer Model 337 spectrometer. Nmr spectra were recorded on a Varian A-60D spectrometer at the University of San Francisco or on a Varian HA-100 spectrometer at Stanford. Unless otherwise noted, chloroform-*d* was used as nmr solvent, and chemical shifts were reported in parts per million downfield from tetramethylsilane taken as internal reference. Product purity was confirmed where noted by thin layer chromatography on silica gel coated glass plates.[14a] Evaporations were conducted under reduced pressure with bath temperatures below 40°.

Meso (15/24) Diastereomer, Mp 158°, of (Para) 2,5-Dibenzylmercapto-1,4-cyclohexanediol (9).—Benzyl mercaptan (8.0 g) was added to a solution of 0.60 g of sodium metal in 20 ml of dry methanol under dry nitrogen. To this mixture was added a solution of 1.30 g of 1,4-cyclohexadiene[14b] dioxide (mixture about 64% trans, 36% cis)[8] in 60 ml of dry methanol. A higher yield could probably be obtained by using the pure cis dioxide as starting material.

The mixture was boiled under reflux for 20 hr (dry nitrogen), cooled, and mixed with 200 g of ice–water, and the resulting mixture was extracted with ether. The extract was washed with water, dried, and evaporated. The crystalline residue was purified by chromatography on a silica gel column. The column was eluted with chloroform to remove excess benzyl mercaptan. Elution with chloroform–acetone (15:1) then yielded the desired product: 200 mg (4.8%); mp 157–158°, after recrystallization from benzene; colorless crystals; infrared maximum (KBr) 3250, 3350 cm^{-1} (OH stretch). The nmr spectrum was recorded at 60 and 100 MHz (see discussion).

Anal. Calcd for $C_{20}H_{24}O_2S_2$ (360.538): C, 66.628; H, 6.710; O, 8.875; S, 17.787. Found: C, 66.56; H, 6.68; (O, 8.79); S, 17.97.

DL (14/25) Diastereomer, Mp 92°, of (Para) 2,5-Dibenzylmercapto-1,4-cyclohexanediol (10).—After elution of the para-meso (15/24) isomer (see above), the silica gel column was further eluted with chloroform–acetone (15:1). On evaporation of this eluate, there was obtained 3.0 g (72%) of an isomer melting at 91–92° after recrystallization from ether–hexane: colorless crystals; infrared maximum (KBr) 3400 cm^{-1} (OH stretch). The nmr spectrum was recorded at 60 and 100 MHz (see discussion).

Anal. Calcd for $C_{20}H_{24}O_2S_2$ (360.538): C, 66.628; H, 6.710; O, 8.875; S, 17.787. Found: C, 66.80; H, 6.66; (O, 8.83); S, 17.71.

DL (14/36) Diastereomer, Mp 109°, of (Meta) 4,6-Dibenzylmercapto-1,3-cyclohexanediol (8).—After elution of the para-DL (14/25) isomer (see above), the silica gel column was eluted further with chloroform–acetone (15:1). On evaporation of this eluate there was obtained 630 mg (15%) of an isomer melting at 108–109° after recrystallization from diethyl ether: infrared maximum (KBr) 3275 cm^{-1} (OH stretch). The nmr spectrum was recorded at 60 and 100 MHz (see discussion).

Anal. Calcd for $C_{20}H_{24}O_2S_2$ (360.538): C, 66.628; H, 6.710; O, 8.875; S, 17.787. Found: C, 66.92, H, 6.84; (O, 8.58); S, 17.66.

A higher yield of the mp 109° product could probably be obtained by using the pure trans dioxide in the reaction with sodium benzylmercaptide.

Chemical Correlation of the Dibenzylmercaptocyclohexanediol Isomer, Mp 109°, with DL-*trans*-1,3-Cyclohexanediol Dibenzoate (11).—A mixture of 102 mg of the meta-DL (14/36) isomer, mp 108–109°, with 20 ml of ethanol and about 2.0 g of Raney nickel catalyst was boiled under reflux for 5 hr. The catalyst was removed by filtration and the filtrate evaporated, giving 40 mg of a colorless syrup. This syrup was dissolved in 0.60 ml of pyridine, and 0.20 ml of benzoyl chloride was added with stirring. After 2 days, the mixture was stirred with 20 g of ice–water. The oil which separated was taken up in chloroform, and the extract was washed with sodium bicarbonate solution and with water. The dried extract on evaporation yielded a syrup, which on treatment with benzene–hexane gave 60 mg (65%) of colorless crystals, mp 123–124° after recrystallization from methanol (reported[12] mp 124°). A mixture melting point with an authentic sample[12] was not depressed, and the infrared spectra were identical.

Registry No.—DL (14/25), 33536-56-0; DL (14/36), 33536-57-1; meso (15/24), 33536-58-2.

Acknowledgment.—This research was made possible by a grant (AM-11433) from the National Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service. The 100-MHz nmr spectra were recorded and interpreted with the help of Dr. Malcolm R. Bramwell, Stanford University. We would like to thank Professor L. N. Owen (Imperial College of Science and Technology, University of London) for an authentic sample of *trans*-1,3-cyclohexanediol dibenzoate. Use of the IBM 360/67 computer system[13] at the Stanford University Campus Facility was supported by a Regional Network Grant from the National Science Foundation to the University of San Francisco (James N. Haag, Principal Investigator). We would like to thank Professor Haag and the Campus Facility consultants for helpful assistance. The Varian A-60D nmr spectrometer used was purchased with the help of a grant from the National Science Foundation to the University of San Francisco.

(12) M. F. Clarke and L. N. Owen, *J. Chem. Soc.*, 2105 (1950).

(13) One of us (G. E. M.) has written a computer program which is very convenient for printing out molecular formulas, molecular weights, and calculated elementary analyses for any elements over specified ranges. For example, for the present article it provided a 143-page table covering the ranges C, 6–36; H, 6–48; O, 0–12; and S, 0–9. By limiting the ranges, the execution time is kept to a reasonable value. Use of the ranges mentioned involved performing more than 150,000 calculations; the execution time was about 68 sec (IBM 360/67, WATFIV, Quick Partition).

(14) The reagents mentioned were products of (a) Mallinckrodt Chemical Works, New York, N. Y.; (b) Chemical Samples Co., Columbus, Ohio.

Neighboring-Group Effects on the Proton Chemical Shift of the *tert*-Butyl Group. Rotational Conformations in the Diastereomers of 1,3-Di-*tert*-butylpropargyl 2-Phenylpropionate

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The proton nmr spectra of 1,3-di-*tert*-butylpropargyl alcohol (1) and 11 derivatives and *tert*-butyl-containing model compounds have been examined in an attempt to assign the chemical shifts of the two *tert*-butyl resonances in 1. It was found that, in the absence of "special effects," the ethynyl *tert*-butyl absorption (EBu) fell at lower field (δ 1.23 ± 0.02) than the alkyl *tert*-butyl resonance, ABu (δ 0.97 ± 0.03), in these compounds, and this has been interpreted as an experimental determination of the shielding and deshielding regions surrounding the triple bond. The "special effects" include long-range shielding by a benzene ring, which is manifested in the tosylate of 1 and in 2,4,4-trimethyl-2-(*p*-hydroxyphenyl)pentane. The reaction of 1 with 2-phenylpropionoyl chloride (7) in pyridine led to a mixture of two (enantiomeric pairs of) diastereomers of 1,3-di-*tert*-butylpropargyl 2-phenylpropionate (8) in nearly equal amounts. One of these (pairs), A, has a normally positioned ABu and a shielded EBu, while the other (B) has a normal EBu and a shielded ABu. The reaction of (*R*)-(+)-1 with (*S*)-(+)-7 (both of known enantiomeric purity) led to (*RS*)-(+)-8, which was identified with B. Thus the *RR*, *SS* pair corresponds to A. A simple statistical model that allows calculation of relative amounts of each of the four stereoisomers produced in such a reaction is presented and found to give reasonable agreement with experiment. The differences in the pmr spectra of A and B are explained on the basis of opposite preferences in the rotational conformations of A and B allowing, on the time average, selective shielding of the EBu in A and the ABu in B by the remote aromatic ring.

During the course of our studies involving the 1,3-di-*tert*-butylpropargyl system[1,2] it became necessary to unambiguously assign the *tert*-butyl resonances in the proton nmr spectrum of 1,3-di-*tert*-butylpropargyl alcohol (1).[1-3] One approach to the problem seemed to be comparison of the chemical shifts found for 1 with those of similarly constituted model compounds, but unfortunately few such data were available in the literature. Thus we undertook measurements on several known and some new compounds, the results of which are presented, together with several literature values, in Table I. The chemical shifts of the *tert*-butyl resonances in these compounds were, as expected, quite insensitive to concentration and nature of the solvent (less than 0.03 ppm upon changing from deuteriochloroform to carbon tetrachloride) in support of the meaningfulness of these comparisons.

It is immediately tempting to assign the higher field resonance of 1 (δ 0.95) to the alkyl *tert*-butyl group (ABu) and the lower field absorption (δ 1.22) to the ethynyl *tert*-butyl group (EBu), because the latter matches the value for *tert*-butylacetylene, which in turn is 0.28 ppm to lower field than that of neopentane. Substitution of an acetoxy group (2) for the hydroxyl in 1 has essentially no effect on the ABu and EBu chemical shifts, an observation that will become important later. The methyl-bearing derivative (3) of 1 further serves to establish the trends in chemical shifts: the EBu absorptions occur at δ 1.23 ± 0.02, while ABu falls in the region δ 0.97 ± 0.03. Tri-*tert*-butylpropargyl alcohol (4) unambiguously confirms the $\delta_{EBu} > \delta_{ABu}$ ordering with an 18-proton singlet at δ 1.13[4] and a 9-proton singlet at δ 1.24.

The assignment $\delta_{EBu} > \delta_{ABu}$ has a further consequence. Induced diamagnetic electron circulation in the carbon–carbon triple bond is believed to account for the *shielded* nature of acetylenic protons and presumably other groups situated *on or near* the internuclear axis of the triple bond. However, comparison of the second and fourth entries in Table I would suggest that an EBu is *deshielded* by *ca.* 0.25 ppm with respect to a saturated analog (*e.g.*, the ABu). This enables one to experimentally locate the "lines" of induced magnetic flux density surrounding the triple bond in such a way that the *tert*-butyl protons experience, on the time average, a net *deshielding* effect (Figure 1). This model can be contrasted with the results of semiempirical calculations. An early approach,[5] which treated the triple bond as a point dipole located at the midpoint of the bond, suggested that the volume surrounding the triple bond be bifurcated into shielding (+) and deshielding (−) regions as shown by the dashed lines in Figure 1. More recently Pople and Untch[6] used a model which locates point dipoles at each end of the triple bond, giving rise to eq 1.

$$\Delta\sigma = \Delta\chi \sum_n \frac{1-3\cos^2\theta_n}{3R_n^3} \qquad (1)$$

Clearly the former treatment incorrectly predicts that the EBu protons should lie within the shielding region. A calculation with eq 1 using values[6] of $\Delta\chi = -1.96 \times 10^{-5}$ Å^3, $R_1 = 2.78$ Å, $\theta_1 = 140°$, $R_2 = 3.80$ Å, and $\theta_2 = 151.5°$ (these values representing the rotationally averaged position of the EBu protons, shown by the asterisk in Figure 1) also predicts a 0.39-ppm shielding effect, again in contrast to our observation. It seems quite unlikely that the observed deshielding could result from a long range effect of the electronegative sp-hybridized carbon atom. Intermediate between an acetylenic proton and those in an EBu is the situation of a methyl group attached to a triple

(1) R. S. Macomber, *Tetrahedron Lett.*, 4639 (1970).
(2) R. S. Macomber, *J. Org. Chem.*, **36**, 2713 (1971).
(3) E. J. Corey and W. T. Borden, *Tetrahedron Lett.*, 313 (1969).
(4) The downfield shift of the ABu absorptions in 4 can be attributed in part to the increased *s* character in the *C-tert*-butyl bonds caused by the "spreading" steric interaction between the two geminal *tert*-butyl groups, and in part to the movement of the ABu groups into the deshielding region of the triple bond (*vide infra*).
(5) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959.
(6) J. A. Pople and K. G. Untch, *J. Amer. Chem. Soc.*, **88**, 4811 (1966). The value given here for $\Delta\chi$ (-11.8×10^{-6} cm^3/mol) is equivalent to the one used in the present calculations.

TABLE I

CHEMICAL SHIFTS OF THE *tert*-BUTYL RESONANCES OF 1 AND MODEL COMPOUNDS[a]

Compound	Solvent	ABu	EBu	Ref
tert-BuC≡C—CHOH-*tert*-Bu (1)	CCl_4 ($CDCl_3$)	0.95 (0.97)	1.22 (1.22)	*b*
$(CH_3)_4C$		0.94		*c*
tert-$BuCH_2OH$	CCl_4	0.88		*b*
tert-BuC≡CH	CCl_4 (neat)		1.22 (1.22)	*b*
tert-BuC≡CCH($OCOCH_3$)-*tert*-Bu (2)	CCl_4	0.95	1.21	*d*
tert-BuC≡CC(OH)(CH_3)-*tert*-Bu (3)	CCl_4	1.00	1.22	*e*
tert-BuC≡CC(OH)(*tert*-Bu)$_2$ (4)	CCl_4	1.13	1.24	*f*
tert-BuC≡CCH(OTs)-*tert*-Bu (5)	CCl_4	1.00	1.00	*b*
p-$HOC_6H_4C(CH_3)_2CH_2$-*tert*-Bu	$CDCl_3$	0.72		*g*
A	CCl_4	0.92	1.13	*b*
B	CCl_4	0.79	1.21	*b*
o-$HOOCC_6H_4CO_2CH$(*tert*-Bu)C≡C-*tert*-Bu	CCl_4	1.05	1.25	*b*

[a] Shift values (60 MHz) in parts per million downfield from internal TMS. [b] Present study. [c] L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959. [d] Reference 1. [e] This compound was prepared in our laboratories using a published procedure: A. I. Zehkarova and G. M. Murashov, *Zh. Obshch. Khim.*, **23**, 1981 (1953). [f] The full details of the synthesis of this compound will appear later in connection with another study. [g] Varian Associates, "High Resolution NMR Spectra Catalog," spectrum 315.

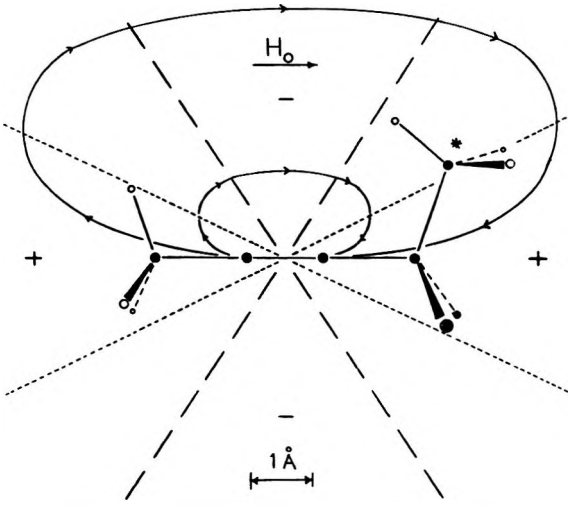
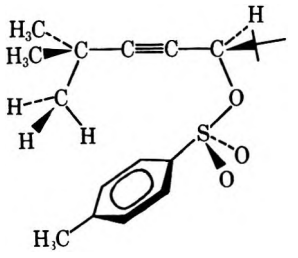


Figure 1.—Geometric model for the shielded (+) and deshielded (1) regions surrounding a carbon–carbon triple bond substituted on the left with a methyl group and on the right by a *tert*-butyl group. ● = carbon, ○ = hydrogen; bond lengths and angles are scaled to published values (J. March, "Advanced Organic Chemistry," McGraw-Hill, New York, N. Y., 1968). Dashed lines show the previously calculated regions;[5] dotted lines demarcate the experimentally verified regions. The asterisk locates the average position of the EBu protons.

bond, which appears at δ 1.80,[7] reflecting *net* deshielding. It is difficult to say whether this results from long range *deshielding* by the triple bond, through bond deshielding by the sp carbon atom, or the latter effect coupled with compensating *shielding* by the triple bond. Equation 1 predicts a shielding contribution of 0.69 ppm, but this would require through-bond sp deshielding of 1.6 ppm to account for the observed resonance at 1.80. Our model places the methyl protons very near the lines separating the shielded and deshielded regions (dotted lines in Figure 1). It is perhaps also significant that the ABu in 1 occurs 0.07 ppm to lower field than the ABu in neopentyl alcohol. This too may be due to triple bond deshielding in the former, but the magnitude of the effect is too small to be unequivocal.

With the chemical shift assignments secure, the situation appeared relatively simple until we found that with 1,3-di-*tert*-butylpropargyl tosylate[1,3] (5, Table I) *both* *tert*-butyl resonances occur exactly at δ 1.00! This suggests that the remote aromatic ring spends a significant fraction of its conformational time near enough to the EBu that the *deshielding* effect of the triple bond is exactly compensated by the *shielding* influence of the face of the benzene ring. Such long range shielding effects are not without precedent,[5] as shown by the ninth entry in Table I.



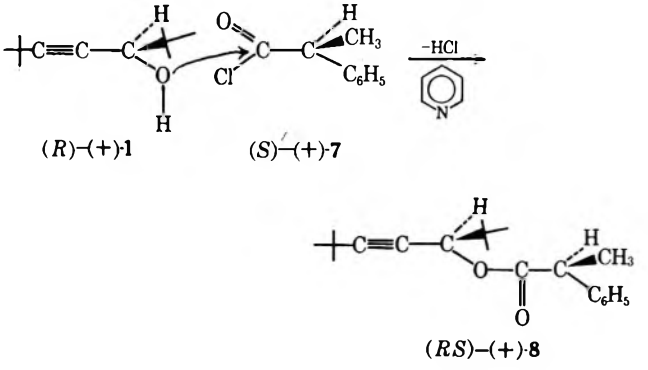
In order to assess the generality and limitations of these types of interaction we chose to prepare derivatives of 1 similar in nature to 5 with remote phenyl substituents. The most significant results arose from the reaction of 1 with 2-phenylpropionic (hydratropic) acid 6 (*via* the acid chloride, 7). Because both 1 and 6 possess a center of chirality it was likely that the reaction would lead to a mixture of (enantiomeric pairs of) diastereomers, but preliminary examination of space-filling molecular models did not permit a decision as to which pair might be preferentially formed or, once formed, if they would be easily separable on steric grounds. Reaction of 1 with an equimolar amount of 7 in pyridine led, in 81% yield, to a high boiling oil with the composition of the anticipated ester(s) 1,3-di-*tert*-butylpropargyl 2-phenylpropionate (8). After several unsuccessful attempts, the oil was ultimately resolved by glpc on a Carbowax 20M column and shown to be a mixture of two components, A and B (in the order of their elution), in the ratio 48.6:51.4%. Although the ir spectra of the two compounds were virtually identical, the proton nmr spectra (Experimental Section) differed significantly in the *tert*-butyl regions (Table I). Comparison of these values with the previously considered ones suggested that diastereomer A had an essentially "normal" ABu and a significantly (0.10 ppm) *shielded* EBu, while isomer B had

(7) Varian Associates, "High Resolution NMR Spectra Catalog," Spectrum No. 16.

a normal EBu and a significantly (0.18 ppm) *shielded* ABu!

In order to ascertain the absolute configuration of the diastereomers, we proceeded to resolve the reactants using published procedures. Acid **6** was resolved by means of its strychnine salt[8-10] to yield (*S*)-(+)-**6**, $[\alpha]^{24.3}D$ +85.8° (*c* 3.48, benzene), which corresponds to an optical purity[11] of 92.8% and an enantiomeric purity of 96.4%. (*S*)-(+)-**6** was converted to the acid chloride, (*S*)-(+)-**7**, with thionyl chloride, the product having $[\alpha]^{24.8}D$ +74.2° (*c* 2.83, chloroform).[12] Alcohol **1** was resolved *via* the brucine salt of its phthalate half ester[3] to yield (*R*)-(+)-**1**, $[\alpha]^{24.5}_{578}$ +4.66° (*c* 1.310, chloroform), which indicates an optical purity of 97.0% and an enantiomeric purity of 98.5%.[14]

SCHEME I



(*R*)-(+)-**1** (*S*)-(+)-**7**

(*RS*)-(+)-**8**

The product from the resolved reactants should then be nearly pure (*R*)-1,3-di-*tert*-butylpropargyl (*S*)-2-phenylpropionate [(*RS*)-**8**]. But how nearly pure? A fairly simple statistical analysis can be developed to estimate the relative amounts of all four stereoisomers of **8**, given the enantiomeric purity of **1** (x), the enantiomeric purity of **7** (y), and the factor (f) by which the major diasteromer is favored over the minor diastereomer *under racemic conditions*. Provided we start with equimolar amounts of **1** and **7** and addition of reactants is much faster than the reaction itself, the relative amount of a given diastereomer, for example *RS*, should be determined by the relative probability of finding an (*R*)-**1** molecule (x) times the relative probability of finding an (*S*)-**7** molecule (y) multiplied by the favoring factor f. Thus if the *RS* and *SR* diastereomers were the favored ones (*vide infra*) the relative amounts would be given by

$$\% (RS)\text{-}8 = 100xyf/N$$
$$\% (SR)\text{-}8 = 100(1-x)(1-y)f/N$$
$$\% (RR)\text{-}8 = 100x(1-y)(1-f)/N$$
$$\% (SS)\text{-}8 = 100(1-x)y(1-f)/N$$

where N, the normalization factor, is given by

$$N = (2f-1)(2xy-x-y)+f$$

Using the values $x = 0.985$, $y = 0.964$, and $f = 0.514$, (*vide supra*), the predicted amounts, assuming no mechanical or optical loss, are

$$\% (RS)\text{-}8 = 95.3$$
$$\% (SR)\text{-}8 < 0.1$$
$$\% (RR)\text{-}8 = 3.3$$
$$\% (SS)\text{-}8 = 1.4$$

Because the glpc separation will not distinguish enantiomers, we would expect to observe one peak [(*RS*)- + (*SR*)-**8**] comprising 95.3% of the product and another [(*RR*)- + (*SS*)-**8**] comprising 4.7%.

When the reaction mixture was analyzed under the same conditions as for the racemic materials, two components emerged, the first (A) constituting 4.0%, the second (B) constituting 96% in excellent agreement with the expectation! Thus the *RS* and *SR* stereoisomers can be identified with B (Table I) while the *RR* and *SS* isomers correspond to A. The mixture had $[\alpha]^{25}D$ +86.2° (c 1.614, chloroform).

Before correlating the absolute configuration with proton nmr behavior in **8**, several facts should be noted. Although the ratio of A to B is near unity, it is significantly dependent on reaction conditions. The two experiments above involved addition of a pyridine solution of **1** to a cooled sample of **7** and stirring from 0 to 25° for 2.5 hr. It was found, however, that addition of **1** to a solution of excess **7** in pyridine at room temperature and stirring for 14 hr led in ~79% yield to a mixture with ratio 60:40 (A:B). One possible explanation was that pyridine served to promote an enolization epimerization[13] (*RS* → *RR*, *SR* → *SS*) of **8**, but this was ruled out by the observation that the diastereomer ratio (A:B) was unchanged after 11.5 hr in pyridine. Another likely explanation would invoke the formation of a pyridinium complex with **7** under the second set of conditions and that this intermediate had different steric requirements than uncomplexed **7**. One might also argue that the less than quantitative yields (80–85%, but see Experimental Section) make the data a little difficult to interpret, but the close correspondence between the calculated and observed amounts of the two diastereomers (*vide supra*) suggest that, if some loss or destruction of esters occurs during work-up, there is little or no selection between the diastereomers. At any rate the above data taken *in toto* verify that the published specific rotations for optically pure **1** and **6** are correct,[3,8-14] as is the above procedure for estimation of stereoisomer populations.

Returning to a discussion of the nmr spectra, why is the *ABu* in (*RS*)- [and (*SR*)-] **8** shielded, while it is the *EBu* in the *RR* and *SS* isomers that is shielded? The explanation cannot be a simple function of the adjacent ester linkage in **8**, for, as we have already seen, going from **1** to **2** has no measurable effect on the chemical shifts of either *tert*-butyl group. We feel that the observations are best explained by examining the rotational conformations available in the two diastereomers.

If we consider two of the diastereomers, the *RS* and the *RR*, it is immediately clear that the differentiating

(8) C. L. Arcus and J. Kenyon, *J. Chem. Soc.*, 916 (1939).

(9) F. A. Abd Elhafez and D. J. Cram, *J. Amer. Chem. Soc.*, **74**, 5846 (1952).

(10) B. Sjoberg, *Ark. Kemi*, **13**, 1 (1959).

(11) In determining these purities we used the value $[\alpha]^{25}D$ +92.5° (c 3.4825, benzene)[8] which corresponds to $[M]^{25}D$ +138.8° (benzene)[10] for optically pure (*S*)-(+)-**6**.

(12) Although one can visualize ready racemization of **6** and **7** *via* acid- or base-catalyzed enolization, the assumption seems to have been made that formation of (*S*)-(+)-**7** from (*S*)-(+)-**6** entails no loss of optical purity.[8,9] This has been experimentally verified by the observation that **6**, converted to **7** then hydrolyzed back to **6**, showed only a 3% loss in optical rotation.[13] We have assumed no loss in optical purity during our preparation of the chloride, and thus the specific rotation of (*S*)-(+)-**7** can be estimated to be $[\alpha]^{28.8}D$ +79.9° (*c* 2.83, chloroform).

(13) J. Smejkal and J. Farkas, *Collect. Czech. Chem. Commun.*, **28**, 481 (1963).

(14) It should be noted that (+)-**1** was previously[3] given the incorrect designation *S*, while the isomer shown there and in Scheme I should carry the designation *R*, as the *tert*-butylethynyl group has precedence by complementation, over a *tert*-butyl group.[15]

(15) E. L. Eliel, private communication.

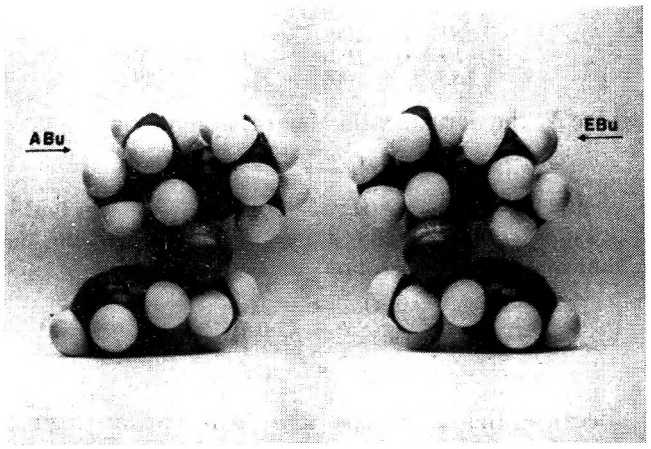
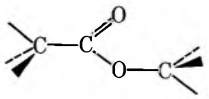


Figure 2.—Space-filling molecular models of (*RS*)-8 (left) and (*RR*)-8 (right). Notice the mirror-image relationship of the acid fragments and the similar configuration of the alkoxy residues.

factor(s) must intimately involve the methyl groups on the acid residues, for if they were replaced by hydrogen both molecules would be identical. Careful consideration of space-filling models of the diastereomers shows that both are relatively bulky and free rotation of most single bonds is limited. Two factors appear dominant in assuring minimized nonbonded repulsions throughout the molecules: first is the desire for one of the ortho hydrogens on the phenyl ring to be nestled between the methyl and carbonyl oxygen of the acid moiety, and second is the selection of the *s-trans* conformation of the ester linkage.



Given these two constraints, it is fairly easy to see that in (*RS*)-8 the ABu can be brought, without significant increase in conformational energy, into the shielding region of the benzene ring,[16] while steric buttressing prevents free rotation of the alcohol fragment in such a way as to bring the EBu into the shielding zone. The situation with the *RR* stereoisomer is just reversed; the conformation with the EBu over the ring is favored, while one which places the ABu in the shielding region possesses considerable nonbonded interactions throughout the molecule. Further evidence for these conclusions can be adduced from the fact that the more distended diastereomer (the *RS*) also has the longer glpc retention time. Molecular models (Figure 2) clarify these situations. These findings further confirm the correctness of the *R*[14] configuration of (+)-1. One final interesting observation is the apparent absence of shielding influence by the benzene ring in the phthalate half ester of 1 (Experimental Section), with ABu at δ 1.05 and EBu at δ 1.25. This can be explanied by the fact that no conformation exists which simultaneously allows either *tert*-butyl group to pass over the aromatic ring while maintaining conjugation between the ring and the C=O.

To summarize, it appears that the *tert*-butyl chemical shift is a relatively sensitive probe of molecular stucture. In the absence of "special effects" an alkyl *tert*-butyl group will fall into the region of δ 0.97. Special effects include attachment to a triple bond, which has a deshielding influence (δ 1.23), and the possibility of rotation into the shielding region of an aromatic ring.[17,17a]

(16) The upfield shifts caused by the aromatic ring are of the magnitude (~0.15 ppm) expected for protons whose (time-averaged) location rests at *p* (the in-plane distance from the center of the ring) = 2.8 Å, and *z* (normal distance from center of ring) = 5.6 Å: J. W. Emsley, J. Feeney and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 1, Pergamon Press, New York, N. Y., 1965, Appendix B.

Experimental Section

General.—The following instruments were employed: pmr spectra, Varian A-60; optical rotations, Cary 60 in ORD mode; ir spectra, Perkin-Elmer Model 700; mass spectra, Hitachi RMU 7 operated at 70 eV; glpc, Hewlett-Packard Model 700 equipped with TC detector and fitted with an 8 ft × 1/8 in. column packed with 12% Carbowax 20M on 80/100 Chromosorb W, AW-DMSC (column temperature 140°, injection block 159°, detector 160°, flow rate 30 ml/min). Quoted glpc percentages were derived from disc-integrated peak areas and are not corrected for response factor differences, which should be small for diastereomers A and B; these percentages were reproducible to ±0.2%. Elemental analyses were performed by Chemalytics, Tempe, Ariz.

1,3-Di-*tert*-butylpropargyl alcohol (1) was prepared by the published procedure.[1,3] Resolution[3] of 1 was initiated by esterifying 1 with phthalic anhydride in pyridine[18] to yield the half ester: mp 112.5–113°; ir (carbon tetrachloride solution) 2260 1725, 1700, 1600, 1580, 1280 cm^{-1}; pmr (carbon tetrachloride, internal TMS) δ 13.17 (s, 1 H), 7.6 (br m, 4 H), 5.30 (s, 1 H), 1.25 (s, 9 H), 1.05 (s, 9 H). The brucine salt of the phthalate half ester was recrystallized four times from 80% aqueous acetone to yield a salt with $[\alpha]^{25}D$ −13.4° (c 0.911, acetone). This material gave (*R*)-(+)-1, mp 58.5–60.0° (lit.[3] 58.8–60.3°) and rotation given in the text.

2-Phenylpropionic acid (6) was prepared in 69% yield by silver oxide oxidation of 2-phenylpropionaldehyde.[19] This material had bp 104–105° (1.0 mm) [lit.[19] 144–147° (11 mm)]; ir (carbon tetrachloride) 3000 (very broad), 1705, 1603 cm^{-1}; pmr (carbon tetrachloride, internal TMS) δ 12.04 (s, 1 H), 7.28 (br s, 5 H), 3.67 (q, *J* = 7 Hz, 1 H), 1.47 (d, *J* = 7 Hz, 3 H).

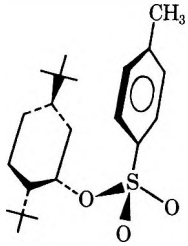
Five recrystallization of the strychnine salt from 75% aqueous ethanol yielded the salt with $[\alpha]^{25}D$ −29.2° (*c* 0.896, ethanol). The (*S*)-(+)-acid isolated therefrom, mp 29–30° (lit.[8] 29°), had specific rotation given in text.

2-Phenylpropionoyl chloride (7) was prepared in 89% yield by use of thionyl chloride.[20] This material had bp 80° (4 mm) [lit.[20] 100–101° (13 mm)]; pmr (carbon tetrachloride, internal TMS) δ 7.31 (br s, 5 H), 4.06 (q, *J* = 7.3 Hz, 1 H), 1.53 (d, *J* = 7.3 Hz, 3 H).

When the reaction was carried out with acid of $[\alpha]^{24.3}D$ +85.8°

(17) For recent examples on the use of chemical shift in elucidating rotational preferences, see G. Montaudo, *et al.*, *J. Amer. Chem. Soc.*, **93**, 4202, 4208 (1971).

(17a) NOTE ADDED IN PROOF.—A recent X-ray study [D. H. Faber and C. Altona, *Chem. Commun.*, 1210 (1971)] has revealed that the *p*-toluenesulfonyl group in *cis,trans*-2,5-di-*tert*-butylcyclohexyl tosylate adopts a folded conformation in the crystalline state as shown. To the extent that



this conformation persists in solution, one would expect from the results described herein that the 5-*tert*-butyl group would experience net shielding by the aromatic ring while the 2-*tert*-butyl group should be unaffected. Professor Pasto [D. J. Pasto and D. R. Rao, *J. Amer. Chem. Soc.*, **92**, 5151 (1970)] has informed us that the *cis,trans*-tosylate exhibits two *tert*-butyl resonances, one at δ 0.89 (a normal value), the other at 0.667 (shielded by ~0.3 ppm), exactly in accord with expectation. Of course the possibility that the 2-*tert*-butyl becomes the shielded one in solution cannot at this point be excluded, but clearly one of the groups is significantly shielded while the other is not.

(18) For details of a similar resolution, see T. L. Jacobs, R. Macomber, and D. Zunker, *J. Amer. Chem. Soc.*, **89**, 7001 (1967).

(19) E. L. Eliel and J. P. Freeman, *ibid.*, **74**, 923 (1952).

(20) R. Delaby, P. Reynaud, and F. Lilly, *Bull. Soc. Chim. Fr.*, 2067 (1961).

(c 3.48, benzene) the product, (*S*)-(+)-**7**, had specific rotation given in the text.

Reaction of 1 with 7.—A solution of 998.8 mg (5.89 mmol) of **1** in 5 ml of dry pyridine was added rapidly, with magnetic stirring to 990.6 mg (5.88 mmol) of **7** cooled to 0° by means of an ice bath. Reaction, as gauged by the appearance of pyridine hydrochloride, was immediate. The reaction mixture, protected from moisture, was stirred for 2.5 hr, while the temperature climbed from 0 to 25°. The solution was poured over an equal volume of ice and extracted with ether (five 8-ml portions), which was then washed repeatedly with 1 *N* sulfuric acid until all pyridine had been removed, and once with saturated sodium chloride solution. The ether solution was dried, then rotary evaporated, leaving 1418.1 mg (81%)[21] of the product as an oil which did not freeze above −20°. Glpc showed two components, one at 8.4 min (48.6%) and one at 9.8 min (51.4%). Distillation gave an analytically pure mixture, slightly enriched in A, the lower boiling isomer (ratio of A to B 51:49), bp 88–91° (0.2 mm); *m/e* 300; ir (carbon tetrachloride) 2970, 2275, 1730, 1605, 1165 cm^{-1}. The pmr spectrum (carbon tetrachloride, internal TMS) clearly showed two sets of absorptions, the relative isomer distributions from which corresponded to within 1% of the ratio found with glpc. Isomer A: δ 7.27 (br s, 5 H), 5.05 (s, 1 H), 3.69 (q, *J* = 7.3 Hz, 1 H), 1.48 (d, *J* = 7.3 Hz, 3 H), 1.13 (s, 9 H), 0.92 (s, 9 H); Isomer B: δ 7.27 (br s, 5 H), 5.08 (s, 1 H), 3.68 (q, *J* = 7.3 Hz, 1 H), 1.48 (d, *J* = 7.3 Hz, 3 H), 1.21 (s, 9 H), 0.79 (s, 9 H).

(21) It is significant to note that although isolated yields are somewhat less than quantitative, glpc analysis of the crude product mixtures showed unreacted **1** as the only contaminant.

Anal. Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39. Found: C, 79.76; H, 9.41.

When the reaction was carried out with the resolved materials, the product, isolated in 86%[21] yield, gave an ir spectrum virtually superimposable on that of the diastereomer mixture (*vide supra*). This material, predominantly (*RS*)-(+)-**8**, did solidify to a glass at 0°, and remelted at ~30°; its specific rotation is given in the text. The pmr spectrum of the product was identical with that of B above, with *ca.* 5% of A discernible. Glpc showed a ratio of 4.0:96.0 (A:B). A 198-mg sample of racemic ester mixture was dissolved in 2 ml of dry pyridine and allowed to stand for 11.5 hr at ambient temperature. Work-up as above and then glpc analysis showed that the constitution of the mixture had changed by less than 2%.

Registry No.—**1**, 22688-43-3; **1** phthalic half ester, 33122-22-4; **1** phthalic half ester brucine salt, 33069-02-2; **6**, 7782-24-3; **6** strychnine salt, 33069-04-4; **7**, 25145-43-1; *R,R*-**8**, 33069-06-6; *S,S*-**8**, 33069-07-7; (+)-*R,S*-**8**, 33069-08-8; *S,R*-**8**, 33122-23-5.

Acknowledgments.—We wish to thank Mr. Eugene R. Kennedy for preparing compounds **3** and **4** (Table I) and the University of Cincinnati Graduate School for partial support in the form of a Summer Research Fellowship to R. S. M. Acknowledgment is further made to the Donors of the Petroleum Research Fund administered by the American Chemical Society for partial support of this work.

Magnetic Circular Dichroism Investigations of Some Conjugated Olefins[1,2]

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Received August 11, 1971

The magnetic circular dichroism (MCD) curves of 12 conjugated dienes are reported. The series studied includes both acyclic and cyclic *s-cis*- and *s-trans*-dienes as well as compounds having a large range in skew angle values. From the lack of variation in the signs and magnitudes of the B/D values measured for the dienes studied, it is concluded that MCD, in the 200–300-nm region, has no distinct advantage over absorption spectroscopy for the structural identification of different diene systems. 1,3,5-Cycloheptatriene exhibits a more complex MCD spectrum than anticipated.

Magnetic circular dichroism (MCD) and magnetic optical rotatory dispersion (MORD) have been useful tools in the investigation of molecular structure[1] and in some cases have been found to be more sensitive to molecular structrual differences than either CD or ORD.[5] MCD has also been used to clarify spectroscopic assignments, detect hidden transitions, and characterize the symmetry and angular momentum properties of molecules in their ground and excited states.[6] The most important advantage of MCD is that it can be applied to optically inactive or racemic material.

A resurgence of interest during the past several years is clearly in evidence.[1] The impetus for this renewed interest comes primarily from Buckingham and Stephens' theoretical treatment of magnetic optical activity within absorption bands.[6a] The magnetic molar ellipticity, $[\theta]_M$, associated with an isolated electronic transition $a \rightarrow j$, can be expressed by eq 1.[6b] In this

$$[\theta_{(a \rightarrow j)}]_M = -21.3458 \{f_1 A_{(a \rightarrow j)} + f_2[B_{(a \rightarrow j)} + C_{(a \rightarrow j)}/kT]\} \quad (1)$$

equation, the B term results from the mixing of energy levels by the magnetic field and is present for all molecules. The A and C terms result from Zeeman splitting of degenerate levels by the external field, and nonzero values for these magnetic rotational strengths will be oberved only for highly symmetrical molecules. The B and C terms are described by the same shape function, f_2, and have the bell shape characteristic of an absorption band. The curve observed for the A term, described by f_1, is the resultant of two oppositely

(1) Part XVI in the series Magnetic Circular Dichroism Studies. For part XV, see C. Djerassi, E. Bunnenberg, and D. L. Elder, *Pure Appl. Chem.*, **25**, 57 (1971), a review of the applications of MCD in organic chemistry.

(2) This work was supported in part by the National Institutes of Arthritis and Metabolic Diseases, U. S. Public Health Service (Grant No. AM-00709 to W. G. D.), the National Institutes of Health (Grant No. AM 12758 to C. D.), and the Stanford University Center for Materials Sciences.

(3) National Institutes of Health Predoctoral Fellow, 1968–1971.

(4) National Science Foundation Predoctoral Fellow, 1967–1971.

(5) (a) W. Voelter, G. Barth, R. Records, E. Bunnenberg, and C. Djerassi, *J. Amer. Chem. Soc.*, **91**, 6165 (1969); (b) W. Voelter, R. Records, E. Bunnenberg, and C. Djerassi, *ibid.*, **90**, 6163 (1968).

(6) (a) A. D. Buckingham and P. J. Stephens, *Ann. Rev. Phys. Chem.*, **17**, 399 (1966); (b) P. N. Schatz and A. J. McCaffery, *Quart. Rev., Chem. Soc.*, **23**, 552 (1969), and references cited therein.

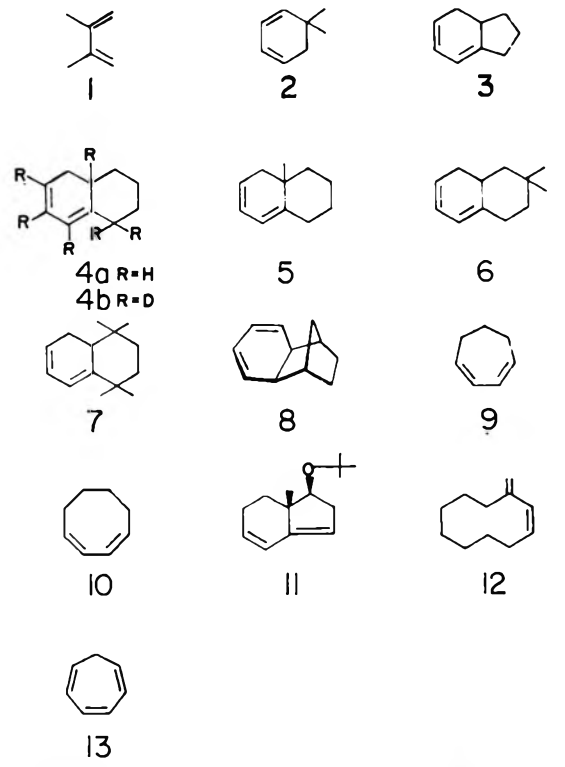

Figure 1.—Structures of the olefins investigated.

signed bell-shaped components which are symmetrically located on either side of the absorption band maximum. Thus, in the general case, the MCD curve observed for an isolated electronic transition can be expected to have a complex envelope.

Much attention has been directed toward the evaluation of the A and C terms, since these magnetic rotational strengths provide extremely useful spectroscopic information about the excited and ground states for both organic and inorganic systems having the appropriate symmetry.[6b,7f] However, accurate values for these two terms are difficult to extract from experimental curves when several transitions are closely spaced. Furthermore, the curve resulting from two overlapping oppositely signed B terms can closely resemble the curve from an A term, a situation which may lead to incorrect transition assignments.

On the other hand, values for the ubiquitous B terms have been determined only for a limited number of organic compounds and then only in the course of extracting A values. A general interpretation of the MCD spectra of compounds which are of such low symmetry as to show only B terms is difficult since, in principle, the entire manifold of states must be considered. Consequently, interpretations of the MCD spectra of the vast majority of organic compounds is likely to be empirical in nature. In the present communication we report the MCD spectra and the B/D values (D = dipole strength) for a number of different conjugated dienes. The series studied includes both

(7) (a) P. J. Stephens, W. Suëtaka, and P. N. Schatz, *J. Chem. Phys.*, **44**, 4592 (1966); (b) P. N. Schatz, A. J. McCafferty, W. Suetaka, G. N. Henning, A. B. Ritchie, and P. J. Stephens, *ibid.*, **45**, 722 (1966); (c) C. H. Henry, S. E. Schnatterly, and C. P. Slichter, *Phys. Rev.*, **137**, A583 (1965); (d) P. J. Stephens, *J. Chem. Phys.*, **52**, 3489 (1970); (e) B. Briat, D. A. Schooley, R. Records, E. Bunnenberg, and C. Djerassi, *J. Amer. Chem. Soc.*, **89**, 7062 (1967); (f) P. J. Stephens, R. L. Mowry, and P. N. Schatz, *J. Chem. Phys.*, **55**, 224 (1971).

TABLE I
ABSORPTION AND MCD SPECTRA OF CONJUGATED OLEFINS IN HEXANE

Compd	Absorption[a] λ, nm (10^{-3} ε)	MCD[b,c,d] λ_0, nm ($10^3[\theta]_M$)	Γ, nm	B/D × 10^6
1	228 (10)	215 (neg)[e]		
2	258 (6.1)	256 (−83)	37	4.8
3	268 (4.9)	270 (−58)	40	3.3
4a	267 (6.8)	270 (−66)	29	2.4
4b	267 (6.6)	267 (−62)	38	3.4
5	264 (6.5)	264 (−51)	34	2.6
	274 (sh)	275 (−47)		
6	267 (6.4)	270 (−37)	41	1.9
7	269 (5.2)	270 (−47)	40	2.8
	278 (5.0)	282 (−40)		
8[f]	268 (4.3)	263 (−38)	47	3.4
	279 (4.0)	271 (−47)		
	288 (sh)	283 (−39)		
		294 (−19)		
9	246 (7.5)	255 (−47)	30	2.2
10	228 (5.5)	220 (neg)[e]		
11[g]	236 (15.0)	235 (−96)	28	2.1
	242 (15.0)	243 (−104)		
12[h]	214 (7.0)	210 (neg)[e]		
13	265 (4.2)	251 (−153)	35[i]	9.9[j]
		284 (+5)		
		302 (−10)		

[a] Only well-defined shoulders are given. [b] $[\theta]_M$ is molar magnetic ellipticity in deg cm² dmol^{-1} G^{-1}. [c] Γ is the full width of the MCD at one-half maximum height. [d] The ratio of the magnetic rotational strength to the dipole strength was computed by the moment analysis procedure outlined in ref 7d and 7f. $B/D = -3.25 \int([\theta]_M/\nu)d\nu / \int(\epsilon/\nu)d\nu$ in β_M/cm^{-1} and β_M is the Bohr magneton. [e] $[\theta]_M$ is negative but a clearly defined maximum was not reached at the wavelength indicated. [f] Supplied by M. S. Kellogg. [g] Supplied by T. J. Dietsche. [h] Supplied by C. Suter. [i] Half band width of the 251 nm MCD band. [j] See comments in text.

acyclic and cyclic *s-cis*- and *s-trans*-dienes and includes compounds having a large range in skew angle values and molecular environments. These latter features are of interest since the ORD[8a,b] of chiral dienes is known to be unusually sensitive to structural parameters.

In the simple two-state case where a nondegenerate ground state a is coupled with only two nondegenerate excited states j and k, theory[6] predicts that the magnetic rotational strengths associated with the transitions $a \rightarrow j$ and $a \rightarrow k$ will be of equal magnitude but of opposite sign. The sign of the B terms depends on the polarization of the transitions and, hence, cannot be determined because of the arbitrary orientation of the molecule in the symmetry axis and the Hermitian character of the magnetic and electric momentum operators.[9,10a] The expression for the B term involves the scalar triple product of the two electric dipole moments and the connecting magnetic dipole moment as given in the simplified expression,[10a] eq 2,

$$B_{(a \rightarrow j)} = I_m \sum_{k \neq j} \frac{\boldsymbol{\mu}_{jk} \cdot \mathbf{m}_{aj} \cdot \mathbf{m}_{ka}}{\nu_{kj}} \qquad (2)$$

where $\mathbf{m}$ and $\boldsymbol{\mu}$ are the electric and magnetic dipole transition moments, respectively, and ν_{kj} is the energy

(8) (a) A. Moscowitz, E. Charney, U. Weiss, and H. Ziffer, *J. Amer. Chem. Soc.*, **83**, 4661 (1961), and subsequent publications; (b) A. W. Burgstahler and R. C. Barkhurst, *ibid.*, **92**, 7601 (1970).

(9) I. Tinoco, Jr., and C. A. Bush, *Biopolym. Symp.*, **1**, 235 (1964).

(10) (a) B. Briat, D. A. Schooley, R. Records, E. Bunnenberg, C. Djerassi, and E. Vogel, *J. Amer. Chem. Soc.*, **90**, 4691 (1968); (b) B. Briat, D. A. Schooley, R. Records, E. Bunnenberg and C. Djerassi, *ibid.*, **89**, 6170 (1967).

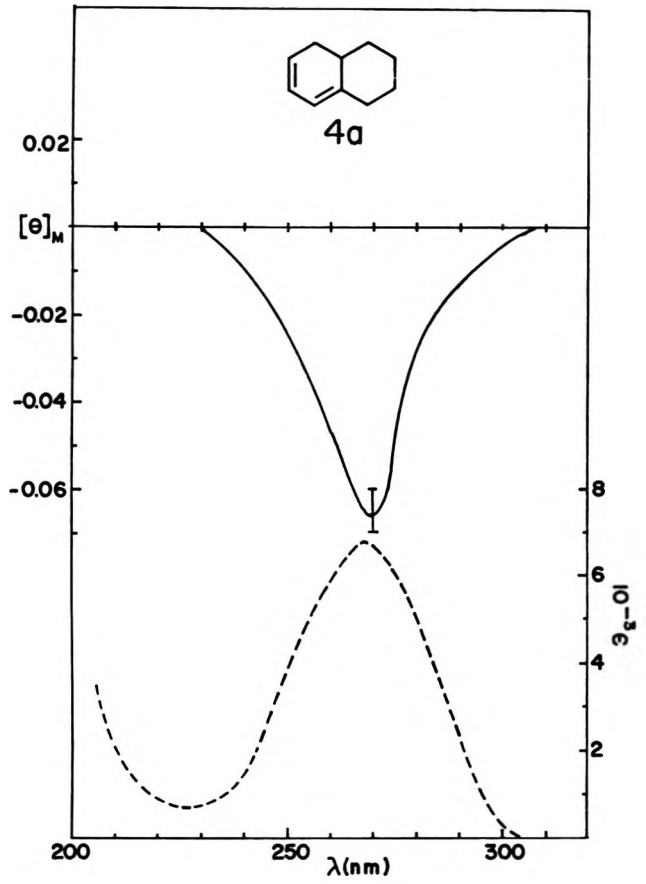

Figure 2.—Absorption (——) and MCD (– – –) spectra of 1,2,3,4,8,9-hexahydronaphthalene (**4a**) in hexane.

difference between the states j and k. The dipole strength for the nondegenerate transition $a \rightarrow j$ is given by eq 3. Equations 2 and 3 illustrate one of the

$$D_{(a \rightarrow j)} = |\mathbf{m}_{(a \rightarrow j)}|^2 \quad (3)$$

analytical applications of MCD; namely, that a weak absorption band may lead to a strong MCD band. Several examples can be found in the MCD spectra of purine derivatives[5] and, more dramatically, in the MCD associated with the Q_0^x and Q_0^y absorption bands of chlorin derivatives.[10b]

The compounds studied are shown in Figure 1 and their absorption and MCD properties are given in Table I. The MCD and absorption spectra of **4a** (Figure 2) are typical of the dienes studied, except for compounds **1**, **10**, and **12**, for which a negative MCD was measured although a clear maximum was not detected at wavelengths corresponding to their absorption maxima. For the remaining dienes only the lowest energy B term is observed since the higher energy B term(s) was not accessible with our instrument. The position of the observed λ_0 of the maximum molar ellipticity, $[\theta]_M$, of these dienes is in the vicinity of their absorption maxima, λ_{max}, as predicted by theory for allowed transitions. In addition, those compounds which exhibit fine structure in their absorption spectra also show similar fine structure in the MCD curves. Indeed, in most cases, the MCD is virtually a mirror image of the absorption spectra. The lack of a clearly defined maximum in the MCD spectra of the compounds having either a large degree of conformational mobility, **1**, or sterically imposed large skew angles,[11]

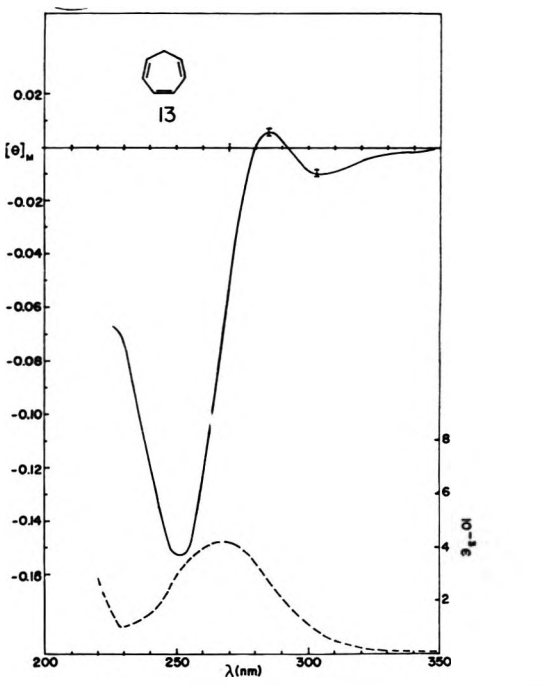

Figure 3.—Absorption (——) and MCD (——) spectra of 1,3,5-cycloheptatriene (**13**) in hexane.

10 and **12**, may be attributed to the low signal-to-noise ratios prevailing at lower wavelengths. On the basis of the lack of variation in the signs of the B terms observed for the *s-cis*- and *s-trans*-dienes (*e.g.*, **4a** and **11**, respectively) as well as the lack of variation in the ratio B/D for the dienes studied, it appears that MCD does not, in fact, exhibit the conformational sensitivity. Furthermore, examination of the values of B/D reported for several organic systems (Table II) shows that

TABLE II
B/D VALUES REPORTED FOR SOME ORGANIC COMPOUNDS

Compd	Transition (λ_{max}, nm)	B/D × 10^6 (β_M/cm^{-1})	Ref
Dienes	230–290	1.9–4.8	
Annulenes	330–370	4.8–9.1	7e
Coronene	303	0.396	7f
Triphenylene	255	−2.32	7f
Zn Hematoporphyrin	578 (Q_0)	−134	7a
	413 (Soret)	3.47	
Coproporphyrin II	625 (Q_0^x)	216	7a
tetramethyl ester	526 (Q_0^y)	−95.9	

this ratio cannot be used to characterize a particular chromophore, since factors such as the energy separation between states, the relative orientation of transition moments, the vagaries attending complex mixing of more than two excited states, and the particular data analysis procedure used must also be considered.

As the data in Table I and Figure 3 indicate, the MCD of cycloheptatriene does not conform to any of the previous generalizations. The experimental curve in Figure 3 can be visualized as the sum of overlapping oppositely signed B terms. Nmr evidence[12] would seem to render the rationalization of a cycloheptatriene–norcaradiene equilibrium untenable. Among

(11) (a) N. L. Allinger and M. A. Miller, *J. Amer. Chem. Soc.*, **86**, 2811 (1964); (b) N. L. Allinger and J. C. Tai, *ibid.*, **87**, 2081 (1965); (c) N. L. Allinger, M. A. Miller L. W. Chow R. A. Ford, and J. C. Graham, *ibid.*, **87**, 3430 (1965).

(12) F. R. Jensen and L. A. Smith, *ibid.*, **86**, 956 (1964).

the other explanations which might be considered are (1) vibrational effects; (2) separate contributions from planar and nonplanar conformers;[12] (3) mixing of a singlet state with a nearby triplet state; and (4) complex mixing with low-lying singlet states. Clearly, further work is required; however, some support for low-lying states can be found in the electron impact excitation spectrum of cycloheptatriene recently reported by Oosterhoff.[14] It should be noted that the ratio $B/D = 9.9 \times 10^{-5}\ \beta_M/cm^{-1}$, although distinctly larger than the mean of the diene values, was determined by moment analysis[7f] and has significance only if the complex MCD is of vibrational rather than electronic origin.

In conclusion, our results support the current theoretical treatment of the Faraday effect and provide additional spectroscopic evidence for the prediction[11] of but a single electronic transition in the 200–300 nm region of conjugated dienes. Furthermore, these results provide the basis, and indeed the impetus, for further measurements in the vacuum ultraviolet. Although MCD in the 200–300 nm region has no distinct advantage over absorption spectroscopy for the structural identification of different diene systems, further work in this region on triene systems is definitely warranted.

(13) F. A. L. Anet, *J. Amer. Chem. Soc.*, **86**, 458 (1964).

(14) F. W. E. Knoop, J. Kistemaker, and L. J. Oosterhoff, *Chem. Phys. Lett.*, **No. 3**, 73 (1969).

Experimental Section

The synthesis and photochemical transformations of these compounds will be described in a future publication.

MCD measurements were made using a Japan Spectroscopic Company spectropolarimeter (Durrum-JASCO Model ORD/UV/CD-5) modified to accept a Lockheed Palo Alto Research Laboratories superconducting magnet (Model OSCM-103). The directions of the light beam and the positive sense of the magnetic field are coincident. All measurements were made at 21° in a magnetic field of 49.5 kG. The solvent was Spectrograde hexane.

Registry No.—**1**, 513-81-5; **2**, 33482-80-3; **3**, 33482-81-4; **4a**, 13376-06-2; **4b**, 33482-83-6; **5**, 33482-84-7; **6**, 33482-85-8; **7**, 33482-86-9; **8**, 33482-87-0; **9**, 4054-38-0; **10**, 3806-59-5; **11**, 33495-82-8; **12**, 31351-58-3; **13**, 544-25-2.

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Stereospecific Introduction of Functionalized Angular Methyl Groups *via* the Claisen Rearrangement. The Octalin and Hydrindenyl Ring Systems[1,2]

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The one-step Claisen rearrangement using ethyl vinyl ether, *N,N*-dimethylacetamide dimethyl acetal, or triethyl orthoacetate provides a useful method for the preparation of octalin systems with functionalized angular methyl groups from octalols. This method fails with the hydrindenyl ring system. However, preparation and purification of vinyl ethers followed by thermolysis lead to functionalized methyl groups in both ring systems. The use of decalin as solvent in the thermolysis increases the amount of Claisen product in the hydrindenyl system. When the temperature is lowered, the rate of rearrangement is decreased and the amount of elimination increased.

In the synthesis of polycyclic sesqui- and diterpenes, the need often has arisen for a general stereospecific preparation of fused ring systems with functionalized angular methyl groups. Such a group has usually been introduced into the ring systems by a conjugated addition of hydrocyanic acid[3] or by functionalizing[4] an already present angular group. Previous studies[5] in this laboratory with regard to the stereospecific introduction of an angular methyl group *via* cyclopropanation of an allylic alcohol called attention to this latter system as a potential starting point for other stereospecific syntheses. Indeed, such a system has been utilized by conversion to a vinyl ether followed by a Claisen rearrangement to a γ,δ-unsaturated aldehyde.[6] The reports in the recent literature[7-9] of three different one-step methods (eq 1–3) for bringing about this conversion made this an attractive pathway to evaluate.

These three reaction sequences were studied using the allylic alcohols **1** and **4**, ring systems which typify those found in natural products. It wasf ound that, when the one-step method using ethyl vinyl ether (eq 1) with the recommended trace of phosphoric acid as a catalyst was employed, the sole products of the reac-

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(2) In this paper the term hydrindenyl is used to describe the tetrahydroindan system represented by structures such as **4** and **5**.

(3) W. Nagata, M. Yoshioka, T. Okumura, and M. Murakami, *J. Chem. Soc. C*, 2355 (1970), and references cited therein.

(4) For a recent review of the Barton reaction see (a) R. H. Hesse in "Advances in Free Radical Chemistry," Vol. 3, G. H. Williams, Ed., Academic Press, New York, N. Y., 1969, pp 83–137. See also (b) A. Bowers, R. Villotti, J. A. Edwards, E. Denst, and O. Halpern, *J. Amer. Chem. Soc.*, **84**, 3204 (1962); (c) A. L. Nussbaum and C. H. Robinson, *Tetrahedron*, **17**, 35 (1962); (d) K. Hensler and J. Kalvoda, *Angew. Chem., Int. Ed. Engl.*, **3**, 525 (1964); (e) M. Aktar in "Advances in Photochemistry," Vol. 2, W. A. Noyes, Jr., G. S. Hammond, and J. N. Pitts, Jr., Ed., Interscience, New York, N. Y., 1964, pp 263–303.

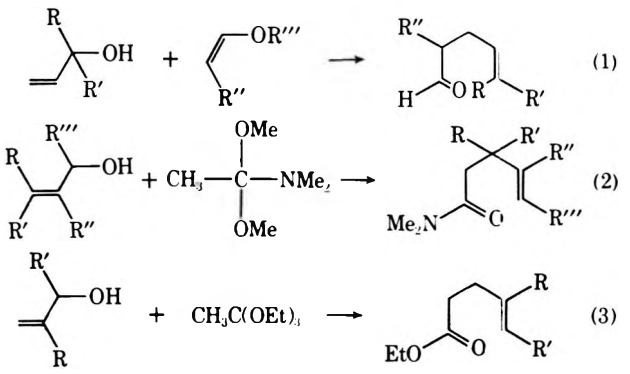
(5) (a) W. G. Dauben and G. H. Berezin, *J. Amer. Chem. Soc.*, **85**, 468 (1963); (b) W. G. Dauben and E. J. Deviny, *J. Org. Chem.*, **31**, 3794 (1966); (c) W. G. Dauben and D. S. Fullerton, *ibid.*, **36**, 3277 (1971).

(6) (a) A. W. Burgstahler and I. C. Nordin, *J. Amer. Chem. Soc.*, **81**, 3151 (1959); A. W. Burgstahler and I. C. Nordin, *ibid.*, **83**, 198 (1961); (b) R. F. Church, R. E. Ireland, and J. A. Marshall, *J. Org. Chem.*, **31**, 2526 (1966); (c) D. J. Dawson and R. E. Ireland, *Tetrahedron Lett.*, 1899 (1968).

(7) (a) R. Marbet and G. Saucy, *Helv. Chim. Acta*, **50**, 1158 (1967); (b) R. Marbet and G. Saucy, *ibid.*, **50**, 2091 (1967); (c) R. Marbet and G. Saucy, *ibid.*, **50**, 2095 (1967).

(8) (a) A. E. Wick, D. Felix, K. Steen, and A. Eschenmoser, *ibid.*, **47**, 2425 (1964); (b) D. Felix, K. Gschwend-Steen, A. E. Wick, and A. Eschenmoser, *ibid.*, **52**, 1030 (1969).

(9) (a) W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, T. Li, D. J. Faulkner, and M. R. Petersen, *J. Amer. Chem. Soc.*, **92**, 741 (1970); (b) W. S. Johnson, T. J. Brocksom, P. Loew, B. H. Rich, L. Werthemann, R. A. Arnold, T. Li, and D. J. Faulkner, *ibid.*, **92**, 4463 (1970).



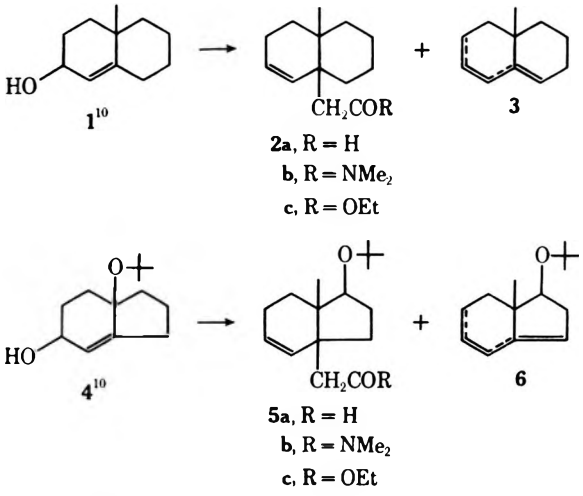
tions were the dienes **3** and **6**; no aldehydes **2a** and **5a** could be detected. An alternate procedure using mercuric acetate as the catalyst was tried and the results are recorded in Table I. This method works quite well

TABLE I
RESULTS OF ONE-STEP CLAISEN REARRANGEMENTS

Alcohol	Reaction	Reaction time, hr	Products,[a] % Starting material	Claisen product	Dienes
1	$CH_3CH_2OCH{=}CH_2$, 200°	12	0	85 (**2a**)	15 (**3**)
4	$CH_3CH_2OCH{=}CH_2$, 200°	12	0	40 (**5a**)	60 (**6**)
1	$CH_3C(OMe)_2NMe_2$, 138°	24	50	50 (**2b**)	0 (**3**)
4	$CH_3C(OMe)_2NMe_2$, 138°	40	0	0 (**5b**)	100 (**6**)
1	$CH_3(OEt)_3$, 137°	24	40	60 (**2c**)	0 (**3**)
4	$CH_3(OEt)_3$, 137°	24	50	Trace (**5c**)	50 (**6**)

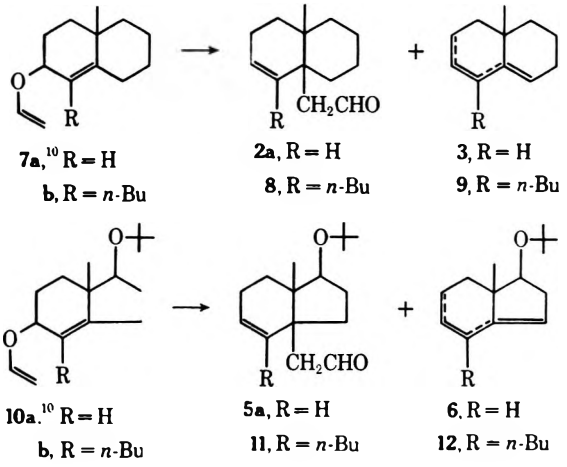
[a] Determined by nmr and/or glpc, and normalized.

for the octalin system **1**,[10] but with the hydrindenyl system **4** twice as much elimination as rearrangement resulted.



The dimethyl amide method (eq 2) was next studied. This process has been previously used on a system[6c] related to **1** and, indeed, the amide **2b** was found in high yield as reported in Table I. However, the products obtained from the hydrindenyl alcohol **4** were only the dienes **6**. Using the triethyl orthoacetate procedure (eq 3), similar results were obtained. A good yield of the ester **2c** resulted (Table I) but the hydrindenyl alcohol **4** gave only a trace of ester **5c** and a high yield of dienes **6**.

Thus, the one-step processes are excellent procedures for introducing various functionalized angular methyl groups in an octalin ring system but not in the hydrindenyl system. In view of the partial success of the modified vinyl ether approach with this latter system, the original two-step procedure of Burgstahler[6a] involving preparation of pure vinyl ether was studied in order to give some ideas as to where the one-step procedure met with difficulty.



The vinyl ethers (**7a,b** and **10a,b**) could be prepared in good yield (75–90%) from ethyl vinyl ether in the presence of mercuric acetate.[11] Unless special care was taken to obtain pure ether, larger amounts of diene were formed in the thermal rearrangement. The most efficient purification procedure was found to be chromatography on Florisil. The results of the vinyl ether thermolyses are given in Table II; the use of decalin as a solvent had been reported by Burgstahler.[6a] It is seen that, with the unsubstituted components **7a** and **10a**, the reaction proceeded very well and the use of decalin noticeably increased the yield of aldehyde **5a**. The presence of a substituent as in **7b** and **10b** had a small effect (~10% decrease) on the yield in the octalin system but in the hydrindenyl system the yield was

TABLE II
RESULTS OF VINYL ETHER THERMOLYSES[a]

Vinyl ether	Phase	Products,[b] % Aldehyde	Diene
7a	Neat	90 (**2a**)	10 (**3**)
7a	Decalin	90 (**2a**)	10 (**3**)
10a	Neat	70 (**5a**)	30 (**6**)
10a	Decalin	90 (**5a**)	10 (**6**)
7b	Neat	80 (**8**)	20 (**9**)
7b	Decalin	80 (**8**)	20 (**9**)
10b	Neat	45 (**11**)	55 (**12**)
10b	Decalin	65 (**11**)	35 (**12**)

[a] The thermolyses were run at 195–200° for 3–5 hr. [b] Determined by nmr and glpc, and normalized.

(10) Structure **1** represents a mixture of 87% β isomer and 13% α isomer by glpc analysis. Nmr analysis of compounds represented by structures **2a–c**, **7a**, **13**, and **14** consist of a mixture with approximately the same isomer ratio. Structure **4** represents a mixture of 95% β isomer and 5% α isomer by glpc analysis. Nmr analysis of compounds represented by structures **5a**, **5c**, and **10a** indicates no more than 5% isomer.

The alcohol from which **7b** is formed consists of a mixture of 80% β isomer and 20% α isomer by glpc. Though it is impossible to determine by nmr analysis the isomer ratio for **7b** and **8**, it is assumed, by analogy with the unsubstituted octalin **1**, to be the same as the alcohol precursor. The alcohol precursor for **10b** shows only β isomer.

(11) W. H. Watanabe and L. E. Conlon, *J. Amer. Chem. Soc.*, **79**, 2828 (1957).

greatly affected. The use of decalin as solvent in this latter case brought the yield of aldehyde **11** back to 65%.

Although Claisen rearrangements have been run over a wide range of temperatures (100–425°), there is lacking a study of the effect of temperature on the side reactions. Table III shows the effect of temperature

TABLE III
THE EFFECT OF TEMPERATURE ON VINYL ETHER THERMOLYSES

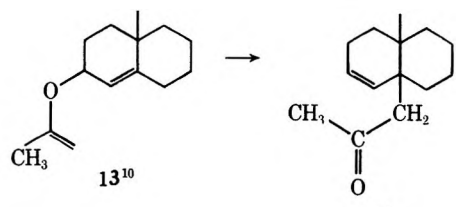
Vinyl ether	Temp, °C	Reaction time, hr	% Reaction	Products,[a] % Starting material	Aldehyde	Diene
10a	229	2.5	100	0	70 (5a)	30 (6)
10a	193	4	100	0	70	30
10a	160	23	100	0	70	30
10a	139	23	55	45	30	25
10a	116	23	<5	>95	Trace	Trace
7a	193	4	100	0	90 (2a)	10 (3)
7a	139	23	60	40	40	20

[a] Determined by nmr and normalized.

on the product distribution from the thermolysis of **10a**. At higher temperature (160° and above) the aldehyde to diene ratio remained the same. At 139° not only did the aldehyde to diene ratio drop but the rate of reaction was slowed down appreciably. Indeed, at 116° the rate of reaction was too slow to be of any synthetic value. The only study on the octalin system **7a** at 139° showed similar results in that the rate of the reaction slowed down and the aldehyde to diene ratio dropped off slightly.

This study of the two-step process indicated that the difficulty encountered with the hydrindenyl system in the one-step process most likely was in the formation of the vinyl ether. The overall results still show, however, that even with the preformed vinyl ether the elimination to form diene is a more competitive reaction in the hydrindenyl system. There is no clear-cut reason for this effect. Inspection of molecular models showed that the angular methyl group in both ring systems inhibited the more favorable chair conformation for the transition state so that the Claisen rearrangement must occur in the more energetic flexible boat conformation.[12] In this conformation the hydrindenyl vinyl ether displayed more steric interference between the terminal hydrogen on the vinyl ether with the angular methyl group, and this extra strain may be responsible for the effect found.

In an extention of their one-step process using vinyl ethers, Marbet and Saucy found that γ,δ-unsaturated methyl ketones could be prepared by utilization of the corresponding isopropenyl ethers.[7b] Following their procedure, alcohol **1** gave none of the desired ketone **14**. Using the two-step procedure, isopropenyl ethers from



13[10] **14**[10]

(12) The need for high temperature might also be indicative of the involvement of a higher energy pathway.

1 and **4** could be prepared in low yield (10–20%). Thermolysis of ether **13** gave methyl ketone **14** in 35% yield plus 65% diene; reaction of the related hydrindenyl ether **15** gave only diene.

The alcohols (**1** and **4**) prepared by $LiAlH_4$ reduction gave a mixture of epimer which consisted of approximately 85–95% of the β alcohol, as could be determined by analytical glpc or nmr analysis.[10] In this study the preparation of vinyl ethers and their thermolyses showed no preference as to stereochemistry and nmr analysis showed the same relative amounts of epimers. Burgstahler[6a] reported that, though the 3α-cholestenyl vinyl ether underwent thermolysis with ease, the formation of the α-vinyl ether went in only 5% yield as compared to the β-vinyl ether (65%). The higher flexibility of the more simple compounds may be responsible for this difference.

Experimental Section

Melting points were determined on a Büchi Schmelzpunktbestimmungsapporat and are uncorrected, as are boiling points. Reactions were monitored and product mixtures were analyzed by gas–liquid phase chromatography (glpc) on a Varian Aerograph A-90-P using a 10-ft column, 5% SE-30 on Chromosorb W, unless otherwise stated. Infrared (ir) spectra were measured on a Perkin-Elmer 137 spectrophotometer with carbon tetrachloride as solvent. Nuclear magnetic resonance (nmr) spectra were obtained as carbon tetrachloride solutions with a Varian T-60 spectrometer, and peak positions are given in parts per million downfield from tetramethylsilane as an internal standard. Mass spectra were recorded on Consolidated Electrodynamics Corp. type 21-103C and Varian M-66 spectrometers. Elemental analyses were conducted by the Microanalytical Laboratory, College of Chemistry, University of California, Berkeley.

10-Methyl-$\Delta^{1(9)}$-2-octalol (1).—To a suspension of lithium aluminum hydride (3.8 g, 0.100 mol) in 100 ml of dry ether was added, dropwise, 10-methyl-$\Delta^{1(9)}$-2-octalone (16.4 g, 0.100 mol) in 100 ml of dry ether. The mixture was refluxed overnight. Water was added until a white, flocculent material formed, and the ether was filtered, dried ($MgSO_4$), and rotary evaporated. Distillation in a short-path still gave 14.3 g (86%) of **1**: bp 89–90° (0.5 mm) [lit.[13] bp 73.5–76° (0.2 mm)]; ir 3350, 1050 cm^{-1}; nmr δ 5.4 (d, J = 4.5 Hz, vinyl proton, α alcohol), 5.2 (s, vinyl proton, β alcohol, total 1 H), 4.0 (m, 1, carbinol H), 1.1 (s, angular methyl, β alcohol) and 1.0 (s, angular methyl, α alcohol, total 3 H). Glpc analysis[14] showed 87% β alcohol and 13% α alcohol.[15]

9-Formylmethyl-10-methyl-Δ^1-octalin (2a).—The allylic alcohol **1** (0.3 g, 1.80 mmol), mercuric acetate (0.2 g), and 1.5 ml of ethyl vinyl ether were sealed in a Carius tube and heated for 12 hr at 200°. Glpc and nmr analyses showed 85% of the aldehyde **2a** and 15% of the dienes **3** (collected by preparative glpc): mass spectrum (70 eV) m/e 133 (base peak), 148 (molecular ion). The aldehyde **2a** was collected for spectral analysis by preparative glpc: ir 2720, 1720 cm^{-1}; nmr δ 9.8 (m, 1, two overlapping triplets from α- and β-formylmethyl groups), 5.7 (m, 2, vinyl), 1.0 (s, angular methyl, α aldehyde) and 0.9 (s, angular methyl, β aldehyde) (total 3 H, ratio 85β:15α); mass spectrum (70 eV) m/e 149 (base peak), 192 (molecular ion).

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.23; H, 10.67.

9-(N,N-Dimethyl)formamidomethyl-10-methyl-Δ^1-octalin (2b).—The allylic alcohol **1** (1.66 g, 0.010 mol) and N,N-dimethylacetamide dimethyl acetal[16] (2.0 g, 0.015 mol) were stirred in refluxing xylene for 24 hr. The excess acetal and xylene were rotary evaporated to give 1.9 g of crude material which by nmr was found to be a 50:50 mixture of starting material **1** and amide **2b**. The amide was collected for spectral analysis by preparative glpc: ir 1660 and 1640 cm^{-1}; nmr δ 5.52 (s, 2, vinyl), 2.95 and 2.85

(13) H. B. Henbest and J. McEntee, *J. Chem. Soc.*, 4478 (1961).
(14) 5 ft, 5% KOH, 5% Carbowax on Chromosorb G.
(15) A. C. Ashcraft, Jr., Dissertation, University of California, Berkeley, 1963.
(16) Fluka A. G., stabilized with 5–10% methanol.

(two s, 6, *N,N*-dimethyl), 1.0 (s, angular methyl, α amide) and 0.92 (s, angular methyl, β amide) (total 3 H, ratio 85β:15α); mass spectrum (70 eV) *m/e* 87 (base peak), 235 (molecular ion).

Anal. Calcd for $C_{15}H_{25}ON$: C, 76.55; H, 10.71; N, 5.95. Found: C, 76.46; H, 10.70; N, 5.76.

9-Carbethoxymethyl-10-methyl-Δ¹-octalin (2c).—The allylic alcohol 1 (1.66 g, 0.010 mol), triethyl orthoacetate (16.2 g, 0.1 mol), and propionic acid (0.037 g, 0.5 mmol) were heated for 24 hr at 137° under conditions for distillative removal of ethanol. The nmr of the reaction mixture showed 40% of starting material 1 and 60% of ester 2c. The ester was collected for spectral analysis by preparative glpc; ir 1730 cm^{-1}; nmr δ 5.55 (s, 2, vinyl), 4.0 (q, 2, J = 7 Hz, ester CH_2O), 2.25 (s, 2, carbethoxy methylene), 1.2 (t, 3, J = 7 Hz, ester CH_3), 1.0 (s, angular methyl, α ester) and 0.9 (s, angular methyl, β ester) (total 3 H, ratio 85β:15α); mass spectrum (70 eV) *m/e* 149 (base peak), 148 (98% of base peak), 236 (molecular ion).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.49; H, 10.38.

1β-*tert*-Butoxy-5,6,7,7a-tetrahydro-7aβ-methyl-5-indanol (4).—The ketone, 1β-*tert*-butoxy-7,7a-dihydro-7aβ-methyl-5(6*H*)-indanone[17] (22.2 g, 0.100 mol) was reduced with $LiAlH_4$ (3.8 g, 0.100 mol) in the standard fashion (as for 1) to yield 21.2 g of crude product 4. Glpc analysis[18] showed 95% β alcohol and 5% α alcohol. A small sample was recrystallized from ice-cold petroleum ether (bp 30–60°) to give a white, granular powder: mp 67–68°; ir 3400 cm^{-1}; nmr δ 5.23 (broad s, 1, vinyl), 4.03 (m, 1, carbinol H), 3.3 (m, 1, *tert*-butyl–OCH), 1.1 (s, 9, *tert*-butyl), 0.94 (s, 3, angular methyl); mass spectrum (70 eV) *m/e* 150 (base peak), no molecular ion.

Anal. Calcd for $C_{14}H_{24}O_2$: C, 74.95; H, 10.78. Found: C, 75.18; H, 10.95.

1β-*tert*-Butoxy-3a-formylmethyl-3a,6,7,7a-tetrahydro-7aβ-methylindan (5a).—The allylic alcohol 4 (0.3 g, 1.30 mmol), mercuric acetate (0.2 g), and 1.5 ml of ethyl vinyl ether were sealed in a Carius tube and heated for 12 hr at 200°. Glpc and nmr analyses showed 40% of aldehyde 5a and 60% of dienes 6. The dienes were collected by preparative glpc: ir 3030 cm^{-1}; nmr δ 5.7 (m, 3, vinyl), 3.7 (m, 1, *tert*-butyl–OCH), 1.15 (s, 9, *tert*-butyl), 0.83 and 0.85 (two s, 3 H, angular methyls); mass spectrum (70 eV) *m/e* 206 (molecular ion).

Anal. Calcd for $C_{14}H_{24}O$: C, 81.50; H, 10.75. Found: C, 81.30; H, 10.72.

The aldehyde 5a was collected for spectral analysis by preparative glpc: ir 2720, 1725 cm^{-1}; nmr δ 9.77 (t, 1, J = 3 Hz), 5.55 (s, 2, vinyl), 3.8 (m, 1, *tert*-butyl–OCH), 2.35 (d, 2, J = 3 Hz, formylmethylene), 1.15 (s, 9, *tert*-butyl), 0.9 (s, 3, angular methyl); mass spectrum (70 eV) *m/e* 150 (base peak), no molecular ion.

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.49; H, 10.52.

Reaction of 4 with *N,N*-Dimethylacetamide Dimethyl Acetal.—The allylic alcohol 4 (0.33 g, 1.50 mmol) and *N,N*-dimethylacetamide dimethyl acetal (0.23 g, 2.00 mmol) were stirred in refluxing xylene for 40 hr. The excess acetal and xylene were rotary evaporated to leave 0.2 g of crude product which by nmr and ir proved to be the dienes 6.

Reaction of 4 with Triethyl Orthoacetate.—The allylic alcohol 4 (2.24 g, 0.010 mol), triethyl orthoacetate (16.2 g, 0.100 mol), and propionic acid (0.037 g, 0.5 mmol) were heated for 24 hr at 137° under conditions for distillative removal of ethanol. The reaction mixture was subjected to analytical glpc analysis which revealed starting material 4 and dienes 6 in a 1:1 ratio and a trace of material which was collected by preparative glpc and shown by spectral analysis to be the ester 5c: ir 1730 cm^{-1}; nmr δ 5.45 (s, 2, vinyl), 4.1 (q, 2, J = 7 Hz, ester CH_2O), 3.8 (m, 1, *tert*-butyl–OCH), 1.3 (t, 3, J = J Hz, ester CH_3), 1.2 (s, 9, *tert*-butyl), 0.8 (s, 3, angular methyl).

Preparation of Vinyl Ethers. 10-Methyl-Δ¹⁽⁹⁾-2-octalyl Vinyl Ether (7a).—The vinyl ethers of the cyclic allylic alcohols were prepared using mercuric acetate as catalyst.[11] In a typical reaction 10-methyl-Δ¹⁽⁹⁾-2-octalol (1, 2.96 g, 0.018 mol) and 1.0 g of freshly recrystallized mercuric acetate (from absolute ethanol containing 0.025% glacial acetic acid) were stirred in 200 ml of refluxing ethyl vinyl ether (distilled after reflux from sodium and stored over sodium) for 10 hr. Best results were obtained when an additional 0.5–1.0 g of mercuric acetate was added every 2 hr.[6a] After the final addition of mercuric acetate, the mixture was refluxed overnight. To the cooled mixture, 0.25 ml of glacial acetic acid was added and stirring was continued for 3 hr.[6b] The mixture was diluted with an equal volume of petroleum ether, washed with 50 ml of 5% aqueous potassium hydroxide, dried (K_2CO_3), and rotary evaporated. The residue was chromatographed on 100 g of Florisil (60–100 mesh) with petroleum ether as the eluent. Distillation in a short-path still gave 3.4 g (74%) of the vinyl ether 7a: bp 51–55° (0.06 mm); ir 3105, 3025, 1625, 1600, 1175 cm^{-1}; nmr δ 6.25 (dd, 1, J_{AX} = 7, J_{BX} = 14 Hz), 5.3 (broad s, 1, vinyl), 4.13 (dd, 1, J_{BX} = 14, J_{AB} = 1.5 Hz), 3.87 (dd, 1, J_{AX} = 7, J_{AB} = 1.5 Hz), 4.2 (m, 1, carbinol H), 1.1 (s, angular methyl, β-vinyl ether) and 1.02 (s, angular methyl, α-vinyl ether) (total 3 H, ratio 85β:15α); mass spectrum (70 eV) *m/e* 149 (base peak), 192 (molecular ion).

Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 80.96; H, 10.73.

Thermolysis of Vinyl Ethers. Thermolysis of 7a.—The vinyl ethers were sealed in a Carius tube under nitrogen, neat or in freshly distilled decalin,[6a] and heated for 3–5 hr at 195–200°. In a typical run a 150-mg portion of the 10-methyl-Δ¹⁽⁹⁾-2-octalyl vinyl ether 7a was sealed neat or sealed with 1.5 ml of decalin in two separate Carius tubes, and heated for 5 hr at 200°. Nmr and glpc analyses of the reaction material in both cases showed 90% of the aldehyde 2a and 10% of the dienes 3.

1-Butyl-10-methyl-Δ¹⁽⁹⁾-2-octalyl Vinyl Ether (7b).—The precursor to the vinyl ether was prepared by alkylating 10-methyl-Δ¹⁽⁹⁾-2-octalone.[19] Sodium hydride (3.3 g of a 55% dispersion in mineral oil, 0.075 mol), washed with pentane and dried under nitrogen, was stirred in 100 ml of DMSO for 1.5 hr at 65°, under nitrogen. To the cooled mixture, the octalone (10.9 g, 0.066 mol) in 100 ml of DMSO was added over several minutes and stirred for 3.5 hr. *n*-Butyl bromide (9.6 g, 0.070 mol) in 50 ml of DMSO was added and the mixture was stirred for 3 days at room temperature. A 300-ml portion of a saturated ammonium chloride solution was added and the mixture was extracted with four 100-ml portions of ether. The ether layer was washed with saturated sodium chloride, dried ($MgSO_4$), and rotary evaporated to leave a crude yellow oil which by spectral and glpc analyses contained, in addition to starting material, mono- and dialkylated material and O-alkylated material. The crude oil was stirred in 100 ml of glacial acetic acid and 15 ml of water for 4 hr at 65° and overnight at room temperature. The solution was cooled in an ice bath, neutralized to pH 9 with 10% sodium hydroxide, and extracted with ether. The solvent was evaporated and 9.5 g of a crude oil was chromatographed on 700 g of silica gel using 2% ethyl acetate in hexane as the eluent. The first eluate contained 1.0 g of dialkylated product: ir 1705 cm^{-1}; nmr δ 5.4 (m, 1, vinyl), 0.95 (s, 3, angular methyl); mass spectrum (70 eV) *m/e* 276 (molecular ion). The second eluate yielded 3.9 g (27%) of the monoalkylated product: ir 1660, 1620 cm^{-1}; nmr δ 1.2 (s, 3, angular methyl); mass spectrum (70 eV) *m/e* 163 (base peak), 220 (molecular ion). The final eluate yielded 2.8 g of the starting enone. The monoalkylated enone (3.63 g, 0.0165 mol) was reduced with $LiAlH_4$ (0.63 g, 0.0165 mol) in the standard fashion (as for 1) to yield 3.44 g of crude product. A small amount of the material was bulb-to-bulb distilled: ir 3500 cm^{-1}; nmr δ 3.9 (m, 1, carbinol H), 1.1 (s, angular methyl, β alcohol) and 1.0 (s, angular methyl, α alcohol) (total 3 H); mass spectrum (70 eV) *m/e* 165 (base peak), 222 (molecular ion). Glpc analysis[18] showed 80% β alcohol and 20% α alcohol.

Anal. Calcd for $C_{15}H_{26}O$: C, 81.02; H, 11.79. Found: C, 8.10; H, 11.52.

To the alcohol (0.77 g, 3.50 mmol) in 100 ml of refluxing ethyl vinyl ether was added 1.0 g of mercuric acetate every 2 hr for 8 hr and reflux was continued overnight. Work-up as for 7a provided 0.7 g (81%) of analytically pure vinyl ether 7b after passing through 50 g of Florisil: ir 3105, 1625, 1600, 1175 cm^{-1}; nmr δ 6.25 (dd, 1, J_{AX} = 7, J_{BX} = 14 Hz), 4.19 (dd, 1, J_{BX} = 14, J_{AB} = 2 Hz), 3.82 (dd, 1, J_{AX} = 7, J_{AB} = 2 Hz), 4.2 (m, 1, carbinol H), 1.1 (s, angular methyl, β alcohol) and 1.0 (s, angular methyl, α alcohol) (total = 3 H, ratio assumed 80β:20α); mass spectrum (70 eV) *m/e* 248 (molecular ion).

Anal. Calcd for $C_{17}H_{28}O$: C, 82.20; H, 11.36. Found: C, 82.36; H, 11.35.

Thermolysis of 7b.—A 200-mg portion of the vinyl ether 7b

(17) A gift from Hoffmann-La Roche, Inc., Nutley, N. J.

(18) 5 ft, 10% KOH, 10% Carbowax on Chromosorb W.

(19) Z. G. Hajos, R. A. Micheli, D. R. Parrish, and E. P. Oliveto, *J. Org. Chem.*, **32**, 3008 (1967).

was sealed neat or sealed with 2 ml of decalin in two separate Carius tubes, and heated for 3 hr at 195°. Nmr and glpc analyses of the reaction material in both cases showed 80% of the aldehyde **8** and 20% of the dienes **9**. The dienes were collected by preparative glpc: nmr δ 5.6 (m, 2, vinyl), 0.95 and 0.9 (s, 3, angular methyls); mass spectrum (70 eV) *m/e* 204 (molecular ion).

Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.84. Found: C, 88.41; H, 11.74.

The aldehyde **8** was collected for spectral analysis by preparative glpc: ir 2720, 1725 cm^{-1}; nmr δ 9.7 (two overlapping t, 1, α and β formylmethyls), 5.55 (m, 1, vinyl), 1.0 (s, angular methyl); mass spectrum (70 eV) *m/e* 248 (molecular ion).

Anal. Calcd for $C_{17}H_{28}O$: C, 82.20; H, 11.36. Found: C, 82.09; H, 11.33.

1β-*tert*-Butoxy-5,6,7,7a-tetrahydro-7aβ-methyl-5-indanyl Vinyl Ether (10a).—To the alcohol **4** (3.7 g, 0.0165 mol) in 250 ml of refluxing ethyl vinyl ether was added 1.0 g of mercuric acetate every 2 hr for 8 hr and reflux was continued overnight. Work-up as for **7a** provided 3.26 g (79%) of vinyl ether **10a**: bp 97–100° (0.1 mm); ir 3105, 1625, 1600, 1175 cm^{-1}; nmr δ 6.25 (dd, 1, J_{AX} = 7, J_{BX} = 14 Hz), 5.35 (s, 1, vinyl), 4.13 (dd, 1, J_{BX} = 14, J_{AB} = 1.5 Hz), 3.85 (dd, 1, J_{AX} = 7, J_{AB} = 1.5 Hz), 4.3 (m, 1, carbinol H), 3.35 (m, 1, *tert*-butyl–OCH), 1.15 (s, 9, *tert*-butyl), 1.0 (s, 3 H, angular methyl); mass spectrum (70 eV) *m/e* 151 (base peak), no molecular ion.

Anal. Calcd for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47. Found: C, 76.80; H, 10.40.

Thermolysis of 10a.—A 200-mg portion of the vinyl ether was sealed neat or sealed with 1.5 ml of decalin in two separate Carius tubes and heated for 4 hr at 195°. Nmr and glpc analyses of the reaction material showed (i) neat, 70% aldehyde **5a** and 30% dienes **6**; (ii) decalin, 90% aldehyde **5a** and 10% dienes **6**.

1β-*tert*-Butoxy-4-*n*-butyl-5,6,7,7a-tetrahydro-7aβ-methyl-5-indanyl Vinyl Ether (10b).—Sodium hydride (5.0 g of a 55% suspension in mineral oil, 0.115 mol), washed with pentane and dried under nitrogen, was stirred in 100 ml of DMSO for 1.5 hr at 70° under nitrogen. To the cooled mixture 1β-*tert*-butoxy-7,7a-dihydro-7aβ-methyl-5(6*H*)-indanone[17] (22.2 g, 0.100 mol) in 100 ml of DMSO was added over several minutes and stirred for 2 hr. *n*-Butyl bromide (15.7 g, 0.115 mol) in 50 ml of DMSO was added and the mixture was stirred for 2 days at room temperature. Work-up and removal of O-alkylated material was carried out as in the preparation of **7b** to yield 27 g of crude oil. The oil was vacuum distilled to yield 13 g of a fraction containing 85% of monoalkylated material. This mixture was chromatographed on 700 g of silica gel with 2% ethyl acetate in hexane as the eluent to yield as first eluate 0.55 g of the dialkylated material: ir 1705 cm^{-1}; nmr δ 5.25 (m, 1, vinyl), 4.75 (m, 1, *tert*-butyl–OCH), 1.15 (s, 9, *tert*-butyl), 1.0 (s, 3, angular methyl). The second eluate yielded 3.5 g of a 2:1 mixture of mono- to dialkylated material. The third eluate yielded 8.13 g which was distilled to give 7.6 g of the monoalkylated material: bp 120–125° (0.1 nm); ir, 1660, 1605 cm^{-1}; nmr δ 3.5 (m, 1, *tert*-butyl–OCH), 1.15 (s, 9, *tert*-butyl), 1.05 (s, 3, angular methyl); mass spectrum (70 eV) *m/e* 222 (base peak), 278 (molecular ion).

Anal. Calcd for $C_{18}H_{30}O_2$: C, 77.65; H, 10.86. Found: C, 77.92; H, 10.65.

The monoalkylated enone (6.11 g, 0.022 mol) was reduced with $LiAlH_4$ (0.84 g, 0.022 mol) in the standard fashion (as for **1**) to yield 6.09 g of a white solid. A small amount of the alcohol was bulb-to-bulb distilled: ir 3400 cm^{-1}; nmr δ 4.0 (m, 1, carbinol H), 3.25 (m, 1, *tert*-butyl–OCH), 1.15 (s, 9, *tert*-butyl), 0.93 (s, 3, angular methyl); mass spectrum (70 eV) *m/e* 161 (base peak), no molecular ion. Glpc analysis[18] showed only the β alcohol.

Anal. Calcd for $C_{18}H_{32}O_2$: C, 77.09; H, 11.50. Found: C, 76.94; H, 11.49.

To the crude alcohol (2.8 g, 0.010 mol) in 100 ml of refluxing ethyl vinyl ether was added 1.0 g of mercuric acetate every 2 hr for 8 hr and reflux was continued overnight. Work-up as for **7a** provided 2.8 g (92%) of analytically pure vinyl ether **10b** after passing through 50 g of Florisil: ir 3105, 3125, 1625, 1600, 1175 cm^{-1}; nmr δ 6.25 (dd, 1, J_{AX} = 7, J_{BX} = 14 Hz), 4.19 (dd, 1, J_{BX} = 14, J_{AB} = 1.5 Hz), 3.85 (dd, 1, J_{AX} = 7, J_{AB} = 1.5 Hz), 4.2 (m, 1, carbinol H), 3.27 (m, 1, *tert*-butyl–OCH), 1.15 (s, 9, *tert*-butyl), 0.95 (s, 3, angular methyl); mass spectrum (70 eV) *m/e* 119 (base peak), no molecular ion.

Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18. Found: C, 78.58; H, 11.23.

Thermolysis of 10b.—A 200-mg portion of the vinyl ether was sealed neat or sealed with 2 ml of decalin in two separate Carius tubes and heated for 3 hr at 195°. Nmr and glpc analyses of the reaction material showed (i) neat, 45% aldehyde **11** and 55% dienes **12**; (ii) decalin, 65% aldehyde **11** and 35% dienes **12**. The dienes were collected for spectral analyses by preparative glpc: ir 3030 cm^{-1}; nmr δ 5.4 (m, 2, vinyl), 3.65 (m, 1, *tert*-butyl–OCH), 1.15 (s, 9, *tert*-butyl), 0.83 and 0.80 (s, 3, angular methyls); mass spectrum (70 eV) *m/e* 119 (base peak), 262 (molecular ion).

Anal. Calcd for $C_{18}H_{30}O$: C, 82.38; H, 11.52. Found: C, 82.17; H, 11.47.

The aldehyde **11** was collected for spectral analyses by preparative glpc: ir 2720, 1725 cm^{-1}; nmr δ 9.65 (t, 1 H, J = 3 Hz), 5.5 (m, 1, vinyl), 3.7 (m, 1, *tert*-butyl–OCH), 2.4 (d, 2, J = 3 Hz, formylmethylene), 1.15 (s, 9, *tert*-butyl), 0.83 (s, 3, angular methyl); mass spectrum (70 eV) *m/e* 57 (base peak), no molecular ion.

Anal. Calcd for $C_{20}H_{34}O_2$: C, 78.38; H, 11.18. Found: C, 78.51; H, 11.24.

10-Methyl-$\Delta^{1(9)}$-2-octalyl Isopropenyl Ether (13).—To the alcohol **1** (1.5 g, 0.090 mol) in 100 ml of refluxing methyl isopropenyl ether[7b] was added 1.0 g of mercuric acetate every 2 hr for 8 hr and reflux was continued overnight. Work-up as for **7a** provided 200 mg of analytically pure vinyl ether **13**: ir 1650, 1610 cm^{-1}; nmr δ 5.33 (m, 1, vinyl), 4.32 (m, 1, carbinol H), 3.73 (s, 2, methylene), 1.70 (s, 3, vinyl methyl), 1.1 (s, angular methyl, β-vinyl ether) and 1.02 (s, angular methyl, α-vinyl ether) (total 3 H, ratio 85β:15α); mass spectrum (70 eV) *m/e* 149 (base peak), 206 (molecular ion).

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.38; H, 10.60.

Thermolyses of 13.—A 200-mg portion of the isopropenyl ether was sealed neat in a Carius tube and heated for 2.5 hr at 200°. Glpc analysis showed 65% of dienes **3** and 35% of methyl ketone **14**. The ketone was collected by preparative glpc: ir 1715 cm^{-1}; nmr δ 5.55 (s, 2 H, vinyl), 2.0 (s, 3, methyl ketone), 0.95 (s, angular methyl, β-methyl ketone) and 0.90 (s, angular methyl, α-methyl ketone) (total 3 H, ratio 85β:15α); mass spectrum (70 eV) *m/e* 58 (base peak), 57 (83% of base peak), 206 (molecular ion).

Anal. Calcd for $C_{14}H_{22}O$: C, 81.50; H, 10.75. Found: C, 81.35; H, 10.54.

1β-*tert*-Butoxy-5,6,7,7a-tetrahydro-7aβ-methyl-5-indanyl Isopropenyl Ether (15).—To the alcohol **4** (1.12 g, 5.00 mmol) in 30 ml of refluxing methyl isopropenyl ether[7b] was added 0.5 g of mercuric acetate every 2 hr for 8 hr and reflux was continued overnight. Work-up as for **7a** provided 200 mg of analytically pure vinyl ether **15**: ir 1650, 1610 cm^{-1}; nmr δ 5.4 (s, 1, vinyl), 4.4 (m, 1, carbinol H), 3.71 (s, 2, methylene) 3.4 (m, 1, *tert*-butyl–OCH), 1.74 (s, 3, vinyl methyl), 1.15 (s, 9, *tert*-butyl), 1.0 (s, 3, angular methyl); mass spectrum (70 eV) *m/e* 57 (base peak), 264 (molecular ion).

Anal. Calcd for $C_{17}H_{28}O_2$: C, 72.22; H, 10.67. Found: C, 77.18; H, 10.56.

Thermolysis of 15.—A 200-mg portion of the isopropenyl ether was sealed neat in a Carius tube and heated for 2.5 hr at 200°. Nmr and glpc analyses showed only the dienes **6**.

Registry No.—**1**, 26675-10-5; **2a**, 33834-80-9; **2b**, 33872-31-0; **2c**, 33834-81-0; **4**, 33835-35-7; **5a**, 33835-36-8; **5c**, 33835-37-9; **7a**, 33834-82-1; **7b**, 33890-39-0; **8**, 33834-83-2; **10a**, 33835-38-0; **10b**, 33835-39-1; **11**, 33834-84-3; **13**, 33834-85-4; **14**, 33834-86-5; **15**, 33872-32-1; alcoholic precursor of **7b**, 33834-87-6; monoalkylated enone (precursor of **10b**), 33835-40-4; alcoholic precursor of **10b**, 33835-41-5; ethyl vinyl ether, 109-92-2; *N,N*-dimethylacetamide dimethyl acetal, 18871-66-4; triethyl orthoacetate, 78-39-7; decalin, 91-17-8.

Configurational Preference of the *P*-Methyl Group in Some Phosphorinane Derivatives[1]

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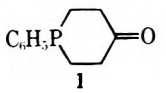
Received July 12, 1971

The same isomer mixture (about 55% cis, 45% trans) of 1-methyl-4-phosphorinanol (**4**) resulted from the reduction of 1-methyl-4-phosphorinanone (**3**) with seven different systems. The composition was not altered by equilibration techniques. The results were interpreted as indicating a lack of configurational preference of P-CH_3 for equatorial or axial positions and are consistent in this respect with earlier results on 1-methyl-4-substituted phosphorinanols. The observation that the dimethyl ketal of **3** exhibits a single OCH_3 nmr signal is also explainable on this basis; a conformationally biased system should exhibit two signals. *cis,trans*-1-Methyl-4-*tert*-butyl-4-phosphorinanol was prepared by addition of *tert*-butyllithium to **3**. The isomer mixture was separated by gas chromatography. The rate of quaternization of these (presumably) conformationally rigid compounds did not differ significantly, indicating little steric influence on the approach of the alkyl group to the axial or equatorial position about phosphorus.

The configurational stability of trivalent phosphorus, first demonstrated in 1961,[2] ensures that C-substituted cyclic tertiary phosphines will exist in cis,trans forms, and isomers of this type were later found to be separable.[3,4] The phosphorinane system[3,5] is of particular interest, for the configurational stability of phosphorus suggests that there could be two structures, with an axial or an equatorial exocyclic P substituent, for whatever conformation the ring adopts. We have established by single-crystal X-ray analysis that the conformation adopted by the ring in 1-phenyl-4-phosphorinanone (**1**)[6] and its dimethyl ketal (**2**) is a chair, somewhat flattened relative to cyclohexane by rather low (about 45°) torsion angles about phosphorus.[7] In both compounds, the substituent on phosphorus is directed axially,[8] as is true for the proton on phosphorinane itself (nmr studies).[9]



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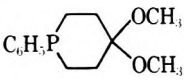
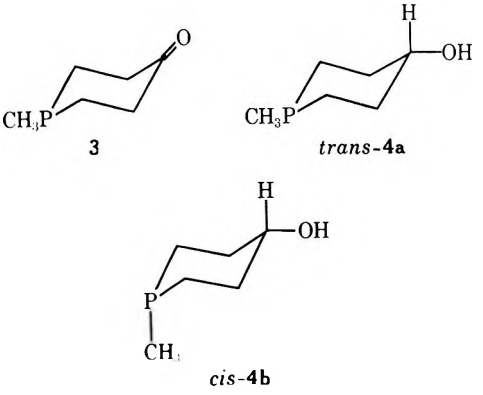


2

In this paper are presented some observations on P-methylphosphorinane derivatives; for this substituent, it has been suggested[5] that little conformational preference is expressed.

Reduction of 1-Methyl-4-phosphorinanone.—Some of our previous work[5] included reduction of the carbonyl of 1-methyl-4-phosphorinanone (**3**). With either lithium aluminum hydride or aluminum isopropoxide–isopropyl alcohol, the same ratio (55% cis, 45% trans) of isomers of 1-methyl-4-phosphorinanol (**4**) was obtained. Unlike some tertiary phosphorinanols, the isomers could not be separated by either fractional distillation or gas chromatography, but their presence in the reduction product was indicated by two ^{31}P nmr signals of nearly equal height and by two PCH_3 doublets in the proton nmr spectrum in benzene. The cis structure was assigned to that isomer with downfield PCH_3; both isomers were suggested tentatively from spectral features to differ in configurations at phosphorus, rather than at the carbinol carbon, as is known to be true for 4-methylcyclohexanol. Another point of interest is that reduction of 4-methylcyclohexanone with aluminum isopropoxide–isopropyl alcohol or lithium aluminum hydride has been reported to give different amounts (68 and 75%, respectively) of the thermodynamically more stable *trans*-4-methylcyclohexanol.[10] Our observation that ketone **3** was reduced by both of these reagents to give a nearly 1:1 mixture of **4a** and **4b** therefore seemed unusual.



3 *trans*-**4a** *cis*-**4b**

In the present work, we have used four other reducing systems [KBH_4, $NaB(H)(OCH_3)_3$, $LiAl(H)(O\text{-}tert\text{-}Bu)_3$, and Na–C_2H_5OH] on **3** and all gave, within experimental error, the same isomer ratio as before. In addition, an attempt to add *tert*-butylmagnesium chloride to the carbonyl of **3** failed; only reduction occurred, forming the same isomer mixture of **4**. The identity of the composition of **4** from the seven reductions cannot be ascribed to a change in the isomer ratio from that formed initially in a reduction to that of the equilibrium value; some of the reducing conditions are not reversible, and equilibration by inversion at phosphorus should occur at higher temperatures[11] than those involved in the reduction procedures. The result with

(1) Supported in part by Public Health Service Research Grant CA-05507, National Cancer Institute. Presented at the Southeastern-Southwestern Regional Meeting of the American Chemical Society, New Orleans, La., Dec 2, 1970. Taken from the Ph.D. Dissertation of J. H. S., Duke University, 1970.

(2) L. Horner, H. Winkler, A. Rapp, A. Mentrup, H. Hoffmann, and P. Beck, *Tetrahedron Lett.*, 161 (1961).

(3) L. D. Quin and H. E. Shook, Jr., *ibid.*, 2193 (1965).

(4) L. D. Quin, J. P. Gratz, and R. E. Montgomery, *ibid.*, 2187 (1965).

(5) H. E. Shook, Jr., and L. D. Quin, *J. Amer. Chem. Soc.*, **89**, 1841 (1967).

(6) A. T. McPhail, J. J. Breen, and L. D. Quin, *ibid.*, **93**, 2574 (1971).

(7) A. T. McPhail, J. J. Breen, J. H. Somers, J. C. H. Steele, Jr., and L. D. Quin, *Chem. Commun.*, 1020 (1971).

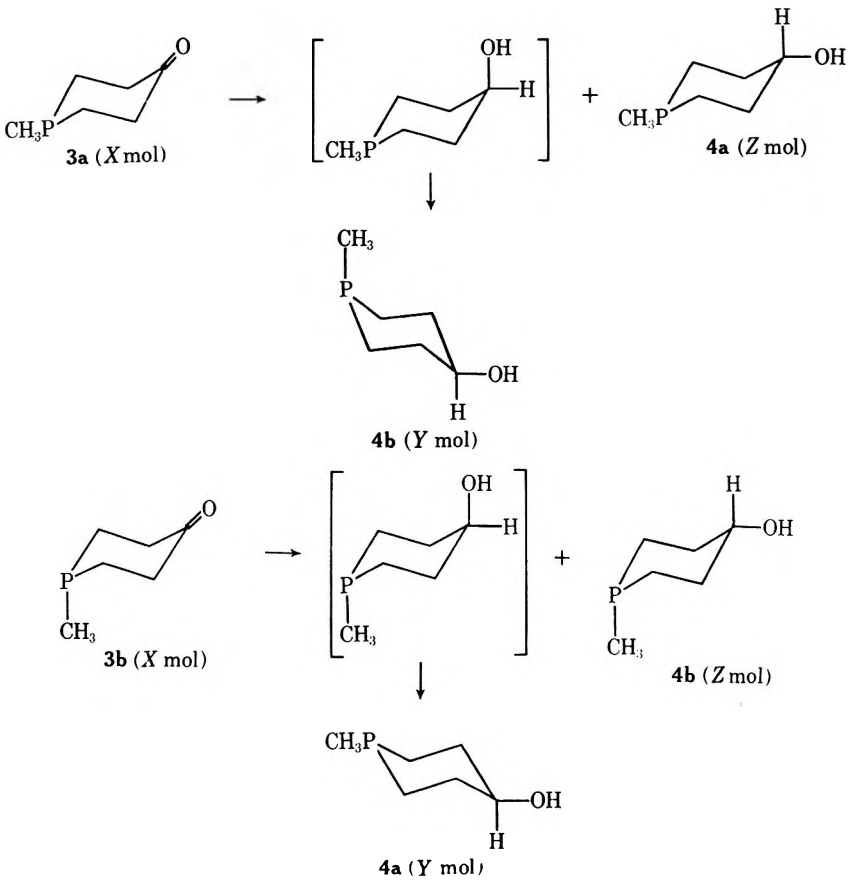
(8) J. P. Albrand, D. Gagnaire, J. Martin, and J. B. Robert, *Bull. Soc. Chim. Fr.*, 40 (1969), have arrived at the opposite conclusion for **1** from nmr studies. Their approach, however, does not seem capable of providing an unequivocal answer.[6]

(9) J. B. Lambert, W. L. Oliver, and G. F. Jackson, *Tetrahedron Lett.*, 2027 (1969).

(10) K. D. Hardy and R. J. Wicker, *J. Amer. Chem. Soc.*, **80**, 640 (1958).

(11) R. D. Baechler and K. Mislow, *ibid.*, **92**, 3090 (1970).

SCHEME I



$Na-C_2H_5OH$ is of particular interest, since in 4-methylcyclohexanone reduction it gives a very high percentage (83%) of trans isomer.[9] Lithium trimethoxyaluminohydride also normally gives a product whose composition reflects the relative stabilities of the isomers.[12]

The formation of nearly 1:1 mixture of *cis,trans*-**4** can be explained if the starting 1-methyl-4-phosphorinanone lacks conformational bias and contains roughly equal amounts of conformers with axial (**3b**) and equatorial (**3a**) PCH_3 at equilibrium. The argument may be developed as follows. (1) Methyl is sterically remote from the carbonyl group; the environment around this group should be similar in both conformations of the ketone. This means that the rates of reduction of *both* conformers by equatorial approach of the reducing agent must be similar, for the two transition states would be of similar energy. For the same reason, the rates of reduction by axial approach should be similar. (2) The extent of equatorial approach of a given reducing agent may not be the same as the extent of axial approach, and relative extents may vary from one reducing agent to another. (3) Initially formed products with axial hydroxyl will undergo ring flipping to the equilibrium composition presumed to be dominated by the conformer with equatorial hydroxyl. Scheme I expresses the result of application of these points to the reduction of an equimolar mixture of the ketone conformers; the total amount of alcohol **4a** formed is seen to equal that of **4b**, independently of the reducing agent used.

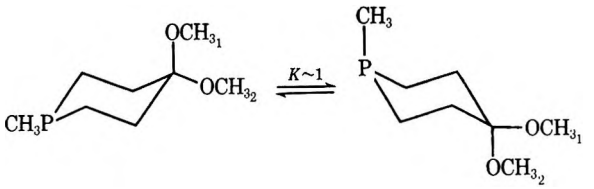
If the postulate of equal-energy conformers for ketone **3** is correct, then the same should be true for the isomers of phosphorinanol **4**, since steric effects on PCH_3 should be similar. Therefore, an equilibrium mixture for **4** should contain equal amounts of each isomer. This is very nearly the composition for **4** resulting from the several reductions of ketone **3**. If the isomers are not of equal energy, then this composition should be capable of modification by equilibration techniques. Equilibration at C-4 with the $AlHCl_2$ system[13] was attempted but no significant change occurred in the isomer ratio of the recovered alcohol. Equilibration by inverting at phosphorus was then attempted; since acyclic optically active phosphines can be racemized at 130°,[11] a temperature of 170° seemed quite adequate for this purpose. However, there was no change in the isomer ratio throughout 18 days, by which time extensive decomposition had occurred. The failure of these equilibration attempts suggests that the reductions of the ketone may have provided the equilibrium mixture in the first place, and provide further indication that axial and equatorial PCH_3 are of similar energy.

The consistency with which *cis*-**4** slightly predominates may be significant. If the structural assignments are correct, it is implied that axial PCH_3 is of slightly lower energy than equatorial. The system would therefore resemble phosphorinane and the *P*-phenyl derivatives **1** and **2** in this sense.

Dimethyl Ketal of 1-Methyl-4-phosphorinanone.—This ketal (**5**) proved of relevance to the conformational argument developed above through its exhibiting a

(12) H. C. Brown and H. R. Deck, *J. Amer. Chem. Soc.*, **87**, 5620 (1965).

(13) E. L. Eliel and M. N. Rerick, *ibid.*, **82**, 1367 (1960).



single sharp methoxy signal, either neat or in nonaromatic solvents, over a wide temperature range (−40 to 100°). This observation is explicable on the basis of the conformational equilibrium not being appreciably biased by PCH_3. This is the situation that holds for the *P*-phenyl ketal **2**; in the crystal, and also apparently in solution, phenyl prefers the axial position,[7] leading to nonequivalence in the OCH_3 groups (3-Hz separation). This behavior is also exhibited by ketals of biased 4-alkyl cyclohexanones.[14,15] While consistent with other data, however, this observation does not *prove* this conformational point, for the possibility must be considered that compensating chemical shift effects produced the apparent singlet. However, it seems unlikely that the effects would exactly compensate over a 140° range, and it is believed that the best explanation is that based on the conformational equilibrium constant being nearly unity.

We have also observed that a significant aromatic solvent effect occurs for ketal **5**; in benzene, for example, two methoxy signals appeared (180.0 and 181.7 Hz), both being upfield relative to the position of a sample measured neat or in nonaromatic solvents (Table I).

Table I

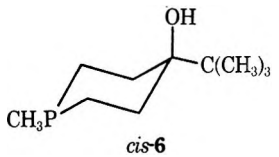
Nmr Spectra[a] of 1-Methyl-4,4-dimethoxyphosphorinane (5) in Various Solvents at 35°

Solvent	Wt % 5	—PCH_3 signal— δ	J, Hz	OCH_3 signal, ν, Hz
Neat[b]		0.98	3.0	187.8
Deuterioacetone[b]	30.2	0.98	2.9	186.2
Cyclohexane[c]	16.7	0.91	3.4	194.3
Methanol[c]	21.3	1.03	2.5	190.2
Toluene[b]	14.8	0.86	3.0	178.6, 180.2
Benzene[b]	33.3	1.05	3.2	180.0, 181.7
Pyridine[c]	27.5	0.98	3.1	188.2, 186.9

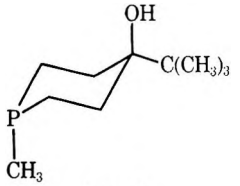
[a] Internal TMS reference. [b] Taken on Varian A-60 spectrometer. [c] Taken on Varian T-60 spectrometer.

The effect is specific for the methyls on oxygen, for the methyl on phosphorus retains its doublet character. Apparently the solvent acts to provide a different shielding environment for each methoxy, possibly through formation of a collision complex. Such complexes with benzene are known for methoxy groups.[16] Since this behavior does not appear to have been recorded for cyclohexanone ketals, we examined the ketal of 4-methylcyclohexanone in benzene, and found the peak separation (2.0 Hz neat) to be increased to 3.4 Hz in benzene. The same was true of the ketal of 4-*tert*-butylcyclohexanone (2.8 Hz separation in deuteriochloroform, 4.1 Hz in benzene). The magnitude of the effect is thus similar (1.3–1.7 Hz) for the two cyclohexanes and for the phosphorinane studied. The presence of a ring substituent is required for the nonequivalence to become detectable, since the ketal of cyclohexanone itself failed to show the effect.

***cis*- and *trans*-1-Methyl-4-*tert*-butyl-4-phosphorinanol.**—This alcohol (**6**) was prepared by adding *tert*-butyllithium to ketone **3**; the isomers were separated by preparative gas chromatography. As has been previously noted for other 1,4-dialkyl-4-phosphorinanols,[5] the isomers differed in the chemical shifts and coupling constants of the PCH_3 group (in benzene, δ 0.89, J = 4 Hz; δ 0.95, J = 2.1 Hz). These values resemble those reported for related structures,[5] but are of special importance in that they pertain to a system more clearly possessing the 4-alkyl group in the equatorial position in each isomer because of its bulk. The consistency of the values thus places on firmer ground the proposal made previously that, in a cis,trans pair of 1-methyl-4-alkylphosphorinanols, the configurational difference occurs at phosphorus rather than C-4. Cis and trans structures are tentatively assigned[5] to those isomers with the downfield and upfield PCH_3 signal, respectively.[17] They were formed in the ratio 42:58.



cis-**6**



trans-**6**

The availability of this phosphorinane system presumably of fixed ring geometry permitted an investigation of the relative rates of quaternization at phosphorus to determine if a difference existed due to the attacking group approaching an axial (as in *cis*-**6**) or an equatorial (*trans*-**6**) position. Reaction of the separate isomers in kinetic studies with ethyl bromide and the bulkier isobutyl idodide showed semiquantitatively that the rates did not differ significantly. Quaternization of a mixture of the two isomers showed more conclusively that this was the case; with isobutyl bromide or iodide, the ratio of the unreacted isomers of **6** was determined periodically by gas chromatography, and found to remain very nearly constant during the reaction period.

An explanation for the similar reaction rates for *cis*- and *trans*-**6** may be derived from the argument already advanced that isomers of *P*-methylphosphorinanes possess similar energy. The nearly identical reaction rates imply similar activation energies for the two isomers, and therefore that the energies of the two transition states must be nearly the same. That this can be the case is perhaps due to the partial carbon–phosphorus bond of the transition state being of such length as to hold the incoming alkyl substituent away from serious nonbonded interactions in axial approach, thus minimizing energy differences in the two modes of approach.

We have observed that shielding effects on phospho-

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(16) R. G. Wilson, J. H. Bowie, and D. H. Williams, *Tetrahedron*, **24**, 1407 (1968).
(17) These isomers are solids, and their structure may be conclusively established by X-ray studies, now in progress. The arguments presented in this paper will hold regardless of the correctness of the tentative assignment.

rus differ in *cis*- and *trans*-**6**, as had been noticed previously for *cis*- and *trans*-**4**.[5] In a mixture, that isomer believed to be *cis*-**6** had a ^{31}P chemical shift of 57.7 ppm, while the trans isomer had a value of 67.3 ppm. Hopefully, the acquisition of values for molecular parameters from X-ray studies will make it possible to account for this important effect.

Conclusions

The available data consistently suggest that little energy difference prevails among conformers or isomers of the phosphorinane system which differ in possessing a PCH_3 group in axial or in equatorial position.[18] The phosphorinane system therefore is quite unlike the cyclohexane system, where it is well known that the equatorial disposition for a methyl substituent is highly favored energetically. (Indeed, there may even be a slight preference for axial PCH_3 in the phosphorinanes.) Although bond lengths and angles involving phosphorus are appreciably different from those about carbon, models reveal that an axial P substituent in a chair conformation will still be subject to nonbonded interactions with the axial 3,5 protons. The factor that causes the axial position to be adopted in spite of this cannot be defined at present; London attractive forces have been proposed to explain the axial preference of oxygen in thiane monoxides,[19,20] and may be involved here. The strain introduced by the axial positioning of the substituent could be partially relieved if the external C–P–C angle is increased. This possibility, which implies greater sp^3 character in phosphorus, already has been advanced to account for J_{PCH} being greater for axial than for equatorial PCH_3.[5] Alternatively, the nonbonded interactions associated with an axial substituent could be diminished if in this ring a conformation was adopted which was somewhat flattened at phosphorus; smaller C–P–C–C torsion angles have the effect of removing the P substituent away from the 3,5-diaxial protons. It is expected that X-ray studies on the individual isomers of 1-methyl-4-*tert*-butyl-4-phosphorinanol will reveal structural differences of these or other types.

A similar conformational situation has very recently been encountered in the 1,3,2-dioxaphosphorinane ring; *P*-phenyl[21] as well as *P*-methyl[22] prefer the axial position. The lone pairs on oxygen, along with other bonds, have been mentioned as being involved in interactions with the phosphorus lone pair in these compounds, but finding the same steric result in the phosphorinane ring raises some doubt about this interpretation, at least as far as the oxygen lone pairs are concerned. Clearly, additional experimental work is needed before the unusual conformational preferences of phosphorinanes can be understood.

(18) Another effect has been noted which points to the same conclusion. In substituted (and biased) cyclohexylidene acetic esters and acids, carbonyl exerts a deshielding effect on the equatorial allylic proton of the ring cis to the ester group. In 1-methyl-4-(carbethoxymethylene)phosphorinane *both* protons of the cis allylic position are deshielded. This can be explained if the ring is not conformationally biased by PCH_3. L. D. Quin, J. W. Russell, Jr., R. H. Prince, and H. E. Shook, Jr., *J. Org. Chem.*, **36**, 1495 (1971).

(19) C. R. Johnson and D. B. McCants, Jr., *J. Amer. Chem. Soc.*, **87**, 1109 (1965).

(20) N. L. Allinger, J. A. Hirsh, M. A. Miller, and I. J. Tyminski, *ibid.*, **91**, 337 (1969).

(21) W. G. Bentrude and K. C. Yee, *Tetrahedron Lett.*, 3999 (1970).

(22) W. G. Bentrude, K. C. Yee, R. D. Bertrand, and D. M. Grant, *J. Amer. Chem. Soc.*, **93**, 797 (1971).

Experimental Section[23]

Reductions of 1-Methyl-4-phosphorinanone (3).—The product (**4**) of all reductions had the reported[5] boiling point and ^1H and ^{31}P nmr spectra. Product compositions listed in each reduction experiment refer to peak measurements from the ^1H spectra; a few were confirmed by ^{31}P signal measurements. Some measurements were made prior to product distillation; no change in the isomer ratio was detected in the distilled product.

With Sodium and Ethanol.—Freshly cut sodium metal (0.80 g, 0.035 g-atom) in 30 ml of sodium-dried toluene was heated to approximately 100° with vigorous stirring to melt and disperse the sodium. 1-Methyl-4-phosphorinanone[5] (1.50 g, 0.0115 mol) in absolute ethanol (1.6 g, 0.035 mol) was slowly added while maintaining the temperature below 20°. The solution was stirred for 2 hr at 10°. Water (15 ml) was then cautiously added to destroy any excess sodium. The organic layer was extracted with three 40-ml ether portions. Vacuum distillation after solvent removal on a rotary evaporator gave 1.14 g (76%) of 1-methyl-4-phosphorinanol (cis, 54%; trans, 46%).

With Potassium Borohydride.—**3** (2 g, 0.016 mol) in 10 ml of isopropyl alcohol was added dropwise to a refluxing slurry of potassium borohydride (0.54 g, 0.010 mol) in 20 ml of isopropyl alcohol. After refluxing for 3 hr and stirring at room temperature for 12 hr, the mixture was hydrolyzed with 30 ml of 10% KOH. The organic layer was removed, and the aqueous layer was extracted with four 40-ml benzene portions. After removing the solvent from the combined organic layers on a rotary evaporator, the residue was vacuum distilled to give 1.5 g (70%) of **4** (cis, 55%; trans, 45%).

With Sodium Trimethoxyborohydride.—**3** (3 g, 0.023 mol) in 25 ml of tetrahydrofuran was added dropwise to a slurry of sodium trimethoxyborohydride (7.0 g, 0.055 mol) in 250 ml of THF. After a 3-hr reflux period, the solution was cooled to 0° and cautiously hydrolyzed by dropwise addition of 40 ml of 20% NaOH. After stirring at room temperature for 1 hr, the solution was extracted with four 75-ml benzene portions. Removal of the organic solvent on a rotary evaporator followed by vacuum distillation of the residue gave a single fraction (1.7 g) shown by gas chromatography to contain 18% **3** and 82% **4**. The crude product was added to a solution of thiosemicarbazide (2.0 g, 0.022 mol) and sodium acetate (1.0 g) in methyl alcohol and the mixture was refluxed for 2 hr, removing **3** as its crystalline thiosemicarbazone. Rotary evaporation left a gummy solid residue. Water and ether (20 ml each) were added to the residue; the ether layer was separated, and the aqueous layer was extracted with four 20-ml ether portions. The ether was removed on a rotary evaporator, and the residue was distilled to give 0.5 g of **4** (cis, 55%; trans, 45%).

With Lithium Tri-*tert*-butoxyaluminohydride.—**3** (4 g, 0.031 mol) in 40 ml of THF was added dropwise over 30 min to a slurry of lithium tri-*tert*-butoxyaluminohydride (10.9 g, 0.043 mol) in 80 ml of THF. The solution was then refluxed for 2 hr and stirred at room temperature for 8 hr. Water (20 ml) was cautiously added while keeping the temperature at 0°. The solution was stirred overnight and then 20 ml of saturated sodium sulfate solution was added. The mixture was extracted with four 50-ml ether portions. Rotary evaporation, followed by vacuum distillation, gave 2.62 g (64%) of **4** (cis, 56%; trans, 44%).

With *tert*-Butylmagnesium Chloride.—**3** (7 g, 0.054 mol) in 25 ml of ether was added dropwise to 60 ml of 2.7 *M* *tert*-butylmagnesium chloride (0.16 mol) in ether, as obtained from Matheson Coleman, and Bell, East Rutherford, N. J. After refluxing for 7 hr and stirring overnight, the mixture was hydrolyzed at 0° with 50 ml of 25% NH_4Cl. The product was extracted with six 50-ml ether portions, and solvent was then removed. Both nmr and infrared spectra as well as gas chromatography showed a substantial amount (47%) of **3** to be present; this was removed as its thiosemicarbazone as above. Gas chromatography of the recovered product (16% overall yield) showed 5% of **3** still present. No evidence was obtained for addi-

(23) All manipulations of phosphines were conducted in a nitrogen atmosphere. Proton nmr spectra were obtained with a Varian A-60 spectrometer unless otherwise noted and are referenced to internal TMS. Phosphorus nmr spectra were obtained with a Varian V-4300B system at 19.3 MHz with 85% phosphoric acid as reference.

tion of the Grignard reagent to the carbonyl group. The 4 formed contained 52% cis and 48% trans isomers.

Attempted Equilibration of 1-Methyl-4-phosphorinanol with Lithium Aluminum Hydride–Aluminum Chloride.[13]—Anhydrous $AlCl_3$ (3.3 g, 0.025 mol) was placed in a 50-ml erlenmeyer flask connected by Gooch tubing to a 100-ml three-neck flask containing $LiAlH_4$ (0.30 g, 0.0080 mol) in 20 ml of THF. The $AlCl_3$ was added slowly to the flask with vigorous stirring. After the exothermic reaction had subsided, 3.0 g (0.023 mol) of 1-methyl-4-phosphorinanol (55% cis, 45% trans) was added dropwise over a 10-min period. The solution was then refluxed for 2 hr, cooled to room temperature, and treated with acetone (0.87 g, 0.015 mol). After 1 hr reflux, the solution was cooled with an ice bath and cautiously hydrolyzed first with 5 ml of water and then with 10 ml of 10 *N* NaOH. The product was extracted with two 30-ml ether portions. After removing the ether on the rotary evaporator, the residue was distilled to give 1.0 g of **4**, having the expected ir spectrum. The nmr spectrum in benzene showed the isomer composition to be 53% cis, 47% trans.

In another approach, the $AlCl_3$–phosphine complex was formed first by adding 4.06 g (0.0304 mol) of $AlCl_3$ to 4.00 g (0.0304 mol) of **4**. The complex from 4.06 g (0.0304 mol) of $AlCl_3$ and 0.300 g (0.00815 mol) of $LiAlH_4$ was formed separately in 20 ml of THF. The lumpy phosphine complex was added to the lithium aluminum hydride–aluminum chloride compound (exothermic). The solution was refluxed for 4 hr and cooled to room temperature. Acetone (0.87 g, 0.015 mol) and a drop of 1-methyl-4-phosphorinanone were added; the solution was refluxed for 18 hr and worked up as before. Distillation gave 1.55 g of **4** (56% cis, 44% trans). Repetitions with variations in the molar ratios of the reagents caused no significant difference in isomer ratio.

Thermal Equilibration of 1-Methyl-4-phosphorinanol (4).—A sample of **4** (55% cis, 45% trans) was held at 170 ± 10° under nitrogen. Samples were withdrawn at various intervals and nmr spectra were taken. Infrared spectra were also taken to determine if any dehydration to 1-methyl-1,2,5,6-tetrahydrophosphorin occurred. Although the spectra after 9 and 12 days of heating showed no dehydration, the sample after 18 days did show slight double-bond absorption at 1660 cm^{-1}. The nmr spectra of the various samples showed no change in the starting isomer ratio. After 22 days, the sample had become very viscous, although it was still colorless, and was no longer soluble in benzene.

1-Methyl-4,4-dimethoxyphosphorinane (5).—Trimethyl orthoformate (8.2 g, 0.039 mol) was added to a solution of 1-methyl-4-phosphorinanone (5.00 g, 0.039 mol) in 100 ml of anhydrous methanol. Hydrogen chloride was generated by adding NaCl (16 g, 0.27 mol) to concentrated H_2SO_4, and passed into the phosphine mixture. An exotherm occurred and the hydrochloride of the phosphine usually precipitated; this dissolved with vigorous stirring and heating. The solution was then refluxed for 2 hr and stirred at room temperature for 2 days. The methyl formate formed (bp 31°) was removed by distilling to the boiling point of methanol (64°). More trimethyl orthoformate was added, and after 2 days the methyl formate was again removed. This process was repeated three additional times to drive the reaction to completion. The solution was then made basic with sodium methoxide in methanol, and the methanol was removed on a rotary evaporator. After addition of water (20 ml) to dissolve the salt, the phosphine was extracted with five 50-ml portions of ether. The ether was removed on a rotary evaporator, and the residue was distilled to give crude **5** (1.88 g, 27%), bp 43–45° (0.33 mm). The infrared spectrum showed a small carbonyl signal, and gas chromatography on an SE-30 column at 150° indicated the composition as 91% **5**, 9% **3**. The sample was purified by preparative gas chromatography (25% SE-30 on Chromosorb W, 60–80 mesh, at 150°), using 100-μl injections of a 50% solution in benzene. The eluate was collected in benzene, which was later removed by vacuum sublimation. Attempts were made to convert the phosphine to a less sensitive salt for analysis, but it proved necessary to analyze the phosphine directly, with moderate success.

Anal. Calcd for $C_8H_{17}O_2P$: C, 54.93; H, 9.73; P, 17.58. Found: C, 54.55; H, 9.85; P, 17.02.

Nmr Study of 1-Methyl-4,4-dimethoxyphosphorinane (5).—The nmr spectrum (neat) of **5** (containing about 4% of ketone **3**) had the expected features: 3 H doublet (PCH_3) (J = 3.0 Hz) at δ 0.98, 6 H singlet (OCH_3, sharp) at δ 3.13, and a multiplet for the ring methylenes centered at about δ 2. The spectra over the range −40 to 100° were essentially the same. Spectra in various solvents are described in Table I, and a temperature study in toluene in Table II.

Table II

Nmr Temperature Study of 1-Methyl-4,4-dimethoxyphosphorinane (5) in Toluene[a]

Temp, °C	Wt % 5	PCH_3 signal, δ	PCH_3 signal, J, Hz	OCH_3 signals, ν Hz
−47	14.8	0.72	3.0	170.4, 173.1
40	7	0.78	3.1	171.7, 173.4
75	7	0.81	3.1	175.4, 176.7
95	7	0.84	3.0	177.1, 178.4

[a] Taken on a Varian A-60 spectrometer with external TMS.

Ketals of Cyclohexanones.—The ketals were prepared by treating the ketones with trimethyl orthoformate.[24] 1,1-Dimethoxycyclohexane had bp 60° (20 mm) [lit.[25] bp 63° (20 mm)], and gave a single OCH_3 nmr signal (δ 3.10 neat, 3.03 in toluene). 1,1-Dimethoxy-4-methylcyclohexane[12] had bp 57° (20 mm); a neat sample at room temperature had two OCH_3 signals (1:1) centered at δ 3.10, separated by 2.0 Hz. No significant change occurred in the spectrum when taken at 120°. A 0.095-g sample in 0.327 g of benzene had these signals centered at δ 3.08, separated by 3.4 Hz. 1,1-Dimethoxy-4-*tert*-butylcyclohexane, mp 36–37° (lit.[24] mp 38°), in $CDCl_3$ had two OCH_3 peaks (1:1) centered at δ 3.20, separated by 2.8 Hz. A 0.142-g sample in 0.59 g of benzene had the signals at δ 3.11, with separation of 4.1 Hz.

1-Methyl-4-*tert*-butyl-4-phosphorinanol (6).—1-Methyl-4-phosphorinanone (**3**, 10.0 g, 0.077 mol) in 100 ml of pentane was added dropwise over 1 hr to 135 ml of 1.54 *M* *tert*-butyllithium (0.20 mol) in pentane. An exotherm was noted, and a white solid precipitated. The solution was refluxed for 24 hr, cooled with an ice bath, and then cautiously hydrolyzed by adding 40 ml of water dropwise. After separation of the organic layer, the aqueous layer was extracted with three 100-ml ether portions. The combined organic layers were stripped of solvent on a rotary evaporator, leaving a solid yellow residue. Vacuum distillation gave 2.0 g of unreacted **3** at 55–60° (0.20–0.25 mm) and a product fraction (8.1 g, 56%) at 70–80° (0.20 mm) with mp 62–65°.

Anal. Calcd for $C_{10}H_{21}OP$: C, 63.80; H, 11.24; P, 16.46. Found: C, 63.97; H, 11.55; P, 16.38.

Gas chromatography on OV-17 or SE-30 columns at 175° showed the presence of two isomers, that with the lower retention time comprising 42% of the mixture. The nmr spectrum in benzene showed two PCH_3 doublets at δ 0.96 (J = 2 Hz) and 0.91 (J about 3–4 Hz). The latter doublet was partly obscured by the *tert*-butyl protons (two sharp singlets centered at δ 0.87 with a separation of about 1 Hz) and was broader than the downfield doublet. The ^{31}P nmr spectrum of a 35.2% solution in benzene had two peaks at 57.7 and 67.3 ppm, in the ratio 40:60.

The isomers were separated (retention times, cis 9.5, trans 11.8 min) by gas chromatography on a 1 × 150 cm column of OV-17 on Chromosorb G (4%), 175°, 75 ml of helium per minute, collecting the eluate in distilled benzene. The benzene was removed by vacuum sublimation of a frozen sample, leaving the crystalline isomer. Gas chromatography of the products showed complete separation of the two isomers. Each isomer was further purified by vacuum sublimation. The nmr spectrum of a 35.1% solution of the major isomer (trans) in benzene had the PCH_3 doublet at δ 0.89 (J = 4 Hz) and the *tert*-butyl singlet at δ 0.85. The ^{31}P nmr signal (in benzene) appeared at 64.6 ppm. The melting point was 84–85°. The sample was resublimed and analyzed. *Anal.* Found: C, 64.05; H, 11.20; P, 16.75.

The nmr spectrum of a 13.1% solution of *cis*-**6** in benzene had the PCH_3 doublet (sharp) at δ 0.95 (J = 2.1 Hz) and the *tert*-butyl singlet at δ 0.84. The methylene region (δ 1–2) of this isomer was simpler than that of the trans isomer, but for neither were the signals well defined.

Quaternization of *cis,trans*-1-Methyl-4-*tert*-butyl-4-phosphorinanol (6).—A 0.114 *M* solution of the isomers of **6** (42% cis, 58% trans) in methanol was mixed with a tenfold excess of 0.157 *M* isobutyl iodide in methanol at 25.0°. The isomer ratio for unreacted **6** was determined periodically for 78% of the reaction

(24) E. L. Eliel, V. G. Badding, and M. N. Rerick, *J. Amer. Chem. Soc.*, **84**, 2371 (1962).

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(200 min) by gas chromatography. The ratio did not vary more than could be attributed to experimental error, and the final composition was 40% cis, 60% trans. There was also no change in the isomer ratio during reaction of excess isobutyl bromide (2.43 *M*) with **6** (0.112 *M*; 45% cis, 55% trans), which was followed to 47% completion (230 min).

Registry No.—**3**, 16327-48-3; **4a**, 16327-50-7; **4b**, 16327-49-4; **5**, 33834-95-6; *cis*-**6**, 33835-61-9; *trans*-**6**, 33835-62-0.

Acknowledgment.—We are grateful to Mr. Sidney Featherman for assistance in developing gas chromatographic conditions for **6**, and to Mr. Joseph J. Breen for obtaining ^{31}P nmr data.

Synthesis of Some Benzeneazo Derivatives of Phosphonic Acid Monoesters

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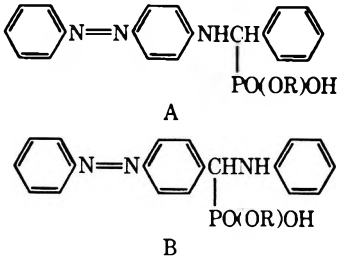
Neutral esters of α-anilinobenzylphosphonic acid were prepared by addition of dialkyl phosphites to Schiff's base. Their hydrolysis with alcoholic sodium hydroxide solution, followed by the acidification of the sodium salts obtained, afforded the corresponding monoesters.

Since the first benzeneazophosphonic acid was reported,[1] a number of various benzeneazo or naphthylazo derivatives of phosphonic acid and its neutral esters have been prepared.[2-4] However, no attempt has been made to synthesize arylazo derivatives of phosphonic acid monoesters. As the syntheses of some monoesters of α-anilinobenzylphosphonic acid were described earlier[5,6] we have undertaken the present investigation to prepare several arylazo derivatives of α-anilinobenzylphosphonic acid.

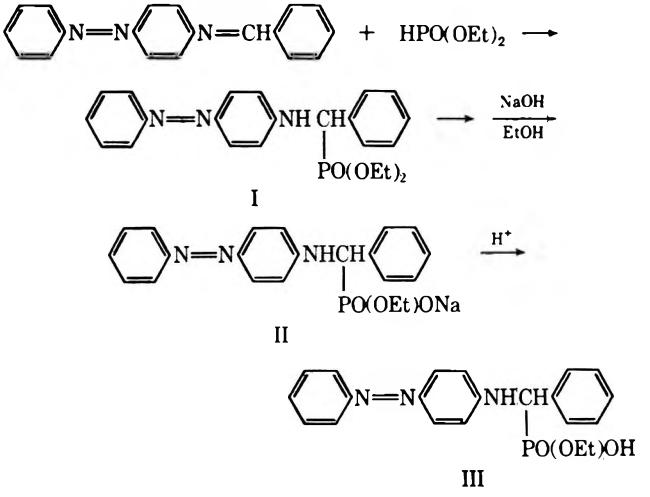
Results and Discussion

Monoesters of [α-(4-benzeneazoanilino)-*N*-benzyl]phosphonic acid (type A) and of [4-benzeneazo-α-(anilino)benzyl]phosphonic acid (type B) have been synthesized. In addition to the monoesters the corresponding diesters, *i.e.*, diethyl and dibutyl [α-(4-benzeneazoanilino)-*N*-benzyl]phosphonate (I and IV) and diethyl and dibutyl [4-benzeneazo-α-(anilino)benzyl]phosphonate (VII and IX), were prepared. Only sodium salts of monoethyl and monobutyl esters [α-(benzeneazoanilino)-*N*-benzyl]phosphonic acid (II and V, respectively), obtained by hydrolysis of I and IV, were isolated in pure form. Neutral esters were obtained by reaction of dialkyl phosphites to Schiff's bases. They were subjected to alkaline hydrolysis to give sodium salts of the monoesters. The latter were converted to the free monoesters by acidification with a diluted mineral acid. Essentially the same reaction was applied to prepare both types of compounds. An illustration (Scheme I) is given for the preparation of the type A only. All phosphonic acid diesters are stable compounds. However, when subjected to alkaline hydrolysis they exhibit various degrees of stability. The compounds of the A type appear to be more stable than that of the B type. Thus the monoesters III and VI were obtained from the corresponding diesters I and IV in over 60% yield. Hydrolysis of diesters VII and IX yielded only about 25% of the monoesters VIII and X, together with an unidentified product (25–30%), which was insoluble in water and did not contain phosphorus, and a product (about 17%) which was identified as benzeneazocarboxylic acid-(4) (XIII) (Table I). The acid was obtained from its sodium salt by acidification with diluted hydrochloric acid and separated from a monoester due to better solubility in ethanol.



R = C_2H_5, compound III
R = C_4H_9, compound VI
R = C_2H_5, compound VIII
R = C_4H_9, compound X

SCHEME I



Attempts have been made to prepare the monoester of the following formula.

(1) G. M. Kosolapoff and G. G. Priest, *J. Amer. Chem. Soc.*, **75**, 4847 (1953).

(2) T. M. Moshkina and A. N. Pudovik, *Zh. Obshch. Khim.*, **35**, 2042 (1965).

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(4) Houben-Weyl, "Methoden der Organischen Chemie," Vol. XII/2, Georg Thieme Verlag, Stuttgart, 1964, pp 545–547.

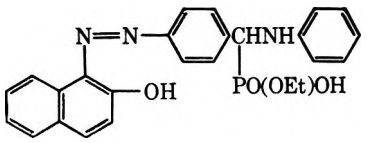
(5) V. Jagodič, *Chem. Ber.*, **93**, 2308 (1960).

(6) V. Jagodič and M. J. Herak, *J. Inorg. Nucl. Chem.*, **32**, 1323 (1970).

TABLE I

Compd	Formula	Mp, °C	Yield, %	Calcd, % C	H	N	P	H_2O	Found, % C	H	N	P	H_2O
I	$C_{23}H_{26}N_3O_3P$	134.5–135	90	65.23	6.19	9.92	7.32		65.02	6.44	10.15	7.21	
II	$C_{21}H_{21}N_3O_3PNa \cdot 1.5H_2O$	232	66	56.75	5.45	9.46	6.97	6.08	56.83	5.61	9.62	6.79	5.92
III	$C_{21}H_{22}N_3O_3P$	182	82	63.79	5.61	10.63	7.83		64.04	5.80	10.87	7.70	
IV	$C_{27}H_{34}N_3O_3P$	122.5–123	92	67.63	7.14	8.76	6.64		67.79	7.15	8.68	6.29	
V	$C_{23}H_{25}N_3O_3PNa \cdot H_2O$	243	60	59.61	5.87	9.07	6.68	3.88	59.57	5.96	8.93	6.66	3.09
VI	$C_{23}H_{26}N_3O_3P$	167	59	65.23	6.19	9.92	7.32		65.42	6.11	10.14	7.27	
VII	$C_{23}H_{26}N_3O_3P$	157–158	86	65.23	6.19	9.92	7.32		64.99	6.12	10.17	7.17	
VIII	$C_{21}H_{22}N_3O_3P$	177.5–178	25	63.79	5.61	10.63	7.83		63.97	5.58	10.84	7.74	
IX	$C_{27}H_{34}N_3O_3P$	112.5–113	82	67.63	7.14	8.76	6.46		67.81	7.35	8.82	6.33	
X	$C_{23}H_{26}N_3O_3P$	178–178.5	26.6	65.23	6.19	9.92	7.32		65.15	6.34	9.81	7.22	
XI	$C_{23}H_{17}N_3O_2$	160.5–161	68.8	78.61	4.88	11.96			78.54	4.83	12.04		
XII	$C_{27}H_{28}N_3O_4P$	149–150	82	66.25	5.77	8.58	6.33		66.11	5.96	8.60	6.08	
XIII	$C_{13}H_{10}N_2O_2$	246–247[a]	17	69.02	4.45	12.38			68.85	4.71	12.53		

[a] Mp 248.5–249.5°: H. D. Anspon, *Org. Syn.*, **25**, 86 (1945).



Although the corresponding diethyl [4-(2-naphtholazo)-α-anilinobenzyl]phosphonate (XII) was prepared in over 80% yield and was quite stable, we were not able to prepare the above monoester. Regardless of the temperature on which the hydrolysis was carried out, kind of the solvent applied (ethanol or water), or duration of hydrolysis, only a mixture consisting of various proportions of decomposition products and unchanged XII resulted. When the product of hydrolysis was dissolved in water and acidified with a mineral acid a compound was obtained which showed in the ir spectrum a strong band at 1680 cm^{-1}, characteristic for the carboxylic acids. This indicates that here, similarly to the hydrolysis of diesters VII and IX, the rupture of the C–P bond and the formation of a carboxylic acid took place. Such a great instability of diester XII in alkaline medium is probably due to the presence of the naphthyl OH group.

The color of the products varies from orange to red. Monoesters of the A type are more readily soluble in common organic solvents than those of the B type.

Experimental Section

The yields and physical properties of the compounds prepared are listed in Table I. The analyses were obtained from the Microanalytical Laboratory, Rudjer Bošković Institute. Melting points are uncorrected.

Preparation of Diesters I, IV, VII, IX, and XII.—Neutral esters of phosphonic acids were prepared by heating an equimolar mixture of Schiff's base and dialkyl phosphite in a water bath for 8 hr. Contrary to the original method[7] this addition was carried out without any catalyst. The reaction products solidified upon cooling and were recrystallized from ethanol.

Hydrolysis of Diesters.—Approximately 5% solution of neutral esters in ethanol was refluxed with an excess of sodium hydroxide (2–2.5 mol/mol of diester) for 20 hr. To precipitate the excess of the base, carbon dioxide was introduced into the solution. Sodium carbonate formed was filtered off and the resulting solution was evaporated to dryness *in vacuo*. Sodium salts II and V, obtained from the corresponding diesters I and IV, were recrystallized from absolute ethanol. Sodium salts obtained from diesters VII and IX were used in a crude form to prepare the free monoesters.

Preparation of Monesters III, VI, VIII, and X.—Sodium salts were dissolved in water and the solution was filtered to remove any insoluble impurities. The resultant solution was stirred and a small excess of 5% hydrochloric or sulfuric acid was added dropwise causing the monoesters to separate as a precipitate. They were collected by filtration, dried, and recrystallized as follows: monoesters I and VI from a benzene–ether (1:50) mixture; VIII from ethanol; and X from a ethanol–ether mixture.

Preparation of Schiff's Bases.—4-Benzeneazo-*N*-benzalaniline[8] and 4-(benzeneazobenzal)aniline[9] were prepared as described. 4-(2-Naphtholazo)benzalaniline (XI) was obtained by heating a mixture of 0.4 g (0.00143 mol) of 4-(2-naphtholazo)benzaldehyde[10] and 0.15 g (0.0015 mol) of aniline on a steam bath for 0.5 hr. After standing overnight at room temperature a solid product formed. It was recrystallized from ethanol giving 0.35 g (68.8%) of XI, mp ~150°. Repeated recrystallization from ether yielded a red product melting at 160.5–161°.

Registry No.—I, 33521-43-6; II, 33521-44-7; III, 33521-45-8; IV, 33521-46-9; V, 33521-47-0; VI, 33521-48-1; VII, 33521-49-2; VIII, 33521-50-5; IX, 33521-51-6; X, 33521-52-7; XI, 33521-53-8; XII, 33521-54-9.

Acknowledgments.—The authors are indebted to Dr. Š. Mesarić and Associates for the microanalyses and to Mr. Z. Despotović for the thermogravimetric analyses of water.

(7) A. N. Pudovik and M. V. Korchemkina, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 940 (1952).

(8) F. G. Pope and W. I. Willett, *J. Chem. Soc.*, **103**, 1258 (1913).

(9) F. J. Alwey, *Amer. Chem. J.*, **28**, 47 (1902).

(10) P. Friendländer and E. Lenk, *Chem. Ber.*, **45**, 2084 (1912).

Preparation and Properties of β-Lactones from Steroidal 17,20-Dihydroxy-21-oic Acids[1]

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The major neutral products from the reaction of the 17,20-dihydroxy-21-oic acids **1a** and **1b** with acetic anhydride–pyridine are the 20-acetyl-21,17α-lactones **4a** and **4b**. A mechanism is presented to explain the controlling effect of configuration at C-20 on the extent of acetylation at C-17 *vs.* C-21,C-17 cyclization. Spontaneous or thermal decarboxylation of **4a** and **4b** leads stereospecifically to **6** and **7**, the respective trans and cis enol acetates of the 17-aldehyde **8**. Reaction of glycolic acids **1a** and **1b** with ethyl chlorocarbonate–pyridine affords the 20-cathyl-21,17α-lactones **13a** and **13b**. Treatment of **13a** with methanolic sodium hydroxide results both in cleavage of the β-lactone ring and formation of an epimeric mixture of the methyl ester 17,20-cyclic carbonates **18a** and **18b**, in which the 20β epimer predominates. Similar treatment of β-lactone **13b** gives the methyl ester cyclic carbonate without epimerization of C-20. Decarboxylation of **13a** and **13b** in refluxing methanol affords the trans and cis enol cathylates **16** and **17**. Configurational assignments for both the latter compounds and the enol acetates **6** and **7** were made on the basis of their nmr spectral properties. Selective peracid oxidation of **16** and **17** furnished their respective 17,20-epoxides **20** and **21**. Successive reaction of the epoxides with methanolic potassium bicarbonate and methanolic hydrogen chloride gave the 17α-hydroxy-20,20-dimethoxy derivative **22** as a common product. In order to assess the contribution of the oxygen function at C-20 in β-lactone formation, the 20-deoxy acid **34** was prepared. The essential role of the 20-acyl group is evident since treatment of **34** with either acylating reagent resulted in no appreciable formation of β-lactone. Instead, reaction with acetic anhydride–pyridine provided the 17-acetate **36**, and reaction with ethyl chlorocarbonate–pyridine gave the ethyl ester **37**, presumably by acylative decarboxylation.

In an earlier communication[2] we noted that reaction of the 17,20-dihydroxy-21-oic acids **1a** and **1b** (Scheme I) with acetic anhydride–pyridine at room temperature affords the 17,20-diacetoxy-21-oic acids **2a** and **2b** as major products. We also recorded that a significant neutral fraction was generated in the reaction, but this material was not studied in detail at that time. Our more recent interest in cyclic derivatives of the pregnane side chain led us to reinvestigate this reaction. We have found, as originally postulated,[3] that the major neutral products are the 20-acetoxy-21,17α-lactones **4a** and **4b**. This paper describes a general procedure for the direct preparation of 21,17α-lactones, some of the typical reactions which these compounds undergo, and a study of the structural features which favor β-lactone formation.

Treatment of the 17,20α-dihydroxy-21-oic acid **1a** with equal volumes of acetic anhydride and pyridine for 18 hr at 5° followed by careful partitioning of the reaction mixture between methylene chloride and cold, dilute sodium bicarbonate solution provided roughly equal amounts of acidic and neutral fractions. In accord with our previous findings the 17,20α-diacetoxy-21-oic acid **2a** was obtained in a yield of 41%. Direct crystallization of the neutral fraction gave the β-lactone **4a** in a yield of 33%. Similar treatment of the 17,20β-dihydroxy-21-oic acid **1b** resulted in the formation of predominantly acidic material from which both the 17,20β-diacetoxy-21-oic acid **2b** and the 17-hydroxy-20β-acetoxy-21-oic acid **3b** (as the methyl ester) were each obtained in a yield of 33%. The minor neutral fraction furnished the β-lactone **4b** in 8% yield.

Assignment of β-lactone structures to **4a** and **4b** was made on the basis of the following evidence: (a) the ir spectrum which showed no hydroxyl absorption and the presence of a new intense carbonyl band at 1820 cm^{-1} which is characteristic of β-lactones;[4] (b) the ready loss of carbon dioxide in the mass spectrograph coupled with a fragmentation pattern consistent with the proposed structures; and (c) the conversion of **4a** and **4b** in methanolic sodium hydroxide to the known methyl esters **5a** and **5b**.

Only a few examples of the direct formation of β-lactones from β-hydroxy acids have been recorded in the literature[5] since an earlier review by Zaugg[6] stated categorically that "...β-lactones cannot be prepared from their corresponding hydroxy acids or esters." It is of interest to speculate on the mechanism of the reaction which must necessarily be highly dependent on the steric factors which promote either acetylation at C-17 or cyclization to β-lactones. A plausible mechanism (Scheme II) involves initial conversion of the dihydroxy acid (a) to the mixed anhydride (b). The point of nucleophilic attack by the hydroxyl oxygen at C-17 determines the nature of the resulting products. Attack on the acetate carbonyl group followed by cleavage of the anhydride bond (pathway 1) affords the 17-acetoxy acid (c); attack on the carboxyl carbonyl group followed by elimination of acetic acid (pathway 2) gives the β-lactone (d). Such a mechanism is similar to that postulated by Diassi and Dylion in the conversion of yohimbine to its β-lactone, β-yohimbine.[7] Examination of Dreiding models of the glycolic acids **1a** and **1b** serves to explain the lower yields of β-lactone from the 20β epimer. Pathway 2 is less favored in the reaction of **1b** because approach of the C-17 oxygen to the anhydride carboxyl carbonyl group would be accompanied by serious impingement of the 20-hydroxyl (or acetoxyl) on the angular methyl group at C-18. This steric hindrance also manifests itself in an inhibition of pathway 1, since only half of the isolated acidic material was acetylated at C-17.

(1) This work was supported largely by a research grant, AM01255, from the National Institute of Arthritis and Metabolic Diseases, National Institutes of Health, U. S. Public Health Service. We are grateful to this institute for its continued and generous support of our research.

(2) M. L. Lewbart and V. R. Mattox, *J. Org. Chem.*, **28**, 1773 (1963).

(3) M. L. Lewbart, Ph.D. Thesis, University of Minnesota, Minneapolis, Minn., 1961.

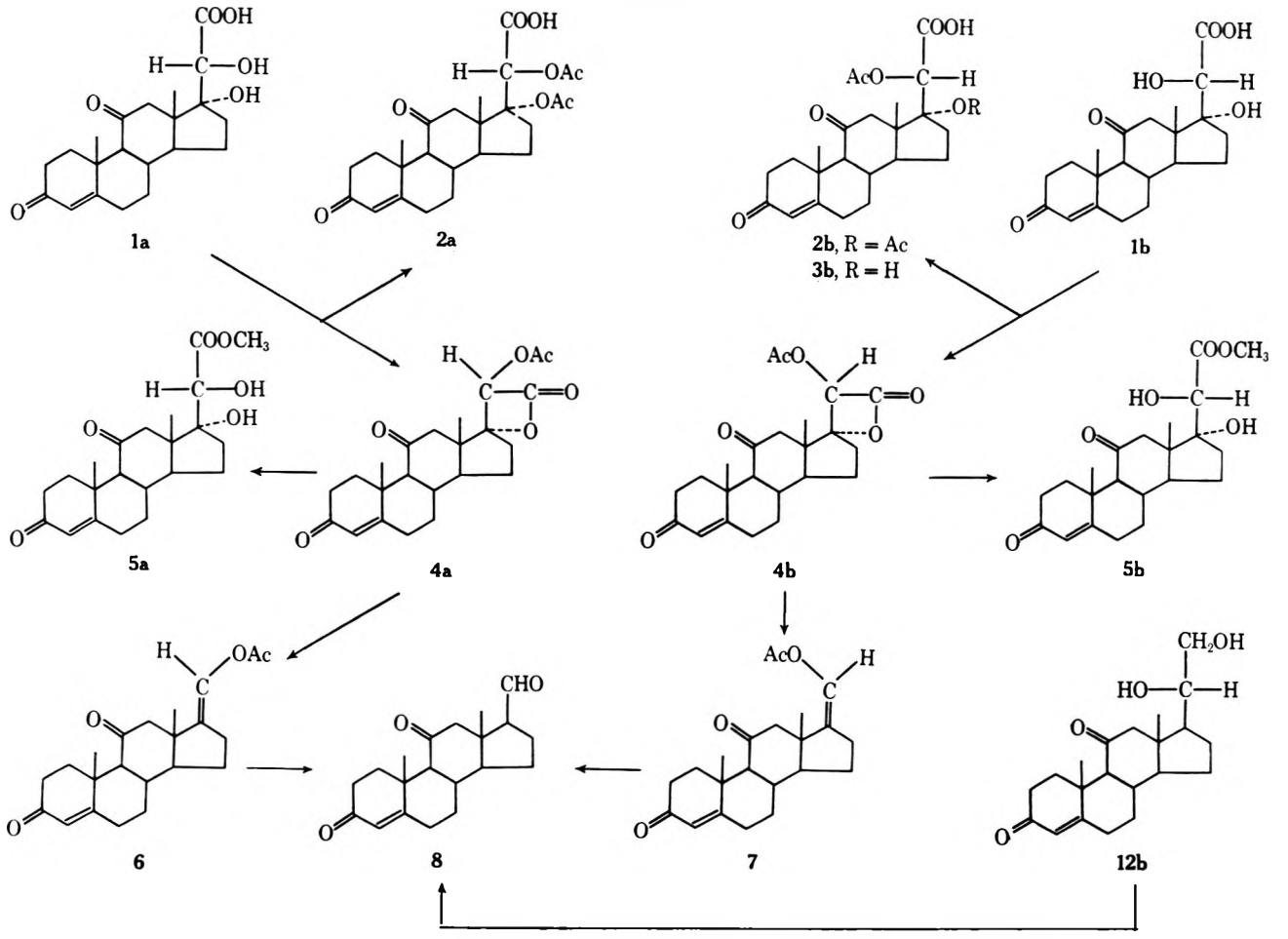
(4) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, p 179.

(5) F. Merger, *Chem. Ber.*, **101**, 2413 (1968), and other work cited.

(6) H. E. Zaugg, *Org. React.*, **8**, 305 (1954).

(7) P. A. Diassi and C. M. Dylion, *J. Amer. Chem. Soc.*, **80**, 3746 (1958).

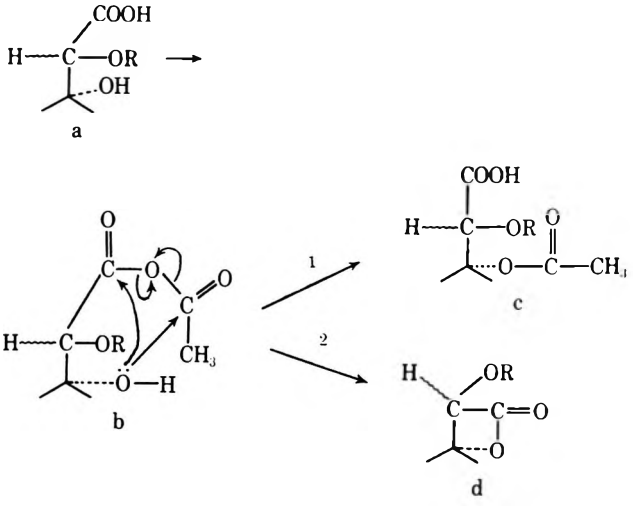
SCHEME I[a]



[a] In this and other schemes, the substituent at C-20 is α oriented in "a" compounds and β oriented in "b" compounds.

The crystalline β-lactones **4a** and **4b** are stable at −20° but decompose slowly at room temperature as evidenced by a progressive decrease in their melting points and the formation from each of a chromatographically more mobile product. The same products could be obtained by refluxing **4a** and **4b** in benzene for several days and were identified as decarboxylation products, namely the trans and cis enol acetates **6** and **7**. The stereochemical assignments were made on the basis of nmr spectral properties (*vide infra*). Enol acetates of this type have not been described previously, and it is likely that they can be prepared only by decarboxylation of 21,17α-lactones, since forced acetylation of the aldehyde **8** affords the geminate diacetate as sole product.[8] Treatment of the enol acetates **6** and **7** with methanolic sodium hydroxide afforded the aldehyde **8** as a common product. Confirmation of the structure of **8** was obtained by its independent synthesis from the glycol **12** by oxidation with 1 equiv of metaperiodic acid.[9]

SCHEME II



In view of the successful use by Diassi and Dylion of ethyl chlorocarbonate–pyridine in the preparation of β-yohimbine, it seemed of interest to study the reaction of glycolic acids **1a** and **1b** (Scheme III) with this reagent. Treatment of **1a** in cold pyridine with excess ethyl chlorocarbonate for 1 hr at room temperature gave the 20α-cathyl-β-lactone **13a** in nearly quantitative yield. The reaction of **1b** proved to be considerably more complex in that a significant acidic fraction was obtained, and the neutral fraction consisted of several components. From the acidic fraction was re-

(8) M. L. Lewbart, unpublished experiments.

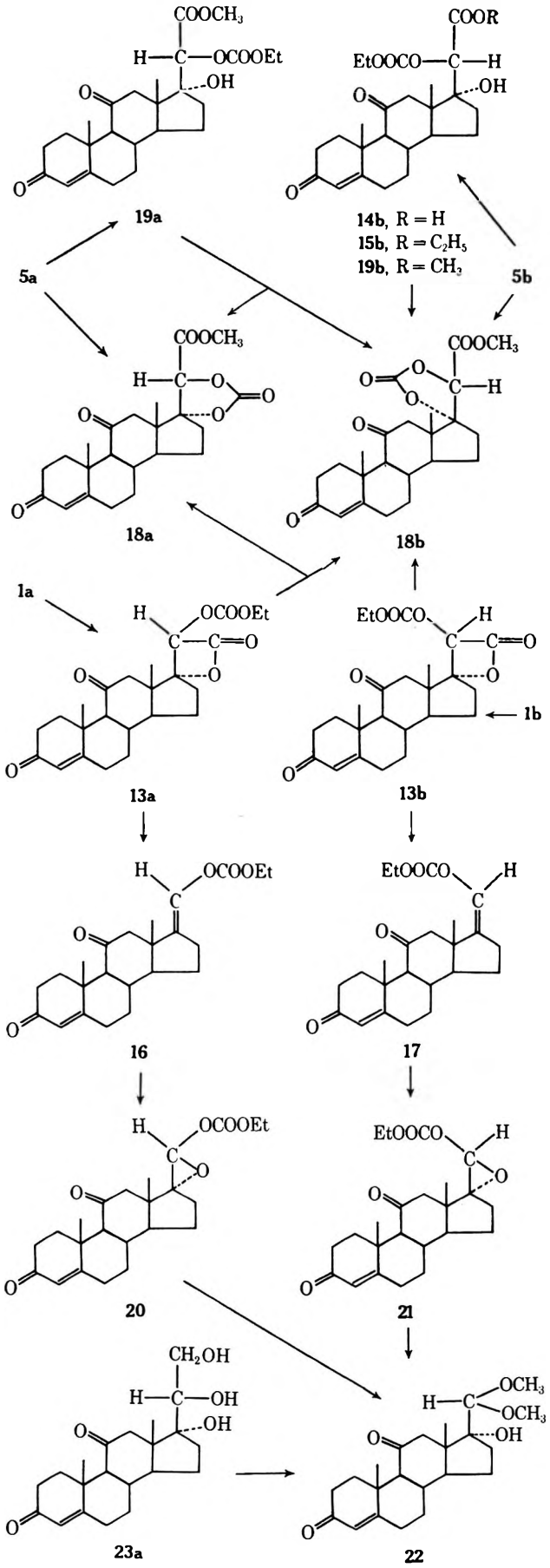
(9) M. Steiger and T. Reichstein, *Helv. Chim. Acta*, **21**, 161 (1938). The glycol **12** which had first been described by Sarett,[10] was prepared for the present study by a three-step reaction sequence from 11β,20β,21-trihydroxypregn-4-en-3-one (**9**).[11] Acetonation of **9** in the usual manner[12] furnished 20β,21-isopropylidenedioxy-11β-hydroxypregn-4-en-3-one (**10**) which was oxidized with chromic anhydride–pyridine to 20β,21-isopropylidenedioxypregn-4-ene-3,11-dione (**11**). The oxidation product **11** was then hydrolyzed to the desired glycol **12** in 60% acetic acid.[12]

(10) L. H. Sarett, *J. Amer. Chem. Soc.*, **68**, 2478 (1946).

(11) D. Taub, R. D. Hoffsommer, and N. L. Wendler, *ibid.*, **81**, 3291 (1959).

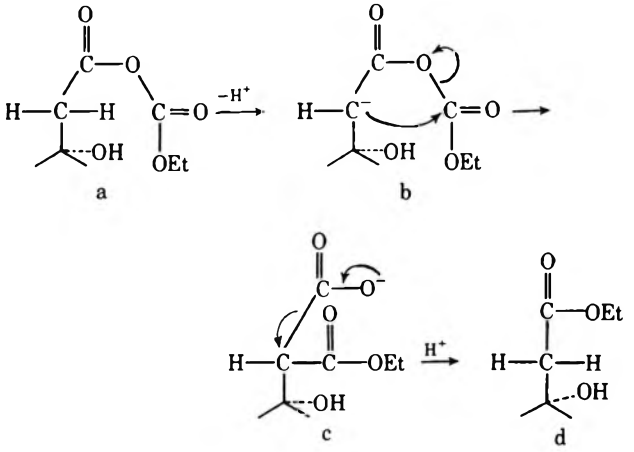
(12) M. L. Lewbart and J. J. Schneider, *J. Org. Chem.*, **34**, 3505 (1969).

SCHEME III



covered the 17-hydroxy-20β-cathyl-21-oic acid **14b**. Silica gel chromatography of the neutral fraction provided in addition to the desired 20β-cathyl-β-lactone

SCHEME IV



13b (18%) its decarboxylation product **17** (*vide infra*) which was generated during chromatography. Further development of the column gave the 20β-cathyl ethyl and methyl esters **15b** and **19b** whose identity was established by independent synthesis. The formation of the ethyl ester **15b** probably results from acylative decarboxylation of the mixed anhydride (Scheme IV); the methyl ester **19b** probably arises as a transesterification artifact resulting from manipulation of the original neutral fraction in methanol. The much lower yield of β-lactone from **1b** as compared with its 20α epimer, together with the nature of the by-products formed in the reaction with ethyl chlorocarbonate–pyridine, again confirms the reduced ability of mixed anhydrides from 17,20β-dihydroxy-21-oic acids to undergo 17,21 interaction. It is also of interest to note that acylation at C-17 does not occur with this reagent, most probably because the negative ethoxyl group inactivates inductively the cathyl carbonyl group in the mixed anhydride.

Reaction of the 20β-cathyl-β-lactone **13b** with methanolic sodium hydroxide gave a single product which by ir analysis lacked hydroxyl groups and possessed an intense carbonyl band at 1812 cm^{-1}. Its identity as the methyl ester 17,20β-cyclic carbonate **18b** was established by its independent synthesis from the methyl ester **5b** both by treating its cathylation product **19b** with methanolic sodium hydroxide and by reaction of **5b** with phosgene in pyridine.[13] Reaction of the 20α-cathyl-β-lactone **13a** with methanolic sodium hydroxide resulted in a more complex mixture which gave after chromatography a small amount of the dihydroxy methyl ester **5a** and a mixture ($[\alpha]_D$ 151°) of methyl ester 17,20-cyclic carbonates **18a** and **18b**, in which the 20β epimer predominated (for pure **18a**, $[\alpha]_D$ 120°; for pure **18b**, $[\alpha]_D$ 160°). Of the synthetic pathways explored, the methyl ester 17,20α-cyclic carbonate **18a** could be prepared only by reaction of the methyl ester **5a** with phosgene in pyridine, since treatment of the 20α-cathylate **19a** with methanolic sodium hydroxide also afforded an epimeric mixture of cyclic carbonates. Similar reaction of the cyclic carbonate **18a** also effected epimerization at carbon 20 giving a mixture with $[\alpha]_D$ 157°. We believe that this unidirectional epimerization is analogous to that seen in 17,20-acetonido-21-oates[14] and that the steric factors which

(13) M. L. Lewbart, *J. Org. Chem.*, **37**, 1233 (1972).
(14) M. L. Lewbart and J. J. Schneider, *J. Org. Chem.*, **34**, 3513 (1969).

favor formation of the 20β epimer are also operative in the case of methyl ester 17,20-cyclic carbonates. A practical application of the epimerization undergone by methyl ester 17,20α-cyclic carbonates was made to improve the yield of the 20β-hydroxyglycolic acid **1b** obtained in the alkaline rearrangement of 17-hydroxy-3,11,20-trioxopregn-4-en-21-al (cortisone glyoxal). Normally the yields of 20α and 20β epimers are approximately 50 and 30%, respectively.[2] However, when the original crude methyl esters were converted to the 17,20-cyclic carbonates *via* the 20-cathylates and epimerized in methanolic alkali, the yield of 20β epimer (as the methyl ester 20-acetate) was nearly doubled (55%) at the expense of the 20α epimer (9%).

Decarboxylation of the 20-cathyl-β-lactones **13a** and **13b** to the respective trans and cis enol cathylates **16** and **17** could be effected in refluxing methanol. Also formed in small amounts were the respective methyl ester 20-cathylates **19a** and **19b**. Preparation of the enol cathylates **16** and **17** was also achieved without isolation of the β-lactones by successive reaction of the glycolic acids **1a** and **1b** with ethyl chlorocarbonate–pyridine and refluxing methanol. Following column chromatography the trans and cis enol cathylates were obtained in overall yields of 75 and 37%, respectively.

Stereochemical assignments of the enol acetates **6** and **7** and the enol cathylates **16** and **17** were made by comparison of their nmr spectra.[15] The most important criteria are as follows: (1) the larger long-range coupling constants of the vinylic protons at C-20 in **6** and **16** (J = 2.7 Hz) are associated with the transoid form;[16] (2) the presence of a selectively deshielded 12β proton near τ 7 in **7** and **17** is indicative of a substituent close to the C ring; and (3) the slight downfield shifts of about 0.05 ppm in **7** and **17** of the C-18 angular methyl groups are as expected because of the greater proximity of the acyl groups in the cis isomers.

Further information as to the properties of the enol cathylates **16** and **17** was obtained by treating them with *m*-chloroperbenzoic acid in methylene chloride. From each reaction mixture was isolated a product in which the cathyl group and the Δ^4-3-keto system were intact. These products which have been designated the epoxy cathylates **20** and **21** gave, after sequential reaction with methanolic potassium bicarbonate and methanolic hydrogen chloride, a common product, namely the 17α-hydroxy-17β-formyl dimethyl acetal **22**. This compound was also prepared in 86% yield by reaction of the glycerol **23a**[14] with 1 equiv of metaperiodic acid in aqueous methanol followed by treatment of the crude aldehyde with methanolic hydrogen chloride.

As an approach to the better definition of steric requirements for β-lactone formation in the reaction of the glycolic acids **1a** and **1b** with acetic anhydride– and ethyl chlorocarbonate–pyridine, it seemed of interest to establish what role if any is played by the hydroxyl group at C-20. This study required the synthesis of the 20-deoxy acid **34** (Scheme V). A key intermediate in the projected reaction sequence is the heretofore undescribed 20-deoxycortisol **29**. We have previously described the preparation of 17,21-diols in the 5β-pregnane series by lithium aluminum hydride reduction of 17,20-oxido-21-ols.[17] Utilizing this same approach, both possible epoxides **26a** and **26b** were prepared, the 20β epimer by reaction with alkali of the 20α-tosylate **25a** [which was obtained from 21-acetoxy-11β,17,20α-trihydroxypregn-4-en-3-one (**24a**)[14] with tosyl chloride in pyridine]; the 20α epimer by perbenzoic acid oxidation of the commercially available *cis* dienediol **28**.[18] Lithium aluminum hydride reduction of either **26a** or **26b** followed by selective oxidation at C-3 with DDQ[19] and column chromatography gave the 17,21-diol **29** in a yield of 40–50%. The compound was recovered either as a nicely crystalline solvate with methylene chloride or as its 21-acetate **30**. Oxidation of **30** with chromic anhydride–pyridine afforded the 11-ketone **32** which on saponification gave 20-deoxycortisone **31**. Oxidation of **31** with chromic anhydride in acetic acid followed by treatment of the acidic fraction with diazomethane gave the methyl ester **33** in a yield of 30%; saponification of **33** furnished the desired β-hydroxy acid **34**.

Reaction of **34** with acetic anhydride–pyridine under the same conditions used in the synthesis of β-lactones **4a** and **4b** from glycolic acids **1a** and **1b** provided only a small neutral fraction which was composed of three products in roughly equal amounts. Since the ir spectrum of this mixture showed no significant absorption in the carbonyl region above 1750 cm^{-1}, it was concluded that β-lactone formation did not occur. After treatment of the acidic fraction with diazomethane, the major product was isolated and identified as the methyl ester 17-acetate **35**. It is therefore evident that in the reaction of the 20-deoxy acid **34** with acetic anhydride–pyridine formation of the 17-acetoxy acid **36** predominates. The structure of **35** was proven by its synthesis in low yield from the 17-hydroxy methyl ester **33** by forced acetylation.

In contrast to the reaction of the 20-deoxy acid **34** with acetic anhydride–pyridine, treatment with ethyl chlorocarbonate–pyridine gave a negligible acidic fraction. Examination of the neutral fraction by ir analysis showed a moderate band at 1822 cm^{-1}, indicating only minimal conversion of **34** to its β-lactone. The major product was the ethyl ester **37**, as confirmed by its synthesis from the methyl ester **33** by transesterification in ethanolic sodium hydroxide. These experiments demonstrate the necessity of the 20-hydroxyl group (as its acylate) in β-lactone formation. This finding is in agreement with the general view[20] that the presence of electronegative substituents in the α position facilitates ring closure. Further comment may be made on the divergent reaction pathways from the 20-deoxy acid **34** brought about by the two acylating reagents. As in the reaction of glycolic acids **1a** and **1b** with acetic anhydride–pyridine, acetylation at C-17 in **34** occurs *via* pathway 1 in Scheme II. In the reaction of **34** with ethyl chlorocarbonate–pyridine, however, neither pathway in Scheme II occurs to a significant extent. Instead, we propose that the mixed anhydride (a, Scheme IV) undergoes acylative decarboxyla-

(15) We wish to thank Dr. Byron H. Arison of the Merck Institute for the determination and interpretation of the nmr spectra.

(16) S. Steinhell and G. P. Newsoroff, *Tetrahedron Lett.*, **No. 58**, 6117 (1968).

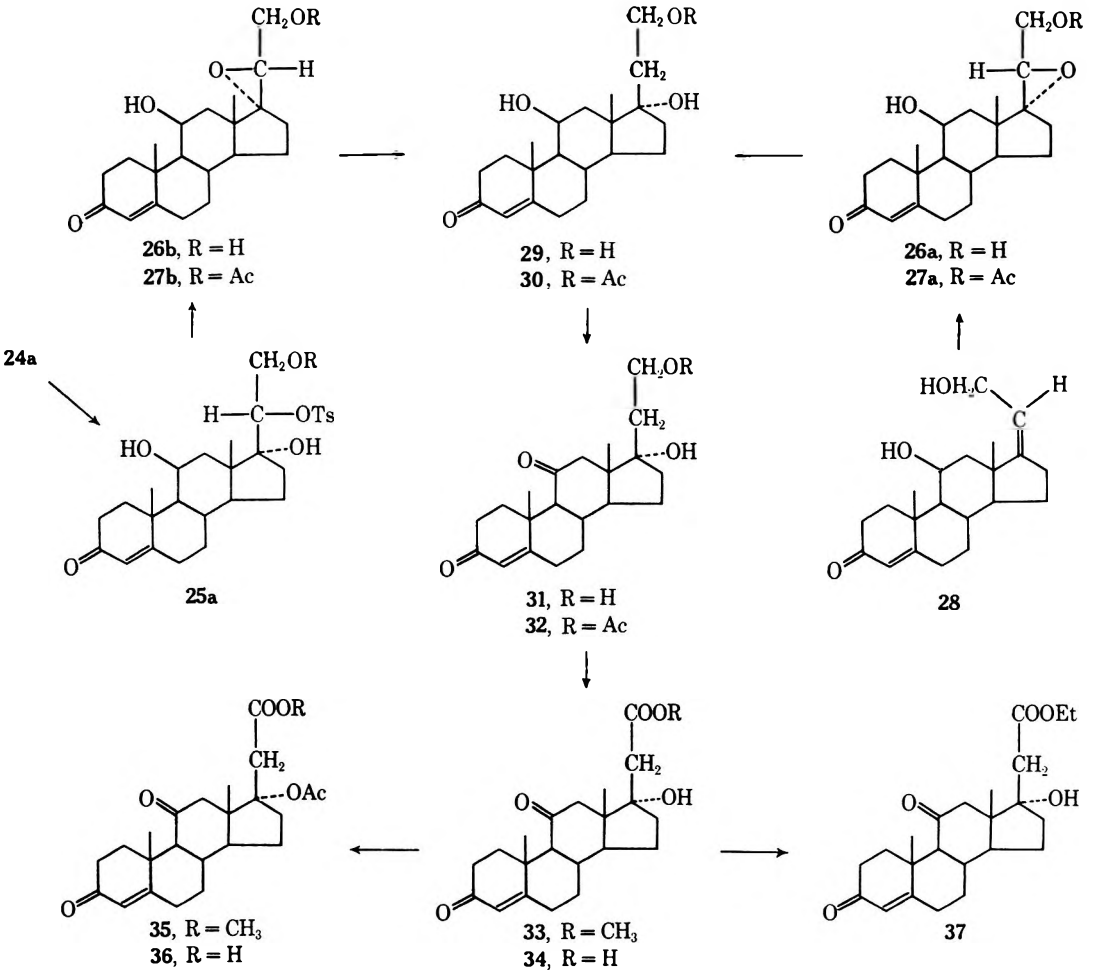
(17) M. L. Lewbart and J. J. Schneider, *J. Org. Chem.*, **33**, 1707 (1968).

(18) J. A. Hogg, P. F. Beal, A. H. Nathan, F. H. Lincoln, W. P. Schneider, B. J. Magerlein, A. R. Hanze, and R. W. Jackson, *J. Amer. Chem. Soc.*, **77**, 4436 (1955).

(19) D. Burn, V. Petrow, and G. O. Weston, *Tetrahedron Lett.*, **No. 9**, 14 (1960).

(20) Y. Etienne and N. Fischer, *Chem. Heterocycl. Compounds*, **19** (2), 796 (1964).

SCHEME V



tion[21] through initial loss of a proton at C-20, giving the anion (b). Attack by the carbanion on the cathylate carbonyl group accompanied by an electron shift gives the carboxylate (c) which readily loses carbon dioxide, and affords after protonation the ethyl ester (d).

Experimental Section

Melting points were taken on a Fisher-Johns apparatus and are uncorrected. Optical rotations were determined at 365 and 589 mμ (D line of sodium) in a Zeiss 0.005° photoelectric polarimeter. Unless noted otherwise measurements were made in chloroform solution in a 0.5-dm tube at a concentration of about 1% and at a temperature of 26 ± 1°. Infrared (ir) spectra were determined as KBr pellets with a Beckman IR-8 instrument. Nmr spectra were determined with a Varian HA-100D instrument in $CDCl_3$, using TMS as an internal standard. Ultraviolet (uv) spectra were obtained in methanol solution with a Zeiss PRQ 20A recording spectrophotometer. General procedures for column and thin layer (tlc) chromatographic techniques and the processing of reaction mixtures have been cited earlier.[12] Elemental analyses were by August Peisker-Ritter, Brugg, Switzerland, E. Thommen, Basel, Switzerland, and the Merck Institute, Rahway, N. J.

Reaction of 17,20α-Dihydroxy-3,11-dioxopregn-4-en-21-oic Acid (1a) with Acetic Anhydride–Pyridine.—The glycolic acid[2] (500 mg) was treated with 1 ml each of acetic anhydride and pyridine for 20 hr at 5°. The solution was added to an ice–water mixture and the milky suspension was extracted with methylene chloride. An initial wash with cold, dilute hydrochloric acid was discarded. The organic layer was washed with two 25-ml portions of cold, 2% sodium bicarbonate solution. The combined aqueous washings were carefully acidified with 1 *N* hydrochloric acid and the liberated acid was extracted with methylene chloride. Concentration of the water-washed organic solvent to dryness gave the acidic fraction (333 mg). Crystallization from acetone–ether afforded 252 mg (41%) of prisms, mp 204.5–206°, which possessed an ir spectrum identical with that of **17,20α-diacetoxy-3,11-dioxopregn-4-en-21-oic acid (2a)**.[2]

The neutral fraction (270 mg) was obtained from the original methylene chloride extract. Crystallization from methanol provided **20α-acetoxy-3,11-dioxopregn-4-ene-21,17α-lactone (4a)** as fine needles (174 mg, mp 109–110°) in a yield of 33%: $[\alpha]_{365}$ 719°, $[\alpha]_D$ 187° (methanol); λ_{max} 238.5 mμ (ε 15,600); ν_{max} 1838 (β-lactone), 1758, 1215 cm^{-1} (acetoxyl).

Anal. Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05; CH_3CO, 10.75. Found: C, 69.41; H, 7.25; CH_3CO, 11.04.

Treatment of **4a** (10 mg) in methanol (1.9 ml) with 1 *N* methanolic sodium hydroxide (0.1 ml) for 1.5 hr and partitioning of the reaction mixture between methylene chloride and water afforded 8 mg of prisms from acetone–*n*-hexane, mp 198–200°. A mixture melting point with **methyl 17,20α-dihydroxy-3,11-dioxopregn-4-en-21-oate (5a)**[2] was 197–199.5° and their ir spectra were identical.

Reaction of 17,20β-Dihydroxy-3,11-dioxopregn-4-en-21-oic Acid (1b) with Acetic Anhydride–Pyridine.—Treatment of the glycolic acid (500 mg) with acetic anhydride–pyridine and separation of the crude product into acidic and neutral fractions was carried out as in the reaction of **1a**. From the acidic fraction (534 mg) was obtained 204 mg (33%) of prisms, mp 156–158°, which possessed an ir spectrum indistinguishable from that of **17,20β-diacetoxy-3,11-dioxopregn-4-en-21-oic acid (2b)**.[2] The mother liquor was treated with excess diazomethane and the crude methyl ester was chromatographed on a 20 × 750 mm silica gel column in ethyl acetate–isooctane (65:35). Fractions (6 ml) were collected at 10-min intervals. Crystallization of the contents of **fractions 121–300** from acetone–ether furnished **methyl 20β-acetoxy-17-hydroxy-3,11-dioxopregn-4-en-21-oate** (methyl ester of **3b**)[2] as rosettes (137 mg, mp 190–190.5°; 53 mg, mp 181–183°) in a yield of 33%.

Crystallization of the neutral fraction (74 mg) from methanol

(21) R. B. Woodward, M. P. Cava, W. D. Ollis, A. Hunger, H. Daeniker, and K. Schenker, *Tetrahedron*, **19**, 247 (1963).

furnished 42 mg (8%) of **20β-acetoxy-3,11-dioxopregn-4-ene-21-17α-lactone (4b)** as needles: mp 117–118.5°, 146–147°; $[\alpha]_{365}$ 697°, $[\alpha]_D$ 180° (methanol); λ_{max} 238.5 mμ (ε 15,200); ν_{max} 1838 (β-lactone), 1759, 1212 cm^{-1} (acetoxyl).

Anal. Calcd for $C_{23}H_{28}O_6$: C, 68.98; H, 7.05; CH_3CO, 10.75. Found: C, 69.36; H, 7.40; CH_3CO, 10.61.

Treatment of **4b** (10 mg) with methanolic sodium hydroxide afforded 8.6 mg of prisms from acetone–ether, mp 211–213°. This product was identical in all respects with a reference sample of **methyl 17,20β-dihydroxy-3,11-dioxopregn-4-en-21-oate (5b)**.[2]

20-Acetoxy-21-norpregna-4,*trans*-17(20)-diene-3,11-dione (6). From Spontaneous Decarboxylation of 4a.—A crystalline sample of 20α-acetoxy-3,11-dioxopregn-4-ene-21,17α-lactone (88 mg) which had been stored at room temperature for 2 months had mp <95°. Tlc analysis in isooctane–ethyl acetate (3:2) showed considerable conversion of the β-lactone (R_f 0.12) to a more mobile artifact (R_f 0.23). Silica gel chromatography of the mixture on a 20 × 750 mm column in ethyl acetate–isooctane (1:1) was carried out, collecting 3-ml fractions every 10 min. **Fractions 126–221** furnished 49 mg of prismatic needles from ether: mp 177–178°; $[\alpha]_{365}$ 718°, $[\alpha]_D$ 186°; λ_{max} 233 mμ (ε 17,200); ν_{max} 1750, 1225 cm^{-1} (enolic acetoxyl);[4] nmr δ 9.13 (s, 3, 18-CH_3), 8.57 (s, 3, 19-CH_3), 7.88 (s, 3, CH_3CO), 3.15 (t, 1, J = 2.7 Hz, 20 H).

Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92; CH_3CO, 12.07. Found: C, 74.60; H, 8.13; CH_3CO, 11.18.

From Refluxing Benzene on 4a.—A solution of 20α-acetoxy-3,11-dioxopregn-4-ene-21,17α-lactone (95 mg) in benzene (20 ml) was refluxed for 49 hr. The residue was chromatographed on a 13 × 550 mm silica gel column under the same conditions used in the recovery of **6** from the spontaneous decarboxylation of **4a**. **Fractions 27–55** (52 mg) afforded 38 mg of prisms from methanol, mp 177–178°. The ir spectrum was identical with that of the spontaneous decarboxylation product **6**.

20-Acetoxy-21-norpregna-4,*cis*-17(20)-diene-3,11-dione (7). From Spontaneous Decarboxylation of 4b.—A crystalline sample of 20β-acetoxy-3,11-dioxopregn-4-ene-21,17α-lactone (46 mg) which had been stored at room temperature for several months had mp <100° and contained a more mobile artifact with the same R_f as the trans enol acetate **6**. Silica gel chromatography furnished 5.6 mg of prisms from ether: mp 159.5–160.5°; $[\alpha]_{365}$ 680°, $[\alpha]_D$ 178°; λ_{max} 233 mμ (ε 17,650); ν_{max} 1750, 1220 cm^{-1} (enolic acetoxyl);[4] nmr δ 9.08 (s, 3, 18-CH_3), 8.57 (s, 3, 19-CH_3), 7.88 (s, 3, CH_3CO), 7.05, 6.92 (d, 1, 12β H), 3.11 (t, 1, J = 2.0 Hz, 20 H).

Anal. Calcd for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92; CH_3CO, 12.07. Found: C, 73.99; H, 8.31; CH_3CO, 11.45.

From Refluxing Benzene on 4b.—A solution of 20β-acetoxy-3,11-dioxopregn-4-ene-21,17α-lactone (98 mg) in benzene (20 ml) was refluxed for 49 hr. Silica gel chromatography of the residue provided fine needles from ethyl acetate–*n*-hexane (20 mg, mp 159–160°; 27 mg, mp 143–144°). Both crops were homogeneous by tlc analysis. The ir spectrum was identical with that of the spontaneous decarboxylation product **7**.

20β,21-Isopropylidenedioxy-11β-hydroxypregn-4-en-3-one (10b) from 9b.—Acetonation of 11β,20β,21-trihydroxypregn-4-en-3-one[11] [1.5 g; mp 213–215°; $[\alpha]_D$ 136°; λ_{max} 242 mμ (ε 15,600)] by the usual method[12] furnished **10b** as prisms from methanol (1150 mg, mp 213–214.5°; 200 mg, mp 205–209°): $[\alpha]_{365}$ 182°, $[\alpha]_D$ 142°; λ_{max} 242 mμ (ε 15,550); ν_{max} 1209, 1160 and 849 cm^{-1} (20,21-acetonide).[12]

Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.17; H, 9.31.

20β,21-Isopropylidenedioxypregn-4-ene-3,11-dione (11b) from 10b.—Oxidation of 20β,21-isopropylidenedioxy-11β-hydroxypregn-4-en-3-one (200 mg) in pyridine (28 ml) with an equal weight of chromic anhydride for 17 hr and crystallization of the product from acetone gave 197 mg of prisms: mp 186.5–187°; $[\alpha]_{365}$ 770°, $[\alpha]_D$ 189°; λ_{max} 238 mμ (ε 15,300); ν_{max} 1702 (11-ketone), 1212, 1159, and 851 cm^{-1} (20,21-acetonide).[12]

Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.60; H, 8.85.

20β-21-Dihydroxypregn-4-ene-3,11-dione (12b) from 11b.—Treatment of 20β,21-isopropylidenedioxypregn-4-ene-3,11-dione (500 mg) with 60% acetic acid (50 ml) for 18 hr at room temperature[12] and crystallization of the product from ethyl acetate provided 410 mg (92%) of needles: mp 223–224°; $[\alpha]_{365}$ 837°, $[\alpha]_D$ 207°; λ_{max} 238 mμ (ε 15,300) [lit.[10] mp 223.5–224.5°; $[\alpha]_D$ 176° (acetone)].

Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.92; H, 8.75.

17β-Formylandrost-4-ene-3,11-dione (8) from 12b.—To a solution of 20β,21-dihydroxypregn-4-ene-3,11-dione (160 mg, 0.46 mmol) in methanol (20 ml) was added sodium metaperiodate (114 mg, 0.50 mmol) in water (10 ml). After 18 hr at room temperature several drops of ethylene glycol were added, and, after 1 hr, the solution was concentrated *in vacuo* and the aqueous residue was extracted with methylene chloride. Analysis of the reaction mixture by tlc in ethyl acetate–isooctane (1:1) showed roughly equal amounts of two products (R_f 0.12 and 0.23). On the assumption that the more mobile component was the dimethyl acetal of **8**, the mixture was treated in a small volume of methanol with hot water (50 ml) and several drops of 1 *N* hydrochloric acid for 1 hr on the steam bath. Extraction of the cooled reaction mixture with methylene chloride and reexamination by tlc showed a trace only of the more mobile component. Crystallization of the retreated material from ether furnished 106 mg (66%) of prisms: mp 138–140°; $[\alpha]_{365}$ 1630°, $[\alpha]_D$ 402°; λ_{max} 238 mμ (ε 15,100); ν_{max} 2740 cm^{-1} (aldehyde).

Anal. Calcd for $C_{20}H_{26}O_3$: C, 76.40; H, 8.34. Found: C, 76.24; H, 8.34.

8 from 6 and 7.—Treatment of 14 mg each of the *trans*- and *cis*-20-acetoxy-21-norpregna-4,17(20)-dienes in methanol (0.9 ml) with 0.2 *N* methanolic sodium hydroxide (0.1 ml) for 15 min at room temperature furnished in each case 6 mg of prisms from acetone–*n*-hexane, mp 138–140°. The products possessed an infrared spectrum identical with that of **8** prepared by periodic acid oxidation of the glycol **12b**.

20α-Carbethoxy-3,11-dioxopregn-4-ene-21,17α-lactone (13a) from 1a.—To a solution of 17,20α-dihydroxy-3,11-dioxopregn-4-en-21-oic acid (275 mg) in cold pyridine (3.75 ml) was added ethyl chlorocarbonate (0.21 ml). After 1 hr at room temperature the crude product was recovered and separated into acidic and neutral fractions as in the preparation of **4a**. The acidic fraction (14 mg) was discarded. The neutral fraction (326 mg) crystallized readily from methanol as prisms (295 mg, mp 124°) in a yield of 97%: $[\alpha]_{365}$ 720°, $[\alpha]_D$ 198°; λ_{max} 238 mμ (ε 16,050); ν_{max} 1839 (β-lactone), 1760, 1255, and 785 cm^{-1} (cathylate).[13]

Anal. Calcd for $C_{24}H_{30}O_7$: C, 66.96; H, 7.02; C_2H_5O, 10.48. Found: C, 66.73; H, 7.10; C_2H_5O, 10.57.

Reaction of 1b with Ethyl Chlorocarbonate–Pyridine.—Treatment of 17,20β-dihydroxy-3,11-dioxopregn-4-en-21-oic acid (275 mg) was carried out as in the preparation of **13a** from **1a**.

20β-Carbethoxy-17-hydroxy-3,11-dioxopregn-4-en-21-oic Acid (14b).—Successive crystallization of the acidic fraction (48 mg) from methanol–ether and methanol furnished 24 mg of prisms: mp 145–149°; $[\alpha]_{365}$ 624°, $[\alpha]_D$ 148°; λ_{max} 238 mμ (ε 14,800); ν_{max} 1745, 1260, and 790 cm^{-1} (cathylate).[13]

Anal. Calcd for $C_{24}H_{32}O_8 \cdot 2H_2O$: C, 59.49; H, 7.49. Found: C, 59.63; H, 7.50.

20β-Carbethoxy-3,11-dioxopregn-4-ene-21,17α-lactone (13b).—Two crystallizations of the neutral fraction from methanol gave 10 mg of fine needles: mp 108–109°; $[\alpha]_{365}$ 703°, $[\alpha]_D$ 183°; λ_{max} 238 mμ (ε 16,200); ν_{max} 1840 (β-lactone), 1758, 1250, and 785 cm^{-1} (cathylate).[13]

Anal. Calcd for $C_{24}H_{30}O_7$: C, 66.96; H, 7.02; C_2H_5O, 10.48. Found: C, 66.94; H, 7.03; C_2H_5O, 10.60.

The mother liquor residue (237 mg) was chromatographed on a 20 × 700 mm silica gel column in isooctane–ethyl acetate (55:45), collecting 5-ml fractions every 10 min. From **fractions 65–115** was obtained **20-carbethoxy-21-norpregna-4,*cis*-17(20)-diene (17**, *vide infra*) as needles from methanol (16 mg, mp 201–202°). From **fractions 125–165** (68 mg) was recovered an additional 46 mg of β-lactone **13b**, mp 112–114°.

Ethyl 20β-Carbethoxy-17-hydroxy-3,11-dioxopregn-4-en-21-oate (15b).—The residue from **fractions 186–246** (32 mg) crystallized as platelets from aqueous methanol: mp 93–95°; $[\alpha]_{365}$ 561°, $[\alpha]_D$ 133°; λ_{max} 238 mμ (ε 15,400); ν_{max} 1745, 1255, and 788 cm^{-1} (cathylate).[13]

Anal. Calcd for $C_{26}H_{36}O_8 \cdot H_2O$: C, 63.84; H, 8.06; $2C_2H_5O$, 18.83. Found: C, 63.72; H, 7.68; $2C_2H_5O$, 17.15.

Sequential reaction of methyl 17,20β-dihydroxy-3,11-dioxopregn-4-en-21-oate (**5b**, 60 mg) with ethanolic sodium hydroxide and ethyl chlorocarbonate–pyridine as described previously afforded 64 mg of platelets from aqueous ethanol: mp 94–96°; $[\alpha]_{365}$ 568°, $[\alpha]_D$ 132°. The ir spectrum was identical with that of **15b** obtained from **fractions 186–246**.

Methyl 20β-Carbethoxy-17-hydroxy-3,11-dioxopregn-4-en-21-oate (19b).—The contents of **fractions 281–380** (23 mg) crystal-

lized from aqueous methanol as prisms, mp 153–154°. The infrared spectrum was indistinguishable from that of the cathylation product from methyl 17,20β-dihydroxy-3,11-dioxopregn-4-en-21-oate (**5b**, *vide infra*).

Methyl 20α-Carbethoxy-17-hydroxy-3,11-dioxopregn-4-en-21-oate (19a) from 5a.—To a solution of methyl 17,20α-dihydroxy-3,11-dioxopregn-4-en-21-oate (100 mg) in cold pyridine (1 ml) was added ethyl chlorocarbonate (0.075 ml). After 2 hr at room temperature the product was recovered and crystallized from methanol as needles (98 mg, mp 172–173.5°; 13 mg, mp 171–172.5°) in a yield of 94%: $[\alpha]_{365}$ 548°, $[\alpha]_D$ 138°; λ_{max} 238 mμ (ε 15,200); ν_{max} 1745, 1255, and 791 cm^{-1} (cathylate).[13]

Anal. Calcd for $C_{25}H_{34}O_8$: C, 64.92; H, 7.41; CH_3O and C_2H_5O, 16.45. Found: C, 64.30; H, 7.13; C_2H_5O, 17.78.

Methyl 20β-Carbethoxy-17-hydroxy-3,11-dioxopregn-4-en-21-oate (19b) from 5b.—Cathylation of methyl 17,20β-dihydroxy-3,11-dioxopregn-4-en-21-oate (100 mg) for 1.5 hr as in the preparation of **19a** afforded 119 mg (98%) of platelets from aqueous methanol: mp 153.5–155°; $[\alpha]_{365}$ 600°, $[\alpha]_D$ 142°; λ_{max} 238 mμ (ε 15,300); ν_{max} 1745, 1255, and 790 cm^{-1} (cathylate).

Anal. Calcd for $C_{25}H_{34}O_8 \cdot 0.5H_2O$: C, 63.68; H, 7.48; CH_3O and C_2H_5O, 16.14. Found: C, 63.90; H, 7 21; C_2H_5O, 18.08.

Methyl 17,20α-Cyclocarbonyldioxy-3,11-dioxopregn-4-en-21-oate (18a) from 5a.—To a solution of methyl 17,20α-dihydroxy-3,11-dioxopregn-4-en-21-oate (190 mg) in cold pyridine (5 ml) was added a 12.5% solution of phosgene in benzene (1.25 ml). After 1 hr at room temperature the product was recovered and crystallized from methanol as prismatic needles (157 mg, mp 263–265°; 22 mg, mp 248–250°) in a yield of 88%: $[\alpha]_{365}$ 491°, $[\alpha]_D$ 120°; λ_{max} 238 mμ (ε 15,800); ν_{max} 1815 and 781 cm^{-1} (cyclic carbonate).[13]

Anal. Calcd for $C_{23}H_{28}O_7$: C, 66.33; H, 6.78; CH_3O, 7.45. Found: C, 66.21; H, 6.80; CH_3O, 7.56.

Methyl 17,20β-Cyclocarbonyldioxy-3,11-dioxopregn-4-en-21-oate (18b) from 5b.—Treatment of methyl 17,20β-dihydroxy-3,11-dioxopregn-4-en-21-oate (78 mg) in pyridine (1 ml) with the phosgene solution (0.25 ml) for 1 hr and crystallization from methanol gave needles (70 mg, mp 264–266°; 4 mg, mp 253–255°) in a yield of 88%: $[\alpha]_{365}$ 633°, $[\alpha]_D$ 160°; λ_{max} 238 mμ (ε 15,800); ν_{max} 1810 and 778 cm^{-1} (cyclic carbonate).[13]

Anal. Calcd for $C_{23}H_{28}O_7$: C, 66.33; H, 6.78; CH_3O, 7.45. Found: C, 66.26; H, 6.84; CH_3O, 7.65.

18b from 19b.—Treatment of methyl 20β-carbethoxy-17-hydroxy-3,11-dioxopregn-4-en-21-oate (50 mg) in methanol (9.5 ml) with 0.1 *N* methanolic sodium hydroxide (0.5 ml) for 15 min at room temperature and crystallization of the product from methanol supplied 40 mg (86%) of needles, mp 264–266°, which were identical in all respects with the phosgenation product of **5b**.

18b from 13b.—Reaction of 20β-carbethoxy-3,11-dioxopregn-4-ene-21,17α-lactone (17 mg) in methanol (3.9 ml) with 0.2 *N* methanolic sodium hydroxide (0.1 ml) for 15 min gave 12 mg of needles from methanol, mp 263–265°. A mixture melting point with **18b** prepared from **5b** showed no depression and their ir spectra were identical.

18b from 18a.—Treatment of methyl 17,20α-cyclocarbonyldioxy-3,11-dioxopregn-4-en-21-oate (100 mg) in methanol (38 ml) with 0.1 *N* methanolic sodium hydroxide (2 ml) for 15 min at room temperature and processing in the usual manner gave 71 mg of needles: mp 260–261°; $[\alpha]_{365}$ 617°, $[\alpha]_D$ 157°. A mixture melting point with starting material was 252–257°; the ir spectrum was identical with that of **18b** prepared from **5b**. Chromatography of the mother liquor residue on a 15 × 600 mm silica gel column in ethyl acetate–isooctane (2:1) was carried out, collecting fractions (2.5 ml) every 10 min. Acetylation of the residue from **fractions 211–400** furnished 12 mg of platelets from methanol, mp 205.5–207°. The ir spectrum was identical with that of **methyl 20α-acetoxy-17-hydroxy-3,11-dioxopregn-4-en-21-oate.**[2]

18a and 18b from 13a.—To a solution of 20α-carbethoxy-3,11-dioxopregn-4-ene-21,17α-lactone (50 mg) in methanol (9.5 ml) was added 0.1 *N* methanolic sodium hydroxide (0.5 ml). After 15 min the material was recovered and crystallized from methanol as leaflets: mp 245–247°; $[\alpha]_{365}$ 600°, $[\alpha]_D$ 151°. The mother liquor residue was chromatographed on a 10 × 480 mm silica gel column in ethyl acetate–isooctane (2:1), collecting 2-ml fractions every 10 min. **Fractions 29–42** afforded an additional 10 mg of the cyclic carbonate mixture, mp 241–243°. The contents of **fractions 61–160** crystallized from ethyl acetate as prisms (6 mg, mp 197–199°) which possessed an ir spectrum identical with that of **methyl 17,20α-dihydroxy-3,11-dioxopregn-4-en-21-oate (5a)**.

Enhanced Yield of Methyl 17,20β-Dihydroxy-3,11-dioxopregn-4-en-21-oate (5b) from Cortisone Glyoxal *via* Epimerization of 18a.—Rearrangement of cortisone glyoxal hemiacetal (3.12 g) with alkali and esterification of the acidic products with diazomethane afforded an epimeric mixture of **5a** and **5b** as described previously.[2] To the crude product in cold pyridine (25 ml) was added ethyl chlorocarbonate (3 ml). After 17 hr at room temperature ice was added to decompose the excess reagent. Repeated addition of a benzene-ethanol mixture and concentration *in vacuo* removed most of the pyridine. The residue was partitioned between methylene chloride and water, and the organic layer was taken to dryness. To the methyl ester 20-cathylate mixture in methanol (200 ml) was added 1 *N* methanolic sodium hydroxide (50 ml). After 1 min 1 *N* aqueous sodium hydroxide (250 ml) was added to the epimerized material and the solution stood for 10 min at room temperature. After concentration *in vacuo* removed most of the methanol, excess hydrochloric acid was added and the liberated glycolic acids were extracted with ethyl acetate. Successive reaction with diazomethane and acetic anhydride–pyridine afforded an epimeric mixture of methyl ester 20-acetates which were chromatographed on a 54 × 840 mm Celite column in toluene–isooctane–formamide (1500:750:250 ml), collecting 12-ml fractions every 10 min. The contents of **fractions 620–830** gave 322 mg (9.3%) of **methyl 20α-acetoxy-17-hydroxy-3,11-dioxopregn-4-en-21-oate,**[2] mp 205–206.5°. From **fractions 871–1200** was obtained 1911 mg (55.3%) of methyl 20β-acetoxy-17-hydroxy-3,11-dioxopregn-4-en-21-oate,[2] mp 199–200°.

20-Carbethoxy-21-norpregna-4,*trans*-17(20)-diene-3,11-dione (16) and Methyl 20α-Carbethoxy-17-hydroxy-3,11-dioxopregn-4-en-21-oate (19a) from 13a.—A solution of 20α-carbethoxy-3,11-dioxopregn-4-ene-21,17α-lactone (100 mg) in methanol (20 ml) was refluxed for 4 hr. Analysis of the reaction mixture by tlc in ethyl acetate–isooctane (1:1) showed that starting material (R_f 0.22) had been completely converted to two products (R_f 0.33 and 0.13). The mixture was chromatographed on a 15 × 630 mm silica gel column in the same system, collecting 2-ml fractions every 10 min.

Fractions 46–76.—Crystallization from ether gave the enol cathylate **16** as prismatic needles (56 mg, mp 137.5–138°) in a yield of 76%: $[\alpha]_{365}$ 644°, $[\alpha]_D$ 169°; λ_{max} 238 mμ (ε 15,500); ν_{max} 1755, 1250, and 785 cm^{-1} (enolic cathylate); nmr δ 9.15 (s, 3, 18-CH_3), 8.68 (s, 3, cathyl methyl), 8.58 (s, 3, 19-CH_3), 5.75 (q, 2, J = 7 Hz, cathyl methylene), 3.37 (t, 1, J = 2.7 Hz, 20 H).

Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82; C_2H_5O, 11.66. Found: C, 71.42; H, 7.82; C_2H_5O, 11.73.

Fractions 131–230.—The residue (21 mg, 20%) crystallized from acetone as platelets, mp 166.5–168.5°. A mixture melting point with the cathylation product from **5a** was 170–173° and their ir spectra were identical.

16 from 1a.—Treatment of 17,20α-dihydroxy-3,11-dioxopregn-4-en-21-oic acid (275 mg) with ethyl chlorocarbonate–pyridine was carried out in the usual manner. The combined acidic and neutral fractions were refluxed in methanol (50 ml) for 4 hr. The crude product gave, following silica gel chromatography, 210 mg (74%) of the enol cathylate **16**, mp 138–138.5°.

20-Carbethoxy-21-norpregna-4,*cis*-17(20)-diene-3,11-dione (17) and Methyl 20β-Carbethoxy-17-hydroxy-3,11-dioxopregn-4-en-21-oate (19b) from 13b.—A solution of 20β-carbethoxy-3,11-dioxopregn-4-ene-21,17α-lactone (49 mg) in methanol (4 ml) was refluxed for 4 hr. Tlc analysis in ethyl acetate–isooctane (1:1) revealed a major mobile product (R_f 0.30) and two minor components (R_f 0.08 and 0.17). The residue was chromatographed on a 13 × 620 mm silica gel column in the same system, collecting 2-ml fractions every 10 min.

Fractions 32–60.—Crystallization from methanol furnished the enol cathylate **17** as prisms (31 mg, mp 205–207°) in a yield of 71%: $[\alpha]_{365}$ 691°, $[\alpha]_D$ 179°; λ_{max} 238 mμ (ε 16,000); ν_{max} 1754, 1250, and 788 cm^{-1} (enolic cathylate); nmr δ 9.09 (s, 3, 18-CH_3), 8.68 (s, 3, cathyl methyl), 8.58 (s, 3, 19-CH_3), 6.98, 6.84 (d, 1, 12β H), 5.78 (q, 2, J = 7 Hz, cathyl methylene), 3.31 (t, 1, J = 2.0 Hz, 20 H).

Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82; C_2H_5O, 11.66. Found: C, 71.19; H, 7.80; C_2H_5O, 11.71.

Fractions 70–105.—The crude residue possessed an ir spectrum identical with that of starting material (**13b**).

Fractions 120–220.—The pooled material (8 mg) crystallized from methanol as platelets, mp 154–155.5°. The ir spectrum was identical with that of **19b**, the cathylation product of **5b**.

17 from 1b.—Sequential reaction of 17,20β-dihydroxy-3,11-dioxopregn-4-en-21-oic acid with ethyl chlorocarbonate–pyridine and refluxing methanol as described in the preparation of **16** from **1a** afforded 104 mg (37%) of enol cathylate **17** as prisms from methanol, mp 208–210°.

17,20α-Oxido-20-carbethoxy-21-norpregn-4-ene-3,11-dione (20) from 16.—To a solution of 20-carbethoxy-21-norpregna-4, *trans*-17(20)-diene-3,11-dione (90 mg, 0.24 mmol) in methylene chloride (5 ml) was added 80 mg (0.46 mmol) of *m*-chloroperbenzoic acid. After 3.5 hr at room temperature the solution was washed with dilute alkali and water and concentrated to dryness. Direct crystallization of the product did not free it from an uv-negative contaminant. The mixture was therefore chromatographed on a 13 × 600 mm silica gel column in isooctane–ethyl acetate (7:3), collecting 3-ml fractions at 10-min intervals. **Fractions 118–170** afforded 39 mg of prisms from methanol: mp 201.5–202°; $[\alpha]_{365}$ 716°, $[\alpha]_D$ 187°; λ_{max} 238 mμ (ε 15,000); ν_{max} 1760, 1255, and 786 (cathylate), 882 cm^{-1} (epoxide).[22]

Anal. Calcd for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51; C_2H_5O, 11.20. Found: C, 68.97; H, 7.71; C_2H_5O, 10.61.

17,20β-Oxido-20-carbethoxy-21-norpregn-4-ene-3,11-dione (21) from 17.—Peracid oxidation of 20-carbethoxy-21-norpregna-4,*cis*-17(20)-diene-3,11-dione (90 mg) was effected as in the preparation of **20** from **16** and the crude product was similarly chromatographed on silica gel. From **fractions 151–215** were obtained 36 mg of prisms from methanol: mp 191–192°; $[\alpha]_{365}$ 620°, $[\alpha]_D$ 141°; λ_{max} 238 mμ (ε 15,050); ν_{max} 1760, 1250, and 792 (cathylate), 878 cm^{-1} (epoxide).[22]

Anal. Calcd for $C_{23}H_{30}O_6$: C, 68.63; H, 7.51; C_2H_5O, 11.20. Found: C, 68.82; H, 7.70; C_2H_5O, 10.99.

20,20-Dimethoxy-17-hydroxy-21-norpregn-4-ene-3,11-dione (22) from 23a.—To a solution of 17,20α,21-trihydroxypregn-4-ene-3,11-dione[14] (181 mg, 0.5 mmol) in methanol (20 ml) was added 114 mg (0.5 mmol) of metaperiodic acid in water (10 ml). After 2 hr at room temperature several drops of ethylene glycol were added, and after 1 hr the product was recovered by extraction with methylene chloride. The crude aldehyde was treated with methanol, 0.75 *N*, in hydrogen chloride (80 ml) for 1 hr at room temperature. The reaction mixture was added to methylene chloride (250 ml) and after being washed twice with water the solution was concentrated to dryness. The residue was chromatographed on a 20 × 700 mm Celite column in the system *n*-hexane–toluene–formamide (85:65:10 ml), collecting fractions of 4 ml every 10 min. Crystallization of the residue from **fractions 146–195** gave prisms (147 mg, mp 228–229°; 15 mg, mp 226–229°) in a yield of 86%: $[\alpha]_{365}$ 777°, $[\alpha]_D$ 181°; λ_{max} 238 mμ (ε 15,500).

Anal. Calcd for $C_{22}H_{32}O_5$: C, 70.18; H, 8.57; CH_3O, 16.48. Found: C, 70.74; H, 8.85; CH_3O, 16.28.

22 from 20 and 21.—Solutions of the 17,20α- (and 20β-)oxido-20-carbethoxy-21-norpregn-4-ene-3,11-diones (25 mg) in methanol (5 ml) were treated with an equal volume of 0.5% methanolic potassium bicarbonate. Tlc analysis in ethyl acetate–isooctane (2:1) of the reaction mixtures after 2.5 hr at room temperature showed complete conversion of both epoxy cathylates to a more polar product (R_f 0.24). However, the recovered material consisted in each case of a binary mixture (R_f 0.24 and 0.10). To each mixture in methanol (1.5 ml) was added 3 *N* hydrogen chloride in methanol. After 1 hr at room temperature a new binary mixture (R_f 0.14 and 0.10) was recovered and chromatographed on a 12 × 580 mm silica gel column in ethyl acetate–isooctane (3:2), collecting 2.5-ml fractions every 15 min. From the 17,20α-oxide **20** was obtained a mobile component (**fractions 106–155**, 7 mg) which crystallized from methanol as prisms, mp 216–219°, and a polar component (**fractions 196–300**, 8 mg) which could not be crystallized. The 17,20β-oxide **21** also furnished a mobile product (**fractions 111–180**, 11 mg) which crystallized from methanol as prisms, mp 218–221°, and a polar product (**fractions 221–350**, 4 mg) which had the same ir spectrum as the polar product from **20**. The mobile products were identical by ir spectroscopy with the dimethyl acetal **22** obtained by periodic acid oxidation of the glycerol **23a**.

20α-Tosyloxy-21-acetoxy-11β,17-dihydroxypregn-4-en-3-one (25a) from 24a.—A solution of 11β,17,20α,21-tetrahydroxypregn-4-en-3-one 21-acetate[14] (5 g) and tosyl chloride (5 g) in pyridine (25 ml) stood for 115 hr at 5°. Addition of ice and water gave a crystalline precipitate which was washed with water and dried *in vacuo* over anhydrous calcium chloride (7.02 g, mp 175° dec). The analytical sample was obtained by recrystallization from methanol: mp 176–177° dec; $[\alpha]_{365}$ −143°, $[\alpha]_D$ 20.8°; λ_{max} 228 mμ (ε 23,100) and 242 (16,850); ν_{max} 1600, 1495, 1189, 1175, 1099, 815, and 670 (tosylate),[22] 1742 and 1230 cm^{-1} (acetate).

Anal. Calcd for $C_{30}H_{40}O_8S$: C, 64.26; H, 7.19. Found: C, 64.18; H, 7.20.

17,20β-Oxido-11β,21-dihydroxypregn-4-en-3-one (26b) from 25a.—To a solution of 20α-tosyloxy-21-acetoxy-11β,17-dihydroxypregn-4-en-3-one (7.02 g) in methanol (300 ml) was added 1 *N* aqueous sodium hydroxide (30 ml). After 18 hr at room temperature excess ethyl acetate was added and the solution was concentrated *in vacuo* to a small volume. The product was extracted with methylene chloride and crystallized from methanol as plates (3.60 g, 85% overall from **24a**): mp 155–157° (softening at 148°); $[\alpha]_{365}$ 113°, $[\alpha]_D$ 133°; λ_{max} 242 mμ (ε 15,500); ν_{max} 1168 and 870 cm^{-1} (17,20-epoxide).[22]

Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.67; H, 8.70.

Treatment of **26b** with acetic anhydride–pyridine and crystallization of the product from ether gave **17,20β-oxido-21-acetoxy-11β-hydroxypregn-4-en-3-one (27b)** as needles: mp 145–147°; $[\alpha]_{365}$ 166°, $[\alpha]_D$ 143°; λ_{max} 242 mμ (ε 16,050); ν_{max} 1742 and 1230 (acetate), 1169 and 870 cm^{-1} (17,20-epoxide).

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30. Found: C, 71.09; H, 8.35.

17,20α-Oxido-11β,21-dihydroxypregn-4-en-3-one (26a) from 28.—To a solution of 11β,21-dihydroxypregna-4,*cis*-17(20)-dien-3-one[18] (3.5 g) in chloroform (50 ml) was added solid perbenzoic acid (1.75 g). A crystalline precipitate began to separate after several minutes. After 2 hr at room temperature the product was filtered off and recrystallized from methanol as needles (1.95 g, mp 225–227°). The original supernatant liquid was washed with dilute alkali and water, and the residue afforded an additional 0.89 g of product, mp 222–224°, raising the yield to 77%: $[\alpha]_{365}$ 106°, $[\alpha]_D$ 137°; λ_{max} 242 mμ (ε 15,950); ν_{max} 1159 and 880 cm^{-1} (17,20-epoxide).

Treatment of **26a** with acetic anhydride–pyridine and crystallization from methanol provided **17,20α-oxido-21-acetoxy-11β-hydropregn-4-en-3-one** as needles: mp 220–222°; $[\alpha]_{365}$ 135°, $[\alpha]_D$ 133°; λ_{max} 242 mμ (ε 15,600); ν_{max} 1740 and 1230 (acetate), 1162 and 881 cm^{-1} (17,20-epoxide).

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30; CH_3CO, 11.08. Found: C, 71.30; H, 8.26; CH_3CO, 13.10.

11β,17,21-Trihydroxypregn-4-en-3-one (29) from 26a.—A solution of 3 g each of 17,20α-oxido-11β,21-dihydroxypregn-4-en-3-one and lithium aluminum hydride in tetrahydrofuran (250 ml) was refluxed for 2 hr. The crude product, recovered by the cautious addition of ethyl acetate and water followed by extraction with ethyl acetate, was treated in *tert*-butyl alcohol (250 ml) with DDQ (3 g) for 2.5 hr with stirring. The orange-red solution was concentrated *in vacuo* and diluted well with methylene chloride. The solution was washed successively with cold 2 *N* sodium hydroxide and water, filtered through anhydrous sodium sulfate, and concentrated to dryness. The residue was chromatographed on a 46 × 940 mm Celite column in the system chloroform–formamide (40% impregnation),[23] collecting 12-ml fractions every 10 min. The residue from **fractions 90–125** crystallized from methylene chloride as well-formed prisms (1874 mg, mp 87–90° and 145–145.5°) in a yield of 50%. For analysis a sample was crystallized from benzene (rosettes): mp 106–108°; $[\alpha]_{365}$ 35.2°, $[\alpha]_D$ 111°; λ_{max} 242 mμ (ε 15,500).

Anal. Calcd for $C_{21}H_{32}O_4 \cdot 0.5C_6H_6$: C, 74.38; H, 9.10. Found: C, 74.24; H, 9.12.

21-Acetoxy-11β,17-dihydroxypregn-4-en-3-one (30) from 29.—Treatment of 11β,17,21-trihydroxypregn-4-en-3-one (1500 mg) with 2 ml each of pyridine and acetic anhydride for 20 hr at room temperature and crystallization of the product from ethyl acetate afforded 1330 mg of prisms: mp 173.5–175.5°; $[\alpha]_{365}$ 17.3°, $[\alpha]_D$ 98.9°; λ_{max} 242 mμ (ε 15,700); ν_{max} 1730 and 1240 cm^{-1} (acetate).

Anal. Calcd for $C_{23}H_{34}O_5$: C, 70.74; H, 8.78; CH_3CO, 11.02. Found: C, 70.66; H, 8.79; CH_3CO, 11.30.

30 from 26b.—A solution of 2.95 g each of 17,20β-oxido-11β,21-dihydroxypregn-4-en-3-one and lithium aluminum hydride in

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tetrahydrofuran (240 ml) was refluxed for 2 hr. The product was recovered, treated with DDQ, and chromatographed as in the preparation of **29** from **26a**. The residue from fractions **108–140** was treated with 2 ml each of pyridine and acetic anhydride for 18 hr at room temperature, affording the 21-acetate **30** as prisms from ethyl acetate (1086 mg, mp 174–175°; 84 mg, mp 172–174°) in a yield of 39%.

21-Acetoxy-17-hydroxypregn-4-ene-3,11-dione (32) from 30.—Oxidation of 21-acetoxy-11β,17-dihydroxypregn-4-en-3-one (500 mg) with an equal weight of chromic anhydride in pyridine (70 ml) was carried out for 17.5 hr. The product crystallized from methanol as prisms (485 mg, mp 180.5–181.5°) in a yield of 98%: $[\alpha]_{365}$ 665°, $[\alpha]_D$ 153°; λ_{max} 238 mμ (ϵ 15,500); ν_{max} 1735 (sh) and 1240 (acetate), 1703 cm^{-1} (11-ketone).

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30; CH_3CO, 11.08. Found: C, 71.20; H, 8.32; CH_3CO, 11.23.

17,21-Dihydroxypregn-4-ene-3,11-dione (31) from 32.—Saponification of 21-acetoxy-17-hydroxypregn-4-ene-3,11-dione (485 mg) in methanol (10 ml) with 1 *N* aqueous sodium hydroxide (1.5 ml) for 30 min at room temperature and crystallization of the product from acetone provided prisms (394 mg, mp 188–189°; 15 mg, mp 183–184°) in a yield of 95%: $[\alpha]_{365}$ 825°, $[\alpha]_D$ 191°; λ_{max} 238 mμ (ϵ 15,350).

Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.60; H, 8.75.

Methyl 17-Hydroxy-3,11-dioxopregn-4-en-21-oate (33) from 31.—To a solution of 17,21-dihydroxypregn-4-ene-3,11-dione (1485 mg) in acetic acid (57 ml) was added chromic anhydride (1290 mg) in water (3 ml). After 20 hr at 5° excess methanol was added and the reaction mixture was concentrated *in vacuo* to a small volume. The residue was divided into acidic and neutral fractions by partitioning between ethyl acetate and dilute sodium hydroxide solution. The neutral fraction (150 mg) was discarded; the acidic fraction (1200 mg) was treated with excess diazomethane and the crude methyl ester was chromatographed on a 35 × 700 mm silica gel column in ethyl acetate–isooctane (3:2), collecting 8-ml fractions at 10-min intervals. The contents of fractions **224–340** crystallized from ether as prisms (474 mg, mp 183–185°) in a yield of 30%: $[\alpha]_{365}$ 709°, $[\alpha]_D$ 167°; λ_{max} 238 mμ (ϵ 16,100); ν_{max} 1735 (sh) and 1720 (sh) cm^{-1} (carbomethoxyl).

Anal. Calcd for $C_{22}H_{30}O_5$: C, 70.56; H, 8.08; CH_3O, 8.29. Found: C, 70.50; H, 8.04; CH_3O, 8.48.

17-Hydroxy-3,11-dioxopregn-4-en-21-oic Acid (34) from 33.—Saponification of methyl 17-hydroxy-3,11-dioxopregn-4-en-21-oate (374 mg) in methanol (3 ml) with 1 *N* sodium hydroxide (1.5 ml) was carried out for 20 min at room temperature. After most of the methanol was removed with a nitrogen stream, the aqueous residue was acidified and extracted with ethyl acetate. Crystallization from acetone gave leaflets (225 mg, mp 204–206°; 62 mg, mp 202–205°) in a yield of 80%: $[\alpha]_{365}$ 758°, $[\alpha]_D$ 173°; λ_{max} 238 mμ (ϵ 15,400).

Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 69.84; H, 7.78.

Methyl 17-Acetoxy-3,11-dioxopregn-4-en-21-oate (35) from 34.—A solution of 17-hydroxy-3,11-dioxopregn-4-en-21-oic acid (50 mg) in 0.2 ml each of pyridine and acetic anhydride stood for 3 hr at 5°. After addition of ice and water the product was extracted with methylene chloride. The residue, which possessed no significant absorption in the carbonyl region above 1750 cm^{-1}, was treated with excess diazomethane and chromatographed on a 12.5 × 560 mm silica gel column in benzene–ethyl acetate (7:3), collecting 3 ml every 10 min. The residue from fractions **76–146** crystallized from ether as prisms (33 mg, mp 200–201°) in a yield of 57%: $[\alpha]_{365}$ 477°, $[\alpha]_D$ 110°; λ_{max} 238 mμ (ϵ 15,600); ν_{max} 1735 and 1235 (acetate), 1755 (sh) and 1740 (sh) cm^{-1} (carbomethoxyl).

Anal. Calcd for $C_{24}H_{32}O_6$: C, 69.21; H, 7.74; CH_3CO, 10.34; OCH_3, 7.45. Found: C, 69.31; H, 7.78; CH_3CO, 9.71; OCH_3, 7.17.

35 from 33.—To a solution of methyl 17-hydroxy-3,11-dioxopregn-4-en-21-oate (50 mg) in a mixture of acetic acid (2 ml) and acetic anhydride (0.4 ml) was added *p*-TSA (40 mg). After 2.7 hr at room temperature several drops of water were added and the reaction mixture was partitioned between methylene chloride and dilute sodium hydroxide solution. Examination of the reaction mixture by tlc in isooctane–ethyl acetate (3:2) showed a complex mixture having a minor component with the same mobility (R_f 0.11) as the methyl ester **35**. The residue was chromatographed on a 12 × 550 mm silica gel column in the same system, collecting 2-ml fractions every 10 min. The contents of fractions **22–40** (11 mg) was shown by ir analysis to consist chiefly of the 17-hydroxy-$\Delta^{3,5}$-enol acetate. Fractions **71–150** (37 mg) consisted of a mixture which was judged by ir analysis to be largely $\Delta^{4,17(20)}$-dienes. From fractions **191–280** (5 mg) was obtained 2.4 mg of prisms (ether–*n*-hexane), mp 198–199.5°. A mixture melting point with **35** prepared from **34** was 199–200.5° and their ir spectra were identical.

Ethyl 17-Hydroxy-3,11-dioxopregn-4-en-21-oate (37) from 34.—To a solution of 17-hydroxy-3,11-dioxopregn-4-en-21-oic acid (108 mg) in a cold pyridine (1.5 ml) was added ethyl chlorocarbonate (0.09 ml). After 1 hr at room temperature the product was recovered and chromatographed on a 13 × 620 mm silica gel column in isooctane–ethyl acetate (65:35), collecting 2-ml fractions at 10-min intervals. Beginning at fraction 69 the broad band which emerged was collected and the pooled material (70 mg) afforded prisms from methanol: mp 203–205° (softening at 197°); $[\alpha]_{365}$ 706°, $[\alpha]_D$ 165°; λ_{max} 238 mμ (ϵ 15,850).

Anal. Calcd for $C_{23}H_{32}O_5$: C, 71.10; H, 8.30; C_2H_5O, 11.60. Found: C, 70.99; H, 8.26; C_2H_5O, 12.73.

37 from 33.—Treatment of methyl 17-hydroxy-3,11-dioxopregn-4-en-21-oate (20 mg) in ethanol (1.9 ml) with 0.1 *N* ethanolic sodium hydroxide (0.1 ml) for 30 min at room temperature and crystallization of the product from ethanol gave prisms (15 mg), mp 203–205°, which were identical in all respects with **37** prepared from the reaction of **34** with ethyl chlorocarbonate–pyridine.

Registry No.—**4a**, 34647-08-0; **4b**, 34621-18-6; **5a**, 34621-19-7; **5b**, 34621-20-0; **6**, 34621-21-1; **7**, 34621-22-1; **8**, 34621-23-3; **10b**, 19448-40-9; **11b**, 18089-36-6; **12b**, 600-70-4; **13a**, 34647-09-1; **13b**, 34621-27-7; **14b**, 34621-28-8; **15b**, 34621-29-9; **16**, 34621-30-2; **17**, 34621-31-3; **18a**, 34621-32-4; **18b**, 34621-33-5; **19a**, 34621-34-6; **19b**, 34621-35-7; **20**, 34621-36-8; **21**, 34621-37-9; **22**, 34621-38-0; **25a**, 34621-39-1; **26a**, 34647-10-4; **26b**, 34621-40-4; **27a**, 34621-41-5; **29**, 34621-42-6; **30**, 34621-43-7; **31**, 34621-44-8; **32**, 34621-45-9; **33**, 34621-46-0; **34**, 34621-47-1; **35**, 34621-48-2; **37**, 34621-49-3.

Preparation and Properties of Steroidal 17,20- and 20,21-Cyclic Carbonates Epimeric at C-20[1]

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Several methods for the preparation of 17,20- and 20,21-cyclic carbonates from steroidal 17,20α(and 20β),21-triols are described. Direct preparation of the former can be achieved by reaction of the glycerol 21-acetates **1a** and **1b** with phosgene in pyridine, whereas the latter compounds can be obtained by similar treatment of the free glycerols. In addition, the 17,20-cyclocarbonyldioxy-21-ols **5a** and **5b** or the 17-hydroxy-20,21-cyclic carbonates **4a** and **4b** can be prepared selectively from the 17,20-cyclocarbonyldioxy-21-acetates **2a** and **2b** or 20-cathyl-21-acetates **3a** and **3b** under conditions which promote deacetylation and/or cyclization with or without isomerization of the cyclic carbonate grouping. The influence of configuration at C-20 on the relative amounts of 17,20- and 20,21-cyclic carbonates which are formed is discussed in stereochemical terms. The utility of side-chain cyclic carbonates as intermediates in partial syntheses was demonstrated by the ready conversion of certain 11β-ols to the 11-ones with chromic anhydride in pyridine and by the development of an improved route to 17,20-diols **12a** and **12b** *via* 17,20-cyclocarbonyldioxy-21-tosylates **11a** and **11b**. Cyclic carbonates from the glycols **12a** and **12b** have also been prepared either directly by reaction with phosgene in pyridine or by alkaline cyclization of the 20-cathylates **16a** and **16b**. In contrast to side-chain acetonides which are strongly resistant to alkaline hydrolysis, cyclic carbonates are easily cleaved by aqueous alkali. However, they are unaffected by relatively strong mineral acid. The resistance of these new derivatives to forcing acetylation conditions was shown in the reaction of the 11β,17-dihydroxy-20,21-cyclic carbonates **4a** and **4b**. Acetylation proceeds readily at C-11, but the presence of the bulky substituent on the side chain greatly inhibits acetylation at C-17.

In the preceding communication[2] we describe the ready formation of methyl ester 17,20-cyclic carbonates from 20-cathyl-21,17-lactones in methanolic sodium hydroxide. These findings with the glycolic acid derivatives prompted a systematic study of the formation and reactions of cyclic carbonates derived from the glycerol side chain since compounds of this type have not been described previously. In this paper will be detailed methods for preparation of both 17,20- and 20,21-cyclic carbonates epimeric at C-20, the stereochemical factors which influence their isomerization, and examples of their use in partial syntheses.

Treatment of the 21-monoacetates of 11β,17,20α,21-tetrahydroxypregn-4-en-3-one (Reichstein's substance epi-E)[3] and 11β,17,20β,21-tetrahydroxypregn-4-en-3-one (Reichstein's substance E)[4] (**1a** and **1b**, Scheme I) with phosgene in a mixture of benzene and pyridine at 0° gave the respective 17,20-cyclic carbonates **2a** and **2b**, each in a yield of 88%. An attempt was made to prepare **2a** and **2b** by cyclization of the 20-cathyl-21-acetates **3a** and **3b**. However, reaction of both **3a** and **3b** in methanolic sodium hydroxide or methanolic potassium bicarbonate resulted in rapid loss of the acetoxyl group. From either the 20β-cathylate **3b** or the 17,20β-cyclic carbonate **2b** was obtained a single product readily identified as the 17,20β-cyclocarbonyldioxy-21-ol **5b** since treatment with acetic anhydride–pyridine afforded the 21-acetate **2b**. Reaction of the 20α epimers **2a** or **3a** with methanolic alkali resulted in the formation of two products. The minor, more polar product was identified as the 17,20α-cyclic carbonate **5a** because its acetylation product was identical with **2a**. Since the major, more mobile cyclic carbonate contained an unacetylable hydroxyl group, it was assigned the 17-hydroxy-20α,21-cyclic carbonate structure **4a**. Confirmation was obtained through its independent synthesis from Reichstein's substance epi-E[5] by reaction with phosgene in pyridine. Treatment of either **4a** or **5a** with methanolic alkali gave the same equilibration mixture of both cyclic carbonates.

The reaction of the epimeric cyclic carbonates **2a** and **2b** and cathylates **3a** and **3b** with ethanolic sulfuric acid was also studied. From **2a** was obtained the 17,20α-cyclocarbonyldioxy-21-ol **5a** in a yield of 88%; in contrast, **3a** afforded the 17-hydroxy-20α,21-cyclic carbonate **4a** in the same yield. Treatment of **2b** with ethanolic sulfuric acid provided the 17,20β-cyclocarbonyldioxy-21-ol **5b** in a yield of 80%. However, under the same conditions **3b** was converted to a roughly 1:1 mixture of **5b** and the 17-hydroxy-20β,21-cyclic carbonate **4b**. The latter compound was synthesized independently by reaction of Reichstein's substance E with phosgene in pyridine. Treatment of **4b** with alcoholic base resulted in its complete isomerization to the 17,20β-cyclic carbonate **5b**. It is evident from these results that by proper choice of substrate and reaction conditions any of the four possible hydroxy cyclic carbonates can be prepared selectively.

A likely explanation for the differences in reactivity of the epimeric cyclic carbonates **2a** and **2b** and cathylates **3a** and **3b** in alcoholic alkali stems from our previous observations on the relative stabilities of 17,20-acetonides.[6] The additional C-21/C-18 interaction undergone by 17,20α-cyclic carbonates would tend to favor partial isomerization to the 17-hydroxy-20α,21-cyclic derivatives *via* the 20-carbomethoxyl intermediate. The greater stability of 17,20β-cyclocarbonyldioxy-21-ols is to be expected since the terminal hydroxymethyl group faces away from the angular methyl group at C-18. That the direction of reaction is independent of the original location of an actual or potential cyclic carbonate grouping in the side chain was shown with the 21-cathylates **6a** and **6b**. The location of the cathyl group in these derivatives, prepared by selective reaction of the respective glycerols

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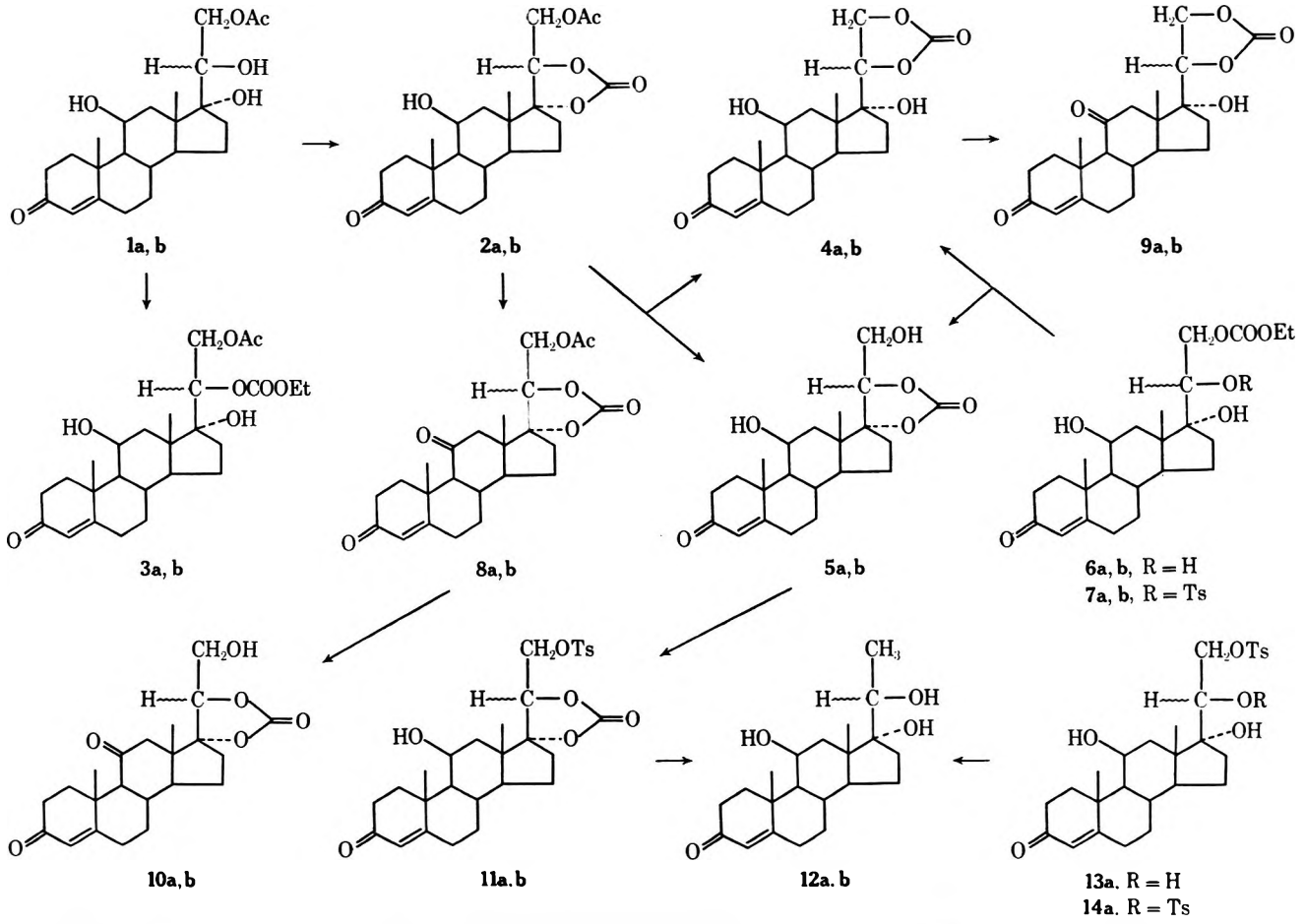
SCHEME I[a]



[a] In this and other schemes, the substituent at C-20 is α oriented in "a" compounds and β oriented in "b" compounds.

with ethyl chlorocarbonate–pyridine, was established by preparing the 20-acetates **7a** and **7b**. These possessed infrared spectra similar to but not identical with those of the isomeric 20-cathyl-21-acetates **3a** and **3b**. Reaction of **6b** with ethanolic alkali gave the 17,20β-cyclocarbonyldioxy-21-ol **5b** as the sole product; similar treatment of **6a** afforded the same equilibrium mixture obtained from **2a** and **3a**.

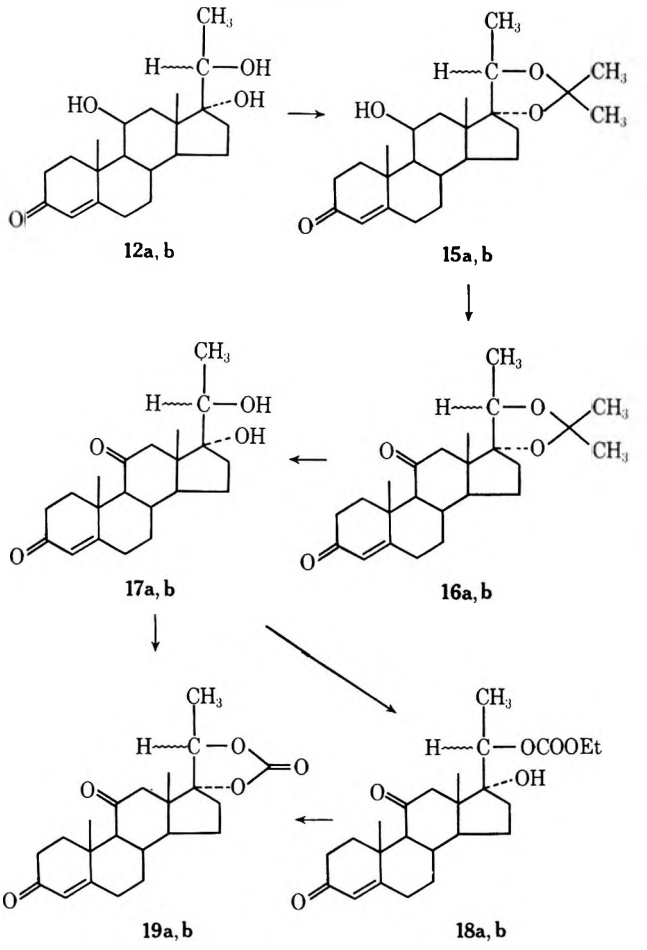
The conversion of both 17,20-cyclocarbonyldioxy-21-acetates (**2a** and **2b**) to the corresponding 21-ols in ethanolic sulfuric acid suggested that isomerization cannot occur in this medium. Confirmation of this lack of interconvertibility was obtained by demonstrating that the 17-hydroxy-20,21-cyclic carbonates **4a** and **4b** were unaffected by treatment with ethanolic sulfuric acid for 1 week at room temperature. In the reaction of the 20-cathyl-21-acetates **3a** and **3b** under acidic conditions the situation differs in that the possibility of cyclization in either direction exists. Presumably the steric factors which are operative in the behavior in alcoholic alkali also obtain in this case since the 20α epimer affords the sterically unstrained 17-hydroxy-20,21-cyclic carbonate **4a** as the only product in a yield of 88%. On the other hand, treatment of the 20β-cathyl-21-acetate **3b** with ethanolic sulfuric acid provided roughly equal amounts of both possible hydroxy cyclic carbonates which suggests that competition between rates of deactylation at C-21 and cyclization involving the tertiary hydroxyl group at C-17 are the controlling factors.

The stability of the cyclocarbonyldioxy system to oxidation with chromic anhydride in pyridine was shown by the following reaction sequence. Oxidation of the 17,20-cyclocarbonyldioxy-21-acetates **2a** and **2b** gave the 11-ketones **8a** and **8b** in excellent yield. Similar treatment of the 17-hydroxy-20,21-cyclic carbonates **4a** and **4b** afforded the corresponding 11-ketones **9a** and **9b**. The controlling effect of configuration at C-20 on the direction of reaction which was established in the 11β-ols was utilized to complete the 11-ketone series. Reaction of **8a** with ethanolic sulfuric acid gave the 17,20α-cyclocarbonyldioxy-21-ol **10a**; treatment of **8b** with ethanolic sodium hydroxide furnished with 20β epimer **10b**.

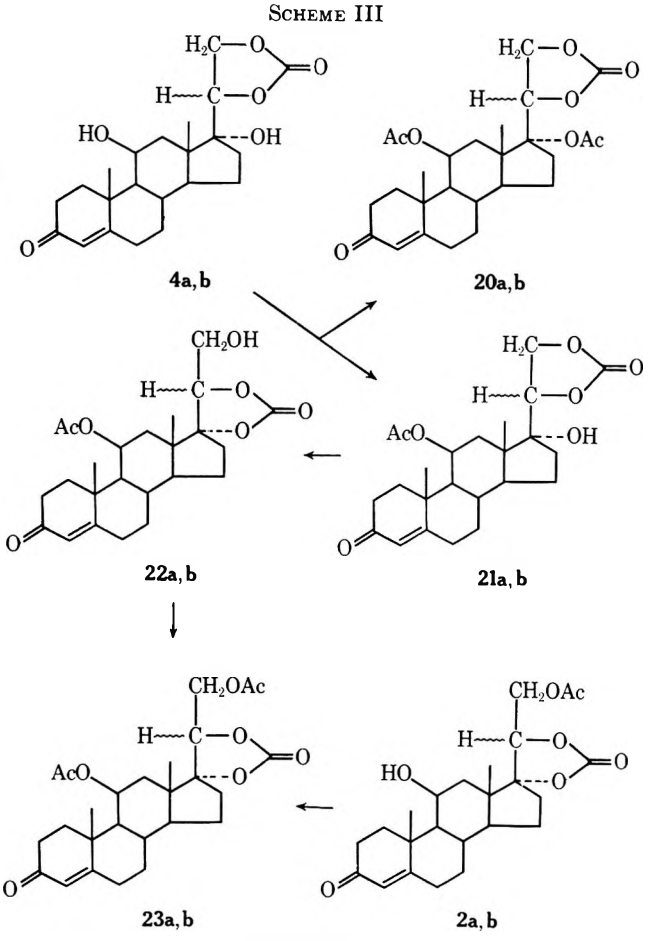
A practical use of cyclic carbonates as intermediates was made in the synthesis of the 21-deoxy analogs of Reichstein's substances epi-E and E (**12a** and **12b**). Reaction of the 17,20-cyclocarbonyldioxy-21-ols **5a** and **5b** with tosyl chloride in pyridine provided the respective 21-tosylates **11a** and **11b**. Lithium aluminum hydride reduction followed by selective oxidation at C-3 with DDQ[7] gave the desired triols **12a** and **12b** in overall yields from **5a** and **5b** in excess of 50%. The superiority of this route to **12a** and **12b** was easily demonstrated since the yield of **12a** *via* the glycerol 21-tosylate **13a** was only 31%. The reason for the lower yield by the more conventional route is in part

(7) D. Burn, V. Petrow, and G. O. Weston, *Tetrahedron Lett.*, **No. 9**, 14 (1960).

SCHEME II



SCHEME III



due to the formation in 10% yield of the 20,21-ditosylate **14a** from the tosylation of the free glycerol.

The triols **12a** and **12b** served as convenient starting materials for the preparation of 11-keto-17,20-cyclic carbonates in the 21-deoxy series. Oxidation of their acetonation products **15a** and **15b** (Scheme II) with chromic anhydride in pyridine afforded the 11-ketones **16a** and **16b**. These were hydrolyzed respectively with 60% acetic acid at room temperature and 80% refluxing acetic acid, as described previously,[6] to the diol-diones **17a** and **17b**. Preparation of the 17,20-cyclic carbonates **19a** and **19b** was carried out either directly by reaction with phosgene in pyridine or *via* alkaline cyclization of the 20-cathylates **18a** and **18b**.

In striking contrast to the great resistance of steroidal side-chain acetonides to alkaline hydrolysis, the corresponding cyclic carbonates are readily cleaved even in dilute, aqueous bicarbonate solution. Cyclic carbonates, however, are very stable to acidic reagents. For example, treatment of the 17,20-cyclic carbonates **19a** and **19b** with aqueous ethanolic sulfuric acid for 70 hr at room temperature was without effect; refluxing in the same reagent for 2 hr resulted in only approximately 10% hydrolysis to the 17,20-diols. It would therefore appear that as in the carbohydrate field[8] cyclocarbonyldioxy derivatives of the steroid side chain can be used as protecting groups for transformations elsewhere in the molecule involving acidic reagents. In this connection it seemed of interest to study the reactivity and/or stability of the 11β,17-dihydroxy-20,21-cyclic carbonates (**4a** and **4b**, Scheme III) to forcing acetylation conditions. Treatment of **4a** with *p*-TSA in a mixture of acetic acid and acetic anhydride at room temperature followed by silica gel column chromatography afforded a major mobile product (71%) and a minor polar product (11%). Similar treatment of **4b** gave a minor mobile product (10%) and a major polar product (64%). The hydroxyl-free minor products from each epimer were assigned the 11,17-diacetate structures **20a** and **20b**. The monohydroxylic major products were identified as the 11β-acetates **21a** and **21b** rather than the 17-acetates since they were not affected by chromic anhydride in pyridine. These results show that the bulky cyclic carbonate ring prevents the complete acetylation at C-17 which normally occurs with this reagent.[9] The facile acetylation of 11β-ols under these conditions was first described by Oliveto, *et al.*[10] The preparation of a complete series of 11β-acetoxy cyclic carbonates was completed as follows: alkaline rearrangement of the 20,21-cyclic carbonates **21a** and **21b** provided the 17,20-cyclocarbonyldioxy-21-ols **22a** and **22b**; treatment of **22a** and **22b** with acetic anhydride–pyridine furnished the 11β,21-diacetates **23a** and **23b**. Alternatively, the latter compounds could be prepared by forced acetylation at C-11 of the 17,20-cyclocarbonyldioxy-21-acetates **2a** and **2b**.

Oliveto, *et al.*, recorded that acetylation of an 11β-hydroxyl group results in a hypsochromic shift of 2 mμ for the λ_{max} of the Δ^4-3-keto system.[10] The ultra-

(8) L. Hough, J. E. Priddle, and R. S. Theobald, *Advan. Carbohyd. Chem.*, **15**, 1 (1960).

(9) R. B. Turner, *J. Amer. Chem Soc.*, **75**, 3489 (1953).

(10) E. P. Oliveto, C. Gerold, L. Weber, H. E. Jorgensen, R. Rausser, and E. B. Hershberg, *ibid.*, **75**, 5486 (1953).

TABLE I

λ_{max} VALUES AND MD INCREMENTS OF 11β-ACETOXY CYCLIC CARBONATES

Pairs	C-11	C-17	C-20	C-21	λ_{max}, mμ 20α	λ_{max}, mμ 20β	MD 20α	MD 20β	ΔMD 20α	ΔMD 20β
1	OH	OH	CCS[a]		242	242	+272	+237	+102	+149
2	OAc	OH			240	240	+374	+386		
3	OH		CCS	OH	240	242	+106	+488	+108	+82
4	OAc		CCS	OH	239	239	+214	+570		
5	OH		CCS	OAc	242	242	+162	+565	−8	−1
6	OAc		CCS	OAc	238	238	+154	+564		
7	OAc	OAc	CCS		239.5	239.5	+366	+195		

[a] CCS denotes cyclic carbonate system.

violet absorption maxima of the 11β-acetates prepared in the present study appear to reflect subtle influences of the side-chain substituents, showing a gradation of hypsochromic shifts from 2 to 4 mμ (Table I). The molecular rotational increments resulting from 11β-acetylation are also presented in Table I. The values, ranging from +82 to +149 units for pairs 1–4, are within the range of from +3 to +165 units given by Fox, *et al.*[11] In contrast, acetylation at C-11 of the 17,20-cyclocarbonyldioxy-21-acetates is associated with a slight negative shift in optical rotation (pairs 5 and 6).

Although no significant trends in optical activity were noted for 20,21-cyclic carbonates generally, consistent differences between C-20 epimeric 17,20-cyclic carbonates were present. In all cases 17,20β-cyclic carbonates were considerably more dextrorotatory than their 20α counterparts, with α − β differences of from −283 to −430 MD units, a range similar to that recorded by us for 20-acetates.[12] It should therefore be possible to assign configurations at C-20 for new pairs of 17,20 cyclic carbonates which may be encountered.

The infrared spectral properties of the new steroidal cathylates and cyclic carbonates were also studied. Eleven side-chain cathylates had a very strong band at 1265–1260 cm^{-1} and a strong to very strong band at 792–784 cm^{-1}. Of the 26 five-membered ring cyclic carbonates examined, all gave rise to a very strong band in the carbonyl region ranging from 1818 to 1778 cm^{-1}. In a number of instances, splitting of the carbonyl band occurs with the two maxima separated by approximately 25 cm^{-1}. Another strong to very strong band characteristic of all 17,20- and 20,21-cyclic carbonates is present in the region from 789 to 769 cm^{-1}. However, in the 21-tosylates **11a** and **11b** this band is apparently displaced to 750 cm^{-1}. Ready differentiation between the two types of side-chain cyclic carbonates by infrared analysis is therefore not possible.

Experimental Section

General experimental procedures are detailed in the previous paper.[2]

20α-Carbethoxy-21-acetoxy-11β,17-dihydroxypregn-4-en-3-one (3a) from 1a.—To a solution of 21-acetoxy-11β,17,20α-trihydroxypregn-4-en-3-one[3] (5 g) in cold pyridine (50 ml) was added ethyl chlorocarbonate (ECC) (5 ml), and the mixture was stored at 5°. Tlc analysis of an aliquot removed after 18 hr showed approximately 50% conversion to a more mobile product. The reaction mixture was therefore retreated with 5 ml of ECC for an additional 5 hr at 5°. Repeat tlc analysis showed a small amount only of starting material. The product was recovered in the usual manner and crystallized from methanol as long, fine needles (4.0 g, mp 216.5–218.5°; 0.4 g, mp 213.5–215°) in a yield of 81%: $[\alpha]_{365}$ −79.5°, $[\alpha]_D$ 48.7°; λ_{max} 242 mμ (ε 16,000); ν_{max} 1740 1265, and 790 (cathylate), 1740 and 1230 cm^{-1} (acetate).

Anal. Calcd for $C_{26}H_{38}O_8$: C, 65.25; H, 8.00; CH_3CO, 8.99; C_2H_5O, 9.41. Found: C, 64.87; H, 8.12; CH_3CO, 9.60; C_2H_5O, 9.72.

20β-Carbethoxy-21-acetoxy-11β,17-dihydroxypregn-4-en-3-one (3b) from 1b.—To a solution of 21-acetoxy-11β,17,20β-trihydroxypregn-4-en-3-one (500 mg) in cold pyridine (5 ml) was added ECC (0.3 ml). Tlc analysis after 3 hr at room temperature showed only a roughly 20% conversion to the desired product. The crude product was recovered and retreated in pyridine (5 ml) with ECC (0.6 ml) for three additional times. Repeated crystallization from ethanol of the final reaction mixture afforded plates (250 mg): mp 225–227°; $[\alpha]_{365}$ 310°, $[\alpha]_D$ 175°; λ_{max} 242 mμ (ε 15,750); ν_{max} 1740, 1260, and 784 (cathylate), 1740 and 1230 cm^{-1} (acetate).

Anal. Calcd for $C_{26}H_{38}O_8$: C, 65.25; H, 8.00. Found: C, 65.24; H, 8.01.

17,20α-Cyclocarbonyldioxy-21-acetoxy-11β-hydroxypregn-4-en-3-one (2a) from 1a.—To a solution of 21-acetoxy-11β,17,20α-trihydroxypregn-4-en-3-one (4.06 g, 10 mmol) in pyridine (50 ml) at 0° was added dropwise with magnetic stirring a mixture of 12.5% phosgene in benzene (15 ml) and benzene (35 ml) over a 1.5-hr period. After an additional 15 min at 0°, the product was recovered and crystallized from methanol as needles (3.7 g, mp 239–241°; 0.1 g, mp 237.5–239°) in a yield of 88%: $[\alpha]_{365}$ −123°, $[\alpha]_D$ 37.5°; λ_{max} 242 mμ (ε 16,100); ν_{max} 1790 and 776 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{24}H_{32}O_7$: C, 66.65; H, 7.46. Found: C, 66.63; H, 7.49.

17,20β-Cyclocarbonyldioxy-21-acetoxy-11β-hydroxypregn-4-en-3-one (2b) from 1b.—A solution of 21-acetoxy-11β,17,20β-trihydroxypregn-4-en-3-one (1624 mg, 4 mmol) in pyridine (20 ml) was treated with a mixture of 12.5% phosgene in benzene (7 ml) and benzene (18 ml) for 2 hr as in the preparation of 2a from 1a. The product crystallized from methanol as needles (1360 mg, mp 250–253°; 160 mg, mp 244–246°) in a yield of 88%: $[\alpha]_{365}$ 142°, $[\alpha]_D$ 131°; λ_{max} 242 mμ (ε 15,900); ν_{max} 1792 and 769 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{24}H_{32}O_7$: C, 66.65; H, 7.46. Found: C, 66.62; H, 7.44.

20α,21-Cyclocarbonyldioxy-11β,17-dihydroxypregn-4-en-3-one (4a). From Phosgene–Pyridine on Reichstein's Substance Epi-E.—To a stirred solution of 11β,17,20α,21-tetrahydroxypregn-4-en-3-one (182 mg) in pyridine (2.5 ml) at 0° was added a mixture of phosgene solution (0.75 ml) and benzene (1.75 ml). After 10 min at 0° the product was recovered and crystallized from methanol as prisms (148 mg, mp 235–236.5°; 16 mg, mp 236.5–238.5°) in a yield of 84%: $[\alpha]_{365}$ −24.6°, $[\alpha]_D$ 69.7°; λ_{max} 242 mμ (ε 16,050); ν_{max} 1788 and 777 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.29; H, 7.66.

From Ethanolic Sulfuric Acid on 3a.—To a solution of 20α-carbethoxy-21-acetoxy-11β,17-dihydroxypregn-4-en-3-one (200 mg) in ethanol (40 ml) was added concentrated sulfuric acid (0.1 ml). After 48 hr at room temperature methylene chloride (250 ml) was added; the solution was washed with water and concentrated to dryness. Crystallization from methanol afforded leaflets (115 mg, mp 232.5–235°; 40 mg, mp 234–236°) in a yield of 88%. The ir spectrum was identical with that of the phosgenation product from Reichstein's Substance epi-E.

17,20α-Cyclocarbonyldioxy-11β,21-dihydroxypregn-4-en-3-one

(11) S. M. Fox, V. E. Origoni, and L. L. Smith, *J. Amer. Chem. Soc.*, **82**, 2580 (1960).

(12) M. L. Lewbart and J. J. Schneider, *J. Org. Chem.*, **33**, 1707 (1968).

(5a) from 2a.—To a solution of 17,20α-cyclocarbonyldioxy-21-acetoxy-11β-hydroxypregn-4-en-3-one (1 g) in a mixture of methylene chloride (100 ml) and ethanol (500 ml) was added concentrated sulfuric acid (1.2 ml). After 10 days at room temperature anhydrous sodium acetate (1.8 g) was added and the reaction mixture was concentrated *in vacuo* nearly to dryness. The product was recovered by extraction with methylene chloride and successive washing with dilute sodium hydroxide and water. Crystallization of the residue from methanol afforded prisms (735 mg, mp 246–248°; 60 mg, mp 244–246°) in a yield of 88%: $[\alpha]_{365}$ −130°, $[\alpha]_D$ 27.1° (methanol); λ_{max} 240 mμ (ε 15,800); ν_{max} 1788 and 778 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.32; H, 7.58.

Treatment of **5a** with acetic anhydride–pyridine afforded a product identical in all respects with the starting material.

20α,21-Cyclocarbonyldioxy-11β,17-dihydroxypregn-4-en-3-one (4a) and 17,20α-Cyclocarbonyldioxy-11β,21-dihydroxypregn-4-en-3-one (5a) from 3a.—To a solution of 20α-carbethoxy-21-acetoxy-11β,17-dihydroxypregn-4-en-3-one (4 g) in ethanol (250 ml) was added 0.1 *N* ethanolic sodium hydroxide (12.5 ml). After 10 min at room temperature, 1 *N* hydrochloric acid (1.25 ml) was added, and the solution was concentrated *in vacuo* to a small volume, and the residue was partitioned between methylene chloride and water. The reaction mixture was applied in pyridine (10 ml) to a 70 × 540 mm silica gel column prepared with the system ethyl acetate–isooctane (3:1). Fractions (15 ml) were collected at intervals of 10 min. At fraction number 750 the system was changed to ethyl acetate.

20α,21-Cyclocarbonyldioxy-11β,17-dihydroxypregn-4-en-3-one. Fractions 300–800.—Crystallization from methanol gave prisms (1510 mg, mp 235–237°; 190 mg, mp 230–232°) in a yield of 48%. The ir spectrum was identical with that of the phosgenation product from Reichstein's substance epi-E.

17,20α-Cyclocarbonyldioxy-11β,21-hydroxypregn-4-en-3-one. Fractions 850 to End of Band.—Crystallization from methanol furnished small prisms (750 mg, mp 244–247°; 50 mg, mp 240–243°) in a yield of 23%. The ir spectrum was identical with that of **5a** prepared from **2a**.

4a and 5a from 2a.—To a solution of 17,20α-cyclocarbonyldioxy-21-acetoxy-11β-hydroxypregn-4-en-3-one (3.82 g) in ethanol (500 ml) was added 0.1 *N* ethanolic sodium hydroxide (25 ml). After 10 min the reaction mixture was processed and chromatographed as in the preparation of **4a** and **5a** from **3a**.

Fractions 331–800.—The 20,21-cyclic carbonate **4a** crystallized from methanol (1940 mg, mp 235–237°) in a yield of 56%.

Fractions 831 to End of Band.—The 17,20-cyclic carbonate **5a** crystallized from methanol (877 mg, mp 245–247°) in a yield of 25%.

20β,21-Cyclocarbonyldioxy-11β,17-dihydroxypregn-4-en-3-one (4b) from Reichstein's Substance E.—Phosgenation of 11β,17,20β,21-tetrahydroxypregn-4-en-3-one monohydrate (182 mg) as in the preparation of **4a** from Reichstein's substance epi-E and crystallization of the product from ethanol provided 151 mg of long needles, mp 155–160° and 229–230° in a yield of 82%: $[\alpha]_{365}$ −11.6°, $[\alpha]_D$ 60.7° (methanol); λ_{max} 242 mμ (ε 15,050); ν_{max} 1803 (1781) and 777 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{22}H_{30}O_6 \cdot H_2O$: C, 64.68; H, 7.90. Found: C, 65.03; H, 8.10.

17,20β-Cyclocarbonyldioxy-11β,21-dihydroxypregn-4-en-3-one (5b) from 2b. With Ethanolic Sodium Hydroxide.—To a solution of 17,20β-cyclocarbonyldioxy-21-acetoxy-11β-hydroxypregn-4-en-3-one (1200 mg) in ethanol (230 ml) was added 0.1 *N* ethanolic sodium hydroxide (12 ml). After 10 min the solution was neutralized with hydrochloric acid and the recovered product crystallized from methanol as needles (934 mg, mp 242–243°) in a yield of 86%: $[\alpha]_{365}$ 173°, $[\alpha]_D$ 125° (methanol); λ_{max} 242 mμ (ε 15,750); ν_{max} 1778 and 774 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.73; H, 7.79.

With Ethanolic Sulfuric Acid.—Treatment of **2b** (100 mg) in ethanol (40 ml) with sulfuric acid (0.1 ml) for 90 hr at room temperature was followed by chromatography of the crude product on a 16 × 600 mm silica gel column in ethyl acetate–isooctane (3:1). Fractions of 3 ml were collected at 10-min intervals. After the emergence of fraction 160 the system was changed to ethyl acetate. From **fractions 61–150** was obtained 6.6 mg of needles, mp 252–253.5°, which possessed an ir spectrum identical with that of the starting material. The residue from **fractions 171–320** (72.3 mg, 80%) afforded **5b** as prismatic needles from methanol, mp 242–243.5°.

20β,21-Cyclocarbonyldioxy-11β,17-dihydroxypregn-4-en-3-one (4b) and 17,20β-Cyclocarbonyldioxy-11β,21-dihydroxypregn-4-en-3-one (5b) from 3b.—Treatment of 20β-carbethoxy-21-acetoxy-11β,17-dihydroxypregn-4-en-3-one (100 mg) with ethanolic sulfuric acid for 90 hr followed by silica gel column chromatography was carried out as in the reaction of **2b**.

20β,21-Cyclocarbonyldioxy-11β,17-dihydroxypregn-4-en-3-one. Fractions 66–145.—The pooled material (47.5 mg, 52.5%) gave long needles from aqueous methanol, mp 193.5–195.5°. Recrystallization from ethanol afforded needles, mp 155–160° and 223–225°, which possessed an ir spectrum identical with that of the phosgenation product obtained from Reichstein's substance E.

17,20β-Cyclocarbonyldioxy-11β,21-dihydroxypregn-4-en-3-one. Fractions 188–290.—Crystallization of the crude residue (37.7 mg, 41.7%) from ethyl acetate gave needles, mp 242–243.5°, which were identical in all respects with **5b** prepared from **2b**.

21-Carbethoxy-11β,17,20α-trihydroxypregn-4-en-3-one (6a) from Reichstein's Substance Epi-E.—To a solution of 11β,17,20α,21-tetrahydroxypregn-4-en-3-one (500 mg) in pyridine (5 ml) was added ECC (0.15 ml). After 17.5 hr at 5° the product was recovered as platelets by several crystallizations from methanol (329 mg, mp 138–140° and 208–211°) in a yield of 55%: $[\alpha]_{365}$ 54.2°, $[\alpha]_D$ 96.3°; λ_{max} 242 mμ (ε 15,550); ν_{max} 1738, 1260, and 789 cm^{-1} (cathylate).

Anal. Calcd for $C_{24}H_{36}O_7$: C, 66.03; H, 8.31; C_2H_5O, 10.32. Found: C, 65.88; H, 8.29; C_2H_5O, 10.42.

7a from 6a.—Treatment of the 21-cathylate with pyridine and acetic anhydride for 18 hr at room temperature and crystallization of the product from ethyl acetate gave **21-carbethoxy-20α-acetoxy-11β,17-dihydroxypregn-4-en-3-one** as hairy needles: mp 204–205°; $[\alpha]_{365}$ −60.5°, $[\alpha]_D$ 55.6°; λ_{max} 242 mμ (ε 15,700); ν_{max} 1738, 1265, and 789 (cathylate), 1738 and 1230 cm^{-1} (acetate).

Anal. Calcd for $C_{26}H_{38}O_8 \cdot 0.5H_2O$: C, 64.04; H, 8.06. Found: C, 64.18; H, 7.72.

A mixture melting point of **7a** with **3a** showed no depression, and they possessed the same mobility (R_f 0.10) by tlc in ethyl acetate–isooctane (1:1). However, the ir fingerprint regions were distinctly different.

21-Carbethoxy-11β,17,20β-trihydroxypregn-4-en-3-one (6b) from Reichstein's Substance E.—Cathylation of 11β,17,20β,21-tetrahydroxypregn-4-en-3-one (500 mg) was carried out as in the preparation of **6a**. Several crystallizations from ethyl acetate provided 309 mg (52%) of prisms: mp 167–168.5°; $[\alpha]_{365}$ 89.5°, $[\alpha]_D$ 109°; λ_{max} 242 mμ (ε 15,300); ν_{max} 1738, 1263, and 790 cm^{-1} (cathylate).

Anal. Calcd for $C_{24}H_{36}O_7$: C, 66.03; H, 8.31; C_2H_5O, 10.32. Found: C, 65.69; H, 8.39; C_2H_5O, 10.30.

7b from 6b.—Acetylation of the 21-cathylate in the usual manner and crystallization of the product from ethanol gave **21-carbethoxy-20β-acetoxy-11β,17-dihydroxypregn-4-en-3-one** as platelets: mp 212–214°; $[\alpha]_{365}$ 289°, $[\alpha]_D$ 168°; λ_{max} 242 mμ (ε 15,700); ν_{max} 1740, 1262, and 790 (cathylate), 1740 and 1230 cm^{-1} (acetate).

Anal. Calcd for $C_{26}H_{38}O_8$: C, 65.25; H, 8.00. Found: C, 65.20; H, 8.07.

17,20α-Cyclocarbonyldioxy-21-acetoxypregn-4-ene-3,11-dione (8a) from 2a.—Oxidation of 17,20α-cyclocarbonyldioxy-21-acetoxy-11β-hydroxypregn-4-en-3-one (2 g) in pyridine (80 ml) with chromic anhydride (2 g) was carried out for 19 hr in the usual manner. Crystallization of the product from methanol afforded prisms (1730 mg, mp 237–238°; 83 mg, mp 233–234°) in a yield of 91%: $[\alpha]_{365}$ 356°, $[\alpha]_D$ 72°; λ_{max} 238 mμ (ε 16,300); ν_{max} 1805 and 776 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{24}H_{30}O_7$: C, 66.96; H, 7.02. Found: C, 66.98; H, 7.05.

17,20β-Cyclocarbonyldioxy-21-acetoxypregn-4-ene-3,11-dione (8b) from 2b.—Oxidation of 17,20β-cyclocarbonyldioxy-21-acetoxy-11β-hydroxypregn-4-en-3-one (300 mg) in pyridine (12 ml) with an equal weight of chromic anhydride for 19 hr afforded the 11-ketone as plates from methanol (254 mg, mp 222–225°; 18 mg, mp 213–216°) in a yield of 91%: $[\alpha]_{365}$ 647°, $[\alpha]_D$ 172°; λ_{max} 238 mμ (ε 15,650); ν_{max} 1802 and 770 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{24}H_{30}O_7$: C, 66.96; H, 7.02. Found: C, 66.81; H, 7.05.

17,20α-Cyclocarbonyldioxy-21-hydroxypregn-4-ene-3,11-dione

(10a) from 8a.—To a solution of 17,20α-cyclocarbonyldioxy-21-acetoxypregn-4-ene-3,11-dione (1 g) in a mixture of methylene chloride (100 ml) and ethanol (500 ml) was added 1.2 ml of sulfuric acid. After 10 days at room temperature the product was recovered as in the preparation of 5a from 2a. Crystallization from methanol gave 869 mg (96%) of leaflets: mp 226–226.5°; $[\alpha]_{365}$ 362°, $[\alpha]_D$ 70.3° (methanol); λ_{max} 238 mμ (ε 15,400); ν_{max} 1801 and 773 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{22}H_{28}O_6$: C, 68.02; H, 7.27. Found: C, 67.80; H, 7.50.

17,20β-Cyclocarbonyldioxy-21-hydroxypregn-4-ene-3,11-dione (10b) from 8b.—To a solution of 17,20β-cyclocarbonyldioxy-21-acetoxypregn-4-ene-3,11-dione (240 mg) in ethanol (46 ml) was added 0.1 *N* ethanolic sodium hydroxide (2.4 ml). After 10 min the solution was neutralized and the product was recovered in the usual manner. Crystallization from methanol gave 174 mg (80%) of needles: mp 266–268°; $[\alpha]_{365}$ 618°, $[\alpha]_D$ 143° (methanol); λ_{max} 238 mμ (ε 15,450); ν_{max} 1790 and 784 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{22}H_{28}O_6$: C, 68.02; H, 7.27. Found: C, 68.01; H, 7.29.

20α,21-Cyclocarbonyldioxy-17-hydroxypregn-4-ene-3,11-dione (9a) from 4a.—Oxidation of 20α,21-cyclocarbonyldioxy-11β,17-dihydroxypregn-4-en-3-one (2 g) with chromic anhydride in pyridine as in the previous examples gave, from methanol, 1940 mg (97%) of platelets: mp 204–206°; $[\alpha]_{365}$ 531°, $[\alpha]_D$ 122° (methanol); λ_{max} 238 mμ (ε 15,500); ν_{max} 1795 and 771 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{22}H_{28}O_6$: C, 68.02; H, 7.27. Found: C, 68.00; H, 7.30.

20β,21-Cyclocarbonyldioxy-17-hydroxypregn-4-ene-3,11-dione (9b) from 4b.—Oxidation of 20β,21-cyclocarbonyldioxy-11β,17-dihydroxypregn-4-en-3-one (100 mg), as in the preparation of 9a from 4a, gave 83 mg of prisms from methanol: mp 170–175, 225–230, and 259–261°; $[\alpha]_{365}$ 433°, $[\alpha]_D$ 85.7° (methanol); λ_{max} 238 mμ (ε 14,900); ν_{max} 1810 (1784) and 780 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{22}H_{28}O_6$: C, 68.02; H, 7.27. Found: C, 67.68; H, 7.89.

17,20α-Cyclocarbonyldioxy-21-tosyloxy-11β-hydroxypregn-4-en-3-one (11a) from 5a.—Treatment of 17,20α-cyclocarbonyldioxy-11β,21-dihydroxypregn-4-en-3-one (1 g) in pyridine (10 ml) with an equal weight of tosyl chloride for 64 hr at 5°, and crystallization of the product from methanol gave 1380 mg of platelets: mp 252–252.5°; $[\alpha]_{365}$ −326°, $[\alpha]_D$ −29.5°; λ_{max} 242 mμ (ε 16,850) (sh) and 228 (ε 23,600); ν_{max} 1800 and 749 (cyclic carbonate), 1595, 1490, 1350, 1189, 1175, 1093, 810, and 662 cm^{-1} (tosylate).[13]

Anal. Calcd for $C_{29}H_{36}O_8S$: C, 63.95; H, 6.66. Found: C, 63.74; H, 6.48.

11β,17,20α-Trihydroxypregn-4-en-3-one (12a) from 11a.—A solution of 17,20α-cyclocarbonyldioxy-21-tosyloxy-11β-hydroxypregn-4-en-3-one (1380 mg) and lithium aluminum hydride (1380 mg) in tetrahydrofuran (75 ml) was refluxed for 2.5 hr. The product, recovered in the usual manner, was treated in *tert*-butyl alcohol (100 ml) with DDQ (1 g) for 3 hr as described earlier.[2] The reaction mixture was chromatographed on a 30 × 730 mm silica gel column in ethyl acetate, collecting 12-ml fractions every 12 min. From fractions 116–275 was obtained 490 mg of prisms (ethyl acetate), mp 202–204°, in an overall yield of 55% from 5a: $[\alpha]_{365}$ 16.4°, $[\alpha]_D$ 105°; λ_{max} 242 mμ (ε 15,050) [lit.[14] mp 193–194° (210–214°), $[\alpha]_D$ 107 ± 2° (chloroform)].

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.28; H, 9.25.

21-Tosyloxy-11β,17,20α-trihydroxypregn-4-en-3-one (13a) from Reichstein's Substance Epi-E.—To a solution of 11β,17,-20α,21-tetrahydroxypregn-4-en-3-one (2 g) in pyridine (10 ml) was added 1450 mg of tosyl chloride. After 24 hr at room temperature the product was recovered and crystallized from acetone as platelets (2.1 g, mp 144.5° dec): $[\alpha]_{365}$ −72.2°, $[\alpha]_D$ 49.9°; λ_{max} 242 mμ (ε 17,600) (sh) and 228 (22,800); λ_{max} 1600, 1495, 1358, 1191, 1176, 1098, 817, and 665 cm^{-1} (tosylate).[13]

Anal. Calcd for $C_{28}H_{38}O_7S$: C, 64.84: H, 7.38. Found: C, 64.91; H, 7.49.

The mother liquor residue was chromatographed on a 35 × 800 mm silica gel column in ethyl acetate–isooctane (1:1), collecting 7.5-ml fractions every 10 min. Fractions 211–385 afforded a more mobile by-product which crystallized from acetone as needles (358 mg, mp 135–138°). Since ir analysis showed an intensification of the characteristic tosylate bands, the compound was tentatively identified as **20α,21-ditosyloxy-11β,17-dihydroxypregn-4-en-3-one (14a)**: $[\alpha]_{365}$ −117°, $[\alpha]_D$ 20.4°; λ_{max} 242 mμ (ε 17,600) (sh) and 228 (33,800). From fractions 461–690 was obtained an additional 300 mg of the 21-tosylate, mp 145° dec, raising the yield to 2.4 g (84%).

12a from 13a.—Lithium aluminum hydride reduction of 21-tosyloxy-11β,17,20α-trihydroxypregn-4-en-3-one (2 g) followed by selective reoxidation with DDQ were carried out as in the preparation of 12a from 11a. The crude product (1.27 g) was chromatographed on a 42 × 700 mm silica gel column in ethyl acetate–isooctane (85:15), collecting 8 ml per 10 min. Crystallization of the residue from fractions 451–840 afforded 488 mg (36%) of the triolone, mp 199–202°.

17,20β-Cyclocarbonyldioxy-21-tosyloxy-11β-hydroxypregn-4-en-3-one (11b) from 5b.—Tosylation of 17,20β-cyclocarbonyldioxy-11β,21-dihydroxypregn-4-en-3-one (750 mg) was carried out as in the preparation of 11a. The product crystallized from methanol as platelets (825 mg, mp 232.5–233°; 100 mg, mp 230–231°): $[\alpha]_{365}$ 168°, $[\alpha]_D$ 123°; λ_{max} 242 mμ (ε 16,250) (sh) and 228 (22,900); ν_{max} 1798 and 750 (cyclic carbonate), 1595, 1490, 1358, 1189, 1175, 1091, 811, and 662 cm^{-1} (tosylate).[13]

Anal. Calcd for $C_{29}H_{36}O_8S$: C, 63.95; H, 6.66. Found: C, 63.91; H, 6.65.

11β,17,20β-Trihydroxypregn-4-en-3-one (12b) from 11b.—Subjection of 17,20β-cyclocarbonyldioxy-21-tosyloxy-11β-hydroxypregn-4-en-3-one (900 mg) to sequential reaction with lithium aluminum hydride and DDQ as in the reaction of 11a followed by silica gel column chromatography afforded 359 mg of needles from acetone, mp 162–163°, in an overall yield from 5a of 54%: $[\alpha]_{365}$ 68.8°, $[\alpha]_D$ 125°; λ_{max} 242 mμ (ε 15,250) [lit.[14] mp 149–151°, $[\alpha]_D$ 122 ± 2° (chloroform)].

Anal. Calcd for $C_{21}H_{32}O_4$: C, 72.38; H, 9.26. Found: C, 72.00; H, 9.18.

17,20α-Isopropylidenedioxy-11β-hydroxypregn-4-en-3-one (15a) from 12a.—Acetonation of 11β,17,20α-trihydroxypregn-4-en-3-one (400 mg) with *p*-TSA as catalyst was carried out for 17 hr.[6] Crystallization of the product from acetone–*n*-hexane afforded prismatic needles (220 mg, mp 204.5–206.5°; 126 mg, mp 200–202°; 70 mg, mp 190–192°) in a yield of 93%: $[\alpha]_{365}$ −45.2°, $[\alpha]_D$ 69.8°; λ_{max} 242 mμ (ε 15,050); ν_{max} 1236, 1210, 1154, and 1003 cm^{-1} (17,20α-acetonide).[6]

Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.02; H, 9.30.

17,20α-Isopropylidenedioxypregn-4-ene-3,11-dione (16a) from 15a.—Oxidation of 17,20α-isopropylidenedioxy-11β-hydroxypregn-4-en-3-one (360 mg) with chromic anhydride in pyridine as in the previous examples provided needles from acetone–*n*-hexane (327 mg, mp 175–177°; 14 mg, mp 164–168°) in a yield of 95%: $[\alpha]_{365}$ 599°, $[\alpha]_D$ 135°; λ_{max} 238 mμ (ε 14,900); ν_{max} 1237, 1214, 1148, and 1003 cm^{-1} (17,20α-acetonide).[6]

Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.21; H, 8.70.

17,20α-Dihydroxypregn-4-ene-3,11-dione (17a) from 16a.—A solution of 17,20α-isopropylidenedioxypregn-4-ene-3,11-dione (300 mg) in 60% acetic acid (100 ml) stood for 72 hr at room temperature. The solution was concentrated *in vacuo* to dryness and the product crystallized from acetone as needles (234 mg, mp 216–218°) in a yield of 87%: $[\alpha]_{365}$ 770°, $[\alpha]_D$ 180°; λ_{max} 238 mμ (ε 14,700).

Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.63; H, 8.71.

17,20β-Isopropylidenedioxy-11β-hydroxypregn-4-en-3-one (15b) from 12b.—To a solution of 11β,17-dihydroxypregn-4-ene-3,20-dione (2 g) in dimethylformamide (50 ml) were added sodium borohydride (150 mg) and sodium bicarbonate (300 mg), each in 2.5 ml of water.[4] After 2 hr at room temperature the crude triolone was recovered and treated in acetone (1 l.) with *p*-TSA (500 mg) for 6 hr. The reaction mixture was chromatographed on a 50 × 890 mm silica gel column in isooctane–ethyl acetate (3:2), collecting 12 ml per 10 min. Several crystallizations of the residue from fractions 367–656 (acetone and ether) afforded 759 mg (34%) of plates: mp 205–206°; $[\alpha]_{365}$ −33.1°, $[\alpha]_D$ 87.3°; λ_{max} 242 mμ (ε 15,300); ν_{max} 1248, 1216, 1154, and 1008 cm^{-1} (17,20β-acetonide).[6]

Anal. Calcd for $C_{24}H_{36}O_4$: C, 74.19; H, 9.34. Found: C, 74.39; H, 9.18.

17,20β-Isopropylidenedioxypregn-4-ene-3,11-dione (16b) from

(13) M. L. Lewbart, *J. Org. Chem.*, **33**, 1695 (1968).

(14) G. I. Poos, *J. Amer. Chem. Soc.*, **77**, 4438 (1955).

15b.—Oxidation of 17,20β-isopropylidenedioxy-11β-hydroxypregn-4-en-3-one (500 mg) with chromic anhydride in pyridine in the usual manner and crystallization of the product gave prisms (408 mg, mp 195–197°; 85 mg, mp 185–187°) in a yield of 99%: $[\alpha]_{365}$ 643°, $[\alpha]_D$ 150°; λ_{max} 238 mμ (ε 15,150); ν_{max} 1248, 1220, 1156, and 1002 cm^{-1} (17,20β-acetonide).[6]

Anal. Calcd for $C_{24}H_{34}O_4$: C, 74.57; H, 8.87. Found: C, 74.56; H, 8.90.

17,20β-Dihydroxypregn-4-ene-3,11-dione (17b) from 16b.—A solution of 17,20β-isopropylidenedioxypregn-4-ene-3,11-dione (300 mg) in 80% acetic acid (100 ml) was refluxed for 1 hr. The reaction mixture was chromatographed on a 25 × 700 mm silica gel column in ethyl acetate–isooctane (85:15), collecting 6 ml per 10 min. From **fractions 31–55** was obtained 26 mg of starting material, mp 197–201°. The major product emerged in **fractions 140–225** and crystallized from acetone as rosettes (94 mg, mp 197–198°; 79 mg, mp 195–198°): $[\alpha]_{365}$ 840°, $[\alpha]_D$ 198°; λ_{max} 238 mμ (ε 15,000) [lit.[15] mp 108–110° (hydrate)].

Anal. Calcd for $C_{21}H_{30}O_4$: C, 72.80; H, 8.73. Found: C, 72.91; H, 8.65.

20α-Carbethoxy-17-hydroxypregn-4-ene-3,11-dione (18a) from 17a.—Cathylation of 17,20α-dihydroxypregn-4-ene-3,11-dione (100 mg) in pyridine (1 ml) with ECC (0.075 ml) was carried out for 3 hr at room temperature. Several crystallizations from methanol gave 98 mg (88%) of product: mp 205–207°; $[\alpha]_{365}$ 583°, $[\alpha]_D$ 132°; λ_{max} 238 mμ (ε 13,900); ν_{max} 1736, 1260, and 791 cm^{-1} (cathylate).

Anal. Calcd for $C_{24}H_{34}O_6$: C, 68.87; H, 8.19; C_2H_5O, 10.77. Found: C, 68.79; H, 8.24; C_2H_5O, 11.10.

17,20α-Cyclocarbonyldioxypregn-4-ene-3,11-dione (19a) from 18a.—To a solution of 20α-carbethoxy-17-hydroxypregn-4-ene-3,11-dione (20 mg) in ethanol (3.8 ml) was added 0.1 *N* ethanolic sodium hydroxide (0.2 ml). After 5 min the reaction mixture was added to methylene chloride (300 ml), and after being washed with water the solution was concentrated to dryness. Crystallization from ethyl acetate provided 17 mg (86%) of prisms: mp 264–265°; $[\alpha]_{365}$ 520°, $[\alpha]_D$ 120°; λ_{max} 238 mμ (ε 15,350); ν_{max} 1792 and 779 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 70.91; H, 7.52.

19a from 17a.—To a solution of 17,20α-dihydroxypregn-4-ene-3,11-dione (35 mg) in pyridine (0.5 ml) was added 12.5% phosgene in benzene (0.15 ml). After 1 hr at room temperature the product was recovered and crystallized from ethyl acetate (29 mg, mp 264–265°; 5 mg, mp 260–262°) in a yield of 91%. The ir spectrum was identical with that of the cyclization product from **18a**.

20β-Carbethoxy-17-hydroxypregn-4-ene-3,11-dione (18b) from 17b.—Cathylation of 17,20β-dihydroxypregn-4-ene-3,11-dione (100 mg) was carried out as in the preparation of **18a**. However, examination of the reaction mixture by tlc showed only roughly 50% conversion to the cathylate. The material was therefore retreated with ECC–pyridine overnight at room temperature. The crude product was chromatographed on a 16 × 580 mm silica gel column in ethyl acetate–isooctane (3:1), collecting 3 ml per 10 min. At fraction 172 the system was changed to ethyl acetate. **Fractions 31–100** afforded the 20-cathylate as prismatic needles from methanol (76 mg, mp 92–93°) in a yield of 69%: $[\alpha]_{365}$ 742°, $[\alpha]_D$ 189°; λ_{max} 238 mμ (ε 14,450); ν_{max} 1738, 1261, and 792 cm^{-1} (cathylate).

Anal. Calcd for $C_{24}H_{34}O_6 \cdot CH_3OH$: C, 66.64; H, 8.50; CH_3O- and C_2H_5O, 16.89. Found: C, 66.69; H, 8.69; C_2H_5O, 19.63.

From **fractions 171–270** was obtained 27 mg (27%) of starting material, mp 197–199°.

17,20β-Cyclocarbonyldioxypregn-4-ene-3,11-dione (19b) from 18b.—Treatment of 20β-carbethoxy-17-hydroxypregn-4-ene-3,11-dione (20 mg) with ethanolic sodium hydroxide as in the preparation of **19a** from **18a** and crystallization from methanol provided needles (15 mg, mp 241–242°) in a yield of 79%: $[\alpha]_{365}$ 700°, $[\alpha]_D$ 179°; λ_{max} 238 mμ (ε 16,150); ν_{max} 1792 and 777 cm^{-1} (cyclic carbonate).

Anal. Calcd for $C_{22}H_{28}O_5$: C, 70.94; H, 7.58. Found: C, 70.93; H, 7.52.

19b from 17b.—Phosgenation of 17,20β-dihydroxypregn-4-ene-3,11-dione (35 mg) as in the preparation of **19a** from **17a** and crystallization of the product from methanol furnished needles (29 mg, mp 243–245°; 5 mg, mp 239–240°) in a yield of 92%. The ir spectrum was identical with that of the cyclization product from **18b**.

Forced Acetylation of 20α,21-Cyclocarbonyldioxy-11β,17-dihydroxypregn-4-en-3-one (4a).—To a solution of the cyclic carbonate (1 g) in a mixture of acetic acid (40 ml) and acetic anhydride (8 ml) was added *p*-TSA (800 mg). After 90 min at room temperature the product was recovered and chromatographed on a 38 × 900 mm silica gel column in ethyl acetate–isooctane (55:45). Fractions (8 ml) were collected at 10-min intervals.

20α,21-Cyclocarbonyldioxy-11β-acetoxy-17-hydroxypregn-4-en-3-one (21a). Fractions 396–570.—Crystallization from methanol gave needles (789 mg, mp 236–238°) in a yield of 71%. The compound was not affected by treatment with chromic anhydride in pyridine: $[\alpha]_{365}$ 0°, $[\alpha]_D$ 86.7°; λ_{max} 240 mμ (ε 15,150); ν_{max} 1800 and 788 (cyclic carbonate), 1734 and 1255 (acetate), 3450 cm^{-1} (hydroxyl).

Anal. Calcd for $C_{24}H_{32}O_7$: C, 66.64; H, 7.46. Found: C, 66.38; H, 7.42.

20α,21-Cyclocarbonyldioxy-11β,17-diacetoxypregn-4-en-3-one (20a). Fractions 591–780.—Crystallization from ethyl acetate gave platelets (130 mg, mp 129–132°) in a yield of 11%: $[\alpha]_{365}$ −23.5°, $[\alpha]_D$ 77.5°; λ_{max} 239.5 mμ (ε 15,200); ν_{max} 1815 and 775 (cyclic carbonate), 1740 and 1245 (very strong) cm^{-1} (acetate).

Anal. Calcd for $C_{26}H_{34}O_8$: C, 65.80; H, 7.22. Found: C, 66.33; H, 6.86.

Forced Acetylation of 20β,21-Cyclocarbonyldioxy-11β,17-dihydroxypregn-4-en-3-one (4b).—Treatment of the 20β,21-cyclic carbonate (1 g) with acetic acid–acetic anhydride–*p*-TSA as in the reaction of **4a** and crystallization of the crude product from ethanol furnished 490 mg of **20β,21-cyclocarbonyldioxy-11β-acetoxy-17-hydroxypregn-4-en-3-one (21b)** as needles: mp 154–156°; $[\alpha]_{365}$ 10.7°, $[\alpha]_D$ 89.4°; λ_{max} 240 mμ (ε 15,300); λ_{max} 1810 (1788) and 775 (cyclic carbonate), 1735 and 1255 (acetate), 3500 cm^{-1} (hydroxyl).

Anal. Calcd for $C_{24}H_{32}O_7 \cdot 0.5H_2O$: C, 65.28; H, 7.53. Found: C, 65.00; H, 7.18.

The compound was unchanged after treatment with chromic anhydride in pyridine. Chromatography of the mother liquor on a 30 × 800 mm silica gel column was carried out under the same conditions used for the 20α epimer.

20β,21-Cyclocarbonyldioxy-11β,17-diacetoxypregn-4-en-3-one (20b). Fractions 401–480.—The pooled residue weighed 125 mg (10%) and could be obtained only as a filterable solid from aqueous methanol: mp 130–132°; $[\alpha]_{365}$ −144°, $[\alpha]_D$ 41.2°; λ_{max} 239.5° mμ (ε 16,050); ν_{max} 1818 (1792) and 775 (cyclic carbonate), 1738 and 1240 (very strong) cm^{-1} (acetate).

Anal. Calcd for $C_{26}H_{34}O_8$: C, 65.80; H, 7.22. Found: C, 65.95; H, 7.03.

Further development of the column gave from **fractions 501–700** an additional 221 mg of the 11β-monoacetate, mp 153.5–155°, raising the yield to 64%.

17,20α-Cyclocarbonyldioxy-11β-acetoxy-21-hydroxypregn-4-en-3-one (22a) from 21a.—To a solution of 20α,21-cyclocarbonyldioxy-11β-acetoxy-17-hydroxypregn-4-en-3-one (100 mg) in a mixture of ethanol (8 ml) and water (4 ml) was added 5% aqueous sodium bicarbonate solution (4 ml). After 15 min at room temperature the solution was added to methylene chloride (100 ml) and washed with water. The residue was chromatographed on a 16 × 680 mm silica gel column in ethyl acetate–isooctane (3:1). At fraction 128 the system was changed to ethyl acetate. **Fractions 64–111** afforded 56 mg of starting material, mp 239–239.5°. **Fractions 162–220** provided **22a** (41 mg) as prisms from acetone: mp 202.5–205°; $[\alpha]_{365}$ −126°, $[\alpha]_D$ 49.5°; λ_{max} 239 mμ (ε 16,400); ν_{max} 1805 and 783 (cyclic carbonate), 1734 and 1255 cm^{-1} (acetate).

Anal. Calcd for $C_{24}H_{32}O_7 \cdot H_2O$: C, 63.98; H, 7.60. Found: C, 64.23; H, 7.04.

17,20β-Cyclocarbonyldioxy-11β-acetoxy-21-hydroxypregn-4-en-3-one (22b) from 21b.—To a solution of 20β,21-cyclocarbonyldioxy-11β-acetoxy-17-hydroxypregn-4-en-3-one (100 mg) in methanol (25 ml) was added an equal volume of 0.5% methanolic potassium bicarbonate. After 30 min at room temperature the solvent was removed *in vacuo* and the residue was partitioned between methylene chloride and water. Crystallization from methanol gave prisms (66 mg, mp 267–268° dec; 6 mg, mp 255–256°) in a yield of 72%: $[\alpha]_{365}$ 130°, $[\alpha]_D$ 132°; λ_{max} 239 mμ (ε 16,500); ν_{max} 1798 and 780 (cyclic carbonate), 1736 and 1255 cm^{-1} (acetate).

(15) L. H. Sarett, *J. Amer. Chem. Soc.*, **68**, 2478 (1946).

Anal. Calcd for $C_{24}H_{32}O_7$: C, 66.64; H, 7.46. Found: C, 66.83; H, 7.61.

17,20α-Cyclocarbonyldioxy-11β,21-diacetoxypregn-4-en-3-one (23a) from 22a.—Treatment of 17,20α-cyclocarbonyldioxy-11β-acetoxy-21-hydroxypregn-4-en-3-one (20 mg) with acetic anhydride–pyridine for 2 hr and crystallization of the product from ethyl acetate gave 14 mg of prisms: mp 207.5–209.5°; $[\alpha]_{365}$ −141°, $[\alpha]_D$ 32.5°; λ_{max} 238 mμ (ε 16,600); ν_{max} 1805 and 782 (cyclic carbonate), 1738 and 1245 (very strong) cm^{-1} (acetate).

Anal. Calcd for $C_{26}H_{34}O_8$: C, 65.80; H, 7.22. Found: C, 65.80; H, 7.37.

23a from 2a.—To a solution of 17,20α-cyclocarbonyldioxy-21-acetoxy-11β-hydroxypregn-4-en-3-one (500 mg) in acetic acid (20 ml) and acetic anhydride (4 ml) was added *p*-TSA (400 mg). After 2 hr the product was recovered and chromatographed on a 25 × 760 mm silica gel column in ethyl acetate–isooctane (65:35), collecting 6 ml of effluent every 10 min. Fractions 161–400 afforded prisms from ethyl acetate (335 mg, mp 206.5–209.5°; 37 mg, mp 199–202°) in a yield of 68%. The ir spectrum was identical with the acetylation product from **22a**.

17,20β-Cyclocarbonyldioxy-11β,21-diacetoxypregn-4-en-3-one (23b) from 22b.—Acetylation of 17,20β-cyclocarbonyldioxy-11β-acetoxy-21-hydroxypregn-4-en-3-one (20 mg) as in the preparation of **23a** from **22a** furnished 17 mg of prisms from ethyl acetate: mp 232–234°; $[\alpha]_{365}$ 120°, $[\alpha]_D$ 119°; λ_{max} 238 mμ (ε 16,200); ν_{max} 1805 and 778 (cyclic carbonate), 1740 and 1240 (very strong) cm^{-1} (acetate).

Anal. Calcd for $C_{26}H_{34}O_8$: C, 65.80; H, 7.22. Found: C, 65.83; H, 7.18.

23b from 2b.—A suspension of 17,20β-cyclocarbonyldioxy-21-acetoxy-11β-hydroxypregn-4-en-3-one (500 mg) in acetic acid (20 ml) and acetic anhydride (4 ml) containing *p*-TSA (400 mg) was stirred and warmed slightly to effect solution. After an additional hour at room temperature the product was recovered and crystallized from ethyl acetate (272 mg, mp 231.5–233.5°). The mother liquor was chromatographed on a 20 × 700 mm silica gel column in ethyl acetate–isooctane (3:2), collecting 4-ml fractions at 10-min intervals. From fractions 166–350 was obtained an additional 96 mg of product, mp 230–232°, raising the yield to 67%. The ir spectrum was identical with that of the acetylation product from **22b**.

Registry No.—**2a**, 33537-28-9; **2b**, 33487-57-9; **3a**, 33487-58-0; **3b**, 33487-59-1; **4a**, 33487-60-4; **4b**, 33487-61-5; **5a**, 33537-24-5; **5b**, 33487-62-6; **6a**, 33608-34-3; **6b**, 33487-63-7; **7a**, 33487-64-8; **7b** 33487-65-9; **8a**, 33487-66-0; **8b**, 33487-67-1; **9a**, 33487-68-2; **9b**, 33487-69-3; **10a**, 33487-70-6; **10b**, 33487-71-7; **11a**, 33487-72-8; **11b**, 33487-73-9; **12a**, 33537-25-6; **12b**, 33487-74-0; **13a**, 33537-26-7; **14a**, 33487-75-1; **15a**, 33487-76-2; **15b**, 33487-77-3; **16a**, 33487-78-4; **16b**, 33487-79-5; **17a**, 33487-81-9; **17b**, 33487-80-8; **18a**, 33487-82-0; **18b**, 33487-83-1; **19a**, 33537-27-8; **19b**, 33487-84-2; **20a**, 33487-85-3; **20b**, 33487-86-4; **21a**, 33487-87-5; **21b**, 33487-88-6; **22a**, 33487-89-7; **22b**, 33487-90-0; **23a**, 33487-91-1; **23b**, 33487-92-2.

The Olefin Selectivity for the Dehydration of 2-Octanol by Alumina and Thoria

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The primary olefin distribution was determined for the dehydration of 2-octanol over several alumina and thoria catalysts. Rather than attempt the elimination of secondary reactions, the isomerization of a very similar olefin, 1-heptene, was used to determine the extent of isomerization of the primary olefin products. For acidic alumina the initial olefin products were 45% 1-octene, 5% *trans*-2-octene, and 50% *cis*-2-octene. The presence of alkali metals in the alumina to decrease acidity caused an increase in the amount of the trans isomer and a corresponding decrease in the 1 isomer.

The mechanism for alcohol dehydration has been widely studied. The results of an early kinetic study with ethanol were interpreted by Brey and Krieger[1] to favor a carbonium ion intermediate. More recent investigators have altered or abandoned a carbonium ion intermediate for secondary alcohols. For instance, Pines and coworkers[2] have expanded the idea of Schwab and coworkers[3] that dehydration occurred in the catalyst pores. Pines attributed a pseudosolvent character to alumina and thus explained dehydration as a typical concerted trans elimination reaction.[4]

A large portion of the data used for mechanism proof has been olefin product distributions. For this distribution to be meaningful one must use the primary olefin product distribution unaltered by later isomerization. Various means have been used to reduce isomerization: adding alkali metal ions to the catalyst, addition of nitrogen bases during the reaction, low conversion, etc. The use of these additives requires us to assume that the isomerization may be poisoned more easily than dehydration if both reactions occur on the same catalyst site or that dehydration and isomerization occur on different sites.

In the present study we have determined the olefin product distribution from 2-octanol dehydration using several alumina and thoria catalyst preparations. Rather than try to eliminate secondary isomerization reactions we have used the isomerization of a very similar olefin, 1-heptene added to the reactant, to determine the extent of isomerization of the olefin product during the dehydration of 2-octanol.

Results

In Table I the selectivity for olefin formation (1-, *trans*-2-, and *cis*-2-octene) from 2-octanol over several catalysts are presented with some results from the literature for other 2-ols. Our selectivity data are taken for the sample collected after about 150–200 min on stream. It is noted that there are two sets of selectivity: over acidic alumina where the amount of *trans*-2-octene is less than 10% of the total octenes and non-acidic alumina, chromia, and molybdena catalysts where the trans isomer comprised 10–25% of the olefin products. Over all catalysts, including those from the

(1) W. S. Brey, Jr., and K. A. Krieger, *J. Amer. Chem. Soc.*, **71**, 3637 (1949).

(2) E. J. Blanc and H. Pines, *J. Org. Chem.*, **33**, 2035 (1968), and references cited therein.

(3) G. M. Schwab and E. Schwab-Agallidis, *J. Amer. Chem. Soc.*, **71**, 1806 (1949).

(4) R. T. Morrison and R. N. Boyd, "Organic Chemistry," Allyn and Bacon, Boston, Mass., 1966.

literature, the amount of cis isomer is nearly 50% of the total olefins. In our runs with only 2-octanol, it was observed that at early time on stream the olefin distribution was different from that at later time on stream. Initially a large relative amount of *trans*-2-octene was formed but decreased to nearly a constant value at later times. The total conversion of 2-octanol usually decreased slowly as the catalyst aged with time on stream. The first sample is usually not representative, since a chromatographic effect allows the olefins to exit from the catalyst bed more rapidly than the alcohol.

To determine the amount of isomerization of the olefin product after desorption, we made runs in which 1-heptene was added to the 2-octanol charge. The added 1-heptene should undergo the same isomerization reactions as the olefin dehydration product (see isomerization paths 1 and 2 in the Discussion). As shown in Table II, the added 1-heptene underwent isomerization at early time on stream but the amount of isomerized heptene decreased to a very small amount at later times on stream. The decrease in 1-heptene isomerization parallels that of the decrease in *trans*-2-octene formation. Thus, isomerization of the octene product after desorption does not occur to a great extent at later time on stream.

TABLE I

CONVERSION OF 2 ALCOHOLS OVER ALUMINA CATALYSTS

Alcohol	Alumina	Temp, °C	Olefin distribution, % 1	t-2	c-2
2-Octanol	Al_2O_3–A[a]	180	43	9	48
2-Octanol	Al_2O_3 ex $AlCl_3$[a]	180	47	6	47
2-Octanol	Cr_2O_3–Al_2O_3[b]	250	38	18	47
2-Octanol	MoO_3–Al_2O_3[c]	180	42	11	47
2-Octanol	Al_2O_3–K (0.4%)[d]	250	41	13	47
2-Octanol	Al_2O_3–K (1.0%)[d]	250	37	19	44
2-Octanol	Al_2O_3–Li (5%)[d]	250	33	24	43
2-Octanol	Al_2O_3[e]	180	46	7	47
2-Octanol	Al_2O_3[f]	180	44	10	46
2-Butanol[g]	Al_2O_3–K	350	44	14	42
2-Pentanol[g]	Al_2O_3–K	350	34	13	54
2-Heptanol[h]	Al_2O_3	280; N_2[h]	34	16	50
		280; CO_2	36	16	48
		280, H_2	38	14	49
		280; NH_3	36	16	48

[a] Acidic alumina. [b] Chromia (16%) supported on nonacidic alumina. [c] Molybdena (10%) supported on nonacidic alumina. [d] Nonacidic alumina. [e] Acidic alumina prepared by hydrolysis of Al–Hg amalgam. [f] Commercial alumina from Continental Oil Co. [g] Results from H. Pines and J. Manassen, *Advan. Catal.*, 16, 49 (1966). [h] Results from M. Laroche, A. Pazdzerski, and B. Blouri, *Bull. Soc. Chim. Fr.*, 2541 (1968); the gas given under conditions was added during the run as a carrier gas.

TABLE II

CONVERSION OF 2-OCTANOL CONTAINING 1-HEPTENE OVER VARIOUS ALUMINA CATALYSTS (LHSV[a] 0.32, NO CARRIER GAS)

Catalyst	Temp, °C	Time, min	Conversion, %[b]	Octenes, % 1	t-2	c-2	Heptenes, % 1	t-2	c-2
Al_2O_3 from Al isopropoxide	180	87	85	43	24	33	63	26	11
		124	53	43	10	47	97	1.5	1.5
		167	39	42	10	48	97	1.5	1.5
		217	41	43	9.9	47	98	1	1
Al_2O_3–K (0.1% K)	250	60	95	40	30	30	59	25	17
		99	95	34	27	39	79	12	9.5
		186	95	34	25	41	86	7.2	8.6
		211	95	33	22	45	90	5	5
Al_2O_3–K (1.0% K)	250	66	45	36	29	35	85	9	6
		125	44	38	18	44	94	3	3
		195	39	39	18	43	93	3	3
		215	37	37	19	44	94	3	3
Al_2O_3–Li (5% Li)	250	50	29	34	27	37	97	1.8	1.7
		115	15	32	25	42	98	1	1
		165	15	35	23	42	99		
		225	15	33	24	43	99		
Al_2O_3 from Al chloride	180	88	96	46	21	33	68	18	14
		144	93	39	10	50	94	3	3
		208	89	38	10	52	98	1	1
		258	86	38	9.4	53	99		
		293	85	38	8.7	53	99		

[a] Liquid hourly space velocity. [b] Conversion is given for conversion to olefins plus other products.

2-Octanol, with 1-heptene added, was also converted over several thoria catalysts that had been found to be nonselective for α-olefin formation.[5] Over thoria there is little isomerization of the added 1-heptene even at early time on stream. However, the octene product contained large amounts of the *cis*- and *trans*-2-octene and in several runs the 2-octene isomers are the major product.

1-Heptanol with 1-octene added was also converted over thoria and alumina. The conversion of 1-heptanol is quite different over the two catalyst systems. 1-Heptene is the major olefin over alumina and approaches 100% at later time on stream. The isomerization of the added 1-octene parallels the formation of the *cis*- and *trans*-2-heptene. Also, diheptyl ether is formed over alumina and the amount even surpasses the amount of dehydration. In contrast, significant amounts of diheptyl ether do not form over thoria, but in some cases a large amount of the dihexyl ketone (identified by gc retention time) is formed by condensation of two alcohol molecules with the loss of CO or CO_2. Also, much more of the *cis*- and *trans*-2-heptenes are formed over these thoria samples than over alumina. The relative amount of the *cis*- and *trans*-2-heptene is larger than the corresponding isomerization of the added 1-octene. This is true even for low conversions;

(5) B. H. Davis and W. S. Brey, Jr., *J. Catal.*, in press.

TABLE III

CONVERSION OF 2-OCTANOL CONTAINING 1-HEPTENE OVER VARIOUS THORIUM OXIDE CATALYSTS

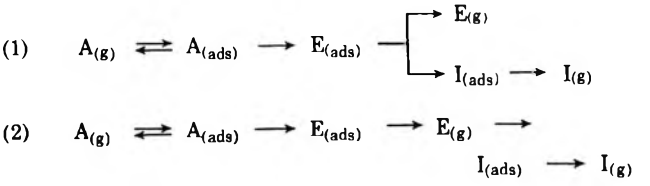
Catalyst[a]	Time, min	Conversion, %[b,c]	Octenes, % 1	Octenes, % t-2	Octenes, % c-2	Heptenes, % 1	Heptenes, % t-2	Heptenes, % c-2
25-Z	80	30	37	26	38	96	2	2
	135	16	35	24	41	99		
	200	8						
	250	9	39	23	38	99		
ThO_2 from	33	45	33	28	39	92	4	4
$ThCl_4$	89	66	29	32	39	97	1.5	1.5
	145	60	28	30	42	98	1	1
	205	52	28	30	42	98	1	1
	230	46	28	29	43	99		
ThO_2 (1.8 *M*)	80	44	50	26	25	93	3.5	3.5
	166	27	56	20	24	96	2	2
	205	17	58	20	22	99		
ThO_2 from	63	88	51	26	23	58	23	19
thorium	115	56	66	17	17	92	4	4
carbonate	175	64	68	16	16	92	4	4
	245	59	67	17	16	96	2	2

[a] All catalysts were pretreated at 600° for 4 hr in oxygen. [b] Conversion is for 2-octanol to octenes and 2-octanone. [c] Temperature was 250° except for ThO_2 from thorium chloride, where it was 190°.

more occurred over both catalysts in the 1-heptanol runs. This is probably due to the higher temperature required to obtain a similar conversion for 1-heptanol as for 2-octanol.

Discussion

The experimental olefin distribution may be altered by two reaction pathways (A, alcohol; E, initial olefin product; I, isomerized olefin; g, gas phase; ads, adsorbed phase).



In reaction pathway 1 the product distribution is determined by the adsorbed intermediate before desorption, and the addition of 1-heptene to the 2-octanol would not give a measure of the product isomerization, but in pathway 2 the olefin product desorbs to the gas phase and is isomerized only after readsorption. For 2 the addition of 1-heptene to 2-octanol would provide a measure of the influence of isomerization on the experimental olefin distribution.

Considering the data in Tables II, III, and IV, it appears that, at later time on stream, the octene isomer distribution is not being altered by pathway 2. Also, if the octene distribution is being altered by pathway 1, over acidic alumina the isomerization must be a selec-

TABLE IV

CONVERSION OF 1-HEPTANOL WITH ADDED 1-OCTENE OVER THORIA AND ALUMINA CATALYSTS

Catalyst[a]	Temp, °C	Time, min	Conversion, %[b]	Ether or ketone,[c] %	Heptenes 1	Heptenes t-2	Heptenes c-2	Octenes 1	Octenes t-2	Octenes c-2
ThO_2 (Cl)	240	50	100		40	39	21	61	27	13
		87	91	2.1	39	39	22	58	27	15
		141	68	1.3	41	38	21	63	21	17
		180	70	1.6	39	32	29	74	13	13
		205	70	1.4	40	32	28	73	15	12
ThO_2 (0.03 *M*)	380	60	21	1.1	67	13	20	93	3	4
		100	21	1.2	68	14	19	92	5	3
		170	26	3.3	68	14	18	92	5	3
		185	25	2.9	68	14	18	91	4	6
ThO_2 (25-Z)	360	65	80	10	46	31	23	68	18	13
		120	63	22	61	20	18	83	7.9	7.9
		175	60	23	59	21	20	84	9.1	7.3
		220	62	21	62	20	18	85	7	8
		260	60	26	64	17	19	85	7	8
ThO_2 (0.6 *M*)	400	80	74	23	68	16	17	80	10	10
		120	80	13	78	4.4	17	82	9	9
		190	70	12	76	5.1	18	95	2.5	2.5
		210	78	15	76	8.4	16	96	2	2
Al_2O_3–K (1% K)	330	95	57	30	92	2.4	6.1	90	4	6
		138	62	28	93	1.7	5	95	2.5	2.5
		188	56	27	93	1.8	5.4	93	3	4
Al_2O_3–A	220	40	90	25	63	26	10	79	12	9
		65	77	50	96	2	2	98	1	1
		125	74	51	98			98		
		225	74	50	98			98		
		270	78	52	98			98		

[a] Thoria and alumina catalysts were pretreated at 600° in flowing hydrogen for 3 hr before the run was started. [b] Conversion is the total alcohol conversion to heptenes and ketone or ether. [c] Over thoria this would be the dihexyl ketone; over alumina this would be diheptyl ether.

for example, over the thoria precipitated from 0.03 *M* thorium nitrate solution the amount of heptene formed is about the same as the amount of added octene, but the amount of 2-heptenes is greater than the amount of 2-octenes. Thus, if the olefins undergo an equal amount of isomerization from the gas phase olefins, some 1-heptene isomerization must occur before desorption. A comparison of the olefin isomerization for the runs with 1-heptanol and 2-octanol shows that

tive one: 1-octene ⇄ *cis*-2-octene. Over nonacidic alumina we can eliminate pathway 2 for altering the octene distribution but not pathway 1. Over thoria, pathway 2 can make only a minor contribution to the olefin distribution. Thus, the larger amount of *trans*-2-octene formed over thoria cannot be accounted for by pathway 2.

To obtain more information about the contribution of pathway 1 on the olefin products, we converted a mixture of 1-heptanol and 1-octene over alumina and thoria. For pathway 1, presumably the only product of dehydration (1-heptene) would undergo isomerization to a similar extent as the 1-octene product from 2-octanol dehydration. For later time on stream, acidic alumina gave less than 5% isomerization and nonacidic alumina less than 10% isomerization of the 1-heptene product, but for thoria the isomerization of 1-heptene to 2-heptenes is considerably larger than the isomerization of the added 1-octene.

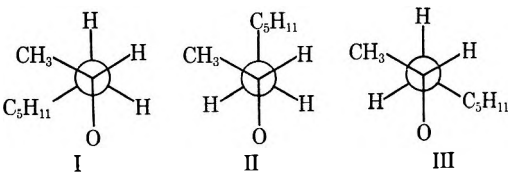
This would mean that over both aluminas isomerization by pathway 1, as well as 2, is small and the experimental octene distribution is very close to that obtained as primary products of the dehydration. Over thoria the olefin product distribution is not altered by pathway 2 but it is altered to a large extent by pathway 1 over some thoria samples. Thus we believe that the olefin distribution from 2-octanol dehydration may be summarized as shown in Table V.

TABLE V
SUMMARY OF INITIAL OLEFIN PRODUCTS FROM 2-OCTANOL DEHYDRATION

	Olefin distribution, %		
Catalyst	1-Octene	*trans*-2-Octene	*cis*-2-Octene
Acidic alumina	40–45	5–10	50
Nonacidic alumina	30–40	10–25	45–50
Thoria (selective)	100[a]		

[a] See ref 5 for octene distributions from several thoria samples. These show that 100% 1-octene is approached over some thoria preparations.

A trans elimination of water is the mechanism favored by most investigators for the dehydration of alcohols by alumina.[6,7] However, the present results can be explained by a cis elimination as well as by a trans elimination. If the alcohol is adsorbed on the catalyst surface by the OH group, three conformations are possible.



Adsorption by the OH group is probable, since both alumina and thoria are more selective dehydration catalysts when pretreated with hydrogen (and probably have an oxygen anion deficient surface) than when pretreated with oxygen.[5,8] If all three conformations are equally probable, a cis elimination would give about a 1:1 ratio of cis:trans isomer. Trans elimination should give a similar ratio, but alumina adsorbs olefins and may be used for gc columns to separate olefins or paraffins. For example, alkene retention times on alumina at 210° show that the free energy of adsorption is approximately −0.55 kcal/mol for each $-CH_2-$ group.[9] The adsorption would probably be weaker on hydrated alumina but would still be significant. This would mean that configurations similar to I and III would be favored, since they allow the C_5H_{11} alkyl group to be more easily adsorbed on the surface. The free energy of adsorption would be approximately −2.7 kcal/mol if all five $-CH_2-$ groups were adsorbed on dehydrated alumina. This should be sufficient to compensate for some increased conformational steric interaction in structures I and III and skew conformations similar to I and III. Thus, structures similar to I and III should predominate during dehydration reactions, but we would still obtain a 1:1 *cis*- to *trans*-2-octene ratio. However, the above conformations could determine the olefin selectivity provided I → *cis*-2-octene and III → 1-octene + *trans*-2-octene. Models of 2-octanol would suggest that, due to the C_5H_{11} alkyl group, the adsorption of the methyl group on the surface should be more difficult in conformation I than in III.

The dehydration using the nonacidic alumina yielded 2–4 times more *trans*-2-octene than acidic alumina. This could be due to the higher temperature required to obtain a given conversion over nonacidic alumina than was required for the acidic alumina. However, the small amount of 2-heptene from 1-heptanol dehydration would suggest that this is not the case. Another possibility is that the alkali metal, or the nitrogen base, added to decrease the acidity is responsible. This could be due to a decrease in the adsorption potential for the alkyl groups on a base-poisoned surface so that configuration II, which could yield all three isomers, contributes more over these catalyst. Another possibility is that the base is present close enough to the dehydration site so that it alters the bond angles in conformations I and III sufficiently to effect the formation of larger amounts of the trans isomer.

The deuterium tracer study of acyclic alcohol dehydration by Lundeen and Van Hoozer[10] provides convincing evidence for a cis elimination mechanism over thoria catalysts. The present olefin distribution can be accounted for by a cis mechanism. A cis elimination mechanism would mean that a single mechanism would be sufficient to describe the dehydration of secondary acyclic alcohols over both thoria and alumina.

Catalysts. **Al_2O_3-A** was prepared by the hydrolysis of aluminum isopropoxide (1 kg/3 l. isopropyl alcohol) with water.[11]

Al_2O_3-K.—Alcoa alumina (99.99%) was dissolved in potassium hydroxide. Alumina was precipitated by the addition of CO_2.[11] The precipitate was washed with water; the amount of washing determined the final potassium content.

Al_2O_3-Li.—Alcoa aluminum was added to a lithium hydroxide solution. The lithium aluminate precipitate was washed with water to reduce the Li to 5% in the calcined (600°) catalyst.

(6) H. Pines and J. Manassen, *Advan. Catal.*, **16**, 49 (1966).
(7) K. Narayana and C. N. Pillai, *Indian J. Chem.*, **7**, 409 (1969).
(8) B. H. Davis, unpublished work.
(9) R. M. Lane, B. C. Lane, and C. S. G. Phillips, *J. Catal.*, **18**, 281 (1971).
(10) A. J. Lundeen and R. Van Hoozer, *J. Org. Chem.*, **32**, 3386 (1967).
(11) H. Pines and W. O. Haag, *J. Amer. Chem. Soc.*, **82**, 2471 (1960).

MoO_3–Al_2O_3.—Al_2O_3–K (1% K) was impregnated with aqueous ammonium molybdate to give 10 wt % MoO_3.

Cr_2O_3–Al_2O_3.—Al_2O_3–K (0.1% K) was impregnated with chromic acid solution to give 13 wt % Cr.

Al_2O_3–B.—Alcoa aluminum was hydrolyzed by forming the mercury amalgam using mercuric chloride.

Al_2O_3–C.—Ammonium hydroxide was added to aluminum chloride (2 *M*) to form the hydroxide; the precipitate was washed with water until a negative test for chloride in the wash was obtained with $AgNO_3$.

Thoria.—25-Z was prepared by the thermal decomposition of thorium nitrate hydrate; the heating program was similar to 25-H in reference 12. ThO_2 (1.8 *M*): thorium hydroxide was precipitated from a 1.8 *M* thorium nitrate solution (or other concentration if given) and washed to give high surface area thoria.[13] ThO_2–Cl: the hydroxide was precipitated from 1 *M* thorium chloride solution with ammonium hydroxide and washed to a negative Cl test.[12] ThO_2–C: thorium carbonate was heated to 600° in air.

Dehydration Procedure.—The catalyst was heated in hydrogen or oxygen *in situ* for 4 hr at 600°. 2-Octanol was fed by a displacement pump (LHSV 0.3) and the liquid products were collected after passing through a water-cooled condensor. The 2-octanol contained about 1.8% 2-octanone. The samples were analyzed for conversion by temperature-programmed gc using a Carbowax 20M column. The octene isomers and heptene isomers (1-, *trans*-2-, and *cis*-2-olefin) were analyzed using the same column isothermally at 60°. These three isomers could be determined quantitatively in the *absence* of the 3 and 4 isomers. For several runs, the octene isomer peaks were trapped and no 3 or 4 isomers were detected by ir. The presence of large amounts of the 3- and 4-octene isomers could be detected by gc because of peak broadening and retention time changes, even though a complete separation of all octene isomers were not possible.

Registry No.—2-Octanol, 123-96-6; 1-heptene, 592 76-7; 1-heptanol, 111-70-6; 1-octene, 111-66-0; Al_2O_3, 1344-28-1; ThO_2, 1314-20-1.

(12) B. H. Davis, Dissertation, University of Florida, Gainesville, Fla., 1965.

(13) W. S. Brey, Jr., B. H. Davis, P. G. Schmidt, and C. G. Moreland, *J. Catal.*, **3**, 303 (1964).

Metal Nitrides in Organic Reactions. II. Reactions of Lithium Nitride with Aromatic Aldehydes[1a-c]

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Aromatic aldehydes react with lithium nitride (Li_3N) in refluxing carbon tetrachloride to give numerous products, which have resulted from a combination of diverse reactions. Benzaldehyde gives primarily Tishchenko or Cannizzaro reaction products, as well as 2,4,5-triphenylimidazole, *cis*-*N*-(2-benzamido-1,2-diphenylethenyl)benzamide, and *threo*-1,2-diphenyl-2-benzamidoethanol. The isolation and structure determination of the various products will be discussed.

Early reports indicated that nitride (N^{-3}) failed to react with alkyl halides,[2] acid chlorides,[3] and other compounds.[2-4] However, nitrides with acid anhydrides have been reported to give nitriles[2] or imides,[5] and more recently nitrides with acid chlorides afforded amides[1a,b] and cyclic imides.[6] Various other diverse reactions of ionic nitrides have been observed.[1b] In this paper, we describe the assorted reactions of aromatic aldehydes with lithium nitride.

Results and Discussion

When benzaldehyde was allowed to react with lithium nitride in refluxing carbon tetrachloride under nitrogen, the following products were isolated (Table I): benzyl benzoate (**2a**), benzoic acid (**3a**), benzyl alcohol (**4a**), benzamide (**5a**), benzonitrile (**6a**), *cis*-*N*-(2-benzamido-1,2-diphenylethenyl)benzamide (**7a**), 2,4,5-triphenylimidazole (**8a**), and *threo*-1,2-diphenyl-2-benzamidoethanol (**9a**).

Non-nitrogen-Containing Products.—Benzyl benzoate (**2a**) is the major product (60%) of the reaction arising by either a Cannizzaro or Tishchenko reaction. It has been well established that benzaldehyde gives exclusively the Cannizzaro reaction products (benzyl alcohol and benzoic acid) when treated with either strong sodium hydroxide or other strong bases,[7] while under aprotic basic reaction conditions, using most commonly aluminum ethoxide[8] or sodium in tetrahydrofuran,[9] the Tishchenko reaction product (benzyl benzoate) is formed.[10] However, either reaction mechanism involves an oxidation–reduction sequence, which produces an adduct that transfers a hydride ion to another molecule of aldehyde. Since both hydride

(1) (a) Paper I: F. P. Baldwin, E. J. Blanchard, and P. E. Koenig, *J. Org. Chem.*, **30**, 671 (1965). (b) Preliminary communication: P. E. Koenig, J. M. Morris, E. J. Blanchard, and P. S. Mason, *ibid.*, **26**, 4777 (1961). (c) We gratefully acknowledge the support of the National Science Foundation through Grant No. G 22021 for partial support of this research. (d) Abstracted in part from the Ph.D. Dissertation submitted to Louisiana State University, Aug 1969. (e) National Science Foundation College Teacher Research Participant, Louisiana State University, summers, 1962–1964.

(2) F. Briegleb and A. Geuther, *Justus Liebigs Ann. Chem.*, **123**, 237 (1862).

(3) O. Emmerling, *Chem. Ber.*, **29**, 1634 (1896).

(4) M. A. Smits, *Recl. Trav. Chim. Pays-Bas*, **12**, 202 (1893).

(5) G. Beck, *Z. Anorg. Allg. Chem.*, **233**, 155 (1937).

(6) A. J. Gordon and R. L. E. Ehrenkaufer, *J. Org. Chem.*, **36**, 44 (1971).

(7) T. A. Geissman, *Org. React.*, **2**, 94 (1944).

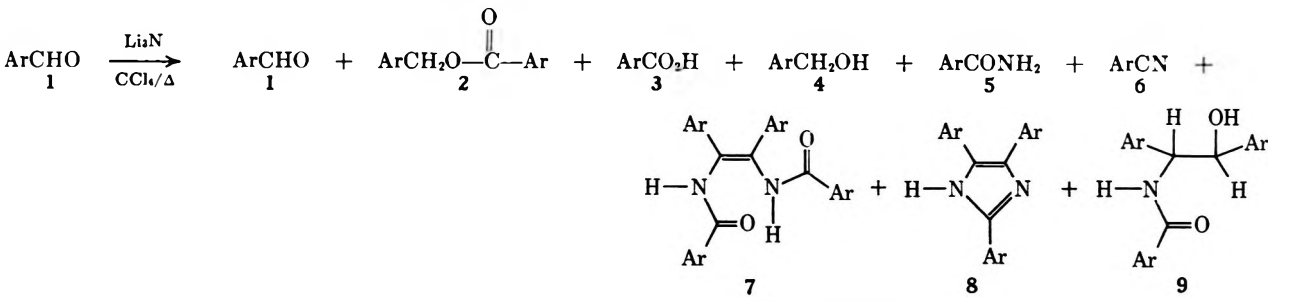
(8) Y. Ogata and A. Kawasaki, *Tetrahedron*, **25**, 929, 2845 (1969).

(9) C. E. Handlovits and J. B. Louch, U. S. Patent 3,387,020; *Chem. Abstr.*, **69**, 27052e (1968).

(10) See J. March, "Advanced Organic Chemistry: Reactions, Mechanisms, and Structures," McGraw-Hill, New York, N. Y., 1968, pp 908–910.

TABLE I

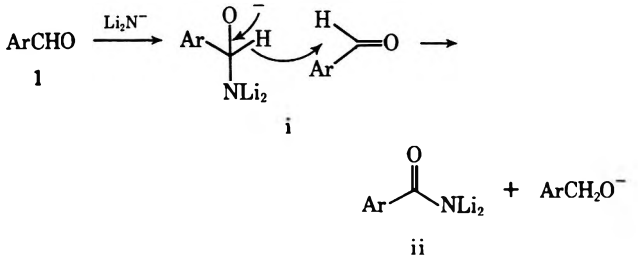
STRUCTURE AND YIELDS OF PRODUCTS DERIVED FROM THE REACTION OF ARYLALDEHYDES WITH LITHIUM NITRIDE



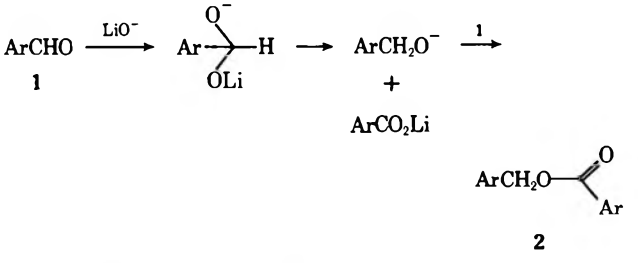
	Mol %[a]								
	1	2	3	4	5	6	7	8	9
1a, Ar = C_6H_5–	2.9	56	9.3	10.0	Traces	Traces	5.5	6.3	9.5
b, Ar = p-$CH_3C_6H_4$–	1.4	55	16.8	10.5	Traces	Traces	1.3	3.6	0[b]

[a] Yields are based on moles of isolated products per mole of aldehyde. [b] *N*-*p*-Xylyl-*p*-toluamide (10) was isolated (4.4%); 9b was not detected in the reaction mixture.

ion[11] and the generated benzylate ion[12] are known to catalyze the formation of benzyl benzoate from benzaldehyde, the formulation of i seems reasonable. However, the subsequent formation of *N*,*N*-dilithiobenzamide (ii) would be expected to give at least some sec-



ondary or tertiary amides; no such products were detected in our reaction mixtures. Although trace quantities of benzamide are formed, an alternate scheme suggests that oxygen-containing impurities on the surface of the nitride, formed from atmospheric oxygen and/or moisture, react with adsorbed aldehyde by a Cannizzaro mechanism[13] to produce lithium benzoate and lithium benzylate. It is the latter which then proceeds to generate the benzyl benzoate *via* the Tishchenko reaction.



In addition to the ester, the Cannizzaro products were isolated in substantial quantities (see Table I). The somewhat unexpected isolation of the alcohol indicates that the Cannizzaro reaction proceeds, at least in part, after all the nitride has been consumed or poisoned in other reactions. Slow hydrolysis of the esters by lithium hydroxide could yield the alcohol and acid salts observed; such a slow organic-phase hydrolysis has been proposed[14] as one of the mechanisms by which heterogeneous Cannizzaro reactions proceed. The mole ratio of benzoate salts to benzyl alcohol observed with benzaldehyde is consistent with this possibility, while the higher ratio of acid to alcohol observed with *p*-tolualdehyde (**1b**) could result from oxidation of the alcohol (or aldehyde) to the acid.

Nitrogen-Containing Products.—*threo*-1,2-Diphenyl-2-benzamidoethanol (**9a**) was obtained (*ca.* 4%) from the reaction of benzaldehyde with lithium nitride. The structure follows from the nmr spectrum which shows a structural sequence [$NH^xCH^aCH^bOH^y$]; $\delta^x = 8.6$, $J_{ax} = 8$ Hz; $\delta^a = 5.35$, $J_{ax} = 8$ Hz, $J_{ab} = 7$ Hz; $\delta^b = 5.05$, $J_{ab} = 7$ Hz, $J_{by} = 6$ Hz; and $\delta^y = 5.7$, $J_{by} = 6$ Hz. Also consistent with this structure is the lack of a molecular ion in the mass spectrum with the prominent *m*/*e* 299 and 212 which corresponds to loss of H_2O and $C_6H_5CO^+$, respectively. Hydrolysis of **9a** afforded equal quantities of benzoic acid and *threo*-1,2-diphenyl-2-aminoethanol;[15] therefore, the synthesis of **9a** from the authentic *threo*-amino alcohol confirmed both its structure and stereochemistry. From all indications, the threo isomer is the predominant stereoisomer with little or no erythro isomer being detected.

Along with amide **9a**, *cis*-*N*-(2-benzamido-1,2-diphenylethenyl)benzamide (**7a**) and 2,4,5-triphenylimidazole (**8a**) were isolated. Amide **7a** was degraded by (1) ozonolysis in formic acid[16] affording only benzil and benzamide in a 1:2 mole ratio, (2) potassium dichromate oxidation in glacial acetic acid giving only dibenzamide (**11**), and (3) hydrolysis in aqueous sulfuric acid[17] quantitatively affording 2,4,5-triphenyloxazole (**12a**) *via* partial hydrolysis followed by rapid cyclization of the resultant α-acylamino ketone. The mass spectrum of **7a** indicates no parent ion but rather *m*/*e* 400, which suggests the pyrolylic loss of water.

(11) T. W. Swamer and C. R. Hauser, *J. Amer. Chem. Soc.*, **68**, 2647 (1946).

(12) H. Gilman and A. H. Blatt, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1941, p 104.

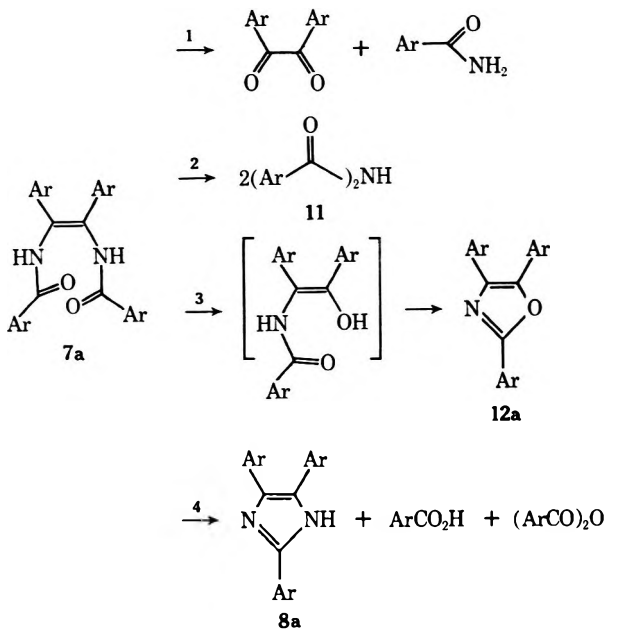
(13) G. E. Lewis [*J. Org. Chem.*, **30**, 2433 (1965)] proposes a similar explanation for the formation of Cannizzaro products in the reaction of *p*-nitrobenzaldehyde with sodium hydride.

(14) E. E. Royals, "Advanced Organic Chemistry," Prentice-Hall, Englewood Cliffs, N. J., 1954, p 718.

(15) A. McKenzie and D. J. C. Pirie, *Chem. Ber.*, **69B**, 876 (1936).

(16) W. Krabbe, H. Bohlk, and K. Schmidt [*ibid.*, **71**, 644 (1938)] used excess ozone in 97% formic acid for the degradation of the related *N*-(2,2-diphenylethenyl)benzamide.

(17) M. N. K. Irving and R. M. Parkins, *J. Inorg. Nucl. Chem.*, **27**, 270 (1965).



For an attempted mass spectral comparison, both *cis*- and *trans*-*N*-(2-benzamidoethenyl)benzamides (**13**) were synthesized; the mass spectrum of both *cis*- and *trans*-**13** indicated a comparable strong parent ion (*m/e* 266) and the lack of the $M^+ - 18$ ($-H_2O$) species. Since *trans*-**13** was initially synthesized by thermal isomerization of the cis isomer, *cis*-**13** under our mass spectral conditions (probe temperature >200°) must have isomerized to the more stable *trans*-**13** prior to fragmentation. The tetrasubstituted olefin **7** shows no signs of thermal isomerization at elevated temperatures which would correspond to the approximate probe temperature (refluxing phenyl ether), but under these conditions does slowly eliminate water to form a trisubstituted imidazole. In light of the concomitant elimination of water under mass spectral conditions as well as exclusive formation of 2,4,5-triphenylimidazole (**8a**),[18] both when **7a** was treated with benzoyl chloride at 100° and upon pyrolysis at 300° under nitrogen, **7** probably possesses the cis configuration.

The mechanism of formation of the amides and imidazoles is not easily visualized. Since we could obtain no such products by heating benzyl benzoate with lithium nitride, the nitrogen-containing compounds are apparently produced by a distinct path and are not secondary products of the Tishchenko reaction. Although the diamide products have not been reported previously, the formation of triarylimidazoles from substituted benzaldehydes has been observed under a variety of conditions.[19] Very little, however, has been published concerning the mechanisms by which imidazoles are formed. Since (1) the amides and imidazoles have apparent structural similarities (ArC=CAr), (2) amides **7** are converted thermally or chemically to imidazoles **8**, and (3) amides **7** could not be obtained from imidazoles (**8**) under varied rigorous conditions, we conclude that the imidazoles **8** arise from **7** or an immediate precursor of **7** containing the proper cis stereochemistry.

(18) D. Davidson, M. Weiss, and M. Jelling, *J. Org. Chem.*, **2**, 319 (1937).

(19) See K. Hofmann in "Imidazole and its Derivatives. Part I. The Chemistry of Heterocyclic Compounds," A. Weissberger, Ed., Interscience, New York, N. Y., 1953, and R. C. Elderfield in "Heterocyclic Compounds," Vol. 5, R. C. Elderfield, Ed., Wiley, New York, N. Y., 1957, Chapter 3.

Attempts were made to isolate various proposed intermediates by interrupting the reaction at various times before completion; however, none of the envisioned intermediates nor the trans isomer of **7** could be isolated. Although the lingering possibility that **7** is the trans isomer cannot be readily dispelled by these data, we are attempting to elucidate a definitive stereochemistry of **7** by synthesis, and are conducting solvent studies of this reaction.

Experimental Section[20]

Reagents.—Benzaldehydes, free of trace acid contaminants, were purified by extraction with a 5% sodium carbonate solution, dried over anhydrous sodium carbonate and distilled at reduced pressures under an inert atmosphere.

The lithium nitride was generously supplied gratis by Foote Mineral Co., Exton, Pa., but could be prepared by the method of E. Masdupuy and F. Gallais.[21]

Reaction of Benzaldehyde with Lithium Nitride.—Benzaldehyde (171.2 g, 1.62 mol) was slowly added under nitrogen to a mechanically stirred suspension of Li_3N (12.25 g, 0.248 mol) in 700 ml of CCl_4 at 75°. The mixture was refluxed for 19 hr maintaining a slow nitrogen flow, which removed any ammonia produced. After cooling, the resultant precipitate (59.2 g) was filtered, washed successively with 100-ml portions of CCl_4, acetone, water, and ethanol, then dried *in vacuo*, affording crude *cis*-*N*-(2-benzamido-1,2-diphenylethenyl)benzamide (**7a**), mp 270–272°. Recrystallization from DMSO gave 9.2 g of pure **7a**: mp 292–294°; ir (Nujol) 3310, 1950, 1900, 1820, 1620 cm^{-1}; mass spectrum *m/e* (rel intensity) 418 (M^+, 9.7), 400 (8), 324 (4), 310, 297 (22), 210 (12), 105 (C_6H_5CO, 100), 89 (C_7H_5, 7.5), 77 (C_6H_5, 35).

Anal. Calcd for $C_{28}H_{22}N_2O_2$: C, 80.34; H, 5.31; N, 6.70; mol wt, 418.1688. Found: C, 80.22; H, 5.40; N, 6.68; mol wt, 418.1587 (mass spectrum).

Evaporation *in vacuo* of the aqueous washing of the crude precipitate gave a white solid, which upon acidification yielded 18.5 g of pure benzoic acid, mp 121–122°.

The reaction filtrate (*ca.* 1 l.) was concentrated *in vacuo*, giving a red viscous oil (125.2 g), which comprised about 80% of volatile components. The oil was fractionally distilled: fraction 1, bp 45–55° (10 mm), contained unreacted benzaldehyde (5 g); fraction 2, bp 60–75° (10 mm), contained benzyl alcohol (17.3 g) contaminated with traces of benzaldehyde and benzonitrile; fraction 3, bp 120° (1 mm), contained benzyl benzoate (94.5 g); and fraction 4, bp 130–140° (1 mm), contained last traces of benzyl benzoate and *threo*-1,2-diphenyl-2-benzamidoethanol (**9a**, 16 g), which solidified in the condenser. Recrystallization from ethanol afforded analytically pure **9a**: mp 223–224° (lit.[22] mp 225°); ir (Nujol) 3310, 3220 (w), 1630 cm^{-1} (C=O); nmr (DMSO-d_6) δ 5.05 (t, J = 7.0 and 6.0 Hz), 5.35 (t, J = 7.0 and 8 Hz), 7.4 (m, C_{arom} H), 7.6 (m, 2 H), and 8.6 (c, J = 8 Hz); mass spectrum *m/e* (rel intensity) 299 ($M^+ - 18$, 2), 213 (10), 212 (95), 211 (50), 194 (28), 180 (4.5), 179 (4), 164 (8), 106 (70), 105 (C_6H_5CO, 99), 104 (26), 90 (8), 79 (26), 78 (25), 77 (C_6H_5, 100).

Anal. Calcd for $C_{21}H_{19}NO_2$: C, 79.5; H, 6.00; H, 4.42. Found: C, 79.6; H, 5.92; N, 4.28.

Column chromatography [alumina (Alcoa F-20), benzene–ethanol (70:30)] of the concentrate from the combined mother liquors of **9a** afforded 10 mg of crystalline benzamide, mp 123–124°, which was identical with an authentic sample.

The residue from the vacuum distillation was recrystallized several times from ethanol, giving 10 g of pure 2,4,5-triphenylimidazole (**8a**), mp 268–272° (lit.[18] mp 274°).

(20) Melting points were recorded on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer 137B spectrophotometer. Nmr spectra were determined on a Varian Associates Model A-60A spectrometer; chemical shifts are given in parts per million relative to TMS as an internal standard. Mass spectral data were determined in this laboratory using a Varian Associates Model M-66 mass spectrometer. Analyses were performed either by Mr. R. Seab in these laboratories or by Galbraith Laboratory, Inc., Knoxville, Tenn.

(21) E. Masdupuy and F. Gallais, *Inorg. Syn.*, **4**, 1 (1953).

(22) F. R. Japp and J. Moir, *J. Chem. Soc.*, **77**, 608 (1900); (b) T. Ishimaru, *Nippon Kagaku Zasshi*, **81**, 769 (1960); *Chem. Abstr.*, **56**, 369a (1962).

Hydrolysis of *cis*-*N*-(2-Benzamido-1,2-diphenylethenyl)benzamide (7a).—Amide **7a** (6.0 g, 14 mmol) suspended in 15 *M* aqueous sulfuric acid was steam distilled. Although undissolved amide rapidly disappeared, the distillation was continued until 230 ml of distillate had been collected. The distillate was made basic with sodium carbonate, concentrated, and acidified, affording 1.3 g (79%) of benzoic acid, mp 120–122°.

After the reaction vessel was cooled, the residue was carefully diluted with ice water (850 ml), causing a precipitation. Recrystallization of this dried solid from ethanol–acetone (99:1) gave 4.07 g (98%) of pure 2,4,5-triphenyloxazole (**12a**), mp 113–115° (lit.[23] mp 114–115°). A mixture melting point gave no depression and spectral data were identical with those of an authentic sample prepared by the method of Schonberg.[23]

Pyrolysis of *cis*-*N*-(2-Benzamido-1,2-diphenylethenyl)benzamide.—Amide **7a** (750 mg, 1.8 mmol) was heated at 300° for 15 min under a slow stream of dry nitrogen. During pyrolysis, a white solid and a colorless liquid were collected in a cooled trap; this pyrolysate was shown by glc and spectral data to be a mixture of benzonitrile (42 mg), benzoic acid (148 mg), and benzoic anhydride (20 mg). The residue (530 mg, 98%), free of **7a**, was decolorized with Norite and recrystallized from ethanol–water, affording 400 mg of pure 2,4,5-triphenylimidazole (**8a**), mp 273–274° (lit.[18] mp 274°).

Reaction of 7a with Benzoyl Chloride.[24]—A mixture of **7a** (1.0 g, 2.4 mmol) and benzoyl chloride (5 ml) was heated to 100° under nitrogen for 30 min. After cooling, the solution was treated with cold aqueous sodium hydroxide solution (10 ml, 20%) and then extracted with ether, dried over $MgSO_4$, and concentrated, affording 400 mg (50%) of 2,4,5-triphenylimidazole.

Recrystallization from pyridine–water gave pure **8a**, mp 273–274°.

Degradation of 7a. A. Ozonolysis in Formic Acid.—Amide **7a** (1.0 g, 2.4 mmol) was suspended in 97% formic acid (50 ml) and subjected at room temperature for 6 hr to excess ozone, which was produced by a Welsbach generator. The formic acid was removed *in vacuo*, giving a residue, which was dissolved in petroleum ether (400 ml, bp 30–60°). Upon concentration to 40 ml, benzamide (188 mg) crystallized, mp 125–127°. Further concentration to about 10 ml gave 212 mg of benzil, mp 94.5–95.5°. Mixture melting points with authentic samples of benzamide and benzil gave no depression.

Evaporation of the remaining solvent gave a yellow mixture, which contained only benzamide and benzil.

B. Oxidation of 7a.—To a stirred suspension of amide **7a** (1.0 g, 2.4 mmol) in glacial acetic acid (100 ml) was added potassium dichromate (1.0 g, 3.4 mmol) over 5 hr under nitrogen. The mixture was stirred at room temperature until the solution became green. Addition of water (400 ml) precipitated an unidentified solid (80 mg),[25] mp 200–230°.

The green filtrate was extracted with ether (two 100-ml portions). The ether extract was washed with water, dried over Drierite, and concentrated to *ca.* 10 ml. Addition of water (40 ml) and cooling gave a suspension, which slowly crystallized, mp 130–142°. Washing with ether and recrystallization from benzene gave 510 mg (48%) of pure dibenzamide: mp 148–149° (lit.[26] mp 148–150°); ir (KBr) 3180 (NH), 1695, 1665 cm^{-1} (C=O). A mixture melting point with an authentic sample produced by the method of Titherley[26] gave no depression.

The ether washings and the mother liquors were combined and concentrated. Column chromatography on silica gel (2 ft × 1 in). with ether–petroleum ether gave 113 mg of pure benzil: mp 94–95°; ir (KBr) 1680, 1600 cm^{-1} (C=O). This sample was identical in all respects with an authentic sample.

Hydrolysis of *threo*-1,2-Diphenyl-2-benzamidoethanol.—Amide **9a** (93.8 mg, 0.296 mmol, mp 223–224°) and potassium hydroxide (9.0 g) in ethanol (25 ml) were refluxed under nitrogen for 18 hr. After cooling, water (70 ml) was added. The solution was extracted with methylene chloride, dried, and concentrated *in vacuo*, giving 52 mg (83%) of crude *threo*-2-amino-1,2-diphenylethanol, mp 108–118°.[27] Recrystallization from chloroform gave threo isomer: mp 122–123° (lit.[15,22a] mp 129–130°); ir ($CHCl_3$) 3670 (–OH), 3400 cm^{-1} (–NH); mass spectrum *m/e* (rel intensity) 195 ($M^+ - 18$, 7.7), 194 (10), 180 (14), 179 (14), 178 (14), 165 (16), 107 (95), 106 (100), 105 (50), 104 (60), 90 (20), 79 (90), 77 (98). A mixture melting point with *threo*-2-amino-1,2-diphenylethanol, prepared by the method of Japp and Moir,[22a] was undepressed.

***cis*-*N*-(2-Benzamidoethenyl)benzamide.**—Excess benzoyl chloride was slowly added to imidazole (300 mg, 40 mmol) dissolved in 10% aqueous sodium hydroxide (10 ml). The precipitate was filtered, washed with water, and recrystallized from aqueous ethanol, affording 270 mg (35%) of *cis*-*N*-(2-benzamidoethenyl)benzamide: mp 204–206° (lit.[29] mp 205–206°); ir (Nujol) 3300, 3220 cm^{-1} (NH); mass spectrum *m/e* (rel intensity) 266 (M^+, 26.5), 145 ($M^+ - 121$, 5.9), 121 (7.0), 105 (C_6H_5CO, 100), 77 (C_6H_5, 47); nmr (DMSO-d_6) δ 6.4 (m, cis HC=CH, 2 H), 7.6 (m, C_{arom} H, 6 H), 7.9 (m, C_{arom} H, 4 H), 10.1 (d, J = 8 Hz, NH, 2 H).

Anal. Calcd for $C_{16}H_{14}N_2O_2$: C, 72.30; H, 5.26. Found: C, 72.40; H, 5.31.

***trans*-*N*-(2-Benzamidoethenyl)benzamide.**—The cis isomer (100 mg, 4 mmol) was heated under nitrogen at 210° for 10 min. Recrystallization from 95% ethanol gave 50 mg (50%) of the trans isomer: mp 289–290° (lit.[30] mp 280–290°); ir (Nujol) 3310 cm^{-1} (NH); mass spectrum *m/e* (rel intensity) 266 (M^+, 28), 145 ($M^+ - 121$, 6), 121 (8.5), 105 (C_6H_5CO, 100), 77 (C_6H_5, 50); nmr (DMSO-d_6) δ 7.3 (m, trans HC=CH, 2 H), 7.6 (m, C_{arom} H, 6 H), 8.0 (m, C_{arom} H, 4 H), 10.2 (d, J = 8 Hz, NH, 2 H).

Reaction of *p*-Tolualdehyde with Lithium Nitride.—*p*-Tolualdehyde (7.74 g, 64.5 mmol) in CCl_4 (20 ml) was added over 30 min to a refluxing stirred suspension of Li_3N (1.0 g, 28 mmol) in CCl_4 (80 ml) under nitrogen. After 10 hr, additional CCl_4 (100 ml) was added. The solution was cooled to 0° and the precipitate was filtered, washed with cold acetone, and extracted with a 20% sodium hydroxide solution. After filtration, the filtrate was acidified, affording 1.47 g of *p*-toluic acid, mp 175–179°, which was identical with an authentic sample. The base-insoluble residue was recrystallized from phenyl ether, giving 952 mg of pure *cis*-*N*-(2-*p*-toluamido-1,2-di-*p*-tolylethenyl)-*p*-toluamide (**7b**): mp 304–305°; ir (Nujol) 3210 (NH), 1640 cm^{-1} (C=O); mass spectrum *m/e* (rel intensity) 474 (M^+, 4) 472 (3), 353 (47), 339 (8), 238 (5), 119 (100), 91 (70); nmr (DMSO-d_6) δ 2.23 (s, C_{arom} CH_3, 6 H), 6.85–7.45 (m, C_{arom} H, 12 H), 7.68–7.95 (broad d, C_{arom} H, 4 H), 9.78 (s, NH, 2 H).

Anal. Calcd for $C_{32}H_{30}N_2O_2$: C, 81.00; H, 6.38; N, 5.96. Found: C, 81.15; H, 6.18; N, 5.63.

Column chromatography of the combined concentrated filtrates (5.2 g) on silica gel G (3 ft × 1 in.) eluting with cyclohexane–benzene–ethanol (65:25:10) and collecting 10-ml aliquots gave the following: fractions 11–13, *p*-xylyl *p*-toluate, 4.23 g, bp 234–240° (33 mm) [lit.[31] bp 213–217° (15 mm)], nmr (CCl_4) δ 2.30 (s, C_{arom} CH_3, 5 H), 2.33 (s, C_{arom} CH_3, 3 H), 5.19 (s, $-CH_2-$, 2 H), 7.1 (m, C_{arom} H, 6 H), 7.87 (d, J_{AB} = 8 Hz, 2 H); fraction 14, *p*-tolualdehyde, 109 mg, DNP mp 238–240° (lit.[32] mp 238–240°), and 2,4,5-tris-*p*-tolylimidazole, recrystallized from ethanol–water, 262 mg, mp 232–233° (lit.[33] mp 232–233°), nmr ($CDCl_3$) δ 2.38 (broad s, C_{arom} CH_3, 9 H), 7–8 (m, C_{arom} H, 12 H); fraction 15–22, *p*-methylbenzyl alcohol, 820 mg, mp 58° (lit.[34] mp 60°), ir (neat) 3320 (OH), 1035 cm^{-1}, nmr ($CDCl_3$) δ 1.87 (s, OH, 1 H, lost with added D_2O), 2.32 (s, C_{arom} CH_3, 3 H), 4.60 (s, $-CH_2-$, 2 H), 7.18 (s, C_{arom} H, 4 H); fraction 23–40, *N*-*p*-xylyl-*p*-toluamide, 337 mg, mp 164–166°, ir (Nujol) 3300 (NH), 1640 cm^{-1} (C=O), nmr (DMSO-d_6), δ 2.29 and 2.37

(23) A. Schonberg, *Chem. Ber.*, **54**, 242 (1921).

(24) Benzoic acid anhydride containing sodium benzoate was successfully used (84%) in this conversion, while acetic anhydride or propionic anhydride failed, and only unreacted **7a** was recovered.

(25) This solid is probably an intermediate, since further oxidation resulted in the same product distribution.

(26) A. W. Titherley, *J. Chem. Soc.*, **85**, 1673 (1904).

(27) The crude threo isomer was contaminated with traces of the erythro isomer[28] and the resultant mixture of diastereomers could be crystallized only with difficulty. The facts show that only minor amounts of erythro isomer were produced.

(28) *erythro*-2-Amino-1,2-diphenylethanol (mp 161–162°) was prepared by comparison purposes by the method of R. Lukes, J. Kovar, and K. Blaka [*Collect. Czech. Chem. Commun.*, **25** 2179 (1960)].

(29) A. Windaus and F. Knopp, *Chem. Ber.*, **38**, 1169 (1905).

(30) P. Ruggli, R. Ratti, and E. Henzi, *Helv. Chim. Acta*, **12**, 332 (1929).

(31) L. Mascarelli and G. Russi, *Gazz. Chim. Ital.*, **42**, 92 (1912).

(32) J. Borstein, S. F. Bedell, P. E. Drummond, and C. L. Kosloski, *J. Amer. Chem. Soc.*, **78**, 86 (1956).

(33) Al. Spasov, St. Robev, and D. Popov, *God. Sofii. Univ., Fiz.-Mat. Fak. Kniga 2-Khim.*, **49**, 119 (1956); *Chem. Abstr.*, **51**, 12075*g* (1957).

(34) A. Schaap, L. Brandsma, and J. F. Arens, *Recl. Trav. Chim. Pays-Bas*, **84**, 1200 (1965).

(s, C_{arom} CH_3, 3 H), 4.46 (d, J = 6 Hz, $-CH_2-$, 2 H), 7.0 (d, J = 8 Hz, C_{arom} H, 2 H), 7.16 (s, C_{arom} H, 4 H), 8.1 (d, J = 8 Hz, C_{arom} H, 2 H), 8.82 (m, NH, 1 H).

Anal. Calcd for $C_{16}H_{17}NO$: C, 80.29; H, 7.16. Found: C, 80.35; H, 7.07.

Hydrolysis of *cis*-*N*-(2-*p*-Toluamido-1,2-di-*p*-tolylethenyl)toluamide.—Amide **7b** (54 mg, 1.1 mmol) was hydrolyzed, in an identical manner with amide **7a**, affording *p*-toluic acid, mp 177–180°, and 24 mg (91%) of 2,4,5-tris-*p*-tolyloxazole, which was recrystallized from absolute ethanol, mp 143–145° (lit.[24] mp 145°).

Pyrolysis of *cis*-*N*-(2-*p*-Toluamido-1,2-di-*p*-tolylethenyl)toluamide.—Amide **7a** (200 mg, 0.43 mmol) was pyrolyzed, in an identical manner with amide **7a**, affording a distillate (*p*-tolunitrile, *p*-toluic acid, and *p*-toluic acid anhydride) and a residue, which was recrystallized from ethanol giving 130 mg (90%) of 2,4,5-tris-*p*-tolylimidazole, mp 232–233°. Each compound was substantiated by spectral comparisons with authentic samples.

Registry No.—**7a**, 33511-25-0; **7b**, 33511-26-1; **9a**, 33511-27-2; lithium nitride, 26134-62-3; benzaldehyde, 100-52-7; *threo*-2-amino-1,2-diphenylethanol, 13286-63-0; *cis*-*N*-(2-benzamidoethenyl)benzamide, 33511-28-3; *trans*-*N*-(2-benzamidoethenyl)benzamide, 33511-29-4; *p*-tolualdehyde, 104-87-0; *p*-xylyl *p*-toluate, 21086-87-3; 2,4,5-*tris*-*p*-tolylimidazole, 33515-43-4; *p*-methylbenzyl alcohol, 589-18-4; *N*-*p*-xylyl-*p*-toluamide, 33515-44-5.

The Preparation and Oxidation of α-Hydroxyaldehydes[1]

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Received May 17, 1971

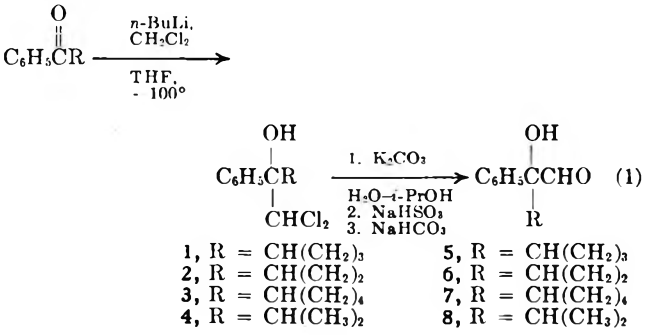
A series of α-hydroxyaldehydes have been prepared in 33–62% yield *via* the hydrolysis of the corresponding dichloromethylcarbinols. The latter compounds were conveniently prepared by the addition of dichloromethyllithium to the appropriate ketone at −100° in tetrahydrofuran. The glycolic aldehydes were oxidized to the corresponding glycolic acids by cold, neutral potassium permanganate in yields of 40–55%. Hydrolysis of trichloromethylcarbinols, obtained by the addition of trichloromethyllithium and the appropriate ketone, resulted in the elimination of chloroform to regenerate the parent ketone.

The syntheses of α-hydroxyaldehydes have been severely limited in the past. Freon[2] has added Grignard reagents to the oximes of difficultly accessible α-keto aldehydes to yield α-hydroxyaldoximes which could then be hydrolyzed by acid to the corresponding α-hydroxyaldehyde in low yields. Also, the hydrolysis of α-haloaldehydes[3,4] affords α-hydroxyaldehydes in low yields.

The purpose of this work, in part, was to investigate the synthesis of α-hydroxyaldehydes by the reaction of dichloromethyllithium with an alkyl aryl ketone followed by hydrolysis of the resulting dichloromethylcarbinols. Avy[5] reported the synthesis of dimethyldichloromethylcarbinol, but no aldehyde was isolated upon hydrolysis of this compound with calcium carbonate. Avy noted that hydrolysis of diethyldichloromethylcarbinol with boiling aqueous calcium carbonate did afford diethyl glycolic aldehyde, isolated as the semicarbazide derivative.

In our work, we found that dichloromethyllithium adds readily to alkyl aryl ketones at −100° in tetrahydrofuran to yield the corresponding dichloromethylcarbinols in yields of 75–85% (eq 1).[6] One example of this reaction was reported in 1964 by Kobrich and coworkers[6b] who treated benzophenone with the same reagent to obtain the corresponding dichloromethylcarbinol.

Hydrolysis of the dichloromethylcarbinols with potassium carbonate in aqueous isopropyl alcohol afforded a mixture of products which was shown by ir spectroscopy to contain the desired glycolic aldehyde. Distillation of the mixture resulted in extensive decomposition. However, the desired aldehydes could be isolated as the bisulfite adducts from which the free aldehydes could be readily regenerated.[7] The overall equations are shown in eq 1.



Investigation of the hydrolysis of compound **2** led also to the isolation of a solid α-hydroxyaldehyde dimer. The structure was assigned on the basis of ir and nmr spectral data and an acceptable elemental analysis. Treatment of the dimer with 4% meth-

(1) (a) This work was conducted at Ash Stevens Inc. under Edgewood Arsenal Contract No. DAAA15-67-C-0519. (b) Presented in part at the 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 1969.

(2) P. Freon, *Ann. Chim. (Paris)*, **11**, 480 (1939).

(3) A. Kirrmann and J. Druesne, *C. R. Acad. Sci.*, **259**, 3285 (1964).

(4) A. Kirrmann, P. Chancel, M. Vignalou, and P. Federling, *Bull. Soc. Chim. Fr.*, 707 (1950).

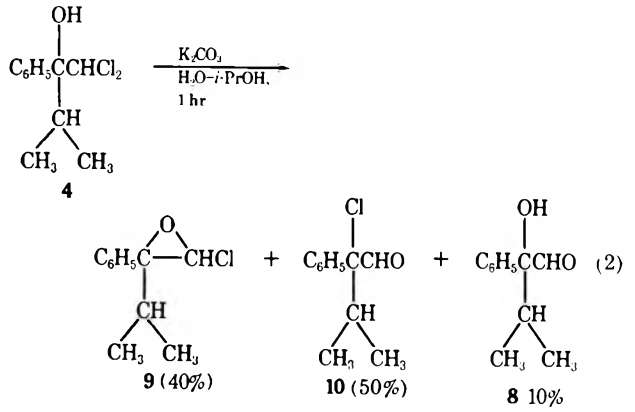
(5) M. A. Avy, *ibid.*, **49**, 12 (1931).

(6) Recent literature has described the preparation of α-chloroalkyllithium compounds by the reaction of polyhalomethanes with *n*-butyllithium in tetrahydrofuran or tetrahydrofuran–ether mixtures at −100°. These salts were reported to be stable indefinitely at −100° but decomposed spontaneously above −65°. Tetrahydrofuran was observed to have a great stabilizing influence on α-chloroalkyllithium structures. (a) D. Hoeg, D. Lusk, and A. L. Crumbliss, *J. Amer. Chem. Soc.*, **87**, 4147 (1965); (b) G. Kobrich, K. Flory, and W. Drischel, *Angew. Chem.*, **76**, 536 (1964); (c) G. Kobrich, H. R. Merkle, and H. Trapp, *Tetrahedron Lett.*, 969 (1965).

(7) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, "The Systematic Identification of Organic Compounds," 4th ed, Wiley, New York, N. Y., 1962, p 149.

anolic potassium hydroxide solution led to a partial regeneration of the monomeric aldehyde, evidenced by the appearance of a carbonyl group in the ir spectrum. The regenerated aldehyde was isolated as its bisulfite adduct, subsequently reconverted to pure monomeric glycolic aldehyde. When this procedure was applied to the crude hydrolysis mother liquor of compound 2, the yield of aldehyde **6** was raised from 31 to 54%. By a similar procedure, aldehyde **5** was obtained in 62% yield.

Kobrich and Weiner reported recently[8] the conversion of an α-dichloromethylcarbinol to an α-chloro epoxide by treatment with *n*-butyllithium in tetrahydrofuran solvent. Upon heating, the epoxide rearranged to an α-chloroaldehyde. The hydrolysis conditions, employed in the present work, consist of potassium carbonate in a 2-propanol–water solvent mixture at room temperature for 17 hr. In an effort to determine if, under these mild reaction conditions, the α-chloro epoxide rearranged to an α-chloroaldehyde prior to hydrolysis, the hydrolysis reaction of compound **4** was quenched after 1 hr. Examination of the reaction mixture by ir and nmr spectroscopy showed the epoxide **9** and chloroaldehyde **10** to be the major components (eq 2). Based on these data, at least 80% of

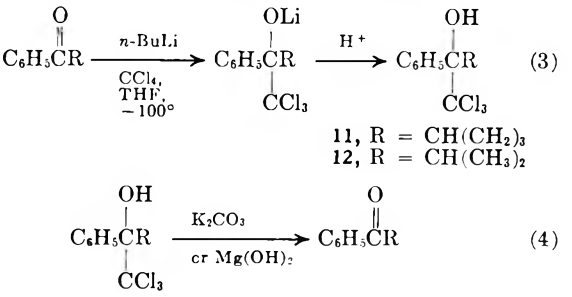


the α-chloro epoxide rearranges to an α-chloroaldehyde prior to hydrolysis.

Pure samples of **9** were prepared by treating **4** with either potassium hydroxide or potassium carbonate in dry methanol. Ir and nmr spectral analyses of the crude reaction product showed no α-chloroaldehyde or α-hydroxyaldehyde to be present. Distillation of **9** under reduced pressure at 50° caused a partial rearrangement to yield a mixture of **9** and α-chloroaldehyde **10**. The rearrangement proceeded readily at 80° to yield pure 2-chloro-2-phenyl-3-methylbutyraldehyde. Pure **10** could also be prepared by a reaction of dichloromethylcarbinol **4** with 1 equiv of butyllithium in THF. Upon warming the cold (−30°) reaction solution to room temperature, α-chloro epoxide **9** was formed, as evidenced by the formation of lithium chloride. Heating this solution at reflux for 1 hr produced pure **10**. In this case, the presence of lithium chloride hastens the rearrangement. These results are in agreement with those reported by Kobrich and Weiner.[8] The rearrangement of the epoxide is also catalyzed by silica gel. When pure **9** was placed on a silica gel column and eluted with petroleum ether, a mixture of **9** and **10** was obtained.

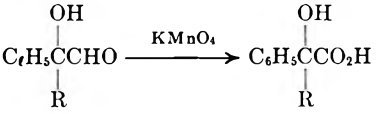
(8) G. Kobrich and W. Weiner, *Tetrahedron Lett.*, 2181 (1969).

Trichloromethylcarbinols **11** and **12** were prepared in 44 and 54% yield, respectively, *via* addition of trichloromethyllithium to the appropriate ketones (eq 3). However, it was found that these compounds were stable to dilute acid and attempted hydrolysis under a variety of basic conditions resulted in the elimination of chloroform to regenerate the parent ketone (eq 4).



Next, the oxidation of α-hydroxyaldehydes **5**–**8** was investigated as a possible synthetic route for α-hydroxy acids. Oxidizing agent studies included silver oxide as a suspended solid or dissolved in ammonium hydroxide, chromium trioxide in aqueous acetone and in pyridine, bromine, nitric acid, peracetic acid, Caro's acid, potassium permanganate and air oxidation with a cobalt catalyst. With the exception of potassium permanganate, the parent alkyl aryl ketone was the sole oxidation product. Potassium permanganate oxidation gave a moderate yield of the glycolic acid although the alkyl aryl ketone still was a major side product. Several solvent systems were evaluated with dioxane–water (1:1) being the preferred solvent. The results are shown in Table I.

TABLE I
PERMANGANATE OXIDATION OF α-HYDROXYALDEHYDES



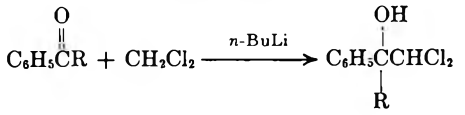
Hydroxy acid	R	Yield, %	Mp, °C
13	$CH(CH_2)_2$	43	138–139
14	$CH(CH_2)_2$	37	88.5–89.5
15	$CH(CH_2)_4$	48	146.5–147.5
16	$CH(CH_3)_2$	40	148–149

The stability of an α-hydroxy acid toward two of the oxidizing agents was established. Thus, 2-hydroxy-2-cyclobutylphenylacetic acid was stable to silver oxide under the reaction conditions employed for the oxidation of the corresponding α-hydroxyaldehyde. Chromium trioxide, however, converted the acid to cyclobutyl phenyl ketone and potassium permanganate gave partial conversion to ketone.

Another possible route to α-hydroxy acids would be the oxidation of α-chloroaldehyde **10** to the α-chloro acid which, if it did not hydrolyze under the reaction conditions, could be converted readily to α-hydroxy acid. It was found that the oxidation of **10** with potassium permanganate in acid media afforded the desired α-hydroxy acid in 61% yield (eq 5). Apparently, the chloro acid hydrolyzed as it was formed. The nonacidic material was found to be starting material which could be recycled. For synthetic purposes, this route appears to be preferred over the oxidation of the α-hydroxyaldehydes.

TABLE II

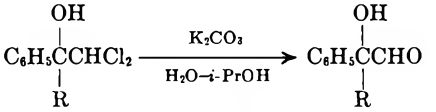
PREPARATION OF DICHLOROMETHYLCARBINOLS



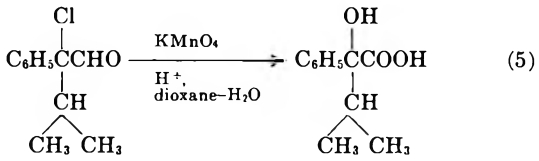
Carbinol	R	Yield, %	Bp, °C	Calcd, % C	Calcd, % H	Found, % C	Found, % H
1	$CH(CH_2)_3$	84	98 (0.22)	58.79	5.76	58.88	5.76
2	$CH(CH_2)_2$	82	83 (0.15)	57.17	5.23	57.44	5.35
3	$CH(CH_2)_4$	75	108 (0.30)	60.26	6.22	60.51	6.24
4	$CH(CH_3)_2$	73	83–84 (0.15)	56.67	6.05	56.58	5.98

TABLE III

HYDROLYSIS OF DICHLOROMETHYLCARBINOLS



Aldehyde	R	Yield, %	Mp, °C	Calcd, % C	Calcd, % H	Found, % C	Found, % H
5	$CH(CH_2)_3$	62	35.5–36.5	75.76	7.42	75.98	7.34
6	$CH(CH_2)_2$	54	51.5–52.5	74.98	6.86	74.73	6.92
7	$CH(CH_2)_4$	44	75–76.5	76.44	7.90	76.70	7.80
8	$CH(CH_3)_2$	33	37–38.5	74.13	7.92	74.31	7.84



(5)

Experimental Section

Boiling points and melting points are uncorrected. Microanalyses were performed by Midwest Microlab, Ltd., Indianapolis, Ind. The ir spectra were measured on a Perkin-Elmer Model 237B spectrophotometer. The nmr spectra were measured on a Varian Model T-60 nmr spectrometer.

Preparation of Dichloromethylcarbinols. General Procedure. Cyclobutyl dichloromethylphenylcarbinol (1).—A solution of methylene chloride (10 ml) in dry tetrahydrofuran (225 ml) was cooled to −100° with a liquid nitrogen bath. To this cooled solution was added dropwise a hexane solution of *n*-butyllithium (88 ml, 0.14 mol) over approximately 45 min. After the addition was complete, the mixture was stirred at −100° for 45 min. Cyclobutyl phenyl ketone (20.8 g, 0.13 mol) was added slowly over *ca.* 30 min. After an additional 30 min at −100°, the mixture was allowed to warm to −20° and poured onto an ice–water mixture (400 ml) containing concentrated sulfuric acid (10 ml). Ether was added and the layers were separated. The aqueous layer was extracted once more with ether. The combined organic phase was dried (sodium sulfate) and the solvent was removed. The residue was distilled under reduced pressure. The results are shown in Table II.

Hydrolysis of Dichloromethylcarbinols. General Procedure. 2-Hydroxy-2-cyclobutylphenylacetaldehyde (5). **A.**—Potassium carbonate (10 g) was added to a solution of cyclobutyldichloromethylphenylcarbinol (10 g, 41 mmol) in 1:1 2-propanol–water (400 ml). The mixture was stirred at room temperature for 19 hr and extracted with ether (200 ml). The ether extract was dried (Na_2SO_4) and the ether was removed under reduced pressure. The residue was treated with standard[7] sodium bisulfite solution, the mixture filtered, and the solid washed with ether to yield 5 g of the bisulfite adduct. The filtrate and ether washings were saved (see B). The bisulfite adduct was added to a saturated aqueous sodium bicarbonate solution (100 ml) and ether (100 ml) and the two-phase system was stirred at room temperature for 4 hr. The layers were separated and the ether layer was concentrated under reduced pressure to yield 3.2 g of the glycolic aldehyde as an oil which solidified on standing.

B.—For the title aldehyde 5 and 2-hydroxy-2-cyclopropylphenylacetaldehyde (6), the yields were improved by the following procedure. The aqueous filtrate and ether washings from the bisulfite adduct formation were combined and shaken and the layers separated. The ether was removed and the residual oil was stirred with 4% methanolic potassium hydroxide (50 ml) for 1 hr at room temperature. The solution was diluted with water (100 ml) and extracted with ether (two 60-ml portions). The ether was removed and the residue treated with sodium bisulfite solution followed by aqueous sodium bicarbonate, as in A, to yield additional glycolic aldehyde. The combined crude product was purified by sublimation at room temperature (0.1 mm). The hydrolysis results are summarized in Table III.

α-Isospropyl-β-chlorostyrene Oxide (9).—To a solution of potassium hydroxide (1.1 g) in anhydrous methanol (35 ml) at 10° was added dichloromethylisopropylphenylcarbinol (2.15 g, 9.3 mmol). The solution was allowed to warm to room temperature and stirred for 1 hr. The solution was then poured into water (150 ml) and extracted twice with petroleum ether (bp 30–60°). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure at 0–5°. Examination of the reaction mixture by nmr showed it to contain *ca.* 50% of chloroaldehyde 10, 40% of epoxide 9, and about 10% of α-hydroxyaldehyde 8.

Preparation of Trichloromethylcarbinols. General Procedure. Cyclobutylphenyltrichloromethylcarbinol (11).—To a solution of carbon tetrachloride (10.05 g, 65 mmol) in tetrahydrofuran (150 ml) cooled to −105° was added dropwise a hexane solution of *n*-butyllithium (44 ml, 70 mmol). After the addition was complete, the solution was stirred at −100° for 1 hr and cyclobutyl phenyl ketone (10.4 g, 65 mmol) was added. The reaction mixture was stirred an additional 40 min at −100°, then allowed to warm to −20°, and poured into ice water (500 ml) containing 5 ml of concentrated sulfuric acid. The mixture was extracted with ether. The ether extract was washed with water, followed by saturated sodium chloride solution, and dried over sodium sulfate. Removal of the ether gave a viscous oil which was distilled *in vacuo*. The first fraction, bp to 90° (0.07 mm), consisted of a mixture of cyclobutyl phenyl ketone and the product. The subsequent fractions, bp 85–95° (0.04 mm), consisted of nearly pure product. The material was purified by recrystallization from petroleum ether and amounted to 7.93 g (44%), mp 59–61°.

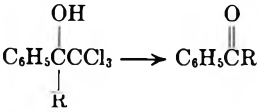
Anal. Calcd for $C_{12}H_{13}Cl_3O$: C, 51.55; H, 4.69; Cl, 38.04. Found: C, 51.78; H, 4.73; Cl, 38.02.

Isopropylphenyltrichloromethylcarbinol (12).—Isobutyrophenone (10.4 g, 0.07 mol) was allowed to react with trichloromethyllithium by the general procedure and gave 9.9 g (53%) of the carbinol 12, mp 37–38.5° (petroleum ether).

Anal. Calcd for $C_{11}H_{13}Cl_3O$: C, 49.38; H, 4.90; Cl, 39.75. Found: C, 49.59; H, 4.97; Cl, 39.49.

Studies of the Hydrolysis of Alkylphenyltrichloromethylcarbinols.—A number of attempts were made to hydrolyze alkyl-

TABLE IV
HYDROLYSIS OF ALKYLPHENYLTRICHLOROMETHYLCARBINOLS



R	Reagent	Product	Yield, %
Cyclobutyl	H_2SO_4	Starting material	71
Cyclobutyl	K_2CO_3	Ketone	94
Cyclobutyl	ZnO	Starting material	98
Cyclobutyl	MgO	Starting material	98
Cyclobutyl	Pyridine	Starting material	95
Cyclobutyl	$AgNO_3$	Starting material + ketone	
Isopropyl	K_2CO_3	Ketone	83

phenyltrichloromethylcarbinols to the respective α-hydroxy acids. The results are shown in Table IV. In all cases studied, the only product formed was the parent ketone, arising from the elimination of chloroform. In the cases in which no ketone was formed, starting carbinol was nearly quantitatively recovered.

Oxidation of Glycolic Aldehydes. General Procedure. 2-Hydroxy-2-cyclobutylphenylacetic Acid (13).—To 2-hydroxy-2-cyclobutylphenylacetaldehyde (300 mg, 1.58 mmol) in dioxane (10 ml) at 10–15° was added potassium permanganate (250 mg) in water (10 ml). The solution was filtered to remove manganese dioxide and 5% sodium hydroxide was added to pH 10. The solution was extracted with ether (two 10-ml portions) to afford an oil (110 mg). The ir spectrum indicated the oil contained about 65% of cyclobutyl phenyl ketone and 35% of unreacted aldehyde. The aqueous basic solution was acidified with hydrochloric acid and extracted with ether (two 10-ml portions) to afford crude acid **13** which was recrystallized from chloroform to yield 140 mg (43%) of pure acid, mp 138–139° (lit.[9] mp 143–143.5°).

2-Hydroxy-2-cyclopropylphenylacetic Acid (14).—2-Hydroxy-2-cyclopropylphenylacetaldehyde (300 mg, 1.7 mmol) was oxidized with permanganate by the general procedure. The crude material was recrystallized from benzene–petroleum ether to yield 122 mg (37%) of pure product, mp 88.5–89.5° (lit.[9] mp 91–92°).

(9) S. B. Kadin and J. G. Cannon, *J. Org. Chem.*, **27**, 240 (1962).

2-Hydroxy-2-cyclopentylphenylacetic Acid (15).—The glycolaldehyde **7** (300 mg, 1.47 mmol) was converted to the acid by the general procedure. The crude product was recrystallized from chloroform and gave 155 mg (48%) of pure acid, mp 146.5–147.5° (lit.[10] mp 147–148°).

2-Hydroxy-2-phenyl-3-methylbutanoic Acid (16). A.—2-Hydroxy-2-phenyl-3-methylbutyraldehyde (300 mg, 1.7 mmol) was oxidized with permanganate by the general procedure. The product was recrystallized from chloroform and amounted to 130 mg (40%), mp 148–149°.

Anal. Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.26. Found: C, 68.22; H, 7.55.

B.—To a cooled solution of 2-chloro-2-phenyl-3-methylbutyraldehyde (1.4 g, 71 mmol) in dioxane (110 ml) and concentrated HCl (6 ml) was added potassium permanganate (4.5 g, 28.5 mol) in water (55 ml). The solution was stirred in an ice bath for 45 min, at which time all potassium permanganate was consumed. The solution was filtered and extracted with chloroform (three 30-ml portions). The organic layer was dried ($MgSO_4$) and concentrated. The residue was dissolved in chloroform (5 ml) and petroleum ether (60 ml) and the solution was washed with saturated sodium bicarbonate solution (two 20-ml portions). The bicarbonate solution was acidified with HCl and filtered to yield 0.85 g (61%) of crude hydroxy acid **16**, mp 144–145°. A sample was recrystallized from chloroform and melted at 148–149°; the ir spectrum ($CHCl_3$) was identical with that of the material prepared above. The petroleum ether solution was dried and concentrated to yield 0.35 g of an oil which was shown by ir analysis to be predominantly unreacted α-chloroaldehyde.

Registry No.—**1**, 33483-07-7; **2**, 33483-08-8; **3**, 33483-09-9; **4**, 33483-10-2; **5**, 33483-11-3; **6**, 33483-12-4; **7**, 31142-50-4; **8**, 33483-14-6; **11**, 33487-50-2; **12**, 33487-51-3; **13**, 1460-47-5; **14**, 1460-46-4; **15**, 427-49-6; **16**, 15879-60-4.

Acknowledgment.—The authors wish to acknowledge Mr. James P. Lockhard for his valuable technical assistance.

(10) J. H. Biel, H. L. Friedman, H. A. Leiser, and E. P. Sprengler, *J. Amer. Chem. Soc.*, **74**, 1485 (1952).

Notes

Charge Distribution in the Addition of Dichlorocarbene to Olefins

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Received September 30, 1971

Although numerous qualitative observations have demonstrated the electrophilic nature of dichlorocarbene in its addition to carbon–carbon double bonds,[2,3] quantitative measurements of the extent of charge development have been meager and are summarized in Table I. The addition of the carbene to styrenes[4] and α-methylstyrenes[5] was best correlated by σ^+, with the more reactive (more nucleophilic) α-methylstyrene system yielding the smaller ρ value. The order of magnitude of these ρ values reflects only modest charge development at the benzylic position in the transition state relative to the ground state in accord with expectations for a concerted but unsymmetrical addition passing through a transition state with unequal bond formation to the two carbon atoms of the double bond.[5-7]

In contrast to the above studies was a report by

(1) Taken from the Ph.D. dissertation of E. V. Couch. Partial support from the Petroleum Research Fund is hereby acknowledged.

(2) W. Kirmse, "Carbene Chemistry," Academic Press, New York, N. Y., 1964, p 163.

(3) D. Bethell, *Advan. Phys. Org. Chem.*, **7**, 153 (1969).

(4) D. Seyferth, J. Y-P. Mui, and R. Damrauer, *J. Amer. Chem. Soc.*, **90**, 6182 (1968).

(5) I. H. Sadler, *J. Chem. Soc. B*, 1024 (1969).

(6) R. Hoffmann, *J. Amer. Chem. Soc.*, **90**, 1475 (1968).

(7) Such results do not clearly distinguish between the unsymmetrical concerted reaction or a two-step process involving a zwitterionic intermediate with a transition state which occurs early along the reaction coordinate.

TABLE I

SUMMARY OF LFE CORRELATIONS FOR DICHLOROCARBENE ADDITIONS TO CARBON–CARBON DOUBLE BONDS

Olefin type	Method of $:CCl_2$ generation	Substituent constant	Reaction constant	Ref
p-$RC_6H_4CH{=}CH_2$	$PhHgCBrCl_2$	σ^+	-0.619 ± 0.045	4
$RC_6H_4(CH_3)C{=}CH_2$	$CHCl_3$ + KO-*tert*-Bu	σ^+	-0.378 ± 0.015	5
$R_1R_2C{=}CR_3R_4$		$\Sigma\sigma^*$	-4.3	8
$RCH{=}CH_2$	Cl_3CCO_2Et + NaOMe	σ^+	-0.74 ± 0.02	This work

Skell[8] that dichlorocarbene addition to a variety of simple aliphatic olefins could be correlated with the Taft σ^* parameter with $\rho^* \cong -4.3$, a value which seems unexpectedly negative. However, interpretation is complicated because the use of olefins with differing numbers of substituents led these authors to sum the substituent constants for all aliphatic groups on the double bond, a practice which is questionable in view of the well-known reactivity differences in 1,1- and 1,2-disubstituted olefins[2] each of which would possess the same $\Sigma\sigma^*$.

Results and Discussion

In the present study, dichlorocarbene generated by the method of Parham[9] was added to a series of monosubstituted olefins, **1**, in which the substituents were

$$\underset{\mathbf{1}}{RCH{=}CH_2} + Cl_3CCO_2Et \xrightarrow[\text{pentane, 0–5°}]{NaOMe} \underset{\mathbf{2}}{R\text{-}\triangle\text{-}Cl_2}$$

a = n-C_4H_9 **d** = $PhCH_2CH_2$
b = CH_3OCH_2 **e** = $PhOCH_2$
c = $ClCH_2$

chosen so as to avoid undesirable side reactions, resonance effects, and differences in steric effects.[10] The exclusive product in each case was the expected dichlorocyclopropane (**2**) except for olefin **1b** which also resulted in a very small amount of 3-methoxy-4,4-dichloro-1-butene from insertion of the carbene into an allylic carbon–hydrogen bond. A suitable control experiment showed that under the reaction conditions the allylic chlorine atom of **1c** was not displaced by methoxide.

Values of ρ^* calculated for several pairs of olefins by use of eq 1 in which P_1, P_2, O_1, and O_2 represent the

$$\log [(P_1O_2)/(P_2O_1)] = \rho^*(\sigma_1^* - \sigma_2^*) \quad (1)$$

relative amounts of product 1, product 2, initial olefin 1, and initial olefin 2, respectively, are in good agreement (Table II).

In order to ensure that the term (P_1O_2/P_2O_1) would be essentially equal to k_1/k_2, the ratio of total initial olefin to ethyl trichloroacetate was at least 10 for each competition.[4,11] The apparent molar product ratios determined by vapor phase chromatography were corrected from a detector sensitivity curve established from a series of known mixtures of products and an internal standard.

Although it is not possible to make a simple direct comparison of the values derived from σ^+ and σ^* correlations, respectively, the small negative values of the reaction constants listed in Table I suggest that the sensitivity of both styrenes and other monosubstituted olefins toward dichlorocarbene addition are comparable. The observed value of -0.74 in our study is similar to the values of -0.742 and -0.606 reported for the reaction of primary alkyl p-toluenesulfonates with ethanol (100°) and primary alkyl bromides with thiophenoxide in methanol (20°), respectively, neither of which would be expected to involve substantial charge separation in the transition state relative to the ground state.[12]

TABLE II

DICHLOROCARBENE COMPETITIONS IN ADDITIONS TO SELECTED MONOSUBSTITUTED OLEFINS

Substituent	σ^*	ρ^*
n-C_4H_9	-0.13	-0.71
CH_3OCH_2	0.52	-0.75
$ClCH_2$	1.05	
$PhCH_2CH_2$	0.08	-0.75
$PhOCH_2$	0.85	
	Av =	-0.74 ± 0.02

Experimental Section[13]

Methyl allyl ether was synthesized in 65% yield from allyl bromide (freshly distilled, dry) and sodium methoxide (commercial) according to the method of Bailey.[1] The product ether was separated from excess allyl bromide by fractional distillation (50-cm wire spiral column), bp 42° (lit.[14] bp 43°).

Attempted Reaction of Allyl Bromide with Sodium Methoxide under Conditions of Dichlorocarbene Generation.—Allyl bromide (6.05 g, 0.05 mol, freshly distilled, dry) was added to a cooled mixture of sodium methoxide (1.08 g, 0.02 mol, commercial) in pentane (20 ml) and stirred (2 hr, ice bath), followed by filtration, several water washes, and drying ($MgSO_4$). Careful distillation (50-cm wire spiral column) followed by observation of the nmr and ir spectra for the distillate with the same boiling range as methyl allyl ether showed no peaks attributable to it.

1,1-Dichloro-2-*n*-butylcyclopropane (2a) was prepared by the method of Parham[9] except for the work-up. The reaction mixture was washed with water and dried ($MgSO_4$), washed with concentrated sulfuric acid followed by water, and dried ($MgSO_4$), followed by removal of the pentane and distillation to give product (4.1 g, 0.024 mol, 61.4%), bp 68° (10 mm) [lit.[11] bp 71.6–72° (20 mm)].

The nmr spectrum contained a large broad singlet at τ 8.45 and two peaks at 9.07 and 9.12 protruding from the multiplet which extends from 8 to 9.32. The ir spectrum (CCl_4) contains

(8) P. S. Skell and M. S. Cholod, *J. Amer. Chem. Soc.*, **91**, 7131 (1969).
(9) W. E. Parham and E. E. Schweizer, *J. Org. Chem.*, **24**, 1773 (1959).
(10) R. A. Moss and A. Mamantov, *Tetrahedron Lett.*, 3425 (1968).
(11) W. von E. Doering and W. A. Henderson, Jr., *J. Amer. Chem. Soc.*, **80**, 5274 (1958).
(12) A. Streitwieser, Jr., *ibid.*, **78**, 4935 (1956).
(13) Elemental analyses were performed by the Department of Medicinal Chemistry at the University of Kansas or by the Galbraith Laboratories, Inc., Knoxville, Tenn., unless otherwise noted. Melting points and boiling points (capillary method) are uncorrected. Infrared spectra were obtained from a Beckman IR-8 instrument (sodium chloride optics) with a 1604 cm^{-1} (polystyrene *vs.* air) as a reference standard. Analyses of halides by vpc were performed with an F & M Model 700 instrument (thermal conductivity detector) and the following columns: 20% QF-1 on 30–60 Chromosorb P (15 ft × 0.25 in.); 20% Carbowax 20M on 30–60 Chromosorb P (12 ft × 0.25 in.); 20% tris(cyanoethoxy)propane on 30–60 Chromosorb P (12 ft × 0.25 in.); 15% SE-30 on 30–60 Chromosorb W (10 ft × 0.25 in.); and 10% OV-210 on 80–100 Gas Chrome Q (6 ft × 1/8 in. glass column). Area measurements were performed with a Disc Integrator. A Varian A-60 or A-60-A spectrometer was used to determine nmr spectra of compounds as solutions in carbon tetrachloride containing 3–6% tetramethylsilane.
(14) W. J. Bailey and L. Nicholas, *J. Org. Chem.*, **21**, 648 (1956).

peaks at 2950 (s), 2870 (s), 2870 (s), 1425, 1375, 1218 (w), 1190 (w), 1118, 1040 (w), 1015 (w), 948 (w), 909, and 750 cm^{-1}.

1,1-Dichloro-2-(chloromethyl)cyclopropane (2c) was prepared in 25.1% overall yield from allyl chloride (freshly distilled, dry) *via* a method similar to the preparation of compound **2a**. The crude reaction mixture was washed and dried ($MgSO_4$) and the solvent removed. 1,1-Dichloro-2-(chloromethyl)cyclopropane was separated from the other components by preparative vpc (Aerograph Autoprep Model A-700, 15% Carbowax 20M). The observed boiling point was 162° [lit.[15] bp 56° (17 mm)].

The nmr spectrum shows a perturbed doublet with the smaller peak at τ 6.3, the larger at 6.42 (2 H, J = 8 Hz, $Cl-CH_2$) and also a multiplet from 7.6 to 8.8 (3 H, cyclopropyl). The ir spectrum (CS_2) contains peaks at 2950 (w), 1425, 1370, 1265, 1220 and 1201 (doublet), 1113 and 1096 (doublet), 1043, 1025, 965 (w), 948, 918, 871 (w), 809 (w), 775 (s, sh), 755 (s), and 714 cm^{-1} (s).

Methyl 2,2-dichlorocyclopropylcarbinyl ether (2b) was prepared from methyl allyl ether in 7.45% yield by the procedure described for compound **2a**. The crude reaction mixture was washed and the solvent removed. The residue was stirred and kept at reflux for 3 hr with sodium hydroxide solution (a volume excess, 20% by weight). The basic solution was extracted with pentane; the pentane layer was washed and dried ($MgSO_4$); and the pentane was removed. The residual liquid was distilled to give colorless product, bp 155°, 73° (37 mm).

The nmr spectrum displays a doublet centered at τ 6.5 (2 H, J = 6 Hz, OCH_2CH), a singlet at 6.66 (3 H, CH_3O-), and a multiplet from 7.82 to 8.98 (3 H, cyclopropyl). The ir spectrum contains peaks at 2990 (w), 2920, 2880, 2820, 1430, 1400, 1220 (w), 1195, 1142, 1100 (s), 1052 (w), 1032 (w), 1009 (w), 985 (w), 915 (w), and 747 cm^{-1} (s).

Anal. Calcd for $C_5H_8OCl_2$: C, 38.74; H, 5.20. Found: C, 38.61; H, 4.96.

4,4-Dichloro-3-methoxy-1-butene is apparently formed as a minor (*ca.* 5%) product resulting from dichlorocarbene insertion into an allylic carbon–hydrogen bond during the formation of methyl 2,2-dichlorocyclopropylcarbinyl ether. A few drops of this insertion product were obtained by preparative vpc (F & M Model 700, 15% QF-1). The nmr spectrum shows a doublet centered at τ 4.4 (J = 5 Hz, $-CCl_2H$) superimposed upon a multiplet absorbing from 3.82 to 4.9 (total area 4 H) which resembles an ABC splitting pattern ($-CH=CH_2$). Additionally the spectrum contains a poorly resolved triplet at 6.16 (1 H, J = 6 Hz, $-OCHCH=CH_2$) and a sharp singlet at 6.6 (3 H, CH_3O-). The ir spectrum (CS_2) has peaks at 1180 (w), 1100, 980 (w), and 932 in common with those of methyl allyl ether, as well as a major peak at 778 cm^{-1} (CCl_2), some 35 cm^{-1} removed from the corresponding peak in the spectrum of the expected carbene addition product **2b**.

1,1-Dichloro-2-(2-phenylethyl)cyclopropane (2d), bp 69° (0.15 mm) [lit.[16] bp 96° (4 mm)], was obtained in 10% yield from 4-phenyl-1-butene (freshly distilled, Aldrich) *via* the process described for compound **2a**. The nmr spectrum contains a singlet at τ 2.82 (5 H, aryl), a triplet centered at 7.2 (2 H, J = 8 Hz, benzyl), and a multiplet from 8.0 to 9.1 (5 H, CH_2–cyclopropyl). The ir spectrum coincides with that reported.[16]

Phenyl 2,2-dichlorocyclopropylcarbinyl ether (2e) was synthesized from allyl phenyl ether in 12.1% yield according to the procedure described previously, bp 79° (0.28 mm). The nmr spectrum consisted of a complex multiplet from τ 2.55 to 3.3 (5 H, aryl), a doublet centered at 5.97 (2 H, J = 6 Hz, $-OCH_2-$), and a multiplet from 7.66 to 8.89 (3 H, cyclopropyl). The ir spectrum (CS_2) shows peaks at 3032 (w), 2934 (w), 2875 (w), 1592 (s), 1398, 1330 (w), 1298, 1237 (s), 1218 (s), 1168, 1112, 1077, 1041 (s), 884 (w), 800, 748 (s), and 687 cm^{-1} (s).

Anal. Calcd for $C_{10}H_{10}OCl_2$: C, 55.32; H, 4.64. Found: C, 55.59; H, 4.81.

Competitive Addition of Dichlorocarbene to Olefins.—To a magnetically stirred mixture of pentane (30 ml, dry, alkene free) and sodium methoxide (1.62 g, 0.03 mol, commercial) cooled in an ice bath were added, by syringe through a rubber septum, equimolar quantities (0.125 mol) of each olefin. The syringe cap was quickly replaced by a pressure compensated addition funnel containing ethyl trichloroacetate (4.78 g, 0.025 mol) and the system was held tightly closed by rubber bands. The ester was added dropwise (*ca.* 1.5 hr) and the reaction mixture left stirring an additional 1.5 hr. The reaction mixture was gravity filtered, the residual sodium methoxide rinsed with pentane (two 15-ml portions), and this washing combined with the filtrate. The solution was washed (four 30-ml portions) and dried ($MgSO_4$) and the solvent removed under vacuum at room temperature. Vpc analysis of the distillate indicated complete absence of any dichlorocyclopropyl product.

For olefins with an aryl substituent the reaction mixture was filtered, washed twice (two 20-ml portions), and dried ($MgSO_4$). The pentane was removed and the product mixture partially distilled under vacuum (50-cm wire spiral column). Methyl ethyl carbonate distilled from the mixture at room temperature (0.1 mm). Most of the excess olefin likewise distilled at a bath temperature of 75° (0.1 mm). The head temperature was not permitted to rise above 30° (0.1 mm). Vpc analysis of the distillate indicated complete absence of any dichlorocyclopropyl product.

Weighed portions (*ca.* 27 μl) of the product mixture were thoroughly mixed with weighed amounts (*ca.* 3 μl) of internal standard in small screw cap vials sealed with a square of polyethylene sheet. 7,7-Dichloronorcarane was used as the internal standard for all the olefin competitions except that of phenyl allyl ether *vs.* 4-phenyl-1-butene for which 1,1-dichloro-2-benzylcyclopropane was used. Several aliquots (*ca.* 1 μl) were withdrawn from each of the vials by a syringe (Hamilton, 10 μl) and injected directly into the vpc. Each column used was calibrated by injecting solutions containing internal standard in known and varied quantities of the carbene adduct products in order to provide an experimental correlation of peak area ratios with compound mole fractions. The observed peak area ratios were corrected to actual mole fractions by reference to this sensitivity calibration curve.

Registry No.—**2a**, 3722-08-5; **2b**, 33707-14-1; **2c**, 3722-05-2; **2d**, 20849-80-3; **2e**, 33666-40-9; dichlorocarbene, 1605-72-7; 4,4-dichloro-3-methoxy-1-butene, 33712-31-1.

(15) W. M. Wagner, H. Kloosterziel, and S. Van der Ven, *Recl. Trav. Chim. Pays-Bas*, **80**, 740 (1961).

(16) V. S. Aksenov, I. A. Dyakonov, and R. R. Ksotokov, *Zh. Org. Khim.*, **4**, 1680 (1968).

Palladium-Catalyzed Reactions of Allene with Diolefins

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Several examples of transition metal catalyzed oligomerizations of allenes have been reported.[1] However, such reactions of allenes with other olefins are relatively rare.[2] In this regard we wish to report two novel examples of catalyzed reactions of allene with diolefins.

When a mixture of allene, butadiene, and a catalytic amount of bis(triphenylphosphine)(maleic anhydride)-palladium[3] was heated to 120°, a 39% yield of a 3:1 mixture of *trans*- and *cis*-2-methyl-3-methylene-1,5,7-octatriene (**1**), respectively, was obtained. Hydrogenation of **1** over 5% Pd on charcoal yielded 2,3-dimethyloctane.

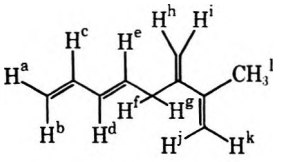
During the preparation of **1**, concurrent dimerizations of the butadiene to a mixture of 4-vinylcyclo-

(1) (a) F. N. Jones and R. V. Lindsey, Jr., *J. Org. Chem.*, **33**, 3838 (1968); (b) R. E. Benson and R. V. Lindsey, Jr., *J. Amer. Chem. Soc.*, **81**, 4247 (1959); (c) G. Shier, *J. Organometal. Chem.*, **10**, 15 (1967); (d) E. L. Jenner and R. V. Lindsey, Jr., U. S. Patent 2,876,254 (1959); (e) S. Otsuka, *et al.*, *Chem. Commun.*, 191 (1969); (f) T. Susuki and J. Tsuji, *Bull. Chem. Soc. Jap.*, **41**, 1954 (1968).

(2) A. Greco, A. Carbonaro, and G. Dall'Asta, *Tetrahedron Lett.*, No. **57**, 5009 (1969); *J. Org. Chem.*, **35**, 271 (1969).

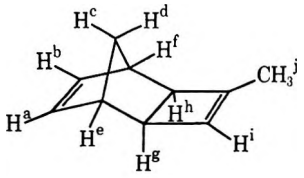
(3) S. Takahashi, T. Sibano, and N. Hagihara, *Bull. Chem. Soc. Jap.*, **41**, 454 (1968).

hexene and 1,3,7-octatriene[4] were also observed. These competing reactions consumed almost all the excess butadiene. When isoprene or 1,3-pentadiene was used in this reaction, only the corresponding dimers could be isolated.



1

A similar study of the reaction of allene with bicyclo[2.2.1]hepta-2,5-diene was made. Under conditions similar to those applied to butadiene, a *ca.* 25% yield of *exo*-3-methyltricyclo[4.2.1.$0^{2,5}$]nona-3,7-diene (2) was obtained.



2

The preparation appeared to yield a single isomer and differentiation between the two possible ring junction isomers was made possible by an analysis of the nmr spectrum. Spin decoupling of the pairs H^a, H^e and H^b, H^f verified the assignments of H^e and H^f. Computer simulation[5] of the region containing the H^{e-h} protons gave a closest fit with $J_{g,h} \cong 4$; $J_{e,g} = J_{f,h} \leqslant 2$ and $J_{g,i} \cong 0.5$ Hz. The second coupling constant, in the cases of *endo*- and *exo*-tricyclo[4.2.1.$0^{2,5}$]nona-3,7-diene, has been reported[6] to be 3.5 and $\leqslant 1$ Hz, respectively. Also, the proton chemical shifts reported for the latter isomer closely resembled comparable shifts found with **2**. Hence, we have assigned the exo configuration to the reaction product. Catalytic hydrogenation of **2** gave a single, saturated hydrocarbon following an uptake of 2.04 equiv of hydrogen.

Substantial amounts of an impure, higher boiling material [bp 53–54° (0.12 mm)] were also isolated from the reaction. Although elemental analysis suggested a 2:1 allene–bicyclo[2.2.1]hepta-2,5-diene adduct, a complete structural assignment was thwarted by the lack of sufficiently pure material.

It may be noted that **2** could conceivably arise from a cycloaddition of methylacetylene, formed *in situ* from allene, to bicyclo[2.2.1]hepta-2,5-diene.[7] However, no evidence for the formation of **2** was found upon substitution of methylacetylene for allene in the reaction.

Experimental Section

Boiling points are uncorrected. The relative proton intensities, determined by nmr, may be assumed to be within ±3% where not noted otherwise.

***trans*- and *cis*-2-Methyl-3-methylene-1,5,7-octatriene (1).**—A solution of bis(triphenylphosphine)(maleic anhydride)palladium (1.47 g, 0.002 mol) in 25 ml of tetrahydrofuran was charged to a 400-cc stainless steel lined autoclave. To this solution was added allene (20 g, 0.50 mol) and butadiene (162 g, 3.0 mol). The mixture was heated to 120° for 5 hr with stirring. The resulting liquid was directly distilled giving a fraction of bp 45–100° (16 mm). Redistillation of this crude fraction through a 24-in. spinning-band column gave **1** (14.8 g, >90% purity, 39% yield). A pure sample was prepared by glc collection: bp 67.5–69° (16 mm); ir (neat) 1595, 1630, and 1650 cm^{-1} (C=C); uv (ethanol) λ_{max} 225 mμ (ε 35,600); nmr (220 MHz, CCl_4) δ 1.88 (H^l, s), 2.97 (H^f, H^g, d, J = 7 Hz, trans), 3.08 (H^f, H^g, d, J = 7 Hz, cis), 4.82–5.20 (H^a, H^b, H^h, H^i, H^j, H^k, m), 5.40–6.65 (H^c, H^d, H^e, m, $J_{c,d,cis}$ = 9 Hz, $J_{c,d,trans}$ = 14 Hz).

Anal. Calcd for $C_{10}H_{14}$: C, 89.50; H, 10.51. Found: C, 89.60; H, 10.60.

Hydrogenation of *trans*- and *cis*-2-Methyl-3-methylene-1,5,7-octatriene (1).—A sample of **1** (1.34 g, 0.0097 mol, >97% purity) and 5% palladium on charcoal (0.1 g) were mixed with 10 ml of absolute ethanol and exposed to hydrogen with stirring. The mixture absorbed 944 ml of hydrogen. The mixture was filtered to remove catalyst and the solvent was evaporated from the filtrate to give 1.2 g of colorless liquid. Glc purification of this material gave a liquid which had an infrared spectrum and a glc retention time identical with that of an authentic sample of 2,3-dimethyloctane.

***exo*-3-Methyltricyclo[4.2.1.$0^{2,5}$]nona-3,7-diene (2).**—A solution of bicyclo[2.2.1]hepta-2,5-diene (660 ml, 6.57 mol) and bis(triphenylphosphine)(maleic anhydride)palladium (8.75 g, 0.01 mol) was charged to a 1000-ml stainless steel lined autoclave. The system was then charged with allene (57.5 g, 1.40 mol) and heated to 145° for 5 hr. The resulting solution was distilled through a 24-in. spinning-band column, giving **2** (45.6 g, 25% yield): bp 49–50.5° (16 mm); ir (neat) 1630, 1590, and 1561 cm^{-1} (C=C); nmr (220 MHz, CCl_4) δ 1.31 (H^c, H^d, AB pattern, $J_{c,d}$ = 8 Hz), 1.67 (H^j, s), 2.18 and 2.15 (H^g and H^h, s), 2.32 (H^e, H^f, m), 5.85 (H^i, s), 6.00 (H^a, H^b, s).

Anal. Calcd for $C_{10}H_{12}$: C, 90.8; H, 9.20. Found: C, 90.67; H, 9.26.

Hydrogenation of *exo*-3-Methyltricyclo[4.2.1.$0^{2,5}$]nona-3,7-diene (2).—A mixture of **2** (0.661 g, 0.005 mol) and 0.05 g of 5% palladium on charcoal in 5 ml of ethanol was exposed to 1 atm of hydrogen with stirring. A total of 252.2 ml of hydrogen was absorbed. Filtration and evaporation of the ethanol gave an oil which appeared to be a single compound by glc analysis (retention time 17 min, on 20% silicone gum nitrile, 4 ft × 1/4 in., 78°). Glc collection afforded a pure sample: nmr (60 MHz, CCl_4) δ 1.6–3.3 (m, 7 protons), 0.8–1.6 (m, 9 protons).

Anal. Calcd for $C_{10}H_{16}$: C, 88.25; H, 11.85. Found: C, 88.64; H, 12.22.

Registry No.—*trans*-**1**, 33885-13-1; *cis*-**1**, 33885-14-2; **2**, 33885-15-3; hydrogenation product of **2**, 33885-16-4; palladium, 7440-05-3; allene, 463-49-0; bicyclo[2.2.1]-hepta-2,5-diene, 121-46-0; butadiene, 106-99-0.

Acknowledgment.—I thank Dr. Raymond C. Ferguson for the nmr simulation studies.

(4) E. J. Smutny, *J. Amer. Chem. Soc.*, **89**, 6793 (1967).

(5) A five-spin approximation using a modified LAOCOON-type program developed by C. W. Haigh, University College, Swansea, Wales.

(6) (a) L. Watts, J. D. Fitzpatrick, and R. Pettit, *J. Amer. Chem. Soc.*, **88**, 623 (1966); (b) L. G. Cannell, *Tetrahedron Lett.*, **No. 48**, 5967 (1966).

(7) G. N. Schrauzer and P. Glockner, *Chem. Ber.*, **97**, 2451 (1964).

Photochemical Conversion of Primary and Secondary Amines to Carbonyl Compounds

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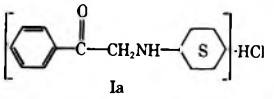
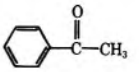
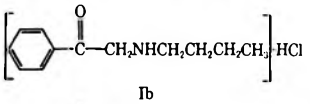
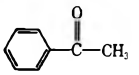
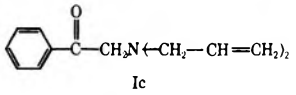
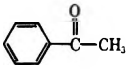
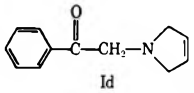
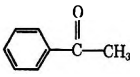
The occurrence of the Norrish type II elimination as the major process[1] in the photolysis of α-phenacylamines prompted an investigation of the utility of this reaction in effecting the conversion of amines to car-

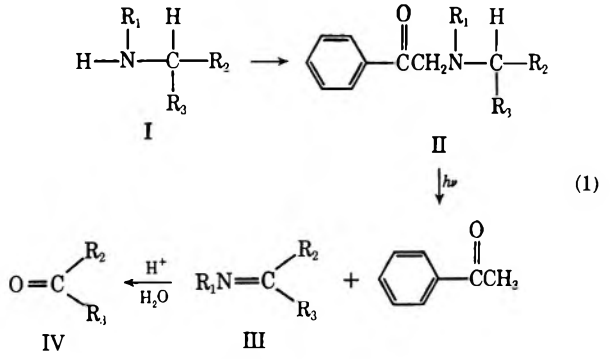
(1) A. Padwa, W. Eisenhardt, R. Gruber, and D. Pashayan, *J. Amer. Chem. Soc.*, **91**, 1857 (1939).

TABLE I

Starting material	Product	Yield, %	Other product	Solvent	Irradiation time, hr	Conversion, %
 Ia		71		1% H_2O in CH_3OH	28	60
 Ib	$CH_3CH_2CH_2CHO$	57		1% H_2O in CH_3OH	13	35
 Ic		90	Polymer	C_6H_6	7	100
 Id		92		C_6H_6	5	100

bonyl compounds. We wish to report here that the photolysis of phenacyl derivatives of primary and secondary amines is a preparatively useful method for the conversion of the amino group to a carbonyl function under mild, nonoxidative conditions.

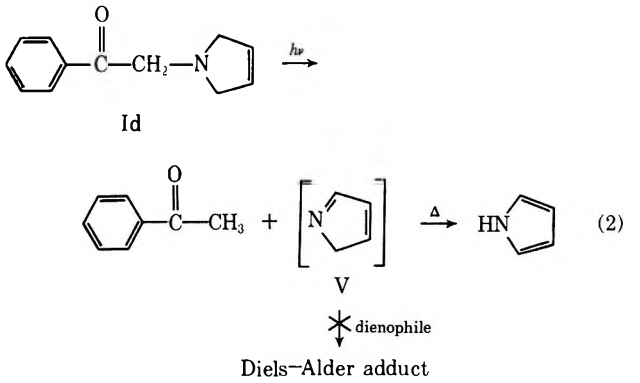
The instability of *N*-phenacyl derivatives of primary amines (II, R_1 = H) relative to dihydropyrazines[2] requires the isolation and use of these compounds as their salts. It is demonstrated here that photolysis of these salts proceeds cleanly with formation of Norrish type II products; *in situ* hydrolysis of the imine photoproduct III yields the desired carbonyl compound[3] (eq 1). Results typical of the photolysis of some *N*-phenacylamines are given in Table I.



(1)

As noted in Table I, photolysis of the hydrochloride salts proceeds slowly, but no competing reactions are observed. Shorter irradiation times suffice to give complete conversion of free allylamine derivatives such as *N*-phenacyldiallylamine and *N*-phenacyl-3-pyrroline, however.

Production of pyrrole in the photolysis of *N*-phenacyl-3-pyrroline intimates the transient existence of the valence-bond tautomer V of pyrrole (eq 2). However, all attempts to trap the tautomer as a Diels–Alder adduct (maleic anhydride, dimethylacetylene dicarboxylate, and dichloroethylene, *in situ* and added after irradiation at ambient and low temperatures) failed to give identifiable products other than pyrrole and acetophenone. The lack of Diels–Alder reactivity of heterodienes of the type N=C–C=C has been noted.[5]



(2)

Experimental Section[6]

***N*-Phenacylcyclohexylamine Hydrochloride.**—Material prepared according to the procedure of Cromwell and Mercer[7] and recrystallized from ethanol had mp 252–253° (lit.[7] mp 250–252°).

***N*-Phenacyl-*n*-butylamine Hydrochloride.**—Material prepared according to Hyde, *et al.*,[8] and recrystallized from acetone–ethanol had mp 223–225° (lit.[8] mp 214–215°).

***N*-Phenacyldiallylamine.**—Freshly distilled diallylamine (32 g, 0.34 mol) was dissolved in a mixture of 70 ml of ether and 40 ml of benzene, cooled to 0°, and stirred.

A solution of 32 g (0.16 mol) of α-bromoacetophenone in a mixture of 50 ml of ether and 20 ml of benzene was added dropwise to the diallylamine solution. The stirred reaction mixture was allowed to warm to room temperature when the addition was complete and was finally heated at reflux for 0.5 hr. The precipitate of diallylamine hydrobromide was removed by filtration and the filtrate was treated with dry hydrogen chloride to yield the hydrochloride salt of the product as a syrup.

Treatment of the hydrochloride salt with 50 ml of 15% aqueous NaOH and ether extraction yielded, upon removal of ether *in vacuo*, the desired product as a yellow oil. Distillation through a 4-in. Vigreux column gave 7.0 g (71%) of faintly yellow product: bp 94–95° (0.02 mm); ir 5.90 (s), 6.24 μ (s); nmr δ 8.0–7.5 (m, 5 H), 6.3–5.6 (m, 2 H), 5.4–4.9 (m, 4 H), 3.87 (s, 2 H), 3.27 (broad d, 4 H); mass spectrum *m/e* 215 (parent) (calcd *m/e* 215).

Anal. Calcd for $C_{14}H_{17}NO$: C, 78.10; H, 7.96; N, 6.51. Found: C, 77.78; H, 8.00; N, 6.58.

3-Pyrroline.—Material prepared by the method of Andrews and McElvain[9] had bp 90–91° (lit.[9] bp 89–92°).

***N*-Phenacyl-3-pyrroline.**—3-Pyrroline (6.9 g, 0.10 mol) and

(2) Y. T. Pratt, *Heterocycl. Compounds*, **6**, 377 (1957).

(3) The possible formation of substituted 3-azetidinols[4] in small amounts was not investigated in this study.

(4) E. H. Gold, *J. Amer. Chem. Soc.*, **93**, 2793 (1971).

(5) A. Oneshchenko, "Diene Synthesis," O. Davey, New York, N. Y., 1964, p 596 ff.

(6) Melting points and boiling points are uncorrected. Ir spectra were taken as Nujol mulls or neat films on a Perkin-Elmer 137 spectrophotometer; nmr spectra were obtained at 60 MHz on a Varian instrument. Mass spectra were determined on an AEI MS-9 instrument. Product mixtures were analyzed and collected by glpc, using SE-30 and PDEAS columns. Microanalyses were performed by W. Rond, The Ohio State University.

(7) H. N. Cromwell and G. D. Mercer, *J. Amer. Chem. Soc.*, **79**, 3815 (1957).

(8) J. F. Hyde, E. Browning, and R. Adams, *ibid.*, **50**, 2287 (1928).

(9) L. H. Andrews and S. M. McElvain, *ibid.*, **51**, 887 (1929).

10.1 g (0.10 mol) of triethylamine were taken up in a mixture of 100 ml of benzene and 25 ml of ether, and cooled to 0° with stirring under N_2.

A solution of 20 g (0.10 mol) of α-bromoacetophenone in 60 ml of benzene was added dropwise over 1 hr, and the reaction mixture was allowed to warm to room temperature. Filtration to remove triethylamine hydrobromide and treatment of the filtrate with dry hydrogen chloride yielded the crude hydrochloride salt of the product as a syrup. Recrystallization from 2-propanol afforded 8.0 g (35%) of the salt as an off-white solid, mp 170–172°.

Samples of the free base for photolysis were secured by ether extraction of a basic aqueous suspension of the salt. The final product was a yellow oil: ir 5.90 (s), 6.18 (s); nmr δ 8.0–7.5 (m, 5 H), 5.98 (s, 2 H), 4.16 (s, 2 H), 3.70 (s, 4 H).

This compound is very susceptible to oxidation to *N*-phenacylpyrrole, and gave unsatisfactory elemental analyses. Its high-resolution mass spectrum showed a parent ion at *m/e* 187.0994 (calcd 187.0997).

Photolyses.—The phenacylamine salts were irradiated in 100-mg quantities as 1% solution in 1:99 water–methanol with a Pyrex-filtered 450-W Hanovia source; the free allylamine derivatives were irradiated as 1% benzene solution in a Rayonet "merry-go-round" apparatus using 3000-Å lamps. Irradiations were carried out in an atmosphere of purified nitrogen.

Products were isolated by preparative gas phase chromatography of the photolysis reaction mixtures following removal of solvent by atmospheric pressure distillation.

Registry No.—Ic, 33777-39-8; Id, 33777-40-1.

Acknowledgment.—The author is grateful to Dr J. S. Swenton for suggestions and use of laboratory facilities during the course of this work. J. A. H. acknowledges an Ohio State University predoctoral fellowship, 1970.

α Anions of Carboxylic Acids. V. A Simple High Yield Presentation of α-Alkylhydracrylic Acids and α-Alkylacrylic Acids[1]

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Received September 8, 1971

The facile preparation of α-metalated carboxylate salts (dianions) (I) (eq 1) has provided unique opportunities for derivatizing long-chain fatty acids at the α-methylene carbon.[3–5]

$$RCH_2COOH + 2LiN(i\text{-}Pr)_2 \xrightarrow[HMPA]{THF} \underset{\underset{Li}{|}}{RCHCOOLi} + 2HN(i\text{-}Pr)_2 \quad (1)$$

I

The reaction of α-metalated carboxylate salts with formaldehyde is shown in this report to be a facile, high-yield synthesis of α-alkylhydracrylic and α-alkylacrylic acids. Prior to this development, low-molecular-weight derivatives of both classes of compounds were inconveniently prepared by multistep reactions, generally in low yields (20–60%).[6] Several single-step syntheses have been described in the patent literature, although yields in general never exceed 20%.[7]

The synthesis of β-hydroxy acids or esters by reaction of carbonyl compounds with metalated carboxylic acids or esters has been previously reported by other investigators.[8–10] However, the reaction of formaldehyde was not included among their aldehydes examined, an omission that would have provided the key hydracrylic acid intermediates—the primary methylol derivatives—for convenient preparations of α-alkylacrylic acids.

The initial reaction of formaldehyde with the metalated carboxylates produces α-alkylhydracrylic acids (II) (eq 2) and the latter compounds are readily

$$R\bar{C}HCOO^- + HCHO \longrightarrow {}^-OCH_2\underset{\underset{R}{|}}{C}HCOO^- \xrightarrow{H^+} \underset{\underset{R}{|}}{HOCH_2}CHCOOH \quad (2)$$

II

dehydrated by acid catalyst to α-alkylacrylic acids (III) (eq 3). The α-alkylacrylic acids (III) are advantageously distilled from the reaction zone during the dehydration process. In the present development, each of the two classes of derivatives is isolated in yields generally exceeding 90%.

$$\underset{\underset{R}{|}}{HOCH_2}CHCOOH \xrightarrow[\text{distillation}]{H^-,\ \Delta,} CH_2{=}\underset{\underset{R}{|}}{C}COOH + H_2O \quad (3)$$

III

The advantages of using hexamethylphosphoramide (HMPA) as a cosolvent in tetrahydrofuran (THF) solution for solubilizing salts and dianions of low solubility has been demonstrated for several reactions.[4,5] Recent reports on alkylations of dianions[11,12] have indicated that mixed cationic species of metalated carboxylates, *e.g.*, $[LiNa]^{2+}$, impart improved reactivity to dianions compared to the dilithiated salts and that heterogeneity due to poorly solubilized dianions is not a barrier to a successful reaction.[12,13] The use of mixed cations would provide an alternative to the use of HMPA, were the advantages of the former found to be general for reactions other than alkylations. In order to determine the relative merits of mixed cations and HMPA in the formylation reactions, the

(1) Paper IV: P. E. Pfeffer and L. S. Silbert, *J. Org. Chem.*, **36**, 3290 (1971).

(2) Eastern Marketing and Nutrition Research Division, Agriculture Research Service, U. S. Department of Agriculture.

(3) P. L. Creger, *J. Amer. Chem. Soc.*, **89**, 2500 (1967).

(4) P. E. Pfeffer and L. S. Silbert, *J. Org. Chem.*, **35**, 262 (1970).

(5) P. E. Pfeffer, L. S. Silbert, and J. M. Chirinko, Jr., *J. Org. Chem.*, **37**, 451 (1972).

(6) (a) S. Reformatsky, *J. Prakt. Chem.*, 469 (1896); (b) C. Mannich and K. Ritsert, *Ber.*, **57B**, 1116 (1924); (c) K. Chikanishi and T. Tsuruta, *Makromol. Chem.*, **81**, 198 (1965); (d) C. F. Allen and M. J. Kalm, "Organic Syntheses, Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 616; (e) Y. Yamashita, H. Kato, K. Hisano, T. Ito, and M. Hasegawa, *Kogyo Kagaku Zasshi*, **65**, 2050 (1962); *Chem. Abstr.*, **58**, 12774c (1963).

(7) (a) B. C. Redmon, U. S. Patent 2,734,074 (Feb 7, 1956); (b) T. A. Koch and I. M. Robinson, U. S. Patent 3,014,958 (Dec 26, 1961); (c) J. M. Leathers and G. E. Woodward, U. S. Patent 3,051,747 (Aug 28, 1962); (d) V. A. Sims and J. F. Vitcha, U. S. Patent 3,247,248 (Apr 19, 1966).

(8) B. Angelo, *C. R. Acad. Sci., Ser. C*, **270**, 1471 (1970).

(9) G. W. Moersch and A. R. Burkett, *J. Org. Chem.*, **36**, 1149 (1971).

(10) M. W. Rathke, *J. Amer. Chem. Soc.*, **92**, 3222 (1970).

(11) P. L. Creger, *ibid.*, **92**, 1396 (1970).

(12) P. L. Creger, *Org. Syn.*, **50**, 58 (1970).

(13) These assertions appear to have a limited validity for alkylations of some dianions. The opposed arguments are discussed in more detail in a former paper (see ref 5).

TABLE I
YIELDS AND PROPERTIES OF α-ALKYLHYDRACRYLIC ACIDS, $HOCH_2C(R)HCOOH$. REACTION OF α ANIONS WITH FORMALDEHYDE

Starting acid	Registry no.	R	Mp or bp, °C (mm)	Yield,[a] % THF	Yield,[a] % THF–HMPA[b]
Hexanoic	33785-85-2	Butyl	114–116 (10)[c]	97	
Nonanoic	33785-86-3	Heptyl	47–48[d]		
			88 (0.3)[c]	96, 65,[e] 12[f]	90, 31[f]
Tetradecanoic	33785-87-4	Dodecyl	75–75.3		89
Hexadecanoic	33785-88-5	Tetradecyl	81–8[illegible].7		85,[g] 61
Octadecanoic	33785-89-6	Hexadecyl	85.5–87.0	29	80[g]
cis-9,10-Octadecenoic	33780-97-1	*cis*-7,8-Hexadecenyl	*h*		93
Phenylacetic[i]	529-64-6	Phenyl	117–118[j]		93

[a] Yields determined by glc. All purified products analyzed satisfactorily by elemental analysis, nmr, and mass spectra. [b] One mole of hexamethylphosphoramide (HMPA) per mole of carboxylic acid in tetrahydrofuran (THF) except where indicated. [c] Methyl ester. [d] Lit. mp 47–48°: E. E. Blaise and A. Luttringer, *Bull. Soc. Chim. Fr.*, **33**, 635 (1905). [e] Dianion present in reaction with $[LiNa]^{2+}$ mixed cations; prepared from the sodium salt of the carboxylic acid. [f] Dianion present in reaction with $[LiK]^{2+}$ mixed cations; prepared from the potassium salt of the carboxylic acid. [g] 2 mol of HMPA. [h] Methyl ester decomposes on distillation to a mixture of unsaturated acid and esters. [i] Included as a representative example of an aromatic preparation. [j] Lit. mp 116–117°: A. McKenzie and J. K. Wood, *J. Chem. Soc.*, **115**, 828 (1919).

formylations of dianions with varied counterions were carried out in the presence and absence of HMPA.

α-Alkylhydracrylic Acids.—The results of these preparations are assembled in Table I and show the importance of conducting the formylations in homogeneous solutions to attain high yields of α-alkylhydracrylic acids. Short-chain dianions such as dilithiated nonanoate are sufficiently soluble in THF in the absence of HMPA to achieve an efficacious formaldehyde reaction (96% yield), whereas long-chain dianions such as octadecanoate require dissolution by HMPA for successful formylations (80% in HMPA *vs.* 29% without HMPA). The results also highlight the importance of the counterion type, since yields diminish in the order $[LiLi]^{2+}$ (96%) > $[LiNa]^{2+}$ (65%) > $[LiK]^{2+}$ (12%). These results are explained in part by the low solubility of the $[LiNa]^{2+}$ and $[LiK]^{2+}$ dicationic species in THF solutions, indicating a slow progressive reaction between formaldehyde and the heterogeneous phase of the metalated carboxylates. It is evident from the example of α-heptylhydracrylic acid (Table I) that yields increase as the solubility of the mixed salt species, *e.g.*, $[LiK]^{2+}$, is increased by inclusion of HMPA as cosolvent, thereby providing a convincing argument for carrying out dianion reactions in homogeneous solutions.

α-Alkylacrylic Acids.—Dehydration of an α-alkyl hydracrylic acid is conveniently carried out in a distillation flask for subsequent *in vacuo* distillation of the α-alkylacrylic acid. The α-alkylhydracrylic acid containing one drop of phosphoric acid as catalyst is heated *in vacuo* at 180° for 30 min to promote formation of estolides (intermolecular polyesters of undetermined size), the presence of which was indicated by their ir spectra. Elevation of the temperature to 270° pyrolyzed the estolides, and the dehydrated product was distilled at reduced pressure. Distillation of the acrylic acids during the dehydration process is essential to effect a disproportionation of estolide to olefinic acid and hydroxy acid as well as to minimize destruction of the liberated products by the acid catalyst. Excellent yields of isomerically pure α-alkylacrylic acids (Table II) are simply obtained. Absence of isomer IV as a possible product by isomerization of III (eq 4) was indicated by glc and nmr analysis.

Thermal dehydration of α-alkylhydracrylic acids by use of sulfuric acid as catalyst or in the absence of catalyst results in lower product yields. Dehydrations by means of sulfuric acid as catalyst are accompanied by excessive charring, while in the absence of catalyst prolonged reaction times are required.

TABLE II
α-ALKYLACRYLIC ACID PREPARATION *via* DEHYDRATION OF α-ALKYLHYDRACRYLIC ACIDS, $HOCH_2C(R)HCOOH$. YIELD AND PROPERTIES OF α-ALKYLACRYLIC ACIDS, $CH_2=C(R)COOH$

R	Registry no.	α-Alkylacrylic acid Mp or bp, °C (mm)	α-Alkylacrylic acid Yield,[a] %
Butyl	4380-88-5	111–113 (10)[b]	94
Heptyl	1118-61-8	122 (0.5)[c]	94, 70,[d] 79[e]
Dodecyl	33785-92-1	44–45	
		157 (0.2)	90
Tetradecyl	6818-50-4	55–55.8	84
Hexadecyl	6818-51-5	60–61.0	
		205–209 (0.25)	90
cis-7,8-Hexadecenyl	33780-98-2	196–197 (0.4)	90

[a] Yields determined on distilled product by glc. All products analyzed satisfactorily by glc, elemental analysis, nmr, and mass spectra. [b] Lit. bp 109–110° (10 mm): E. E. Blaise and A. Luttringer, *Bull. Soc. Chim. Fr.*, **33**, 760 (1905). [c] Lit. bp 128–134° (2 mm): Y. Yamashita, H. Kato, K. Hisano, T. Ito, and M. Hasegawa, *Kogyo Kagaka Zasshi*, **65**, 2050 (1962); *Chem. Abstr.*, **58**, 12774e (1963). [d] Uncatalyzed dehydration. [e] Sulfuric acid catalyzed dehydration.

$$\underset{\text{III}}{CH_2=\overset{R}{\overset{|}{C}}COOH} \longrightarrow \underset{\text{IV}}{R'CH=\overset{CH_3}{\overset{|}{C}}COOH} \qquad (4)$$

Experimental Section

Tetrahydrofuran, hexamethylphosphoramide, and diisopropylamine were purified as previously described.[4,5]

Paraformaldehyde was dried over phosphorus pentoxide before use.

Sodium and potassium salts of carboxylic acids were crystallized from methanol–THF, dried at 110° for 12 hr, and stored in a desiccator over phosphorus pentoxide.

Purity of methyl esters of acrylic and hydracrylic acid derivatives was examined by glc [Dow Corning 710 silicone oil (10%)].

Preparation of 2-Heptylhydracrylic Acid.—The following preparation of 2-heptylhydracrylic acid and 2-heptylacrylic acid typifies the general procedures for preparing these classes of compounds. Preparation of α-metalated carboxylate salts has been described in previous papers.[4,5]

Paraformaldehyde (8 g) was heated at 180–200° to generate

formaldehyde[14] and the formaldehyde vapors were carried by a stream of N_2 over the surface of a stirred THF solution (50 ml) of α-lithiated lithium nonanoate (3.28 g, 0.02 mol) containing 1 molar equiv of HMPA. The reaction was terminated after complete depolymerization of paraformaldehyde. The reaction solution was cooled in an ice bath and neutralized with dilute (10%) hydrochloric acid until acidic. The aqueous layer was separated and extracted with ethyl ether. To ensure complete removal of HMPA, the ether layer was extracted with four portions of dilute hydrochloric acid. The ether layer was dried and α-heptylhydracrylic acid was recovered by evaporation of solvent, yield 2.85 g (90%). The crude product was purified by crystallization from acetonitrile.

Other similarly prepared α-alkylhydracrylic acids (Table I) were purified by crystallization (solvent in parenthesis): α-dodecyl, α-tetradecyl, and α-hexadecyl (hexane); α-phenyl (ethyl alcohol). α-Butylhydracrylic acid was distilled in vacuum.

Preparation of 2-Heptylacrylic Acid.—2-Heptylhydracrylic acid (2.0 g, 0.01 mol) and phosphoric acid (one drop) were stirred in a R.B. flask (10 ml) equipped with a short-path distillation head and heated to 180° in a Wood's metal bath under vacuum (0.5 mm) for 30 min. The temperature was raised to 270° to decompose the estolides and to distil pure 2-heptylacrylic acid (head temperature, 122°), yield 1.7 g (94%). The long-chain derivatives were also recrystallized, 2-dodecylacrylic acid from hexane and 2-tetradecyl- and 2-hexadecylacrylic acids from acetone. Table II records properties and yields.

Registry No.—Formaldehyde, 50-00-0.

(14) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 397.

Investigations on Vinylogous Fries and Photo-Fries Rearrangements[1]

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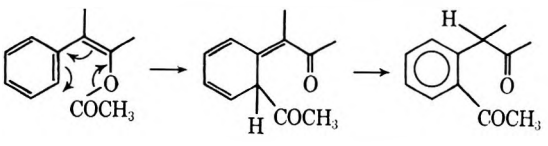
Received September 29, 1971

The photo-Fries rearrangement has been widely investigated and extended to simple vinyl esters,[2] as well as to the 1,3-dienyl acetate system, which is reported to undergo both 1,3- and 1,5-acyl migration.[3] The latter finding raises questions concerning the photoreactivity of β-phenyl vinyl acetate derivatives which may *a priori* undergo 1,3-acyl migration as a simple vinyl system or 1,5 migration to the ortho ring position, which would constitute a vinylogous Fries rearrangement (eq 1), a new reaction of potential synthetic and



(1)

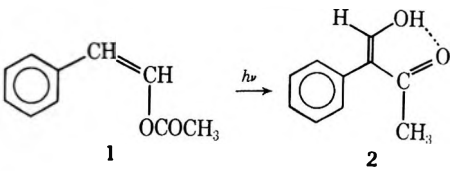
mechanistic importance. Furthermore, this prospect prompted studies on the thermal reactivity of this system which were carried out both in the presence and absence of Lewis acids.

(1) (a) Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. (b) Taken in part from the Ph.D. thesis of J. E. A., North Dakota State University.

(2) (a) V. I. Stenberg in "Organic Photochemistry," Vol. I, O. L. Chapman, Ed., Marcel Dekker, New York, N. Y., 1967, pp 127–153; (b) D. Bellus and P. Hrdlovic, *Chem. Rev.*, **67**, 599 (1967).

(3) Y. Mazur and M. Gorodetsky, *J. Amer. Chem. Soc.*, **86**, 5213 (1964).

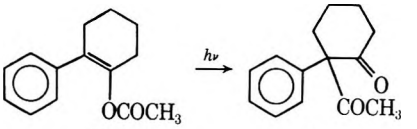
Irradiation (254 nm) of phenylacetaldehyde enol acetate (**1**), as a mixture of the cis and trans isomers,[4] in benzene or acetonitrile solution, yielded the known α-acetyl phenylacetaldehyde (**2**)[5] as the only apparent



1 2

primary photoproduct, which was determined by monitoring (glc) the reaction at less than 5% conversion with the use of an internal standard. Throughout the reaction course, no additional products were in evidence in significant amounts, although **2** was found to be photolabile and attained a maximum concentration of about 25%. The product **2**, mp 69–70°, was isolated by silica gel chromatography and characterized by elemental and spectral analysis (see Experimental Section). This result parallels the known photorearrangement of β-phenyl enamides, which also undergo 1,3-acyl migration.[6]

With the hope of enhancing the prospect of 1,5-acyl migration, the photochemistry of 1-acetoxy-2-phenylcyclohexene (**3**)[7] was also investigated, in which case (1) the phenyl and acetoxy groups are fixed in the requisite cis configuration for concerted migration, and (2) 1,3 migration is sterically more hindered. However, only the product of 1,3 migration, the previously unknown 2-acetyl-2-phenylcyclohexanone (**4**), was pro-



3 4

duced together with small amounts of 2-phenylcyclohexanone. The assignment of structure **4** was readily deduced from elemental and spectral analysis (see Experimental Section).

In the absence of Lewis acids, this system was found to be remarkably heat stable. Both **1** and **3** were quantitatively recovered after being heated in benzene or acetonitrile solution at 550° for 30 min in sealed tubes, as evidenced by glc and infrared analysis. Compound **3** remained essentially unchanged on passage through a Vycor tube packed with glass helices (1 × 25 cm) at 750°. On the other hand, when the helices were packed to a height of 50 cm, only trace amounts of starting material and volatile products were detected.

On heating **3** at 210° in benzene together with an equimolar amount of boron trifluoride etherate and an internal standard, slow decomposition occurred (about 50% in 1.5 hr); however, only trace amounts of products could be detected by glc analysis, suggestive of a polymerization process. The bulk of the material was apparently polymerized, as well, on treatment of **3** under standard Fries conditions with aluminum chlo-

(4) D. T. Witiak and B. B. Chaudhari, *J. Org. Chem.*, **30**, 1467 (1965).

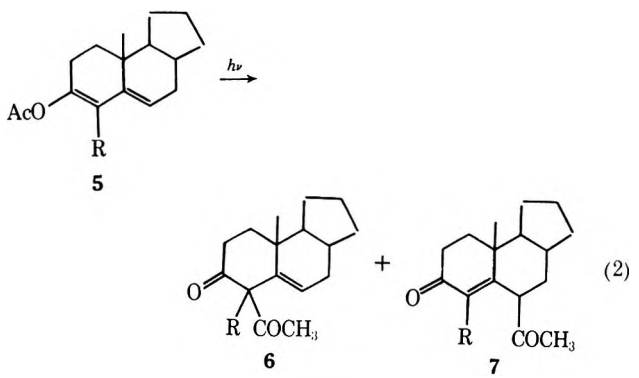
(5) H. Yasuda, *Yakugaku Zasshi*, **79**, 623 (1959); *Chem. Abstr.*, **53**, 21885e (1959).

(6) R. W. Hoffmann and K. R. Eicken, *Tetrahedron Lett.*, 1759 (1968).

(7) A. N. Kost and I. P. Sugrobova, *Vestn. Mosk. Univ., Ser. II*, **18**, 75 (1963); *Chem. Abstr.*, **59**, 7460d (1963).

ride in carbon disulfide, whereupon the only volatile product was 2-phenylcyclohexanone.

Thus, under a variety of experimental conditions involving the use of light, heat, and acid treatment, β-phenyl vinyl acetates were found to resist 1,5-acyl migration to the aromatic ring. Two possible explanations are (1) an unfavorable stereochemical relationship for concerted 1,5-migration, and (2) the requisite loss of aromaticity along this pathway (eq 1). The reported occurrence of both 1,3- and 1,5-acyl migration in a steroidal dienyl acetate system (eq 2)[3] appears to



minimize the importance of the former consideration. However, this conclusion would be invalid if **7** were actually derived from **6** by 1,3-acyl migration[8] rather than directly from **5** by 1,5 migration, a question that does not appear to be resolved.

Experimental Section

Irradiation of Phenylacetaldehyde Enol Acetate (1).—Irradiation of **1**, a mixture of the cis and trans isomers,[4] was carried out in solution at 254 nm with a low-pressure Hg immersion lamp (PCQ9G-1 lamp, supplied by Ultraviolet Products, Inc.). The solution, purged with N_2 prior to and during the irradiation, also contained an internal standard (*n*-tetradecane) for monitoring the reaction course by glc analysis.[9] Irradiation of **1**, 0.02 *M* in either benzene or acetonitrile, yielded a single product, which was photolabile and attained a maximum concentration of about 25%. The product, mp 69–70°, was obtained in 10% yield after silica gel chromatography and crystallization from ether–hexane, and was identified as 2-acetylphenylacetaldehyde (**2**), reported mp 67–68°,[5] on the basis of elemental and spectral analysis. The ultraviolet spectrum exhibited λ_{max}^{MeOH} at 310 nm (ϵ 6.65 × 10^3) and 242 (3.95 × 10^3). The infrared spectrum, obtained in chloroform, featured broad H-bonded OH absorption and strong bands at 1640, 1610, and 1605 cm^{-1}, indicative of the enolized β-dicarbonyl system. The nmr spectrum, obtained in deuteriochloroform, exhibited a sharp singlet at τ 7.85 (3 H, CH_3), a multiplet at τ 2.6 (5 H, aromatic hydrogens), a doublet at τ 1.70 (1 H, J = 6 Hz, vinyl H), and a doublet at τ −5.50 (1 H, J = 6 Hz, OH). Upon addition of D_2O, the OH resonance disappeared and the doublet at τ 1.70 was transformed into a singlet. The parent peak in the mass spectrum corresponded to the molecular ion (*m/e* 162) and the fragmentation pattern was consistent with the assignment.

Anal. Calcd for $C_{10}H_{10}O_2$: C, 74.1; H, 6.2. Found: C, 73.3; H, 6.0.[10]

Irradiation of 1-Acetoxy-2-phenylcyclohexene (3).—Irradiation of **3**,[7] prepared from 2-phenylcyclohexanone by treatment with acetic anhydride and *p*-toluenesulfonic acid,[11] was conducted as described above. In addition to small amounts of 2-phenylcyclohexanone, irradiation of **3** yielded a single product, mp 73–74°, which was obtained in 15% yield after silica gel chromatography and crystallization from ether–hexane. On the basis of elemental and spectral analysis, the product was formulated as the previously unknown compound, 2-acetyl-2-phenylcyclohexanone (**4**). The ultraviolet spectrum exhibited λ_{max}^{MeOH} at 285 nm (ϵ 340) and 260 (430), attributable to the β-phenyl carbonyl system. The infrared spectrum, obtained in chloroform, featured two closely spaced carbonyl bands at about 1710 cm^{-1}. The nmr spectrum, obtained in deuteriochloroform, exhibited a broad multiplet at τ 8.20 (4 H, C-4 and C-5 ring methylenes), a sharp singlet at τ 7.97 (3 H, CH_3), a broad multiplet at τ 7.44 (4 H, C-3 and C-6 ring methylenes), and a multiplet at τ 2.63 (5 H, aromatic hydrogens). In the mass spectrum, the base peak at *m/e* 174 is readily explicable in terms of the loss of ketene (McLafferty rearrangement) from the molecular ion (*m/e* 216), which was also present.

Anal. Calcd for $C_{14}H_{16}O_2$: C, 77.8; H, 7.5. Found: C, 78.1; H, 7.5.

Pyrolysis Experiments.—On heating at 550° for 30 min in sealed Pyrex tubes, the enol acetates **1** and **3**, 0.05 *M* in benzene or acetonitrile which also contained an internal standard (*n*-hexadecane), were recovered unchanged as evidenced by glc and infrared analysis.

A solution of 100 mg of enol acetate **3** in 100 ml of cyclohexane was passed in a slow stream of N_2 over a period of 30 min through a vertical Vycor tube packed with glass helices (1 × 25 cm) and enclosed in an oven at 750°. The enol acetate suffered only slight decomposition under these conditions. However, when the helices were packed to a height of 50 cm, only trace amounts of starting material and volatile products were detected.

Treatment of 1-Acetoxy-2-Phenylcyclohexene (3) with Lewis Acids.—Treatment of **3** with $AlCl_3$ in CS_2 under standard conditions for the Fries rearrangement[12] led primarily to nonvolatile tarry material together with small amounts of 2-phenylcyclohexanone. On heating **3** with boron trifluoride etherate, both 0.1 *M* in benzene which also contained *n*-hexadecane (internal standard), in sealed Pyrex tubes at 210°, the enol acetate reacted slowly (50% in 1.5 hr) but only trace amounts of product could be detected by glc analysis, suggestive of a polymerization process.

Registry No.—**2**, 13055-49-7; **4**, 33777-04-7.

(8) E. Baffiolini, K. Schaffner, and O. Jeger, *Chem. Commun.*, 1103 (1969); also see D. I. Schuster, G. R. Underwood, and T. P. Knudsen, *J. Amer. Chem. Soc.*, **93**, 4304 (1971).

(9) Conducted on a Varian 1740 flame ionization instrument with a 5 ft × 1/8 in. column of 3% SE-30 on 100–120 Varaport.

(10) The relatively large discrepancy in carbon (0.8) is attributed to the instability of **2**, which underwent substantial decomposition on standing at room temperature in the dark over a period of 2 weeks.

(11) H. O. House and V. Kramar, *J. Org. Chem.*, **28**, 3362 (1963).

(12) E. Miller and W. H. Hartung in "Organic Syntheses," Collect. Vol. II, A. H. Blatt, Ed., Wiley, New York, N. Y., 1943, pp 543–545.

Photochemistry of 6-Propyl-2-cyclohexenone

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In extension of previous observations[2,3] on photolysis of cyclopentenones in dilute solution, we have examined the photochemistry of several alkylcyclohexenones.[4] The results indicate that photochemical reactions of the six-membered ring compounds are much less specific; complex mixtures of products result with no single component accounting for more than a fourth or fifth of the

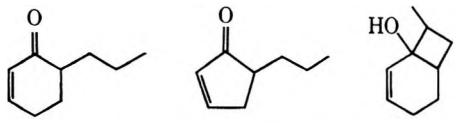
(1) Fellow of the Alfred P. Sloan Foundation and author to whom inquiries should be addressed.

(2) W. C. Agosta and A. B. Smith, III, *J. Amer. Chem. Soc.*, **93**, 5513 (1971).

(3) W. L. Schreiber and W. C. Agosta, *ibid.*, **93**, 3814 (1971).

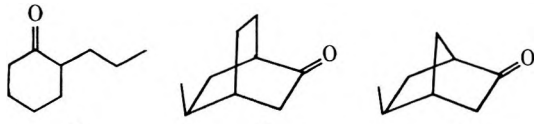
(4) Earlier investigations in this general area, dealing largely with the lumirearrangement of 4,4-dialkyl-2-cyclohexenones, have been summarized and discussed by W. G. Dauben, G. W. Shaffer, and N. D. Vietmeyer, *J. Org. Chem.*, **33**, 4060 (1968).

total. A single example suffices, and we record here observations arising from photolysis of 6-propyl-2-cyclohexenone (**1**). Preparative experiments are described after the photochemical results.

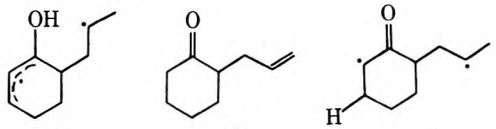


1 **2** **3**

Under irradiation conditions[5] leading to about 75% destruction of 5-propyl-2-cyclopentenone (**2**) in 6 hr, photolysis of the homologous cyclohexenone (**1**) in *tert*-butyl alcohol required 2 weeks for similar conversion and furnished a host of volatile products. Of these we have identified four. The major component (23%[6]) was recognized from its ir and 220-MHz nmr spectra as cyclobutanol **3**. The photoreduction product, 2-propylcyclohexanone (**4**, 2%[6]), was identified by comparison with authentic material. A third component was a cyclization product, *exo*-5-methylbicyclo[2.2.2]-octan-2-one (**5**, 4%[6]), the structure of which was deduced from its spectroscopic properties and analogy with the formation (44%) of its lower homolog **6** from **2**.[2] As earlier with **6**,[2] the stereochemistry of the methyl substituent in **5** was confirmed by an independent synthesis which is detailed below. Also as before,[2] we found no sign (<1%) of the endo isomer of **5** among the photoproducts and ascribe this selectivity to steric control in cyclization of the type II[7] biradical **7**, which is the presumed precursor of both **5** and **3**.



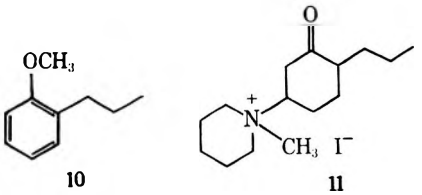
4 **5** **6**



7 **8** **9**

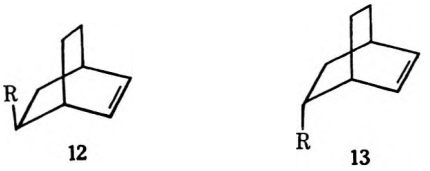
Finally we obtained a small amount of 2-allylcyclohexanone (**8**, 3%), a product representing transfer of unsaturation from ring to side chain. This may be the result of abstraction of hydrogen from the methyl group of **7** by the β carbon atom. Alternatively, the initial abstraction could be by the β carbon atom to form **9**, and this intermediate could then undergo hydrogen transfer from methyl to the α carbon atom. The former pathway seems more likely, since **7** is already implicated in formation of **3** and **6**, although there are known examples of direct hydrogen abstraction by the β carbon atom of unsaturated ketones.[2,3,8]

Starting ketone **1** was prepared from *o*-propylanisole (**10**) by Birch reduction followed by treatment with acid. The desired product was purified through the methiodide **11** of its Michael adduct with piperidine, all according to a procedure developed[9] earlier for closely related cyclohexenones. Pyridine-catalyzed elimination of *N*-methylpiperidine from **11** led to **1**. The corresponding saturated ketone **4** was available on catalytic hydrogenation of **1**.



10 **11**

Synthesis of bicyclic ketone **5** began with the Diels–Alder adduct[10] of methyl acrylate and 1,3-cyclohexadiene. Methoxide-catalyzed equilibration of the adduct gave a 1:2 mixture of exo (**12a**) and endo (**13a**) esters, as reported.[10] Saponification then furnished a mixture of the carboxylic acids **12b** and **13b**, which were separated by selective formation from **13b** of the iodolactone.[11] This left unchanged the desired exo acid **12b**, which was isolated and purified. Diazomethane esterification of **12b** yielded only **12a**, the configuration of which had been previously assigned[10] on the basis of nmr arguments and the base-catalyzed equilibration mentioned above. Acid **12b** was now reduced with lithium aluminum hydride to alcohol **12c**, and this was converted to the tosylate **12d** and again reduced with hydride to form hydrocarbon **12e**. The overall yield from **12b** to **12e** was 85%. Hydroboration[12] of the double bond of **12e**, followed by dichromate oxidation, provided a mixture of **5** and **14**. This mixture was reduced directly to the related alcohols, which were partially separated by preparative vpc of the derived trimethylsilyl ethers.[13] A pure ether **15a** was isolated and converted on acid hydrolysis to a single alcohol **15b**.



12 **13**

a, R = $COOCH_3$
b, R = COOH
c, R = CH_2OH
d, R = CH_2OTs
e, R = CH_3

14 **15**

a, R = $OSi(CH_3)_3$
b, R = H

(5) Complete details are given in ref 2; a uranium glass filter was used to prevent secondary photolysis of products which were saturated ketones.

(6) Yields are approximate only and are based on vpc analysis of the crude photolysate.

(7) J. G. Calvert and J. N. Pitts, Jr., "Photochemistry," Wiley, New York, N. Y., 1966, Chapter 5; P. J. Wagner, *Accounts Chem. Res.*, **4**, 168 (1971).

(8) D. Bellus, D. R. Kearns, and K. Schaffner, *Helv. Chim. Acta*, **52**, 971 (1969), and references cited therein.

(9) G. Stork and W. N. White, *J. Amer. Chem. Soc.*, **78**, 4604 (1956).

(10) R. J. Ouellette and G. E. Booth, *J. Org. Chem.*, **30**, 423 (1965).

(11) W. R. Boehme, E. Schipper, W. G. Scharpf, and J. Nichols, *J. Amer. Chem. Soc.*, **80**, 5488 (1958). In contrast to this earlier report, under our conditions the exo acid did not react in base with iodine.

(12) G. Zweifel and H. C. Brown, *Org. React.*, **13**, 1 (1963).

(13) L. Birkofer and R. Ritter, *Angew. Chem., Int. Ed. Engl.*, **4**, 417 (1965); J. F. Klebe, H. Finkbeiner, and D. M. White, *J. Amer. Chem. Soc.*, **88**, 3390 (1966).

Jones oxidation[14] of this alcohol gave **5**, identical with the photolysis product from **1** by comparison of their vpc retention times and rather complex ir and 220-MHz nmr spectra.

Experimental Section

Materials and Equipment.—Solvent for the photochemical experiments was Matheson Coleman and Bell *tert*-butyl alcohol (chromatoquality). All vpc was done using a Varian Aerograph Model 700 Autoprep or Model A-90-P3 with one of the following columns: A, 30% QF-1, 10 ft × $^3/_8$ in.; B, 30% Carbowax, 10 ft × $^3/_8$ in.; E, 30% QF-1, 50 ft × $^1/_4$ in.; F, 30% SE-30, 10 ft × $^3/_8$ in. The column oven was operated at 90–190°, and helium carrier gas flow rate was 100–120 ml/min. Unless otherwise noted both ir and nmr spectra were obtained for CCl_4 solutions, the former on a Perkin-Elmer Model 237B spectrophotometer and the latter on a Varian Model HR-220 (220 MHz) spectrometer. Melting points are corrected. Photochemical experiments were carried out with a Hanovia Model L mercury lamp (No. 679A-36) in a quartz immersion well and using a uranium glass (Corning No. 3320) filter.

Photolysis of 6-Propyl-2-cyclohexenone (1).—A solution of 400 mg of **1** in 400 ml of *tert*-butyl alcohol was flushed with nitrogen for 15 min and then irradiated for 14 days under nitrogen with magnetic stirring. At the end of this period the mixture was poured into water and extracted with pentane. The pentane was washed with water, dried, and removed to give 308 mg of yellow oil. Analytical vpc on columns B and F indicated the presence of at least 18 products, four of which accounted for 32%[6] of the volatile material. These were isolated and identified. The data are given below in the order of elution from column B; the ratios of the four products were 1:1.11:10:1.74.

The first product was shown to be 2-propylcyclohexanone (**4**) by comparison of its ir spectrum and vpc retention time with those of a sample prepared by hydrogenation of **1** in methanol over palladium on carbon. A semicarbazone of the latter sample was prepared, mp 118–119°, (lit.[15] mp 116–118°, 118–121°, 119–120°), as well as a 2,4-dinitrophenylhydrazone, mp 150–151.5° (lit.[15] mp 153–154°).

The second product was shown to be 2-allylcyclohexanone (**8**). The ir spectra and melting points of the 2,4-dinitrophenylhydrazones derived from the photolysis product and from an authentic[16] sample of **8** were identical [mp 149–151°, mmp 149–151° (lit.[16] mp 149–150°)].

Spectroscopic data established that the third product was 8-methylbicyclo[4.2.0]oct-2-en-1-ol (**3**): ir 3610 (m), 3410 (m), 3010 (m), 1375 (m), 1270 (m), 1220 (m), 1112 (s), 1080 (s), 1025 (m), 995 (m), 940 cm^{-1} (m); nmr δ 0.73–1.27 (m), 1.12 (d, J = 7 Hz), 4 H, 1.32–2.73 (broad m, 8 H), 5.45–5.97 (m, 2 H).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.05; H, 10.11.

The fourth product was identified as 5-methylbicyclo[2.2.2]-octan-2-one from its spectra: ir 2950 (s), 2910 (sh), 2860 (s), 1730 (vs), 1470 (m), 1450 (m), 1400 (m), 1370 (m), 1218 (m), 1075 cm^{-1} (m); nmr δ 1.10 (d, J = 7 Hz, 3 H), 1.20 (m, 1 H), 1.51 (m, 1 H), 1.64–2.27 (m, 9 H); mass spectrum m/e 138.10409 (M^+) (calcd for $C_9H_{14}O$: m/e 138.10446). This assignment, along with the exo stereochemistry (see **5**), was confirmed by establishing the identity of this photoproduct with the synthetic ketone described below. The two samples gave identical complex ir and 220-MHz nmr spectra and had identical vpc retention times.

6-Propyl-2-cyclohexenone (1).—To a solution of 10.0 g of the anisol **10**[17] in 50 ml of ether and 150 ml of dry liquid ammonia was added 2.00 g of lithium ribbon. The mixture was stirred rapidly for 2 hr and then 18.5 ml of absolute ethanol was added. After 1 hr the blue color had disappeared and the ammonia was allowed to evaporate. Water was added with caution, and the mixture was extracted with ether. Removal of the ether left 10.0 g of oil which was treated with 15 ml of 10% HCl and 50 ml of methanol and then heated at reflux for 1 hr. This mixture was then added to water and extracted with ether. The ether solution was washed with saturated $NaHCO_3$ and dried; the solvent was removed through a Vigreux column to leave 8.86 g of liquid which could be purified directly by preparative vpc to give **1**. Alternatively, the crude product was converted to **11** (mp 183–184° from *n*-butyl alcohol) according to the procedure of Stork.[9] Treatment of **11** with pyridine[9] gave **1**. Vpc-purified material was analytically pure: ir 3030 (w), 2955 (s), 2930 (s), 2870 (s), 2725 (w), 1660 (s), 1620 (w), 1380 cm^{-1} (s); nmr δ 0.92 (t, J = 6 Hz, 3 H), 1.32 (m, 3 H), 1.74–2.34 (m, 4 H), 2.04 (m, 2 H), 5.84 (dt, J_1 = 10, J_2 = 2 Hz, 1 H), 6.77 (dt, J_1 = 10, J_2 = 2 Hz, 1 H).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.38; H, 10.37.

***exo*-Bicyclo[2.2.2]oct-2-ene-5-carboxylic Acid (12b).**—A mixture of **12b** and **13b** was prepared as previously described.[10,11] A 34.0-g sample of this mixture was dissolved in 344 ml of methanol, neutralized with 8.95 g of NaOH, and treated with 344 ml of 5% aqueous $NaHCO_3$. To this solution was added at room temperature over 1 hr with stirring a solution of 103.5 g of KI and 56.6 g of iodine in 344 ml of water. After 2 hr sufficient saturated aqueous $NaHSO_3$ was added to reduce all excess iodine, and the iodolactone was extracted into ether. This yielded 38.7 g of iodolactone (mp 72–74.5° from hexane). The aqueous reaction mixture was now acidified and extracted with ether which was washed and dried. This furnished 9.74 g of **12b**, mp 48–50° from pentane or after sublimation (lit.[11] mp 46–47°): ir 3500–2400 (broad), 3040 (s), 2940 (s), 2860 (s), 1705 (vs), 1410 (m), 1225 (s), 690 cm^{-1} (s).

Anal. Calcd for $C_9H_{12}O_2$: C, 71.02; H, 7.95. Found: C, 70.95; H, 7.92.

A 50-mg sample of **12b** was treated with excess CH_2N_2 in ether. Removal of solvent left an oil which by vpc analysis was shown to contain only one component. Preparative vpc on column B gave a liquid which was shown to be **12a** by comparison of its vpc retention time and ir spectrum with those of authentic **12a**.[10]

5-*exo*-Hydroxymethylbicyclo[2.2.2]oct-2-ene (12c).—To a solution of 2.26 g (59.4 mmol) of $LiAlH_4$ in 100 ml of ether was added dropwise at room temperature over 1 hr 6.26 g (39.7 mmol) of **12b** in 50 ml of ether. The mixture was heated at reflux for 22 hr and then quenched[18] with 2.3 ml of water, 2.3 ml of 15% aqueous NaOH, and 6.9 ml of water. Subsequent work-up gave 5.53 g (97%) of **12c**, which was purified by preparative vpc on column A: ir 3635 (m), 3335 (broad), 3045 (m), 2945 (s), 3460 (s), 1625 (w), 1055 (m), 1030 (m), 670 cm^{-1} (s).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.18; H, 10.31.

5-*exo*-Methylbicyclo[2.2.2]oct-2-ene (12e).—A 5.68-g sample of alcohol **12c** was converted to the tosylate with *p*-toluenesulfonyl chloride in pyridine in the usual fashion (10.77 g, 89%). This crude tosylate was dissolved in 60 ml of ether and added dropwise over 30 min to a solution of 20 g of $LiAlH_4$ in 100 ml of ether. The resulting solution was heated at reflux for 28 hr and then worked up as described for **12c** above.[18] Removal of solvent left 4.42 g (99%) of oil, which by vpc on column B was a single component. Preparative vpc gave pure **12e** as a liquid: ir 3045 (m), 2950 (s), 2860 (s), 1615 (w), 1465 (m), 1445 (m), 1370 (m), 1362 (m), 835 (m), 680 cm^{-1} (s); nmr δ 0.84 (m, 1 H), 0.94–1.63 (m), 1.01 (d, J = 7 Hz), 8 H, 1.31 (m, 1 H), 2.14 (m, 1 H), 2.42 (m, 1 H), 6.12 (dd, J_1 = J_2 = 8 Hz, 1 H), 6.32 (dd, J_1 = J_2 = 8 Hz, 1 H).

Anal. Calcd for C_9H_{14}: C, 88.45; H, 11.55. Found: C, 88.40; H, 11.42.

5-*exo*-Methylbicyclo[2.2.2]octan-2-one (5).—To a solution of 419 mg of $LiAlH_4$ in 15 ml of ether was added 2.00 g of olefin **12e**. The solution was cooled to 0° and 1.20 ml of boron trifluoride etherate in 2 ml of ether was added dropwise. The mixture was stirred at 0° for 15 min and then at room temperature for 2 hr. The reaction was quenched with 1.2 ml of water, and the resulting solution was treated dropwise with 3.57 g of $Na_2Cr_2O_7$ in 2.64 ml of concentrated H_2SO_4 and 14.4 ml of water over 1 hr at room temperature. After 2 hr more, water was added and the product was extracted into ether. Removal of ether

(14) A. Bowers, T. G. Halsall, E. R. H. Jones, and A. J. Lemin, *J. Chem. Soc.*, 2548 (1953); C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(15) E. A. Braude and J. A. Coles, *J. Chem. Soc.*, 2014 (1950), and references cited therein.

(16) G. Opitz, H. Mildenberger, and H. Suhr, *Justus Liebigs Ann. Chem.*, **649**, 47 (1961).

(17) This ether was prepared from *o*-propylphenol according to the method of G. N. Vyas and N. M. Shah: "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 836.

(18) V. M. Mićović and M. L. J. Mihailović, *J. Org. Chem.*, **18**, 1140 (1953).

after washing and drying left 2.12 g (94%) of oil, which from ir and nmr evidence appeared to be a mixture of ketones **5** and **14**. A solution of 2.02 g of this mixture of ketones in 20 ml of ether was reduced with $LiAlH_4$ in the usual way to give 1.91 g (93%) of a solid showing hydroxyl but not carbonyl absorption in the ir. To 1.79 g of this solid was added 3.5 ml of bis(trimethylsilyl)-acetamide,[13] and the mixture was allowed to stand for 19 hr. The product was extracted into pentane, washed with water, and dried. There was recovered 2.22 g (82%) of a liquid showing no hydroxyl absorption in the ir. Vpc on column E gave a partial separation of these ethers into three components in the ratios 1:2:1. The third component was collected and shown to be homogeneous on reinjection. Hydrolysis of this ether in 2 *M* aqueous HCl followed by Jones oxidation[14] of the alcohol **15b** gave a single ketone (**5**). This was purified by vpc on column B and was identical with the photoproduct described above.

Registry No.—**1**, 33777-32-1; **3**, 33777-33-2; **5**, 33890-38-9; **12c**, 33780-85-7; **13e**, 14926-88-6.

Acknowledgments.—It is a pleasure to thank Mr. S. T. Bella for microanalyses, Miss Luz Catan for technical assistance, and Mr. Peter Ziegler for 220-MHz nmr spectra.

Synthesis of a Hydroxyxanthone Dicarboxylic Acid, Cassiaxanthone. Reactions of γ-Resorcylic Acid with Phenols

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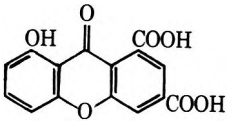
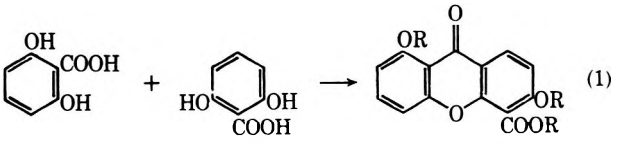
Cassiaxanthone (**1**)[1] and cassiolin (pinselin)[2] (**4h**) are, to our knowledge, the only xanthones from *Cassia*



1

species so far reported. It is interesting that these both have a carboxylic acid function on the xanthone nucleus. None of the other xanthones isolated from higher plants are of this type.[3]

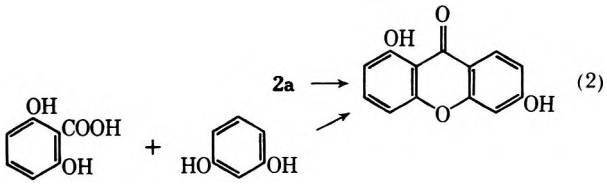
In the course of investigating possible routes to the synthesis of cassiaxanthone, γ-resorcylic acid was condensed with a number of phenols, using either polyphosphoric acid (PPA)[4] or $POCl_3$ and $ZnCl_2$.[5] These reactions generally afforded, besides or instead of the expected xanthone, a mixture of other products. We have examined this mixture and found that the main components are (a) 1,6-dihydroxyxanthone-5-carboxylic acid (**2a**) resulting from self-condensation (eq 1); (b) 1,6-dihydroxyxanthone resulting from self-condensation and subsequent decarboxylation or from condensation of γ-resorcylic acid with resorcinol resulting



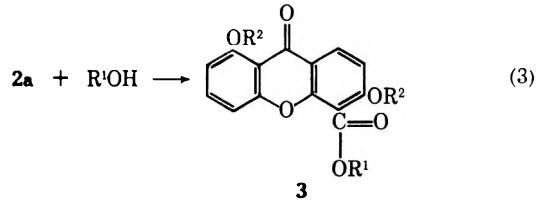
(1)

2a, R = H
b, R = Me

from decarboxylation (eq 2); (c) esters of **2a** (**3a**, **3c**, **3e**) (eq 3); and (d) polymeric products.



(2)



(3)

3

Compd	R^1	R^2
a	Phenyl	H
b	Phenyl	Me
c	3,5-Methylphenyl	H
d	3,5-Methylphenyl	Me
e	Ethyl	H
f	Ethyl	Me

The proportion of the various products obtained is shown in Table I. Most of the crude product (see last column), not accounted for in other columns, was an insoluble material which remained at the origin of a thin layer chromatogram, and is probably polymeric.

It is apparent that the temperature, the reagent, and the nature of the participating phenol all influence the results.

Attempted condensation of γ-resorcylic acid with phenol at lower temperatures yielded only a small amount of the expected product, 1-hydroxyxanthone. The two main products were the result of self-condensation of γ-resorcylic acid. One was 1,6-dihydroxyxanthone-5-carboxylic acid. The second was a compound of mp 196–197°. Preliminary examination suggested that this might be 1,8-dihydroxyxanthone formed by condensation ortho to both hydroxyl groups of resorcinol.[6] This possibility was ruled out by nmr spectrum which showed a peak at δ 8.41 for a proton peri to the xanthone carbonyl.

Clues to the structure of the compound were afforded by its ir spectrum and that of its methylation product, and by its mass spectrum. In the ir spectrum of the methylated product, in contrast to that of the parent compound, there was a peak at 1760 cm^{-1} suggesting the presence of a phenyl ester grouping, the carbonyl

(1) M. S. R. Nair, T. C. McMorris, and M. Anchel, *Phytochem.*, **9**, 1153 (1970).

(2) C. E. Moppett, *J. Chem. Soc. D*, 423 (1971).

(3) J. Carpenter, H. O. Locksley, and F. Scheinmann, *Phytochem.*, **8**, 2013 (1969).

(4) F. Uhlig and H. R. Snyder, *Advan. Org. Chem.*, **1**, 35 (1960).

(5) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 880.

(6) Analytical values for C, H, and O were in good agreement. The R_f was higher than that of 1,6-dihydroxyxanthone. Comparison of the melting point and uv spectrum with those reported in the literature[7-10] for samples prepared by a different method did not permit an unequivocal conclusion as to identity.

(7) A. Baeyer, *Justus Liebigs Ann. Chem.*, **372**, 80 (1910).

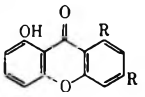
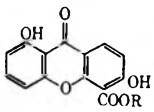
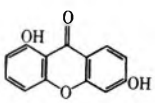
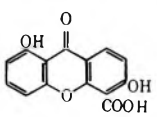
(8) D. L. Dreyer, Ph.D. Thesis, University of Washington, 1960. University Microfilms, Inc., Ann Arbor, Mich.

(9) P. Yates and G. H. Stout, *J. Amer. Chem. Soc.*, **80**, 1691 (1958).

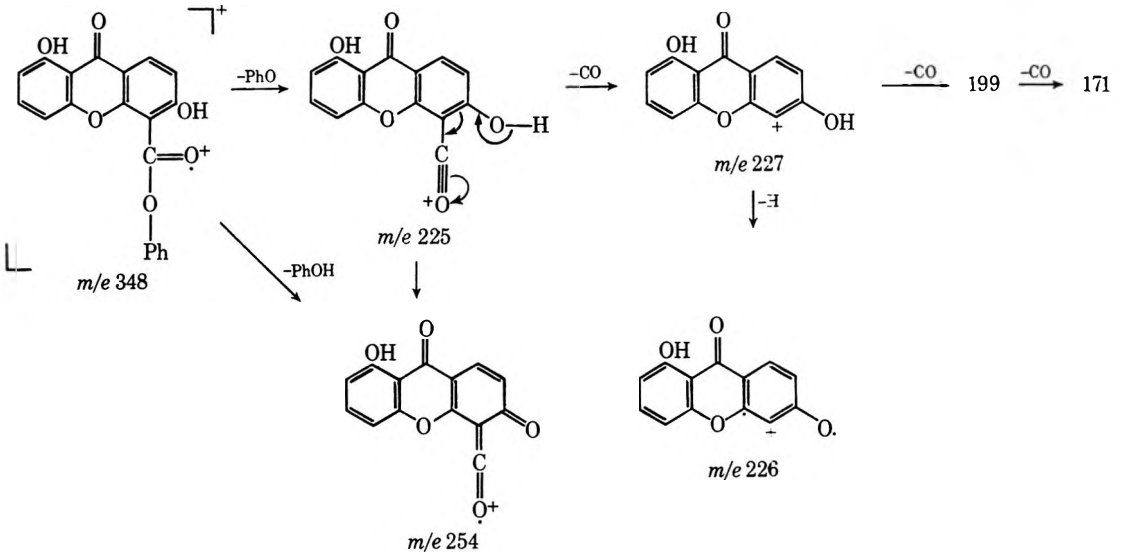
(10) O. R. Gottlieb, M. Taveira Magalhaes, M. Ottoni da Silva Pereira, A. A. Lins Mesquita, D. de Barros Correa, and G. G. De Oliveira, *Tetrahedron*, **24**, 1601 (1968).

TABLE I

YIELD OF PRODUCTS (g) FROM CONDENSATION OF γ-RESORCYLIC ACID (0.01 *M*, 1.54 g) WITH PHENOLS (0.01 *M*)

Phenol	Reagent (A, $POCl_3$–$ZnCl_2$; B, PPA)	Temp (°C), time (hr)	 R	g	 R	g	 g	 g	Wt of crude product, g
Phenol	A	30, 160	H	0.02	Ph	0.12	Trace	0.45	0.9
Phenol	A	60–80, 2	H	0.024	Ph	0.29	Trace	0.25	1.3
Phenol	A	100–110, 2							1.2
Xylenol	A	60–80, 2	Me	0.19	3,5-Dimethylphenyl	0.23	Trace	Trace	2.4
Resorcinol	A	60–80, 2					0.73		1.2
γ-Resorcylic acid	A	30, 160						1.85	2.2
γ-Resorcylic acid	A	60–80, 2					Trace	1.56	1.9
γ-Resorcylic acid	A	100–110, 2					Trace	Trace	1.6
Phenol	B	140, 4	H	0.035	Ph	Trace	0.23	Trace	0.64
Phenol	B	100, 5	H	0.025	Ph	0.015	0.175	0.035	0.52
Phenol	B	75, 5	H	0.02	Ph	0.155	0.065	0.110	0.45
Phenol	B	40, 5	H	0.01	Ph	Trace	Trace	0.155	0.34
Resorcinol	B	140, 4					0.75		1.2
γ-Resorcylic acid	B	140, 4					0.6	Trace	0.95
γ-Resorcylic acid	B	40, 7					0.04	0.8	0.98
Xylenol	B	140, 4	Me	0.85			0.115		1.3

SCHEME I



group of which was bonded to hydroxyl in the parent compound. The mass spectrum, M^+ 348, suggested that the compound might be **3a**, the phenyl ester of **2a**. The fragmentation pattern, peaks at *m/e* 348, 255, 254, 227, 226, 199, 171, and 94 was interpreted as shown in Scheme I. In confirmation of this formulation, hydrolysis yielded **2a** and phenol.

An analogous by-product in the reaction of γ-resorcylic acid with 3,5-dimethylphenol was **3c**. With resorcylic acid itself, besides the free acid **2a** and a polymeric product, a very small amount of the ethyl ester (**3e**) was obtained, presumably formed during the working up procedure which involved extraction with ethanol and chloroform.[11] The corresponding methylated products of **3a**, **3c**, and **3e** in each instance revealed the ester peak, not present in the ir spectrum of the parent compound.

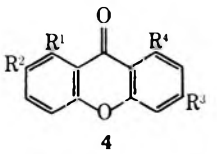
In general, at lower temperatures, larger proportions of **2a** or **3** were obtained, while at higher temperatures the product was mostly polymer or 1,6-dihydroxyxanthone. Evidently, high temperature favors decarboxylation either of the γ-resorcylic acid itself or of **2a**. When γ-resorcylic acid alone is subjected to condensing conditions, the main product at low temperature is **2a**, while at high temperatures it is polymer.

For the synthesis of cassiaxanthone, γ-resorcylic acid was condensed with 3,5-dimethylphenol. The reaction proceeded smoothly under the usual conditions[4,5] to give 1-hydroxy-6,8-dimethylxanthone (**4a**). The structure of this compound was confirmed by analysis and by spectral data. The uv absorption spectrum, max 232, 251, 286, 302, 358 nm, is typical of hydroxyxanthones[12] and resembles very closely that of 1-hydroxyxanthone itself.[13] The ir showed a peak at 1642 cm^{-1} for chelated

(11) The same product may well have been formed in the other reactions, but, since it has the same R_f as **2a** and **2b**, it could have gone undetected.

(12) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," Macmillan, New York, N. Y., 1964, p 158.

(13) A. A. Lins Mesquita, D. DeBarros Correa, O. R. Gottlieb, and M. Taveira Magalhaes, *Anal. Chim. Acta*, **42**, 311 (1968).



4

Compd	R^1	R^2	R^3	R^4
a	OH	H	Me	Me
b	OMe	H	Me	Me
c	OMe	H	COHO	Me
d	OMe	H	COOH	COOH
e	OMe	H	COOMe	Me
f	OMe	H	COOMe	COOMe
g	OH	H	COOH	Me
h	COOMe	OH	Me	OH

carbonyl and the nmr showed signals at δ 2.35 and 2.77 for six methyl protons.

For oxidation, **4a** was converted to the methyl ether (**4b**). With $KMnO_4$ under suitable conditions, this afforded a mixture of the mono- and diacids (**4c** and **4d**) in good yield. Owing to poor solubility, the acid mixture could not be separated. Hence, it was esterified. The resulting mixture, separated by preparative tlc, yielded the mono- and diesters (**4e** and **4f**) in about equal amounts. The uv spectra of the esters showed the expected xanthone maxima. Both showed ester peaks in the ir at 1730 cm^{-1} and carbonyl absorption at 1675 and 1670 cm^{-1}, respectively. In the nmr, **4e** showed signals at δ 2.93 for three protons of the C_8 methyl group, 3.97 for three protons of the ester methyl group, and at 4.02 for three protons of the methoxyl carbon. The diester, **4f**, showed a signal at 3.98 for six protons of the methyl ester groups and at 4.05 for three methoxyl protons. It was identical in all respects (melting point, uv, ir, and R_f on tlc) with the completely methylated product prepared from cassiaxanthone.

Alkaline hydrolysis of **4e** and **4f** yielded the corresponding acids, **4c** and **4d**, in good yield. Treatment of **4e** and **4f** with HBr yielded the hydroxy acid **4g** and the hydroxy diacid 1 (cassiaxanthone), respectively. The synthetic product was identical with natural cassiaxanthone in all respects.

Experimental Section[14]

The following represent typical procedures. Data for the new compounds are reported at the end.

Condensation of γ-Resorcylic Acid with Phenols.—The reactions were carried out with either PPA or $POCl_3$–$ZnCl_2$ at a number of different temperatures.

Procedure A.—To a mixture of γ-resorcylic acid (1.54 g, 0.01 *M*), phenol (0.94 g, 0.01 *M*), and freshly fused and powdered anhydrous $ZnCl_2$ (4.5 g) was added $POCl_3$ (10.5 ml). The mixture was heated around 70° with stirring for 2 hr and then poured into crushed ice. The orange red solid (1.3 g) was dissolved in a minimum volume of 1:1 chloroform–ethanol and chromatographed over silica gel (40 g). Elution with benzene–Skelly-B gave 1-hydroxyxanthone: mp 148–149° (40 mg); uv max 229, 250, 279, 295, 335, 362 nm [lit. mp 147–148°;[15] uv max 230, 250, 282, 298 (sh), 362 nm[13]]. Elution with benzene followed by benzene–chloroform yielded **3a**, mp 196–197° (290 mg). The chloroform fraction furnished traces of 1,6-dihydroxyxanthone: mp 248°; uv max 229, 247, 265, 304, 352 nm (lit. mp 242–243°,[13] 248–250°;[8] uv max 231, 252, 265, 306, 353 nm[13]). Finally, elution with 25% methanol–chloroform yielded **2a**, mp 228–230° (250 mg).

When the reaction was carried out at higher temperatures, mostly polymeric product was obtained.

Procedure B.—A powdered mixture of 0.01 *M* γ-resorcylic acid (1.54 g) and phenol (0.94 g) was added to PPA (freshly prepared from 5 ml of H_3PO_4 and 8 g of P_2O_5), heated with stirring around 75° for 5 hr, and then poured into crushed ice. The brownish yellow solid (450 mg) was taken up in a minimum volume of ethanol–chloroform and chromatographed over silica gel (20 g). Elution with benzene gave 1-hydroxyxanthone (20 mg) and the benzene–chloroform fraction gave **3a** (155 mg). Further elution with chloroform yielded 1,6-dihydroxyxanthone (65 mg), and the chloroform–methanol (5:1) fraction furnished **2a** (110 mg).

Methylation.—Methylation of hydroxyxanthones, including **3a**, was carried out by refluxing with $(CH_3)_2SO_4$ and anhydrous K_2CO_3 in acetone for 12–15 hr. The methylated products were crystallized from ethanol or aqueous ethanol.

Hydrolysis.—On hydrolysis with 10% NaOH at room temperature, **3a** (45 mg) yielded **2a** (20 mg) and phenol (7 mg). Similarly, hydrolysis of **3c** (60 mg) furnished **2a** (30 mg) and 3,5-dimethylphenol (10 mg).

1,6-Dihydroxyxanthone-5-carboxylic Acid (2a).—**2a** was obtained as pale yellow crystals from acetone: mp 228–230°; uv max 225 nm (ϵ 17,000), 245 (sh) (18,300), 256 (20,000), 295 (8500), 310 (9500), and 355 (10,700); in 10% NaOH, uv max 240 (ϵ 21,000), 265 (19,000), 375 (15,500) nm; ir max 3500–2800 (bonded OH), 1675 (chelated COOH), 1647 (chelated C=O), 1608, 1481 (aromatic C=C), 1266, 1235, 1075, 1060 (=COC–), 813, 792, 715, 678 cm^{-1}; nmr (acetone-d_6 and DMSO-d_6) δ 6.77 (d, 1, J = 8.5 Hz, C_2 H), 6.93 (d, 1, J = 8.5 Hz, C_4 H), 7.03 (d, 1, J = 9 Hz, C_7 H), 7.58 (t, 1, J = 8.5 Hz, C_3 H), 8.18 (d, 1, J = 9 Hz, C_8 H).

Anal. Calcd for $C_{14}H_8O_6$: C, 61.77; H, 2.96; O, 35.27; mol wt, 272. Found: C, 61.58; H, 3.06; O, 35.46; mol wt, 273 (by depression of vapor pressure).

1,6-Dimethoxyxanthone-5-carboxylic Acid Methyl Ester (2b).—**2b** was obtained as white crystals from aqueous ethanol: mp 160°; uv max 225 nm (ϵ 34,000), 245 (sh) (29,000), 290 (19,000), 341 (13,400); ir max 1740 (ester C=O), 1665 (xanthone C=O), 1623, 1600, 1480 (aromatic C=C), 1290, 1272, 1242, 1105, 1071 (=COC–), 797 704, 684 cm^{-1}; nmr δ 3.97 (s, 3, $COOCH_3$), 4.02 (s, 6, Ar OCH_3), 6.79 (d, 1, J = 8.5 Hz, C_2 H), 6.97 (d, 2, J = 8.5 Hz, C_4 H and C_7 H), 7.57 (t, 1, J = 8.5 Hz, C_3 H), 8.35 (d, 1, J = 9 Hz, C_8 H).

Anal. Calcd for $C_{17}H_{14}O_6$: C, 64.96; H, 4.49; O, 30.55. Found: C, 65.07; H, 4.56; O, 30.10.

1,6-Dihydroxyxanthone-5-carboxylic Acid Phenyl Ester (3a).—**3a** was obtained as pale yellow crystals from ethanol: mp 196–197°; uv max 225 nm (ϵ 27,800), 252 (28,000), 295 (11,700), 303 (11,750), 355 (10,600); ir max 3300–2700, 1653, 1613, 1600, 1587, 1481, 1261, 1235, 1072, 1058, 810, 788, 760, 750, 730, 718, 678 cm^{-1}; nmr δ 6.83 (d, 1, J = 9 Hz, C_2 H), 7.58 (t, 1, J = 8.5 Hz, C_3 H), 6.9–7.5 (m, 7, Ar H), 8.35 (d, 1, J = 9 Hz, C_8 H), 12.02 (s, 1, OH), 12.41 (s, 1, OH).

Anal. Calcd for $C_{20}H_{12}O_6$: C, 68.96; H, 3.47; O, 27.56; mol wt, 348. Found: C, 68.55; H, 3.44; O, 28.02; mol wt, 348 (by mass spectrum), 339 (by depression of vapor pressure).

The diacetate had mp 203–205°; nmr (DMSO-d_6) δ 2.33 (s, 3), 2.37 (s, 3), (2, $OCOCH_3$).

1,6-Dimethoxyxanthone-5-carboxylic Acid Phenyl Ester (3b).—**3b** was obtained as white crystals from aqueous ethanol: mp 208–210°; uv max 224 nm (ϵ 35,800), 245 (30,000), 290 (16,800), 342 (11,200); ir max 1760 (COOPh), 1667 (xanthone C=O), 1626, 1600, 1481 (aromatic C=C), 1290, 1275, 1242, 1108, 1067, 795, 747, 687 cm^{-1}; nmr δ 4.03 (s, 6, Ar OCH_3), 6.81 (d, 1, J = 9 Hz, C_2 H), 7.58 (t, 1, J = 8.5 Hz, C_3 H), 8.4 (d, 1, J = 9 Hz, C_8 H), 6.9–7.45 (m, 7, Ar H).

Anal. Calcd for $C_{22}H_{16}O_6$: C, 70.21; H, 4.29; O, 25.51; mol wt, 376. Found: C, 70.20; H, 4.25; O, 25.60; mol wt, 384 (by depression of vapor pressure).

1,6-Dihydroxyxanthone-5-carboxylic Acid 3,5-Dimethylphenyl Ester (3c).—**3c** was obtained as crystals from ethanol: mp 185–186°; uv max 225 nm (ϵ 27,400), 252, (27,500), 295 (12,200), 303 (12,450), 355 (11,800); ir max 1672 (chelated ester C=O), 1653 (xanthone C=O), 1613, 1580, 1480 (aromatic), 1238, 1075, 810, 762, 676 cm^{-1}; nmr δ 2.4 (s, 6, Ar CH_3), 6.76 (d, 1, J =

(14) All uv spectra were taken in ethanol on a Cary Model 11 spectrophotometer. The ir spectra were taken in KBr pellets on a Perkin-Elmer Model 21 spectrometer. The nmr spectra were recorded on a Varian A-60A spectrometer, using $CDCl_3$ as solvent (unless otherwise stated) and TMS as internal standard. The melting points were determined on a Kofler hot stage and are uncorrected.

(15) R. P. Mull and F. F. Nord, *Arch. Biochem.*, **4**, 419 (1944).

8.5 Hz, C_2 H), 6.8–7.1 (m, 5, Ar H), 7.53 (t, 1, J = 8.5 Hz, C_3 H), 8.35 (d, 1, J = 9 Hz, C_8 H), 12.05 (s, 1, OH), 12.38 (s, 1, OH).

Anal. Calcd for $C_{22}H_{16}O_6$: C, 70.21; H, 4.29; O, 25.51. Found: C, 70.20; H, 4.38; O, 25.57.

1,6-Dimethoxyxanthone-5-carboxylic Acid 3,5-Dimethylphenyl Ester (3d).—**3d** was obtained as crystals from aqueous ethanol: mp 235–236°; uv max 222 nm (ϵ 36,000), 245 (30,500), 290 (17,000), 341 (11,500); ir max 1754 (ester C=O), 1669 (xanthone C=O), 1623, 1605, 1480, 1290, 1274, 1242, 1103, 1072, 797, 681 cm^{-1}; nmr δ 2.37 (s, 6, Ar CH_3), 4.02 (s, 6, Ar OCH_3), 6.81 (d, 1, J = 9 Hz, C_2 H), 6.85–7.25 (m, 5, Ar H), 7.6 (t, 1, J = 8.5 Hz, C_3 H), 8.39 (d, 1, J = 9 Hz, C_8 H).

Anal. Calcd for $C_{24}H_{20}O_6$: C, 71.28; H, 4.99; O, 23.74. Found: C, 71.31; H, 5.05; O, 23.85.

1,6-Dihydroxyxanthone-5-carboxylic Acid Ethyl Ester (3e).—**3e** was obtained as crystals from ethanol: mp 160°; uv max 225 nm (ϵ 23,500), 243 (sh) (24,600), 254 (26,800), 295 (10,200), 304 (9800), 355 (9600); ir max 1660–1650 (chelated C=O), 1605, 1587, 1481, 1242, 1078, 1040, 812, 766, 678 cm^{-1}; nmr δ 1.53 (t, 3, J = 7 Hz, $COOCH_2CH_3$), 4.53 (q, 2, J = 7 Hz, $COOCH_2CH_3$), 6.6–7 (m, 3, C_2 H, C_4 H, and C_7 H), 7.52 (t, 1, J = 8.5 Hz, C_3 H), 8.26 (d, 1, J = 9 Hz, C_8 H), 12.4 (s, 2, OH).

Anal. Calcd for $C_{16}H_{12}O_6$: C, 64.00; H, 4.03; O, 31.97. Found: C, 63.74; H, 4.00; O, 32.19.

1,6-Dimethoxyxanthone-5-carboxylic Acid Ethyl Ester (3f).—**3f** was obtained as crystals from 1:1 ethyl acetate–petroleum ether (bp 60–70°): mp 187°; uv max 227 nm (ϵ 30,500), 245 (sh), (24,200), 290 (16,500), 341 (11,000); ir max 1737 (ester C=O), 1670, (xanthone C=O), 1626, 1605, 1575, 1481 (aromatic C=C), 1290, 1274, 1242, 1105, 1075, 1020, 793, 684 cm^{-1}; nmr δ 1.45 (t, 3, J = 7 Hz, $COOCH_2CH_3$), 3.98 (s, 3, Ar OCH_3), 4.02 (s, 3, Ar OCH_3), 4.53 (q, 2, J = 7 Hz, $COOCH_2CH_3$), 6.8 (d, 1, J = 8.5 Hz, C_2 H), 6.98 (d, 2, J = 9 Hz, C_4 H and C_7 H), 7.58 (t, 1, J = 8.5 Hz, C_3 H), 8.36 (d, 1, J = 9 Hz, C_8 H).

Anal. Calcd for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91; O, 29.24. Found: C, 65.81; H, 4.63; O, 29.83.

1-Hydroxy-6,8-dimethylxanthone (4a).—**4a** was obtained as light yellow crystals from ethanol: mp 179°; uv max 232 nm (ϵ 25,600) 251 (22,250), 286 (8400), 302 (8050), 358 (4400); ir max 1642, 1618, 1600, 1563, 1481, 1271, 1239, 1062, 901, 840, 780, 672 cm^{-1}; nmr δ 2.35 (s, 3, C_6 Me), 2.77 (s, 3, C_8 Me), 7.45 (t, 1, J = 8.5 Hz, C_3 H), 12.88 (s, 1, OH), 6.6–7.0 (m, 4).

Anal. Calcd for $C_{15}H_{12}O_3$: C, 74.99; H, 5.03; O, 19.98. Found: C, 74.61; H, 4.90; O, 20.35.

The acetate (Ac_2O, NaOAc, reflux) had mp 205°; nmr (DMSO-d_6) 2.46 (s, C_6 H) 2.48 (s, C_3 H).

1-Methoxy-6,8-dimethylxanthone (4b).—A mixture of **4a** (1.3 g), $(CH_3)_2SO_4$ (2 ml), and anhydrous K_2CO_3 (5 g) in acetone (100 ml) was refluxed for 12 hr, during which time the yellow color of the solution disappeared. The solvent was removed *in vacuo* and ice water was added to the residue. The white solid, filtered off and crystallized from ethanol, gave **4b** (1.1 g) as white crystals: mp 156°; uv max 240 nm (ϵ 39,000), 282 (12,700), 295 (11,550), 343 (7,600); ir max 1660, 1621, 1600, 1478, 1258, 1095, 1081, 1055, 952, 880, 841, 811, 777, 670 cm^{-1}; nmr δ 2.33 (s, 3, C_6 Me), 2.82 (s, 3, C_8 Me), 3.93 (s, 3, OCH_3), 6.63 (d, 1, J = 8.5 Hz, C_2 H), 6.74 (d, 2, J = 1.5 Hz, C_5 H), 6.82 (d, 1, J = 8.5 Hz, C_4 H), 6.89 (d, 1, J = 1.5 Hz, C_7 H), 7.38 (t, 1, J = 8.5 Hz, C_3 H).

Anal. Calcd for $C_{16}H_{14}O_3$: C, 75.57; H, 5.55; O, 18.88. Found: C, 75.38; H, 5.48; O, 19.06.

A 130-mg sample of **4b**, heated in 3 ml of HBr at 110–120° for 5 hr, gave a quantitative yield of **4a**.

Oxidation of 1-Methoxy-6,8-dimethylxanthone.—Of the various reagents and conditions used to oxidize the CH_3 groups to COOH, only the following gave good yields:

To a refluxing solution of 4b (4.33 g) in *tert*-butyl alcohol (160 ml) and water (80 ml) was added a solution of 17 g of $KMnO_4$ in 170 ml of water dropwise, with stirring, over a period of 3–4 hr. The refluxing and stirring were continued until the purple color completely disappeared (4–5 hr). The mixture was cooled, acidified with 10% sulfuric acid, refluxed again for 20 min, cooled, and treated with $NaHSO_3$ to remove MnO_2. The pale yellow solid remaining was stirred with a saturated solution of $NaHCO_3$. The bicarbonate extract, acidified with concentrated HCl, yielded a mixture of acids (2.75 g).

For separation of the components, the mixture was esterified (10 ml of $(CH_3)_2SO_4$ and 12 g of anhydrous K_2CO_3 in 200 ml of acetone, refluxed 15 hr). The crude ester (2.9 g) showed two main spots on tlc. It was separated by preparative tlc (silica gel, Merck PF 254 (containing $CaSO_4$) using 1% methanol in chloroform as developer.

1-Methoxy-6-carbomethoxy-8-methylxanthone (4e).—The ester fraction with the higher R_f value (0.55) furnished **4e** (750 mg) as fluffy white crystals from ethanol: mp 183°; uv max 235 nm (ϵ 25,150), 245 (sh, 23,300), 255 (24,400), 285 (5780), 310 (8380), 355 (5030); ir max 1730, 1675, 1613, 1572, 1486, 1242, 1099, 1058, 1000, 970, 927, 885, 817, 772, 727, 679 cm^{-1}; nmr δ 2.93 (s, 3, C_8 Me), 3.97 (s, 3, $COOCH_3$), 4.02 (s, 3, Ar OCH_3), 6.77 (d, 1, J = 8.5 Hz, C_2 H), 6.99 (d, 1, J = 8.5 Hz, C_4 H), 7.58 (t, 1, J = 8.5 Hz, C_3 H), 7.7 (d, 1, J = 1.5 Hz, C_5 H), 7.88 (d, 1, J = 1.5 Hz, C_7 H).

Anal. Calcd for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73; O, 26.82. Found: C, 66.92; H, 5.08; O, 27.74.

This compound apparently is difficult to free of solvent. About 9% ethanol would account for the analytical results.

1-Methoxy-6,8-dicarbomethoxyxanthone (4f).—The ester fraction with the lower R_f value (0.25) yielded 1.05 g of **4f** as white crystals from ethanol: mp 239–240°; uv max 235 nm (ϵ 22,800), 260 (23,180), 286 (5700), 298 (5890), 310 (7130), 356 (5030); ir max 1730, 1670, 1608, 1570, 1477, 1235, 1092, 1080, 1018, 813, 775, 767, 760, 725, 722, 667 cm^{-1}; nmr δ 3.98 (s, 6, $COOCH_3$), 4.05 (s, 3, Ar OCH_3), 6.82 (d, 1, J = 8.5 Hz, C_2 H), 7.05 (d, 1, J = 8.5 Hz, C_4 H), 7.63 (t, 2, J = 8.5 Hz, C_3 H), 7.88 (d, 2, J = 1.5 Hz, C_5 H), 8.14 (d, 1, J = 1.5 Hz, C_7 H). This compound was identical in all respects (melting point, uv, ir, nmr, tlc) with that obtained by refluxing natural cassiaxanthone with $(CH_3)_2SO_4$ and anhydrous K_2CO_3 in acetone.

Anal. Calcd for $C_{18}H_{14}O_7$: C, 63.16; H, 4.12; O, 32.72. Found: C, 63.07; H, 4.02; O, 32.70.

When pyridine was used instead of *tert*-butyl alcohol as solvent, the yield of both mono- and diester was decreased.

1-Methoxy-8-methylxanthone-6-carboxylic Acid (4c).—Hydrolysis of **4e** (60 mg) with aqueous NaOH furnished the acid **4c** (35 mg) as white crystals from ethanol: mp 302–305°; uv max 235 nm (ϵ 25,700), 252 (25,250), 286 (6900), 309 (8500), 355 (5360); ir max 3300–2800, 1725, 1647, 1625, 1608, 1570, 1480, 1278, 1180, 1092, 1082, 1053, 946, 882, 815, 784, 750, 713, 670 cm^{-1}.

Anal. Calcd for $C_{16}H_{12}O_5$: C, 67.60; H, 4.26; O, 28.14. Found: C, 66.93; H, 4.29; O, 28.27.

1-Methoxyxanthone-6,8-dicarboxylic Acid Cassiaxanthone Methyl Ether (4d).—Hydrolysis of **4f** (60 mg) with aqueous NaOH yielded the acid **4d** (30 mg) as crystals from acetic acid: mp 285–290° dec; uv max 235 nm (ϵ 23,700) 256 (22,900), 286 (5800), 308 (5900), 355 (5100); ir max 3250–2800, 1730, 1660, 1613, 1575, 1484, 1275, 1090, 1080, 880, 817, 774, 730, 670 cm^{-1}.

Anal. Calcd for $C_{16}H_{10}O_7$: C, 61.15; H, 3.21; O, 35.64. Found: C, 60.01, H, 3.38; O, 36.65.

The compound apparently holds solvent, even when dried *in vacuo* at 80°.

Anal. Calcd for $C_{16}H_{10}O_7 \cdot 0.25C_2H_4O_2$: C, 60.20; H, 3.37; O, 36.43.

1-Hydroxy-8-methylxanthone-6-carboxylic Acid (4g).—A mixture of **4e** (60 mg) and HBr (47–49%, 5 ml) was heated at 110–120° with stirring for 5 hr, cooled, and diluted with water. Yellow crystals from alcohol were obtained: 45 mg; mp 312–315°; uv max 235 nm (ϵ 26,650), 261 (28,350), 291 (6750), 316 (9500), 370 (5800); $uv_{max}^{EtOH-NaOH}$ 239 nm (ϵ 33,350), 268 (23,250) 314 (11,600), 322 (12,300), 400 (7560); ir max 3300–2800, 1710, 1653, 1613, 1565, 1475, 1235, 1212, 1058, 890, 817, 772, 767, 723, 682, 666 cm^{-1}.

Anal. Calcd for $C_{15}H_{10}O_5$: C, 66.67; H, 3.73; O, 29.60. Found: C, 66.52; H, 3.76; O, 29.24.

1-Hydroxyxanthone-6,8-dicarboxylic Acid (1) (Cassiaxanthone).—The diester **4f** (60 mg) was heated with 2 ml of HBr at 110–120° for 5 hr, cooled, and diluted with H_2O. The product, a yellow solid, was crystallized from acetic acid, yielding 40 mg of cassiaxanthone as pale yellow crystals: mp 330–333°; uv max 235 nm (ϵ 27,100) 262 (28,500), 290 (7500), 314 (8000) (the peak at 314 nm was originally reported in error as being at 300 nm[1]); ir max 1704, 1653 (reported in error as 1635[1]), 1613, 1575, 1471, 1265, 1220, 1050, 995, 890, 813, 763, 730, 695, 672 cm^{-1}. The synthetic sample was identical in all respects (melting point, uv, ir) with that obtained from *Cassia reticulata*.

Anal. Calcd for $C_{15}H_8O_7$: C, 60.01; H, 2.69; O, 37.31. Found: C, 59.74; H, 2.71; O, 37.13.

Registry No.—**1**, 28917-02-4; **2a**, 33780-61-9; **2b**, 33777-15-0; **3a**, 33777-16-1; **3b**, 33777-17-2; **3c**, 33777-18-3; **3d**, 33777-19-4; **3e**, 33777-20-7; **3f**, 33777-21-8; **4a**, 33777-22-9; **4a** acetate, 33777-23-0; **4b**, 33777-24-1; **4c**, 33777-25-2; **4d**, 33777-26-3; **4e**, 33780-62-0; **4f**, 33780-63-1; **4g**, 33780-64-2.

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Synthesis of Imino Derivatives of *Cecropia* Juvenile Hormone[1]

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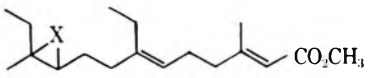
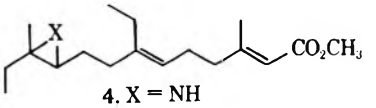
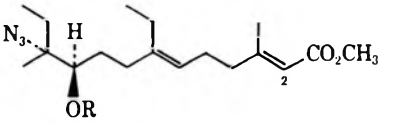
In connection with our studies of the effects of the juvenile hormones[2] of *Hyalophora cecropia* on insect metamorphosis, we were encouraged to devise an efficient synthesis for the imino analog **1**, particularly in view of a report[3a] of the preparation of **1**, by an undetailed method,[3b] and of its interesting biological properties.



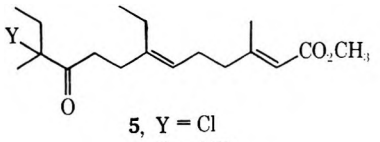
1. X = NH
2, X = O



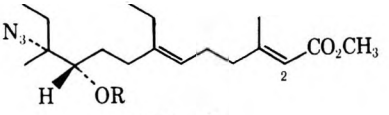
4. X = NH
11, X = O



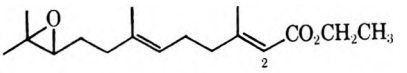
3, R = H
9, R = SO_2CH_3



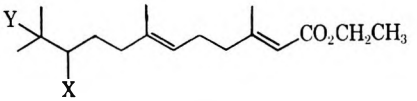
5, Y = Cl
6, Y = NH_2
7, Y = N_3



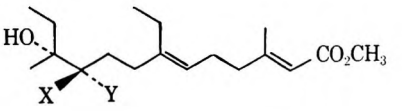
8, R = H
10, R = SO_2CH_3



12



13. X = N_3; Y = OH
14. X = OH; Y = N_3



15, X = N_3; Y = H
16, X = H; Y = N_3

Initial attempts to prepare **1** from the racemic Röller juvenile hormone **2** *via* opening of the epoxide ring with either azide ion or with hydrazoic acid under a variety of conditions failed, although a later variation (see below) did allow the preparation of **1** by this method but in poor yield. In this connection it was found that treatment of **2** with excess lithium azide in dimethoxyethane–acetic acid at 25° for 24 hr failed to give any of the required azido alcohol **3** (*cf.* 3b).

An efficient synthesis of the racemic imino C_{18} juvenile hormone (JH) analogs **1** and **4** was developed starting with the available chloro ketone **5**.[4] Since initial attempts to convert **5** to the amino ketone **6** were unsuccessful, we prepared the corresponding azido ketone **7** from the chloro ketone **5** in 90% yield using sodium azide in dimethylformamide (100° for 3 hr). Reduction of **7** with 1 equiv of sodium borohydride in methanol gave a mixture of the diastereoisomeric azido alcohols **3** and **8** (ratio 3:2), which was separated by thin layer chromatography in an overall combined yield of 65% from **5**. Each pure alcohol was separately converted into its corresponding azido mesylate using methanesulfonyl chloride in triethylamine–pentane[5] (yield 80–85% after purification *via* preparative tlc). The final conversion of the azido mesylates **9** and **10** into the aziridines **1** and **4**, respectively, was best carried out by reduction using hydrazine hydrate and Raney nickel in ethanol.[6] Preparative tlc of the reduction products gave **1** (62% yield) and **4** (55% yield) in high purity. Use of an alternative reduction system, cobaltous bromide–dipyridyl–sodium borohydride,[7] also gave the aziridines, but some selective saturation[8] of the α,β-unsaturated ester double bond also occurred. The two aziridines **1** and **4** could be differentiated by glc and by the different chemical shift of the C-11 methyl in their nmr spectra.

The diastereoisomeric azido alcohols **3** and **8**, and thus the aziridines derived from them, were assigned their stereochemistry on the basis of the correlations with the synthetic trans,trans,cis hormone **2** and the all-trans isomer **11**, respectively,[4] providing also an alternative synthesis of the imino JH analogs. These correlations were established using an epoxide opening

(1) Contribution No. 5 from the Research Laboratory of Zoecon Corp. This work was presented in part at the XXIII International Congress of Pure and Applied Chemistry, Boston, Mass., July 1971.

(2) H. Röller, K. H. Dahm, C. C. Sweeley, and B. M. Trost, *Angew. Chem., Int. Ed. Engl.*, **6**, 179 (1967); A. S. Meyer, H. A. Schneidermann, E. Hanzmann, and J. H. Ko, *Proc. Nat. Acad. Sci. U. S.*, **60**, 853 (1968).

(3) (a) Report by Dr. E. J. Corey at the International Conference on Juvenile Hormones, Basel, Switzerland, Oct 1970; (b) L. M. Riddiford, A. M. Ajami, E. J. Corey, H. Yamamoto, and J. E. Anderson, *J. Amer. Chem. Soc.*, **93**, 1815 (1971).

(4) P. Loew, J. B. Siddall, V. L. Spain, and L. Werthemann, *Proc. Nat. Acad. Sci. U. S.*, **67**, 1462, 1824 (1970).

(5) R. K. Crossland and K. L. Servis, *J. Org. Chem.*, **35**, 3195 (1970).

(6) R. D. Guthrie and D. Murphy, *J. Chem. Soc.*, 5288 (1963); K. Ponsold, *Chem. Ber.*, **97**, 3524 (1964).

(7) K. Ponsold, *J. Prakt. Chem.*, **36**, 148 (1967).

(8) T. Satoh, J. Nanba, and S. Suzuki, *Chem. Pharm. Bull.*, **19**, 817 (1971).

method developed initially with the model epoxide **12**.[9] When **12** was treated with an excess of lithium azide and acetic acid (azide:acid = 2:1) in hexamethylphosphoramide (HMPA) at room temperature for 6 days, the azido alcohols **13** and **14** were isolated in yields of 42 and 18%, respectively. At 95° (20 hr) only **14** could be isolated (in 11% yield) and no other product could be identified. At the higher temperature some 2-ene isomerization also occurred. Reaction of racemic *Cecropia* hormone **2** under the above conditions in HMPA (7 days at 25°) gave the azido alcohols **3** (20% yield) and **15** (60% yield). At 105° (19 hr) only **3** could be isolated in 10% yield (with some isomerization to cis at Δ^2). Similarly, the all-trans epoxide **11** at room temperature gave *only* the azido alcohols **8** (17% yield) and **16** (41% yield) with no detectable **3** or **15**.

To establish the trans nature of the epoxide ring opening under our reaction conditions, cyclohexane epoxide was treated with lithium azide–acetic acid (2:1) in HMPA (4 days at room temperature). The only product was shown to be *trans*-2-azidocyclohexanol, identical with material prepared as described[10] in the literature with sodium azide in refluxing aqueous dioxane. However, it is necessary to point out that the epoxide **12** was recovered unchanged under the latter conditions and treatment of **12** with lithium azide in HMPA in the absence of acetic acid at room temperature gave a mixture which contained a negligible proportion of the required ring-opening product **14**. Thus the above correlations depend in some way on the presence of acid in the reaction mixture used for the epoxide ring opening.

The biological properties of the aziridines **1** and **4** have been investigated in detail and the results are reported in part elsewhere.[1]

Experimental Section

Infrared spectra were determined with a UNICAM SP 200 G infrared spectrophotometer; nmr spectra were obtained using a Varian T-60 spectrometer with TMS as internal standard. The gas chromatograph used was a Hewlett-Packard Model 402 equipped with flame detector. Microanalyses were performed by Bernhardt Microanalytical Laboratories, Elbach, West Germany.

Methyl 11-Azido-3,11-dimethyl-7-ethyl-10-oxo-2-*trans*,6-*trans*-tridecadienoate (7).—To 4.32 g (13.2 mmol) of chloro ketone **5**[4] in 40 ml of dry dimethylformamide under argon was added 0.91 g (14 mmol) of sodium azide and the mixture was heated at 90° for 6 hr. After sitting overnight at room temperature, the suspension was poured into water and extracted three times with pentane–ether (9:1). The combined organic fractions were washed with saturated sodium chloride, dried ($MgSO_4$), and evaporated to give the azido ketone **7** (4.0 g, 91% yield): ir (CCl_4) 2100 ($-N_3$), 1720 (ester C=O), 1710 (shoulder, ketone C=O), 1650 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.40 (s, 3, CH_3CN_3), 2.18 (d, 3, J = 1 Hz, CH_3C=CCOOR), 3.72 (s, 3, $COOCH_3$), 5.10 (m, 1, C=CH), and 5.72 ppm (broad s, 1, C=CHCOOR).

Anal. Calcd for $C_{18}H_{29}N_3O_3$: C, 64.45; H, 8.72; N, 12.53. Found: C, 64.27; H, 8.69; N, 12.49.

Reduction of Azido Ketone 7.—To 4.0 g of the ketone **7** in 25 ml of methanol was added 300 mg of sodium borohydride. After 45 min, reduction was quenched by the addition of ether and water, the aqueous phase was twice more extracted with ether, and the combined ether fractions were washed to neutrality (saturated sodium chloride). After drying ($MgSO_4$) 3.85 g of crude alcohol mixture was recovered. The diastereoisomers **3** and **8** were separated by use of preparative tlc: each 1 m × 20 cm plate (1.3 mm PF silica gel) was charged with 250 mg of the mixture of **3** and **8** and was developed five times with 12% ether in hexane. In this manner, it was possible to obtain from the above mixture 1.43 g of pure **3** (larger R_f) and 1.09 g of pure **8** (smaller R_f). This recovery (2.52 g) represents a 62% overall yield from azido ketone **7**.

Both diastereoisomers were completely characterized. **3** had ir (film) 3510 (OH), 2100 (N_3), 1720 (ester C=O), and 1640 cm^{-1} (C=C); nmr ($CDCl_3$) δ 0.97 (t, 6, J = 7 Hz, CH_3CH_2–), 1.23 (s, 3, CH_3CN_3), 2.18 (d, 3, J = 1 Hz, CH_3C=CCOOR), 3.72 (s, 3, $COOCH_3$), 5.14 (m, 1, C=CH), and 5.71 ppm (broad s, 1, C=CHCOOR).

Anal. Calcd for $C_{18}H_{31}N_3O_3$: C, 64.06; H, 9.26; N, 12.45. Found: C, 64.25; H, 9.13; N, 12.44.

8 had ir (film) 3510 (OH), 2100 (N_3), 1720 (ester C=O), and 1640 cm^{-1} (C=C); nmr δ 0.97 (t, 6, J = 7 Hz, CH_3CH_2–), 1.28 (s, 3, CH_3CN_3), 2.17 (d, 3, J = 1 Hz, CH_3C=CCOOR), 3.71 (s, 3, $COOCH_3$), 5.15 (m, 1, C=CH), and 5.72 ppm (broad s, 1, C=CHCOOR).

Anal. Calcd for $C_{18}H_{31}N_3O_3$: C, 64.06; H, 9.26; N, 12.45. Found: C, 64.26; H, 9.24; N, 12.40.

Conversion of Azido Alcohols 3 and 8 to the Methanesulfonates 9 and 10.—The azido alcohol **3** (1.14 g, 3.4 mmol), dissolved in 33 ml of 0.3 *M* triethylamine in pentane, was cooled to −10° under argon, and 0.58 ml (7.5 mmol) of methanesulfonyl chloride was added dropwise. After 1 hr the gummy suspension was poured into ice and ether, and the organic phase was washed successively with cold 5% hydrochloric acid, saturated sodium bicarbonate, and saturated sodium chloride solutions. After drying ($MgSO_4$), 1.45 g of crude material was isolated and applied directly to three 1 m × 20 cm silica gel PF preparative plates (1.3 mm thickness). After developing with 20% ethyl acetate in hexane, 1.09 g (2.64 mmol) of pure azido mesylate **9** (R_f 0.29) could be recovered (78% yield): ir (CCl_4) 2100 (N_3), 1720 (C=O), 1650 (C=C), 1365 and 1190 cm^{-1} (OSO_2); nmr ($CDCl_3$) δ 0.98 (t, 6, J = 7 Hz, CH_3CH_2–), 1.28 (s, 3, CH_3CN_3), 2.17 (d, 3, J = 1 Hz, CH_3C=CCOOR), 3.15 (s, 3, CH_3SO_2O), 3.72 (s, 3, $COOCH_3$), 4.60 (t, 1, J = 6 Hz, HCOMs), 5.15 (m, 1, C=CH), and 5.71 ppm (broad s, 1, C=CHCOOR).

Anal. Calcd for $C_{19}H_{33}N_3O_5S$: C, 54.92; H, 8.01; N, 10.11; S, 7.70. Found: C, 54.86; H, 7.97; N, 10.21; S, 7.80.

The preparation of the second diastereoisomer **10** was identical with that of **9**. Thus 0.90 g (2.67 mmol) of azido alcohol **8** gave 0.96 g (2.30 mmol, 86% yield) of pure azido mesylate **10**: ir (film) 2100 (N_3), 1720 (ester C=O), 1640 (C=C), 1350, and 1180 cm^{-1} (OSO_2); nmr ($CDCl_3$) δ 0.98 (t, 6, J = 7 Hz, CH_3CH_2–), 1.37 (s, 3, CH_3CN_3), 2.18 (d, 3, J = 1 Hz, CH_3C=CCOOR), 3.15 (s, 3, CH_3SO_2O), 3.72 (s, 3, $COOCH_3$), 4.64 (t, 1, J = 6 Hz, HCOMs), 5.17 (m, 1, C=CH), and 5.72 ppm (broad s, 1, C=CHCOOR).

Anal. Calcd for $C_{19}H_{33}N_3O_5S$: C, 54.92; H, 8.01; N, 10.11; S, 7.70. Found: C, 55.05; H, 8.00; N, 10.26; S, 7.94.

Methyl 3,11-Dimethyl-10,11-*cis*-imino-7-ethyl-2-*trans*,6-*trans*-tridecadienoate (1).—To 1.10 g (2.65 mmol) of mesylate **9** in 30 ml of ethanol under argon was added 2 ml of 85% hydrazine hydrate and about 0.2 g of Raney nickel. After stirring for 3 hr at room temperature the catalyst was filtered off and ether and saturated sodium chloride were added to the filtrate. The organic phase was washed to neutrality with brine and dried ($MgSO_4$). The crude product (712 mg) was purified by chromatography on two 1 m × 20 cm preparative silica gel plates (1.3 mm thickness PF), developed with a benzene–methanol–diethylamine system (94:5.4:0.6), to give 483 mg (62% yield) of the aziridine **1**: ir (film) 1720 (ester C=O) and 1640 cm^{-1} (C=C). nmr ($CDCl_3$) δ 0.98 (t, 6, J = 7 Hz, CH_3CH_2), 1.22 [s, 3, CH_3C–N(imino)], 2.18 (d, 3, J = 1 Hz, CH_3C=CCOOR), 3.72 (s, 3, $COOCH_3$), 5.14 (m, 1, C=CH), and 5.72 ppm (broad s, 1, C=CHCOOR); mass spectrum (70 eV) *m/e* (rel intensity) M^+ 293 (1), 180 (13), 98 (100).

Anal. Calcd for $C_{18}H_{31}NO_2$: C, 73.67; H, 10.65; N, 4.77. Found: C, 73.48; H, 10.51; N, 4.60.

Methyl 3,11-Dimethyl-10,11,*trans*-imino-7-ethyl-2-*trans*,6-*trans*-tridecadienoate (4).—Azido mesylate **10** (0.88 g, 2.12 mmol) on reduction with hydrazine hydrate and Raney nickel in ethanol as above gave 0.54 g of crude **4**. Preparative tlc gave 339 mg (55% yield) of pure **4**: ir (film) 1720 (ester C=O) and 1640 cm^{-1} (C=C); nmr ($CDCl_3$) δ 0.97 (t, 6, J = 7 Hz, CH_3CH_2), 1.15

(9) R. J. Anderson, C. A. Henrick, and J. B. Siddall, unpublished work. The corresponding methyl ester has been prepared; see W. S. Bowers, M. J. Thompson, and E. C. Uebel, *Life Sci.*, **4**, 2323 (1965); E. E. van Tamelen, M. A. Schwartz, E. J. Hessler, and A. Storni, *Chem. Commun.*, 409 (1966).

(10) C. A. VanderWerf, R. H. Heisler, and W. E. McEwen, *J. Amer. Chem. Soc.*, **76**, 1231 (1954).

[s, 3, CH_3C–N(imino)], 2.18 (d, 3, J = 1 Hz, CH_3C=CCOOR), 3.71 (s, 3, $COOCH_3$), 5.12 (m, 1, C=CH), and 5.72 (broad s, 1, C=CHCOOR); mass spectrum (70 eV) m/e M^+ 293.

Anal. Calcd for $C_{18}H_{31}NO_2$: C, 73.67; H, 10.65; N, 4.77. Found: C, 73.42; H, 10.46; N, 4.89.

Reduction of 9 and 10 with Cobaltous Bromide–Sodium Borohydride.—An alternate method of reduction of the mixture of azido mesylates (9 and 10) was also investigated. The reducing agent[7] was first prepared as follows: 146 mg (0.67 mmol) of anhydrous cobaltous bromide was dissolved in 10 ml of absolute ethanol (blue solution) and 312 mg (2 mmol) of dipyridyl was added (orange solution). To this solution at 0° under argon was added 76 mg (2 mmol) of sodium borohydride (blue-black solution). In a second flask, 35 mg (0.085 mmol) of a mixture of azido mesylates 9 and 10 was dissolved in 0.8 ml of dry ethanol at 0° under argon and to this solution was added dropwise 0.7 ml of the reducing solution. After 0.5 hr, the solution was poured into ether and water, and the organic phase was washed to neutrality (saturated sodium chloride) and dried ($MgSO_4$). The residue was applied to one 20 × 20 cm silica gel plate (0.5 mm thickness) and developed with a benzene–methanol–diethylamine system (94:5.4:0.6); 7 mg (R_f 0.29) of aziridines 1 and 4 was recovered. However, some saturation of the α,β-unsaturated ester function also occurred (to the extent of about 25%).

Ring Opening of 12 with Lithium Azide–Acetic Acid.—The epoxide 12 (100 mg, 0.36 mmol), lithium azide (175 mg, 3.6 mmol), and acetic acid (0.10 ml, 1.8 mmol) were stirred together in 4 ml of dry hexamethylphosphoramide for 6 days at room temperature under argon. Hexane–ether (95:5) and water were added and the phases were separated; the organic phase was washed to neutrality (saturated NaCl) and dried ($MgSO_4$) and the solvent was removed. The crude residue was applied to one 20 × 20 cm preparative silica gel plate (1.3 mm thickness) and developed twice with 20% ethyl acetate in hexane. The upper product band (R_f 0.38, 19 mg) was shown to be 14 and the lower band (R_f 0.30, 46 mg) the position isomer 13. In addition, 5 mg of starting material 12 was recovered.

Isomer 13 had ir (CCl_4) 3630, 3590, 3520 (m, OH), 2110 (N_3), 1725 (ester C=O), 1655 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.23 [s, 6, $(CH_3)_2COH$], 1.27 (t, 3, J = 7 Hz, CH_3CH_2O–), 1.63 (broad s, 3, CH_3C=C), 2.17 (d, 3, J = 1 Hz, CH_3C=CCOOR), 3.12 (d of d, 1, HCN_3), 4.17 (q, 2, J = 7 Hz, $-CH_2O$–), 5.20 (m, 1, C=CH), and 5.70 ppm (broad s, 1, C=CHCOOR).

Anal. Calcd for $C_{17}H_{29}N_3O_3$: C, 63.13; H, 9.04; N, 12.99. Found: C, 63.31; H, 9.12; N, 12.92.

Isomer 14 had ir (CCl_4) 3590 (OH), 2110 (N_3), 1725 (ester C=O), and 1650 cm^{-1} (C=C); nmr ($CDCl_3$) δ 1.30 [s, 6, $(CH_3)_2CN_3$], 1.63 (broad s, 3, CH_3C=C), 2.18 (d, 3, J = 1 Hz, CH_3C=CCOOR), 3.35 (m, 1, HCOH), 4.18 (q, 2, J = 7 Hz, $-CH_2O$–), 5.20 (m, 1, C=CH), and 5.71 ppm (broad s, 1, C=CHCOOR).

Anal. Calcd for $C_{17}H_{29}N_3O_3$: C, 63.13; H, 9.04; N, 12.99. Found: C, 63.04; H, 8.94; N, 13.10.

On treatment of the two isomers separately with acetic anhydride–pyridine at room temperature for 6 hr, the top band (*i.e.*, 14) gave an acetate [ir (CCl_4) 1740 cm^{-1} (acetate C=O); nmr ($CDCl_3$) δ 2.13 (s, 3, CH_3COO)] while the lower band gave only recovered starting material 13 (*via* infrared).

Ring Opening of 2 and 11.—Synthetic juvenile hormone 2[4] (60 mg, 0.20 mmol), lithium azide (350 mg, 7.2 mmol), and glacial acetic acid (0.20 ml, 3.6 mmol) were dissolved in 4 ml of dry hexamethylphosphoramide and stirred under argon for 7 days at room temperature. Pentane–ether (95:5) and water were then added, and the organic phase was washed with 2 M sodium carbonate and saturated sodium chloride, dried ($MgSO_4$), and evaporated. The residue was placed on one 20 × 20 cm silica gel plate (1.3 mm PF) and developed with 12% ethyl acetate in hexane three times. In this manner two products were isolated: 3 (14 mg, 20% yield) and the position isomer 15 (40 mg, 59% yield). Azido alcohol 3 was identical with the faster eluting isomer obtained above from reduction of azido ketone 7. Isomer 15 was completely characterized: ir (CCl_4) 3630, 3590, 3520 (broad multiplet, OH), 2110 (N_3), 1725 (ester C=O), and 1655 cm^{-1} (C=C); nmr ($CDCl_3$) δ 0.93 (t, 3, J = 7 Hz, CH_3CH_2–), 0.98 (t, 3, J = 7 Hz, CH_3CH_2), 1.15 (s, 3, CH_3COH), 2.18 (d, 3, J = 1 Hz, CH_3C=CCOOR), 3.22 (d of d, 1, HCN_3), 3.72 (s, 3, $COOCH_3$), 5.15 (m, 1, C=CH), and 5.72 ppm (broad s, 1, C=CHCOOR).

Anal. Calcd for $C_{18}H_{31}N_3O_3$: C, 64.06; H, 9.26; N, 12.45. Found: C, 64.29; H, 9.12; N, 12.30.

Similarly, the all-trans isomer 11[4] (53 mg, 0.18 mmol), lithium azide (350 mg, 7.2 mmol), and glacial acetic acid (0.20 ml, 3.6 mmol) were dissolved in 4 ml of dry hexamethylphosphoramide and stirred for 9 days. Work-up as above gave a residue which was applied to one 20 × 20 cm silica gel plate (1.3 mm PF) and developed eight times with 10% ethyl acetate in hexane. Again, two bands were recovered and identified. The upper band was shown to be identical with that of the azido alcohol 8 (10 mg, 17% yield) and the lower band (25 mg, 41% yield) was shown to be that of the position isomer 16: ir (CCl_4) 3630, 3590, 3530 (broad multiplet, OH), 2110 (N_3), 1730 (ester C=O), and 1655 cm^{-1} (C=C); nmr ($CDCl_3$) δ 0.93 (t, 3, J = 7 Hz, CH_3CH_2–), 0.98 (t, 3, J = 7 Hz, CH_3CH_2–), 1.18 (s, 3, CH_3COH), 2.18 (d, 3, J = 1 Hz, CH_3C=CCOOR), 3.18 (d of d, 1, HCN_3), 3.72 (s, 3, $COOCH_3$), 5.16 (m, 1, C=CH), and 5.71 ppm (broad s, 1, C=CHCOOR).

Anal. Calcd for $C_{18}H_{31}N_3O_3$: C, 64.06; H, 9.26; N, 12.45. Found: C, 64.22; H, 9.10; N, 12.20.

***trans*-2-Azidocyclohexanol.**—To 3.9 g (0.08 mol) of lithium azide and 2.3 ml (0.04 mol) of glacial acetic acid in 20 ml of hexamethylphosphoramide was added 2.0 g (0.02 mol) of cyclohexane oxide and the milky suspension was stirred at room temperature for 4 days. Pentane–ether (95:5) and 2 M sodium carbonate were added, the layers were separated, and the organic phase was washed to neutrality. After drying ($MgSO_4$), the solvent was removed and the residue was distilled, bp 95° (0.5 mm). This product (both prior to and after distillation) was homogeneous on three vpc columns (2 m 3% OV-225, 98°; 4 m 20% UCON 90M, 170°; 2 m 3% PDEAS, 100°) and was identical in all respects with a sample of *trans*-2-azidocyclohexanol prepared as described,[10] with sodium azide in hot aqueous dioxane.

Registry No.—**1**, 33780-87-9; **3**, 33780-88-0; **4**, 33780-89-1; **7**, 33780-90-4; **8**, 33780-91-5; **9**, 33780-92-6; **10**, 33886-27-0; **13**, 33886-28-1; **14**, 33780-93-7; **15**, 33780-94-8; **16**, 33780-95-9; *trans*-2-azidocyclohexanol, 10027-78-8.

The Synthesis of *trans*-3′-Methylnicotine[1a]

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Recently Rueppel and Rapoport reported that *dl*-1,3-dimethylpyrrolinium-3-$^{14}CH_3$ chloride (1) is incorporated into 3′-methylnicotine (2) by *Nicotiana glutinosa*.[2] The asymmetric center at C-2′ was assigned the *S* configuration on the basis of ORD and CD studies. However, the configuration at C-3′ remained unassigned. The superimposition of the nmr spectrum of *dl-trans*-3′-methylnicotine, synthesized in the present study, with the nmr spectrum of the biosynthesis product[3] establishes the absolute stereochemistry of the biosynthesis product as 2′*S*,3′*S* (2a). The nmr spectrum of 2a displays in addition to the assignable signals for the NCH_3, CCH_3, and aromatic protons, a series of signals between δ 2.6 and 1.4 ppm integrating for five protons and a multiplet centered near δ 3.2 ppm integrating for one proton. The nmr spectrum of

(1) (a) Presented in part at the 162nd Meeting of the American Chemical Society, Washington, D. C., Sept 1971. (b) NDEA Predoctoral Fellow and American Foundation for Pharmaceutical Education Fellow.

(2) M. L. Rueppel and H. Rapoport, *J. Amer. Chem. Soc.*, **92**, 5528 (1970).

(3) The authors are indebted to Professor Henry Rapoport for providing the nmr spectrum of the biosynthesis product.

nicotine (**3**) also displays a multiplet centered near δ 3.2 ppm which however represents two protons.[4] In order to achieve a more thorough understanding of these nmr characteristics, a complete nmr assignment for *trans*-3′-methylnicotine has been carried out (Table I) *via* model deuteration and pseudocontact shift reagent studies.

TABLE I

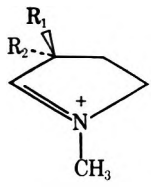
CHEMICAL SHIFTS AND RELATIVE CONTACT SHIFTS FOR **2a** COORDINATED WITH Eu(DPM)$_3$[a]

Proton	δ, ppm	$\Delta\delta$, ppm[b]
H_a	2.55 (d, J = 8 Hz)	1.9
H_b	2.0 (m)[c]	1.7
H_c	2.26 (m)	0.6
H_d	1.32 (m)	0.6
H_e	2.41 (m)	0.6
H_f	3.18 (m)	0.6
CCH_3	0.96 (d, J = 7 Hz)	0.9
NCH_3	2.07 (s)	1.2
$H_{a'}$	8.41 (m)	10.0
$H_{b'}$	7.60 (m)	2.8
$H_{c'}$	7.15 (m)	3.1
$H_{d'}$	8.41 (m)	7.9

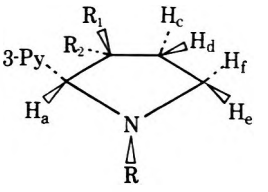
[a] Spectra were recorded at 100 MHz in CCl_4 at 0, 20, 27, 35, and 55 mol % Eu(DPM)$_3$ with TMS as internal standard. [b] Relative contact shifts calculated from the four Eu(DPM)$_3$ spectra and normalized to give a value of 10.0 for the largest proton shift ($H_{a'}$). [c] Calculated from relative contact shift value.

As part of our synthetic studies on analogs of nicotine,[5] we have prepared 1-hydroxy-2-(3-pyridyl)-3,3-dimethylpyrrolidine (**4**).[6] The nmr spectrum of **4** shows two singlets for the *gem*-dimethyl groups at δ 1.12 and 0.62 ppm. The high-field signal was assigned to the methyl group cis to the pyridine ring since it should be shifted upfield due to the shielding effect of the aromatic π cloud. We have observed similar field effects in the *trans*- and *cis*-1-cyclohexyl-4-methoxycarbonyl-5-aryl-2-pyrrolidinones (**5a** and **5b**, respectively) in which the signals for the methoxycarbonyl methyl groups of the trans compounds occur near δ 3.7 ppm, 0.5 ppm downfield relative to the corresponding cis compounds.[7] Based on the above considerations and the fact that the *C*-methyl group doublet of **2** centers at δ 0.96 ppm near the *trans*-methyl group of **4**, we decided to prepare the trans isomer **2a** as the more likely candidate for the biosynthetic product.

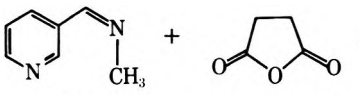
The synthesis of **2a** was achieved according to the following reaction sequence. Paralleling our previous studies,[8] the condensation of *N*-3-pyridylidenemethylamine (**6**) and succinic anhydride gave *trans*-1-methyl-5-(3-pyridyl)-2-pyrrolidinone (**7**). As previously observed[8] the coupling constant for the C-5 methine proton doublet was 5 Hz as expected for the trans configuration. Attempted lithium aluminum hydride reduction of **7** to the hydroxymethylpyrrolidine **8** in ether or tetrahydrofuran was accompanied by partial reduction of the pyridine ring. However, the corresponding methyl ester **9** was smoothly converted to **8** by lithium aluminum hydride. Confirmation of the 4,5 trans stereochemistry was obtained from the nmr of the methyl ester **9** since the methoxycarbonyl methyl signal appeared at δ 3.75 ppm, whereas the corresponding signal in the cis ester would be expected to occur near δ 3.2 ppm.[7,8] Subsequent reduction of the tosylate **10** with lithium aluminum hydride yielded *trans*-3′-methylnicotine (**2a**). The high-resolution mass and



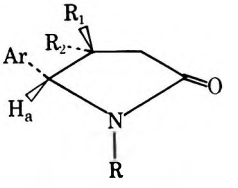
1a, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$



2a, $R = R_1 = CH_3$; $R_2 = H_b$
b, $R = R_2 = CH_3$; $R_1 = H_b$
3, $R = CH_3$; $R_1 = R_2 = H$
4, $R = OH$; $R_1 = R_2 = CH_3$
8, $R = CH_3$; $R_1 = CH_2OH$; $R_2 = H_b$
10, $R = CH_3$; $R_1 = p\text{-}CH_2OTs$; $R_2 = H_b$



6



5a, R = cyclohexyl; $R_1 = COOCH_3$; $R_2 = H$
b, R = cyclohexyl; $R_1 = H$; $R_2 = COOCH_3$
7, $R = CH_3$; Ar = 3-pyridyl; $R_1 = COOH$; $R_2 = H$
9, $R = CH_3$; Ar = 3-pyridyl; $R_1 = COOCH_3$; $R_2 = H$
11, $R = CH_3$; Ar = 3-pyridyl; $R_1 = R_2 = H$

nmr spectra were consistent with the reported spectra.[2] Thus it is possible to assign the relative stereochemistry of **2** as trans and, based on the reported ORD and CD curves,[2] the absolute stereochemistry of the biosynthetic product as 2′*S*,3′*S*. Assuming that the enzymatic processes responsible for the formation of **2a** do not involve inversion at the asymmetric center of **1**, it may be concluded that (3*S*)-1,3-dimethyl-1-pyrrolinium chloride (**1a**) and not the 3*R* enantiomer (**1b**) is selectively incorporated into **2a** by *Nicotiana glutinosa*.

At 100 MHz, the δ 3.2 ppm region of the nmr spectrum of **2a** (Figure 1a) integrates for one proton and appears similar to the corresponding region in the spectrum of nicotine which, however, integrates for two protons. The spectrum of 5′,5′-dideuterionicotine (structure **3** in which H_e and H_f are replaced by deuterium atoms), prepared by $LiAlD_4$ reduction[9] of cotinine[10] **11**, shows a one-proton triplet at δ 3.04 ppm (J = 8 Hz) which clearly can be assigned to H_a. Consequently, the second low-field signal in the nicotine spectrum must be due to one of the two C-5′ protons, presumably H_f, which would be expected to appear

(4) M. Ohashi, I. Morishima, and T. Yonezawa, *Bull. Chem. Soc. Jap.*, **44**, 576 (1971).
(5) N. Castagnoli, Jr., A. P. Melikian, and V. Rosnati, *J. Pharm. Sci.*, **58**, 860 (1969).
(6) N. Castagnoli, Jr., and A. P. Melikian, unpublished results.
(7) M. Cushman and N. Castagnoli, Jr., *J. Org. Chem.*, **36**, 3404 (1971).
(8) N. Castagnoli, Jr., *ibid.*, **34**, 3187 (1969).
(9) A. M. Duffied, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, **87**, 2926 (1965).
(10) E. R. Bowman and H. McKennis, *Biochem. Prep.*, **10**, 36 (1963).

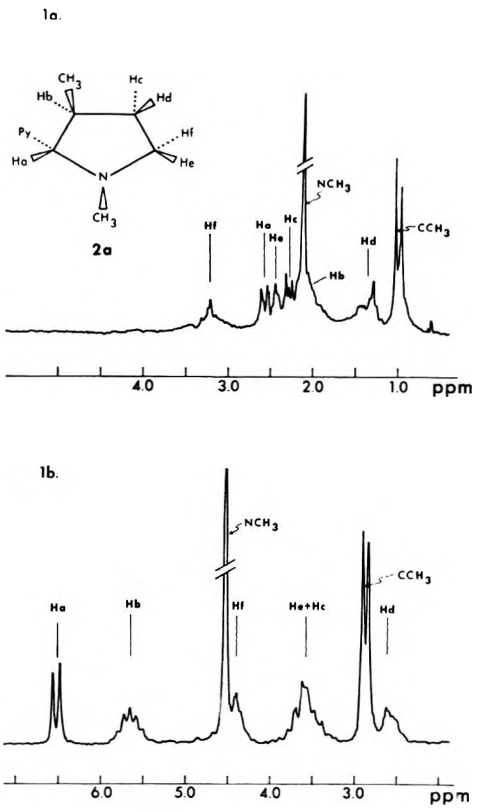


Figure 1.—(a) 100-MHz nmr spectrum of **2a** in CCl_4. (b) 100-MHz nmr spectrum of **2a** in CCl_4 complexed with 55 mol % $Eu(DPM)_3$.

downfield relative to H_e.[11] Based on these observations, the δ 3.2 ppm multiplet in the spectrum of **2a** must also be assigned to H_f. The partially resolved doublet at δ 2.55 ppm (J = 8 Hz) can therefore tentatively be assigned to H_a.

Confirmation of these assignments was obtained with the aid of the pseudocontact shift reagent tris(dipivalomethanato)europium [$Eu(DPM)_3$].[12] At a concentration of 55 mol % $Eu(DPM)_3$, the signals for the nonaromatic protons of **2a** (Figure 1b) are well separated except for two overlapping multiplets centered at δ 3.6 ppm. As was recently observed with nicotine,[4] the europium coordinates with the pyridine and not the pyrrolidine nitrogen of **2a** since the relative contact shifts of the aromatic proton signals are much greater than the corresponding shifts of the nonaromatic proton signals (Table I). On the basis of geometry, one would predict that the signal for H_a should be shifted downfield to a greater extent than the remaining pyrrolidine proton signals of **2a**, a prediction consistent with the assignment of H_a to the doublet at δ 2.55 ppm. The proton which should be next most deshielded is H_b which appears in Figure 1b as the multiplet at δ 5.66 ppm. Knowing the chemical shift of this multiplet at various concentrations of $Eu(DPM)_3$, it was possible to extrapolate to zero concentration and locate this signal at δ 2.0 ppm, overlapping with the signal for the *N*-methyl group (Figure 1a). In a similar way, the signals centered at δ 4.42 and 2.63 ppm (Figure 1b) were shown to correspond to the multiplets at δ 3.18 and 1.32 ppm, respectively, while the two-proton multiplet at δ 3.6 ppm (Figure 1b) must correspond to the multiplets at δ 2.41 and 2.26 ppm (Figure 1a). The assignments for these signals are indicated in Figure 1 and Table I. It is of interest to note that the signals for H_a and H_d occur at higher fields than in nicotine due to the shielding effect of the *cis*-methyl group. The observed shielding effect of the methyl group in **2a** of about 0.5 ppm is consistent with methyl group shielding effects observed in other five-membered ring systems.[13]

(11) The observed difference in chemical shift values between H_e and H_f in the nmr spectrum of nicotine implies that the *N*-methyl group assumes a preferred configuration trans to the pyridine ring: I. R. Simpson, J. C. Craig, and W. D. Kumler, *J. Pharm. Sci.*, **56**, 708 (1967); S. Ohki and M. Yoshino, *Chem. Pharm. Bull.*, **16**, 269 (1968). The contribution of the deshielding effect of the nitrogen lone pair on H_f [M. Uskokovic, H. Bruderer, C. von Planta, T. Williams, and A. Brossi, *J. Amer. Chem. Soc.* **86**, 3364 (1964)] relative to the shielding effect of the *N*-methyl group on H_e [J. B. Lambert and R. G. Keske, *Tetrahedron Lett.*, **No. 25**, 2023 (1969)] to this difference in chemical shift remains unresolved.

(12) J. K. M. Sanders and O. H. Williams, *J. Amer. Chem. Soc.*, **93**, 641 (1971).

Experimental Section[14]

***N*-3-Pyridylidenemethylamine** (6).—A solution of CH_3NH_2 (33.37 g, 1.07 mol) and pyridine-3-carboxaldehyde (107.11 g, 1.00 mol) in C_6H_6 (200 ml) containing molecular sieves (75 g) was stirred for 12 hr at room temperature. The residue obtained after filtering and removing the solvent was distilled to give a colorless oil (110.39 g, 92%): bp 37° (0.2 mm); nmr δ 8.84 (m), 8.60 (m), 8.02 (m), 7.27 (m, aromatic signals), 8.24 (q, J = 1.5 Hz, N=CH), 3.88 ppm (d, J = 1.5 Hz, CH_3).

Anal. Calcd for $C_7H_8N_2$: C, 69.97; H, 6.71; N, 23.31. Found: C, 70.01; H, 6.85; N, 23.48.

***trans*-1-Methyl-4-carboxy-5-(3-pyridyl)-2-pyrrolidinone** (7).—The above Schiff base (91.10 g, 0.76 mol) and succinic anhydride (75.85 g, 0.76 mol) were refluxed in xylene (100 ml) for 24 hr. After cooling, the xylene was decanted from the reaction mixture and the remaining brownish oil dissolved in 5% $NaHCO_3$ (800 ml). The resulting solution was washed with $CHCl_3$ (two 800-ml portions), decolorized with activated carbon (3 g), and warmed on a steam cone to remove traces of $CHCl_3$. The pH of the solution was adjusted to 4.7 with H_3PO_4 to precipitate the product (58.62 g, mp 192–194°). An additional crop (33.51 g, mp 187–192°) was obtained after concentrating the filtrate to 225 ml. The combined material (92.13 g, 55%) was crystallized from EtOH (1700 ml) to give the analytical sample: mp 194–194.5°; nmr ($CDCl_3$–Py-d_5, 1:1) δ 14.0 (s, OH), 8.62 (m), 7.63 (m), 7.34 (m) (aromatic signals), 4.95 (d, J = 5 Hz, H_a), 2.95 (m, $CHCH_2$), 2.69 ppm (s, CH_3).

Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.71; H, 5.31; N, 12.92.

***trans*-1-Methyl-4-methoxycarbonyl-5-(3-pyridyl)-2-pyrrolidinone** (9).—A solution of **7** (13.85 g, 0.063 mol) in 2 *N* methanolic H_2SO_4 (110 ml) containing molecular sieves (5.0 g) was stirred for 16 hr at room temperature. The filtered solution was added slowly to 8% $NaHCO_3$ (250 ml) and the resulting mixture extracted with $CHCl_3$ (four 200-ml portions). Evaporation of the dried ($MgSO_4$) extracts yielded a clear, light amber oil (13.78 g, 93%) which gave colorless needles (11.94 g, 81%) from Et_2O–Me_2CO (75 + 15 ml): mp 83–84°; nmr δ 8.63 (m), 7.64 (m), (m) (aromatic signals), 4.86 (d, J = 5 Hz, H_a), 3.75 (s, OCH_3), 2.92 (m, $CHCH_2$), 2.69 ppm (s, NCH_3).

Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.53; H, 6.02; N, 11.96. Found: C, 61.74; H, 5.79; N, 11.96.

***trans*-3′-Hydroxymethylnicotine** (8).—The trans ester 9 (6.00 g, 25.6 mmol) was stirred in a solution of $LiAlH_4$ (3.64 g, 96.0 mmol) in Et_2O (350 ml) for 24 hr at room temperature. The reaction mixture was decomposed by the addition of H_2O (3.5 ml), 15% NaOH (3.5 ml), and finally H_2O (11.0 ml). The suspension was filtered, the filtrate dried ($MgSO_4$), and after removing the solvent the gold-colored residue (3.52 g, 72%) was distilled (short path) to yield an almost colorless oil: bp 87° (10 μ);

(13) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon, Oxford, 1969, pp 236, 237.

(14) All reactions were performed under a nitrogen atmosphere and solvents were concentrated on a rotary evaporator under vacuum. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. Nmr spectra were recorded on a JEOL 100-MHz instrument and, except where noted, in $CDCl_3$ solvent with TMS as internal standard. Microanalyses were performed by the Microanalytical Laboratory, University of California, Berkeley.

nmr δ 8.41 (m), 7.76 (m), 7.21 (m) (aromatic signals), 5.15 (b, OH), 3.56 (d, J = 5 Hz, CH_2O), 2.92 (d, J = 8 Hz, H_a), 2.11 (s, CH_3), 3.19 (m, H_f), 2.00 ppm (m, 4 H).

Anal. Calcd for $C_{11}H_{16}N_2O$: C, 68.72; H, 8.39; N, 14.57. Found: C, 68.72; H, 8.17; N, 14.46.

trans-**3′-Methylnicotine (2a).**—The above hydroxymethyl compound **8** (1.81 g, 9.41 mmol) in pyridine (40 ml) was treated with tosyl chloride (1.79 g, 9.40 mmol) at 1° for 21 hr. The solution was then added to ice-cold 5% K_2CO_3 (100 ml) and the mixture extracted rapidly with $CHCl_3$ (four 200-ml portions). After drying ($MgSO_4$), the $CHCl_3$ and pyridine were removed *in vacuo* to yield a reddish-brown oil (3.70 g) which was dissolved in Et_2O (200 ml) and treated with $LiAlH_4$ (0.35 g, 9.4 mmol) at room temperature for 12 hr. The reaction mixture was decomposed with H_2O (0.35 ml), 15% NaOH (0.35 ml), and finally H_2O (1.05 ml). After filtering, drying ($MgSO_4$), and removing solvent, the residue (1.59 g) was chromatographed on alumina. Elution with $CHCl_3$ gave the 3′-methylnicotine (**2a**) (0.88 g, 53%) which was purified by short-path distillation: bp 40–42° (1.0 mm). The homogeneity of the distillate was established by observing only one peak on glpc (retention time 245 sec, 1/8 in. × 6 ft, 3% OV 17 on acid-washed Chromosorb W, 100–120 mesh, 146° column temperature, N_2 flow 26 ml/min).

Mass spectrum. Calcd for $C_{11}H_{16}N_2$: m/e 176.1313. Found: 176.1299. Calcd for $C_6H_{12}N$ (1,3-dimethyl-1-pyrrolinium fragment): 98.0970. Found: 98.0966. Mass fragments: m/e 176 (43), 175 (14), 134 (100), 119 (14), 98 (86).

The dipicrate was prepared for analysis, mp 199–200°.

Anal. Calcd for $C_{23}H_{22}N_8O_{14}$: C, 43.54; H, 3.50; N, 17.66. Found: C, 43.47; H, 3.48; N, 17.54.

Registry No.—**2a**, 33223-98-2; **2a** dipicrate, 33223-99-3; **6**, 16273-54-4; **7**, 33224-01-0; **8**, 33224-02-1; **9**, 33224-03-2.

Ferrocenophanes. An Improved Synthesis of 3-Phenyl[5]ferrocenophane-1,5-dione Involving a Reverse Aldol Condensation[1]

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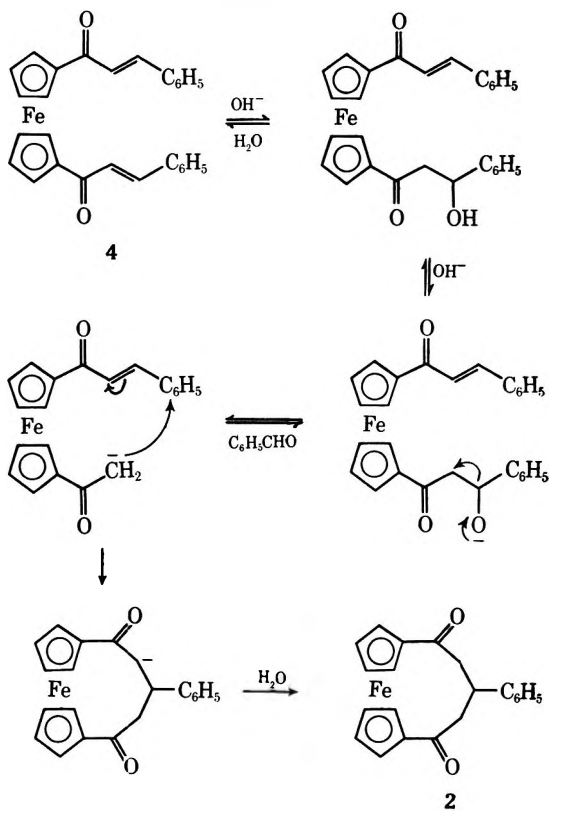
It has been reported[2] that 1,1′-diacetylferrocene (**1**) and benzaldehyde undergo an alkali-catalyzed aldol type condensation to form mono- and dibenzaldehyde derivatives and a yellow product. One of several suggested structures for the yellow product was 3-phenyl-[5]ferrocenophane-1,5-dione (**2**). This structure was later confirmed by Furdik, *et al.*[3] Barr and Watts[4] have synthesized **2** from acetylferrocene by first preparing 1-acetyl-1′-cinnamoylferrocene (**3**) (80% yield) and then by cyclizing the product under alkaline conditions to **2** (69% yield). This results in an overall yield of 55% for the two reactions.

We have recently synthesized **2** in two steps starting with ferrocene. Ferrocene is first dicinnamoylated by the Friedel–Crafts reaction to yield 1,1′-dicinnamoylferrocene (**4**), which is treated with base to yield **2**. The overall yield for the two steps was 73%. This yield is considerably higher than the previously reported yield of 55% and starts with the readily available ferrocene rather than acetylferrocene.

Nielson and Houlihan[5] discussed a number of important syntheses involving a Michael condensation followed by an intramolecular aldol condensation. The synthesis of **2** appears to be a unique example of a reverse aldol condensation step in a synthesis followed by an intramolecular Michael addition. A probable mechanism for this synthesis involves a base-catalyzed reverse aldol type condensation (reverse Claisen–Schmidt) to form the carbanion which is followed by internal Michael addition to form the heteroannular bridge (Scheme I).

SCHEME I



Since **4** is a symmetrical molecule, base attack on either cinnamoyl group leads to the carbanion intermediate after a reverse aldol condensation. In the case of base treatment of **3**, attack on the acetyl group generates the necessary carbanion for ring closure to yield **2**. However, if the cinnamoyl group is attacked, a reverse aldol condensation would lead to the carbanion of **1** which would not lead to the product. This could account for the smaller yield starting with **3**.

Experimental Section

Infrared spectra were recorded as Nujol mulls on a Beckman IR-4 and were calibrated against polystyrene film; nmr spectra were determined in deuteriochloroform on a Varian A-60 using TMS as an internal standard. Analyses were performed at Huffman Laboratories, Inc., Wheatridge, Colo. All melting points were determined using a Reichert Austria melting point apparatus and are uncorrected.

(1) The views expressed herein are those of the author and do not necessarily reflect the views of the United States Air Force or the Department of Defense.

(2) T. A. Mashburn, Jr., C. E. Cain, and C. R. Hauser, *J. Org. Chem.*, **25**, 1982 (1960).

(3) M. Furdik, S. Toma, J. Suchy, and P. Elecko, *Chem. Zvesti*, **15**, 45 (1961); *Chem. Abstr.*, **55**, 18692e (1961).

(4) T. H. Barr and W. E. Watts, *Tetrahedron*, **24**, 3219 (1968).

(5) A. T. Nielson and W. J. Houlihan, *Org. React.*, **16**, 47 (1968).

1,1'-Dicinnamoylferrocene (2).—A solution of cinnamoyl chloride (8.25 g, 0.049 mol) and $AlCl_3$ (6.6 g, 0.049 mol) in dry CH_2Cl_2 (75 ml) was added slowly to a solution of ferrocene (4 g, 0.022 mol) in dry CH_2Cl_2 (75 ml). The mixture was stirred for 4 hr at 25° in a N_2 atmosphere, then poured into 300 ml of ice–water. The organic phase was separated and combined with the CH_2Cl_2 extracts of the aqueous phase. The combined organic phases were washed with water, dried with $MgSO_4$, and taken to dryness. The residue was dissolved in a minimum volume of benzene with heating and allowed to crystallize. After removal of crystalline **4** (7.9 g) the solution was reduced to a small volume and chromatographed on neutral alumina. Petroleum ether (bp 20–40°)–diethyl ether (3:2) eluted a small band of ferrocene and a second small band of cinnamoylferrocene. Methylene chloride eluted an additional 0.6 g of **4**. The 8.5 g of crystalline (red needles) product represents an 88% yield, mp 180.5–182° (lit.[2] mp 208–210°), ir 6.01 μ, nmr τ 2.06–3.07 (m, 14 H, vinyl and Ph protons), 5.06, 5.39 (2 t, 8 H, cyclopentadienyl protons).

Anal. Calcd for $C_{28}H_{22}O_2Fe$: C, 75.35; H, 4.97; Fe, 12.51. Found: C, 75.25; H, 5.01; Fe, 12.85.

Due to the discrepancy in melting point, **4** was synthesized from 1 according to the directions of Mashburn, *et al.*,[2] which after repeated recrystallizations from ethanol–water melted at 180.5–182°. Ir and nmr spectra of this compound were also identical with those of **4** synthesized by Friedel–Crafts dicinnamoylation of ferrocene.

3-Phenyl[5]ferrocenophane-1,5-dione (2).—Aqueous 15% NaOH solution (100 ml) was slowly added to a solution of **4** (5 g, 0.011 mol) in 500 ml of 95% ethanol and 150 ml of THF. The mixture was stirred at 25° in a nitrogen atmosphere for 65 hr and diluted with 800 ml of water. The suspension was extracted with $CHCl_3$. The extract was then dried with $MgSO_4$, concentrated, and chromatographed on neutral alumina. Only one band developed, which was eluted with CH_2Cl_2–$CHCl_3$ (1:1). Crystallization from ethanol yielded 3.7 g of yellow feathers (yield 92%), mp >300° (lit.[2-4] mp >300°), ir 6.03 μ (lit.[4] 6.03 μ).

Anal. Calcd for $C_{21}H_{18}O_2Fe$: C, 70.41; H, 5.06; Fe, 15.59. Found: C, 70.18; H, 5.04; Fe, 15.64.

A Convenient Synthesis of Benzaldehyde-*formyl-d* from Benzil[1]

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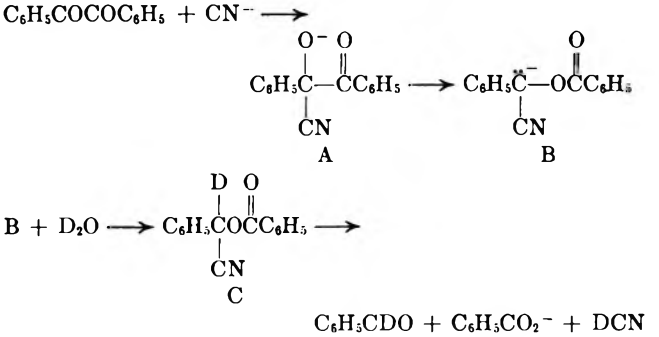
Although various methods[3] are now available for the synthesis of deuterio and tritio aldehydes, practically all of them involve multistep procedures, costly reagents, or extended reaction periods. In seeking a simple, rapid route to benzaldehyde-*formyl-d*, we have found that the facile cleavage of benzil by cyanide ion in the presence of D_2O, occurring apparently through adduct A and its rearrangement products B and C,[4] provides a convenient source of this compound.



When dry potassium cyanide is added at room temperature to 1 equiv of benzil in dioxane containing 10 equiv of D_2O, the yellow α-diketone color gradually disappears. After dilution of the mixture with ordinary water, extraction with ether, and washing of the ether extract, benzaldehyde-*formyl-d* of 98% isotopic purity (by nmr analysis) can be recovered in 55–60% yield by distillation. The remainder of the product consists of an equivalent amount of benzoic acid (separated in the extraction and washing), unchanged benzil, and a mixture of what appears to be α-deuteriobenzoin and its benzoate ester.[4] The benzoin derivatives are evidently formed not by the benzoin condensation but, as shown recently,[4] through trapping of carbanion B by deuteriobenzaldehyde, even though the latter must compete with an appreciable excess of D_2O. (With the use of less than 10 equiv of D_2O more by-products are formed, and the yield of aldehyde is diminished.) When conducted in dioxane–H_2O in the presence of tritium oxide the reaction furnishes benzaldehyde containing benzaldehyde-*formyl-t*.

Although cyanide ion is theoretically required only in catalytic amounts, the reaction is erratic and the yield of aldehyde is lower when less than a full molar equivalent of cyanide is used. In addition, the disappearance of the yellow diketone color occurs much more slowly when less cyanide is used, even when potassium carbonate is added to prevent its loss as DCN. Use of sodium cyanide in place of potassium cyanide is unsatisfactory because of the formation of difficultly soluble salts during the initial stages of the reaction.

Experimental Section

Benzaldehyde-*formyl-d*.—By means of a syringe, 10 ml of D_2O (99.87%, Bio-Rad Laboratories) was added to a magnetically stirred solution of 10.5 g (0.050 mol) of benzil (recrystallized from carbon tetrachloride[5]) in 25 ml of dry 1,4-dioxane under a dry, inert atmosphere (argon or nitrogen) at 20–25°. To the resulting fine suspension of benzil were added, with rapid stirring, at 2-min intervals, four 1-g portions of reagent-grade potassium cyanide (previously dried at 125°). After the second addition of cyanide the mixture became homogeneous, and the yellow color disappeared within 2 min after the last addition. Stirring was continued for 10 min as potassium benzoate gradually precipitated. The mixture was then diluted with 100 ml of distilled water and extracted with two 50-ml portions of ether. The combined ether extracts were washed with 50 ml of 5% sodium carbonate solution, 100 ml of water, and finally with 50 ml of saturated sodium chloride solution. After drying for 2 min over $MgSO_4$ the ether solution was concentrated in a rotary evaporator under aspirator vacuum on a water bath. Distillation of the light yellow residue (5.5 ml) gave, in separate runs, 2.95 to 3.2 g (55–60%) of benzaldehyde-*formyl-d*, bp 84–86° (30 mm). By nmr analysis this contained 0.98 atom of deuterium per molecule. Crystallization of the still-pot residue

(1) This research was supported in part by the National Science Foundation and the National Institutes of Health.

(2) Holder of a Research Career Development Award of the National Institute of General Medical Sciences.

(3) *E.g.*, D. Nasipuri, C. K. Gosh, and R. J. L. Martin, *J. Org. Chem.*, **35**, 657 (1970) [citing D. J. Bennett, G. W. Kirby, and V. A. Mess, *Chem. Commun.*, 218 (1967)]; A. I. Meyers, A. Nabeya, H. W. Adickes, and I. R. Politzer, *J. Amer. Chem. Soc.*, **91**, 763 (1969); T. Axenrod, L. Loew, and P. S. Pregosin, *J. Org. Chem.*, **33**, 1274 (1968); J. Cymerman Craig and L. R. Kray, *ibid.*, **33**, 871 (1968); R. A. Olafson and D. M. Zimmerman, *J. Amer. Chem. Soc.*, **89**, 5057 (1967); D. Seebach, B. W. Erickson, and G. Singh, *J. Org. Chem.*, **31**, 4303 (1966); V. E. Althouse, D. M. Feigl, W. A. Sanderson, and H. S. Mosher, *J. Amer. Chem. Soc.*, **88**, 3595 (1966).

(4) For a recent study and references to earlier work, see J. P. Kuebrich and R. L. Schowen, *J. Amer. Chem. Soc.*, **93**, 1220 (1971).

(5) H. T. Clarke and E. E. Dreger, "Organic Syntheses," Collect. Vol. I, 2nd ed, Wiley, New York, N. Y., 1941, p 87.

(1.8 to 2.2 g) from ethanol afforded *ca.* 1.0 g of recovered benzil, mp and mmp 92–94°.[5] When conducted on 21.0 g (0.10 mol) of benzil in 50 ml of dioxane and 20 ml of D_2O, the reaction furnished 6.0 g (56%) of distilled benzaldehyde-*formyl-d*.

With 5 ml of D_2O in the cleavage of 10.5 g of benzil, the yield of deuterio aldehyde was only 1.6 g (30%), and a larger amount of still-pot residue (3.5 g) remained. Even with 20 ml of D_2O the yield of aldehyde from 10.5 g of benzil did not exceed 3.2 g (60%). With 10 ml of H_2O containing tritium oxide the reaction afforded 3.0 to 3.25 g (57–62%) of tritium-labeled benzaldehyde. Substitution of tetrahydrofuran or 1,2-dimethoxyethane for 1,4-dioxane as solvent offered no apparent advantage, while use of dimethyl sulfoxide resulted in the formation of deeply colored by-products and very little aldehyde.

Registry No.—Benzaldehyde-*formyl-d*, 3592-47-0; benzil, 134-81-6.

Organocopper Chemistry. The Decarboxylation of a Benzhydryl Carboxylic Acid

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In the course of our synthesis of the highly strained hydrocarbon 4,8-dihydrodibenzo[*cd,gh*]pentalene,[3] we became interested in the decarboxylation reactions of benzhydryl carboxylic acids for which a paucity of examples exist in the literature.[4,5] Recent interpretations of the decarboxylation of aromatic and vinyl carboxylic acids invoke the intermediacy of organocopper species.[6–8] A requirement for the π system was assumed on the basis of a lack of a catalytic effect of copper salts on decarboxylation of aliphatic acids. In contrast to this conclusion, decarboxylation of benzhydryl carboxylic acids exhibits a pronounced dependence on the presence of copper and its salts and on the nature of the copper source. To study this phenomenon for preparative purposes, fluorene-9-carboxylic acid was chosen as a suitable model, and this compound was consequently subjected to a variety of classical and new decarboxylation procedures. A study of these reactions has evolved some new and unusual chemistry attributable to organocopper intermediates.

Heating fluorene-9-carboxylic acid to 290° for several minutes (material sublimes from the reaction mixture) afforded fluorene in 38% yield and 9,9′-bifluorenyl in 12% yield (Scheme I, Table I). The products here and in the following cases were separated by preparative thick layer chromatography on silica gel, and identified by comparison of spectral data and melting points with those of authentic samples. Bifluorenyl was prepared by the reductive coupling of 9-bromofluorene.[9]

SCHEME I

DECARBOXYLATION OF FLUORENE-9-CARBOXYLIC ACID

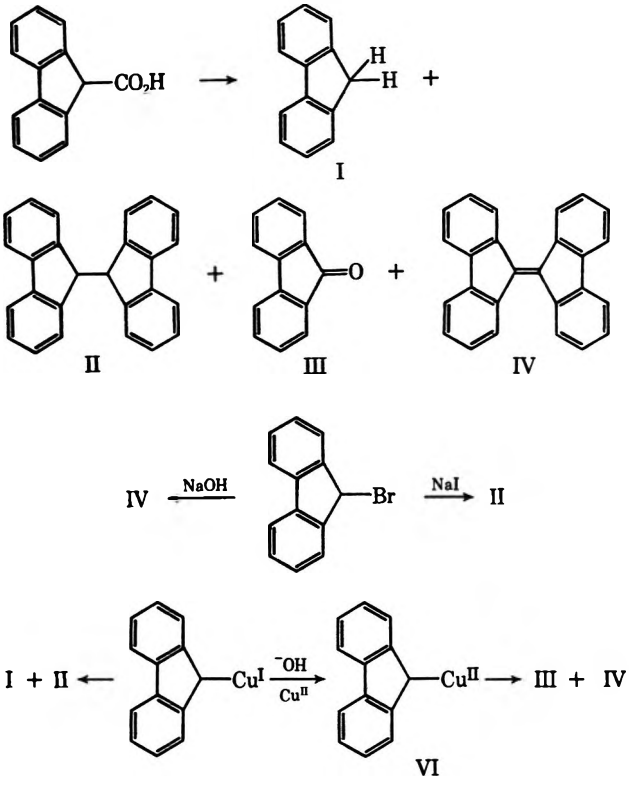

TABLE I

YIELDS OF PRODUCTS OBTAINED ON DECARBOXYLATION OF FLUORENE-9-CARBOXYLIC ACID

Reaction conditions	Yield, % I	II	III	IV
1. Δ 290°	38	12		
2. 0.03 equiv $CuCO_3Cu(OH)_2$ (265°)	48	10	11	3
3. 2.0 equiv $CuCO_3Cu(OH)_2$ (265°)			56	10
4. Cu–quinoline (reflux)	85	6		4
5. Pentafluorophenylcopper quinoline (reflux)	90	Trace		Trace

Heating fluorene-9-carboxylic acid to 265° (material sublimes from the reaction mixture) with 0.03 molar equiv of basic copper carbonate [$CuCO_3Cu(OH)_2$] afforded fluorene (48% yield), 9,9′-bifluorenyl (10% yield), and, unexpectedly, fluorenone (3% yield) and 9,9′-bifluorenylidene (11% yield). Bifluorenylidene was available by base treatment of 9-bromofluorene.[10] Repeating this reaction with 2.0 molar equiv of basic copper carbonate afforded only fluorenone (56% yield) and 9,9′-bifluorenylidene (10% yield). This case represents the first example of a direct oxidative decarboxylation utilizing copper salts catalysis and has clear synthetic utility.[11]

The copper–quinoline decarboxylation[7] is another method which has found wide utility. Employment of copper powder[5] in refluxing quinoline (1 hr) afforded an 85% yield of fluorene, a 6% yield of bifluorenyl, and a 4% yield of bifluorenylidene from fluorenecarboxylic acid. Alternatively, treatment of fluorene-9-carboxylic acid with 0.1 equiv of pentafluorophenylcopper[6] in quinoline for 3 min at 220° followed by addition of a

(1) Camille and Henry Dreyfus Teacher–Scholar.
(2) National Institutes of Health Predoctoral Fellow.
(3) B. M. Trost and P. L. Kinson, *J. Amer. Chem. Soc.*, **92**, 2591 (1970); B. M. Trost, P. L. Kinson, C. A. Maier, and I. C. Paul, *ibid.*, in press.
(4) P. Friedlander, *Chem. Ber.*, **10**, 536 (1877).
(5) G. Werber and F. Maggio, *Ann. Chim (Rome)*, **50**, 1438 (1960).
(6) A. Cairncross and W. M. Sheppard, *J. Amer. Chem. Soc.*, **92**, 3187 (1970).
(7) T. Cohen and R. A. Schambach, *ibid.*, **92**, 3189 (1970).
(8) M. Nilsson, *Acta Chem. Scand.*, **20**, 423 (1966); C. Bjorklund and M. Nilsson, *ibid.*, **22**, 2585 (1968).
(9) Compare J. Thiele and A. Wanscheidt, *Justus Liebigs Ann. Chem.*, **376**, 269 (1910); A. Wanscheidt, *Chem. Ber.*, **59**, 2092 (1926).
(10) R. C. Fuson and H. D. Porter, *J. Amer. Chem. Soc.*, **70**, 895 (1948).
(11) Compare chromic acid procedure [I. M. Hunsberger and E. D. Amstutz, *ibid.*, **71**, 2635 (1949)] and pyridine *N*-oxide procedure [T. Cohen, I. H. Song, and J. H. Fager, *Tetrahedron Lett.*, 237 (1965)].

small amount of water afforded a 90% yield of fluorene accompanied by only traces of 9,9′-bifluorenyl and 9,9′-bifluorenylidene (thin layer comparison). To our knowledge this reaction is the first example of the employment of pentafluorophenylcopper for the decarboxylation of acids other than aromatic and vinyl acids. It is also clearly the reagent of choice.

Table I summarizes the yields of the products obtained in the decarboxylation of fluorene-9-carboxylic acid by the above procedures.

The mechanism of formation of these products, particularly fluorenone and bifluorenylidene, is of considerable interest. Recent investigations[6-8] have shown that aromatic and vinyl carboxylic acids react with a variety of copper salts to afford copper(I) carboxylates. On heating in complexing solvents such as quinoline these materials evolve carbon dioxide with consequent formation of organocopper(I) compounds. These organocoppers, pentafluorophenylcopper, for example, have been isolated in a number of cases. These materials afford the parent hydrocarbon on treatment with acids or water or dimers on heating or oxidation.[12] Analogy of the aryl- and vinylcopper chemistry to our results is apparent. This chemistry thus explains the formation of fluorene and bifluorenyl in the above reactions *via* the intermediacy of 9-fluorenylcopper V (Scheme I). The formation of fluorenone and bifluorenylidene, however, remains unexplained. It is interesting to speculate upon a mechanism for the formation of these products. Organocopper V under the basic conditions could suffer basic oxidation to a copper II fluorenylidene (VI). Such a compound may dimerize to bifluorenylidene or pick up oxygen from the cupric oxide to generate fluorenone.

Experimental Section

Melting points were taken on a Thomas-Hoover melting point apparatus and are corrected. Infrared spectra were determined on a Beckman IR-8 spectrophotometer, and ultraviolet spectra were recorded on Cary Model 11 and Model 15 spectrophotometers. Nmr spectra were determined on a Varian Associates Model A-60A or Model HA-100 spectrometer fitted with a variable temperature probe. Chemical shifts are given in parts per million relative to TMS as an internal standard. Mass spectra were taken on a CEC 103 C or a MS-902 mass spectrometer at an ionizing current of 40 mA and ionizing voltage of 70 V. Chromatographic separations employed silica gel PF-254 (Merck, Darmstadt).

Decarboxylations of Fluorene-9-carboxylic Acid. Method A. Pentafluorophenylcopper.—Under nitrogen, a solution of fluorene-9-carboxylic acid (210 mg, 1.00 mmol) and pentafluorophenylcopper (23 mg, 0.10 mmol) in distilled deaerated quinoline (10 ml) was heated with swirling in a metal bath at 225–230° for 3 min. Rapid bubbling was observed over the first minute. While the reaction mixture was cooling, water (1 ml) was added. The material was taken up in ether (100 ml) and extracted with 20% hydrochloric acid (100 ml), 10% hydrochloric acid (100 ml), water (50 ml), twice with 10% potassium hydroxide (50 ml), and with water (50 ml). The solvent was removed, affording 187 mg (quantitative yield) of a tan solid, mp 90–102° (mp fluorene[13] 116–117°). Acidification of the basic washes, extraction with ether, and removal of solvent afforded only 0.7 mg of a brown oil, indicating that the starting material had been consumed. The neutral material was identified as fluorene by nmr, ir, and thin layer comparison to an authentic sample. Thin layer comparison spots indicated that traces of 9,9′-bifluorenyl and 9,9′-bifluorenylidene were also produced in the reaction, but examination of the nmr indicates that they were produced in less than 3% yield each.

Method B. Copper–Quinoline.—Under nitrogen, fluorene-9-carboxylic acid (200 mg, 0.953 mmol), copper powder [632 mg, 9.96 mmol, Fisher (electrolytic) purified], and distilled deaerated quinoline (3.2 ml) were heated at reflux for 1.1 hr. After cooling, the reaction mixture was taken up in dichloromethane (50 ml), filtered through sintered glass, and extracted twice with 10% aqueous hydrochloric acid. Removal of solvent afforded 191 mg of material. Examination of this material by nmr and thin layer comparison spots indicated that the reaction afforded fluorene, 9,9′-bifluorenyl, and 9,9′-bifluorenylidene in yields of 85, 6, and 4%, respectively.

Method C. Thermal Decarboxylation.—Under nitrogen, fluorene-9-carboxylic acid (50.0 mg, 23.8 mmol) in a sublimation apparatus was heated to 290° for 5 min, subliming material (34 mg) onto the cold finger. This material was examined by nmr and thin layer, and identified on that basis as being mainly comprised of a mixture of fluorene (38% yield), fluorene-9-carboxylic acid (6% yield), and 9,9′-bifluorenyl (12% yield).

Method D. Basic Copper Carbonate (0.03 Molar Equiv).—Fluorene-9-carboxylic acid (61.4 mg, 0.28 mmol) and basic copper carbonate (1.9 mg, 0.0086 mmol) were mixed and heated under nitrogen in a sublimation apparatus to 265° for 5 min. After cooling, the material was removed from the cold finger with dichloromethane and extracted with 5% potassium carbonate solution, and the solvent was removed on a rotary evaporator. The basic aqueous extract was acidified with hydrochloric acid and extracted with dichloromethane, and the solvent was removed on a rotary evaporator, affording 18 mg (30% recovery) of starting material, mp 221–224° (lit.[4] mp 225–228°), confirmed by nmr comparisons. The neutral materials were applied to a preparative thick layer plate, and eluted twice with 3:1 pentane–dichloromethane. The four major bands were removed with chloroform, and identified by comparison of R_f's, melting points, and spectral data with authentic samples of material. The yields (based on starting material consumed) and R_f's of these materials are shown in Table II.

Table II

Products of Basic Copper Carbonate Decarboxylation of Fluorene-9-carboxylic Acid

Material	R_f	Yield, mg (%)
Fluorene	0.85	16.3 (48)
Fluorenone	0.21	4.2 (11)
9,9′-Bifluorenyl	0.66	3.5 (10)
9,9′-Bifluorenylidene	0.75	1.0 (3)

Method E. Basic Copper Carbonate (2.0 Molar Equiv).—Fluorene-9-carboxylic acid (50 mg, 0.24 mmol) and basic copper carbonate (106 mg, 0.48 mmol) were mixed and heated to 265° for 5 min under nitrogen in a sublimation apparatus. The material was removed from the cold finger with dichloromethane. The material was applied to a preparative thick layer plate and eluted twice with 3:1 pentane–dichloromethane, affording 24 mg (56% yield) of fluorenone, mp 80–82° (lit.[14] mp 83°), and 4 mg (10% yield) of 9,9′-bifluorenyl, identified by spectral data and thin layer comparison with authentic material.

Preparation of 9,9′-Bifluorenylidene.—Utilizing the method of Fuson and Porter,[10] 9-bromofluorene (1.00 g, 4.09 mmol) generated 391 mg (58% yield) of bifluorenylidene, mp 186.0–187.5° (lit.[10] mp 188–190°) after recrystallization from ethanol–benzene.

Preparation of 9,9′-Bifluorenyl.[9]—9-Bromofluorene (764 mg, 3.1 mmol) was dissolved in 30.5 ml of hot acetone. A solution of 915 mg (6.2 mmol) of sodium iodide in 6.1 ml of acetone was added, and the mixture was refluxed for 5.5 hr. The solution was cooled to 40°, and 4 ml of 10% aqueous sodium thiosulfate and 30 ml of water were added. The resultant crystals were filtered, washed with water, and air dried. The material was recrystallized from 2.5 ml of xylene, filtered, washed with 0.5 ml of xylene, and air dried, affording 357 mg (70% yield) of 9,9′-bifluorenyl: mp 243.5–245.0° (lit.[15] mp 247°); nmr (CCl_4) δ 7.68–6.82 (16 H, m), 4.76 (2 H, s), ir ($CHCl_3$) 1475, 1450 cm^{-1}.

(12) (a) M. Nilsson, *Tetrahedron Lett.*, 679 (1966); (b) M. Nilsson and O. Wennerström, *ibid.*, 3307 (1968); (c) G. M. Whitesides, W. F. Fischer, Jr., J. San Filippo, Jr., R. W. Bashe, and H. O. House, *J. Amer. Chem. Soc.*, **91**, 4871 (1969); (d) R. J. De Pasquale and C. Tamborski, *J. Org. Chem.*, **34**, 1736 (1969).

(13) R. C. Weast, Ed., "Handbook of Chemistry and Physics," 46th ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1965, p C-324.

(14) Reference 13, p C-325.

(15) Reference 13, p C-206.

Registry No.—Fluorene-9-carboxylic acid, 1989-33-9.

Acknowledgment.—We wish to thank the Petroleum Research Fund for their generous support of our programs. We are indebted to Dr. William Sheppard for a generous gift of pentafluorophenylcopper.

The Friedel–Crafts Reaction with 1-Bromo-1-phenyl-2-propanone

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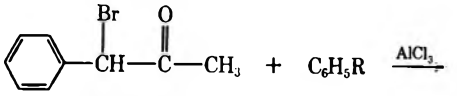
Received September 20, 1971

Under Friedel–Crafts reaction conditions, 1-bromo-1-phenyl-2-propanone (**1**) reacts with benzene to give 1,1-diphenyl-2-propanone (**2a**) in good yield.[1] As an extension of this method, Cragoe, *et al.*,[2] reacted **1** with substituted benzene to prepare substituted diphenyl-2-propanones (**2**). However, when they reacted **1** with



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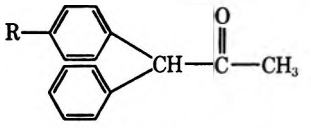
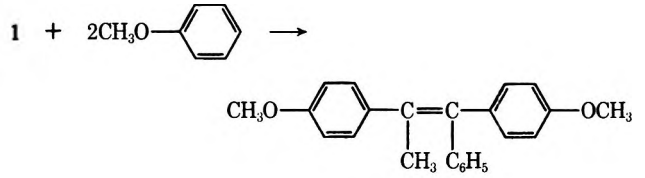


2a, R = H
b, R = CH_3
c, R = Cl

anisole, they isolated 1,2-bis(*p*-methoxyphenyl)-1-phenylpropene (**3**) in good yield.



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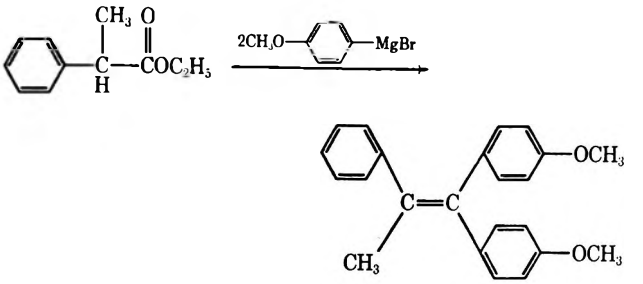
The structure assignment was based on elemental analysis and infrared data. Similar reaction[3,4] has been reported for acetyl chloride and anisole with aluminum chloride which gave 1,1-bis(*p*-methoxyphenyl)ethylene.

In our synthetic program, we had the occasion to prepare 1,1-bis(*p*-methoxyphenyl)-2-phenylpropene (**4**) by treating ethyl 2-phenylpropionate with *p*-methoxyphenylmagnesium bromide.

The melting point and boiling point of **4** were identical with those of **3** as reported by Cragoe.[2] It seemed unusual that two isomeric compounds should have the same melting point and boiling point. The preparation of **3** was repeated according to the literature procedure.[2]



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The product was found to be identical in every respect (mixture melting point, ir, uv, nmr, and tlc) with **4**.

It remained to be determined which structure was correct. Ozonolysis of **3** would give 4-methoxyacetophenone and 4-methoxybenzophenone, while ozonolysis of **4** would give acetophenone and 4,4′-dimethoxybenzophenone. Ozonolysis and characterization of the reaction products of 1-bromo-1-phenyl-2-propanone (**1**) with anisole and ethyl 2-phenylpropionate with *p*-methoxyphenylmagnesium bromide confirmed that in both cases the end products are 4,4′-dimethoxybenzophenone and acetophenone, thus proving that **4** is the correct structure.

Ketones are known to rearrange under acidic conditions[5–7] and this may partly explain the formation of **4** from **1** under Friedel–Crafts reaction conditions.

Experimental Section[8]

Ethyl 2-Phenylpropionate.—To a solution of 34 g (0.13 mol) of 2-phenylpropionic acid in 100 ml of ethyl iodide cooled in an ice bath was added 26 g (0.07 mol) of Ag_2O in small portions with stirring. Stirring was continued at room temperature for 2 hr. The AgI was filtered and the filtrate was dried and concentrated. The ester was distilled to give 28.2 g of colorless liquid: bp 112–115° (15 mm); $n^{22}D$ 1.4932; ir 1730 cm^{-1} (ester); nmr δ 7.30 (s, 5, aromatic), 4.10 (q, 2, CH_2 next to CH_3), 3.70 (q, 1, CH), 1.5 (d, 3, CH_3), and 1.17 (t, 3, CH_3).

Anal. Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.92; H, 7.79.

1,1-Bis(*p*-methoxyphenyl)-2-phenylpropene. Method A.—To a mixture of *p*-methoxyphenyl Grignard reagent [formed by reacting 41.1 g (0.22 mol) of *p*-bromoanisole and 5.76 g (0.24 g-atom) of Mg in 100 ml of ether] was added slowly 17.8 g (0.1 mol) of ethyl 2-phenylpropionate dissolved in 50 ml of ether. The mixture was refluxed with stirring for 1 hr and then was poured into ice water. The mixture was acidified with concentrated HCl, extracted with ether, and dried. Removal of ether gave a viscous brown residue. The crude product was dissolved in hot hexane to give a pale yellow solution. The hexane was removed under reduced pressure and the residue was distilled to give 25 g of colorless product that solidified immediately, bp 190–195° (0.08 mm). The product was recrystallized from hexane and then from methanol to give 18 g of colorless crystals: mp 93–94.5°; ir 1602 cm^{-1} (C=C conjugated); uv λ_{max} (isooctane) 285 mμ (ε 14,736) and 247 (21,530); nmr δ 7.13 (s, 5, aromatic), 7.3 (q, 4, aromatic, J_{AB} = 9 Hz), 6.68 (q, 4, aromatic, J_{AB} = 9 Hz), 3.8 (s, 3, OCH_3), 3.66 (s, 3, OCH_3), and 2.13 (s, 3, CH_3).

Anal. Calcd for $C_{23}H_{22}O_2$: C, 83.60; H, 6.71. Found: C, 83.29; H, 6.63.

Method B[2].—To a stirring solution of 55.5 g (0.41 mol) of 1-phenyl-2-propanone in 250 g of CS_2 was added 67 g (0.42 mol)

(1) E. M. Schultz, *Org. Syn.*, **29**, 38 (1949).
(2) E. J. Cragoe, Jr., A. M. Pietruskiewiez, and C. M. Robb, *J. Org. Chem.*, **23**, 973 (1958).
(3) L. Gattermann, *Ber.*, **22**, 1129 (1889).
(4) L. Gattermann, R. Ehrhardt, and H. Maisch, *ibid.*, **23**, 1199 (1890).
(5) S. Barton and C. R. Porter, *J. Chem. Soc.*, 2483 (1956).
(6) H. D. Zook and S. C. Paviak, *J. Amer. Chem. Soc.*, **77**, 2501 (1955).
(7) H. D. Zook, W E. Smith, and J. C. Green, *ibid.*, **79**, 4436 (1957).
(8) Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Nuclear magnetic resonance spectra were recorded on a Varian A-60A spectrometer using $CDCl_3$ as solvent and TMS as internal standard. Ultraviolet spectra were obtained on a Cary Model 14 spectrophotometer using spectral grade solvents. Microanalyses were performed by Chemical Analytical Services, University of California, Berkeley, Calif. 94701.

of bromine dropwise. This bromination solution was added to a mixture of 340 ml of anisole and 113 g (0.84 mol) of $AlCl_3$ in a 1-l. three-necked flask equipped with mechanical stirrer. The mixture was heated to 80–90° for 1 hr with stirring and then was stirred at room temperature for 2 hr. The mixture was poured into 500 g of ice and acidified with 75 ml of concentrated HCl. The organic layer was separated and the aqueous layer was extracted with 1 l. of ether. The combined organic layers were washed with water, dilute NaOH, and water. The dried solution was concentrated under reduced pressure. The residue was distilled to give 80 g of product bp 180–190° (0.08 mm). Recrystallization of the product from methanol twice gave 54 g of colorless crystals: mp 93–94.5°; ir 1602 cm^{-1} (C=C conjugated); uv λ_{max} (isooctane) 285 mμ (ε 14,840) and 247 (21,653); nmr δ 7.13 (s, 5, aromatic), 7.3 (q, 4, aromatic, J_{AB} = 9 Hz), 6.68 (q, 4, aromatic, J_{AB} = 9 Hz), 3.8 (s, 3, OCH_3), 3.66 (s, 3, OCH_3), and 2.13 (s, 3, CH_3). A mixture melting point with the product obtained from method A showed no depression.

Ozonolysis of 1,1-Bis(*p*-methoxyphenyl)-2-phenylpropene (4).—A solution of 3 g of the olefin **4** in 200 ml of ethyl acetate was cooled in a Dry Ice–acetone bath. A stream of ozone was passed into the solution. After about 20 min, the solution became light blue. Ozone was passed into the solution for another 30 min. The ozone generator was switched off and oxygen was passed through the solution for 20 min. The flask was removed from the Dry Ice–acetone bath and dry nitrogen was passed through the solution for 20 min. The solvent was removed under reduced pressure to give a yellow mixture of solid and oil. The residue was stirred in 25 ml of acetic acid and 1 g of Zn dust for 1 hr at room temperature. The mixture was diluted with 300 ml of ether and was filtered through Celite. The clear filtrate was washed with 2 × 200 ml of water and dilute $NaHCO_3$ solution until neutral. The ether solution was dried and concentrated to give a semisolid. Recrystallization from alcohol gave 1.5 g of product, mp 141–143°. Recrystallization again from hexane gave tiny needles, mp 142–143°. Dimethoxybenzophenone from Aldrich, recrystallized twice, melted at 142–144°. A mixture melting point showed no depression. Both materials showed the same spot on tlc (20% ethyl acetate in benzene). The ir, uv, and nmr spectra of both materials were also identical.

Acetophenone was detected by tlc in the alcoholic mother liquor, but no attempt was made to isolate it.

Registry No.—**1**, 23022-83-5; **4**, 33835-17-5; ethyl 2-phenylpropionate, 2510-99-8.

Acknowledgment.—This research was supported by a grant from the Population Council, Contract No. AID/csd-2491.

Glyoxal Derivatives. IV. 2-Dimethoxymethyl-4,5-dimethoxy-1,3-dioxolane and 2,2′-Bis(4,5-dimethoxy-1,3-dioxolane)

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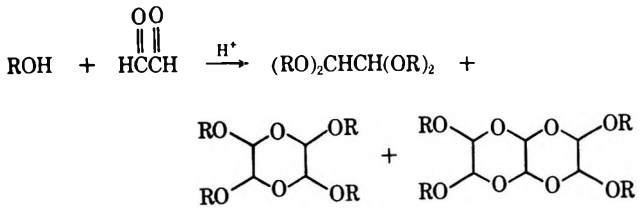
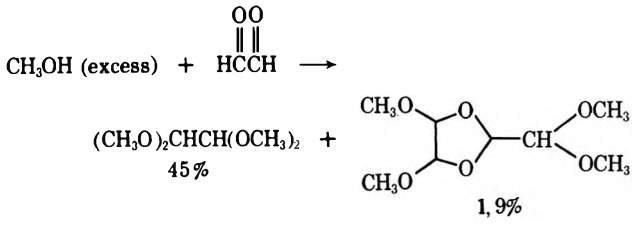
The reaction of aqueous glyoxal with alcohols to give bisacetals is well known and has been the subject of two basic patents.[2] General descriptions of the preparation of tetraalkoxyethanes, tetraalkoxydioxanes, and tetraalkoxynaphthodioxanes from aqueous glyoxal and

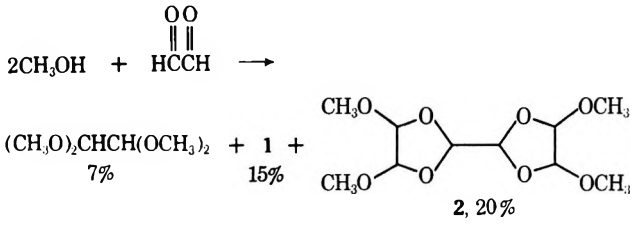


butanol or isopropyl alcohol have also been published.[3] The reaction of glyoxal with methyl alcohol, or glyoxal sulfate with methyl alcohol in the presence of calcium chloride, has also been reported.[4,5] In those cases the only product isolated was 1,1,2,2-tetrakis(methoxy)-ethane. In this paper we report the isolation and identification of two totally new acetal derivatives of glyoxal based upon the dimeric and trimeric forms of glyoxal.

We have found that 80% glyoxal reacts with methyl alcohol under acid conditions to give, as previously reported, 1,1,2,2-tetrakis(methoxy)ethane and a new compound, 2-dimethoxymethyl-4,5-dimethoxy-1,3-dioxolane (**1**), in 45 and 9% yields, respectively. If the



reaction is run with only 2 mol of methyl alcohol/mol of glyoxal the higher molecular weight dimer and a trimer, **2**, predominate. In both of these reactions



substantial amounts of intractable residues were produced.

The structures of compounds **1** and **2** were deduced from their molecular weights, carbon and hydrogen analyses, and proton magnetic resonance spectra. In the case of compound **2**, no reasonable alternative to the assigned structure exists, apart from diastereoisomerism. The final choice between two possible structures for compound **1** is based upon interpolation between the rigorously assigned structure of glyoxal dimer[6] and compound **2**.

The elemental analysis and molecular weight of compound **2** are supportive for a trimer of glyoxal with four methoxyl groups. The pmr spectrum in deuteriochloroform at 60 MHz shows one strong line at 3.41 ppm (downfield from tetramethylsilane) representing the four methoxyl groups and three equally intense

(1) (a) Tarrytown; (b) South Charleston.

(2) (a) C. B. Purves, U. S. Patent 2,194,405 (March 19, 1940); (b) L. G. MacDowell and R. W. McNamee, British Patent 559,362 (Feb 16, 1944).

(3) "General Chemistry of Glyoxal," Union Carbide Product Booklet, 1965, p F-41296.

(4) H. O. L. Fisher and C. Taube, *Chem. Ber.*, **59B**, 851 (1926).

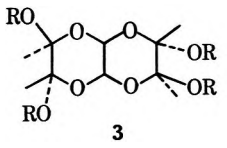
(5) D. H. Graangard and C. B. Purves, *J. Amer. Chem. Soc.*, **61**, 755 (1939); *ibid*, **61**, 428 (1939).

(6) E. B. Whipple, *ibid*, **92**, 7183 (1970).

singlets at 4.98, 5.03, and 5.13 ppm for the skeletal CH protons.

In order for the six protons from the three glyoxal units to give only three equally intense lines, it is necessary that the protons occur in three equivalent pairs. Since no hyperfine splittings are apparent in the spectrum, one might naturally suspect that each equivalent pair consists of vicinal protons from a glyoxal unit in the methylated trimer. This would require that each glyoxal unit lie across a symmetry element in the molecule, and that no two of these glyoxal units be alike.

Two structures (**3** and **4**) that can satisfy these condi-



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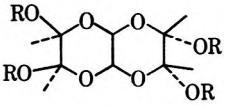


4

tions involve the heretofore presumed 1,4,5,8-naphthodioxane rings.

The equivalence of any pair of CH groups is removed in the ^{13}C satellite spectrum, since one of the protons will couple strongly to the directly bonded ^{13}C and the probability that the other is also attached to ^{13}C is small (the natural abundance of ^{13}C is 1.1%). One can therefore tell from the satellite spectrum whether the absence of resolvable coupling constants results from the equivalence of coupled groups.[7] This experiment, which requires time averaging to yield detectable signals, gives the result shown in Figure 1. Only one of the three ring proton lines is found to undergo additional splitting ($J_{H,H}$ = 6.76 Hz) from a vicinal proton when viewed in the ^{13}C satellite spectrum; therefore, of the three equivalent proton pairs, only one contains mutually coupled members.

Neither of the fused dioxane structures **3** or **4** is compatible with this result. The trans fused structure **3** would have two geminal proton pairs in a trans diaxial configuration, leading one to expect at least two strongly coupled pairs. A cis ring fusion would, on the other hand, require three axial–equatorial pairs, so that either all would be visibly coupled or none would be. One is forced, therefore, to abandon all the structural possibilities in which the members of all three vicinal proton pairs are equivalent and seek alternatives in which there is only one such pair, the other two glyoxal units being symmetrically located with respect to each other, but with dissimilar environments for their two CH groups. The coupling between the nonequivalent vicinial pairs must then be small by virtue of electronegative substitution and an unfavorable conformation, as in glyoxal dimer.[6,8]

A simple extension of the dioxolane structure therefore permits one to satisfy the conditions imposed by the ^{13}C satellite nmr spectrum, including reasonable agreement with the observed magnitude of the resolved vicinal coupling. There are, moreover, two such structures which correspond to a meso and racemic combination of two optically active dioxolane rings (**5** and **6**). One might therefore expect to find two diastereo-

(7) A. D. Cohen, J. Sheppard, and J. J. Turner, *Proc. Chem. Soc. London*, 118 (1958).

(8) See, however, F. A. L. Anet, *J. Amer. Chem. Soc.*, **84**, 747 (1962), where quite substantial trans vicinal couplings are observed in methyl-substituted dioxolane rings.

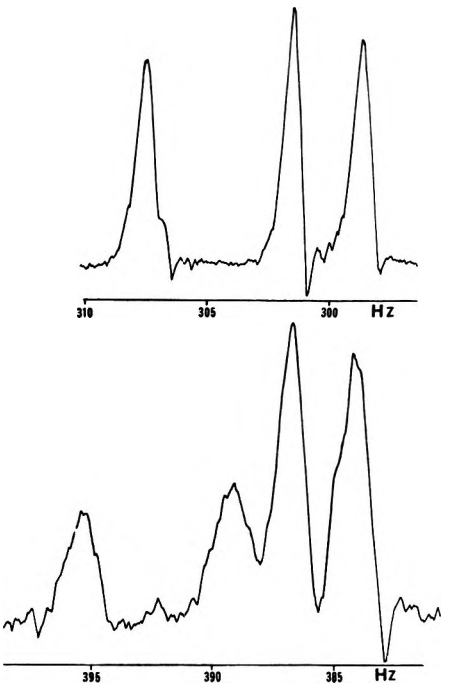
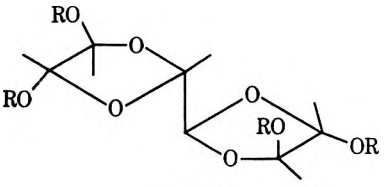
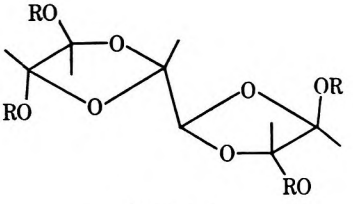


Figure 1.—Top: proton magnetic resonance spectrum (60 MHz) of skeletal protons in compound **2** in $CDCl_3$ (TMS) solution. Bottom: time averaged (300 accumulations) low-field ^{13}C satellite spectrum of the corresponding protons. The frequency scales in both spectra are referenced to tetramethylsilane.



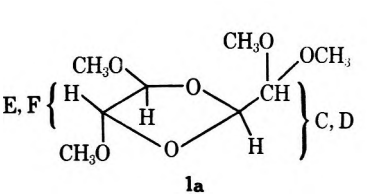
5 (*dl*)



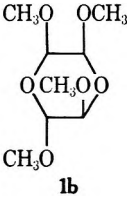
6 (meso)

isomers of compound **2**, and studies combining solvent effects and high magnetic fields do indeed permit every line in its nmr spectrum (Figure 2) to be resolved into two components present in about a 2:1 ratio (no significance can be attached to the isomer ratio which is reported here for an isolated product of the reaction). The methylated trimer can, therefore, be assigned structures **5** and **6** with confidence.

The pmr spectrum of compound **1** at 60 MHz in deuteriochloroform is shown in Figure 3. Only two structures corresponding to a tetramethoxylated dimer are compatible. These are **1a** and **1b**.



1a



1b

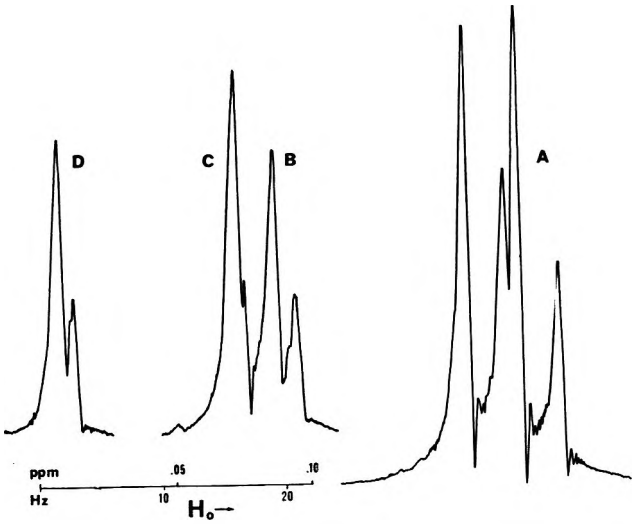
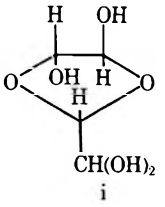


Figure 2.—Pmr absorption bands of compound 2 at 220 MHz in benzene solution, showing partially resolved lines from disastereoisomeric structures. The spectrometer gain in region A is reduced by half. The positions of the principal lines are given in Table II.

The ring proton signals C, D, E, and F of compound 1 are strikingly similar to the resonances observed for the ring protons of glyoxal dimer, which has been shown to have structure i.[6] The ring protons (E and



i

F) are nonequivalent, but are weakly coupled, as in 2 and in glyoxal dimer. Protons C and D are vicinal, nonequivalent, and favorably oriented for spin coupling, and therefore appear as a typical AB pattern. The chemical shifts of compound 1 in D_2O solution (dioxane reference) bear a simple relation to those of glyoxal dimer. Ring protons D, E, and F show incremental upfield shifts due to methoxylation of 0.0, 0.3, and 0.3 ppm, respectively, while the side-chain proton C shifts upfield by 0.6 ppm. All of the shifts are thus in accord with a simple rule that substitution of methyl groups for hydroxyl protons causes an additive, 0.3-ppm upfield shift of protons on carbon attached to the oxygen atom on which the substitution occurs, and causes negligible shifts elsewhere.

In strong magnetic fields or in pyridine solution, the methoxyl signals from compound 1 can be resolved into four lines. With increasing temperature, two of these lines approach coalescence, while the separation between the others increases very slightly, and the vicinal coupling constant between protons C and D diminishes. This behavior is typical for rotation of a group about an asymmetric environment. This fact,[9] coupled with the shape and shift similarity to glyoxal dimer, gives further support to the assignment of **1a** as the structure.

These results also suggest, but do not prove, that glyoxal trimer also consists of coupled dioxolane rings.

(9) This analysis is not conclusive; however, it is much easier to rationalize on the basis of conformational changes in **1a** than **1b**: L. M. Jackson and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Oxford Pergamon Press," London, 1969, Chapter 5-2.

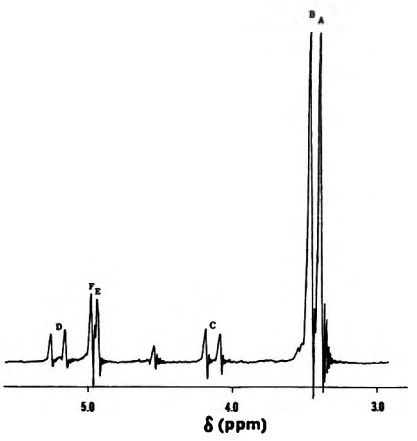


Figure 3.—Pmr spectrum (60 MHz) of compound 1 in $CDCl_3$ (TMS) solution. The line at 4.5 ppm is an impurity, suspected to be water.

An effort was therefore made to detect corresponding lines in the nmr spectrum of aqueous glyoxal solutions. One might expect to find these lines near their counterparts in glyoxal dimer, particularly in view of the earlier observation that incremental shifts on O-alkylation of the dimer were small except for CH groups attached directly to the oxygen involved. Two lines (lines 10, and 14 in reference 6) due to trimers have been reported in about the right places, and show evidence of additional structure (line 9) which is most reasonably attributed to diastereoisomeric pairs. Moreover, the spectrum of our compound 2 in D_2O solution shows a complex, single band at 1.45 ppm downfield from internal dioxane, in reasonable accord with the incremental shifts derived earlier for methoxylation of the dimer. It is also noteable that bands 10 and 14 in aqueous glyoxal are not shifted or broadened by borate salts,[6] indicating that they are due to a structure which does not contain eclipsed hydroxyl groups. It therefore appears that structures corresponding to **5** and **6** do exist as a minor component in aqueous glyoxal solutions along with at least one other trimeric species (line 16) in comparable amounts.[6]

Experimental Section[10]

A.—A mixture of 290.0 g of 80% aqueous glyoxal (4.0 mol), 1000.0 g of methyl alcohol (32.3 mol), and 182.0 g of *p*-toluenesulfonic acid (0.96 mol) in 2 l. of chloroform was heated at reflux for 4 days. No water azeotrope was observed; so the chloroform–methanol azeotrope was distilled with the addition of fresh chloroform until no more methyl alcohol was in the distillate. At that point, a water–chloroform azeotrope began to come over, and the mixture was neutralized with sodium carbonate and filtered and the water was removed by azeotropic distillation with chloroform. Distillation of the resultant product mixture through a Nester–Faust spinning-band column gave 1,1,2,2-tetrakis(methoxy)ethane, bp 83–85° (48 mm), $n^{25}D$ 1.4006 [lit.[2b,5] bp 78–79° (50 mm), $n^{25}D$ 1.4010], 271.2 g (45% yield), and 2-dimethoxymethyl-4,5-dimethoxy-1,3-dioxolane (1), bp 98–99° (5 mm), $n^{25}D$ 1.4225, 36.0 g (9% yield).

Anal. Calcd for $C_8H_{16}O_6$: C, 46.16; H, 7.69; mol wt, 208. Found: C, 46.23; H, 7.63, mol wt, 229.

B.—In another type of experiment, 64.0 g of methanol (2.0 mol), 72.5 g of 80% glyoxal (1.0 mol), and 2.0 g of *p*-toluenesulfonic acid (0.01 mol) were heated at reflux for 20 hr, chloroform was added, and the unreacted methanol was removed

(10) All melting and boiling points are uncorrected. Infrared spectra were measured on a Perkin-Elmer Infracord. Nmr spectra were recorded on Varian 60-MHz and 220-MHz instruments. Molecular weights were determined by Crobaugh Laboratories, Cleveland, Ohio, and microanalysis were performed by Union Carbide staff members.

azeotropically. After no more methanol was present, the water was removed azeotropically with the chloroform. The remaining chloroform was distilled away from the reaction mixture, 32.0 g of methyl alcohol (1.0 mol) was added, and the solution was brought to reflux for another 24 hr. The above procedure was then repeated and the resultant product mixture was distilled through the Nester–Faust spinning-band column to give 1,1,2,2-tetrakis(methoxy)ethane, bp 85–90° (25 mm), 6.6 g (4% yield), 2-dimethoxymethyl-4,5-dimethoxy-1,3-dioxolane (1), bp 95–98° (5 mm), 16.0 g (15% yield), and 2,2′-bis(4,5-dimethoxy-1,3-dioxolane) (2), bp 105–108° (5 mm), mp 109–110°, 17.9 g (20% yield).

Anal. Calcd for $C_{10}H_{18}O_8$: C, 45.11; H, 6.77; mol wt, 266. Found: C, 45.11; H, 6.81; mol wt, 263.

The infrared spectra of both compounds 1 and 2 showed no carbonyl or hydroxyl bonds, but had strong absorption in that region expected for ethers or acetals.

Registry No.—1, 33834-89-8; 2, 33834-90-1.

The Photochemistry of *S*-Methyl Diazothioacetate[1]

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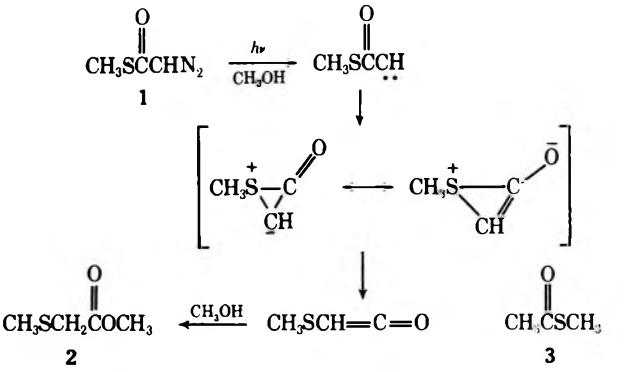
The photochemistry of α-diazo esters has received much attention recently both from chemists interested in the nature and mechanisms of the reactions undergone by these species[2a-e] and from others interested in using them as labeling reagents for active sites of enzymes.[3a-f] However, Wolff rearrangement of the carbenes produced upon irradiation of the diazo esters has diminished the utility of these compounds as labeling reagents, particularly in the case of diazoacetylglyceraldehyde-3-phosphate dehydrogenase[4] (only Wolff rearrangement observed) but also in diazoacetylchymotrypsin[3a,b] (15–20% rearrangement). In the former case, to date the only investigation of an α-diazothio ester, the per cent Wolff rearrangement was not determined since other products arising from, for example, solvent insertion would have gone undetected.

Since we are interested in enzyme labeling with diazo esters and because many enzymes contain the -SH group of a cysteine moiety at their active sites, we wished to examine the extent of Wolff rearrangement of an excited diazothio ester relative to oxygen (ester) and nitrogen (amide) analogs, and the effect of excited state multiplicity on the rearrangement. For these purposes the photochemistry of *S*-methyl diazothioacetate (1) has been studied.

Ester 1 was prepared in 25% yield from diazomethane and methyl chlorothiolformate. Direct photolysis of 1 in methanol with 310–380 nm light afforded in 86% yield only one detectable volatile product with a gc retention time identical with that of known methyl methylthioacetate (2). A dark control showed no reaction. The identity of the product was firmly established by distilling the final solution carefully to remove the methanol; the infrared spectrum of the remaining oil was identical with that of known 2.

The sensitized decomposition was carried out using xanthone as sensitizer and light of wavelengths 310–355 nm. Gas chromatographic analysis of the reaction mixture present when 95% of 1 had disappeared revealed only a small amount of one product with a retention time identical with that of known *S*-methyl thioacetate (3) corresponding in area to a 7% yield



from 1.[5] Benzophenone sensitization gave similar results. As expected, xanthone-sensitized decomposition of 1 in isopropyl alcohol, a better hydrogen atom donor than methanol, gave an increased yield (23%) of this product. Once again dark controls showed no loss of 1.

Assuming that the direct photolysis of 1 generates a singlet carbene, our results show that this carbene undergoes a very rapid Wolff rearrangement. No products arising from insertion into the solvent -OH bond or from hydrogen abstraction were detected by our methods of analysis. This is in contrast to the case with α-diazo esters and amides, which show a lower (20–60%) per cent rearrangement and give a significant amount of the other products.[2d] This enhanced migratory aptitude of a sulfur atom to a carbene center has also been found in carbenes generated from *p*-tosylhydrazone decomposition.[6,7]

The results of the sensitized decomposition demonstrate that multiplicity has a profound effect on the Wolff rearrangement in that the latter is eliminated entirely and only a moderate amount of what is probably the reduction product 3, presumably formed *via* stepwise hydrogen abstraction by a triplet carbene, is

(1) This work was supported by a grant (GB 27644) from the National Science Foundation and by a Faculty Research Grant from the Research Council of the University of Massachusetts, Amherst, Mass.

(2) Good leading references are (a) T. Dominh and O. P. Strausz, *J. Amer. Chem. Soc.*, **92**, 1766 (1970); (b) D. E. Thornton, R. K. Gosavi, and O. P. Strausz, *ibid.*, **92**, 1768 (1970); (c) W. Ando, *et al.*, *J. Org. Chem.*, **36**, 1732 (1971); (d) H. Chaimovich, R. J. Vaughan, and F. H. Westheimer, *J. Amer. Chem. Soc.*, **90**, 4088 (1968); (e) G. O. Schenck and A. Ritter, *Tetrahedron Lett.*, 3189 (1968).

(3) (a) A. Singh, E. R. Thornton, and F. H. Westheimer, *J. Biol. Chem.*, **237**, 3006 (1962); (b) J. Schafer, P. Baronowsky, R. Laursen, F. Finn, and F. H. Westheimer, *ibid.*, **241**, 421 (1966); (c) R. J. Vaughan and F. H. Westheimer, *J. Amer. Chem. Soc.*, **91**, 217 (1969); (d) D. T. Browne, S. S. Hixson, and F. H. Westheimer, *J. Biol. Chem.*, **246**, 4477 (1971). (e) C. Hexter and F. H. Westheimer, *ibid.*, **246**, 3928, 3934 (1971); (f) see also R. R. Rando, *J. Amer. Chem. Soc.*, **92**, 6706 (1970).

(4) J. H. Scott, unpublished results, Harvard University, 1965. Part of this work is cited in ref 2d.

(5) Due to the high absorption of 1 and the low solubility of sensitizer, it was necessary to use a dilute solution containing a relatively large amount of sensitizer in the presence of a very small amount of 1 in order to ensure complete absorption of light by the sensitizer. This precluded an extensive search for unknown products.

(6) J. H. Robson and H. Schechter, *J. Amer. Chem. Soc.*, **89**, 7112 (1967).

(7) Wolff rearrangement *via* an oxirene formation–hydrogen shift sequence, a minor process in diazo ester photolysis (vapor phase),[2b] seems unlikely in the present case, but it cannot be ruled out.

found.[8a] Most likely nonvolatile materials or products of very short retention time (see Experimental Section) formed *via* radical reactions account for the balance of the products. Triplet carbenes might be expected to show radical-like behavior; we have found that even when a very good migrating group is present they do not undergo the Wolff rearrangement.[8a,b]

Perhaps most importantly these results suggest that the sensitized decomposition of diazoacyl enzymes may prove to be a fruitful method for labeling active sites. We are actively investigating this area.

Experimental Section

Photolyses were carried out in a Rayonet photochemical reactor (Southern N. E. Ultraviolet Co.) equipped with RPR-3500 Å lamps. The reaction vessel was immersed in the well of a Pyrex cooling chamber around which water at 23–27° was pumped. The well was filled with water for the direct photolysis and with filter solution for the sensitized photolysis.

Gas chromatography was carried out on a Perkin-Elmer Model 990 gas chromatograph using a 7 ft × $^1/_8$ in. Poropak Q, 80/100 mesh column. Column temperature was 200°, injector and manifold temperatures 250°, and He flow rate 50 cc/min.

The ir spectra were determined on a Beckman IR-10 spectrophotometer, and nmr spectra on a Varian A-60 spectrometer using TMS as internal standard. The uv spectra were run on a Cary 14 spectrophotometer.

Microanalyses were performed by Mr. Charles Meade of the University of Massachusetts Microanalytical Laboratory.

S-Methyl Diazothioacetate (1).—To 500 ml of a stirred solution of diazomethane in ether [prepared[9] from 27 g of bis(*N*-methyl-*N*-nitroso)terephthalamide] cooled in an ice bath was added dropwise a solution of 5.0 ml (56.9 mmol) of methyl chlorothiolformate in 100 ml of anhydrous ether over 15 min. The reaction flask was kept stoppered overnight at room temperature in the dark. The ether and excess diazomethane were blown off with a stream of dry nitrogen. An additional 50-ml aliquot of anhydrous ether was added and blown off to give 7.97 g of a deep yellow oil which was then stored in the refrigerator and protected from light. Portions of the crude oil were chromatographed before use, and the pure product was either used immediately or stored up to several months in the freezer before use.

In a typical purification 1.40 g of the crude oil was chromatographed on a silical gel column packed and eluted with 1:20 anhydrous ether–Skelly F (v/v). Fractions showing only material with R_f 0.42 on silica gel tlc in 1:5 ether–Skelly F were combined, and the solvent was removed with a nitrogen stream to give a thin yellow oil, *S*-methyl diazothioacetate (**1**, 0.292 g, 25%): ir (neat) 2095 (diazo), 1620 (C=O), 1335, 1133, 1028, and 856 cm^{-1}; nmr ($CDCl_3$) δ 2.56 (s, 3, CH_3) and 5.70 (s, 1, CH); uv max (MeOH) 278 nm (ε 13,300) and 241 (9120).

Anal. Calcd for $C_3H_4SON_2$: C, 31.04; H, 3.47; N, 24.14; S, 27.56. Found: C, 31.00; H, 3.50; N, 24.10; S, 27.50.

Carbon Disulfide Extractions.—In order to eliminate the big methanol peak on the gc traces, samples in methanol were routinely extracted into CS_2. CS_2 (1 ml), 2 ml of saturated sodium chloride solution, 0.25 ml of water, and 1 ml of the methanol solution to be analyzed were shaken together, and the CS_2 layer was then separated and examined by gc. In extractions with known samples of methyl methylthioacetate[10] (**2**) and *S*-methyl thioacetate[11] (**3**) at least 70 and 80%, respectively, of the amounts of these compounds originally in the methanol layer could be brought into the CS_2 layer. Similar products in the photolysis mixtures, then, can be expected to appear in the CS_2 layer.

CS_2 extractions were carried out as above only with pure methanol. Gc of the CS_2 layers reproducibly gave a certain pattern of peaks in the 0–4-min range which are referred to below as the "background peaks;" because of these peaks, products of retention times less than 4 min would go undetected.

Direct Photolysis of *S*-Methyl Diazothioacetate (1).—A solution of 0.0795 g (0.685 mmol) of **1** in 20 ml of anhydrous methanol in a Pyrex tube stoppered with a serum cap was purged with nitrogen for 20 min. The solution was photolyzed for 5.5 hr. After this time less than 1% of the original absorption at 278 nm remained. A similar solution kept at room temperature in the dark for 14 hr showed no decrease in the absorption at 278 nm.

Gc of the final solution revealed, in addition to the methanol peak, only a peak of retention time 17.3 min, identical with the retention time of known methyl methylthioacetate (**2**) on the same column. The peak area corresponded to an 86% yield of **2** from **1**. In addition, a 0.5-ml aliquot of the final photolysis solution was diluted with 0.5 ml of methanol and carried through a CS_2 extraction. Gc of the CS_2 layer showed only the background peaks and the peak at 17.3 min. When 0.5 ml of the original reaction solution, before photolysis, was treated similarly only background peaks were seen.

A portion of the final reaction solution was distilled at atmospheric pressure until no further methanol distilled, 10 ml of anhydrous ether was added to the liquid remaining, and the ether solution was treated with $MgSO_4$, filtered, and blown down under nitrogen. An ir spectrum (neat) of the thin oil remaining was identical with that of known **2**.

Sensitized Photolysis of *S*-Methyl Diazothioacetate (1).—A solution of 0.0150 g (0.129 mmol) of **1** and 0.2503 g (1.23 mmol) of xanthone (Aldrich Chemical Co., recrystallized twice from ethanol) in 50 ml of anhydrous methanol in a Pyrex vessel stoppered with a serum cap was purged with nitrogen for 20 min. The reaction solution was surrounded by a filter solution (270 g of $NiSO_4 \cdot 6H_2O$ and 169 g of $CoSO_4 \cdot 7H_2O$ diluted to 870 ml) which cut off light of wavelengths greater than 355 nm (2.4-cm path length).

The solution was photolyzed for 8 hr. Throughout the photolysis aliquots of the reaction solution were taken and the change in absorption at 284 nm after 1 drop of concentrated HCl was added was noted. The original reaction solution showed a 20% loss in absorption at 284 nm after treatment with acid. After 8 hr of photolysis a 1% decrease was noted. A similar solution kept in the dark for 14 hr at room temperature still showed a 20% decrease on acid treatment.

Gc of the original reaction solution gave, in addition to the methanol peak, a peak at 16.3 min. The final solution gave only a methanol peak. (In preliminary tests, gc of methanol solutions of **1** were found to give a peak of retention time 16–17 min, whereas gc of CS_2 solutions of **1** gave no peaks other than background peaks. Xanthone was retained on the column.)

When 1 ml of the final reaction solution was carried through a standard CS_2 extraction, the CS_2 layer on gc showed the background peaks and a peak at 4.3 min, identical with the retention time of known **3** on the same column, and corresponding in area to a 7% yield of **3** from **1**. When 1 ml of the original reaction solution, before photolysis, was carried through the same procedure, only background peaks were seen.

Registry No.—**1**, 33821-93-1.

Acknowledgment.—We thank Professor Peter C. Uden for helpful suggestions concerning the gas chromatography.

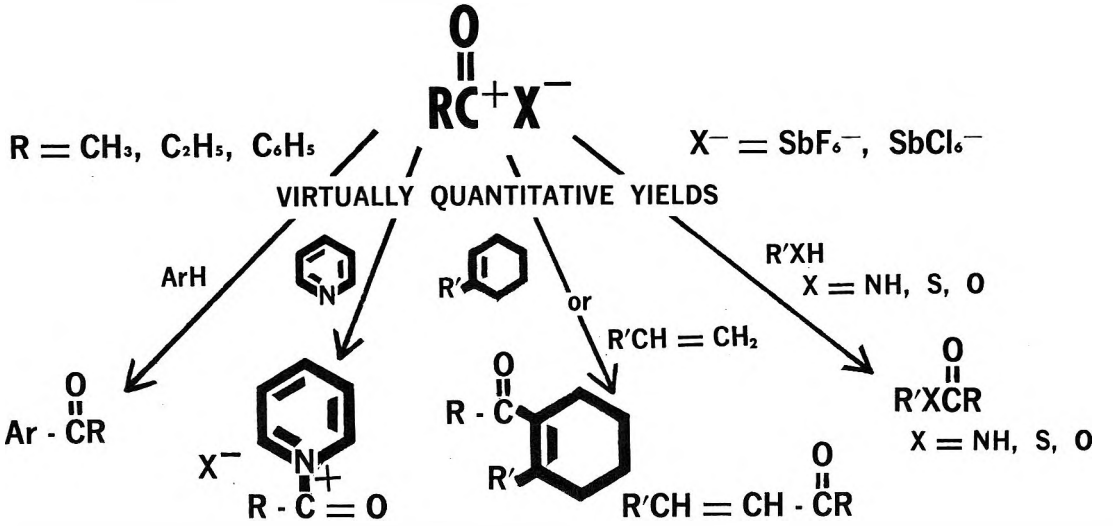
(8) (a) We assume by analogy to other cases[8b] that triplet sensitization, presumably a diffusion-controlled process, leading to a triplet carbene has occurred. (b) Triplet carboethoxycarbene derived from the benzophenone sensitization of ethyl diazoacetate apparently also does not undergo the Wolff rearrangement but rather gives products expected of a diradical-like species: see ref 2a, footnote 3. Similar results are found with α-diazo ketones: M. Jones, Jr., and W. Ando, *J. Amer. Chem. Soc.*, **90**, 2200 (1968); A. Padwa and R. Layton, *Tetrahedron Lett.*, 2167 (1965).

(9) J. A. Moore and D. E. Reed, *Org. Syn.*, **41**, 16 (1961).

(10) K. S. Boustany, *J. Chem. U. A. R.*, **9**, 317 (1966).

(11) F. W. Wenzel, Jr., and E. E. Reid, *J. Amer. Chem. Soc.*, **59**, 1089 (1937), method C.

OXOCARBENIUM (ACYL CATION) SALTS



Oxocarbenium (acyl) salts[1] are a class of very reactive cationic intermediates. In Friedel-Crafts acylations, highly polarized or ionic complexes are formed between the acylating agent and Lewis acid[2] and, in some instances, they can indeed be isolated as stable, crystalline salts. Acetyl hexachloroantimonate and benzoyl hexafluoroantimonate exist as oxocarbenium (acyl) salts; whereas, propionyl chloride – antimony pentachloride and benzoyl chloride – antimony pentachloride complexes exhibit ionic character in solution but exist as donor : acceptor complexes in the solid state. These crystalline stable compounds are remarkably reactive acylating reagents capable of acylating aromatic and aliphatic hydrocarbons (including olefins and acetylenes) in high yield.[1,3] In addition, amines, thiols and alcohols are acetylated or benzoylated in nearly quantitative yields.[1] These salts in addition to our currently available trityl salts, form a group of highly reactive cationic compounds which allow the synthetic chemist an opportunity to perform selective, regiospecific transformations.

1. (a) G. A. Olah, **et al., J. Amer. Chem. Soc., 84,** 2733 (1962). (b) G. A. Olah, **Rev. Chimie, 7,** 1139 (1962). (c) G. A. Olah, **et al., J. Amer. Chem. Soc., 85,** 1328 (1963).
2. For a review see "Friedel-Crafts and Related Reactions" ed. G. A. Olah, Vols. I-III, Wiley-Interscience Publishers, New York, N. Y. 1963-65, and references given therein.
3. G. A. Olah, S. J. Kuhn, S. H. Flood and B. A. Hardie, **J. Amer. Chem. Soc., 86,** 2203 (1964); G. A. Olah, J. Lukas and E. Lukas, **ibid., 91,** 5319 (1959).

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