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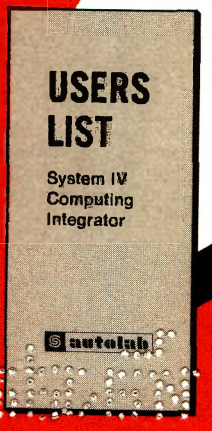

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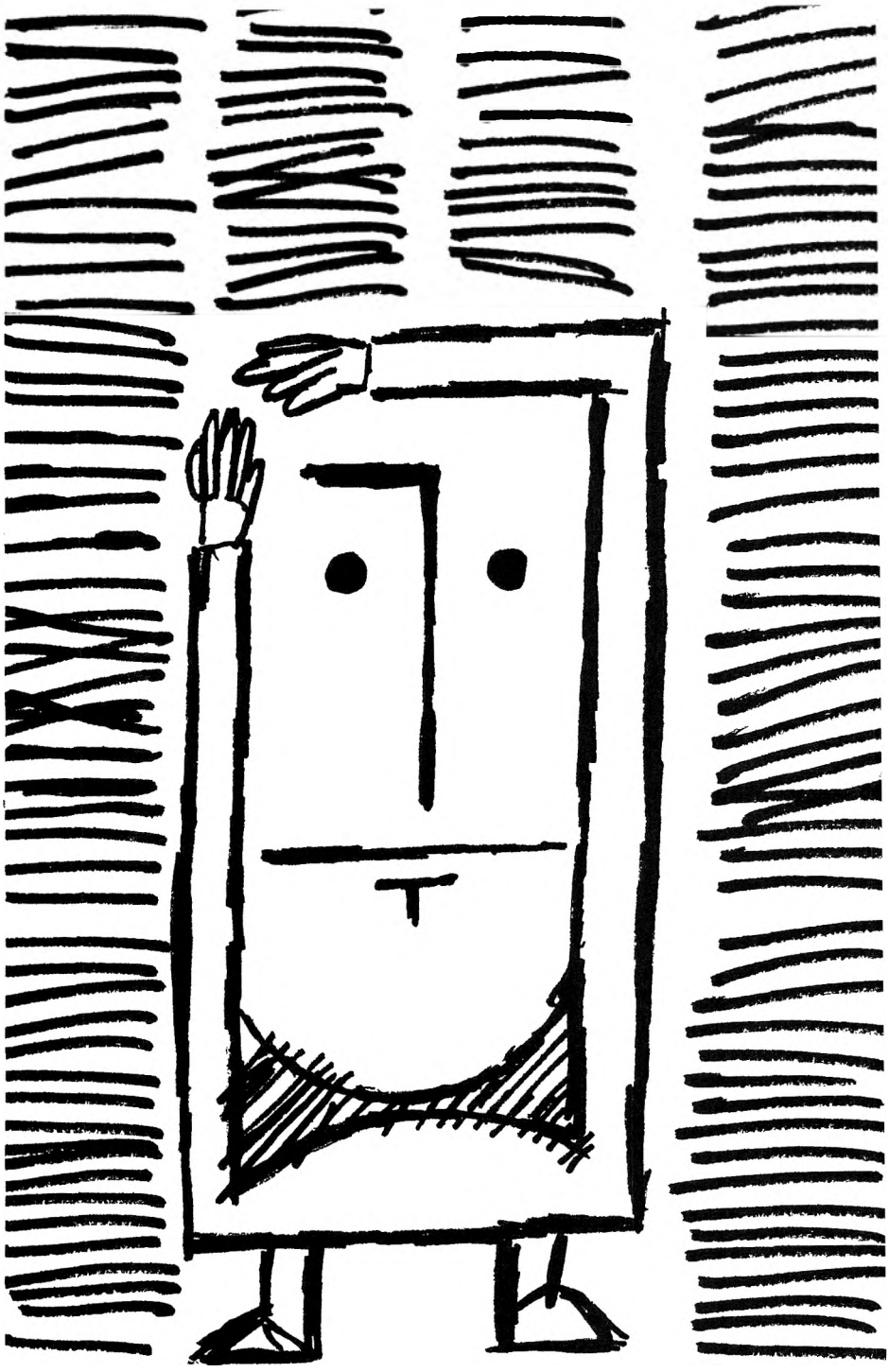

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VOLUME 38, NUMBER 12

JUNE 15, 1973

Preparation of Substituted Spiro[4.5]decan-7-ones. An Approach to the Synthesis of the Acorenones[1]

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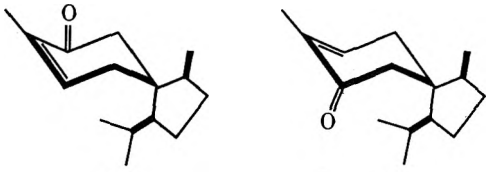
Department of Chemistry, University of Guelph, Guelph, Ontario, Canada

Received October 10, 1972

Uv irradiation of 2-acetoxy-2-cyclopentenone (**3**) and methylenecyclopentane (**8**) in benzene or acetonitrile yielded five products. By varying the irradiation conditions it was possible to favor the formation of certain products. Two of the photoproducts were shown to be α-acetoxy ketones formed by head-to-tail (**9**) and head-to-head (**13**) cycloaddition reactions of **3** and **8** while another two (**12** and **16**, respectively) were the type I cleavage products of these cycloadducts. The fifth product was 2-acetoxy-3-(1-cyclopentenylmethyl)cyclopentanone (**17**) and a mechanism for its formation is suggested. Rearrangement of adducts **9** and **13** under basic conditions followed by lead tetraacetate oxidation of the resultant ketols yielded spiro[4.5]decan-7-one-10-carboxylic acid (**11a**) and spiro[4.5]decan-6-one-9-carboxylic acid (**15a**), respectively. Application of this approach to the synthesis of the spiro sesquiterpenes, acorenone, and acorenone B, is discussed.

The sesquiterpene acorenone B was recently isolated from a hybrid grass of *Bothriochloa intermedia* and was shown by X-ray crystallographic studies to possess structure **1**.[2] The related sesquiterpene, acorenone (**2**) had previously been isolated from sweetflag

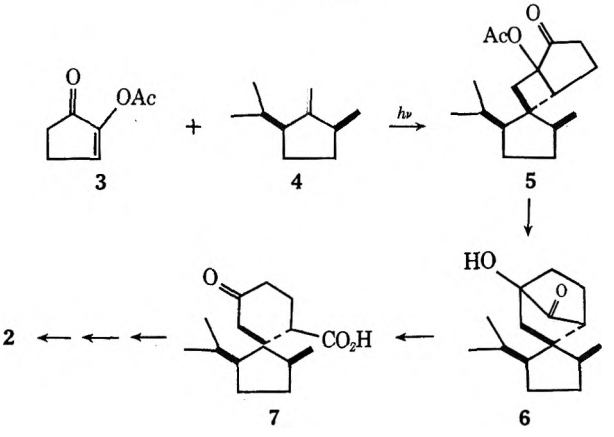


1 **2**

oil[3] and presumably differs only in its configuration at the spiro carbon atom.[2] We wish to describe a versatile approach to the synthesis of substituted spiro[4.5]decan-7-ones with the ultimate objective being the synthesis of one or both of the acorenones.

The proposed synthetic approach is outlined in Scheme I. Photochemical cycloaddition of 2-acetoxy-2-cyclopentenone (**3**) to the less hindered α face of the cis-disubstituted methylenecyclopentane **4** would be expected to yield adduct **5** as one of the major products. Photochemical cycloaddition of **3** to alkenes has previously been reported.[4] The rearrangement of **5** to **6** in basic solution followed by oxidative cleavage to give **7** is analogous to reported conversions.[4]

SCHEME I



The remaining steps to achieve the synthesis of acorenone (**2**) (esterification, alkylation, bromination, dehydrobromination, hydrolysis, and vinylogous decarboxylation) would not be expected to present any major obstacles. Cycloaddition of **3** to the more hindered β face of **4** would ultimately give acorenone B (**1**) as one of the possible products. The critical and potentially the most troublesome step in the scheme is the photochemical cycloaddition. Consequently, this step was studied in detail using the unsubstituted methylenecyclopentane (**8**) and the results are reported here.

Irradiation of benzene or acetonitrile solutions of **3** and **8** (tenfold excess) in a Pyrex vessel using a 350-nm source[5] resulted in the formation of five major prod-

(1) This work was supported by the Research Advisory Board, University of Guelph, and the National Research Council of Canada.

(2) R. J. McClure, K. S. Schorno, J. A. Bertrand, and L. H. Zalkow, *Chem. Commun.*, 1135 (1968).

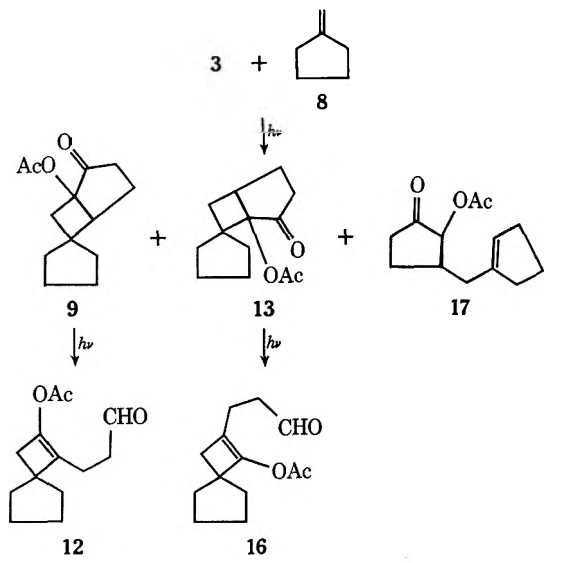
(3) J. Vrkoc, V. Herout, and F. Sorm, *Collect. Czech. Chem. Commun.*, **26**, 3183 (1961).

(4) (a) D. Helmlinger, P. de Mayo, M. Nye, L. Westfelt, and R. B. Yeats, *Tetrahedron Lett.*, 349 (1970); (b) P. G. Bauslaugh, *Synthesis*, 287 (1970); (c) T. Matsumoto, H. Shirahama, A. Ichihara, S. Kagawa, and S. Matsumoto, *Tetrahedron Lett.*, 4103 (1969).

(5) The reaction proceeded at a much slower rate when a 300-nm source was used.

ucts (Scheme II) (but only four resolved peaks) as determined by gas–liquid chromatography (glc). The

SCHEME II



product distribution in the two solvents for normal and extended periods of irradiation is shown in Table I, runs 1–4. Comparison of runs 1 and 2 or 3 and 4

TABLE I

PRODUCT DISTRIBUTION FROM IRRADIATION OF 3 AND 8

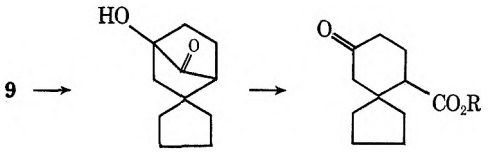
Run	Solvent	Irradiation time, hr	Unreacted 3, %	Filter	Photoproducts, %[a] 13 + 16[b]	12	9	17
1	Benzene	30	5	Pyrex	22	14	28	36
2	Benzene	75	0	Pyrex	20	35	8	30[c]
3	Acetonitrile	30	21	Pyrex	20	11	38	31
4	Acetonitrile	100	0	Pyrex	17	36	14	26[c]
5	Benzene	65	16	Uranium glass	21	6	36	37
6	Acetonitrile	67	20	Uranium glass	20	7	41	32

[a] Product distribution was determined by glc and the components are listed in order of elution from the column. The percentages are based on reacted 3 and are not corrected for differences in relative thermal response. [b] These two products were not resolved by glc. [c] In addition, 7% of a new product with a retention time slightly longer than that of 9 was detected.

suggested that 9 was being converted to 12 during the course of the irradiation. Similarly, although products 13 and 16 could not be resolved by glc, it was noted that during the extended irradiations a shoulder appeared on the front side of this peak which gradually increased in size until it masked the original peak. Also, the combined percentages of 9 + 12 or 13 + 16 remained essentially constant in runs 1 and 2 or 3 and 4. These photochemical conversions will be of importance when discussing the structural elucidation of the products.

The four major peaks were collected by preparative glc and the structures of the products were determined in the following manner.

Photoproduct 9.—This component, the third to be eluted from the glc column, exhibited strong ir absorption bands at 1755 and 1740 cm^{-1} which were attributed to cyclopentanone and acetate carbonyl groups. In the nmr spectrum, a three-proton singlet at τ 8.00 also supported the presence of the acetate group. The mass spectrum of the compound showed a molecular ion at *m/e* 222 as expected for the union of 3 and 8. Further structural information was obtained by conversion of 9 to 10 (95%) in dilute base. The ir spectrum of the product indicated the presence of a hydroxyl group and a strained cycloalkanone (1782 cm^{-1}), which suggested that the desired acyloin rearrangement[4] had occurred. Oxidation of ketol 10 with lead



tetraacetate gave keto acid **11a** (74%), which upon esterification with diazomethane gave keto ester **11b**. Treatment of **11b** with deuterium oxide and potassium carbonate gave the tetradeuterio derivative, as determined by nmr and mass spectrometry. This result requires that four hydrogen atoms be placed α to the ketone group in **11a** and supports the structure as depicted rather than the isomer in which the ketone group is adjacent to the spiro carbon atom. Further evidence to support this assignment will be presented when discussing compound **13**. Having proven the structure of the keto acid **11a** it was then possible to assign structures to **9** and **10** on the basis of their interconversions.

The formation of the head-to-tail cycloadduct **9** (41%, see Table I, run 6) and its subsequent conversion in high yield to the desired **11a** confirms that this is a practical approach to the synthesis of substituted spiro[4.5]decan-7-ones. In order to gain a better understanding of the photochemical step, the structures of the other products were also elucidated.

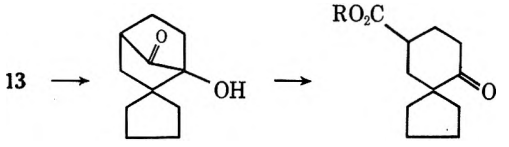
Photoproduct 12.—The ir spectrum of **12** indicated the presence of an aldehyde function (2820, 2720, 1730 cm^{-1})[6] and an enol acetate moiety (1755, 1710, 1210 cm^{-1}).[6] This assignment was supported by the nmr spectrum, which showed an aldehyde proton at τ 0.22 and a three-proton singlet for the acetate methyl group at τ 7.94. The mass spectrum had a molecular ion at *m/e* 222 as expected for 3 + 8. The ir spectrum of the hydrolysis product of **12** showed absorptions at 1775 and 1730 cm^{-1} for the cyclobutanone and aldehyde carbonyl groups, respectively. As mentioned above, the precursor of **12** appeared to be cycloadduct **9** and thus the structure of the aldehyde must be as depicted (Scheme II). To prove this conversion, a pure sample of **9** was irradiated in benzene in a Pyrex tube and was converted cleanly to **12**. This photochemical transformation is an example of the well-known type I cleavage.[7] Examination of Table I, runs 5 and 6, indicates that this cleavage reaction could be suppressed by the use of a uranium glass

(6) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, San Francisco, Calif., 1962, pp 43–44.

(7) J. C. Dalton, K. Dawes, N. J. Turro, D. S. Weiss, J. A. Barltrop, and J. D. Coyle, *J. Amer. Chem. Soc.*, **93**, 7213 (1971), and references cited therein.

filter ($\lambda > 330$ nm),[8] which protected the saturated ketone **9** while allowing absorption of irradiation by the enone **3**.

Photoproducts 13 and 16.—The first product peak (**13**) eluted from glc separation of the irradiation mixtures described in Table I, runs 5 and 6 ($\lambda > 330$), was collected. The ir spectrum (strong absorptions at 1740 and 1250 cm^{-1}), the nmr spectrum (three-proton singlet at τ 8.00), and the mass spectrum (parent peak at m/e 222) suggested that this component was an acetoxycyclopentanone isomeric to **9**. Rearrangement of **13** in dilute base gave a strained hydroxy ke-

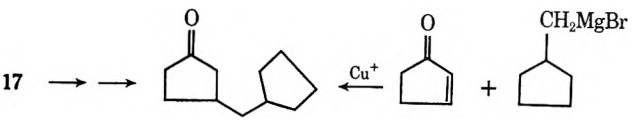


14 **15a**, R = H; **b**, R = Me

tone (1775 cm^{-1}) which upon oxidation with lead tetraacetate yielded keto acid **15a**, which in turn gave keto ester **15b** upon treatment with diazomethane. Both **15a** and **15b** were identical with authentic samples.[9] Thus the hydroxy ketone must have structure **14** and the acetoxy ketone must be the head-to-head cycloadduct **13** by virtue of the reactions which they undergo and the known products to which they are converted.

Upon prolonged irradiation of **3** and **8** in a Pyrex vessel (Table I, runs 2 and 4), cycloadduct **13** was converted to a compound (**16**) (Scheme II) which had almost the same glc retention time as **13** (discussed above) but which had completely different spectral properties. The ir spectrum indicated the presence of an aldehyde group (2810, 2710, 1730 cm^{-1})[6] and an enol acetate moiety (1755, 1700, 1205 cm^{-1})[6] and these assignments were supported by the nmr spectrum (one proton at τ 0.26 and a three-proton singlet at τ 7.90). The ir spectrum of the hydrolysis product of **16** showed absorptions at 1770 and 1725 cm^{-1} for the cyclobutanone and aldehyde carbonyl groups, respectively. Thus the structure of the acetoxy aldehyde must be **16**, the type I cleavage product of **13**. It was not possible to obtain analytical samples of **13** and **16** because of their very similar glc retention times on several different columns, and in all the irradiations described there was always a small amount of one of the components as an impurity in the other. Cleavage reactions of α-acetoxycyclopentanones related to **9** and **13** may have some synthetic utility, as these compounds appear to be converted rather cleanly to products with unusual structural features.[10]

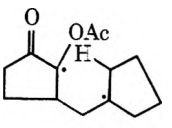
Photoproduct 17.—The ir spectrum of the fourth product (**17**) to be eluted from the glc column indicated two carbonyl bands (1748 and 1762 cm^{-1}), the former attributed to an acetate group (1230 cm^{-1}) and the latter to a cyclopentanone ring. The nmr spectrum exhibited a one-proton vinyl resonance at τ 4.57 and a one-proton doublet (J = 9 Hz) at τ 5.19 assigned to the methine proton on the carbon atom bearing the acetoxy group (methyl at τ 7.95). Upon hydrogenation of this photoproduct the resonance at τ 4.57 disappeared and upon treatment of this dihydro product with zinc in refluxing acetic acid the acetoxy group was removed to give the substituted cyclopentanone **18** (1743 cm^{-1}). The latter experiment suggests that the acetoxy group is on a carbon atom α to the ketone group.[11] The structure of degradation product **18** was proven by an unambiguous syn-



18

thesis. Conjugate addition of the Grignard reagent of cyclopentylmethyl bromide to 2-cyclopentenone in the presence of cuprous bromide gave 3-(cyclopentylmethyl)cyclopentanone, which was identical with the product derived from **17**. Thus, the most reasonable structure for **17** is 2-acetoxy-3-(1-cyclopentenylmethyl)cyclopentanone (Scheme II).

The formation of **17** upon irradiation of **3** and **8** is analogous to the formation of 2-(β-methallyl)cyclohexanone upon irradiation of 2-cyclohexenone and isobutylene as reported by Corey.[12] A plausible mechanism would involve the conversion of the initially formed diradical **19** to **17** *via* a hydrogen atom transfer in a six-membered transition state.



19

Compounds **9** and **12** may be characterized as being products of a head-to-tail union of **3** and **8**, while **13**, **16**, and **17** are the result of a head-to-head union. Table I shows that in benzene the head-to-tail products comprised ~42% of the irradiation mixture while in acetonitrile this percentage increased to ~49%. Similar changes in product ratios upon varying the dielectric constant of the solvent have been noted.[13]

Preparation of the optically active alkene **4** is presently underway. In the irradiation of **3** and **4** it is hoped that the steric hindrance of the added alkyl substituents will enhance further the proportion of the desired head-to-tail adduct **5**.

Experimental Section

The infrared spectra were determined with a Beckman Model IR-5A or IR-12 infrared spectrophotometer. Ultraviolet spectra were recorded on a Unicam SP 800 spectrophotometer and the mass spectra were obtained with a Varian Mat CH7 spectrometer. Nuclear magnetic resonance spectra were recorded on a Varian A-60A spectrometer using the internal standard tetramethylsilane (TMS, τ 10.0). Gas chromatographic separations and collections were carried out on an Aerograph Autoprep

(8) (a) G. S. Hammond, J. Saltiel, A. A. Lamola, N. J. Turro, J. S. Bradshaw, D. O. Cowan, R. C. Counsell, V. Vogt, and C. Dalton, *J. Amer. Chem. Soc.*, **86**, 3197 (1964); (b) W. C. Agosta and Amos B. Smith, III, *ibid.*, **93**, 5513 (1971).

(9) We thank Professor Lawton for generously supplying us with samples of **15a** and **15b**. See D. J. Dunham and R. G. Lawton, *J. Amer. Chem. Soc.*, **93**, 2074 (1971).

(10) The cycloadduct of enone **3** and cyclopentene was found to undergo the same cleavage reaction.

(11) H. O. House, "Modern Synthetic Reactions," 2nd ed, W. A. Benjamin, Menlo Park, Calif., 1972, p 158.

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

(13) B. D. Challand and P. de Mayo, *Chem. Commun.*, 982 (1968).

Model A-700 using a column of 20% Carbowax 20M on Chromosorb W, 60–80 mesh, 6 ft × 0.25 in. The peak areas were determined by triangulation and were not corrected for differences in thermal response. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. Elemental analyses were performed by H. S. McKinnon, Chemistry Department, University of Guelph, and A. B. Gygli, Toronto.

Photochemical irradiations were performed in a Rayonet Model RPR 208 preparative reactor equipped with 350-nm lamps. Spectrograde benzene and acetonitrile were distilled before use in the irradiations. Methylenecyclopentane was prepared using Corey's general procedure.[14]

Preparation of 2-Acetoxy-2-cyclopentenone (3).—A solution of 4.0 g (41 mmol) of 1,2-cyclopentanedione[15] in 250 ml of dry Et_2O was placed in a two-neck 500-ml round-bottomed flask equipped with a gas dispersion tube and a Dry Ice–acetone condenser with a drying tube at the top. An excess of ketene, prepared by pyrolysis at 550° of 30 ml of freshly distilled diketene,[16] was passed into the solution for 5–6 hr at 0° with stirring. The mixture was stirred for an additional 5–6 hr to complete the reaction and the excess ketene was swept out with dry nitrogen. Removal of the solvent left a pale yellow solid, which was recrystallized from petroleum ether (bp 60–90°) to give 4.7 g (82%) of **3** as white crystals: mp 57–58°; ir (CCl_4) 1775 (s), 1735 (s), 1370 (m), 1200 (vs), 1085 cm^{-1} (m); uv max (EtOH) 228 nm (ϵ 9250), 308 (51); nmr (CCl_4) τ 7.79 (3 H, s), 7.64 (2 H, m), 7.35 (2 H, m), 2.73 (1 H, t, J = 3 Hz).

Anal. Calcd for $C_7H_8O_3$: C, 59.99; H, 5.74. Found: C, 60.18; H, 5.89.

Irradiations of 3 and 8.—In each of the irradiations listed in Table I, a solution of 0.25 g (1.78 mmol) of **3** and 1.46 g (17.8 mmol, tenfold excess) of **8** in 4 ml of solvent (either benzene or acetonitrile) was placed in a Pyrex or uranium glass (Corning no. 3320)[8] tube and degassed with purified dry nitrogen. The tube was sealed with a serum cap, placed in a water-cooled jacket (~15°) inside the reactor, and irradiated for the indicated period of time. The reaction was followed by glc analysis of aliquots removed at various times. At the end of the irradiation period the solvent was removed and the product composition was determined by glc to give the results recorded in Table I. At a column temperature of 183° the starting enone and products were eluted in the following order (retention time in minutes): **3** (6.8), **13** and **16** (13.7), **12** (17.5), **9** (20.0), and **17** (32.2). Each fraction was collected by preparative glc to give the five photoproducts described below.

Photoproduct 9.—This product was most effectively prepared using the irradiation conditions described in Table I, run 6. Pure **9** exhibited the following properties: ir (CCl_4) 1755 (s), 1740 (s), 1255 (s) cm^{-1}; nmr (CCl_4) τ 8.05–8.52 (8 H, m), 8.00 (3 H, s), 6.87–7.93 (7 H, m); mass spectrum m/e (rel intensity) 222 (3, M^+), 162 (40), 137 (29), 80 (31), 67 (66), 43 (100).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.31; H, 8.35.

Preparation of Ketol 10.—A solution of 2 ml of 1% methanolic NaOH (0.50 mmol) and 109 mg (0.49 mmol) of **9** was allowed to stand in a nitrogen atmosphere for 1 hr. After addition of 20 ml of H_2O, the solution was extracted with Et_2O (five times), and the combined extracts were washed with saturated brine and dried ($MgSO_4$). Removal of the solvent gave 84 mg (95%) of an oil which was >95% pure by glc analysis. An analytical sample of **10** was obtained by glc: ir (CCl_4) 3550 (w), 3460 (w), 1782 cm^{-1} (s); nmr (CCl_4) τ 8.18–8.72 (9 H, m), 8.02–8.18 (3 H, m), 7.00–8.02 (3 H, m), 6.56 (1 H, s, exchanges with D_2O); mass spectrum m/e (rel intensity) 180 (9, M^+), 134 (34), 95 (66), 94 (100), 79 (31), 67 (35).

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.28; H, 8.95. Found: C, 73.40; H, 9.00.

Preparation of 11a and 11b.—To a solution of 125 mg (0.69 mmol) of ketol **10** in 2.3 ml of dry benzene was added 0.34 g (0.77 mmol) of $Pb(OAc)_4$ and the suspension was stirred for 4 hr at room temperature. The reaction mixture was filtered, the solid was washed with 20 ml of benzene, and the combined organic phase was extracted with 25 ml of saturated $NaHCO_3$ solution (four times). The combined aqueous phase was acidified to Congo red with HCl and extracted with Et_2O (five times). The combined Et_2O extract was washed with saturated brine and dried. Removal of the solvent gave 101 mg (74%) of **11a** which crystallized on cooling. Recrystallization of this product from Et_2O–petroleum ether gave an analytical sample of keto acid **11a**: mp 86–87°; ir (CCl_4) 3000–2500 (s), 1712 cm^{-1} (vs, broad); nmr (CCl_4) τ 8.0–8.6 (8 H, m), 7.4–8.0 (4 H, m), 7.0–7.4 (3 H, m), −1.50 (1 H, broad s); mass spectrum m/e (rel intensity) 196 (53, M^+), 109 (100).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.42; H, 8.28.

Treatment of an Et_2O solution of **11a** with diazomethane gave a quantitative yield of the methyl ester **11b**, which exhibited only one peak on glc analysis: ir (CCl_4) 1738 (s), 1716 (s), 1166 cm^{-1} (s); nmr (CCl_4) τ 8.1–8.6 (8 H, m), 7.5–8.1 (4 H, m), 7.1–7.5 (3 H, m), 6.30 (3 H, s); mass spectrum m/e (rel intensity) 210 (32, M^+), 150 (55), 109 (100), 100 (72).

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63. Found: C, 68.58; H, 8.66.

Preparation of Tetradeuterio 11b.—A mixture of 54 mg (0.26 mmol) of keto ester **11b**, 1.14 ml of D_2O, and 0.11 g of K_2CO_3[17] was refluxed with stirring for 5.5 hr. The product was extracted with Et_2O and examination of the residue showed that exchange was not complete. The procedure was repeated to give 24 mg of an acid fraction and 26 mg of tetradeuterio **11b**: ir (CCl_4) 1738 (s), 1714 cm^{-1} (s); nmr (CCl_4) τ 8.1–8.6 (8 H, m), 7.93 (2 H, d, J = 5 Hz), 7.42 (1 H, t, J = 5 Hz), 6.30 (3 H, s); mass spectrum m/e (rel intensity) 214 (79, M^+), 154 (73), 110 (73), 102 (100).

Photoproduct 12.—This product was prepared most effectively using the irradiation conditions described in Table I, runs 2 or 4. Preparative glc yielded a pure sample of **12**: ir (CCl_4) 2820 (w), 2720 (w), 1755 (s), 1730 (s), 1710 (m) 1210 cm^{-1} (vs); nmr (CCl_4) τ 8.3–8.4 (8 H, broad s), 7.94 (3 H, s), 6.9–7.9 (6 H, m), 0.22 (1 H, s); mass spectrum m/e (rel intensity) 222 (3, M^+), 67 (37), 43 (100).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.13; H, 8.30.

To definitely establish the origin of **12**, a solution of 71 mg of pure **9** and 2.5 ml of benzene in a Pyrex tube was degassed and irradiated under the usual conditions for 42 hr. Glc analysis of the solution indicated an 80% conversion to **12** and no other products were observed.

A sample of 116 mg (0.52 mmol) of **12** was hydrolyzed using the conditions described for the preparation of ketol **10** to give 76 mg (66%) of a yellow oil which glc analysis showed to contain one major peak (>90%) plus minor impurities. The ir spectrum of the sample exhibited strong bands at 1775 and 1730 cm^{-1}.

Photoproduct 13.—The irradiation conditions that produced this compound most effectively are recorded in Table I, runs 5 and 6. Preparative glc of this first product peak gave a fraction which was >90% **13**: ir (CCl_4) 1740 (s), 1250 cm^{-1} (s); nmr (CCl_4) τ 8.1–8.7 (10 H, m), 8.00 (3 H, s), 6.9–7.9 (5 H, m), a minor peak at 0.26 indicated **16** was the impurity in this fraction; mass spectrum m/e (rel intensity) 222 (9, M^+), 141 (100), 99 (100), 43 (95).

Preparation of 15a and 15b *via* Ketol 14.—A sample of 38 mg (0.17 mmol) of **13** (>90% in purity) was treated with methanolic NaOH as described in the preparation of ketol **10**. The residue (27 mg, 87%) was shown by glc to be a 94:6 mixture of two components. The ir spectrum of the mixture showed an hydroxyl band at 3440 cm^{-1} and a strong carbonyl band at 1775 cm^{-1}.

This crude ketol fraction was oxidized with $Pb(OAc)_4$ as described for the preparation of **11a** to give 19 mg (66%) of keto acid **15a** which crystallized on cooling. This sample was shown to be identical with spiro[4.5]decan-6-one-9-carboxylic acid synthesized independently by Lawton.[9] The methyl ester **15b** was prepared by treatment of **15a** with diazomethane and was similarly found to be identical with an authentic sample.[9]

Photoproduct 16.—This product was prepared by prolonged irradiation of **3** and **8** as described in Table I, runs 2 and 4. Preparative glc of the first product peak eluted gave a fraction which was rich in **16** (~75%): ir (CCl_4) 2810 (w), 2710 (w), 1755 (s), 1730 (s), 1700 (w), 1205 cm^{-1} (vs); nmr (CCl_4) τ 0.26 (~1 H, s), 7.90 (~3 H, s), a much smaller singlet at 8.00 for **13** also observed. Hydrolysis of **16** using conditions previously described gave a fraction which exhibited ir bands at 1770 and 1725 cm^{-1} and which showed by glc analysis the presence of two

(14) R. Greenwald, M. Chaykovsky, and E. J. Corey, *J. Org. Chem.*, **28**, 1128 (1963).

(15) H. Herloffinhoffen and H. Kramer, *Chem. Ber.*, **87**, 488 (1954).

(16) S. Andreades and H. D. Carlson, *Org. Syn.*, **45**, 50 (1965).

(17) M. St-Jacques and C. Vaziri, *Can. J. Chem.*, **49**, 1256 (1971).

components in a ratio of 74:26, the latter having the same retention time as ketol **14**.

Photoproduct 17.—The compound was prepared by carrying out the irradiation in benzene as described in Table I, runs 1 or 5. Preparative glc collection of this last peak gave a pure sample of **17**: ir (CCl_4) 1762 (s), 1748 (s), 1234 cm^{-1} (s); nmr (CCl_4) τ 7.4–8.5 (13 H, m), 7.95 (3 H, s), 5.19 (1 H, d with additional fine splitting, J = 9 Hz), 4.57 (1 H, broad s); mass spectrum m/e (rel intensity) 222 (4, M^+), 120, (98), 80 (90), 43 (100).

Anal. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 70.22; H, 8.37.

Degradation of 17.—To a solution of 130 mg (0.59 mmol) of **17** in 20 ml of AcOH was added 20 mg of 10% Pd on charcoal and the suspension was stirred under 1 atm of hydrogen until 1 equiv had been consumed. The catalyst was filtered, the solvent was removed, and the residue was examined by nmr, which showed that the resonance at τ 4.57 was no longer present.

This sample of dihydro **17** was dissolved in 15 ml of AcOH and heated to reflux for 24 hr with 4 g of Zn powder. The cooled reaction mixture was filtered, most of the AcOH was removed under reduced pressure, and 150 ml of Et_2O was added to this concentrate. The organic phase was extracted with saturated with Na_2CO_3 solution (three times) and dried. Removal of the solvent gave 80 mg (82%) of a brown oil which showed only one peak on glc analysis. Preparative glc yielded a pure sample of **18**: ir (CCl_4) 1743 (s), 1160 cm^{-1} (m); nmr (CCl_4) τ 7.5–9.0 (complex multiplet of all protons); mass spectrum m/e (rel intensity) 166 (5, M^+), 83 (80), 55 (56), 41 (100).

Anal. Calcd for $C_{11}H_{18}O$: C, 79.45; H, 10.91. Found: C, 79.29; H, 10.77.

Preparation of 3-(Cyclopentylmethyl)cyclopentanone (18).—A solution of 3.75 g (23 mmol) of bromomethylcyclopentane[18] in 30 ml of dry tetrahydrofuran (THF) was added over 30 min to 0.486 g (0.020 g-atoms) of Mg turnings and the reaction was refluxed for an additional 30 min. The Grignard solution was added to a stirred suspension of 0.144 g (1 mmol) of freshly prepared CuBr[19,20] in 30 ml dry THF at 0° to give a yellowish-brown solution. A solution of 0.82 g (10 mmol) of 2-cyclopentenone in 30 ml of dry THF was added dropwise over 30 min to the Grignard–CuBr solution at 0°. The reaction mixture was allowed to warm to room temperature over 30 min then heated to reflux. The cooled reaction mixture was poured into 50 ml of NH_4Cl solution, the aqueous phase was separated and extracted with Et_2O (two times), and the combined organic phase was washed with saturated brine (two times) and dried. Removal of the solvent yielded 2.4 g of an oil which upon glc analysis showed two major components, the minor (21%) and more volatile compound being the coupling product, 1,2-dicyclopentylethane (mass spectrum m/e 166, M^+; ir indicated no carbonyl group), and the other being the desired ketone (68%). This residue was distilled to give 0.84 g (51%) of **18**, bp 93–96° (0.7 mm). The spectroscopic properties of this product were identical with those described above for the degradation product of **17**.

(18) E. E. Royals and A. H. Neal, *J. Org. Chem.*, **21**, 1448 (1956).

Registry No.—**3**, 28742-34-9; **8**, 1528-30-9; **9**, 39837-66-6; **10**, 39837-67-7; **11a**, 39837-68-8; **11b**, 39837-69-9; **11b** (tetradeuterio derivative), 39837-70-2; **12**, 39837-71-3; **13**, 39837-72-4; **14**, 39837-73-5; **15a**, 39837-74-6; **16**, 39837-75-7; **17**, 39837-76-8; **17** (dihydro derivative), 39837-77-9; **18**, 39837-78-0; 1,2-cyclopentanedione, 3008-40-0; ketene, 463-51-4; bromomethylcyclopentane, 3814-30-0; 2-cyclopentenone, 930-30-3.

(19) J. L. Hartwell, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 185.

(20) If the cuprous bromide is not freshly prepared the major product isolated from the reaction is 1,2-dicyclopentylethane, formed by coupling of the Grignard reagent.

The Reaction of Cyclopentanones with Methylsulfinyl Carbanion

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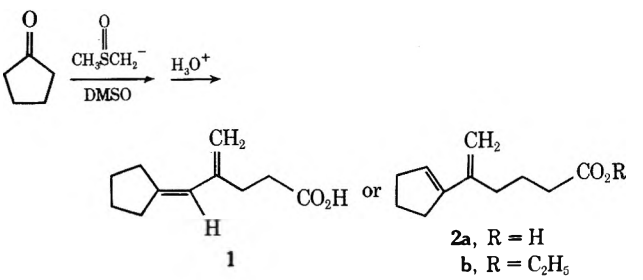
Methylsulfinyl carbanion reacts with cyclopentanone at ambient temperature to afford the unexpected δ-methylene-1-cyclopentene-1-pentanoic acid (**2a**) in good yield. This reaction appears limited to cyclopentanones, with only low yields isolated from 2- and 3-methylcyclopentanones. Mechanistic considerations and some reactions of the dienoic acid are discussed.

While investigating the reaction of methylsulfinyl carbanion with some enolizable ketones, we were surprised to observe that cyclopentanone does not react as does cyclohexanone. According to Corey and Chaykovsky,[1,2] the enolate anion and the β-hydroxy sulfoxide adduct are the major products from cyclohexanone and cycloheptanone. However, when cyclopentanone is added dropwise to dimsyl sodium in DMSO at 25°, the sodium salt of an 11-carbon dienoic acid was isolated from CH_2Cl_2–ether after a few hours. This observation prompted a study of the product structure and the reaction scope and mechanism.

Structure Proof.—Aqueous acidification of the isolated sodium salts yields (59% overall) a carboxylic acid as the sole organic product. The purified acid melts at 44.5–46.0°, analyzes for $C_{11}H_{16}O_2$, and shows a molecular ion of 180 mass units (31% relative abundance) and ions of 135 ($M\cdot^+ - CO_2H$, 4%) and 107 mass units ($M\cdot^+ - CH_2CH_2CO_2H$, 75%) in the mass spectrum. The uv spectrum has a single absorption at 237 nm (ε 16,300), suggestive of a trisubstituted, conjugated diene; ir peaks at 1580 and 1620 cm^{-1} are indicative of a conjugated diene; and the nmr spectrum has olefinic proton signals at 5.87 (s, 1, C=CH) and 4.98 ppm (s, 2, $C{=}CH_2$). The product reacts rapidly with maleic anhydride to form an adduct, mp 112.0–113.0°. The acid is converted to its ethyl ester with *N*,*N*′-carbonyldiimidazole and ethanol, and the ester is readily hydrogenated on 10% Pd/C in ethanol to an oil with a molecular ion of 212 mass units whose nmr spectrum shows a methyl signal at 0.90 ppm (broad singlet). From these data we considered structures **1** and **2a** for



1 **2a**, R = H; **b**, R = C_2H_5

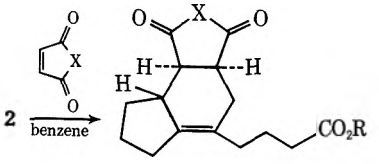
(1) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **84**, 866 (1962).

(2) E. J. Corey and M. Chaykovsky, *J. Amer. Chem. Soc.*, **87**, 1345 (1965).

the initial acid product. The apparent lack of coupling for the methine signal at 5.87 ppm (line width at half height of 4 Hz) might favor **1**, whereas the ion of 107 mass units would favor **2** owing to predominance of allylic cleavage and stability of the allylic radical cation,[3] even though double-bond rearrangements are possible.

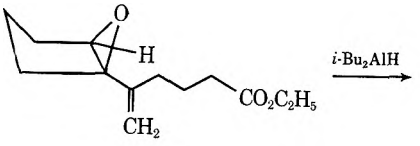
After oxidation of the acid by periodate–permanganate,[4] only glutaric acid was isolated (as diethyl ester) in 24% yield. This oxidative fragmentation establishes **2** as the correct structure, since **1** should yield succinic acid and cyclopentanone. In retrospect, the broadened singlet at 5.87 ppm can be rationalized for structure **2** by noting that similar vinyl protons from other cyclopentene systems are observed as broadened singlets.[5]

Additional support for structure **2** was obtained by examining some reactions of the dienoic acid. Adducts were obtained from maleic anhydride in fast, exothermic reactions, whereas the adduct from 4-cyclopentene-1,3-dione formed with a reaction half-life of 7.5 hr. None of these adducts show an olefinic proton signal in the nmr except **4**, which shows an exchangeable enol–olefinic proton at 4.88 ppm. The spiro adduct formed from structure **1** would contain an olefinic proton.

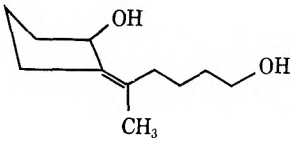


3a, X = O; R = H
3b, X = O; R = C_2H_5
4, X = CH_2; R = H

The ester **2b** reacted with *m*-chloroperbenzoic acid to give a single epoxide, **5**. The nmr spectrum of **5** contains a doublet at 5.00 ppm and one at 5.25 ppm for the methylene protons with geminal coupling constants $J \cong 1$ Hz, and a singlet for the epoxide OCH at 3.38 ppm with a line width at half height of 1.7 Hz. The lack of AB_2 coupling may be attributed to the probable boat conformation for epoxycyclopentanes,[6] which would minimize J_{cis}. Similar observations have been made for steroidal ring D epoxides.[7] The mass spectrum of **5** shows a molecular ion of 224 mass units and



5



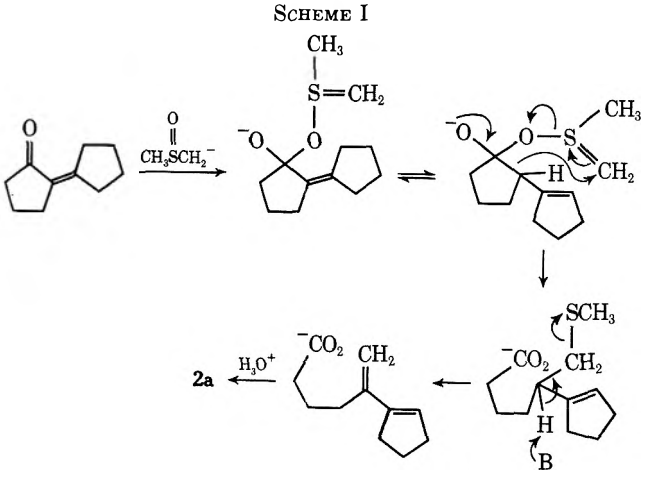
6

an allylic ion of 123 mass units ($M \cdot^+ - CH_2CH_2CO_2C_2H_5$, 67% relative abundance). Reduction of the epoxide **5** with $LiAlH_4$ yielded a mixture of two diols, both containing a C=CH_2 group according to their nmr spectra. However, a selective reduction of **5** with diisobutylaluminum hydride in benzene[8] afforded **6** in good yield. In addition to a broad one-proton singlet for the alcohol methine at 4.68 ppm, a methyl resonance near 1.80 ppm is observed in the nmr spectrum of **6**. These spectral properties of **6** support the epoxide being derived from **2** rather than **1**.

Reaction Mechanism.—The structure **2a** for the product of this unusual reaction suggests that the reaction may proceed *via* base-catalyzed dimerization of cyclopentanone followed by a one-carbon alkylation and oxidation. An aldol condensation of cyclopentanone to form 2-cyclopentylidenecyclopentanone could be expected in the basic DMSO medium, although self-condensation of enolate anions from cyclohexanone and cycloheptanone was not observed under similar conditions.[1,2] A sample of cyclopentylidenecyclopentanone was prepared[9] and added to 1 equiv of methylsulfinyl carbanion in DMSO. The same carboxylic acid product **2a** was isolated in 26% yield, which strongly implicates self-condensation as the initial step.

Although we presently have no direct mechanistic evidence for the subsequent alkylation and oxidation, we offer a feasible pathway in Scheme I. The oxidation

SCHEME I



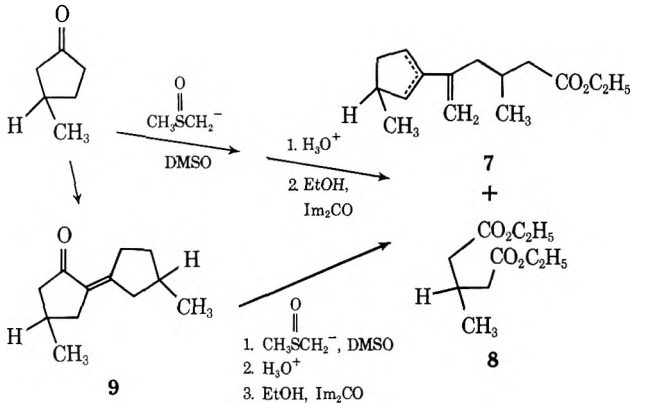
may be explained by nucleophilic attack at the carbonyl carbon by sulfoxide oxygen rather than attack by carbon as with larger cycloalkanones.[1] Gassman and coworkers suggest a similar mechanism for the oxidative cleavage of nonenolizable ketones.[10] The endocyclic double bond shift is reasonable with loss of the conjugated enone; then an allowed [2,3]-sigmatropic shift[11] would form the product following loss of methylmercaptan.[12] The nmr spectrum of the salts as isolated from the reaction mixture is essentially identical with the spectrum of purified acid **2a**; hence the carboxylate product is formed under the reaction conditions and aqueous acid merely converts the carboxylate anion to free acid.

(3) H. A. Bondarovich and S. K. Freeman, "Interpretive Spectroscopy," S. K. Freeman, Ed., Reinhold, New York, N. Y., 1965, p 193.
(4) R. U. Lemieux and E. von Rudloff, *Can. J. Chem.*, **33**, 1701, 1710, 1714 (1955).
(5) A. D. Ketley and J. L. McClanahan, *J. Org. Chem.*, **30**, 940 (1965).
(6) J. J. McCullough, H. B. Henbest, R. J. Bishop, G. M. Glover, and L. E. Sutton, *J. Chem. Soc.*, 5496 (1965).
(7) K. Tori, T. Komeno, and T. Nakagawa, *J. Org. Chem.*, **29**, 1136 (1964).
(8) L. I. Zakharkin and I. M. Khorlina, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **65**, 862 (1965); *Chem. Abstr.*, **63**, 5574*f* (1965).
(9) H. S. French and L. Wiley, *J. Amer. Chem. Soc.*, **71**, 3702 (1949).
(10) P. G. Gassman, J. T. Lumb, and F. V. Zalar, *J. Amer. Chem. Soc.*, **89**, 946 (1967).
(11) J. E. Baldwin and C. N. Armstrong, *Chem. Commun.*, 631 (1970).
(12) T. J. Wallace, J. E. Hofmann, and A. Schriesheim, *J. Amer. Chem. Soc.*, **85**, 2739 (1963).

Further support for these mechanistic considerations was obtained by adding cyclopentanone to deuterated dimsyl sodium, generated from DMSO-d_6 (99.5% isotope purity). The dienoic acid isolated was partially deuterated at the methylene group (40%) and the ring vinyl proton (75%). Although exchange undoubtedly occurs, we feel that deuteration of the ring vinyl proton is consistent with the endocyclic double bond rearrangement, and deuteration of the methylene group establishes that it derives from DMSO. Mass spectral analysis of the deuterated sample showed 3% containing no D, 5% one D, 18% two D's, 38% three D's, 24% four D's, and 12% five D's. The presence of material containing up to five deuterium atoms is consistent with Scheme I and the nmr data.

Reaction Scope.—When cyclobutanone was added to dimsyl sodium in DMSO at room temperature, a complex mixture of carboxylic acid salts was isolated with no evidence supporting a dienoic acid analogous to **2**. Substituted cyclopentanones were then investigated under the same reaction conditions. The least hindered ketone, 3-methylcyclopentanone, gave a mixture of acids in low yield (Scheme II). The oily acids

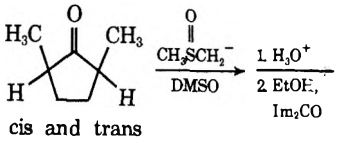
SCHEME II



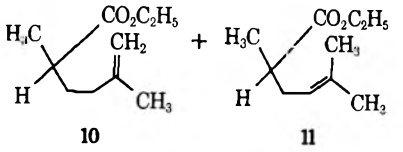
were esterified with *N*,*N*′-carbonyldiimidazole in EtOH, and the esters were fractionated at reduced pressure. A material analogous to **2b** was isolated in 5.3% yield, and vpc analysis shows **7** to be a mixture of two compounds which are isomeric with respect to the ring methyl and double bond; a molecular ion of 236 mass units was observed in the mass spectrum. Compound **7** reacted with maleic anhydride to give an adduct, which was purified by column chromatography. The adduct is analogous to **3a**, but its nmr spectrum indicates a mixture of methyl positional isomers. The self-condensation product **9** was also prepared[9] and added to dimsyl sodium; from this reaction **7** was obtained in low yield. Since the enone **9** is readily formed, the low yield of **7** compared to **2** may be due to steric hindrance by the 3-methyl group in the sigmatropic rearrangement.

A more volatile ester was also recovered from the reaction mixture in 2% yield and assigned structure **8**. 3-Methyl glutarate is presumably derived from 3-methylcyclopentanone *via* a semidione intermediate formed in the presence of some oxygen.[13]

When 2,5-dimethylcyclopentanone was added to dimsyl sodium, and the crude acids esterified as for **2b**, a mixture of monomeric carboxylates was obtained; **10** and **11** were each formed in 1% yield. An nmr spec-

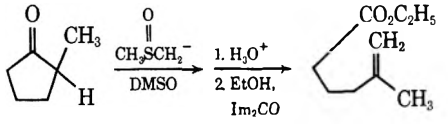


cis and trans



trum of the ester mixture showed olefinic signals at 5.25 (m, 1, C=CH) and 4.70 ppm (m, 2, C=CH_2), with a molecular ion of 170 mass units. A moderate yield of the sodium enolate of 2,5-dimethylcyclopentanone was also present in the initial reaction product. Since the methyl groups of this ketone prevent self-condensation, it is not surprising that only monomeric products were isolated. Nevertheless, the structures **10** and **11** substantiate the mechanistic considerations of Scheme I and the ambident character of the DMSO anion.

Finally, 2-methylcyclopentanone was added to dimsyl sodium. The mixture of carboxylate salts thus obtained was acidified and then esterified to give a mixture of five esters (vpc, 10% SE-30 on Chromosorb W, 120–180°). The most abundant component had the shortest retention time, and was isolated by fractional distillation, bp 84° (1.5 mm). This volatile component represents the product obtained from oxidation and alkylation of 2-methylcyclopentanone itself rather than the dimeric enone, presumably *via* a mechanism similar to Scheme I, and is assigned structure **12**; it had char-



12

acteristic nmr peaks at 4.70 (s, 2, C=CH_2) and 1.75 ppm (s, 3, C=CCH_3), with a molecular ion of 156 mass units. Three of the remaining four esters distilled as a mixture, and demonstrated similar vpc retention times. An nmr spectrum of the mixture resembled that of structures **2b** and **7**; olefinic proton signals were seen at 4.80 (s, 2, C=CH_2) and 5.75 ppm (s, 1, C=CH). The mass spectrum showed *m/e* 236 ($M\cdot^+$, 1.7%), 148 ($M\cdot^+ - CO_2C_2H_5$ and CH_3, 25%), 135 ($M\cdot^+ - CH_3CHCO_2C_2H_5$), and 121 ($M\cdot^+ - CH_2CH_3CHCO_2C_2H_5$). The mixture gave a single adduct with maleic anhydride which was separated from unreacted esters on a silica gel column, but the exact identity of these three dimeric esters is still being investigated.

Although the aldol condensation of 2-methylcyclopentanone has not been reported, we find that it does occur under rigorous conditions to give a mixture of enones which is being further investigated.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary apparatus according to USP Class 1, and are corrected. Elemental analyses were determined with an F & M Model 185

(13) G. A. Russell, E. R. Talaty, and R. H. Horrocks, *J. Org. Chem.*, **32**, 353 (1967).

analyzer. Gas chromatographic (vpc) separations were obtained with a Perkin-Elmer F11 gas chromatograph using 0.125 × 36 in. columns with 10% SE-30 on Chromosorb W. Infrared spectra were recorded on a Beckman IR-18A using KBr pellets for solids. Uv spectra were obtained on absolute ethanol solutions and recorded with a Cary Model 14 spectrophotometer. Nmr spectra were obtained with $CDCl_3$ solutions and recorded by a Varian XL-100 spectrometer using TMS as an internal standard. Mass spectral data were obtained with a CEC Model 21-104 spectrometer.

δ-Methylene-1-cyclopentene-1-pentanoic Acid (2a).—A suspension of NaH (54.0 g of 57% mineral oil dispersion, 1.28 mol) in 250 ml of dry DMSO was vigorously stirred under a dry nitrogen atmosphere and heated gradually (oil bath) to 71°, then maintained at that temperature until solution resulted and hydrogen evolution was no longer observed.[1,14] The gray mixture was immediately cooled to 25°[15,16] and maintained at <25° while cyclopentanone (100 g, 1.19 mol) was added dropwise. The mixture was stirred for 30 min with cooling to moderate the exothermic reaction, then at 25° for 5 hr. The reaction mixture was poured into 2 l. of chilled methylene chloride–ether (1:1), and the resulting suspension was refrigerated overnight. The fine solid was filtered on a sintered-glass filter, washed with ether–methylene chloride (9:1), and then thoroughly dried. The crude salts were dissolved in water and the solution was neutralized with 6 *N* HCl. The odorous mixture was extracted with ether, and the extract was dried ($MgSO_4$), filtered from Darco G-60, and evaporated to give 62.8 g (59%) of orange oil which crystallized on standing. Purification was achieved by dissolving the crude acid in aqueous alkali followed by acidification to yield white crystals: mp 44.5–46.0; tlc on silica gel ($CHCl_3$–CH_3OH, 9:1), R_f 0.60.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95. Found: C, 73.20; H, 8.83.

Ethyl δ-Methylene-1-cyclopentene-1-pentanoate (2b).—To the acid **2a** (11.6 g, 0.065 mol) in 50 ml of dry THF was added *N*,*N*′-carbonyldiimidazole (11.3 g, 0.070 mol) in small portions. When CO_2 evolution had ceased, 50 ml of dry ethanol with a catalytic amount of sodium ethoxide was added and the mixture was stirred at room temperature for 2 hr. The solvent was evaporated and the residue was dissolved in ether, then washed with water, cold 1 *N* NaOH, and cold 1 *N* HCl. The ether extract was dried ($MgSO_4$), evaporated, and distilled to give 13.5 g (100%) of the ethyl ester: bp 70–71° (0.2 mm); $n^{26}D$ 1.484; ir (film) 1740 cm^{-1} (ester C=O).

Anal. Calcd for $C_{13}H_{20}O_2$: C, 74.96; H, 9.68. Found: C, 74.88; H, 9.77.

Ethyl 5-Cyclopentylhexanoate.—The ester **2b** (6.65 g, 0.032 mol) in 50 ml of dry ethanol was hydrogenated with 0.1 g of 10% Pd/C at 60 psi and ambient temperature in a Parr apparatus. The theoretical amount of hydrogen was absorbed in 1 hr, the catalyst was filtered, and the solution was evaporated and then distilled to give a colorless oil: 6.6 g (98%); bp 75–76° (0.2 mm); $n^{26}D$ 1.455; ir (film) 1730 cm^{-1} (ester C=O).

Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.40. Found: C, 73.84; H, 11.29.

7-(3-Carboxypropyl)-2,3,3a,4,5,6-hexahydroindene-4,5-*cis*-dicarboxylic Acid Anhydride (3a).—To the acid **2a** (5.00 g, 0.0277 mol) in 25 ml of dry benzene, maleic anhydride (2.74 g, 0.028 mol) was added slowly. The exothermic reaction was moderated with an ice bath, and then the mixture was stirred at room temperature for 1 hr. Ether (100 ml) was added and the brown solution was filtered from Darco G-60, then evaporated to give an oil which crystallized on standing, 7.7 g (99%). The solid recrystallized from ether to give white crystals: mp 100.0–106.0°; ir (KBr) 1710 (acid C=O), 1780, 1840 cm^{-1} (anhydride C=O).

Anal. Calcd for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 64.60; H, 6.49.

7-[3-(Ethoxycarbonyl)propyl]-2,3,3a,4,5,6-hexahydroindene-4,5-*cis*-dicarboxylic Acid Anhydride (3b).—This ester adduct was prepared as described for the acid adduct **3a**, and the oily orange crystals (87%) were recrystallized from ether–petroleum ether (bp 30–60°) to give off-white crystals: mp 85.5–87.0°; ir (KBr) 1720 (ester C=O), 1770, 1840 cm^{-1} (anhydride C=O).

Anal. Calcd for $C_{17}H_{22}O_5$: C, 66.65; H, 7.24. Found: C, 66.70; H, 7.49.

1,2,3,5,5aα,6,7,8,8aα,8b-Decahydro-6,8-dioxo-*cis*-indacene-4-butyric Acid (4).—To the acid **2a** (1.00 g, 5.56 mmol) in 1.0 ml of dry benzene, 4-cyclopentene-1,3-dione (0.534 g, 5.56 mmol) was added and the mixture was stirred at room temperature for 24 hr. The reaction mixture was filtered to give a white solid, 0.80 g (52%), which recrystallized from acetone to yield white crystals: mp 154–157°; ir (KBr) 1715 (acid C=O), 1590 cm^{-1} (β diketone); nmr ($CDCl_3$) δ 4.88 (s, 1, COCH=CO), 2.75 (s, broad, 2, cis CHCO).

Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30. Found: C, 69.74; H, 7.06.

5-(2-Hydroxycyclohexylidene)-1-hexanol (6).—To a solution of the ester **2b** (27.10 g, 0.130 mol) in 150 ml of dry CH_2Cl_2 was added dropwise 85% *m*-chloroperbenzoic acid (29.4 g, 0.144 mol) in 300 ml of dry CH_2Cl_2 with stirring at 0°. After the addition was complete, the mixture was stirred at 25° for 2 hr, and then the *m*-chlorobenzoic acid was filtered. The filtrate was twice washed with 100 ml of Na_2SO_3 solution followed by 100 ml of cold 1 *N* NaOH. The organic layer was dried ($MgSO_4$) and evaporated to give 28.10 g (97%) of a yellow oil. The product was purified by chromatography (silica gel, ether) to yield the colorless, thermally unstable epoxide **5**: nmr ($CDCl_3$) δ 5.00 (d, 1, $J_{gem} \cong 1$ Hz, C=CH_2), 5.25 (d, 1, $J_{gem} \cong 1$ Hz, C=CH_2), 3.38 (s, 1, OCH); mass spectrum *m/e* (rel intensity) 224 (3.3), 123 (67).

The epoxide **5** (4.67 g, 0.0208 mol) in 5 ml of dry benzene was directly added dropwise to diisobutylaluminum hydride (46.7 ml of 24.8% in benzene, 0.0686 mol, Texas Alkyls Inc.) with stirring at 0°. The mixture was stirred at 0° for 16 hr; then 1 ml of methanol was added, followed by 2 ml of water. The solids were filtered and rinsed with ether. The filtrates were evaporated to an oil which was chromatographed (silica gel, ether) to give a colorless, viscous oil, **6**: nmr ($CDCl_3$) δ 4.68 (s, 1, OCH), 1.80 (s, 3, C=CCH_3); ir (KBr) 3370 cm^{-1} (OH); mass spectrum *m/e* (rel intensity) 184 (1.1), 166 (18), 149 (36).

Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.68; H, 10.75.

Ethyl β-Methyl-δ-methylene-(3- or 4-methyl-1-cyclopentene)-1-pentanoate (7).—3-Methylcyclopentanone reacted with methylsulfinyl carbanion as described for the preparation of **2a**, and then the reaction products were esterified as for **2b**, giving a yellow oil which was distilled to yield diethyl 3-methylglutarate, (**8**), bp 89° (0.3 mm), mass spectrum *m/e* (rel intensity) 157 (21, $M \cdot^+ - OC_2H_5$), followed by **7**: bp 116° (0.3 mm); $n^{23}D$ 1.3074; nmr ($CDCl_3$) δ 5.75 (s, 1, C=CH), 4.80 (s, 2, C=CH_2); mass spectrum *m/e* (rel intensity) 236 (35), 191 (20).

Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.20; H, 10.20.

7-[2-(Ethoxycarbonyl)-2-methylpropyl]-2- or -3-methyl-2,3,3a,-4,5,6-hexahydro-4,5-indene-*cis*-dicarboxylic Acid Anhydride.—This adduct was prepared from **7** and maleic anhydride as described for **3a**. The crude adduct (100%) was purified by elution chromatography (silica gel, ether–petroleum ether), giving a yellow oil: $n^{23}D$ 1.5007; ir (KBr) 1720 (ester C=O), 1770, 1840 cm^{-1} (anhydride C=O).

Anal. Calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 68.05; H, 8.11.

Registry No.—**2a**, 39495-68-6; **2b**, 39495-69-7; **3a**, 39495-70-0; **3b**, 39495-71-1; **4**, 39495-72-2; **5**, 39495-78-8; **6**, 39495-79-9; **7** (3-methyl), 39495-80-2; **7** (4-methyl), 39495-81-3; **12**, 39495-82-4; methylsulfinyl carbanion, 13810-16-7; cyclopentanone, 120-92-3; ethyl 5-cyclopentylhexanoate, 39495-83-5; maleic anhydride, 108-31-6; 4-cyclopentene-1,3-dione, 930-60-9; 3-methylcyclopentanone, 1757-42-2; 7-[2-(ethoxycarbonyl)-2-methylpropyl]-2-methyl-2,3,3a,4,5,6-hexahydro-4,5-indene-*cis*-dicarboxylic acid anhydride, 39495-84-6; 7-[2-(ethoxycarbonyl)-2-methylpropyl]-3-methyl-2,3,-3a,4,5,6-hexahydro-4,5-indene-*cis*-dicarboxylic acid anhydride, 39495-85-7.

(14) The same acid **2a** was formed in comparable yield by using fresh KO-*t*-Bu in dry DMSO at room temperature instead of NaH.

(15) Prolonged standing of this reagent above 25° resulted in explosive decomposition on one occasion.

(16) Hazards of generating dimsylsodium are cited in *Chem. Eng. News*, June 13, 1966, p 7.

Acknowledgments.—The authors thank Mr. James Rayburn for the initial isolation of 2, Mr. Charles Combs for some nmr and mass spectral interpretations, and Professor David M. Lemal of Dartmouth College for helpful discussions concerning structure assignments and spectral interpretations.

Intramolecular Alkylations of Bicyclic α,β-Unsaturated Ketones[1]

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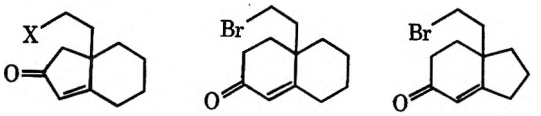
Bicyclic α,β-unsaturated ketones **1**, **2**, and **3**, having 2-bromoethyl groups as angular substituents, were prepared and their cyclizations by intramolecular alkylation investigated. High selectivities for α′-alkylation were found; tricyclic ketones **10**, **15**, and **17** were the major or sole products of cyclization.

Intramolecular alkylation of ketones is an attractive and popular synthetic route to polycyclic ketones. In most cases the synthetic scheme is designed such that only one mode of cyclization is possible. We here describe the intramolecular alkylations of a series of bicyclic α,β-unsaturated ketones (**1**, **2**, and **3**) in

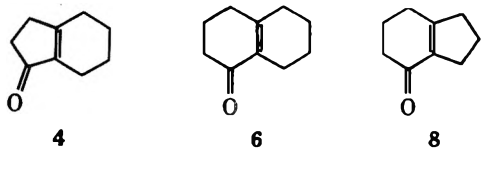


1a, X = Br
b, X = OMs

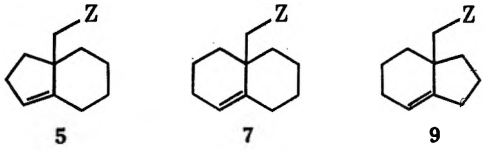
2 **3**

which, *a priori*, three possibilities for cyclization exist, *i. e.*, alkylation at the α position, at the γ position, or at the α′ position. Several examples of intramolecular alkylations of α,β-unsaturated ketones have been reported.[2-7] In some cases, the stereochemistry of the compound to be cyclized was such that only γ-alkylation was feasible;[2,3] however, in other cases in which competition among the several sites for alkylation seemed possible, selectivities for cyclization to the γ position[4,5] and to the α position[6,7] were observed.

The preparative route to ketones **1**, **2**, and **3** was based on Burgstahler's procedure for angular substitution[8] and the allylic oxidation method introduced by Dauben.[9] Thus, improvement[10] of the previously reported procedures for the conversion of **4** into **5a**[11] and **6** into **7a**[9] and extension to **8** to provide **9a** gave good yields of the angularly substituted bicyclic olefins.[12] Reduction of the aldehydes **5a**, **7a**, and **9a** gave the corresponding alcohols **5b**, **7b**, and **9b**, which were converted to the mesylates **5c**, **7c**, and **9c** and



4 **6** **8**



5 **7** **9**

a, Z = CHO
b, Z = CH_2OH
c, Z = CH_2OMs
d, Z = CH_2Br

treated with lithium bromide[13] to afford the bromo olefins **5d**, **7d**, and **9d**.[14] Oxidation[9] of the olefins with chromium trioxide–dipyridine complex, formed *in situ*,[15] provided the desired α,β-unsaturated ketones **1a**, **2**, and **3** (and **1b** from **5c**).

When cyclopentenone **1a** (or **1b**) was treated with potassium *tert*-butoxide in *tert*-butyl alcohol,[3] a mixture of ketones was obtained in which α,β-unsaturated ketone **10**, the product of α′-alkylation, and β,γ-unsaturated ketone **11**, the product of α-alkylation, were present in the ratio of 95:5. That the α,β-unsaturated ketone produced was **10** rather than **12**, the product of γ-alkylation, was demonstrated by catalytic reduction of the double bond to saturated ketone **13** followed by mild basic exchange of the active methylene hydrogens in methanol-*O*-*D*. The presence of only two exchangeable hydrogens confirmed the assignment of structures **13** and **10**; the saturated ketone **14**, derivable from **12**, would have had four exchangeable hydrogens.

(1) Presented in part at the 164th National Meeting of the American Chemical Society, New York, N. Y., Aug 1972, Abstracts, ORGN140.

(2) R. B. Bates, G. Büchi, T. Matsura, and R. R. Shaffer, *J. Amer. Chem. Soc.*, **82**, 2327 (1960). See also G. Büchi, W. Hofheinz, and J. V. Paukstelis *ibid.*, **91**, 6473 (1969).

(3) Intramolecular cyclization to the 4 position of the phenol can be considered γ-alkylation of an α,β-unsaturated ketone. For example, see S. Masamune, *ibid.*, **83**, 1009 (1961).

(4) (a) J. J. Bonet, H. Wehrli, and K. Schaffner, *Helv. Chim. Acta.*, **45**, 2615 (1962); (b) O. Halpern, P. Crabbe, A. D. Cross, I. Delfin, L. Cervantes, and A. Bowers, *Steroids*, **4**, 1 (1964).

(5) P. C. Mukharji and A. N. Ganguly, *Tetrahedron*, **25**, 5281 (1969).

(6) P. Grafen, H. J. Kabbe, O. Roos, G. D. Diana, Tsung-tee Li, and R. B. Turner, *J. Amer. Chem. Soc.*, **90**, 6131 (1968).

(7) C. Mercier, A. R. Addas, and P. Deslongshamps, *Can. J. Chem.*, **50**, 1882 (1972).

(8) A. W. Burgstahler and I. C. Nordin, *J. Amer. Chem. Soc.*, **83**, 198 (1961).

(9) W. G. Dauben, M. Lorber, and D. S. Fullerton, *J. Org. Chem.*, **34**, 3587 (1969).

(10) Longer reaction times in formation of the vinyl ethers of the allylic alcohols obtained upon reduction of **4**, **6**, and **8** resulted in much improved yields.

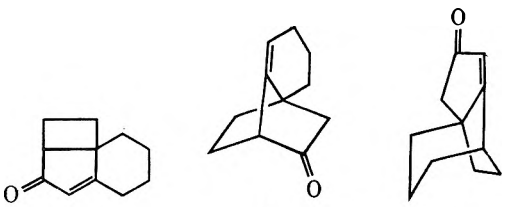
(11) (a) R. L. Cargill and A. M. Foster, *J. Org. Chem.*, **35**, 1971 (1970); (b) A. M. Foster, Ph.D. Thesis, University of South Carolina, Columbia, S. C., 1970.

(12) Attempts to convert the alcohol obtained from **4** into the methyl ester corresponding to **5a** by the orthoacetate method [W. S. Johnson, L. Werthemann, W. R. Bartlett, T. J. Brocksom, Tsung-tee Li, D. J. Faulkner, and M. R. Petersen, *J. Amer. Chem. Soc.*, **92**, 741 (1970)] failed owing to elimination from the allylic alcohol, which is unstable to storage.

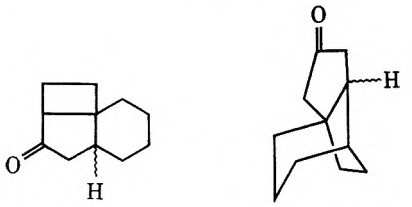
(13) J. W. Cornforth, R. H. Cornforth, and K. K. Mathew, *J. Chem. Soc.*, 2539 (1959).

(14) The bromides were preferred to the mesylates owing to easier purification of the bromo olefins and bromo enones.

(15) R. Ratcliffe and R. Rodehurst, *J. Org. Chem.*, **35**, 4000 (1970).

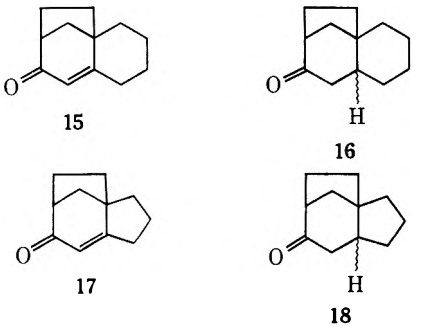


10 11 12



13 14

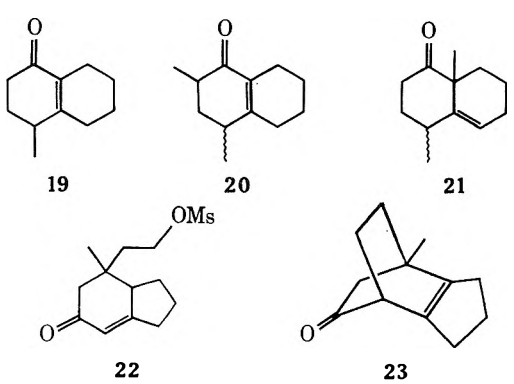
The selectivity for α'-alkylation found with the cyclopentenone increased to the point of specificity with the cyclohexenones. Similar cyclization of cyclohexenone **2** gave α,β-unsaturated ketone **15**, which was reduced to saturated ketone **16** having two ex-



15 16 17 18

changeable hydrogens; cyclohexenone **3** yielded α,β-unsaturated ketone **17**, which was converted to saturated ketone **18** with two exchangeable hydrogens.

That the kinetically formed enolate anion of such α,β-unsaturated ketones is the α' anion and the conjugated α (or γ) anion is the more stable anion has been demonstrated.[16] Thus, treatment of the kinetically formed enolate anion of **19** with methyl iodide resulted in formation of **20**, the product of α'-alkylation, but the equilibrated anion yielded **21**, the product of α-alkylation. This suggests that the selectivities noted in the intramolecular alkylations might result from trapping of the kinetically formed α'-enolate anion; however, this does not seem to be the best explanation. The use of equilibrating conditions for the cyclizations, the isolation of β,γ-unsaturated ketone **11**, and the recent report[7] that the major product of cyclization of cyclohexenone **22** under equilibrating conditions was β,γ-unsaturated ketone **23** argue against trapping of the kinetically formed anion. Examination of appropriate models in each case (including **23**) indicates that the observed product is the least strained of those possible. The products obtained from **1**, **2**, **3**, and **22** result from the lowest energy transition state available for intramolecular alkylation of an equilibrating mixture of α' and extended enolate anions.



19 20 21

22 23

(16) P. S. Wharton and E. C. Sundin, *J. Org. Chem.*, **33**, 4255 (1968). See also G. Stork and J. Benaim, *J. Amer. Chem. Soc.*, **93**, 5939 (1971).

Experimental Section

Microanalyses were performed by Bernhardt Microanalytisches Laboratorium, Elbach uber Engelskirchen, West Germany. Melting points and boiling points are uncorrected. Analytical gas–liquid partition chromatography (glpc) was carried out on an Aerograph Model 1200 Hy-FI employing 3% SE-30, 8 ft × 0.125 in.; 3% DEGS, 8 ft × 0.125 in.; 3% DC-710, 8 ft × 0.125 in.; and 10% Carbowax 1000, 6 ft × 0.125 in. columns. Preparative glpc was carried out on an Aerograph Model A-90-P3 using a 20% SE-30, 5 ft × 0.25 in. column. Silica gel used for column chromatography was E. Merck 0.05–0.20 mm silica gel. The following spectrometers were used: uv, Perkin-Elmer 202; ir, Perkin-Elmer 337 and 257; nmr, Varian A-60 and XL-100; mass spectrum, Hitachi RM-U6D. Generally, only absorptions important for characterization or identification and particularly strong absorptions are reported.

6-(2-Hydroxyethyl)bicyclo[4.3.0]non-1(9)-ene (5b).—Bicyclo[4.3.0]non-1(6)-en-7-one (**4**)[17] (26.2 g, 192 mmol) in dry ether (473 ml) under a drying tube was cooled in an ice–water bath and lithium aluminum hydride (6.2 g, 164 mmol) was added to the stirred solution. The ice bath was removed and the mixture was stirred at room temperature for 1 hr before it was again cooled with an ice–water bath and treated with H_2O (6.2 ml), 15% NaOH (6.2 ml), and H_2O (18.6 ml). After an additional 1 hr of stirring, the white precipitate was filtered and washed a few times with ether. The combined ethereal solution was dried ($MgSO_4$) and concentrated *in vacuo* to give bicyclo[4.3.0]non-1(6)-en-7-ol[12] as a clear oil (26.0 g, 98%) which had the expected ir spectrum[11] and was used at once for vinyl ether formation. The freshly prepared alcohol (26.0 g, 188 mmol) in ethyl vinyl ether (1.2 l.) (freshly distilled from sodium hydride) under N_2 was treated with mercuric acetate (15.0 g) (recrystallized from absolute ethanol containing 1% glacial acetic acid), and the resulting solution was heated under reflux for 57 hr. Glacial acetic acid (0.74 ml) was added, and reflux was continued for an additional 3 hr. The cooled reaction mixture was diluted to 1750 ml with pentane, washed with 5% NaOH (500 ml), dried (K_2CO_3), and concentrated *in vacuo* to a yellow oil (40 g) which was immediately washed through a column of Alcoa F-20 alumina (300 g) with pentane. Combination of the fractions containing the desired ether gave bicyclo[4.3.0]non-1(6)-en-7-yl vinyl ether (22.2 g, 71.5%) with ir and nmr spectra identical with those reported.[11] A portion of this vinyl ether (21.3 g, 130 mmol) was stirred while N_2 was bubbled through it for 1 hr; then the flask was equipped with an uncooled condenser and an N_2 bubbler and placed in an oil bath. The oil bath was warmed to 190° during 15 min. When the bath temperature reached 185°, a brief period of gas evolution caused foaming, which was controlled by cooling the condenser. After 1 hr at 190°, the oil was allowed to cool to room temperature, giving bicyclo[4.3.0]non-1(9)-ene-6-acetaldehyde (**5a**) (20.8 g, 97.7%) with the expected spectral characteristics.[11] A portion of the aldehyde (20.3 g, 124 mmol) in dry ether (473 ml) under a drying tube was cooled in an ice–water bath and treated with lithium aluminum hydride (4.7 g, 124 mmol). The bath was removed and the reaction mixture was stirred at room temperature for 70 min before it was again cooled with an ice–water bath and treated successively with H_2O (4.7 ml), 15% NaOH (4.7 ml), and H_2O (14.1 ml). Work-up in the usual way gave the alcohol **5b** (17.6 g, 86%) as an oil

(17) The preparation of **4** from cyclohexene and acrylic acid using polyphosphoric acid (PPA) [S. Dev, *J. Indian Chem. Soc.*, **34**, 169 (1957)] is limited in scale owing to the difficulty in stirring the viscous PPA mixture. Substitution of methanesulfonic acid containing phosphorus pentoxide [P. E. Eaton and R. H. Mueller, *J. Amer. Chem. Soc.*, **94**, 1014 (1972), footnote 11] for PPA allows easy scale-up and affords purer product.

containing only traces of impurities by glpc: ir (CCl_4) 3300, 3040, 2940, 2870, 1450 cm^{-1}; nmr ($CDCl_3$) δ 5.20 (m, 1), 3.60 (t, 2, J = 7 Hz), 1.0–2.5 (m, 15). An analytical sample was obtained by preparative glpc.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.38; H, 10.75.

6-(2-Bromoethyl)bicyclo[4.3.0]non-1(9)-ene (5d).—The above alcohol **5b** (12.50 g, 75.2 mmol) in dry pyridine (50 ml) under a drying tube was cooled in an ice–water bath and treated with methanesulfonyl chloride (7 ml, 11.5 g, 100 mmol). After a few minutes of stirring, a large amount of precipitate formed. The bath was removed and the mixture was kept at room temperature for 0.5 hr before H_2O (2 ml) was carefully added. The resulting mixture was taken up in ether–water. After the phases were separated and the aqueous phase was back-washed with ether, the combined ethereal solution was washed with 3 *N* HCl (five times, until the washings remained strongly acidic), H_2O, saturated $NaHCO_3$ (twice), and saturated NaCl, dried ($MgSO_4$), and concentrated *in vacuo* to give **5c** (14.63 g, 80%) as a yellowish oil: ir (CCl_4) 3020, 2920, 2840, 1370, 1350, 1170, 950 cm^{-1}; nmr ($CDCl_3$) δ 5.2 (m, 1), 4.13 (m, 2), 2.95 (s, 3), 1.0–2.5 (m, 14). The mesylate (14.6 g, 60.0 mmol) was dissolved in acetone (60 ml), treated with anhydrous lithium bromide (15.55 g, 180 mmol), and heated at reflux under a drying tube for 3 hr.[13] The cooled reaction mixture was diluted with acetone; then the solid was filtered and washed with acetone. The combined acetone solution was concentrated *in vacuo* to an oil which was taken up in ether–water. After the phases were separated, the ether solution was washed with water, saturated $NaHCO_3$, and saturated NaCl, dried ($MgSO_4$), and concentrated *in vacuo* to give the bromide **5d** as an orange liquid (12.2 g) which was vacuum distilled to give two fractions which were pure by glpc [(1) bp 62–64° (0.2 mm), 2.52 g; (2) bp 69–73° (0.15 mm), 8.76 g (combined yield 11.28 g, 82% from **5c**, 66% from **5b**)]: ir (CCl_4) 3020, 2910, 2830, 1450, 1215 cm^{-1}; nmr ($CDCl_3$) δ 5.22 (m, 1), 3.25 (m, 2), 1.0–2.5 (m, 14). An analytical sample was obtained by preparative glpc.

Anal. Calcd for $C_{11}H_{17}Br$: C, 57.65; H, 7.48; Br, 34.87. Found: C, 57.61; H, 7.37; Br, 34.83.

6-(2-Bromoethyl)bicyclo[4.3.0]non-1(9)-en-8-one (1a).[9]—To the burgundy colored solution[15] resulting from the addition of CrO_3 (20 g, 200 mmol = 300 mmol [O]) (ground and dried over P_2O_5 in a vacuum desiccator) to an ice–water bath cooled solution of pyridine (32.2 ml, 400 mmol) (distilled from BaO) in CH_2Cl_2 (500 ml) (distilled from P_2O_5) under N_2 with 15 min stirring (mechanical stirrer, blade in top of liquid) was added the bromo olefin **5d** (5.01 g, 21.8 mmol) in CH_2Cl_2 (10 ml). The ice–water bath was removed and the mixture was stirred for 17.5 hr before CH_2Cl_2 (250 ml), pyridine (16.1 ml, 200 mmol), and CrO_3 (10.0 g, 100 mmol = 150 mmol [O]), successively, were added.[18] After an additional 7 hr of stirring, the CH_2Cl_2 solution was decanted, the solid residue was washed several times with CH_2Cl_2, and the combined CH_2Cl_2 solution was washed with saturated $NaHCO_3$ (four times). Concentration *in vacuo* gave an oil which was taken up in ether (500 ml). The ether solution was washed with saturated $NaHCO_3$ (twice), H_2O, 3 *N* HCl (twice), H_2O, saturated $NaHCO_3$, and saturated NaCl before it was dried ($MgSO_4$) and concentrated *in vacuo* to a yellow liquid (4.39 g). Chromatography over silica gel (102 g) (1:1 hexane–ether) followed by recrystallization (ether–hexane) of the combined fractions containing bromo ketone gave crystalline **1a** (3.09 g, 58%) in several crops. Further recrystallization of a sample for spectra and analysis gave **1a**: mp 55.5–56.5°; uv max (95% EtOH) 233 nm (ϵ 13,300); ir (CCl_4) 2915, 2840, 1710, 1625, 1450, 1225, 855 cm^{-1}; nmr ($CDCl_3$) δ 5.80 (m, 1), 3.15 (m, 2), 1.1–2.7 (m, 12).

Anal. Calcd for $C_{11}H_{15}BrO$: C, 54.34; H, 6.22; Br, 32.86. Found: C, 54.25; H, 6.02; Br, 32.84.

Cyclization of 1a.[19]—The bromo ketone **1a** (1.000 g, 4.12 mmol) under Ar was dissolved in dry *tert*-butyl alcohol (40 ml) and treated with 1 *M* potassium *tert*-butoxide in *tert*-butyl alcohol (5 ml). A white precipitate formed at once in the clear solution. The stirred suspension was heated at gentle reflux for 22 hr,[20] allowed to cool, and poured into pentane-saturated NaCl. After the phases were separated, the aqueous phase was back-washed with pentane, and the combined pentane solution was washed several times with saturated NaCl, H_2O, and saturated NaCl, dried ($MgSO_4$), and concentrated by distillation of the pentane to give the product as a pale yellow liquid (0.300 g, 45%). Examination by glpc (assuming equal response factors) showed the presence of two components in a ratio of *ca.* 95:5; spectra indicated that the major product was an α,β-unsaturated ketone and the minor product a nonconjugated ketone. For separation of the components, the product was chromatographed over a column of silica gel (30 g), using 9:1 hexane–ethyl acetate to remove the ketones. First collected was the less polar tricyclo[5.2.2.$0^{1,6}$]undec-5-en-9-one (**11**) (16 mg, 2.4%): ir (CCl_4) 2990 (weak), 2915, 1755, 1705 cm^{-1} (weak); nmr ($CDCl_3$) δ 5.47 (t, 1, J = 7.5 Hz), 2.85 (m, 1), 1.2–2.2 (m, 12); mass spectrum (20 eV) *m/e* (rel intensity) 162 (14), 120 (100), 118 (61). Second was collected the more polar α,β-unsaturated ketone tricyclo[7.2.0.$0^{4,9}$]undec-3-en-2-one (**10**) (281 mg, 42.2%). A sample of this ketone collected by glpc for spectra and analysis had uv max (95% EtOH) 236 nm (ϵ 13,200); ir (CCl_4) 2910, 2830, 1695, 1450, 1440, 1170, 870 cm^{-1}; nmr ($CDCl_3$) δ 5.90 (finely split s, 1), 1.2–2.9 (m, 13).

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.42; H, 8.77.

Structure determination of the α,β-unsaturated ketone was carried out by hydrogenation of 187 mg (1.15 mmol) in ethyl acetate (6 ml) with 10% Pd/C (13 mg) as catalyst at ambient temperature and pressure. When hydrogenation (1 equiv of H_2) was complete, the catalyst was filtered with the aid of Celite, and the resulting solution was concentrated to give the saturated ketone tricyclo[7.2.0.$0^{4,9}$]undecan-2-one (**13**)[21] as a clear oil (184 mg, 97%). A portion collected by glpc for spectra and analysis had ir (CCl_4) 2905, 2840, 1740, 1450 cm^{-1}; nmr ($CDCl_3$) δ 2.5–1.1 (m, 16); mass spectrum (70 eV) *m/e* (rel intensity) 164 (22), 136 (100).

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.08; H, 9.63.

The number of active hydrogens was determined by base-catalyzed exchange. A portion of saturated ketone **13** (30.5 mg) was dissolved in a solution of $NaOCH_3$ in CH_3OD (1 ml) (prepared by addition of a small piece of sodium to CH_3OD). After 1.5 hr at room temperature the solvent was removed *in vacuo*, and the residue was taken up in D_2O–ether. After separation of the phases and further extraction of the D_2O with ether, the combined ethereal solution was dried (K_2CO_3) and concentrated *in vacuo* to a clear oil (29.8 mg). Examination by nmr showed a decrease in intensity of some, but not all, of the signals in the region δ 2.1–2.5. Analysis by mass spectroscopy and comparison with the mass spectrum of the untreated saturated ketone showed the product of exchange contained 7 mol % $C_{11}H_{16}O$, 32 mol % $C_{11}H_{15}DO$, 61 mol % $C_{11}H_{14}D_2O$, no $C_{11}H_{13}D_3O$, and no $C_{11}H_{12}D_4O$. The presence of only two exchangeable hydrogens confirmed that the α,β-unsaturated ketone was **10**.

6-(2-Hydroxyethyl)bicyclo[4.4.0]decene (7b).—Bicyclo[4.4.0]-dec-1(6)-en-2-one (**6**) was converted to the alcohol and the vinyl ether in the same manner described above for **4**. The vinyl ether (8.3 g) was stirred under aspirator vacuum until all bubbling ceased, then for an additional 1 hr, Ar was bubbled through the stirred liquid for 0.5 hr, and the liquid was again stirred under vacuum until gas evolution ceased. The resulting liquid, stirred under N_2 under an uncooled short-path (Alembic) still, was heated to 190° during 5 min and stirred at that temperature for 0.5 hr with a slight amount of foaming. The resulting product was a clear oil (7.1 g, 86%) (73% from **6**) having the infrared spectrum expected for **7a**.[8] The crude aldehyde **7a** (7.1 g, 40 mmol) was reduced with $LiAlH_4$ (1.0 g, 26 mmol) as previously described for **5a**; the crude product (7.4 g, 103%) was a clear, colorless oil containing a few droplets of another phase and two significant impurities by glpc (possibly from the starting material). For spectra and analysis, a sample of pure alcohol **7b** was collected by glpc as a clear oil: ir (CCl_4) 3590, 3300 (broad), 3020, 2910,

(18) This second addition of oxidant[9] is necessary; in preliminary experiments, oxidation of **5d** to **1a** and of **5c** to **1b** without the second addition of oxidant resulted in *ca.* 20% remaining unoxidized starting material.

(19) Similar results were obtained on cyclization of crude **1b**.[14] When **1a** containing *ca.* 20% **5d**[18] was cyclized in a preliminary experiment, the **5d** was recovered unchanged; thus elimination (which would require removal of a proton from a neopentyl-type carbon) does not occur significantly under these conditions.

(20) Further experiments with the cyclohexenones indicated that the period of reflux is unnecessary.

(21) The stereochemistry of the angular hydrogen introduced upon hydrogenation of the double bond is unassigned owing to lack of evidence; for the structural assignments this information is unimportant.

2840, 1450, 1050, 1040 cm^{-1}; nmr ($CDCl_3$) δ 5.35 (m, 1), 3.63 (t, 2, J = 7.5 Hz), 1.3–2.1 (m, 17).

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18; Found: C, 79.86; H, 11.28.

6-(2-Bromoethyl)bicyclo[4.4.0]dec-1-ene (7d).—The crude alcohol **7b** (7.3 g, 40 mmol) was treated with methanesulfonyl chloride in pyridine as described for the conversion of **5b** to **5c**. The crude mesylate **7c**, obtained as a clear oil (8.0 g, 31 mmol, 78%) with ir (CCl_4) 2920, 2840, 1370, 1350, 1170, 940 cm^{-1}, was treated with lithium bromide in acetone as described for the preparation of **5d**. The crude bromide **7d** was obtained as a red oil (6.5 g, 80%). Analysis by glpc showed the same two impurities present in the alcohol and new, minor ones. Samples for spectra and analysis were collected by glpc giving **7d** as a clear oil: ir (CCl_4) 2910, 2840, 1450 cm^{-1}; nmr ($CDCl_3$) δ 5.38 (m, 1), 3.30 (m, 2), 1.1–2.3 (m, 16).

Anal. Calcd for $C_{12}H_{19}Br$: C, 59.27; H, 7.88; Br, 32.86. Found: C, 59.16; H, 7.98; Br, 32.77.

6-(2-Bromoethyl)bicyclo[4.4.0]dec-1-en-3-one (2).—By the procedure described for the preparation of **1a**, the crude bromide **7d** (6.3 g, 26 mmol) was oxidized to the bromo enone **2**. Chromatography of the crude product, a yellow oil (4.6 g), over silica gel using mixtures of hexane and ethyl acetate, followed by recrystallization (hexane–ether) of the fractions containing **2**, gave white, crystalline **2** (1.26 g, 19%) and an uncrystallized yellow oil (0.48 g, 7%) of essentially pure **2**. A sample of **2** further recrystallized for spectra and analysis was a white, crystalline solid: mp 51.5–52°; uv max (95% EtOH) 241 nm (ϵ 14,000); ir (CCl_4) 2920, 2850, 1680, 1625, 1465, 1330, 860 cm^{-1}; nmr ($CDCl_3$) δ 5.75 (finely split s, 1), 3.3 (m, 2), 1.2–2.6 (m, 14).

Anal. Calcd for $C_{12}H_{17}BrO$: C, 56.02; H, 6.67; Br, 31.09. Found: C, 55.81; H, 6.89; Br, 30.88.

Cyclization of 2.—A portion of crystalline **2** (287 mg, 1.12 mmol) under Ar was dissolved in dry *tert*-butyl alcohol (12 ml) and treated with 1 *M* potassium *tert*-butoxide in *tert*-butyl alcohol (2 ml). A white precipitate formed at once in the reaction mixture, which was stirred at 35–40° for 6.5 hr before it was worked up as described for the cyclization of **1a**. Examination of the crude product, a slightly yellow oil (153 mg, 78%), by glpc and ir showed the only product to be tricyclo[7.2.1.0^{4,9}]dodec-3-en-2-one (**15**). Spectra of **15** were obtained from the product of a different preparation, and purified by passage through a column of silica gel (9:1 hexane–ethyl acetate) and preparative glpc, giving **15** as a clear oil: uv max (95% EtOH) 244 nm (ϵ 11,900); ir (CCl_4) 3020, 2940, 2860, 1680, 1610, 1450, 1260 cm^{-1}; nmr ($CDCl_3$) δ 5.58 (m, 1) 2.80 (m, 1), 1.2–2.6 (m, 14). An analytical sample was prepared by filtration of the product of the above described preparation through a small column of silica gel (1:1 hexane–ether) followed by collection from glpc.

Anal. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15. Found: C, 81.64; H, 8.98.

Catalytic hydrogenation of **15** as described for the conversion of **10** to **13** gave tricyclo[7.2.1.0^{4,9}]dodecan-2-one (**16**)[21] as a colorless oil: ir (CCl_4) 2920, 2850, 1710, 1450 cm^{-1}; nmr ($CDCl_3$) δ 2.63 (m, 1), 1.0–2.4 (m, 17); mass spectrum (70 eV) *m/e* (rel intensity) 178 (67), 41 (100).

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.74; H, 10.03.

Although the structural assignments for **15** and **16** were clear from the spectra (*i.e.*, bridgehead proton α to ketone at δ 2.63 in **16**), the deuterium exchange experiment was carried out as before, resulting in a product mixture containing 3 mol % $C_{12}H_{18}O$, 19 mol % $C_{12}H_{17}DO$, 78 mol % $C_{12}H_{16}D_2O$, no $C_{12}H_{15}D_3O$, and no $C_{12}H_{14}D_4O$ and confirming the structural assignments.

Bicyclo[4.3.0]non-1-ene-6-acetaldehyde (9a).—By procedures similar to those described previously, bicyclo[4.3.0]non-1(6)-en-2-one (**8**)[22] (9.43 g, 69.4 mmol) was converted successively into the alcohol [ir (CCl_4) 3580, 3400 cm^{-1} (broad)[1]] (8.8 g, 63.7 mmol, 92%), the vinyl ether [ir (CCl_4) 3100, 2920, 2825, 1630, 1610 cm^{-1}; nmr ($CDCl_3$) δ 6.32 (d of d, 1, J = 14 Hz, J = 7.5 Hz), 4.27 (d of d, 1, J = 14 Hz, J = 1.5 Hz), 4.22 (m, 1), 3.92 (d of d, 1, J = 7.5 Hz, J = 1.5 Hz), 1.5–2.6 (m, 12)] (8.22 g, 50 mmol, 78.5%), and the aldehyde **9a** [7.14 g, 43.5 mmol (87%); 63% from **8**]. Pure **9a** collected by glpc was a clear oil: ir (CCl_4) 2920, 2825, 2710, 1720 cm^{-1}; nmr ($CDCl_3$) δ 9.70 (t, 1, J = 3 Hz), 5.37 (m, 1), 1.2–2.6 [m, 14, including 2.35 (d, 2, J = 3 Hz)].

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.09; H, 9.80.

6-(2-Hydroxyethyl)bicyclo[4.3.0]non-1-ene (9b).—Reduction of **9a** (6.82 g, 41.5 mmol) (containing an impurity from the rearrangement) as described for the similar aldehydes gave **9b** (5.82 g, 78%) (still containing the impurity). A purer sample of **9b** (from another preparation) had ir (CCl_4) 3590, 3300 (broad), 3020 (weak), 2910, 1450, 1043 cm^{-1}; nmr ($CDCl_3$) δ 5.3 (m, 1), 3.60 (t, 2, J = 7.5 Hz), 2.68 (s, 1), 1.0–2.5 (m, 14). An analytical sample was collected from glpc.

Anal. Calcd for $C_{11}H_{18}O$: C, 79.46; H, 10.92. Found: C, 79.41; H, 10.92.

6-(2-Bromoethyl)bicyclo[4.3.0]non-1-ene (9d).[23]—The above described crude alcohol **9b** (5.33 g, 32 mmol) and a small amount of *o*-phenanthroline were dissolved in ether (100 ml) under Ar. The solution was cooled to 0° with an isopropyl alcohol–Dry Ice bath and treated with methyllithium (14 ml of 1.9 *M* solution, 27 mmol) at 0° until the reaction mixture became a coffee-colored suspension. The suspension was then treated at −10 to 0° with methanesulfonyl chloride (2.3 ml, 30 mmol). The bath was removed and the suspension was allowed to warm to room temperature before it was treated with anhydrous lithium bromide (8.7 g, 100 mmol) and allowed to stir for 21 hr. The reaction mixture was poured into saturated $NaHCO_3$. After phases were separated, the ether solution was washed with water and saturated $NaHCO_3$, dried (K_2CO_3), and concentrated *in vacuo* to give crude **9d** as an orange oil (6.78 g, 92.5%). Examination by glpc showed that the impurity present in **9a** and **9b** (retention time 0.8 min) remained as essentially the only impurity in **9d** (retention time 3.2 min). The impurity was removed by distillation at room temperature under high vacuum, using a Dry Ice cooled alembic still. The resulting **9d** (5.07 g), containing *ca.* 3% impurity, had ir (CCl_4) 3040, 2940, 2870, 2840, 1455, 1440 cm^{-1}; nmr ($CDCl_3$) δ 5.3 (m, 1), 3.2 (m, 2), 1.0–2.5 (m, 14). An analytical sample was obtained by glpc.

Anal. Calcd for $C_{11}H_{17}Br$: C, 57.65; H, 7.48; Br, 34.87. Found: C, 57.47; H, 7.44; Br, 34.81.

6-(2-Bromoethyl)bicyclo[4.3.0]non-1-en-3-one (3).[24]—By the procedure described for the preparation of **1a** and **2**, the above described bromide **9d** (2.05 g, 8.95 mmol) was converted into enone **3**. The crude product (1.4 g) was chromatographed over silica gel (50 g), using mixtures of hexane–ethyl acetate, yielding a pure fraction of **3** (491 mg, 24%) as an oil which resisted attempts at crystallization, and which cyclized to **17** upon injection into the glpc instrument. The bromo enone **3** was thus characterized as an oil: uv max (95% EtOH) 240 nm; ir (CCl_4) 2950, 2870, 1675, 1630 cm^{-1}; nmr ($CDCl_3$) δ 5.77 (m, 1), 3.43 (t, 2, J = 8.5 Hz), 1.2–2.8 (m, 12); mass spectrum (70 eV) *m/e* (rel intensity) 244 (6), 242 (6), 216 (21), 214 (21), 202 (8), 200 (8), 163 (42), 79 (100).

Cyclization of 3.—A portion of **3** (273 mg, 1.12 mmol) under Ar was dissolved in dry *tert*-butyl alcohol (20 ml) and treated with 1 *M* potassium *tert*-butoxide in *tert*-butyl alcohol (2 ml). A precipitate formed at once. After 15 min of stirring, the reaction mixture was worked up as described for the cyclizations of **1a** and **2**. The crude product (83 mg, 46%) was a yellow oil which was found to contain tricyclo[6.2.1.0^{4,8}]undec-3-en-2-one (**17**) as the only ketone present. Purification over a column of silica gel (1:1 hexane–ether) gave pure **17** (75 mg, 41%) as a clear oil. For spectra and analysis, **17** collected by glpc was a clear oil: uv max (95% EtOH) 242 nm (ϵ 11,700); ir (CCl_4) 2940, 2850, 1670, 875 cm^{-1}; nmr ($CDCl_3$) δ 5.7 (m, 1), 1.2–3.0 (m, 13); mass spectrum (70 eV) *m/e* (rel intensity) 162 (30), 134 (18), 121 (100).

Anal. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70. Found: C, 81.28; H, 8.82.

Catalytic hydrogenation of **17** as previously described gave tricyclo[6.2.1.0^{4,8}]undecan-2-one (**18**)[21] as a clear oil: ir (CCl_4) 2950, 2860, 1710 cm^{-1}; nmr ($CDCl_3$) δ 2.63 (m, 1), 1.1–2.5 (m,

(22) An improved procedure for the preparation of **8** results from use of methanesulfonic acid–phosphorus pentoxide (see footnote 17) instead of PPA, which is used in the previously described preparation: R. K. Hill and R. T. Conley, *J. Amer. Chem. Soc.*, **82**, 645 (1960). More convenient purification of the product is afforded by distillation, bp 43° (0.10 mm).

(23) When the procedure used for the preparation of **5d** from **5b** and **7d** from **7b** was applied to **9b**, a mixture of **5d** and **9d** was obtained, apparently as a result of isomerization of **9c** in the work-up procedure. The procedure used for preparation of **9d** is a better and more convenient one for this transformation of alcohol to bromide.

(24) For a synthesis of the 2-acetoxyethyl compound corresponding to **3**, see N. P. Peet and R. L. Cargill, *J. Org. Chem.*, **38**, 1215 (1973).

15); mass spectrum (70 eV) *m/e* (rel intensity) 164 (42), 41 (100). An analytical sample was prepared by glpc.

Anal. Calcd for $C_{11}H_{16}O$: C, 80.44; H, 9.83. Found: C, 80.01; H, 9.77.

Again the shift (δ 2.63) of the bridgehead hydrogen adjacent to the ketone in **18** confirmed the structural assignment, but the deuterium experiment was carried out, giving a product containing 3 mol % $C_{11}H_{16}O$, 14 mol % $C_{11}H_{15}DO$, 83 mol % $C_{11}H_{14}D_2O$, no $C_{11}H_{13}D_3O$, and no $C_{11}H_{12}D_4O$ and confirming the structural assignments.

Registry No.—**1a,** 39837-99-5; **2,** 39832-73-0; **3,** 39832-74-1; **4,** 22118-00-9; **5a,** 24097-40-3; **5b,** 39832-76-3; **5c,** 39832-77-4; **5d,** 39832-78-5; **6,** 18631-96-4; **7a,** 39832-80-9; **7b,** 39832-81-0; **7c,** 39832-82-1; **7d,** 39832-83-2; **8,** 22118-01-0; **9a,** 39832-85-4; **9b,** 39832-86-5; **9d,** 39832-87-6; **10,** 39832-88-7; **11,** 39832-89-8; **13,** 24736-69-4; **15,** 39832-91-2; **16,** 39832-92-3; **17,** 39832-93-4; **18,** 39832-94-5; bicyclo[4.3.0]non-1(6)-en-7-ol, 39832-95-6; bicyclo[4.3.0]non-1(6)-en-7-yl vinyl ether, 39832-96-7; methanesulfonyl chloride, 124-63-0.

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The Synthesis of α-Branched Ketones from Dihydro-1,3-oxazines *via* the Ketenimine Intermediate. α-Substituted Ketones from a Stable Ketenimine[1]

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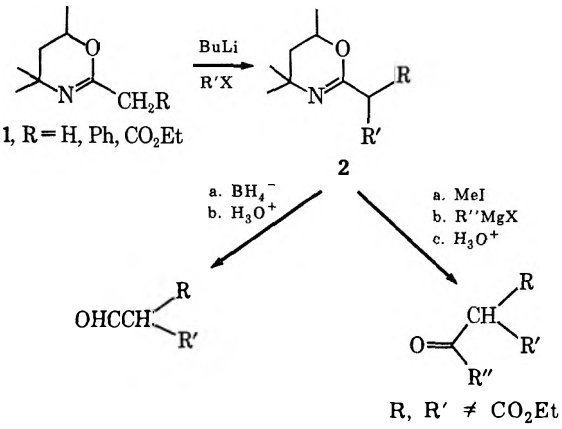
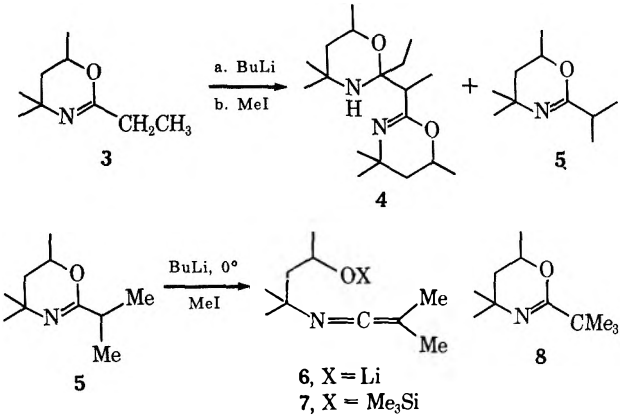
The tertiary proton abstraction from 2-isoalkyloxazines (**12**) by organolithiums leads to rapid ketenimine rearrangement. The ketenimines are shown to be useful precursors to a variety of highly substituted ketones by virtue of successive alkylations. The ketenimine intermediate was verified by isolation as its trimethylsilyl ether (**7**) and also used as a precursor to substituted ketones by addition of Grignard or organolithium reagents.

The readily available tetramethyldihydro-1,3-oxazine **1** (R = H) has been shown to serve as a useful precursor to aldehydes[4] and ketones[5] by the equations set forth in Scheme I. In addition, the corresponding

SCHEME I



2-benzyl (R = Ph) and 2-carboethoxy (R = CO_2Et) derivatives led to substituted oxazines by virtue of alkylation of their respective carbanions. These, in turn, were transformed into carbonyl compounds by similar manipulations. Among the limitations noted for these methods[4,5] was the failure of oxazines possessing *n*-alkyl (**1**, R = Me, Et, Pr, etc.) or isoalkyl (**2**, R, R′ = Me, Et, etc.) substituents to form a stable carbanion capable of further alkylation. For example, the 2-ethyloxazine **3** gave mainly the dimer **4** upon treatment with butyllithium (or other comparable bases) and methyl iodide under a variety of conditions. The expected product **5** was produced in only 10–15% yield. Similar treatment of the 2-isopropyloxazine **5** indicated complete inertness to strong base below ~0°; yet above this temperature (0–25°) it was rapidly transformed into the ketenimine **6**. The latter was trapped by addition of trimethylchlorosilane and **7** was isolated in 35–40% yield. Only a trace of the 2-*tert*-butyloxazine **8** was found among the product. It is evident,



therefore, that secondary and tertiary carbanions α to the oxazine ring are unstable to the temperatures at which they are formed, rearranging to open-chain ketenimines which react further with nucleophiles present. This oxazine–ketenimine rearrangement thus prohibits the synthesis of α-alkylaldehydes *via* Scheme I but was deemed sufficiently novel that a study to assess its potential was undertaken.[6]

(1) Part XX of a study on the chemistry of dihydro-1,3-oxazines. For previous papers in this series see A. I. Meyers and N. Nazarenko, *J. Org. Chem.*, **38**, 175 (1973).

(2) Address all correspondence to this author at the Department of Chemistry, Colorado State University, Fort Collins, Colo. 80521.

(3) Postdoctoral Fellow of the Medical Research Council of Canada, 1968–1970.

(4) A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen, and R. C. Portnoy, *J. Org. Chem.*, **38**, 36 (1973).

(5) A. I. Meyers and E. M. Smith, *J. Org. Chem.*, **37**, 4289 (1972).

(6) The synthesis of α-alkylaldehydes was accomplished, nevertheless, using the 2-vinyloxazine and successive addition of Grignard reagent and alkyl iodides (see ref 4).

Results and Discussion

The reaction of **5** with 1.0 equiv of *n*-butyllithium (0°, THF) gave the tetrahydro-1,3-oxazine **10**, which, upon hydrolysis in aqueous oxalic acid, afforded the ketone **11** in ~30% yield. This result may be explained by the slow rate of tertiary proton removal followed by rapid rearrangement of the unstable α carbanion and addition of unreacted *n*-butyllithium leading to **9**. Introduction of trimethylchlorosilane subsequent to the addition of *n*-butyllithium leads to **7** and **9a** after quenching. The tetrahydro-1,3-oxazine **10** was not obtained pure and was probably contaminated with **9a** (Me_3Si singlet in nmr of crude **10**). Nevertheless, both **10** and **9a** would lead to the ketone **11** on hydrolytic cleavage. It was a simple matter to render this process more efficient by adding 2.0 equiv of *n*-butyllithium to the isopropyloxazine, **5**. In this fashion there was sufficient base to abstract completely the tertiary proton and also allow addition to the resulting ketenimine. The yield of ketone **11** rose to 75% after this modification. A series of ketones **13** were prepared *via* this route (Scheme II) using various isoalkyloxazines **12** and organolithium reagents (Table I, entries 1–12). A significant extension to this process was developed by taking advantage of the *in situ* formation of the lithioenamine intermediate **14**. If, prior to quenching, the solution containing **14** is treated with an alkyl halide, **15** is produced by a nucleophilic attack of the lithioenamine upon the alkyl halide. This provides the quaternary carbon adduct, which, after quenching and oxalic acid hydrolysis, leads to the α-quaternary carbon ketones **16**. Thus, a stepwise technique based upon four alkyl groups being introduced in sequence is available for the formation of highly substituted ketones (Table I, entries 13–17).[7] The relationship of the alkylation step (**14** → **15**) to that reported by Stork[8] is obvious. Transformation of aldehydes and ketones to their imine derivative, followed by salt formation with a Grignard reagent, leads to the magnesioenamine **17**, which similarly alkylates at the β carbon, affording, after hydrolysis, the α-alkylated ketone **18**. It is noteworthy that only the magnesioenamine **17** is formed and not the more highly substituted isomer, **19**. This confirms the absence of an equilibrium between the two metalated enamines **17** and **19** and this was also observed in the enamine salts derived from ketenimines. Furthermore, both methods complement each other nicely in that Stork's procedure leads to ketones containing the alkyl group on the least substituted carbon, whereas this method produces ketones alkylated at the more highly substituted carbon.

In the case where the oxazine bears a benzyl proton (*e.g.*, **20**) it may be removed at −78° with *n*-butyllithium, since the conjugated effect of the phenyl group assists in stabilizing the carbanion, **21**. At −78° this carbanion may be alkylated smoothly[4] but, if **21** is allowed to warm up, rearrangement to the ketenimine **22** ensues. At this point, other nucleophilic reagents may be introduced (*i.e.*, RMgX), furnishing the magnesioenamine **23** which is ultimately carried on to either the ketone **24** or **25**. This route possesses two distinct advantages: (a) it reduces the necessity for using 2.0 equiv of an organolithium reagent whose availability or carbon skeleton may be either time-consuming or expensive, and (b) allows the preparation of methyl ketones which could not be obtained using 2.0 equiv of methyllithium, since the latter fails to

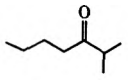
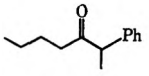
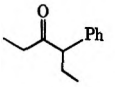
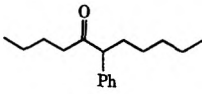
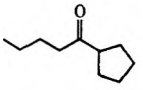
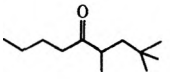
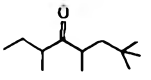
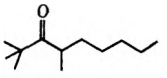
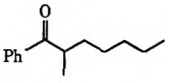
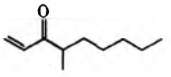
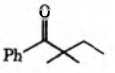
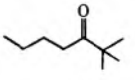
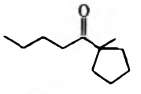
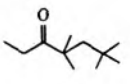
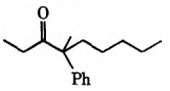
SCHEME II

(7) A Preliminary report has appeared: A. I. Meyers, E. M. Smith, and A. F. Jurjevich, *J. Amer. Chem. Soc.*, **93**, 2314 (1971).

(8) G. Stork and S. Dowd, *J. Amer. Chem. Soc.*, **85**, 2178 (1963).

TABLE I

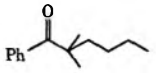
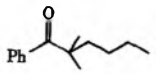
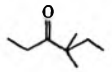
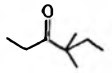
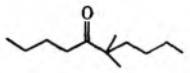
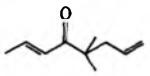
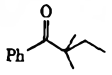
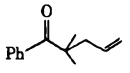
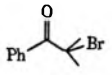
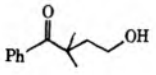
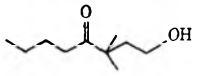
KETONES 16 AND 13 *via* SCHEME II

Entry	Registry no. of 12	Oxazine, 12[a] R1	R2	Organolithium R3	Registry no.	Alkyl iodide R4	Ketone	Registry no.	Yield, %[b]	Registry no.	ν, cm⁻¹ (film)
					Ketones 13[c]						
1	39575-96-7	Me	Me	*n*-Bu	109-72-8			13019-20-0	73		1705
2		Me	Me	*t*-Bu	594-19-4			5857-36-3	49		1700
3		Me	Me	Ph	591-51-5			611-70-1	80		1694
4	39575-97-8	Ph	Me	*n*-Bu				7661-44-1	70[d]	39576-16-4	1709
5	36867-26-2	Ph	Et	Et	811-49-4			6957-17-1	92[e]	39576-17-5	1712
6	30078-61-6	Ph	*n*-Amyl	*n*-Bu				25387-03-5	77		1710
7	39576-00-6			*n*-Bu				6636-80-2	88[f]	39576-18-6	1701
8	39575-86-5	Me	Neopent	*n*-Bu				26933-75-5	61		1709
9		Me	Neopent	*sec*-Bu	598-30-1			39576-08-4	57		1702
10	36871-42-8	Me	*n*-Amyl	*t*-Bu				32557-59-8	63		1703
11		Me	*n*-Amyl	Ph				39576-10-8	47		1685
12		Me	*n*-Amyl	CH_2=CH	917-57-7			32524-99-5	45		1699 1679 1613
					Ketones 16						
13		Me	Me	Ph	75-03-6	Et		829-10-7	51		1681
14		Me	Me	*n*-Bu	74-88-4	Me		19078-97-8	60[g]	39576-19-7	1715
15				*n*-Bu		Me		32524-97-3	63		1709
16		Me	Neopent	Et		Me		32557-57-6	65		1700
17		Ph	*n*-Amyl	Et		Me		39576-15-3	73		1710

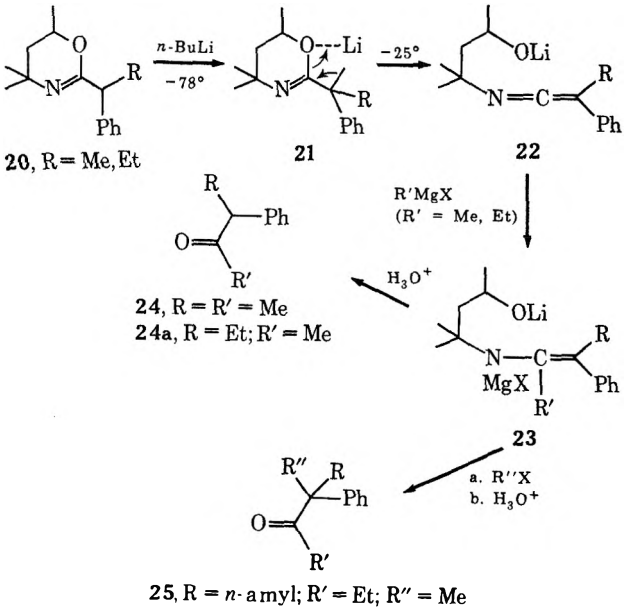
[a] Oxazines were distilled prior to reaction with organolithium reagents. [b] Yields based upon 2-isoalkyloxazines (12). [c] All compounds gave satisfactory elemental (±0.03%) and mass analyses. Nmr spectra were consistent with structures in all cases. [d] Semicarbazone, mp 119–120°. [e] Semicarbazone, mp 138–140°. [f] Semicarbazone, mp 120–121°. [g] Semicarbazone, mp 143–145°.

TABLE II

α-SUBSTITUTED KETONES (27) FROM KETENIMINE O-TRIMETHYLSILYL ETHER (7)

Entry	Registry no.	RMgBr	E	Registry no.	Ketone 27[a]	Registry no.	Yield, %	ν, cm⁻¹ (film)
1	100-58-3	Ph	*n*-BuI	542-69-8		17234-63-8	74	1680
2		Ph	*n*-BuBr	109-65-9			81	
3	925-90-6	Et	EtI			19550-14-2	87	1712
4		Et	EtBr	74-96-4			78	
5	693-03-8	*n*-Bu	*n*-BuI			39576-22-2	79	1704
6	1730-25-2	Allyl	Allyl Br	106-95-6		39576-23-3	70[b]	1683, 1628
7		Ph	EtI				74[e]	1681
8		Ph	Allyl Br			39576-24-4	60	1678
9		Ph	Br_2	7726-95-6		10409-54-8	40	1670
10		Ph	Ethylene oxide	75-21-8		39576-26-6	30[c]	3480
11		*n*-Bu[d]	Ethylene oxide			39576-27-7	65[c]	1688, 3500

[a] All compounds gave satisfactory elemental (±0.03%) and mass analyses. Nmr spectra were consistent with structures in all cases. [b] Obtained as a mixture (9:1) of conjugated and nonconjugated isomer. [c] Exists in hemiketal form. [d] Butyllithium was used since poor yields (~15%) were obtained using *n*-butylmagnesium bromide. [e] Identical with **13** (entry 13) in Table I.



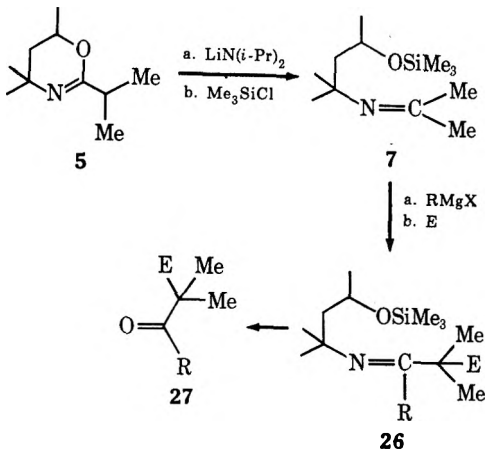
abstract the tertiary proton from the oxazines.[9] Unfortunately, this route was limited to oxazines whose α protons can be removed at low temperatures, thus avoiding interference by the ketenimine.

The use of lithium diisopropylamide as a base provided a partial solution to the problem of employing 2.0 equiv of an organolithium reagent. Treatment of 2-isopropyloxazine **5** with lithium diisopropylamide at 0° in THF, followed by addition of trimethylchlorosilane, gave the ketenimine silyl ether **7** in 80% yield. This was in sharp contrast to the results mentioned earlier using butyllithium. The efficient preparation of **7**, in sufficient quantity to classify it as a suitable starting material, allowed its chemistry to be further evaluated. The ketenimine was found to be completely stable to water and alkali for several hours (25°), but very unstable to aqueous acid.[10]

A variety of Grignard reagents were added to **7** followed by introduction of an electrophile (E) leading to the imine **26**. Hydrolysis of the latter in oxalic acid afforded the ketones **27** in variable yields (Table II). It is seen from Table II that bromine and ethylene oxide also served as electrophilic agents producing α-bromo and γ-hydroxy ketones, respectively. Among the electrophiles which did not add were chlorine, iodine, acyl halides, esters, and epoxides carrying sub-

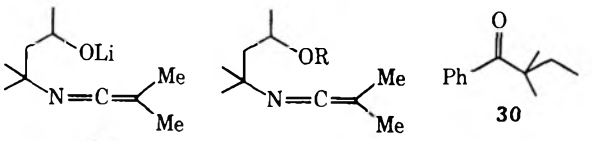
(9) Methyllithium failed to function as a base at low temperature in all the oxalines studied to date.[4] (However, see ref 13.)

(10) C. L. Stevens and J. C. French, *J. Amer. Chem. Soc.*, **75**, 657 (1953).

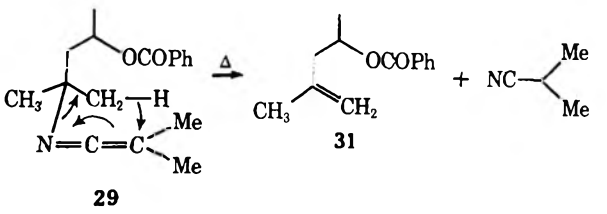


stituents (ethyl, phenyl). *sec*-Butyl and 3-cyclohexenyl bromide also failed to react with the intermediate magnesioenamine. Of further note was the sluggish nature of the Grignard addition to **7**. After these reactants had been stirred at room temperature for 18 hr there was still a considerable quantity of unreacted **7**. This is in contrast to the more facile addition (25°, 8 hr) of Grignard reagents to the *O*-lithioketenimines **6** and **22**. Similarly, the addition of alkyl halides to the magnesioenamine derived from **7** proceeded slowly at room temperature. The yields of ketones in Table II were achieved only after heating the ketenimine and Grignard reagents to reflux (~18 hr) and similarly heating the reaction after introduction of the electrophile (except bromine).

It is difficult to explain the slow reaction rate of **7** as compared to that of the *O*-lithio salt **6** except on steric grounds. Yet the bulky trimethylsilyl group must be hindering attack by both the Grignard and electrophilic agent. Why this should occur in an open-chain compound is not clear. In order to test this hypothesis, the ketenimine *O*-methyl ether **28** was prepared by addition of dimethyl sulfate to the *O*-lithioketenimine **6**. This compound could not be obtained pure since it was accompanied by 10% of the 2-isopropyloxazine, and separation attempts were all fruitless. Nevertheless, **28** was used in ~90% purity in reaction with Grignard reagents and subsequently with ethyl iodide. There was no concern over the presence of 10% oxazine in the ketenimine, since it is now well known that oxazines are completely inert to Grignard reagents.[4] Addition of phenyl Grignard to **28** followed by ethyl iodide proceeded smoothly at room temperature to give, after work-up, the phenyl ketone **30** in 90% yield (based upon

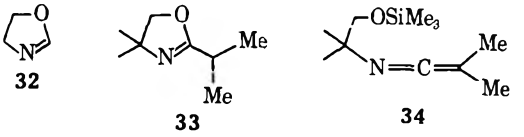


the ketenimine present). Thus, the smaller methoxyl group in **28** results in greater accessibility to the magnesioenamine by ethyl iodide. During attempts to purify **28**, vpc examination above 175° showed several additional highly volatile peaks, one of which was collected and found to be isobutyronitrile. The origin of this material was subsequently determined by subjecting the higher boiling ketenimine benzoate **29** to pyrolysis (160–200°). In addition to isobutyronitrile, the unsaturated ester **31** was isolated in 80% yield.



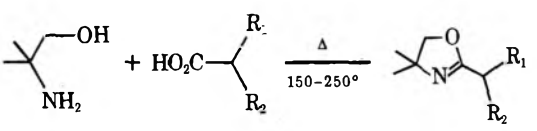
While this study was in progress, Ciganek reported the pyrolytic conversion of ketenimines to olefins and nitriles.[11]

In view of the synthetic utility exhibited by the related 2-oxazoline system **32** as a source of carboxylic acids and esters,[12] it was of interest to examine its behavior in the carbanion–ketenimine rearrangement. As expected, the carbanion of **33** was formed using *n*-butyllithium and in the presence of an excess of the latter base provided *n*-butyl isopropyl ketone **11** in 84% yield. Furthermore, addition of lithium diisopropylamide to **33** followed by trimethylsilyl chloride produced the trimethylsilyl ketenimine **34** in 65% yield.



Several experiments were performed on **34** in order to assess its utility toward the synthesis of ketones. Addition of phenylmagnesium bromide followed by *n*-butyl iodide gave after extended heating the corresponding ketone **26** (Table II, entry 1) in only 40% yield. On the basis of this experiment, it would appear that the trimethylsilyl group is exerting an even greater retarding effect than was observed in the ketenimine derived from the oxazine. In view of these results, no further effort was expended on the 2-oxazoline. A report by Dubois[13] has demonstrated that excellent yields of α-branched ketones were obtained by the use of 2.0 equiv of organolithium reagents on **33** according to the method given in Scheme II. The main advantage to the use of the oxazoline as a precursor to ketones was stated by Dubois to lie in their ease of preparation. Thus, by heating 2-methyl-2-aminopropanol with carboxylic acids according to Scheme III,

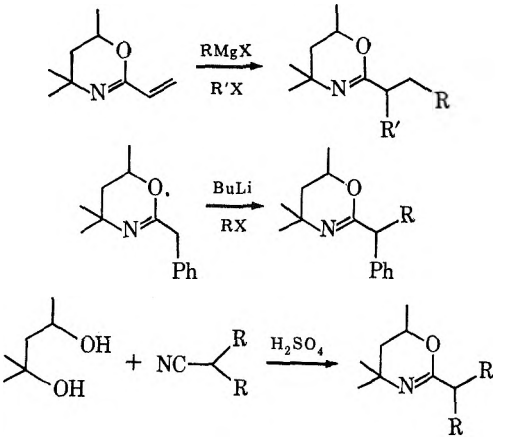
SCHEME III



various 2-isoalkyl-2-oxazolines were obtained in 30–68% yield. Although this may be an efficient route to simple oxazolines ($R_1 = R_2 = Me$), the yields drop off rapidly as the substituents on the carboxylic acid increase in bulk. On the other hand, the use of oxazines as precursors to ketones allows a variety of alkyl substituents to be employed by the efficient elaborative techniques outlined in Scheme IV. The oxazines **12** in Table I

(11) E. Ciganek, *Tetrahedron Lett.*, 5179 (1969).
(12) A. I. Meyers and D. L. Temple, *J. Amer. Chem. Soc.*, **92**, 6644, 6646 (1970).
(13) J. E. Dubois and C. Lion, *C. R. Acad. Sci.*, **274**, 203 (1972).

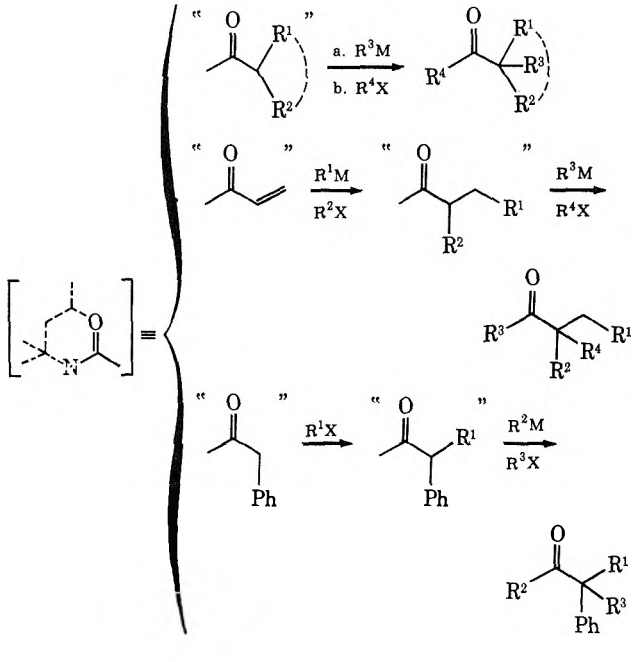
SCHEME IV



were all prepared from these three methods, and except for the last one, involving the glycol–nitrile condensation, are much more versatile than that in Scheme III. It should also be mentioned that the 2-vinyl- and 2-benzyloxazines are easy to prepare in quantity[4] or may be obtained from commercial sources.[14]

In summary, the oxazine ketone synthesis relies on a successive introduction of alkyl groups into the variously substituted oxazines whose carbonyl synthetic equivalents are depicted in quotes in Scheme V. These

SCHEME V



synthons are derived from the readily available oxazines shown in Scheme IV. Although several elegant and useful approaches to highly branched ketones have been recently reported,[15-18] they all involve substrates with preconstructed substituents or the use of bulky organometallic reagents. The oxazine ketone synthesis should provide a useful alternative to a number of these approaches.

(14) Columbia Organic Chemicals, Columbia, S. C.

(15) (a) J. E. Dubois, C. Lion, and C. Moulineau, *Tetrahedron Lett.*, 177 (1971); (b) J. E. Dubois, M. Busso, and C. Lion, *ibid.*, 829 (1971).

(16) G. H. Posner and C. E. Whitten, *Tetrahedron Lett.*, 4647 (1970).

(17) R. M. Coates and R. L. Sowerby, *J. Amer. Chem. Soc.*, **93**, 1029 (1971).

(18) H. C. Brown and G. W. Kabalka, *ibid.*, **92**, 714 (1970), and references cited therein.

Experimental Section[19]

2-Substituted 4,4-Dimethyl-5,6-dihydro-1,3-oxazines 12 (Table I). **A. 12 (R_1 = R_2 = Me, 5)** was prepared according to previously described procedures[4] from 76.0 g (1.1 mol) of isobutyronitrile, 118 g (1.0 mol) of 2-methyl-2,4-pentanediol, and 100 ml of concentrated sulfuric acid. The isopropyl oxazine was obtained in 62% yield (105 g): bp 64–65° (2 mm); ir (film) 1666 cm^{-1}; nmr (CCl_4) δ 4.0 (m, 1), 2.1 (m, 1), 1.5 (d of t, 2), 1.2 (d, 3), 1.1 (s, 6), 1.0 (d, 6).

Anal. Calcd for $C_{10}H_{19}NO$: C, 70.96; H, 11.31; N, 8.27. Found: C, 71.08; H, 11.31; N, 8.33.

B. 12 (R_1 = Ph, R_2 = Me, 20) was prepared according to previously described procedures[4] from the 2-benzyloxazine (10.85 g), methyl iodide (7.81 g), and *n*-butyllithium: yield 11.6 g (99%); bp 85–90° (0.2 mm); ir (film) 1661 cm^{-1}; nmr (CCl_4) δ 7.0–7.4 (m, 5), 4.0 (m, 1), 3.4 (q, 1), 1.5 (d of t, 2), 1.0–1.4 (m, 12).

Anal. Calcd for $C_{15}H_{21}NO$: C, 77.88; H, 9.15; N, 6.05. Found: C, 78.00; H, 9.13; N, 5.99.

C. 12 (R_1 = Ph, R_2 = Et, 20) has been previously described.[4]

D. 12 (R_1 = Ph, R_2 = *n*-amyl, 20) was prepared by alkylation of 2-benzyloxazine (10.85 g) with *n*-amyl iodide (10.25 g) with *n*-butyllithium:[4] yield 13.0 g (91%); bp 120° (0.05 mm); ir (film) 1663 cm^{-1}; nmr (CCl_4) δ 7.1–7.4 (m, 5), 4.0 (m, 1) 3.2 (d of d, 1), 1.5 (d of t, 2), 0.8–1.4 (m, 20).

Anal. Calcd for $C_{19}H_{29}NO$: C, 79.39; H, 10.17; N, 4.87. Found: C, 79.31; H, 10.21; N, 4.69.

E. 12 (R_1 = Ph, R_2 = *n*-butyl) was prepared by alkylation of 2-benzyloxazine (10.85 g) with *n*-butyl bromide (7.54 g) according to previous procedures:[4] yield 13.4 g (98%); bp 108–110° (0.2 mm); ir (film) 1665 cm^{-1}; nmr (CCl_4) δ 7.0–7.4 (m, 5), 4.0 (m, 1), 3.2 (t, 1), 0.8–2.1 (m, 21).

Anal. Calcd for $C_{18}H_{27}NO$: C, 79.07; H, 9.95; N, 5.12. Found: C, 79.17; H, 10.08; N, 5.00.

F. 12 (R_1 = Me, R_2 = neopentyl) has been described elsewhere.[20]

G. 12 (R_1 = Me, R_2 = *n*-amyl) has been previously described.[4]

H. 12 [R_1 = R_2 = $-(CH_2)_4-$] was prepared from cyclopentyl cyanide and 2-methyl-2,4-pentanediol according to the previously described[4] method: yield 62%; bp 54–56° (0.3 mm); ir (film) 1667 cm^{-1}; nmr (CCl_4) δ 4.0 (m, 1), 2.5 (m, 1), 1.5–2.0 (m, 10), 1.3 (d, J = 7 Hz, 3), 1.1 (s, 6).

Anal. Calcd for $C_{12}H_{21}NO$: C, 73.80; H, 10.84; N, 7.17. Found: C, 73.67; H, 10.95; N, 7.07.

Dimethylketen-*N*-(4-trimethylsiloxy-2-methyl)-2-pentylimine (7).—A solution of lithium diisopropylamide in THF (0.22 mol in 150 ml) prepared from equivalent amounts of *n*-butyllithium and diisopropylamine mixed at 0°, was treated under nitrogen with 33.7 g (0.2 mol) of **5** (**12**, R_1 = R_2 = Me) at 0°. After the dropwise addition was complete, the yellow solution was allowed to warm to room temperature and stirring was continued for 3 hr. Upon recooling to 0°, 22 g (0.2 mol) of trimethylchlorosilane was slowly added and the resulting cloudy solution was stirred for an additional 2 hr at room temperature. The precipitated lithium chloride was removed by filtration and the filtrate was concentrated, leaving a yellow oily residue. Distillation gave 37 g (80%) of a colorless liquid: bp 65–68° (0.3 mm); ir (film) 2020, 843 cm^{-1}; nmr (CCl_4) δ 3.9 (m, 1), 1.5 (s, 6), 1.4 (m, 2), 0.9–1.1 (m, 9), 0.5 (s, 9).

Anal. Calcd for $C_{13}H_{27}NOSi$: C, 64.67; H, 11.27; N, 5.80. Found: C, 64.98, H, 11.17; N, 6.03.

2-Isopropyl-4,4-dimethyl-2-oxazoline (33).[21]—A mixture of 88.1 g (1.0 mol) of isobutyric acid and 89.1 g (1.0 mol) of 2-amino-2-methylpropanol was heated (~220°) in the presence of

(19) Microanalyses were performed by Midwest Microlab, Indianapolis, Ind. The nmr, infrared, and mass spectra were taken on a Varian T-60, Perkin-Elmer 257, and AEI MS-9 instrument, respectively. The organolithium reagents were kindly supplied by the Lithium Corporation, Bessemer City, N. C. The 2-vinyl-, 2-benzyl-, and 2-isopropyloxazines in Scheme IV were purchased from Columbia Organic Chemicals, Columbia, S. C., or prepared as previously described.[4]

(20) A. I. Meyers, A. C. Kovelesky, and A. F. Jurjevich, *J. Org. Chem.*, **38**, 2136 (1973).

(21) Adapted from the procedure reported by P. Allen and J. Ginos, *J. Org. Chem.*, **28**, 2759 (1963).

a 6-in. Vigreux column until 2.0 mol (~36 ml) of water was visible in the distillate [hexane (~300 ml) was present in the receiving flask to facilitate monitoring of the distilled water]. The temperature of the distillate then rose to 130–140° and the distillate was also collected in the hexane. When distillation ceased, the aqueous layer was separated and extracted repeatedly with fresh hexane, and the latter extracts were combined with the main hexane solution. Drying (K_2CO_3), concentration, and distillation of the hexane residue gave 96 g (68%) of **33**: bp 135–136°; ir (film) 1665 cm^{-1}; nmr (CCl_4) δ 3.8 (s, 2), 2.4 (m, 1), 1.0–1.2 (s, 6; d, 6).

Anal. Calcd for $C_8H_{15}NO$: C, 68.04; H, 10.71; N, 9.92. Found: C, 68.34; H, 10.94; N, 10.00.

Dimethylketen-*N*-(3-trimethylsiloxy-2-methyl)-2-propylimine (34).—The preparation was the same as that described for **7** using 0.12 mol of lithium diisopropylamide, 14.1 g (0.1 mol) of 2-isopropyl-2-oxazoline (**33**), and 7.68 g (0.12 mol) of trimethylchlorosilane in 70 ml of THF: yield 13.2 g (62%); bp 65–67° (17 mm); ir (film) 2021 cm^{-1}; nmr (CCl_4) δ 3.3 (s, 2), 1.6 (s, 6), 1.05 (s, 6), 0.5 (s, 9).

Anal. Calcd for $C_{11}H_{23}NOSi$: C, 61.97; H, 10.86; N, 6.57. Found: C, 61.69; H, 10.58; N, 6.73.

Ketones 13. General Procedure.—The following procedure is typical for all ketones **13** in Table I listed in entries 1–12.

A 1 *M* THF solution of the 2-isoalkyloxazines **12**, previously cooled to −78° under nitrogen with stirring, was treated in a dropwise manner with 2.1 equiv of the organolithium reagent. After addition was complete, the solution was allowed to warm to room temperature and stirred for 3 hr (overnight stirring was also performed with no detrimental effects). The resulting solution was quenched in 3–4 volumes of water and the aqueous mixture was extracted repeatedly (3–4 times) with ether, dried (K_2CO_3), and concentrated. The crude tetrahydrooxazine (0.02 mol) was dissolved in aqueous oxalic acid (5 g of oxalic acid in 40 ml of water) and heated to reflux for 1.5 hr, after which the aqueous solution was extracted with ether. The latter extracts were washed with 10% sodium carbonate solution, dried (K_2CO_3), and concentrated, affording the crude ketones **13**. Purification was accomplished by distillation and verified by vapor phase chromatography, infrared, nmr, and mass spectra. Known ketones were identified through solid derivatives. (See footnote *c*, Table I).

Ketones 16. General Procedure.—The following procedure is typical for ketones **16** in Table I, entries 13–17.

Prior to the aqueous quenching step in the procedure for **13** above, the solution containing the lithioenamine adduct was cooled to 0–5°. Addition of 1.1 equiv of an alkyl iodide was performed slowly in a dropwise fashion owing to the exothermic nature of the reaction. Stirring was continued after complete addition for 4–12 hr and then the reaction mixture was quenched in water, isolated, and identified as above.

Ketones 24 and 25 Prepared by Successive Addition of *n*-Butyllithium and a Grignard Reagent.—The preparation leading to **24a** is typical of this technique. A 1 *M* solution of **20** (R = Et) in THF was treated with 1.0 equiv of *n*-butyllithium at −78° and the resulting solution was allowed to warm to room temperature under nitrogen and with continuous stirring. The addition of 1.1 equiv of ethereal methylmagnesium bromide followed at room temperature and the mixture was stirred for 12–15 hr. Quenching in water, extraction with ether, drying (K_2CO_3), and concentration left an oil (tetrahydro-1,3-oxazine). The infrared spectrum exhibited medium-intensity bands for NH and OH (3200–3300 cm^{-1}) and C=N (1660 cm^{-1}). The C=N and OH absorptions are due to the open-chain tautomer of the tetrahydro-1,3-oxazine. Hydrolysis in 2 *M* oxalic acid solution (reflux 1.5 hr) gave, after ethereal extraction, the ketone **24a** [60% based upon **20** (R = Et)]: ir (film) 1710 cm^{-1}; nmr (CCl_4) δ 7.2 (br s, 5), 3.4 (t, J = 7 Hz, 1), 1.9 (s, 3), 1.8 (m, 2), 0.8 (t, 3); *m/e* 162; semicarbazone mp 198–199° (lit.[22] mp 189–190°).

The preparation of **24** was accomplished in the same manner using **20** (R = Me), *tert*-butyllithium, and methylmagnesium bromide. The yield based upon **20** was 59.3%: ir (film) 1709 cm^{-1}; nmr (CCl_4) δ 7.3 (br s, 5), 3.7 (q, 1), 1.9 (s, 3), 1.4 (d, 3); *m/e* 148; semicarbazone mp 173–175° (lit.[23] mp 172–173°).

The preparation of **25** was accomplished in a similar manner using a 1 *M* solution of **20** (R = *n*-amyl) and 1.0 equiv of *tert*-butyllithium, followed by 1.0 equiv of ethylmagnesium bromide. After stirring for 12–15 hr, the solution was cooled to 0° and 1.0 equiv of methyl iodide was added dropwise. The solution, containing a pale yellow suspension was stirred for 15 hr at room temperature and quenched in water. Extraction and drying in the usual manner gave 76% of **25** which was identical in all respects with **16** (entry 17 in Table I).

Ketones 27 from the Ketenimine *O*-Trimethylsilyl Ether 7. A. 2-Benzoyl-2-methylhexane (27, Entry 1).—The preparation of this ketone may be considered typical for entries 1–8 in Table II.

A solution containing 0.03 mol of phenylmagnesium bromide in 40 ml of THF was treated with 4.83 g (0.02 mol) of the ketenimine **7** and heated to reflux overnight. The reaction mixture was cooled to 0° and *n*-butyl iodide (4.05 g, 0.02 mol) was added dropwise at this temperature (exothermic reaction). After complete addition, the solution was heated to reflux overnight and then concentrated *in vacuo*. The residue was dissolved in aqueous oxalic acid (80 ml of 10% solution) and heated to reflux for 2 hr. Ether extraction of the aqueous solution, washing of the extracts with saturated sodium bicarbonate, drying (Na_2SO_4), and evaporation left 4.01 g (95%) of crude ketone. Distillation afforded 3.01 g (74%): bp 64–65° (0.2 mm); ir (film) 1680 cm^{-1}; nmr (CCl_4) δ 7.6–7.8 (m, 2), 7.2–7.5 (m, 3), 0.6–1.8 (m, 15).

Anal. Calcd for $C_{14}H_{20}O$: C, 82.30; H, 9.87. Found: C, 82.03; H, 9.75.

B. 2-Benzoyl-2-bromopropane (27, Entry 9).—A solution containing 0.03 mol of phenylmagnesium bromide in 40 ml of THF was treated with 4.83 g (0.02 mol) of **7** and heated to reflux for 16 hr. Upon cooling to 0°, bromine (4.8 g) was added dropwise and the solution was allowed to stir at room temperature for 15 hr, after which it had solidified. The mass was heated at reflux for 1 hr and then the solvent was removed under rotary evaporation. Hydrolysis of the residue with 80 ml of 10% oxalic followed by ethereal extraction, bicarbonate washing, drying, and concentration gave the bromo ketone:[24] 1.8 g (39.7%); bp 81–83° (0.65 mm); ir (film) 1670 cm^{-1}; nmr (CCl_4) δ 8.0–8.3 (m, 2), 7.4–7.6 (m, 3), 2.0 (s, 3).

Anal. Calcd for $C_{10}H_{11}OBr$: C, 52.86; H, 4.84. Found: C, 52.47; H, 4.69.

C. 1-Hydroxy-3,3-dimethyl-4-octanone (27, Entry 11).—Addition of *n*-butyllithium(0.03 mol) to **7** (4.83 g, 0.02 mol) in 40 ml of THF at room temperature gave a clear solution which was stirred at this temperature for 15 hr. Ethylene oxide (2.64 g, 0.06 mol) was added at 0° and heated to reflux for 3 hr in the presence of a Dry Ice–acetone condenser. Most of the solvent was removed by rotary evaporation and 80 ml of 10% oxalic acid was carefully added. After this exothermic reaction had subsided, the mixture was heated to reflux for 30 min and isolation of the organic material was accomplished in the manner given above. The residual crude product was distilled to yield 1.8 g (60%) of the hydroxy ketone, bp 113–116° (0.5 mm); ir (neat) showed weak carbonyl (1710 cm^{-1}) and enol ether (1688 cm^{-1}) bands as well as a weak OH (3400–3500 cm^{-1}). The nmr spectrum was also indicative of a mixture of ketone, hemiacetal, and enol ether (dehydrated hemiacetal). The mass spectrum (8, 70 eV) gave a parent ion only at *m/e* 154 (dehydrated hemiacetal). The moisture sensitivity of this compound was indicated by its elemental analysis which corresponded to the hydroxy ketone and/or the hemiacetal.

Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.78; H, 11.63.

Ketone 27 (entry 10) was prepared in the same manner as the ketone above using phenylmagnesium bromide, **7**, and ethylene oxide: yield 30%; mp 119–120°; *m/e* 192; ir (KBr) 3480 cm^{-1}; nmr ($CDCl_3$) δ 7.2–7.8 (m, 5), 4.0–4.3 (d of d, 2), 2.6 (s, 1, exchanged with D_2O), 1.4–2.5 (m, 2), 1.2 (s, 3), 0.6 (s, 3). This compound existed solely as the hemiacetal.

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.70; H, 8.35.

Dimethylketen-*N*-(4 methoxy-2-methyl)-2-pentylimine (28).—2-Isopropyl-4,4-dimethyl-5,6-dihydro-1,3-oxazine (**5**, 16.9 g, 0.1 mol) was added to a solution of lithium diisopropylamide (0.11 mol) in THF at 0°. The reaction mixture was stirred for

(22) "Dictionary of Organic Compounds," Oxford University Press, New York, N. Y., 1965, p 2709.

(23) A. Witzel, A. Botta, and K. Dimroth, *Chem. Ber.*, **98**, 1465 (1965).

(24) Trimethylphenylsilane was observed as a minor product (15–25%) in this and all other reactions of **7** with phenylmagnesium bromide. Hence the excess of Grignard reagent utilized in these experiments.

3 hr at room temperature, 19.0 g (0.15 mol) of dimethyl sulfate was added, and stirring was continued for an additional 3 hr. After addition of dilute potassium hydroxide solution (1 *M*) at 0–5°, the solution was stirred for 45 min to decompose excess dimethyl sulfate. The aqueous solution was extracted with ether, and the extracts were dried (K_2CO_3) and concentrated. The residue was distilled, producing several fractions: (a) 25–35° (0.4 mm), (b) 35–40° (0.4 mm), and (c) 40–44° (0.4 mm). Fraction c contained the ketenimine ether **28** along with ~10% of starting oxazine **5**. Repeated attempts at column chromatography failed to completely remove **5**. Total ketenimine recovery was 6.6 g (35%), which included 10% oxazine: ir (neat) 2021, 1667 cm^{-1}; nmr ($CDCl_3$) δ 4.0 (m, 0.1 oxazine), 3.4 (m, 0.9), 3.2 (s, 2.7), 1.7 (s, ~6), 0.9–1.4 (m, 11).

Reaction of 28 with Phenylmagnesium Bromide and Ethyl Iodide to Give 30.—Crude **28** (~90% purity) from above was treated in the usual manner with phenylmagnesium bromide (1.5 equiv) at room temperature in THF for 12 hr. This was followed by addition of 1.1 equiv of ethyl iodide to the cooled solution (0°) and the solution was again stirred for 12 hr. The usual isolation procedure led to the ketone **30** in 90% yield, which was identical in every respect with **27** (entry 7, Table II) obtained from **7**.

Dimethylketen-*N*-(4-benzoyloxy-2-methyl)-2-pentylimine (29) and Its Pyrolysis to 31.—The benzoyloxyketenimine **29** was prepared in a manner analogous to **28** by the addition of benzoyl chloride to the lithioketenimine **6** prepared above. The main difference in preparation lies in the fact that the solution was heated to reflux for 1 hr after addition of the benzoyl chloride. The mixture was decomposed in cold 1 *N* potassium hydroxide and rapidly extracted with ether, dried (K_2CO_3), and concentrated. Bulb-to-bulb distillation at 0.2 mm gave a colorless oil (~30%) which was <90% pure: ir (neat) 2020, 1718 cm^{-1}; nmr ($CDCl_3$) δ 8.02 (m, 2), 7.45 (m, 3), 5.0 (m, 1), 1.6 (s, 6), 1.5 (m, 2), 1.2 (d, 3), 1.0 (s, 6). This product contained ~10% of the starting oxazine **5**. Pyrolysis of **29** was accomplished by heating (160–200°) at 0.5 mm until a distillate appeared (110–130°). Vpc examination of the distillate gave three peaks which were collected. The minor peaks were characterized as isobutyronitrile and the 2-isopropyloxazine **5** originally present. The major peak collected was consisted with the unsaturated ester **31**: ir (neat) 1715 cm^{-1}; nmr (CCl_4) δ 8.0 (m, 2), 7.3 (m, 3), 5.3 (sextet, 1), 4.8 (br s, 2), 2.3 (d of t, 2), 1.8 (s, 3), 1.3 (d, 3); *m/e* 204.

Anal. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90. Found: C, 76.37; H, 7.79.

Registry No.—**7**, 36867-23-9; **12** (R_1 = Ph; R_2 = *n*-Bu), 39576-28-8; **24**, 769-59-5; **24a**, 1528-39-8; **28**, 39576-31-3; **29**, 39576-32-4; **31**, 39576-33-5; **33**, 34575-25-2; **34**, 39575-64-9; isobutyric acid, 79-31-2; 2-amino-2-methylpropanol, 124-68-3.

Acknowledgment.—The authors are grateful to the National Science Foundation (GP 22541), the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Institutes of Health for financial support of this work. Generous supplies of organolithium reagents from the Lithium Corporation of America are also gratefully acknowledged.

1,4 Addition of Organometallics to 2-Alkenyldihydro-1,3-oxazines. A Synthesis of α-Substituted Aldehydes and Ketones[1]

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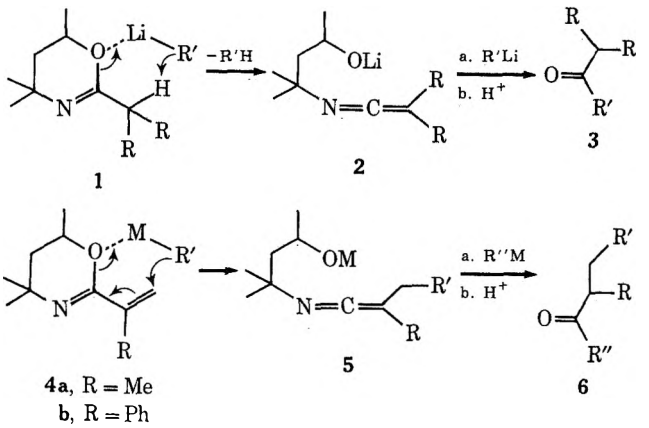
Received February 6, 1973

Addition of organolithium and Grignard reagents to 2-alkenyloxazines (**4a** and **4b**) leads to alkylation *via* the ketenimine intermediate (**10**). The latter may be converted to α-methyl- or α-phenylaldehydes or, in turn, may be sequentially alkylated with alkyl halides to the corresponding ketones. The formation of ketenimines may be accomplished by nucleophilic addition to the alkenyloxazines, thus eliminating the necessity of a strong base to effect these transformations. The scope and limitation to this carbonyl synthesis are presented.

The base-induced rearrangement of 2-isoalkyloxazines (**1**) to ketenimines (**2**) following proton abstraction has been shown to lead to a variety of α-branched ketones (**3**).[3] It was of interest to determine if the oxazine–ketenimine rearrangement could be effected by addition of organometallics to 2-alkenylozaxines (**4**). Implementation of this process would further expand the scope of the ketone synthesis by incorporation of an additional β-methylene group in the ketenimine **5** and the resulting ketone **6**. Furthermore, organometallic addition to **4**, since it does not require proton abstraction as in **1**, may be possible with Grignard reagents as well as organolithiums. This, in itself, would be worthwhile modification owing to the more convenient nature of Grignard reagents.



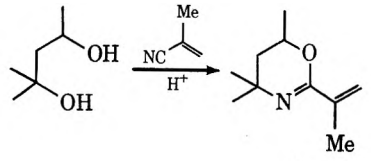
The oxazines chosen for this study were the 2-isopropenyl (**4a**) and the 2-(α-styryl) (**4b**) derivatives prepared from methacrylonitrile and the diol (eq 1) and condensation of the benzyloxazine with formaldehyde (eq 2), respectively. Organometallic addition to the 2-vinyloxazine **4** (R = H) were precluded owing to the polymerization already noted for this system.[4]

(1) Part XXI of a study on the chemistry of dihydro-1,3-oxazines. For previous papers in this series see ref 3.

(2) Address all correspondence to this author at the Department of Chemistry, Colorado State University, Fort Collins, Colo. 80521.

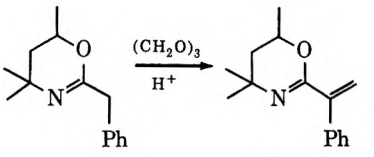
(3) A. I. Meyers, E. M. Smith, and M. S. Ao, *J. Org. Chem.*, **38**, 2129 (1973).

(4) A. I. Meyers, A. Nabeya, H. W. Adickes, I. R. Politzer, G. R. Malone, A. C. Kovelesky, R. L. Nolen, and R. C. Portnoy, *J. Org. Chem.*, **38**, 36 (1973).



(1)

4a

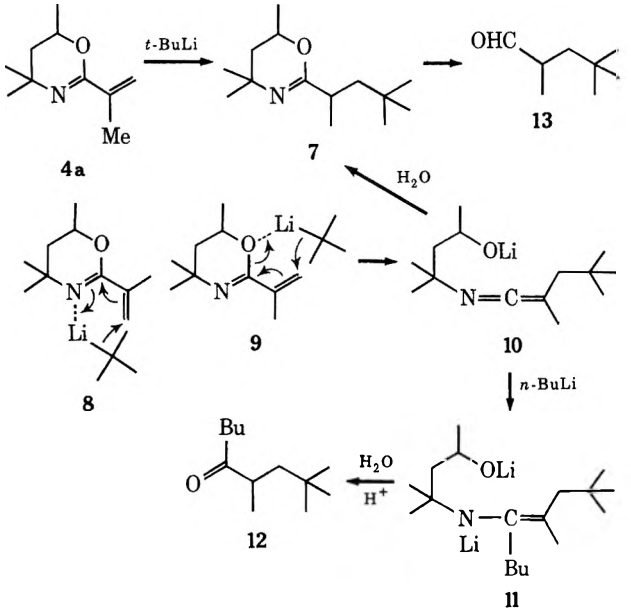


(2)

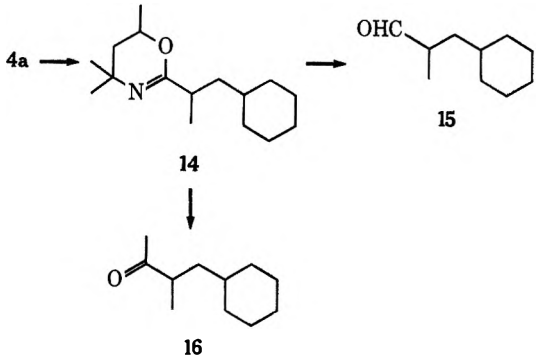
4b

Results and Discussion

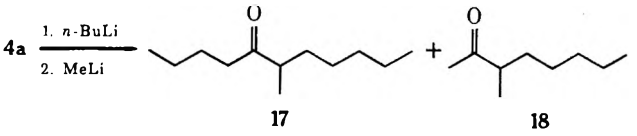
The addition of 1.0 equiv of *tert*-butyllithium to **4a** in THF at −78° produced after quenching a high yield of an oxazine which was characterized as the *tert*-butyl adduct **7**. Although the product may be assumed to merely arise by the familiar 1,4-conjugate addition (**8**), this was not in keeping with the alkylation mechanism in other oxazine systems.[3] A more reasonable mechanism should involve the initial complex **9** followed by ring opening to the ketenimine **10**. Hydrolysis then results in recyclization to the oxazine **7**. In order to confirm this mode of reaction, *tert*-butyllithium was again added to **4a** at −78° and, after 1 hr, 1.2 equiv of *n*-butyllithium was introduced. If the ketenimine **10** is indeed an intermediate, the presence of *n*-butyllithium should convert it to the adduct **11**. The latter is most easily characterized by hydrolysis to the corresponding ketone **12**. This was found to be the case, as the ketone **12** was isolated in 77% overall yield (from **4a**). These data confirm that the oxazines **4a** may be smoothly alkylated and transformed into the ketenimine by addition of organometallics. The initial goal of the study was therefore achieved. Furthermore, the oxazine **7** was readily reduced ($NaBH_4$) and hydrolyzed (oxalic acid) to the aldehyde **13** by the previously described technique.[4] It was now



necessary to determine whether Grignard reagent addition to **4a** would lead to similar results. Treatment of **4a** with cyclohexylmagnesium bromide at −60° in THF provided the cyclohexyloxazine **14**, which was transformed into the aldehyde **15** in 78% overall yield. If the addition of the Grignard reagent was followed by methyllithium, the corresponding ketone **16** was ob-



tained in 82% overall yield. Thus, it is clear that, without the necessity of a strong base, the alkenyloxazines may also serve as useful precursors to carbonyl compounds by utilizing Grignard reagents, organolithiums, or a combination of both. A serious limitation of this method soon became apparent when a primary organometallic (*n*-BuLi, −78°) was added to **4a** followed by methyllithium. The product isolated was found to contain both the *n*-butyl (**17**) and methyl (**18**) ketones



17 18

in approximately a 1:1 ratio. This behavior is consistent with the fact that relatively unhindered organometallics will readily add to the newly formed ketenimines (*i.e.*, **10**) giving rise to precursors which lead to **17**. The methyllithium, added subsequently, then must compete with the *n*-butyllithium still present. This result further suggested that the use of 2 equiv of organometallic introduced into a solution of **4a** should lead to a more efficient synthesis of **17**. This was indeed found to be the case, as 2 equiv of *n*-butylmagnesium bromide gave **17** in 79% yield upon addition to **4a**. When 2 equiv of *tert*-butyllithium was added to **4a** under reflux conditions, in an attempt to form **19**, the major product recovered was **7** (40%) along with **19** (6%) and **20** (31%). It may be concluded from this experiment that the bulky *tert*-butyllithium reacts only at "elevated temperatures" (>20°) with the ketenimine, and prolonged heating (or standing at room temperature) results in attack by the base upon the solvent. Tetrahydrofuran is converted to its anion **21** by butyllithium, which is known to cleave to

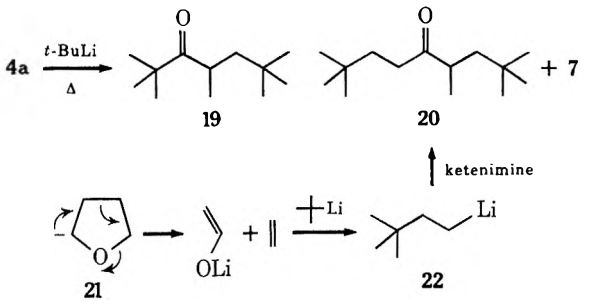
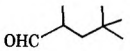
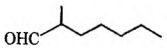
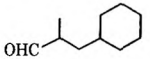
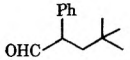
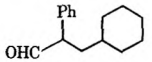
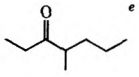
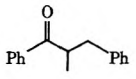
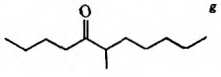
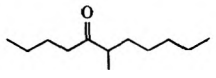
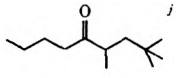
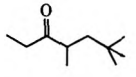
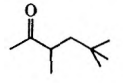
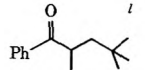
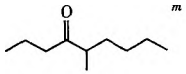
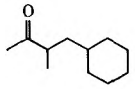
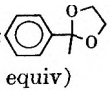
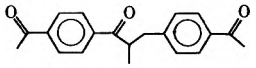
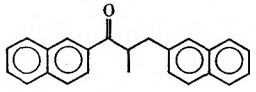
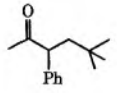
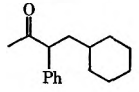
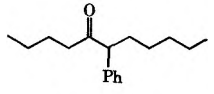
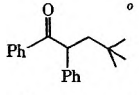
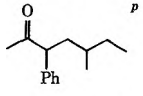
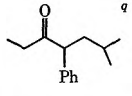


TABLE I

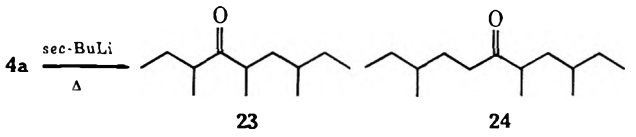
ALDEHYDES AND KETONES FROM 2-ALKENYLDIHYDRO-1,3-OXAZINES 4a AND 4b

Entry	Oxazine	RM	Registry no.	R′M	Carbonyl compd[a]	Registry no.	Yield, %	2,4-DNP mp, °C	2,4-DNP registry no.	Mp or bp, °C (mm)	M+	ν, cm⁻¹ (film)
1	4a[r]	*t*-BuLi	594-19-4	$NaBH_4$		17414-46-9	43	145–146[b]	39575-80-9	44–46 (20)	128	1720, 2695
2	4a	*n*-BuLi	109-72-8	$NaBH_4$		16630-91-4	32	104–105[c]	39576-31-9	50–52 (20)	128	1720, 2697
3	4a	$C_6H_{11}MgBr$	931-50-0	$NaBH_4$		20514-52-7	78	146–148[d]	20514-53-8	106–109 (20)	154	1720, 2699
4	4b[s]	*t*-BuLi		$NaBH_4$		25387-09-1	71	172–173[d]	25387-10-4	64–66 (0.1)	190	1722, 2701
5	4b	$C_6H_{11}MgBr$		$NaBH_4$		25387-11-5	94	155–157[d]	25387-12-6	95–97 (0.08)	216	1720, 2699
6	4a	EtMgBr	925-90-6	EtMgBr		6137-11-7	67	47–48[d]	14807-81-9	52–55 (25)	128	1707
7	4a	PhMgBr	100-58-3	PhMgBr		4842-43-7	47	131–133[f]	17282-48-3	113–115 (0.05)	224	1675
8	4a	*n*-BuLi		*n*-BuLi		26825-70-7	23	Oil[h]	39575-84-3	63–64 (0.45)	184	1705
9	4a	*n*-BuMgBr	693-03-8	*n*-BuMgBr			79					
10	4a	*t*-BuLi		*n*-BuLi		26933-75-5	60	86–87[d,i]	39751-38-7	73–76 (2)	184	1709
11	4a	*t*-BuLi		EtMgBr		26825-72-9	67	77–79[d,i]	39575-85-4	77–80 (2)	156	1710
12	4a	*t*-BuLi		MeLi		26825-71-8	73	64–65[k]	39575-75-2	68–70 (25)	142	1710
13	4a	*t*-BuLi		PhMgBr		39575-71-8	31	115–116	39575-76-3	83–85 (0.3)	204	1680

14	4a	*n*-PrMgBr	927-77-5	*n*-PrMgBr		26825-73-0	79	Oil[h]	39575-77-4	90–95 (25)	156	1705
15	4a	$C_6H_{11}MgBr$		MeLi		27206-64-0	82	104–106[d]	39575-78-5	120–123 (25)	168	1705
16	4a	 (3.1 equiv)	39575-67-2			39575-73-0	62	72–73[n]		72–73	308	1680
17	4a	2-NaphthMgBr (3.2 equiv)	21473-01-8			39575-74-1	92	61–63[n]		61–64	324	1672
18	4b	*t*-BuLi		MeLi		25386-99-6	84	120–122[d]	25387-00-2	74–78 (1.5)	204	1712
19	4b	$C_6H_{11}MgBr$		MeLi		25387-01-3	79	126–127[d]	25387-02-4	102–105 (0.05)	230	1708
20	4b	*n*-BuMgBr		*n*-BuMgBr		25387-03-5	68	Oil[d,h]	39575-79-6	96–97 (0.01)	246	1710
21	4b	*t*-BuLi		PhMgBr			<10%			Semisolid		1670
22	4b	*sec*-BuLi	598-30-1	MeLi		25387-05-7	65	84–86[d]	25387-06-8	84–88 (0.2)	204	1710
23	4b	*i*-PrLi	1888-75-1	EtMgBr		25387-07-9	65	93–95[d]	25387-08-0	70–71 (0.2)		1710

[a] All compounds (except entry 41) gave satisfactory elemental analyses (±0.03%). [b] A. Byers and W. J. Hickenbottom, *J. Chem. Soc.*, 1328 (1948). [c] H. Normant and C. Crisan, *Bull. Soc. Chim. Fr.*, 459 (1959). [d] New compounds, analytical data in *a* above. [e] J. Dubois and R. Luft, *Bull. Soc. Chim. Fr.*, 1184 (1954), report bp 53–54° (10 mm). [f] L. I. Smith and J. R. Holum, *J. Amer. Chem. Soc.*, **78**, 3417 (1956). [g] F. H. Owens, W. L. Myers, and F. W. Zimmerman, *J. Org. Chem.*, **26**, 2288 (1961), report bp 76–78° (0.8 mm). [h] 2,4-DNP derivative was an oil and semicarbazone could not be prepared. [i] Semicarbazone. [j] Distilled product contained 13% of ketone in entry 8. Pure material collected by vpc (10% UC-W98, 130°). [k] M. F. Ansell, W. H. Hickenbottom, and A. A. Hyatt, *J. Chem. Soc.*, 1592 (1955). [l] H. Riviere-Larramona, *C. R. Acad. Sci.*, **244**, 1653 (1957), reports bp 80–82° (0.5 mm). [m] S. G. Powell and A. T. Nielsen, *J. Amer. Chem. Soc.*, **70**, 3677 (1948), report bp 68–69° (6 mm). [n] Melting point of ketone; no derivative was prepared. [o] Product could not be obtained pure although spectral evidence was consistent with structure. This appears to be a limiting case for this process. [p] Crude product contained 24% lower boiling ketone, which was identified as 3-phenyl-4-pentanone. [q] Distilled ketone contained 16% of another carbonyl compound, presumably 4-phenyl-3-heptanone. Pure material collected by vpc; see ref *j* above. [r] Registry no., 39575-65-0. [s] Registry no., 38709-86-3.

the enolate of acetaldehyde and ethylene.[5] Reaction of *tert*-butyllithium with ethylene gave the homologated alkyllithium **22**, which adds to the ketenimine producing **20**. In a similar reaction, **4a** was treated with 2–2.5 equiv of *sec*-butyllithium and afforded a mixture of ketones, **23** (35%) and **24** (5%). The latter ketone

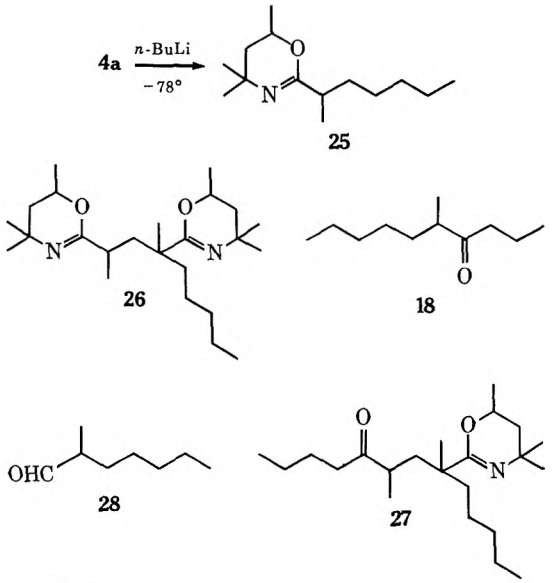


23 24

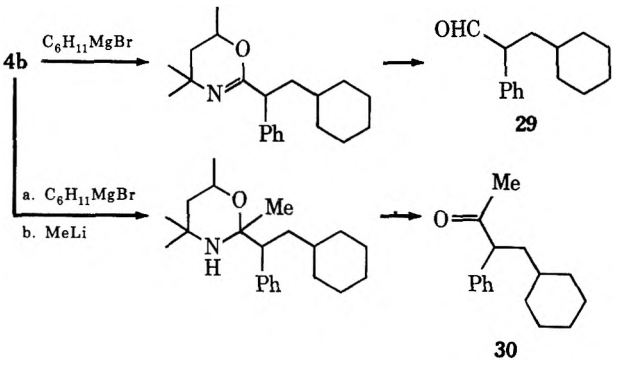
was formed by conversion of *sec*-butyllithium to its ethylene homolog prior to attack on the ketenimine. It should be noted that the "normal" ketone **23** is by far the major product, which implies that *sec*-butyllithium is not so efficient a base as *tert*-butyllithium with regard to proton abstraction on THF. In other studies,[3] it was found that *tert*-butyl- and *sec*-butyllithium were quite useful as nucleophiles for addition to ketenimines. Thus, it is possible to utilize these bulky alkyllithiums to introduce two alkyl groups into the final ketone. By introduction of these reagents at −78°, the likelihood of sequential addition is remote and subsequent treatment with an excess (20–25%) of the more reactive primary organometallic leads to ketones virtually free of isomers.

Several attempts at reaction of 1.0 equiv of a primary organometallic to **4a** were made. Since both *tert*-butyl and cyclohexyl moieties were successfully incorporated into the oxazine (**7** and **14**, respectively), *n*-butyllithium was examined under various conditions in order to obtain **25**. Careful temperature control, rates of addition, orders of addition, and stoichiometric variations all lead to four products (**25**, **26**, **18**, and **27**). The latter two were isolated after oxalic acid hydrolysis. Although **25** was the desired product, its initially formed carbanion (from butyllithium addition to **4a**) undoubtedly was sufficiently long lived to add once again to **4a**, producing **26**. The isolation of ketooxazine **27** must have been the result of the reaction of ketenimine of **26** with butyllithium.

However, **25** could be isolated in 45% yield and transformed by borohydride reduction and oxalic acid

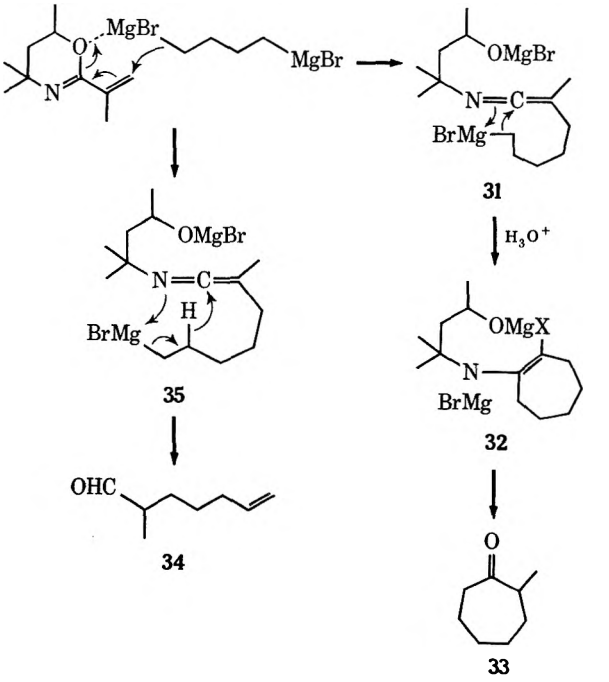


hydrolysis to the aldehyde **28**. Investigation of the 2-(α-styryl)oxazine **4b** as a source of α-phenylaldehydes (**28**) and ketones (**29**) provided the expected results.



The reactions were performed in a manner comparable to those involving **4a** and the limitations encountered were likewise similar. The carbonyl compounds prepared[6] by singular or multiple organometallic treatment with **4a** and **4b** are summarized in Table I. It may be mentioned that the steric retardation to addition of bulky organometallics to the ketenimine intermediate (entries 13 and 21) is manifested in the lower yields of ketones. This effect has already been noted in reactions with other ketenimines.[3]

In an effort to synthesize α-methyl cyclic ketones *via* this method, it was anticipated that a double Grignard reagent would add twice in an intramolecular fashion. Treatment of **4a** in refluxing ether with the *di*-Grignard reagent of 1,4-dibromobutane led to **18** (16.5%), 2-methylcycloheptanone (**33**) (12%), and the unsaturated aldehyde **34** (71.5%). The unexpectedly high percentage of the aldehyde must have arisen *via* reduction of the ketenimine intermediate **35**, whereas the cycloheptanone is derived from the anticipated intermediates **31** and **32**. Changing the solvent to THF and repeating the reaction at room temperature gave the cycloheptanone in 10% yield and **18** in 90%



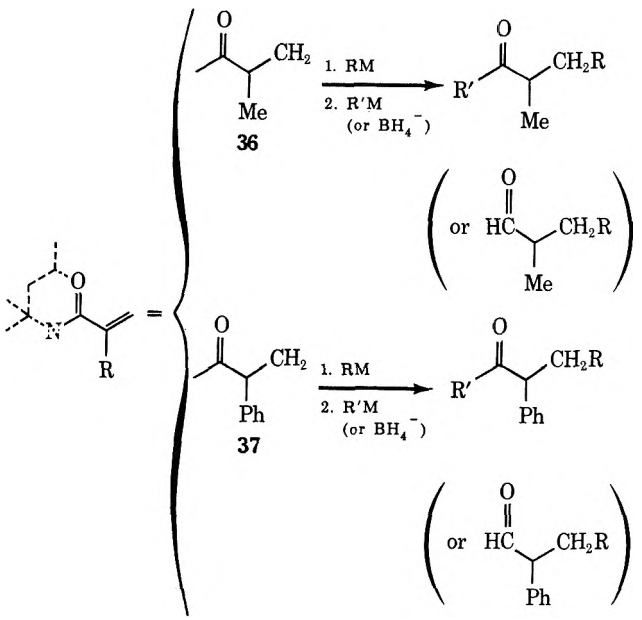
(5) P. D. Bartlett and M. Stiles, *J. Amer. Chem. Soc.*, **77**, 2806 (1955); P. Tamboulian, *et al.*, *J. Org. Chem.*, **38**, 322 (1973).

(6) Preliminary reports have appeared: A. I. Meyers and A. C. Kovelesky, *J. Amer. Chem. Soc.*, **91**, 5887 (1969); A. I. Meyers and A. C. Kovelesky, *Tetrahedron Lett.*, 4809 (1969).

yield. The aldehyde **34** was present in only trace amounts. Thus, the reduction (*via* **35**) was severely retarded in THF and this could be due to enhanced solvation of the metal in **35** minimizing the need for coordination with the lone pair on nitrogen. Since the goal of this effort was to open a route to α-methyl cyclic ketones and the results in this direction were disappointing, the study was discontinued.

In summary, the synthetic utility of **4a** and **4b** has been demonstrated by their ability to serve as synthons (**36** and **37**) for α-branched ketones and aldehydes. The mode of introduction of substituents into these synthons is outlined in Scheme I.

SCHEME I



Experimental Section[7]

The organolithium reagents used in this study were obtained from The Lithium Corporation of America, Bessemer City, N. C., as the following solutions: methyllithium (1.5 *M* in ether), *n*-butyllithium (1.6 *M* in hexane), *sec*-butyllithium (1.2 *M* in hexane), isopropyllithium (1.6 *M* in hexane), *tert*-butyllithium (1.24 *M* in pentane). All the Grignard reagents were prepared in ether (~3 *M*) just prior to use.

2-Isopropenyl-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (**4a**) was prepared by the previously described procedure[4] using 118 g (1.0 mol) of 2-methyl-2,4-pentanediol, 74.0 g (1.1 mol) of methacrylonitrile, and 200 ml (96–98%) of sulfuric acid. There was obtained 83.7 g (50.2%) of a colorless liquid: bp 74–76° (25 mm); ir (film) 3100, 1650, 1620 cm^{-1}; nmr ($CDCl_3$) δ 5.7 (br s, 1), 5.2 (br s, 1), 4.1 (m, 1), 1.9 (br s, 3), 1.6 (d of t, 2), 1.2 (d, 3), 1.1 (s, 6).

Anal. Calcd for $C_{10}H_{17}NO$: C, 71.85; H, 10.18; N, 8.38. Found: C, 71.77; H, 10.12; N, 8.29.

2-(α-Styryl)-4,4,6-trimethyl-5,6-dihydro-1,3-oxazine (**4b**) was prepared by heating a solution of 75.4 g (0.32 mol) of the 2-benzyloxazine[4,8] in 250 ml of toluene to which 12.2 g (0.38 mole) of paraformaldehyde and 2 ml of trifluoroacetic acid had been added. The solution was heated for 24 hr with continuous removal of water *via* an azeotrope trap. The toluene solution was added to water, acidified to pH 2–3, and then shaken vigorously. The toluene layer was withdrawn and discarded. Neutralization of the aqueous solution gave an oil which was taken up in ether, dried (K_2CO_3), and concentrated. Distillation provided 17.5 g (47.2%) of the product: bp 93–95° (0.2 mm); ir (film) 1640 cm^{-1}; nmr ($CDCl_3$) δ 7.1–7.6 (m, 5), 5.9 (d, 1), 5.6 (d, 1), 4.2 (m, 1), 1.7 (m, 2), 1.3 (d, 3), 1.2 (s, 6).

Anal. Calcd for $C_{15}H_{19}NO$: C, 78.60; H, 8.30; N, 6.11. Found: C, 78.74; H, 8.26; N, 6.09.

Typical Procedures. 2,4,4-Trimethylpentanal (**13**).—A solution composed of 10.5 g (63 mmol) of **4a** in 125 ml of dry tetrahydrofuran was cooled to −78° under nitrogen. To the stirred solution was added 55.6 ml of *tert*-butyllithium in pentane (1.24 *M*) in a dropwise manner over a 30-min period. After stirring at −78° for 1 hr, the reaction mixture was decomposed by careful addition of water and the entire mixture was diluted into 250 ml of ice water. The solution was acidified (pH 2–3) and extracted with pentane. The pentane extracts were discarded and the aqueous solution was neutralized with 35% sodium hydroxide. The alkaline solution was extracted with ether, dried (K_2CO_3), and concentrated, leaving 13.3 g of an oil. A portion was distilled, bp 110–113° (25 mm), to give pure **7**, ir (film) 1660 cm^{-1}.

Anal. Calcd for $C_{14}H_{27}NO$: C 74.61; H, 12.08; N, 6.21. Found: C, 74.74; H, 11.95; N, 6.18.

The crude oxazine **7** was subjected to borohydride reduction in the following manner. To a 600-ml beaker was added 100 ml of THF, 100 ml of 95% ethanol, and 12.0 g (0.053 mol) of **7**. The mixture was cooled between −35 and −40° with an acetone bath to which Dry Ice was added as needed. Hydrochloric acid (9 *N*) was added to the magnetically stirred solution until an approximate pH of 7 was obtained. The pH was monitored by periodic checks with pH paper. Sodium borohydride solution was prepared by dissolving 2.0 g (0.053 mol) in a minimum amount of water (4–5 ml) to which one drop of 40% sodium hydroxide was added. The sodium borohydride solution and the 9 *N* hydrochloric acid solution were added to the stirred solution alternately so that a pH of 6–8 was maintained. During the addition care was taken to maintain a temperature between −35 and −45°. After addition of this borohydride solution was complete, the solution was stirred with cooling for 2 hr (pH 7 was maintained by the occasional addition of hydrochloric acid solution). The contents were then poured into approximately 100 ml of water and made basic by the addition of 40% sodium hydroxide solution. The layers were separated and the aqueous solution was extracted with three 25-ml portions of diethyl ether. The combined organic extracts were washed with 100 ml of saturated sodium chloride solution and dried over anhydrous potassium carbonate. The ether was removed by rotary evaporation to give 11.7 g of crude tetrahydro-1,3-oxazine. Only a slight band at 1660 cm^{-1} was evident in the infrared, indicating almost complete reduction. The crude tetrahydro-1,3-oxazine from above (11.4 g 0.051 mol) and an oxalic solution (32.0 g per 100 ml of water) were heated to reflux for 2 hr. The cloudy solution was extracted with diethyl ether (three 50-ml portions) and the extracts were washed with 5% sodium bicarbonate solution and dried (Na_2SO_4). Removal of the solvent and distillation gave 3.1 g (48%) of **13** (43% overall).

1-Methyl-3-cyclohexylpropionaldehyde (**15**).—Alkylation of **4a** was performed by addition of a solution of cyclohexylmagnesium bromide (prepared in 75 ml of ether from 23.4 ml of cyclohexyl bromide and 5.6 g of triply sublimed magnesium) to 9.9 g (59 mmol) of **4a** in 150 ml of THF at −60°. The solution was allowed to slowly warm to room temperature overnight under a nitrogen atmosphere with magnetic stirring. Isolation of the oxazine **14**, reduction, and cleavage to the ketone **15** were also accomplished as described in the preceding experiment. Pertinent data are presented in Table I.

3-Methyl-4-cyclohexyl-2-butanone (**16**).—A solution of 10.3 g (61 mmol) of **4a** in 150 ml of THF was cooled to −60° under nitrogen. To the stirred solution was added 75 ml of 2.5 *M* ethereal cyclohexylmagnesium bromide over a 30-min period. After addition was complete, the reaction was slowly allowed to reach room temperature, at which point 49.2 ml of 1.5 *M* ethereal methyllithium was added. The reaction mixture was stirred overnight at room temperature and then the excess Grignard was carefully decomposed by water. Dilution of the mixture in 250 ml of ice–water was followed by acidification with 2 *N* hydrochloric acid. The two-phase mixture was extracted several times with pentane and the pentane solutions were discarded. The aqueous solution was neutralized with 40% sodium hydroxide and subsequently extracted with ether. Drying (K_2CO_3) and concentration of the ethereal extracts provided 16.2 g of crude product whose infrared spectrum displayed only a slight C=N absorption at 1660 cm^{-1}. The oily tetrahydrooxazine (13.7 g)

(7) Microanalyses performed by Galbraith Laboratories, Knoxville, Tenn., and Atlantic Microlabs, Atlanta, Ga. Mass, infrared, and nmr spectra were taken on Hitachi RMU-6, Perkin-Elmer 257, and Varian A-60 instruments, respectively. Melting points and boiling points are uncorrected.

(8) R. G. Neville, *J. Org. Chem.*, **24**, 111 (1959).

was added to an oxalic solution (34.3 g in 100 ml of water) and heated to reflux for 2 hr. Ethereal extraction of the cooled solution afforded the ketone, which after distillation provided 8.3 g (82% based on **4a**). Physical data are presented in Table I.

5,5-Dimethyl-3-phenyl-2-hexanone (Table I, Entry 18).—A solution of 6.9 g (30 mmol) of **4b** in 150 ml of THF was cooled to −78° under nitrogen. To the stirred solution was added 20.2 ml (1.8 *M*) of *tert*-butyllithium over a period of 20 min. The reaction was then stirred at −78° for 2 hr, after which 25.0 ml of ethereal (1.5 *M*) methyllithium was added dropwise. The reaction mixture was allowed to warm to room temperature overnight with continual stirring under nitrogen. The excess organolithium reagents were decomposed by careful addition of water (10 ml) and the contents of the flask were poured into 400 ml of ice–water. The solution was acidified (2 *N* HCl) to pH 2–3 and then extracted (3 × 75 ml) with pentane. The latter was discarded and the solution was neutralized, extracted with ether, dried (K_2CO_3), and concentrated. The residue (8.5 g, 93%) was heated for 2 hr in oxalic acid solution (18 g per 150 ml) yielding the ketone, 5.1 g (84.3% based upon **4b**).

2-Methyl-1,3-bis(4-acetylphenyl)-1-propanone (Table I, Entry 17).—A portion of a solution of 5.70 g (0.023 mol) of 2-(4-bromophenyl)-2-methyl-1,3-dioxolane[8] in 10 ml of THF was added to 0.66 g (0.027 g-atom) of triply sublimed magnesium in 10 ml of THF and the resulting mixture was warmed in a hot-water bath with stirring to initiate the reaction. The remainder of the dioxolane solution was added dropwise at a rate sufficient to keep the reaction mixture warm. As the Grignard precipitated after addition of 80% of the solution, an additional 10 ml of THF was added.

To the warm, light yellow slurry was added 1.25 g (7.5 mmol) of **4a** in 10 ml of THF. After 2.5 hr, the mixture had turned deep purple. After stirring for 22 hr at room temperature, the reaction mixture was added to 60 ml of an ice–water mixture. Upon acidification (pH ~2) and extraction with pentane, an insoluble oil separated from the aqueous phase. When the two phases were made alkaline (~pH 8) and extracted with ether, the oil dissolved with difficulty. The ethereal extracts were dried with anhydrous potassium carbonate and the ether was removed on the rotary evaporator to give 3.24 g (87%) of a light yellow, fluorescent oil. The above residue was refluxed for 2.5 hr with 14.8 g (0.12 mol) of oxalic acid dihydrate and 120 ml of water under argon. The mixture was cooled, dichloromethane was added, and the material was stirred overnight. The layers were separated and the aqueous phase was extracted further. The combined extracts were dried with anhydrous sodium sulfate and the solvent was removed to give 1.88 g (81%) of a viscous oil which solidified on standing. Recrystallization from petroleum ether (bp 30–60°)–ether gave 1.32 g (57%), mp 72–73°. Pertinent data are given in Table I, ref *a*.

2-Methyl-1,3-bis(2-naphthyl)-1-propanone (Table I, Entry 17).—The procedure of the preceding experiment was repeated with 0.920 g (0.038 g-atom) of magnesium in 5 ml of THF, 6.47 g (0.031 mol) of 2-bromonaphthalene in 10 ml of THF, and 1.65 g (0.010 mol) of 2-isopropenyloxazine in 3 ml of THF. During the isolation of the tetrahydrooxazine, its insoluble solid hydrochloride was collected, washed with pentane, and converted back to the free base by ammonium hydroxide. The crude yield was 4.3 g (102%) of an orange-brown, taffy-like substance.

The cleavage was accomplished with 6.3 g (0.05 mol) of oxalic acid, 20 ml of water, and 30 ml of acetic acid. The dichloromethane extracts were washed with aqueous 5% sodium bicarbonate. The crude yield was 3.2 g (100%). This material was passed through an alumina column with carbon tetrachloride to give an orange oil, 2.94 g (92%), which gradually solidified. The product was purified by passage through an alumina column (pentane–ether), mp 61–64°. Pertinent data are given in Table I, ref *a*.

Reaction of 4a with 1.0 Equiv of *n*-Butyllithium.—A cold solution (−78°) [20 ml of THF and 8.8 ml of 2.25 *M* (0.02 equiv) of *n*-butyllithium in hexane] was added in a steady stream from a syringe to a cold solution (−78°) of 3.35 g (0.02 mol) of **4a** in 50 ml of THF. After stirring at −78° for 0.5 hr, 1 ml of water was added to the reaction solution. Stirring was continued for several minutes and then the mixture was added to ~200 ml of an ice–water mixture. This aqueous mixture was acidified, extracted with low-boiling ligroin, made basic, and extracted with ether. The ether extracts were dried over anhydrous $MgSO_4$, the ether was evaporated, and the residue was distilled at 1.5 mm to give three fractions: (1) 76–81°, 1.865 g; (2) 81–152°, 0.635 g; and (3) 152–155°, 0.885 g. Fraction 1 was mainly **25** (45%); fractions 2 and 3 were mixtures but fraction 3 was mainly **26** (22%). Fraction 3 was redistilled to give 0.410 g of **26**, ir (film) 1660 cm^{-1}. The mass spectrum had a very weak molecular ion at *m/e* 392 and major peaks at *m/e* 226, 168, 155, 86, and 84.

Anal. Calcd for $C_{24}H_{44}N_2O_2$: C, 73.41; H, 11.30; N, 7.14. Found: C, 73.54; H, 11.05; N, 7.28.

Fraction 1 was subjected to the standard borohydride reduction and hydrolytic cleavage to give 2-methylheptanal (**28**) (Table I, entry 2). If the crude ethereal residue obtained above was subjected to oxalic acid hydrolysis, two carbonyl compounds were produced upon distillation: (a) 6-methyl-5-undecanone (**18**, 13%), bp 63–65° (0.4 mm), and (b) **27** (~8%), bp 124–126 (0.25 mm), ir (film) 1707, 1660 cm^{-1}. The mass spectrum did not give a parent ion at *m/e* 351, but only at *m/e* 226, indicating normal ketone fragmentation, loss of *n*-butyl radical, followed by loss of carbon monoxide. This fragmentation pattern was also seen in the mass spectrum of **26**, which also exhibited a base peak at *m/e* 226.

Anal. Calcd for $C_{22}H_{41}NO_2$: C, 75.16; H, 11.75; N, 3.98. Found: C, 74.96; H, 11.86; N, 3.89.

Reaction of 4a with *sec*-Butyllithium under Reflux Conditions.—To a solution of 2.283 g (0.01366 mol) of **4a** in 30 ml of THF at −78° was slowly added 40 ml of 1.1 *M* (0.044 equiv) of *sec*-butyllithium. The resulting solution was refluxed with stirring for 59 hr. Isolation was performed in the normal manner. A crude yield of 2.34 g of ketonic products was obtained. Vpc peak area weight per cents were 80.7 and 19.3 for the desired and unexpected ketones, respectively. This corresponds to crude yields of 75% of **23** and 15.5% of **24**. Distillation from glass wool gave 0.94 g (37%) of the desired compound, **23**, bp 54–56° (0.8 mm), *m/e* 184.

Anal. Calcd for $C_{12}H_{24}O$: C, 78.20; H, 13.12. Found: C, 78.03; H, 12.99.

The first minor fraction and the material left in the pot were redistilled to give four fractions, the last of which, bp 80–85° (0.8 mm), appeared to be at least 95% higher boiling ketone. The fractions were collected from vpc to give 0.128 g (4.6%) of 3,5,9-trimethyl-6-undecanone (**24**), *m/e* 212.

Anal. Calcd for $C_{14}H_{28}O$: C, 79.18; H, 13.29. Found: C, 78.99; H, 13.17.

Reaction of 4a with *tert*-Butyllithium under Reflux Conditions.—The same procedure as in the preceding experiment was used. The reaction utilized 37 ml of 1.22 *M* (0.045 equiv) *tert*-butyllithium in pentane–hexane and 2.403 g (0.0144 mol) of **4a** in 30 ml of THF. There was obtained 0.15 g (~6%) of 2,2,4,6,6-pentamethyl-3-heptanone (**19**), bp 54–58° (1.5 mm), $n^{23}D$ 1.4286 [lit.[9] bp 87–90° (16–18 mm), $n^{20}D$ 1.4288–1.4290, *m/e* 184, nmr (CCl_4) δ 0.86 [s, $CH_2C(CH_3)_3$] and 1.13 [s, $COC(CH_3)_3$], ir (neat) 1700 cm^{-1} (C=O), and 0.906 g (~31%) of 2,2,4,8,8-pentamethyl-5-nonanone (**20**), bp ~76–85° (1.5 mm), *m/e* 212, nmr (CCl_4) δ 0.83 [s, $C(CH_3)_3$] and 0.88 [s, $C(CH_3)_3$], ir (neat) 1713 cm^{-1} (C=O).

Anal. Calcd for $C_{14}H_{28}O$: C, 79.18; H, 13.29. Found: C, 79.30; H, 13.36.

Reaction of 4a with the Di-Grignard Reagent of 1,4-Dibromobutane.—To a refluxing mixture of 2.300 g (0.094 g-atom) of magnesium in 200 ml of ether was added dropwise 9.24 g (0.043 mol) of 1,4-dibromobutane in 200 ml of ether. After an additional 2.5-hr reflux, two liquid phases were present. A solution of 4.27 g (0.025 mol) of **4a** in 150 ml of ether was added dropwise to the refluxing Grignard. The reflux was continued with stirring for an additional 21 hr. The tetrahydrooxazine was isolated and cleaved in the usual manner to give a three-component mixture. Separation on a 10-ft 10% SE-30 vpc column, monitored by ir, showed the major component to have absorption at 3075 (vinyl protons), 2705 (aldehyde proton), and 1725 cm^{-1} (aldehyde carbonyl). The second component had an absorption at 1700 cm^{-1} (cycloheptanone, 1699 cm^{-1}), and the third at 1710 cm^{-1} (straight-chain ketone). The three components were identified as 2-methylcycloheptanone (**33**) (12%), 6-methyl-5-undecanone (**18**)[10] (16.5%), and 2-methyl-6-heptenal (**34**) (71.5%). The latter was characterized by its molecular ion (*m/e* 126) and elemental analysis.

(9) F. C. Whitmore, H. S. Whitaker, W. A. Mosher, O. N. Breivik, W. R. Wheeler, C. S. Minor, L. H. Sutherland, R. B. Wagner, T. W. Clopper, C. E. Lewis, A. R. Lux, and A. H. Poppin, *J. Amer. Chem. Soc.*, **63**, 643 (1941).

(10) G. Stork and S. Dowd, *ibid.*, **85**, 2180 (1963).

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 75.93; H, 11.09.

This reaction was repeated in pure THF at room temperature with 2.29 g (0.094 g-atom) of magnesium in 175 ml of THF, 8.80 g (0.041 mol) of 1,4-dibromobutane in 200 ml of THF, and 3.81 g (0.023 mol) of **4a** in 175 ml of THF. The products isolated consisted of 2-methylcycloheptanone (10%) and 6-methyl-5-undecanone (90%) which were compared with authentic samples. *Only a trace (0.2%) of the unsaturated aldehyde* **34** was detected.

Registry No.—**7**, 39575-86-5; **19**, 25368-59-6; **20**, 39575-88-7; **23**, 39575-89-8; **24**, 39575-90-1; **25**, 36871-42-8; **26**, 39575-92-3; **27**, 39575-93-4; **33**, 932-56-9; **34**, 17206-63-2; 2-benzyl-4,4,6-trimethyloxazine, 26939-22-0; paraformaldehyde, 30525-89-4.

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Correlation of Configuration and ^{19}F Chemical Shifts of α-Methoxy-α-trifluoromethylphenylacetate Derivatives[1]

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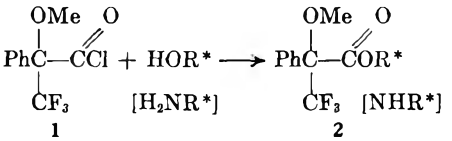
An empirically derived correlation of configuration of diastereomeric α-methoxy-α-trifluoromethylphenylacetic (MTPA) esters and amides with the ^{19}F chemical shifts has been developed. The data have been rationalized in terms of a configuration-correlation model **5**. The inherently large ^{19}F chemical shifts ($CDCl_3$ solvent, external trifluoroacetic acid) and their location in an otherwise uncongested region of the nmr spectrum makes this correlation of considerable value in connection with stereochemical studies involving chiral secondary alcohols and primary amines. Of the 25 examples studied, 19 MTPA esters and 6 MTPA amides, 18 clearly group themselves in a general pattern which is discussed in terms of the configuration-correlation model. Three MTPA esters showed no significant chemical shift nonequivalence for the ^{19}F α-CF_3 signals between *R,R–S,S vs. R,S–S,R* diastereomers. Of the four cases which might be considered exceptions to this nmr configurational correlation model, namely isobutyl-*tert*-butylcarbinol, *n*-butyl-*tert*-butylcarbinol, trifluoromethyl-*tert*-butylcarbinol, and borneol, the first three can be rationalized while only borneol stands as a clear exception to the model. *All of the 6 MTPA diastereomeric amides studied conform to the same model.*

The nonequivalence of various diastereomeric esters and amides has been utilized for the quantitative determination of enantiomeric composition of chiral alcohols and amines.[3] These studies recently have been extended to include correlations of configurations with proton nmr chemical shift differences of these diastereomers.[4] We now report on an empirically derived correlation of configuration and ^{19}F nmr chemical shift differences for esters and amides of α-methoxy-α-trifluoromethylphenylacetic acid (MTPA) which are readily prepared from α-methoxy-α-trifluoromethylphenylacetyl chloride (MTPA-Cl, **1**). This derivative was chosen because of its availability in optically active forms,[3c,5] stability to racemization, and proven utility in earlier proton nmr studies.[4]



1 **2**

This method has the inherent advantage that the ^{19}F nmr chemical shift differences for the α-CF_3 group of such diastereomeric derivatives (**2**) are generally greater than those of the corresponding proton signals in the same compounds. With the usual substrates the ^{19}F signals are found in a completely unobstructed region of the spectrum. If there are other fluorine substituents on the carbinyl moiety of the MTPA esters or amides, their signals are generally discernible by spin–spin coupling patterns.

The ^{19}F chemical shifts for the diastereomers in this study are listed in Table I. They are recorded in parts per million downfield relative to external trifluoroacetic acid (TFA) in deuteriochloroform solvent. From these data are obtained the diastereomer chemical shift differences ($\delta_X - \delta_Y$). These values are also compared to those reported previously[3c] using internal TFA as a reference standard (Table I, last three columns). In our previous studies we had noted that internal TFA, as well as solvent, had a pronounced effect on the position of the α-CF_3 resonances and on the chemical shift differences of the α-CF_3 signals of diastereomeric MTPA esters. We further observed that in some cases there was no diastereomer chemical shift difference for these α-CF_3 until TFA was added. These initial observations had discouraged us from seriously considering a correlation scheme based upon the nonequivalence of these α-CF_3 resonances. We now find that, in spite of the fact that some MTPA diastereomers give coincident α-CF_3 signals in the absence of TFA (3 out of 25 examples in Table I), very significant nonequivalences are observed in most cases. In the present study all values were obtained using external TFA.

(1) We acknowledge with gratitude support of these studies by the National Science Foundation, Grant GP 27448.

(2) Taken in part from the Ph.D. Thesis of James A. Dale, Stanford University, 1970.

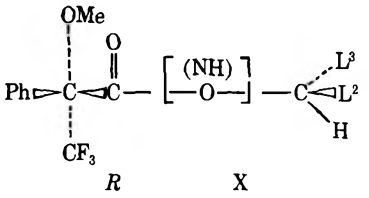
(3) (a) M. Raban and K. Mislow, *Tetrahedron Lett.*, 4249 (1966); (b) *Top. Stereochem.*, **2**, 199 (1967); (c) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969); (d) J. A. Dale and H. S. Mosher, *J. Amer. Chem. Soc.*, **90**, 3732 (1968); (e) G. Helmchen, R. Ott, and K. Sauber, *Tetrahedron Lett.*, 3873 (1972).

(4) J. A. Dale and H. S. Mosher, *J. Amer. Chem. Soc.*, **95**, 512 (1973), and references cited therein.

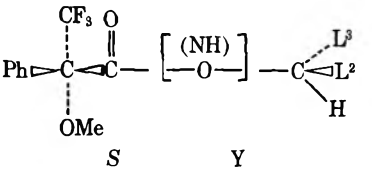
(5) Resolved MTPA[5d] is available from Aldrich Chemical Co., Inc., Milwaukee, Wis., Norse Chemicals, Santa Barbara, Calif., and Fluka AG, Buchs, Switzerland.

TABLE I

^{19}F NMR CHEMICAL SHIFT DIFFERENCES FOR DIASTEREOMERIC MTPA DERIVATIVES[a]



R X



S Y

Registry no. X	Registry no. Y	Carbinol moiety L²	Carbinol moiety L³	Configuration[b]	Nmr chemical shift of α-CF₃, downfield from TFA[c] External TFA[a] −δX, ppm	External TFA[a] −δY, ppm	External TFA[a] (−δX) − (−δY), ppm	Internal TFA[a] −δX, ppm	Internal TFA[a] −δY, ppm	Internal TFA[a] (−δX) − (−δY), ppm
20445-05-0	39532-60-0	Me	Et	*R*[d]	7.25	7.25	0.0	5.73	5.65	0.08
20445-07-2	39532-61-1	Me	*i*-Pr	*R*[d]	6.57	6.39	0.18	6.17	6.00	0.17
20445-09-4	39532-62-2	Me	*n*-Hex	*R*[d]	7.31	7.26	0.05	6.12	5.80	0.32
20445-13-0	39532-63-3	Me	CF_3	*R*[e]	7.00	6.63	0.37	4.48	4.20	0.28
20445-11-8	39532-64-4	Me	*t*-Bu	*R*[f]	6.79	6.57	0.22	6.39	6.17	0.22
39532-26-8	39532-65-5	Me	CO_2Et	*R*[g]	7.09	6.64	0.45			
39532-27-9	39532-66-6	Me	CH_2NMe_2	*R*[h]	7.85	7.71	0.14			
39532-28-0	39532-67-7	*t*-Bu	CF_3	*R*[e]	7.67	6.94	0.73	6.38	6.38	0.0
39532-29-1	39532-68-8	*t*-Bu	*i*-Bu	*S*[f]	8.11	7.71	0.40			
39532-30-4	39532-69-9	Me	Ph	*R*[i]	7.97	7.77	0.20	5.81	5.30	0.51
39532-31-5	39532-70-2	*n*-Pr	Ph	*R*[i]	7.92	7.65	0.27			
39532-33-7	39532-71-3	*i*-Pr	Ph	*R*[i]	8.15	7.80	0.35			
20445-20-9	39532-47-3	*t*-Bu	Ph	*R*[i]	8.43	8.00	0.43	7.12	6.62	0.50
20445-16-3	39532-48-4	CF_3	Ph	*S*[e]	6.95	6.95	0.0	5.86	5.32	0.54
39532-36-0	39532-49-5	*t*-Bu	*n*-Bu	*S*[f]	7.96	7.71	0.25			
39532-37-1	39532-50-8	Ph	Trityl	*R*[j]	7.27	7.13	0.14			
39532-44-0	39532-51-9		*d*-Bornyl	*S*[k]	7.37	7.27	0.10			
39532-38-2	39532-52-0		*l*-Menthyl	*R*[l]	7.46	7.34	0.12			
39532-45-1	39532-53-1		Cholesteryl	*S*	7.17	7.17	0.0			
		Amine moiety								
39532-46-2	39532-54-2	Me	Et	*R*[d]	10.51	10.41	0.10			
39532-39-3	39532-55-3	Me	*n*-Hex	*R*[m]	9.90	9.81	0.09			
20445-26-5	39532-56-4	Me	Ph	*R*[m]	8.02	7.77	0.25	7.55	7.30	0.25
20445-24-3	39532-57-5	Me	CH_2Ph	*R*[d]	10.66	10.35	0.31	7.39	6.89	0.50
39532-42-8	39532-58-6	Me	α-Naph	*R*[n]	10.87	10.58	0.29	7.85	7.39	0.46
39532-43-9	39532-59-7		*l*-Menthyl	*R*[l]	9.94	9.84	0.10			

[a] Data determined at 94.1 MHz on a Varian XL-100 spectrometer using deuteriochloroform solvent, with trifluoroacetic acid (TFA) external standard; internal TFA, ref 3c. [b] Configurations as per formulas X and Y in the heading. The actual data may have been determined on the opposite isomer but corrected for the configuration shown. [c] The convention used for reporting chemical shifts is such that signals upfield from TFA have positive values and signals downfield from TFA have negative values. All chemical shifts reported here are downfield from TFA. [d] J. A. Mills and W. Klyne, *Progr. Stereochem.*, **1**, 177 (1954); J. H. Brewster, *J. Amer. Chem. Soc.*, **81**, 5475 (1959). [e] H. Peters, D. M. Feigl, and H. S. Mosher, *J. Org. Chem.*, **33**, 4245 (1968). [f] W. M. Foley, F. J. Welch, E. M. LaCombe, and H. S. Mosher, *J. Amer. Chem. Soc.*, **81**, 2779 (1959). [g] J. A. Mills and W. Klyne, *Progr. Stereochem.*, **1**, 187 (1954). [h] A. H. Beckett, N. J. Harper, and J. W. Cletherow, *J. Pharm. Pharmacol.*, **15**, 8577g (1963). [i] R. MacLeod, F. J. Welch, and H. S. Mosher, *J. Amer. Chem. Soc.*, **82**, 876 (1960). [j] V. Prelog, E. Philbin, E. Watanabe, and M. Wilhelm, *Helv. Chim. Acta*, **39**, 1086 (1956). [k] Configuration at carbinyl center; the 2 position is designated L^2 and the 6 position L^3. This example is complicated by multiple chiral centers. [l] (−)-Menthyl configuration at carbinyl carbon, in which the α-isopropyl substituent is designated L^3 and the α-methylene as L^2. For configuration see J. L. Simonsen and L. N. Owen, "The Terpenes," Vol. 1, 2nd ed, Cambridge University Press, London, 1947, p 245. [m] J. H. Brewster, *J. Amer. Chem. Soc.*, **81**, 5475 (1959). [n] M. G. B. Drew, *Acta Crystallogr.*, **B25**, 1320 (1971).

Table I has been so organized that the configurations of the carbinyl moiety in X and Y are the same, while those of the MTPA moiety are *R* in X and *S* in Y. The enantiomers of X and Y will of course have identical nmr spectra. Thus Table I accommodates the data for the configurations shown as well as those for the enantiomers of X and Y. These data will be first considered from a strictly empirical viewpoint followed by an attempt to rationalize them in terms of a conformationally based stereochemical correlation model.

The chemical shift data in Table I are arranged so that the α-CF_3 group of diastereomer X has its resonance to lower field than that of Y. Once this is done, the designation of the groups on the carbinyl carbon as L^2 *vs.* L^3 is not arbitrary since each example in Table I is of known configuration. The data for any new MTPA ester or amide can be fitted into Table I in like manner; however, if the configuration of such a new example is unknown, then there is a choice which must be made for the designation of the substituents attached to the carbinyl carbon as either L^2 or L^3. This designation of L^2 and L^3 serves to establish the assigned configuration of X and Y. Without additional information such a designation would be arbitrary. An inspection of columns 3 and 4 of Table I shows that in all but four somewhat special cases the L^2 group is "smaller" than the L^3 group. The decision as to which of two groups is sterically smaller is very clear in cases such as methyl *vs.* *tert*-butyl and methyl

vs. phenyl, but it is not so obvious in cases such as *tert*-butyl *vs.* phenyl, trifluoromethyl, isobutyl, or even *n*-butyl. This problem has been discussed in general.[6] Nevertheless, *if it is possible to decisively designate one group attached to the carbinyl carbon as sterically smaller than the other group*, then by specifying the "smaller group" L^2 and the "larger group" L^3 the new example will fit the general pattern of the data in Table I. Thus the configuration of such a new compound can be determined by this empirical correlation. The specification of the carbinyl moiety as *R* or *S* follows from the application of the Cahn–Ingold–Prelog configurational nomenclature rules. It is important to note that steric bulk considerations alone may be invalid for electronegative groups such as CF_3 and for groups containing other heteroatoms.

The six MTPA amides of primary amines which are chiral at the carbinyl carbon, in analogy with the secondary carbinols, show completely comparable nmr nonequivalences for the α-CF_3 resonances. Thus the same empirical correlation used for the esters will presumably be applicable to a variety of corresponding MTPA amides of primary amines. The situation with respect to amides of secondary amines may be quite different, as shown by the proton nmr studies by Jacobus and Jones[7] and Helmchen.[8]

A configuration-correlation model has already been proposed for rationalizing the nonequivalence *proton* nmr spectra of MTPA diastereomeric esters.[4] This is shown in formulas **3A** and **3B** and **4A** and **4B** (Chart I).[9] No attempt was made to use models **4A** and **4B** to account for the $-CF_3$ chemical shift differences.[4] We now believe that the effect which leads to the nonequivalence of the α-CF_3 resonances in these diastereomers is an anisotropic deshielding of the α-CF_3 substituent by the ester carbonyl. Normally this might be a small effect, but, if other influential factors[10] are relatively constant between two diastereomers, then the anisotropic deshielding by the carbonyl group could be the determining factor responsible for the observed chemical shift differences. The magnitude of the observed ^{19}F diastereomer nonequivalence (up to 0.73 ppm) is in the range anticipated for such

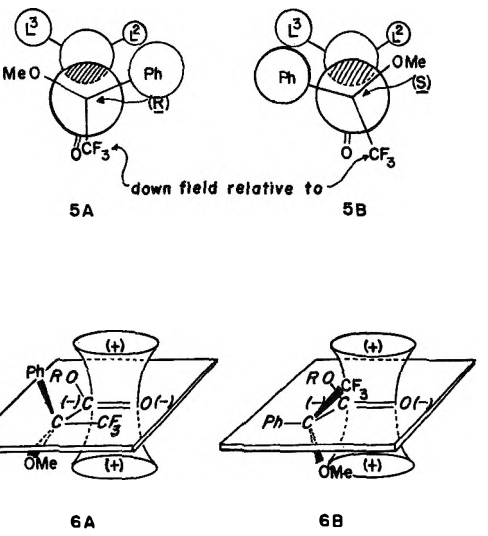
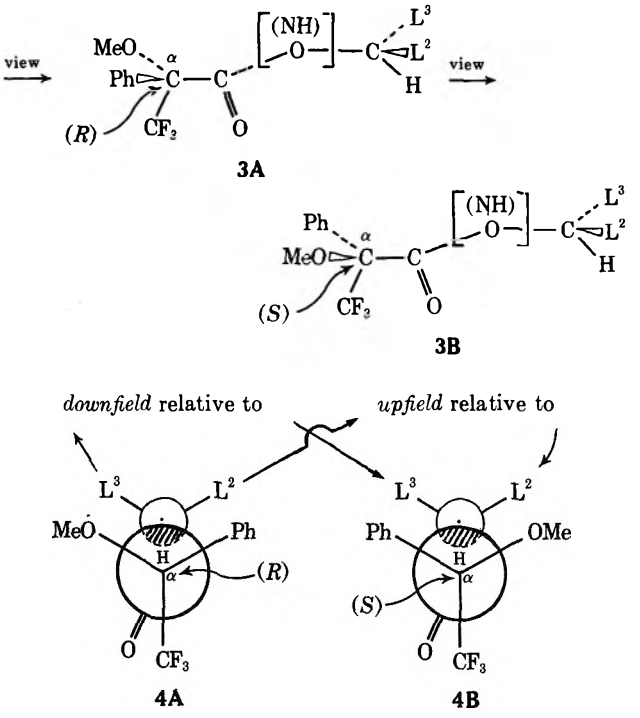


Figure 1.—Nmr ^{19}F configurational correlation models for diastereomeric MTPA derivatives. The cone-shaped field shown here is only an approximation; the carbonyl shielding environment is delineated more precisely in ref 12.

CHART I

CONFIGURATIONAL CORRELATION MODEL FOR (*R*)-MTPA DERIVATIVES (**4A**) AND (*S*)-MTPA DERIVATIVES (**4B**)



an effect[12] in which the α-CF_3 group finds itself either in a relatively deshielded environment (relatively downfield) as represented in **5A** or in a relatively more shielded environment (relatively upfield) as in **5B** (Figure 1). In these proposed models (**5A** *vs.* **5B**) the extent of deshielding of the α-CF_3 group will depend upon the extent that the α-CF_3 group is forced out of coplanarity by the interactions of L^2 and L^3 with the α-methoxy and phenyl groups. These interactions can be either steric, electronic, or both. The results are best rationalized by focusing on the α-phenyl group.

(6) J. D. Morrison and H. S. Mosher, "Asymmetric Organic Reactions," Prentice-Hall, Englewood Cliffs, N. J., 1971, pp 36–37, 55–57, 89, 363.

(7) J. Jacobus and T. B. Jones, *J. Amer. Chem. Soc.*, **92**, 4583 (1970).

(8) G. Helmchen, private communication, University of Stuttgart, Germany.

(9) It has been previously emphasized[2,4] and should be restated that formulas **4A** and **4B** are intended to represent a model which successfully correlates the known results. These are not intended to represent the preferred ground state conformation of the molecules under consideration. They may in fact measure an effective average of many conformations or may represent a minor conformation which, however, exerts a proportionately large differential shielding of the L^2 and L^3 groups. Admittedly the success of the correlation tends to reinforce the belief that these do indeed represent major conformations of the molecules in question, but it must still be borne in mind that the possibility exists that this is a fortuitous array which happens to serve as an empirical correlation of the results.

(10) The paramagnetic contribution to the shielding of the fluorine nuclei is approximately 100 times that of the diamagnetic contribution and is responsible for the generally large variance observed for ^{19}F chemical shifts.[11] In the examples under consideration the α-CF_3 resonances are all found within a range of 2 ppm. It seems reasonable, therefore, to propose that the paramagnetic contribution within diastereomeric pairs is relatively constant and that the differences in α-CF_3 resonances observed between such pairs can result from diamagnetic inequalities in the environment caused by its orientation with respect to the carbonyl group as proposed here.

(11) (a) N. F. Ramsey, *Phys. Rev.*, **86**, 243 (1952); (b) J. W. Emsley, J. Feeroy, and L. H. Sutcliffe, "High Resolution Nuclear Magnetic Resonance Spectroscopy," Vol. 2, Pergamon Press, Oxford, 1965, p 874.

(12) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969, pp 88–92.

Let us first assume (1) that the interactions with which we are concerned in the basic model represented by **5** are primarily steric in nature, (2) that phenyl is sterically more bulky than methoxyl, and (3) that L^3 is more bulky than L^2. Under these conditions, diastereomer **5A** should have the α-CF_3 group more nearly coplanar with the carbonyl group than diastereomer **5B**. In **5A** the steric interactions are minimized by [(L^3||OMe) + (L^2||Ph)] with the larger substituent L^3 opposed to the smaller methoxy and the smaller L^2 opposed to the larger phenyl. In the alternate diastereomer **5B** the interactions will be [(L^3||Ph) + (L^2||OMe)], which juxtapose the two large groups on one side and the two small groups on the other. The overall result should be a rotation (on the average) of the α-CF_3 group out of coplanarity with the carbonyl group in diastereomer **5B**. As a consequence, the diastereomer represented by **5B** should have the α-CF_3 group in a less deshielded environment of the carbonyl group as represented in **6B** and its resonance should be upfield relative to that in diastereomer **6A**.

The explicit use of this configuration-correlation model for prediction of configuration based on the ^{19}F nmr nonequivalence of MTPA diastereomers (with external TFA in $CDCl_3$ solvent) is as follows. That diastereomer prepared from (*R*)-(+)-MTPA with the downfield α-CF_3 signal relative to the α-CF_3 resonance of the alternate diastereomer will have configuration **5B** (equivalent to **3B**) where L^2 is sterically smaller than L^3. If (*S*)-(−)-MTPA is used in preparing the derivatives, then that diastereomer with the relatively downfield α-CF_3 resonance will be the enantiomer of **5B**. The configurational designation follows from application of the Cahn–Ingold–Prelog nomenclature rules.

This model clearly and simply rationalizes the α-CF_3 nmr data in Table I, with the exception of the MTPA esters of phenyl-*tert*-butylcarbinol, *n*-butyl-*tert*-butylcarbinol, isobutyl-*tert*-butylcarbinol, trifluoromethyl-*tert*-butylcarbinol, and borneol; these examples represent special cases requiring further consideration. The phenyl-*tert*-butylcarbinyl MTPA ester of known configuration follows the correlation model when L^2 is *tert*-butyl and L^3 is phenyl; *i. e.*, when phenyl is considered to be larger than *tert*-butyl. This is in accord with the most asymmetric synthesis;[6] therefore, it is the expected result, although the apparent relative sizes of phenyl and *tert*-butyl are not obvious.[13]

Correlation of the α-CF_3 nmr resonances of the *n*-butyl-*tert*-butylcarbinol and isobutyl-*tert*-butylcarbinol MTPA esters of known configuration requires that one consider for the purpose of this correlation scheme that *n*-butyl and isobutyl both act as though they are more bulky than *tert*-butyl. This is contrary to findings based upon asymmetric Grignard reductions.[14] However, the observation that asymmetric synthesis using *n*-butyl-*tert*-butylcarbinyl benzoylformate gives a reversal in stereoselectivity depending upon its reaction with either methyl Grignard reagent or lithium tri-*tert*-butoxyaluminohydride[15] emphasizes the complexity of the group size concept.[8] Certainly *tert*-butyl acts as the more bulky group in comparison to the *n*-butyl and isobutyl groups in those cases where the focus of steric interaction is located adjacent to these substituents (as in the asymmetric reduction of Me_3CCOR ketones). However, in cases where the prochiral reaction center is more remote from the inducing chiral center [as in the PhCOCOO-CHR(CMe_3) reactions][15] the longer *n*-butyl and isobutyl groups may be able to extend their influence to the remote carbonyl reaction center better than the shorter *tert*-butyl group. The present study of diastereomer differences in the α-CF_3 nmr resonances of MTPA derivatives must reflect conformational interactions resembling the situation which exists with the benzoylformate esters. Similar observations were made by Landor and coworkers[16] in asymmetric reduction of various ketones using the chiral lithium aluminum hydride–3-*O*-benzyl-1,2-*O*-cyclohexylidene-α-D-glucofuranose complex.

It is unrealistic to hope to correlate interactions of electronegative groups such as phenyl and trifluoromethyl on steric grounds alone. The present data confirm this. In the MTPA esters of trifluoromethylphenylcarbinol, the group interactions for the two diastereomers represented by **5** are [(CF_3||OMe) + (pH||Ph)] and [(CF_3||Ph) + Ph||OMe)]. An intuitive evaluation of the electronic and steric factors in this situation indicates that they are essentially equivalent and thus the rotation out of coplanarity for **5A** *vs.* **5B** would be minimal. This is in accord with the observation of no significant α-CF_3 nmr nonequivalence in these diastereomers.

However, when we consider the diastereomeric MTPA esters of trifluoromethyl-*tert*-butylcarbinol we find a different situation with the following interactions: [(*t*-Bu||OMe) + (CF_3||Ph)] *vs.* [(CF_3||OMe) + (*t*-Bu||Ph)]. Previous asymmetric reduction studies[17] indicate that the CF_3||Ph repulsive interaction is especially large, and we therefore conclude that the largest rotation out of coplanarity as represented in **5B** will be for that diastereomer in which L^3 is designated to be CF_3 and L^2 to be *tert*-butyl,[6] but it is altogether reasonable to postulate that electronic repulsions exert a dominant influence here. This interpretation is in accord with the published absolute configuration of trifluoromethyl-*tert*-butylcarbinol.[18] Thus the discrepancy in this case based upon steric interactions alone is successfully rationalized by taking electronic interactions into considerations.

The MTPA esters of menthol, cholesterol, and borneol represent examples in which the chiral alcohol moiety contains asymmetric centers other than the one to which the ester is bonded. In such cases it may be that one or more of these additional asymmetric centers is influential in determining the nmr nonequivalence. In spite of this, both the menthyl ester and

(13) For instance, the relative axial *vs.* equatorial conformational energy values for phenyl *vs.* *tert*-butyl in cyclohexane systems indicate that *tert*-butyl is substantially more bulky: J. A. Hirsch, *Top. Stereochem.*, **1**, 207 (1967). This is in contrast to the general experience in asymmetric synthesis studies.[6]

(14) See ref 6, pp 182–186.

(15) S. Yamaguchi, J. A. Dale, and H. S. Mosher, *J. Org. Chem.*, **37**, 9254 (1972).

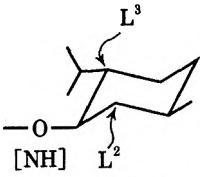
(16) S. R. Landor, B. J. Miller, and A. R. Tatchell, *J. Chem. Soc. C*, 2280 (1966).

(17) Reference 6, pp 190–193.

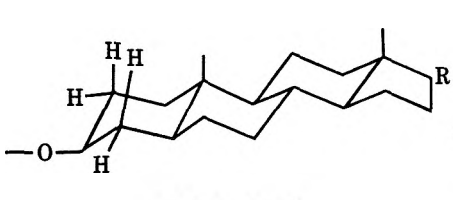
(18) The absolute configuration of trifluoromethyl-*tert*-butylcarbinol has not been proven unequivocally but has been deduced based upon reasonable correlations: H. Peters, D. M. Feigl, and H. S. Mosher, *J. Org. Chem.*, **33**, 4245 (1968).

the amide examples fit the general scheme of L^2 being smaller than L^3.

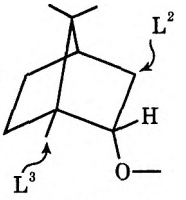
The carbinyl carbon in cholesterol (7) is flanked on each side by a methylene group; accordingly one might anticipate that there would be little difference in the α-CF_3 nmr resonances for these MTPA diastereomers. This is what we observe.



6, *l*-menthyl



7, cholesteryl



8, *d*-bornyl

However, we have checked both (−)- and (+)-bornyl MTPA esters and confirm that the *d*-bornyl ester with the *S* configuration at the carbinyl carbon shows the α-CF_3 resonance of the (*R*)-MTPA ester downfield with respect to that of the (*S*)-MTPA ester. In borneol the methylene group at C-2 is clearly designated L^2 (smaller) while the quaternary carbon at C-2 is L^3 (larger). Thus this lone example stands as a clear exception to the general correlation scheme for the α-CF_3 resonances.

Finally, the presence of heteroatoms in either L^2 or L^3, as in entries 6 and 7, Table I, may profoundly change the molecular conformations upon which the correlation is based. The fact that the correlation does hold in a case such as ethyl lactate does not necessarily mean that this will be generally so for all α-hydroxy esters. These examples must be taken only as indication that it may be possible to successfully extend the correlation to these types by further study.

Experimental Section

Instruments.—All ^{19}F resonance measurements were made on a Varian XL-100 nmr spectrometer[19] at 94.1 MHz using 5-mm nmr tubes, $CDCl_3$ solvent, and external trifluoroacetic acid (TFA) as standard. The TFA was contained in a sealed, precision ground, coaxial cell which was necked down at the bottom to a concentric 25 × 2 mm o.d. capillary stem containing the degassed TFA.

Reagent.—(+)-α-Methoxy-α-trifluoromethylphenylacetyl chloride, (+)-MTPA-Cl, was prepared from (*R*)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid,[5] (*R*)-(+)-MTPA, according to the previously described method.[3c,4]

MTPA Derivatives.—The MTPA esters and amides were prepared from (+)-MTPA-Cl according to the previously described procedure.[4] Two derivatives were usually prepared, one from enantiomerically pure carbinol and amine and (+)-MTPA-Cl and a second using MTPA-Cl which was about 70% (+)-MTPA-Cl and 30% (−)-MTPA-Cl. This permitted the unequivocal establishment of the nmr chemical shift for each diastereomer.

Chiral Carbinols and Amines.—These compounds were available from previous studies in these laboratories by the methods indicated by the references to Table I.

Acknowledgment.—We are grateful to Dr. Lois Durham, Director of the Stanford Chemistry Department Nmr Laboratories, for her continued help and cooperation.

(19) We gratefully acknowledge Grant GP 28142 from the National Science Foundation to the Stanford Chemistry Department for the purchase of this instrument.

The 2:1 Adduct from Diphenylketene and 1,1-Diphenylethylene. 3,4-Dihydro-1,4,4-triphenyl-2-naphthyl Diphenylacetate[1,2]

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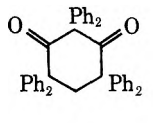
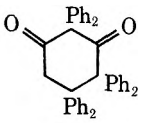
The 2:1 adduct from the thermal reaction of diphenylketene and 1,1-diphenylethylene has been conclusively identified as 3,4-dihydro-1,4,4-triphenyl-2-naphthyl diphenylacetate, and part of the degradation of the adduct reported in 1958 by Farooq and Abraham has been repeated and reinterpreted.

The 2:1 adduct derived from the reaction of diphenylketene with 1,1-diphenylethylene at 150° was first obtained by Staudinger and Suter[3] in 1920. Their original structural proposal, 2,2,4,4,6,6-hexaphenylcyclohexane-1,3-dione (1), was revised by Farooq and Abraham[4] in 1958 to 2,2,4,4,5,5-hexaphenylcyclohexane-1,3-dione (2).



1



2

The later proposal was bolstered by results obtained through a degradation of the 2:1 adduct, a degradation which led eventually to some 1,1,4,4-tetraphenyl-1-butene, claimed to be identical with an authentic, independently synthesized sample of this hydrocarbon. Salient features of degradation are outlined in Scheme I.

In the course of a thorough kinetic investigation of the cycloaddition reaction between diphenylketene and 1,1-diarylethylenes[5] we secured infrared and nmr spectral data on five adducts of this class. These data were inconsistent with cyclohexanedione structural postu-

(1) Supported by the National Science Foundation and Hoffmann-La Roche Inc.

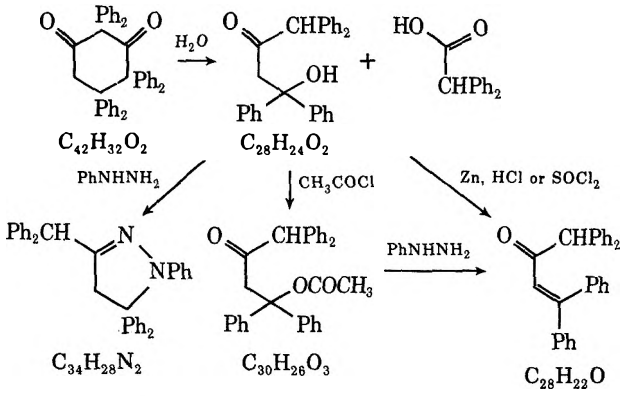
(2) A preliminary account of this work has appeared: J. E. Baldwin, M. F. Breckinridge, and D. S. Johnson, *Tetrahedron Lett.*, 1635 (1972).

(3) H. Staudinger and E. Suter, *Ber. Deut. Chem. Ges.*, **53**, 1092 (1920).

(4) M. O. Farooq and N. A. Abraham, *Bull. Soc. Chim. Fr.*, 832 (1958).

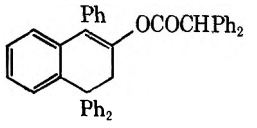
(5) J. E. Baldwin and J. A. Kapecki, *J. Amer. Chem. Soc.*, **92**, 4868 (1970).

SCHEME I[4]



lates **1** and **2**, and led us to a repetition of the degradative studies reported by Farooq and Abraham.

We thereby found that the 2:1 adduct is 3,4-dihydro-1,4,4-triphenyl-2-naphthyl diphenylacetate (**3**),[2,6,7] and



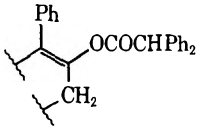
3

have unraveled and are thus able to reinterpret satisfactorily most of the degradation reported earlier.

Results

The 2:1 adduct from diphenylketene and 1,1-diphenylethylene has prominent infrared bands at 1745 and 1490 cm^{-1} and, in addition to absorptions from 29 aromatic protons at τ 2.5–3.4, singlets at τ 5.10 and 6.55 with integrated intensities appropriate to one and two protons, respectively.

These data were viewed as suggestive of an enol diphenylacetate partial structure (**4**).



4

The diphenylacetate ester of 2,3,4-triphenyl-1-naphthol, by comparison, shows a singlet for the α H at τ 5.15.[8]

Hydrolysis of the 2:1 adduct with alcoholic sodium hydroxide and subsequent acidification gave diphenylacetic acid, while reduction of the adduct with lithium aluminum hydride gave 2,2-diphenylethanol. Both results are easily comprehended in terms of partial formula **4**.

There was initial surprise, however, when we found that, in addition to diphenylacetic acid or diphenylethanol, both hydrolysis and reduction gave the same product, mp 195–196°, having the formula $C_{28}H_{22}O_2$. Farooq and Abraham had identified this material, obtained through hydrolysis, as 4-hydroxy-1,1,4,4-tetraphenylbutan-2-one, $C_{28}H_{24}O_2$.

This two-hydrogen discrepancy between previously assigned and actual molecular formula, easily understandable since the earlier workers had depended on combustion analyses alone, was unmistakable through mass spectrometric molecular weight determinations. The discrepancy was sustained in the three degradation products from "$C_{28}H_{24}O_2$" in Scheme I; all three were found to have two hydrogens fewer than originally believed.

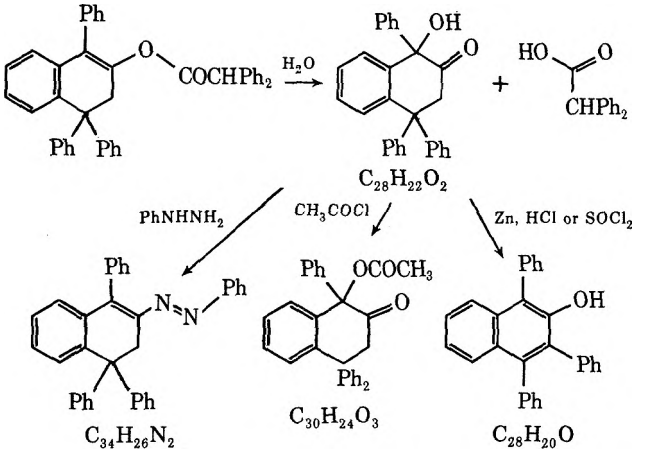
The nmr spectrum of the $C_{28}H_{22}O_2$ product showed absorptions from three nonaromatic protons: a singlet at τ 5.46 and an AB pattern centered at τ 6.35 with J_{AB} = 12.5 Hz. The singlet vanished when the solution of sample was shaken momentarily with D_2O.

In the infrared, there were indications of carbonyl (1725 cm^{-1}) and hydroxyl (3450 cm^{-1}) functionality. The hydroxyl reacted with acetyl chloride smoothly to give a keto ester (1743 and 1730 cm^{-1}) having nonidentical geminal protons as before, centered at τ 6.50 (J_{AB} = 16 Hz).

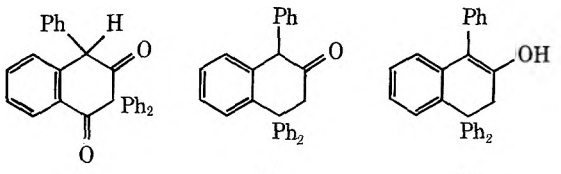
Reaction of the keto alcohol with phenylhydrazine gave an oxygen-free derivative in which the geminal protons now appeared as a sharp singlet at τ 6.1.

With these reactions and spectral data as guides, and conscious of the extreme ease with which a doubly benzylic and α-to-carbonyl hydrogen might suffer autoxidation by air, the structural postulates of Scheme II were made.

SCHEME II



The diphenylketene dimer **5** must be prepared and recrystallized under a nitrogen atmosphere to avoid air oxidation.[8] Heller and coworkers[6] have been able to isolate and observe nmr absorptions appropriate to the unoxidized hydrolysis products **6** and **7** by conducting the basic hydrolysis of **3** under an inert atmosphere.



5 **6** **7**

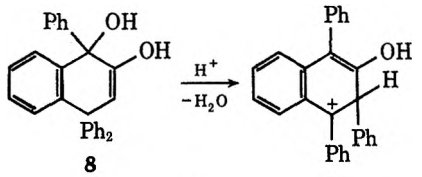
The final reaction in Scheme II, acid-catalyzed dehydration, would then require a molecular rearrangement. Acid-catalyzed formation of the enol form **8**

(6) An independent investigation has also led to the correct structural representation for the 2:1 adduct: J. S. Hastings, H. G. Heller, and R. M. Megit, The Chemical Society Autumn Meeting, University of York, Sept 27–30, 1971, Abstract A25.

(7) J. S. Hastings and H. G. Heller, *J. Chem. Soc., Perkin Trans. 1*, 1839 (1972).

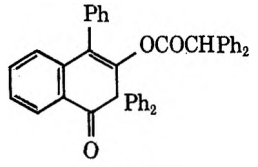
(8) H. Das and E. C. Kooyman, *Recl. Trav. Chim. Pays-Bas*, **84**, 965 (1965).

would greatly facilitate ionization of the protonated alcohol function with concomitant or rapidly following 1,2-phenyl shift to the other end of the allylic cationic system. Loss of a proton from **9** would then afford 1,3,4-triphenyl-2-naphthol.



8 **9**

The triphenylnaphthol we obtained had mp 232–233°. Das and Kooyman[8] secured a small amount of a triphenylnaphthol, mp 228–231°, from the reaction of the diphenylacetate **10** with red phosphorus and hydriodic acid in a sealed tube at 200–210° for 70 hr.

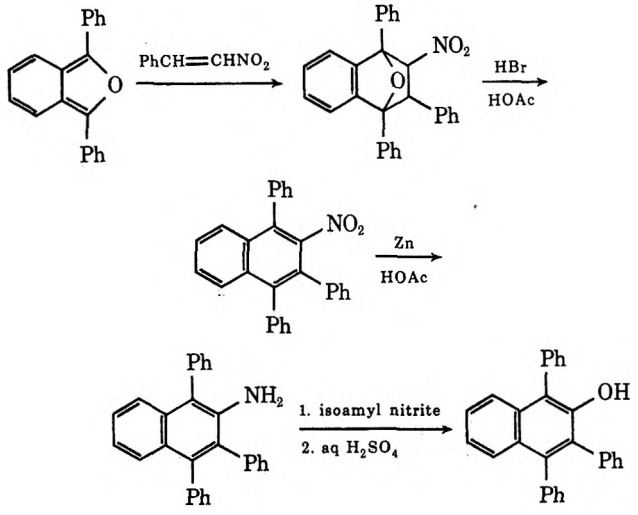


10

While they proposed[8] a mechanistic rationale for the formation of 1,3,4-triphenyl-2-naphthol derivatives under these reaction conditions, they carefully refrained from claiming a sure structural characterization of the degradation product.

To make our identification secure, then, we prepared an authentic sample through the route given in Scheme III.

SCHEME III



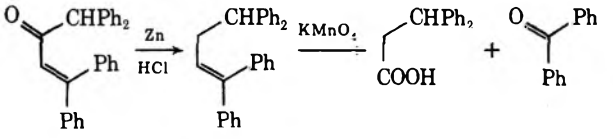
Diels–Alder reaction between β-nitrostyrene[9] and 1,3-diphenyl[c]benzofuran[10,11] gave the known oxidotetrahydronaphthalene adduct,[11] which was converted[12] through the four steps shown in Scheme III to the desired 1,3,4-triphenyl-2-naphthol, mp 231–233°. This material and the sample obtained through acid-catalyzed rearrangement of the $C_{28}H_{22}O_2$ product (Scheme II) proved to be identical in infrared and nmr spectral characteristics.

Thus the proposed revision (Scheme II) of the degradation first studied by Farooq and Abraham is anchored by a direct correlation between an authentic sample and a degradation product, and the other proposed formulations are thereby strengthened. Staudinger's 2:1 adduct now seems properly represented by structure **3**.

Discussion

Everything fits, except the report[4] that the product of mp 231°, thought to be 1,1,4,4-tetraphenyl-3-buten-2-one but now known to be 1,3,4-triphenyl-2-naphthol, may be reduced with zinc amalgam in acidic media to give 1,1,4,4-tetraphenyl-1-butene, identical with an authentic sample, and oxidized by permanganate to benzophenone and β,β-diphenylpropionic acid (Scheme IV).

SCHEME IV[4]

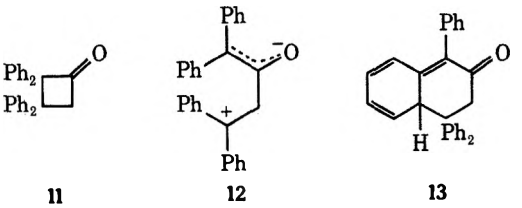


We have been unable to clarify this claim, since all our attempts to reduce the naphthol with zinc amalgam and hydrochloric acid have been unsuccessful.

Authentic 1,1,4,4-tetraphenyl-1-butene, mp 97–98°, was prepared by Farooq and Abraham[4] according to a procedure introduced by Wittig and Lupin.[13,14] A sample of mp 103° secured by other means in 1970,[15] which exhibited an appropriate nmr spectrum, is identical with 1,1,4,4-tetraphenyl-1-butene prepared according to Wittig and Lupin.[16] Thus either the zinc amalgam reduction of 1,3,4-triphenyl-2-naphthol reported earlier resulted in extensive isomerization or the comparison of the two samples of 1,1,4,4-tetraphenylbut-1-ene through a mixture melting point determination may have lacked adequate discriminatory sensitivity.

What mechanism may be responsible for formation of the 2:1 adduct **3**?

One possibility is through formation of a dipolar intermediate **12**, either directly or subsequent to a rate-determining cycloaddition producing the cyclobutanone **11**.



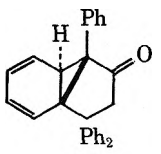
11 **12** **13**

The dipolar species **12** could cyclize intramolecularly, affording system **13**, which could easily react further in the presence of excess diphenylketene to yield the observed 2:1 product. Alternatively, **13** may be

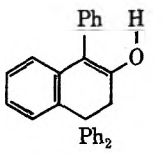
(9) D. E. Worrall, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N.Y., 1941, p 413.
(10) C. R. Hauser, M. T. Tetenbaum, and D. S. Hoffenberg, *J. Org. Chem.*, **23**, 861 (1958).
(11) M. S. Newman, *ibid.*, **26**, 2630 (1961).
(12) *Cf.* C. F. Allen, A. Bell, and J. W. Gates, Jr., *ibid.*, **8**, 373 (1943).
(13) G. Wittig and F. von Lupin, *Ber. Deut. Chem. Ges.*, **61**, 1627 (1928).
(14) G. Wittig, *ibid.*, **64**, 437 (1931).
(15) G. Köbrich and I. Stöber, *Chem. Ber.*, **103**, 2744 (1970).
(16) D. S. Johnson, unpublished work.

envisaged as arising directly through Diels–Alder combination of diphenylketene and 1,1-diphenylethylene.

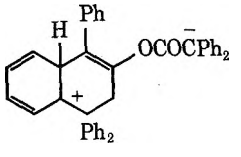
Finally, the unusual behavior of diphenylketene in its cycloadditions with alkoxyacetylenes,[17,18] if repeated with 1,1-diphenylethylene, would give as the initial 1:1 adduct structure **14**, an assemblage of atoms just a six-centered hydrogen migration to oxygen away from the enol **15**. As a variation on this possibility, the initial adduct **14** could react with diphenylketene with realization of its potential for a cyclopropylcarbinyl to homoallylic skeletal rearrangement to give **16** and, in turn, through a hydrogen transfer, **3**.



14



15



16

Clarification of the structure of the 2:1 adduct thus does not settle any mechanistic problems; it merely poses them. Several reasonable possibilities exist; choices among them may be made only through additional and carefully engineered experimental tests.

Experimental Section

Melting points were obtained on a Kofler micro heating stage using a calibrated thermometer; boiling points are uncorrected. Infrared spectra were recorded on a Beckman IR-7 or a Beckman IR-5A using chloroform solutions unless otherwise noted. Nuclear magnetic resonance spectra were obtained on Varian Associates T-60, HA-100, and XL-100 spectrometers using deuteriochloroform solutions unless otherwise noted and are reported in τ units, parts per million relative to tetramethylsilane at τ 10. Ultraviolet spectra were obtained using a Cary Model 15. Mass spectra were obtained on a CEC-110-21B and elemental analyses were determined by Dr. Susan Rottschaefer.

Diphenylketene was prepared through the dehydrohalogenation of diphenylacetyl chloride[19] with dry triethylamine in benzene;[5] it had bp 100–101° (1 mm) [lit.[20] bp 119–120° (3.5 mm)].

1,1-Diphenylethylene was prepared through reaction of phenylmagnesium bromide with ethyl acetate, followed by dehydration of the resultant carbinol with 20% sulfuric acid. The product had bp 129–131° (10 mm) [lit.[21] bp 113° (2 mm)].

Cycloaddition of Diphenylketene and 1,1-Diphenylethylene.—In a combustion tube were placed 8.75 g (42 mmol) of diphenylketene and 4.07 g (23 mmol) of 1,1-diphenylethylene. The tube was degassed on a vacuum line and sealed under 330 mm of nitrogen, then heated at 150° for 3 days. The tube was allowed to cool and was opened carefully. The reaction mixture was dissolved in a minimum of benzene, then petroleum ether (bp 30–60°) was added until precipitation seemed imminent. The following day a crystalline material was collected. This crude product, 7.4 g (58%), mp 170–173°, was washed with acetone and recrystallized from benzene–petroleum ether to afford material of mp 185–186° [lit.[4] mp 182°]; nmr absorptions at τ 2.7–3.5 (29 H), 5.10 (s, 1 H), and 6.55 (s, 2 H); mass spectrum M$^+$ m/e 568 (calcd for $C_{42}H_{32}O_2$, 568).

Anal. Calcd for $C_{42}H_{32}O_2$: C, 88.70; H, 5.67. Found:[4] C, 89.15; H, 5.72.

Lithium Aluminum Hydride Reduction of the 2:1 Adduct.—In a 250-ml round-bottomed flask were placed 1.0 g (26 mmol) of lithium aluminum hydride and 100 ml of THF. The flask was cooled and 3.75 g (6.6 mmol) of the 2:1 adduct dissolved in 50 ml of THF was added; the reaction mixture was stirred for 1 hr at room temperature. After cooling again, 1 ml of water was added, followed by 1 ml of 15% potassium hydroxide solution and 2 ml of water. The reaction mixture was filtered and the solid cake obtained was thoroughly washed with ether. The total filtrate was concentrated on a steam bath to 5 ml and was purified by column chromatography on Woelm acidic alumina to give 0.87 g (34%) of a solid having mp 195–196° [lit.[4] mp 195–196°]; ir (Nujol mull) 1725 (CO) and 3450 cm^{-1} (OH); nmr τ 2.5–3.3 (aromatic), 5.46 (s, 1 H), and 6.35 (AB pattern, J_{AB} = 12.5 Hz, 2 H); mass spectrum M$^+$ m/e 390 (calcd for $C_{28}H_{22}O_2$, 390).

Anal. Calcd for $C_{28}H_{22}O_2$: C, 86.13; H, 5.68. Found:[4] C, 86.18; H, 5.62.

After elution was complete, the alumina was subject to continuous extraction with methanol for 8 hr. The resulting solution was concentrated and the residue was sublimed twice at 60° to give a product melting at 52–53°, identified as 2,2-diphenylethanol [lit.[22] mp 54–55°] through direct spectral comparisons with an authentic sample prepared through reduction of diphenylacetic acid with lithium aluminum hydride.

Alcoholic Sodium Hydroxide Hydrolysis of the 2:1 Adduct.—In a 100-ml round-bottomed flask were combined 0.2 g (9.9 mmol) of sodium, 20 ml of 95% ethanol, and a few drops of water. After all the sodium had reacted, 0.15 g (0.26 mmol) of the 2:1 adduct was added, and the mixture was heated to reflux for 1 hr. An additional 25 ml of ethanol was added and the mixture was heated to reflux for another 15 min. It was then concentrated to about 5 ml, allowed to cool, and diluted with 25 ml of water; the white precipitate which formed was collected and recrystallized from benzene–petroleum ether; there was obtained 0.10 g (95%) of product, mp 193–196° (lit.[4] mp 195–196°), identical with that obtained from the lithium aluminum hydride reduction. The filtrate was acidified with dilute acid and the resulting solid was filtered and dried; it had mp 144–146° (lit.[23] mp 148°); admixture of authentic diphenylacetic acid caused no melting point depression.

Acetylation of the Reduction Product.—In a 10-ml round-bottomed flask were placed 0.15 g (0.38 mmol) of the reduction product and 4 ml (4.4 g, 5.6 mmol) of freshly distilled acetyl chloride. The reaction mixture was heated to reflux overnight, and then the excess acetyl chloride was removed at reduced pressure. The crude product was dissolved in methylene chloride and precipitated by the addition of petroleum ether. After two recrystallizations there was obtained 0.11 g (65%) of product: mp 165–168° (lit.[4] mp 163°); ir (CCl_4) 1743 (CO), 1730 cm^{-1} (CO); nmr τ 2.6–3.2 (aromatic), 6.50 (AB pattern, J_{AB} = 16 Hz, 2 H), and 7.9 (s, 3 H); mass spectrum M$^+$ m/e 432 (calcd for $C_{30}H_{24}O_3$, 432).

Anal. Calcd for $C_{30}H_{24}O_3$: C, 83.31; H, 5.59. Found:[4] C, 83.43; H, 5.91.

Phenylhydrazone of the Reduction Product.—To 0.94 g (2.4 mmol) of the reduction product in a 10-ml round-bottomed flask was added 1 ml of acetic acid and 1 ml (1.1 g, 0.10 mmol) of phenylhydrazine. The mixture was heated at 100° for 15 min. The orange solid obtained was collected and recrystallized from methylene chloride–acetone. The purified derivative (0.60 g, 54%) had mp 278–281° (lit.[4] mp 171°); ir (CCl_4) 1448 (m), 1299 (m), 696 (s), and 683 cm^{-1} (s); nmr τ 2.4–3.2 (aromatic), 6.1 (s, 2); mass spectrum M$^+$ m/e 462 (calcd for $C_{34}H_{26}N_2$, 462).

Anal. Calcd for $C_{34}H_{26}N_2$: C, 88.28; H, 5.67; N, 6.06. Found:[4] C, 88.16; H, 5.58; N, 5.80.

(17) H. Teufel and E. F. Jenny, *Tetrahedron Lett.*, 1769 (1971), and references cited therein.

(18) Another instance of such a "crisscross" thermal addition to a diene unit has been uncovered in the reaction of 1,8-dehydronaphthalene with cyclopentadiene: J. Meinwald and G. W. Gruber, *J. Amer. Chem. Soc.*, **93**, 3802 (1971).

(19) L. Hellerman, M. L. Cohen, and R. E. Hoen, *ibid.*, **50**, 1725 (1928).

(20) L. I. Smith and H. H. Hoehn, "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 357.

(21) C. F. H. Allen and S. Converse, "Organic Syntheses," Collect. Vol. I, Wiley, New York, N. Y., 1932, p 226.

(22) "Dictionary of Organic Compounds," Vol. III, 4th ed, Oxford University Press, New York, N. Y., 1965, p 1280.

(23) "Handbook of Tables for Organic Compound Identification," 3rd ed, compiled by Z. Rappoport, The Chemical Rubber Co., Cleveland, Ohio, 1967, p 202.

1,3,4-Triphenyl-2-naphthol.—Dry gaseous hydrogen chloride was bubbled through a solution of 100 mg (0.25 mmol) of the reduction product in 5 ml of acetic acid at reflux for 1.5 hr. The reaction mixture was cooled and poured into water. The aqueous solution was extracted with two 10-ml portions of ether; the ethereal solution was dried over sodium sulfate, filtered, and concentrated to give a crystalline material which, after being washed with cold, anhydrous ether, was collected. There was obtained 80 mg (84%) of 1,3,4-triphenyl-2-naphthol, mp 231°. Recrystallization from benzene–ligroin gave crystals of mp 232–233°; ir 3400 (s), 1190 (s), 1280 (s), and 950 cm^{-1} (s); nmr τ 2.4–3.0 (aromatic), 4.9 (s, 1 H); mass spectrum M^+ *m/e* 372 (calcd for $C_{28}H_{20}O$, 372).

Anal. Calcd for $C_{28}H_{20}O$: C, 90.29; H, 5.41. Found: C, 90.11; H, 5.55.

β-Nitrostyrene was prepared according to the "Organic Syntheses" procedure[9] on a 0.2-mol scale; after recrystallization from ethanol the product (23.7 g, 79%) had mp 58–59° (lit.[9] mp 59°).

3-Phenylphthalide from the reduction of *o*-benzoylbenzoic acid with zinc dust in aqueous acetic acid had mp 114–115° (lit.[10] mp 114–115°).

1,3-Diphenyl[*c*]benzofuran.—Phenylmagnesium bromide and 3-phenylphthalide in a solution of THF and ether led to the benzofuran product; after recrystallization from benzene–ethanol, it had mp 129–131° (lit.[10] mp 128–131°).

1,2,4-Triphenyl-3-nitro-1,4-oxido-1,2,3,4-tetrahydronaphthalene was prepared by heating 0.7 g (2.6 mmol) of 1,3-diphenyl[*c*]-benzofuran, 0.4 g (2.6 mmol) of nitrostyrene, and 20 ml of ethanol at reflux for 3 hr. The reaction mixture was cooled and filtered; the pale yellow material collected (1.1 g, 100%) had mp 155–158° (lit.[12] mp 163°).

1,2,4-Triphenyl-3-nitronaphthalene.—A suspension of 0.85 g (2.0 mmol) of the oxidotetrahydronaphthalene addition product in 5 ml of 30–32% hydrobromic acid in acetic acid (Eastman Organic Chemicals) was allowed to stand for 4 hr. It was then heated to reflux for several minutes, cooled in an ice bath, and filtered. The tan, crystalline material was washed with acetic acid; the white, crystalline material obtained (0.40 g, 51%) had mp 206–210° (lit.[12] mp 216–218°).

1,2,4-Triphenyl-3-aminonaphthalene.—1,2,4-Triphenyl-3-nitronaphthalene (0.45 g, 1.1 mmol), 2 g (31 g-atoms) of zinc, and 20 ml of glacial acetic acid were heated at reflux for 3.5 hr. The reaction mixture was poured into water and extracted with ether. The ethereal solution was dried, filtered, and concentrated to give white, crystalline product (0.3 g, 75%) having mp 254–256° (lit.[12] mp 256–257°).

1,3,4-Triphenyl-2-naphthol was obtained by adding 0.3 g (0.9 mmol) of the corresponding amine to 3 ml of glacial acetic acid and 0.5 g (4.5 mmol) of isoamyl nitrite. The reaction mixture was allowed to stand for 15 min; it was then slowly poured into a boiling 10% aqueous solution of sulfuric acid. As soon as the addition was complete, the solution was cooled in an ice bath and the precipitate was collected, washed with cold ether, and dried. This material, mp 231–233°, was identical in spectral characteristics with that formed through the degradation of the 2:1 adduct.

Anal. Calcd for $C_{28}H_{20}O$: C, 90.29; H, 5.41. Found: C, 89.98; H, 5.62.

Registry No.—1, 39495-51-7; 2, 39495-52-8; 3, 38028-34-1; diphenylketene, 525-06-4; 1,1-diphenylethylene, 530-48-3; 3,4-dihydro-1-hydroxy-1,4,4-triphenyl-2(1*H*)-naphthalenone, 38028-35-2; 3,4-dihydro-1-hydroxy-1,4,4-triphenyl-2(1*H*)-naphthalenone acetate, 38028-36-3; 3,4-dihydro-1,4,4-triphenyl-2-naphthalenazobenzene, 38028-37-4; 1,3,4-triphenyl-2-naphthol, 38028-38-5; 1,3-diphenyl[*c*]benzofuran, 5471-63-6; β-nitrostyrene, 102-96-5; 1,2,4-triphenyl-3-nitro-1,4-oxido-1,2,3,4-tetrahydronaphthalene, 39495-59-5; 1,2,4-triphenyl-3-nitronaphthalene, 39495-60-8; 1,2,4-triphenyl-3-aminonaphthalene, 39495-61-9.

The Oxidative Hydrolysis of *p*-Hydroxyphenyl Phosphates[1]

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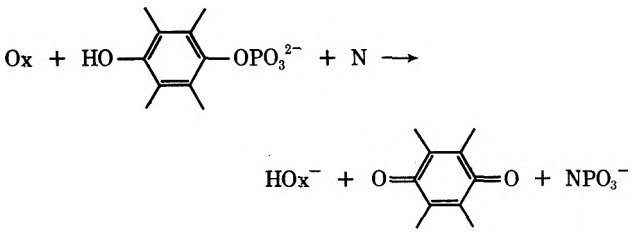
Periodic acid and its anions react with *p*-hydroxyphenyl phosphate (I) and the mono- (II) and dimethyl (III) esters, following second-order kinetics with no evidence for buildup of a periodate intermediate in high concentration. Both periodic acid and its monoanion are reactive species, and the reaction rates are greatest at low pH except for I, where the fastest reaction, at pH 7–8, involves a trianionic transition state, probably with elimination of a metaphosphate ion. Phosphorus–oxygen fission is important in the reaction of I at pH 1 and 6.5.

The oxidation of quinol phosphates can generate a phosphorylating agent, and the reaction has been examined and used synthetically.[2,3] The oxidants have generally been halogens or metal ions.

These reactions have been discussed as models for oxidative phosphorylation in biological systems, and the isolation of *p*-quinones from biological systems supported this hypothesis.[4] In addition, the involvement of quinones in biological phosphorylation has been demonstrated,[5] and quinone-induced phosphorylations have been observed in chemical systems.[6] Oxidatively induced chemical phosphorylations have recently been reviewed.[7] There are, however, certain weaknesses to this hypothesis, notably the difficulty of explaining the initial formation of the quinol phosphate and the observation that the oxidation in some



(where OX and N are respectively the oxidant and nucleophile)

(1) Support of this work by the Arthritis and Metabolic Diseases Institute of the USPHS is gratefully acknowledged.

(2) V. M. Clark, D. W. Hutchinson, G. W. Kirby, and A. R. Todd, *J. Chem. Soc.*, 715 (1961).

(3) T. Wieland and F. Patterman, *Ber.*, **92**, 2917 (1959); C. D. Chambers and J. Q. Chambers, *J. Amer. Chem. Soc.*, **88**, 2922 (1966); C. D. Snyder and H. Rapoport, *ibid.*, **89**, 1269 (1967).

(4) For general discussion, see T. C. Bruice and S. Benkovic, "Biorganic Mechanisms," Vol. II, W. A. Benjamin, New York, N. Y., 1968, p 91.

(5) P. G. Phillips, B. Revsin, E. G. Drell, and A. F. Brodie, *Arch. Biochem. Biophys.*, **139**, 59 (1970).

(6) V. M. Clark, D. W. Hutchinson, A. R. Lyons, and R. J. Roschnik, *J. Chem. Soc. C*, 233 (1969).

(7) G. M. Blackburn and J. S. Cohen, *Top. Phosphorus Chem.*, **6**, 187 (1969).

cases is not a phosphorylation, but gives carbon–oxygen fission,[8,9] and alternative reactions have been considered as chemical models for oxidative phosphorylation.

Periodic acid and its anions will quantitatively oxidize quinols and their esters to quinones,[10] and the kinetics of these oxidations have been thoroughly examined.[11] Kaiser and his coworkers have also considered the oxidative cleavage of *p*-hydroxyphenyl sulfate as a model for biological sulfate transfer, although in cleavage of the sulfates, as with the phosphates, there is considerable aryl–oxygen fission.[12]

Aqueous periodic acid will oxidatively hydrolyze carboxylic esters of *p*-quinol, and this reaction has been studied kinetically;[13] we have extended this investigation to the oxidative hydrolysis of *p*-hydroxyphenyl phosphates. A preliminary account of part of this work has been given.[14] The reaction occurs in water under mild conditions, whereas other oxidants have to be used in nonaqueous solvents, and the halogens can substitute into the aromatic group unless the reactive positions are blocked.[2-4]

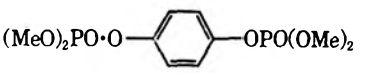
The formation of an intermediate, probably metaphosphate ion, PO_3^-, in the rate-limiting step of hydrolysis of mono- and dianions of many monosubstituted phosphate esters is generally assumed,[4,15] and a key aim of this research was to find evidence for formation of this intermediate in the oxidative cleavage of a quinol phosphate under mild aqueous conditions. With this aim in mind we used *p*-hydroxyphenyl phosphate (I), which can generate an intermediate which could eliminate metaphosphate ion, and compared its reactivity with those of the corresponding mono- and dimethyl esters (II and III) where metaphosphate ion elimination cannot occur.

Experimental Section

Materials.—*p*-Hydroxyphenyl phosphate (I) was prepared as its barium or cyclohexylamine salt by the method of Wieland and Patterman.[3] The barium salt was converted into the acid using Dowex 50W-X8 in its acid form, and neutralization with cyclohexylamine at pH 7.0 gave the bicyclohexylammonium salt, mp 202° dec (lit. mp 205°).[3]

The dimethyl ester III[16,17] was prepared by refluxing *p*-quinone (56 mmol) with dimethyl phosphite (56 mmol) in 300 ml of dry benzene under dry N_2,[16] or in anhydrous methanol with a catalytic amount of NaOMe.[17] The crude product was precipitated from benzene by addition of petroleum ether (bp 30–60°) and was purified by recrystallization from hot water, mp 73–75° (lit. mp 71–72°,[16] 75°[17]). The nmr spectrum (60 MHz, $CDCl_3$) had a doublet at δ 3.70 and 3.88 and a multiplet at δ 6.9 with areas 1.4:1.

When this reaction was carried out with excess dimethyl phosphite and no added solvent, we obtained a white solid, mp 109–114°. Comparison of the mass spectrum of this solid with that of the dimethyl ester suggested that reaction with excess dimethyl phosphite gave the tetramethyl ester IV.



IV

The monomethyl ester II was prepared as its lithium salt by demethylating III (0.0144 mol) in refluxing dried acetone (350 ml) with dried LiCl (0.014 mol) and glacial acetic acid (0.01 ml) for 12 hr. (The acetic acid was added to suppress formation of the phenoxide ion.) The lithium salt of II separated as fine white crystals, and it was washed several times with dry acetone. The melting point was 282° dec. The nmr spectrum (60 MHz, D_2O) had a doublet δ 3.46 and 3.64 (J = 11 Hz) and a multiplet at δ 6.63–7.11 with relative areas 2.9:4.0. The ir spectrum (Nujol mull) had free and hydrogen-bonded hydroxyl absorptions at 3450–3510 and 3100–3200 cm^{-1}.

Anal. Calcd. for $C_7H_8LiO_5P$: C, 40.0; H, 3.8; P, 14.7. Found: C, 39.9; H, 3.9; P, 14.5.

The periodate solutions were made up using periodic acid or sodium periodate in deoxygenated, distilled, deionized water, and were stored in the dark under N_2. Their concentrations were determined using KI in hydrogen carbonate buffer followed by titration with thiosulfate.

pK Measurements.—The pK values of I and II were determined using solutions of the free acid obtained by treating the salts with Dowex 50W-X8 resin (acid form). The conventional titration method[18] using KOH was used to determine pK_2 = 6.14 at 25° for I.

The values of pK_1 = 1.4 at 25° for both I and II were determined by pH measurements at various concentrations of the aryl phosphoric acids.[19] The concentration of I was determined by hydrolyzing it using alkaline phosphatase followed by the colorimetric determination of inorganic phosphate.[20] The diester II was hydrolyzed using snake venom alkaline phosphodiesterase followed by alkaline phosphatase.

Kinetics.—The reactions were followed spectrophotometrically with excess periodate under first-order conditions, using a Gilford spectrophotometer with a water-jacketed cell compartment. The increasing absorbance due to formation of *p*-quinone was followed at 247 nm, and the ester concentrations were 6–10 × 10^{-5} M. The first-order rate constants, k_ψ, sec^{-1}, were unaffected by these changes in ester concentration. Generally the reactions were followed using 1-mm stoppered cells, but for the slower reactions of the dimethyl ester III samples were withdrawn from stoppered volumetric flasks. The rate constants were calculated using the simple integrated rate equation or by Guggenheim's method.[21] Because of instability of *p*-quinone in alkali we could not work at high pH.

The pH was controlled with dilute acid at low pH. Periodate acts as its own buffer at pH 2.5–4.0 and 8.0, and the other buffers were acetate, pH 4–6; phosphate, pH 6–7.5; borate, pH >8. Added salt or buffer slightly affects k_ψ, and the values quoted were obtained at a given periodate concentration by extrapolation to zero added buffer, except for runs at low pH in acid. For experiments at low pH, the rate constants were very similar for reactions catalyzed by H_2SO_4 or $HClO_4$.

Bond Fission.—The oxidative hydrolysis of *p*-hydroxyphenyl phosphate was carried out at pH 1.0 and 6.5 at 25° in $H_2{}^{18}O$. The substrate concentration was *ca.* 0.1 M, 0.4 M periodic acid was used for the reaction at pH 1, and 0.12 M periodate at pH 6.5. Inorganic phosphate was isolated and analyzed mass spectrometrically by methods described elsewhere.[22] There is considerable P–O fission (Table I).

Results

Kinetics.—Under all our conditions oxidation was much faster than hydrolysis. The values of k_ψ ex-

(8) W. Durckheimer and L. A. Cohen, *Biochemistry*, **3**, 1948 (1964).
(9) A. Lapidot and D. Samuel, *Biochim. Biophys. Acta*, **65**, 164 (1962); *J. Amer. Chem. Soc.*, **86**, 1886 (1964).
(10) E. Alder, I. Falkehag, and B. Smith, *Acta Chem. Scand.*, **16**, 529 (1962).
(11) E. T. Kaiser and S. W. Weidman, *J. Amer. Chem. Soc.*, **86**, 4354 (1964); *Tetrahedron Lett.*, 497 (1965).
(12) E. T. Kaiser, D. F. Mayers, S. W. Wiedman, and O. R. Zaborsky, *J. Amer. Chem. Soc.*, **86**, 4555 (1967).
(13) C. A. Bunton and J. M. Hellyer, *J. Amer. Chem. Soc.*, **89**, 6252 (1967).
(14) C. A. Bunton and J. M. Hellyer, *Tetrahedron Lett.*, 187 (1969).
(15) J. R. Cox and O. B. Ramsay, *Chem. Rev.*, **64**, 317 (1964); ref 4, Chapter 5; C. A. Bunton, *Accounts Chem. Res.*, **3**, 257 (1970).
(16) F. Ramirez and S. Dershowitz, *J. Org. Chem.*, **22**, 1282 (1957); F. Ramirez, H. J. Kugler, and C. P. Smith, *Tetrahedron Lett.*, 261 (1965).
(17) P. I. Sanin, E. S. Voronkv, E. S. Shepelva, and B. I. Ionin, *Dokl. Akad. Nauk SSSR*, **132**, 145 (1960); *Chem. Abstr.*, **57**, 11120 (1962).
(18) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Wiley, New York, N. Y., 1962, p 30.
(19) C. A. Bunton, E. J. Fendler, E. Humeres, and K.-U. Yang, *J. Org. Chem.*, **32**, 2806 (1967).
(20) C. H. Fiske and Y. Subba Row, *J. Biol. Chem.*, **66**, 375 (1925).
(21) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1961, Chapter 3.
(22) C. A. Bunton and J. M. Hellyer *J. Org. Chem.*, **34**, 2798 (1969).

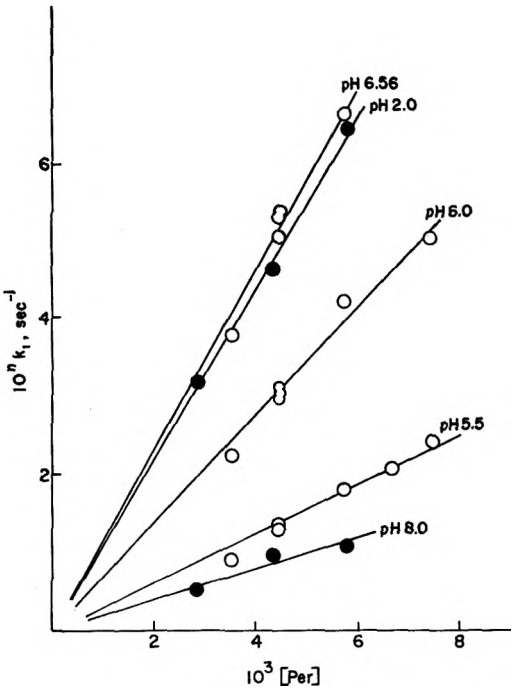


Figure 1.—Variation of first-order rate constants with periodate concentration for *p*-hydroxyphenyl phosphate (I), open circles, $n = 3$, and for *p*-hydroxyphenyl methylphosphate (II), solid circles, $n = 4$.

TABLE I

BOND FISSION IN THE REACTION OF *p*-HYDROXYPHENYL PHOSPHATE[a]

pH	N_{H_2O}	$N_{KH_2PO_4}$	P–O fission %
1.0	1.37	0.22	64
1.0	1.37	0.21	61
6.5	0.75	0.17	91
6.5	0.75	0.17	91

[a] At 25.0°; the isotopic abundances, N, are in atom % excess over normal.

trapolated to zero added buffer gave k_1, the first-order rate constant with respect to phosphate ester. Plots of k_1 against the periodate concentration (Per) were linear with close to zero intercepts (some examples are shown in Figure 1), and their slopes gave the second-order rate constants, k_2, for oxidation of the phosphate esters by periodate (Figures 2 and 3 and Table II).

TABLE II

REACTION OF *p*-HYDROXYPHENYL DIMETHYLPHOSPHATE[a]

Acid	[LiClO$_4$], M	-10^2k, l. mol^{-1} sec^{-1}— Obsd	Calcd[c]
3 M HClO$_4$		1.96	
3 M HClO$_4$	0.50	3.24	
3 M HClO$_4$	1.00	5.00	
2 M HClO$_4$		0.95	
2 M HClO$_4$	0.50	1.37	
2 M HClO$_4$	1.00	1.92	
2 M H_2SO_4		0.95	
1 M HClO$_4$		0.46	
1 M HClO$_4$	0.50	0.55	
1 M HClO$_4$	1.00	0.65	0.36
0.50[b]		0.32	0.32
1.00[b]		0.28	0.26
1.50[b]		0.17	0.18
2.00[b]		0.12	0.12

[a] At 25.0°. [b] pH. [c] Calcd for k_2^0, = 3.4×10^{-3} l. mol^{-1} sec^{-1}.

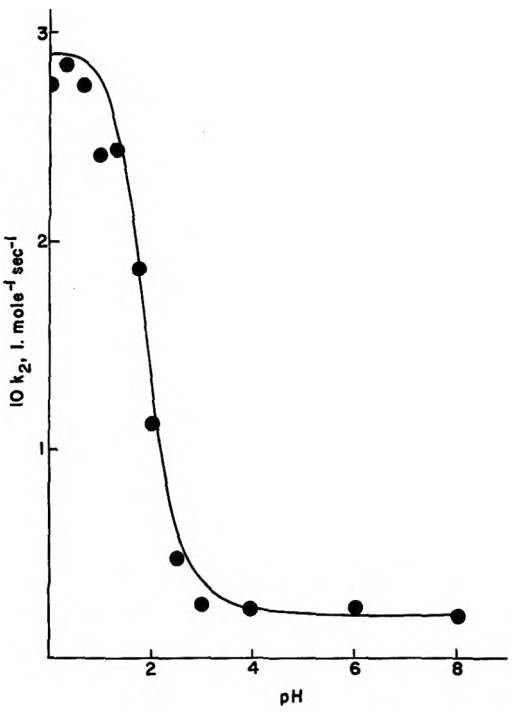


Figure 2.—Variation of the second-order rate constants, k_2, with pH for the reaction of *p*-hydroxyphenyl methylphosphate (II) at 25.0°. The line is calculated.

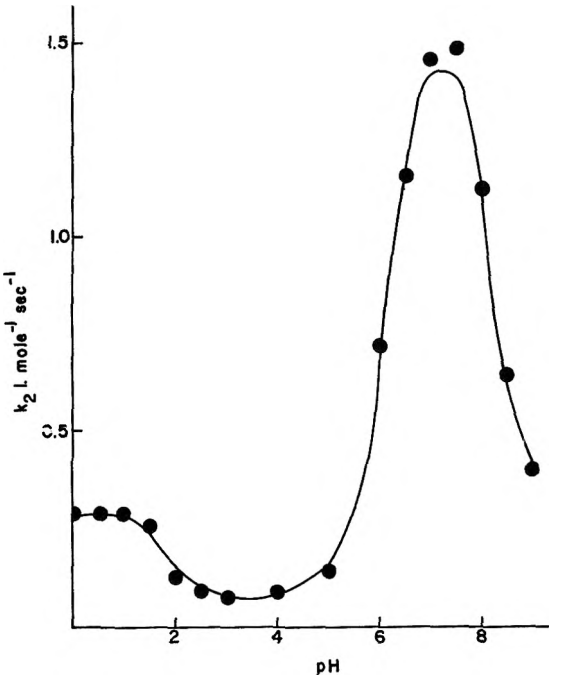


Figure 3.—Variation of second-order rate constants, k_2, with pH for the reaction of *p*-hydroxyphenyl phosphate (I) at 25.0°. The line is calculated.

The observations of second-order kinetics under all conditions show that there is no buildup of a periodate–substrate complex, in accord with the existing evidence on periodate oxidations of quinols and related compounds.[11,13]

Relation between Rate and pH. Reaction of *p*-Hydroxyphenyl Dimethylphosphate (III).—The rates of oxidative hydrolysis of the dimethyl ester show a very simple pH dependence. The periodate dianion, $H_3IO_6^{2-}$

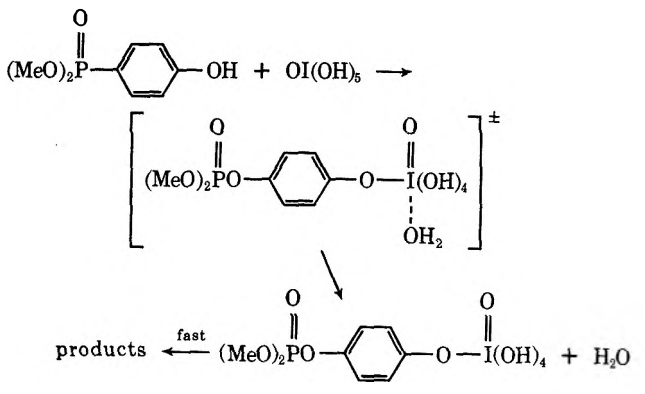
(Per^{2-}), appears unreactive toward quinols and their derivatives, and for reaction of III we can write

$$v = k_2[Per][P] = \{k_2^0[Per^0] + k_2^-[Per^-]\}[P] \quad (1)$$

where P is the phosphate ester, the superscripts denote charge, and [Per] is the stoichiometric concentration of periodate.

The relative amounts of undissociated acid and periodate monoanion can be calculated using the apparent first dissociation constant, K_1, at the various ionic strengths of the solutions interpolated from existing results.[23] (The values of 10^2K_1 were 5.5, 3.5, and 2.0 at ionic strengths of 1.0, 0.1, and 0.01, respectively.) Our kinetic treatment does not distinguish between the hydrated ($H_4IO_6^-$) and dehydrated (IO_4^-) forms of the periodate monoanion. However, IO_4^- is the predominant species,[23] and should be a better oxidant than $H_4IO_6^-$.

The second-order rate constants, k_2, for reaction of III vary linearly with the relative amount of undissociated periodic acid in the pH range 0.5–2, with $k_2^0 = 0.34 \times 10^{-2}$ l. mol^{-1} sec^{-1}, and k_2^- is negligibly small. These rate constants are compared with those for the other reactions in Table III. The observed and calculated rate constants are in satisfactory agreement for pH 0.5–2 (Table II). Undissociated periodic acid in dilute aqueous solution exists as H_5IO_6, and we assume that it is the reactive oxidant except possibly in solutions of high ionic strength. The positive electrolyte effects and the increase in k_ψ at acid concentrations >1 M (Table II) could be caused by partial dehydration of H_5IO_6 giving H_3IO_5, which should be a more effective electrophile and oxidant (HIO_4 is a strong electrolyte and would not exist to any appreciable extent under the reaction conditions).[23] Another possibility is that formation of the transition state is assisted by loss of water, *e.g.*,



and that moderately concentrated acid or added electrolyte "dehydrates" the transition state.

TABLE III
SECOND-ORDER RATE CONSTANTS[a]

Substrate	Second-order rate constants[a] k_2^0	k_2^-	k_2^{2-}	k_2^{3-}
I	0.26	0.91	0.08	1.65
II	0.26	0.64	0.02	
III	0.0034	~0		

[a] At 25.0°.

One problem with this explanation based on dehydration is that for the oxidation of *p*-hydroxyphenyl phosphate and its monomethyl ester II the values of k_ψ are independent of acid concentration once the reagents are converted fully into their undissociated acids, *i.e.*, at acid concentrations > 0.1 M (Figures 2 and 3). Therefore there are differences in the relations between rate constant and acid concentration (or ionic strength) for reactions of the dimethyl ester III and I and II. These differences may not be related to differences in mechanism, but could be caused by different electrolyte effects upon the activity coefficients of the hydrophobic dimethyl ester III and the more hydrophilic compounds I and II. Electrolyte effects are often observed in hydrolyses of hydrophobic phosphate esters.[24]

Reaction of *p*-Hydroxyphenyl Methylphosphate (II).—In the oxidative hydrolysis of the monomethyl ester II, periodic acid (Per^0) or its monoanion (Per^-, *i.e.*, $IO_4^- + H_4IO_6^{2-}$) could attack the undissociated phosphoric acid or its monoanion, and the overall rate equation is

$$v = k_2^0[P^0][Per^0] + k_2^-[P^0][Per^-] + k_2^{2-}[P^-][Per^-] \quad (2)$$

where P^- is the monoanion of II.

In formulating eq 2 we assume that periodate dianion is unreactive toward the phosphate monoanion, because the observed second-order rate constants, k_2, fall to a constant value (Figure 2) and do not increase when the concentration of $H_3IO_6^{2-}$ increases. The second and third terms of eq 2 could be written as involving other ionic species; *e.g.*, kinetically we cannot differentiate between the terms $[P^0][Per^-]$ and $[P^-][Per^0]$.

In calculating the rate constants in eq 2 we take $k_2^{2-} = 0.02$ l. mol^{-1} sec^{-1} (the limiting value of k_2 in the region pH 6–8). The rate constants k_2^0 and k_2^- were then calculated by using the concentrations of the various ionic species calculated from the dissociation constants of the phosphate ester and periodic acid, and the values of k_2 at the pH's used in the kinetic runs. From these data we calculate $k_2^0 = 0.26$ l. mol^{-1} sec^{-1}, and $k_2^- = 0.64$ l. mol^{-1} sec^{-1}.

There is good agreement between the observed and calculated values of k_2 (Figure 2).

Reaction of *p*-Hydroxyphenyl Phosphate (I).—In analyzing the variation of k_2 with pH for reaction of I we have to take into account the undissociated phosphoric acid as well as its mono- and dianions, and the various periodate species, and again we cannot differentiate kinetically between reactions of various ionic species which generate transition states of like charge. We arbitrarily write the rate equation as

$$v = (k_2^0[P^0] + k_2^-[P^-])[Per^0] + (k_2^{2-}[P^-] + k_2^{3-}[P^{2-}])[Per^-] \quad (3)$$

The rate constants in eq 3 were calculated by considering various pH regions separately; *e.g.*, at low pH we can ignore reactions of the phosphate dianion, and at high pH we can ignore reactions of the undissociated phosphoric acid, because the concentrations of these species are so low that reactions involving

(23) C. E. Crouthamel, H. V. Meek, D. S. Martin, and C. V. Banks, *J. Amer. Chem. Soc.*, **71**, 3031 (1949); C. E. Crouthamel, A. M. Hayes, and D. S. Martin, *ibid.*, **73**, 82 (1951); G. J. Buist and J. D. Lewis, *Chem. Commun.*, 66 (1965).

(24) P. W. C. Barnard, C. A. Bunton, D. Kellerman, M. M. Mhata, B. Silver, C. A. Vernon, and V. A. Welch, *J. Chem. Soc. B*, 227 (1966); C. A. Bunton, S. J. Farber, and E. J. Fendler, *J. Org. Chem.*, **33**, 29 (1968).

them would have to have rate constants as large as those for diffusion-controlled reactions to contribute to the overall reaction.

We calculate the following rate constants (l. mol^{-1} sec^{-1})—k_2^0 = 0.27, k_2^- = 0.91, k_2^{2-} = 0.02, and k_2^{3-} = 1.65—using the second-order rate constants for the overall reaction and the acid dissociation constants of the reactants, taking the apparent second dissociation constant of periodic acid[23] as 4.7 × 10^{-9}. The calculated values of k_2 (Table III) fit the experimental points reasonably well (Figure 3). (The values of k_2^- and k_2^{2-} differ from those given in ref 14, because in calculating the earlier values we did not take into account ionic strength effects on the acid dissociation of periodic acid.) There is no decrease of reaction rate with increasing acid; *e.g.*, in 2 *M* $HClO_4$, the second-order rate constant is 2.87 l. mol^{-1} sec^{-1}, and in 1 *M* acid it is 2.88 (*cf.* Figure 3).

Discussion

Under all conditions there was no buildup of a periodate ester, and the rate-limiting step is formation of a periodate ester which decomposes rapidly to products, or the periodate ester (E) is in equilibrium with reactants and decomposes slowly to products, *i.e.*, $k_b \gg k_p$, in Scheme I.

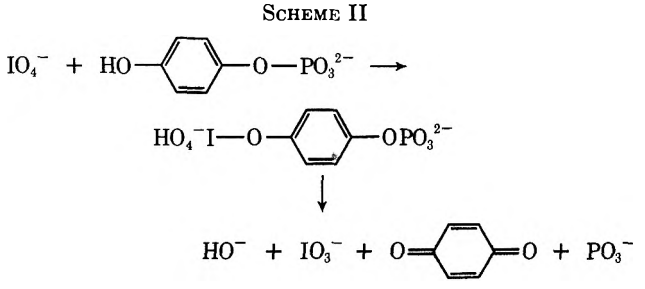
SCHEME I

$$P + Per \underset{k_b}{\overset{k_f}{\rightleftharpoons}} E \xrightarrow{k_p} \text{products}$$

We cannot distinguish between these two possibilities using only kinetic measurements, but at least for the oxidative hydrolysis of *p*-hydroxyphenyl phosphate (I) we can draw mechanistic conclusions.

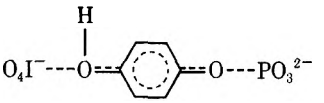
Mechanism of Oxidation of *p*-Hydroxyphenyl Phosphate.—The obvious feature of Figure 3 is the rate maximum at pH 7–7.5. In this pH region the probable reactants are the phosphate dianion, which should be a better nucleophile than the monoanion. In Scheme II,

SCHEME II



we assume that the reactive form of the periodate monoanion is IO_4^- (*cf.* ref 23). This mechanism explains the phosphorus–oxygen fission observed at pH 6.5 (Table I).

In Scheme II we show formation and breakdown of the periodate ester as discrete steps, but they could be concerted. Elimination of metaphosphate ion from phosphate ester dianions occurs readily if P–O bond breaking is favored,[25] as it could be in forming periodate ester, *e.g.*, IV, or in species generated by loss of IO_3^- from it.



IV

This monoanion–dianion reaction appears to involve metaphosphate elimination in a slow step following the general mechanism proposed by Todd and his coworkers,[2] and it occurs under physiological conditions.

The reaction involving a dianionic transition state makes little overall contribution to the overall reaction, and there is considerable uncertainty in the actual value of k_2^{2-} for reaction of *p*-hydroxyphenyl phosphate (Table III).

The rate constant, k_2^0, is calculated for the reaction between two undissociated acids, although other reaction schemes could give the same kinetic form, and, in the same way, the reaction involving a monoanionic transition state (rate constant k_2^-) could be written differently. These reactions may not involve elimination of metaphosphate ion, although there is considerable P–O fission at pH 1. Either formation of a periodate–substrate complex is the rate-limiting step or the complex decomposes slowly, probably by attack of water.

To date analogies between the oxidative hydrolysis of quinol phosphates and their possible biological role have not been clear-cut, largely because extensive carbon–oxygen fission was observed in the chemical systems.[4,7-9] The reaction between a periodate monoanion and the dianion of *p*-hydroxyphenyl phosphate occurs at low temperature and under mild conditions in water and with extensive phosphorus–oxygen bond fission, and could therefore provide a simple chemical model for oxidation-induced phosphorylation.

Reactions of the Methyl Esters.—Three reactions are involved in the oxidative cleavage of the monomethyl ester II. Although k_2^- is relatively large (Table III), the contribution of the corresponding reaction is not large because at no pH are both reactants the predominant species. The rate constant k_2^0 is not particularly large, probably because formation of a periodate ester from H_5IO_6 involves elimination of water, but it is difficult to study the mechanisms of any of these three reactions in isolation.

The second-order rate constant for the reaction of periodic acid with the dimethyl ester III is slower than the corresponding reactions of the other esters (Table III). Two factors could be involved in this low reactivity of the dimethyl ester.

(1) The PO_3Me_2 group could be more electron attracting than either PO_3HMe or PO_3H_2 because of hydrogen bonding of water to the acidic hydrogens. The Hammett σ_p values are more negative for OH than OMe.[26]

(2) Nucleophilic attack upon the aryl or phosphoryl groups of the intermediates could be sterically hindered by the methyl groups.

Although the fit between the observed and calculated k_2 values is satisfactory over most of the pH

(25) G. DiSabato and W. P. Jencks, *J. Amer. Chem. Soc.*, **83**, 1268, 4400 (1961); A. J. Kirby and A. G. Varvoglis, *ibid.*, **88**, 1823 (1966); C. A. Bunton, E. J. Fendler, and J. H. Fendler, *ibid.*, **89**, 1221 (1967).

(26) J. Hine, "Physical Organic Chemistry," McGraw-Hill, New York, N. Y., 1962, p 87.

range (Figures 1 and 2, Table III), there are some deviations at relatively high concentrations of acid, the observed values being lower than those calculated for the monomethyl phosphate II, as was observed in the periodate oxidation of quinols,[11] but not of their carboxylic esters.[13] However, for the dimethyl ester the observed values are greater than those calculated (Table II), but because of the complex equilibria it is difficult to predict the sign or magnitude of what are probably kinetic or equilibrium electrolyte effects.

Relation with Periodate Oxidations of Quinols and Their Derivatives.—The reactions of *p*-quinol or its monomethyl ether with periodic acid are much faster than those of the undissociated phosphate esters, or the corresponding carboxylic esters.[11,13] For reaction of periodic acid with *p*-quinol the second-order rate constant is 71.7 l. mol^{-1} sec^{-1} at 25°,[11] whereas for *p*-hydroxyphenyl acetate[13] it is 19.6 × 10^{-4} l. mol^{-1} sec^{-1}, and for the phosphates I and II it is 0.26 l. mol^{-1} sec^{-1}. These low reactivities of the esters can be explained in part in terms of electron withdrawal by the acetyl and phosphoryl groups. (The σ_p values follow: $^{26}CH_3CO$, +0.50, and PO_3H^-, +0.26.) In addition, decomposition of intermediates requires an extensive molecular reorganization, much more than in the decomposition of the corresponding intermediates in the oxidation of *p*-quinol. This explanation implies that formation of the periodate intermediate in the ester oxidations is reversible, with an unfavorable equilibrium constant, because it would be difficult to explain the rate constants solely in terms of the electronic effects of the phosphoryl groups upon formation of a periodate ester.

Registry No.—I, 940-75-0; II lithium salt, 39478-13-2; III, 1665-78-7; IV, 39478-14-3; dimethyl phosphite, 868-85-9.

Sulfonium Salts. VI. The Halogenation of Thiophane. Reaction Products

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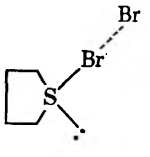
Received February 21, 1973

Bromination of thiophane in methylene chloride solution provides *trans*-2,3-dibromothiophane, isolated after methanolysis as *trans*-3-bromo-2-methoxythiophane (**3**). Chlorination of thiophane in methylene chloride solution provides 2-chlorothiophane (**10**) and 2,3-dichlorothiophane (**11**) identified after methanolysis as 2-methoxythiophane (**9**) and *trans*-3-chloro-2-methoxythiophane (**10**). The nmr spectrum of **3** suggests a highly favored conformation in solution with the substituents disposed diaxially on the thiophane ring.

The bromination of diethyl sulfide to produce unidentified fuming oils was described by Rathke in 1869.[2] The reaction was investigated by others, who obtained α-halo sulfides[3] and α,β-unsaturated sulfides[4] using a variety of halogenating agents. In some cases halogenation led to rupture of the carbon–sulfur bond with subsequent reactions ensuing from the sulfenyl halide generated.[3,5] In most cases such fragmentation appeared to be favored over α-substitution because decomposition of the halosulfonium salt intermediate could lead to a stable carbonium ion. We considered that a comparison of the results for halogenations of thiophanes with those of oxathiolanes[5a] would help in evaluating the importance of conformational effects on α-substitution in a five-membered ring and the importance of carbonium ion stabilization as an aid to carbon–sulfur bond fragmentation. Here we report results for the halogenation of the parent compound, thiophane, which indicate that α-substitution can be highly favorable in five-membered, sulfur-containing rings.

Results and Discussion

Bromination.—Bromination of thiophane in cold carbon tetrachloride solution provided an orange, crystalline adduct of sulfide with bromine. Recrystallization at low temperature from methylene chloride provided crystals whose molecular structure was found to be as shown.[6]



When the bromine complex of thiophane was allowed to react with cyclohexene, *trans*-1,2-dibromocyclohexane was produced. With water, the sulfoxide was formed. In methylene chloride solution at temperatures as low as 10°, hydrogen bromide was evolved and the orange color of the solution faded to a faint yellow. Thiophane could be readily identified by vpc as a reaction product, but the remaining materials were too unstable to handle. Removal of methylene chloride

(1) (a) Taken in part from the dissertation of Richard Albert, submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the Polytechnic Institute of Brooklyn. (b) NASA Trainee, 1966–1969.

(2) B. Rathke, *Justus Liebigs Ann. Chem.*, **152**, 181 (1869).

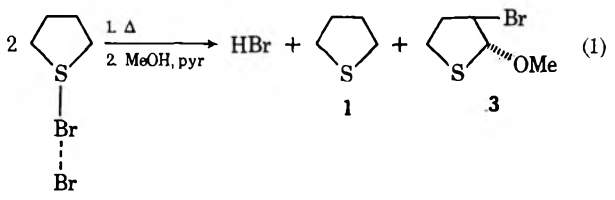
(3) For lead references, see G. E. Wilson, Jr., and M. G. Huang, *J. Org. Chem.*, **35**, 3002 (1970).

(4) H. Bohme and H. Gran, *Justus Liebigs Ann. Chem.*, **577**, 6B (1952).

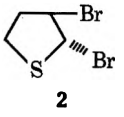
(5) (a) G. E. Wilson, Jr., *J. Amer. Chem. Soc.*, **87**, 3785 (1965); (b) D. S. Tarbell and D. P. Harnish, *ibid.*, **74**, 1862 (1952); (c) D. C. Gregg, K. Hazelton, and T. F. McKeon, Jr., *J. Org. Chem.*, **18**, 36 (1953); (d) K. C. Schreiber and V. P. Fernandez, *ibid.*, **26**, 2478 (1961); (e) M. L. Wolfrom, H. G. Garg, and D. Horton, *ibid.*, **29**, 3280 (1964), and references cited therein; (f) H. Kwart and P. S. Strilko, *Chem. Commun.*, **767** (1967), and references cited therein; (g) J. M. Stewart and C. H. Burnside, *J. Amer. Chem. Soc.*, **75**, 243 (1953); (h) N. J. Leonard and G. E. Wilson, Jr., *ibid.*, **86**, 5307 (1964).

(6) G. Allegra, G. E. Wilson, Jr., E. Benedetti, C. Pedone, and R. Albert, *J. Amer. Chem. Soc.*, **92**, 4002 (1970).

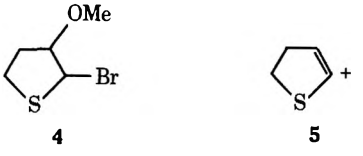
at room temperature under vacuum led to decomposition of the products with evolution of hydrogen bromide. Addition of pyridine and methanol to the original reaction mixture provided pyridinium bromide and a solution containing equimolar quantities of thiophane (**1**) and an unknown methoxylated derivative (**3**) of the bromine-containing product (**2**). In subsequent experiments the hydrogen bromide was isolated as silver bromide, and the stoichiometry of the decomposition was established to be as shown in eq 1.



Spectral data for the bromination product and its methoxylated derivative were consistent with the assigned structures **2** and **3**. The nmr spectrum of **3**



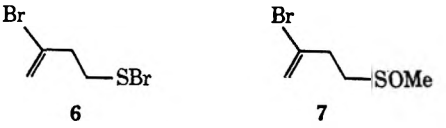
consisted of a triplet of doublets for one proton at 4.45 (J = 3.2, 1.5 Hz), a one-proton doublet at 5.07 (J = 1.5 Hz), a three-proton singlet at 3.24, and two broad two-proton multiplets centered at 3.0 and 2.5 ppm downfield from TMS. The coupling patterns of the downfield protons and the existence of the two-proton resonance at 3.0 ppm, consistent with the normal position of methylene groups adjacent to sulfur atoms, appeared to rule out isomers other than **3** or **4**. The downfield resonances of **2** were a structured single peak at 5.02 ppm and a tightly coupled multiplet at 5.80 ppm. The mass spectral fragmentation pattern of **3** (M^+, 196, 198) showed loss of Br· (m/e 117, 95%) followed by loss of methanol (m/e 85, 100%) to give ion **5**. Alternatively, loss of the methoxy radical (m/e



165, 167; 41%, 40%) may have occurred first followed by loss of HBr to give ion **5**.

Dibromide **2** undergoes a very rapid reaction with iodide ion in DMF at room temperature to produce copious quantities of iodine. Under the conditions of the reaction, the dihydrothiophene formed apparently polymerizes. The rapidity of this reaction is noteworthy, for 1,2-dibromocyclopentane requires a reaction temperature of 75° before it reacts smoothly with iodide ion in methanol solution to produce cyclopentene.[7] We consider that this provides additional evidence for trans substitution in a rather rigid ring system (*vide infra*).

The experimental data to this point could also be reconciled with an alternative pair of structures (**6** and **7**) for the dibrominated product and the methoxyl-

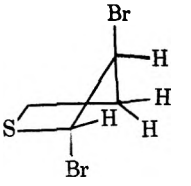


ated derivative, respectively;[8] however, these were eliminated from consideration when bromination of dihydrothiophene was demonstrated to produce products identical with those obtained by bromination of thiophane. Assignment of structure **3** rather than **4** is based on the high reactivity of α-halo sulfides to nucleophilic substitution reactions[9] and comparison of the chemical shifts of the methinyl protons with those of model compounds (Table I).

TABLE I
DOWNFIELD CHEMICAL SHIFTS OF METHINE PROTONS α AND β TO SULFUR IN THIOPHANES

Compd	δ in CCl_4, ppm α	β	Compd	δ in CCl_4, ppm α	β
	5.80	5.02		5.04	
	5.07	4.45			4.72
	5.03	4.45		5.63	
				5.65	

The nmr spectra of the 2-methoxy-3-halothiophanes and 2,3-dibromothiophane indicate a system with a strongly preferred conformation and they are instrumental in assigning the trans stereochemistry. If rapid and complete pseudorotation through equienergy conformations were occurring in any of these compounds, the vicinal coupling constant between the methine protons would be in the range of 5–8 Hz for either cis or trans disubstitution. The small magnitude of this coupling, 1.5 Hz in **3** and less than 1.0 Hz in 2-methoxy-3-chlorothiophane (**10**), requires that there be *highly* favored conformations restricted so that the dihedral angle between the methine protons be close to 90°. This can be true only for trans-1,2-disubstitution and only if the substituents are diaxially disposed on a thiophane ring which itself is very nearly of C_2 symmetry[10] (see structure below). In the favored conformation the dihedral angles between the β proton and both β′ protons are equal, thus explaining the triplet of doublets for the β proton.



(7) J. Weinstock, S. N. Lewis, and F. G. Bordwell, *J. Amer. Chem. Soc.*, **78**, 6072 (1956).

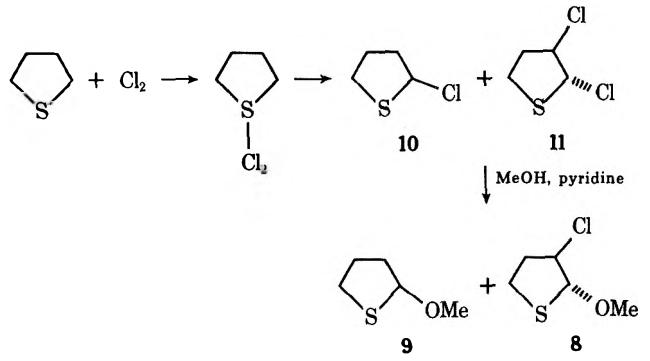
(8) G. E. Wilson, Jr., and R. Albert, *Tetrahedron Lett.*, 6271 (1968).

(9) F. G. Bordwell and W. T. Brannen, Jr., *J. Amer. Chem. Soc.*, **86**, 4645 (1964).

(10) The coupling constants are also certainly in line with that envelope conformation with the flap atom at the 2 position. This represents only a negligible distortion of the proposed most favorable conformation.

Chlorination.—Chlorination of thiophane in carbon tetrachloride produced a complex believed to be of 1:1 stoichiometry similar to that with bromine. This material is stable at −20° at pressures as low as 10^{-5} Torr, but it decomposes as it warms to room temperature with the evolution of hydrogen chloride. Decomposition ensues even when the material is formed at low temperature on the vacuum line and overlayered with an atmosphere of argon before the sample temperature is allowed to increase.[11]

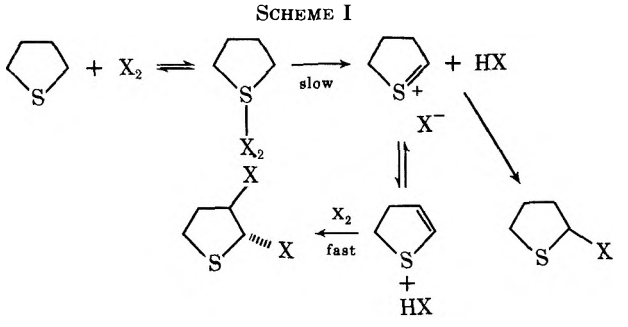
Two products in addition to thiophane were obtained when a methylene chloride solution of the chlorine complex of thiophane was warmed. These were immediately converted to methoxylated derivatives for identification. The first was identified as 2-methoxythiophane (**9**) by spectroscopic methods, and by comparison to an authentic sample generated by addition of hydrogen chloride to dihydrothiophene. The second product was identified as 2-methoxy-3-chlorothiophane (**8**) based on spectral similarities to the bromo compound **3**. Thus the precursors must be α-chlorothiophane (**10**) and 2,3-dichlorothiophane (**11**).



Bordwell and Pitt[12] suggested that **11** was produced by treatment of thiophane with sulfuryl chloride. They isolated in 2% yield a material considered to be 2-phenyl-3-chlorosulfolane (**12**), mp 154–155°, with an analysis consistent with the empirical formula $C_{10}H_{11}ClO_2S$ after treatment of the chlorinated thiophane with phenylmagnesium bromide and oxidation to a sulfone. Our results on a sample known to be almost pure 2,3-dichlorothiophane completely substantiate the previous results.

We consider that the mechanism depicted in Scheme I is most consistent with the available facts. In this

SCHEME I



context and particularly germane for synthetic applications is the fact that modification of the bromination reaction by addition of triethylamine to the reaction medium results in formation of nearly pure α-bromothiophane. We believe that the course of the bromination is altered in this way because the amine ties up the available halogen and thus retards the bromination of the dihydrothiophene.

Experimental Section[13]

1-Bromothiophanium Bromide.—To a solution of 8.8 g (0.10 mol) of thiophane in 50 ml of carbon tetrachloride at 4° was added dropwise and with stirring 16.0 g (0.10 mol) of bromine in 25 ml of cold carbon tetrachloride, causing a deposition of orange crystals. The crystals were removed by filtration, washed with cold carbon tetrachloride, and dried under vacuum: mp 80–81°; uv $\lambda_{max}^{CH_2Cl_2}$ 285 nm (ε 1800); ir ν_{max}^{KBr} 3420, 2930, 1411, 1312, 1265, 1194, and 1137 cm^{-1}; nmr ($CDCl_3$) τ 6.47 (4 H, m) and 7.59 (4 H, m); nmr (CD_3CN) τ 6.13 (4 H, m) and 7.58 (4 H, m). A satisfactory analysis could not be obtained, probably because of the instability of 1-bromothiophanium bromide at room temperature even when stored in a sealed ampoule under nitrogen or *in vacuo*. The structure was confirmed by single-crystal X-ray techniques.[6]

Reaction of 1-Bromothiophanium Bromide with Cyclohexene.—To 0.25 ml of cyclohexene in 10 ml of cold methylene chloride was added an unmeasured quantity of solid 1-bromothiophanium bromide. The solution was immediately decolorized. A sample of the solution was then injected into the vpc (20% SE-30, 9 ft × 0.25 in., Chromosorb P, 60/80 mesh) column; and the product peak corresponding to *trans*-1,2-dibromocyclohexane was identified by mixed injection with an authentic sample.

***trans*-2-Methoxy-3-bromothiophane (3).**—To a solution of 5.0 g (0.057 mol) of thiophane in 150 ml of methylene chloride at −10° was added dropwise and with stirring 9.0 g (0.057 mol) of bromine. An orange, crystalline precipitate formed which dissolved when the solution was warmed to 40°. Stirring was continued under a nitrogen current at 40° until hydrogen bromide gas was no longer evolved. In another run the hydrogen bromide evolved was conducted through silver nitrate solution, where it produced 9.5 g (0.05 mol) of silver bromide. The solution was cooled to ambient temperature, and to it was added with stirring 2.0 g (0.063 mol) of methanol followed by 5.0 g (0.063 mol) of pyridine in small portions. The mixture was allowed to stand overnight, and the deposited crystals of pyridinium bromide were removed by filtration. The filtrate was then washed several times with 100-ml portions of water. The separated organic layer was then dried over sodium sulfate, and the solvent was removed on the rotary evaporator. From the 4.87 g (87% yield) of crude product, pure 2-methoxy-3-bromothiophane (2.96 g) was obtained by chromatography on 100 g of silica gel (Fisher Scientific Co., Grade 923 ASTM D 1319-61T, 100–200 mesh) in a column 1.8 × 60.0 cm. The crude material was added neat and then eluted using methylene chloride. The first six 50-ml fractions were combined, and the eluent was removed by rotary evaporation, resulting in 2.57 g (98% yield) of analytically pure 2-methoxy-3-bromothiophane: $n^{25}D$ 1.5430; uv λ_{max}^{EtOH} 212 nm (ε 720); ir ν_{max}^{neat} 2994 (CH), 2946 (CH), 2823, 1441, and 1075 cm^{-1} (OCH_3); nmr (CCl_4) τ 4.92 (1 H, d), 5.52 (1 H, t-d), 6.77 (3 H, s), 7.02 (2 H, m), and 7.57 (2 H, m).

Anal. Calcd for C_5H_9OSBr: C, 30.46; H, 4.60; S, 16.25; mol wt, 197.109. Found: C, 30.84; H, 4.60; S, 16.55; mol wt, 196, 198 (mass spectrum, molecular ion).

***trans*-2-Methoxy-3-chlorothiophane (8).**—To a deep yellow solution of 5.0 g (0.057 mol) of thiophane in 100 ml of liquid sulfur dioxide at −10° was added 4.0 g (0.057 mol) of chlorine in a stream of nitrogen and with stirring. The color disappeared immediately. Stirring was continued at −10° for 2 days, then the sulfur dioxide was replaced with 40 ml of methylene chloride,

(11) We wish to thank Dr. Thomas Bazzone for performing these experiments.

(12) F. G. Bordwell and B. M. Pitt, *J. Amer. Chem. Soc.*, **77**, 572 (1955).

(13) Nmr spectra were obtained using a Varian Associates Model A-60 spectrometer equipped with a variable-temperature probe, and chemical shifts were measured using tetramethylsilane as an internal standard. Mass spectra were obtained using a Hitachi Perkin-Elmer RMU-6E mass spectrometer. Infrared spectra were obtained using a Perkin-Elmer automatic recording infrared spectrometer, Model 521. All elemental analyses were done by Galbraith Laboratories, Inc., Knoxville, Tenn. An Aerograph Model 200B gas chromotograph with 0.25 in. × 9 ft columns packed with 15% SE-30 on Chromosorb P 60/80 A/W was employed for vpc analyses unless otherwise stated.

and the solution was allowed to reach ambient temperature. To this was added with stirring 10.0 g (0.315 mol) of methanol followed by 10.0 g (0.126 mol) of pyridine in small portions. The mixture was allowed to stand overnight, and the deposited crystals of pyridinium chloride were removed by filtration. The filtrate was washed several times with 100-ml portions of water. The separated organic layer was dried over sodium sulfate, and the solvent was removed on the rotary evaporator. The volatile portion of the product was shown by vpc to consist of 2.1 g (66%) of *trans*-2-methoxy-3-chlorothiophane. An analytical sample was obtained by preparative vpc: ir ν_{max}^{neat} 2932 (CH), 2826 (OCH_3), 1481, and 1080 cm^{-1} (OCH_3); nmr (CCl_4) τ 4.97 (1 H), 5.55 (1 H), 6.74 (5 H), and 7.72 (2 H).

Anal. Calcd for C_5H_9ClOS: C, 39.34; H, 5.94; Cl, 23.22; S, 21.00; mol wt, 152.65. Found: C, 39.37; H, 5.94; Cl, 23.24; S, 20.96; mol wt, 152, 154 (mass spectrum, molecular ion).

α-Methoxythiophane (9).—To a solution of 5.0 g (0.057 mol) of thiophane in 150 ml of carbon tetrachloride at 4° was added in a stream of nitrogen and with stirring 4.0 g (0.057 mol) of chlorine. A fluffy white precipitate formed which dissolved when the mixture was warmed to 40°. Stirring was continued at 40° until hydrogen chloride gas was no longer evolved in the nitrogen stream when the solution was cooled to ambient temperature, and to it was added with stirring 2.0 g (0.063 mol) of pyridine in small portions. The mixture was allowed to stand overnight, and the deposited crystals of pyridinium chloride were removed by filtration, the filtrate having been washed several times with 100-ml portions of water. The separated organic layer was dried over sodium sulfate and the solvent was removed on the rotary evaporator. The crude material was shown by vpc to consist of 5.6 g (80% yield) of α-methoxythiophane. An analytical sample was obtained by preparative vpc: $n^{20}D$ 1.496; ir ν_{max}^{neat} 2950 (CH), 2860 (OCH_3), 1437, and 1252 cm^{-1} (OCH_3); nmr (CCl_4) τ 5.00 (1 H, m), 6.82 (2 H, m), 7.15 (3 H, s), and 7.95 (4 H, m).

Anal. Calcd for $C_5H_{10}OS$: C, 50.81; H, 8.52; S, 27.13, mol wt, 118.20. Found: C, 50.79; H, 8.51; S, 27.16; mol wt, 118 (mass spectrum, molecular ion).

2-Phenyl-3-chlorosulfolane (12).—A three-step procedure was carried out in order to convert 2,3-dichlorothiophane into a stable derivative the physical properties of which could be compared to those of the material prepared by Bordwell and Pitt.[12]

To a solution of 2,3-dichlorothiophane, prepared from 5.0 g (0.056 mol) of thiophane, in carbon tetrachloride was added with stirring 0.1 mol of phenylmagnesium bromide in 60 ml of ether. Stirring was continued at ambient temperature overnight, and then the excess Grignard reagent was hydrolyzed with 4 ml of water, extracted with ether, and dried over anhydrous potassium carbonate. The solvent was removed on a rotary evaporator, yielding 6 g of residue. The residue was taken up in 100 ml of glacial acetic acid containing 30 ml of 30% hydrogen peroxide and heated under reflux for 15 min, after which it was diluted with water and extracted with methylene chloride. The organic layer was dried and the solid residue after removal of solvent was dissolved in a minimum amount of benzene and allowed to crystallize under external cooling with an ice bath. The product, 2-phenyl-3-chlorothiophane, was collected as microcrystals: 0.267 g (4% yield); mp 153–154° (lit. mp 154–155°);[12] uv λ_{max}^{EtOH} 218 nm (ε 7000) and 259 (300); ir ν_{max}^{Nujol} 1310 and 1120 cm^{-1} ($-SO_2$); nmr ($CDCl_3$) τ 2.51 (6 H, s), 5.41 (1 H, m), 5.64 (1 H, m), 6.61 (2 H, m), and 7.31 (2 H, m).

Anal. Calcd for $C_{10}H_{11}ClOS$: C, 52.06; H, 4.80; S, 13.90; mol wt, 230.721. Found: C, 52.22; H, 4.67; S, 13.53; mol wt, 230 (molecular ion, mass spectrum).

3-Hydroxythiophane.—To a solution of 5.0 g (0.049 mol) of 3-thiophanone in 50 ml of methanol precooled to 4° was added with stirring a solution of 8.4 g (0.10 mol) of sodium acetate and 4.0 g (0.104 mol) of sodium borohydride in 30 ml of water at such a rate that the solution temperature remained between 4 and 10°. After addition was complete, the solution was stirred at 4° for 1 hr and then neutralized with several milliliters of concentrated sulfuric acid, and the product, in three 50-ml portions, was extracted into ether. The ether extract was dried over magnesium sulfate and the solvent was removed by rotary evaporation, leaving 4.3 g (83% yield) of 3-hydroxythiophane. The product was purified by distillation, bp 53° (0.25 mm), giving 3.8 g (72% yield) of 3-hydroxythiophane: $n^{20}D$ 1.5374; ir ν_{max}^{neat} 3382 (OH), 2943 (CH), 1451, 1336, 1262, 1195, 1027, 956, and 830 cm^{-1}; nmr (neat) τ 5.52 (q, 1 H, J = 4 Hz), 5.37 (s, 1 H), 7.00 (m, 4 H), and 7.92 (m, 2 H).

Anal. Calcd for C_4H_8OS: C, 46.12; H, 7.74; S, 30.78; mol wt, 104.17. Found: C, 46.16; H, 7.74; S, 30.75; mol wt, 104 (mass spectrum, molecular ion).

3-Bromothiophane.—To a solution of 4.0 g (0.0385 mol) of 3-thiophanol in 30 ml of methylene chloride was added slowly with stirring 10.5 g (0.0385 mol) of phosphorus tribromide. Upon completion of the phosphorus tribromide addition, the reaction mixture was allowed to reach ambient temperature over a period of 12 hr. The reaction mixture was washed twice with 50-ml portions of 10% aqueous sodium bicarbonate. The organic layer was separated and dried over sodium sulfate; the solvent was removed by rotary evaporation and the residue was distilled, bp 33° (0.4 mm), yielding 4.74 g (71% yield) of 3-bromothiophane: ir ν_{max}^{neat} 2944 (CH), 2862, 1421, 1372, 1233, 891, 735, 692, 656, and 515 cm^{-1}; nmr (CCl_4) τ 5.27 (q, 1 H, J = 6 Hz), 6.85 (m, 4 H), and 7.50 (t, 2 H, J = 6 Hz).

Anal. Calcd for C_4H_7BrS: C, 28.75; H, 4.24; S, 19.19; mol wt, 167.10. Found: C, 28.77; H, 4.19; S, 19.26; mol wt, 166, 168 (mass spectrum, molecular ion).

Dihydrothiophene.—A solution of 10.4 g (0.10 mol) of tetramethylene sulfoxide and 22.6 g (0.10 mol) of benzoic anhydride in 60 ml of benzene was heated under reflux for 5 hr, then cooled. The benzoic acid was then extracted with several 100-ml portions of 5% aqueous sodium bicarbonate. The separated organic layer was dried over sodium sulfate, and the solvent was removed on the rotary evaporator. The residue, 20.1 g of crude 2-benzoyloxythiophane, was distilled through a 15-cm Vigreux column at 80° (760 mm) yielding 2.0 g (23% yield) of dihydrothiophene: nmr (C_6H_6) τ 4.05 (doublet of triplets, 1 H, J = 6.0, 2.0 Hz), 4.72 (1 H, J = 6.0, 2.0 Hz), 7.02 (m, 1 H), and 7.29 (m, 1 H). The nmr (CCl_4) τ 3.94 (doublet of triplets, 1 H, J = 6.0, 2.0 Hz), 4.52 (m, 1 H, J = 5.8, 2.2 Hz), 6.92 (m, 1 H), and 7.38 (m, 1 H) (lit. J = 6.06, 2.2 Hz) was identical with that of the compound prepared by the method of Korver, *et al.*[14]

Addition of Chlorine and Bromine to Dihydrothiophene.—To 86 mg (1 mmol) of dihydrothiophene was added 1.25 ml of 1.25 *N* chlorine in $DCCl_3$ solution at 40°. The two envelopes at τ 3.94 and 4.52 were replaced by two new envelopes at τ 4.31 (m, 1 H, J = 8 Hz) and 5.19 (m, 1 H). Addition of 0.8 ml of 1.25 *N* bromine in CCl_4 solution led at first to a cloudy precipitate that dissolved and produced peaks at τ 4.15 (m, 1 H, J = 1 Hz) and 5.05 (m, 1 H).

Saturating the solution of 86 mg (1 mmol) of dihydrothiophene in 1 ml of carbon tetrachloride with chlorine gas annihilated the absorptions at τ 4.31, and the multiplet at 5.19 collapsed to a doublet of doublets. The resulting spectrum was similar to the one obtained from treating thiophane with excess chlorine.

Addition of Hydrogen Chloride to Dihydrothiophene.—Saturating a solution of 86 mg (1 mmol) of dihydrothiophene in 1 ml of carbon tetrachloride with hydrogen chloride annihilated the absorptions at τ 3.94 and 4.52 and formed a new multiplet at 4.32 giving a spectrum identical with that of 2-chlorothiophane.

Registry No.—**1**, 110-01-0; **3**, 39010-39-4; **8**, 39010-40-7; **9**, 33794-77-3; **11**, 39010-41-8; **12**, 39013-63-3; 1-bromothiophanium bromide, 22053-77-6; 3-thiophanone, 1003-04-9; 3-hydroxythiophane, 3334-05-2; 3-bromothiophane, 39013-66-6; tetramethylene sulfoxide, 1600-44-8; benzoic anhydride, 93-97-0; dihydrothiophene, 1120-59-8.

Acknowledgment.—We thank the donors of the Petroleum Research Fund, admimistered by the American Chemical Society, for a grant in partial support of this work. A NASA graduate traineeship awarded to R. A. is gratefully acknowledged.

(14) P. K. Korver, P. J. VanDerHaak, H. Steinberg, and T. J. DeBoes, *Recl. Trav. Chim. Pays-Bas*, **84**, 129 (1965).

Sulfonium Salts. VII. Halogenation of Thiophane. Studies on the Mechanism of the Pummerer Reaction[1]

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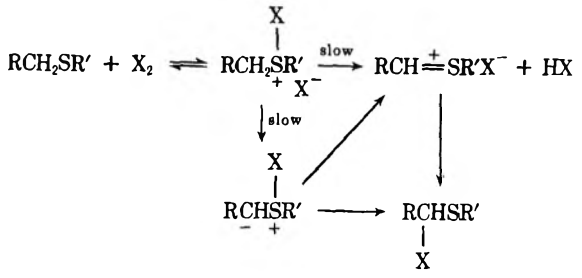
The effects of solvent and added reagents on the product distributions for the chlorination and bromination of thiophane were examined. Addition of common acid or triethylamine leads to an increase in the ratio of 2-halothiophane, but trifluoroacetic acid, *p*-toluenesulfonic acid, and boron trifluoride lead to an increase in the amount of 2,3-dihalothiophane. Competitive kinetic isotope effects of 5.1 and 3.6 were measured for chlorination and bromination, respectively.

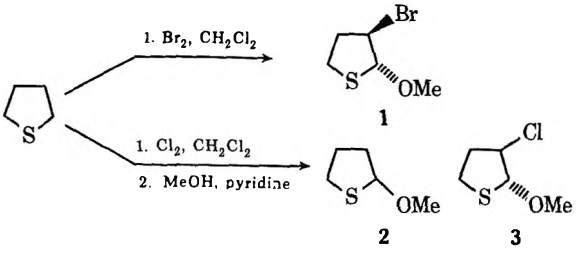
The Pummerer reaction of halosulfonium salts formed by halogenation of sulfides has received considerable attention because of its mechanistic subtleties and its utility in synthetic schemes.[3] The possible series of steps generally considered to be involved in this reaction is shown below.



Recent work[4] has established that the complex of bromine with thiophane in the solid state is a greatly distorted charge-transfer complex, probably with a high degree of ionic character. By contrast, the complex of chlorine with bis-*p*-chlorophenyl sulfide adopts a trigonal bipyramidal structure in the solid state.[5] In solution complexation of bis-*p*-fluorophenyl sulfide with chlorine is rapidly reversible between a seemingly covalent complex and starting materials.[6] Thus true halosulfonium salts may be present in very small concentrations.

The nature of the transformation of the halosulfonium salt to the α-halo sulfide is not yet completely resolved. Both a concerted process involving a sulfocarbonium ion[7] and a stepwise procedure through an ylide[8,9] have been proposed. Recent evidence suggests that the reactive species in *N*-chlorosuccinimide reactions may be a succinimidyl sulfonium salt[10] rather than a chlorosulfonium salt, as previously supposed.[9] Although it has been clear for some time that a sulfocarbonium ion may exist as a reaction intermediate, no firm proof for this species has been reported.

Bromination of thiophane in methylene chloride followed by treatment with methanol and pyridine leads to *trans*-3-bromo-2-methoxythiophane (**1**) and recovered thiophane in equimolar quantities.[2] Similarly, treatment of thiophane with chlorine followed by methanolysis led to both the normal Pummerer rearrangement product, 2-methoxythiophane (**2**), and *trans*-3-chloro-2-methoxythiophane (**3**) in a ratio of 2.4:1, as well as recovered thiophane.[2] Here we report studies concerning the effects of solvents and added reagents on the halogenation reactions which establish the presence of a sulfocarbonium ion intermediate in the Pummerer rearrangement of a halosulfonium salt.



Results

Solvent and Other Medium Effects on the Halogenation Reaction.—The chlorination of thiophane conducted in CCl_4 and followed by methanolysis produced two products, 2-methoxythiophane and 3-chloro-2-methoxythiophane, in a ratio ($\alpha/\alpha,\beta$) of 18.3. Chlorination in methylene chloride gave a ratio of 2.4. In each case chlorine was added at 0–5°, after which the temperature was raised to 40° and maintained there until hydrogen halide evolution was complete. The results in a series of solvents are shown in Table I.

TABLE I

EFFECT OF SOLVENTS ON THE PRODUCT RATIO FOR THE CHLORINATION OF THIOPHANE[a] AT 40°

Solvent	$\alpha/\alpha,\beta$[b]	Solvent	$\alpha/\alpha,\beta$[b]
CCl_4	18.3	$PhNO_2$	1.4
CH_2Cl_2	2.5	PhH	14.5
SO_2[c]	0.12	CH_3CN	0.50
CH_3NO_2	0.51		

[a] Initial thiophane concentration was 0.76 mol/l. [b] Molar ratio of α-methoxythiophane to α-methoxy-β-chlorothiophane. [c] Run at −15°.

Generally, the more polar the solvent the smaller the ratio of 2-substituted to disubstituted material ($\alpha/\alpha,\beta$); however, there were several inconsistencies with this in-

(1) Previous paper: G. E. Wilson, Jr., and R. Albert, *J. Org. Chem.*, **38**, 2156 (1973).

(2) Taken from the dissertation of Richard Albert, submitted to the Polytechnic Institute of Brooklyn in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry.

(3) For a review of the Pummerer reaction, see G. A. Russell and G. J. Mikol in B. S. Thyagarajan, Ed., "Mechanisms of Molecular Migrations," Vol. 1, Wiley, New York, N. Y., 1968, p 157.

(4) G. Allegra, G. E. Wilson, Jr., C. Pedone, E. Benedetti, and R. Albert, *J. Amer. Chem. Soc.*, **92**, 4002 (1970).

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

(6) G. E. Wilson, Jr., and M. M. Y. Chang, *Tetrahedron Lett.*, 875 (1971).

(7) For lead references, see G. E. Wilson, Jr., and M. G. Huang, *J. Org. Chem.*, **35**, 3002 (1970).

(8) F. G. Bordwell and B. M. Pitt, *J. Amer. Chem. Soc.*, **77**, 572 (1955).

(9) D. L. Tuleen and T. B. Stephens, *J. Org. Chem.*, **34**, 31 (1969), and references cited therein.

(10) E. Vilsmaier and W. Sprugel, *Justus Liebigs Ann. Chem.*, **747**, 151 (1971).

verse dependency on polarity. Nitromethane and nitrobenzene have dielectric constants of 39.4 and 36.1, respectively, but gave product ratios of 0.51 and 1.4, respectively. Acetonitrile, with a dielectric constant of 38.8, gave a product ratio of 0.50.

Chlorination conducted in CCl_4 with 10% boron trifluoride changed the ratio $\alpha/\alpha,\beta$ from 18.3 to 0.21. Trifluoroacetic and *p*-toluenesulfonic acid reduced the product ratio to 0.31 and 0.25, respectively. Addition of triethylamine to a methylene chloride solution of bromothiophanium bromide led to 2-bromothiophane. Addition of lutidinium chloride to the chlorination mixture led to the formation of only α-chlorothiophane. Lithium perchlorate acted in a fashion imitating a special salt effect; a solution 6.2×10^{-3} *M* in lithium perchlorate and 0.37 *M* in thiophane increased the ratio $\alpha/\alpha,\beta$ from 2.5 to 5.0. In contrast to the observation with benzyl sulfide,[7] the ratio $\alpha/\alpha,\beta$ is insensitive to initial concentration of reagents, not varying by more than 40% as the concentration of thiophane and halogen was varied by 600%. These results are displayed in Tables II and III.

TABLE II

REAGENT EFFECTS ON THE HALOGENATION OF THIOPHANE[a]

Reagent	Concn, mol/l.	$\alpha/\alpha,\beta$
None added		2.5
Hydrogen chloride	0.88	>80
	1.3	>80
	2.6	>80
Lutidinium chloride	0.53	>80
Hydrogen bromide[b]	0.0	0.09
	1.1	0.18
Trifluoroacetic acid	0.76	0.3
p-Toluenesulfonic acid	0.13	0.3
Triethylamine[b]	0.80	80
Sulfuryl chloride	0.76	0.3
Boron trifluoride	0.80	0.2

[a] The concentrations of thiophane and halogen were 0.38 mol/l. [b] Refers to the bromination of thiophane.

TABLE III

EFFECT OF INITIAL CONCENTRATION OF HALOGEN AND THIOPHANE IN METHYLENE CHLORIDE ON THE PRODUCT RATIO $\alpha/\alpha,\beta$

Concn, mol/l.		
Thiophane	Chlorine	$\alpha/\alpha,\beta$[a]
0.19	0.19	2.3
0.38	0.38	2.6
0.75	0.75	1.6
1.14	1.14	1.8

[a] Molar ratio of α-methoxythiophane to α-methoxy-, chlorothiophane.

Kinetic Isotope Effects.—Competitive hydrogen–deuterium kinetic isotope effects were measured for both the chlorination and bromination reactions in carbon tetrachloride and chloroform, using 2,2-dideuteriothiophane. The deuterated thiophane was obtained by lithium aluminum deuteride reduction of γ-butyrolactone to 1,1-dideuterio-1,4-butanediol, conversion to 1,1-dideuterio-1,4-dichlorobutane using thionyl chloride, and cyclization to the desired compound with sodium sulfide in ethanol. The kinetic isotope effect for chlorination in carbon tetrachloride ($k_H/k_D = 5.1$) in which there was less than 5% of **3** could be obtained by nmr methods in the following manner. The area of the methine signal (A_1) is proportional to the number of moles of α-chlorothiophane formed by proton removal. The area of the upfield multiplet (A_2) is proportional to four times the molar concentration of 2-chlorothiophane formed by proton removal plus six times the molar concentration of 2-chlorothiophane formed by deuterium removal. Thus k_H/k_D is given by

$$k_H/k_D = \frac{6A_1}{A_2 - 4A_1}$$

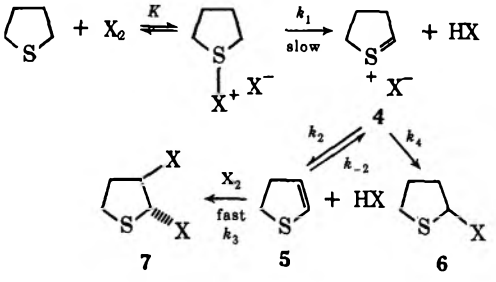
The isotope effect for the bromination reaction (3.6) is easily obtained by nmr because the two methine absorptions are separated from each other. Thus, the area of the downfield absorption (A_1), due to the 2 proton of 2,3-dibromothiophane, represents the rate of proton removal. The upfield methine absorption (A_2) is common to both products. Thus,

$$k_H/k_D = \frac{A_1}{A_2 - A_1}$$

Discussion

The reagent and solvent effects on the halogenations of thiophane are all consistent with the series of steps shown in Scheme I.

SCHEME I



In this scheme the initial equilibrium is considered to be fast and proton removal is considered rate limiting. The relative magnitudes of k_2, k_{-2}, k_3, and k_4 are important in determining the partitioning of the products. Thus, a preponderance of **7** in the case of bromination of thiophane could occur because $k_4 < k_3$ or because $k_2 > k_{-2}$. If formation of **6** were reversible, the reaction would drain into **7** until the supply of the necessary halogenating agent was depleted. That this was not the case was demonstrated for both 2-bromo- and 2-chlorothiophane, which were stable under the reaction conditions in the absence of halogenating agent.

Some solvent sensitivity would be expected for the equilibrium **4** ⇌ **5**, but not enough to account for the observed dramatic reversal in the favored product when changing from carbon tetrachloride to sulfur dioxide. Thus, changes in the relative magnitudes of k_2 and k_{-2} cannot be used to explain the results.

When $k_3 > k_4$, the product ratio reflects the difference between the activation energies for proton loss from the sulfocarbonium ion **4** and attack by anion at the α-carbon atom.

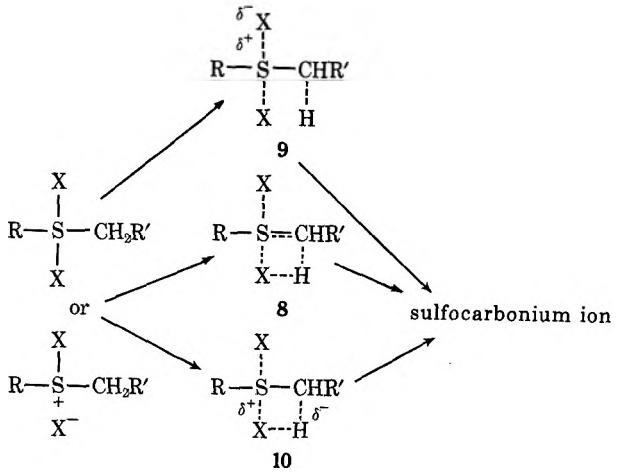
The relative magnitudes of the activation energies for formation of **5** and **6** from **4** can be rationalized in

terms of the hard and soft acid and base theory developed by Pearson[11a] and Klopman.[11b] Klopman[11b] has shown theoretically that, as the solvent becomes more polar, hydrogen chloride ionizes more, becoming a stronger acid. The proton becomes harder, the chloride ion becomes softer, and the bond between them becomes weaker. Thus, the energy of the transition state for olefin protonation by hydrogen chloride, and also the energy of the transition state for deprotonation of the sulfocarbonium ion **4**, decreases with increased solvent polarity. By contrast, attack of chloride ion at the relatively hard carbonium carbon atom of **4** should become less favorable as the solvent is made more polar. Both of these effects operate in the direction to reduce the ratio $\alpha/\alpha,\beta$, which is consistent with the observations.

Addition of the common acid has the expected dramatic effect of increasing the proportion of **4** by shifting the equilibrium **4** $\rightleftharpoons$ **5** toward **4**. The effect of lutidinium chloride may be quite similar with the lutidinium ion supplying the proton.

That $\alpha/\alpha,\beta$ drops with addition of trifluoroacetic acid, *p*-toluenesulfonic acid, and boron trifluoride etherate may be due to a reduction of the nucleophilic activity of the chloride ion caused by complexation, in the first two cases by the proton and in the last case by the boron trifluoride. Even the weak bases in solution, however, can act as proton acceptors for the conversion of **4** to **5**.

The data now available in this and other systems permit, we believe, a detailed picture for the removal of the α proton in the generalized Pummerer reaction. In this transformation, which may best be described in the terminology of Ko and Parker[12] as an E2S elimination, the transition state for this postulated mechanism (**8**) involves weak bonding between the nucleophile–base and both the sulfur atom and the α-hydrogen atom and synchronous weakening of the remaining sulfur–leaving group bond. This transition state may also be looked at as the central transition state in the variable E2 transition-state theory[13,14] as applied to C–S double bond formation. For this modified theory the reference central transition state (**8**) possesses geometry similar to the sulfurane and is one in which bond breaking of the two S–X bonds is about equal. The E1 extreme (**9**) involves cleavage of the S–X bond preceding H–X loss. Finally, the E1cB extreme (**10**) involves loss of HX proceeding ahead of S–X cleavage to provide an ylide-like transition state.



It is clear that any of these transition states may be arrived at from either a sulfurane or a sulfonium salt, both of which have been shown to be possible structures for formalized sulfonium salts in the solid state[5,15,16] and in the solution.[6,17]

In analogy with carbon systems, one would expect that, in symmetric systems with the nucleophile–base structurally identical with the leaving group on sulfur, exchange of the electronegative ligand might be faster than proton removal and that reprotonation of a sulfocarbonium ion intermediate would be an unfavorable step because of the necessity for a termolecular collision. In fact, it is clear from work with "halosulfonium salts"[6] and alkoxysulfonium salts[18] that, for those compounds which do not exist as the sulfurane, displacement of the electronegative ligand from the sulfonium sulfur atom by an anionic nucleophile can occur more rapidly than the Pummerer reaction. For acetoxysulfonium salts, however, it has been shown that the rate of the Pummerer reaction of aryl methyl sulfoxides is greater than the rate of oxygen exchange.[19] Finally, we[7,20] and others[21–23] have been unable to demonstrate significant exchange of the α proton accompanying the Pummerer reaction.

For the E2S mechanisms, one would predict that weakly basic anions which allow bonding to sulfur through a strongly electron-withdrawing atom will be characterized by relatively central transition states. However, strongly basic anions might show a preference for attack at the proton leading to an ylide.

The relatively central transition state should be accompanied by a high kinetic isotope effect, and transition states at either extreme should give isotope effects tending toward unity. The observed isotope effects for the halogenations of thiophane eliminate an E1cB mechanism; all variations of such a mechanism require that k_H/k_D be equal to unity.[24] The observation that the value for the competitive isotope effect of the chlorosulfonium salt is higher than that of the bromosulfonium salt is readily explained in terms of the proposed mechanism using the theory of hard and soft acids and bases. The sulfur atom of a sulfonium salt should be moderately hard in analogy with the sulfur atom in sulfinyl and sulfonyl derivatives.[25] Thus, one would expect relatively stronger bonding between sulfur and chlorine than between sulfur and bromine in the transition state. Similarly, the chlorine should develop bonding with hydrogen more easily than

(11) (a) R. G. Pearson and J. Songstad, *J. Amer. Chem. Soc.*, **89**, 1827 (1967); (b) G. Klopman, *ibid.*, **90**, 223 (1968).
(12) E. C. F. Ko and A. J. Parker, *J. Amer. Chem. Soc.*, **90**, 6447 (1968).
(13) J. F. Bunnett, *Angew. Chem., Int. Ed. Engl.*, **1**, 225 (1962).
(14) R. A. Bartsch and J. F. Bunnett, *J. Amer. Chem. Soc.*, **91**, 1376 (1969).
(15) I. Kapovitz and A. Kalman, *Chem. Commun.*, 649 (1971).
(16) I. C. Paul, J. C. Martin, and E. F. Perazzi, *J. Amer. Chem. Soc.*, **93**, 6674 (1971).
(17) W. A. Sheppard, *J. Amer. Chem. Soc.*, **93**, 5597 (1971).
(18) C. R. Johnson and W. G. Phillips, *Tetrahedron Lett.*, 2101 (1965).
(19) S. Oae and M. Kise, *Tetrahedron Lett.*, 2261 (1968).
(20) G. E. Wilson, Jr., and C. J. Strong, *J. Org. Chem.*, **37**, 2376 (1972).
(21) C. R. Johnson and W. G. Phillips, *J. Org. Chem.*, **32**, 1926 (1967).
(22) C. R. Johnson, J. C. Sharp, and W. G. Phillips, *Tetrahedron Lett.*, 5299 (1967).
(23) W. G. Phillips and K. W. Ratts, *J. Org. Chem.*, **36**, 3145 (1971).
(24) W. K. Kwok, W. G. Lee, and S. I. Miller, *J. Amer. Chem. Soc.*, **91**, 468 (1969); Z. Rappoport, *Tetrahedron Lett.*, 3401 (1968).
(25) J. L. Kice and G. B. Large, *J. Amer. Chem. Soc.*, **90**, 4076 (1968); J. L. Kice and G. Guaraldi, *Tetrahedron Lett.*, 6135 (1966).

should the bromine. Thus the bromination reaction would be expected to tend toward the E1 extreme transition state, **9**. For acetoxysulfonium salts, because of the hardness of the oxygen atoms, one would expect the transition state to be relatively more central than that for the bromosulfonium salt, and, indeed, the reaction of dibenzyl sulfoxide with acetic anhydride provided a high competitive hydrogen kinetic isotope effect.[21] Finally, it is clear that the relative magnitudes of the isotope effects are not a function of the geometrical constraint imposed by the thiophane ring, for a similar order was observed with benzyl sulfide.[7]

Where other factors are equal, a preference for removal of the most acidic proton might be expected for the Pummerer reaction. The reaction, however, should be highly sensitive to steric effects as the size of the anion–base increases if coplanarity of the proton, the leaving group, and the nucleophile–base is required. This would agree with the observed preference methyl < ethyl ≈ *n*-propyl < isopropyl observed by Tuleen and coworkers[26] for the *N*-chlorosuccinimide reaction, assuming chloride ion to be the anion, and with the order methyl > *n*-propyl, isopropyl, *n*-butyl observed by Johnson and coworkers[22] for acetic anhydride reactions with sulfoxides.

Finally, it is clear that the E2S mechanism also is in accord with observations of racemization and reduction of sulfoxides by hydrogen halides in aqueous solutions[27] where the activity of the anion is reduced by coordination to water so that there is little tendency to remove the α proton from the sulfonium salt intermediate.

Experimental Section

1,1-Dideuterio-1,4-dichlorobutane.—To a solution of 8.0 g (0.087 mol) of 1,1-dideuterio-1,4-dihydroxybutane in 50 ml of benzene was slowly added with stirring 25.0 g (0.21 mol) of thionyl chloride in 30 ml of benzene at such a rate that the temperature remained between 25 and 30°. After complete addition of the thionyl chloride, the solution was stirred at ambient temperature for 12 hr, then the solvent was removed on the rotary evaporator, and the residue was distilled, bp 35° (1.8 mm), providing 8.7 g (79% yield) of 1,1-dideuterio-1,4-dichlorobutane, nmr ($DCCl_3$) τ 6.01 (m, 2 H) and 8.19 (m, 4 H).

α,α-Dideuteriothiophane.—To 100 ml of refluxing dimethylformamide was added simultaneously a solution of 25 g (0.105 mol) of sodium sulfide nonahydrate in 40 ml of hot water and a solution of 8.7 g (0.07 mol) of 1,1-dideuterio-1,4-dichlorobutane in 20 ml of dimethylformamide at such a rate that gentle reflux was maintained. After addition of the reagents was completed, the system was heated under reflux for an additional 6 hr, and then 50 ml of the solution was removed by distillation. The aqueous distillate was made alkaline with 4.0 g (0.10 mol) of solid sodium hydroxide and brought to saturation with sodium chloride, after which the organic layer was separated, dried, and distilled through a 15-cm Vigreux column, bp 110° (760 mm), giving 3.5 g (57% yield) of α,α-dideuteriothiophane: ir λ_{max}^{neat} 2948, 2863, 2213, 2138, 1681, 1439 cm^{-1}; nmr (CCl_4) τ 7.30 (m, 2 H) and 8.14 (m, 4 H).

Solvent Effects on the Halogenation of Thiophane.—To a solution of 2.5 g (0.028 mol) of thiophane in 75 ml of solvent was added in a nitrogen carrier 2.0 g (0.62 ml, 0.028 mol) of chlorine with stirring and while maintaining the temperature between 5 and 10°. After chlorine addition was complete, the temperature was rapidly raised to 40°, and stirring was continued until all hydrogen chloride evolution ceased. Then the solution was cooled and charged with 1.0 g (0.031 mol) of methanol and 2.2 g (0.03 mol) of pyridine in small portions, and stirring was continued overnight. The crude reaction mixture was analyzed on the vpc. Components were identified by mixed injections with authentic samples on SE-30 and FFAP columns. The mole percentage of thiophane, α-methoxythiophane, and α-methoxy-β-chlorothiophane were averaged over three to five runs and two to three injections per run. The vpc columns employed were a 9 ft × 0.25 in. aluminum column packed with 15% SE-30 on 60/80 mesh Chromosorb P and a 6 ft × 0.25 in. steel column packed with 20% FFAP on 60/80 mesh Chromosorb W.

Reagent Effects on the Halogenation of Thiophane.—To a solution of 2.5 g (0.028 mol) of thiophane and one of the following [5.7 g (0.04 mol) of lutidinium chloride, 7.65 g (0.0567 mol) of sulfuryl chloride, 50 mg (4.7×10^{-4} mol) of lithium perchlorate, 1.74 g (0.010 mol) of boron trifluoride, or 0.24, 0.48, or 0.72 g (0.066, 0.098, or 0.196 mol) of hydrogen chloride] in 75 ml of methylene chloride was added in a nitrogen carrier 2.0 g (0.028 mol) of chlorine with stirring while the temperature was maintained between 5 and 10°. The hydrogen chloride run was allowed to reflux under a Dry Ice trap sealed with an inflatable balloon. After chlorine addition was complete, the temperature was rapidly raised to 40°, and stirring was continued until all hydrogen chloride evolution had ceased. The solution was cooled, charged with 1.0 g (0.031 mol) of methanol and then with 2.2 g (0.03 mol) of pyridine in small portions, and stirring was continued overnight. Work-up and analysis were as above.

Effect of Hydrogen Bromide on the Bromination of Thiophane.—To a solution of 2.5 g (0.028 mol) of thiophane and 0.082 mol of hydrogen bromide in 75 ml of methylene chlorine was added 2.0 g (0.028 mol) of bromine with stirring while the temperature was maintained between 5 and 10°. Hydrogen bromide was refluxed under a liquid nitrogen trap which was closed by an inflatable balloon. After bromine addition was complete, the temperature was rapidly raised to 40°, and stirring was continued overnight. The solution was cooled and charged with 1.0 g (0.031 mol) of methanol and then with 2.2 g (0.03 mol) of pyridine in small portions, and stirring was continued overnight. The crude reaction mixture was analyzed on the vpc as above.

Kinetic Isotope Study.—To 88 mg (1 mmol) of α,α-dideuteriothiophane was added 0.80 ml of 1.25 *N* chlorine in deuteriochloroform at 40°. When the reaction was complete, the absorptions 4.15 and 7.12 ppm downfield from TMS were scanned at 100 and 500 cps sweep widths using a Varian Associates Model A-60 spectrometer. Averaging the area integration over five passes yielded the product isotopic ratio. A similar procedure was employed for the bromination of thiophane-d_2 except that the resonance peaks examined were 4.03 and 4.88 ppm downfield from TMS.

α-Acetoxythiophane.—Tetramethylene sulfoxide (16.7 g, 0.160 mol) and 16.6 g (0.160 mol) of acetic anhydride in 50 ml of benzene were heated under reflux under nitrogen for 4 hr, then allowed to cool to room temperature. The solution was washed with 5% aqueous sodium bicarbonate until the aqueous layer was no longer acidic. The organic layer was dried over sodium sulfate, the solvent was removed on a rotary evaporator, and the 14.6 g of residue was distilled, bp 47° (0.4 mm), giving 12.0 g (51% yield) of α-acetoxythiophane: n^{25}D 1.4896; ir ν_{max}^{neat} 2996 (CH), 2910 (CH), 1732 (C=O), 1200 (CO), and 912 cm^{-1}; nmr (CCl_4) τ 3.85 (1 H, m), 7.09 (2 H, m), 7.90 (4 H, m), and 7.97 (3 H, s).

Anal. Calcd for $C_6H_{10}O_2S$: C, 49.29; H, 6.90; S, 21.93; mol wt, 146.20. Found: C, 49.07; H, 6.86; S, 21.89; mol wt, 146 (*m/e* 104, mass spectrum, $M^+ - CH_2CO$).

2-(2-Thiophanyl)-2,3-dihydrothiophene.—Tetramethylene sulfoxide (10.4 g, 0.10 mol) and 50 ml of acetic acid were heated under nitrogen at 100° overnight. The solution was diluted with 150 ml of methylene chloride and washed several times with 100-ml portions of water and several times with portions of aqueous 5% sodium bicarbonate until the aqueous layer was neutral. The organic layer was dried over sodium sulfate, and the solvent was removed by rotary evaporation, leaving 6.65 g (83% yield) of crude material, 2.0 g of which was purified by chromatography on 100 g of alumina (M. Woelm, Woelm neutral, activity grade I) in a column of 1.8 × 60.0 cm. The crude product was added neat and then eluted using benzene, thus providing 1.5 g of pure 2-(2-thiophanyl)-2,3-dihydrothiophene in 62% yield: ir ν_{max}^{neat} 3000 (C=CH), 2842 (CH), 1648 (C=C), 1445, 1253, and 841 cm^{-1}; nmr τ 4.00 (1 H, m), 5.17 (1 H, m), 6.97 (4 H, m), and 7.98 (6 H, m).

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

(27) See, for example, D. Landini, G. Modena, F. Montanari, and G. Scorrano, *J. Amer. Chem. Soc.*, **92**, 7168 (1970); R. A. Strecker and K. K. Andersen, *J. Org. Chem.*, **33**, 2234 (1968).

Anal. Calcd for $C_8H_{12}S_2$: C, 55.76; H, 7.02; S, 37.22; mol wt, 172.316. Found: C, 55.35; H, 6.72; S, 37.72; mol wt, 172 (mass spectrum, molecular ion).

Reaction of Tetramethylene Sulfoxide with Acetyl Bromide.—To a solution of 5.2 g (0.05 mol) of tetramethylene sulfoxide in 100 ml of carbon tetrachloride was added with stirring an equimolar quantity of acetyl bromide at 0°; 1-bromothiophanium bromide deposited out of solution and was identified by nmr spectrometry.

Reaction of Tetramethylene Sulfoxide with Acetyl Chloride.—To a solution of 5.2 g (0.05 mol) of tetramethylene sulfoxide in 100 ml of methylene chloride was added with stirring an equimolar quantity of acetyl chloride at ambient temperature. After addition of the acetyl chloride was complete, the temperature was raised and kept at 40–50° until all hydrogen chloride evolution ceased. Then 4 g (0.125 mol) of methanol was added followed by 7.0 g (0.09 mol) of pyridine in small portions, and the mixture was stirred overnight.

With acetyl bromide, when carbon tetrachloride was employed as the solvent, bromothiophanium bromide was deposited out of solution. Analysis by mixed injection of the crude reaction mixture was by vpc as previously described.

Registry No.—Thiophane, 110-01-0; 1,1-dideuterio-1,4-dichlorobutane, 39495-73-3; 1,1-dideuterio-1,4-dihydroxybutane, 39495-74-4; thionyl chloride, 7719-09-7; α,α-dideuteriothiophane, 39495-75-5; α-acetoxythiophane, 1608-66-8; tetramethylene sulfoxide, 1600-44-8; 2-(2-thiophanyl)-2,3-dihydrothiophene, 39495-77-7.

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Quaternization of Thiazoles

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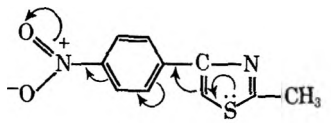
Different thiazoles have been prepared and their rate of quaternization with methyl iodide studied by the conductance method. The lower reactivity of quinaldine (10) over 2-methylbenzothiazole (5) has been explained on the basis of the β value of sulfur atom and the vinyl group. A charge transfer complex has been proposed to explain the rate retardation effect of an amino group, which otherwise should have accelerated the rate. The pK_a values of these thiazoles have been calculated by employing Edward's equation. The rate of quaternization in a series of isomeric alcohols has been investigated.

Quaternization has been a subject of interest since the days of Menschutkin.[1] The quaternization kinetics of heterocyclic bases like pyridine[2] and tetrahydroquinoline[3] have been investigated, but thiazoles have not been utilized for such studies. The quaternary salts of these thiazoles have been used by Rout, *et al.*,[4] for the synthesis of various dyes. The relative basicities of these thiazoles have been evaluated with the aid of Brooker's deviation factor.[5]

Results and Discussion

Thiazoles react with methyl iodide to form a quaternary salt. The rate data, Arrhenius parameters, and entropy of activation values are given in Table I. The reactivity of different 4-aryl substituted 2-methylthiazoles conform to the order **1** > **2** > **3** > **4**. This order of reactivity of different substituents is justifiable, since they oppose the main resonance of the sulfur atom with the thiazole ring[6] (I). The order of reactivity of other bases is **12** > **11** > **10** > **5** > **7** > **9** > **6** > **8**. The compounds **5**, **10**, and **11** belong to the same series of even alternant hydrocarbons. Quinaldine reacts more slowly than lepidine, possibly owing to the ortho effect. At 80°, the k values (extrapolated) are reversed, presumably owing to the loss of steric effect and the operation of the polar effects alone. Quinaldine reacts *ca.* four times slower than 2-methylbenzothiazole in agreement with the observation that the β value of sulfur is 25% lower than that of a vinyl group.[7]



I

The greater rate of reactivity of **1** over **8** is surprising, since an amino group would (1) increase the negative charge density around nitrogen in the reactant state and (2) stabilize the transition state. This decrease in rate may be due to the existence of an equilibrium between loose contact pairs and a charge trans-

(1) M. Menschutkin, *Z. Phys. Chem.*, **5**, 589 (1890).

(2) E. M. Kosower, *J. Amer. Chem. Soc.*, **80**, 3267 (1958).

(3) J. Wolford, G. Toth, G. Bernathi, and J. Kobor, *Tetrahedron Lett.*, **43**, 43, 4019 (1971).

(4) (a) P. K. Misra, B. K. Patnaik, and M. K. Rout, *J. Indian Chem. Soc.*, **36**, 35 (1959); (b) B. K. Sabata, B. K. Patnaik, and M. K. Rout, *ibid.*, **37**, 613 (1960); (c) K. Mukherjee, R. C. Parida, A. Nayak, and M. K. Rout, *ibid.*, **47**, 1121 (1970); (d) P. B. Tripathy and M. K. Rout, *J. Indian Chem. Soc.*, **39**, 103 (1962); (e) B. K. Sabata, B. K. Patnaik, and M. K. Rout, *ibid.*, **38**, 679 (1970); **47**, 1121 (1970); (f) D. C. Pati and M. K. Rout, *ibid.*, **45**, 425 (1968); (g) K. Mukherjee, C. S. Panda, S. Misra, G. B. Behera, and M. K. Rout, *ibid.*, **47**, 323 (1970).

(5) L. G. S. Brooker, S. G. De nt, D. W. Heseltine, and E. VanLare, *J. Amer. Chem. Soc.*, **75**, 4335 (1953).

(6) A. M. Acheson, "An Introduction to the Chemistry of Heterocyclic Compounds," The Queens College, Oxford, 1967.

(7) A. Streitweiser, Jr., "Molecular Orbital Theory for Organic Chemists," Wiley, New York, N. Y., 1962, p 127.

TABLE I

VALUES OF RATE CONSTANTS, ARRHENIUS PARAMETERS, ENTROPY OF ACTIVATION, n, E_n, AND H VALUES OF THE HETEROCYCLIC BASES IN THEIR QUATERNIZATION REACTION WITH METHYL IODIDE IN NITROBENZENE

Compd no.	Compd	$k \times 10^4$, sec^{-1} 50°	55°	60°	65°	80°[a]	E, kcal/mol	Log PZ	$-\Delta S^{\pm}$, eu	n	E_n	H	pK_a
1	4-Phenyl-2-methylthiazole	3.84	6.21	10.30	15.91	40.62	20.32	10.14	14.3	3.69	1.076	4.40	2.66
2	4-(m-Nitrophenyl)-2-methylthiazole	1.75	3.20	3.84	5.75		17.00	7.66	23.8				
3	4-(p-Chlorophenyl)-2-methylthiazole	1.72	2.30	2.90	4.37		11.60	4.02	40.6				
4	4-(p-Nitrophenyl)-2-methylthiazole	1.28	1.77	2.30	3.22		13.30	5.03	35.9				
5	2-Methylbenzothiazole	2.26	2.88	4.72	6.41	13.76	14.90	6.36	25.2	3.35	0.98	4.0	2.26
6	2-Methylbenzoxazole	1.53	2.16	3.00	4.60	9.30	15.71	6.73	32.7	3.23	0.94	2.53	0.79
7	6-Amino-2-methylbenzothiazole	1.92	2.56	3.20	3.84	5.35	12.10	4.39	34.3	3.25	0.95	3.86	2.12
8	2-Amino-4-phenylthiazole	0.96	1.28	1.84	2.99	4.02	18.83	8.63	19.4	3.06	0.89	3.60	1.86
9	2-Methyl-4,5-diphenylthiazole	1.61	2.30	3.70	7.67	9.92	26.80	14.21	−6.2	2.97	0.87	3.46	1.72
10	Quinaldine[b]	1.59	2.69	5.37	8.07	99.68	21.63	10.45	6.4	3.96	1.15	4.80	3.06
11	Lepidine[b]	4.03	6.35	8.53	9.69	89.86	15.00	7.02	26.8	3.93	1.14	4.66	2.92
12	2-Methylbenzimidazole	4.69	6.83	9.56	10.90	63.62	9.41	3.36	43.6	3.83	1.12	4.53	2.79

[a] Extrapolated values. [b] Data are at 35, 40, 45, and 50°, respectively.

TABLE II

QUATERNIZATION OF 2-METHYL-4-PHENYLTHIAZOLE WITH CH_3I IN DIFFERENT SOLVENTS

Solvent	$k \times 10^4$, sec^{-1} 50°	55°	60°	65°	E, kcal/mol	Log PZ	$-\Delta S^{\pm}$, eu
Nitrobenzene	3.84	6.21	10.3	15.91	20.32	10.14	14.3
n-Butyl alcohol	2.68	5.18	7.3		23.00	11.88	4.3
sec-Butyl alcohol	1.84	3.00	6.00	9.59	23.57	12.10	3.3
$tert$-Butyl alcohol	0.84	1.28	1.53	2.99	19.50	9.00	17.50
Isobutyl alcohol	1.53	3.00	5.00	8.40	24.60	13.45	−2.8

fer complex.[8] This also can be a plausible explanation for the reduced reactivity of **7** over **5**. The values $k_5/k_7 = 1.2$ and $k_1/k_8 = 4.0$ may possibly be due to the steric effect arising out of charge transfer complex formation at the neighboring amino group in **8**.

A phenyl group at position 5 in the thiazole ring retards the rate of reaction of 4-phenyl-2-methylthiazole. The presence of the benzene ring at both the 4 and 5 positions of the thiazole ring produces strain on the molecule; as a result the benzene rings at position 4 become noncoplanar, decreasing thereby the interaction of the 4-phenyl group with the ring.[9]

The value of n, the nucleophilic constant of the Swain–Scott equation,[10] has been evaluated with $S_{CH_3I} = 1.4$[11] and log k_0 (hydrolysis of methyl iodide) = 8.4432.[12] The E_n values of the Edwards equation[13] have been obtained for different thiazoles. With these E_n values and values for $\alpha = 4.5$ and $\beta = 0.075$ for methyl iodide,[14] the pK_a values of these thiazoles have been calculated. All these data are presented in Table I. The order of basicity thus obtained agrees with the order derived by Rout, *et al.*, from the absorption spectra of the unsymmetrical cyanines.[4]

The reactivity of 4-phenyl-2-methylthiazole (**1**) in different pure solvents follows the order nitrobenzene > n-butyl alcohol > sec-butyl alcohol = isobutyl alcohol > $tert$-butyl alcohol (Table II). The trend in reactivity in different isomeric alcohols is quite interesting. The entropy of activation values for n-, iso-, and sec-butyl alcohols are very near to each other (+2 to −5 eu) whereas that in $tert$-butyl alcohol is −17.5 eu. The boiling point and density data of all these alcohols indicate $tert$-butyl alcohol to be less H bonded and so less ordered.[15] The solubility of all these alcohols in water,[16] however, indicates the greater capacity of the $tert$-butyl alcohol to form an intermolecular H bond over the rest. The polar transition state, therefore, is solvated to a greater extent in $tert$-butyl alcohol. These tendencies have possibly contributed to such a large negative entropy of activation.

Experimental Section

The purity of the compounds used in the kinetic study was checked on a silica gel G tlc plate. The following compounds were obtained from Schudart and Co.: 2 methylbenzothiazole, bp 242° (lit.[17] bp 240°); 2-methylbenzimidazole, recrystallized from water, mp 175° (lit.[18] mp 176°); 2-methylbenzoxazole, bp 202.3° [lit.[19] bp 204° (760 mm)]; quinaldine, bp 245–247° (lit.[20] bp 257°); 2-methyl-6-aminobenzothiazole, mp 129° (lit.[21] mp 126°).

The thiazoles (1–4, 9) were prepared from appropriately substituted phenacyl bromides and thioacetamide by the method of Hantzsch.[22] The compounds are 2-methyl-4-phenylthiazole, mp 66° (lit.[22] mp 67°); 2-methyl-4-(m-nitrophenyl)thiazole, mp 104°; 2-methyl-4-(p-chlorophenyl)thiazole, mp 110°; 2-methyl-4-(p-nitrophenyl)thiazole, mp 147° (lit.[23] mp 145°); 2 methyl-4,5-diphenylthiazole, mp 110°.

2-Amino-4-phenylthiazole was prepared by the condensation

(8) Inone and Kato [H. Inone and Y. Kato, *Tetrahedron*, **28**, 527 (1972)] have observed such an equilibrium between aniline and nitrobenzene. Behera, *et al.*, have also proposed a charge transfer complex between *O*-phenylenediamine and nitrobenzene [G. B. Behera, R. C. Acharya, and M. K. Rout, *J. Indian Chem. Soc.*, **48**, 917 (1971)].

(9) E. D. Sych and A. I. Kripianov, *Chem. Abstr.*, **57**, 9834 (1962).

(10) C. G. Swain and C. B. Scott, *J. Amer. Chem. Soc.*, **75**, 151 (1963).

(11) R. G. Pearson, H. Sobel, and J. Songstead, *ibid.*, **90**, 319 (1968).

(12) S. S. Radhakrishna Murti and G. P. Panigrahi, *J. Indian Chem. Soc.*, **46**, 320 (1969).

(13) J. O. Edwards, *J. Amer. Chem. Soc.*, **76**, 1540 (1954).

(14) R. E. Davis, "Survey of Progress in Chemistry," A. Scott, Ed., Academic Press, New York, N. Y., 1964.

(15) F. Franks and D. T. G. Ives, *Quart. Rev. Chem. Soc.*, **20**, 1 (1966).

(16) A. I. Vogel, "A Textbook of Practical Organic Chemistry," 3rd ed, Longmans Green and Co., London, 1956, p 1046.

(17) J. Fraser and F. M. Hammer, *J. Chem. Soc.*, 507 (1936).

(18) M. A. Phillips, *ibid.*, 2395 (1928).

(19) W. Theilacher, *J. Prakt. Chem.*, **153**, 54 (1939).

(20) J. T. Hackman and J. P. Wibant, *Recl. Trav. Chim. Pays-Bas*, **62**, 237 (1943).

(21) K. Fries and A. Wolter, *Justus Liebigs Ann. Chem.*, **527**, 60 (1936).

(22) A. Hantzsch, *ibid.*, **250**, 269 (1889).

(23) E. D. Sych, *Chem. Abstr.*, **54**, 5619*f* (1948).

of phenacyl bromide and thiourea by the method of Hurd, *et al.*[24] The compound melted at 148° (lit.[23] mp 147°).

The solvents used were of AnalaR B. D. H. variety. They had the following characteristics: nitrobenzene, bp 210–211°; *sec*-butyl alcohol, bp 99°; *n*-butyl alcohol, bp 118°; *tert*-butyl alcohol, bp 83°.

Kinetic Measurements.—The rate of reaction of the thiazoles with methyl iodide was studied in nitrobenzene at different temperatures in a thermostat (±0.1°) by monitoring the change in electrical conductivity with a Phillips model conductivity bridge at 1000 Hz. The platinum electrodes of the conductivity cell were coated with platinum black. Pseudo-first-order kinetics were maintained during the course of a kinetic run where [thiazole] was 0.01 *M* and [CH_3I] was 0.2 *M* (20-fold e Pseudo-first-order rate plots of log $R_t/R_t - R_\infty$ *vs.* time, w R_t and R_∞ are the electrical resistances at time *t* and at infin. time, respectively, were linear. The pseudo-first-order rate constants were calculated from the slopes of these linear plots and were reproducible to within ±0.2 units.

(24) C. D. Hurd and H. L. Herhrmeister, *J. Amer. Chem. Soc.*, **71**, 4007 (1949).

Registry No.—**1**, 1826-16-0; **2**, 39541-91-8; **3**, 24840-75-3; **4**, 33102-81-7; **5**, 120-75-2; **6**, 95-21-6; **7**, 2941-62-0; **8**, 2010-06-2; **9**, 3755-83-7; **10**, 91-63-4; **11**, 491-35-0; **12**, 615-15-6; methyl iodide, 74-88-4.

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Reactions of 3-Carboxyacryloylhydrazines. II.[1] Acid-Induced Rearrangement of Isomaleimides

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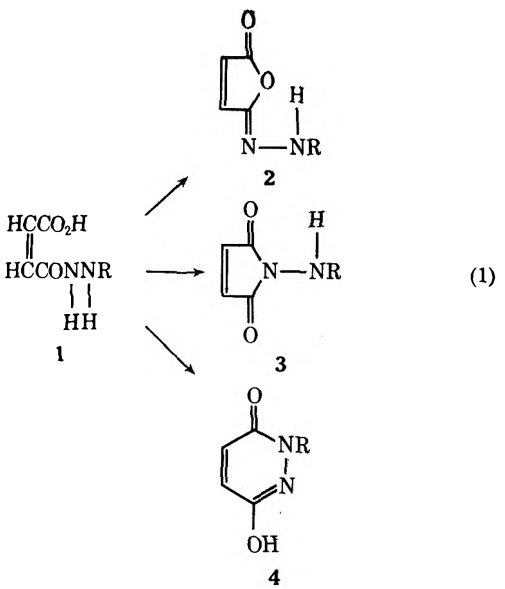
3-Carboxyacryloyl derivatives of several nitrophenylhydrazines undergo cyclization in acetic anhydride to the corresponding aminoisomaleimides. The latter in acid solutions rearrange to aminomaleimides or pyridazinones. Contrary to reports in the literature, these aminomaleimides do not rearrange to pyridazinones in acid media but are recovered unchanged.

Recently, Rubinstein, Skarbek, and Feuer[1] have discussed conditions under which 3-carboxyacryloylhydrazines **1** undergo cyclization to aminoisomaleimides **2**, aminomaleimides **3**, or pyridazinones **4** (eq 1).



They have also presented criteria for distinguishing between these structures.

In 1968, Baloniak[2] reported that the dehydration with acetic anhydride of various nitrophenyl-2-(3-carboxyacryloyl)hydrazines **1** led to the corresponding nitrophenylaminomaleimides **3**. It was further reported that these compounds were converted to pyridazinones **4** on treatment with sulfuric acid or with a mixture of sulfuric and acetic acids.[2-8]

These results, as well as previous reports in the literature[9,10] on ring formation and rearrangement, seemed incongruous when examined by the newly established criteria[1] and other recent work.[11,12] In light of the many discrepancies, it seemed important to reexamine the formation and interconversion of the various ring compounds formed by cyclization of **1** in acid solutions, and to reconcile the results obtained by previous workers.[2-10]

Results

Various aminoisomaleimide derivatives **2a–f** were prepared from the corresponding 3-carboxyacryloylhydrazines on treatment with acetic anhydride or thionyl chloride.[1] On treatment with acetic acid *N*-acetylaminoisomaleimide (**2a**), *N*-benzenesulfonylaminoisomaleimide (**2b**), 1-(2-nitrophenyl)aminoisomaleimide (**2c**), and 1-(2,4-dinitrophenyl)aminoisomaleimide (**2f**) rearranged to the corresponding aminomaleimides **3**. However, 1-(3-nitrophenyl)aminoisomaleimide (**2d**) was converted to the pyridazinone **4d**, while 1-(4-nitro-

(1) H. Rubinstein, J. Skarbek, and H. Feuer, *J. Org. Chem.*, **36**, 3372 (1971).

(2) S. Baloniak, *Rocz. Chem.*, **42**, 1231 (1968).

(3) S. Baloniak, Abstracts, Third International Congress of Heterocyclic Chemistry, Sendai, Japan, 1971, p 323.

(4) S. Baloniak, *Rocz. Chem.*, **43**, 1187 (1969).

(5) S. Baloniak, *ibid.*, **42**, 1867 (1968).

(6) S. Baloniak, *ibid.*, **43**, 315 (1969).

(7) S. Baloniak and U. Wrzeciono, *ibid.*, **45**, 567 (1971).

(8) S. Baloniak and A. Mroczkiewicz, *ibid.*, **45**, 659 (1971).

(9) H. Feuer and H. Rubinstein, *J. Amer. Chem. Soc.*, **80**, 5873 (1958).

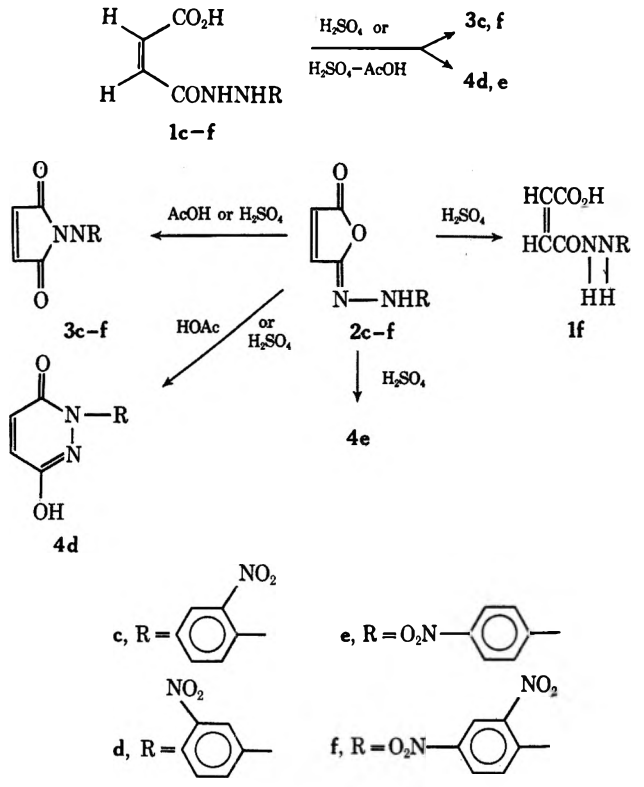
(10) H. Feuer and J. Asunskis, *J. Org. Chem.*, **27**, 4684 (1962).

(11) E. Hedaya, R. L. Hinman, and S. Theodoropulos, *ibid.*, **31**, 1311 (1966).

(12) A. Le Berre, J. Godin, and R. Garreau, *C. R. Acad. Sci., Ser. C*, **265**, 570 (1967).

phenyl)aminoisomaleimide (**2e**) was recovered unchanged (Scheme I).

SCHEME I



When the nitrophenylaminoisomaleimides were treated with sulfuric acid according to the procedure of Baloniak,[2,5,6] **2c** was converted to the aminomaleimide **3c**, **2d** and **2e** to the corresponding pyridazinones **4d** and **4e**, but **2f** to a mixture composed of **1f** and **3f** (Scheme I).

That the rearrangements shown in Scheme I were those of aminoisomaleimides **2** and not of aminomaleimides **3** was established by the fact that samples of **3** were recovered unchanged when subjected to similar reaction conditions.

When the nitrophenyl-3-carboxyacryloylhydrazines **1c–f** were treated with sulfuric acid or with mixtures of sulfuric–acetic acids according to the procedure reported by Baloniak,[2] **1c** and **1f** were converted to the aminomaleimides **3c** and **3f**, while **1d** and **1e** gave the pyridazinones **4d** and **4e** (Scheme I).

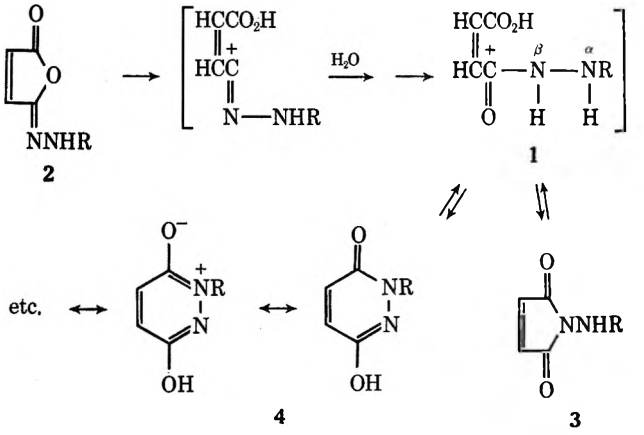
A summary of the physical properties of the compounds isolated from these experiments is presented in Table I.

Discussion

The data presented in this paper indicate that our previously reported substituted aminomaleimide rearrangements[9,10] are instead aminoisomaleimide rearrangements. Furthermore, the data show that the starting materials which Baloniak[2,3] considered to be nitrophenylaminomaleimides were all nitrophenylaminoisomaleimides.

Rearrangement of the aminoisomaleimides does not lead exclusively to the formation of aminomaleimides or to pyridazinones. Rather it is dependent on the acidity of the medium used to effect the rearrangement and on the electronegativity of the group attached to the α nitrogen (Scheme II). Thus, the less electronegative 1-(3-nitrophenyl)aminoisomaleimide (**2d**) is converted to the pyridazinone **4d** and the more electronegative aminoisomaleimides **2c** and **2f** give the aminomaleimides **3c** and **3f**. The 4-nitrophenyl compound **2e**, which lies in electronegativity between **2d** and **2c** or **2f**, gives no reaction in acetic acid but is converted to the pyridazinone **4e** in sulfuric acid. It is of interest to note that the open-chain compound **1e** undergoes ring closure to the aminomaleimide **3e** in acetic acid.

SCHEME II



The course of the rearrangement of **2** which is illustrated in Scheme II presumes the formation of **1** as an intermediate through the addition of water to the immonium center as proposed by Ernst[13] and demonstrated by Sauers[14,15] for the isoimide system. It is reasonable to expect that ring formation from **1** (or some related intermediate) then proceeds by nucleophilic attack of the α or β nitrogen atom, leading to the six- or five-membered ring compound. Electron-withdrawing substituents on the α nitrogen favor aminomaleimide formation by inhibiting attack at the α nitrogen. The results obtained on dehydration of **1** with acetic or sulfuric acid give further evidence for the mechanism proposed in Scheme II. The results were similar to those observed in the rearrangement reactions except that cyclization of **1e** in acetic acid gave the aminomaleimide **3e** while in sulfuric acid it was converted to the pyridazinone **4e**. The difference observed in acetic and sulfuric acid with **1e** can be ascribed to the stabilization of the pyridazinone ring (through its resonance forms) which would be expected to be favored in a strongly acidic polar medium.

The rearrangement and product formation which have been observed in this investigation can readily be used to explain some of the anomalous results reported[4] in the literature. For example, it has been stated, "In contrast with some reactions of 4-nitrophenyl- and 3-nitrophenyl-, the corresponding reactions of 2-nitrophenyl- and 2,4-dinitrophenylpyridazinones with acetic anhydride, dimethyl sulfate, and phosphorus oxychloride and pentachloride failed." These differences, as well as differences in the ir and uv spectra,

(13) M. L. Ernst and G. L. Schmir, *J. Amer. Chem. Soc.*, **88**, 5001 (1966).
(14) C. K. Sauers, *Tetrahedron Lett.*, 1149 (1970).
(15) C. K. Sauers, C. L. Gould, and E. S. Ivannou, *J. Org. Chem.*, **36**, 1941 (1971).

TABLE I

PHYSICAL AND SPECTRAL PROPERTIES OF NITROPHENYLHYDRAZINE DERIVATIVES

R1	R2	R3	Ir, cm⁻¹,[a] obsd	CO stretch, lit.[i]	Nmr[b-d] Olefinic protons, δ	J, Hz	Aromatic protons, δ	Mp, °C Obsd	Mp, °C Lit.[j]
			3-Carboxyacryloylhydrazines						
NO_2	H	H (1c)	1705		6.53 d, 6.26 d	12	8.29–6.27 m	163–164	158–159
H	NO_2	H (1d)	1703		6.68 d, 6.34 d[e]	13	6.68–7.28 m	147.5–148	145–146
H	H	NO_2 (1e)	1694		6.32 d, 6.26 d	12	7.92 d–6.78 d	172.5–173	165–166
NO_2	H	NO_2 (1f)	1706		6.57 d, 6.32 d[f]	13	8.95–7.49 m	192.5–193	189–190
			Aminoisomaleimides						
NO_2	H	H (2c)	1780		8.10 d, 7.00 d	6.0	8.40–7.14 m	129–131	155–157[g]
H	NO_2	H (2d)	1774, 1748		7.83 d, 6.63 d	5.5	7.74–7.52 m	213.5–214.5	213–214[g]
H	H	NO_2 (2e)	1790		7.76 d, 6.68 d	6.0	8.16 d–7.36 d	277–278	260[g]
NO_2	H	NO_2 (2f)	1792		7.99 d, 6.99 d	6.0	8.84–7.33 m	182.5–183.5	184–186[g]
			Aminomaleimides						
NO_2	H	H (3c)	1730, 1715	1750	7.19 s		8.24–6.68 m	136–137.5	140–142[h]
H	H	NO_2 (3e)	1704		7.19 s		8.10 d–6.88 d	179–180.5	
NO_2	H	NO_2 (3f)	1714	1750	7.30 s		8.97–7.37 m	232.5–233	230–232[h]
			Pyridazinones						
H	NO_2	H (4d)	1662	1672	7.28 d, 7.06 d	10.5	8.61–7.63 m	272–273 d	269–270
H	H	NO_2 (4e)	1665	1675	7.26 d, 7.08 d	9.5	8.36 d–8.00 d	308–310 d	302–303

[a] Run as a Nujol mull. [b] Parts per million. [c] All spectra were run in DMSO-d_6 using P.E. R-20 unless indicated otherwise. [d] d = doublet, m = multiplet, s = singlet. [e] Run in acetone-d_6. [f] Run using P.E. R-24. [g] Assumed by authors to be aminomaleimides. [h] Assumed by authors to be pyridazinones. [i] References 4–6. [j] Reference 2.

were attributed to the fact that some of these compounds are in the diketo form while others are in the enol form of the pyridazinone. However, our results indicate that the reported differences are those expected between pyridazinones and aminomaleimides. The former would be expected to react with the above reagents[16] while the latter would not. The observed spectral differences can be explained by the same reasoning. Furthermore, the many anomalous bromination reactions and rearrangements reported in the literature[3-8] can now be understood in the light of structure assignments in this paper and should be reinvestigated.

Experimental Section

All infrared spectra were obtained on a Beckman IR-10 instrument using sodium chloride cells and Nujol mulls. The nmr spectra were obtained on Perkin-Elmer R-20 and R-24 spectrometers. Melting points were obtained using a Thomas-Hoover melting point apparatus, and are corrected.

Hydrazines.—All hydrazines were purchased commercially or prepared by previously described procedures,[1,9] except for *m*-nitrophenylhydrazine, which was prepared by an adaptation of a method described in the literature.[17]

3-Carboxyacryloylhydrazines (1).—The 3-carboxyacryloylhydrazines were prepared by the methods indicated in the literature: 1-acetyl-2-(3-carboxyacryloyl)hydrazine,[9] 1,1-dimethyl-2-(3-carboxyacryloyl)hydrazine,[18] 1-benzenesulfonyl-2-(3-carboxyacrylcyl)hydrazine,[9] 1,2-bis(3-carboxyacryloyl)hydrazine,[9] 1-(2-nitrophenyl)-2-(3-carboxyacryloyl)hydrazine,[2] 1-(3-nitrophenyl)-2-(3-carboxyacryloyl)hydrazine,[2] 1-(4-nitrophenyl)-2-(3-carboxyacryloyl)hydrazine,[2] and 1-(2,4-dinitro)-2-(3-carboxyacryloyl)-hydrazine.[10]

Aminoisomaleimides (2).—The aminoisomaleimides were prepared according to methods published in the literature for the formation of aminomaleimides, except in the case of the dimethyl-substituted compound, which was reported as the aminoisomaleimide, 1-acetylaminoisomaleimide,[10] 1,1-dimethylaminoisomaleimide,[1] 1-benzenesulfonylaminoisomaleimide,[10] 1,2-biisomaleimide,[9] and 1-(2,4-dinitrophenyl)aminoisomaleimide.[10]

1-(2-Nitrophenyl)aminoisomaleimide[2] (2c).—Acetic anhydride (120 ml) was added to 6.0 g of 1-(2-nitrophenyl)-2-(3-carboxyacryloyl)hydrazine and the mixture was stirred at room temperature. Upon solution of the hydrazine, 18 ml of water was added and stirring was continued. The solvent was removed *in vacuo*, leaving a red solid which upon recrystallization from acetic acid

(16) S. Druey, *et al.*, *Helv. Chim. Acta*, **37**, 510 (1954).

(17) (a) A. Bischler and S. Bradsky, *Chem. Ber.*, **22**, 2809 (1889); (b) A. W. vander Haar Utrecht, *Chem. Weekbl.*, **14**, 147 (1917).

(18) H. H. Hagemann and W. L. Hubbard, Belgian Patent 613,799 (Feb 28, 1962).

gave 5.56 g of product, mp 129.5–131.0° (lit.[2] mp 155–157°). We cannot account for the difference in the melting points, but all of our physical data confirm the structure of **2c**.

Anal. Calcd for $C_{10}H_7N_3O_4$: C, 51.51; H, 3.03; N, 18.02. Found: C, 51.28; H, 3.07; N, 18.09.

Aminomaleimides (3).—The aminomaleimides were prepared according to methods reported in the literature for the preparation of pyridazinones, except for the dimethyl derivative, which was reported as the aminomaleimide, 1-acetylaminomaleimide,[9] 1,1-dimethylaminomaleimide,[1] 1-benzenesulfonylaminomaleimide,[9] and 1-(2,4-dinitrophenyl)aminomaleimide.[10]

1-(2-Nitrophenyl)aminomaleimide (3c).—Glacial acetic acid (100 ml) was added to 4.0 g of 1-(2-nitrophenyl)-2-(3-carboxyacryloyl)hydrazine. The resulting dark red solution was refluxed for 3 hr and the solvent was removed *in vacuo* to give a red-orange solid. Recrystallization from 95% ethanol produced 0.64 g of the aminomaleimide, mp 136.0–137.5°.

Anal. Calcd for $C_{10}H_7N_3O_4$: C, 51.51; H, 3.03; N, 18.02. Found: C, 51.47; H, 3.08; N, 17.94.

1-(4-Nitrophenyl)aminomaleimide (3e).—The experiment was performed as described for the preparation of **3c**. 1-(4-Nitrophenyl)-2-(3-carboxyacryloyl)hydrazine gave 1.3 g of dark orange **3e**, mp 179.0–180.5° (EtOH).

Anal. Calcd for $C_{10}H_7N_3O_4$: C, 51.51; H, 3.03; N, 18.02. Found: 51.69; H, 3.22; N, 17.74.

Rearrangement of Aminoisomaleimides (2). A. In Acetic Acid.—Glacial acetic acid was added to 0.006 mol of the aminoisomaleimide and the mixture was refluxed for the time indicated with each compound. The solvent was removed *in vacuo* and the product was purified by recrystallization: 1-acetylaminoisomaleimide, 5 hr; 1,1-dimethylaminoisomaleimide, 2 hr; 1-benzenesulfonylaminoisomaleimide, 6 hr; 1-(2,4-dinitrophenyl)-aminoisomaleimide, 4 days; 1-(2-nitrophenyl)aminoisomaleimide, 18 hr; 1-(3-nitrophenyl)aminoisomaleimide, 6 days; and 1-(4-nitrophenyl)aminoisomaleimide, 2 days (no transformation took place).

In all but one case, the product formed was found to be identical with the corresponding aminomaleimide. The exception was the 3-nitrophenyl derivative, which rearranged to the pyridazinone.

B. In Sulfuric Acid.—The various nitrophenylaminoisomaleimides **2c–f** were treated with sulfuric acid according to the methods described by Baloniak.[2] **2d** and **2e** formed the corresponding pyridazinones **4d** and **4e** and **2c** gave the aminomaleimide **3c**. The 2,4-dinitrophenyl derivative **2f** was converted to a mixture consisting of the aminomaleimide **3f** and 3-carboxyacryloylhydrazine **1f**. The nmr spectrum of this mixture was identical with the spectrum of a 1:1 mixture of authentic **3f** and **1f**.

Reaction of 3-Carboxyacryloylhydrazines with Sulfuric Acid or Sulfuric–Acetic Acid Mixture.—The various nitrophenyl 3-carboxyacryloylhydrazines were treated according to methods reported by Baloniak.[2] The 3-nitrophenyl- and 4-nitrophenyl-substituted hydrazines **1d** and **1e** formed the corresponding pyridazinones **4d** and **4e**. The 2-nitrophenyl and 2,4-dinitrophenyl derivatives **1c** and **1f** gave the corresponding aminomaleimides **3c** and **3f**.

In the case of **1d** treatment with refluxing acetic acid also produced the corresponding pyridazinone **4d**.

Attempted Rearrangement of Aminomaleimides with Sulfuric Acid or Sulfuric–Acetic Acid. A. Sulfuric Acid.—A 0.5-g sample of the 2-nitro- and a 0.42-g sample of the 4-nitrophenylaminomaleimides were dissolved in 2.5 and 2 ml of concentrated sulfuric acid, respectively. The solutions obtained were added to 10 and 8 ml of distilled water to produce 0.46 and 0.40 g of recovered starting material.

B. Sulfuric–Acetic Acid.—Glacial acetic acid (50 ml) was added to 50 ml of concentrated sulfuric acid and the resulting solution was cooled to room temperature. A 1.64-g sample of 1-(2,4-dinitrophenyl)aminomaleimide was dissolved in the acid mixture and the mixture was stirred for 24 hr. On addition of water a solid (1.30 g) precipitated which was identified as starting material.

Registry No.—**1c**, 39704-29-5; **1d**, 39704-30-8; **1e**, 39704-31-9; **1f**, 31413-88-4; **2a**, 6903-87-3; **2b**, 30986-27-7; **2c**, 39704-35-3; **2d**, 39838-39-6; **2e**, 39704-36-4; **2f**, 31413-91-9; **3c**, 14938-99-9; **3e**, 20970-39-2; **3f**, 20970-35-8; **4d**, 39704-40-0; **4e**, 39704-41-1.

Acknowledgment.—We are indebted to Mr. Michael Wuerthele of Scott Graphics Inc., Holyoke, Mass., for the microanalyses.

Rates of Intramolecular Diels–Alder Reactions of Pentadienylacrylamides

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Among the substrates derived from 4,5-diphenylpentadienylamines **4**, prepared for a study of the intramolecular Diels–Alder reaction, the highly reactive N–CH_3 amide of fumaric acid ethyl ester **7a** directly produces the endo cycloadduct **8a** at 0°, whereas the *N*-demethyl derivative **7b** is far less reactive. The N–CH_3 cinnamamide **9** and *N*-allylamine **11** give predominantly the cycloadducts *trans*-**10** at 90° and *cis*-**12** at 140°, respectively, while the acrylamide **13a** produces an equal mixture of *trans–cis*-**14a**. The structures and relative configurations of the cycloadducts are discussed and elaborated. The kinetic parameters for the intramolecular cycloadditions of **13a–d** reveal that $\Delta G^{\ddagger}$ decreases from 28.7 kcal/mol for **13a** by increments of $\Delta\Delta G^{\ddagger} \cong 1.2$ kcal/mol for the homologs **13b** and **13c** to 25.3 kcal/mol for **13d**. This phenomenon is discussed in terms of a conformational equilibrium on part of the substrate, as evinced by nmr studies.

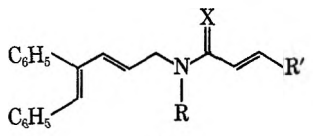
The marked rate-increasing or -decreasing effects of alkyl substituents in the [4 + 2] cycloaddition of dienes with dienophiles has been observed in numerous cases and is well documented.[1–3] The reactivity of a diene increases if appropriate alkyl substituents, such as in the 2 and 3 positions of butadiene, move the conformational equilibrium to the s-cis form, the prerequisite diene conformation for the Diels–Alder reaction. Conversely, bulky substituents at the dienophile generally have a rate-decreasing effect. The present study of the intramolecular Diels–Alder reaction with amides of α,β-unsaturated acids reveals still another phenomenon: the rate-accelerating influence of a bulky substituent attached neither to the diene nor to the dienophile component but to an atom linking the two together.

(1) S. Seltzer in "Advances in Alicyclic Chemistry," Vol. 2, Academic Press, New York, N. Y., 1968, pp 17–32.

(2) R. Huisgen, R. Grashey, and J. Sauer in "The Chemistry of Alkenes," S. Patai, Ed., Wiley-Interscience, New York, N. Y., 1964, pp 878–929.

(3) J. G. Martin and R. K. Hill, *Chem. Rev.*, **61**, 537 (1961).

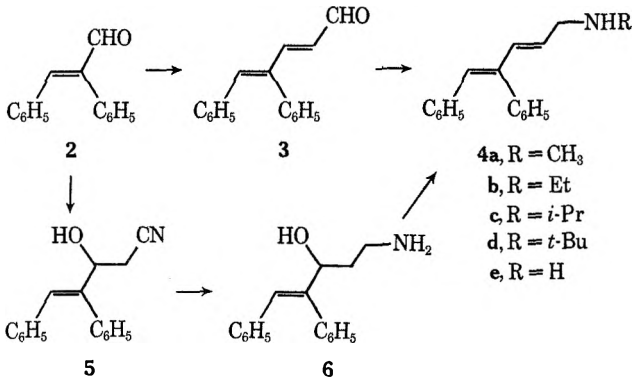
Synthesis of Substrates.—For various reasons the acrylamides 1 were chosen as substrates for this study



1

of the intramolecular [4 + 2] cycloaddition. The initial goal then was the preparation of the parent 4,5-diphenyl-2,4-pentadienylamines in which the size of R would be varied from H to *t*-Bu. The synthesis of these amines **4** is outlined in Scheme I.

SCHEME I



α-Phenylcinnamaldehyde (**2**) was readily obtained according to methods described previously.[4] The cis arrangement of the two phenyl groups was confirmed by the uv data of the known[5] α-phenylcinnamyl alcohol obtained by $LiAlH_4$ reduction of **2**. Homologization to the aldehyde **3** is most cleanly accomplished *via* the directed aldol condensation[6a,b] of **2** with the lithiated cyclohexylimine of acetaldehyde and subsequent hydrolysis and dehydration. The trans stereochemistry of the newly introduced double bond is secured by the nmr data: the vinylic proton next to the aldehyde function, appearing at δ 5.78 ppm, exhibits the large trans coupling constant of 15.5 Hz in addition to the 8-Hz coupling with the aldehydic proton. Formation of the appropriate imines[7] and subsequent reduction with $NaBH_4$ gave access to the desired amines **4**, which were characterized as their hydrochloride salts. Their uv spectra are most characteristic and show absorption maxima at 206 nm (log ε 4.38), 224 (4.13), 232 (4.08), 288 (4.49), and 308 (4.26). In order to confirm the assumption that the cis relationship of the two phenyl groups was retained during the steps **2** → **4**, one of which involved the intermediacy of an allylic carbonium ion, the disubstituted double bond of **4c** was cleanly and selectively reduced with $(Ph_3P)_3RhCl$–H_2. The uv data of the dihydro product [257 nm (log ε 4.03)] are clearly in good agreement with the *cis*-stilbene chromophore. The primary amine **4e** was accessible *via* the alternate route outlined in Scheme I. Condensation of **2** with α-lithioacetonitrile[8] afforded a good yield of the hydroxy nitrile **5**, which after $LiAlH_4$ reduction and acid-catalyzed dehydration of the crystalline amino alcohol **6** produced the well-identified primary amine **4e**.

The next step toward a substrate **1** consisted in linking the amines **4** with an appropriate dienophile moiety. We were in fact looking for a substrate **1** which would meet the following criteria for a kinetic study: (a) solubility in a nonpolar solvent suitable for uv measurements; (b) crystalline, easily purified compounds; (c) undergo the intramolecular [4 + 2] cycloaddition in a practical temperature range, such as 25–150°. Scheme II outlines the substrates actually prepared by acylation or alkylation of the corresponding amines **4**.

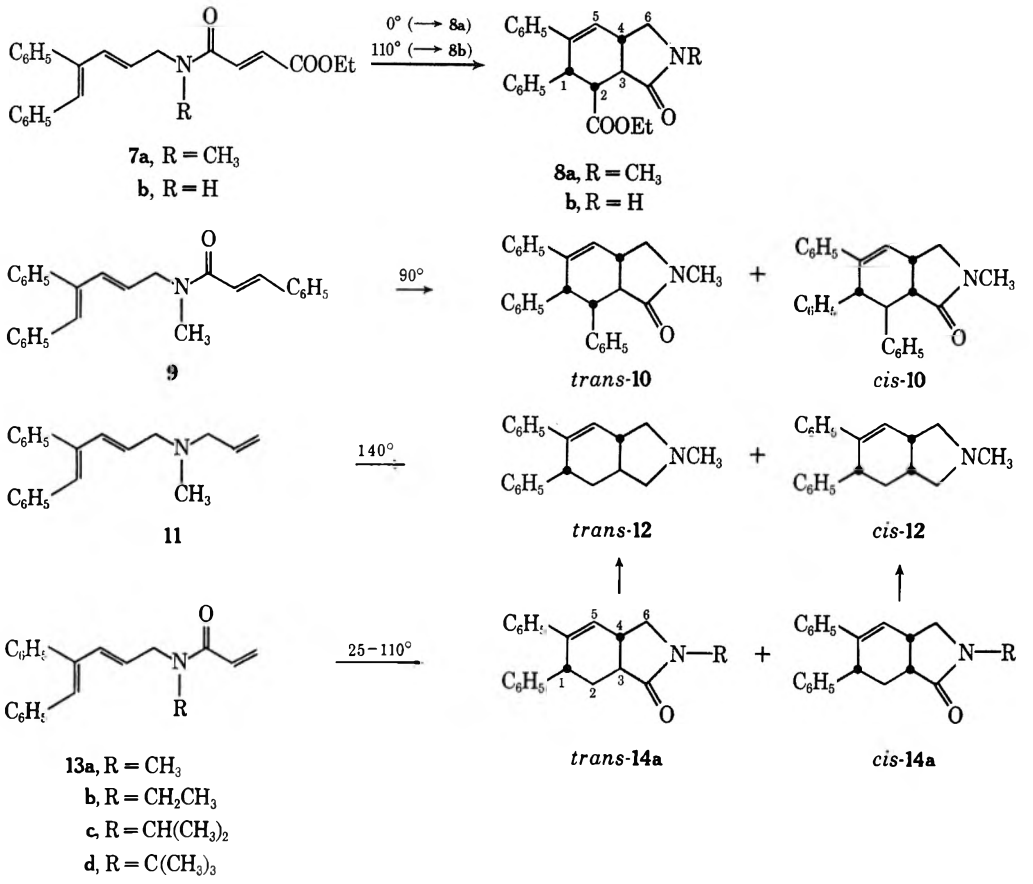
As we have experienced with other examples,[9,10] the intermediate amide **7a** of fumaric acid ethyl ester was far too reactive and could not be isolated. Instead, the product of an endo addition **8a** was isolated directly in 63% yield. In sharp contrast to **7a**, which undergoes the cycloaddition at 0° or below, the demethylamide **7b** could be isolated without difficulty. Intramolecular cycloaddition occurs only above 100° to produce **8b** in 58% yield. The respective structures and the relative configurational relationships of the four asymmetric centers of these two adducts are firmly supported by the analytical and spectral data. Both cycloadducts **8a** and **8b** exhibit the styrene chromophore at 242 nm (log ε 4.06). The ir carbonyl frequencies for ester and γ-lactam are at 1718 and 1686 (**8a**) and at 1713 and 1664 cm^{-1} (**8b**), respectively. A 100-MHz nmr spectrum with double-resonance experiments permitted the assignment of all the important protons in **8a**. With the cis arrangement of phenyl and carboethoxy group, the ester protons are heavily shielded by the aromatic ring current and appear at 0.90 and 3.75 ppm (ABX_3 system owing to hindered rotation). The benzylic hydrogen at 4.57 ppm is coupled to H_2 (3.22 ppm) with J = 7 Hz. The latter, forming nearly a 180° angle with H_3 (2.8 ppm), exhibits the large trans-diaxial coupling of 13 Hz. The N–CH_3 group appears normal at 2.9 ppm and the adjacent CH_2 protons (H_6) as a multiplet at 3.4 ppm. The vinylic proton H_5 at δ 6.26 forms approximately a 90° angle with H_4 (2.82 ppm) and is virtually uncoupled. The signal does sharpen somewhat by irradiating at the frequency of the benzylic proton (H_1).

The cinnamamide **9**, incorporating a less powerful dienophile, was isolated in crystalline form and with an approximate half-life of 2 hr underwent cycloaddition at 90° to a 8:1 mixture of the endo and exo adducts **10** separable by preparative tlc.

The isolated and unactivated double bond, representing the least reactive dienophile available, was tested by preparing the *N*-allylamine **11**. The free base, isolated and characterized as its hydrochloride salt, was in fact amenable to a [4 + 2] cycloaddition under relatively mild conditions. After 12 hr at 140° the product mixture consisted, according to nmr and glc analysis, of 84% *cis*-**12** and 16% *trans*-**12** identical

(4) K. Alder, J. Haydn, K. Heimbach, and K. Neufang, *Justus Liebigs Ann. Chem.*, **586**, 128 (1954).
(5) J. H. Brewster and H. O. Baya, *J. Org. Chem.*, **29**, 105 (1964).
(6) (a) G. Wittig and H. Reiff, *Angew. Chem.*, **80**, 8 (1968); (b) G. Wittig and P. Suchanek, *Tetrahedron, Suppl. 8*, Part I, 347 (1966).
(7) E. M. Kosower and T. S. Sorensen, *J. Org. Chem.*, **28**, 692 (1963).
(8) E. M. Kaiser and C. R. Hauser, *J. Org. Chem.*, **33**, 3402 (1968).
(9) H. W. Gschwend and H. P. Meier, *Angew. Chem., Int. Ed. Engl.*, **11**, 294 (1972).
(10) H. W. Gschwend, *Helv. Chim. Acta*, in preparation.

SCHEME II



spectroscopically with the reduction products obtained from *cis–trans*-**14** (see below).

The most convenient substrates, meeting all our criteria for a kinetic study, were found to be the acrylamides **13**. The amides **13a–d** were all obtained in crystalline form *via* standard procedures. The intramolecular cycloaddition was carried out preparatively in the case of **13a**. Upon refluxing a solution of the amide for 8 hr in toluene and subsequent separation of the product mixture, 42% *trans*-**14a**, 40% *cis*-**14**, and 8% unreacted starting material were isolated. The assignment of the relative configurations at C_3–C_4 is based partly on the observation that base-catalyzed isomerization of a 1:1 mixture of *cis–trans*-**14a** leads to an enrichment of the cis component, which is considered to be the thermodynamically more stable isomer. More significant, however, are the nmr data. In *cis*-**14a** the coupling constant of 5.5 Hz between H_1 and both methylene protons at C_2 suggests an axial position of the phenyl group at C_1. An axial phenyl ring would be expected to exert a shielding effect on the N–CH_3 group, which indeed appears shifted by 0.2 ppm to higher field in comparison to *trans*-**14a** the trans fused lactam. Additionally, the coupling constant of 4 Hz between H_5 and H_4 reflects a dihedral angle of 20–30°, whereas in *trans*-**14a** the angle is closer to 90° and the coupling very small (1.5 Hz). The spectrum of *trans*-**14a** is very similar to the one of **8a**, also assigned the trans ring fusion (*cf.* Figure 1).

Kinetics.—The characteristic uv spectra of the substrates **13a–d** with a maximal extinction coefficient in the 290-nm area, an absorption which is absent in the products, made it possible to monitor the course of the cycloaddition by uv spectroscopic measurements of the concentration of the starting material. Another feasible, though less accurate, method was the nmr spectroscopic following of the reaction, which, however, was used only for a rough determination of the most convenient reaction temperature as well as for an estimation of the trans:cis product ratio. All kinetic measurements were carried out at uv concentrations in decahydronaphthalene (6×10^{-5} *M*, approximately corresponding to infinite dilution) and the samples (7–13 per run) were analyzed without further dilution. The data points which were collected up to 80% conversion were analyzed by a simple linear regression computer program for the determination of first-order rate constants.[11] The calculated standard deviations of the slope were used as the limits of error for the rate constants. The first-order rate constants k determined by this method clearly include both k_{trans} and k_{cis}, since both possible products *trans–cis*-**14a–d** were formed during the cycloaddition. As determined by nmr integration of the product mixture, k_{trans} was nearly equal to k_{cis} for all four substrates **13a–d**. The activation parameters were determined by the least-squares method using standard computer programs.[12] The limits of error include both the maximal deviations in the rate constants and temperature. Table I records the data.

Discussion

A qualitative comparison of the results of the intramolecular [4 + 2] cycloaddition of the substrates **7a**

(11) A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," 2nd ed, Wiley, New York, N. Y., 1961.

(12) ACTENG, written by D. F. deTar, Department of Chemistry, Florida State University.

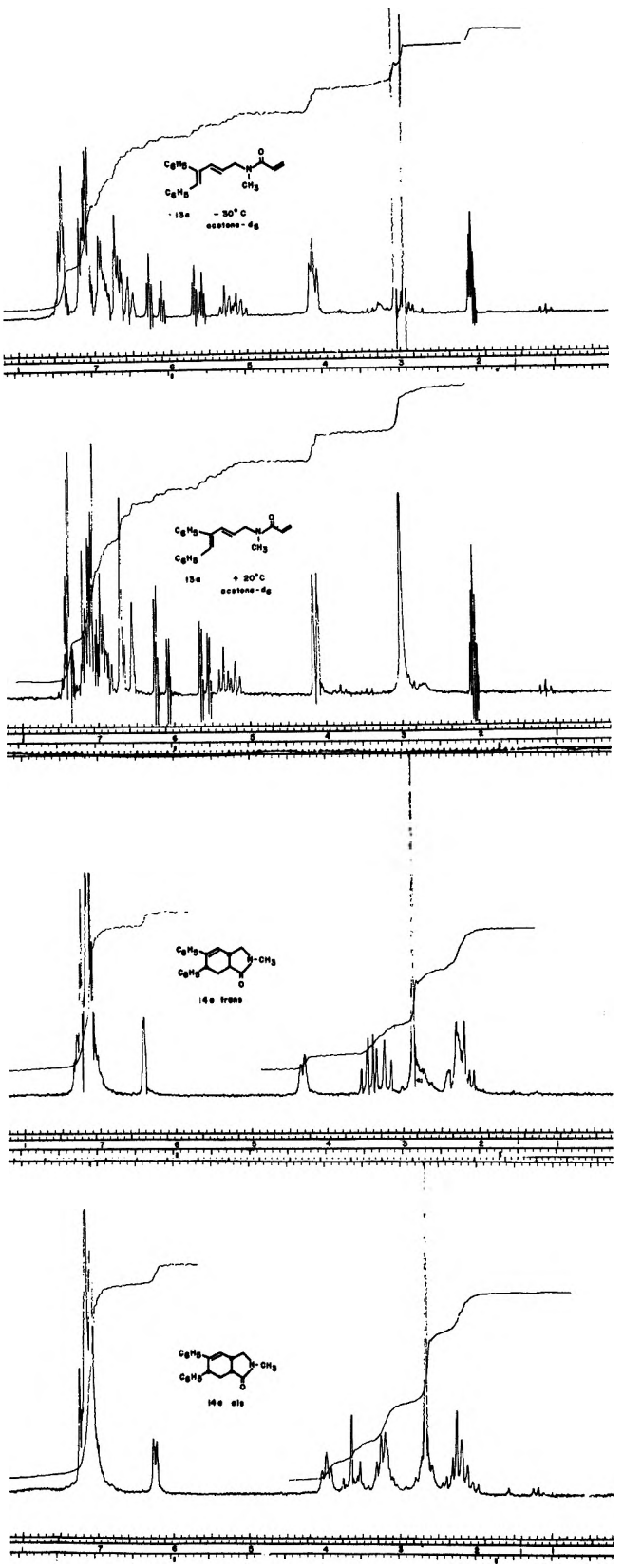


Figure 1.—Nmr spectra (100 MHz) of **13a** in acetone-d_6 and of *trans*-**14a** and *cis*-**14a** in $CDCl_3$.

and **9** with those described earlier[9,10] reveals surprisingly that the additional phenyl substituent in the 4 position of the pentadienylamine moiety did not affect the rate of the reaction in any dramatic way. A quite remarkable effect, however, on the rate of cycloaddition is noticed by replacing the $N-CH_3$ group with a hydrogen. Aside from the influence on the gross conformational equilibrium of the substrate exerted by size of the N substituent, as outlined below, intermolecular hydrogen bonding in nonpolar solvents in the case of **7b** would, relative to **7a**, not only alter the electronic properties of the dienophile part of the molecule but most certainly also change the conformational situation *via* bimolecular interactions. The possibility of intermolecular H bonding in **7b** is thus considered to be the dominant factor for its markedly decreased reactivity as compared to **7a**. It would be expected that the cycloaddition would be considerably accelerated in a polar solvent, such as DMF.

Intramolecular Diels–Alder reactions, in which isolated nonactivated double bonds add to the highly reactive, substituted cyclopentadienes and *o*-quinodimethanes, have been reported previously.[13,14] More recently it was observed[15] that *N*-allylamines undergo an intramolecular cycloaddition to an endocyclic cis–cis butadiene system, although the temperatures required were rather high (180°) and the yields of cycloadducts low. It was therefore surprising and remarkable that the cycloaddition of the *N*-allylamine **11**, in which the diene moiety has a trans–trans geometry and is not particularly activated, proceeds under relatively mild conditions. It is also of interest to note that in the absence of a terminal π system, which otherwise stabilizes a transition state leading to the trans-fused cycloadducts, such as in **7a** or **9**, the cis-fused product is favored by a respectable margin, namely, 84:16. This observation parallels the results of Oppolzer in the cycloadditions of *o*-quinodimethanes.[14a,b] The transition from an *N*-allyl to an *N*-acryloyl system (**13a–d**) leads only to a modest increase in reactivity. This is rationalized by the fact that in the transition state of **13a** → **14a** the terminal double bond can no longer assume coplanarity with the amide carbonyl, thus losing some of the reactivity of an α,β-unsaturated double bond system. Again, in the absence of a terminal π system the trans-fused product is not favored and the cis:trans ratio remains through all the products **14a–d** virtually the same, namely, approximately unity. The kinetic measurements for the cycloadditions of **13a–d** (Table I) clearly indicate that the free energy of activation ($\Delta G^{\pm}$) decreases with increasing size of the N substituent. In the four examples studied, namely, methyl, ethyl, isopropyl, and *tert*-butyl, the average decrease in $\Delta G^{\pm}$ ($\Delta\Delta G^{\pm}$) is 1.2 kcal/mol. Although the size of the respective $\Delta\Delta G^{\pm}$'s is not very large, it is nevertheless significant, but quite definitely of a different order of magnitude than the probable, yet not actually determined, $\Delta\Delta G^{\pm}$ between **7a** and **7b** ($N-CH_3$ *vs.* N–H). The values of approximately 1.2 kcal/mol happen to be very close to the differences in the inversion barriers of N-substituted aziridines ($N-CH_3$ to N–Et, $\Delta\Delta G^{\pm}$ = 1.4 kcal/mol).[16]

(13) (a) G. Brieger, *J. Amer. Chem. Soc.*, **85**, 3783 (1963); (b) E. T. McBee, J. O. Stoffer, and H. P. Braendlin, *J. Amer. Chem. Soc.*, **84**, 4540 (1962).

(14) (a) W. Oppolzer, *J. Amer. Chem. Soc.*, **93**, 3833, 3834, 3836 (1971); (b) W. Oppolzer, 13th Medicinal Chemistry Symposium, Iowa City, Iowa, June 18–22, 1972.

(15) A. L. Johnson and H. E. Simmons, *J. Org. Chem.*, **34**, 1140 (1969).

(16) (a) J. B. Lambert and W. L. Oliver, *J. Amer. Chem. Soc.*, **91**, 7774 (1969); (b) J. M. Lehn and J. Wagner, *Chem. Commun.*, 148 (1968); (c) A. Loewenstein, J. F. Neumer, and J. D. Roberts, *J. Amer. Chem. Soc.*, **82**, 3599 (1960); (d) A. T. Bottini and J. D. Roberts, *ibid.*, **90**, 5203 (1968); (e) S. L. Brois, *ibid.*, **89**, 4242 (1967).

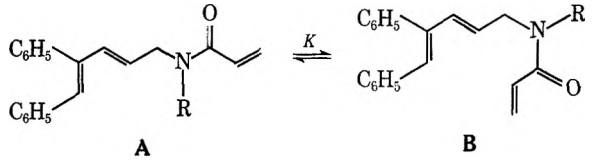
TABLE I
KINETIC DATA FOR THE INTRAMOLECULAR CYCLOADDITIONS

13a–d ⟶ *cis–trans*-**14a–d**

Compd	Temp, °C (±0.1)	Rate constant $K = k_{trans} + k_{cis} \times 10^{-5}$, sec^{-1}	Activation parameters $\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, cal/°K mol	$\Delta G^{\ddagger}_{298}$, kcal/mol
	90.2	1.2275 ± 0.0147			
13a	96.9	2.3797 ± 0.0141	24.7 ± 0.3	−13.4 ± 0.7	28.7 ± 0.5
	101.6	3.5570 ± 0.0211			
	109.4	7.3025 ± 0.0857			
	90.0	2.1003 ± 0.0147			
13b	96.9	3.8192 ± 0.0264	22.2 ± 0.6	−19.2 ± 1.5	27.9 ± 1.0
	101.6	5.4197 ± 0.0672			
	109.4	10.9470 ± 0.2551			
	69.4	1.7056 ± 0.0142			
13c	76.0	3.1147 ± 0.0090	20.4 ± 0.4	−21.2 ± 1.0	26.7 ± 0.7
	82.3	5.2758 ± 0.0670			
	90.0	9.8378 ± 0.1781			
	34.0	0.5233 ± 0.0051			
13d	45.2	1.8986 ± 0.0127	21.0 ± 0.1	−14.4 ± 0.3	25.3 ± 0.2
	52.0	3.8217 ± 0.0248			
	60.7	8.9581 ± 0.0636			

It seems appealing to explain this phenomenon in terms of the conformational differences among the four substrates **13a–d**. Since both diene and dienophile moieties are part of the same substrate undergoing an intramolecular Diels–Alder reaction, a new conformational equilibrium becomes a codeterminant factor. In addition to the prerequisite s-cis conformation of the diene part, the rate of cycloaddition depends upon the population of the one conformer in which the spatial relationship of the four reaction centers starts to resemble the geometry of the transition state. Thus, the conformational equilibrium of the least reactive N–CH_3 amide **13a** would appear to be almost exclusively on the side of the "stretched" or linear conformer A (Scheme III), whereas the reactive **13d**, the other extreme, would virtually be frozen as the bent conformer B.

SCHEME III



A B

Nmr spectroscopy provides a practical tool to determine conformational equilibria, which in this particular case seem to be determined essentially by the energy barrier to rotation around the amide bond. However, the known dependence of such measurements upon concentration and in particular the solvent[17] made it rather difficult if not impossible to correlate the kinetic data (infinite dilution, in decahydronaphthalene) with any nmr data. A series of nmr studies (in acetone-d_6) revealed that **13d** was exclusively one conformer (B) between −30 and 20° (at higher temperatures cycloaddition occurs). At −30° the other three substrates (**13a–c**) exhibited the sharp and distinctly different signals of two conformers in the ratios of 1:1 (**13a**) (see Figure 1), 3:2 (**13b**), and 1:2 (**13c**). Between 0 and 10° the signals coalesce and appear sharp at 20°. The established presence of such a conformation equilibrium makes the meaning of the calculated activation parameters somewhat questionable. The first-order rate constants for the formation of the products may actually be composite: $dP/dt = k'R$ with $k' = kK(1 + K)$.[18] The conformational equilibrium between forms A and B is described by the constant K, and k' would be the rate constant for the disappearance of the reactive conformer B. Thus, only with extreme K values (very small or large) would a standard transition-state theory plot produce accurate activation parameters. Since **13d** appears to exist almost exclusively as the reactive conformer B (K large) as evinced in the nmr studies, the rather crude (solvent difference) correlation of this fact with the measurements of the rate constants seems to indicate that the activation parameters for **13d** are probably the most meaningful ones. The calculated values for the entropies and enthalpies of activation for the other congeners, in particular though for **13b** and **13c**, are likely to be less reliable.

(17) (a) J. V. Hatton and W. G. Schneider, *Can. J. Chem.*, **40**, 1285 (1963); M. L. Blanchard, A. Chevallier, and G. J. Martin, *Tetrahedron Lett.*, 5057 (1967). (c) R. C. Newmann, Jr., and L. B. Young, *J. Phys. Chem.*, **69**, 2570 (1965).

Experimental Section

The physical data were obtained as follows: melting points in a Thomas-Hoover melting point apparatus (uncorrected); ir spectra on a Perkin-Elmer 521; uv curves on a Cary Model 14; mass spectra on a AEI MS 902 by direct insertion; nmr spectra on either a Varian A-60 or a XL-100 using tetramethylsilane as internal standard. The following abbreviations are used: b, broad; w, weak; sh, shoulder; ex, exchangeable with D_2O; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

4,5-Diphenyl-2,4-pentadienal (3).—To a solution of 36.5 ml of diisopropylamine in 260 ml of dry ether was added 162 ml 1.6 *M* BuLi–hexane, the temperature being kept below −10°. Then 32.4 g (259 mmol) of cyclohexylacetaldimine in 260 ml of ether was added dropwise. After 15 min the temperature was lowered to −70° and a solution of the aldehyde **2** (45 g, 216 mmol) in 1.2 l. of ether was added dropwise. After the addition the temperature was raised to 20°, then again lowered to −10°, and 450 ml of water was added. The ethereal layer was then separated and stirred for 16 hr vigorously with 300 ml of benzene, 108 ml of AcOH, and 270 ml of H_2O. The organic layer was again separated and washed with dilute H_2SO_4, ice water, dilute NaOH, and finally brine. After drying the sol-

(18) Suggestion of a referee of this paper.

vent and evaporation, the residue (49 g) was crystallized from EtOH to give 32.2 g of **3**, mp 92–94°, and a second and third crop of 9.4 g, mp 85–92° (83%): ir (Nujol) 1675, 760, 710, 690 cm^{-1}; uv (CH_3OH) 228 mμ (ε 10,500), 236 (10,900), 326 (39,400); nmr ($CDCl_3$) δ 5.78 (q, J = 15.5 and 8 Hz, 1 H), 6.7–7.6 (m, 12 H), 9.65 (d, J = 8 Hz, 1 H).

Anal. Calcd for $C_{17}H_{14}O$: C, 87.15; H, 6.02. Found: C, 87.12; H, 6.21.

N-(4,5-Diphenyl-2,4-pentadienyl)-N-methylamine (4a).—The aldehyde **3**, 23.1 g (99 mmol), was stirred together with 53 g of Na_2SO_4 in 230 ml of 1.73 N CH_3NH_2–benzene for 4 hr at room temperature. The heterogenous mixture was then filtered and the benzene was evaporated to give 25 g of crude methylimine. This imine was dissolved in 415 ml of ethanol and cooled to 0° and 5.8 g of $NaBH_4$ was added. After an additional 1 hr at room temperature, the ethanol was evaporated *in vacuo*, the residue was made acidic with 5 N aqueous HCl, then made basic with 30% NaOH, and the amine was extracted into CH_2Cl_2. After drying over Na_2SO_4 and removal of the solvent, 25.9 g of crude product was obtained. This was dissolved in ethanol and 1 molar equiv of ethereal HCl was added. A total of 19.7 g of hydrochloride was thus collected: mp 154–158° (70%); ir (Nujol) 760, 700 cm^{-1} (broad); uv (CH_3OH) 207 mμ (ε 19,300), 224 (12,300), 232 (11,900), 288 (27,800); on free base nmr ($CDCl_3$) δ 1.08 (s, ex, 1 H), 2.37 (s, 3 H), 3.24 (d, J = 6.5 Hz, 2 H), 5.4 (td, J = 6.5, 16 Hz, 1 H), 6.56 (s, 1 H), 6.58 (d, J = 16 Hz, 1 H), 6.7–7.5 (m, 10 H).

Anal. Calcd for $C_{18}H_{19}N \cdot HCl$: C, 75.64; H, 7.05; N, 4.90. Found: C, 75.48; H, 7.13; N, 5.20.

N-(4,5-Diphenyl-2,4-pentadienyl)-N-ethylamine (4b).—From 2 g of aldehyde **3** was obtained 2.28 g of imine by following the above procedure. This was reduced as described for **4a** to give 2.2 g of crude amine. From ethanol a total of 2.1 g of hydrochloride salt was collected: mp 154–156° (80%); ir (Nujol) 980, 760, 700, 690 cm^{-1}; uv (CH_3OH) 207 mμ (ε 23,400), 233 (12,100), 288 (30,800), 308 (18,000).

Anal. Calcd for $C_{19}H_{21}N \cdot HCl$: C, 76.11; H, 7.40; N, 4.67. Found: C, 76.33; H, 7.64; N, 4.66.

N-(4,5-Diphenyl-2,4-pentadienyl)-N-isopropylamine (4c).—From 2 g (8.6 mmol) of aldehyde **3** and 19.2 ml of 1.8 N isopropylamine in benzene one obtained, after a reaction of 20 hr at room temperature, 2.4 g of crude imine. Reduction with $NaBH_4$ for 2 hr and work-up as outlined for **4a** produced 2.3 g of crude amine. From ethanol a total of 2.17 g of hydrochloride salt was collected: mp 192–193° (80%); ir (Nujol) 980, 750, 700, 680 cm^{-1}; uv (CH_3OH) 232 mμ (ε 13,000), 288 (31,360), 308 (18,200).

Anal. Calcd for $C_{20}H_{23}N \cdot HCl$: C, 76.53; H, 7.70; N, 4.46. Found: C, 76.57; H, 7.63; N, 4.50.

N-tert-Butyl-N-4,5-diphenyl-2,4-pentadienylamine (4d).—The aldehyde **3** (2.0 g, 8.6 mmol) was stirred with 29 ml of 1.8 M t-$BuNH_2$–benzene for 44 hr. The crude product, 2.5 g, was reduced as described above to give 2.5 g of crude amine. From hexane, 1.1 g of crystalline **4a** was obtained, mp 98°. To the mother liquor in ethanol was added ethereal HCl and an additional 1.16 g of hydrochloride salt was collected, mp 196–198° (total yield 78%). The analytical data were obtained on the free base: ir (Nujol) 970, 750, 700, 688 cm^{-1}; uv (CH_3OH) 206 mμ (ε 24,970), 224 (13,400), 232 (12,100), 288 (31,200), 308 (18,000).

Anal. Calcd for $C_{21}H_{25}N$: C, 86.55; H, 8.65; N, 4.81. Found: C, 86.78; H, 8.85; N, 4.67.

4,5-Diphenyl-2,4-pentadienylamine (4e) (2 → 5 → 6 → 4e).—In a three-necked flask 16.5 ml of 1.6 M BuLi in hexane was cooled to −75° under a N_2 atmosphere. Then 16.5 ml of dry THF was added all at once and immediately thereafter a solution of 980 mg of CH_3CN in 24 ml of THF over 5 min. Stirring was continued for 1 hr at −70° and then a solution of 5 g (24 mmol) of aldehyde **2** was added. The cold bath was removed, stirring was continued for 1 hr and then ice and dilute HCl were added. The organic layer was diluted with ether. After drying the organic part over Na_2SO_4 and removal of the solvent, a solid residue of 6 g was obtained (**5**). This material was dissolved in 350 ml of ether and carefully added to a cold suspension of 1.5 g of $LiAlH_4$ in 90 ml of ether. After stirring at room temperature for 16 hr, excess hydride was destroyed by the addition of 1.5 ml of H_2O, 1.5 ml of 15% NaOH, and 4.5 ml of H_2O. The mixture was filtered and the filtrate was evaporated to give a residue of 5.6 g. Crystallization from ether gave a total of 3.6 g of hydroxyamine **6**: mp 114–116° (60% overall); ir (Nujol) 3350, 3290, 700, 690 cm^{-1}; uv (CH_3OH) 217–224 mμ (ε 15,400), 255 (13,500).

Anal. Calcd for $C_{17}H_{19}NO$: C, 80.57; H, 7.56; N, 5.53. Found: C, 80.20; H, 7.68; N, 5.65.

The hydroxy amine **6** (15.5 g, 61.3 mmol) was refluxed in 150 ml of dioxane and 460 ml of 2 N H_2SO_4 for 5 hr. The mixture was cooled, made basic with 30% NaOH, and extracted into $CHCl_3$. After drying over Na_2SO_4 and removal of the solvent, the residue weighed 14.8 g. From ethanol and an equivalent amount of ethereal HCl 11.4 g of the hydrochloride salt of **4e** was obtained: mp 212°; ir (Nujol) 1610, 1660, 1510, 790, 705, 690 cm^{-1}; uv (CH_3OH) 224 mμ (ε 12,400), 232 (11,240), 287 (28,000), 308 (17,000).

Anal. Calcd for $C_{17}H_{17}N \cdot HCl$: C, 75.13; H, 6.68; N, 5.15. Found: C, 75.22; H, 6.89; N, 4.95.

Ethyl 5,6-Diphenyl-2-methyl-3-oxo-4,5,3a,7a-tetrahydroisoindoline-4-carboxylate [4a → (7a) → 8a].—A solution of 11.1 g (44.7 mmol) of **4a** (free base) in 450 ml of CH_2Cl_2 was stirred in an ice bath. Then 4.4 ml of pyridine and a solution of 7.7 g of fumaric acid chloride ethyl ester in 90 ml of CH_2Cl_2 were added. The mixture was stirred at 25° overnight. The dark solution was subsequently washed with a cold Na_2CO_3 solution and dried over Na_2SO_4. After evaporation of the solvent, the residue of 17 g was crystallized from benzene to give a first crop of 7.9 g of **8a**, mp 247–251°, and a second crop of 2.5 g, mp 230–240° (63% yield): ir (Nujol) 1718, 1686 cm^{-1}; uv (CH_3OH) 242 mμ (ε 11,450); nmr ($CDCl_3$, 100 MHz) δ 0.86 (t, J = 7 Hz, 3 H), 2.82 (m, 2 H), 2.85 (s, 3 H), 3.22 (J = 12 and 7 Hz, 1 H), 3.0–4.0 (m, 3 H), 4.57 (d, J = 7 Hz, 1 H), 6.26 (s, 1 H), 7.0–7.3 (m, 10 H).

Anal. Calcd for $C_{24}H_{25}NO_3$: C, 76.77; H, 6.71; N, 3.73. Found: C, 76.90; H, 6.72; N, 3.84.

Ethyl N-(4,5-diphenyl-2,4-pentadienyl)fumaramate (7b).—From 9.7 g (41.3 mmol) of amine **4e** was obtained, in the same manner as outlined for **7a**, 14.7 g of crude amide **7b**. This crude material (700 mg) was crystallized from ether to give 200 mg: mp 87–89°; ir (Nujol) 1713, 1664, 1644, 1632, 1556 cm^{-1}; uv (CH_3OH) 208 mμ (ε 38,300), 224 (27,100), 288 (36,000), 308 (21,600); nmr ($CDCl_3$) δ 1.23 (t, J = 7 Hz, 3 H), 4.2 (q, J = 7 Hz, 2 H), 4.0 (dd, $J \cong$ Hz, 2 H), 5.25 (t d, J = 6, 16 Hz, 1 H), 6.52 (s, 1 H), 6.55 (d, J = 16 Hz, 1 H), 6.7–7.5 (11 H).

Anal. Calcd for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88. Found: C, 76.81; H, 6.54; N, 4.17.

Ethyl 5,6-Diphenyl-3-oxo-4,5,3a,7a-tetrahydroisoindoline-4-carboxylate (8b).—The crude amide **7b** (14.5 g) was refluxed in 700 ml of benzene for 5 hr. After cooling, the precipitated product was filtered off (8.5 g, 58%): mp 200–207°; ir (Nujol) 3200, 3100, 1725, 1700 cm^{-1}; uv (CH_3OH) 242 mμ (ε 11,300).

Anal. Calcd for $C_{23}H_{23}NO_3$: C, 76.43; H, 6.41; N, 3.88. Found: C, 76.45; H, 6.46; N, 3.82.

N-(4,5-Diphenyl-2,4-pentadienyl)-N-methylcinnamamide (9).—To an ice-cold solution of 1.1 g (4.4 mmol) of amine **4a** and 0.44 ml of pyridine in 50 ml of CH_2Cl_2 was added a solution of 0.78 g of cinnamoyl chloride in 10 ml of CH_2Cl_2. After 2 hr the mixture was washed with cold dilute HCl and dilute Na_2CO_3 and dried. After evaporation of the solvent the residue (1.8 g) was crystallized from ether to give 1.1 g of **9**, mp 118°, and a second crop of 400 mg, mp 105–115° (84%): ir (Nujol) 1638, 1598 cm^{-1}; uv (CH_3OH) 213 mμ (ε 27,100), 223 (24,200), 290 (47,900); nmr ($CDCl_3$) δ 3.05 (s, 3 H), 4.13 (d, broad, J = 5.5 Hz 2 H), 5.3 (six lines, J = 5.5 and 15.5 Hz, 1 H), 6.4–7.6 (m, 18 H), 7.75 (d, J = 15.5 Hz, 1 H).

Anal. Calcd for $C_{27}H_{25}NO$: C, 85.45; H, 6.64; N, 3.69. Found: C, 85.65; H, 6.88; N, 3.63.

N-Allyl-N-methyl-4,5-diphenyl-2,4-pentadienylamine (11).—A solution of 2.38 g (9.5 mmol) of amine **4a** in 100 ml of dry ether was cooled to −40° and (under N_2) 7.16 ml of BuLi–hexane was added, followed by 1.5 g (12.4 mmol) of allyl bromide in 20 ml of ether. The mixture was warmed to 25° and stirred at that temperature for 16 hr. Water was added, and the ether was separated, dried over Na_2SO_4, and evaporated. The residue of 2.47 g, containing, according to nmr, some starting material, was acylated with AcCl under Schotten–Baumann conditions. The basic material was then extracted into dilute HCl, the aqueous layer was separated, and the pH was adjusted to 11. Extraction with ether gave a residue of 1.5 g. From acetone 1.1 g of hydrochloride salt was obtained: mp 138–141° [recrystallization from acetone raised the melting point to 149–151° (300 mg)]: uv (CH_3OH) 222 mμ (ε 14,100), 232 (13,000), 289 (32,300), 306 (21,000).

Anal. Calcd for $C_{21}H_{23}N \cdot HCl$: C, 77.40; H, 7.42; N, 4.30. Found: C, 77.66; H, 7.54; N, 4.41.

Intramolecular Cycloaddition of 11 → *trans*-12 + *cis*-12.—A solution of 170 mg of **11** (free base) in 0.37 ml of C_6D_6 was heated in a sealed nmr tube at 140–142° and the reaction was monitored nmr spectroscopically. Rough estimates indicated that after 3 hr 60–70% and after 12 hr more than 95% of products **12** were formed. Glc analysis revealed a ratio of 84% *cis*-**12** and 16% *trans*-12. The characteristics of the pure compounds **12** are given below.

Preparation of Acrylamides 13a–d.—Generally a solution of the amine (**4a–d**) (2.75 mmol) and 260 mg of pyridine in 12 ml of CH_2Cl_2 was added at 0° to a solution of 300 mg (3.3 mmol) of acryloyl chloride in 40 ml of CH_2Cl_2. After 16 hr at 0–20° (0° for **13c** and **13d**) the CH_2Cl_2 was evaporated, and the residue was taken up in ether and washed with cold dilute HCl, then with Na_2CO_3 solution, and finally with brine. Drying over Na_2SO_4 and removal of the solvent *in vacuo* (temperature <30° for **13c** and **13d**) produced the crude amides, which were recrystallized.

13a had mp 98–101° (from ether); ir (Nujol) 1642, 1606 cm^{-1}; uv (CH_3OH) 224–236 mμ (ϵ 14,900), 288 (32,300), 307 (18,800); nmr, see Figure 1.

Anal. Calcd for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.62. Found: C, 83.14; H, 7.20; N, 4.46.

13b had mp 84–86° (from ether); ir (Nujol) 1643, 1609 cm^{-1}; uv (CH_3OH) 224 mμ (ϵ 15,500), 234 (15,200), 289 (32,100), 308 (18,500).

Anal. Calcd for $C_{22}H_{23}NO$: C, 83.24; H, 7.30; N, 4.41. Found: C, 83.06; H, 6.96; N, 4.58.

13c had mp 112–114° (from ether); ir (Nujol) 1650, 1609 cm^{-1}; uv (CH_3OH) 226 mμ (ϵ 15,700), 234 (15,600), 289 (32,000), 308 (19,200).

Anal. Calcd for $C_{23}H_{25}NO$: C, 83.34; H, 7.60; N, 4.23. Found: C, 83.38; H, 7.34; N, 4.31.

13d had mp 118–119° (from ether); ir (Nujol) 1648, 1607 cm^{-1}; uv (CH_3OH) 224 mμ (ϵ 14,200), 234 (14,100), 289 (30,400), 307 (18,800).

Anal. Calcd for $C_{24}H_{27}NO$: C, 83.44; H, 7.88; N, 4.05. Found: C, 83.74; H, 8.11; N, 3.91.

Intramolecular Cycloaddition of 13a → *trans*-14a + *cis*-14a.—A solution of 470 mg of amide **13a** in 20 ml of toluene was refluxed for 8 hr. Removal of the solvent and preparative tlc separation of the residue (silica gel, AcOEt/$CHCl_3$ 1:4) gave 198 mg of *trans*-**14a** (R_f 0.2, 42%) and 189 mg of *cis*-**14a** (R_f 0.4, 40%) besides 37 mg of starting material (8%) and 70 mg of material remaining at the origin. Crystallization of the main fractions from ether gave 120 mg of *trans*-**14a** and 100 mg of *cis*-**14a** crystalline material.

trans-**14a** had mp 131–133°; ir (Nujol) 1680 cm^{-1} (sh at 1685); uv (CH_3OH) 245 mμ (ϵ 12,100); nmr ($CDCl_3$, 100 MHz) δ 2.0–2.5 (m, 3 H), 2.6–3.0 (m, 1 H), 2.88 (s, 3 H), 3.15–3.6 (m, 2 H), 4.32 (d, J = 5 Hz, 1 H), 6.42 (d, $J \cong 1.5$ Hz, 1 H), 6.9–7.4 (m, 10 H).

Anal. Calcd for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.62. Found: C, 81.71; H, 6.95; N, 4.58 (crystallized with $^1/_3$ mol of ether).

cis-**14a** had mp 127–129°; ir (Nujol) 1672 cm^{-1} (sh at 1677); uv (CH_3OH) 243 mμ (ϵ 12,700); nmr ($CDCl_3$, 100 MHz) δ 2.25 (m, 2 H), 2.68 (s, 3 H), 2.7 (m, 1 H), 3.0–3.8 (m, 2 H), 3.21 (m, 1 H), 3.98 (dd, J = 5.5, 5.5 Hz, 1 H), 6.13 (d, J = 4 Hz, 1 H), 6.9–7.3 (m, 10 H).

Anal. Calcd for $C_{21}H_{21}NO$: C, 83.13; H, 6.98; N, 4.62. Found: C, 83.41; H, 7.22; N, 4.41.

Reduction of *cis*-14a to *cis*-12.—A solution of 350 mg of lactam *cis*-**14a** in 40 ml of ether was refluxed for 4 hr with 90 mg of $LiAlH_4$. Excess reagent was destroyed with 0.09 ml of H_2O, 0.09 ml of 15% NaOH, and 0.27 ml of H_2O. Filtration from the inorganic material and removal of the ether gave a residue of 350 mg which was dissolved in 3 ml of acetone. Upon addition of an equimolar amount of ethereal HCl, 270 mg of the hydrochloride salt, mp 255° (72%), was collected: ir (Nujol) 1490, 777, 755, 700, 690 cm^{-1}; uv (CH_3OH) 241 mμ (ϵ 12,300); nmr ($CDCl_3$) on free base δ 1.4–3.7 (m, 8 H), 2.33 (s, 3 H), 3.95 (m, 1 H), 6.17 (dd, J = 4, 2 Hz, 1 H), 6.9–7.5 (m, 10 H).

Anal. Calcd for $C_{21}H_{23}N \cdot HCl$: C, 77.40; H, 7.42; N, 4.30. Found: C, 77.34; H, 7.46; N, 4.39.

Reduction of *trans*-14a to *trans*-12.—The reduction was carried out analogously to *cis*-**14a** → *cis*-**12**. The product *trans*-**12** was isolated in 53% yield (250 mg from 300 mg of *trans*-**14a**) as the cyclohexylsulfamate salt: mp >115° dec; ir (Nujol) 1490, 760, 745, 695 cm^{-1}; uv (CH_3OH) 243 mμ (ϵ 10,000); nmr ($CDCl_3$) on free base δ 1.7–3.2 (m, 8 H), 2.45 (s, 3 H), 4.27 (m, 1 H), 6.48 (s, W_H = 3 Hz, 1 H), 6.9–7.5 (m, 10 H).

Anal. Calcd for $C_{21}H_{23}N \cdot C_6H_{13}NO_3S$: C, 69.19; H, 7.74; N, 5.97. Found: C, 68.95; H, 7.64; N, 5.67.

Reduction of 4c.—A solution of 310 mg of **4c** (hydrochloride salt) and 20 mg of $(Ph_3P)_3RhCl$ in 5 ml of ethanol was hydrogenated at atmospheric pressure until 1 mmol of H_2 was taken up. After filtration and removal of the solvent, the dihydro derivative was crystallized from ethanol–ether to give 90 mg: mp 154–156°; uv (CH_3OH) 218 mμ (ϵ 14,900), 257 (10,700), 260 (3100); mass spectrum m/e 279 (M^+), 264, 205, 178, 98.

Intramolecular Cycloaddition 9 → 10.—A solution of 67 mg of **9** in 0.42 ml of C_6D_6 was sealed in a nmr tube and heated in an oil bath of 91–92°. The reaction was completed after 6 hr and the product mixture consisted of eight parts trans and one part cis adduct, according to the nmr integrations.

A solution of 800 mg of **9** in 50 ml of toluene was heated in an oil bath at 91° for 9 hr. After removal of the solvent *in vacuo* the solid residue was separated by preparative tlc (silica, $CHCl_3$: AcOEt 4:1) to give 650 mg of *trans*-**10** (81%) and 85 mg of *cis*-**10** (10.6%).

The two compounds were recrystallized for analytical purposes.

trans-**10** (from CH_2Cl_2–ether) had mp 217–219°; ir (Nujol) 1693 cm^{-1}; nmr ($CDCl_3$, 100 MHz) δ 2.80 (s, 3 H), 2.75–3.5 (m, 4 H), 3.62 (dd, J = 6 and 11 Hz, 1 H), 4.25 (d, J = 6 Hz, 1 H), 6.4 (s, 1 H), 6.7 (m, 4 H), 6.8–7.3 (m, 11 H).

Anal. Calcd for $C_{27}H_{25}NO$: C, 85.45; H, 6.64; N, 3.69. Found: C, 85.08; H, 6.84; N, 3.69.

cis-**10** (from CH_2Cl_2–hexane) had mp 168–169°; ir (Nujol) 1703 cm^{-1}; nmr ($CDCl_3$, 100 MHz) δ 2.62 (s, 3 H), 2.81 (d broad, J = 9 Hz, 1 H), 3.3 (m, 2 H), 3.67 (t, J = 9 Hz, 1 H), 3.93 (t, J = 2.5 Hz, 1 H), 4.2 (s broad, 1 H) 6.45 (d, J = 4 Hz, 1 H), 7.0–7.4 (m, 15 H).

Anal. Calcd for $C_{27}H_{25}NO$: C, 85.45; H, 6.64; N, 3.69. Found: C, 85.10; H, 6.77; N, 3.65.

Registry No.—**2**, 1755-47-1; **3**, 39549-82-1; **4a**, 39549-83-2; **4a** HCl, 39549-84-3; **4b**, 39549-85-4; **4b** HCl, 39549-86-5; **4c**, 39549-87-6; **4c** HCl, 39549-88-7; **4c** dihydro derivative, 39549-89-8; **4d**, 39549-90-1; **4d** HCl, 39549-91-2; **4e**, 39549-92-3; **4e** HCl, 39549-93-4; **5**, 39549-94-5; **6**, 39549-95-6; **7b**, 39549-96-7; **8a**, 39549-97-8; **8b**, 39549-98-9; **9**, 39549-99-0; *cis*-**10**, 39550-00-0; *trans*-**10**, 39550-01-1; **11**, 39550-02-0; **11** HCl, 39550-03-3; *cis*-**12** HCl, 39550-04-4; *trans*-**12** cyclohexylsulfamate salt, 39550-05-5; **13a**, 39550-06-6; **13b**, 39550-07-7; **13c**, 39550-08-8; **13d**, 39550-09-9; *trans*-**14a**, 39550-10-2; *cis*-**14a**, 39550-11-3; lithiated cyclohexylimine of acetaldehyde, 39550-12-4; methylamine, 74-89-5; ethylamine, 75-04-7; isopropylamine, 75-31-0; *tert*-butylamine, 75-64-9; acetonitrile, 75-05-8; fumaric acid chloride ethyl ester, 26367-48-6; *trans*-cinnamoyl chloride, 17082-09-6; acryloyl chloride, 814-68-6.

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Quinoxaline Derivatives. XI.[1] The Reaction of Quinoxaline 1,4-Dioxide and Some of Its Derivatives with Acetyl Chloride

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Quinoxaline 1,4-dioxide (Ia) with acetyl chloride gives 6-chloroquinoxaline 1-oxide (IIa). On heating, and progressively increasing the time of reaction, the yield of IIa increases, and 3-chloroquinoxaline 1-oxide (IIIa) and 6,7-dichloroquinoxaline appear as additional products. 7-Ethoxy- (Ib), 7-methoxy- (Ic), and 7-methylquinoxaline 1,4-dioxides (Id) show a similar behavior, giving corresponding 6-chloro (IIb–d) and 3-chloro derivatives (IIIb–d), as main products. Further increase in the reaction time results in the formation of 2,6-dichloro (Vb–d) and 2,3-dichloro (VIb–d) compounds as additional products. However none of the 2-chloro 4-oxide derivatives (IVb–d) were isolated. The mechanisms for these transformations have been proposed and discussed.

The chlorination of the heterocyclic ring in reactions of *N*-oxides with acyl chlorides has been reported.[3,4] Derivatives of pyridine *N*-oxide, quinoline *N*-oxide, and quinoxaline *N*-oxide with acetyl chloride give the corresponding 2- (or 4-) chloro compounds in good yields. This chlorination can be visualized to take place through the acylation of the *N*-oxide function, whereby the adjacent C-2 (or the vinylogous C-4) position becomes electron deficient and hence prone to nucleophilic attack by the chloride anion, with simultaneous loss of an acetic acid molecule. However, when the position adjacent to the *N*-oxide is occupied by a methyl group, chlorine substitution takes place in the methyl group. Thus 2,3-dimethylquinoxaline 1-oxide and 1,4-dioxide on reaction with acetyl chloride give[4] 2-chloromethyl-3-methylquinoxaline and 2,3-di-(chloromethyl)quinoxaline, respectively.

In contrast to these findings we have observed[5] that the chlorination is entirely directed to C-6 in quinoxaline 1-oxides which have a substituted C-2 position and also carry an oxygen function at C-3. Similar observations had been made earlier by Newbold and Spring,[6] Usherwood and Whitely,[7] and Clark-Lewis and Katekar.[8] However, the importance of the oxygen function at C-3 in directing the chlorine substitution to C-6 was not fully recognized. This novel pattern of a nucleophilic chlorine substitution in the *N*-oxides of the quinoxaline derivatives, and generality of this reaction, has been well established in these laboratories.

Elina has recently reported[9] that quinoxaline 1,4-dioxide with benzenesulfonyl chloride in the cold gives only 3% yield of the expected 3-chloroquinoxaline 1-oxide. The major product[10] is the benzenesulfonate of 2-chloroquinoxaline 1-oxide. These unusual findings prompted us to extend the study of the reaction of acetyl chloride to simpler quinoxaline *N*-oxides with unsubstituted heterocyclic rings.

Quinoxaline 1-oxide remained unchanged[11] (over 90% recovery) when heated under reflux with an excess of acetyl chloride for 24 hr. On the other hand, quinoxaline 1,4-dioxide (Ia) readily reacted with acetyl chloride. On stirring with an excess of acetyl chloride at room temperature for 1 hr, Ia gave 6-chloroquinoxaline 1-oxide (IIa) (about 20% yield). The latter compound was established by treating it with acetic anhydride and quantitatively isolating 6-chloro-2-hydroxyquinoxaline[12] (VIIa). When Ia was heated under reflux with acetyl chloride, the amount of IIa progressively increased until it reached a maximum yield of 60–65% after 8 hr. A second product (yield about 35%), isolated from the mother liquor of the reaction mixture after removal of IIa, proved to be 3-chloroquinoxaline 1-oxide (IIIa) by (1) hydrolysis with aqueous alkali to 3-hydroxyquinoxaline 1-oxide;[13] (2) reaction with $POCl_3$ to 2,3-dichloroquinoxaline[14] (VIa); and (3) reaction with acetic anhydride to 2-chloro-3-hydroxyquinoxaline, converted into VIa with $POCl_3$. When the heating time was increased to 16 hr the quantity of IIa in the reaction mixture decreased, the amount of IIIa remained unaltered, and a third product (yield 10–15%), identical with 6,7-dichloroquinoxaline,[14] was also isolated. The last named product was probably formed at the expense of IIa.

After an 8-hr reflux time, 6-methylquinoxaline 1,4-dioxide (Id) with acetyl chloride yielded two compounds. The insoluble product was identical with 6-chloro-7-methylquinoxaline 1-oxide[14] (IIId), a sample of which for comparison was kindly supplied by Dr. Landquist. This constitution of the product was initially indicated by the fact that it showed no absorption in the carbonyl region of its ir spectrum, and with acetic anhydride it underwent the familiar rearrangement of quinoxaline *N*-oxides to quinoxalinones, and the isomeric 6-chloro-2-hydroxy-7-methylquinoxaline (VIId) thus obtained with $POCl_3$ gave the same 2,6-dichloro-7-methylquinoxaline (Vd) as was obtained directly by the action of $POCl_3$ on the starting compound IId. The mother liquor of the reaction mixture afforded a second compound, an isomeric *N*-oxide of the structure IIId, since it showed no absorption in the carbonyl region of its ir spectrum and on reaction with $POCl_3$ yielded a

(1) Part X: Y. Ahmad, M. S. Habib, A. Mohammadi, B. Bakhtiari, and S. A. Shamsi, *J. Org. Chem.*, **38**, 201 (1968).

(2) M. S. H. presented this paper at the 3rd International Congress of Heterocyclic Chemistry, Sendai, Japan, Aug 1971.

(3) T. Itai, *J. Pharm. Soc. Jap.*, **65**, 70 (1945); *Chem. Abstr.*, **45**, 8525*b* (1951).

(4) Y. Ahmad, M. S. Habib, Ziauddin, and B. Bakhtiari, *J. Org. Chem.*, **31**, 2613 (1966).

(5) Y. Ahmad, M. S. Habib, Ziauddin, and N. Bashir, *Bull. Chem. Soc. Jap.*, **38**, 1654 (1965).

(6) (a) G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 519 (1948); (b) W. Dawson, G. T. Newbold, and F. S. Spring, *ibid.*, 2579 (1949).

(7) E. A. Usherwood and M. A. Whitely, *ibid.*, **123**, 1069 (1923).

(8) J. W. Clark-Lewis and G. F. Katekar, *ibid.*, 2825 (1959).

(9) A. S. Elina, *Khim. Geterotsikl. Soedin.*, 545 (1968); *Chem. Abstr.*, **69**, 96660p (1968).

(10) Isolation of a very minor product having chlorine in the benzene portion of the molecule (on the evidence of nmr studies) has been reported by Elina.[9] The position of chlorine in the molecule, however, has remained undetermined.

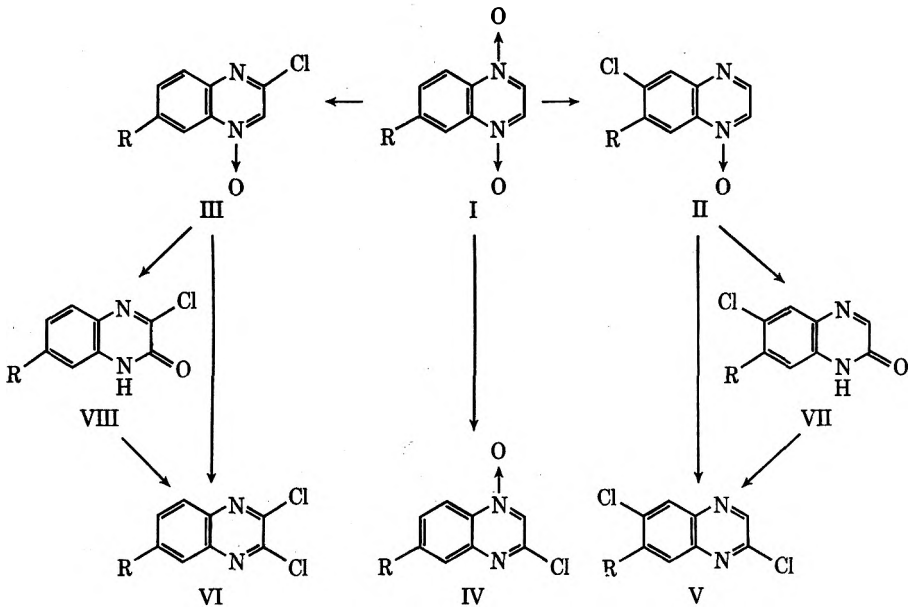
(11) Unpublished work.

(12) Y. Ahmad, M. S. Habib, M. Iqbal, M. I. Qureshi, and Ziauddiu, *Bull. Chem. Soc. Jap.*, **38**, 1659 (1965).

(13) G. Tennant, *J. Chem. Soc.*, 2428 (1963).

(14) J. K. Landquist, *ibid.*, 2816 (1953).

SCHEME I



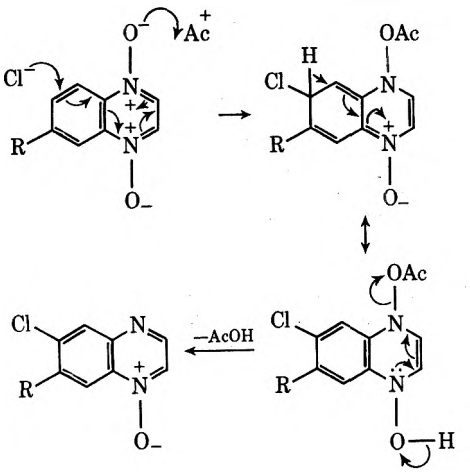
a, R = H b, R = EtO
c, R = MeO d, R = Me

product identical with 2,3-dichloro-7-methylquinoxaline[14] (VId).

When the time of heating was increased to 16 hr, in addition to IId and IIId, two more products were isolated by column chromatography over alumina. The latter compounds proved to be 2,3-dichloro- (VId) and 2,6-dichloro-7-methylquinoxaline (Vd) on comparison with authentic samples described above. These compounds were probably formed by the action of acetyl chloride on the primary products IId and IIId, initially produced in the reaction mixture.

6-Methoxyquinoxaline 1,4-dioxide (Ic) with acetyl chloride showed analogous behavior. Two corresponding primary products, the *N*-oxides IIc and IIIc, were isolated in 50–60 and 30–35% yields, after 8 hr of heating. When the heating time was increased to 16 hr, in addition to IIc and IIIc, the corresponding secondary products Vc and VIc were also isolated. Similarly, from 6-ethoxyquinoxaline 1,4-dioxide (Ib) two products (IIb and IIIb) were obtained after 8 hr of heating, whereas all four products (IIb, IIIb, Vb, and VIb) were isolated after heating for 16 hr. See Scheme I.

The mechanism illustrated below is proposed for the chlorine substitution in the benzene portion of the molecule during the reaction of quinoxaline 1,4-dioxides with acetyl chloride.



The mechanism of chlorine substitution into the heterocyclic ring is well known and has already been described in the opening paragraph of this paper.

These nucleophilic chlorinations seem to be influenced by certain factors as yet not understood, because none of the 2,3-dichloroquinoxaline from Ia and other 3-chloro 1-oxide derivatives (IVb–d) from Ib–d) could be isolated in these reactions, as expected from the above mechanisms.

Experimental Section[15]

Materials.—Quinoxaline 1,4-dioxide (Ia), 6-ethoxyquinoxaline 1,4-dioxide (Ib), 6-methoxyquinoxaline 1,4-dioxide (Ic), and 6-methylquinoxaline 1,4-dioxide (Id) were prepared by the reported[14] methods.

Reaction of Quinoxaline 1,4-Dioxide (Ia) with Acetyl Chloride. Reaction at Room Temperature.—A suspension of Ia (2.0 g) in acetyl chloride (30 ml) was vigorously stirred at room temperature for 1 hr. The filtrate, after removal of solid, on distillation left a negligible residue. The solid was exhaustively extracted with hot light petroleum. The insoluble part proved to be the starting material. The solution on evaporation left a residue (0.5 g, 20% yield) which on crystallization from ethanol gave colorless needles, mp 137–138°, which proved to be 6-chloroquinoxaline 1-oxide[16] (IIa).

Anal. Calcd for $C_8H_5ClN_2O$: C, 53.19; H, 2.77; Cl, 19.66; N, 15.52. Found: C, 53.06; H, 2.79; Cl, 19.62; N, 15.30.

(15) All melting points are uncorrected. The light petroleum used was of the boiling range 60–80°. Freshly distilled pure acetyl chloride was used and reasonable precautions against the ingress of moisture were observed throughout various operations in these reactions. Infrared spectra were measured in Nujol mulls with a Perkin-Elmer Model 137-B instrument. The compounds were considered identical when their mixture melting points remained undepressed and their ir spectra were superimposable. Brockmann alumina (activity I grade) was used for chromatography.

(16) The compound, mp 151–152°, obtained from Dr. Landquist for comparison, and reported[14] by him to be 6-chloroquinoxaline *N*-oxide, proved in fact to be the 7-chloroquinoxaline 1-oxide. The repetition of Landquist's oxidation of 6-chloroquinoxaline gave in our hands a mixture of two mono-*N*-oxides, mp 151–152 and 137–138°, which could be separated by chromatography on alumina and elution with light petroleum. Since the compound with mp 137–138° has now definitely been proved to be 6-chloroquinoxaline 1-oxide, the compound with mp 151–152° should therefore be 7-chloroquinoxaline 1-oxide.

On heating under reflux with acetic anhydride, and removal of solvent *in vacuo*, IIa gave in almost quantitative yield 6-chloro-2-hydroxyquinoxaline (VIIa), mp 320° dec, which was identical with its authentic sample[12] prepared, for comparison, by the decarboxylation of 6-chloro-2-hydroxyquinoxaline-3-carboxylic acid.

Reaction under Reflux for 8 Hr (Procedure A).—A mixture of the dioxide Ia (4.0 g) and acetyl chloride (60 ml) was heated under reflux for 8 hr. After the mixture was cooled to room temperature the solid was removed by filtration, washed with a little light petroleum, and crystallized from ethanol to give IIa in 65% yield. None of the unreacted Ia was recovered. The filtrate upon evaporation under reduced pressure left a sticky mass, which solidified after addition of a little water and storage overnight in the refrigerator. The solid was collected and crystallized from ethanol, and 3-chloroquinoxaline 1-oxide (IIIa) was isolated as yellow needles, mp 147–148° (yield 35%).

Anal. Calcd for $C_8H_5ClN_2O$: C, 53.19; H, 2.77; Cl, 19.66; N, 15.52. Found: C, 53.21; H, 2.71; Cl, 19.69; N, 15.54.

This material was identified by the following methods.

(1) On hydrolysis with 2.5 *N* potassium hydroxide on a water bath for 2 hr, it gave a clear solution, which on acidification precipitated a solid. Crystallization of the solid from glacial acetic acid gave greyish-white needles of 3-hydroxyquinoxaline 1-oxide (IIIa, OH for Cl), mp 271–273°, identical with an authentic sample.[13]

(2) After cautious addition of the above IIIa (0.3 g) to cooled $POCl_3$ (2 ml), the mixture was allowed to come to room temperature, and then refluxed for 15 min. Removal of excess $POCl_3$ under reduced pressure left a residue, which was triturated with ice-cold water, filtered, dried, and crystallized from light petroleum, whereby colorless needles of a solid identical with 2,3-dichloroquinoxaline[14] (VIa), mp 148–149°, were obtained.

(3) The compound (0.5 g) was refluxed with an excess of acetic anhydride (7 ml). After removal of the solvent *in vacuo* and work-up in the usual manner, the reaction product was recrystallized from ethanol and identified as 3-chloro-2-hydroxyquinoxaline (VIIIa), mp 322–324°.

Anal. Calcd for $C_8H_5ClN_2O$: C, 53.19; H, 2.77; Cl, 19.66; N, 15.52. Found: C, 53.48; H, 2.74; Cl, 19.61; N, 15.37.

The structure of the above compound (VIIIa) was further confirmed by its conversion to the known 2,3-dichloroquinoxaline by treatment with $POCl_3$.

Reaction under Reflux for 16 Hr (Procedure B).—Quinoxaline 1,4-dioxide (Ia) (4.0 g) and acetyl chloride (60 ml) were refluxed together for 16 hr. The dark grey, insoluble solid was removed by filtration. On working up as before and crystallization from ethanol, colorless needles of IIa were isolated, mp 137–138° (yield 40%). The filtrate on evaporation under reduced pressure left a dark brown, sticky residue which was triturated with cold water to decompose a trace of acetyl chloride. After being left overnight in a refrigerator it was collected and washed with water. The dried solid (2.1 g) was taken up in dry benzene and adsorbed onto alumina, dried again, and put on a column of alumina prepared in light petroleum. The chromatographic column was eluted with light petroleum. The first fraction (about 1 l.) afforded a colorless, crystalline product, mp 208–210° (10–15% yield), which proved to be 6,7-dichloroquinoxaline on comparison with an authentic sample[14] (reported mp 210°).

Anal. Calcd for $C_8H_4Cl_2N_2$: C, 48.23; H, 2.01; Cl, 35.68; N, 14.07. Found: C, 48.18; H, 2.16; Cl, 35.69; N, 14.10.

On further elution until exhaustion of the column with the same solvent (about 2 l. more), 3-chloroquinoxaline 1-oxide (IIIa) was obtained (30% yield) as the second crystalline product.

Reaction[17] of 6-Methylquinoxaline 1,4-Dioxide (Id) with Acetyl Chloride. Procedure A.—(1) The insoluble part of the reaction mixture afforded on crystallization from ethanol greyish-white needles of 6-chloro-7-methylquinoxaline 1-oxide (IId), mp 168–169° (lit.[14] mp 166–168°) (yield 55%).

Anal. Calcd for $C_9H_7ClN_2O$: C, 55.52; H, 3.59; Cl, 18.25; N, 14.40. Found: C, 55.49; H, 3.43; Cl, 18.18; N, 14.38.

For further confirmation IId was treated with acetic anhydride and converted into 6-chloro-2-hydroxy-7-methylquinoxaline (VIId), mp 294–295° (greyish-white flakes from ethanol).

Anal. Calcd for $C_9H_7ClN_2O$: C, 55.52; H, 3.59; N, 14.40. Found: C, 55.81; H, 3.70; N, 14.17.

Compound VIId was treated with $POCl_3$ and worked up in the usual manner to give 2,6-dichloro-7-methylquinoxaline (Vd), which crystallized from light petroleum as colorless needles, mp 136–137°.

Anal. Calcd for $C_9H_6Cl_2N_2$: C, 50.70; H, 2.81; Cl, 33.34; N, 13.14. Found: C, 50.78; H, 2.87; Cl, 33.31; N, 13.05.

(2) The filtrate from the reaction mixture after removal of acetyl chloride left a residue, which on processing as described earlier gave 3-chloro-7-methylquinoxaline 1-oxide (IIId) as pink needles (from ethanol), mp 142–143°, yield 34%.

Anal. Calcd for $C_9H_7ClN_2O$: C, 55.52; H, 3.59; Cl, 18.25; N, 14.40. Found: C, 55.52; H, 3.53; Cl, 18.25; N, 14.39.

This isomeric product showed no absorption peak in the carbonyl region of its ir spectrum and on treatment with $POCl_3$ was converted to 2,3-dichloro-7-methylquinoxaline[14] (VId), which unambiguously established the structure of the compound as IIId.

Procedure B.—Upon heating for 16 hr no insoluble material was isolated but instead a clear red solution was obtained. The dark red residue left after removal of acetyl chloride was chromatographed on alumina in the usual manner. Three crystalline products eluted out with light petroleum in the following order.

The first 700 ml of eluent gave colorless needles of a compound (12% yield) identical with 2,6-dichloro-7-methylquinoxaline (Vd), mp 136–137°. The next 1 l. afforded pinkish-white crystals of a product (about 13% yield) identical with 2,3-dichloro-7-methylquinoxaline (VId), mp 114–115°. The third fraction (about 2 l.) gave pink needles of a compound (11% yield) identical with 3-chloro-7-methylquinoxaline 1-oxide (IIId), mp 142–143°. Further elution of the column failed to give any identifiable crystalline product.

Reaction[17] of 6-Methoxyquinoxaline 1,4-Dioxide (Ic) with Acetyl Chloride. Procedure A.—In this reaction Ic showed behavior comparable to that of Id described above, and corresponding products were obtained in this case.

(1) The insoluble part on crystallization from ethanol gave greyish-white needles of 6-chloro-7-methoxyquinoxaline 1-oxide (IIc), mp 190–192° (yield 57%).

Anal. Calcd for $C_9H_7ClN_2O_2$: C, 51.31; H, 3.32; Cl, 16.87; N, 13.30. Found: C, 50.76; H, 3.25; Cl, 16.79; N, 13.22.

With acetic anhydride IIc gave 6-chloro-2-hydroxy-7-methoxyquinoxaline (VIIc), mp 273–275° dec (cream-colored grains from ethanol).

Anal. Calcd for $C_9H_7ClN_2O_2$: C, 51.31; H, 3.32; N, 13.30. Found: C, 51.21; H, 3.18; N, 13.31.

On treatment with $POCl_3$ IIc and VIIc both yielded 2,6-dichloro-7-methoxyquinoxaline (Vc), which crystallized from light petroleum as colorless needles, mp 177–179°.

Anal. Calcd for $C_9H_6Cl_2N_2O$: C, 47.17; H, 2.62; Cl, 31.10; N, 12.23. Found: C, 47.41; H, 2.96; Cl, 30.68; N, 12.26.

(2) The residue, obtained from the filtrate after removal of acetyl chloride, afforded on crystallization from ethanol light brown flakes of 3-chloro-7-methoxyquinoxaline 1-oxide (IIIc), mp 150–152° (yield 33%).

Anal. Calcd for $C_9H_7ClN_2O_2$: C, 51.31; H, 3.32; Cl, 16.87; N, 13.30. Found: C, 51.16; H, 3.21; Cl, 16.81; N, 13.04.

With $POCl_3$ IIIc gave 2,3-dichloro-7-methoxyquinoxaline[18] (VIc), which crystallized from light petroleum as pinkish white needles, mp 160–161°.

Procedure B.—When Ic (4.0 g) in acetyl chloride (60 ml) was heated under reflux for 16 hr a brown-colored, clear solution resulted. The residue, obtained after removal of acetyl chloride, was chromatographed over alumina and eluted with light petroleum. The first fraction (about 1 l.) gave colorless needles of 2,6-dichloro-7-methoxyquinoxaline (Vc), mp 177–179° (yield 10–15%). The second fraction (about 1 l.) afforded pinkish-white flakes of 2,3-dichloro-7-methoxyquinoxaline (VIc), mp 160–161° (yield 14%). Further elution, even with change of solvents, failed to give any other identifiable product.

Reaction[17] of 6-Ethoxyquinoxaline 1,4-Dioxide (Ib) with Acetyl Chloride. Procedure A.—(1) The insoluble part on crystallization from ethanol gave greyish-white needles of 6-chloro-7-ethoxyquinoxaline 1-oxide (IIb), mp 188–189° (yield 58%).

(17) Unless otherwise stated, the same general procedures (A and B) and the same quantities (4.0 g and 60 ml) of the two reactants were used in the reaction study of the dioxides Ib, Ic, and Id with acetyl chloride.

(18) F. H. S. Curd, D. G. Davey, and G. J. Stacey, *J. Chem. Soc.*, 1271 (1949).

Anal. Calcd for $C_{10}H_9ClN_2O_2$: C, 53.46; H, 4.00; Cl, 15.81; N, 12.47. Found: C, 53.36; H, 4.08; Cl, 15.95; N, 12.60.

With acetic anhydride the *N*-oxide (IIb) rearranged to 6-chloro-7-ethoxy-2-hydroxyquinoxaline (VIIb) as light brown needles from ethanol, mp 255° dec.

Anal. Calcd for $C_{10}H_9ClN_2O_2$: C, 53.46; H, 4.00; N, 12.47. Found: C, 53.37; H, 4.04; N, 12.33.

Both IIb and VIIb with $POCl_3$ were converted to the same compound, 2,6-dichloro-7-ethoxyquinoxaline (Vb), as greyish-white needles from light petroleum, mp 133°.

Anal. Calcd for $C_{10}H_8Cl_2N_2O$: C, 49.39; H, 3.29; Cl, 29.22; N, 11.52. Found: C, 49.16; H, 3.33; Cl, 29.04; N, 11.55.

(2) The residue, obtained from the filtrate after removal of acetyl chloride, gave on crystallization from ethanol pink microneedles of 3-chloro-7-ethoxyquinoxaline 1-oxide (IIIb), mp 143–145°, yield 37%.

Anal. Calcd for $C_{10}H_9ClN_2O_2$: C, 53.46; H, 4.00; Cl, 15.81; N, 12.47. Found: C, 53.30; H, 4.10; Cl, 15.71; N, 12.56.

With $POCl_3$ IIIb gave a compound, mp 137–138° (pinkish white flakes from light petroleum), identical with 2,3-dichloro-7-ethoxyquinoxaline (VIb) prepared by the reaction of 2,3-dihydroxy-7-ethoxyquinoxaline[19] with $POCl_3$.

Procedure B.—A dark brown, clear solution was obtained after 16 hr of heating. The dark red, sticky residue left after removal of acetyl chloride was chromatographed on alumina and eluted with light petroleum. The first fraction (about 800 ml) of the eluent yielded colorless needles of 2,6-dichloro-7-ethoxyquinoxaline (Vb), mp 135° (yield 12%). The subsequent fraction (1 l.) gave light pink needles of 2,3-dichloro-7-ethoxyquinoxaline (VIb), mp 137–138° (yield 15%). Further elution with various solvent failed to give any more identifiable products.

(19) W. Autenrieth and O. Hinsberg, *Ber.*, **25**, 492 (1892).

Registry No.—Ia, 2423-66-7; Ib, 39266-91-6; Ic, 39266-92-7; Id, 33368-89-7; IIa, 39266-93-8; IIb, 39266-94-9; IIc, 39266-95-0; IId, 39266-96-1; IIIa, 5227-59-8; IIIb, 39266-98-3; IIIc, 39266-99-4; IIId, 39267-00-0; Vb, 39267-01-1; Vc, 39267-02-2; Vd, 39267-03-3; VIc, 39267-04-4; VId, 39267-05-5; VIIa, 39267-06-6; VIIb, 39267-07-7; VIIc, 39267-08-8; VIId, 39267-09-9; VIIIa, 35676-70-1; acetyl, 75-36-5; 6,7-dichloroquinoxaline, 19853-64-6; 7-chloroquinoxaline 1-oxide, 39267-11-3.

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The Reaction of Phenyl 2-*O*-Acetyl-4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-glucopyranoside with Alkali Azide

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The title compound **3** reacts with sodium azide or lithium azide in various media to yield predominantly one of the following products by selecting appropriate conditions: nitro azide **5**, triazole **6**, and **7**. The key factor in determining product was found to be the basicity of the medium. Similar results were obtained when nitro olefin **4**, derived from the title compound, or nitro azide **5** was used as a starting material. Structures **6** and **7** were deduced from their nmr, mass, and ir spectra, and the mechanisms involved in the formation of **5**, **6**, and **7** are discussed.

In previous papers[2,3] we have dealt with the synthesis of a new type of nucleosides, in which the purine or pyrimidine moiety is linked to the C-2 position of a 3-nitroglucopyranoside. In this reaction α-nitro olefin 2, formed from methyl 2-*O*-acetyl-4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-glucopyranoside (1) by the elimination of acetic acid, was assumed to be an intermediate.[4]

Recently the following similar substitution reaction was observed. The thermodynamically unstable *all-cis*- (1*r*,2*c*,3*c*) and *cis,trans*- (DL-1*r*,2*c*,3*t*) dianilino derivatives were isolated in 30 and 20% yields, respectively, on treatment of 1*r*,3*c*-diacetoxy-2*t*-nitrocyclohexane with aniline, but only a trace of thermodynamically more stable *all-trans* (1*r*,2*t*,3*c*) isomer was detectable by tlc.[5] The fact that the thermodynamically stable isomer was not formed in quantity in this reaction can be explained by assuming that subsequent epimerization of the two products is slow. If the reaction proceeds *via* a nitro olefin intermediate, the products may be formed by kinetic control; on the other hand, they may conceivably be formed by an SN2 reaction with starting material. We have therefore studied further the reaction of **3** with alkali azide, which is generally accepted as a typical SN2-type nucleophile, in a variety of media and we have found that this reaction affords the corresponding nitro azide **5** and/or the triazole derivatives (**6**, **7**) in excellent yield (Scheme I) and that one of the three products can be obtained exclusively by selecting appropriate reaction conditions. The details are described herewith.

Results and Discussions

Structural Assignment of the Products.—Phenyl 2-azido-4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-glucopyranoside (**5**), phenyl 4,6-*O*-benzylidene-2,3-dideoxy-β-D-*erythro*-hexopyranosido[2,3-*d*]triazole (**6**), and phenyl 4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-2-(phenyl 4′,6′-*O*-benzylidene-2′,3′-dideoxy-β-D-*erythro*-hexopyranosido[2′,3′-*d*]triazolyl)-β-D-glycopyranoside (**7**) were obtained as exclusive products by the reaction

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(2) T. Nakagawa, T. Sakakibara, and S. Kumazawa, *Tetrahedron Lett.*, 1645 (1970).

(3) T. Sakakibara, S. Kumazawa, R. Sudoh, and T. Nakagawa, *Carbohyd. Res.*, in press.

(4) The chemistry of nitro sugars was reviewed by H. H. Baer: H. H. Baer, *Advan. Carbohyd. Chem.*, **24**, 69 (1969).

(5) T. Nakagawa, T. Sakakibara, and F. W. Lichtenthaler, *Bull. Chem. Soc. Jap.*, **43**, 3861 (1970).

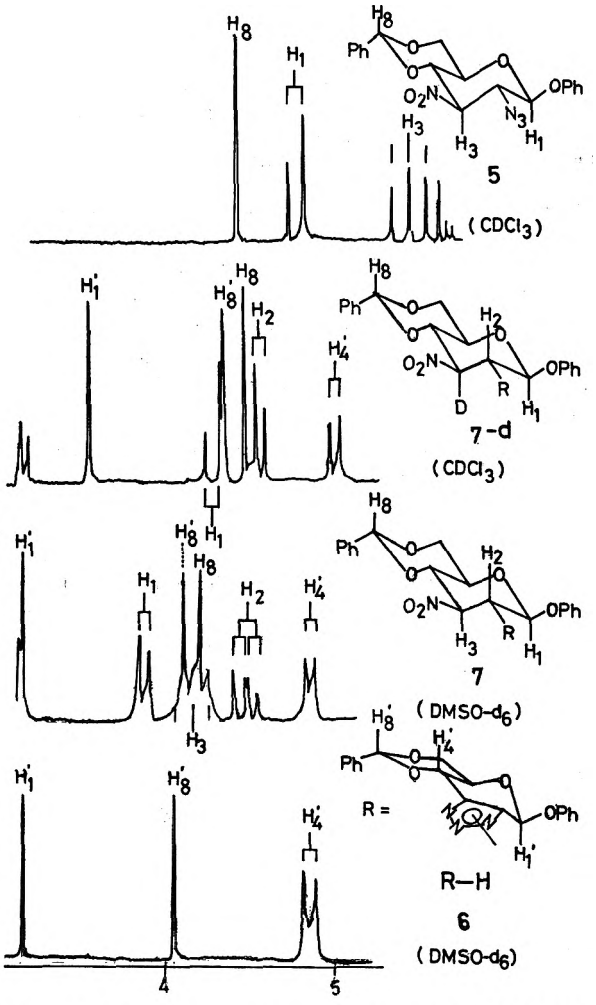


Figure 1.—Partial nmr spectra of **5**, **6**, and **7** at 100 MHz.

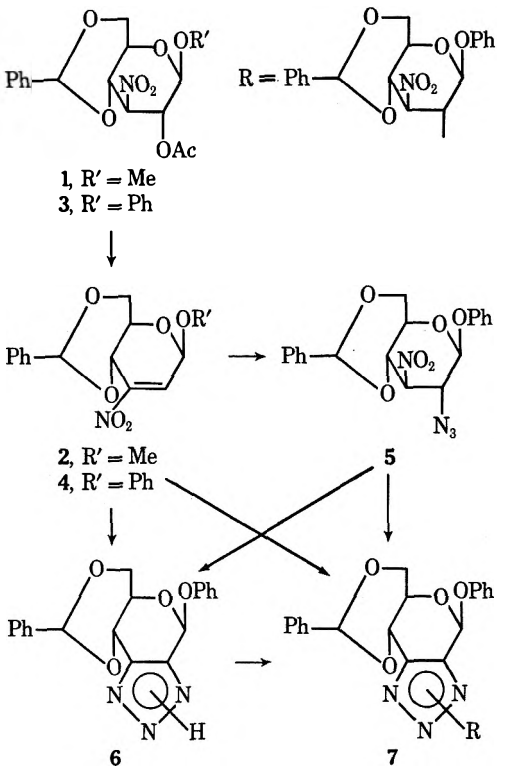
of **3** with alkali azide when reaction conditions which will be described later are employed. Structural assignment of **5**, **6**, and **7** was based on the following data.

5.—Its ir spectrum (KBr) shows the presence of an azide group (2100 cm^{-1}) and of a nonconjugated nitro group (1560 cm^{-1}). The large value of the coupling constants of the nmr signals of the ring protons, *i.e.*, $J_{1,2} = 7.5$, $J_{2,3} = J_{3,4} = 10$ Hz, indicates the β-gluco configuration.

6.—No ir absorption bands corresponding to nitro and azide group were observed. The elemental analysis of this product is in full accordance with the formula $C_{19}H_{17}H_3O_4$ which was, in addition, supported by the observation of a mass spectral peak at *m/e* 351. The sugar moiety contains only five protons as shown by the nmr spectrum (Figure 1). A sharp 1 H singlet at τ 3.16 and a 1 H doublet at 4.86 with a spacing of 7.5 Hz are assigned to H-1 and H-4, respectively, suggesting the absence of protons on the C-2 and C-3 atoms. From these data, and in the view of the results reported by Zefirov, *et al.*,[6] on the similar reaction of nitrostyrenes with sodium azide in DMSO giving triazoles, compound **6** is deduced to have a triazole skeleton, but the location of the hydrogen on the ring has not yet been determined.

7.—The ir spectrum (KBr) of this product showed

SCHEME I



no absorption of an azide group but a nitro group (1560 cm^{-1}). Its elemental analysis corresponded to $C_{38}H_{34}N_4O_{10}$, which is further confirmed by the appearance of the molecular ion peak at *m/e* 706. Catalytic reduction of **7** with Raney nickel in dioxane containing a trace amount of triethylamine afforded colorless crystalline phenyl 3-amino-4,6-*O*-benzylidene-2,3-dideoxy-2-(phenyl 4′,6′-*O*-benzylidene-2′,3′-dideoxy-β-D-*erythro*-hexopyranosido[2′,3′-*d*]triazolyl)-β-D-glucopyranoside (**8**), which was characterized as its *N*-acetyl derivative **9** after acetylation as usual. In the nmr spectrum of **7** (Figure 1) 1 H signals at τ 3.13 (s), 4.07 (s), and 4.85 (d) could be assigned to H-1′, H-8′ (benzylidene methine proton), and H-4′, respectively, by comparison with those of **6**; hence the other signals at τ 3.83 (d), 4.19 (s), 4.15 (t), and 4.45 (q) corresponded to H-1, H-8 (benzylidene methine proton), H-3, and H-2, respectively. These assignments were further confirmed by comparison with the spectrum of the C-3-deuterated derivative of **7** (Figure 1). **7** was deduced to have the β-gluco configuration for its nitro sugar moiety on the basis of the coupling constants $J_{1,2} = 7.5$, $J_{2,3} = J_{3,4} = 10$ Hz. The presence of the triazole nucleus[7] was indirectly confirmed by determining the uv spectrum of methyl 4,6-*O*-bromoethylidene-2,3-dideoxy-2-(methyl 4′,6′-*O*-bromoethylidene-2′,3′-dideoxy-β-D-hexopyranosido[2′,3′-*d*]triazolyl)-3-nitro-β-D-hexopyranoside (**10**) at 228.5 nm, (ε 1.1 × 10^4), which was prepared from methyl 2-*O*-acetyl-4,6-*O*-bromoethylidene-3-deoxy-3-nitro-β-D-glucopyranoside (**14**) and sodium azide by treatment under the same condition as had been employed in the reaction of **3**. This fact is, moreover, in good agreement with the proposed mechanism for the formation of **7** which will be

(6) N. S. Zefirov, N. K. Chapovakaya, and V. V. Kolesnikov, *Chem. Commun.*, 1001 (1971). 8-Azapurines and *v*-triazole[4,5-*b*]pyridines were obtained on the treatment of 5-nitropyrimidines and 5-nitropyridines with sodium azide, respectively: H. Ulrich, I. Wempen, and J. J. Fox, *J. Org. Chem.*, **35**, 1131 (1970).

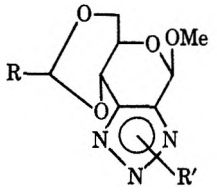
(7) These compounds involving such a nucleus generally show an uv absorption band in the vicinity of 225 nm with molar extinction coefficient of ~4 × 10^4. *E.g.*, L. W. Hartzel and F. R. Benson, *J. Amer. Chem. Soc.*, **76**, 667 (1954); G. B. Barlin, *J. Chem. Soc., B*, 641 (1967).

TABLE I

REACTIONS WITH SODIUM AZIDE AND HYDRAZOIC ACID

Expt	Starting material (S)	Reagents (R)	Mole ratios of R to S	Solvent systems[a]	Yields, %, of products[b] 5 (5-*d*)	6	7 (7-*d*)
1	3	NaN_3	1	A	93	t	t
2	3	NaN_3	1	B or C		t	85
3	3	NaN_3, NaOH	1, 1	A		t	q
11	4	NaN_3	1	A		t	83
12	4	NaN_3	2	A		t	q
13	4	NaN_3	1	B or C		t	q
14	4	HN_3, AcONa	excess, 1	D			
	4	NaN_3, AcOH	1, 1	A	q		
15	4	NaN_3, AcOH	1, 1	B		t	q
16	4	HN_3	1	A	q		
17	4	HN_3	1	A-*d*	50 (50)		
18	4	NaN_3, HN_3	1, excess	A	q	t	
19	4	NaN_3, HN_3	1, excess	A-*d*	(q)	t	
20	4	NaN_3	1	E			q
21	5	NaN_3	1	A-*d*	(q)		
22	5	NaN_3	1	B-*d*		t	(q)
23	5	NaOAc	1	A	q		
24	5	NaOAc	1	B		t	q
25	5	NaN_3	1	DMF or DMSO	t	q	t
26	5	NaN_3	1	THF-D_2O	(q)	t	t

[a] A, CH_3CN-H_2O (8:1, v/v); A-*d*, CH_3CN-D_2O (8:1, v/v); B, DMF-H_2O (8:1, v/v); B-*d*, DMF-D_2O (8:1, v/v); C, DMSO-H_2O (8:1, v/v); D, $CHCl_3$-H_2O (8:1, v/v); E, Carbitol. [b] t, trace; q, quantitative or almost so; blank indicates that product could not be detected by tlc.



10, R = CH_2Br
11, R = Ph

discussed later, but final determination of the bonding position of the nitro sugar moiety on the triazole skeleton has not yet been accomplished, although it likely linked to N-2 of the triazole nucleus on steric grounds.

Incidentally, the mass spectra of **6** and **7** were examined in detail. Although carbohydrates[8] and aliphatic and alicyclic nitro compounds[9] are generally said to exhibit no molecular ion peaks, weak peaks corresponding to the molecular ion were observed in the case of **6** and **7** at *m/e* 351 and 706, respectively. Comparatively strong peaks appear in mass spectra of **7** at *m/e* 613.1972, 583.1854, 507.1538, and 477.1453, which are in accord with M − C_6H_5O (613.1934), M − $C_7H_7O_2$ (583.1828), M − $C_{13}H_{11}O_2$ (507.1515), and M − $C_{14}H_{13}O_3$ (477.1410), respectively. Analogous peaks were observed in **6** at *m/e* 258, 228, 152, and 122. These results may be explained as follows. The phenoxy radical is split off from the molecular ions Ia,b to give cations IIa,b, which were presumably subjected to a successive elimination of formaldehyde and benzaldehyde affording oxetane ions IIIa,b, IVa,b, and pyran ions Va,b, respectively (Scheme II).

Correlation of Products and Reaction Conditions.— As previously described, the structure of the product varies depending on the reaction conditions. The details are discussed in this section.

The reaction of nitro acetate **3** with an equivalent of sodium azide in acetonitrile–water (8:1 v/v) at room temperature gave nitro azide **5** in 93% yield, along with trace amounts of the triazole derivatives **6** and **7** (expt 1, Table I). Under similar conditions, on the other hand, nitro olefin **4** afforded a different product, *i.e.*, **7**, in 83% yield. A trace of **6** was also detected by tlc (expt 11), but no **5**. On the basis of these results **4** can not be assumed to be the intermediate for the reaction leading from **3** to **5**, but this assumption ignores the potential participation of acetic acid, which may equilibrate with sodium azide as shown in eq 1 and is thus

$$NaN_3 + CH_3COOH \rightleftharpoons HN_3 + CH_3COONa \quad (1)$$

released in the course of the reaction. Therefore, the reaction of **4** with hydrazoic acid in aqueous chloroform with sodium azide in aqueous acetonitrile was studied in the presence of sodium acetate and acetic acid, respectively. Both reaction conditions afforded **5** exclusively and no **7** (expt 14). If sufficient amounts of a base were present to neutralize the acetic acid produced, the reaction of **3** with sodium azide could be expected to proceed similarly to that of **4**. In fact, treatment of **3** with sodium azide in the presence of an equivalent of sodium hydroxide yielded only **7** (expt 3). Consequently, the assumption that **4** is not the reaction intermediate can be said to be erroneous.

A striking solvent effect was observed in the reaction of **3** with sodium azide. When either aqueous DMF or aqueous DMSO was used as the solvent, **7**, but no **5**, was isolated in 85% yield (expt 2). In most instances, the amount of **6** produced was too small to isolate and it was only detected by tlc. However, the reaction of **5** with sodium azide in freshly distilled DMF afforded **6** as the major product, which was isolated by silica gel column chromatography (expt 25). The application of lithium

(8) N. K. Kochetkov and O. S. Chizhvov, *Advan. Carbohyd. Chem.*, **21**, 39 (1966).

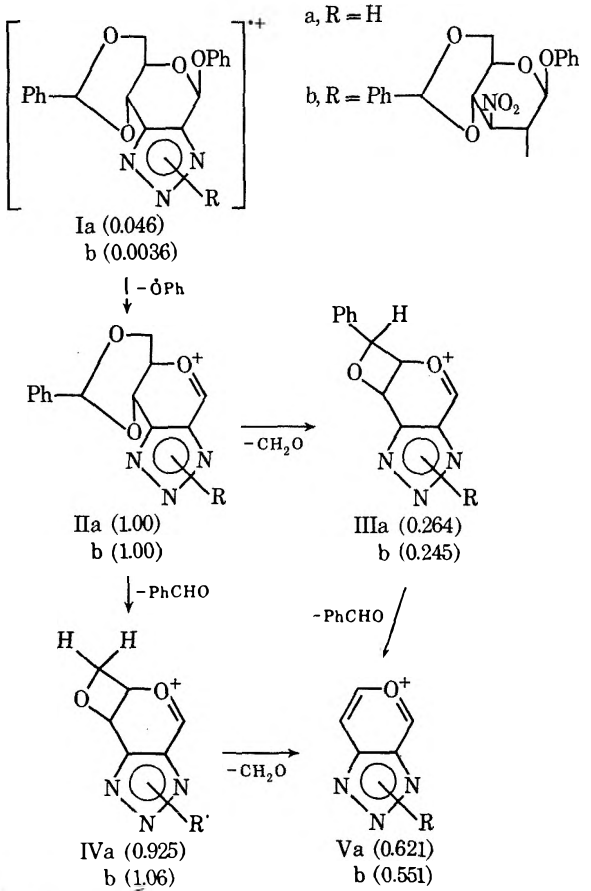
(9) R. T. Aplin, M. Fischer, D. Becher, H. Budzikiewicz, and C. Djerassi, *J. Amer. Chem. Soc.*, **87**, 4888 (1965).

TABLE II
REACTIONS WITH LITHIUM AZIDE

Expt	Starting materials (S)[a]	Reagents (R)[a]	Solvent	Yields of products 5	6	7
31	3	LiN_3	EtOH	q		t
32	3	LiN_3	THF	q		
33	3	LiN_3	CH_3CN	q		
34	3	LiN_3	DMF		q	
35	3	LiN_3	DMSO		q	
41	4	LiN_3	EtOH	t	t	q
42	4	LiN_3	THF	t	t	q
43	4	LiN_3	CH_3CN			q
44	4	LiN_3	DMF		q	t
45	4	LiN_3	DMSO		q	t
46	4	6	CH_3CN			q
51	5	LiN_3	CH_3CN	q	t	t
52	5	LiN_3	THF	q	t	t
53	5	LiN_3	DMF		q	t
54	5	LiOAc	CH_3CN	q	t	
55	5	LiOAc	DMF		q	t

[a] Mole ratio of reagent to starting material is 1:1.

SCHEME II[a]



[a] Figures in parentheses mean relative intensity to II.

azide as a nucleophile in these aprotic solvents made the exclusive formation of **6** possible (expt 34, 35, 44, 45, and 53, Table II).

The reaction of **4** with hydrazoic acid was studied by use of deuterium oxide in order to shed light on the possibilities that the reaction may proceed through 1,4 addition[10] to afford an *aci*-nitro form which isomerizes to the corresponding nitro form by an intermolecular proton exchange, that reversal of the Michael-type addition[11] could occur with great ease, and that the rate of deuterium exchange between deuterium oxide and hydrazoic acid may be much more rapid than that of the addition. If this were the case, deuteration at the 3 position should go to completion. Treatment of **4** with hydrazoic acid in acetonitrile–deuterium oxide (8:1, v/v), however, gave **5** containing the deuterated derivative in only 50% yield, which was determined from the nmr spectrum (expt 17). This suggests that the reaction of hydrazoic acid with **4** may involve, at least partly, irreversible 1,2 addition of hydrazoic acid to the C_2–C_3 double bond of **4**, and that the rate of reaction 2 is comparable with that of the addition reaction.

$$HN_3 + D_2O \rightleftharpoons DN_3 + HOD \qquad (2)$$

To our knowledge, no example is known of a one-step cyclization involving the powerfully nucleophilic azide ion. It has been accepted that the reaction of nitriles with lithium azide to give tetrazoles proceeds by a two-step mechanism involving initial nucleophilic attack of the azide ion on the carbon atom of the cyano group followed by cyclization of the adduct to the tetrazole.[12] On this basis, the reaction of **4** with sodium azide giving triazole **6** seems to proceed by a two-step mechanism, a conclusion which may be supported by the fact that nitro azide **5** also afforded triazole **6** or **7** depending on the reaction condition. In this case, nitrite ion must be eliminated from nitro azide **5** or its nitronate **5′**. Two routes may be considered for this process: (i) one *via* a vinyl azide or a carbene,[6] (ii) the other *via* a sodium nitronate. Of these the former may be discounted since the Michael-type addition is, in general, considered as one involving a reversible process,[11] and elimination of hydrazoic acid would occur more easily than that of nitrous acid. In fact, treatment of **5** with sodium methoxide in methanol gave phenyl 4,6-*O*-benzylidene-3-deoxy-2-*O*-methyl-3-nitro-β-D-glucopyranoside (**12**) by a reaction involving only exchange of the azide group for the methoxy group. Thus the reaction should proceed by the second route: sodium 2-azido-3-nitronate **5′**, which was formed directly by the attack of sodium

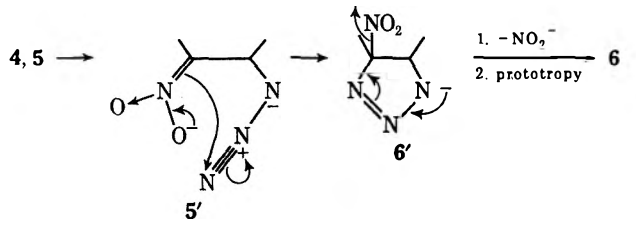
(10) The Michael-type addition is generally accepted to proceed through 1,4 addition. *E.g.*, J. March, "Advanced Organic Chemistry. Reactions, Mechanisms, and Structure," McGraw-Hill, London, 1968, pp 567–568.

(11) S. Patai and Z. Rappoport in "The Chemistry of Alkenes," S. Patai, Ed., Interscience, London, 1964, Chapter 8.

(12) A. I. Meyers and J. C. Sircar in "The Chemistry of the Cyano Group," Z. Rappoport, Ed., Interscience, London, 1970, Chapter 8.

azide on **4** (1,4 addition) or indirectly from **5**, cyclizes irreversibly to an unstable intermediate triazoline **6'**, which leads to the more stable triazole **6** by rapid elimination of a nitrite ion[13] and subsequent prototropy (Scheme III).

SCHEME III



With regard to the formation of **7** from **3** or **4**, it is deduced to be formed not by 1,3 cycloaddition of **5** to **4**, but by Michael-type addition of intermediate **6** to **4** on the basis of the following facts: (i) treatment of **6** with **4** affords **7** exclusively and with great ease even in the absence of ctalysts (expt 46), similar to the reaction of heterocyclic compounds such as theophylline, 2,6-dichloropurine, and uracil with nitro acetate **1** or nitro olefin **2**;[2,3] (ii) nitro azide **5** does not react with methyl 2-eno-3-nitropyranoside **2** without catalyst and both compounds were recovered quantitatively [in the presence of an equivalent of sodium azide in aqueous acetonitrile, on the other hand, **2** was converted into **11** (the methyl glycoside analog of **7**) in 62% yield, whereas most of **5** was recovered]; (iii) nitro olefin **4** does not react at room temperature in the absence of catalyst with picryl azide,[14] which is known as a typical reagent for 1,3 cycloaddition.

Tables I and II show the following trends: (i) **3**, **4**, and **5** in anhydrous DMF or DMSO gave **6** exclusively (expt 25, 34, 35, 44, 45, and 53); (ii) **3**, **4**, and **5** gave **7** exclusively in aqueous DMF or DMSO (expt 2, 13, and 22); (iii) treatment of **3** and **5** in anhydrous or aqueous ethanol, THF, chloroform, or acetonitrile afforded no product other than **5** (expt 1, 21, 26, 31, 32, 33, 51, and 52); (iv) treatment of **4** under the same conditions as described in iii afforded only **7** (expt 11, 12, 41, 42, and 43).

Experimental Section

Melting points were determined in capillaries and are uncorrected. Specific rotations were measured with a Carl Zeiss photoelectric polarimeter. Nmr spectra were recorded at 100 MHz with a spectrometer JNM-4H-100 (JEOL), using tetramethylsilane as an internal standard. Column chromatography was carried out on silica gel (100 mesh powder, Mallinckrodt, St. Louis) and developed with benzene. Tlc were performed on silica gel (Wakogel B-5, Japan) with a solvent system of xylene–acetonitrile (10:1, v/v). Mass spectra were taken on a spectrometer JMS-01SG (JEOL).

Solvents.—Anhydrous acetonitrile was prepared by treatment with anhydrous potassium carbonate, followed by several distillations from phosphorus pentoxide. Ethanol was purified by adding ~5% benzene as azeotroping agent followed by fractional distillation. Tetrahydrofuran was purified by treatment with potassium hydroxide and distilled from sodium. Dimethylformamide, dimethyl sulfoxide, and Carbitol were purified by distilling under reduced pressure followed by treatment with molecular sieves 3A (1/16).

Materials.—Hydrazoic acid was prepared according to Wolff.[15] Commercial sodium azide was used without further purification. Lithium azide prepared from lithium sulfate and sodium azide was recrystallized twice from water and dried [90°, (20 mm), 3 hr] before use. Typical procedures for the reaction of nitro acetate **3** and nitro olefin **4** with sodium azide and lithium azide are described. These procedures are almost exact prototypes for the experiments summarized in Tables I and II.

Phenyl 2-*O*-Acetyl-4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-glucopyranoside (3).—Phenyl 3-deoxy-3-nitro-β-D-glucopyranoside (30 g),[16] zinc chloride (50 g), and benzaldehyde (125 g) were stirred together at room temperature for 30 hr. Water (500 ml) was added to this mixture. A semicrystalline mass, separated upon addition of petroleum ether (600 ml, bp 30–60°), was collected and washed twice with 200 ml of petroleum ether. Without further purification, to a solution of pyridine (200 ml) dissolved in the benzylidene derivative was added acetic anhydride (65 ml) under cooling with ice water. The reaction mixture was left overnight at room temperature and then poured into 800 ml of ice water. The separated crude acetate was washed thoroughly with water to remove all traces of pyridine and dried. Crystallization from benzene furnished the acetate **3** (35 g): mp 204–205°; $[\alpha]^{20}D$ −109° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{21}H_{21}NO_8$: C, 60.72; H, 5.10; N, 3.37. Found: C, 60.67; H, 5.23; N, 3.22.

Phenyl 4,6-*O*-Benzylidene-2,3-dideoxy-3-nitro-β-D-*erythro*-hex-2-enopyranoside (4).—**3** (80 g) and dry sodium bicarbonate (120 g) in distilled benzene (600 ml) were refluxed, with stirring, for 60 hr. The reaction mixture was allowed to cool and filtered, and the filtrate was evaporated to give a nearly colorless crystalline residue of **4**. Recrystallization from benzene afforded compound **4** (80%): mp 144–145°; $[\alpha]^{20}D$ −142° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{19}H_{17}NO_6$: C, 64.22; H, 4.82; N, 3.94. Found: C, 64.38; H, 4.98; N, 3.72.

Methyl 4,6-*O*-Bromoethylidene-3-deoxy-3-nitro-β-D-glucopyranoside (13).—Methyl 3-deoxy-3-nitro-β-D-glucopyranoside (1.9 g), bromo acetal (4 ml), and concentrated sulfuric acid (0.1 ml) in diethyl ether (15 ml) were stirred for 3 days at room temperature. The mixture was neutralized of 1 *N* sodium hydroxide and poured into 10 ml of water. A semicrystalline material, precipitated upon addition of petroleum ether (80 ml), was collected and washed twice with 10 ml of petroleum ether. Recrystallization from ethanol afforded **13** (75%): mp 215–216° dec; $[\alpha]^{20}D$ −78.5° (*c* 1, acetone).

Anal. Calcd for $C_9H_{14}NO_7Br$: C, 32.93; H, 4.27; N, 4.27. Found: C, 32.75; H, 4.21; N, 4.29.

Methyl 2-*O*-Acetyl-4,6-*O*-bromoethylidene-3-deoxy-3-nitro-β-D-glucopyranoside (14).—To a solution of 3.2 g of **13** in pyridine (20 ml) was added 12 ml of acetic anhydride under cooling with ice water. The reaction mixture was allowed to stand overnight at room temperature and then poured into 150 ml of ice water. The precipitated crude acetate was washed thoroughly with water. Crystallization from aqueous ethanol furnished the acetate **14** (95%): mp 177.0–177.5°; $[\alpha]^{20}D$ −46.8° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{11}H_{16}NO_8Br$: C, 35.68; H, 4.32; N, 3.78. Found: C, 35.67; H, 4.06; N, 3.85.

Reaction of Phenyl 2-*O*-Acetyl-4,6-*O*-benzylidene-3-deoxy-3-nitro-β-D-glucopyranoside (3) with Sodium Azide. i. Using Acetonitrile as the Solvent.—To a solution of **3** (830 mg, 2.0 mmol) in acetonitrile (24 ml) containing water (3 ml) was added sodium azide (143 mg, 2.2 mmol). The mixture was gently agitated for 10 hr at room temperature by means of a magnetic stirrer and then evaporated *in vacuo* at 40°. The remaining material was washed with water and crystallized from ethanol to give 740 mg (93%) of **5** as needles of mp 180° dec, R_f 0.78, and $[\alpha]^{20}D$ −43.1° (*c* 1, $CHCl_3$).

Anal. Calcd for $C_{19}H_{18}N_4O_8$: C, 57.28; H, 4.55; N, 14.07. Found: C, 57.47; H, 4.68; N, 14.10.

ii. **Using Dimethylformamide as the Solvent.**—To a solution of **3** (830 mg, 2.0 mmol) in DMF (12 ml) and water (1.5 ml) was added sodium azide (143 mg, 2.2 mmol). The mixture was stirred for 10 hr at room temperature and then poured into 100 ml of water. A separated semicrystalline mass was collected. Recrystallization from acetone–ethanol afforded **7** (600 mg, 85%): mp 238–239° dec; R_f 0.69; $[\alpha]^{20}D$ −36.7° (*c* 1, $CHCl_3$).

(13) If the nitro group is situated at the β position of carbonyl or ester group, nitrous acid can be eliminated easily. *E.g.*, M. C. Kloetzel, *J. Amer. Chem. Soc.*, **70**, 3571 (1948); H. H. Baer and W. Rank, *Can. J. Chem.*, **47**, 2811 (1969).

(14) A. S. Bailey and J. E. White, *J. Chem. Soc., B*, 819 (1966).

(15) H. Wolff, *Org. React.*, **3**, 307 (1946).

(16) T. Nakagawa, Y. Sato, T. Takamoto, F. W. Lichtenthaler, and N. Majer, *Bull. Chem. Soc. Jap.*, **43**, 3866 (1970).

Anal. Calcd for $C_{38}H_{34}N_4O_{10}$: C, 64.58; H, 4.85; N, 7.93. Found: C, 64.77; H, 4.98; N, 8.15.

Reaction of Phenyl 4,6-*O*-Benzylidene-2,3-dideoxy-3-nitro-β-D-*erythro*-hex-2-enopyranoside (4) with Hydrazoic Acid.—To 4 (355 mg, 1 mmol) in acetonitrile (8 ml) was added a chloroform solution containing excess hydrazoic acid. The mixture was stirred for 10 hr at room temperature and then evaporated *in vacuo* to give a crystalline residue. Recrystallization from ethanol afforded an almost quantitative yield of 5 which was found to be identical with the product obtained above by tlc, ir, and nmr comparison.

Reaction of Phenyl 2-Azido-4,6-*O*-benzylidene-2,3-dideoxy-3-nitro-β-D-glucopyranoside (5) with Sodium Azide.—Nitro azide 5 (398 mg, 1 mmol) and sodium azide (65 mg, 1 mmol) were stirred in distilled DMF (10 ml) for 10 hr at room temperature. The mixture was evaporated *in vacuo* to afford a white material which was washed with water. Recrystallization from ethanol to give 6 with contamination of a trace of 7. Column chromatography on silica gel with benzene removed the trace of 7 completely to afford pure 6: mp 188.5–189.0°; R_f 0.08; $[\alpha]^{20}D$ −108° (*c* 1, acetone).

Anal. Calcd for $C_{19}H_{17}N_3O_4$: C, 64.95; H, 4.88; N, 11.96. Found: C, 65.13; H, 4.80; N, 12.27.

Hydrogenation of 7.—7 (706 mg, 1 mmol) was stirred under hydrogen with prereduced Raney nickel in dioxane containing a catalytic amount of triethylamine for 2 days. After the reaction mixture was filtered, evaporation of the filtrate afforded white powder. Recrystallization from ethanol afforded crystalline 8 (85%): mp 215° dec; $[\alpha]^{20}D$ −93.9° (c 0.25, DMSO); ir (KBr) 3350 cm^{-1} (NH).

Anal. Calcd for $C_{38}H_{36}N_4O_8$: C, 67.44; H, 5.36; N, 8.28. Found: C, 67.17; H, 5.65; N, 8.25.

To a solution of 8 (338 mg, 0.5 mmol) in methanol (40 ml) was added acetic anhydride (5 ml). The solution was allowed to stand for 2 hr and then evaporated *in vacuo*. The remaining material was washed with water and recrystallized from DMF–water to give a white powder phenyl 3-acetamido-4,6-*O*-benzylidene-2,3-dideoxy-2-(phenyl 4′,6′-*O*-benzylidene-2′,3′-dideoxy-β-D-*erythro*-hexopyranosido[2′,3′-*d*]triazolyl)-β-D-glucopyranoside (9) in 87% yield: mp 222–224° dec; $[\alpha]^{20}D$ −17.0° (*c* 0.5, DMSO); ir (KBr) 3270 (NH) and 1660 cm^{-1} (NHAc).

Anal. Calcd for $C_{40}H_{38}N_4O_9$: C, 66.84; H, 5.33; N, 7.80. Found: C, 66.40; H, 5.47; N, 7.85.

Reaction of 4 with 6.—4 (355 mg, 1 mmol) and triazole 6 (351 mg, 1 mmol) were stirred in acetonitrile (24 ml) for 10 hr at room temperature, and the mixture was then evaporated *in vacuo* to afford a white crystalline material. Recrystallization from ethanol–acetone gave 7 (88%).

Phenyl 4,6-*O*-Benzylidene-3-deoxy-2-*O*-methyl-3-nitro-β-D-glycopyranoside (12).—To a solution of 5 (398 mg, 1 mmol) in absolute methanol (30 ml) was added a catalytic amount of sodium methoxide. The mixture was stirred for 8 hr at room temperature and evaporated *in vacuo*. The remaining material was washed with water and crystallized from ethanol to give 12 (290 mg, 75%): mp 170.0–170.5°; $[\alpha]^{20}D$ −64.6° (*c* 1, $CHCl_3$); ir (KBr) 1560 cm^{-1} (NO_2); nmr ($CDCl_3$) τ 4.92 (d, 1, J = 7 Hz, H-1), 5.22 (t, 1, J = 10 Hz, H-3), 6.40 (s, 3, OMe).

Anal. Calcd for $C_{20}H_{21}NO_7$: C, 62.01; H, 5.46; N, 3.62. Found: C, 61.72; H, 5.42; N, 3.65.

Reaction of Methyl 4,6-*O*-Benzylidene-2,3-dideoxy-3-nitro-β-D-*erythro*-hex-2-enopyranoside (2) with Sodium Azide in the Presence of 5.—To solution of 5 (398 mg, 1 mmol) and 2[17] (293 mg, 1 mmol) in acetonitrile (16 ml) and water (2 ml) was added sodium azide (65 mg, 1 mmol). After stirring for 3 hr at room temperature, the reaction mixture was evaporated *in vacuo*. The remaining material was washed with water and chromatographed on a column (3 × 14 cm) of silica gel using benzene as an eluent. The azide 5, which was eluted as the first portion, was recovered in 70% yield and a trace amount of several products were fractionally isolated, although their structures have not yet been determined. Methyl 4,6-*O*-benzylidene-2,3-dideoxy-2-(methyl 4′,6′-*O*-benzylidene-2′,3′-dideoxy-β-D-*erythro*-hexopyranosido-[2′,3′-*d*]triazolyl)-3-nitro-β-D-hexopyranoside (11), corresponding to 7, but its configuration at C-2 of the nitro sugar moiety has not been determined, was eluted as the last portion and obtained in 62% yield: mp 222° dec; $[\alpha]^{20}D$ −62.5° (*c* 1, $CHCl_3$); ir (KBr) 1560 cm^{-1} (NO_2); nmr ($CDCl_3$) τ 4.18 (s, 1, H-1′), 6.49 (s, 3, OMe), 6.64 (s, 3, OMe).

Anal. Calcd for $C_{28}H_{30}N_4O_{10}$: C, 57.73; H, 5.19; N, 9.62. Found: C, 57.79; H, 5.32; N, 9.80.

Reaction of Nitro Olefin 4 with Picryl Azide.—To a solution of nitro olefin 4 (355 mg, 1 mmol) and picryl azide (254 mg, 1 mmol) in distilled dioxane (20 ml) was added 1 *N* sodium hydroxide (0.4 ml). The reaction mixture was allowed to stand at room temperature for 12 hr and then evaporated *in vacuo*. Diethyl ether (70 ml) was added to the residue, and the resultant solid was filtered. The precipitate was recrystallized from ethanol–benzene to give 240 mg (68%) of 7.

Reaction of Methyl 2-*O*-Acetyl-4,6-*O*-bromoethylidene-3-deoxy-3-nitro-β-D-glucopyranoside (14) with Sodium Azide.—To a solution of 14 (740 mg, 2 mmol) in DMF (16 ml) and water (2 ml) was added sodium azide (130 mg, 2 mmol). The mixture was stirred for 10 hr at room temperature and poured into water (100 ml). Separated semicrystalline material was collected. Recrystallization from ethanol afforded 10 (72%): mp 170.0–170.5°; $[\alpha]^{20}D$ −40.7° (*c* 1, CH_3Cl_3); ir (KBr) 1560 cm^{-1} (NO_2); nmr ($CDCl_3$) τ 4.13 (s, 1, H-1′), 6.42 (s, 3, OMe), 6.58 (s, 3, OMe).

Anal. Calcd for $C_{18}H_{24}N_4O_{10}Br_2$: C, 35.07; H, 3.90; N, 9.09. Found: C, 35.47; H, 4.05; N, 9.35.

Registry No.—2, 25541-58-6; 3, 39727-45-2; 4, 39727-46-3; 5, 39727-47-4; 6, 39710-80-0; 7, 37342-70-4; 8, 37342-71-5; 9, 37342-72-6; 10, 37342-68-0; 11, 37342-69-1; 12, 39727-48-5; 13, 39727-49-6; 14, 39727-50-9; phenyl 3-deoxy-3-nitro-β-D-glucopyranoside, 39727-51-0; methyl 3-deoxy-3-nitro-β-D-glucopyranoside, 39727-52-1; sodium azide, 26628-22-8.

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(17) H. H. Baer and T. Neilson, *Can. J. Chem.*, **43**, 840 (1965).

The Synthesis of Pteridine-6-carboxamides. 9-Oxofolic Acid and 9-Oxoaminopterin[1]

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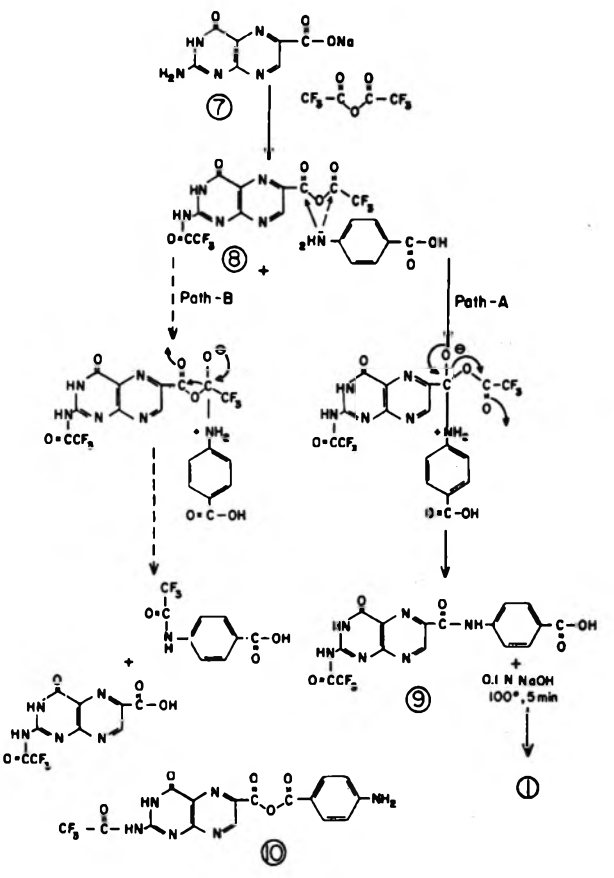
A new and general method for the preparation of several 7-unsubstituted pteridine-6-carboxamides has been developed. This method has been successfully employed for the synthesis of 9-oxofolic acid and 9-oxoaminopterin as well as certain γ-glutamyl derivatives of these analogs. These procedures involve the simultaneous protection, solubilization, and mixed anhydride formation of a pteridine-6-carboxylic acid by reaction with trifluoroacetic anhydride. The activated pteridines have proven to be stable enough to permit removal of excess trifluoroacetic anhydride and trifluoroacetic acid followed by direct coupling to various nucleophiles such as amines and amino acids. In addition we report the preparation of α-amino-*p*-toluic acid.

A number of substituted pteridine-6-carboxamides have been prepared by the condensation of an appropriately substituted 6-amino-5-nitrosopyrimidine with cyanoacetamides or malonamides.[2,3] In either case the resulting product is a 7-amino- *and* a 7-hydroxypteridine-6-carboxamide, depending on reaction conditions and the nature of the substituted amides used. No general method has, to our knowledge, been reported for the synthesis of 7-unsubstituted pteridine-6-carboxamides. We here describe the preparation of several such compounds which are analogs of folic acid.

The intermediate 2-amino-4-hydroxypteridine-6-carboxylic acid (P-6-COOH) is accessible by the oxidation of the corresponding 6-hydroxymethylpteridine.[4] The use of the free acid directly in the preparation of carboxamides was impaired owing to its insolubility. Several attempts to make suitable soluble derivatives were unsuccessful. In the case of pteroic acid, solubilization in dimethylformamide (DMF) can be accomplished by trifluoroacetylation at the 2- and 10-amino functions, and the trifluoroacetylated derivative can be successfully used for peptide bond formation at the carboxyl group by several standard procedures.[5] A similar attempt to prepare *N*-2-trifluoroacetyl-P-6-COOH was unsuccessful. However, the reaction of the sodium salt **7** (Scheme I) with trifluoroacetic anhydride for 4 hr gave a product soluble in DMF. Excess anhydride and acid were removed by codistillation with benzene from the DMF solution at 40° *in vacuo*. This product, upon treatment with dilute base, was converted cleanly to **7**, a result which precludes trifluoroacetylation of the pteridine nucleus.[6]

Emmons,[7] Bourne,[8] and Duckworth[9] have studied the reaction of various carboxylic acids with trifluoroacetic anhydride and established the formation of the mixed anhydride of the corresponding acids by infrared spectral studies in solution. It appeared that our

SCHEME I



product in DMF was the trifluoroacetyl mixed anhydride of pteridine-6-carboxylic acid (**8**); this suggested its use for preparing the desired carboxamides by way of the unprecedented peptide-forming reaction shown in Scheme I. The process envisioned here would require the attack of the nucleophile on the carbonyl group attached to the pteridine moiety (path A, solid arrows) in preference to the carbonyl group of the trifluoroacetyl function (path B, broken arrows) with subsequent displacement of the trifluoroacetate anion, to give compound **9**. It is apparent that a partial positive charge at the carbonyl function attached to C_6 can be easily accommodated by delocalization with the pteridine ring, and path A would then be the preferred route. In the absence of such a stabilizing effect, as in the case of the reaction of acetyl trifluoroacetate or benzoyl trifluoroacetate with amines, the reaction would be expected to proceed predominantly by the

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(2) O. Vogel and E. C. Taylor, *J. Amer. Chem. Soc.*, **79**, 1518 (1957).

(3) T. S. Osdene, A. A. Santilli, L. E. McCardle, and M. E. Rosenthale, *J. Med. Chem.*, **9**, 697 (1966).

(4) C. M. Baugh and E. Shaw, *J. Org. Chem.*, **29**, 3610 (1964).

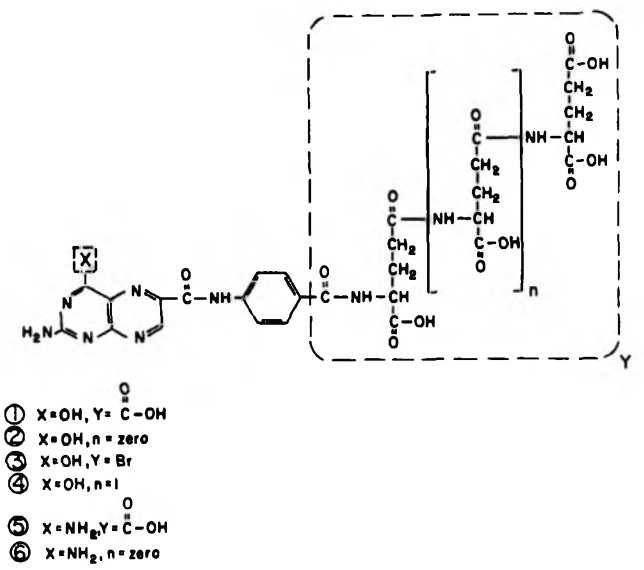
(5) C. L. Krumdieck and C. M. Baugh, *Biochemistry*, **8**, 1568 (1969).

(6) A. G. Anderson, Jr., and R. G. Anderson, *J. Org. Chem.*, **27**, 3578 (1962).

(7) W. D. Emmons, K. S. McCallum, and A. F. Ferris, *J. Amer. Chem. Soc.*, **75**, 6047 (1953).

(8) E. F. Bourne, M. Stacey, J. C. Tatlow, and R. Worrall, *J. Chem. Soc.*, 2006 (1954).

(9) A. C. Duckworth, *J. Org. Chem.*, **27**, 3146 (1962).



① X=OH, Y= O=C-OH
② X=OH, n = zero
③ X=OH, Y = Br
④ X=OH, n=1
⑤ X=NH_2, Y= O=C-OH
⑥ X=NH_2, n = zero

Figure 1.

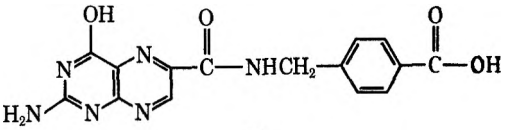
alternate route (path B). Indeed, when benzoyl trifluoroacetate is treated with aniline, trifluoroacetanilide was the only product detected.[8]

The reaction of molar equivalents of intermediate **8** and *p*-aminobenzoic acid at room temperature for 18 hr, and subsequent work-up, gave 2-trifluoroacetylamino-9-oxopteroic acid (**9**). Removal of the trifluoroacetyl group by base treatment shifts the λ_{max} of the uv absorption of this compound to shorter wavelengths of 370 and 279 nm with a shoulder at 310 nm. This shift of the uv maxima is general in the 9-oxopteroic acid series and serves as a diagnostic tool to study the progress of the deprotection reaction. The nmr spectrum of **1**[10] showed the expected signals due to the aromatic protons at 7.95 and 7.61 ppm as two doublets (J = 8 cps), and the C_7 proton of the pteridine ring resonated as a singlet at a field strength of 9.18 ppm. This is 36 cps deshielded, as compared to the resonance of the C_7 proton of folic acid,[11] which can be readily accounted for by considering the peri effect of the carbonyl group at C_9. Compound **1** did not show any infrared absorption indicative of the alternate structure **10**. Attempts were made to improve the yield of **1** beyond the initial 45% by increasing the amount of the nucleophile relative to **8**. In contrast to expectations, a detrimental effect resulted. Protection of the carboxyl group of *p*-aminobenzoic acid by trimethylsilylation[12] also did not increase the formation of the desired product. An attempt was made to reactivate any *N*-2-trifluoroacetyl-P-6-COOH, if present in the reaction mixture, by the isobutyl chloroformate method, prior to the addition of the nucleophile. This again led to no further improvement in the yield. As further evidence in substantiating the structure,[10] product **1** was hydrolyzed cleanly with 6 *N* HCl in glacial HOAc to the starting materials.

Compound **2**, 9-oxofolic acid[13] (Figure 1), was similarly prepared by using *p*-aminobenzoyl-L-glutamate as the nucleophile. The 9-oxofolic acid was obtained in 40% yield after DEAE cellulose chromatography. This structure was confirmed by acid hydrolysis to P-6-COOH, *p*-aminobenzoic acid, and glutamic acid, identified by comparison with authentic samples, and further substantiated by the presence of the characteristic nmr resonances expected of this compound. The generality of this reaction was established by using a simple aromatic amine as the nucleophile as in the preparation of **3**.

The required triglutamate of *p*-aminobenzoic acid for the synthesis of compound **4** was prepared by solid-phase peptide synthesis.[5] Solubilization of the peptide was accomplished by trimethylsilylation with hexamethyldisilazane using an acid catalyst.[12] The trimethylsilyl derivative was then coupled directly with **8** and the product was purified by ion exchange chromatography. The structure of **4** was apparent from its uv spectrum in 0.1 *N* NaOH, which showed λ_{max} at 370, 310, and 278 nm, characteristic of the 9-oxopteroic acid analogs **1**, **2**, and **3**. The structure of the triglutamate was established beyond doubt earlier.[5] On vigorous acid hydrolysis, **4** gave P-6-COOH, *p*-aminobenzoic acid, and glutamic acid.

It appears that a general method is at hand to prepare a large variety of pteridine-6-carboxamides from an appropriate amine or amino acid and pteridine-6-carboxylic acid. The synthesis of 9-oxoisohomopteroic



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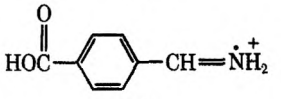


12

acid (**11**) was of interest since homofolic acid has considerable biological significance.[14-16] The nucleophile, α-amino-*p*-toluic acid, required for coupling with **8** was synthesized as follows. The oxime of the commercially available *p*-carboxybenzaldehyde was prepared according to standard procedure. This was hydrogenated with 5% Pd/C to the amino acid. The white, crystalline material thus obtained in our hands, with mp 294–295° on a Fisher-Johns apparatus and 273–274° in a sealed tube, differed considerably in physical properties from the pink compound reported by Levine and Sedlecky,[17] mp 347.5°, and Dewing.[18] The oxime showed the expected nmr signals at 10.2 (s, carboxy), 8.3 (s, vinyl, no exchange with D_2O), and 7.9 ppm (q, J = 7 cps, 4 protons) typical of the AB system of aromatic protons. In α-amino-*p*-toluic acid, the benzylic protons resonated as a quartet at 4.15 (2 protons, J =

(10) The difficulties encountered in obtaining correct elemental analyses of pteridines and pteroic acids are well known. Although no difficulties were experienced with regard to the analyses of these compounds, the authors felt it necessary to characterize these by nmr and degradation.

(11) E. J. Pastore, *Ann. N. Y. Acad. Sci.*, **186**, 43 (1971).

(12) D. Birkofer and A. Ritter, *Angew. Chem., Int. Ed. Engl.*, **4**, 417 (1965).

(13) When *n* in Figure 1 is zero, the second and terminal glutamyl moieties drop out and the monoglutamyl derivative results.

(14) L. Goodman, J. DeGraw, R. L. Kisliuk, M. Friedkin, E. J. Pastore, E. J. Crawford, L. T. Plante, A. A. Nahas, J. F. Morningstar, G. Kwok, L. Wilson, E. F. Donovan, and J. Ratzan, *J. Amer. Chem. Soc.*, **86**, 308 (1964).

(15) J. A. R. Mead, A. Goldin, R. L. Kisliuk, M. Friedkin, L. Plante, E. J. Crawford, and G. Kwok, *Cancer Res.*, **26**, 2374 (1966).

(16) R. L. Kisliuk, M. Friedkin, L. H. Schmidt, and R. N. Rossan, *Science*, **156**, 1616 (1967).

(17) M. Levine and R. Sedlecky, *J. Org. Chem.*, **24**, 115 (1959).

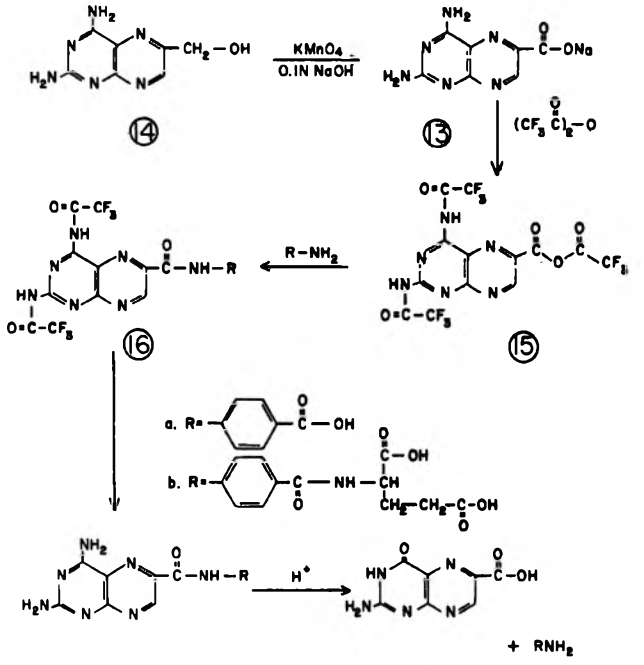
(18) T. Dewing, *J. Chem. Soc.*, 466 (1946).

6 cps) and a doublet of doublets at 7.3 and 7.9 ppm (J = 8 cps), which we attribute to the aromatic protons adjacent to the aminomethyl group and the carboxyl group, respectively. A parent peak in the mass spectrum of α-amino-*p*-toluic acid at m/e 150 was seen, which is also the observable molecular ion. This is a characteristic phenomenon associated with benzyl amines owing to the formation of ionic species **12**.[19] These findings conclusively established the accuracy of the structure, the identity of our material, and that the previous claim[17,18] on this material is in error.

After α-amino-*p*-toluic acid was coupled with **8** in the usual manner, the crude product was deprotected and purified by DEAE cellulose ion exchange chromatography. Compound **11** had the expected uv characteristics and nmr signals.

We next directed our attention to the synthesis of the 9-oxo analog of aminopterin (**6**) and 2,4-diamino-4-deoxy-9-oxopteroic acid (**5**).[20] This required the preparation of the sodium salt of 2,4-diaminopteridine-6-carboxylic acid (**13**). A 2,4-diaminopteridine is quite prone to deamination at the 4 position.[20] Therefore, mild conditions had to be used for the preparation of **13**, which was accomplished after a great deal of experimentation. Thus the carefully controlled oxidation of 2,4-diamino-6-hydroxymethylpteridine[4] (**14**) with $KMnO_4$ gives a mixture of **13** and **7** in about 6:1 ratio, which was readily separated by ion exchange chromatography. It was expected that, on treatment of **13** with trifluoroacetic anhydride, both the amino functions would be trifluoroacetylated, and the resulting compound, **15**, would be stable under the reaction conditions. These reactions are summarized in Scheme II.

SCHEME II[a]



[a] For **5**, R = benzoic acid, "a" series; for **6**, R = benzoyl-glutamic acid, "b" series.

p-Aminobenzoic acid and *p*-aminobenzoyl-L-glutamic acid were used as nucleophiles for coupling with intermediate **15** to prepare 4-amino-4-deoxy-9-oxopteroic acid (**5**) and 9-oxoaminopterin (**6**), respectively. Unlike **7**, compound **13**, when stirred with trifluoroacetic anhydride at room temperature, goes into solution. Removal of excess anhydride was carried out by codistillation with benzene *in vacuo*, and the coupling reaction was carried out in DMF. Deprotection of the 2- and 4-amino groups was accomplished by allowing the reaction mixture to sit at room temperature for 72 hr at pH 7.5. The final purifications were carried out by ion exchange chromatography. Both **5** and **6** had ultraviolet spectra very similar to those of **1** and **2** in 0.1 *N* NaOH, but could easily be distinguished from them by their profound differences in λ_{max} when examined in 0.1 *N* HCl, where both **5** and **6** absorb at 346 and 271 nm.

Experimental Section

Melting points are uncorrected and were determined on a Fisher-Johns apparatus. Nmr spectra were run in 0.1 *N* NaOD in D_2O on a HA-60-Varian spectrometer or Varian XL-100 with TMS as lock signal unless otherwise specified. Field strengths of the various proton resonances are expressed in parts per million and coupling constants as cycles per second. Peak multiplicity is depicted as usual: s for singlet, d for doublet, t for triplet, q for quartet, and c for complex. Ultraviolet spectra were determined on a Beckman DU or a Bausch and Lomb Spectronic 505 spectrophotometer. All chromatography was carried out on DEAE cellulose in the chloride form with 1.2 × 22 cm packing. A linear NaCl gradient, 0.005 *M* phosphate buffer pH 7.0 from zero to 0.5 *M* with respect to NaCl, was used to elute the column in a total volume of 2 l. Infrared spectra were run on a Beckman infrared spectrophotometer. Mass spectra were determined at the Research Triangle Institute by Dr. David Rosenthal. Elemental analyses[21] (Table I) were by Galbraith Laboratories, Inc., Knoxville, Tenn. Yields represent the actual amount of pure compound isolated, assuming 100% reaction.

TABLE I
ANALYSES

Compd	Molecular formula	
P-6-COOH	$C_7H_5N_5O_3 \cdot {}^1/_2H_2O$	C, H, N[a]
1	$C_{14}H_{10}N_6O_4 \cdot 2H_2O$	C, H,[b] N, O
2	$C_{19}H_{17}N_7O_7$	C, H, N, O
3	$C_{13}H_9BrN_6O_2 \cdot {}^1/_2H_2O$	C, H, N
5	$C_{14}H_{11}N_7O_3 \cdot {}^1/_2H_2O$	C, H,[c] N
6	$C_{19}H_{18}N_8O_6$	C, H, N
11	$C_{15}H_{12}N_6O_4 \cdot {}^1/_2H_2O$	C, H, N
α-Amino-*p*-toluic acid	$C_8H_9NO_2$	C, H, N, O

[a] N: calcd 32.41; found, 31.96. [b] H: calcd 3.86; found 3.30. [c] H: calcd 3.16; found 3.66.

Preparation of the Sodium Salt of Pteridine-6-carboxylic Acid (7).—Pteridine-6-carboxylic acid was prepared according to the procedure of Baugh and Shaw[4] and was dissolved in a minimum amount of 1 *N* NaOH at 50° and allowed to cool. Absolute EtOH was then added while stirring until the solution became cloudy. On standing in the refrigerator, it crystallized as yellow needles. The solid was collected by filtration, washed with 95% EtOH to remove excess NaOH, and dried *in vacuo* for several hours at 80°.

Preparation of the Protected, Solubilized, and Activated Trifluoroacetyl Mixed Anhydride of Pteridine-6-carboxylic Acid (8) and Hydrolysis to P-6-COOH.—In a typical procedure 1 mmol of **7** was stirred at room temperature with 9 ml of trifluoroacetic anhydride for 4 hr. The reaction mixture was carefully protected from moisture. The white fluffy solid which remained after this

(19) D. Rosenthal, Research Triangle Institute, N. C.

(20) D. R. Seeger, D. B. Cosulich, J. M. Smith, Jr., and M. E. Hultquist, *J. Amer. Chem. Soc.*, **71**, 1753 (1949).

(21) Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements or functions were within 0.4% of the theoretical values.

period was collected by filtration and dried *in vacuo*.[22] This material, on treatment with 0.1 *N* NaOH at 100° for 5 min and acidification, gave P-6-COOH, uv λ_{max} 365 and 265 nm, $\lambda_{365}/\lambda_{265}$ = 2.7 in 0.1 *N* NaOH.[4]

General Procedure for the Preparation of Reactive Intermediate 8.—Reaction of 1 mmol of P-6-COOH with trifluoroacetic anhydride was carried out as described above. At the end of the reaction period 4 ml of dry DMF was added. After the solid had dissolved, 25 ml of dry benzene was added to the clear yellow solution and the solution was concentrated *in vacuo* to about 5 ml. The process of adding benzene and concentration of the resulting solution was repeated at least three additional times to ensure the complete removal of excess anhydride. These operations were carried out under strictly anhydrous conditions, and the temperature at no stage was allowed to rise above 40°. Intermediate 8, thus prepared, was used directly for coupling with various amines.

Preparation of 9-Oxopteroic Acid (1).—The above solution containing reactive intermediate 8 was allowed to react with 1 mmol of *p*-aminobenzoic acid at room temperature for 18 hr under anhydrous conditions. Ice (40 g) was added to the reaction mixture and the pH of the solution was adjusted to 2. The resulting precipitate was collected by centrifugation, λ_{max} 300 and 382 nm, λ_{min} at 340 and 365 nm in 0.1 *N* NaOH. The precipitate was dissolved in 0.1 *N* NaOH and heated on a water bath and the progress of hydrolysis of the trifluoroacetyl group from the 2-amino function (*vide infra*) was monitored by the characteristic change in the uv spectrum. After 5 min the spectrum showed λ_{max} at 370 nm (ϵ 11,830), 310 (17,290), and 279 (24,115); further heat treatment did not change the spectrum. The solution was adjusted to pH 7.3, applied to a DEAE cellulose Cl^- column, and eluted with a linear NaCl gradient. Three compounds were eluted at 0.05, 0.11, and 0.315 *M* NaCl concentrations. These were identified by their spectral characteristics as *p*-aminobenzoic acid, P-6-COOH, and 9, respectively. The major product was then eluted with concentrated NH_4OH. It should be noted that retreatment of the peak eluting at 0.315 *M* NaCl with 0.1 *N* NaOH at 100° for 5 min converted it to the product eluting with NH_4OH. The ammoniacal peak was pooled and evaporated to a small volume *in vacuo*. When the pH was lowered to 2.0 a yellow precipitate was formed. The solid was filtered, washed, and dried to give 45% yield of the desired product, 1, as a golden yellow solid. In 0.1 *N* HCl λ_{max} are found at 320 and 255 nm and λ_{min} at 350 and 290 nm; nmr 9.18 (s, one proton, H_7), 7.95 (d, two protons, J = 8 cps, $H_{2',6'}$), and 7.61 ppm (d, two protons, J = 8 cps, $H_{3',5'}$). No ir bands were seen between 1750 and 1850 cm^{-1}.

Hydrolysis of 9-Oxopteroic Acid as a Confirmation of Structure.—This is typical of the general method employed for the hydrolysis of all 9-oxo analogs. 9-Oxopteroic acid (10 mg) was dissolved in 5 ml of 6 *N* HCl and 5 ml of glacial HOAc and refluxed for 1 hr. The solution was then evaporated to dryness. Water (5 ml) was added and the pH was adjusted to 7.5. This solution was chromatographed on the standard DEAE cellulose Cl^- column as described. P-6-COOH and *p*-aminobenzoic acid were recovered as substantiated by their uv spectra and the molarity of NaCl required for elution.

Preparation of 9-Oxofolic Acid (2).—8 and *p*-aminobenzoyl-L-glutamic acid (1 mmol of each) were treated for 18 hr. The procedure to obtain the crude product was the same as described for 1. Deprotection was carried out by dissolving the product in 40 ml of water with the dropwise addition of 1 *N* NaOH until the pH of the solution was 10. The solution was then heated for 5 min in a boiling water bath. Further heating did not produce further changes in the uv spectrum. Therefore, deprotection was assumed to be complete. The pH was adjusted to 7.3 and the reaction mixture was chromatographed on DEAE cellulose as described for 1. In addition to 7 and *p*-aminobenzoyl glutamate, two peaks were eluted, a minor peak at 0.29 *M* NaCl showed the uv characteristics of the protected product with λ_{max} at 300 and 384 nm, and a major peak at 0.39 *M* NaCl, which is the fully deprotected product. Re-treatment of the minor peak with base and heat quantitatively converted it to product 2. The major peak was pooled and concentrated to dryness *in vacuo*. The residue was suspended in 50 ml of 0.1 *N* HCl and the bright yellow solid was collected by filtration. After washing and drying, a yield of 44% was calculated. The melting point was above 300°. In 0.1 *N* NaOH λ_{max} are found at 374 nm (ϵ 12,512), 310 (17,420), and 279 (24,960); nmr in 0.1 *N* NaOD 9.20 (s, one proton, H_7), 7.89 (d, two protons, J = 8 cps, $H_{2',6'}$), 7.65 (d, two protons, J = 8 cps, $H_{3',5'}$), 4.65 (t, α proton of glutamic acid), and 2.60 ppm (c, four protons, glutamic acid).

Preparation of 2-Amino-4-hydroxy-N^{10}-(*p*-bromophenyl)pteridine-6-carboxamide (3).—The coupling reaction was carried out in the usual manner, using 1 mmol each of 8 and *p*-bromoaniline. At the end of the reaction, 40 g of ice was added, the pH was adjusted to 10.2, the reaction mixture was heated for 5 min at 100° and cooled, and the pH was adjusted to 7.2. A yellow precipitate was rapidly formed; this was collected by centrifugation, redissolved in 0.1 *N* NaOH, and diluted to 50 ml so that the pH was 10. The pH was again lowered to 7.2 and the precipitate was collected. This process was repeated three times to remove traces of 7. The product was washed several times with water, then dried to obtain the analytical sample, mp >300°, yield 50%. The nmr spectrum of 3 showed the expected resonance of the aromatic protons as a clean AB quartet at 6.9 ppm (J = 8 cps) and the C_7 proton as a singlet at 8.73 ppm. The uv spectrum showed the characteristic maxima at 375, 310, and 275 nm, generally observed for all 9-oxo analogs of folic acid. These observations provide further evidence to the validity of the structures 1 and 2.

Preparation of 9-Oxopteroylglutamyl-γ-glutamyl-γ-glutamic Acid (4).—The hydrochloride of the triglutamate of *p*-aminobenzoic acid (1 mmol) was suspended in 4 ml of hexamethyldisilazane and heated under reflux. After 1.5 hr solution was complete. Refluxing was continued for an additional 0.5 hr. Excess reagent was removed *in vacuo*. Freshly distilled triethylamine (1 ml) was added with stirring for 5 min. The excess triethylamine was taken off at reduced pressure and the product was dried *in vacuo* for 4 hr. This was dissolved in 4 ml of DMF and coupled in the usual manner with intermediate 8. After work-up and deprotection, the compound was purified by chromatography. The desired product was eluted at 0.5 *M* NaCl as a single band. The compound showed λ_{max} in 0.1 *N* NaOH at 379 and 276 nm with a shoulder at 310 nm; the spectrum is very similar to that of 9-oxofolic acid. Hydrolysis of this compound in the usual manner gave 7, *p*-aminobenzoic acid, and glutamic acid, all identified by comparison with authentic samples.

Preparation of 2,4-Diaminopteridine-6-carboxylic Acid.—The parent compound, 14, was obtained by a previously known procedure.[4] The hydroxymethylpteridine (100 mg) was dissolved in 20 ml of 0.1 *N* NaOH at room temperature and stirred. $KMnO_4$ (200 mg) was added dropwise from a saturated solution. The temperature was maintained at 25° for 1 hr, then EtOH was added to destroy excess permanganate. The coagulated precipitate, MnO_2, was removed by filtration and washed two times with 20-ml portions of water. The combined extracts were then brought to pH 4.0 and a yellow precipitate formed. This was collected, after cooling, by centrifugation and washed with water to obtain crude 2,4-diaminopteridine-6-carboxylic acid.

Purification was achieved by chromatography on DEAE cellulose Cl^-. A small amount of starting material and 2-amino-4-hydroxypteridine-6-carboxylic acid were separated from the product. These products were identified by their characteristic uv spectra and also by cochromatography with authentic samples. The 2,4-diaminopteridine-6-carboxylic acid in 0.1 *N* HCl showed λ_{max} at 332 and 255 nm. The crude product was used directly for subsequent syntheses.

The sodium salt of the carboxylic acid, 13, was prepared by suspending the acid in water and the gradual addition of 0.1 *N* NaOH so that the pH of the solution did not exceed 8. When all the material had gone into solution, the pH was adjusted back to 7 and the solution was evaporated to dryness. This was then dried *in vacuo* for several hours and was found to be satisfactory for the synthesis of 6.

Synthesis of 9-Oxoaminopterin (6) and 2,4-Diamino-4-deoxy-9-oxopteroic Acid (5).—The preparation of the trifluoroacetyl mixed anhydride, 15, was accomplished in a manner identical with that used for the preparation of 8. This intermediate was then coupled with 1 equiv of *p*-aminobenzoyl-L-glutamic acid at room temperature for 18 hr. The reaction mixture was then adjusted to pH 2.5 after dilution. The precipitate, 16b, thus formed was collected by centrifugation, resuspended in water, and adjusted to pH 7.5 by the addition of 0.1 *N* NaOH. After 4 days the solution was chromatographed on DEAE cellulose Cl^- and 9-oxoaminopterin was eluted at 0.39 *M* NaCl concentration. The product peak from the column was evapo-

(22) The analytical data on this substance could not be collected because of its extreme instability, as is expected of a trifluoroacetyl mixed anhydride.

rated to a small volume and acidified to pH 4 using 0.1 *N* HCl. The precipitate thus formed was collected by centrifugation, washed several times with water, and dried *in vacuo* to give 30% yield of the product, **6**, as a brown powder, mp >300°. In 0.1 *N* NaOH λ_{max} were found at 380 nm (ϵ 10,117) and 275 (23,690), and in 0.1 *N* HCl at 346 and 271 nm; nmr 9.10 (s, one proton, H_7), 7.75 (d, two protons, J = 8 cps, $H_{2',6'}$), 7.48 (d, two protons, J = 8 cps, $H_{3',5'}$), 4.62 (t, α proton of glutamic acid), and 2.65 ppm (c, four protons of glutamic acid). Hydrolysis of **6** by HCl in glacial HOAc gave P-6-COOH, *p*-aminobenzoic acid, and glutamic acid. Compound **5** was prepared in the same manner using *p*-aminobenzoic acid as the nucleophile. The product which eluted at 0.43 *M* NaCl showed λ_{max} in 0.1 *N* NaOH at 380 nm (ϵ 10,507) and 275 (22,809), and in 0.1 *N* HCl at 350 and 275 nm. On acid hydrolysis **5** gave P-6-COOH and *p*-aminobenzoic acid.

Synthesis of 9-Oxoisohomopterioc Acid (11). A. Preparation of α-Amino-*p*-toluic Acid.—*p*-Carboxybenzaldehyde (1.5 g) and 1.2 g of hydroxylamine hydrochloride were dissolved in 20 ml of EtOH and brought to reflux; a clear solution was obtained. To this was added dropwise 1.7 g of NaOH dissolved in 7 ml of water, over a period of 0.5 hr. Water (0.5 ml) was then added to bring the suspension into solution. Refluxing was continued for an additional 15 min and the reaction mixture was poured into 100 ml of ice-cold 20% HCl. The precipitate was collected by filtration and recrystallized from MeOH: yield 1.1 g; mp 223–224°; nmr (DMSO) 7.9 (q, four protons, J = 7 cps, aromatic), 8.3 (s, one proton), and 10.2 ppm (s, one proton, carboxyl).

The above oxime (1 g) was dissolved in 100 ml of 95% EtOH, 100 mg of 5% Pd/C was added, and hydrogenation was carried out for 18 hr at 30 psi. Filtration and washing the residue with two 20-ml portions of hot glacial HOAc gave a solution which was evaporated to dryness. The solid thus obtained was triturated with absolute EtOH and filtered, producing 850 mg of solid. This was crystallized from water to give the white crystalline α-amino-*p*-toluic acid: mp 294–295°; λ_{max} 234 nm (H_2O); nmr (TFA) 4.15 (q, J = 6 cps), 7.3 (d, J = 8 cps, two protons adjacent to the aminomethyl group), and 7.9 ppm (d, J = 8 cps, two protons adjacent to the carboxyl group).

Treatment of this material with diazomethane gave the corresponding methyl ester, whose high-resolution mass spectrum showed the molecular ion at 164.0708 (calculated for $C_8H_{10}NO_2$, 164.0711), again representing the loss of a hydrogen from the benzylic position.

B. Synthesis of 9-Oxoisohomopteroic Acid (11).—α-Amino-*p*-toluic acid and **8** (1 mmol of each) were treated as usual. After deprotection and chromatography on DEAE cellulose Cl^-, **11** eluted as a single band at 0.22 *M* NaCl, and was recovered from the pooled peak in about 36% yield. The uv spectral data revealed λ_{max} at 370 nm (ϵ 10,750) and 270 (25,240) and λ_{min} at 320 and 250 nm in 0.1 *N* NaOH; nmr 9.25 (s, one proton, H_7), 8.15 (d, two protons, J = 8 cps, $H_{2',6'}$), 7.7 (d, two protons, J = 8 cps, $H_{3',5'}$), and 4.67 ppm (s, two protons, benzylic). Hydrolysis of **11** with 6 *N* HCl in glacial HOAc cleanly gave P-6-COOH and α-amino-*p*-toluic acid, identified by comparison with authentic samples.

Registry No.—**1**, 39707-60-3; **2**, 39707-61-4; **3**, 39707-62-5; **5**, 39707-63-6; **6**, 39707-65-8; **8**, 39707-64-7; **11**, 39707-66-9; **15**, 39707-67-0; **16b**, 39707-68-1; P-6-COOH, 948-60-7; trifluoroacetic anhydride, 407-25-0; *p*-aminobenzoic acid, 150-13-0; *p*-aminobenzoyl-L-glutamic acid, 4271-30-1; *p*-bromoaniline, 106-40-1; α-amino-*p*-toluic acid, 56-91-7; *p*-carboxybenzaldehyde, 619-66-9; hydroxylamine hydrochloride, 5470-11-1; diazomethane, 334-88-3; α-amino-*p*-toluic acid methyl ester, 18469-52-8.

Structural Elucidation of Novel Tumor-Inhibitory Sesquiterpene Lactones from *Eupatorium cuneifolium*[1,2]

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Five new cytotoxic germacranolide lactones have been isolated from *Eupatorium cuneifolium* Willd. The structures of eupacunin (**1**) and eupacunoxin (**2**) were elaborated by chemical and spectral arguments, and confirmed by X-ray crystallographic analysis of their *o*-bromobenzoate (**4**) and *m*-bromobenzoate (**5**) derivatives, respectively. Eupatocunin (**6**) was interrelated with **1** by conversion of each to the epoxy ketone **9**, and spin-decoupling studies of **6** and **9** confirmed the structural assignments. Eupatocunoxin, isomeric with eupacunoxin (**2**), was assigned structure **7** on the basis of spectral arguments. Eupacunolin (**19**) has been characterized as a hydroxy eupacunin. Eupacunin (**1**) and its companions **2** and **19** appear to be the first recognized naturally occurring germacranolide *cis,cis*-dienes. The most abundant lactone, eupacunin, was tested *in vivo* and was found to show inhibitory activity against the P-388 leukemia in mice and the Walker 256 carcinosarcoma in rats.

In the course of a continuing search for tumor inhibitors of plant origin,[4] an alcoholic extract of *Eupatorium cuneifolium* Willd. (Compositae)[5] was found to show significant inhibitory activity *in vitro* against cells derived from human carcinoma of the nasopharynx (KB) carried in tissue culture.[6] Consequently, a systematic study aimed at the isolation of the KB inhibitory principles of *E. cuneifolium* was undertaken.

A preliminary communication[7] described the isolation and structural elucidation of the novel antileukemic germacranolide eupacunin (**1**), and of two other cytotoxic germacranolides, eupacunoxin (**2**) and eupatocunin (**6**). It is the purpose of this paper to present in detail the structural elucidation of these materials and of the companion germacranolides, eupatocunoxin (**7**)

(1) Tumor Inhibitors. LXXXV. Part LXXXIV is ref 3.

(2) This investigation was supported by grants from the National Cancer Institute (CA-11718) and the American Cancer Society (IC-57), and a contract with the Division of Cancer Treatment, National Cancer Institute (NIH-NCI-C-71-2099).

(3) S. M. Kupchan, T. Fujita, M. Maruyama, and R. W. Britton, *J. Org. Chem.*, **38**, 1260 (1973).

(4) S. M. Kupchan, *Trans. N. Y. Acad. Sci.*, **32**, 85 (1970).

(5) Whole plant gathered in Florida in 1966 and 1969. The authors acknowledge receipt of the dried plant material from Dr. Robert E. Perdue, Jr., U. S. Department of Agriculture, Beltsville, Md., in accordance with the program developed with the USDA by the National Cancer Institute.

(6) Cytotoxicity and *in vivo* inhibitory activity were assayed under the auspices of the National Cancer Institute. The procedures were those described in *Cancer Chemother. Rep.*, **25**, 1 (1962).

(7) S. M. Kupchan, M. Maruyama, R. J. Hemingway, J. C. Hemingway, S. Shibuya, and T. Fujita, *J. Amer. Chem. Soc.*, **93**, 4914 (1971).

and eupacunolin (19). A sixth germacranolide, eupaserrin, was identical with a cytotoxic lactone which was characterized in the course of a parallel study of the active principles of *Eupatorium semiserratum*.[3]

Fractionation of the ethanol extract (Chart I), guided by assay against KB (Table I), revealed that the

CHART I

FRACTIONATION OF THE CYTOTOXIC PRINCIPLES OF *Eupatorium cuneifolium* WILLD.

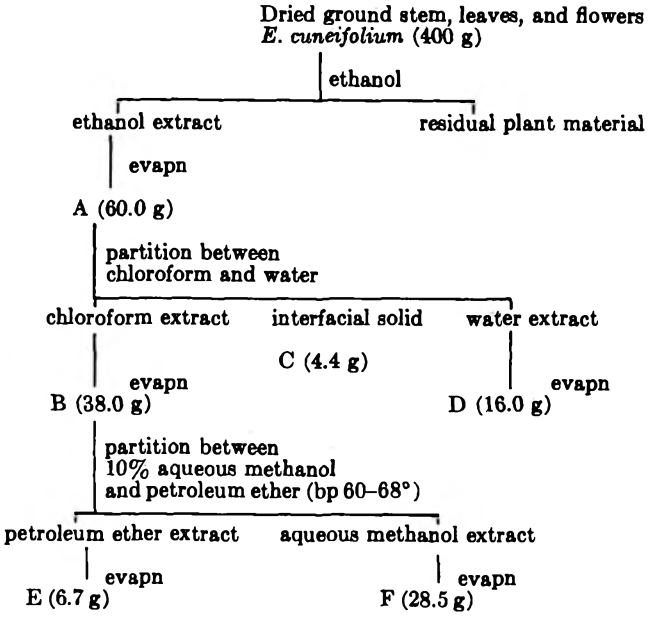


TABLE I

ACTIVITY OF FRACTIONS FROM *E. cuneifolium* AGAINST KB TISSUE CULTURE

Fraction	ED_{50}, μg/ml	Fraction	ED_{50}, μg/ml
A	1.8	L	0.5
B	2.8	M	3.9
C	19	N	2.4
D	>100	O	1.7
E	>100	P	5.6
F	1.8	1	2.1
G	1.6	2	2.1
H	2.3	6	0.11
I	6.7	7	1.7
J	3.7	19	3.7
K	7.0		

active principles were concentrated, successively, in the chloroform layer of a chloroform–water partition and in the aqueous methanol layer of a 10% aqueous methanol–petroleum ether partition. The active fraction was chromatographed on silicic acid. Eupacunin (1) and eupatocunin (6) were eluted with chloroform in two separate fractions. Eupacunoxin (2) and eupatocunoxin (7) were eluted together with 1% methanol in chloroform. They were subsequently separated by rechromatography on silicic acid and silica gel and purified by crystallization. Eupacunolin (19) was eluted with 2% methanol in chloroform and further purified by silica gel chromatography. All five compounds showed ultraviolet high intensity end absorption and infrared bands near 5.7 and 6.1 μ, which was suggestive of the presence of an α,β-unsaturated γ-lactone, a structural feature common in other sesquiterpenoids of *Eupatorium* species.[8-10] All of the lactones showed *in vitro* cytotoxicity against KB cell culture, but only eupacunin has significant *in vivo* activity against lymphocytic leukemia (PS) in mice and Walker 256 intramuscular carcinosarcoma in rats.

Elemental analysis and mass spectrometry established that eupacunin (1) and eupatocunin (6) had the same molecular formula, $C_{22}H_{28}O_7$. Similarities in spectral data indicated a close structural relationship. Spectra for eupatocunin (6) indicated the presence of a hydroxyl group (ir 2.86 μ), an acetate [ir 5.73 and 8.08 μ, nmr, τ 7.97 (3 H, s)], an α,β-exocyclic methylene γ-lactone [uv 212 nm (ε 28,000), ir 5.68 μ, and characteristic nmr signals at τ 3.76 (d, J = 2.5 Hz) and τ 4.04 (d, J = 2 Hz)] and an ester (ir 5.82 μ). These groups accounted for all of the oxygen functions of 6. The same functionalities were also indicated as present in eupacunin (1).

The nature of the ester group of eupatocunin was revealed by its nmr spectrum, which showed characteristic signals for the methyl [τ 8.10 (6 H)] and vinyl [τ 3.91 (1 H)] protons of an angeloyl residue. The corresponding signals for the isomeric tiglyoyl residue occur at somewhat different chemical shifts.[11] Methanolysis of eupatocunin yielded methyl angelate.

While the signals in the 100-MHz nmr spectrum for eupacunin (1) were not all well resolved and could not be specifically assigned (see Experimental Section), the nmr spectrum of eupatocunin (6) (see Table II) was clearly resolved and by utilizing double-resonance studies a structure for eupatocunin could be postulated. The typical pair of doublets (J = 2 and 2.5 Hz) characteristic of exocyclic (C-13) methylene protons in germacranolides[12] was collapsed to two singlets on irradiation of the multiplet at τ 6.70, which could therefore be assigned as the C-7 proton. The two well-resolved signals at τ 4.22 (dd, J = 2.5 and 11 Hz) and 4.36 (dd, J = 1 and 3 Hz), each corresponding to one proton, could be assigned to either the C-6 or C-8 proton, since the signals collapsed to doublets (J = 11 and 3 Hz, respectively) on irradiation of the C-7 proton signal. The proton giving rise to the signal at τ 4.36 was further coupled to a proton on carbon bearing hydroxyl which appeared as a multiplet at τ 5.54 and collapsed to a doublet (J = 3 Hz) on addition of D_2O. In addition the proton giving rise to the signal at τ 4.22 was further coupled to an olefinic proton which appeared as a doublet of quartets at τ 4.82 (J = 1.5 and 11 Hz). The olefinic proton was also coupled to a methyl group, τ 8.21 (d, J = 1.5 Hz). These facts supported postulation of partial structure A for eupatocunin.

A complex signal at τ 8.10, integrating for nine protons, was assigned to the two methyl groups of the angelate ester, and the other germacrane methyl group. The remaining high-field signals were two doublets of doublets at τ 7.24 (J = 2.5, 10, 14 Hz) and 7.62 (J = 4, 7, 14 Hz). On irradiation of the proton signal appearing as a doublet of doublets at τ 4.80

(8) S. M. Kupchan, J. C. Hemingway, J. M. Cassady, J. R. Knox, A. T. McPhail, and G. A. Sim, *J. Amer. Chem. Soc.*, **89**, 465 (1967).

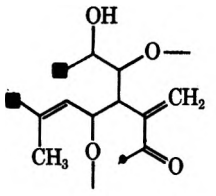
(9) S. M. Kupchan, J. E. Kelsey, M. Maruyama, and J. M. Cassady, *Tetrahedron Lett.*, 3517 (1968).

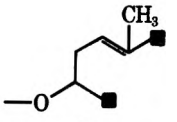
(10) S. M. Kupchan, J. E. Kelsey, M. Maruyama, J. M. Cassady, J. C. Hemingway, and J. R. Knox, *J. Org. Chem.*, **34**, 3876 (1969).

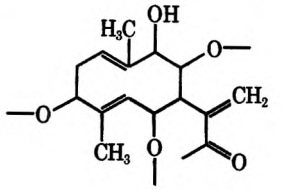
(11) H. Morimoto, Y. Sanno, and H. Oshio, *Tetrahedron*, **27**, 3173 (1966).

(12) Z. Samek, *Tetrahedron Lett.*, 671 (1970).

(J = 2.5, 4 Hz), these complex signals were simplified to doublets of doublets. Furthermore, irradiation at τ 7.24 resulted in collapse of the signals at τ 4.80 and 4.60 (m) to a doublet and narrower multiplet, respectively. These decoupling experiments suggested partial structure B for eupatocunin. Partial structures A and B could only be linked as in partial structure C, a biogenetically reasonable germacrane skeleton.

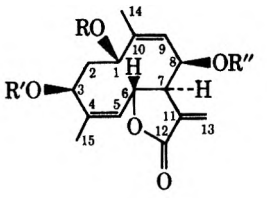

A

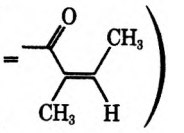

B

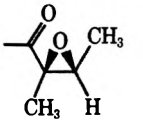

C

Eupatocunin (6) was further characterized by hydrolysis. Treatment of 6 with sodium methoxide gave a product (8) which still retained an acetyl group, but had lost an angeloyl group. This suggested that the angeloyl group in 6 was vicinal[13] to the C-9 hydroxyl group, and therefore at C-8. Consequently, the acetyl group in 6 could be assigned to C-3 and eupatocunin represented as structure 6. Additional support for this structure was furnished by its interrelationship with eupacunin (1). Oxidation of 1 and 6 with Jones reagent afforded the same product (9). The nmr spectrum of 9 was similar to that of eupatocunin. The significant changes were the disappearance of one of the vinyl methyl signals at τ 8.10 and an olefinic proton multiplet at τ 4.60, and the appearance of a methyl singlet at τ 8.53 and a doublet of doublets at τ 6.07 (J = 2, 11 Hz). These changes suggested formation of a C-1, C-10 epoxide ring in 9. Reactions of this type, involving epoxidation of allylic alcohols, have been observed previously with chromate oxidations.[14,15] The nmr spectrum of 9 also lacked the doublet at τ 5.54 (J = 3 Hz) assigned to the C-9 proton in 6, and had a new doublet at τ 4.36 (J = 3.5 Hz) which corresponded to the doublet of doublets at τ 4.36 (J = 1, 3 Hz) in the spectrum of 6. This was in good accord with the formation of a carbonyl group at C-9. Therefore the common oxidation product of 1 and 6 possessed a 1,10-epoxy 9-ketone structure. This was a reasonable proposition based on the postulated structure of 6 and suggested that 1 and 6 differed only at C-1, C-9, and C-10. Most reasonably, eupacunin (1) was presumably converted to 9 by an allylic rearrangement followed by epoxidation and oxidation.

In addition to 9, the Jones oxidation of eupacunin (1) afforded a second, more polar product 11. Elemental analysis and mass spectrometry supported a $C_{22}H_{28}O_8$

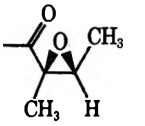


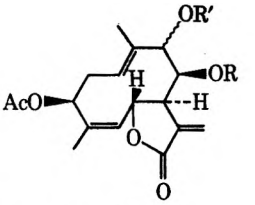
1, R = H; R′ = Ac; R″ = Ang 

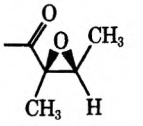

2, R = H; R′ = Ac; R″ =

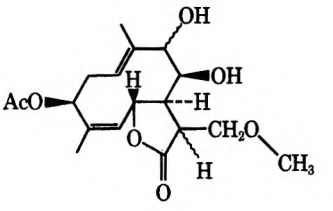
3, R = R′ = H; R″ = Ang

4, R = *o*-bromobenzoyl; R′ = Ac; R″ = Ang


5, R = *m*-bromobenzoyl; R′ = Ac; R″ =


6, R = Ang; R′ = H


7, R = H; R′ =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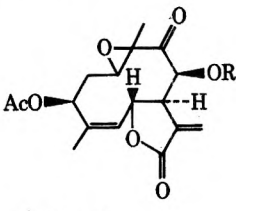
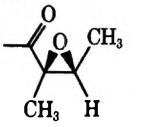

9, R = Ang


10, R =

formula for 11. The nmr spectrum of 11 showed the absence of one of the vinyl methyl signals at τ 8.10 and the presence of a methyl singlet at τ 8.66. The uv spectrum of 11 exhibited a maximum at 210 nm with an extinction somewhat lower than that for eupacunin, and the ir spectrum still showed a hydroxyl group at 2.86 μ. These spectral data were most consistent with a structure for a product which arose from 1 by an allylic rearrangement followed by epoxidation.

The postulated structures for the oxidation products of 1 and 6 were supported by the methanolysis[10,16,17] of eupacunin (1), which yielded deacetyldeangeloyl-13-methoxydihydroeupacunin (12). The C-10 methyl

(13) S. M. Kupchan, P. Slade, R. J. Young, and G. W. A. Milne, *Tetrahedron*, **18**, 499 (1962).

(14) J. Iriarte, J. N. Shoolery, and C. Djerassi, *J. Org. Chem.*, **27**, 1139 (1962).

(15) E. Glotter, S. Greenfield, and D. Lavie, *J. Chem. Soc. C*, 1646 (1968).

(16) G. H. Kulkarni, A. Paul, A. S. Rao, G. R. Kelkar, and S. C. Bhattacharya, *Tetrahedron*, **12**, 178 (1961).

(17) S. M. Kupchan, J. M. Cassady, J. E. Kelsey, H. K. Schnoes, D. H. Smith, and A. L. Burlingame, *J. Amer. Chem. Soc.*, **88**, 5292 (1966).

TABLE II

NUCLEAR MAGNETIC RESONANCE DATA[a]

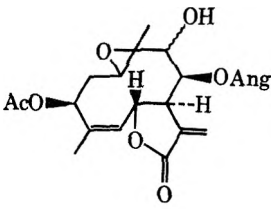
Compd	C-1	C-2	C-3	C-5	C-6	C-7	C-8	C-9	C-13	C-14	C-15	OCOR, OH, other
6	4.60 m	7.24 ddd (2.5, 10, 14) 7.62 ddd (4, 7, 14)	4.80 dd (2.5, 4)	4.82 dq (1.5, 11)	4.22 dd (2.5, 11)	6.70 m	4.36 dd (1, 3)	5.54 d (3)	3.76 d (2.5) 4.04 d (2)	8.10 s	8.21 d (1.5)	OH, 6.77 m 1-H, 3.91 m 2-CH$_3$, 8.1 m Ac, 7.97 s
7	4.8 m	7.64 ddd (3.7, 7, 15) 7.27 ddd (3, 9, 15)	4.8 m	4.8 m	4.21 dd (2, 10.5)	6.9 m	5.85 m	4.72 d (2)	3.81 d (2.5) 4.20 d (2)	8.17 br s	8.27 d (1.5)	1-H, 6.90 q (5.5) CH$_3$, 8.73 d (5.5) CH$_3$, 8.46 s Ac, 7.98 s
9[b]	6.07 dd (2, 11)	7.55 ddd (2, 5, 15) 8.30 ddd (3, 11, 15)	4.7 m	4.67 dd (1.5, 11)	4.38 dd (8, 11)	6.7 m	4.36 d (3.5)		3.63 d (3) 4.21 d (3)	8.53 s	8.11 d (1.5)	1-H, 3.80 q (7) CH$_3$, 8.13 br s CH$_3$, 8.05 br s Ac, 7.91 s
10[b]	6.29 dd (2.2, 11)	7.46 ddd (2.2, 5, 15) 8.36 ddd (2, 11,15)	4.64 dd (2, 5)	4.60 br d (11)	4.52 dd (7, 11)	6.7 m	4.22 d		4.60 d (3) 4.06 d (2.8)	8.46 s or 8.44 s	8.06 br s	1-H, 6.95 q (5.5) CH$_3$, 8.67 d (5.5) CH$_3$, 8.44 s or 8.46 s Ac, 7.85 s
12	5.61 br d (5)	8.17 m	4.19 dd (2, 5, 11)	4.92 br d (10)	3.56 t (10)	7.8 m	5.49 br d (5)	4.90 dd (1.5, 5)	6.37 m	8.35 m	8.35 m	OCH$_3$, 6.22 s C-11, 7.06 dt (3.5, 11.5)
18[c]	4.40 m	7.50 m 8.30 m	4.73 m	4.73 m	4.40 m	7.05 m	4.40 m	5.70 d	8.87 d (7)	8.12 br s	8.19 d (1.5)	OH, 7.05 m; H, 3.95 m Ac, 7.98 s CH$_3$, 8.12 s; CH$_3$, 8.15 s

[a] Spectra were determined on a Varian HR-100 spectrometer in acetone-d_6 unless otherwise indicated. [b] Spectra measured in deuteriochloroform. [c] Spectrum measured in deuteriochloroform on a Varian A-60A spectrometer. Values are given in τ units relative to tetramethylsilane as internal standard. Multiplicity of signals is designated as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet; br, broad. Absence of designation implies that signal is overlapped with another signal and multiplicity is unclear. Numbers in parentheses denote coupling constants in hertz.

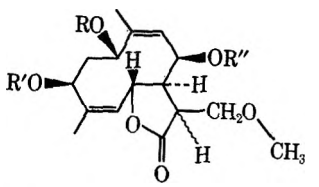
(τ 8.35) of **12** was coupled to both the C-8 [τ 5.49 (br d, J = 5 Hz)] and C-9 [τ 4.90 (dd, J = 1.5, 5 Hz)] protons. This fact could be explained by a homoallylic arrangement[18,19] and supported the location of a double bond at C-9, C-10. Location of the hydroxyl group at C-1 was thereby substantiated also.

The nmr spectrum of **12** measured with addition of trichloroacetylisocyanate showed downfield shifts of 1.1, 0.87, and 1.36 ppm for the signals assigned to the C-1, C-3, and C-8 protons, respectively, while the C-6 proton signal was shifted upfield as much as 0.25 ppm.[20] Accordingly, the three hydroxyl groups in **12** could be located at C-1, C-3, and C-8, thus showing that the γ-lactone closure of **12**, and consequently of **1** and **6**, was oriented at C-6.

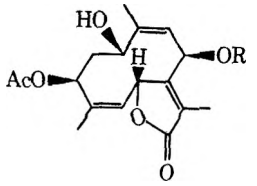
Eupacunin (**1**) was further characterized by its saponification products. Treatment of **1** with 2% sodium hydroxide in aqueous dioxane gave deacetyleupacunin (**3**), while treatment with 2% sodium hydroxide in aqueous methanol gave deacetyl-13-methoxydihydroeupacunin (**13**). The latter product was acetylated to give the diacetate **14**.



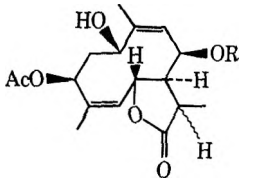
11



12, R = R' = R'' = H
13, R = R' = H; R'' = Ang
14, R = R' = Ac; R'' = Ang



15, R = Ang
16, R = COCH(CH$_3$)CH$_2$CH$_3$



17, R = COCH(CH$_3$)CH$_2$CH$_3$

All of these studies provided firm chemical support for the postulation of structures **1** and **6** for eupacunin and eupatocunin, respectively. Unequivocal proof of the structure, stereochemistry, and absolute configuration of eupacunin shown in **1** was achieved by X-ray crystallographic analysis[21] of eupacunin *o*-bromobenzoate (**4**).

Hydrogenation of eupacunin using 10% palladium on charcoal as catalyst yielded several products, three of which were isolated. In one of these, an isomeric compound, the nmr spectrum showed peaks for five vinyl methyl groups, two at τ 7.95, two at τ 8.10, and one at τ 8.30. This suggested that the exocyclic double bond had been isomerized to the endo position and that the product could be assigned structure **15**.[22] The second product was shown by its mass spectrum [*m/e* 305, M − 101 ($C_5H_9O_2$)] and nmr spectrum to be the dihydro isomeric compound, **16**, in which the double bond of the angelate group was reduced. The six-proton methyl singlet at τ 8.05 of eupacunin was no longer present, but was replaced in **16** by a three-proton doublet at τ 8.82 (J = 7 Hz) and a three-proton triplet (J = 7 Hz) at τ 9.07. In addition, signals for three vinylic methyl groups remained. The final hydrogenation product was the tetrahydro compound **17**. The intensity of absorption in the uv spectrum of **17** was substantially lessened, indicative that the conjugated double bonds of the ester and lactone had been reduced.

Dihydroeupatocunin (**18**) was obtained by the treatment of eupatocunin with sodium borohydride.[23]

(18) J. T. Pinhey and S. Sternhell, *Tetrahedron Lett.*, 275 (1963).
(19) J. T. Pinhey and S. Sternhell, *Aust. J. Chem.*, **18**, 543 (1965).
(20) V. W. Goodlet, *Anal. Chem.*, **37**, 431 (1965).
(21) X-Ray crystallographic analysis was carried out by Dr. G. A. Sim, P. D. Cradwick, and A. D. U. Hardy. A complete description of the X-ray results will be published separately by Professor Sim.
(22) *E.g.*, L. A. P. Anderson, W. T. deKock, W. Nel, K. G. R. Pachler, and G. van Tonder, *Tetrahedron*, **24**, 1687 (1968).
(23) W. Renold, H. Yoshioka, and T. J. Mabry, *J. Org. Chem.*, **35**, 4264 (1970).

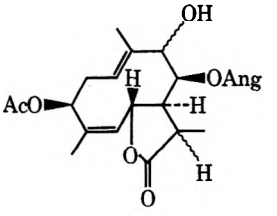
For **18** the intensity of the uv end absorption was decreased, and the nmr spectrum no longer showed the doublets typical of the exocyclic methylene. A new doublet methyl appeared at τ 8.87 (J = 7 Hz).

The molecular formula $C_{22}H_{28}O_8$ was assigned for eupacunoxin (**2**) on the basis of elemental analysis and mass spectrometry. The presence of an α-methyl-α,β-epoxybutyrate side-chain ester was indicated by the nmr spectrum, which showed two methyl signals at τ 8.82 (d, J = 5.5 Hz) and 8.38 (s), and a signal at τ 6.95 (q, J = 5.5 Hz) which could be assigned to a proton on an epoxide ring. Otherwise, the spectrum of **2** was very similar to the spectrum of **1**. The uv extinction coefficient of **2** was less than that of eupacunin (**1**), suggesting the absence of one of the two conjugated systems present in the latter. Methanolysis of **2** gave methyl α-methyl-*trans*-α,β-epoxybutyrate and deacetyldeangeloyl-13-methoxydihydroeupacunin (**12**). Consequently, structure **2** was proposed for eupacunoxin. Jones oxidation of **2** yielded the epoxy ketone **10**, the nmr of which was very similar to that of **9** except for the signals due to the side chain at C-8. Proof of structure **2** was furnished by the X-ray crystallographic structure[21] of eupacunoxin *m*-bromobenzoate (**5**), $C_{29}H_{31}O_9Br$.

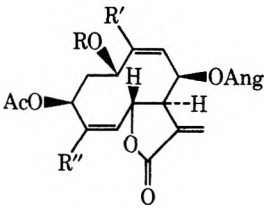
The uv spectrum of eupatocunoxin (**7**), $C_{22}H_{28}O_8$, was essentially the same as that of **2**. A methyl doublet at τ 8.73 (J = 5.5 Hz), a methyl singlet at τ 8.46, and a quartet at τ 6.90 (J = 5.5 Hz) in the nmr spectrum of **7** suggested the presence of an α-methyl-*trans*-α,β-epoxybutyrate as in **2**. Location of the epoxy ester at C-9 was supported by the downfield shift of the signal assigned to the C-9 proton [τ 4.72 (d, J = 2 Hz)] and the upfield shift of the signal assigned to the C-8 proton [τ 5.85 (m)] relative to the signals for the C-9 proton [τ 5.54 (d, J = 3 Hz)] and C-8 proton [τ 4.36 (dd, 1 H, J = 3 Hz)] in the nmr spectrum of eupatocunin (**6**). Otherwise the spectrum of **7** was very similar to the spectrum of **6**. In contrast to other sesquiterpene lactones in this series, eupatocunoxin (**7**) was resistant to Jones oxidation, giving additional support to the absence of a C-9 hydroxyl group. This evidence suggested that eupatocunoxin had the same germacrane skeleton as **6** and differed in the nature and location of the side-chain ester as shown by structure **7**.

Eupacunolin (**19**), $C_{22}H_{28}O_8$, showed the same uv spectrum as eupacunin (**1**) and a stronger hydroxyl absorption band at 2.88 μ in the ir than **1**. Many features of the nmr spectrum of **19** were similar to those of the spectrum of **1**. However, **19** lacked one of the vinyl methyl signals at τ 8.10, showing instead a two-proton signal at τ 5.90. In addition, the nmr spectrum exhibited a two-proton signal at τ 7.25 which was D_2O exchangeable. It therefore appeared that compounds **1** and **19** were similar, and the extra oxygen in **19** was present as a hydroxymethyl group.

Further evidence for the diol structure was obtained by acetylation, which afforded two oily products. The nmr spectra of these were consistent with the mono- and diacetate structures **20** and **21**. The nmr spectrum of compound **20** showed one new acetate signal at τ 7.86, and the signal for the methylene protons at τ 5.90 in **19** were shifted to τ 5.40. Since the remainder of the low-field signals were essentially the same in compounds **19** and **20**, compound **20** could be assigned a primary acetate function. In the nmr spectrum of **21**, resonance for three acetate methyl groups appeared between τ 7.82 and 7.88 and the signal for the methylene protons (at τ 5.90 in **19**) again resonated at lower field (τ 5.45), indicative of a primary acetate. This spectrum showed no change on addition of D_2O. Oxidation of **19** with manganese dioxide gave, in good yield, an oily product, **22**. The nmr spectrum of this material lacked the methylene signal at τ 5.90, but showed instead a singlet at τ 0.54 characteristic of an aldehyde proton. In other respects the nmr spectrum of **19** and **22** were similar. The aldehyde was characterized as the *p*-bromophenylhydrazone **23**.



18



19, R = H; R' = CH_3; R'' = CH_2OH or R' = CH_2OH; R'' = CH_3
20, R = H; R' = CH_3; R'' = CH_2OAc or R' = CH_2OAc; R'' = CH_3
21, R = Ac; R' = CH_3; R'' = CH_2OAc or R' = CH_2OAc; R'' = CH_3
22, R = H; R' = CH_3; R'' = CHO or R' = CHO; R'' = CH_3
23, R = H; R' = CH_3; R'' = CH=NNH-*p*-C_6H_4Br or R' = CH=NNH-*p*-C_6H_4Br; R'' = CH_3

To confirm the suspected relationship between **1** and **19**, a sample of eupacunolin (**19**) was hydrogenated using 10% palladium on charcoal as catalyst. The reaction yielded a complex mixture of products from which dihydroisoeupacunin (**16**) and tetrahydroeupacunin (**17**) were obtained by chromatography on silicic acid. This experiment confirmed that **19** was a hydroxy eupacunin. Whether that hydroxyl group is at C-14 or C-15 remains to be established.

Eupacunin (**1**) and its companions **2** and **19** appear to be the first recognized naturally occurring germacranolide *cis,cis*-dienes. Furthermore, the unique location of the double bonds (Δ^4, Δ^9) renders the skeletal structures essentially symmetrical about the C-2, C-7 axis. In an earlier communication, we noted the ambiguity of prior practices for describing germacranolides, and proposed the convention that each germacranolide be represented with the alkyl group β at C-7 and with the ring numbering running counterclockwise.[24] However, it was subsequently noted that the numbering produced by these rules for melampodin was ambiguous until the absolute configuration was

(24) S. M. Kupchan, J. E. Kelsey, and G. A. Sim, *Tetrahedron Lett.*, 2863 (1967).

known.[25] Consequently, the proposal (rule 1) was advanced that the distinction between the α and β faces should be based not on the configuration at C-7, but on other evidence which can be firmly related to the asymmetry of the molecule's mode of biogenesis.[24] Such features as positions of double bonds or their equivalents (*e.g.*, epoxides) or patterns of oxygen functions that are indicative of the former positions of the double bonds were proposed. The symmetry of the structures of eupacunin (1) and its companions 2 and 19 makes the numbering produced for these molecules by the newly proposed convention ambiguous without a prior knowledge of the absolute configuration. We applaud the efforts of Rogers, *et al.*, to eliminate the ambiguity and confusion in the representation of germacranolides, and approve of their proposed rules 2, 3, and 4. However, for the distinction of the α and β faces, we favor adoption of a generally applicable rule which includes the configuration at tetrahedral C-7 as *one of the primary asymmetric features* to be considered.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are corrected. Infrared spectra were determined on a Beckman Model IR-9 and Perkin-Elmer 257 recording spectrophotometers. Ultraviolet absorption spectra were determined on Beckman DK2A and Coleman EPS-3T spectrophotometers. Nmr spectra were determined on Varian A-60, Varian HA-100, and Hitachi H20 spectrometers using tetramethylsilane as internal standard. Nmr data are listed in Table II for compounds with well-resolved signals which were assignable to specific protons. Otherwise, partial data are reported under the compound in the Experimental Section. Gas-phase chromatography (glpc) was carried out on a Varian Aerograph Model 1860 gas chromatograph. Specific rotations were determined on a Zeiss Winkel polarimeter and are approximated to the nearest degree. The petroleum ether used was Skellysolve B, bp 60–68°. Evaporations were carried out at temperatures less than 40°. Tlc was carried out on silica gel (E. Merck) plates and chromatograms were visualized by spraying with a 3% $Ce(SO_4)_2$–3 *N* H_2SO_4 solution followed by heating. Microanalyses were performed by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Extraction and Preliminary Fractionation.—The dried ground stems, leaves, and flowers (400 g) of *Eupatorium cuneifolium* were continuously extracted with 95% ethanol for 16 hr, and the ethanol extract was evaporated under reduced pressure to yield a dark green gum, A (60 g). Fraction A was partitioned between water (500 ml) and three 500-ml portions of chloroform; the combined chloroform layers were finally washed with water (200 ml) and evaporated under reduced pressure to yield a dark green foam, B (38.0 g). Evaporation of the combined aqueous layer and washings under reduced pressure yielded a brown syrup, D (16.0 g). The interfacial material, after drying, yielded the solid C (4.4 g).

The chloroform-soluble fraction (B) was partitioned between 10% aqueous methanol (300 ml) and three 200-ml portions of petroleum ether. The combined petroleum ether layers, after washing with three 100-ml portions of 10% aqueous methanol, were evaporated to dryness under reduced pressure to yield a green oil, E (6.7 g). Evaporation of the aqueous methanol layer and washings under reduced pressure yielded a green gum, F (28.5 g).

Isolation of Sesquiterpene Lactones.—Fraction F (7.5 g) was fractionated by chromatography on silicic acid by elution with chloroform (20 l.). After 10 l. of eluate, fractions (20 ml) were collected and analyzed by tlc. Tubes 176–205 were combined to yield fraction G (0.273 g) and tubes 231–275 formed fraction H (0.159 g). Continued elution with 1% methanol in chloroform (11 l.) afforded fraction I (1.21 g). Subsequent elution with 2% methanol in chloroform (10 l.) yielded fraction J (2.58 g). Repeated chromatographies, as described above, yielded larger quantities of each fraction. A larger batch of fraction G (2.6 g) was crystallized from methanol and ether to yield eupacunin (1, 1.8 g) as colorless needles: mp 166–167°; $[\alpha]^{26}D$ +55° (*c* 1.24, acetone); uv max (MeOH) 211 nm (ϵ 23,900); ir ($CHCl_3$) 2.77, 3.40, 5.70, 5.75, 5.84, 6.10, 7.26, 7.32, 8.02, 8.78, and 9.60 μ; nmr (CD_3COCD_3) τ 6.42 (1 H, br d, J = 3 Hz), 6.90 (1 H, m), 7.25 (1 H, br s), 7.58 (1 H, dd, J = 3, 15 Hz), 7.94 (3 H, s), 7.96 (3 H, br s), 8.05 (3 H, br s), 8.17 (3 H, br s), 8.26 (3 H, br s); mass spectrum *m/e* 404 (M^+), 345, 313, 305, 283, 263, 253, 245, 227, 163, and 111.

Anal. Calcd for $C_{22}H_{28}O_7$: C, 65.33; H, 6.98. Found: C, 65.88; H, 7.08.

A fraction equivalent to H (0.485 g) was crystallized from methanol–ether to yield eupatocunin (6, 0.224 g) as colorless prisms: mp 163–164°; $[\alpha]^{25}D$ −129° (*c* 1.36, acetone); uv (MeOH) end absorption 212 nm (ϵ 28,000); ir ($CHCl_3$) 2.86, 3.30, 5.68, 5.73, 5.82, 6.06, 7.24, 7.36, 8.08, 8.67, and 9.60 μ; mass spectrum *m/e* 404 (M^+), 387, 362, 344, 321, 305, 261, 244, 214, 165, 149, 137, 83, and 55.

Anal. Calcd for $C_{22}H_{28}O_7$: C, 65.33; H, 6.98. Found: C, 65.51; H, 7.13.

Silicic acid chromatography of fraction I by elution with 0.5% methanol–chloroform afforded fraction K (6.09 g), which appeared mainly as a large yellow-brown spot on tlc after visualization. A portion of this fraction (5.0 g) was rechromatographed on a silica gel column by elution with acetone–methanol–chloroform (10.0:1.5:88.5) to afford fraction L (2.71 g). This material (200 mg) crystallized from ether to yield eupacunoxin (2, 23 mg) as colorless needles: mp 171–172°; $[\alpha]^{26}D$ +27° (*c* 1.0, acetone); uv (MeOH) end absorption 209 nm (ϵ 17,000); ir (KBr) 2.84, 5.67, 5.71, 7.88, 8.03, 8.66, 10.20, 10.44, 10.55, and 10.99 μ; nmr (CD_3COCD_3) τ 3.82 (1 H, d, J = 4 Hz), 7.23 (2 H, br s), 7.92 (3 H, s), 8.15 (3 H, d, J = 1.5 Hz), 8.25 (3 H, d, J = 1.0 Hz), 8.38 (3 H, s), 8.82 (3 H, d, J = 5.5 Hz); mass spectrum *m/e* 420 (M^+), 361, 305, 263, 245, 163, 95, and 43.

Anal. Calcd for $C_{22}H_{28}O_8$: C, 62.84; H, 6.71. Found: C, 62.52; H, 6.54.

Further elution of the fraction I column gave fraction M (2.25 g), a two-component mixture by tlc. Rechromatography of M on silica gel by elution with acetone–methanol–chloroforom (10.0:1.5:88.5) gave fraction N (267 mg), which crystallized from acetone to yield eupatocunoxin (7, 81 mg) as colorless needles: mp 200–201°; $[\alpha]^{26}D$ −209° (*c* 1.0, acetone); uv (MeOH) end absorption 210 nm (ϵ 15,500); ir (KBr) 2.92, 5.76, 8.66, 9.25, 9.66, 10.31, and 10.47 μ; mass spectrum *m/e* 420 (M^+), 403, 361, 360, 305, 262, 244, 237, 165, 137, 97, 71, and 43.

Anal. Calcd for $C_{22}H_{28}O_8$: C, 62.84; H, 6.71. Found: C, 62.87; H, 6.66.

Further elution of the fraction M column gave fraction O (200 mg), which crystallized from methanol–ether to yield eupaserrin (25 mg) as colorless needles, mp 153–154°. The material was characterized by melting point, mixture melting point, ir, nmr, and mass spectral comparison with a sample isolated from *Eupatorium semiserratum*.[3]

A sample of fraction J (1.07 g) from the initial silicic acid column was rechromatographed on a second silicic acid column to afford fraction P (147 mg). Finally, fraction P was chromatographed on a silica gel column by elution with acetone–methanol–chloroform (10:2:88) to afford a fraction (84 mg) which crystallized to yield eupacunolin (19) as colorless needles: mp 164–165°; $[\alpha]^{26}D$ +46° (*c* 1.02, acetone); uv max (MeOH) 211 nm (ϵ 23,800); ir ($CHCl_3$) 2.88, 3.40, 5.66, 5.72, 5.80, 6.06, 8.02, and 8.88 μ; nmr ($CDCl_3$) τ 3.68 (1 H, d, J = 4 Hz), 5.90 (2 H, br s), 7.25 (2 H, m), 7.90 (3 H, s), 7.92 (3 H, s), 8.02 (6 H, s), 8.28 (3 H, s); mass spectrum *m/e* 420 (M^+), 361, 321, 303, 261, 242, 215, 95, 83, 58, and 43.

Anal. Calcd for $C_{22}H_{28}O_8$: C, 62.84; H, 6.71. Found: C, 63.11; H, 6.87.

1,10-Epoxyeupacunin (11) and 1,10-Epoxy-9-dehydroeupacunin (9).—A solution of eupacunin (1, 240 mg) in acetone (8 ml) at 0° was treated with Jones reagent (1 ml) and allowed to react for 6 min. The reaction mixture was poured into ice water (40 ml) and extracted with chloroform. The chloroform extract was dried (Na_2SO_4), filtered, and evaporated under reduced pressure to yield an oily residue. Chromatography on SilicAR CC-7 (Mallinckrodt, 100–200 mesh) by elution with chloroform gave three fractions, a (50 mg), b (55 mg), and c (60 mg). Crystallization of fraction b from methanol–ether gave 11 as colorless prisms: mp 195–196°; $[\alpha]^{26}D$ +54° (c 0.90, acetone); uv max (MeOH) 210 nm (ϵ 15,400); ir ($CHCl_3$) 2.86, 3.30, 5.67, 5.72,

(25) D. Rogers, G. P. Moss, and S. Neidle, *J. Chem. Soc., Chem. Commun.*, 142 (1972).

6.10, 8.06, and 8.76 μ; nmr ($CDCl_3$) τ 3.59 (1 H, d, J = 3 Hz), 4.60 (1 H, dm, J = 12 Hz), 4.66 (1 H, dd, J = 2, 3 Hz), 6.00 (1 H, d, J = 4 Hz), 6.08 (1 H, dd, J = 3.5, 11 Hz), 7.00 (1 H, m), 7.89 (3 H, s), 8.10 (9 H, s), 8.66 (3 H, s); mass spectrum m/e 420 (M^+), 378, 360, 316, 279, 260, 177, 165, 147, 109, 83, 55, and 43.

Anal. Calcd for $C_{22}H_{28}O_8$: C, 62.84; H, 6.71. Found: C, 62.83; H, 6.36.

Crystallization of fraction a afforded 9 (30 mg) as colorless prisms: mp 200–201°; $[\alpha]^{26}D$ +66° (c 1.11, acetone); uv max (MeOH) 210 nm (ε 14,600); ir ($CHCl_3$) 3.29, 5.65, 5.75, 6.00, 6.08, 8.04, and 8.78 μ; mass spectrum m/e 418 (M^+), 376, 334, 319, 277, 275, 259, 165, 151, 109, 83, 55, and 43.

Using a procedure identical with the one above, eupatocunin (2, 40 mg) was treated with the Jones reagent to afford (after normal work-up) 1,10-epoxy-9-dehydroeupacunin (9), shown to be identical with the material obtained from eupacunin (1) by melting point, mixture melting point, and ir and nmr spectral comparison.

Eupacunin *o*-Bromobenzoate (4).—A solution of eupacunin (1, 50 mg) in pyridine (1 ml) was treated with *o*-bromobenzoyl chloride (100 mg). The reaction mixture was allowed to stand at room temperature for 24 hr, and was then poured into ice water, acidified with HCl, and extracted with chloroform. The organic layer was washed with sodium bicarbonate solution and water, dried (Na_2SO_4), and evaporated under reduced pressure to give an oily residue. Preparative thin layer chromatography on silica gel afforded crystals (80 mg), which were recrystallized from methanol to afford 4 (29 mg) as colorless prisms: mp 184.5–186°; uv (MeOH) end absorption 210 nm (ε 42,000), 284 (1000); ir (KBr) 5.65, 5.73, 5.76, 5.84, 5.95, 6.08, and 6.28 μ.

Anal. Calcd for $C_{29}H_{31}O_8Br$: C, 59.28; H, 5.31; Br, 13.62. Found: C, 59.03; H, 5.43; Br, 13.67.

Deacetyldeangeloyl-11,13-dihydro-13-methoxyeupacunin (12).

A.—A solution of eupacunoxin (2, 70 mg) in methanol (2 ml) was treated with a 2% solution of sodium hydroxide in 10% aqueous methanol (7 ml) and allowed to react at room temperature for 16 hr. The reaction mixture was acidified with 5% sulfuric acid and extracted with chloroform. The chloroform extract was dried (Na_2SO_4), filtered, and evaporated under reduced pressure to yield a colorless oil (14 mg). Crystallization from methanol–ether yielded 12 as colorless prisms: mp 202–203°; uv (MeOH) end absorption 210 nm (ε 4368); ir (KBr) 2.84, 2.91, 5.66, 8.13, 8.27, 9.23, 10.36, 10.99, and 11.49 μ; mass spectrum m/e 312 (M^+), 294, 287, 277, 263, 192, 166, 149, 100, 95, 71, and 45.

Anal. Calcd for $C_{16}H_{24}O_6$: C, 61.52; H, 7.75. Found: C, 61.50; H, 7.84.

B.—A solution of deacetyl-11,13-dihydro-13-methoxyeupacunin (13, 70 mg) in methanol was hydrogenated in the presence of 10% palladium on charcoal (20 mg) at atmospheric pressure and room temperature. Uptake of hydrogen stopped after 15 min, at which time 1 molar equiv of hydrogen had been absorbed. The suspension was filtered and concentrated to give a colorless oil (60 mg). A solution of the product (50 mg) in methanol (2 ml) was treated by the above procedure (conversion of 2 to 12) to yield a colorless glass (10 mg) which crystallized to give 12 as colorless prisms (7 mg) shown to be identical with the material obtained from eupacunoxin (2) by mixture melting point and infrared and mass spectral comparison.

C.—A solution of eupacunin (1, 250 mg) in anhydrous methanol (25 ml) was treated with sodium methoxide (100 mg) and kept at room temperature for 7 days. The reaction mixture was acidified with acetic acid, evaporated under reduced pressure, dissolved in water, and extracted with chloroform. The organic solution was washed with water, dried (Na_2SO_4), and evaporated to give an oil. Preparative thin layer chromatography on silica gel afforded a material which crystallized from methanol–water to afford 12 as colorless prisms. This material was shown to be identical with the product obtained from eupacunoxin (2) by mixture melting point.

Deacetyleupacunin (3).—A solution of eupacunin (1, 50 mg) in dioxane (3 ml) was treated with 2% potassium hydroxide in water (2.5 ml) and kept at room temperature for 16 hr. The reaction mixture was diluted with water (10 ml), acidified with 5% hydrochloric acid, and extracted with ether. The ether was dried (Na_2SO_4), filtered, and evaporated under reduced pressure to yield the crude product (25 mg). Crystallization from ether–hexane afforded deacetyleupacunin (3) as colorless crystals: mp 155–156°; $[\alpha]^{25}D$ +114° (c 1.50, acetone); uv (MeOH) end absorption 208 nm (ε 14,100); ir (KBr) 2.87, 5.71, 5.76, 8.00, 8.69, 10.00, 10.34, and 10.47 μ; nmr ($CDCl_3$–CD_3COCD_3) τ 3.77 (1 H, d, J = 3.5 Hz), 5.45 (1 H, m), 8.05 (3 H, s), 8.25 (9 H, br s).

Anal. Calcd for $C_{20}H_{26}O_6$: C, 66.28; H, 7.23. Found: C, 66.61; H, 7.26.

Deacetyl-11,13-dihydro-13-methoxyeupacunin (13).—A solution of eupacunin (1, 250 mg) in 20% aqueous methanol (5 ml) containing sodium hydroxide (100 mg) was kept at room temperature for 16 hr. The reaction mixture was cooled, diluted with water (15 ml), acidified with concentrated hydrochloric acid, and extracted with chloroform. The extract was washed with water, dried (Na_2SO_4), filtered, and evaporated to afford an oil (260 mg). Chromatography on silicic acid by elution with methanol–chloroform (1:99) gave a fraction (127 mg) which crystallized from ether–petroleum ether to afford 13 as colorless prisms (91 mg): mp 150–151°; $[\alpha]^{26}D$ +76.5° (c 0.63, acetone); uv max (MeOH) 217 nm (ε 11,000); ir ($CHCl_3$) 2.77, 2.90, 5.65, 5.83, 6.08, and 8.66 μ; nmr ($CDCl_3$) τ 6.62 (3 H, s), 7.96 (6 H, br s), 8.28 (6 H, br s); mass spectrum m/e 394 (M^+), 377, 364, 363, 362, 361, 360, 310, 293, 275, 231, 215, 199, 191, 173, 149, 135, 95, 83, and 55.

Anal. Calcd for $C_{21}H_{30}O_7$: C, 63.94; H, 7.66. Found: C, 64.20; H, 7.87.

11,13-Dihydro-13-methoxyeupacunin Acetate (14).—A solution of deacetyl-11,13-dihydro-13-methoxyeupacunin (13, 48 mg) in isopropenyl acetate (2 ml) containing *p*-TsOH (2 mg) was kept at 40° for 16 hr, after which the reaction mixture was evaporated to dryness under reduced pressure. Chromatography on silicic acid by elution with chloroform yielded one main fraction (61 mg) which crystallized from ether–petroleum ether to yield 14 (32 mg) as colorless prisms: mp 136–137°; $[\alpha]^{20}D$ −12° (c 1.53, acetone); uv max (MeOH) 216 nm (ε 10,900); ir ($CHCl_3$) 3.23, 3.42, 5.65, 5.77, 6.05, 7.23, 7.32, and 8.00 μ; nmr ($CDCl_3$) τ 6.65 (3 H, s), 7.82 (3 H, s), 8.00 (6 H, br s), 8.10 (3 H, s), 8.22 (3 H, d, J = 2 Hz), 8.26 (3 H, d, J = 2 Hz); mass spectrum m/e 478 (M^+), 419, 370, 337, 327, 259, 245, 231, 227, 215, 199, 173, 83, and 55.

Anal. Calcd for $C_{25}H_{34}O_9$: C, 62.75; H, 7.16. Found: C, 63.06; H, 7.24.

Partial Methanolysis of Eupatocunin (6).—A solution of eupatocunin (6, 81 mg) and sodium methoxide (11 mg) in anhydrous methanol was kept at room temperature for 21 hr. The reaction mixture was neutralized with acetic acid and evaporated. The residue was dissolved in chloroform, washed with 5% sodium carbonate solution and water, dried (Na_2SO_4), and evaporated to afford an amorphous solid (53 mg). Preparative thin layer chromatography yielded homogeneous 8: ir ($CHCl_3$) 2.79, 2.81, 5.72, 5.76, 6.01, 6.91, 7.28, 7.32, 8.04, 8.37, 9.17, 9.69, and 10.30 μ; mass spectrum m/e 354 (M^+), 337, 309, 295, 294, 275, 262, 69, 46, and 43.

Isoeupacunin (15).—A solution of eupacunin (1, 200 mg) in methanol (20 ml) was hydrogenated using 10% palladium on charcoal (50 mg) as catalyst at atmospheric pressure and room temperature. Uptake of hydrogen stopped after 11 min, at which time 1 molar equiv of hydrogen had been absorbed. The suspension was filtered and concentrated to give a colorless oil (180 mg). Chromatography on silica gel and elution with acetone–methanol–chloroform (10:1:89) yielded three fractions. The major fraction (100 mg) crystallized from ether–hexane to afford isoeupacunin (15): mp 144–145°; $[\alpha]^{25}D$ −66° (c 0.77, acetone); uv (MeOH) end absorption 213 nm (ε 15,800); ir (KBr) 2.93, 5.70, 5.72, 5.81, 8.08, and 9.00 μ; nmr ($CDCl_3$) τ 2.70 (1 H, br d, J = 10 Hz), 3.77 (1 H, br d, J = 10 Hz), 4.44 (1 H, m), 4.85 (1 H, br d, J = 10 Hz), 5.22 (1 H, br d, J = 10 Hz), 7.95 (6 H, s), 8.10 (6 H, s), 8.30 (3 H, s).

Anal. Calcd for $C_{22}H_{28}O_7$: C, 65.33; H, 6.98. Found: C, 65.50; H, 7.10.

Dihydroisoeupacunin (16).

A.—A solution of eupacunin (1, 200 mg) in methanol (10 ml) was hydrogenated using 10% palladium on charcoal (80 mg) as catalyst at atmospheric pressure and room temperature. Uptake of hydrogen stopped after 20 min, at which time 3 molar equiv of hydrogen had been absorbed. The suspension was filtered and concentrated to give a colorless oil. Chromatography on silic acid by elution with chloroform yielded two main fractions, a (53 mg) and b (59 mg), respectively. Recrystallization of fraction a from ether–petroleum ether yielded dihydroisoeupacunin (16) as colorless prisms: mp 130–131°; $[\alpha]^{28}D$ −45° (c 1.11, acetone); ir ($CHCl_3$) 2.87, 3.36, 5.72, 5.96, 8.04, 8.94, and 9.90 μ; nmr ($CDCl_3$) τ 2.71 (1 H, br d, J = 10 Hz), 3.79 (1 H, br d, J = 10 Hz), 4.42 (1 H, m),

4.88 (1 H, br d, J = 10 Hz), 5.21 (1 H, br d, J = 10 Hz), 7.94 (6 H, s), 8.10, (3 H, d, J = 2 Hz), 8.30 (3 H, d, J = 2 Hz), 8.82 (3 H, d, J = 7 Hz), 9.07 (3 H, t, J = 7 Hz).

Anal. Calcd for $C_{22}H_{30}O_7$: C, 65.01; H, 7.44. Found: C, 65.20; H, 7.63.

B.—A solution of eupacunolin (**19**, 140 mg) in methanol (15 ml) was hydrogenated using 30% palladium on charcoal (50 mg) as catalyst at atmospheric pressure and room temperature. Uptake of hydrogen stopped after 100 min, at which time 3 molar equiv of hydrogen had been absorbed. The suspension was filtered and concentrated to give a colorless oil. Careful chromatography on SilicAR CC-7 by elution with methanol–chloroform (1:99) yielded two fractions, a (15 mg) and b (30 mg). Crystallization of fraction a from ether–hexane yielded dihydroisoeupacunin (**16**, 7 mg) as prism rosettes shown to be identical with the material obtained from eupacunin by melting point, mixture melting point, and infrared spectral comparison.

Tetrahydroeupacunin (17). A.—Crystallization of the fraction b (from the hydrogenation of eupacunin to give dihydroisoeupacunin) from ether–petroleum ether yielded tetrahydroeupacunin (**17**, 45 mg) as colorless prisms: mp 152–153°; $[\alpha]^{28}D$ +99° (c 1.00, acetone); uv max (MeOH) 209 nm (ϵ 3600); ir ($CHCl_3$) 2.87, 3.35, 5.64, 5.75, 6.06, 7.24, 8.03, and 8.70 μ; nmr ($CDCl_3$) τ 7.92 (3 H, s), 8.10 (3 H, br s), 8.30 (3 H, br s), 8.60 (3 H, d, J = 7 Hz), 8.88 (3 H, d, J = 7 Hz), 9.07 (3 H, t, J = 7 Hz); mass spectrum m/e 408 (M^+), 349, 307, 265, 246, 239, 219, 201, 191, 173, 165, 122, 119, 95, 85, and 57.

Anal. Calcd for $C_{22}H_{32}O_7$: C, 64.68; H, 7.90. Found: C, 64.74; H, 8.13.

B.—Crystallization of fraction b (from hydrogenation of eupacunolin) from ether–hexane yielded tetrahydroeupacunin (**17**, 19 mg) shown to be identical with the material obtained from **1** by mixture melting point and infrared spectral comparison.

11,13-Dihydroeupatocunin (18).—A solution of eupatocunin (**6**) (90 mg) in methanol (3 ml) was treated with a methanolic solution (30 ml) of sodium borohydride (90 mg) at room temperature for 3 hr. The reaction mixture was diluted with water (20 ml) and extracted with chloroform. The chloroform extract was washed with water and dried (Na_2SO_4), filtered, and evaporated under reduced pressure to yield 70 mg of product which was crystallized from ether–hexane to yield dihydroeupatocunin (**18**, 40 mg) as colorless crystals: mp 184–185°; $[\alpha]^{25}D$ −68° (c 0.93, acetone); uv (MeOH) end absorption 210 nm (ϵ 10,500); ir (KBr) 2.89, 5.67, 5.78, 10.08, 10.44 μ; mass spectrum m/e 406 (M^+), 323, 307, 263, 245, 165, 95, 83, 55, and 43.

Anal. Calcd for $C_{22}H_{30}O_7$: C, 65.01; H, 7.44. Found: C, 65.16; H, 7.23.

1,10-Epoxy-9-dehydroeupacunoxin (10).—A solution of eupacunoxin (**2**, 40 mg) in acetone (3 ml) at 4° was treated with Jones reagent (1 ml) and stirred for 8 min. The reaction mixture was poured into ice water (20 ml) and extracted with chloroform. The chloroform extract was dried (Na_2SO_4), filtered, and evaporated. The residue was chromatographed on silica gel by elution with acetone–methanol–chloroform (20:1:79). The main fraction (34 mg) crystallized to afford colorless needles (20 mg) of **10**: mp 205–206°; $[\alpha]^{26}D$ +82.5° (c 0.94, acetone); uv max (MeOH) 210 nm (ϵ 15,600); ir (KBr) 5.64, 5.60, 5.76, 6.90, 7.23, 8.05, 8.12, 8.63, and 10.20 μ; mass spectrum m/e 434 (M^+), 335, 319, 275, 259, 109, 97, 95, 69, 55, and 43.

Anal. Calcd for $C_{22}H_{26}O_9$: C, 60.82; H, 6.03. Found: C, 60.78; H, 6.01.

Eupacunoxin *m*-Bromobenzoate (5).—To a solution of eupacunoxin (**2**, 71 mg) in pyridine (0.5 ml) was added a mixture of *m*-bromobenzoyl chloride (0.5 ml) in pyridine (0.5 ml). The reaction mixture was kept for 24 hr at room temperature, poured into ice water, stirred for 3 hr, and extracted with chloroform. The chloroform layer was washed with sodium bicarbonate solution, and water, dried (Na_2SO_4), and evaporated to dryness *in vacuo*. Preparative thin layer chromatography on silica gel plates afforded 117 mg of crystals, which were recrystallized from methanol to yield the *m*-bromobenzoate **5** as needles: mp 191–192°; ir (KBr) 5.72, 5.75, 5.82, 5.95, 6.30, 8.00, 8.13, 8.82, and 12.60 μ.

Anal. Calcd for $C_{29}H_{31}O_9Br$: C, 57.77; H, 5.17; Br, 13.24. Found: C, 57.82; H, 5.18; Br, 13.16.

Eupacunolin Acetate (20) and Eupacunolin Diacetate (21).—To a solution of eupacunolin (**19**, 100 mg) in dry pyridine (4 ml) was added acetic anhydride (200 mg) and the solution was kept at room temperature for 12 hr. The reaction mixture was evaporated at room temperature *in vacuo*, and the residue was chromatographed on SilicAR CC-7 by elution with chloroform and 0.5% methanol in chloroform. Two main fractions, a (90 mg) and b (48 mg), were obtained. Spectral data for a were consistent with the structure proposed for eupacunolin diacetate (**21**): ir (neat) 3.30, 3.40, 5.65, 5.73, 6.06, 7.30, 8.00, and 8.78 μ; nmr ($CDCl_3$) τ 3.65 (1 H, d, J = 3 Hz), 5.45 (2 H, br s), 7.82 (3 H, s), 7.88 (6 H, s), 8.07 (6 H, br s), 8.22 (3 H, br s). Spectral data for b were consistent with the structure proposed for eucapunolin acetate (**20**): ir (neat) 2.72, 3.30, 3.40, 5.65, 5.73, 6.06, 7.30, 8.08, and 8.78 μ; nmr ($CDCl_3$) τ 3.62 (1 H, d, J = 3 Hz), 5.40 (2 H, br s), 7.86 (9 H, br s), 8.00 (3 H, s), 8.22 (3 H, br s).

Dehydroeupacunolin (22).—To a solution of eupacunolin (**19**, 120 mg) in chloroform (5 ml) was added manganese dioxide (1.0 g) and the suspension was stirred at 35° for 36 hr. The suspension was filtered and concentrated to give an oily product which was chromatographed on silicic acid to afford a homogeneous, colorless oil (80 mg). Spectral evidence was consistent with structure **22**: uv max (MeOH) 212 nm (ϵ 22,100); ir (neat) 2.86, 3.38, 5.63, 5.71, 5.80, 5.91, 6.05, 8.17, and 8.80 μ; nmr ($CDCl_3$) τ 0.54 (1 H, s), 3.61 (1 H, d, J = 3 Hz), 6.85 (1 H, m), 7.91 (6 H, s), 8.03 (3 H, s), 8.43 (3 H, br s).

Dehydroeupacunolin *p*-Bromophenylhydrazone (23).—A solution of dehydroeupacunolin (**12**, 54 mg) in 50% aqueous methanol (2 ml) was treated with a solution of *p*-bromophenylhydrazine hydrochloride (75 mg) in 50% aqueous methanol (1 ml). The reaction mixture was cooled, diluted with water, and extracted with chloroform. The chloroform was dried (Na_2SO_4), filtered, and evaporated to give a brown oil (60 mg). Chromatography on silicic acid by elution with methanol–chloroform (1:99) yielded one main fraction (47 mg). Recrystallization from methanol–ether–hexane afforded the hydrazone **23** (23 mg) as pale yellow crystals: mp 173–180° dec; ir (KBr) 2.83, 3.03, 3.38, 5.67, 5.73, 6.06, 6.26, 6.37, 6.72, 8.16, 8.73, 9.58, 10.25, and 12.20 μ.

Anal. Calcd for $C_{28}H_{31}BrN_2O_7$: C, 57.24; H, 5.32; Br, 13.61. Found: C, 57.05; H, 5.33; Br, 13.69.

Methanolysis of Eupatocunoxin.—A solution of eupatocunoxin (**7**, 50 mg) and sodium methoxide (10 mg) in absolute methanol (50 ml) was refluxed for 6 days. The mixture was acidified with acetic acid, diluted with water (50 ml), and extracted with ether. The ether layer was washed with water, dried (Na_2SO_4), and evaporated. Glpc of the residue showed one short retention time peak which was identified as methyl 2-methyl-*trans*-2,3-epoxybutyrate by comparison of retention times with an authentic sample.

Methanolysis of Eupatocunin.—A solution of eupatocunin (**6**, 165 mg) and sodium methoxide in absolute methanol (16 ml) was kept at room temperature for 11 days. The reaction mixture was acidified with concentrated HCl, diluted with water (60 ml), and extracted with ether. The ether layer was separated into acid and neutral fractions in the usual way. The neutral fraction was dried (Na_2SO_4) and evaporated. Glpc of the residue showed a peak which was identified as methyl angelate by comparison of its retention time with that of an authentic sample. Methyl tiglate had a different retention time.

Registry No.—**1**, 33854-15-8; **2**, 33853-88-2; **3**, 33853-82-6; **4**, 33853-89-3; **5**, 33853-90-6; **6**, 33853-87-1; **7**, 39204-36-9; **8**, 39204-37-0; **9**, 33853-86-0; **10**, 39204-39-2; **11**, 33911-41-0; **12**, 33853-85-9; **13**, 33853-83-7; **14**, 33853-84-8; **15**, 39266-89-2; **16**, 39204-44-9; **17**, 39204-45-0; **18**, 39204-46-1; **19**, 39152-57-3; **20**, 39152-58-4; **21**, 39152-59-5; **22**, 39152-60-8; **23**, 39152-61-9.

Reduction of the Steroidal Sapogenin Spiro Ketal System[1]

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Reduction of tigogenin (1a) and deoxytigogenin (1b) with lithium aluminum deuteride–aluminum chloride was shown to involve incorporation of hydride at the 22 position by an intermolecular mechanism. A possible alternative involving an intramolecular hydride shift from the 26 position was excluded. Position of the deuterium label was conclusively shown by pmr measurements and by chemical methods. An attempt to employ mass spectral evidence for assigning the deuterium position led to the observation of a rare seven-center transition state in an electron impact fragmentation sequence.

In our initial study of steroidal sapogenin reduction employing metal hydrides[2] it was suggested that reduction (1 → 2) of the spiro ketal system with lithium aluminum hydride–aluminum chloride might proceed *via* a hydride transfer mechanism. However, the possibility of either direct reduction of an oxonium ion intermediate or a completely different mechanism was also considered feasible. The oxonium ion possibility would be expected to proceed as outlined[3] for reduction of acetals and ketals by lithium aluminum hydride–aluminum chloride. Some evidence for the oxonium ion route was presented by Leggetter and Brown in 1964.[4] The most compelling evidence for this mechanistic pathway was provided by Eliel and colleagues from a deuterium labeling and mass spectral investigation of cyclohexanone ketal reduction with lithium aluminum deuteride–aluminum chloride.[5] By this means it was found that deuterium was only incorporated into the cyclohexane ring thereby demonstrating that no hydride shift had occurred. These results could not completely preclude the possibility of a hydride shift occurring with rather specialized spiro ketals of the steroidal sapogenin type. To either confirm or eliminate the latter mechanistic possibility we undertook the following examination of tigogenin (**1a**) and deoxytigogenin (**1b**) (Chart I) reduction by lithium aluminum deuteride–aluminum chloride.

As originally planned, this investigation simply required preparation of deuterium-labeled dihydrotigogenin (**2a**) using lithium aluminum deuteride–aluminum chloride and comparison of the mass and pmr spectra with those of the nondeuterated compound. If reduction yielded a monodeuterated product, spectral interpretation would help differentiate among (1) direct reduction of intermediate **3** to dihydrosapogenin **2**; (2) reduction of complex **4** to dihydro derivative **2** preceded by an intramolecular hydride transfer (**3** → **4**); (3) both mechanisms operative; or (4) an entirely different mechanism. With direct reduction (**3** → **2**) the deuterium label would be found at the 22 position. In the case of an intramolecular hydride shift (**3** → **4**), the label would appear at the 26 position.

To make use of pmr data it became necessary to determine the chemical shifts of dihydrosapogenin low field protons and this was accomplished using model systems. The pmr spectrum of 5α-furostan (**5**) demonstrated that the C-16 and C-22 protons have different chemical shifts (Table I). From the spirostan (no C-22 proton) spectra it was evident that the C-16 proton appears farthest down field. The dihydrosapogenins and their derivatives displayed a pair of broad peaks (δ ~3.30 and 4.26) corresponding to the α protons of the furan system in addition to the C-26 proton doublet. When dihydrosapogenins **2a** and **2c** were prepared using lithium aluminum deuteride–aluminum chloride, the C-22 proton signal at δ 3.30 was no longer present and the doublet corresponding to the C-26 protons remained unchanged. Similar results were also obtained with labeled acetate **2b** and ester **6b** (Table I). Thus, from the pmr data, it was apparent that the deuterium label resided at the 22 position.

Although the pmr data was considered unequivocal it was decided to add further support for the C-22 labeling using mass spectral data. In the mass spectrum of dihydrotigogenin (**2a**, Figure 1) the first major fragment observed (*m/e* 331) corresponded to anticipated[6] loss of the side chain. Located between this fragment and the molecular ion were several minor yet important fragments. Besides the M − 1, M − 2, M − CH_3 (*m/e* 403), M − H_2O (*m/e* 400), and M − CH_3 − H_2O (*m/e* 385) fragments, possible structures[7] for the four remaining important ions are pictured in Chart II.

For the two most likely reduction mechanisms, deuterium incorporation would be at positions 22 or 26. Location of the label at C-22 would be indicated by fragments **7** and **10** moving up 1 amu, while **8** and **9** would remain unchanged.[7] A C-26 deuteron would be detected by means of a change in the M − 1 and M − 2 peak heights compared with those of the unlabeled com-

(1) (a) This investigation was supported by U. S. Public Health Service Research Grants CA-10612-02 and CA-10612-05 from the National Cancer Institute, National Institutes of Health, and by National Science Foundation Grants GB-4939 and GP-6979 which provided financial assistance for purchase of the Atlas CH-4B and SM-1B mass spectrometers. The present contribution represents Steroids and Related Natural Products. 81. For part 80, see G. R. Pettit and Y. Kamano, *J. Chem. Soc., Perkin Trans. 1*, in press. (b) Abstracted in part from the Ph.D. dissertation submitted by A. A. to the graduate school, Arizona State University, Feb 1971. A preliminary communication based on part of the mass spectral study reported herein has been prepared by P. Brown, A. H. Albert, and G. R. Pettit, *J. Amer. Chem. Soc.*, **92**, 3212 (1970). After completing the present investigation an evaluation of reductive ring opening with the spiro ketal 9,9-dimethyl-1,6-dioxaspiro[4.5]decane was also completed; see G. R. Pettit, A. H. Albert, and P. Brown, *J. Amer. Chem. Soc.*, **94**, 8095 (1972).

(2) G. R. Pettit and W. J. Bowyer, *J. Org. Chem.*, **25**, 84 (1960).

(3) E. L. Eliel and M. Rerick, *J. Org. Chem.*, **23**, 1088 (1958).

(4) B. E. Leggetter and R. K. Brown, *Can. J. Chem.*, **42**, 990 (1964).

(5) E. L. Eliel, V. G. Badding, and M. N. Rerick, *J. Amer. Chem. Soc.*, **84**, 2371 (1962).

(6) The most abundant fragment in the spectra of α-alkylated tetrahydrofurans results from α cleavage of the alkyl group. This cleavage leaves the very stable cyclic oxonium ion. See H. Budzikiewiez, C. Djerassi, and D. H. Williams, "Mass Spectrometry of Organic Compounds," Holden-Day, San Francisco, Calif., 1967, p 253; and K. Bieman, "Mass Spectrometry—Organic Chemical Applications," McGraw-Hill, New York, N. Y., 1962, p 97.

(7) This fragmentation pattern is analogous to one proposed for the spirostans: C. Djerassi, personal communication, 1969; H. Budzikiewiez, C. Djerassi, and D. H. Williams, "Structure Elucidation of Natural Products by Mass Spectrometry," Vol. II, Holden-Day, San Francisco, Calif., 1964; H. Budzikiewiez, K. Takada, and K. Schreiber, *Monatsh. Chem.*, **101**, 1003 (1970); W. H. Faul and C. Djerassi, *Org. Mass Spectrom.*, **3**, 1187 (1970).

TABLE I

ASSIGNMENT OF LOW FIELD SIGNALS IN THE PMR SPECTRA OF SPIROSTANS AND FUROSTANS[a,b]

Spirostan (1)

Registry no.	Substituent, R	Chemical shifts, ppm C-3	C-16	C-22	C-26 (J, Hz)[c]
5012-14-6	H		4.40		3.45 (d, 5)
77-60-1	OH	3.57	4.40		3.47 (d, 5)
2530-07-6	CH_3COO	4.62	4.35		3.36 (d, 5)
39636-32-3	p-$CH_3C_6H_4SO_3$	4.43	4.3[d]		3.42 (d, 5)

Furostan (2)

Registry no.	Substituents R	R_1	X	Chemical shifts, ppm C-3	C-16	C-22	C-26 (J, Hz)[c]
39636-33-4	H[e,f]	H	H		4.29	3.32	
39636-34-5	CH_3COO[e]	H	H	4.68	4.28	3.32	
39636-35-6	H	$(CH_3)_3C$	H		4.30	3.33	3.18 (d, 5)
39636-36-7	CH_3COO[g]	CH_3CO	H	4.52	4.14	3.13	3.81 (d, 6)
39636-37-8	$Cl_3CCONHCOO$	$Cl_3CCONHCO$	H	4.80	4.27	3.32	4.17 (d, 5)
39636-38-9	$(CH_3)_2CO$	$(CH_3)_3C$	H	3.2[d]	4.25	3.33	3.13 (d, 6)
39636-39-0	CH_3COO	26-Thio acetal	H	4.65	4.26	3.32	4.55 (d, 6)
39636-40-3	CH_3COO	26-Aldehyde	H	4.68	4.28	3.30	
39636-41-4	H	H	H		4.26	3.30	3.43 (d, 5)
39636-42-5	H	H	D		4.26		3.45 (d, 5)
39636-43-6	H	CH_3CO	H		4.28	3.28	3.92 (dd, 5, 1.5)
39636-44-7	H	CH_3CO	D		4.26		3.92 (dd, 5, 1.5)
39636-45-8	H	26-Methoxycarbonyl	H		4.26	3.30	
39636-46-9	H	26-Methoxycarbonyl	D		4.27		
39636-47-0	OH	OH	H	3.59	4.24	3.30	3.45 (d, 6)
39636-48-1	OH	OH	D	3.60	4.25		3.47 (d, 6)

[a] Protons not below δ 3 or absent are left blank. [b] Solvent was $CDCl_3$ in all cases except where noted. [c] d, doublet; dd, doublet of doublets. [d] Approximate. [e] Supplied by Dr. J. C. Knight. [f] 5β hydrogen. [g] Carbon tetrachloride as solvent.

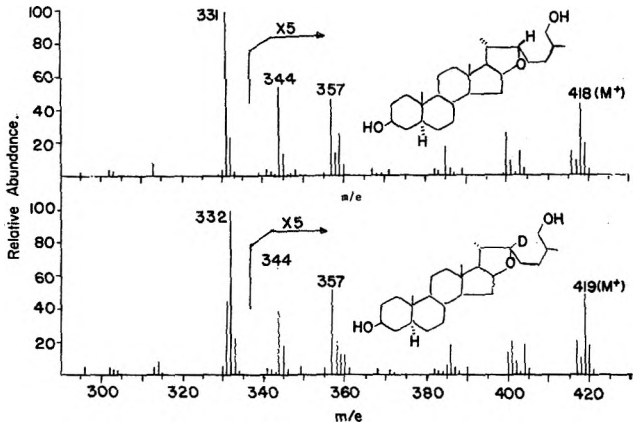


Figure 1.—Mass spectra of labeled and unlabeled dihydrotigogenin (2a).

pound plus the appearance of an M − 3 peak and no change in the mass of all other fragments. In practice, the product (**2d**) of lithium aluminum deuteride–aluminum chloride reduction of tigogenin displayed a high degree of monodeuteration, but the fragmentation pattern (Figure 1) presented a challenge. From the mass spectral data it was possible to rule out a C-26 deuterium label, but it was not possible to confirm a C-22 deuteron owing to the presence of both M − 87 (*m/e* 332) and M − 88 (*m/e* 331) peaks (Chart II, fragment **10**).

To determine whether an oxygen-containing fragment, other than loss of the side chain, was responsible for the M − 88 (*m/e* 331) peak in the mass spectrum of dihydrotigogenin-d_1 (**2d**), a study of 3-deoxytigogenin was made. The appropriate dihydro derivatives (**2c** and **2e**) were prepared by reduction with either lithium aluminum hydride or deuteride with aluminum chloride. The respective mass spectral fragments, between the molecular ion and loss of the side chain, are listed in Table II. Again, both the M − 87 (*m/e* 316) and

TABLE II

MASS SPECTRA OF UNLABELED (2c) AND DEUTERIUM-LABELED (2e) DIHYDRO-3-DEOXYTIGOGENIN

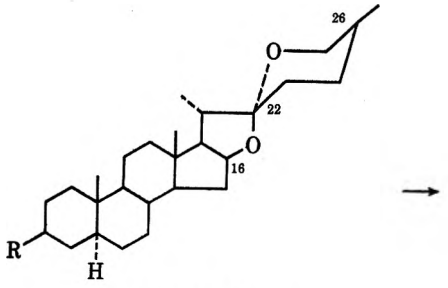
Unlabeled (2c) *m/e* (rel intensity)	Labeled (2e) Fragment	Labeled (2e) *m/e* (rel intensity)
402 (10)	M^+	403 (11)
401 (1)	M − 1	402 (2)
400 (4)	M − 2	401 (5)
387 (3)	M − 15	388 (3)
384 (5)	M − H_2O	385 (3)
	M − HDO	384 (2)
369 (3)	M − 15 − H_2O	370 (2)
	M − 15 − HDO	369 (1)
343 (4)	7	344 (2)
	7	343 (2)
341 (8)	8	341 (11)
328 (11)	9	328 (14)
315 (100)	10	316 (100)
	10	315 (37)

M − 88 (*m/e* 315) fragments were present in the labeled derivative (**2e**) spectrum. Thus, it appeared that a C-3 oxygen containing fragment was not responsible for the M − 88 peak. High resolution mass studies further demonstrated that the peak at *m/e* 315 of dihydro-3-deoxytigogenin (**2c**) was due to a fragment with composition $C_{22}H_{33}O$ (**10**). We next excluded multiple pathways leading to M − 87 (*m/e* 316) and M − 88 (*m/e* 315) ions by observing the electron energy independence of the peak ratio [315]/[316] from 70 eV to threshold.[1b]

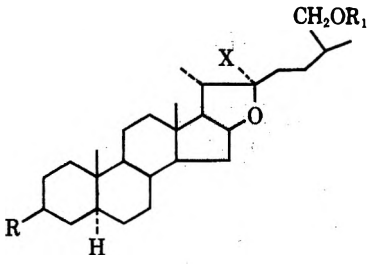
When labeled dihydro-3-deoxytigogenin was con-

verted to acetate **2f** and subjected to electron impact, a marked effect upon composition of the oxonium ion fragment **10** was apparent. As shown in Table III, a peak corresponding to the M − 88 (*m/e* 315) ion was no longer present. Similarly, when dihydro-3-deoxytigogenins **2c** and **2e** were oxidized and methylated to yield methyl-(22*R*,25ε)-5α-furostan-26-oates (**6a** and **6b**) only the M − 87 (*m/e* 316) peak was found in the labeled derivative (**6b**) mass spectrum (Table IV). These results indicated that the 26-hydroxyl group was responsible for the ambiguous mass spectral results obtained with the dihydrotigogenins.

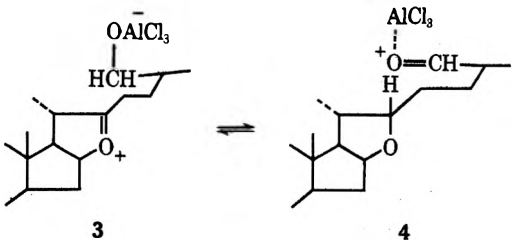
CHART I



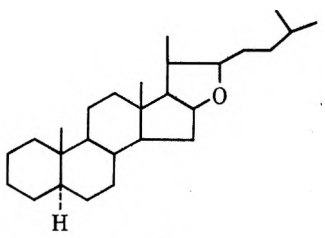
1a, R = OH
b, R = H



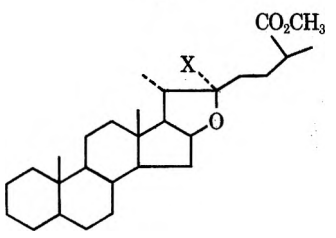
2a, R = OH; R_1 = X = H; M^+ 418
b, R = OH; R_1 = $COCH_3$
c, R = R_1 = X = H; M^+ 402
d, R = OH; R_1 = H; X = D; M^+ 419
e, R = R_1 = H; X = D; M^+ 403
f, R = H; R_1 = $COCH_3$; X = D
g, R = H; R_1 = $COCH_3$; X = H
h, R = H; R_1 = D



3 **4**

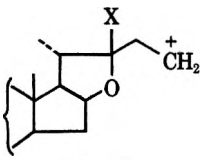


5



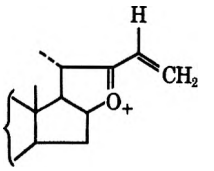
6a, X = H
b, X = D

CHART II



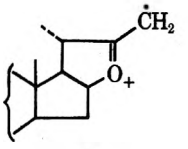
7

m/e 359; R = OH; X = H
m/e 360; R = OH; X = D
m/e 343; R = H; X = H
m/e 344; R = H; X = D



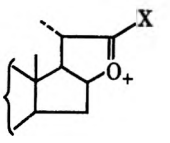
8

m/e 357, R = OH
m/e 341, R = H



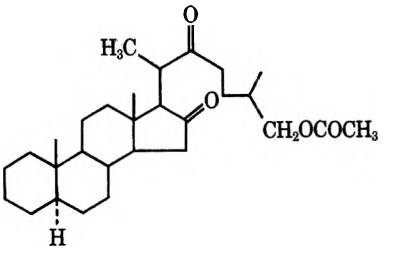
9

m/e 344, R = OH
m/e 328, R = H



10

m/e 331, R = OH; X = H
m/e 332, R = OH; X = D
m/e 315, R = H; X = H
m/e 316, R = H; X = D



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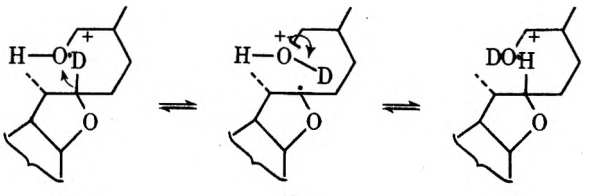

12 **13** **14**

TABLE III
MASS SPECTRA OF UNLABELED (**2g**) AND DEUTERIUM-LABELED (**2h**) DIHYDRO-3-DEOXYTIGOGENIN ACETATE

Unlabeled (**2g**)	Labeled (**2h**)	
m/e (rel intensity)	Fragment	*m/e* (rel intensity)
444 (12)	M^+	445 (13)
429 (19)	M − 15	430 (18)
427 (5)	M − 17	428 (2)
426 (6)	M − H_2O	427 (4)
	M − HDO	426 (4)
411 (3)	M − H_2O − CH_3	412 (2)
400 (2)	M − 44	401 (17)
384 (19)	M − HOAC	385 (11)
	M − DOAC	384 (8)
369 (9)	M − HOAC − CH_3	370 (6)
355 (15)	*m/e* 384 − 29	355 (12)
341 (32)	*m/e* 384 − 43	341 (27)
328 (15)	9	328 (11)
315 (100)	10	316 (100)

TABLE IV

MASS SPECTRA OF UNLABELED (6a) AND DEUTERIUM-LABELED (6b) METHYL-5α-(22R,25ε)-FUROSTAN-26-OATE

Unlabeled (6a) m/e (rel intensity)	Fragment	Labeled (6b) m/e (rel intensity)
431 (17)	M^+	430 (28)
416 (9)	M − 15	415 (11)
413 (10)	M − H_2O	412 (21)
412 (14)	M − HDO	
400 (7)	M − OCH_3	399 (8)
	M − CH_3OH	398 (8)
398 (9)	M − CH_3OD M − CH_3 − H_2O	397 (7)
384 (10)	M − CH_3OH − CH_3	383 (12)
371 (6)	M − CH_3OH − CO	370 (9)
370 (4)	M − CH_3OD − CO	
361 (5)		360 (5)
344 (16)		343 (17)
328 (27)	M − $CH_3CHCOOCH_3$	328 (45)
316 (100)		315 (100)

The best evidence that deuterium had been incorporated only into the 22 position was obtained by oxidizing deuterium-labeled dihydro-3-deoxytigogenin acetate (2f) to 26-acetoxy-16,22-dioxo-(25R)-5α-cholestane (11) and comparing its mass spectrum with that of a sample prepared from the nondeuterated analog 2c. In this manner it was shown that deuterium had indeed been incorporated into the 22 position since all label was lost.

To account for the presence of both M − 87 and M − 88 peaks (see 10) in the spectra of the labeled dihydrotigogenins, a reciprocal H/D exchange between C-22 and the alcohol O atom was proposed (12 ⇄ 13).[1b] This novel exchange not only accounts for the presence of both the labeled and unlabeled oxonium ion fragments (10) but also the anomalous HDO loss and M − 60 fragment (*cf.* 7). In such an exchange mechanism, dihydrosapogenins containing an O-*d* label should also display both M − 87 (7, X = D) and M − 88 (7, X = H) peaks, but the ratio of the two peaks would be exactly opposite to that found in the C-22 labeled analogs. This situation was in fact found to be the case for dihydro-3-deoxytigogenin-*O*-*d* (2h, Table V). Thus, the hydrogen (deuterium) atom of position 22 can exchange with the hydroxyl proton (deuteron) *via* a novel[8] seven-centered transition state.[1b] Undoubtedly, the relative position of the tetrahydrofuran ring (which gives rise to a very stable radical) to the hydroxyl group is responsible for this unusual reaction.

From the above pmr and mass spectral results, it was concluded that the mechanism of metal hydride reduction of the steroidal sapogenin spiro ketal system is best represented by an intermolecular hydride insertion (3 → 2). Stereochemical aspects were next considered. An X-ray crystallographic study of the sapogenins[9] has substantiated[10a] that the configuration about C-22 is "*R*."[10b] However, the configuration at C-22 in the dihydrosapogenins has not been established. Since metal hydride reduction of the spiro ketal gives a nearly quantitative yield of sharp melting solid, it would appear that the dihydrotigogenins must consist of one isomer rather than a mixture of epimers.[11] By examining a model, it can be seen that the 18-methyl group poses a greater amount of steric hinderance to a group approaching at C-22 than the 21-methyl group. For these steric reasons it should be easier for the incoming group to approach from the remote α side of the steroid resulting in an *R* configuration at C-22. Also, as the alcohol resulting from steric approach control accounts for 90% of the camphor–lithium aluminum hydride reduction product,[12] it seems quite plausible that the larger[5,13] $AlHCl_2$ might attack the slightly less hindered oxonium ion 3 with selectivity.[14]

Instead of steric approach control, the reduction product might result from product development control. Inspection of models suggests that the most stable final product (2) should have the bulky side chain in the α position and thereby removed from the 18-methyl group. In this configuration the side chain would remain cis and in close proximity to the 21α-methyl group. If, on the other hand, the side chain were to assume the β or *R* configuration, a change in conformation of the E ring would allow a positioning remote to both methyl groups. Thus, it appears that by approaching the stereochemical problem from either steric approach or product development control the same configuration (*R*) is indicated for the dihydrosapogenin 22 position.

An alternative to the stepwise reduction mechanism discussed above is a concerted one. For example, certain stereoselective reductions of epoxides have been postulated[14] to proceed by simultaneous ring opening and hydride insertion. With epoxides it has been suggested[14] that only the weaker Lewis acid AlH_3 (stronger hydride donor) is involved in a concerted attack. With spiro ketals, it is possible that the electron density around the incipient carbonium ion is sufficiently altered by the adjacent oxygen atom to allow the weaker hydride donor $AlHCl_2$ to also react in a concerted manner. If, indeed, reduction is concerted, the C-22 stereochemistry should be maintained and lead to the (22*R*)-dihydrosapogenin. Regardless of whether the mechanism is stepwise or concerted the configuration at C-22 should be *R*. Similar arguments for the stereo-

(8) See, for example, J. H. Beynon, B. E. Job, and A. E. Williams, *Zeit. Fur Naturforsch.*, **20a**, 883 (1965); S. Meyerson and J. L. Corbin, *J. Amer. Chem. Soc.*, **87**, 3045 (1965); A. N. H. Yeo and D. H. Williams, *ibid.*, **91**, 3582 (1969); and G. A. Smith, and D. H. Williams, *ibid.*, **91**, 5254 (1969).

(9) R. Callow, *J. Chem. Soc. C*, 288 (1966).

(10) (a) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 822; (b) G. R. Pettit, *Experientia*, **19**, 124 (1963).

(11) Although the yield was quantitative, this does not preclude the possibility that a small amount of an epimeric mixture was removed during recrystallization.

(12) D. S. Noyce and D. B. Denney, *J. Amer. Chem. Soc.*, **72**, 5743 (1950); H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 31.

(13) E. C. Ashby and J. Prather, *J. Amer. Chem. Soc.*, **88**, 729 (1966); U. E. Diner, H. A. Davis, and R. K. Brown, *Can. J. Chem.*, **45**, 207 (1967); E. L. Eliel, *Rec. Chem. Progr.*, **22**, 129 (1961); E. Wiberg and M. Schmidt, *Z. Natu-forsch.*, **6B**, 333 (1951); E. Wiberg and M. Schmidt, *ibid.*, **6B**, 460 (1951). The actual reducing species in mixed hydride reductions are AlH_3, AlH_2Cl, $AlHCl_2$, and $AlHCl_2 \cdot AlCl_3$ when the ratio of aluminum chloride to lithium aluminum hydride is 1:3, 1:1, 3:1, and 4:1, respectively. See E. C. Ashby and B. Cooke, *J. Amer. Chem. Soc.*, **90**, 1625 (1968). The excess aluminum chloride in the 4:1 ratio ($AlCl_3$:$LiAlH_4$) was found not to take part in the reduction of epoxides.

(14) Generally, it is assumed that the reduction of a ketone with lithium aluminum hydride proceeds *via* a four-centered transition state. The metal atom is coordinated with the oxygen and a hydride with the electron-deficient carbon atom. This mode of action has been considered for other hydride-donating species (see ref 13).

TABLE V

HYDROGEN–DEUTERIUM EXCHANGE[a]

Dihydro-3-deoxytigogenin			Dihydro-3-deoxytigogenin-22-d[b]				Dihydro-3-deoxytigogenin-O-d				
400	401	402	400	401	402	403	400	401	402	403	404
28	3	70	1	29	3	67	33	5	32	29	2
314	315	316	314	315	316	317	313	314	315	316	317
4	96	0	3	25	72	0	2	7	80	11	0
				26	74				76	24[c]	

[a] Corrected for ^{13}C isotopic contributions; all values are in per cent; each peak normalized to 100%; reproducibility ±1%. [b] <97% d_1. [c] Corrected to 100% O-d_1.

chemical course of the hydrogenation[15] route to dihydrosapogenins also points to an *R* configuration at C-22 and our[2] earlier comparison of dehydrosapogenins prepared by catalytic hydrogenation and lithium aluminum hydride–aluminum chloride methods provides compelling support for the stereochemical assignments.

Experimental Section

Boiling points and melting points (Kofler hot stage apparatus) are uncorrected. Each analytical sample was colorless and displayed a single spot on thin layer chromatography. The (Beckman IR-12), pmr (Varian A-60, tetramethylsilane internal standard), and ORD (Jasco ORD/UV-5) spectra were recorded by Miss K. Reimer. An Atlas CH4B instrument equipped with a molecular beam direct inlet system was employed for low resolution mass spectra. The experimental conditions employed were electron energy of 70 eV, trap current of 19 μA, source temperature of 200°, probe temperature of 70–75°, and accelerating voltage of 3 kV. Accurate mass measurements were determined using an Atlas SM1B double focussing instrument with electron energy of 70 eV, trap current of 290 μA, source temperature of 180°, probe temperature of 70–75°, accelerating voltage of 8 kV, and ~10,000 resolutions.

Dihydrotigogenin-*22-d* (**2d**).—Lithium aluminum deuteride–aluminum chloride reduction of tigogenin was accomplished using our previously described[2] method employing lithium aluminum hydride. The deuterated specimen of dihydrotigogenin was isolated in essentially quantitative yield: mp 168–169.5°; ir ($CHCl_3$) 3630 (m), 3450 (m, br), 2100 (w, br), 1040 cm^{-1} (s).

Dihydro-3-deoxytigogenin-*22-d* (**2e**).—The procedure used above for the preparation of deuterium-labeled dihydrotigogenin (**2d**) was applied to 3-deoxytigogenin (**1b**) and dihydro-3-deoxytigogenin-*22-d* was obtained in quantitative yield: mp 92.5–95°; ir ($CHCl_3$) 3370 (m, br), 2090 (w, br), 1055 cm^{-1} (s).

Dihydro-3-deoxytigogenin Acetate [26-Acetoxy-(22*R*,25*R*)-5α-furostan] (**2g**).—A solution of alcohol **2c** (1 g) in 60 ml of an acetic anhydride–perchloric acid acetylating reagent[16] was allowed to remain at room temperature for 10 min. After dilution with saturated sodium bicarbonate solution the corresponding acetate (**2g**) was isolated in 91% yield: bp 165° (bath, 0.008 mm) (the pure product slowly solidified, but melted over the range of 50–60°); ir (CCl_4) 1745 (s), 1175 (m), 1100 (m), 1005 cm^{-1} (w, sh); ORD ($CHCl_3$) $[\alpha]^{26}$, λ (mμ), −9.0 (400), −13.3 (350), −25.5 (312, min), −24.0 (307, infl), −12.2° (290).

Anal. Calcd for $C_{29}H_{48}O_3$: C, 78.32; H, 10.88. Found: C, 78.08; H, 10.80.

Dihydro-3-deoxytigogenin-*22-d* Acetate (**2f**).—The acetate derivative of dihydro-3-deoxytigogenin-*22-d* (**2f**) was obtained as an oil: bp 180° (bath, 0.012 mm); ir (CCl_4) 2080 (w, br), 1740 (s), 1240 cm^{-1} (s); ORD ($CHCl_3$) $[\alpha]^{25}$, λ (mμ), −5.2 (500), −8.4 (400), −13.8 (338, infl), −18.5 (310, max).

26-Acetoxy-16,22-dioxo-(25*R*)-5α-cholestane (**11**).—Dihydro-3-deoxytigogenin acetate (**2g**) was converted to diketone **11** in 81% yield using the general chromium trioxide procedure of Iwasaki.[17] Recrystallization of the product from methanol afforded an analytical sample (colorless needles): mp 95.5–97°; ir (KBr) 1745 (s), 1715 (s), 1253 cm^{-1} (s); pmr ($CDCl_3$) δ 2.08 (s), 2.61 (d, broad, J = 3 Hz), 3.95 ppm (d, J = 5.5 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 458 (0.5, M^+), 398 (20), 383 (8), 329 (51), 302 (90), 301 (100), 287 (44); ORD ($CHCl_3$) $[\alpha]^{25}$, λ (mμ), −1090 (350), −3880 (315, min), −3250 (308, infl), 0.0 (294), +3100 (271, max).

Anal. Calcd for $C_{29}H_{46}O_4$: C, 75.94; H, 10.11. Found: C, 76.20; H, 9.90.

A sample of dihydro-3-deoxytigogenin-*22-d* acetate (**2f**) was oxidized to diketocholestane **11** using the procedure described above (*cf.* **11**). Both ir and mass spectral analysis demonstrated that no deuterium was present in the product (**11**), mp 92–95°.

Methyl (22*R*,25ε)-5α-Furostan-26-oate (**6a**).—Dihydro-3-deoxytigogenin (**2a**) was oxidized and methylated in the same manner as described below for labeled derivative **2e**: mp 85.5–95°; ir (KBr) 1740 (s), 1170 cm^{-1} (m).

Anal. Calcd for $C_{28}H_{46}O_3$: C, 78.09; H, 10.77. Found: C, 77.85; H, 10.88.

Methyl (22*R*,25ε)-5α-Furostan-26-oate-*22-d* (**6b**).—Dihydro-3-deoxytigogenin-*22-d* (**2e**, 0.60 g) in 30 ml of acetone was slowly treated with 1 ml of Jones reagent[18] while the temperature was kept below 10° (ice bath). The mixture was then allowed to remain at room temperature for 25 min. Excess oxidant was destroyed with methanol and the mixture poured into 100 ml of water and continuously extracted with ether for 22 hr. Removal of the solvent *in vacuo* yielded 0.62 g of colorless solid, mp 123–140°. Recrystallization from acetone (twice) at −7° and from hexane (once) gave a product melting at 138–153°. The acid was treated with freshly distilled diazomethane (in ether) to yield an oil. Recrystallization from methanol at Dry Ice–isopropyl alcohol temperature and twice from methanol at −7° gave a colorless solid: mp 76–83°; ir (KBr) 2100 (w, br), 1745 (s), 1170 cm^{-1} (m).

Registry No.—**2c**, 39636-41-4; **2d**, 39636-50-5; **2h**, 39636-51-6; **11**, 39636-52-7.

(15) The catalytic reduction of acetals and ketals has been proposed to proceed *via* an enol ether: M. Acke and M. Anteunis, *Bull. Soc. Chim. Belges*, **74**, 41 (1965), and W. L. Howard and J. H. Brown, *J. Org. Chem.*, **26**, 1026 (1961). If this proposal is extended to the sapogenins, hydrogenation of the unsaturated intermediate (pseudosapogenin) from the least hindered α side would produce the (20*R*,22*R*)-furostan derivative. The product would have the incorrect configuration at C-20. However, it has been demonstrated by R. K. Callow and P. N. Massy-Beresford, *J. Chem. Soc.*, 2645 (1958), that this isomer can readily be converted by acidic hydrogenation media to the more stable 20*S* configuration.

(16) E. D. Edwards and P. N. Rao, *J. Org. Chem.*, **31**, 324 (1966).

(17) M. Iwasaki, *Tetrahedron*, **23**, 2145 (1967).

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

Bufadienolides. 25. Direct Conversion of 14-Dehydrobufalin to Bufalin[1]

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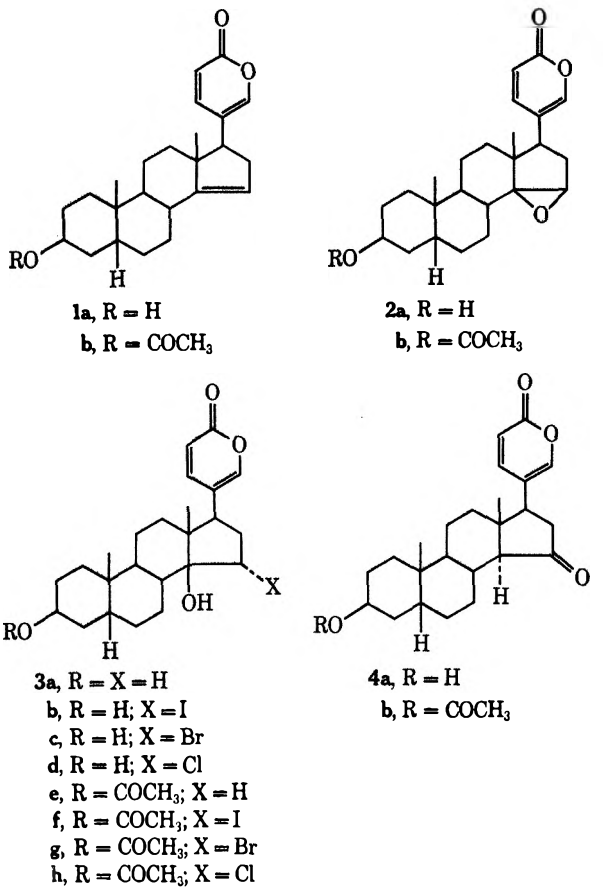
The easily prepared iodo- (**3b**), bromo- (**3c**), and chlorohydrin (**3d**) derivatives of 14-dehydrobufalin (**1a**), when subjected to careful hydrogenolysis using Urushibara nickel A or Raney nickel, readily yield bufalin (**3a**). This experimentally simple route from 14-dehydrobufalin to bufalin obviates the prior necessity of proceeding *via* resibufogenin (**2a**). In related experiments, treatment of resibufogenin (**2a**) with hydrogen chloride was found to yield chlorohydrin **3d**, and the reverse reaction was achieved using hot α-collidine. A new procedure for selective hydrolysis of bufadienolide 3β-acetates was realized employing an acidic ion exchange resin.

Stereoselective addition of hypohalous acid to a steroid 14 olefin followed by selective hydrogenolysis of the carbon–halogen bond provides in principle an attractive means for obtaining certain 14- or 15-hydroxy steroids. Excellent illustrations of this reaction sequence appear in recent transformations of 14-dehydrocardenolides to the corresponding 14β-hydroxy cardenolides[2] and in a synthesis of the plant bufadienolide, scillarenin.[3] These experiments suggested that our earlier synthesis of bufalin[4] which included transformation of 14-dehydrobufalin (**1a**) *via* resibufogenin (**2a**) to bufalin (**3a**) might be simplified employing a halohydrin approach. In practice this proved quite workable and a summary of these experiments is recorded in this report.

In a preceding series of experiments,[4b] reaction of *N*-iodosuccinimide and either *N*-bromosuccinimide or *N*-bromoacetamide was found to readily transform 14-dehydrobufalin (**1a**) to, respectively, iodohydrin **3b** and bromohydrin **3c**. In the present study chlorohydrin **3d** was also prepared using olefin **1a** and *N*-chlorosuccinimide. Unlike the *N*-iodo- and *N*-bromoimide reactions, formation of the chlorohydrin did require presence of a small amount of perchloric acid in the solvent. While iodohydrin **3b** and bromohydrin **3c** could not be isolated in pure form, the chlorohydrin **3d** has been easily isolated and characterized. The chlorohydrin **3d** was also obtained by a modification of the method Meyer[5] applied to resibufogenin (**2a**) using hydrogen chloride. However, this method proved less attractive than using olefin **1a**, as substantial amounts of 14α-artebufogenin (**4a**) were formed. Each of the preceding reactions was also viewed starting with the corresponding 3β-acetate derivative and analogous results were observed.

Careful hydrogenolysis of halohydrins **3b** and **3c** using Urushibara nickel A[6] or Randy nickel[7] readily afforded bufalin (**3a**) in good yield. For example, conversion of 14-dehydrobufalin to iodohydrin **3b** followed by hydrogenolysis with Urushibara nickel A led to bufalin in a 67% overall yield. However, hydrogenolysis of chlorohydrin **3b** did not proceed well in spite of prolonging the reaction; the yield of bufalin (**3a**) was limited to 18%. Comparable results were obtained in the conversion of 3β-acetoxy-14-dehydrobufalin (**1b**) to 3β-acetoxybufalin (**3e**). Again, hydrogenolysis of iodohydrin **3f** and bromohydrin **3g** proceeded very well but chlorohydrin **3h** gave unsatisfactory results. In both series of experiments the Urushibara nickel A and Raney nickel gave similar results. The usual[4a] alumina-catalyzed hydrolysis of bufalin acetate to bufalin was improved by substituting Amberlite CG-120 resin in the acid form. The ion exchange resin catalyzed hydrolysis reaction also proceeded well when applied to conversion of resibufogenin acetate (**3b**) to resibufogenin (**2a**).

One of the synthetic routes we developed[4b] to resibufogenin (**2a**) involved allowing iodohydrin **3b** or bromohydrin **3c** to react with pyridine or basic alumina. With such halohydrins collapse to the corresponding epoxide proceeds very quickly and in essentially quanti-



1a, R = H
b, R = $COCH_3$

2a, R = H
b, R = $COCH_3$

3a, R = X = H
b, R = H; X = I
c, R = H; X = Br
d, R = H; X = Cl
e, R = $COCH_3$; X = H
f, R = $COCH_3$; X = I
g, R = $COCH_3$; X = Br
h, R = $COCH_3$; X = Cl

4a, R = H
b, R = $COCH_3$

(1) The present contribution represents part 84 of the series Steroids and Related Natural Products. For the preceding paper see Y. Kamano and G. R. Pettit, *J. Amer. Chem. Soc.*, **94**, 8592 (1972). This reference also corresponds to a preliminary report of the present study.

(2) W. Fritsch, U. Stache, W. Haede, K. Radscheit, and H. Ruschig, *Justus Liebigs Ann. Chem.*, **721**, 168 (1969); U. Stache, W. Fritsch, W. Haede, and K. Radscheit, *ibid.*, **726**, 136 (1969).

(3) U. Stache, K. Radscheit, W. Fritsch, W. Haede, H. Kohl, and H. Ruschig, *Justus Liebigs Ann. Chem.*, **750**, 149 (1971).

(4) (a) G. R. Pettit, L. E. Houghton, J. C. Knight, and F. Bruschweiler, *J. Org. Chem.*, **35**, 2895 (1970); (b) G. R. Pettit, Y. Kamano, F. Bruschweiler, and P. Brown, *ibid.*, **36**, 3736 (1971).

(5) K. Meyer, *Helv. Chim. Acta*, **35**, 2444 (1952).

(6) Y. Urushibara, S. Nishimura, and H. Uehara, *Bull. Chem. Soc. Jap.* **28**, 446 (1955).

(7) W. Fritsch, H. Kohl, U. Stache, W. Haede, K. Radscheit, and H. Ruschig, *Justus Liebigs Ann. Chem.*, **727**, 110 (1969).

tative yield. However, brief treatment of chlorohydrin **3d** with pyridine has proved unproductive,[5] but in the present study dehydrohalogenation in hot α-collidine did prove effective and provided resibufogenin (**2a**).

Evidence now in hand from the preceding direct synthesis of bufalin from 14-dehydrobufalin combined with analogous results[2,3] obtained in the Farbwerke Hoechst Laboratories clearly indicates that the halohydrin-hydrogenolysis route to 14β-hydroxy steroids from 14-olefin precursors is a most efficient method. Alternatively, photochemically initiated attack on the saturated 14-carbon has been of increasing promise.[8]

Experimental Section

The bufalin and resibufogenin employed in this study were isolated from the Chinese medicinal preparation, Ch'an Su. All melting points were observed using a micro hot-stage apparatus (Reichert, Austria) and are uncorrected. Spectral data was recorded by Miss K. Reimer and Messrs. Richard Scott and Eugene Kelley. The general experimental, chromatographic techniques, and instrumental methods have been summarized in prior contributions.[4b,9]

Bufalin (3a). Method A. From Iodohydrin 3b.—About 2.6 g of Urushibara nickel A[6] in ethanol (18 ml) was saturated with hydrogen employing vigorous stirring. The hydrogen atmosphere was replaced with nitrogen and the ethyl alcohol with methylene chloride. A solution of iodohydrin **3b** (79 mg), prepared[4b] from 80 mg of 14-dehydrobufalin, in methylene chloride (10 ml) was added to the nickel A and the mixture was stirred in a nitrogen atmosphere for 4 hr at 14–16°. The solution was filtered and solvent was removed from the filtrate to provide a 78-mg residue, which was subjected to preparative thin layer chromatography on silica gel using acetone–chloroform–*n*-hexane (3:3:4) as eluent. The zone corresponding to R_f 0.29 was eluted with methanol. Recrystallization of the product from methanol afforded 54 mg of bufalin (**3a**) as colorless needles melting at 240–243°. Our original synthetic specimen[4a] of bufalin melted at 242–243°.[10]

In an analogous series of experiments, iodohydrin **3b** (43 mg) was treated (3 hr at 18–20°) with freshly prepared[7] Raney nickel (approximately 1.2 g) in a nitrogen atmosphere. By means of the isolation procedure described for the Urushibara nickel A experiment 26 mg of bufalin (**3a**), mp 239–242°, was isolated.

Method B. From Bromohydrin 3c.—A 39-mg sample of the crude bromohydrin **3c** prepared from 14-dehydrobufalin and *N*-bromoacetamide was converted to bufalin (**3a**, 25 mg, mp 239–243°) using the hydrogen-saturated Urushibara nickel A (about 1.6 g) procedure (4 hr at 16°) summarized in method A. With the Raney nickel (approximately 1 g) procedure, 37 mg of the crude bromohydrin (**3c** obtained using *N*-bromosuccinimide) provided 23 mg of bufalin (**3a**) melting at 238–241°.

Method C. From Chlorohydrin 3c.—A 35-mg specimen of chlorohydrin **3c** was prepared as summarized in the following experiment and subjected to hydrogenolysis with freshly prepared Urushibara nickel A (*ca.* 1.4 g) in methylene chloride (10 mg). In this case the reaction mixture was stirred in a nitrogen atmosphere for 8 hr at 28–32°. The bufalin (**3a**, 6.2 mg) was isolated as noted in method A and found to melt at 237–241°.

Method D. By Hydrolysis of 3β-Acetoxybufalin (3e).—A mixture prepared from bufalin acetate (**3e**, 33 mg), ethyl alcohol (9 ml)–water (2 ml), and 0.35 g of Amberlite CG-120 (H^+ form) was stirred at room temperature for 18 hr. The solution was filtered and following removal of solvent the crude product (35 mg) was purified by preparative thin layer chromatography and recrystallization as indicated in method A to yield 22.8 mg of bufalin (**3a**) melting at 237–240°.

The specimens of bufalin (**3a**) prepared by methods A–C were found mutually identical[10] and identical with natural bufalin.[11]

3β,14β-Dihydroxy-15α-chloro-5β-bufa-20,22-dienolide (3d). Method A. From 14-Dehydrobufalin (1a).—A solution of *N*-chlorosuccinimide (0.12 g) in dioxane (3 ml)–acetone (1 ml) was added with stirring to a solution composed of 14-dehydrobufalin (**1a**, 0.12 g) in dioxane (6 ml)–acetone (2 ml)–water (1 ml) and perchloric acid (0.1 ml) at room temperature. After a 24-hr period, sodium sulfite (0.12 g) in water (4 ml) was added and approximately two thirds of the solvent was removed under reduced pressure. The mixture was poured into ice–water with stirring and extracted with chloroform. The combined extract was washed with water and concentrated to dryness. The 0.13-g residue was chromatographed on a column of silica gel and the fraction eluted with 4:1 ligroin–acetone was recrystallized from ethyl acetate to provide 58 mg of chlorohydrin **3d**, mp 232–233°, as colorless needles: mass spectrum M^+ 420, 402 ($M^+ - H_2O$), 384 ($M^+ - 2H_2O$ and $M^+ - HCl$), and 366 ($M^+ - 2H_2O - HCl$); uv λ_{max} 299 mμ (log ϵ 3.71 in methanol); ir ν_{max}^{KBr} 3518 (OH), 3460 (OH), 1724, 1695 (conjugated CO), 1633, 1540 (conjugated C=C), 958, 745 (C=C), and 720 cm^{-1} (Cl); pmr (in pentadeuteriopyridine) δ 0.90 (18-methyl), 0.94 (19-methyl), 2.58 (d, J = 4 Hz, 16-protons), 4.31 (broad s, 3α-proton), 4.56 (d, J = 4 Hz, 15β-proton), 6.29 (d, J = 9.5 Hz, 23-proton), about 7.5 (21-proton, indistinct peak overlapped with that of solvent), and 7.68 (q, J = 9.5 and 2.5 Hz, 22-proton).

Anal. Calcd for $C_{24}H_{33}O_4Cl$: C, 68.47; H, 7.90; Cl, 8.42. Found: C, 68.38; H, 7.90; Cl, 8.36.

Method B. From Resibufogenin (2a).—Dry hydrogen chloride was carefully passed (for 8 min) through a solution of resibufogenin (**2a**, 0.15 g) in dry chloroform (3 ml) maintained at −8°. Additional chloroform was added and the solution was poured into water. The chloroform layer was separated, washed with water, dilute sodium bicarbonate solution, and water and then concentrated under reduced pressure to dryness. The residue (0.17 g) was chromatographed on a column of silica gel. The fraction eluted with ligroin–acetone (4:1) was recrystallized from ethyl acetate to yield (82.5 mg) chlorohydrin **3d** melting at 231–233°.

Continued elution of the silica gel column provided 37 mg of 14α-artebufogenin (**4a**, mp 263–265° from acetone) which was identical[10] with an authentic specimen.[4b] Also the specimens of chlorohydrin **3d** prepared by methods A and B were found mutually identical.[10]

When chlorohydrin **3d** (26 mg) was acetylated (room temperature, 24 hr) with acetic anhydride (3 ml)–pyridine (4 ml) and the product was recrystallized from ethyl acetate, a 24-mg sample of 3β-acetoxy-14β-hydroxy-15α-chloro-5β-bufa-20,22-dienolide (**3h**) was obtained as colorless needles melting at 230–233°. The identical acetate (**3h**, 42 mg, mp 230–232°) was obtained from 3β-acetoxy-14-dehydrobufalin (**1b**, 75 mg) and *N*-chlorosuccinimide (76 mg) by method A. In this experiment acetate **3h** was eluted from the silica gel column with 7:1 ligroin–acetone. Further, acetate **3h** (58 mg, mp 229–230°) and 3β-acetoxy-14α-artebufogenin (**4b**, 22 mg, mp 220–221°)[4b] were obtained from 3β-acetoxyresibufogenin (**2b**, 100 mg) using dry hydrogen chloride in chloroform (2.5 ml) by method B. Again, the silica gel column was eluted with 7:1 ligroin–acetone. All three samples of chlorohydrin acetate **3h** were mutually identical.[10]

3β-Acetoxybufalin (3e). Method A. From Iodohydrin Acetate 3f.—A 35-mg quantity of 3β-acetoxy-14-dehydrobufalin (**1b**) was converted to iodohydrin **3f** (36 mg) using *N*-iodosuccinimide was previously reported.[4b] The resulting crude iodohydrin (**3f**, 36 mg) was treated with Urushibara nickel A (about 1.4 g) in methylene chloride (9 ml) as noted in the method A route to bufalin described above. The product was isolated by preparative thin layer chromatography employing 3:3:4 acetone–chloroform–*n*-hexane and the zone corresponding to R_f 0.60 was eluted with 2:1 chloroform–methanol. Recrystallization of the product from acetone gave 3β-acetoxybufalin (**3e**, 24 mg) as needles melting at 239–240° (lit.[12] mp 236–247°).

Method B. From Bromohydrin Acetate 3g.—With 20 mg of 3β-acetoxy-14-dehydrobufalin (**1b**) and *N*-bromoacetamide (20 mg) as starting material the resulting crude bromohydrin (**3g**, 19 mg)[4b] underwent hydrogenolysis with Raney nickel (about 0.6 g) to afford 11.8 mg of bufalin acetate (**3e**) melting at 239–242°. The reaction sequence and isolation procedure was conducted as summarized above for method A.

Method C. From Chlorohydrin 3h.—Chlorohydrin acetate **3f**

(8) For example, consult A. Rotman and Y. Mazur, *J. Amer. Chem. Soc.*, **94**, 6228 (1972).

(9) G. R. Pettit and Y. Kamano, *J. Chem. Soc.*, Perkin *Trans. 1*, in press.

(10) The identical composition of synthetic and natural specimens was confirmed by comparison infrared spectra (in potassium bromide) and thin layer chromatographic behavior.

(11) Y. Kamano, *Chem. Pharm. Bull.*, **17**, 1711 (1969).

(12) M. Barbier, H. Schroter, K. Meyer, O. Schindler, and T. Reichstein, *Helv. Chim. Acta*, **42**, 2486 (1959).

(25 mg) was treated with Urushibara nickel A (about 0.8 g) as noted above for the preparation of bufalin by method C. By this means 4.6 mg of bufalin acetate (3e), mp 237–240°, was obtained.

The samples of bufalin acetate prepared by methods A–C were found identical[10] with an authentic specimen:[11] mass spectrum M^+ 462, 444 ($M^+ - H_2O$), 426 ($M^+ - HCl$), 402 ($M^+ - AcOH$), 384 ($M^+ - H_2O - AcOH$), 366 ($M^+ - AcOH - HCl$), and 348 ($M^+ - H_2O - AcOH - HCl$); uv λ_{max} 299 mμ (log ε 3.48 in methanol); ir ν_{max}^{KBr} 3550 (OH), 1730, 1696 (conjugated CO), 1632, 1540 (conjugated C=C), 1264, 1240, 1228 (CO), 950, 745 (C=C), and 720 cm^{-1} (Cl); pmr (in deuteriochloroform) δ 0.74 (18-methyl), 0.92 (19-methyl), 2.06 (s, 3β-acetoxyl), 2.47 (d, J = 3 Hz, 16-protons), 4.32 (d, J = 3 Hz, 15β-proton), 5.15 (s, 3α-proton), 6.35 (d, J = 10 Hz, 23-proton), 7.34 (d, J = 2.5 Hz, 21-proton), and 7.58 (q, J = 10 and 2.5 Hz, 22-proton).

Anal. Calcd for $C_{26}H_{35}O_5Cl$: C, 67.45; H, 7.62; Cl, 7.66. Found: C, 67.55; H, 7.65; Cl, 7.51.

Resibufogenin (2a). Method A. From Chlorohydrin 3d.—A solution prepared from chlorohydrin **3d** (22 mg) and freshly distilled α-collidine (2.5 ml) was heated at reflux for 4.5 hr. The crude product obtained by removal (under reduced pressure) of solvent was chromatographed on a column of silica gel. The fraction eluted with 5:1 ligroin–acetone was recrystallized from acetone–*n*-hexane to provide 15.8 mg of resibufogenin (2a) with a characteristic double melting point, 108–121 and 149–168°. An earlier[4a] specimen of resibufogenin prepared in our laboratory was found to melt at 110–121 and 148–168°. Both specimens were mutually identical.[10]

Method B. Hydrolysis of Resibufogenin Acetate (2b).—A 28-mg sample of resibufogenin acetate (**2b**) was hydrolyzed in ethanol (18 ml)–water (2 ml) with 0.3 g of Amberlite CG-120 (H^+ form) as summarized above for the hydrolysis of bufalin acetate. The preparative thin layer corresponding to R_f 0.42 was eluted and recrystallized from acetone–*n*-hexane to provide 18 mg of resibufogenin as plates melting at 109–122 and 147–167°. The products of methods A and B were mutually identical.[10]

Resibufogenin Acetate (2b).—Dehydrohalogenation of chlorohydrin acetate **3h** (20 mg) with α-collidine (2.4 ml) was performed as outlined above for the synthesis of resibufogenin. The product was chromatographed on a column of silica gel and the fraction eluted with 8:1 ligroin–acetone was recrystallized from acetone to afford 14.4 mg of resibufogenin acetate (**2b**), as needles melting at 226–228°, identical[10] with a specimen obtained by acetylating natural resibufogenin.

Registry No.—**1a**, 7439-77-2; **2a**, 465-39-[illegible]; **2b**, 4029-64-5; **3a**, 465-21-4; **3b**, 39707-10-3; **3c**, 39707-11-4; **3d**, 39707-12-5; **3e**, 4029-66-7; **3f**, 39707-1[illegible]-7; **3g**, 39707-15-8; **3h**, 39707-16-9; **4b**, 24183-19-5.

Acknowledgment.—This investigation was supported by Public Health Research Grants CA-10612-04 and CA-10612-05 from the National Cancer Institute.

Mass Spectra of Prostaglandins. III. Trimethylsilyl and Alkyl Oxime–Trimethylsilyl Derivatives of Prostaglandins of the E Series[1]

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Received November 9, 1972

The mass spectra of the trimethylsilyl ester–trimethylsilyl ether derivatives of prostaglandins E_1 and E_2 and 8-isoprostaglandin E_2 and of their *O*-methyl oximes are reported and discussed. The high resolution spectra of these compounds are also considered. These spectra are compared with those of the analogous *O*-ethyl oximes and of the corresponding d_9-trimethylsilyl ether–d_9-trimethylsilyl ester and selectively labeled trimethylsilyl ester–d_9-trimethylsilyl ether derivatives. The 11-trimethylsilyloxy substituent had a strong fragmentation-directing influence on the molecular ion, and it was found that there was a marked stereochemical influence on fragmentation. Multiple origins were found for ions of several nominal masses; the most notable were those of m/e 199 and m/e 173. Ions of m/e 217 and m/e 204 were found to be formed by relatively long-range migrations of trimethylsilyl groups.

Prostaglandins of the E series are widely distributed in body fluids of man and of many other animals.[3] The 1,3-ketol moiety of the ring of these compounds is particularly unstable. The trimethylsilyl (TMS) derivatives were found to undergo partial decomposition during gas chromatography (gc),[4] but "clean" spectra of these derivatives could be obtained by combined gas chromatography–mass spectrometry (gc–ms). The oxime–TMS derivatives[5] were much more stable. In continuation of our studies of prostaglandin mass spectrometry,[1,6] we now report on the mass spectra of these derivatives of prostaglandins of the E series. All elemental compositions were compatible with high resolution data.

Results and Discussion

As was the case for the oxime–TMS derivative of prostaglandins of the A series,[6] it was found that those of the E series gave two peaks on gc, presumably the syn and anti isomers. It was reported that such derivatives of the synthetic 8-isoprostaglandins of the E series gave only one peak on gc.[5] We have, however, found that two peaks are obtained, although they are less well separated than those of the naturally occurring E series.[4] As before,[1,6] we have examined the spectra of methyl oxime (MO)–TMS and ethyl oxime (EO)–TMS derivatives, as well as those of the corresponding TMS-d_0 derivatives and of the selectively labeled TMS ester–d_9-TMS ether analogs. Because of space limitations, the spectra of the EO–TMS derivatives are not illustrated here, but have been submitted to the Mass Spectrometry Data Centre, A. W. R. E. Aldermaston, Berks, England.

The spectra of TMS derivatives of prostaglandins E_1 (I) and E_2 (II) and of 8-isoprostaglandin E_2 (III) are shown in Figures 1–3, respectively. The spectra

(1) For paper II, see B. S. Middleditch and D. M. Desiderio, *Prostaglandins*, in press.

(2) Fellow of the Intra-Science Research Foundation, 1971–1975.

(3) B. Samuelsson in "Lipid Metabolism," S. J. Wakil, Ed., Academic Press, New York, N. Y., 1970, p 107.

(4) B. S. Middleditch and D. M. Desiderio, *Prostaglandins*, **2**, 115 (1972).

(5) F. Vane and M. G. Horning, *Anal. Lett.*, **2**, 357 (1969).

(6) Paper I, B. S. Middleditch and D. M. Desiderio, *Lipids*, in press.

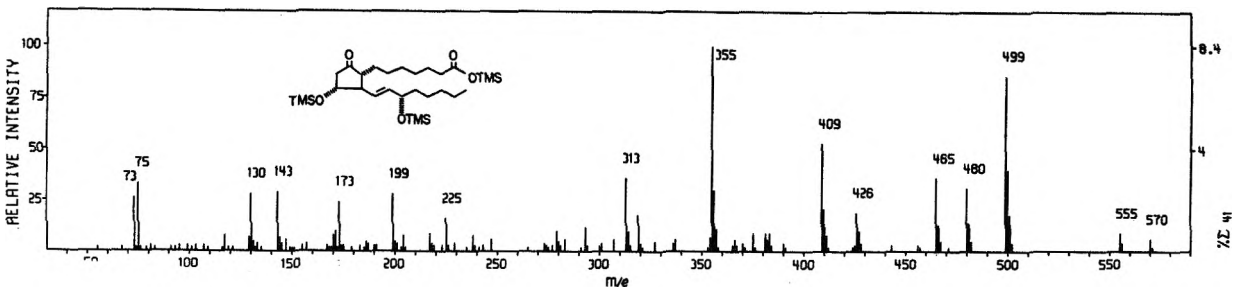


Figure 1.—Mass spectrum (22.5 eV) of TMS derivative of prostaglandin E_1 (I).

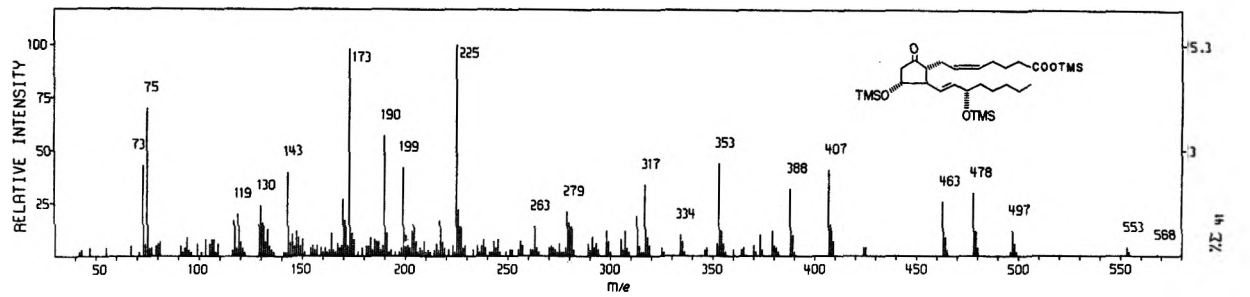


Figure 2.—Mass spectrum (22.5 eV) of TMS derivative of prostaglandin E_2 (II).

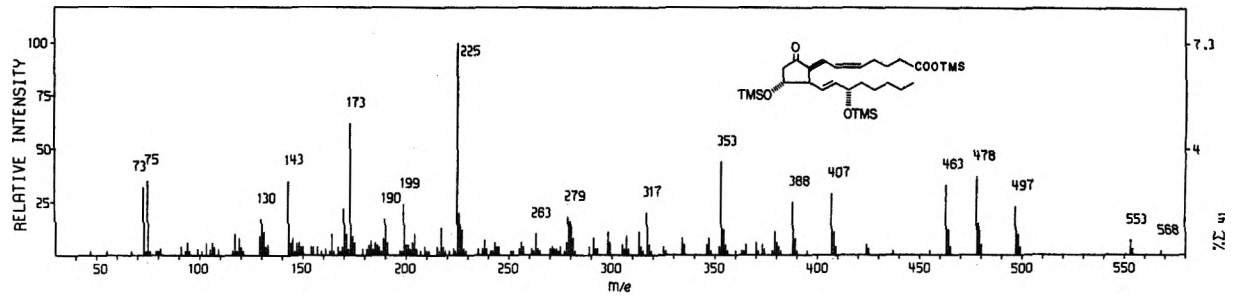
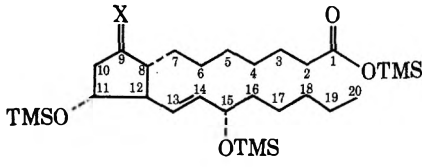


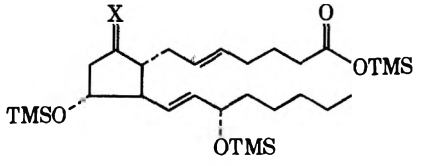
Figure 3.—Mass spectrum (22.5 eV) of TMS derivative of 8-isoprostaglandin E_2 (III).

of the corresponding MO–TMS derivatives (IV–VI) are shown in Figures 4–6. The syn and anti isomers are referred to in the same manner as those of the A series.[6] For example, the first isomer eluted during gas chromatography on SE-30 of the MO–TMS derivatives of prostaglandin E_1 is designated IVa (and the spectrum shown in Figure 4, top) and the second, IVb (Figure 4, bottom).

There is little difference between the spectra of the TMS derivative of the naturally occurring prostaglandin E_2 and that of the corresponding synthetic 8-isoprostaglandin E_2. Also, when the spectra of



I, X = O
IVa, IVb, X = NOMe (syn-anti isomers)



II, X = O
Va, Vb, X = NOMe (syn-anti isomers)

the MO–TMS derivatives of the various isomeric prostaglandins of the E_2 series are compared, it is found that the spectrum of Vb is somewhat similar to that of VIa. Quantitatively, the spectrum of Va is quite different from that of VIb. Nevertheless, the spectra of the MO–TMS derivatives of E_1 prostaglandins are qualitatively alike, as are those of the E_2 prostaglandins. For the sake of brevity in the ensuing discussion, only the spectra of IVa (Figure 4, top) and Va (Figure 5, top) will be considered in detail, although significant quantitative differences in the spectra will not be ignored.

The molecular ions of neither the TMS derivatives nor the MO–TMS derivatives are very intense. Because of the low relative intensities of the ions involved, it is difficult to ascertain the origins of the methyl radicals lost in the formation of $[M - 15]^+$ ions in the spectra of the TMS derivatives, although d_9-TMS labeling shows that they all originate from TMS groups. In the case of the MO–TMS derivatives, however, it is found that IVa fragments by loss of a methyl radical from an ether TMS group, whereas Va loses methyl radicals mainly (80%) from the ester TMS group.

The molecules of trimethylsilanol eliminated from the molecular ions in the formation of $[M - 90]\cdot^+$ peaks have various origins. They are lost exclusively from ether TMS groups of I, but 10% are from the ester

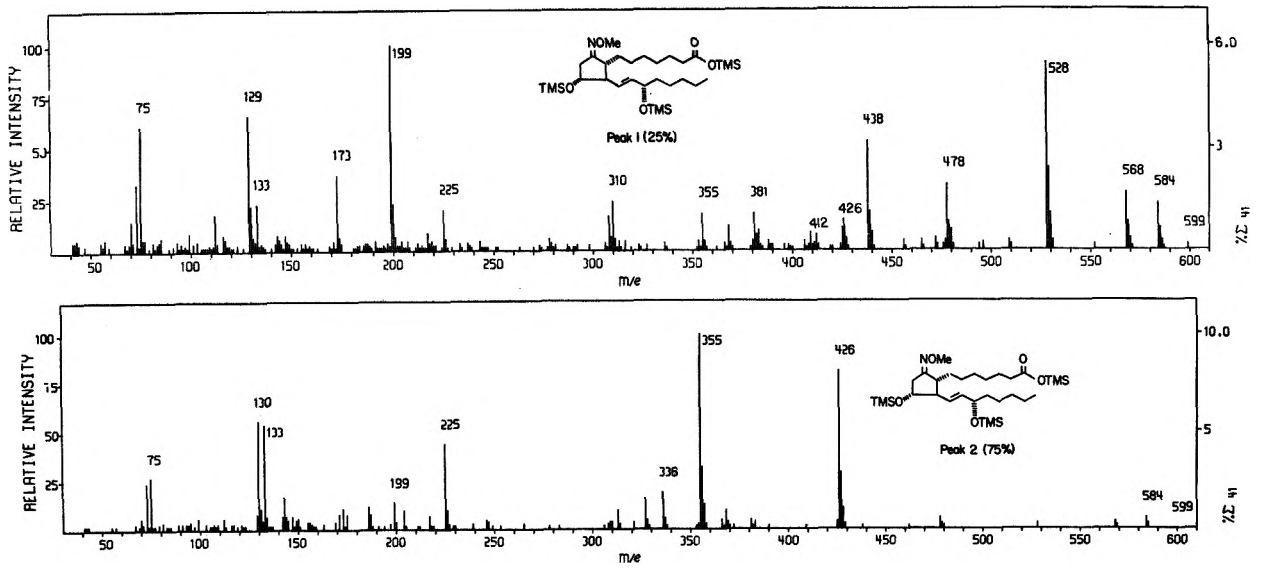


Figure 4.—Mass spectra (22.5 eV) of MO–TMS derivatives of prostaglandin E_1: first (IVa) and second (IVb) gc peaks.

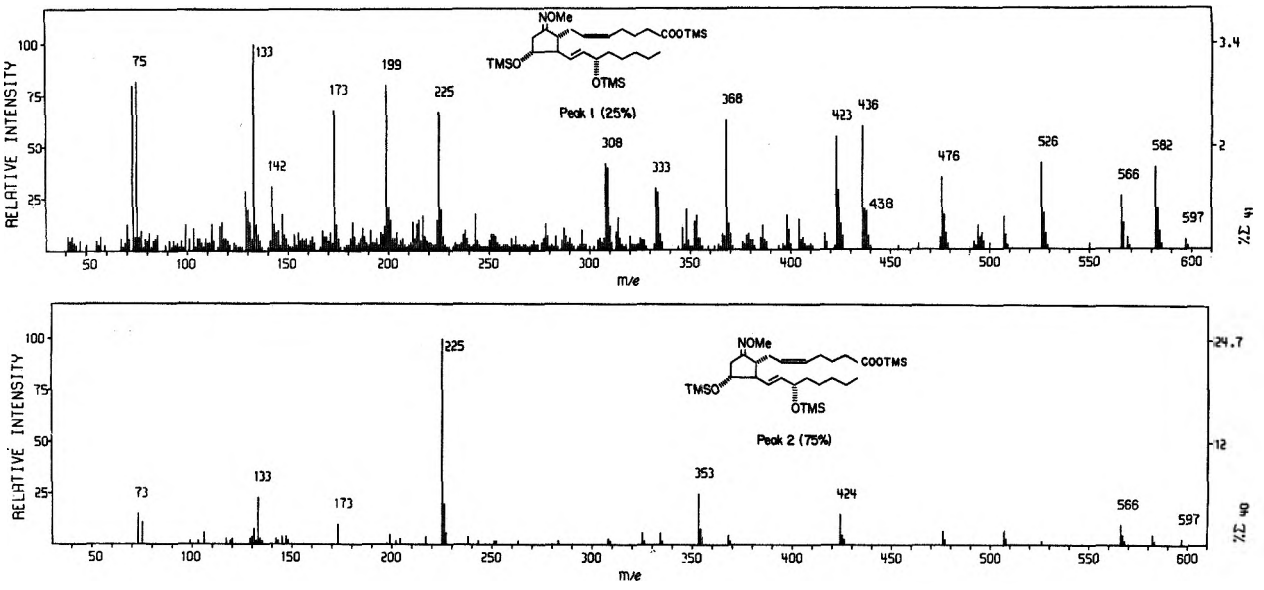


Figure 5.—Mass spectra (22.5 eV) of MO-TMS derivatives of prostaglandin E_2: first (Va) and second (Vb) gc peaks.

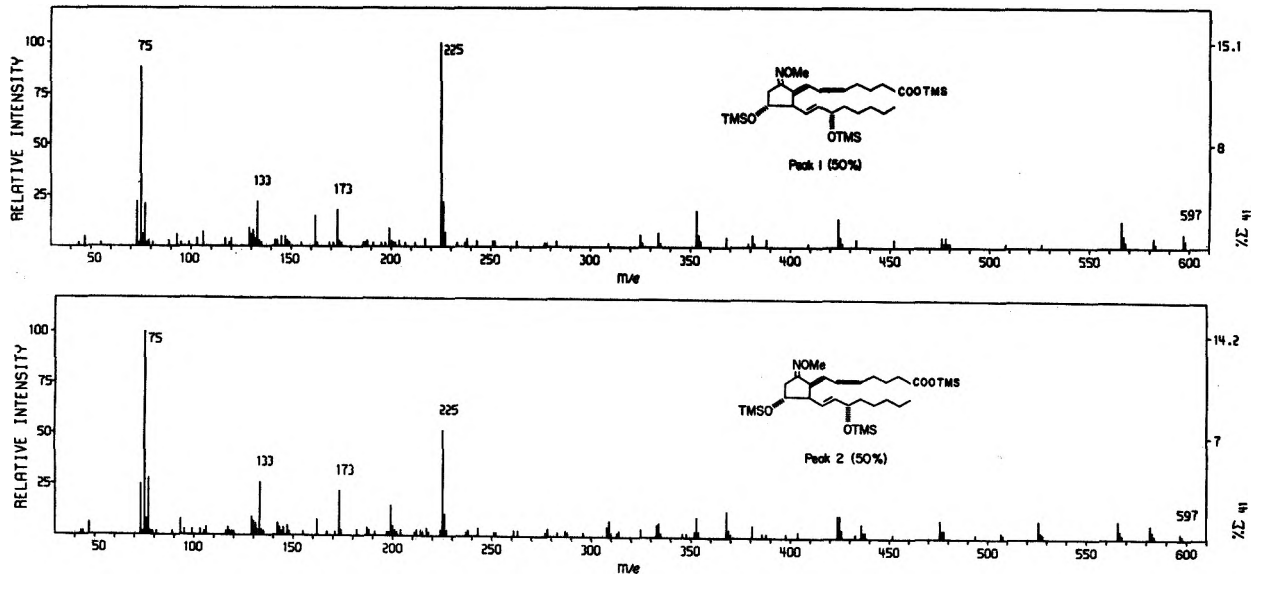
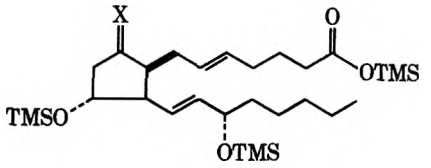
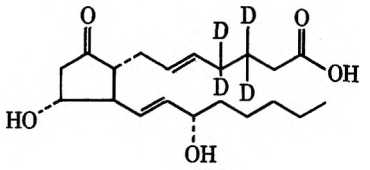


Figure 6.—Mass spectra (22.5 eV) of MO–TMS derivatives of 8-isoprostaglandin E_2: first (VIa) and second (VIb) gc peaks.

TMS group of II. Examination of the spectrum of the TMS derivative of *3,3,4,4-d*$_4$-prostaglandin E_2 (VII, kindly provided by U. Axen[7]) shows that, in



IV, X = O
VIa, VIb, X = NOMe (syn-anti isomers)



VII

the latter case, the hydrogen atom eliminated with the trimethylsilyloxy group originates from C-3 or C-4; Djerassi and co-workers have found (for TMS ethers of cyclohexyl derivatives) that trimethylsilanol may be eliminated *via* a 1,4 process.[8] The $[M - 90]\cdot^+$ ion is weak in the spectrum of IVa, but it can clearly be seen that, in the spectra of labeled analogs of IVa, it is formed by loss of trimethylsilanol from an ether TMS group. A second elimination of trimethylsilanol (also from an ether TMS group) gives rise to an abundant ion only in the spectrum of II (*m/e* 388, 32%). Only weak ions are formed by sequential eliminations of trimethylsilanol in other spectra; these are accompanied also by ions resulting from additional losses of methyl radicals.

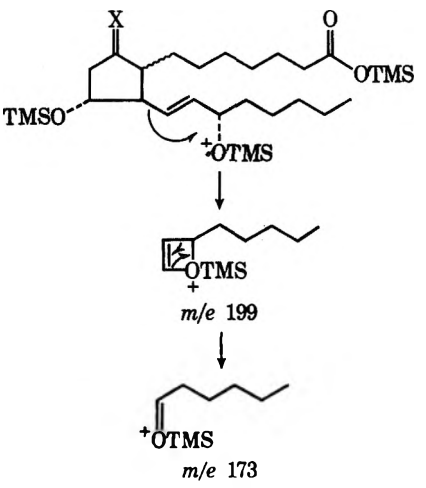
Further fragmentations of the C-1/7 and C-13/20 chains and the C-8/12 ring, and fragmentations directed by the *O*-methyl oxime group will be discussed in turn.

Fragmentations of the C-1/7 Chain.—No major fragment ions are formed by direct fragmentation of this chain. Weak ions are present in the spectra of all of the TMS derivatives which appear to be formed by scission of the C-7/8 bond of the $[M - 90]\cdot^+$ ion formed by loss of an ether TMS group (*m/e* 279). The ions of *m/e* 398 in the spectra of the MO–TMS derivatives appear also to be formed by scission of the C-7/8 bond. These ions were found to contain neither an ester TMS group nor any hydrogen atoms from C-3 or C-4. Further loss of trimethylsilanol leads to the formation of ions of *m/e* 308.

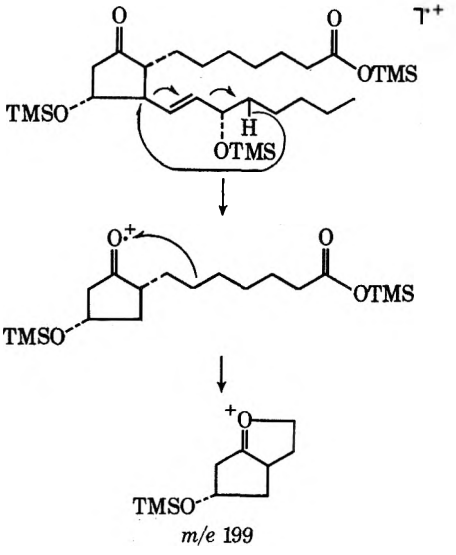
The ion of *m/e* 438 in the spectrum of Va was found not to contain an ester TMS group or hydrogen atoms from C-3 or C-4. It is probably formed by loss of C-1/4, with substituents, from the molecular ion. The rather weak ion of *m/e* 412 in the spectrum of IVa may be produced by α cleavage to the oxime group[9] of the C-6/7 bond.

It was found that, in the spectra of TMS and MO–TMS derivatives of prostaglandins of the A^6 and B^1 series, ions of *m/e* 199 and *m/e* 173 were formed, presumably as shown in Scheme I. Careful examination of the high resolution spectra of derivatives of prostaglandins of the E series, and of the low resolution spectra of labeled analogs, reveals that such ions are also formed by fragmentation of the C-1/7 chain of these compounds. In addition to the ion at *m/e* 199 of Scheme I, the spectra of TMS derivatives of all of the prostaglandins of the E series were found to contain ions of *m/e* 199 with elemental composition $C_{10}H_{19}O_2Si$. This ion in the spectra of the TMS derivatives of prostaglandins E_1 was found to contain an ether TMS group and may be formed as shown in Scheme II.

SCHEME I



SCHEME II

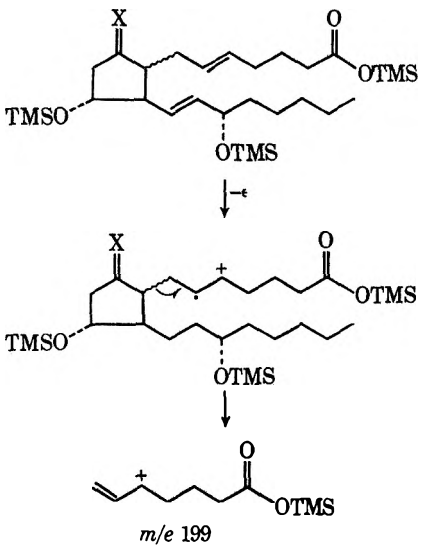


Those in the spectra of the TMS derivatives of prostaglandins E_2 and 8-isoprostaglandin E_2 were, however, found to contain an ester TMS group, and may be formed as in Scheme III. Also, ions of the MO–TMS derivatives of prostaglandins E_2 and 8-isoprostaglandin E_2 were observed which apparently comprise C-1/7 with substituents and are formed as shown in Scheme III.

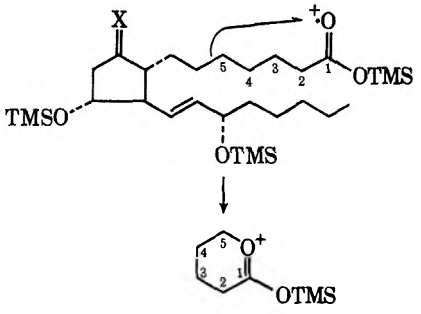
It was found that the ions of *m/e* 173 in the spectra of TMS and MO–TMS derivatives of prostaglandins E_1 were doublets. The major component ($C_9H_{21}OSi$) was formed as in Scheme I, but the minor component ($C_8H_{17}O_2Si$) was found to contain an ester TMS group. The latter could be formed as shown in Scheme IV.

(7) U. Axen, K. Gréen, D. Hörlin, and B. Samuelsson, *Biochem. Biophys. Res. Comm.*, **45**, 519 (1971).
(8) P. D. Woodgate, R. T. Gray, and C. Djerassi, *Org. Mass Spectrom.*, **4**, 257 (1970).
(9) B. S. Middleditch and B. A. Knights, *Org. Mass Spectrom.*, **6**, 179 (1972).

SCHEME III



SCHEME IV



Fragmentations of the C-13/20 Chain.—Scission of the C-15/16 bond, directed by the 15-trimethylsilyloxy group, gives rise to moderately intense ions of type $[M - 71]^+$ in each of the spectra under consideration.[6] A series of ions is formed by successive eliminations of trimethylsilanol from the $[M - 71]^+$ ions.

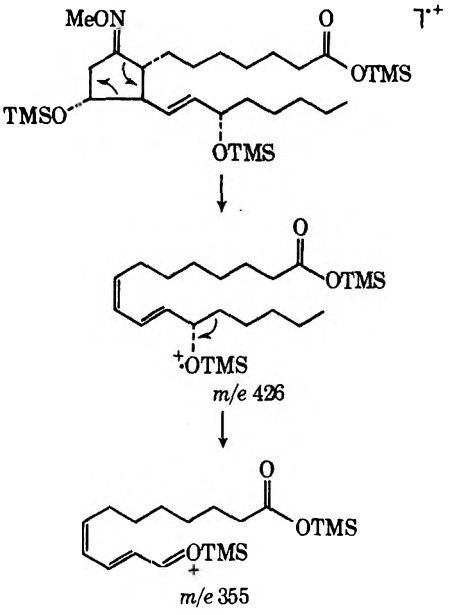
The genesis of ions of *m/e* 173 and *m/e* 199 has already been discussed.

It has been suggested that the ion of *m/e* 426 in the spectrum of the MO–TMS derivative of prostaglandin E_1 (IVa) is formed by loss of C-1/5, with substituents, and that this ion can further lose C_5H_{11} from C-16/20 to afford the ion of *m/e* 355.[5] However, high resolution mass measurement shows that the ion of *m/e* 426 has composition $C_{23}H_{46}O_3Si_2$ (calcd 426.2985, found 426.2986) and that of *m/e* 355 has composition $C_{18}H_{35}O_3Si_2$ (calcd 355.2125, found 355.2138). The corresponding pair of ions is not shifted in mass in the spectra of the EO–TMS derivative. It seems likely that the ion of *m/e* 426 is formed by cleavage of the ring and that the ion of *m/e* 355 is produced by subsequent loss of C_5H_{11} (corresponding to C-16/20) as depicted in Scheme V. A similar fragmentation mode was proposed for the MO–TMS derivative of the methyl ester of prostaglandin E_1.[10]

Fragmentations of the C-8/12 Ring.—Whereas the rings of derivatives of prostaglandins of the A and B series were relatively stable,[1,6] the 11-trimethylsilyloxy group in derivatives of the E series has a strong fragmentation-inducing influence.

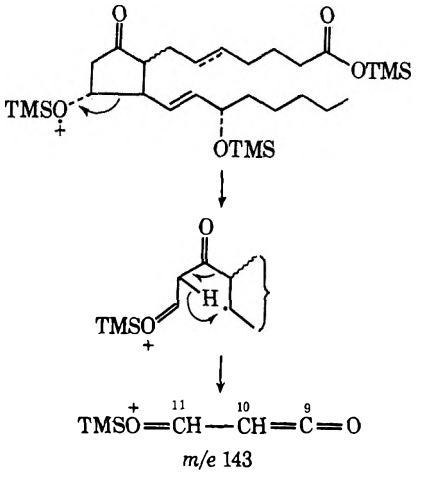
(10) K. Green, *Chem. Phys. Lipids*, 3, 254 (1969).

SCHEME V



A number of ions are formed *via* initial cleavage of the C-11/12 bond. This bond is particularly weak by virtue of its being α to the 11-trimethylsilyloxy group, β to the C-13/14 bond, and (in the case of the MO–TMS derivatives) γ to the oxime moiety. Spectra of the TMS derivatives contain ions of *m/e* 143 which are partially due to fragmentation of the ring ($C_6H_{11}O_2Si$: calcd 143.0528, found 143.0530) as shown in Scheme VI and partialy due to minor components

SCHEME VI

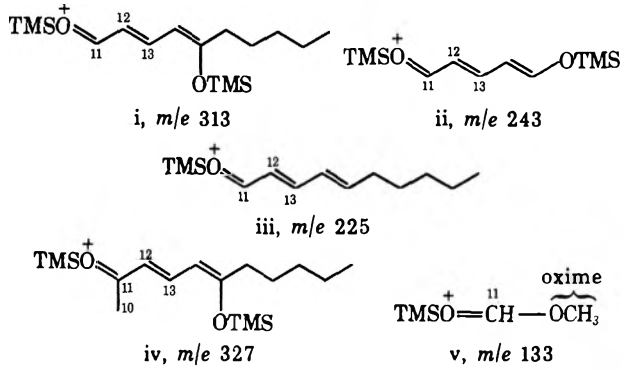


having composition $C_7H_{15}OSi$ (calcd 143.0892, found 143.0882) and containing an ether TMS group. Complementary ions, formed by loss of C-9/11, were observed at *m/e* 426 (E_1 series) or *m/e* 424 (E_2 series) in the spectra of TMS and MO–TMS derivatives (Scheme V).

Numerous fragment ions are formed by eliminations of trimethylsilanol from the ions of *m/e* 426 and 424 (at *m/e* 336, 334, 246, 244) and from the ions of *m/e* 355 and 353 formed by loss of C_5H_{11} (at *m/e* 265, 263).

A second category of ions formed by cleavage of the ring requires initial cleavage of the C-10/11 bond. The driving force for the formation of fragment ions in this manner is apparently the ease of

formation of highly conjugated ions promoted by juxtaposition of the 11- and 15-trimethylsilyloxy groups. The elemental compositions of ions i–iii are all compatible with the high resolution data and with the spectra of labeled analogs.

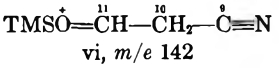


The ion of *m/e* 327 (iv) appears to be formed by loss of C-1/9 from the molecular ions.

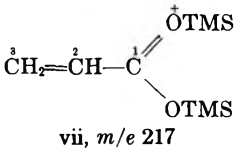
An interesting ion is present in the spectra of the MO–TMS derivatives at *m/e* 133 and of the EO–TMS derivatives at *m/e* 147. The former has composition $C_5H_{13}O_2Si$ (calcd 133.0685, found 133.0663). These data suggest that the ion is formed by migration of the oxime alkoxy group to C-11 in the formation of an ion of type v.

Fragmentations Directed by the *O*-Methyl Oxime Group.—As expected, the molecular ion may lose a methoxy radical from the oxime moiety to give an ion of type $[M - 31]^+$. This ion can undergo further fragmentation by, for example, elimination of molecules of trimethylsilanol. As in the case of the MO–TMS derivatives of prostaglandin A_1, losses of methanol as well as, or instead of, methoxy radicals sometimes take place in combination with other eliminations.[6]

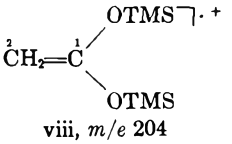
The ion of *m/e* 142 in the spectra of MO–TMS (and EO–TMS) derivatives has elemental composition $C_6H_{12}NOSi$ (calcd 142.0688, found 142.0716). It contains an ether TMS group, but none of the hydrogen atoms at C-3 or C-4. It is probably formed by fission of the ring and loss of the oxime alkoxy group, leading to a structure such as vi.



vi, *m/e* 142



vii, *m/e* 217



viii, *m/e* 204

Fragmentations Influenced by Remote Interactions of TMS Groups.—The influences of remote interactions of TMS groups on mass spectral fragmentation modes are well known.[11] None were observed in the spectra of derivatives of prostaglandins of the A and B series,[1,6] but two such ions are seen in many of the spectra of prostaglandins of the E series, the first at *m/e* 217, the second at *m/e* 204. d_9-TMS labeling shows that both contain two TMS groups and selective d_9-TMS labeling indicates that, in each case, one of the TMS groups derives from the ester moiety. In the spectra of the MO–TMS derivatives of *3,3,4,4-d*$_4$-prostaglandin E_2 (VII), the former ion is shifted to *m/e* 219, whereas the latter remains at *m/e* 204. These ions, then, probably have structures vii and viii.

(11) For leading references, see C. J. W. Brooks and B. S. Middleditch in "Modern Methods of Steroid Analysis," E. Heftmann, Ed., Academic Press, New York, N. Y., in press.

Conclusions

The mass spectra both of the TMS and of the MO–TMS derivatives of prostaglandins of the E series contain many relatively abundant fragment ions. Nevertheless, the majority have been interpreted satisfactorily by comparison with the spectra of labeled analogs and by high resolution measurement. We have found the technique of selective d_9-TMS labeling to be of particular value in these studies when it has been necessary to distinguish between ether and ester TMS groups in fragment ions. In this manner we have been able to recognize several ions formed by long-range TMS migrations.

This discussion would be incomplete without consideration of the effect of stereochemistry on fragmentation, although we have demonstrated that the various isomeric prostaglandin derivatives can be distinguished by gas chromatography.[4] The spectrum of the second gc peak of the MO–TMS derivative of prostaglandin E_1 (IVb, Figure 4, bottom) is dominated by ions of *m/e* 426 and *m/e* 355 (whereas this is not the case in IVa). It has been demonstrated that these ions arise by cleavage of the ring (Scheme V). It could be suggested that the rationale for the ease of fragmentation of the ring is the adjacency of the methoxy group with the side chain since only one of the syn–anti isomers fragments in this manner with such ease. It might then be argued that, on the mass spectrometric evidence, the order of elution of the syn–anti isomer pair is reversed for the 8 isomer. At this stage, however, we feel that such speculation is unwarranted because we are unable to identify unequivocally the syn and anti isomers.

Experimental Section

Prostaglandins were kindly provided by J. E. Pike and U. Axen of The Upjohn Co., Kalamazoo, Mich., and by K. Sano of Ono Pharmaceutical Company, Osaka, Japan. **Derivatives** were prepared as previously described.[6] **Mass spectrometry** was performed using LKB 9000 (low resolution, gc-ms) and CEC 21-110B (high resolution, direct insertion probe) instruments as previously described.[6]

Registry No.—I, 39003-19-5; II, 39003-20-8; III, 39003-21-9; IVa (9*Z* isomer), 39003-22-0; IVb (9*E* isomer), 39062-24-3; Va (9*Z* isomer), 39003-23-1; Vb (9*E* isomer), 39003-24-2; VIa (9*Z* isomer), 39003-25-3; VIb (9*E* isomer), 39003-26-4.

Acknowledgments.—This work was supported by grants from the NIH (GM-13901) and the Robert A. Welch Foundation (Q-125). We thank Miss P. Crain for obtaining the high-resolution mass spectra.

Nucleophilic Ring Opening of Optically Pure (*R*)-(+)-1,2-Epoxybutane. Synthesis of New (*R*)-2-Butanol Derivatives[1]

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Received January 7, 1972

Optically pure (*R*)-(+)-1,2-epoxybutane has been prepared. Treatment of the epoxide with various nucleophiles produces the optically active alcohols resulting from highly selective attack at the 1 position of the epoxide. Reaction of alkyllithium compounds with the epoxide forms some high molecular weight material and conditions are described for minimizing this side reaction. Preparation of four new (*R*)-2-butanol derivatives is reported, including that of (*R*)-(+)-1-methylthio-2-butanol, which previously is unreported even as a racemate. Structure proof of the latter compound by nmr and desulfurization to 2-butanol is described.

Coke and Rice previously have prepared partially resolved (*R*)-(+)-1,2-epoxybutane by Hofmann elimination of the methiodide of (*R*)-(−)-1-dimethylamino-2-butanol.[3] The optically active amino alcohol was prepared from racemic material by recrystallization of the *O,O'*-dibenzoyl (*R*)-tartrate salt. Although the melting point and optical rotation of the salt is unchanged after the first recrystallization, we have found that the optical rotation of the liberated amine increases upon further recrystallizations. As shown in Table I,

TABLE I
OPTICAL ROTATION OF (*R*)-(−)-1-DIMETHYLAMINO-2-BUTANOL AS A FUNCTION OF THE NUMBER OF RECRYSTALLIZATIONS OF ITS *O,O'*-DIBENZOYL (*R*)-(+)-TARTRATE SALT

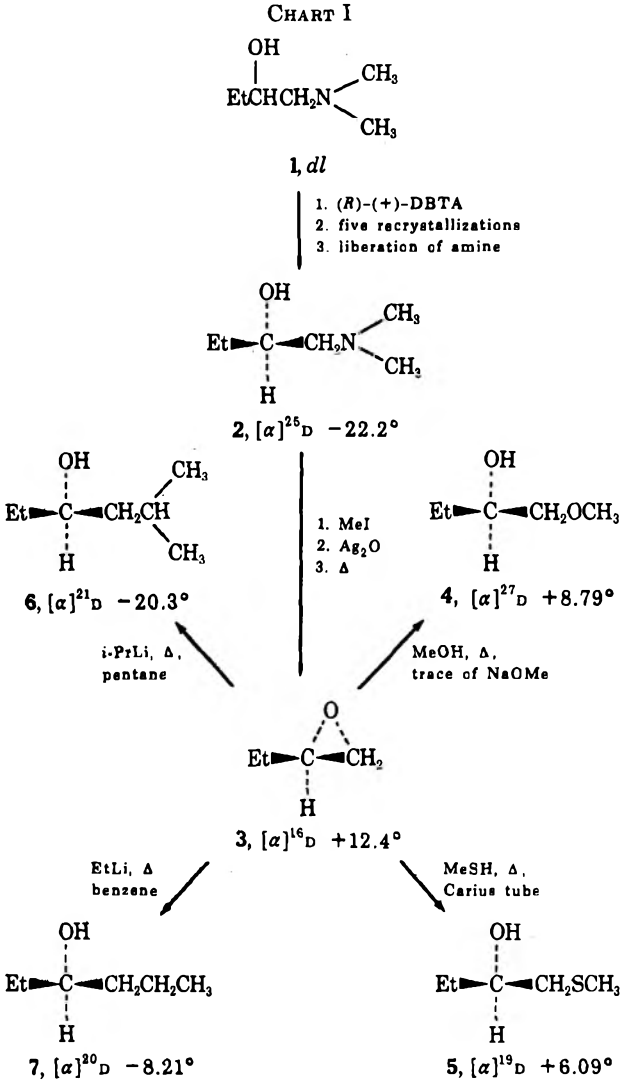
Number of salt recrystallization	Ratio of ml of ethanol to g of salt	Recovery of salt, %	$[\alpha]^{25}D$ of amino alcohol liberated from salt
1	5.4	76	−18.2
2	6.4	77	−20.8
3	6.4	88	−21.5
4	6.4	87	−22.0
5	6.3	84	−22.2
6	6.4	88	−22.1

it is only after five recrystallizations of the salt that the optical rotation of the liberated amine reaches a constant value.[4]

Using (*R*)-(−)-1-dimethylamino-2-butanol liberated after five recrystallizations of its precursor [the *O,O'*-dibenzoyl (*R*)-(+)-tartrate salt] we have prepared (*R*)-(+)-1,2-epoxybutane (**3**) with $[\alpha]^{16}D$ +12.4°. Levene and coworkers[5] have prepared the epoxide from (−)-1-bromo-2-hydroxybutane of 70% optical purity and obtained a value of $[\alpha]^{25}D$ +8.75° for its optical rotation. Since the optical purity of the epoxide prepared by their method should be the same as that of the starting bromo alcohol, the optical rotation of optically pure (*R*)-(+)-1,2-epoxybutane can be calculated to be $[\alpha]^{25}D$ +12.5°, which is in good agreement with our epoxide.

The reaction of various nucleophiles with (*R*)-(+)-1,2-epoxybutane was studied. As is shown in Chart I, all reactions studied produce alcohols by highly

CHART I



selective attack on the 1 position of the epoxide. Methanol containing a trace of sodium methoxide, for example, gives (*R*)-(+)-1-methoxy-2-butanol (**4**) from the epoxide. This compound was characterized by its physical properties (compared with those of the previously reported racemic compound) and by its infrared spectrum. It was easily distinguished from 2-methoxy-1-butanol by its boiling point.

Formation of high molecular weight material is a serious side reaction when the epoxide is treated with alkyllithium compounds. This material presumably arises by attack of intermediate alkoxides on unreacted epoxide to produce a polyether. As would be expected, this side reaction is minimized when the

(1) This investigation was supported in part by Public Health Service Research Grant HE 07050, from the National Heart Institute, U. S. Public Health Service.

(2) National Aeronautics and Space Administration Fellow, 1964–1967.

(3) J. L. Coke and W. Y. Rice, Jr., *J. Org. Chem.*, **30**, 3420 (1965).

(4) The value of $[\alpha]^{25}D$ given in ref 3 for the optical rotation of (*R*)-(−)-1-dimethylamino-2-butanol is for a sample of that amino alcohol liberated after six recrystallizations of the *O,O'*-dibenzoyl (+)-tartrate. The amino alcohol used in the preparation of (*R*)-(+)-1,2-epoxybutane in ref 3 was liberated after one recrystallization, however.

(5) P. A. Levene and A. Walti, *J. Biol. Chem.*, **94**, 367 (1931); P. A. Levene and H. L. Haller, *ibid.*, **74**, 343 (1927).

epoxide is added to the alkyllithium and epoxide excess is avoided, but yields are relatively low even under these conditions. Ethyllithium, for example, reacts with (R)-(+)-1,2-epoxybutane to give a 21% yield of (R)-(−)-3-hexanol (7), which was characterized by its physical properties and infrared spectrum. The boiling point of 7 easily distinguishes it from 2-ethyl-1-butanol, the isomer possible from reverse opening of the epoxide ring. Similarly, isopropyllithium gives a 19% yield of (R)-(−)-5-methyl-3-hexanol (6) from the epoxide.

Treatment of the epoxide with methanethiol under autogeneous pressure at 100° gives an 84% yield of (R)-(+)-1-methylthio-2-butanol (5). Since this compound is unreported previously in either its racemic or optically active forms and since it was synthesized under essentially neutral conditions, it was necessary to fully characterize it. The nmr spectrum of the compound showed a two-proton doublet at τ 7.5 for the methylene on sulfur and an unresolved one-proton pentet at τ 6.0 for the alcohol methine proton. The spectrum was not at all consistent with what would have been expected from 2-methylthio-1-butanol. The structure was confirmed by desulfurization of the compound with W-4 Raney nickel. Vpc analysis of the solution after reaction showed only solvent and 2-butanol. No 1-butanol nor unreacted starting material was detected.

It should be noted that all the compounds prepared from the (R)-(+)-1,2-epoxybutane are assigned the absolute configuration shown in Chart I, and that the optical rotations are assumed to be for the optically pure isomers. This presumes that no racemization occurred during epoxide opening. This seems reasonable because no isomeric products involving opening of the epoxide from the more hindered side were detected in any of the final products and because no mechanism is likely for simple racemization of starting material or products under the conditions used.

Experimental Section

All distillations were done through a 2-ft Podbielniak column and the boiling points are corrected. All melting points were taken on a calibrated Kofler hot stage. Infrared spectra were taken on a Perkin-Elmer Model 237B grating Infracord using neat films. Nuclear magnetic resonance spectra were taken on a Varian Model A-60 spectrometer using neat liquids and tetramethylsilane as an internal standard. Optical rotations were taken on a Perkin-Elmer Model 141 polarimeter. Vapor phase chromatography was done on an F & M Model 500 gas chromatograph using a 2-m column of 25% glyceryl-tricyanoethyl ether on Chromosorb P. All distilled compounds were shown to be pure by vapor phase chromatography.

1-Dimethylamino-2-butanol (1).—The procedure used was similar to that used by Coke and Rice[3] and Hill.[6] A solution of 100 g (1.39 mol) of 1,2-epoxybutane and 100 g (2.22 mol) of anhydrous dimethylamine was heated in an autoclave under autogeneous pressure at 115° for 72 hr. Unreacted starting material was removed on a steam bath and the residue was distilled to give 154 g (96%) of racemic 1-dimethylamino-2-butanol, bp 143–145° (760 mm), d^{20}_4 0.8399 [lit.[7] bp 142–144° (760 mm)].

(R)-(−)-1-Dimethylamino-2-butanol (2).—Racemic 1 was resolved with O,O'-dibenzoyl (R)-(+)-tartaric acid[8] using the procedure of Coke and Rice.[3] Table I gives the ratio of absolute ethanol to salt and the recovery of salt in the repetitive recrystallizations. Values for the optical rotation of the amine liberated[3] from each salt are given in Table I. The amine used below was that liberated after five recrystallizations of the salt, $[\alpha]^{25}_D$ −22.2° (c 2.05 g/100 ml, absolute ethanol) [lit.[3] $[\alpha]^{25}_D$ −21.9° (c 4.18 g/100 ml, absolute ethanol)].

(R)-(+)-1,2-Epoxybutane (3).—The methiodide[3] of 2 was subjected to Hofmann elimination with silver oxide[9] using the procedure of Coke and Rice.[3] The product from 37.5 g of 2 was distilled from anhydrous $MgSO_4$ to give 9.6 g (44%) of 3, bp 59–62.5° (760 mm) [lit.[10] bp 61–62° (760 mm)], $[\alpha]^{16}_D$ +12.4° (c 5.98 g/100 ml, dioxane) [lit.[3] $[\alpha]^{25}_D$ +8.2° (c 4.99 g/100 ml, dioxane)].

(R)-(+)-1-Methoxy-2-butanol (4).—A solution of 3.0 g (0.0417 mol) of 3 in 12 ml of methanol was added slowly under nitrogen to 6 ml of refluxing methanol containing a trace of sodium methoxide. Refluxing was continued for 22.5 hr. The solution was then evaporated under vacuum and the residue was distilled to give 2.7 g (62.5%) of 4: bp 135–136° (760 mm); n^{20}D 1.4118; d^{20}_4 0.9045; $[\alpha]^{27}_D$ +8.79° (c 2.76 g/100 ml, absolute ethanol); ir (neat) 3410 (broad, OH), 2810 (OCH_3), 1170 (COC), 1110 cm^{-1} (COH) [lit.[11] (of racemic material) bp 133–137° (760 mm); n^{20}_D 1.4114].

(R)-(+)-1-Methylthio-2-butanol (5).—Anhydrous methanethiol (2.0 g, 0.0417 mol) and 3 (2.0 g, 0.0278 mol) were sealed in a Carius tube cooled in Dry Ice. The tube was then heated at 100° under autogeneous pressure for 50 hr in a 600-ml autoclave containing 150 ml of MeOH to minimize the pressure difference on the Carius tube. The tube was cooled in Dry Ice, opened, and heated on a steam bath to remove unreacted starting materials. The residue was distilled to give 2.8 g (84%) of 5: bp 179–180.5° (758 mm); $[\alpha]^{19}_D$ +6.09° (c 7.26 g/100 ml, absolute ethanol); n^{25}_D 1.4782; d^{20}_4 0.9821; nmr data given in discussion; ir (neat) 3400 (broad, OH), 1420 (SCH_2), 1315 (SCH_3), 1115 cm^{-1} (COH).

Anal. Calcd for $C_5H_{12}OS$: C, 49.93; H, 10.07. Found: C, 49.96; H, 10.21.

Desulfurization of Racemic 1-Methylthio-2-butanol.—One gram of racemic 1-methylthio-2-butanol (prepared as above, using racemic 1,2-epoxybutane) was refluxed overnight under nitrogen in ethanol containing 15 g of W-4 Raney nickel. The mixture was filtered and the filtrate was concentrated by careful distillation. Vpc analysis of the concentrate showed only ethanol and 2-butanol. No 1-butanol or starting material were detected.

(R)-(−)-5-Methyl-3-hexanol (6).—A solution of 5.67 g (0.079 mol) of 3 in 113 ml of pentane was added slowly and with stirring under nitrogen to 182 ml of 1.64 *M* isopropyllithium in pentane. The solution was refluxed for 48 hr and was then cooled in ice. Water (200 ml) was added slowly with stirring and the layers were separated. The pentane was washed with a small amount of water and the washing was added to the aqueous layer, which was then saturated with NaCl and extracted repeatedly with Et_2O. The ether extracts were combined with the pentane layer and dried over anhydrous Na_2SO_4. Distillation of the mixture gave 1.73 g (19%) of 6: bp 145–147° (760 mm); $[\alpha]^{21}_D$ −20.3° (c 5.25 g/100 ml, absolute ethanol); d^{20}_4 0.8436; n^{20}_D 1.4219; ir (neat) 3350 (broad, OH), 1380 (doublet, *gem*-dimethyl), 1110 cm^{-1} (COH) [lit.[12,13] (of racemic material) bp 146–148° (760 mm); n^{20}_D 1.4220].

(R)-(−)-3-Hexanol (7).—A solution of 9.91 g (0.139 mol) of 3 in 100 ml of benzene was added slowly and with stirring under nitrogen to 515 ml of 0.81 *M* ethyllithium in benzene. The solution was refluxed for 68 hr and was then cooled in ice. Water (400 ml) was added slowly with stirring. Isolation and distillation analogous to that given for 6 gave 2.99 g (21%) of 7: bp 133–136° (760 mm); $[\alpha]^{20}_D$ −8.21° (c 11.5 g/100 ml, absolute ethanol); ir (neat) identical with that of commercial 3-hexanol [lit.[14] bp (of racemic material) 135° (760 mm)].

Registry No.—1, 34487-37-1; 2, 3760-97-2; 2 O,O'-dibenzoyl (R)-(+)-tartrate, 39010-59-8; 2 MeI, 3806-20-0; 3, 3760-95-0; 4, 39010-62-3; 5, 39010-63-4; 6, 39003-07-1; 7, 13471-42-6; O,O'-dibenzoyl (R)-(+)-tartaric acid, 2743-38-6.

(6) R. K. Hill, *J. Amer. Chem. Soc.*, **80**, 1611 (1958).
(7) R. T. Major and H. T. Bonnett, *ibid.*, **58**, 22 (1936).
(8) C. L. Butler and L. H. Cretcher, *ibid.*, **55**, 2605 (1933).
(9) B. Helferich and W. Klein, *Justus Liebigs Ann. Chem.*, **450**, 219 (1926).
(10) "Handbook of Chemistry and Physics," 43rd ed, Chemical Rubber Publishing Co., Cleveland, Ohio, 1961, p C-219.
(11) E. G. E. Hawkins, *J. Chem. Soc.*, 254 (1959).
(12) R. A. Benkeser, J. J. Hazdra, and M. L. Burrous, *J. Amer. Chem. Soc.*, **81**, 5374 (1959).
(13) N. I. Shuikin and I. F. Bel'shii, *Zh. Obshch. Khim.*, **27**, 402 (1957).
(14) Reference 10, p 1032.

Stable Carbocations. CLII.[1] Protonation of Halophenols and Haloanisoles in Superacids

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The protonation of halophenols and haloanisoles was studied in four different superacid media: $HF–SbF_5$ (1:1 mol/mol)–SO_2ClF, $FSO_3H–SbF_5$ (1:1 mol/mol)–SO_2ClF, $FSO_3H–SbF_5$ (4:1 mol/mol), and $FSO_3H–SO_2ClF$ at low temperature by nmr spectroscopy. O- or C-protonation was observed dependent upon the superacid media used. The structure of the formed arenium and oxonium ions was assigned based on their nmr (^1H and ^{19}F) spectra. Isomeric ions derived from the same precursor were also observed. Structural aspects and stability of halogenated arenium, as well as halophenyloxonium, ions are discussed in terms of hydrogen bonding and steric, resonance, and inductive effects.

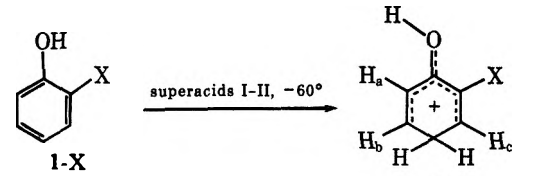
Recently, we have reported the protonation of mono-, di-, and trihydroxybenzenes and their methyl ethers in various superacid media.[3] Independently, hydroxy- and alkoxybenzenium ions have also been studied[4] and reviewed by Brouwer, *et al.*[5] The protonation (in superacid media) of haloarenes has also been investigated in our laboratory,[6] as well as by Brouwer.[7] In continuation of our studies it was of interest to undertake an investigation of the protonation of halophenols and haloanisoles in superacids. Of particular interest is the site of protonation, since phenol and anisole are both C- and O-protonated dependent on the conditions. The inductive and resonance (back-donation[8]) effects of halogens may play an important role in determining the formation of the corresponding arenium and oxonium ions in the protonation of halophenols and haloanisoles.

A systematic study of the protonation of monohalophenols and monohaloanisoles was carried out in the following four superacid systems at low temperature: (I) $HF–SbF_5$(1:1 mol/mol)–SO_2ClF, (II) $FSO_3H–SbF_5$ (1:1 mol/mol)–SO_2ClF, (III) $FSO_3H–SbF_5$ (4:1 mol/mol)–SO_2ClF, and (IV) $FSO_3H–SO_2ClF$.

Results and Discussion

The complete series of isomeric halophenols and haloanisoles was protonated in superacids I–IV. Ions observed are summarized in Table I. The nmr data of halogenated hydroxy- and methoxybenzenium ions formed under various conditions are tabulated in Table II, whereas data of the corresponding oxonium ions are summarized in Table III.

Protonation of *o*-Halophenols (1-X).—Protonation of *o*-halophenols (1-X, X = F, Cl, and Br) in superacids I and II at −60° gave the corresponding C-protonated



1-X

1-F, X = F
1-Cl, X = Cl
1-Br, X = Br

1-Xa

1-Fa, X = F
1-Cla, X = Cl
1-Bra, X = Br

3-halo-4-hydroxybenzenium ions 1-Xa. The structures of ions 1-Xa can be assigned based on their nmr (^1H and ^{19}F) spectra (Tables II and IV). Evidence for the formation of these benzenium ions (*i.e.*, C-protonation) comes from the observed methylene absorption (δ 4.6–4.8) and the marked deshielding effect of the ortho protons (H_b and H_c), as well as the coupling constants ($J_{H_aH_b}$ and J_{H_aF}) (Figure 1a). The meta protons (H_a) of ions 1-Xa are coupled to protons H_b. In the case of ion 1-Fa, it is also coupled to the meta F ($^4J_{HF}$ = 6.0 Hz) (Figure 1a). The pmr absorptions of the two ortho protons (H_b and H_c) are generally more deshielded than that of H_a. They can be distinguished by the observed vincinal proton–proton coupling (8–10 Hz) between protons H_a and H_b. The pmr absorptions of protons H_b and H_c in ions 1-Xa are a doublet of quartets and a quartet, respectively. These data indicate that the two ortho protons are coupled to each other through six bonds ($^6J_{H_bH_c}$ = 1.0 Hz). Similar results have been observed in the protonation of *o*-cresol and *o*-methylanisole.[3b] The OH pmr absorption of ions 1-Xa were not observed, presumably owing to the rapid intermolecular hydrogen exchange with the solvent system.

The ^{19}F nmr spectrum of ion 1-Fa shows a multiplet at ϕ 129.3 (11.7 ppm deshielded from the precursor 1-F). The slight deshielding effect is mainly due to the inductive effect of the halogen. This is consistent with the assigned structure.[6] Thus, the observed fluorine shift is similar to those of the meta F in fluorobenzenium ions.[6a]

Protonation of *o*-iodophenol (1-I) and *o*-iodoanisole (2-I) in superacids I–II was not successful. Solid tar as well as iodine formation was observed. The decomposition of 1-I and 2-I is not surprising, since iodobenzene also decomposes to iodine and unidentified products under similar conditions.[9] On the other hand, iodobenzene can be readily methylated with

(1) Part CLI: G. A. Olah and Y. K. Mo, *J. Amer. Chem. Soc.*, submitted.
(2) Postdoctoral Research Associate, 1972.
(3) (a) G. A. Olah and Y. K. Mo, *J. Amer. Chem. Soc.*, **94**, 5341 (1972); (b) *J. Org. Chem.*, in press.
(4) (a) D. M. Brouwer, E. L. Mackor, and C. MacLean, *Recl. Trav. Chim. Pays-Bas*, **85**, 109, 114 (1966); (b) T. Birchall, A. N. Bourns, R. J. Gillespis, and P. J. Smith, *Can. J. Chem.*, **42**, 1433 (1964); (c) T. Birchall and R. J. Gillespie, *ibid.*, **42**, 502 (1964); (f) C. MacLean and E. L. Mackor, *Discuss. Faraday Soc.*, **34**, 165 (1962); (e) D. M. Brouwer, C. MacLean, and E. L. Mackor, *ibid.*, **39**, 121 (1965); (f) M. P. Hartshorn, K. E. Richards, J. Vaughan, and G. J. Wright, *J. Chem. Soc. B*, 1624 (1971).
(5) D. M. Brouwer, E. L. Mackor, and C. MacLean in "Carbonium Ions," G. A. Olah and P. v. R. Schleyer, Ed., Wiley-Interscience, New York, N. Y., 1970, p 865.
(6) (a) G. A. Olah and T. E. Kiovsky, *J. Amer. Chem. Soc.*, **89**, 5692 (1967); **90**, 2583 (1968); (b) G. A. Olah and Y. K. Mo, *ibid.*, in press.
(7) D. M. Brouwer, *Recl. Trav. Chim. Pays-Bas*, **87**, 335, 342 (1968).
(8) G. A. Olah, Y. K. Mo, and Y. Halpern, *J. Amer. Chem. Soc.*, **94**, 3551 (1972).
(9) G. A. Olah and P. Schilling, *ibid.*, in press.

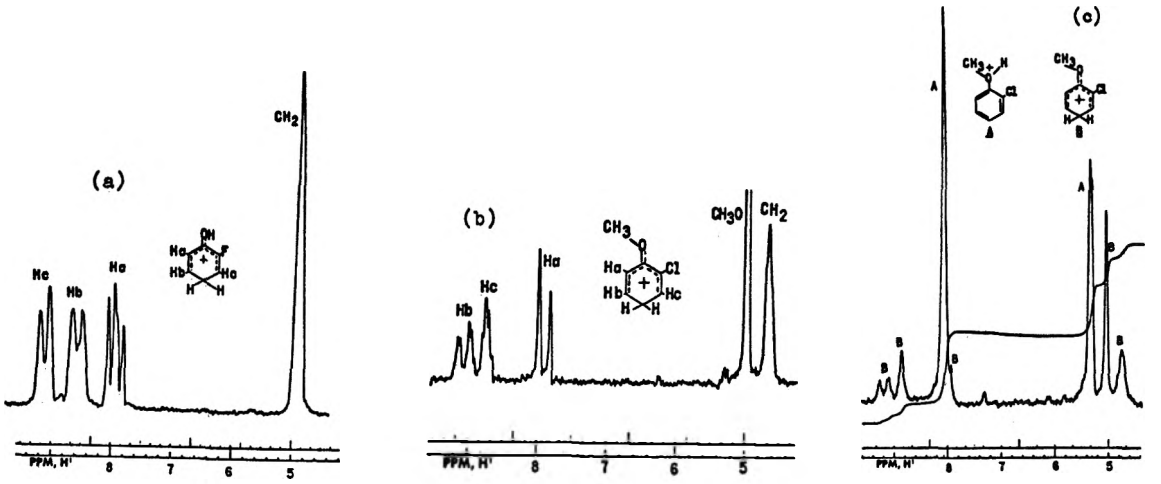


Figure 1.—Pmr spectra of 3-fluoro-4-hydroxybenzenium ion 1-Fa (a), 3-chloro-4-methoxybenzenium ion 2-Cla (b), and a mixture of ions 2-Cla and 2-Clb (c).

TABLE I

ION FORMATION UPON PROTONATION OF HALOGENATED PHENOLS AND ANISOLES[a]

Halogenated phenol and anisole	Ions formed in superacid system			
	I	II	III	IV
1-F	1-Fa	1-Fa	1-Fa, 1-F ⇄ 1-Fb (55%) (45%)	1-F ⇄ 1-Fb
1-Cl	1-Cla	1-Cla	1-Cla, 1-Cl ⇄ 1-Clb (60%) (40%)	1-Cl ⇄ 1-Clb
1-Br	1-Bra	1-Bra	1-Bra	1-Br ⇄ 1-Brb
1-I	Dec	Dec	1-Ia	1-I ⇄ 1-Ib
2-F	2-Fa	2-Fa, 2-F ⇄ 2-Fb (72%) (28%)	2-Fa, 2-F ⇄ 2-Fb (67%) (33%)	1-F ⇄ 1-Fb
2-Cl	2-Cla	2-Cla, 2-Cl ⇄ 2-Clb (33%) (67%)	2-Cla, 2-Cl ⇄ 2-Clb (33%) (67%)	1-Cl ⇄ 1-Clb
2-Br	2-Bra	2-Bra, 2-Br ⇄ 2-Brb (33%) (67%)	2-Bra, 2-Br ⇄ 2-Brb (30%) (70%)	1-Br ⇄ 1-Brb
2-I	Dec	Dec	2-Ia	1-I ⇄ 1-Ib
3-F	3-Fa	3-Fa	3-Fa	3-Fa
3-Cl	3-Cla	3-Cla	3-Cla, 3-Cl ⇄ 3-Clb (55%) (45%)	3-Cla, 3-Cl ⇄ 3-Clb (20%) (80%)
3-Br	3-Bra	3-Bra	3-Bra, 3-Br ⇄ 3-Brb (41%) (59%)	3-Bra, 3-Br ⇄ 3-Brb (28%) (72%)
3-I	Dec	Dec	3-Ia	3-Ia, 3-I ⇄ 3-Ib (60%) (40%)
4-F	4-Fa ⇄ 4-Fa′ (75%) (25%)	4-Fa ⇄ 4-Fa′ (71%) (29%)	4-Fa ⇄ 4-Fa′ (88%) (12%)	4-Fa ⇄ 4-Fa′ (92%) (8%)
4-Cl	4-Cla ⇄ 4-Cla′ (60%) (40%)	4-Cla ⇄ 4-Cla′ (60%) (40%)	4-Cla ⇄ 4-Cla′ (60%) (40%)	4-Cla ⇄ 4-Cla′ (70%) 4-Cl ⇄ 4-Clb (30%)
4-Br	4-Bra ⇄ 4-Bra′ (60%) (40%)	4-Bra ⇄ 4-Bra′ (60%) (40%)	4-Bra ⇄ 4-Bra′ (60%) (40%)	4-Bra ⇄ 4-Bra′ (50%) 4-Br ⇄ 4-Brb (50%)
4-I	4-Ia ⇄ 4-Ia′ (50%) (50%)	4-Ia ⇄ 4-Ia′ (50%) (50%)	4-Ia ⇄ 4-Ia′ (50%) (50%)	4-Ia ⇄ 4-Ia′ (15%) (15%) 4-I ⇄ 4-Ib (70%)
5-F	5-Fb	5-Fb	5-F ⇄ 5-Fb	5-F ⇄ 5-Fb
5-Cl	5-Clb	5-Clb	5-Cl ⇄ 5-Clb	5-Cl ⇄ 5-Clb
5-Br	5-Brb	5-Brb	5-Br ⇄ 5-Brb	5-Br ⇄ 5-Brb
5-I	Dec	Dec	Dec	5-I ⇄ 5-Ib
6-F	6-Fb	6-Fb	6-F ⇄ 6-Fb	6-F ⇄ 6-Fb
6-Cl	6-Clb	6-Clb	6-Cl ⇄ 6-Clb	6-Cl ⇄ 6-Clb
6-Br	6-Brb	6-Brb	6-Br ⇄ 6-Brb	6-Br ⇄ 6-Brb
6-I	Dec	Dec	Dec	6-I ⇄ 6-Ib

[a] For actual experimental conditions (*e.g.*, temperature), see text.

TABLE II

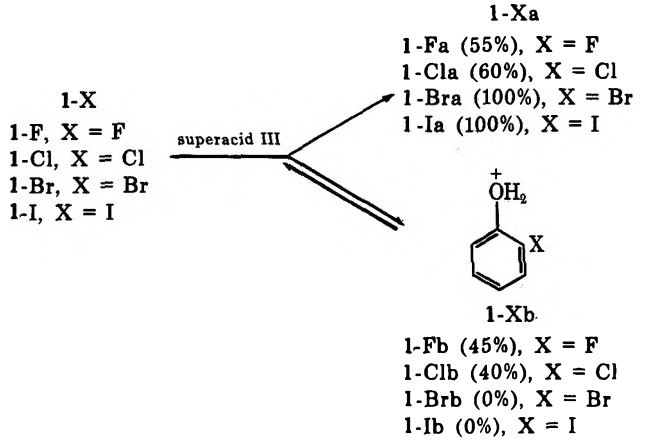
PMR DATA OF HALOGENATED HYDROXY- AND METHOXYBENZENIUM IONS[a,c]

Halogenated aromatic	Ion	Superacid system, temp, °C	δ, OCH_3	δ, CH_2	δ, H_a	δ, H_b	δ, H_c	δ, OH
1-F	1-Fa	I, −20		4.8 (s,br)	7.83 (d,d), J_{HF} = 6 J_{HH} = 9	8.5 (d,br), J_{HH} = 9	9.0 (d,br), J_{HF} = 10	[b]
1-Cl	1-Cla	I, −60		4.8 (s,br)	7.90 (d,br), J_{HH} = 8	9.06 (d,br),	8.95 (s,br)	[b]
1-Br	1-Bra	I, −60		4.73 (t) J_{HH} = 1	7.80 (d), J_{HH} = 9	9.02 (d,q) J_{HH} = 9, 1	9.20 (q), J_{HH} = 1	[b]
1-I	1-Ia	III, −40		4.6 (s,br)	7.7 (d,br), J_{HH} = 9	8.9 (d,br), J = 9	9.3 (s,br)	12.1 (s,br)
2-F	2-Fa	I, −40	5.15 (s)	4.8 (s,br)	8.00 (d,d), J_{HF} = 6 J_{HH} = 10	8.31 (d,q) J_{HH} = 10, 1.5	9.16 (d,q), J_{HF} = 10 J_{HH} = 1.5	[b]
	2-Fa		5.00 (s)	4.7 (s,br)	7.90 (d,d), J_{HH} = 10 J_{HF} = 6	8.23 (d,q), J_{HH} = 10, 1.5	9.10 (d,q), J_{HF} = 10 J_{HH} = 1.5	[b]
2-F	⇅	II, −40						
	2-Fa′		5.20 (s)	4.7 (s,br)	7.90 (d,d), J_{HH} = 10 J_{HH} = 6	8.23 (d,q), J_{HH} = 10, 1.5	9.10 (d,q), J_{HF} = 10 J_{HH} = 1.5	[b]
2-Cl	2-Cla	II, −40	5.00 (s)	4.63 (t) J_{HH} = 2	7.90 (d), J_{HH} = 9	9.04 (d,q), J_{HH} = 9, 1	8.74 (q), J_{HH} = 1	[b]
2-Br	2-Bra	I, −50	4.97 (s)	4.63 (t) J_{HH} = 2	7.90 (d), J_{HH} = 10	9.04 (d,q), J_{HH} = 10, 1	8.97 (q), J_{HH} = 1	[b]
2-I	2-Ia	III, −80	4.80 (s)	4.5 (s,br)	7.8 (br)	9.0 (br)	8.6 (br)	[b]
3-F	3-Fa	I, −16		4.50 (t), J_{HH} = J_{HF} = 3.5	7.31 (d,d), J_{HH} = 10 J_{HF} = 1.5	7.48 (d), J_{HF} = 10	8.4 (m)	11.3 (br)
3-Cl	3-Cla	I, −40		4.70 (d), J_{HH} = 2	7.54 (d), J_{HH} = 9	7.70 (s)	8.73 (d,t), J_{HH} = 9, 2	[b]
3-Br	3-Bra	I, −40		4.70 (d), J_{HH} = 2	7.63 (d,d), J_{HH} = 9, 1	8.00 (d), J_{HH} = 2	8.80 (d,t), J_{HH} = 9, 2	[b]
3-I	3-Ia	III, −60		4.60 (d) J_{HH} = 2	7.50 (d,d), J_{HH} = 10, 1	8.30 (d), J_{HH} = 1	8.68 (d,t), J_{HH} = 10, 2	[b]
	4-Fa		4.88 (s)	4.6 (s,br)	7.4 (m)	7.4 (m)	8.3 (m)	[b]
4-F	⇅	II, −40						
	4-Fa′		4.74 (s)	4.6 (s,br)	7.4 (m)	7.4 (m)	8.3 (m)	[b]
	4-Cla		4.80 (s)	4.60 (d)	7.4 (d,br)	7.8 (s,br)	8.5 (d,br)	[b]
4-Cl	⇅	I, −30		J_{HH} = 2	J_{HH} = 9		J_{HH} = 9	
	4-Cla′		4.80 (s)	4.60 (d) J_{HH} = 2	7.7 (d,br) J_{HH} = 9	7.6 (s,br)	8.8 (d,br) J_{HH} = 9	[b]
	4-Bra		4.80 (s)	4.68 (s)	7.6 (d,br), J_{HH} = 9	8.2 (s)	8.5 (d,br), J_{HH} = 9	[b]
4-Br	⇅	I, −60						
	4-Bra′		4.80 (s)	4.68 (s)	7.8 (d,br), J_{HH} = 9	7.9 (s)	8.9 (d,br), J_{HH} = 9	[b]
	4-Ia		4.72 (s)	4.62 (d)	7.50 (d,d)	8.53 (s), J_{HH} = 1	8.63 (d,t)	[b]
4-I	⇅	III, −60		J_{HH} = 2	J_{HH} = 10, 1		J_{HH} = 10, 2	
	4-Ia′		4.72 (s)	4.62 (d) J_{HH} = 2	7.88 (d,d) J_{HH} = 10, 1	8.22 (d), J_{HH} = 1	8.90 (d,t) J_{HH} = 10, 2	[b]

[a] Proton chemical shifts are referred to external capillary TMS in parts per million (δ). J values are in hertz. [b] OH proton is not observable owing to rapid hydrogen exchange with the solvent systems. [c] Abbreviation used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad.

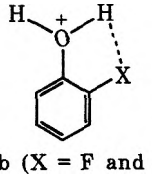
methyl fluoroantimonate to give the methylphenyliodonium ion.[10] Thus, deiodination of iodobenzene as well as 1-I and 2-I may involve initial protonation at iodine and subsequent dehydroiodination to give the corresponding aryl cations, which would immediately arylate excess iodoaromatic compounds. Attempts to directly observe such an intermediate I-protonated species at low temperature were not successful.

Protonation of *o*-halophenols in superacid III gave C-protonated 3-halo-4-hydroxybenzenium ions (I-Xa).



(10) G. A. Olah and E. G. Melby, *J. Amer. Chem. Soc.*, **94**, 6220 (1972).

However, O-protonated oxonium ions 1-Fb (45%) and 1-Cl (40%) were also formed in the protonation of 1-F and 1-Cl, respectively. The pmr spectrum of 1-F in superacid III shows, besides the absorption lines of ion 1-Fa, a multiplet at δ 7.7. This multiplet is similar to that of 1-F when protonated in superacid IV (O-protonation, see subsequent discussion). The ratio of ions 1-Fa:1-Fb can thus be determined by integration of the pmr spectrum. Similar results were also obtained when 1-Cl was protonated in superacid III. The OH proton absorptions of ions 1-Xa and 1-Xb were



1-Xb (X = F and Cl)

not observed under the experimental conditions, owing to obvious rapid exchange with the acid solvent system.

The formation of oxonium ion 1-Fb (45%) and 1-Cl (40%), but not of 1-Brb and 1-Ib from 1-X (X = F, Cl, Br, and I) under identical conditions, is interesting, These data indicate that the substantial inductive effect of the electronegative fluorine and chlorine atoms in the ortho position of a benzenium ion is operative.

TABLE III

PMR PARAMETERS OF HALOGENATED PHENYLOXONIUM IONS[a]

Halogenated phenyloxonium ion	Superacid system and temp, °C	δ, OCH_3	δ, Aromatic	δ, OH	Remarks
1-F ⇄ 1-Fb	IV, −40		7.4 (m)	b	
1-Cl ⇄ 1-Clb	IV, −60		7.4 (m)	b	
1-Br ⇄ 1-Brb	IV, −60		7.3–7.8 (a)	b	
1-I ⇄ 1-Ib	IV, −80		7.3–7.8 (m)	b	
2-F ⇄ 2-Fb	IV, −40	4.54 (s)	7.5 (m)	b	
2-Clb	I, −60	5.30 (d)	8.10 (s)	11.9 (q)	67% with 33% C-protonation
		J_{HH} = 2		J_{HH} = 2	formed initially
2-Cl ⇄ 2-Clb	IV, −60	4.50 (s)	7.60 (s)	b	
2-Brb	II, −60	5.30 (d)	8.0 (m)	c	67% with 33% C-protonation
		J_{HH} = 2			formed initially
2-Br ⇄ 2-Brb	IV, −50	4.5 (s)	7.6–7.7 (m)	b	
2-I ⇄ 2-Ib	IV, −80	4.60 (s)	7.3–7.9 (m)	b	
3-Cl ⇄ 3-Clb	III, −40		7.6 (m)	b	45% with 55% C-protonation
3-Br ⇄ 3-Brb	IV, −40		7.7 (m)	b	72% with 28% C-protonation
3-I ⇄ 3-Ib	IV, −50		7.5–7.7 (m)	b	40% with 60% C-protonation
4-Clb	II, −60	5.23 (d)	7.8 (m)	12.0 (q)	See text
		J_{HH} = 2		J_{HH} = 2	
4-Cl ⇄ 4-Clb	IV, −60	4.6 (s)	7.5 (m)	b	31% with 69% C-protonation
4-Brb	II, −60	5.23 (d)	7.9 (m)	11.7 (q)	10% with 90% C-protonation
		J_{HH} = 3		J_{HH} = 3	formed initially
4-Br ⇄ 4-Brb	IV, −50	4.60 (s)	7.6 (m)	b	50% with 50% C-protonation
4-I ⇄ 4-Ib	IV, −60	4.40 (s)	7.6–7.8 (m)	b	71% with 29% C-protonation
5-Fb	I, −20		7.8 (m)	12.0 (s)	
5-F ⇄ 5-Fb	IV, −20		7.45 (m)	b	
5-Clb	I, −40		7.81 (d), J_{HH} = 10	12.3 (s)	
			8.01 (d), J_{HH} = 10		
5-Cl ⇄ 5-Clb	IV, −60		7.3 (d), J_{HH} = 8	b	
			7.6 (d), J_{HH} = 8		
5-Brb	I, −60		7.90 (d), J_{HH} = 9	12.7 (s)	
			8.26 (d), J_{HH} = 9		
5-Br ⇄ 5-Brb	IV, −60		7.32 (d), J_{HH} = 8	b	
			7.78 (d), J_{HH} = 8		
5-I ⇄ 5-Ib	IV, −80		7.17 (d), J_{HH} = 8	b	
			8.00 (d), J_{HH} = 8		
6-Fb	II, −60	5.22 (d)	7.8 (m)	12.1 (s,br)	
		J_{HH} = 3			
6-F ⇄ 6-Fb	IV, −40	4.73 (s)	7.5 (m)	b	
6-Clb	I, −40	5.22 (d)	7.81 (d), J_{HH} = 9	11.2 (q)	
		J_{HH} = 3	8.03 (d), J_{HH} = 9	J_{HH} = 3	
6-Cl ⇄ 6-Clb	IV, −40	4.60 (s)	7.41 (d), J_{HH} = 9	b	
			7.63 (d), J_{HH} = 9		
6-Brb	I, −40	5.22 (d)	7.81 (d), J_{HH} = 8	11.3 (q)	
		J_{HH} = 3	8.20 (d), J_{HH} = 8	J_{HH} = 3	
6-Br ⇄ 6-Brb	IV, −40	4.60 (s)	7.50 (d), J_{HH} = 9	b	
			7.90 (d), J_{HH} = 9		
6-I ⇄ 6-Ib	IV, −80	4.60 (s)	7.23 (d), J_{HH} = 9	b	
			8.00 (d), J_{HH} = 9		

[a] Proton chemical shifts are referred to external capillary TMS in parts per million (δ): s, singlet; d, doublet; q, quartet; br, broad. J values are in hertz. [b] The OH peak is not observable since it exchanges with the superacids. [c] The broad peak should be a quartet.

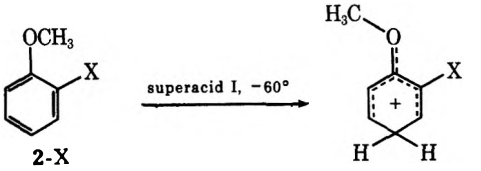
Consequently, ions 1-Fa and 1-Cla are less stable than ions 1-Bra and 1-Ia. In addition, intramolecular hydrogen bonding may be more favorable in oxonium ions 1-Fb and 1-Clb than in ions 1-Brb and 1-Ib.

In superacid IV, all the four *o*-halophenols (1-X) were O-protonated to give the oxonium ions 1-Xb.

$$\text{1-X} \underset{}{\overset{\text{superacid IV, } -70°}{\rightleftharpoons}} \text{1-Xb (X = F, Cl, Br, and I)}$$

The pmr data of oxonium ions 1-Xb in superacid IV are summarized in Table III. The aromatic proton absorptions of 1-X in superacid IV are similar to those of the precursors (in SO_2ClF), but are very much deshielded. The OH proton absorptions of 1-Xb are not observable, indicating rapid intermolecular hydrogen exchange with the solvent system.

Protonation of *o*-Haloanisoles (2-X).—*o*-Haloanisoles behave somewhat differently from *o*-halophenols in the four superacids studied. In superacid I, *o*-haloanisoles (2-X, X = F, Cl, and Br) were C-protonated to give the transoid 3-halo-4-methoxybenzenium ions



2-X

2-F, X = F
2-Cl, X = Cl
2-Br, X = Br

2-Xa

2-Fa, X = F
2-Cla, X = Cl
2-Bra, X = Br

TABLE IV

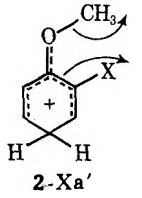
^{19}F NMR DATA OF PROTONATED FLUOROPHENOLS AND FLUOROANISOLES[a]

Fluorophenol and fluoroanisole	Precursor ^{19}F chemical shift, ϕ	Superacid system, temp, °C	Formed ion	ϕ, o-F	ϕ, m-F	ϕ, p-F
1-F	141.0 (m)	I, −16	1-Fa		129.3 (m)	
		IV, −60	1-F ⇌ 1-Fb	137.8 (m)		
2-F	136.7 (m)	I, −45	2-Fa		125.9 (m)	
		II, −80	2-Fa (72%)		126.3 (br)	
			2-F ⇌ 2-Fb (28%)	131.4 (m)		
		IV, −80	2-F ⇌ 2-Fb	134.0 (m)		
3-F	112.6 (m)	I, −16	3-Fa	35.9 (m)		
4-F	130.9 (m)	I, −25	4-Fa ⇌ 4-Fa′	32.4 (m)		
			(75%) (25%)	45.1 (m)		
		IV, −60	4-Fa ⇌ 4-Fa′	33.1 (m)		
			(92%) (8%)	44.9 (m)		
5-F	125.2 (m)	I, −16	5-Fb			110.2 (m)
6-F	125.8 (m)	I, −25	6-Fb			109.3 (m)

[a] Fluorine chemical shifts are referred to external capillary CCl_3F in parts per million (δ).

(2-Xa) exclusively. The pmr spectrum of ion 2-Cla is shown in Figure 1b.

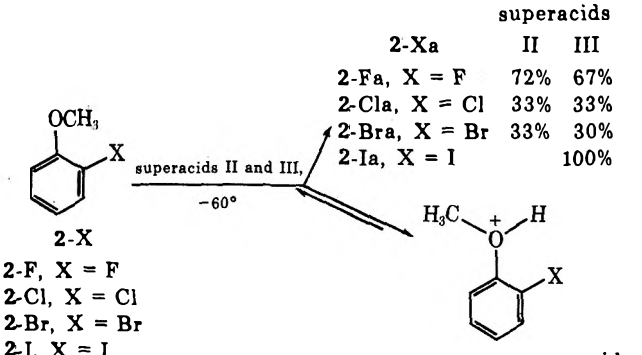
The isomeric cisoid 3-halo-4-methoxybenzenium ions 2-Xa′ were not observed, presumably owing to un-



2-Xa′

favorable steric conditions.[4] The nmr (^{1}H and ^{19}F) spectra of 2-Xa are similar to those of 1-Xa except that an additional methoxyl proton absorption was observed in each pmr spectrum (see Table II).

Both C- and O-protonated ions (2-Xa and 2-Xb) were obtained when o-haloanisoles (2-X) were treated in superacids II and III. The ratio of 2-Xa:2-Xb is dependent on the nature of the halogen atom and the superacids used.



2-X

2-F, X = F
2-Cl, X = Cl
2-Br, X = Br
2-I, X = I

2-Xa	superacids II	III
2-Fa, X = F	72%	67%
2-Cla, X = Cl	33%	33%
2-Bra, X = Br	33%	30%
2-Ia, X = I		100%

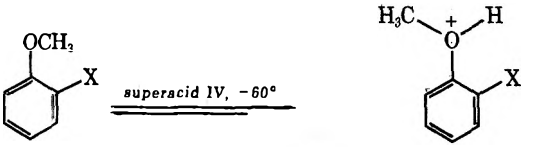
2-Xb	superacids II	III
2-Fb, X = F	28%	33%
2-Clb, X = Cl	67%	67%
2-Brb, X = Br	67%	70%

The pmr spectra of 2-F in superacids II and III are very similar. Besides the pmr absorption lines of ion 2-Fa, there is an additional singlet absorption at δ 5.20 (OCH_3). In the aromatic region an additional multiplet was also observed at δ 7.9. These data show the formation of oxonium ion 2-Fb, although the OH proton absorption is not observed (presumably owing to rapid intermolecular hydrogen exchange with the solvent system). The ratio of ions 2-Fa:2-Fb was determined from the integration of the area of the two methoxy absorptions. The ^{19}F nmr spectrum of 2-F in superacid II shows two multiplets at ϕ 126.3 (2-Fa) and 131.4 (2-Fb). The ratio of the two fluorine absorptions is identical with that of the methoxy protons. The fluorine absorption of the precursor (2-F) shows a multiplet at ϕ 136.7. Thus the slight deshielding effects in both ions 2-Fa and 2-Fb are primarily due to an inductive effect. A similar ^{19}F nmr spectrum was also observed when 2-F was protonated in superacid III.

When 2-Cl was protonated in superacid II at −60°, the pmr spectrum (Figure 1c) of the solution shows, besides the absorption lines of ion 2-Cla, a doublet at δ 5.30 (J_{HH} = 2 Hz, OCH_3), a singlet at δ 8.10 (aromatic protons), and a quartet at δ 11.9 (J_{HH} = 2 Hz, OH). These data clearly indicate the formation of oxonium ion 2-Clb. A similar pmr spectrum was also observed when 2-Cl was treated in superacid III. However, both the methoxyl and the aromatic protons of ion 2-Clb are slightly shielded from those observed in superacid II. Owing to the rapid hydrogen exchange of $>OH^+$ with the solvent system, the OCH_3 proton absorption is a singlet instead of a doublet in superacid III. o-Bromoanisole (2-Br) behaves very similarly to 2-Cl in both superacids II and III.

o-Iodoanisole (2-I) decomposed to unidentified products in superacid II. However, it was protonated in superacid III to give the 3-iodo-4-methoxybenzenium ion (2-Ia), together with some decomposition products. The different behavior of 2-I in superacid II and in superacid III is not yet understood.

In the weakest superacid IV, all the four o-haloanisoles (2-X) were O-protonated to give oxonium ions 2-Xb. The pmr data of these oxonium ions 2-Xb in

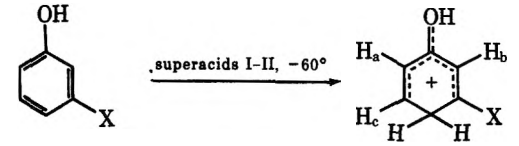


2-X

2-Xb (X = F, Cl, Br, and I)

superacid IV are summarized in Table III. The OH proton absorptions of ions 2-Xb were not observed even at the lowest possible temperature, indicating that they are rapidly exchanging with the solvent system. The ^{19}F nmr spectrum of ion 2-Fb shows a multiplet at ϕ 134.0 (2.7 ppm deshielded from 2-F in SO_2ClF).

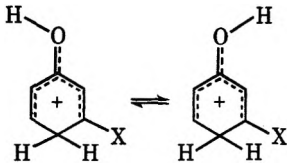
Protonation of *m*-Halophenols (3-X).—Protonation of *m*-halophenols (3-X, X = F, Cl, and Br) in superacids I–II at −60° gave the corresponding 2-halo-4-hydroxybenzenium ions (3-Xa, X = F, Cl, and Br).



3-X
3-F, X = F
3-Cl, X = Cl
3-Br, X = Br

3-Xa
3-Fa, X = F
3-Cla, X = Cl
3-Bra, X = Br

In the pmr spectra of ions 3-Xa, the OH proton either shows a broadened absorption line or is not observable. This indicates rapid equilibration of the isomeric ions



3-Xa (transoid and cisoid). Thus, the nmr (^1H and ^{19}F) spectra of ions 3-Xa are greatly simplified (Figures 2a and 2b).

In the pmr spectrum of ion 3-Fa, it is interesting to note that the methylene protons display a triplet at δ 4.50 ($J_{HH} = J_{HF} = 3.5$ Hz). The triplet indicates that the two equivalent methylene protons have a similar spin–spin interaction with both ortho F and ortho H (H_c) in ion 3-Fa. The meta proton (H_b) adjacent to the ortho F shows a doublet at δ 7.48 ($J_{HH} = 10$ Hz). The less deshielded meta proton (H_a) displays a doublet of doublets at δ 7.31 ($J_{HH} = J_{HF} = 1.5$ Hz). The further splitting is due to the five-bond H–F long-range coupling. The ortho proton shows a multiplet instead of a doublet of triplets at δ 8.4 indicating a six-bond long-range H–F spin–spin interaction.

The pmr spectra of both ions 3-Cla and 3-Bra are much simplified because of the absence of the proton–fluorine coupling as observed in ion 3-Fa. Thus, the CH_2 of both ion 3-Cla and 3-Ba display a doublet at δ 4.70 ($J_{HH} = 3$ Hz). The meta proton (H_a) of ion 3-Bra shows a doublet of doublets at δ 7.63 ($J_{HH} = 9$ and 1 Hz) while the H_a proton of ion 3-Cla shows a doublet at δ 7.54 ($J_{HH} = 9$ Hz). These results indicate that the coupling between the two meta protons (H_a and H_b) is larger in ion 3-Bra (1 Hz) than in ion 3-Cla (less than 0.5 Hz).

Protonation of *m*-iodophenol (3-I) in both superacids I and II was unsuccessful. It decomposed immediately even when the reaction was attempted at −90°.

In superacid III, both *m*-fluorophenol (3-F) and *m*-iodophenol (3-I) were C-protonated at −60° to give

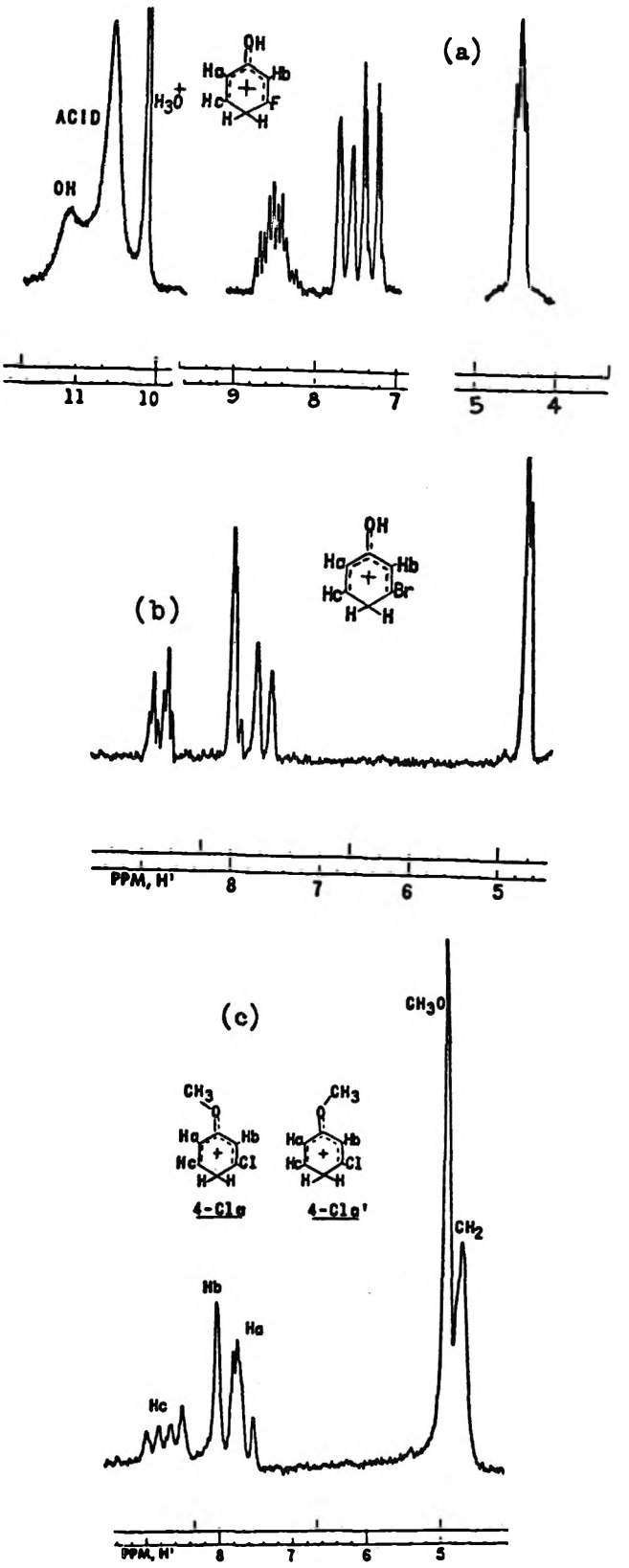
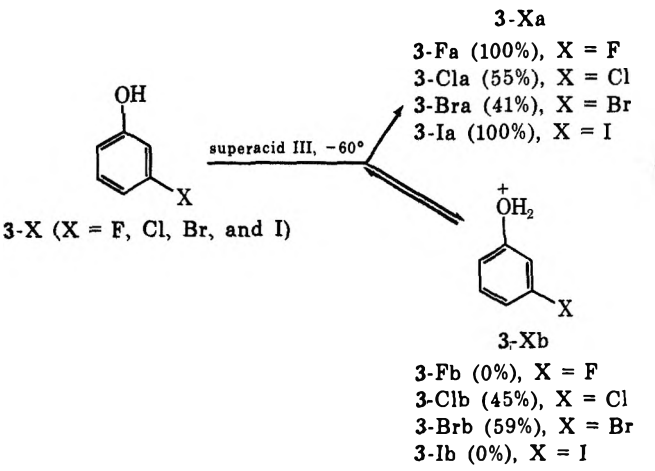


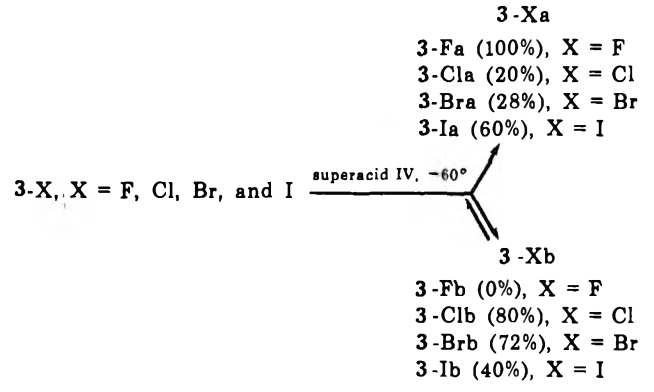
Figure 2.—Pmr spectra of ions 3-Fa (a), 3-Bra (b), and 4-Cla and 4-Cla' (c).

the corresponding 2-fluoro- and 2-iodo-4-hydroxybenzenium ions (3-Fa and 3-Ia), respectively. The pmr spectrum of 3-Ia is similar to that of ion 3-Cla. In the same superacid III, 3-Cl and 3-Br were both C- and O-protonated to give 3-Cla (55%) and 3-Clb (45%), as well as 3-Bra (41%) and 3-Brb (59%), respectively. The formation of oxonium ion 3-Clb and 3-Brb can be



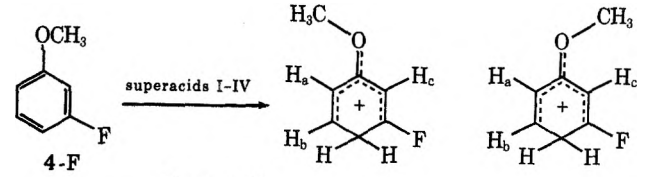
recognized from the additional multiplets observed at δ 7.6 and 7.7, respectively, in their pmr spectra. The $^{+}OH_2$ proton absorption of ions **3**-Clb and **3**-Brb were not observed, indicating rapid intermolecular hydrogen exchange with the superacid system.

In superacid IV, **3**-F was again C-protonated to give **3**-Fa exclusively. However, both **3**-Xa (X = Cl, Br, and I) and **3**-Xb (X = Cl, Br, and I) were obtained when **3**-X (X = Cl, Br, and I) were treated with superacid IV under similar conditions. The formation of



3-Xb was evidenced from the pmr multiplets of the aromatic protons. These multiplets were slightly shielded from those observed in superacid III, indicating that the equilibrium was shifting to the left (or the lifetime of **3**-Xb is shortened). The ratio of ions **3**-Xa:**3**-Xb was determined from integration of peak areas of spectra.

Protonation of *m*-Haloanisoles.—Protonation of *m*-fluoroanisole (**4**-F) in all four superacid systems (I–IV) gave two isomeric ions **4**-Fa and **4**-Fa′ in varying ratios.

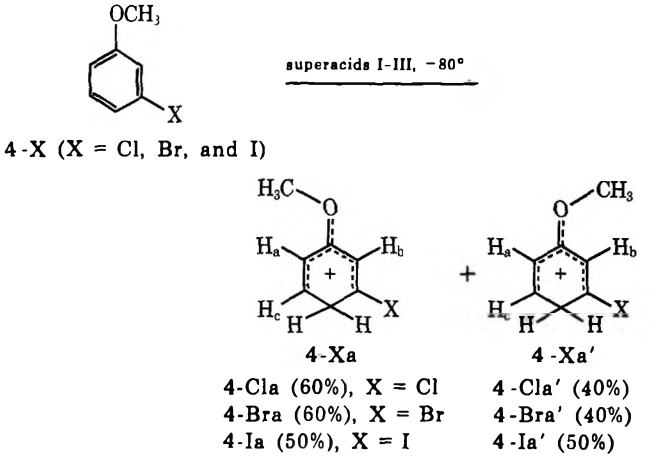


Superacid system	4-Fa	4-Fa′
I	75%	25%
II	71%	29%
III	88%	12%
IV	92%	8%

In increasingly stronger superacids a higher ratio of **4**-Fa:**4**-Fa′ is observed. In the same superacid system, the ratio is independent of the temperature, in the range of −20 to −80°. The ratio can be determined either from the two distinct OCH_3 absorptions of **4**-Fa (δ 4.88) and of **4**-Fa′ (δ 4.74) or from the well-separated ^{19}F nmr absorptions at ϕ 33.1 (**4**-Fa) and 44.9 (**4**-Fa′). The remainder of the pmr resonance lines are not sufficiently different in ions **4**-Fa and **4**-Fa′. The methylene protons of both ions **4**-Fa and **4**-Fa′ show a broadened pmr absorption at δ 4.6. The meta protons of the ions **4**-Fa and **4**-Fa′ display a multiplet centered at δ 7.4 and the ortho proton shows another multiplet at δ 8.3.

The structural differentiation of ions **4**-Fa and **4**-Fa′ is based on their ^{19}F nmr absorptions. Ion **4**-Fa has a more deshielded fluorine absorption (ϕ 33.1) than that of ion **4**-Fa′ (ϕ 44.9) (Table IV). This is because the fluorine atom of ion **4**-Fa is anisotropically deshielded by the nonbonded electron pair of oxygen. Similar results were observed in the protonation of *m*-methylanisole.[4]

The corresponding behavior of other *m*-haloanisoles (**4**-X, X = Cl, Br, and I) in superacids I–IV is slightly different from that of **4**-F. Two isomeric ions (cisoid and transoid) were again observed when **4**-X (X = Cl, Br, and I) were treated with superacids I–III at −80°.

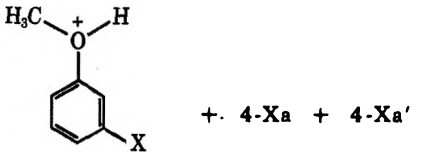


The formation of the two isomeric ions **4**-Xa and **4**-Xa′ can be readily recognized from the two very deshielded pmr triplet of doublets of the ortho protons (H_c). The meta protons (H_a and H_b) in ions **4**-Xa and **4**-Xa′ are also very much different. Owing to the anisotropy effect of the methoxy oxygen lone pair, the proton H_b in ion **4**-Xa is more deshielded than proton H_a in the same ion. Similarly, proton H_a in ions **4**-Xa′ is more deshielded than the corresponding H_b. The anisotropy effect is extended to the ortho proton (H_c). The ortho proton in **4**-Xa is more deshielded than that in **4**-Xa′ (Figure 2c). The methoxy as well as the methylene protons of both ions **4**-Xa and **4**-Xa′ are hardly distinguishable. Thus, the ratios of ions **4**-Xa:**4**-Xa′ were determined from the integration of the H_c proton absorptions. Furthermore, the pmr spectra of ions **4**-Xa and **4**-Xa′ (X = Cl, Br, and I) are temperature dependent (similar to that of C-protonated anisole).[3,5] These data clearly indicate that the interconversion of **4**-Xa and **4**-Xa′ takes place through the rotation of the carbon–oxygen (C=O) partial double bond.

When **4**-Cl and **4**-Br were protonated carefully in superacid II at −80°, some O-protonated ions **4**-Clb (10%) and **4**-Brb (5%) were formed initially. Both

ions 4-Clb and 4-Brb were transformed into C-protonated ion 4-Cla, 4-Cla′ and 4-Bra, 4-Bra′, respec-

4-X (X = Cl and Br)



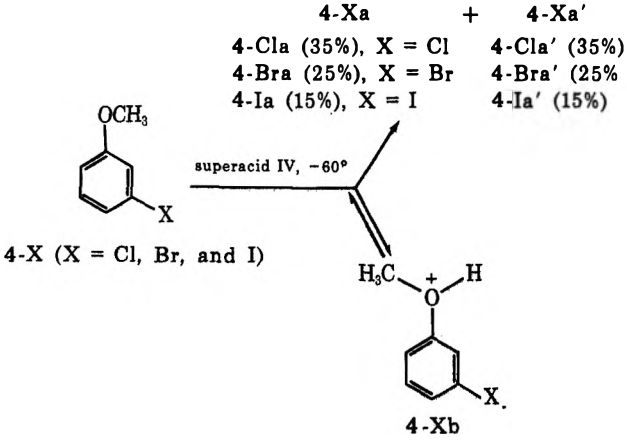
+ 4-Xa + 4-Xa′

4-Xb

4-Clb (10%), X = Cl
4-Brb (5%), X = Br

tively, when the solution was warmed to −20° for 1 min. The process is irreversible. It indicates that initial O-protonation is a kinetically controlled process, while C-protonation is thermodynamically controlled.

When *m*-haloanisoles (4-X, X = Cl, Br, and I) were protonated in superacid IV, both 2-halo-4-methoxybenzenium ions (4-Xa and 4-Xa′) and oxonium ions 4-Xb were obtained. The ratio of C- to O-protonation is dependent upon the nature of the halogens. C-

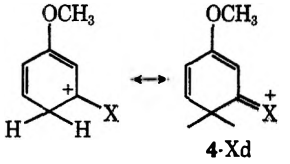


4-X (X = Cl, Br, and I)

4-Xb

4-Clb (30%), X = Cl
4-Brb (50%), X = Br
4-Ib (70%), X = I

protonation increases in the same order as the electronegativity of the halogens (F > Cl > Br > I). This result is in good agreement with observed degree of halogen "back-donation" in halocarbenium ions.[8] In other words, the resonance form of 2-halo-4-methoxybenzenium ion 4-Xd arising through halogen back-

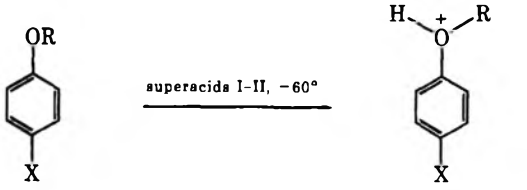


4-Xd

donation is increasingly important with the decrease of the size of the halogen atom.

The methoxy pmr absorptions of ions 4-Clb and 4-Brb are more shielded in superacid IV than those observed in superacid II (see Table III). The OH pmr absorptions of oxonium ions 4-Clb and 4-Brb were not observable even at −78°. These results indicate that the OH proton of oxonium ions 4-Clb and 4-Brb in IV is rapidly exchanging with the solvent system.

Protonation of *p*-Halophenols (5-X) and *p*-Haloanisoles (6-X).—*p*-Halophenols (5-X) and *p*-haloanisoles (6-X) show very similar behavior in the four superacid systems (I–IV). In either superacid I or II, the site of protonation was found to be on the oxygen atom. The $^{+}OH_2$ protons of O-protonated *p*-halophenols (5-Xb) and the $-CH_3OH^{+}$ proton of O-pro-



5-X (R = H)	5-Xb (R = H)
5-F, X = F	5-Fb, X = F
5-Cl, X = Cl	5-Clb, X = Cl
5-Br, X = Br	5-Brb, X = Br
6-X (R = CH_3)	6-X (R = CH_3)
6-F	6-Fb
6-Cl	6-Clb
6-Br	6-Brb

tonated *p*-haloanisoles (6-Xb) were directly observed in their pmr spectra (Figure 3). They are more deshielded than those of protonated alcohols[11] and ethers.[12] Obviously, the deshielding effect is caused by the inductively electron withdrawing aromatic (C_6H_4X) rings. The $^{+}OCH_3$ protons of all the oxonium ions 6-Xb show a doublet at $\sim\delta$ 5.2 (J_{HH} = 3 Hz). The aromatic protons of both oxonium ions 5-Fb and 6-Fb are centered as a multiplet at δ 7.8 while those of oxonium ions 5-Clb, 5-Brb, 6-Clb, and 6-Brb show two doublets (or AB quartet) between δ 7.7 and 8.3 (see Table III). The multiple coupling in oxonium ions 5-Fb and 6-Fb must be due to the proton–fluorine interaction. The ^{19}F nmr spectra of 5-F and 6-F have almost identical chemical shifts at ϕ 125.2 and 125.8, respectively, whereas those of the O-protonated species, 5-Fb and 6-Fb, are both deshielded (by about 15–16 ppm) at ϕ 110.2 and 109.3. The relatively small deshielding (compared to those of C-protonated *o*- and *m*-fluorophenols and fluoroanisoles) indicate that back-donation by the nonbonded electron pairs of fluorine is not affecting much the deshielding for which the inductive effect is mainly responsible.

When superacid III or IV was used to protonate 5-X and 6-X, the $-OH_2^{+}$ and the $-CH_3OH^{+}$ protons of the corresponding oxonium ions 5-Xb and 6-Xb were not observed. The methoxy protons of 5-Xb and 6-Xb show a pmr singlet instead of a doublet. The aromatic proton absorptions of 5-Xb and 6-Xb are similar to those observed in superacids I–II, but are slightly shielded (Table III). Similarly, the fluorine nmr absorptions of 5-F and 6-F in superacids III and IV are also shielded from those observed in superacids I and II. These data indicate a rapid protonation–deprotonation equilibrium between 5-X (6-X) and 5-Xb (6-Xb). Consequently, the pmr absorptions of 5-X and 6-X are

$$\text{5-X or 6-X} \xrightleftharpoons{\text{superacids III–IV}} \text{5-Xb or 6-Xb (X = F, Cl, Br)}$$

(11) G. A. Olah, J. Sommer, and E. Namanworth, *J. Amer. Chem. Soc.*, **89**, 3576 (1967).
(12) G. A. Olah and D. H. O'Brien, *ibid.*, **89**, 1725 (1967).

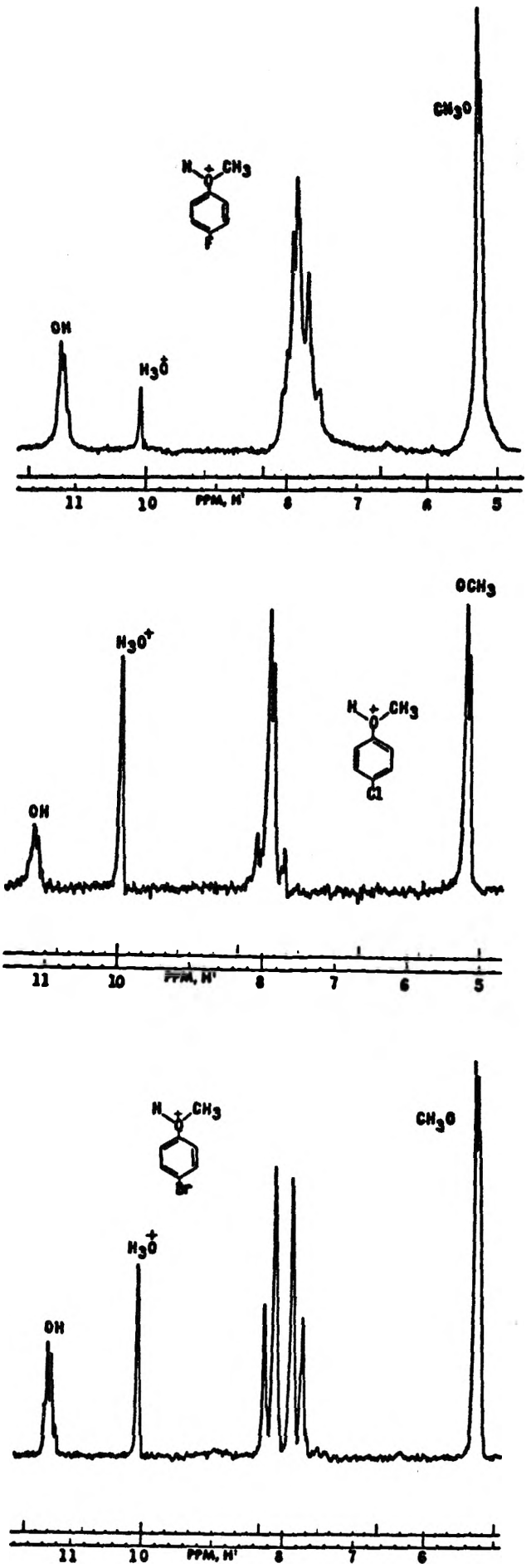
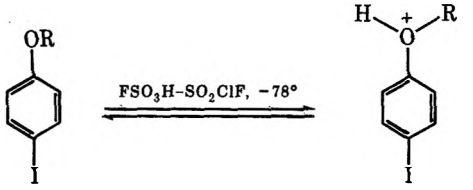


Figure 3.—Pmr spectra of O-protonated *p*-haloanisoles (6-Fb, upper, 6-Clb, middle, and 6-Brb, bottom traces).

also different in superacid III and in superacid IV. They are more deshielded in the former, indicating that the equilibria were shifting to the right or the lifetimes of the oxonium ions 5-Xb or 6-Xb are longer in this media.

We have also studied the protonation of *p*-iodophenol (5-I) and *p*-iodoanisole (6-I) in the four superacid systems (I–IV). When 5-I and 6-I were treated with superacids I–III at −78°, only tar formation and liberation of iodine were observed. The decomposition of 5-I and 6-I in superacids I–III is similar to those of 1-I and 2-I (see previous discussion). However, both 5-I and 6-I were O-protonated in FSO_3H–SO_2ClF (IV) at −78°. The pmr spectra of 5-I and 6-I in FSO_3H–SO_2ClF are similar to those of 5-X (X = Cl and Br) and 6-X (X = Cl and Br) in the same medium. Thus, in oxonium ions 5-Ib and 6-Ib the hydroxyl protons are intermolecularly exchanging with the superacid systems.



5-I, R = H
6-I, R = CH_3

5-Ib, R = H
6-Ib, R = CH_3

Conclusion

The site of protonation of halophenols and haloanisoles was found to be dependent upon the four superacids (I–IV) used as well as the nature of the halogen atoms. In general, C-protonation of halophenols and haloanisoles to give the corresponding halogenated hydroxy(methoxy)benzenium ions was achieved in the strongest superacid I, while O-protonated oxonium ions were formed in the weakest acid IV. Since OH and OCH_3 are stronger activating groups than halogen atoms, protonation of rings always takes place at the position para to the hydroxy or methoxy group. In the case when the para position is substituted by a halogen atom (*e.g.*, *p*-halophenols), no C-protonation was observed. Instead the corresponding O-protonated oxonium ions were formed, even in superacid I.

The nature of the halogen atoms plays an important role in the formation of halogenated hydroxy(methoxy)-benzenium ions (1-Xa–4-Xa). Protonation of *o*-halophenols (1-X) in superacid III is particularly interesting. 1-Br and 1-I were completely C-protonated in superacid III at −60°, while 1-F and 1-Cl were both C- and O-protonated. These results reflect the strong negative inductive effect of fluorine and chlorine atoms, respectively. O-Protonation to give oxonium ions 1-Fb and 1-Clb is favored through involvement of hydrogen bonding (1-Xb). In the case of *m*-halophenols (3-X), complete C-protonation was found when 3-F and 3-I were treated with superacid III. Under identical conditions, 3-Cl and 3-Br were only partially C-protonated. These results indicate that resonance effects (halogen back-donation) stabilize ion 3-Fa the most, while ion 3-Ia is inductively more favorable than related ions 3-Xa (X = F, Cl, and Br). Thus, ions 3-Cla and 3-Bra have lesser resonance stabilization than that of ion 3-Fa and at the same time are destabilized inductively much more than ion 3-Ia.

o-Halophenols (1-X) were completely C-protonated in superacid II, while their methyl ethers (2-X) were only partially C-protonated. These data show that a hydroxy group is better in stabilizing arenium ions than an alkoxy group. Similar results have been observed in the case of other hydroxy- and alkoxybenzenium ions.[3a]

The present study of the protonation of halophenols and haloanisoles in varying superacid media also gives useful information relating to the electrophilic aromatic substitution of these compounds. The site of electrophilic attack in substitution reactions in general should parallel those observed in protonation of halophenols and haloanisoles. Kinetic *vs.* thermodynamic control can be responsible for O- or C-substitution. The former, however, is generally reversible through intermolecular displacement (exchange) reactions.[13]

Experimental Section

Materials.—All the halophenols and haloanisoles were commercially available in high purity and were used without further purification. Antimony pentafluoride (Allied Chemical Co.) was refluxed overnight while passing a stream of dry nitrogen through it. The material was then twice distilled (bp 150°). Fluorosulfuric acid (Allied Chemical Co.) was distilled (bp 160–164°) before use. Hydrogen fluoride was obtained from Baker Chemical Co. Sulfuryl chloride fluoride was obtained from Allied Chemical Co.

Preparation of Ions.—Superacid solutions were prepared by mixing antimony pentafluoride and HF or FSO_3H at −78° in Teflon bottles in the concentrations indicated. The resulting solutions were then diluted with sulfuryl chloride fluoride. Ions for nmr studies were prepared by adding 30–40 mg of the aromatic compound (dissolved in SO_2ClF) to 1 ml of the above superacid solution (at −78°). Upon warming, while stirring or shaking, a clear solution was obtained. After nmr study, solutions were quenched (as previously described)[14] and starting halophenols and haloanisoles were recovered (as indicated by nmr, ir, and glc studies) showing that no side reactions took place, other than described.

Nmr Spectra.—A Varian Associates Model A-56/60A nmr spectrometer equipped with a variable-temperature probe was used for ^1H and ^{19}F nmr spectra. Both ^1H and ^{19}F coupling constants are believed accurate to ±0.1 Hz. Unless otherwise indicated, proton chemical shifts (δ) are from an external capillary of TMS. Fluorine chemical shifts (ϕ) are from an external capillary of CCl_3F.

Registry No.—1-F, 367-12-4; 1-Cl, 95-57-8; 1-Br, 95-56-7; 1-I, 533-58-4; 2-F, 321-28-8; 2-Cl, 766-51-8; 2-Br, 578-57-4; 2-I, 529-28-2; 3-F, 372-20-3; 3-Cl, 108-43-0; 3-Br, 591-20-8; 3-I, 626-02-8; 4-F, 456-49-5; 4-Cl, 2845-89-8; 4-Br, 2398-37-0; 4-I, 766-85-8; 5-F, 371-41-5; 5-Cl, 106-48-9; 5-Br, 106-41-2; 5-I, 540-38-5; 6-F, 459-60-9; 6-Cl, 623-12-1; 6-Br, 104-92-7; 6-I, 696-62-8.

Acknowledgment.—Support of our work by the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Institutes of Health is gratefully acknowledged.

(13) G. A. Olah and E. G. Melby, *J. Amer. Chem. Soc.*, in press.

(14) (a) G. A. Olah and E. Namanworth, *ibid.*, **88**, 5327 (1966); (b) G. A. Olah, M. B. Comisarow, E. Namanworth, and B. Ramsey, *ibid.*, **89**, 5259 (1967).

The Copper-Catalyzed Additions of Diazo Esters to 2,4-Hexadienes

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Received January 16, 1973

Decomposition of ethyl diazoacetate with copper powder in the presence of *trans,trans*-, *cis,trans*-, and *cis,cis*-2,4-hexadiene afforded the eight isomeric ethyl 2-methyl-3-propenylcyclopropanecarboxylates which were separated by preparative glpc. The structures of the isomeric products were established on the basis of their spectral properties and from correlations based on thermolysis and ozonolysis results. The additions took place with a general preference for the orientation of the carboethoxy group trans to the propenyl group. The stereoselectivity of the reaction is discussed.

The addition reactions of carbenes and carbenoids have proven to be of great synthetic utility;[2,3] in particular the copper-catalyzed addition of diazoacetic ester to olefins has allowed the synthesis of numerous cyclopropanecarboxylic acids.[4] In conjunction with a study of their thermochemistry,[5] we required a series of "maximally labeled"[6] vinylcyclopropanes whose stereochemistry was known with certainty so that firm conclusions could be made on the mechanism and stereochemistry of their thermal rearrangements. With these objectives in mind we embarked on a study of the addition of alkyl diazo esters to the isomeric 2,4-hexadienes.

Results

The general procedure for the addition reactions involved adding a mixture of diazo ester in the appropriate diene to a slurry of copper powder (activated by preliminary washing with acetic acid) in the diene. Products were purified by vacuum distillation and the isomers were separated by preparative glpc. Isolated yields in the preparative runs ranged from 51 to 59%.

Product distributions (Table I) were determined by glpc analysis of the crude reaction mixture and were invariant throughout the course of the reaction, indicating that there was no product interconversion. These data are only slightly different from those ob-

(1) Taken from the Ph.D. Thesis of H. J. T., University of Maryland, 1971.

(2) W. Kirmse, "Carbene Chemistry," 2nd ed, Academic Press, New York, N. Y., 1971.

(3) R. A. Moss in "Selective Organic Transformations," Vol. I, B. S. Thyagarajan, Ed., Wiley-Interscience, New York, N. Y., 1970, p 35.

(4) I. A. Dyakonov and V. F. Myznikova, *Sb. Statei Obschch. Khim.*, **1**, 489 (1953); C. von der Heide, *Chem. Ber.*, **37**, 2101 (1904); S. Harper and H. W. Reed, *J. Chem. Soc.*, 779 (1955); R. N. Gmyzina, I. A. Dyakanov, and L. P. Danilkina, *Zh. Org. Khim.*, **6**, 2168 (1970); H. Nozaki, H. Takaya, S. Moriuti, and R. Noyori, *Tetrahedron*, **24**, 3655 (1968); D. L. Garin, *J. Amer. Chem. Soc.*, **92**, 5224 (1970).

(5) P. H. Mazzocchi and H. J. Tamburin, *J. Amer. Chem. Soc.*, **92**, 7220 (1970).

(6) R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Verlag Chemie, Weinheim/Bergstr., Germany, 1970, p 122.

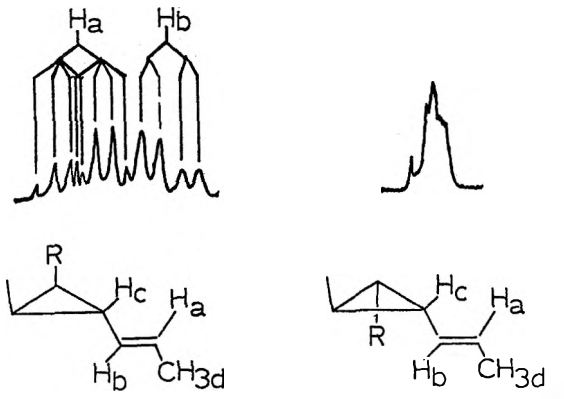
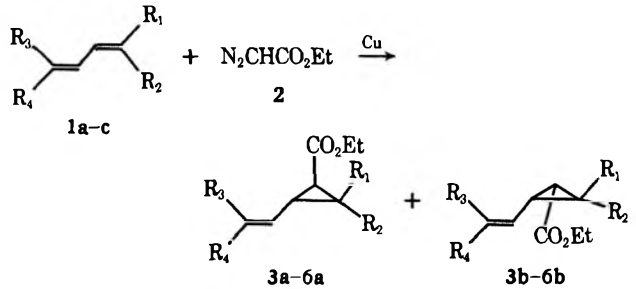


Figure 1.—The vinyl regions of the nmr spectra of **3a** and **3b** (R = CO_2Et).



1a, $R_1 = R_4 = CH_3$; $R_2 = R_3 = H$
b, $R_1 = R_3 = CH_3$; $R_2 = R_4 = H$
c, $R_2 = R_3 = CH_3$; $R_1 = R_4 = H$

3a, $R_1 = R_4 = CH_3$; $R_2 = R_3 = H$
4a, $R_1 = R_3 = CH_3$; $R_2 = R_4 = H$
5a, $R_2 = R_4 = CH_3$; $R_1 = R_3 = H$
6a, $R_2 = R_3 = CH_3$; $R_1 = R_4 = H$

3b, $R_1 = R_4 = CH_3$; $R_2 = R_3 = H$
4b, $R_1 = R_3 = CH_3$; $R_2 = R_4 = H$
5b, $R_2 = R_4 = CH_3$; $R_1 = R_3 = H$
6b, $R_2 = R_3 = CH_3$; $R_1 = R_4 = H$

TABLE I

Reactants	Product ratios, %	
1a + **2**	**3a** (57)	**3b** (43)
1b + **2**	**4a** (17)	**4b** (10)
	5a (41)	**5b** (31)
1c + **2**	**6a** (68)	**6b** (32)

tained for the product after distillation. We attribute these differences to fractionation during distillation rather than product interconversion. A check of the starting dienes after reaction indicted that isomerization of the dienes amounted to less than 2%.

Stereochemistry.—The isomeric vinylcyclopropanes **3**–**6** are listed in Table II along with relevant infrared and nmr data.

TABLE II

CHEMICAL SHIFTS (τ) OF PROTONS H_a AND H_b (CCl4, INTERNAL TMS)

Isomer	Proton absorbance, τ H_a	H_b	H_b shift, τ	$\nu_{max}^{CCl_4}$
3a	4.50	5.05		960
3b	4.53	4.53	0.52	969
4a	4.55	5.17		
4b	4.59	4.59	0.58	
5a	4.34	4.86		960
5b	4.30	4.30	0.56	962
6a	4.40	4.92		
6b	4.40	4.40	0.52	

The products may be initially broken down into three groups on the basis of their method of synthesis; *i.e.*, only **3a** and **3b** could result from addition to *trans,trans*-hexadiene, whereas **4a**, **4b**, **5a**, and **5b** could result from addition to *cis,trans*-2,4-hexadiene and **6a** and **6b** from *cis-cis*-2,4-hexadiene.

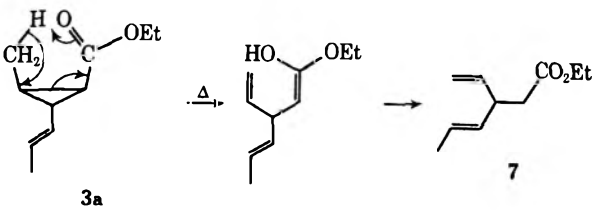
Examination of the infrared spectra allows a further simplification, since those isomers having a trans double bond (960 cm^{-1}) may be identified.[7] The isomers thus can be considered as four pairs, with one member of each pair having the carboethoxy group cis to the propenyl group (as in **3b**–**6b**) and the other having the carboethoxy and propenyl groups trans (as in **3a**–**6a**).

Examination of the vinyl region of the nmr spectra for these compounds reveals an important stereochemical correlation. For the latter group (**3a**–**6a**) the vinyl regions of the spectra are all similar to that of **3a** (Figure 1) showing H_a and H_b separated by *ca.* τ 0.5. This area of the spectrum is analyzable on a first-order basis and shows H_a as a doublet of quartets (J_{ab} = 15.0 Hz, J_{ad} = 6.0 Hz) at τ 4.50 and H_b as a doublet of doublets (J_{ab} = 15.0 Hz, J_{bc} = 7.5 Hz) at τ 5.05.

In contrast the vinyl regions of the nmr spectra of the former group (**3b**–**6b**) are similar to that shown for **3b** (Figure 1) showing H_a and H_b as a broad complex resonance centered at τ 4.53. We[5] ascribe this difference to specific deshielding of H_b by the cis carboethoxy group, a phenomenon which has been well established for the cis β hydrogens of crotonates and acyclic dienoates.[8,9] Examination of data in the literature reveals that this correlation holds for *cis*- and *trans*-(2-benzoyl)- and -(2-acetyl)vinylcyclopropanes[10] and for *cis*- and *trans*-(2-acetyl-1-methyl)vinylcyclopropane.[11] In all cases a vinyl proton (corresponding to H_b) is deshielded in the cis compound with respect to the trans compound.

Irrespective of this analysis, and especially in view of subsequent and apparently anomalous nmr results obtained on **11** (*vide infra*), it was felt that the stereochemistry of at least one pair of cis–trans isomers should be conclusively established.

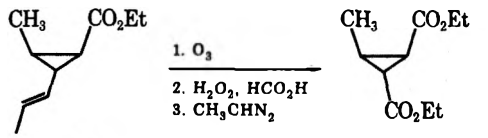
Additional stereochemical evidence was furnished by thermolysis (285°, sealed tube) of **3a** and **3b**. Under these conditions[5] **3a** afforded ethyl 3-vinyl-*trans*-4-hexenoate (**7**) as a major product, whereas **3b** gave little **7**. Since this homocyclic 1,5 hydrogen



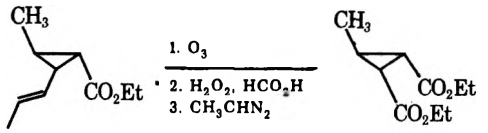
(7) L. J. Bellamy, "Advances in Infrared Group Frequencies," Methuen and Co., London, 1967, p 43.
(8) M. Hocking, *Can. J. Chem.*, **44**, 1581 (1966).
(9) L. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, New York, N. Y., 1969, p 88.
(10) Y. Bahucel, F. Collonges, A. Menet, F. Pautet, A. Poncet, and G. Descotes, *Bull. Soc. Chim. Fr.*, 2209 (1971).
(11) S. J. Rhoads and C. F. Brandenburg, *J. Amer. Chem. Soc.*, **93**, 5805 (1971).

migration requires cis alkyl and carboethoxy groups,[12] the stereochemistry of **3a** should be as indicated.

Conclusive evidence on the stereochemistry of **3a** and **3b** follows from ozonolysis data. Ozonolysis of **3a** and **3b** afforded, after oxidative work-up and esterification with diazoethane, the diesters **8** and **9**, respectively. The structure of **8** and **9** are apparent



3a **8**

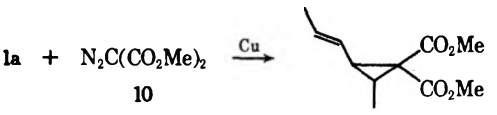


3b **9**

from their nmr spectra. Whereas the methylene groups of the ethyl esters in **9**, which has a plane of symmetry, appear as a single sharp quartet, those of **8**, which has no symmetry plane, appear as a doublet of quartets. These data conclusively establish the stereochemistry of **3a** and **3b** and, by analogy, the stereochemsitry of all of the other isomers.

That nmr analysis should not be trusted as the sole criterion for stereochemical assignments in these systems was graphically demonstrated by the results obtained from addition of methyl diazomalonate to *trans,trans*-2,4-hexadiene.

The vinyl region of the nmr spectrum of diester **11** showed H_a as a doublet of quartets at τ 4.28 (J_{ab} =



10 **11**

15.0, J_{ad} = 6.0 Hz) and H_b as a doublet of doublets at τ 4.97 (J_{ab} = 15.0, J_{bc} = 8.0 Hz). This region of the spectrum is remarkably similar to the vinyl region of **3a**, *i.e.*, the necessarily cis carboethoxy group in **11** does not deshield H_b. We believe that this is due to the preferred conformations of the cis carboethoxy groups in **3a** and **3b** with respect to **11**. For effective deshielding of the transannular vinyl proton the anisotropy of the carbonyl group is such that there must be a significant population of the s-cis conformer (Figure 2).[13] In the case of **11** the presence of the bulky geminal carboethoxy group would tend to destabilize the s-cis conformer, resulting in the virtual disappearance of the long-range deshielding as observed. A similar effect has been shown to be operative in the β-cyclopropyl acrylic esters where a distinct bathochromic shift in the ultraviolet spectrum is observed when a geminal cyclopropyl substituent is added.[13] This has been explained as being due to destabilization of the "maximum overlap" conformation in that system, a

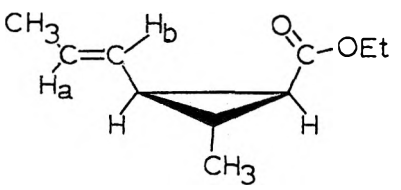


Figure 2.—The required conformation for maximum deshielding of H_a by the transannular carboxyl group.

conformation analogous to that depicted (Figure 2) for **3b**.

Discussion

There are several points that can be made concerning the product ratios in Table I. It is obvious that, in cases where there is a clear distinction, the least hindered product is always formed preferentially.[3,14] This steric discrimination is consistent with addition *via* attack of a bulky copper complex.[14,15] Thus, in the case of additions to a cis double bond to form **5a**, **6a**, **5b**, and **6b**, the anti addition product clearly predominates.

The analysis of the **3a**:**3b** and **4a**:**4b** product ratios is not so clear-cut, however, since it requires an evaluation of the steric requirements of methyl *vs.* propenyl groups. Although conformational free energies are not a direct measure of group size, they do reflect the relative steric requirements of the minimum energy orientations of various groups.[16,17] If the transition state for copper diazoacetate addition resembles one that would result from the approach of the copper complex to a planar s-trans diene, then the conformational free energies are probably reasonable values for the relative steric demands of propenyl and methyl groups in the transition state. The incoming reagent will probably experience less interaction with the planar propenyl group than with the approximately spherical methyl group.[18]

Examination of the **3a**:**3b**, and **4a**:**4b** ratios reveals that in each case the major product has cis carboethoxy and methyl groups, *i.e.*, the major product is the one that would result from the most hindered transition state, and, although the differences are small, they are not insignificant. Although the formation of hindered syn adducts is common in carbene additions, it is unprecedented in diazo ester additions, where the anti product is usually favored.[14]

A possible answer lies in a combination of opposing steric and electrostatic effects. As has been pointed out by Moss,[3] the permanent dipole in the carboethoxy group should interact in a destabilizing manner with any positive charge residing on the olefinic substituents. Since charge in the transition state (Figure 3) will preferentially delocalize into the propenyl rather than the methyl group, this electrostatic effect will

(12) H. M. Frey and R. Walsh, *Chem. Rev.*, **69**, 103 (1969); M. J. Jorgenson and A. F. Thacher, *Tetrahedron Lett.*, 4651 (1969); D. E. McGreer, N. W. K. Chiu, and R. McDaniel, *Proc. Chem. Soc.*, 415 (1964); R. M. Roberts, R. G. Landolt, R. N. Greene, and E. W. Heyer, *J. Amer. Chem. Soc.*, **89**, 1404 (1967); W. Ando, *Tetrahedron Lett.*, 929 (1969).

(13) M. J. Jorgenson and T. Leung, *J. Amer. Chem. Soc.*, **90**, 3769 (1968).

(14) W. R. Moser, *J. Amer. Chem. Soc.*, **91**, 1135 (1969).

(15) H. Nozaki, S. Moriuti, H. Tahaya, and R. Noyori, *Tetrahedron Lett.*, 5239 (1966).

(16) E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, pp 44, 433.

(17) E. L. Eliel, *Angew. Chem., Int. Ed. Engl.*, **4**, 782 (1965); J. A. Hirsch in "Topics in Stereochemistry," Vol. 1, N. L. Allinger and E. L. Eliel, Ed., Interscience, New York, N. Y., 1967, p 199.

(18) The $-\Delta G°$ value for methyl is 1.70 kcal/mol.[17] The values for cis and trans propenyl groups are unknown, but they should be the same as that for the vinyl group ($-\Delta G°$ = 1.35 kcal/mol[17]), since substituents two atoms removed from the ring do not effect these values.[16]

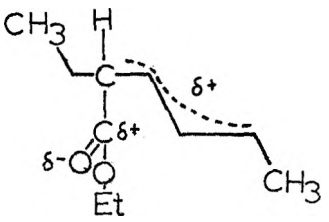


Figure 3.—A model of a possible transition state for carbenoid addition to 1a showing electrostatic interactions. For simplicity copper has not been included.

tend to favor the cis carboethoxy–methyl arrangement. Opposing this is the slight steric preference for cis propenyl and carboethoxy groups. The result is a small but significant preference for **3a** and **4a** over **3b** and **4b**.

Our results also indicate a clear preference for addition to a cis double bond over a trans double bond. This point is graphically illustrated by comparison of the yields obtained from addition to *cis,trans*-2,4-hexadiene (**1b**). It is obvious that the products of insertion into the cis double bond (**5a** and **5b**) are the major ones. In fact **5b**, by far the most hindered product, is formed in better yield than the total yield of products from insertion into the trans double bond (*i.e.*, **4a** and **4b**). This enhanced reactivity undoubtedly reflects the higher ground-state energy of the cis alkenyl moiety.

Experimental Section

The infrared spectra were obtained on a Perkin-Elmer 337 grating infrared spectrophotometer in a 0.1-mm NaCl cell (10% in carbon tetrachloride). The nmr spectra were obtained on a Varian A-60D spectrophotometer in carbon tetrachloride solutions with tetramethylsilane as internal standard. The preparative glpc work was done on a Varian Aerograph series 90 using a thermal conductivity detector; the analytical glpc work was done on a Varian Aerograph series 1200 with flame ionization. A list of glpc columns employed follows: column A, 20% Carbowax 20M on 80/100 Chromosorb P (AW-DMCS), 15 ft × 0.25 in.; B, 15% IGEPAL (CO-880) on 80/100 Chromosorb W (AW-DMCS), 9 ft × 0.25 in.; C, 6 ft × 0.125 in. 5% IGEPAL-CO880 then 4 ft × 0.125 in. 5% XE-60 on 80/100 Chromosorb P (AW-DMCS); D, 11% Carbowax 20M and 4% DEGA on 60/80 Chromosorb W (AW-DMCS), 6 ft × 0.25 in.; E, 15% UCON 50 HB 270X on 80/100 Chromosorb W (AW-DMCS), 15 ft × 0.25 in.; F, 15% UCON 50 HB 270X on 60/80 Chromosorb W (AW-DMCS), 6 ft × 0.125 in.; G, 15% UCON 50 HB 270X on 60/80 Chromosorb W (AW-DMCS), 6 ft × 0.25 in.; H, 10% SE-30 on 100/120 Chromosorb P (AW-DMCS), 10 ft × 0.125 in.; I, 15% Carbowax 20M on 60/80 Chromosorb W (AW-DMCS), 9 ft × 0.125 in.; J, 15% silicone D. C. 550 on 60/80 Chromosorb W (AW-DMCS), 6 ft × 0.25 in.; K, 15% Carbowax 20M on 60/80 Chromosorb W (AW-DMCS), 6 ft × 0.125 in.; L, 15% Carbowax 20M on 60/80 Chromosorb W (AW-DMCS), 6 ft × 0.25 in.

Preparation of the Isomeric Ethyl 2-Methyl-3-propenylcyclopropane-1-carboxylates. A. Addition to *trans,trans*-2,4-Hexadiene (1a).—The insertion reaction was accomplished by a modification of the procedure of Musso and Biethan.[19] Into a 50-ml three-necked round-bottomed flask, fitted with a reflux condenser and addition funnel, were placed 4.5 g (0.055 mol) of **1a** and 0.2 g of finely divided activated (*via* glacial acetic acid) copper powder. The flask was flushed with nitrogen, and while the solution was stirred vigorously at reflux a mixture of 3.2 g (0.028 mol) of ethyl diazoacetate in 4.5 g (0.055 mol) of **1a** was added over a 3-hr period.

After the addition was complete, the light brown solution was filtered *via* a glass funnel to remove the copper. The filtrate was carefully distilled at atmospheric pressure to remove excess hexadiene, which was essentially pure (>98% trans,trans). The residue was distilled *in vacuo* to yield 2.7 g (57.5%), bp 68–70° (0.5 mm).

An analytical sample of the mixture was obtained by preparative glpc (column D, 110°) and submitted for analysis.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.24; H, 9.35.

This material was analyzed by glpc on column I at 125° and showed two peaks in a ratio of 43:57. Separation of the two isomers was accomplished by preparative glpc on column G (135°). The minor isomer was obtained pure by making one pass on column G and one pass on column K (135°). Similarly, the major isomer was purified by making two passes on column K (130°). The minor isomer was assigned the structure ethyl *trans*-2-methyl-*cis*-3-(*trans*-propenyl)cyclopropane-1-carboxylate (**3b**), on the basis of the following data: $\nu_{max}^{CCl_4}$ 3010, 2950, 2910, 1725, 1160, 1180, and 969 cm^{-1}; τ ~4.53 (4.39–4.70, unresolved multiplet, 2 H, vinyl), 5.94 (quartet, 2 H, J = 7.0 Hz, $-COOCH_2CH_3$), 8.35 (doublet, 3 H, vinyl methyl), ~8.60 (8.20–9.00, multiplet, 6 H, cyclopropyl methyl and cyclopropyl), and 8.77 (triplet, 3 H, J = 7.0 Hz, $-COOCH_2CH_3$).

The major product was identified as ethyl *cis*-2-methyl-*trans*-3-(*trans*-propenyl)cyclopropane-1-carboxylate (**3a**) on the basis of the following data: $\nu_{max}^{CCl_4}$ 3010, 2960, 2950, 2910, 1720, 1170, and 960 cm^{-1}; nmr τ 4.50 (doublet of quartets, 1 H, J_{ab} = 15.0, J_{ad} = 6.0 Hz, vinyl H_a), 5.05 (doublet of doublets, 1 H, J_{ab} = 15.0, J_{bc} = 7.5 Hz, vinyl H_b), 5.95 (quartet, 2 H, J = 7.0 Hz, $-COOCH_2CH_3$), 8.37 (doublet, 3 H, vinyl methyl), ~8.60 (8.20–9.00) (complex multiplet, 6 H, cyclopropyl and cyclopropyl methyl), and 8.77 (triplet, 3 H, J = 7.0 Hz, $-COOCH_2CH_3$).

B. Addition to *cis,trans*-2,4-Hexadiene (1b).—The procedure used was the same as above except that pure *cis,trans*-2,4-hexadiene (**1b**) was employed. The yield of product was 2.4 g (51.1%), bp 52–55° (0.8 mm).

An analytical sample of the mixture was obtained by preparative glpc (column D, 150°) and submitted for analysis.

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.27; H, 9.34.

Analysis of this mixture by glpc on column C at 90° showed four peaks in a relative ratio of 14% (retention time 35 min), 8% (46 min), 27% (51 min), and 51% (60 min). The materials corresponding to these peaks were subsequently identified as isomers **4a**, **4b**, **5b**, and **5a** as follows.

The mixture (15-μl injections) was passed through column I (100°) which allowed the isolation of **4a** (**4b**, **5a**, and **5b** were collected together). A second pass on column D (120°) gave pure **4a**. The remaining material, a mixture of **4b**, **5a**, and **5b**, was passed (<15 μl) through column B (100°), which allowed the isolation of **5b** from the mixture of **4b** and **5a**. Two passes on column C (105°) gave pure **5b**. The remaining material, a mixture of **4b** and **5a**, was separated with difficulty by employing small injections (5 μl) on column E (125°). Two passes on column E and one pass on column A (110°) gave pure **5a**. Similarly, **4b** was obtained pure after two passes on column D (105°).

Isomer **4a** was identified as ethyl *cis*-2-methyl-*trans*-3-(*cis*-propenyl)cyclopropane-1 carboxylate on the following basis. The nmr spectrum showed τ 4.55 (doublet of quartets, 1 H, J_{ab} = 10.0, J_{ad} = 6.5 Hz, vinyl H_a), 5.17 (broad triplet, 1 H, J_{ab} = 10.0 Hz, J_{bc} = 10.0 Hz, vinyl H_b), 5.89 (quartet, 2 H, J = 7.0 Hz, $-COOCH_2CH_3$), 8.27 (doublet of doublets, 3 H, vinyl methyl), ~8.50 (7.90–8.90, complex multiplet, 6 H, cyclopropyl methyl and cyclopropyl), 8.73 (triplet, 3 H, J = 7.0 Hz, $-COOCH_2CH_3$); ir showed $\nu_{max}^{CCl_4}$ 3020, 2970, 2950, 2930, 1730, 1170, and 700 cm^{-1}.

Isomer **4b** was identified as ethyl *trans*-2-methyl-*cis*-3-(*cis*-propenyl)cyclopropane-1-carboxylate on the following basis: nmr τ 4.59 (complex multiplet, 2 H, vinyl), 5.93 (quartet, 2 H, J = 7.0 Hz, $-COOCH_2CH_3$), 8.30 (broad doublet, 3 H, vinyl methyl), ~8.50 (8.20–9.00, complex multiplet, 6 H, cyclopropyl methyl and cyclopropyl), and 8.78 (triplet, 3 H, J = 7.0 Hz, $-COOCH_2CH_3$); $\nu_{max}^{CCl_4}$ 3040, 2960, 2930, 2970, 1730, and 1180 cm^{-1}.

Isomer **5b** was assigned the structure ethyl *cis*-2-methyl-*cis*-3-(*trans*-propenyl)cyclopropane-1-carboxylate on the basis of nmr resonance at τ ~4.30 (4.20–4.50) (complex multiplet, 2 H, vinyl), 5.92 (quartet, 2 H, J = 7.0 Hz, $-COOCH_2CH_3$), 8.28 (doublet, 2 H, vinyl methyl), 8.20–8.90 (complex multiplet, 6 H, cyclopropyl methyl and cyclopropyl), 8.76 (triplet, 3 H, J = 4.0 Hz, $-COOCH_2CH_3$).

(19) H. Musso and V. Biethan, *Chem. Ber.*, **97**, 2282 (1964).

The infrared spectrum of **5a** had characteristic peaks at 3010, 2980, 2960, 2940, 1735, 1160, and 962 cm^{-1}.

Isomer **5a** was identified as ethyl *trans* 2-methyl-*trans*-3-(*trans*-propenyl)cyclopropane-1-carboxylate on the following basis. The nmr spectrum exhibited absorption at τ 4.34 (overlapping quartets, 1 H, J_{ab} = 15.0, J_{ad} = 6.0 Hz, vinyl H_a), 4.86 (doublet of doublets, 1 H, J_{ab} = 15.0, J_{bc} = 8.0 Hz, vinyl H_b), 5.94 (quartet, 2 H, J = 7.0 Hz, $-COOCH_2CH_3$), 7.80–9.00 (complex multiplet, 6 H, cyclopropyl methyl and cyclopropyl), 8.30 (doublet, 3 H, vinyl methyl), 8.77 (triplet, 3 H, J = 7.0 Hz, $-COOCH_2CH_3$); ir showed $\nu_{max}^{CCl_4}$ 3010, 2970, 2940, 1735, 1175, and 960 cm^{-1}.

C. Addition to *cis*,*cis*-2,4-Hexadiene (1c).—The yield of product was 1.6 g (59%), bp 48–50° (0.5 mm). The recovered hexadiene was pure **1c** *via* glpc.

An analytical sample of the mixture was obtained by preparative glpc (column H, 150°).

Anal. Calcd for $C_{10}H_{16}O_2$: C, 71.39; H, 9.59. Found: C, 71.03; H, 9.37.

Analysis of this mixture on column H (100°) showed two peaks in a relative ratio of 69:31. The two isomers were separated by preparative glpc on column E (135°). The major isomer was obtained pure after one pass on column L (105°). Similarly, the minor isomer was purified by making one pass on column L (105°).

The major isomer was assigned the structure ethyl *trans*-2-methyl-*trans*-3-(*cis*-propenyl)cyclopropane-1-carboxylate (**6a**) on the basis of the following data: $\nu_{max}^{CCl_4}$ 3025, 2970, 2935, 1730, and 1180 cm^{-1}; nmr τ 4.40 (doublet of quartets, 1 H, J_{ab} = 10.0, J_{ad} = 6.0 Hz, vinyl H_a), 4.92 (doublet of doublets, 1 H, $J_{ab} \cong$ 10.0, $J_{bc} \cong$ 10.0 Hz, vinyl H_b), 5.92 (quartet, 2 H, J = 7.0 Hz, $-COOCH_2CH_3$), 8.27 (slightly split doublet, 3 H, vinyl methyl), 7.70–9.00 (complex multiplet, 6 H, cyclopropyl and cyclopropyl methyl), 8.75 (triplet, 3 H, J = 7.0 Hz, $-COOCH_2CH_3$).

Isomer **6b** was identified as ethyl *cis*-2-methyl-*cis*-3-(*cis*-propenyl)cyclopropane-1-carboxylate on the following basis: $\nu_{max}^{CCl_4}$ 3040, 2975, 2950, 2925, 1720, and 1155 cm^{-1}; nmr τ ~4.40 (4.30–4.65, unresolved multiplet, 2 H, vinyl), 5.95 (quartet, 2 H, J = 7.0 Hz, $-COOCH_2CH_3$), 8.32 (doublet, 2 H, vinyl methyl), 7.80–8.90 (multiplet, 6 H, cyclopropyl and cyclopropyl methyl), and 8.77 (triplet, 3 H, J = 7.0 Hz, $-COOCH_2CH_3$).

Dimethyl *trans*-2-Methyl-3-(*trans*-propenyl)cyclopropane-1,1-dicarboxylate (11).—The general insertion procedure using 4.1 g (0.025 mol) of methyl diazomalonate[19] and 8.2 g (0.100 mol) of **1a** afforded 2.3 g (44%) of **11**, bp 69–70° (0.4 mm). Analysis by glpc showed this material to consist of one major product. The product was purified by preparative glpc (column G, 150°) and identified as dimethyl *trans*-2-methyl-3-(*trans*-propenyl)cyclopropane-1,1-dicarboxylate: nmr (CCl_4) τ 4.28 (doublet of quartets, 1 H, J_{ab} = 15.0, J_{ad} = 6.0 Hz, vinyl H_a), 4.97 (doublet of doublets, 1 H, J_{ab} = 15.0, J_{bc} = 8.0 Hz, vinyl H_b), 6.32 (slightly split singlet, 3 H, carboxymethyl), 7.50–8.30 (complex multiplet, 2 H, methyl cyclopropyl and allylic cyclopropyl), 8.33 (slightly split doublet, 3 H, J = 6.0 Hz, vinyl methyl), 8.92 (doublet, 3 H, J = 6.0 Hz, cyclopropyl methyl); $\nu_{max}^{CCl_4}$ 3010, 2975, 2940, 2920, 1725, 1435, 1290, 1210, and 965 cm^{-1}.

Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 61.97; H, 7.62.

Ozonolysis of Isomers 3a and 3b.—The isomers (0.50 g, 57% **3a** and 43% **3b**) were dissolved in a mixture of chloroform (10 ml) and methanol (10 ml) and cooled to −78°.

A stream of ozone from an Orec Model 03Cl Ozonator was passed through the mixture until the solution was faintly blue (~35 min). The solution was allowed to warm to room temperature and the solvents were evaporated at room temperature under reduced pressure, leaving an oil. This was dissolved in 10 ml of 90% formic acid and 10 ml of 30% hydrogen peroxide and heated gently to 60° until refluxing began. The heat was removed until the initial reaction subsided (~10 min) and then the mixture was refluxed gently for 45 min. Solvent was removed under reduced pressure, leaving an oil. A sample of 300 μl of this oil was esterified to the cyclopropane diesters **8** and **9** by the addition of diazoethane. Analysis of the esterified ether solution on column J (140°) showed two major peaks, which were subsequently identified as **8** (59%) and **9** (41%) as follows. One pass of this mixture on column J (140°) allowed separation of the two isomers. A second pass on the same column gave analytically pure **8** and **9**. The major product was identified as diethyl 3-methylcyclopropane *trans* 1,2-dicarboxylate (**8**) on the following basis: nmr τ 5.87 (doublet of quartets, 4 H, J = 7.0 Hz, $-COOCH_2CH_3$), 7.60–8.40 (complex multiplet, 3 H, cyclopropyl methine), 1.28 (triplet, 3 H, J = 7.0 Hz, $-COOCH_2CH_3$), and 1.25 (doublet, 3 H, cyclopropyl methyl); $\nu_{max}^{CCl_4}$ 2960, 2950, 1715, 1300, and 1185 cm^{-1}.

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.06. Found: C, 59.78; H, 7.91.

The minor product was assigned the structure diethyl *trans*-3-methylcyclopropane-*cis*-1,2-dicarboxylate (**9**): nmr τ 4.09 (quartet, 2 H, J = 7.0 Hz, $-COOCH_2CH_3$), ~8.25 (7.85–8.40, complex multiplet, 3 H, cyclopropyl methine), 8.77 (triplet, 3 H, J = 7.0 Hz, $-COOCH_2CH_3$), and 8.82 (doublet, 3 H, cyclopropyl methyl); $\nu_{max}^{CCl_4}$ 2960, 2950, 1720, and 1175 cm^{-1}.

Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.06. Found: C, 59.76; H, 8.05.

Ozonolysis of 3a.—A sample of 20 μl of >95% pure **3a** was dissolved in 300 μl of ethanol–300 μl of chloroform and ozonized as before. The esterified (diazoethane) product was analyzed by glpc on column K (140°) and found to have the same retention time (coinjection) as the larger product peak in the ozonolysis of the mixture of isomers [which was subsequently identified as **8** (*vide supra*)], thus confirming the stereochemical assignments for **3a** and **3b**.

Registry No.—**1a**, 5194-51-4; **1b**, 5194-50-3; **1c**, 6108-61-8; **2**, 623-73-4; **3a**, 30626-52-9; **3b**, 30626-51-8; **4a**, 39495-86-8; **4b**, 39495-87-9; **5a**, 30634-35-6; **5b**, 30634-34-5; **6a**, 39495-90-4; **6b**, 39495-91-5; **8**, 4104-67-0; **9**, 713-51-9; **10**, 6773-29-1; **11**, 39495-94-8; copper, 7440-50-8.

Catalytic Hydrogenation. VI.[1] The Reaction of Sodium Borohydride with Nickel Salts in Ethanol Solution. P-2 Nickel, A Highly Convenient, New, Selective Hydrogenation Catalyst with Great Sensitivity to Substrate Structure

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Reduction of nickelous acetate with sodium borohydride in ethanolic solution yields a nearly colloidal black suspension (P-2 nickel) which, used *in situ*, is a hydrogenation catalyst of extraordinary sensitivity to the environment of the double bond. Slight increases in hindrance are strongly reflected in the rate of hydrogenation: 1-octene, 1.00; 3-methyl-1-butene, 0.23; 3,3-dimethyl-1-butene, 0.07. Substitution of the olefinic moiety more markedly affects the reduction rate: 1-octene, 1.0; 2-methyl-1-pentene, 0.004; 2-methyl-2-pentene, $\ll$0.001; 2,3-dimethyl-2-butene, 0. Cyclohexene is peculiarly inert among simple cyclic alkenes: cyclopentene, 1.00; cyclohexene, $\sim$0.010; cycloheptene, 0.60; cyclooctene, 0.20. Strained double bonds are readily reduced: bicyclo[2.2.1]heptene, 1.0; cyclopentene, 0.26; *cis*-2-pentene, <0.01. The presence of an aryl group, even nonconjugated, markedly promotes hydrogenation: 1-octene, 1.0; 3,4-methylenedioxyallylbenzene (safrole), >3.5; allylbenzene, 3.0. Double-bond isomerization and disproportionation of cyclohexadienes are minimal. Benzylic compounds are not hydrogenolyzed significantly in 24 hr, and allylic and propargylic compounds are hydrogenated with no detectable hydrogenolysis. Dienes and acetylenes are partially reduced with high selectivity.

Sodium borohydride reacts with various group VIIIB transition metals to yield finely divided black precipitates, some of which are active catalysts for hydrolysis of borohydride.[3,4] Certain of these materials have been shown to be hydrogenation catalysts with activity equaling or exceeding that of conventionally prepared analogs.[5-8]

The catalyst prepared by treatment of aqueous nickel salts with an excess of sodium borohydride (designated P-1 nickel) is a granular material with catalytic activity comparable to that of standard commercial Raney nickel catalyst.[8,9] The P-1 catalyst produces considerably less double bond migration during hydrogenation than does Raney nickel.[8]

Borohydride-reduced noble metal catalysts can be generated and used *in situ* in ethanol.[7,10] In an extension of this procedure to nickel catalysts, ethanolic nickel acetate was treated with sodium borohydride under nitrogen; a nearly colloidal black suspension formed, in contrast to the granular precipitate resulting from reaction in aqueous solution. This material was nonpyrophoric and nonmagnetic (in contrast to Raney nickel). Hydrogenation of a few model substrates demonstrated major differences between P-1 nickel and the new material, designated P-2 nickel.

Therefore, as part of our systematic studies of the uses of borohydride-reduced transition metals, we undertook a survey of hydrogenations using the P-2 catalyst under model synthetic conditions.

Results[11]

P-2 nickel is prepared by treating a vigorously stirred solution of nickelous acetate in 95% ethanol (*ca.* 1.25 *M*) with ethanolic sodium borohydride under an inert atmosphere or hydrogen. When hydrogen evolution ceases, the substrate is injected.

Variations in Preparation.—Reduction of nickelous acetate in ethanol was carried out with sodium borohydride in mole ratios of 2:1, 1:1, and 1:2. The 2:1 ratio catalyst was somewhat less active than the others.

The reduction is normally carried out by rapid addition of the borohydride solution to the vigorously stirred nickel acetate solution. Addition of the borohydride in successive smaller increments (mole ratio of Ni(II):$NaBH_4$ = 1:1 and 1:2) produced no significant change.

In these reductions, some active hydride (from $NaBH_4$) is utilized in the reduction and does not appear as hydrogen from borohydride ethanolysis. Addition of a 2.5-mmol aliquot of $NaBH_4$ to 5.0 mmol of Ni(II) yields 6.2 mmol of hydrogen (10.0 mmol theoretical). Subsequent aliquots yield 6.6, 8.8, 9.7, and 10.0 mmol of hydrogen, respectively. A total of 8.7 mmol of hydride is utilized in the reduction of the catalyst.

Metal catalysts have frequently been employed dispersed on inert supports.[12,13] Preparation of P-2 nickel in the presence of high surface area carbon or silica (23% metal loading by weight) yielded no significant change.

Preparation of the catalyst could be carried out equally satisfactorily under argon, nitrogen, or hydrogen; however, contact with air during the reduction produces a markedly less active catalyst. Once formed, the catalyst appears unaffected by brief exposure (without agitation) to air (as when adding solid substrates).

Catalyst is freshly prepared for each run. Reproducibility is quite high measured by time for an up-

(1) Part V: C. A. Brown, *J. Org. Chem.*, **35**, 1900 (1970).

(2) Uniroyal Summer Research Fellow, 1971.

(3) H. C. Brown, H. I. Schlesinger, A. E. Finholt, J. R. Gilbreath, H. R. Hoekstra, and E. K. Hyde, *J. Amer. Chem. Soc.*, **75**, 215 (1953). This work was carried out during World War II but association with classified research delayed publication for nearly 10 years.

(4) H. C. Brown and C. A. Brown, *J. Amer. Chem. Soc.*, **84**, 1491 (1962).

(5) R. Paul, P. Buisson, and N. Joseph, *C. R. Acad. Sci.*, **232**, 627 (1951).

(6) C. A. Brown and H. C. Brown, *J. Amer. Chem. Soc.*, **85**, 1003 (1963).

(7) H. C. Brown and C. A. Brown, *Tetrahedron, Suppl. 8, Part I*, 149 (1966).

(8) C. A. Brown, *J. Org. Chem.*, **35**, 1900 (1970).

(9) Samples of preformed Raney nickel were obtained from the Raney Catalyst Co., Inc. Chattanooga, Tenn. This catalyst, essentially the W-2 preparation, is that commonly stocked in organic chemical laboratories.

(10) C. A. Brown and H. C. Brown, *J. Org. Chem.*, **31**, 3989 (1966).

(11) Unless specified otherwise, all hydrogenations were carried out on 40.0 mmol of substrate over P-2 nickel prepared under nitrogen from nickel acetate at 25°, 1 atm of hydrogen, in ethanol solution. These are typical preparative conditions for the automatic borohydride hydrogenator.[10]

(12) P. N. Rylander, "Catalytic Hydrogenation over Platinum Metals," Academic Press, New York, N. Y., 1967, p 4.

(13) M. Freifelder, "Practical Catalytic Hydrogenation: Techniques and Applications," Wiley-Interscience, New York, N. Y., 1971, p 75.

take of 0.5 equiv of hydrogen by simple alkenes, generally within ± 10% of the average of a series.[14,15]

Effect of Alkene Structure.—See Tables I and II and Figures 1 and 2. Relative reactivity is reported as ratios of $1/T_{50\%}$.

TABLE I

HYDROGENATION OF REPRESENTATIVE SUBSTRATES OVER 5.0 MMOL OF P-2 Ni[a]

Compd	Initial rate,[b] mmol/min	$T_{50\%}$,[c] min
1-Octene	5.3	4.3
3-Methyl-1-butene	2.0	10
3,3-Dimethyl-1-butene	0.53	48
2-Methyl-1-pentene	0.13	720
2-Methyl-2-pentene	0.01*	>24 hr
2,3-Dimethyl-2-butene	0	∞
cis-2-Pentene	0.31	120
trans-2-Pentene	0.08*	>8 hr
Cyclopentene	0.6	8.0
Cyclohexene	0.08*	>8 hr
Cycloheptene	2.1	13
Cyclooctene	0.67	40
Norbornene	5.6	3.4[e]
α-Methylstyrene[d]	0.25	120
Benzene	0	∞

[a] 40.0 mmol of substrate, 0.8 min, 95% ethanol at 25°, 730-mm pressure. [b] Average from 0.0 to 0.2 H_2. * denotes values measured between 0.0 and 0.05 or 0.1 H_2. [c] Time for uptake of 20.0 mmol of H_2. [d] No reduction of aromatic ring. [e] May reflect slight amount of diffusion limitation.

TABLE II

HYDROGENATION OF REPRESENTATIVE SUBSTRATES OVER 1.25 MMOL OF P-2 Ni[a]

Compd	Initial rate,[b,f] mmol/min	$T_{50\%}$,[c] min
1-Octene	2.7	7.8
1-Octene + cyclohexane[e]	2.7	7.9
1-Octene + benzene[d,e]	2.3	9.5
Norbornene	5.0	4.0
Safrole[d]	8.0	2.5
Allylbenzene[d]	4.0	4.1
Styrene[d]	3.3	5.5

[a–d] See Table I. [e] 40.0 mmol of each compound. [f] Because of lower concentration of salts from *in situ* preparation of 1.25 (*vs.* 5.0) mmol of catalyst, rates are not always proportional to the amount of metal; rates are independent of stirring rate, however.

Substitution of the α position of a 1-alkene markedly interferes with hydrogenation, presumably by increasing hindrance to substrate adsorption: 1-octene, 1.0; 3-methyl-1-butene, 0.23; 3,3-dimethyl-1-butene, 0.07. Direct substitution of the double bond produces even more dramatic effects: 1-octene, 1.0; *cis*-2-pentene, 0.03; 2-methyl-1-pentene, 0.004; *trans*-2-pentene, 0.003; 2-methyl-2-pentene, <0.001; 2,3-dimethyl-2-butene, 0. This extreme sensitivity to substitution is in marked contrast to Pt, Pt/C, and P-1 Ni, which reduce even the tetrasubstituted alkenes without difficulty.

Although most medium-ring alkenes are reduced smoothly, cyclohexene is unexpectedly inert, even less

(14) Hydrogen uptake often slows as hydrogenation proceeds; thus comparison of half-hydrogenation times is preferable to 100% reaction times. The reactions appear to be first order in olefin; a detailed kinetic study of borohydride-reduced catalysts has been initiated.

(15) Reactions are carried out in a magnetically stirred reactor under conditions where hydrogenation rate is independent of agitation rate. Stirrer speeds in excess of 10,000 rpm are available (see Experimental Section).

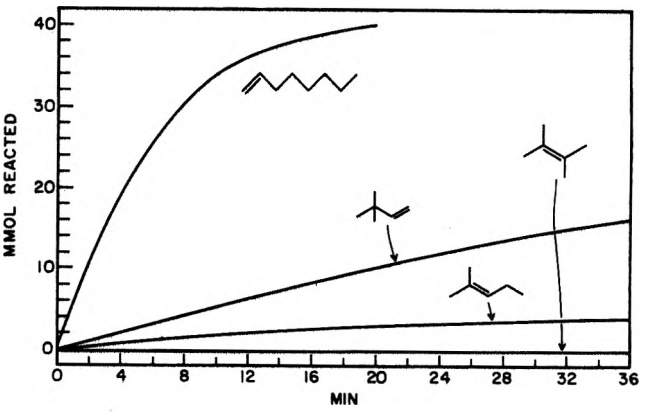


Figure 1.—Hydrogenation of substituted ethylenes over P-2 nickel at 25°: 40.0 mmol of substrate + 5.0 mmol of catalyst.

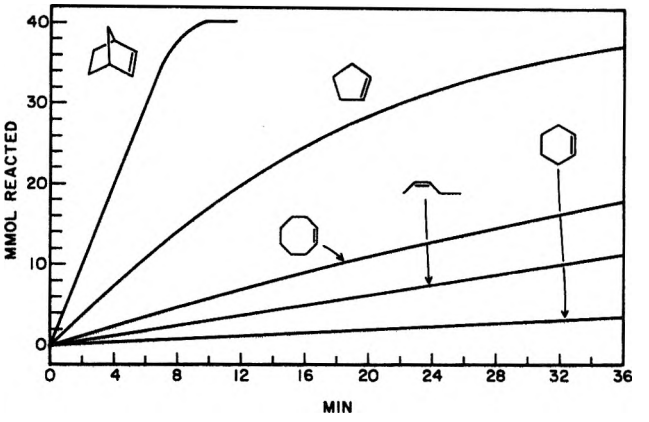


Figure 2.—Hydrogenation of disubstituted alkenes over P-2 nickel at 25°: 40.0 mmol of substrate + 5.0 mmol of catalyst (1.25 mmol for norbornene and cyclopentene).

reactive than *cis*-2-pentene: cyclopentene, 1.0; cycloheptene, 0.60; cyclooctene, 0.20; *cis*-2-pentene, 0.07; cyclohexene, 0.010. This order of reactivity parallels that of P-1 Ni (but is much more pronounced over P-2 Ni), yet differs from that of borohydride-reduced platinum catalysts, which are most active toward cyclohexene.[16]

Benzene was not hydrogenated detectably in 24 hr. Compounds containing both olefinic and aromatic unsaturation (*e.g.*, styrene) absorb only 1.0 equiv of hydrogen. However, hydrogenation is markedly faster than in structurally similar aliphatic olefins: 3,4-methylenedioxyallylbenzene (safrole), >3.5; allylbenzene, 3.0; styrene, 1.6; 1-octene, 1.0. The effect is also felt for hindered bonds: α-methylstyrene, 1.0; 2-methyl-1-pentene, 0.17. The presence of benzene slightly retards hydrogenation of 1-octene.

Double-bond strain promotes hydrogenation markedly (norbornene is even more reactive than 1-octene): norbornene, 1.0; cyclopentene, 0.26; *cis*-2-pentene, <0.01.

Migration of double bonds appears minimal over P-2 nickel. After absorption of 0.5 H_2, 1-pentene yields only 2 mol % 2-pentene (largely trans). Both P-1 nickel and Raney nickel[10] yield substantially more 2-pentene (10 and 23 mol %, respectively).[17]

The initial rates and half-hydrogenation times are

(16) C. A. Brown and V. Ahuja, unpublished observations.

(17) Although hydrogenation predominates over isomerization with nickel, with certain other metals, most notably Pd, isomerization predominates. See ref 7.

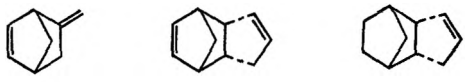
listed in Table I. In a few cases hydrogenations could not be rendered independent of stirring rate with 5.0 mmol of P-2 nickel even at stirring rates of 10,000 rpm. Hydrogenations independent of stirring rate could be obtained over 1.25 mmol of catalyst (Table II).

Selective Hydrogenation of Alkenes.—As the high structural sensitivity suggests, P-2 nickel is highly selective for hydrogenations of one double bond in the presence of another. Hydrogenations proceed smoothly to the equivalence point and then slow sharply. Thus an equimolar mixture of 1-octene and 2-methyl-1-pentene yields (uptake of 1.00 H_2) the respective alkanes in the ratio 16:1. Similarly, 1-octene is reduced in the presence of cyclohexene with a preference of 32:1.

Even in cases where both substrates are readily reduced, addition of 1.0 H_2 yields high selectivity: a mixture of bicyclo[2.2.1]heptene and cyclopentene yields a >13:1 ratio of the respective hydrocarbons. Selectivity, as in the above case, frequently exceeds that predicted from independent initial rates or half-hydrogenation times.

Dienes are hydrogenated with selectivity equal to or greater than that of structurally similar olefin mixtures. Half-hydrogenation of 2-methyl-1,5-hexadiene required 20 min for absorption of 1.04 H_2, 2-methyl-1-hexene accounting for 98% of the olefinic products (49:1 selectivity). Similarly, 4-vinylcyclohexene (1.02 H_2) yielded 4-ethylcyclohexene as 99% of the monounsaturated products.

Methylenenorbornene (**1**) was readily hydrogenated to 2-methylenenorbornene and **2** was reduced to **3** over



1 **2** **3**

P-2 nickel; in both cases only 1–2% of isomeric alkenes and of tetrahydro derivatives were formed.

Reduction of **2** has been carried out on a 3-mol (400 g) scale without difficulty to yield 98.5% pure **3** in 90% distilled yield.

Selective Hydrogenation of Alkynes.—P-2 nickel is an excellent catalyst for selective partial hydrogenation of dialkylacetylenes to cis olefins. Hydrogen uptake is smooth and rapid until 1.00–1.02 H_2 is absorbed. For example, 3-hexyne is hydrogenated over P-2 nickel (mole ratio 8:1) to yield 3-hexene (cis:trans >30:1) quantitatively. Selectivity on a large scale run (200 mmol, substrate:catalyst 20:1) was higher, with cis:trans $\geq$50:1. P-2 nickel has recently been useful for selective hydrogenations of various long-chain acetylenic alcohols in the synthesis of insect sex attractants.[18]

Hydrogenation of 1-hexyne is not so selective as that of disubstituted alkynes; at half-hydrogenation a 1:4:1 ratio of *n*-hexane:1-hexene:1-hexyne is found by glpc (no isomeric hexenes are formed). During hydrogenation, the hexane:hexene ratio is constant at 0.27 as long as 1-hexyne is present.[19]

Conjugated Dienes.—Isoprene is selectively reduced to a mixture of all three methylbutenes. Hydrogen uptake continued after the equivalence point until 3-methyl-1-butene was removed, as expected from the structural sensitivity of P-2 nickel discussed above. Hydrogenation of 1,3-cyclohexadiene nearly ceases after uptake of 0.85 H_2. The product consists mainly of cyclohexene and benzene (formed *via* disproportionation[20] of the diene) in a 10:1 ratio.

Hydrogenolysis.—Benzylic derivatives such as the alcohol and methyl ether are not subject to hydrogenolysis over P-2 nickel for at least 24 hr. Allylic alcohols such as 1-penten-3-ol and 1-vinylcyclohexanol are hydrogenated to the corresponding saturated derivatives without scission of the C–O bond, as is allyl acetate. Similarly, ethynylcarbinols absorb exactly 2.0 H_2 without hydrogenolysis.

Selective hydrogenation data are listed in Table III.

Discussion

Reduction of nickel salts with sodium borohydride represents a convenient direct method to active catalysts. It is surprising, and currently unexplained, that the alteration of preparation solvent from water to ethanol should result in such a pronounced change in properties.

P-2 nickel is probably an amorphous mixture of nickel and boron.[21] Such mixtures usually contain nickel and boron in a mole ratio of 2.0–2.5:1.[21] Reduction of nickel(II) to nickel(0) with borohydride results in utilization of 1.0 equiv of H^-, or 5.0 mmol of H^- for 5.0 mmol of nickelous acetate. The formation of B(0) would utilize 1.5 equiv of H^-, or 3.0–3.75 mmol of H^- for the usual alloy mole ratios. Thus preparation of P-2 nickel requires 8.0–8.75 mmol of H^-, in excellent agreement with the 8.7 mmol actually found to be utilized.

The lack of effect of supports such as high surface area carbon upon P-2 nickel was at first surprising, since a considerable effect is obtained with borohydride-reduced platinum metals.[7] The effect of supports is most probably to increase the available metal surface area; thus the extremely high state of dispersion of P-2 nickel may be unimproved by support. Similar phenomena have been observed for silane-reduced[22] and borane-reduced[23] catalysts.

Hydrogenations over P-2 nickel proceed at a steadily decreasing rate, unlike the zero-order hydrogenations observed over borohydride-reduced platinum catalysts. Studies in progress suggest that hydrogenations over P-2 nickel proceed by kinetics first order in substrate, indicating a weak adsorption of the double bonds for the P-2 nickel surface. Refinements in technique are in progress to allow analysis of the effects of substrate structure.

The study reports a preliminary survey of a novel catalyst system, P-2 nickel. This scan reveals a readily prepared, simple catalyst with considerable selectivity: reduction of one double bond in the presence of others; selective half-hydrogenation of conjugated dienes; reduction of alkynes to pure cis olefins; and hydrogena-

(18) K. W. Greenlee, private communication.

(19) Hexane and 1-hexene are formed *via* a common chemisorbed intermediate; little or no hexane is formed *via* reduction of 1-hexene in competition with 1-hexyne. C. A. Brown, *Chem. Commun.*, 139 (1970).

(20) Such disproportionation occurs with both 1,3- and 1,4-cyclohexadienes over a variety of catalysts, predominating over hydrogenations with Pd/C. Low-temperature aromatization utilizing this effect is under investigation.

(21) See the discussion in ref 8 and the references therein.

(22) C. Eaborn, B. C. Pant, E. R. A. Peeling, and S. C. Taylor, *J. Chem. Soc. C*, 2823 (1969).

(23) C. A. Brown, research in progress.

TABLE III
SELECTIVE HYDROGENATIONS OVER P-2 NICKEL

Compd[a]	Product (%)
1-Hexyne	*n*-Hexane (16)
	1-Hexene (68)
	1-Hexyne (16)
3-Hexyne	*n*-Hexane (1)
	c-3-Hexene (96)
	tert-3-Hexene (3)
	3-Hexyne (0)
1-Octene + 2-methyl-1-pentene	*n*-Octane (48)
	1-Octene (2)
	2-Methylpentane (3)
	2-Methyl-1-pentene (47)
1-Octene + cyclohexene	*n*-Octane (49)
	1-Octene (1)
	Cyclohexane (2)
	Cyclohexene (48)
Norbornene + cyclopentene	Norbornane (47)
	Norbornene (3)
	Cyclopentane (2)
	Cyclopentene (48)
2-Methyl-1,5-hexadiene	2-Methylhexane (2)
	2-Methyl-1-hexene (96)
	Other methylhexenes (2)
	2-Methyl-1,5-hexadiene (0)
4-Vinylcyclohexene	Ethylcyclohexane (2)
	4-Ethylcyclohexene (97)
	Vinylcyclohexane (1)
	4-Vinylcyclohexene (0)
Isoprene	2-Methylbutene (4)
	Methylbutenes (91)
	Isoprene (5)
1,3-Cyclohexadiene[b]	Cyclohexane (2)
	Cyclohexene (89)
	1,3-Cyclohexadiene (0)
	Benzene (9)
5-Methylenenorbornene	Methylnorbornanes (1)
	Methylnorbornenes (2)
	2-Methylenenorbornane (96)
	5-Methylenenorbornene (1)
endo-Dicyclopentadiene (2)	Tricyclodecane (2)
	Dihydro (3) (>97)
	Other dihydro (<1)
	Dicyclopentadiene (0)
1-Penten-3-ol[c]	*n*-Pentane (0)
	3-Pentanol (100%)
1-Vinylcyclohexanol[c]	Ethylcyclohexane (0)
	1-Ethylcyclohexanol (100)
3-Methyl-1-pentyn-3-ol[d]	3-Methylpentane (0)
	3-Methyl-3-pentanol (100)
1-Ethynylcyclohexanol[d]	Ethylcyclohexane (0)
	1-Ethylcyclohexanol (100)

[a] Hydrogenation of 40.0 mmol of substrate (40.0 mmol of each in mixtures) over 5.0 mmol of P-2 nickel in 95% ethanol at 25°, 1 atm; 40 ± 0.8 mmol of hydrogen used. [b] 32.0 mmol of hydrogen. [c] Hydrogen uptake 40.0 mmol. [d] Hydrogen uptake 80.0 mmol.

tion without hydrogenolysis. Future studies will examine these uses individually in detail. The ease of preparation, high selectivity, nonpyrophoric nature, and reproducibility of P-2 nickel make it a potentially powerful new synthetic tool.

Experimental Section

Apparatus.—The all-glass automatic borohydride hydrogenator described in early studies[8] was employed throughout this work.[24] The reactor flask was agitated with a 1.5 × 0.375 in. TFE-covered magnetic stirring bar; the drive magnet was powered by a motor supplied with a 0–145-V continuously variable power source. Under reaction load speeds of at least 11,000 rpm were obtained, as monitored with a stroboscopic tachometer. Speed variations during runs were less than 500 rpm. The reactor was generally a 125-ml modified erlenmeyer flask but special cylindrical flasks of 150-ml capacity with antivortex indentations were employed for faster runs. The reactor was immersed in a water bath maintained at 25 ± 1°. Reaction rates were shown to be independent of stirring rate at the speeds employed.

Reagents.—Nickelous acetate [$Ni(C_2H_3O_2)_2 \cdot 4H_2O$] was obtained from J. T. Baker (Baker A. R. grade).

Sodium borohydride, 98% dry solid, was produced and supplied by Ventron Corp. A stabilized solution suitable for catalyst reduction is prepared by dissolving 4.0 g of sodium borohydride powder in a mixture of 95 ml of absolute ethanol and 5 ml of 2 *N* sodium hydroxide and filtering the resulting solution. This solution is best prepared freshly the day of use for maximum catalyst reproducibility but may be utilized satisfactorily for up to 5 days if kept refrigerated. Formation of small amounts of sediment under refrigeration is not harmful.

Organic substrates were obtained from Phillips Petroleum Co. or Chemical Samples Co. and were distilled under nitrogen before use. If a substrate was colored or had a refractive index significantly varied from published values (American Petroleum Institute), it was fractionally distilled from $LiAlH_4$ or $NaBH_4$. Purified samples were stored at 0° under nitrogen.

Catalyst Preparation and Use.—Nickel acetate tetrahydrate (1.24 g, 5.0 mmol) was dissolved in (50 − *n*) ml (*n* = volume of substrate to be added) of 95% ethanol in a 125-ml erlenmeyer flask (modified for high-speed magnetic stirring). This flask was attached to a borohydride hydrogenator, which was then flushed with nitrogen. With vigorous stirring, 5.0 ml of 1.0 *M* sodium borohydride solution in ethanol (see above) was injected over 15 sec. When gas evolution from the mixture ceased, the catalyst was ready for use. The hydrogenator was purged with hydrogen, and reaction was initiated by injecting substrate. Addition of solid substrates was accomplished with the stirrer stopped just before purging with hydrogen. When two compounds were run, they were either injected as a mixture or else stirring was stopped momentarily while the two were added in rapid succession.

Catalyst for 1.25-mmol runs was prepared *in situ* on 1/4 scale; alcohol was then added to maintain a total volume of 50 ml.

Samples were withdrawn from the reactor with a syringe and stainless steel needle. Sampling did not affect reaction reproducibility.

Analysis.—Samples were analyzed by glpc and compared with known materials. In general, total hydrogen uptake was within ±2% of theoretical; certain runs were also checked with internal standards, confirming quantitative yields (*i.e.*, no substrate polymerization).

Columns made from the following materials proved exceptionally useful in analyzing various olefin and hydrocarbon mixtures: adiponitrile, triethylene glycol–silver nitrate, tris(cyanoethoxy)propane, UCON 50 HB 2000, and squalene.

5,6-Dihydro-*endo*-dicyclopentadiene (3).—Dicyclopentadiene (Matheson Coleman and Bell) was chilled until the major portion had solidified. The material was filtered and the solid was pressed on a Buchner funnel with dental dam to remove as much liquid as possible. The solid was warmed just to melt, and the process was repeated. The resulting solid had mp 28–30° (lit.[25,26] mp 27–28°).

In a 2-l. flask, 37.5 g (150 mmol) of nickel acetate tetrahydrate was dissolved in 200 ml of 95% ethanol. The flask was attached to a Brown□ hydrogenator and flushed with hydrogen. With rapid stirring 150 ml of 1.0 *M* sodium borohydride solution in ethanol was added to reduce the nickel acetate to P-2 nickel. The purified *endo*-dicyclopentadiene (407 g, 3.08 mol) was melted with 200 ml of ethanol and the mixture was injected into the hydrogenator. With vigorous stirring, the reaction proceeded smoothly; hydrogen uptake ceased when 3.08 mol of hydrogen had been absorbed.

Five grams of activated carbon was added to the reaction mixture to aid in catalyst removal and the warm (40°) mixture was filtered through a thin (0.125 in.) pad of carbon on a Buchner funnel. The filter pad was washed with 2 × 100 ml of warm

(24) A commercial model was obtained from Delmar Scientific Laboratories, Maywood, Ill.

(25) H. Staudinger and A. Rheiver, *Helv. Chim. Acta*, **7**, 23 (1924).

(26) C. E. Waring, E. E. Kern, and W. A. Blann, *J. Amer. Chem. Soc.*, **63**, 1767 (1941).

acetone. The combined organic layers were distilled to remove solvent. The residue was distilled through a short Vigreux column to give 370 g, 2.76 mol (90%), of 5,6-dihydro-*endo*-dicyclopentadiene (3), bp 178–180°, mp 48–50°. Recrystallization from methanol gave mp 50° (lit.[27] mp 48.5–50°); nmr (CCl_4, TMS) δ 1.25 (s, 3.8 H), 1.45 (s, 2.2 H), 2.0–3.2 (m, broad, 6.2 H), 5.70 (s, broad, 2.0 H). Product was free from starting material by glpc.

(27) K. Alder and G. Stein, *Justus Liebigs Ann., Chem.*, **485**, 241 (1931).

Registry No.—Nickelous acetate, 373-02-4; sodium borohydride, 16940-66-2.

Acknowledgment.—Financial assistance by the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the DuPont Young Faculty Grant, administered by the Cornell Chemistry Department, are gratefully acknowledged.

Studies on Heterocage Compounds. V.[1] Reaction of 5-Hydroxymethyl-2-norbornene with Dihalocarbene. Novel Synthesis of Some Oxa-Modified Adamantane Analogs

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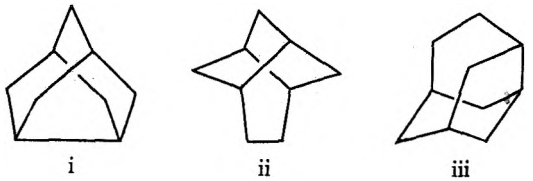
Reaction of *endo*-5-hydroxymethyl-2-norbornene (1) with dichloro- and dibromocarbene afforded oxahomobrendene derivatives, 3-chloro- (2) and 3-bromo-5-oxatricyclo[5.2.1.$0^{4,8}$]dec-2-ene (10), in good yields. Catalytic hydrogenation of 2 and 10 gave 5-oxahomobrendane (6). The Birch reduction of 2 afforded *endo*-6-hydroxymethylbicyclo[3.2.1]oct-2-ene (7), which was shown to be an excellent precursor to 5-oxaprotoadamantane (12) and its 10-acetoxy derivative (13). The mechanism for the reaction of 1 with dihalocarbene was discussed from the product distributions under various conditions.

Much attention has been paid recently to adamantane and its related cage compounds since the discovery of an efficient synthetic route to the adamantyl ring system by Schleyer and Donaldson, and the subsequent findings of the biological activities of a number of compounds with these ring systems.[2] However, studies on the heteroanalogs of the related cage compounds seem to be not extensively investigated compared to the carbocyclic analogs; this might be due to the lack of a very efficient synthetic route to heteroanalogs such as carbonium ion rearrangements.[3] In a continuation of our studies on heterocage compounds,[4] this paper describes a novel and facile synthetic route to 5-oxahomobrendane and 5-oxaprotoadamantane.

endo-6-Substituted bicyclo[3.2.1]octane is involved as the characteristic skeletal moiety in some of the representative modified adamantane skeletons such as noradamantane (i), twistane (ii), and protoadamantane (iii).



i ii iii

On the other hand, dihalocarbene addition to norbornene is known to afford bicyclo[3.2.1]octane derivatives.[5] Furthermore, dihalocarbene in a surfactant-catalyzed emulsion has been found recently to react with substrates very effectively.[6-8] Taking into consideration these facts, we employed readily accessible *endo*-5-hydroxymethyl-2-norbornene (1) as one of the most promising starting materials for synthesis of some oxa-modified adamantane analogs and examined the reactions of 1 with dihalocarbene.

Results and Discussion

Reaction of *endo*-5-Hydroxymethyl-2-norbornene (1) with Dichlorocarbene.—Dichlorocarbene addition to 1[9] in 50% aqueous sodium hydroxide–benzene emulsion catalyzed with benzyltriethylammonium chloride at 20° afforded a mixture of 3-chloro-5-oxatricyclo-[5.2.1.$0^{4,8}$]dec-2-ene (2), 3,3,6-trichlorotricyclo[3.3.-1.$0^{2,4}$]nonane (3), 3,4,6-trichlorobicyclo[3.3.1]non-2-ene (4), and 3,3,7,8-tetrachlorotricyclo[4.3.1.$0^{2,4}$]dec-8-ene (5) (Table I, Scheme I). Both 3 and 5 were isolated by chromatography on basic alumina in 8.4 and 3.2% yields, respectively. Oily products 2 and 4 were purified on preparative glpc. Structural assignment of these products was based on the analytical and physical data, and some chemical conversions. The major product 2 had a formula $C_9H_{11}OCl$ from analysis and characteristic mass spectrum, *m/e* 170 (M^+) and 172 (M + 2) in 3:1 ratio. In the nmr ($CDCl_3$) spectrum, 2 had signals at τ 3.87 (d, 1, $J_{1,2}$ = 7.5 Hz, H_2), 5.58 (d, 1, $J_{4,8}$ = 6.5 Hz, H_4), 5.89 (t, 1, $J_{6,6}$ = $J_{6,7}$ = 8.8 Hz,

(1) Part IV of this series: T. Sasaki, S. Eguchi, T. Kiriyama, and Y. Sakito, *J. Org. Chem.*, **38**, 1648 (1973).

(2) For recent reviews, see (a) R. D. Bingham and P. v. R. Schleyer, "Chemistry of Adamantane," Springer-Verlag, New York, New York, N. Y., 1971; (b) P. v. R. Schleyer, *Fortschr. Chem. Forsch.*, **18**, 1 (1971); (c) Z. Weidenhoffer and S. Hala, *Sb. Vys. Sk. Chem.-Technol. Praze, Technol. Paliv*, **22**, 5 (1971).

(3) For a recent review on heteroadamantane, see G. Gelbard, *Ann. Chim. (Paris)*, 331 (1969).

(4) For example, see (a) T. Sasaki, S. Eguchi, and T. Kiriyama, *J. Amer. Chem. Soc.*, **91**, 212 (1969); (b) T. Sasaki, S. Eguchi, and T. Kiriyama, *Tetrahedron*, **27**, 893 (1971).

(5) C. W. Jefford, S. Mahajan, J. Weslyn, and B. Waegell, *J. Amer. Chem. Soc.*, **87**, 2183 (1965), and references cited therein.

(6) For addition reactions of carbene to olefin, see (a) M. Makosza and M. Warzyniez, *Tetrahedron Lett.*, 4659 (1969); (b) M. Makosza and E. Biskecka, *ibid.*, 4517 (1971).

(7) (a) For insertion reaction of dihalocarbene, see I. Tabushi, Z. Yoshida, and N. Takahashi, *J. Amer. Chem. Soc.*, **92**, 6670 (1970); (b) for reaction of alcohol with dichlorocarbene, see I. Tabushi, Z. Yoshida, and N. Takahashi, *ibid.*, **93**, 1820 (1971).

(8) For the reaction site and the reaction mechanism, see (a) C. M. Starks, *J. Amer. Chem. Soc.*, **93**, 195 (1971); (b) G. C. Joshi, N. Singh, and L. M. Pande, *Tetrahedron Lett.*, 1461 (1972); (c) A. W. Herriott and D. Picker, *ibid.*, 4521 (1972).

(9) An exo–endo mixture (1:4) was used as a practical starting material because a 1:19 mixture gave a similar result (see Table I).

SCHEME I

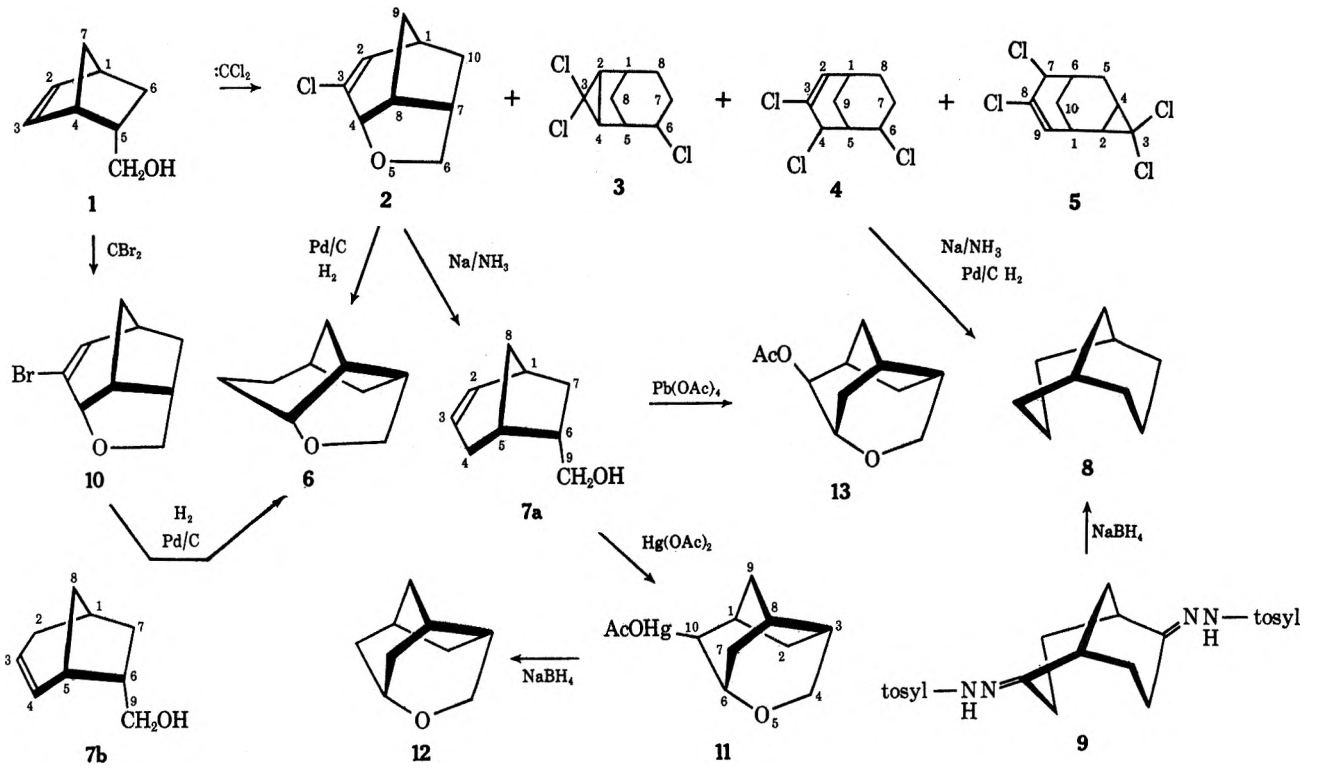


TABLE I

PRODUCT DISTRIBUTION RATIO AT 20°

Alkali metal	Total yield, %	Relative product ratio (on glpc), % 2	3	4	5	Unidentified
NaOH	40[a]	62	21	6	8	Trace
KOH	80[a]	81	9	6	4	Trace
KOH	*b*	67	15	14	4	Trace
KOH	*c*	19	7	26	5	43

[a] An exo–endo mixture (1:4) was used in 50-mmol scale; see ref 9. [b] An exo–endo mixture (1:19) was used in 1-mmol scale. [c] An exo–endo mixture (15:6) was used in 1-mmol scale.

H_{6x}), 6.68 (d of d, 1, $J_{6,6} = 8.8$, $J_{6,7} = 3.8$ Hz, H_{6n}), 7.00–7.70 (m, 3, H_1, H_7, and H_8), and 7.83–8.90 (m, 4, 2 H_9 and 2 H_{10}). The appearance of only one vinyl proton signal as well as an ir (neat) absorption at 1635 cm^{-1} supported the assigned structure. The coupling constants of H_2, H_4, H_{6x}, and H_{6n} were in good accordance with those predicted from the Karplus equation[10] and dihedral angles on a Dreiding stereomodel. The observed values were inconsistent with the predicted coupling constants for another possible structure of 3-chloro-5-oxatricyclo[5.3.0.$0^{4,9}$]dec-2-ene. Catalytic hydrogenation (Pd/C) of **2** in the presence of sodium hydroxide afforded 5-oxatricyclo[5.2.1.$0^{4,8}$]decane (**6**) (5-oxahomobrendane)[11] in 74% yield, which had a mass spectral molecular ion peak at *m/e* 138 (M^+), and nmr signals at τ 5.87 (d, 1, $J_{4,8} = 7.5$ Hz, H_4), 6.41 (s with small split, 2, 2 H_6), 7.50 (m, 2, H_7 and H_8), and 7.8–9.1 (m, 9, other protons). The Birch reduction of **2** with sodium metal in liquid ammonia afforded *endo*-6-hydroxymethylbicyclo[3.2.1]oct-2-ene (**7a**) in 89% yield, which revealed ir (neat) absorptions at 3400 and 1638 cm^{-1} and a molecular ion peak at *m/e* 138 in the mass spectrum. In the nmr ($CDCl_3$) spectrum, **7a** had signals at τ 4.23 and 4.68 (m, each 1, H_3 and H_2), 6.52 (d, 2, J = 6.2 Hz, CH_2OH), 6.98 (s, 1, OH, disappeared on shaking with D_2O), and 7.40–9.33 (m, 9, other ring protons). The position of the double bond in **7a** was supported by the similarity of the relative europium shift values obtained for H_2 and H_3 (Table II): the *S* values

TABLE II

EUROPIUM SHIFT VALUES OF **7** IN $CDCl_3$

Obsd τ	Obsd S	Obsd S/S_{H_9}	Calcd **7a** S/S_{H_9}	Calcd **7b** S/S_{H_9}
4.68	5.2	0.297	0.231 (H_2)	0.247 (H_3)
4.23	5.3	0.303	0.298 (H_3)	0.458 (H_4)
6.52 (H_9)	17.5			

and their ratios to that of H_9 were quite close for both vinyl protons, indicating that the distances between these hydrogens and the complexed europium atom are similar. A study on a Dreiding stereomodel revealed clearly that the assigned structure **7a** is favored over another possible structure **7b**; the estimated relative shift values of the vinyl protons against H_9 by using Cockerill and Rackham's method are also very close for **7a** but not for **7b**.[12,13] All of these conversions of **2** and transannular cyclization of **7a** described below supported the assigned structure of **2**.

The mass spectrum of the second product **3** showed characteristic ion peaks due to the presence of three chlorine atoms at *m/e* (rel intensity) 224 (100), 226 (96), 228 (36), and 230 (4), and analysis indicated a formula $C_9H_{11}Cl_3$. In the nmr spectrum, a multiplet at τ 5.90 (H_6) and a broad singlet at τ 7.40 (H_5), as well as a multiplet at τ 7.55–9.30 (9 H, other protons), were observed but no vinyl proton signals. Taking into consideration

(10) M. J. Karplus, *J. Chem. Phys.*, **30**, 11 (1959).
(11) We prefer this trivial name for **6** in this paper.
(12) A. F. Cockerill and D. M. Rackham, *Tetrahedron Lett.*, 5149 (1970).
(13) For more detailed discussion on paramagnetic shift reagents, see J. K. M. Sanders, S. W. Hanson, and D. H. Williams, *J. Amer. Chem. Soc.*, **94**, 5325 (1972), and references cited therein.

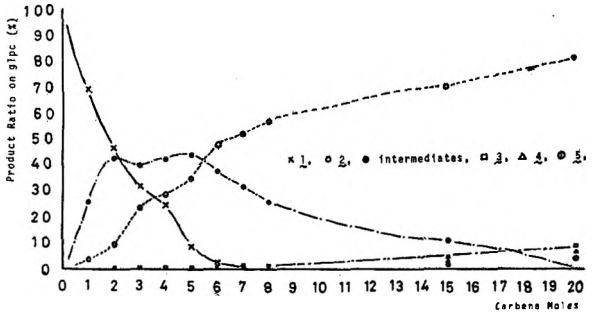


Figure 1.—Change of product distribution by molar ratio of carbene in 50% aqueous KOH–benzene emulsion at 20°.

that 2 mol of dichlorocarbene were trapped by both olefin and hydroxy group in **1**, we assigned **3** as 3,3,6-trichlorotricyclo[3.3.1.$0^{2,4}$]nonane.[14]

Compound **4** was an isomer of **3** from analysis and mass spectrum, but an ir absorption at 1640 cm^{-1} and nmr signals at τ 3.94 and 4.14 for one proton (d, J = 7.8 Hz) suggested the presence of an olefinic moiety in **4**.[15] The Birch reduction of **4**, followed by catalytic hydrogenation (Pd/C) afforded known bicyclo[3.3.1]-nonane (**8**).[16] Hence, **4** was determined as 3,4,6-trichlorobicyclo[3.3.1]non-2-ene, a doubly ring expanded product.

Compound **5** had a formula $C_{10}H_{10}Cl$ from analysis and characteristic mass spectral ion peaks, m/e (rel intensity) 270 (100), 272 (145), 274 (70), 276 (18), 278 (1). The presence of an olefinic moiety was supported by an ir (KBr) absorption at 1641 cm^{-1} and nmr signals at τ 3.85 (d, 1, $J_{1,9}$ = 6.5 Hz, H_9) and 5.82 (s, 1, H_7), which allowed us to assign **5** as 3,3,7,8-tetrachlorotricyclo[4.3.1.$0^{2,4}$]dec-8-ene.

The Carbene Addition Reactions under Various Conditions and Reaction Mechanisms Thereof.—A change of alkali metal from sodium to potassium in aqueous medium improved the overall yield of the adducts and also the relative yield of **2**. Dichlorocarbene generated in the emulsion of 50% aqueous potassium hydroxide and benzene afforded 64.8% of **2**, 7.2% of **3**, 4.8% of **4**, and 3.2% of **5** (Table I). A large excess amount of dichlorocarbene (20-mol excess) was required in order to obtain a better yield of **2**. The reaction with several moles of excess dichlorocarbene resulted only in the formation of the formyl derivative of **1**, which showed a strong ir absorption at 1725 cm^{-1}. The change of the product distribution was followed on glpc by using various molar ratios of dichlorocarbene (Figure 1). The starting material **1** did not disappear for longer reaction time despite the consumption of excess dichlorocarbene; the major product **2** increased very slowly as the intermediate decreased.

The temperature effect on the product distribution was examined at 0, 20, and 60° by using 20 mol of excess dichlorocarbene (Table III). Obviously a considerable temperature effect was observed. Interestingly, the formation of a transannular cyclized product **2** decreased and the formation of the ring-

TABLE III
TEMPERATURE EFFECT (REACTIONS OF 20 EXCESS MOL OF CARBENE IN 50% AQUEOUS KOH–BENZENE EMULSION)

	Yield, %			
Temp, °C	2	3	4	5
0	75	10	8	6
20	81	9	6	4
60	24	30	22	6

expanded products **3** and **4** increased at 60°. On the basis of these observations, dichlorocarbene addition to **1** could be explained by the reaction mechanism illustrated in Scheme II. The long life of **1** may demonstrate the predominant role of a cycling sequence of the reactions, in which an electrophilic attack of CCl_2 on the hydroxy group affords a dichloromethyl ether b *via* an ylide intermediate a, and b can be hydrolyzed to **1** *via* a formate derivative c. On the other hand, the Wagner–Meerwein rearrangement of b followed by a nucleophilic attack of chloride anion leads to **3** with additional equimolar dichlorocarbene. The major product **2** is formed from dichlorocyclopropane derivatives d and f *via* their thermally allowed disrotatory ring openings (e)[17] accompanied by an intramolecular nucleophilic cyclization. The disrotatory ring opening of dichlorocyclopropyl formate intermediate f can afford **4** and **5** *via* h and i followed by the Wagner–Meerwein rearrangement and nucleophilic substitution or elimination as depicted in Scheme II.

Reaction of 1 with Dibromocarbene.—Dibromocarbene addition to **1** in the emulsion of 50% aqueous potassium hydroxide–benzene afforded 3-bromo-5-oxatricyclo[5.2.1.$0^{4,8}$]dec-2-ene (**10**) as a major product. Compound **10** had characteristic mass spectral ion peaks at m/e (rel intensity) 214 (M^+, 100) and 216 (M + 2, 98), and an ir (neat) absorption at 1620 cm^{-1}; its nmr spectrum was very similar to that of **2**. Catalytic hydrogenation (Pd/C) in methanolic sodium hydroxide afforded **6** quantitatively, supporting the assigned structure (Scheme I).

Transannular Cyclizations of 7a.—Compound **7a**, obtained from **2** by the Birch reduction, has a suitable alignment of double bond and hydroxy group for a transannular cyclization. Treatment of **7a** with mercuric acetate in a buffered solution of sodium acetate afforded a mercuric acetate derivative **11** which, on reduction with sodium borohydride, gave 5-oxaprotoadamantane (**12**) in 83% yield. The assigned structure was evidenced by analytical and spectral data. The more symmetrical structure of **12** compared to **6** was reflected in the higher melting point of **12** (175–178°) compared with **6** (92–96°) and also in the nmr spectrum ($CDCl_3$) in which bridgehead methine protons such as H_1,H_3, and H_8 appeared at τ 7.25–8.00 and bridge methylene protons such as H_2, H_7, H_9, and H_{10} at τ 8.00–8.90, similar to those of adamantane,[2] while in the nmr spectrum of **6**, methine and methylene protons appeared in more complex patterns as described above.

Treatment of **7a** with lead tetraacetate afforded also a cyclized product **13** which was characterized as 10-acetoxy-5-oxaprotoadamantane on the basis of analysis and spectral data (Scheme I).

In summary, 5-oxahomobrendane (**6**) and 5-oxaprotoadamantane (**12**) were obtained in good yields from

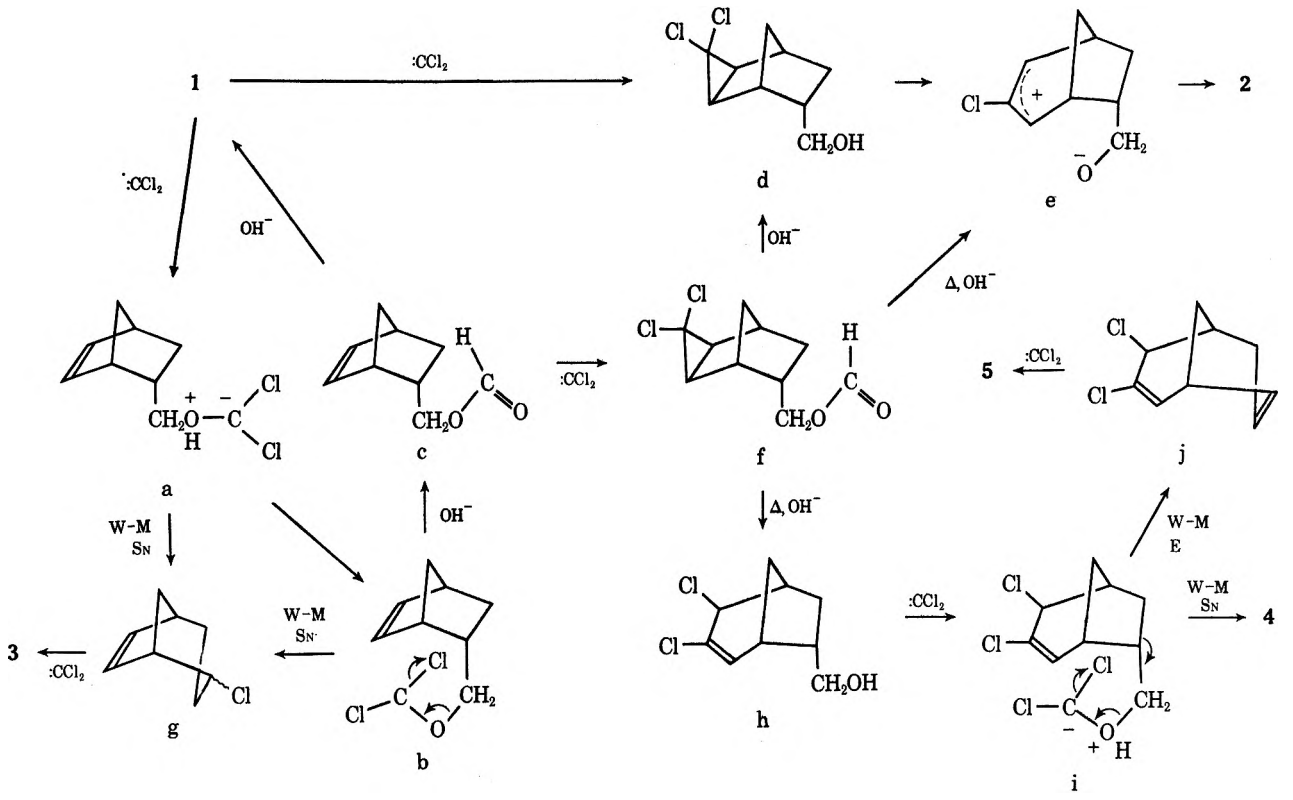
(14) The stereochemistry of dichlorocyclopropane and C_6Cl is uncertain. *Cf.* R. C. De Selms and C. M. Combs, *J. Org. Chem.*, **28**, 2206 (1963).

(15) The appearance of one vinyl proton at τ 3.94 and 4.14 indicates that this product is a 3.5:1 mixture of 6- and 8-chloro isomers. The unsymmetrical peak of **4** on glpc analysis indicates also the presence of isomers.

(16) E. N. Marvell, R. S. Knutson, T. McEwen, D. Sturmer, W. Federici, and K. Salisbury, *J. Org. Chem.*, **35**, 391 (1970).

(17) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).

SCHEME II



readily available *endo*-5-hydroxymethyl-2-norbornene (1) *via* dihalocarbene addition and successive reductions. This synthetic route might be useful for some other heteromodified adamantane analogs.

Experimental Section[18]

Dichlorocarbene Addition Reaction to *endo*-5-Hydroxymethyl-2-norbornene (1). A.—In a 1-l., three-necked flask fitted with a dropping funnel and a mechanical stirrer, a mixture of 50% (w/w) aqueous sodium hydroxide (500 g), benzene (40 ml), benzyltriethylammonium chloride (500 mg, 2.2 mmol), and 1[9] (6.2 g, 50 mmol) was vigorously stirred at 20°. While the stirring was continued, chloroform (80 ml, 1.0 mol) was added slowly to the mixture for 10 hr. After the addition was completed, the mixture was stirred for a further 10 hr. The mixture was diluted with water (1.5 l.) and filtered on a Buchner funnel. The filtrate was extracted with chloroform (3 × 50 ml). The combined extracts were dried on anhydrous sodium sulfate and evaporated to give a dark brownish oil (8.45 g). A short-path chromatography on basic alumina eluting with methylene chloride afforded a mixture of products as an oil (3.41 g) which revealed four peaks on glpc analysis (Table I). Further purification on an alumina column eluting with *n*-hexane–benzene gave 3,3,6-trichlorotricyclo[3.3.1.$0^{2,4}$]nonane (**3**) as the first fraction, which crystallized on standing: mp 55–57°; ir (KBr) 800, 790, and 740 cm^{-1}.

Anal. Calcd for $C_9H_{11}Cl_3$: C, 47.93; H, 4.92. Found: C, 47.89; H, 4.96.

The second fraction gave a mixture of oily product and crystalline product, from which **3,3,7,8-tetrachlorotricyclo[4.3.1.$0^{2,4}$]-dec-8-ene (5)** was obtained, after washing with methanol, as colorless crystals: mp 157–159°; ir (KBr) 3050, 1641, 784, 768, and 716 cm^{-1}; nmr ($CDCl_3$) τ 3.85 (d, 1, H_9), 5.82 (s, 1, H_7), 7.12 (m, 1, H_1), and 7.50–9.0 (m, 7, other protons).

Anal. Calcd for $C_{10}H_{10}Cl_4$: C, 44.16; H, 3.70. Found C, 44.20; H, 3.64.

The third fraction gave **3-chloro-5-oxatricyclo[5.2.1.$0^{4,8}$]dec-2-ene (2)**. An analytical sample was purified by preparative glpc (30% silicone SE-30 on 45/60 mesh Chromosorb W at 180°): $n^{19.0}D$ 1.5366; ir (neat) 1635, 755, and 738 cm^{-1}.

Anal. Calcd for $C_9H_{11}OCl$: C, 63.35; H, 6.50. Found: C, 63.36; H, 6.49.

Purification of the oily portion of the second fraction by preparative glpc afforded **3,4,6-trichlorobicyclo[3.3.1]non-2-ene (4)** as a colorless oil: $n^{22.5}D$ 1.5574; ir (neat) 1640, 770, 760, and 745 cm^{-1}; mass spectrum *m/e* (rel intensity) 224 (M^+, 100), 226 (M + 2, 95), 228 (M + 4, 30), and 230 (M + 6, 5); nmr ($CDCl_3$) τ 3.94 and 4.14 (each d, 1, J = 7.8 Hz, ratio 3.5:1, C=CH), 5.68–6.22 (m, 2, H_4 and H_6), 7.00–7.50 (m, 2, H_1 and H_5), and 7.50–8.85 (m, 6, remaining protons).

Anal. Calcd for $C_9H_{11}Cl_3$: C, 47.93; H, 4.92. Found: C, 47.84; H, 4.91.

B.—Dichlorocarbene addition reaction in 50% potassium hydroxide was carried out similarly as above. Purification of crude product (6.83 g) gave 2–5 (Table I).

The reaction at 0° was carried out similarly by using a mixture of 50% potassium hydroxide (40 g), *n*-hexane (2.5 ml), benzene (2.5 ml), benzyltriethylammonium chloride (50 mg, 0.22 mmol), and 1 (0.12 g, 1.0 mmol). To the vigorously stirred mixture was added chloroform (2.4 g, 20 mmol) in 2 hr at 0°. The work-up gave 155 mg of crude product which was analyzed on glpc (Table III).

The reaction at 60° was carried out similarly but by using benzene (5 ml) instead of *n*-hexane–benzene in a flask fitted with a reflux condenser. Work-up gave crude product (190 mg) which was analyzed on glpc (Table III).

***endo*-6-Hydroxymethylbicyclo[3.2.1]oct-2-ene (7a).**—In a three-necked flask fitted with a sealed mechanical stirrer, a drying tube (soda lime), and a gas inlet was introduced anhydrous liquid ammonia (*ca.* 100 ml) at −78° under nitrogen. Clean metallic sodium (1.5 g, 65 g-atoms) was added into the flask with stirring. To the resulting dark blue solution was added 2 (500 mg, 2.94 mmol) in ethanol (1 ml) dropwise with stirring. After the stirring was continued for 4 hr at −78° and for 1 hr at −40°, ethanol was added at −78° until the color disappeared. The mixture was allowed to warm gradually to room temperature after further addition of ethanol (30 ml). The residual mixture was diluted with water (100 ml) and extracted with chloroform (3 × 50 ml). The combined extracts were dried (Na_2SO_4) and evaporated to

(18) Ir spectra were recorded on a JASCO IRA-1 grating infrared spectrophotometer. Nmr spectra were taken with a JEOL-C-60HL spectrometer using TMS as the internal standard at 60 MHz, and mass spectra with a JEOL-01SG spectrometer at 75 eV. Melting points were determined on a Yanagimoto hot-stage type melting point apparatus and are corrected. Microanalyses were performed with a Perkin-Elmer 240 elemental analyzer. Glpc analyses were performed with a NEVA gas chromatograph Model 1400 and preparative glpc with a Varian Aerograph Model 700.

afford 7a as an oil (360 mg, 89%). An analytical sample was obtained after chromatography on a silica gel column eluting with chloroform as a colorless oil, $n^{20}D$ 1.5163.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.27; H, 10.15.

5-Oxahomobrendane (6).—Catalytic hydrogenation of 2 (1.70 g, 10.0 mmol) with 5% Pd/C (1.7 g) in 4% (w/v) methanolic sodium hydroxide solution (50 ml) at room temperature and under atmospheric pressure afforded a colorless oil (1.02 g, 74%) after work-up as usual. Sublimation of the oil at 80° gave 6 as colorless crystals: mp 92–96° (sealed tube); ir (KBr) 2925, 1456, 1085, 1056, 1038, and 1017 cm^{-1}.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.40; H, 10.02.

Conversion of 4 to Bicyclo[3.3.1]nonane (8).—To a mixture of liquid ammonia (50 ml) and sodium metal (1.0 g, 43 g-atoms) was added an ethanol (0.1 ml) solution of 4 (0.30 g, 1.3 mmol). After the mixture was stirred for 8 hr at −78° and ammonia was removed, the work-up afforded a colorless syrup (40 mg) which revealed ir absorption at 1638 cm^{-1} ($CHCl_3$). Catalytic hydrogenation of this syrup with 5% Pd/C (50 mg) in ethanol afforded 8 as a major product on glpc analysis. An authentic sample of 8[16] prepared from $NaBH_4$ reduction of bicyclo[3.3.1]nonane-2,6-dione bistosylhydrazone (9)[19] had the same retention time on two different columns (10% silicone SE-30 on Chromosorb W and 10% Apiezon on Chromosorb W).

3-Bromo-5-oxatricyclo[5.2.1.0^{4,8}]dec-2-ene (10).—To a vigorously stirred mixture of 50% potassium hydroxide (500 g), benzene (30 ml), benzyltriethylammonium chloride (500 mg, 2.2 mmol), and 1 (2.4 g, 20 mmol) was added bromoform (101 g, 0.40 mol) in 10 hr at 20°. After stirring was continued for a further 12 hr, work-up as above gave a dark brownish oil (4.13 g) which was purified on an alumina column eluting with methylene chloride to give an oily mixture (2.25 g) of 10 (relative yield 58%, total yield 31%) and five other minor products (*ca.* 42%) on glpc analysis. Further purification of this oil on an alumina column eluting with *n*-hexane–benzene afforded 10 as a colorless oil (865 mg, 20%): $n^{28.5}D$ 1.5552; ir (neat) 2930, 2855, 1620, 1032, 796, 765, and 692 cm^{-1}; nmr (CCl_4) τ 3.65 (d, 1, $J_{1,2}$ = 7.3 Hz, H_2), 5.53 (d, 1, $J_{4,8}$ = 6.6 Hz, H_4), 5.91 (t, 1, $J_{5,6}$ = $J_{6,7}$ = 8.8 Hz, H_{6x}), 6.70 (d of d, 1, $J_{6,6}$ = 8.8, $J_{6,7}$ = 3.8 Hz, H_{6n}), 7.00–7.72 (m, 3, H_1, H_7, and H_8), and 7.75–8.80 (m, 4, 2 H_9 and 2 H_{10}).

Anal. Calcd for $C_9H_{11}OBr$: C, 50.26; H, 5.15. Found: C, 50.41; H, 5.00.

On catalytic hydrogenation with 5% Pd/C in methanolic sodium hydroxide solution at room temperature and under atmospheric pressure, 10 afforded 6 (97%).

5-Oxaprotoadamantane (12).—To a solution of mercuric acetate (1.152 g, 3.61 mmol) and sodium acetate (295 mg, 0.360 mmol) in water (10 ml) was added a solution of 7a (414 mg, 3.00 mmol) in methanol (1.5 ml). After the mixture was stirred for 1 hr at room temperature, the mixture was diluted with water (30 ml) and extracted with chloroform (3 × 10 ml). The combined extracts were dried (Na_2SO_4) and evaporated to afford an oily product (11) (1.20 g, 100%), which was treated with sodium borohydride (150 mg, 3.95 mmol) in 3.4% aqueous sodium hydroxide (24 ml) for 6 hr at room temperature. Work-up in the usual way afforded 12 as crystals which were sublimed at 120° (25 mm) to give analytically pure 12 (355 mg, 83%): mp 175–178° (sealed tube); ir (KBr) 2925, 1184, and 1092 cm^{-1}.

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.36; H, 10.06.

10-Acetoxy-5-oxaprotoadamantane (13).—A mixture of 7a (138 mg, 1.00 mmol) and lead tetraacetate (886 mg, 2.00 mmol) in chloroform (40 ml) was refluxed for 1 day. The cooled mixture was washed with 5% aqueous sodium hydroxide (2 × 10 ml) and water (10 ml) successively. The dried (Na_2SO_4) organic layer was evaporated to give 13 as an oil (175 mg, 89%). An analytical sample was obtained by preparative tlc (silica gel, 50% benzene–methylene chloride) as an oil: $n^{23.5}D$ 1.5035; ir (neat) 2940, 1730, 1240, and 1195 cm^{-1}; mass spectrum *m/e* 196 (M^+); nmr ($CDCl_3$) τ 5.24 (m, 1, H_{10}), 5.77–6.47 (m, 3, $2H_4$ and H_6), 7.17–9.06 (m, 9, other ring protons), and 7.95 (s, 3, $COCH_3$).

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.31; H, 8.23.

Registry No.—*endo*-1, 15507-06-9; *exo*-1, 13360-81-1; 2, 39833-55-1; 3, 39833-56-2; 4, 39833-57-3; 5, 39833-58-4; 6, 39837-56-4; 7a, 39837-57-5; 10, 39837-58-6; 11, 39837-59-7; 12, 39837-60-0; 13, 39837-61-1; dichlorocarbene, 1605-72-7; dibromocarbene, 4371-77-1.

(19) H. Musso and U. Biethan, *Chem. Ber.*, **100**, 119 (1967).

Notes

Chemistry of Heterocyclic Compounds. 8. A One-Step Synthesis of 2-Hydroxy-4*H*-quinolizin-4-ones[1]

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In connection with a current project related to construction of heteromacrocycles, we needed large quantities of substituted ethyl 2-pyridylacetates. The simplest preparation of ethyl 2-pyridylacetate is the condensation[2] of 2-picolyllithium with diethyl carbonate under very mild conditions.[3] After prolonged extraction with petroleum ether (bp 30–60°), the major side product, 1,3-di(2-pyridyl)acetone, was recovered in trace amounts, as indicated by analysis of its dipicrate.[2]

Repetition of this procedure is easily accomplished. However, in an initial attempt to isolate increased yields of 1 and 5, during the work-up procedure the strongly alkaline aqueous solution was neutralized to a pH of 7.5–8 by addition of dilute hydrochloric acid; extraction with chloroform afforded additional quantities of 1 and 5, as well as the previously undetected 1-carboethoxy-2-hydroxy-3-(2-pyridyl)-4*H*-quinolizin-4-one (4). Structural assignment[4] of 4 was based

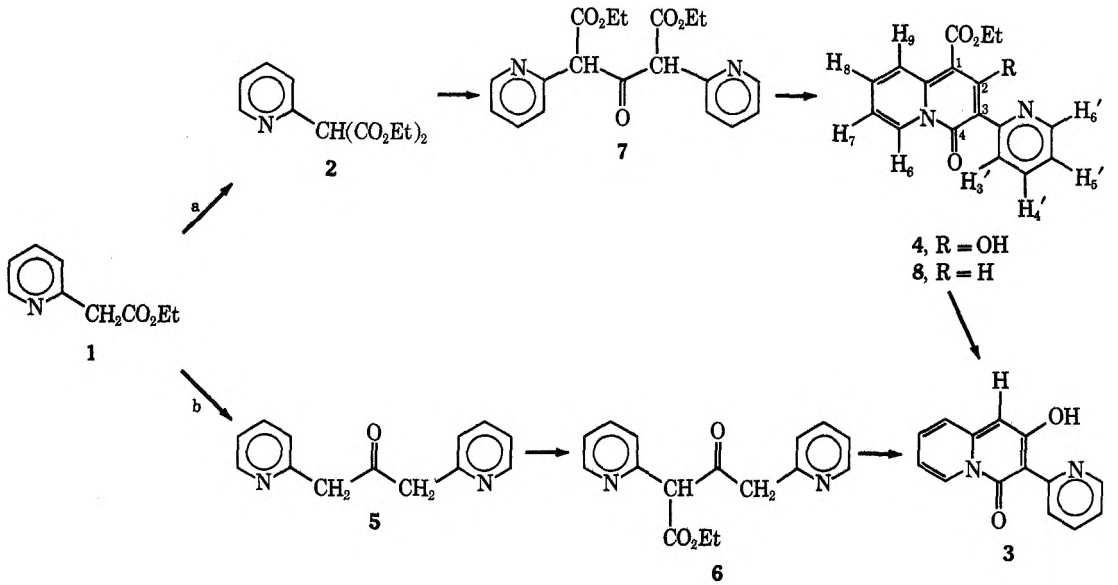
(1) (a) This research has been supported by Public Health Service Grant No. 5-RO1-MS-09930 from the National Institute of Neurological Diseases and Stroke, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the Research Corporation. (b) Presented in part at the 28th Southwest Regional Meeting of the American Chemical Society, Baton Rouge, La., Dec 1972.

(2) N. N. Goldberg, B. M. Perfetti, and R. Levine, *J. Amer. Chem. Soc.*, **75**, 3843 (1953).

(3) Alternate routes are known; see references in ref 2, as well as K. Winterfeld and K. Flick, *Arch. Pharm. (Weinheim)*, 448 (1956), and K. Winterfeld and K. Nonn, *Pharmazie*, **29**, 337 (1965).

(4) The infrared spectral data of related compounds have been previously assigned.

SCHEME I



upon degradation[5] to 2-hydroxy-3-(2-pyridyl)-4*H*-quinolizin-4-one (**3**)[6] and upon nmr analysis. The nmr spectral comparison of **3** and **4** is particularly important in establishing the structure **4**. In **3** and **4**, the most downfield absorptions at δ 18.3 and 19.75, respectively, indicate the presence of a hydroxyl group proton that is strongly hydrogen bonded to the pyridyl ring nitrogen atom. Occurrence of the unusually low-field resonance at δ 9.34 and 9.29 for the pyridyl H-3′ proton in **3** and **4** is possible only if the pyridyl ring exists in a planar conformation with the quinolizinone ring; thus proton H-3′ is subjected to the close proximity of the C-4 carbonyl function. The signals at δ 9.00 and 9.11 in **3** and **4**, respectively, are assigned to H-6.[7] The low-field position is attributed to a combination of a long-range deshielding peri effect due to the C-4 carbonyl function and an α effect of the amido nitrogen atom. In **4**, the H-9 proton experiences a similar peri effect from the C-1 carboethoxy group; however, in **3**, the absence of this long-range interaction causes the H-9 resonance to shift upfield by ~0.5 ppm. The remaining chemical shifts and coupling constants are in excellent accord with the assigned structures.

Self-condensation of ethyl 2-pyridylacetate (**1**) has been demonstrated[6,8] to afford **3** *via* the pathway **1** → **6** → **3**. Similarly, the preparation of 1-carboethoxy-3-(2-pyridyl)-4*H*-quinolizin-4-one (**8**) has been accomplished utilizing ethyl orthoformate as the source of the C-3 ring atom.[9] Unexpected formation of the major isolated quinolizinone **4**, which possesses both the 1-carboethoxy group and functionality in the 2 position, has been envisaged as proceeding through two possible routes (Scheme I). Alterations in reaction conditions permit the distinction between the two routes. More vigorous conditions result in (a) isolation of the intermediate diethyl 2-pyridylmalonate (**2**) along with **4**, and (b) the absence of detectable quantities of ketone **5**, which by further carboethoxylation and subsequent cyclization would generate **3**. These results suggest that the formation of quinolizinone **4** involves carboethoxylation of **1** and then nucleophilic substitution by the carbanion of **1** or **2** forming **7**, which cyclizes to give **4** (route a). The alternative of further carboethoxylation of **6** to give **7** was deemed unlikely under the reaction conditions.

Isolation of **4** is uncomplicated since the major impurities are easily removed by distillation. No attempt has been made to optimize the reaction conditions.

Experimental Section[10]

Ethyl 2-pyridylacetate was prepared by the method of Goldberg, *et al.*,[2] from 2-picolyllithium and diethyl carbonate. Work-up procedure deviated slightly from the literature procedure. The reaction mixture was poured into 200 g of ice water and extracted with several 200-ml portions of ether. The combined ethereal phases were dried with anhydrous magnesium sulfate, concentrated *in vacuo* to remove starting 2-picoline, and distilled to afford 13.4 g (41%) of ethyl 2-pyridylacetate: bp 110–116° (6 mm) [lit.[2] bp 110–113° (6 mm)]; ir (Nujol) 1738 (C=O), 1597, 1160 (CO), 1036 cm^{-1}; nmr ($CDCl_3$) δ 1.23 ($-CH_2CH_3$, t, J = 7 Hz), 3.83 ($-CH_2CO$, s), 4.17 ($-CH_2CH_3$, q, J = 7 Hz), 7.0–7.8 (pyr H, m), and 8.45–8.65 (6-pyr H, m). The residue chromatographed on silica gel G [cyclohexane–ethyl acetate (1:1)] affording an additional 459 mg of ethyl 2-pyridylacetate and 3.0 g (7.1%) of di-2-picolyl ketone: bp 170–180° (0.7 mm) [lit.[4] bp 130–135° (0.05 mm)]; picrate (recrystallized with ethanol) mp 210° (lit.[11] mp 191–191.5°).

Anal. Calcd for dipicrate ($C_{25}H_{18}N_8O_{15}$): C, 44.78; H, 2.71; N, 16.72. Found: C, 44.98; H, 2.62; N, 16.77.

The aqueous layer was then adjusted with dilute acid to pH 7.5–8 and extracted with chloroform. Chromatography of the dried (magnesium sulfate) chloroform extract gave 100 mg of

(5) T. Kappe, *Monatsh. Chem.*, **98**, 874 (1967).

(6) K. Winterfeld, W. Zengerling, and M. Rink, *Justus Liebigs Ann. Chem.*, **597**, 104 (1955).

(7) K. T. Potts and M. Sorm, *J. Org. Chem.*, **36**, 8 (1971).

(8) K. Winterfeld, G. Wald, and M. Rink, *Justus Liebigs Ann. Chem.*, **588**, 125 (1955).

(9) (a) G. R. Clemo, W. M. Morgan, and R. Raper, *J. Chem. Soc.*, 1025 (1936); (b) N. J. Leonard and R. E. Beyler, *J. Amer. Chem. Soc.*, **70**, 2298 (1948); (c) *ibid.*, **72**, 1316 (1950); (d) S. I. Goldberg and A. H. Lipkin, *J. Org. Chem.*, **37**, 1823 (1972).

(10) Melting points were recorded in sealed capillary tubes on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were determined on a Perkin-Elmer 621 spectrophotometer. Nmr spectra were determined on either a Varian Associates Model HA-100 or Perkin-Elmer Model R12-B spectrometers; chemical shifts are given in parts per million relative to TMS as an internal standard. Analyses were performed by Mr. R. Seab in these laboratories.

(11) R. Bodalski, J. Michalski, and B. Mlotkowska, *Rocz. Chem., Ann. Soc. Chim. Polonorum*, **43**, 677 (1969); *Chem. Abstr.*, **71**, 61159w (1969).

ethyl 2-pyridylacetate, 1.11 g of di-2-picolyl ketone, and 24 mg of 1-carboethoxy-2-hydroxy-3-(2-pyridyl)-4*H*-quinolizin-4-one (**4**): mp 166–167°; nmr[12] ($CDCl_3$) δ 1.44 (t, J = 7 Hz, $-CH_2CH_3$), 4.47 (q, J = 7 Hz, $-CH_2CH_3$), 6.82 (ddd, J = 7.5, 6.5, 1.5 Hz, H_7), 7.22 (ddd, J = 7.5, 6.5, 1.2 Hz, H_5'), 7.37 (ddd, J = 9.2, 6.5, 1.4 Hz, H_8), 7.71 (ddd, J = 9.2, 1.5, 0.9 Hz, H_9), 7.92 (ddd, J = 8.6, 7.5, 1.9 Hz, H_4'), 8.29 (ddd, J = 5.3, 1.9, 1.0 Hz, H_6'), 9.11 (ddd, J = 7.5, 1.4, 0.9 Hz, H_6), 9.29 (ddd, J = 8.6, 1.2, 1.0 Hz, H_3'), and 19.75 (broad s, –OH); ir (Nujol) 1700 (ester), 1652, 1630, 1602, 1557, and 1231 cm^{-1}; mass spectrum m/e 310 (M^+), 309, 264 ($M^+ - C_2H_6O$), 237 ($M^+ - C_3H_5O_2$), 181, 146, 91, 78 (C_5H_4N).

Anal. Calcd for $C_{17}H_{14}N_2O_4$: C, 65.78; H, 4.55; N, 9.03. Found: C, 65.56; H, 4.46; N, 8.99.

Reaction of 2-Picolyllithium with Diethyl Carbonate. 1-Carboethoxy-2-hydroxy-3-(2-pyridyl)-4*H*-quinolizin-4-one (4).—To a solution of phenyllithium (Alfa Chemical Co., 0.6 mol, 2.2 *M* in benzene–ether) in 500 ml of ether, 2-picoline (bp 128–129°, 56 g, 0.6 mol) was added over a 10-min period. The solution was refluxed for 30 min, and then diethyl carbonate (47 g, 0.4 mol) in 50 ml of ether was added rapidly. Reflux was maintained for an additional 30 min. The mixture was cooled, poured into ice water, adjusted with acid to pH ~8, and extracted with chloroform. After removal of the solvents, as well as unreacted 2-picoline, the residue was fractionally distilled, affording 2.0 g of ethyl 2-pyridylacetate, bp 110–113° (6 mm).

The distillation residue (11.7 g) was chromatographed, affording 917 mg of ethyl 2-pyridylacetate, 6.0 g (14%) of **4** (mp 166–167°), and 150 mg (1%) of 3-hydroxy-3-(2-pyridyl)-4*H*-quinolizin-4-one (**3**): mp 175–177° (lit.[6] mp 181–182°); nmr ($CDCl_3$) δ 6.30 (d, J = 0.75 Hz, H_1), 6.73 (five lines), 7.21 (ddd, J = 6.0, 5.0, 1.0 Hz, H_5'), 7.21 (m, H_8 and H_9), 7.89 (ddd, J = 8.5, 6.0, 1.0 Hz, H_4'), 8.36 (ddd, J = 5.0, 1.9, 1.0 Hz, H_6'), 9.00 (broad d, H_6), 9.34 (ddd, J = 8.5, 1.0, 1.0 Hz, H_3'), and 18.3 (broad s, –OH); ir (Nujol) 3500–3100 (broad, OH), 1667, 1641, 1613, and 1589 cm^{-1}.

2-Hydroxy-3-(2-pyridyl)-4*H*-quinolizin-4-one (3).—The ester **4** (1.00 g, 3.22 mmol) suspended in 100 ml of a 5% sodium hydroxide solution was refluxed for 8 hr. After cooling to ambient temperature, the pH was adjusted to 7.5–8. The solution was extracted with chloroform, dried with anhydrous sodium sulfate, and concentrated *in vacuo*, affording 630 mg (82%) of 2-hydroxy-3-(2-pyridyl)-4*H*-quinolizin-4-one, mp 174.5–176°. Recrystallization from ethanol gave a sample of pure **3**, mp 176.5–178°.

Reaction of 2-Picoline with Diethyl Carbonate and Sodium Hydride.—Sodium hydride (50% dispersion, 2.15 g, 0.05 mol) in 1,2-dimethoxyethane (DME, 25 ml) was stirred under nitrogen with addition of a solution of 2-picoline (4.65 g, 0.05 mol), diethyl carbonate (11.8 g, 1.10 mol), and DME (20 ml). After the mixture was refluxed for 8 hr, it was poured into ice water. The pH of the aqueous layer was adjusted with dilute acid to 7.5–8 and the layer was extracted with chloroform. The extract was dried with sodium sulfate and concentrated *in vacuo*, removing all solvents and unreacted starting materials. Chromatography of the remaining yellow oil afforded 322 mg (2.7%) of diethyl 2-pyridylmalonate: bp 130–132° (1 mm); nmr ($CDCl_3$) δ 1.21 ($-CH_2CH_3$, t, J = 7 Hz), 4.22 ($-CH_2CH_3$, q, J = 7 Hz), 5.04 (CHCO, s), 7.05–7.88 (pyr H, m), and 8.44–8.65 (6-pyr H, m).

Anal. Calcd for $C_{12}H_{15}NO_4$: C, 60.76; H, 6.38. Found: C, 61.06; H, 6.40.

Further elution afforded 1.099 g (13.3%) of ethyl 2-pyridylacetate [bp 110–117° (6 mm)], 131 mg (1.7%) of 1-carboethoxy-2-hydroxy-3-(2-pyridyl)-4*H*-quinolizin-4-one (**4**, mp 166–168°), and only traces of **3**.

Registry No.—**2**, 39541-69-0; **3**, 39541-70-3; **4**, 39541-71-4; **5** dipicrate, 39541-72-5; 2-picolyllithium, 39541-73-6; diethyl carbonate, 105-58-8; 2-picoline, 109-06-8; sodium hydride, 7646-69-7.

(12) The nmr spectrum of **4** 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. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-2234.

Unambiguous Synthesis of a Monocyclic 5,6-Dihydro-1,2-oxazine[1]

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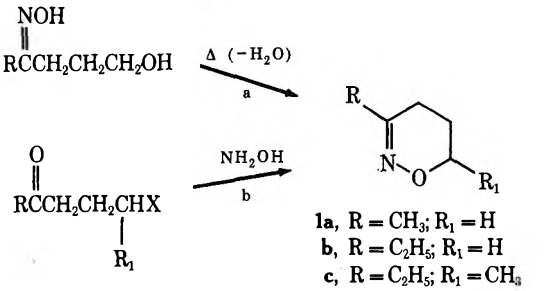
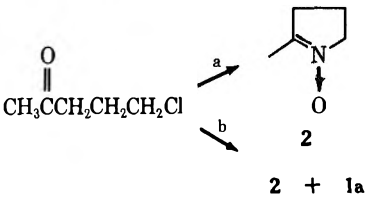
Recent review articles[2] to the contrary, considerable ambiguity exists regarding the published procedures[3,4] for the synthesis of monocyclic 4*H*-5,6-dihydro-1,2-oxazines. Neither Marshall and Perkin's cyclodehydration of a γ-hydroxy oxime (eq 1, path a) nor Wohlgemuth's oximation of a γ-halo ketone unequivocally produces the desired oxazine (eq 1, path b).[5,6]



(1)

Utilizing the procedure of Wohlgemuth,[4] 5-chloro-2-pentanone was treated with hydroxylamine hydrochloride–potassium carbonate in the molar ratio 1.0:1.1:0.5 (eq 2, path a). A compound, **2**, was obtained which analyzed for C_5H_9NO and which possessed all the physical properties previously described.[6] If this were 3-methyl-4*H*-5,6-dihydro-1,2-oxazine (**1a**), it would not be expected to show any significant uv absorption above 220 nm.[8] However, a maximum was observed at 227 nm (ϵ 8700). This, together with the ir data presented in Table I, led us to assign the structure 2-methylpyrroline 1-oxide (**2**) to this material.



(2)

(1) Work done at Seton Hall University, South Orange, N. J. 07079.

(2) (a) R. L. McKee in "Heterocyclic Compounds," Vol. 17, A. Weissberger, Ed., Interscience, New York, N. Y., 1962, p 329; (b) N. H. Cromwell in "Heterocyclic Compounds," Vol. 6, R. E. Elderfield, Ed., Wiley, New York, N. Y., 1957, p 559.

(3) J. R. Marshall and W. H. Perkin, *J. Chem. Soc.*, 861 (1891).

(4) H. Wohlgemuth, *Ann. Chim. (Paris)*, **2**, 403 (1914).

(5) Attempts to reproduce Marshall and Perkin's work have met with conflicting results.[7] Our own attempts to prepare **1a** by the author's procedure were unsuccessful.

(6) Wohlgemuth reported only that the compounds obtained were "water soluble, reduced ammoniacal silver nitrate in the cold and Fehling's solution when boiled."[4]

(7) (a) H. E. Glynn and W. H. Linnell, *Quart J. Pharmacol.*, **5**, 496 (1932); (b) M. Carmack, O. H. Bullitt, Jr., G. R. Handrick, L. W. Kissinger, and I. Von, *J. Amer. Chem. Soc.*, **68**, 1220 (1946).

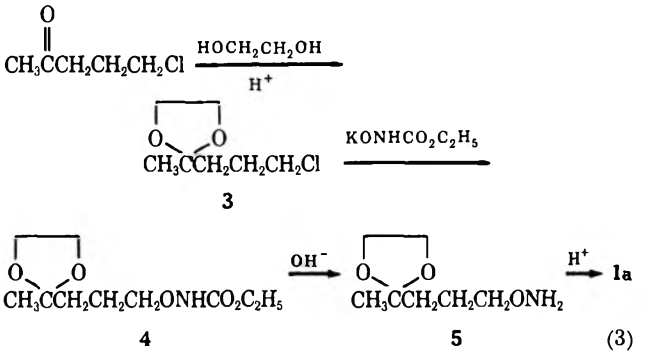
(8) C. N. R. Rao, "Ultraviolet and Visible Spectroscopy," Butterworths, London, 1961, pp 31–32.

TABLE I
UV AND IR SPECTRA OF PYRROLINE 1-OXIDES

Pyrroline 1-oxide	λ_{max}^{EtOH}, nm	ϵ_{max}	$\nu_{C=N}$, cm^{-1}	Ref
2,3,3-Trimethyl-	229	9000	1613 (s)	*a*
2,4,4-Trimethyl-	229	9120	1610 (s)	*b*, *c*
2	227	8700	1610 (s)	*d*

[a] R. Bonnett, S. C. Ho, and J. A. Raleigh, *Can. J. Chem.*, **43**, 2717 (1965). [b] R. Bonnett, R. F. C. Brown, U. M. Clark, and I. O. Sutherland, *J. Chem. Soc.*, 2094 (1959). [c] R. F. C. Brown, U. M. Clark, and A. Todd, *Proc. Chem. Soc.*, 97 (1957). [d] This work.

Repetition of the oximation with a molar ratio of ketone:hydroxylamine hydrochloride:potassium carbonate of 1.0:1.1:1.0 (eq 2, path b) gave a mixture of the previously obtained **2** together with a more volatile compound in a 1.0:1.4 ratio. This new (volatile) compound, although isomeric with **2**, exhibited no uv absorption above 220 nm. The ir spectrum displayed a medium-intensity band at 1620 cm^{-1} and a series of intense bands between 800 and 1010 cm^{-1}. The nmr consisted of a two-proton triplet at τ 6.11 and a three-proton singlet at τ 8.10 in the midst of a four-proton complex multiplet, τ 7.60–8.37. Based on this spectral data the structure **1a** was assigned to this compound. Further confirmation was obtained by a synthetic sequence which employed a preformed –NOC– linkage as outlined in eq 3.



(3)

The material obtained from this route was identical in every respect with the more volatile component from the oximation (eq 2, path b) of 5-chloro-2-pentanone. As far as we can ascertain from the literature, this represents the first unambiguous synthesis of a monocyclic 4*H*-5,6-dihydro-1,2-oxazine.

Experimental Section[9]

Oximation of 5-Chloro-2-pentanone (Eq 2, Path a).—Following the method of Wohlgemuth[4] a solution of 1.21 g (0.010 mol) of 5-chloro-2-pentanone, 0.77 g (0.011 mol) of hydroxylamine hydrochloride, 0.76 g (0.0055 mol) of potassium carbonate, 25 ml of 95% ethanol, and 25 ml of water was refluxed for 45 min. The reaction mixture (which had an approximate pH of 3, pHydrion paper) was cooled, concentrated under reduced pressure, saturated with sodium chloride, and extracted five times with 40-ml portions of methylene chloride. The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated *in vacuo* to leave 0.70 g of a clear liquid. Distillation through a short-path distillation apparatus gave 0.51 g of a colorless liquid (water soluble), bp 71–72° (0.4 mm), $n^{25}D$ 1.5129. On the basis of elemental analysis and ir, uv, and nmr spectral data this material was assigned the structure 2-methylpyrroline 1-oxide (**2**), rather than the expected, isomeric 3-methyl-4*H*-5,6-dihydro-1,2-oxazine (**1a**): ir (neat) 1610 (s), 1265 (s), 1228 cm^{-1} (vs); uv λ_{max}^{EtOH} 227 nm (ϵ 8700); nmr ($CDCl_3$) τ 5.98 (t, 2, J = 8.0 Hz, 5-CH_2), 7.18 (t, 2, J = 7.1 Hz, 3-CH_2), 7.97 (s, 3, 2-CH_3) in midst of complex multiplet, 7.60–8.02 (4-CH_2); mass spectrum (77.5 eV) *m/e* (rel intensity) 99 (58), 98 (16), 84 (3), 83 (2), 69 (6), 55 (10), 41 (100).

Anal. Calcd for C_5H_9NO: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.50; H, 9.30; N, 13.95.

The picrate was prepared in 95% ethanol and washed with several portions of ether, mp 73–74°.

Anal. Calcd for $C_{11}H_{12}N_4O_8$: C, 40.25; H, 3.68; N, 17.07. Found: C, 40.07; H, 3.39; N, 16.95.

Oximation of 5-Chloro-2-pentanone (Eq 2, Path b).—A solution of 1.54 g (0.22 mol) of hydroxylamine hydrochloride and 3.04 g (0.022 mol) of potassium carbonate in 25 ml of water was added to 2.42 g (0.020 mol) of 5-chloro-2-pentanone in 25 ml of 95% ethanol and the resulting mixture was refluxed for 3 hr. The solution was cooled and worked up as before to leave 2.33 g of a colorless liquid. The ir spectrum of this crude material exhibited bands at 1610 cm^{-1} (vs) and a series of five bands of medium intensity between 835 and 1050 cm^{-1}. Distillation through a short-path distillation apparatus yielded two products.

The more volatile component, bp 32–33° (0.4 mm), $n^{25}D$ 1.4607, weighed 0.45 g and was assigned the structure 3-methyl-4*H*-5,6-dihydro-1,2-oxazine (**1a**): ir (neat) 1620 (m), 1050 (s), 1010 (s), 950 (s), 900 (s), 840 (s), 655 cm^{-1} (s); uv featureless above 220 nm; nmr ($CDCl_3$) τ 6.11 (t, 2, J = 5.0 Hz, 6-CH_2), 8.10 (s, 3, 3-CH_3) in midst of complex multiplet, 7.60–8.37 (4, 4-CH_2, 5-CH_2); mass spectrum (77.5 eV) *m/e* (rel intensity) 99 (93), 98 (3), 85 (4), 84 (7), 73 (42), 71 (9), 69 (18), 68 (57), 56 (15), 55 (10), 54 (13), 43 (10), 42 (67), 41 (100).

Anal. Calcd for C_5H_9NO: C, 60.58; H, 9.15; N, 14.13. Found: C, 60.43; H, 9.15; N, 14.25.

The hydrochloride prepared in ether had mp 130–131°.

Anal. Calcd for $C_5H_{10}ClNO$: C, 44.27; H, 7.44; Cl, 10.33. Found: C, 44.29; H, 7.44; Cl, 10.21.

The picrate was prepared in 95% ethanol, mp 108–109°.

Anal. Calcd for $C_{11}H_{12}N_4O_8$: C, 40.25; H, 3.68; N, 17.07. Found: C, 40.44; H, 3.87; N, 17.03.

The second component, 0.33 g of a colorless liquid, bp 72–73° (0.4 mm), was identical in all respects (refractive index and ir, uv, and nmr spectra) to the 2-methylpyrroline 1-oxide previously obtained by path a.

3-Methyl-4*H*-5,6-dihydro-1,2-oxazine (*via* Eq 3). 2-(3-Chloropropyl)-2-methyl-1,3-dioxolane (3).—A mixture of 23 ml of ethylene glycol, 24.2 g (0.2 mol) of 5-chloro-2-pentanone, 0.3 g of *p*-toluenesulfonic acid, and 500 ml of dry benzene was refluxed for 10 hr while the water produced was separated with a Dean–Stark trap. The benzene was removed *in vacuo* and the residue was taken up with chloroform and carefully basified with sodium methoxide. After washing one time with 5% sodium bicarbonate solution and one time with water, the organic layer was dried ($MgSO_4$), filtered, and evaporated under reduced pressure to remove most of the solvent. Distillation through a 15-cm vacuum-jacketed Vigreux column gave 27.0 g (82.5%) of **3**, bp 111–113° (40 mm) [(lit.[10] bp 84–86° (14 mm)].

2-(3-Ethoxycarbonylaminooxypropyl)-2-methyl-1,3-dioxolane (4).—A mixture of 17.7 g (0.10 mol) of **3**, 10.7 g (0.12 mol) of hydroxyurethane,[11] 7.8 g (0.12 mol) of potassium hydroxide (85%), and 30 ml of absolute ethanol was refluxed with stirring for 6.5 hr. After cooling, the reaction mixture was washed onto a filter funnel with ether; the inorganic residue was washed six times with 50-ml portions of ether. The combined filtrates were dried ($MgSO_4$), filtered, and concentrated under reduced pressure to leave 22.15 g of a viscous oil. Distillation through an 8-cm vacuum-jacketed Vigreux column gave 7.10 g of unreacted **3** and 7.70 g (58.3% based on consumed starting material) of **4**: bp 128–130° (0.4 mm); ir (neat) 3280 (m), 2980 (m), 1740 (s), 1480 (m), 1450 (m), 1380 (m), 1250 (s), 1120 (s), 1070 (s), 950 cm^{-1} (m).

Anal. Calcd for $C_{10}H_{19}NO_5$: C, 51.47; H, 8.20; N, 6.03. Found: C, 51.55; H, 8.15; N, 6.20.

(9) Boiling and melting points are uncorrected. Microanalyses were performed by Bernhardt Microanalytisches Laboratorium, Mulheim, Germany. Infrared spectra were recorded on a Beckman IR-10 spectrophotometer, nmr spectra on a Varian A-60A spectrometer, and uv spectra on a Beckman DB spectrophotometer. The mass spectra were recorded on a Consolidated Electrodynamics 21-130 mass spectrometer using a heated inlet system operating at 135°; the energy of the electron beam was 77.5 eV.

(10) C. A. Grob and R. Moesch, *Helv. Chim. Acta*, **42**, 728 (1959).

(11) R. T. Major, F. Dursch, and H. J. Hess, *J. Org. Chem.*, **24**, 431 (1959).

2-(3-Aminooxypropyl)-2-methyl-1,3-dioxolane (5).—A solution of 7.90 g (0.14 mol) of potassium hydroxide in 50 ml of water was added to 7.70 g (0.035 mol) of **4** and the solution was refluxed for 1 hr. After cooling, the reaction mixture was saturated with sodium chloride and extracted five times with 75-ml portions of ether. The combined organic extracts were dried ($MgSO_4$) and filtered and the solvent was removed under reduced pressure. Distillation of the residual liquid through an 8-cm vacuum-jacketed Vigreux column gave 3.58 g (74.3%) of **5**: bp 67–69° (0.5 mm); ir (neat) 3490 (w), 3320 (m), 3230 (w), 3160 (w), 1380 (s), 1255 (s), 1220 (s), 1065 cm^{-1} (vs); nmr ($CDCl_3$) τ 4.55 (br, 2, NH_2), 6.06 (s, 4, OCH_2CH_2O), 6.34 (t, 2, J = 6.0 Hz, CH_2ONH_2), 8.13–8.45 (m, 4, $CH_2CH_2CH_2ONH_2$), 8.70 (s, 3, CH_3).

Anal. Calcd for $C_7H_{15}NO_3$: C, 52.13; H, 9.37; N, 8.72. Found: C, 52.20; H, 9.35; N, 8.60.

Cyclization of Alkoxyamine 5 to 3-Methyl-4*H*-5,6-dihydro-1,2-oxazine (1a).—A solution of 3.50 g (0.23 mol) of **5** in 40 ml of ether was acidified with 10 ml of 3 *N* hydrochloric acid and stirred at room temperature for 30 min. Following removal of the ether under reduced pressure, the aqueous layer was basified with sodium bicarbonate and extracted three times with 75-ml portions of methylene chloride. The combined organic extracts were dried ($MgSO_4$), filtered, and evaporated *in vacuo* to leave 2.43 g of a colorless liquid. Distillation through a short-path distillation apparatus gave 1.25 g (56.5%) of **1a**, bp 32–34° (0.4 mm). This material was identical in every respect with the lower boiling component isolated from the oximation of 5-chloro-2-pentanone with an excess amount of base (eq 2, path b).

The hydrochloride was prepared in ether, mp 130–131° (mixture melting point with the hydrochloride of the previously isolated 3-methyloxazine showed no depression, mp 130–131°).

Registry No.—**1a**, 39703-76-9; **1a** hydrochloride, 39703-77-0; **1a** picrate, 39703-78-1; **2**, 6931-10-8; **2** picrate, 13742-66-0; **3**, 5978-08-5; **4**, 39703-82-7; **5**, 39703-83-8; 5-chloro-2-pentanone, 5891-21-4; hydroxylamine hydrochloride, 5470-11-1; potassium carbonate, 584-08-7; hydroxyurethane, 589-41-3; potassium hydroxide, 1310-58-3.

Pteridines. XXVII. A New Synthetic Route to Pteridines and 7-Azapteridines[1a]

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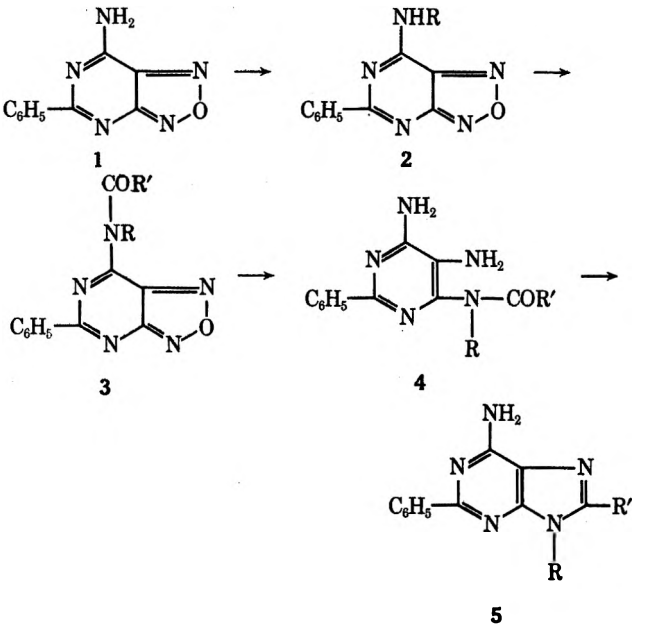
Recent investigations in this laboratory have shown that 7-aminofurazano[3,4-*d*]pyrimidines, prepared by lead tetraacetate oxidation of 4,6-diamino-5-nitrosopyrimidines, are useful, versatile intermediates for the unequivocal preparation of 2-, 8-, and 9-substituted adenines.[2] The sequence of reactions involved consists of introduction of the eventual adenine 9 and 8 substituents by reaction of the 7-aminofurazano-[3,4-*d*]pyrimidine with an alkylamine, followed by acylation; reductive fission of the furazan ring then gives an intermediate 5-amino-6-acylaminopyrimidine which spontaneously cyclizes to the desired adenine. These reactions are summarized in Scheme I.

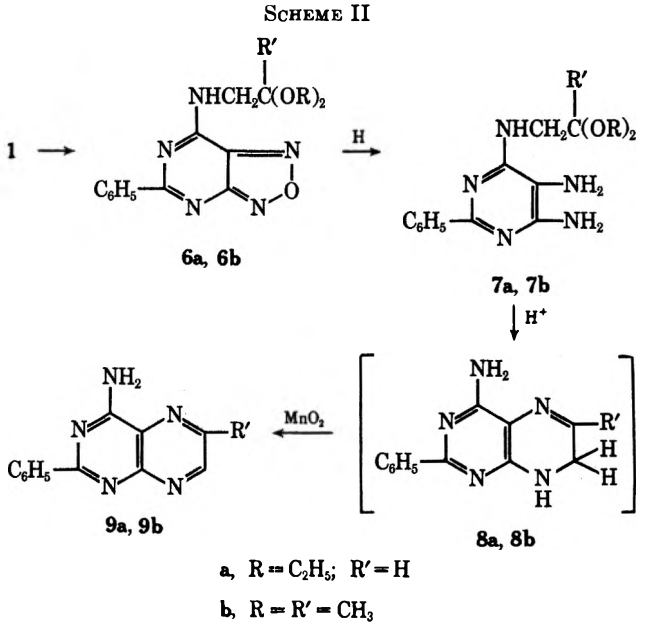
SCHEME I



It occurred to us that displacement of the 7-amino grouping by nucleophiles possessing a carbonyl functionality capable of cyclization with the 5-aminopyrimidine grouping released in the reductive fission of the furazan ring would allow the preparation of other fused pyrimidine systems, with the nature of the second fused ring dependent upon the structure of the initial nucleophile. This note describes the successful application of this concept to the preparation of pteridines and 7-azapteridines.

The conversion of 5-phenyl-7-aminofurazano[3,4-*d*]-pyrimidine (**1**) to pteridines was achieved as follows. The reaction of **1** with aminoacetaldehyde diethyl acetal took place readily at room temperature to give the 7-substituted aminofurazano[3,4-*d*]pyrimidine **6a** in 94% yield (see Scheme II). This latter compound was

SCHEME II



then subjected to catalytic reduction under neutral conditions to give the triaminopyrimidine **7a**. Treat-

(1) (a) For the previous paper in this series, see E. C. Taylor, M. J. Thompson, K. L. Perlman, R. Mengel, and W. Pfleiderer, *J. Org. Chem.*, **36**, 4012 (1971); (b) NIH Predoctoral Fellow, 1969–1972; (c) Gifu College of Pharmacy, Gifu, Japan; (d) NSF Predoctoral Fellow, 1968–1971.

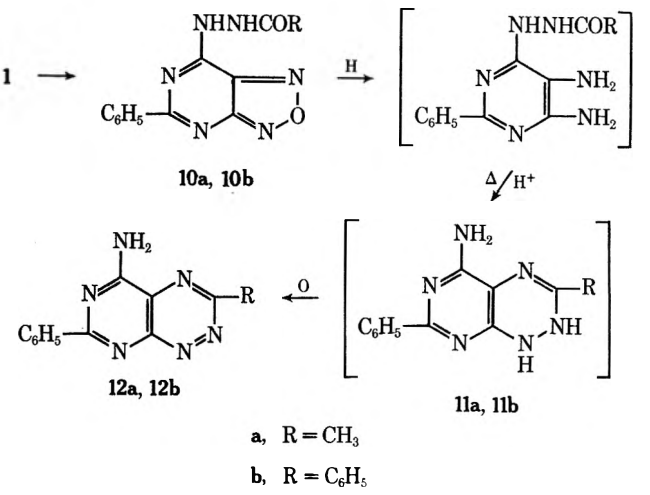
(2) E. C. Taylor, G. P. Beardsley, and Y. Maki, *J. Org. Chem.*, **36**, 3211 (1971).

ment of this latter intermediate with acid resulted in cleavage of the acetal protecting group; spontaneous cyclization then led to the dihydropteridine **8a**, which was not isolated but was oxidized *in situ* with manganese dioxide to give 2-phenyl-4-aminopteridine (**9a**). Obviously, the use of appropriately substituted α-aminocarbonyl components should lead through an analogous sequence of reactions to pteridines substituted selectively at position 6 or 7, or to 6,7-disubstituted derivatives carrying the same or different substituents. The deficiencies of classical pteridine syntheses for the unequivocal preparation of such compounds have been discussed previously.[1a,3]

To illustrate the potential utility of the furazanopyrimidine route to the preparation of 6-substituted pteridines, 2-phenyl-4-amino-6-methylpteridine (**9b**) was prepared by reaction of **1** with aminoacetone dimethyl acetal to give the intermediate 7-substituted aminofurazano[3,4-*d*]pyrimidine **6b**, which was reduced, and the resulting triaminopyrimidine was then treated with acid. Cyclization, followed by manganese dioxide oxidation as in the example described above, led to 2-phenyl-4-amino-6-methylpteridine (**9b**) in an overall yield of 60%. This new approach to the unequivocal synthesis of 6-substituted pteridines should be capable of considerable extension. It should be noted that intermediates analogous to **7** and **8** are also encountered in the classical pteridine synthesis which involves the reaction of a 5-nitro- or 5-arylazo-6-chloropyrimidine with an α-aminocarbonyl compound, followed by reductive cyclization to a 7,8-dihydropteridine and final oxidation.[4] The pteridine synthesis herein described provides an alternate route to the key intermediate **7** and may prove to be more flexible in view of the ready availability of the requisite furazano[3,4-*d*]pyrimidine precursors (**1**).[2]

7-Azapteridines were readily prepared from 5-phenyl-7-aminofurazano[3,4-*d*]pyrimidine (**1**) by utilization of acid hydrazides as the attacking nucleophile, followed by an analogous sequence of reduction and subsequent ring-closure reactions. For example, the reaction of **1** with acethydrazide at room temperature gave 5-phenyl-7-acetylhydrazinofurazano[3,4-*d*]-pyrimidine (**10a**) in 63% yield. Catalytic reduction followed by acid-catalyzed cyclization and final oxidation of the initially formed dihydro-7-azapteridine **11a** with isoamyl nitrite gave 5-amino-3-methyl-7-phenylpyrimido[5,4-*e*]-*as*-triazine (2-phenyl-4-amino-6-methyl-7-azapteridine) (**12a**) in 53% overall yield from **10a** without isolation of any intermediates. Similarly, acid-catalyzed reaction of **1** with benzhydrazide gave the intermediate benzoylhydrazinofurazano[3,4-*d*]pyrimidine **10b** which, when subjected to an analogous sequence of reactions, gave 5-amino-3,7-diphenylpyrimido[5,4-*e*]-*as*-triazine (**12b**) in 80% overall yield. Once again, it would appear that this latter sequence of reactions constitutes a general synthetic route to 6-substituted 7-azapteridines (Scheme III).

SCHEME III



a, $R = CH_3$

b, $R = C_6H_5$

Experimental Section

N-(**5-Phenylfurazano[3,4-*d*]pyrimid-7-yl**)**aminoacetaldehyde Diethyl Acetal** (**6a**).—A mixture of 2.15 g of 5-phenyl-7-aminofurazano[3,4-*d*]pyrimidine (**1**) and 3 ml of aminoacetaldehyde diethyl acetal was stirred overnight at room temperature and then warmed to 70–80° for 1 hr. The oily mixture was dissolved in chloroform, and the solution was extracted several times with water and once with cold 0.1 *N* hydrochloric acid, dried over sodium sulfate, and filtered. The solution was evaporated to dryness, yielding an amber oil which solidified upon addition of a small amount of ether. Recrystallization from a mixture of ether and hexane afforded 3.1 g (94%) of pale yellow prisms, mp 88–90°.

Anal. Calcd for $C_{16}H_{19}N_5O_3$: C, 58.35; H, 5.82; N, 21.27. Found: C, 58.45; H, 5.75; N, 21.48.

N-(**2-Phenyl-5,6-diaminopyrimid-4-yl**)**aminoacetaldehyde Diethyl Acetal** (**7a**).—A solution of 0.50 g of **6a** in 25 ml of ethanol was hydrogenated over 20 mg of 10% Pd/C at room temperature and 1 atm of hydrogen pressure until hydrogen uptake ceased. The solution was filtered and evaporated under reduced pressure to give a reddish oil which solidified upon scratching. Several recrystallizations from a mixture of ether and hexane afforded 0.30 g (62%) of faintly pink plates, mp 101–102°.

Anal. Calcd for $C_{16}H_{23}N_5O_2$: C, 60.55; H, 7.30; N, 22.07. Found: C, 60.61; H, 7.33; N, 22.44.

2-Phenyl-4-aminopteridine (**9a**).—The crude oil from the reduction of 1.0 g of **6a** was dissolved in 50 ml of 0.5 *N* hydrochloric acid. The solution was stirred at room temperature for 4 hr. The resulting suspension was adjusted to pH 7 by addition of saturated aqueous sodium bicarbonate, and the suspended solid was collected by filtration, washed with water, and dissolved in 100 ml of THF. To this solution was added several grams of anhydrous magnesium sulfate and 1 g of activated manganese dioxide.[5] The suspension was stirred at room temperature overnight, filtered, and evaporated to dryness under reduced pressure. The residue was dissolved in cold, dilute hydrochloric acid, the solution was treated with charcoal and filtered, and the product was precipitated by adjusting the filtrate to pH 7 by addition of aqueous ammonia. The solid was collected by filtration and recrystallized from methanol to give colorless plates, mp 241–243° (lit.[6,7] mp 240–241°, 239°). The ultraviolet spectrum of this material was also identical with that reported.[6]

N-(**5-Phenylfurazano[3,4-*d*]pyrimid-7-yl**)**aminoacetone Dimethyl Acetal** (**6b**).—A mixture of 1.0 g of 5-phenyl-7-aminofurazano[3,4-*d*]pyrimidine (**1**) and 1.5 ml of aminoacetone dimethyl acetal was allowed to stand at room temperature overnight. The mixture was diluted with chloroform, washed with cold 1 *N* hydrochloric acid, dried, filtered, and evaporated to afford an amber oil which slowly solidified. Recrystallization

(3) E. C. Taylor in "Chemistry and Biology of Pteridines (Folic Acid Included)," K. Iwai, M. Akino, M. Goto, and Y. Iwanami, Ed., International Academic Printing Co., Tokyo, 1970, pp 79–93.

(4) See, for example, (a) W. R. Boon, W. G. M. Jones, and G. R. Ramage, *J. Chem. Soc.*, 96 (1951); (b) W. R. Boon and W. G. M. Jones, *ibid.*, 591 (1951); (d) W. R. Boon and T. Leigh, *ibid.*, 1497 (1951); (d) A. Stuart and H. C. S. Wood, *ibid.*, 4186 (1963); (e) K. J. M. Andrews, W. E. Barber, and B. P. Tong, *ibid.*, 928 (1969).

(5) L. A. Carpino, *J. Org. Chem.*, **35**, 3971 (1970).

(6) R. M. Evans, P. G. Jones, P. J. Palmer, and F. F. Stevens, *J. Chem. Soc.*, 4106 (1956).

(7) J. Weinstock, R. Y. Dunoff, J. E. Carevic, J. G. Williams, and A. J. Villani, *J. Med. Chem.*, **11**, 618 (1968).

from a mixture of isopropyl ether and hexane afforded 1.35 g (92%) of pale yellow needles, mp 139–141°.

Anal. Calcd for $C_{15}H_{17}N_5O_3$: C, 57.13; H, 5.43; N, 22.21. Found: C, 56.90; H, 5.42; N, 21.93.

2-Phenyl-4-amino-6-methylpteridine (9b).—A solution of 1.0 g of **6b** in 100 ml of ethanol was hydrogenated over 100 mg of 10% Pd/C at room temperature and 50 psi of hydrogen pressure until the uptake of hydrogen ceased. The catalyst was removed by filtration and the solution was evaporated under reduced pressure to afford a yellow oil. This was dissolved in 100 ml of water to which had been added several drops of concentrated hydrochloric acid. The solution was kept at room temperature under an atmosphere of nitrogen overnight. The solution was neutralized with aqueous sodium bicarbonate solution, and the yellow solid which formed was collected by filtration and treated with activated manganese dioxide in THF containing magnesium sulfate. After several hours, the solution was filtered and evaporated and the resulting dark oil was dissolved in cold dilute hydrochloric acid to give a homogeneous solution which was decolorized with charcoal and neutralized with aqueous sodium bicarbonate. The resulting precipitate was collected by filtration and recrystallized from methanol to afford 0.51 g (60%) of pale yellow plates, mp 242–244° (lit.[7] mp 240–241°). Its nmr spectrum was identical with the reported spectrum.[6]

5-Phenyl-7-acetylhydrazinofurazano[3,4-*d*]pyrimidine (10a).—A suspension of 2.00 g (9.38 mmol) of 5-phenyl-7-aminofurazano-[3,4-*d*]pyrimidine (**1**) and 3.44 g (46.8 mmol) of acethydrazide in 40 ml of 1 *N* ethanolic hydrogen chloride was stirred at room temperature for 24 hr and filtered, and the collected solid was recrystallized from ethanol to give 1.58 g (63%) of fine yellow needles, mp 266–267° dec.

Anal. Calcd for $C_{12}H_{10}N_6O_2$: C, 53.33; H, 3.73; N, 31.10. Found: C, 53.50; H, 3.83; N, 31.32.

5-Amino-3-methyl-7-phenylpyrimido[5,4-*e*]-*as*-triazine (12a).—A suspension of 0.30 g (1.11 mmol) of **10a** in 25 ml of ethanol containing 0.05 g of 10% Pd/C and 1.1 ml of 1 *N* ethanolic hydrogen chloride was shaken under 1 atm of hydrogen at room temperature until the hydrogen uptake ceased. The mixture was then refluxed for 2 hr and cooled, isoamyl nitrite (0.30 ml) was added, and stirring was continued for 16 hr at room temperature. Filtration through a Celite pad, evaporation of the filtrate under reduced pressure, and addition of water afforded an orange solid which was recrystallized from aqueous dimethylformamide to give 0.14 g (53%) of orange needles: mp 237° dec; uv $\lambda_{max}^{C_2H_5OH}$ 2.51 nm (log ϵ 3.73), 290 (3.93), 382 (2.96); nmr (DMSO-d_6) δ 3.08 (3 H, s), 7.6 (3 H, m), 8.5 (2 H, m), 9.0 (2 H, br, NH_2).

Anal. Calcd for $C_{12}H_{10}N_6$: C, 60.49; H, 4.23; N, 35.28. Found: C, 60.21; H, 4.08; N, 35.28.

5-Phenyl-7-benzoylhydrazinofurazano[3,4-*d*]pyrimidine (10b).—A suspension of 0.50 g (2.32 mmol) of **1** and 1.59 g (11.7 mmol) of benzhydrazide in 15 ml of 1 *N* ethanolic hydrogen chloride was stirred for 24 hr at room temperature and then filtered. The collected solid was recrystallized from ethanol to give 0.42 g (54%) of powdery flakes, mp 258–259° dec.

Anal. Calcd for $C_{17}H_{12}N_6O_2$: C, 61.44; H, 3.64; N, 25.29. Found: C, 61.64; H, 3.53; N, 25.02.

5-Amino-3,7-diphenylpyrimido[5,4-*e*]-*as*-triazine (12b).—A suspension of 0.25 g (0.75 mmol) of **10a** in 25 ml of ethanol containing 10% Pd/C was shaken under 1 atm of hydrogen at room temperature until hydrogen uptake ceased, 5 ml of 1 *N* ethanolic hydrogen chloride was added, the mixture was heated to boiling and filtered through Celite, and the filtrate then refluxed for 2 hr. Isoamyl nitrite (0.25 ml) was added, and the mixture was stirred for 24 hr at room temperature, neutralized with sodium bicarbonate, and concentrated to dryness under reduced pressure. The residue was triturated with water and then filtered. Recrystallization of the collected solid from aqueous dimethylformamide gave 0.18 g (80%) of fine yellow plates: mp >300°; uv $\lambda_{max}^{C_2H_5OH}$ 254 nm (log ϵ 3.70), 307 (4.22), 396 (3.34); nmr (DMSO-d_6) δ 7.68, 8.5–9.0 (12 H, m).

Anal. Calcd for $C_{17}H_{12}N_6$: C, 67.99; H, 4.03; N, 27.99. Found: C, 67.70; H, 4.15; N, 27.98.

Registry No.—**1**, 30720-36-6; **6a**, 39550-16-8; **6b**, 39550-17-9; **7a**, 39550-18-0; **9a**, 1084-59-9; **9b**, 19830-37-6; **10a**, 39550-21-5; **10b**, 39550-22-6; **12a**, 39550-23-7; **12b**, 39550-24-8; aminoacetaldehyde diethyl acetal, 645-36-3; aminoacetone diethyl acetal, 39550-25-9; acethydrazide, 1068-57-1.

Acknowledgment.—This work was supported in part by grants from the National Cancer Institute (No. CA-12876) and from Eli Lilly and Company.

Reactions of Vinyl Acetate with Carbazole

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Organic transformations brought about by thallium(I) and thallium(III) compounds have received considerable attention.[1] Recently we have demonstrated the usefulness of thallium(I) ethoxide as a base for the alkylation, under mild conditions, of carbazole, phenothiazine, and to a lesser extent 5*H*-dibenz[*b*,*f*]-azepine.[2] A notable feature of this reaction is that alkylation employing thallium(I) ethoxide as the base, unlike those employing potassium metal or potassium amide, is subject to steric limitations, and can only be used for the introduction of primary alkyl groups.

We now wish to report a further instance of the differing behavior of carbazole in reactions induced by potassium hydroxide and thallium(I) ethoxide, respectively.

Lopatinski, *et al.*,[3] have shown that carbazole, vinyl acetate, and potassium hydroxide react in acetone at −10 to −20° to afford *N*-(α-acetoxyethyl)carbazole (**1a**). We have repeated this reaction and confirmed the identity of the product **1a**, although the reaction is best carried out below −30°. Upon treatment with methanol the ester **1a** is converted to *N*-(α-methoxyethyl)carbazole (**1b**), and this product was found to be identical with authentic material prepared from methanol and *N*-vinylcarbazole.[4]

In complete contrast, the reaction of vinyl acetate with carbazole and thallium(I) ethoxide at room temperature in DMF–ether afforded *N*-acetylcarbazole (57%) together with an insoluble, light-sensitive thallium compound. This material was tentatively identified as vinyloxythallium(I) (**3**); however, during subsequent manipulation of this unstable compound an insertion reaction[5] with atmospheric carbon dioxide occurred producing vinylcarbonatothallium (**4**). The infrared spectrum of **4** showed bands at 1550 (br) and 1020 and 920 cm^{-1}, appropriate to a carbonato[6] and vinyl group, respectively. No molecular ion could be detected in the mass spectrum; however, an ion at *m/e* 249 was identified as $^{205}TlCO_2$ by accurate mass measurement.

(1) E. C. Taylor and A. McKillop, *Accounts Chem. Res.*, **3**, 338 (1970).

(2) L. J. Kricka and A. Ledwith, *J. Chem. Soc., Perkin Trans. 1*, 2292 (1972).

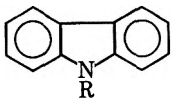
(3) V. P. Lopatinski and Yu. P. Shekhirev, *Izv. Tomsk. Politekh. Inst.*, **136**, 162 (1965); *cf. Chem. Abstr.*, **65**, 16930*e* (1966).

(4) L. P. Ellinger, *Polymer*, **5**, 559 (1964); C. E. H. Bawn, A. Ledwith, and Y. Shih-Lin, *Chem. Ind. (London)*, 769 (1965).

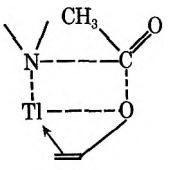
(5) M. F. Lappert, *Advan. Organometal. Chem.*, **5**, 225 (1967); A. G. Lee, *J. Chem. Soc. A*, 467 (1970).

(6) K. Nakamoto, "Infrared Spectra of Inorganic and Coordination Compounds," Wiley, New York, N. Y., 1963, p 159.

It is proposed that the thallium(I)-induced reaction of carbazole and vinyl acetate occurs *via* a four-center transition state (2) in which an important factor is coordination between the vinyl group and thallium,[7] since this reaction fails when the substrate is a simple ester, *e.g.*, ethyl acetate, or a sterically hindered ester, *e.g.*, vinyl pivalate or vinyl benzoate.



1a, R = CHMeOCOMe
b, R = CHMeOMe
c, R = COMe



2

$CH_2{=}CHOTl$ **3**

$CH_2{=}CHOCO_2Tl$ **4**

The potassium-induced reaction is envisaged as occurring *via* addition of potassium carbazole to the carbonyl group of vinyl acetate, and subsequent attack by a carbazolyl anion at the activated α-carbon atom (*cf.*[8] reactivity of vinyl ethers toward nucleophiles); likewise this reaction fails with sterically hindered esters (vinyl pivalate).

The differing mechanisms which operate for the thallium(I)- and potassium-induced reactions are seen to reflect the bonding in the respective metal–nitrogen bonds. Gray[9] has interpreted the somewhat short Tl–N distance (2.98 Å) in thallium(I) azide (*cf.* K–N 2.96 Å in potassium azide; ionic radii Tl^+ 1.49, K^+ 1.33) as indicating that the thallium–nitrogen bond is partially covalent. Further evidence in support of the proposed four-center reaction mechanism is available from Pearson's hard–soft acid–base principle.[10] Thallium(I) is a soft Lewis acid, whereas potassium (K^+) is a hard Lewis acid, and the former would be expected to exhibit a much greater tendency to coordinate to the vinyl group.

It is interesting to note that reaction of carbazole with vinyl acetate catalyzed by mercury(II) compounds yields exclusively *N*-vinylcarbazole.[11]

Experimental Section

Ir spectra were recorded for Nujol mulls. Mass spectra were measured by the Physico-Chemical Measurements Unit, Harwell. ^1H nmr spectra were recorded at 60 MHz with tetramethylsilane as internal standard.

N-Acetylcarbazole, mp 68–69° (lit.[12] mp 68–69°), was prepared from carbazole and acetic anhydride, as described.[11] *N*-(α-Methoxyethyl)carbazole, mp 88–90° (lit.[4] mp 89–90), was prepared from *N*-vinylcarbazole and methanol.

***N*-(α-Acetoxyethyl)carbazole.**—Vinyl acetate (10 g) was added dropwise to a stirred mixture of carbazole (10 g) and powdered potassium hydroxide (0.5 g) in acetone (25 ml) cooled in a carbon tetrachloride–Dry Ice bath (*ca.* −35°). The reaction mixture was stirred for 2 hr and then allowed to warm up to room temperature and filtered. The filtrate was evaporated and the resulting oil was recrystallized from petrol (bp 40–60°) to afford *N*-(α-acetoxyethyl)carbazole[13] (8.5 g, 57%): mp 87–88° (lit.[3] mp 85–87°); ν_{max} 1745, 1730 (C=O), 1598, 1490, 1335, 1238, 1210, 1155, 1085, 1058, 1010, 985, 920, 750, and 720 cm^{-1}; nmr τ [$(CD_3)_2CO$] 1.9–3.0 (9 H, m, ArH and NCHO–), 8.05 (3 H, s, $COCH_3$), and 8.16 (3 H, d, J = 7 Hz, CH_3); mass spectrum *m/e* (rel intensity) 253 (M^+, 12), 194 (M − $MeCO_2$, 20), 193 (M − $C_2H_4O_2$, 42), 192 (10), 168 (12), 167 (M − $C_4H_6O_2$, 100), 166 (14), 140 (20), and 139 (10).

N-(α-Acetoxyethyl)carbazole was refluxed in methanol for 0.5 hr to afford *N*-(α-methoxyethyl)carbazole, mp and mmp 86–88° (lit.[4] mp 89–90°), from methanol: nmr [$(CD_3)_2CO$] 1.9–3.1 (8 H, m, ArH), 4.55 (1 H, q, J = 7 Hz, NCHO), 6.91 (3 H, s, $COCH_3$), and 8.32 (3 H, d, CH_3).

Reaction of Vinyl Acetate with Carbazole and Thallium(I) Ethoxide.—Thallium(I) ethoxide (3.0 g) was added to a solution of carbazole (1.7 g) in DMF–ether (25 ml, 1:1 v/v), and the mixture was stirred at room temperature for 0.5 hr. Vinyl acetate (4.0 g) was then added and the mixture was stirred at room temperature for a further 2 hr, during which time a white precipitate was deposited. The reaction mixture was filtered free of solid material and poured into water, and the aqueous mixture was extracted with ether and dried ($MgSO_4$). Evaporation afforded an oil which was recrystallized from aqueous methanol to give *N*-acetylcarbazole (1.2 g, 57%), mp and mmp 68–70° (lit.[12] mp 68–69°).

The precipitate (1.0 g), mp 80–85° dec, which discolored upon standing in daylight, was tentatively identified as vinyloxythallium(I). *Anal.* Calcd for C_2H_3TlO: C, 9.7; H, 1.2. Found: C, 9.7, H, 1.2. Upon standing this material reacted with carbon dioxide (air) to form vinylcarbonatothallium: ν_{max} 1620–1500 (br, carbonate), 1285, 1210, 1015, 950, and 920 cm^{-1} (vinyl); mass spectrum *m/e* (rel intensity) 249/247 (M − C_2H_3O, 23/5), 221/219 (M − $C_3H_3O_3$, 2/1), 205/203 (100/47, $^{205}Tl^+/^{203}Tl^+$), 60 (60), 45 (72), and 43 (81); measured mass 246.9621 (calcd for $CO_2{}^{203}Tl$, 246.9631).

Registry No.—**3**, 39542-29-5; **4**, 39542-30-8; vinyl acetate, 108-05-4; carbazole, 86-74-8; thallium(I) ethoxide, 20398-06-5.

Acknowledgments.—We thank the SRC for a Research Assistantship (to L. J. K.).

(13) This material was stored below 5°.

(7) F. A. Cotton and L. T. Reynolds, *J. Amer. Chem. Soc.*, **80**, 269 (1958).
(8) Houben-Weyl, "Methoden der Organishen Chemie," Georg Thieme Verlag, Stuttgart, 1965, p 90, 185.
(9) P. Gray, *Quart. Rev., Chem. Soc.*, **17**, 441 (1963); A. G. Lee, "The Chemistry of Thallium," Elsevier, Amsterdam, 1971.
(10) R. G. Pearson, *J. Amer. Chem. Soc.*, **85**, 3533 (1963).
(11) H. Kaye, *Polym. Lett.*, **7**, 1 (1969).
(12) A. A. Berlin, *J. Gen. Chem. USSR*, **14**, 438 (1944); *cf. Chem. Abstr.*, **39**, 4606 (1945).

A Novel Aryl Cyanide Synthesis Using Trichloroacetonitrile

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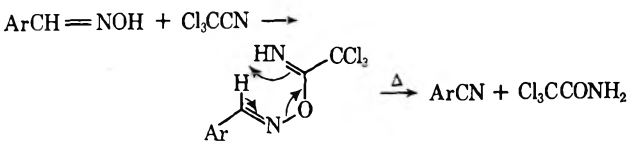
Although there exist a great number of ways to effect dehydration of aldoximes, interest in this area remains unabated.[1] Since most methods either utilize acidic reagents or are attended by the generation of acidic side products which might be detrimental to sensitive molecules, the development of procedures involving strictly neutral conditions is highly desirable. We wish to report a novel method for converting aryl aldoximes to the corresponding cyanides which fulfills this criterion; furthermore, the present procedure is simple, efficient, and economical.

Trichloroacetonitrile exhibits a remarkable capability of mediating the replacement of a hydroxy group by chlorine[2] under very mild conditions; it is also useful

(1) J. K. Chakrabarti and T. M. Hotten, *J. Chem. Soc., Chem. Commun.*, 1226 (1972), and references cited therein.
(2) F. Cramer and H.-J. Baldauf, *Chem. Ber.*, **92**, 370 (1959).

in phosphorylation of alcohols,[3] and conversion of symmetrical pyrophosphates into phosphate diesters.[4] We have now observed that aryl aldoximes are readily dehydrated upon refluxing with trichloroacetonitrile. The by-product, trichloroacetamide, is generally obtained in quantitative yield and can be easily removed. The reaction can be depicted as follows.



The initial configuration of the aldoxime does not seem to affect the results. Dehydration of aliphatic aldoximes under similar conditions is not so efficient.

TABLE I

Cl_3CCN DEHYDRATION OF ArCH=NOH

Oxime of	Registry no.	Nitrile yield, %	Registry no.
C_6H_5CHO	932-90-1	81	100-47-0
4-$CH_3C_6H_4CHO$	3235-02-7	94	104-85-8
3,4-$(CH_3O)_2C_6H_3CHO$	2169-98-4	75	2024-83-1
1-$C_{10}H_7CHO$	13504-46-6	95	86-53-3
C_6H_5CH=CHCHO	13372-81-1	92	4360-47-8

Experimental Section

Dehydration of Aryl Aldoximes. General Procedure.—A mixture of the aldoxime (3 mmol) and trichloroacetonitrile (1 ml) was refluxed for 0.5 hr with the exclusion of atmospheric moisture. The excess reagent was removed *in vacuo*, and the residue was digested thrice with warm hexane. The combined hexane solution was washed with water, dried over $MgSO_4$, and evaporated to afford the nitrile, which was distilled or recrystallized and identified by comparison with authentic sample (ir, nmr, tlc). Yields are given in Table I.

Registry No.—Trichloroacetonitrile, 545-06-2.

Acknowledgment.—We thank the National Research Council of Canada for partial financial support.

(3) F. Cramer, W. Rittersdorf, and W. Böhm, *Justis Liebigs Ann. Chem.*, **654**, 180 (1962).
(4) F. Cramer, K.-H. Scheit, and H.-J. Baldauf, *Chem. Ber.*, **95**, 1657 (1962).

A New Synthesis of Thioimino Esters

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As part of our studies on the synthesis of substituted dithio acids and their derivatives we have had occasion to prepare thioimino esters. The methods most commonly employed for the preparation of these compounds are variants of the original procedure re-

$$RSH + R'CN \xrightarrow{HCl(g)} R'(C{=}NH_2)SR^+Cl^-$$

ported by Autenreith and Bruning.[1] The recent report by Suydam, Greth, and Langerman[2] for the preparation of imino esters from amides and ethyl chloroformate suggested to us the possibility of a parallel synthesis of thioimino esters. We have investigated the reaction of ethyl thiochloroformate with several amides and thio amides. The reaction of amides with ethyl thiochloroformate did not produce the corresponding ethyl thioimino esters. No reaction was observed until the equimolar reaction mixture was heated to reflux temperature, when sudden gas evolution occurred and a white solid was formed which was a mixture of unreacted amide and the amide hemihydrochloride. Suydam[2] reported the formation of acetamide hemihydrochloride in the reaction of acetamide with ethyl chloroformate. The reaction of thio amides with ethyl thiochloroformate, however, produces the corresponding ethyl thioimino esters. When an equimolar amount of ethyl thiochloroformate is added slowly to a thio amide, with exclusion of moisture, a spontaneous exothermic reaction begins

$$RCSNH_2 + C_2H_5SCOCl \longrightarrow R(C{=}NH_2)SC_2H_5^+Cl^-$$

immediately. The product formed has been shown, by nmr and comparison to authentic samples prepared by the classical method,[1] to be the thiomino ester hydrochloride corresponding to the starting thio amide. The results of duplicate runs are shown in Table I.

TABLE I

Reactant RCSNH₂	Registry no.	Yield of product,[a] % R(C=NH₂)-SC₂H₅⁺Cl⁻	Registry no.
R = CH_3	62-55-5	79	5426-05-1
R = C_2H_5	631-58-3	59	39549-80-9
R = C_6H_5	2227-79-4	48	5442-13-7

[a] Based on crude product.

Since thio amides are readily available from nitriles by several methods,[3] the preparation of thioimino esters by this method offers an alternate synthetic route to the classical reaction.

Experimental Section

The following experimental procedure is representative of the method used for the preparation of ethyl thioimino esters.

The addition of 12.4 g (0.1 mol) of ethyl thiochloroformate to 7.5 g (0.1 mol) of thioacetamide results in an immediate exothermic reaction accompanied by gas evolution. After 6 min the reaction is complete and the reaction mixture solidifies to a white semisolid. The crude product is transferred to a fritted glass filter and washed several times with cold anhydrous ether. After removal of the ether by vacuum filtration the white crystalline product is immediately stored in a vacuum desiccator over P_2O_5. The yield of crude product is 11.1 g (79.2%). One recrystallization from chloroform gives a product melting at 139–141° (lit. mp 143°).[4] The physical properties and nmr spectrum of the product are identical with those of an authentic sample of ethyl thioiminoacetate prepared by the classical method.[1]

Registry No.—Ethyl thiochloroformate, 2941-64-2.

Acknowledgment.—We gratefully acknowledge the Robert A. Welch Foundation (Grant No. T-124) and the Office of Organized Research of East Texas State University for supporting this research.

(1) W. Autenreith and A. Brunig, *Ber.*, **36**, 3464 (1903).
(2) F. H. Suydam, W. E. Greth, and N. R. Langerman, *J. Org. Chem.*, **34**, 292 (1969).
(3) E. Emmett Reid, "Organic Chemistry of Bivalent Sulfur," Vol. IV, Chemical Publishing Co., New York, N. Y., 1962, pp 45–52.
(4) A. Hantzsch, *Ber.*, **64**, 665 (1931).

The Addition of α-Metalated Chloromethanesulfonamides to Unsaturated Linkages

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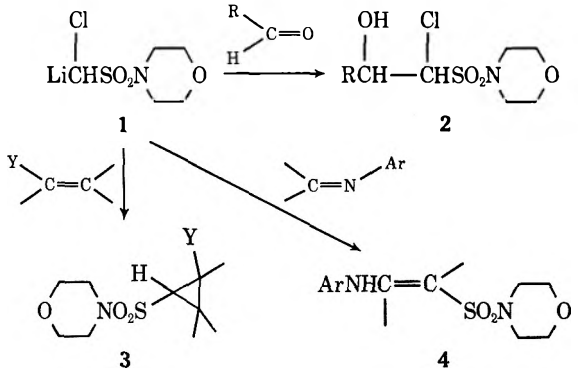
In the course of our investigations utilizing sulfur-stabilized carbanions in synthesis,[1] the reactions of 1-metalated 1-halosulfonic acid derivatives have offered unique synthetic potential.[2] These species couple the advantage of an extremely reactive carbanionic site while maintaining a functionality at the α position which is available for subsequent modification.[2b] Thus, facile, high-yield routes to a variety of novel 1- and 1,2-functionalized sulfur compounds are provided. We wish to report on the diverse reactivity of α-haloalkyllithium systems such as **1** with various classes of unsaturated substrates. Table I and Scheme I

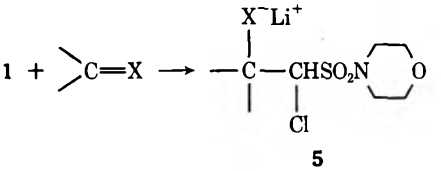
SCHEME I



summarize the results of the reactions of α-lithiochloromethanesulfonmorpholide with such acceptors. Clearly each unsaturated system demonstrates both characteristic and unique behavior. All reactions were carried out in tetrahydrofuran at −65° to minimize side reactions of the "carbenoid" **1**. Characterization of the products is based on chemical properties, elemental analyses, molecular-weight determinations, and infrared and well-defined proton magnetic resonance spectra.

Condensation of **1** with aldehydes afforded a mixture of diastereomeric alcohols. A similar preparation of diastereomeric β-hydroxy-α-chlorosulfones has been reported.[3]

That diastereomeric mixtures are obtained is evidenced both by the wide melting range of analytically pure adduct (Table I) and examination of the nmr spectra, which shows a variation in chemical shift accompanied by a pronounced difference in coupling constants for the erythro and threo isomers.[4,5] However, in most cases separation and isolation of the pure erythro and threo isomers was not systematically attempted. The nature of the products in this condensation parallels directly the interaction of **1** with ketones.[2] This reaction can be pictured as an initial addition of **1** to the unsaturated system giving the ion-pair intermediate **5**. No epoxide could be detected in



5

the crude reaction mixture, indicating that, under the reaction conditions when X is oxygen, ring closure with displacement of chloride ion is not favored.

By contrast, the reaction of **1** with Michael acceptors gives the ring-closed cyclopropanes under the same reaction conditions. Thus, an attractive route is provided to cyclopropanes which are 1,2 disubstituted with electron-withdrawing groups. Such systems are difficult to synthesize or unavailable by alternative cyclopropyl ring forming reactions.[6] It should be noted that, if the reaction proceeds *via* the intermediate carbanion, **5**, a facile intramolecular nucleophilic displacement α to a sulfonamide group must ensue.[7] It is evident that this method of forming disubstituted cyclopropanes is useful synthetically and its extension to other α-halosulfur-containing reactants and diverse Michael acceptor olefins constitutes a general approach to such cyclopropyl systems.

Distinct to these two modes of reactivity, the interaction of **1** with an imine affords a sulfonyl-substituted enamine as product[8] rather than the amine (analogous to carbonyl reactivity) or the aziridine (analogous to carbon–carbon double bond reactivity). The three individual modes of behavior of **1** toward various acceptors may reflect the differences in nucleophilicity and basicity expected for the three different anionic intermediates, **5**. Although such a correlation is attractive, we have little additional data to support such speculation at this time. An indication that perhaps more subtle factors govern the change in the nature of the products is suggested by the lack of reaction between **1** and *N*-benzylidenemethylamine.

These reactions, while providing convenient routes to novel sulfonic acid derivatives, also illustrate the diverse behavior of sulfur-stabilized α-haloalkyllithiums.

(1) (a) W. E. Truce and L. W. Christensen, *Tetrahedron*, **25**, 181 (1969); (b) W. E. Truce and D. J. Vrencur, *J. Org. Chem.*, **35**, 1226 (1970); (c) W. E. Truce and T. C. Klingler, *ibid.*, **35**, 1834 (1970).

(2) (a) W. E. Truce and L. W. Christensen, *Tetrahedron Lett.*, 3075 (1969); (b) *J. Org. Chem.*, **36**, 2538 (1971); (c) *Chem. Commun.*, 588 (1971).

(3) (a) F. Bohlmann and G. Haffer, *Chem. Ber.*, **102**, 4017 (1969); (b) T. Durst and K. C. Tin, *Tetrahedron Lett.*, 2369 (1970); (c) D. F. Tavares, R. E. Estep, and M. Blezard, *ibid.*, 2373 (1970).

(4) Assignment of stereochemistry *via* nmr spectroscopy has been reported: (a) J. B. Hyne, *Can. J. Chem.*, **39**, 2536 (1961); (b) M. E. Munk, M. K. Meilahn, and P. Franklin, *J. Org. Chem.*, **33**, 3480 (1968). Also see ref 1c for similar assignments in diastereomeric sulfones.

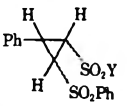
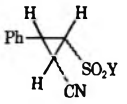
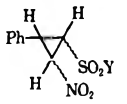
(5) The terms erythro and threo refer to *dl*-erythro and *dl*-threo, respectively.

(6) For analogous reactions of carboxylic acid derivatives, see (a) G. Bonavent, M. Causse, M. Guitard, and R. Fraisse-Jullian, *Bull. Soc. Chim. Fr.*, 2462 (1964); (b) T. Kawakami and T. Tsuruta, *Tetrahedron Lett.*, 1173 (1971).

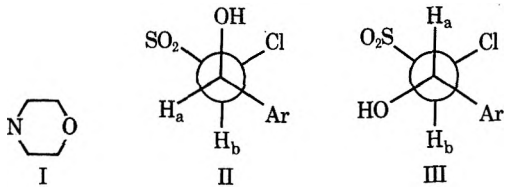
(7) For a comparison of the ease of intra- and intermolecular displacement α to a sulfonyl group, see (a) F. G. Bordwell and B. B. Jarvis, *J. Org. Chem.*, **33**, 1182 (1968); (b) W. E. Truce, T. C. Klingler, J. E. Paar, H. Feuer, and D. K. Wu, *J. Org. Chem.*, **34**, 3104 (1969), and ref 2b.

(8) (a) J. G. Lombardino, *J. Org. Chem.*, **33**, 3938 (1968); (b) W. E. Truce, R. H. Bavry, and P. S. Bailey, Jr., *Tetrahedron Lett.*, 5651 (1968).

TABLE I
REACTION PRODUCTS OF α-LITHIOCHLOROMETHANESULFONMORPHOLIDE WITH DOUBLE BONDS

Registry no.	Acceptor	Product	Product no.	Mp, °C	Yield, %[i]
75-07-0	CH_3CHO	$CH_3CH(OH)CHClSO_2Y$[a]	6	*b*	90[c]
78-84-2	$(CH_3)_2CHCHO$	$(CH_3)_2CH(OH)CHClSO_2Y$	7	114–120[c]	68
100-52-7	C_6H_5CHO	$PhCH(OH)CHClSO_2Y$	8	138–155[d]	39
89-98-5	*o*-ClC_6H_4CHO	*o*-$ClC_6H_4CH(OH)CHClSO_2Y$	9	122–134[c]	93
591-31-1	*m*-$CH_3OC_6H_4CHO$	*m*-$CH_3OC_6H_4CH(OH)CHClSO_2Y$	10	110.5–111.5[e]	81
538-51-2	$C_6H_5CH{=}NC_6H_5$	$C_6H_5NHC(C_6H_5){=}CHSO_2Y$	11	53.5–55	69
16212-06-9	*trans*-$C_6H_5CH{=}CHSO_2C_6H_5$		12	175.5–177[f]	73[g]
1885-38-7	*trans*-$C_6H_5CH{=}CHCN$		13	143–148[h]	70
5153-67-3	*trans*-$C_6H_5CH{=}CHNO_2$		14	104–109[h]	21

[a] Y is the group designated as structure I below. [b] Isolated as a viscous oil which could not be crystallized. [c] An analytically pure mixture of erythro and threo isomers. [d] A single isomer (structure II) was isolated from this mixture, having mp 156.5–158°. This



I II III

isomer is assigned the erythro configuration having the gauche conformation on the basis of the coupling constant J_{ab} = 1.6 Hz. [e] This isomer is tentatively assigned the threo configuration having the anti conformation designated as structure III on the basis of the coupling constant J_{ab} = 9.0 Hz. (See ref 1c and references cited therein for discussion of spectral methods of structural assignment.) [f] Stereochemistry about the cyclopropyl ring has not been determined. [g] 12% of a lower melting (142–143°) geometrical isomer was also isolated. [h] Mixture of geometrical isomers. [i] Isolated products, yields not optimized.

Experimental Section

All melting points are uncorrected. The nmr spectra were obtained in $CDCl_3$ using a Varian A-60 spectrometer with TMS = 0. Microanalyses and molecular weight determinations were performed by Dr. C. S. Yeh and staff of the Purdue University Microanalysis Laboratories or Atlantic Microlab, Inc. *n*-Butyllithium was purchased from Alfa Inorganics as a 2.1 *M* solution in hexane. Reagent grade THF was distilled from $LiAlH_4$ prior to use and all reactions were carried out under a dry nitrogen atmosphere. Aldehydes, olefins, and imines were obtained commercially in reagent grade purity.

Chloromethanesulfonmorpholide.—To a solution of triethylamine (9.58 g, 0.11 mol) and morpholine (11.12 g, 0.11 mol) in 200 ml of tetrahydrofuran stirred under nitrogen at 0° was slowly added a solution of chloromethanesulfonyl chloride (16.30 g, 0.11 mol) in 50 ml of tetrahydrofuran. The mixture was stirred for 1 hr, the precipitated triethylamine hydrochloride was filtered, and the filtrate was evaporated *in vacuo*. The resultant solid was recrystallized from 90% ethanol to afford 16.68 g (76%) of the amide, mp 70.5–71.0°, nmr δ 3.48 (m, 4), 3.72 (m, 4), 4.52 (s, 2).

Anal. Calcd for $C_5H_{10}ClNSO_3$: C, 30.18; H, 5.05; Cl, 17.79. Found: C, 30.30; H, 5.10; Cl, 17.70.

General Procedure for the Condensation of α-Chloromethyllithiumsulfonmorpholide with Carbonyl Compounds.—To a solution of 0.01 mol of chloromethanesulfonmorpholide in 30 ml of THF at −78° was added *n*-butyllithium (0.01 mol, in hexane) while maintaining the temperature below −60°. Immediately upon completion of the addition, the carbonyl compound (0.011 mol) was added and the resulting mixture was stirred at −60 to −65° for 15–20 min, and quenched with 100 ml of a 3% aqueous solution of NH_4Cl. The resultant mixture was extracted with four 50-ml portions of chloroform; the chloroform extracts were dried over Na_2SO_4 and evaporated *in vacuo* to yield the β-hydroxy-α-chlorosulfonamide as either a white solid or a light yellow oil which was purified by appropriate procedures.

1-Chloro-2-hydroxypropanesulfonmorpholide (6).—Chloromethanesulfonmorpholide (1.99 g, 0.01 mol) and acetaldehyde (0.62 ml, 0.011 mol) gave 2.30 g of a viscous yellow oil which could not be induced to crystallize. The oil was therefore washed with cold hexane and cold diethyl ether and subjected to evaporation *in vacuo* for 24 hr. The resultant yellow oil, 2.20 g (90%), gave analytical and spectral evidence of being a diastereomeric mixture of **6**: nmr δ 1.30 (overlapping d, 6, J = 5.0 Hz, $-CH_3$), 3.60 (m, 9, morpholine ring protons plus –OH), 4.42 (m, 1, –CHOH), 4.72 (d, 1, J = 1.5 Hz, erthyro isomer), 4.82 (d, 1, J = 5.0 Hz, threo isomer); mol wt calcd 243, found (mass spectrum) 243.

Anal. Calcd for $C_7H_{14}ClNO_4S$: C, 34.53; H, 5.75; Cl, 14.58. Found: C, 34.40; H, 5.90; Cl, 14.29.

1-Chloro-2-hydroxy-3-methylbutanesulfonmorpholide (7).—Chloromethanesulfonmorpholide (3.00 g, 0.015 mol), *n*-butyllithium (0.015 mol), and isobutylaldehyde (1.23 g, 0.017 mol) afforded a light yellow oil which was taken up in an ether–petroleum ether (bp 30–60°) mixture and cooled to afford a white solid, 2.75 g (68%), which was a diastereomeric mixture of **7**, mp 114–120°, nmr δ 1.00 (m, 6), 2.22 (m, 1), 3.61 (m, 9), 4.02 (m, 1), 4.66 (m, 1).

Anal. Calcd for $C_9H_{18}ClNO_4S$: C, 39.88; H, 6.84; S, 11.40; mol wt, 272. Found: C, 39.98; H, 6.70; S, 11.58; mol wt (in benzene), 269.

1-Chloro-2-hydroxy-2-phenylethanesulfonmorpholide (8).—Chloromethanesulfonmorpholide (1.99 g, 0.01 mol), *n*-butyllithium (0.01 mol), and benzaldehyde (1.17 g, 0.011 mol) afforded a yellow oil which upon crystallization and recrystallization from 95% ethanol gave 1.19 g (39%) of diastereomeric **8**, mp 138–155°, nmr δ 3.65 (m, 9), 4.90–5.80 (m, 2), 7.50 (s, 5).

Anal. Calcd for $C_{12}H_{16}ClNO_4S$: C, 47.12; H, 5.24; Cl, 11.61. Found: C, 46.72; H, 5.34; Cl, 11.52.

Repeated fractional crystallization from 95% ethanol gave 0.62 g (20%) of one pure diastereomer, mp 156.5–158°, which was assigned the erythro configuration (see Table I) on the basis of the nmr spectrum: δ 3.21 (d, 1, J = 4.0 Hz, –OH), 3.70 (m, 8), 4.87 d, 1, J = 1.6 Hz, >CHCl), 5.67 (m, 1, >CHOH). This isomer also gave a satisfactory analysis for $C_{12}H_{16}ClNO_4S$.

1-Chloro-2-hydroxy-2-(*o*-chlorophenyl)ethanesulfonmorpholide (9).—Chloromethanesulfonmorpholide (1.99 g, 0.01 mol) and *o*-chlorobenzaldehyde (1.55 g, 0.011 mol) gave, after recrystallization of the crude product from 95% ethanol, 3.16 g (93%) of diastereomeric **9**, mp 108–141°, nmr δ 3.62 (m, 10), 5.30 (m, 1), 7.60 (m, 4).

Anal. Calcd for $C_{12}H_{15}Cl_2NO_4S$: C, 42.50; H, 4.41; Cl, 20.82. Found: C, 42.46; H, 4.56; Cl, 21.01.

1-Chloro-2-hydroxy-2-(*m*-methoxyphenyl)ethanesulfonmorpholide (10).—Chloromethanesulfonmorpholide (2.20 g, 0.011 mol), *n*-butyllithium (0.011 mol), and *m*-methoxybenzaldehyde (1.53 g, 0.0112 mol) afforded a yellow oil which was recrystallized from 90% ethanol to give a white solid, which was further recrystallized from benzene–hexane to yield 3.00 g (81%) of **10**, tentatively assigned the threo configuration (see Table I), mp 110–111.50°, nmr δ 3.50 (m, 5), 3.72 (m, 4), 3.82 (s, 3), 4.82 (d, 2, J = 9.0 Hz), 5.14 (d, 2, J = 9.0 Hz), 7.12 (m, 4).

Anal. Calcd for $C_{13}H_{18}ClNO_5S$: C, 46.50; H, 5.49; Cl, 10.59; S, 9.56. Found: C, 46.47; H, 5.61; Cl, 10.81; S, 9.27.

General Procedure for Cyclopropane Formation from α-Chloromethyllithium Sulfonamides and Activated Olefins.—To chloromethanesulfonmorpholide (0.020 mol) in 50 ml of dry THF at −75° under N_2 was added *n*-butyllithium (0.020 mol in hexane) while maintaining the temperature below −60°. The olefin (0.021 mol) was then added in THF and the reaction mixture was stirred for 10–15 min and quenched with 150 ml of 3% aqueous NH_4Cl. The resultant mixture was extracted with 5 × 40 ml of chloroform, and the combined chloroform extracts were dried over Na_2SO_4 and then evaporated *in vacuo*, yielding the cyclopropane as a white solid which was recrystallized from ethanol.

Reaction of α-Chloromethyllithiumsulfonmorpholide with *trans*-1-Phenylsulfonyl-2-phenylethene.—Chloromethanesulfonmorpholide (1.99 g, 0.01 mol), *n*-butyllithium (0.01 mol), and *trans*-1-phenylsulfonyl-2-phenylethene (2.68 g, 0.011 mol) afforded 2.92 g (73%) of **12**, mp 175–176.5° (geometric stereochemistry was undefined). In addition 0.45 g (12%) of a second cis–trans configurational isomer was obtained, mp 142–143°. The minor component was much more soluble in 95% ethanol than the major component, nmr of which showed δ 3.10 (m, 4), 3.38 (m, 2), 3.63 (m, 5), 7.28 (s, 5), 7.82 (m, 5).

Anal. Calcd for $C_{19}H_{21}NO_5S_2$: C, 56.28; H, 5.19; N, 3.43; S, 15.69; mol wt, 409. Found: C, 56.10; H, 5.28, N, 3.28; S, 15.55; mol wt (in acetone), 410.

Reaction of α-Chloromethyllithiumsulfonmorpholide with *trans*-Cinnamonitrile.—Chloromethanesulfonmorpholide (2.00 g, 0.01 mol), *n*-butyllithium (0.01 mol), and *trans*-cinnamonitrile (1.42 g, 0.011 mol) gave 2.06 g (70%) of a mixture of geometrical isomers of **13**, mp 143–148 and 165–169°, nmr δ 2.58 (q. 1, J = 5.0 Hz), 3.38 (m, 5), 3.78 (m, 4), 7.40 (s, 5).

Anal. Calcd for $C_{14}H_{16}N_2O_3S$: C, 57.55; H, 5.48; N, 9.58; S, 10.95; mol wt, 292. Found: C, 57.63; H, 5.67; N, 9.88; S, 10.91; mol wt (in benzene), 297.

Reaction of α-Chloromethyllithiumsulfonmorpholide with β-Nitrostyrene.—Chloromethanesulfonmorpholide (1.99 g, 0.01 mol), *n*-butyllithium (0.01 mol), and β-nitrostyrene (1.53 g, 0.011 mol) gave 0.72 g (21%) of geometric isomers of **14**, mp 162–171°, nmr δ 4.26 (q, 1), 3.38 (m, 5), 3.80 (m, 4), 7.40 (s, 5).

Anal. Calcd for $C_{13}H_{15}N_2O_5S$: C, 50.01; H, 5.14; S, 10.22. Found: C, 49.87; H, 5.26; S, 10.25.

Reaction of α-Chloromethyllithiumsulfonmorpholide with *N*-Benzylideneaniline.—Chloromethanesulfonmorpholide (1.99 g, 0.01 mol), *n*-butyllithium (0.01 mol), and *N*-benzylideneaniline (1.99 g, 0.011 mol) gave 2.36 g (69%) of **11**, nmr δ 3.60 (m, 8), 5.20 (m, 2), 7.50 (m, 10).

Anal. Calcd for $C_{18}H_{20}N_2O_3S$: C, 62.95; H, 5.82. Found: C, 62.80; H, 5.96.

Registry No.—**1**, 23917-17-1; (*R**,*R**)-**6**, 39542-15-9; (*R**,*S**)-**6**, 39542-16-0; (*R**,*R**)-**7**, 39542-17-1; (*R**,*S**)-**7**, 39542-18-2; *erythro*-**8**, 39542-19-3; (*R**,*R**)-**9**, 39542-20-6; (*R**,*S**)-**9**, 39542-21-7; *threo*-**10**, 39542-22-8; **11**, 39542-23-9; **12**, 39542-24-0; **13**, 39542-25-1; **14**, 39542-26-2; chloromethanesulfonmorpholide, 39542-27-3; triethylamine, 121-44-8; morpholine, 110-91-8; chloromethanesulfonyl chloride, 3518-65-8; *n*-butyllithium, 109-72-8.

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A Stereospecific Synthesis of (±)-(*E*)-Nuciferol *via* the [2,3]-Sigmatropic Rearrangement of Allylic Sulfoxides

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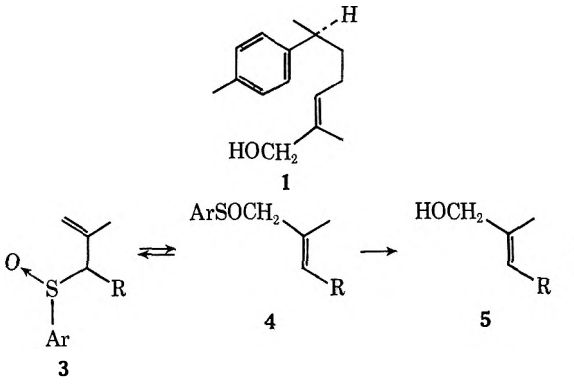
We wish to report a convenient four-step synthesis of racemic (*E*)-nuciferol (**1**)[1] utilizing the concerted nature of the [2,3]-sigmatropic rearrangement[2] of allylic sulfoxides to allylic sulfenate esters (eq 1).



The completely stereospecific nature of the allylic sulfoxide–sulfenate interconversion resulting in the synthesis of trisubstituted olefins of type **5** was recently reported by one of us.[3]

Reduction[4] of β-methyl-4-methylcinnamic acid with excess lithium in liquid ammonia proceeded cleanly to give a 98% yield of the crystalline saturated acid **2a**, mp 90–90.5° (lit.[5] mp 91°). Further reduction of acid **2a** with lithium aluminum hydride afforded a nearly quantitative yield of alcohol **2b**. Standard

(1) T. Sakai, K. Nishimura, and Y. Hirose, *Bull. Chem. Soc. Jap.*, **38**, 381 (1965).

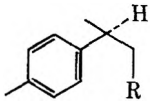
(2) P. Bickart, F. W. Carson, J. Jacobus, E. G. Miller, and K. Mislow, *J. Amer. Chem. Soc.*, **90**, 4869 (1968); R. Tang and K. Mislow, *ibid.*, **92**, 2100 (1970); D. A. Evans, G. C. Andrews, and C. L. Sims, *ibid.*, **93**, 4956 (1971).

(3) P. A. Grieco, *J. Chem. Soc., Chem. Commun.*, 702 (1972).

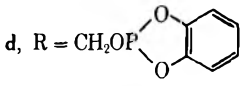
(4) J. E. Shaw and K. K. Knutson, *J. Org. Chem.*, **36**, 1151 (1971).

(5) H. Rupe and F. Wieder-Kehr, *Helv. Chim. Acta*, **7**, 654 (1924).

methods for the preparation of iodide **2c** from **2b** were not satisfactory. However, reaction of alcohol **2b** with *o*-phenylene phosphorochloridite[6] in ether in the presence of pyridine afforded a quantitative yield of the corresponding phosphite **2d**, which was subsequently treated with iodine in methylene chloride.[7] The desired iodide **2c** was thus obtained in 91% yield.



2a, R = COOH
b, R = CH_2OH
c, R = CH_2I



d, R = CH_2OP

Treatment of methallyl alcohol **5** (R = H) with *n*-butyllithium (−20°, THF) followed by addition of *p*-toluenesulfenyl chloride[8] produced the corresponding sulfenate **4** (R = H), which was smoothly transformed into sulfoxide **3** (R = H) in 92% yield. Addition of *n*-butyllithium (−50°) to a THF solution of sulfoxide **3** (R = H) followed by addition of iodide afforded the alkylated allylic sulfoxide **3** (R = 3-*p*-tolylbutyl), which upon subsequent treatment with thiophenoxide[9] in methanol produced the trans allylic alcohol, (±)-(*E*)-nuciferol (**1**), in 58% yield whose infrared and nuclear magnetic resonance spectra were in agreement with those of (±)-(*E*)-nuciferol obtained from natural nuciferal.[1] The chemical shift of the olefinic methyl protons in the nuclear magnetic resonance spectrum of synthetic nuciferol (δ 1.50, CCl_4) is in good agreement with those of other trans (*E*) olefinic methyl protons of type **5**.[10] In contrast, the nuclear magnetic resonance spectrum of natural (*Z*)-nuciferol exhibited the olefinic methyl signal at δ 1.71 (CCl_4).[1] In addition, the protons α to the hydroxyl group appeared as a singlet at δ 3.82, clearly in agreement with the trans (*E*) assignment. The synthesis of racemic (*E*)-nuciferol in *ca.* 50% overall yield from β-methyl-4-methylcinnamic acid is in agreement with and thus confirms the earlier work[1] which established that (*E*)-nuciferol is obtained by reduction of natural nuciferal and that natural nuciferol possesses the *Z* (cis) configuration.

Experimental Section

Microanalyses were performed by Galbraith Microanalytical Laboratories, Knoxville, Tenn. Boiling and melting points are uncorrected. Gas–liquid chromatography was performed on a Varian Aerograph Model 90-P instrument, using silicone rubber gum SE-30. Pre-coated PLC silica gel F-254 Merck plates were used for preparative tlc. The following spectrometers were used: nmr, Varian A-60D and T-60; ir, Perkin-Elmer Model 247; mass spectrum, LKB-9.

3-*p*-Tolylbutanoic Acid (2a).—A solution of β-methyl-4-methylcinnamic acid (4.07 g, 23.1 mmol) in 75 ml of anhydrous ether was rapidly added to a dark blue solution of lithium (660 mg, 0.095 g-atom) in 200 ml of anhydrous liquid ammonia. After stirring for 30 min at −33°, the reaction mixture was quenched by slow addition of ammonium chloride (20.8 g) and the ammonia was allowed to evaporate. The resulting residue was dissolved in water and extracted with ether. The remaining aqueous layer was acidified with 6 *N* hydrochloric acid and extracted twice with ether and the combined ethereal extracts (250 ml) were washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* afforded the crude crystalline saturated acid **2a** in quantitative yield. Recrystallization from ethanol gave 4.02 g (98%) of pure acid: mp 90–90.5° (lit.[5] mp 91°); ir ($CHCl_3$) 1705 cm^{-1} (C=O); nmr ($CDCl_3$) δ 1.28 (d, 3 H), 2.28 (s, 3 H), 2.30–2.70 (m, 2 H), 3.25 (m, 1 H), 7.08 (s, 4 H), 11.51 (s, 1 H); mass spectrum *m/e* 178.

3-*p*-Tolyl-1-butanol (2b).—To a suspension of lithium aluminum hydride (1.0 g, 26 mmol) in 125 ml of anhydrous ether was added dropwise over 15 min 4.0 g (23 mmol) of acid **2a** dissolved in 10 ml of THF and diluted with 50 ml of ether. After stirring for a total of 30 min, the reaction was quenched by the dropwise addition of water. Usual work-up afforded 3.7 g (99%) of alcohol **2b**: bp 80° (0.1 mm) [homogeneous on glc analysis (SE-30 column)]; ir (film) 3350 cm^{-1}; nmr (CCl_4) δ 1.18 (d, 3 H), 1.50–3.00 (m, 2 H), 2.22 (s, 3 H), 2.78 (m, 1 H), 3.38 (t, 2 H), 4.00 (s, 1 H), 6.98 (s, 4 H); mass spectrum *m/e* 164.

Anal. Calcd for $C_{11}H_{16}O$: C, 80.93; H, 9.26. Found: C, 80.74; H, 9.40.

1-Iodo-3-*p*-tolylbutane (2c).—To a mixture of 1.15 g (6.60 mmol) of *o*-phenylene phosphorochloridite[6] and 0.51 g of pyridine in 22 ml of anhydrous ether cooled to 0° was added with stirring 1.02 g (6.20 mmol) of alcohol **2b** in 22 ml of anhydrous ether. After the addition was complete, the reaction was warmed to room temperature. After a total of 15 hr, the pyridine hydrochloride was filtered off. The solvent was removed *in vacuo* to give an oily residue (quantitative yield) which was dissolved in 18 ml of methylene chloride. To the resultant solution was added 1.60 g (6.25 mmol) of iodine. After stirring for 7 hr at 25°, the reaction was diluted with ether and was extracted with 25 ml of 5% sodium hydroxide solution, 25 ml of 5% sodium bisulfite solution, and 10 ml of saturated sodium chloride solution. After drying over anhydrous sodium sulfate, the solvent was removed under reduced pressure. Distillation afforded 1.55 g (91%) of pure iodide **2c** which was homogeneous on glc (SE-30): bp 72° (0.05 mm); nmr (CCl_4) δ 1.22 (d, 3 H), 1.80–2.20 (m, 2 H), 2.28 (s, 3 H), 2.50–3.15 (m, 3 H), 7.01 (s, 4 H); mass spectrum *m/e* 274.

Anal. Calcd for $C_{11}H_{15}I$: C, 48.19; H, 5.52. Found: C, 48.42; H, 5.50.

Methallyl *p*-Tolyl Sulfoxide (3, R = H).—To a solution of anhydrous THF (90 ml) containing 3.24 g (45 mmol) of methallyl alcohol at −20° under an atmosphere of nitrogen was added dropwise 18 ml (45 mmol) of 2.5 *M* *n*-butyllithium in hexane. After addition was complete, 5.56 g (35 mmol) of *p*-toluenesulfenyl chloride[8] in 10 ml of THF was added dropwise and the reaction was warmed to room temperature. The intense orange color of the sulfenyl chloride was discharged immediately upon addition. After 15 min the solvent was removed under reduced pressure and the product was taken up in ether. The resulting ethereal solution was washed with saturated sodium chloride solution and dried (magnesium sulfate). Distillation of the crude product obtained upon removal of the solvents *in vacuo* afforded 6.25 g (92%) of **3** (R = H): bp 107–109° (0.15 mm); ir (film) 1050 (sulfoxide), 898 cm^{-1} (=CH_2); nmr (CCl_4) δ 1.76 (s, 3 H), 2.37 (s, 3 H), 3.32 (s, 2 H), 4.82 (d, 2 H), 7.35 (q, 4 H); mass spectrum *m/e* 194.

Anal. Calcd for $C_{11}H_{14}OS$: C, 67.99; H, 7.26. Found: C, 68.21; H, 7.45.

(±)-(*E*)-Nuciferol (1).—To a solution of 195 mg (1.00 mmol) of allylic sulfoxide **3** (R = H) in 10 ml of freshly distilled THF (from $LiAlH_4$) cooled to −50° under an atmosphere of nitrogen was added dropwise 0.65 ml (1.08 mmol) of 1.66 *M* *n*-butyllithium in hexane. After 15 min, 548 mg of iodide **2c** in 1.0 ml of THF was added dropwise over a 10-min period. After stirring at −50° for 1 hr, the reaction mixture was slowly warmed over a period of 1 hr to room temperature and stirred at room temperature for 2 hr. The reaction contents were poured into a solution of brine and the product was extracted with ether–hexane (3:1) mixture (three times). The crude alkylated sulfoxide was dissolved in 1.5 ml of methanol and added to a solution of 660 mg of benzenethiol in 20 ml of methanol to which had been added

(6) P. C. Crofts, J. H. H. Markes, and H. N. Rydon, *J. Chem. Soc.*, 4250 (1958).

(7) E. J. Corey and J. E. Anderson, *J. Org. Chem.*, **32**, 4160 (1967).

(8) F. Kurzer and J. R. Powell, "Organic Syntheses," Collect. Vol. IV, N. Rabjohn, Ed., Wiley, New York, N. Y., 1962, p 934.

(9) D. J. Abbott and C. J. M. Stirling, *J. Chem. Soc. C*, 818 (1969).

(10) K. C. Chan, R. A. Jewell, W. H. Nutting, and H. Rapoport, *J. Org. Chem.*, **33**, 3382 (1968).

0.70 ml of 1.66 *M* *n*-butyllithium in hexane under nitrogen. The reaction mixture was heated at *ca.* 65° for 7 hr and then left for 10 hr at room temperature. After removal of methanol under reduced pressure, the product was isolated by addition of water and extraction with ether. The combined ethereal extracts were washed with 2% sodium hydroxide solution and saturated sodium chloride solution and dried over magnesium sulfate. Removal of the solvents *in vacuo* produced the crude product. Purification by preparative tlc on silica gel plates using ether–hexane (2:1) afforded 127 mg (58%) of racemic (*E*)-nuciferol which was homogeneous by glc (SE-30): ir (film) 3340 cm^{-1}; nmr (CCl_4) δ 1.21 (d, 3 H), 1.50 (s, 3 H), 1.60–2.15 (m, 5 H), 2.30 (s, 3 H), 2.60 (m, 1 H), 3.82 (s, 2 H), 5.28 (b t, 1 H), 6.98 (s, 4 H); mass spectrum *m/e* 218.

Anal. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.73; H, 10.15.

Registry No.—**1**, 39599-18-3; **2a**, 39533-45-4; **2b**, 39533-46-5; **2c**, 39533-47-6; **3** (R = H), 37616-05-0; **5** (R = H), 513-42-8; β-methyl-4-methylcinnamic acid, 14271-34-2; *p*-toluenesulfenyl chloride, 933-00-6.

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Isotopic Labeling Studies of the Base-Catalyzed Conversion of 1-Methyladenosine to N^6-Methyladenosine

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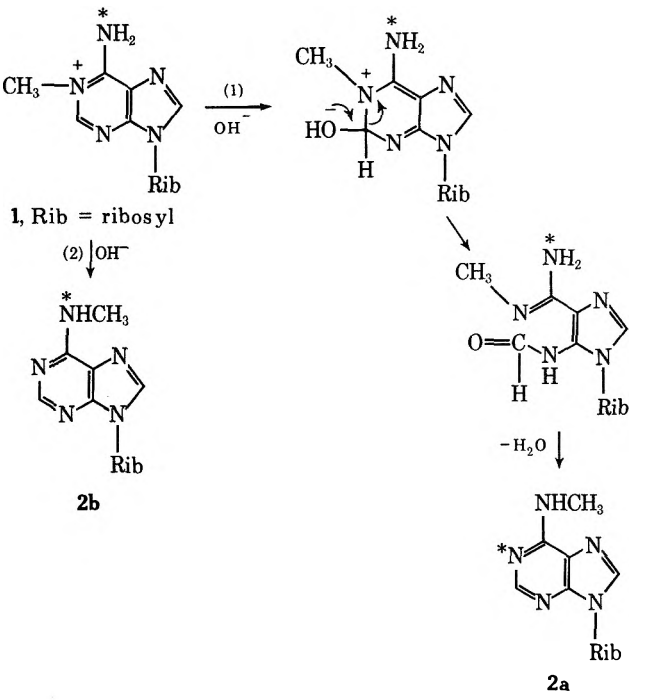
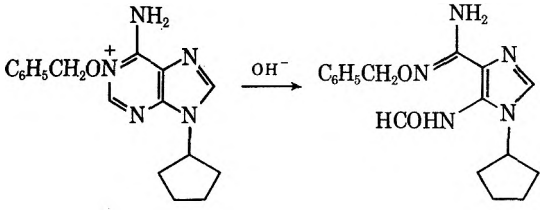
The observation that certain derivatives of 1-methylpurine rearrange in base to N^6-methyladenine was reported over a decade ago,[1,2] and has since been shown to occur for a variety of purine derivatives and has often been the basis for synthesis of N^6-substituted derivatives of adenine.[3] Following the proposal of Taylor and Loeffler, who studied the structurally similar pyrazolo[3,4-*d*]pyrimidine system,[4] the mechanism has been generally presumed to follow that of the Dimroth rearrangement,[5] involving ring opening and recyclization (eq 1) rather than simple methyl migration (eq 2).

In related work, Windmueller and Kaplan studied the ring opening of 1,6-bis(2-hydroxyethylamino)-9-(β-D-ribofuranosyl)purine in base.[6] An intermediate ring-opened product, which does not undergo recyclization



in dilute alkali, was isolated as a diazo derivative, but did not have a structure analogous to the intermediate shown in eq 1. The most detailed study to date is that of Macon and Wolfenden, who failed to detect or trap an intermediate species in the conversion of **1** to **2** but found that the reaction occurs at room temperature from ~pH 7 to 13 and follows pseudo-first-order kinetics.[7] Their data were interpreted in terms of an initial ring opening (eq 1) brought about by attack of hydroxide on the neutral or protonated form of 1-methyladenosine. In more recent work, Montgomery and Thomas have isolated the intermediate formamide derivative **4** derived from 1-benzyloxy-9-cyclopentyladenine (**3**), which was then converted with ring closure



3 **4**

to the N^6-benzyloxy derivative.[8] From these and other less relevant data[9,10] it has been reasonably assumed[7–10] that rearrangement of 1-substituted purines in base follows the Dimroth mechanism, in analogy to the pyrimidines, for which the overall mechanism has been clearly established.[5,11–13]

The present study of the conversion of 1-methyl-6-amino-9-(β-D-ribofuranosyl)purine (**1**) to 6-methylamino-9-(β-D-ribofuranosyl)purine (**2**) was undertaken to directly test the mechanism in eq 1 by use of ^{15}N and

(1) (a) A. R. Todd in "CIBA Foundation Symposium on the Chemistry and Biology of Purines," G. E. W. Wolstenholme and C. M. O'Connor, Ed., Little, Brown and Co., Boston, Mass., 1957, p 57; *cf.* G. B. Elion, ref 1a, p 44.

(2) P. Brookes and P. D. Lawley, *J. Chem. Soc.*, 539 (1960).

(3) For example, (a) A. Codington, *Biochem. Biophys. Acta*, **59**, 472 (1962); (b) G. B. Elion, *J. Org. Chem.*, **27**, 2478 (1962); (c) J. W. Jones and R. K. Robins, *J. Amer. Chem. Soc.*, **85**, 193 (1963); (d) P. D. Lawley and P. Brookes, *Biochem. J.*, **89**, 127 (1963); (e) W. Grimm, T. Fuji, and N. J. Leonard in "Synthetic Procedures in Nucleic Acid Chemistry," Vol. 1, W. W. Zorbach and R. S. Tipson, Ed., Wiley-Interscience, New York, N. Y., 1968, p 212; (f) H. T. Nagasawa, P. S. Fraser, and J. A. Elberling, *J. Org. Chem.*, **37**, 516 (1972).

(4) E. C. Taylor and P. K. Loeffler, *J. Amer. Chem. Soc.*, **82**, 3147 (1960).

(5) For comprehensive review see (a) D. J. Brown in "Mechanisms of Molecular Migrations," Vol. 1, B. S. Thyagarjan, Ed., Wiley-Interscience, New York, N. Y., 1968, pp 209–245; (b) M. Wahren, *Z. Chem.*, **9**, 241 (1969).

(6) H. G. Windmueller and N. O. Kaplan, *J. Biol. Chem.*, **236**, 2716 (1961).

(7) J. B. Macon and R. Wolfenden, *Biochemistry*, **7**, 3453 (1968).

(8) J. A. Montgomery and H. J. Thomas, *J. Med. Chem.*, **15**, 182 (1972).

(9) J. H. Lister, "Fused Pyrimidines. Part II. Purines," D. J. Brown, Ed., Wiley-Interscience, New York, N. Y., 1971, p 313.

(10) "Organic Chemistry of Nucleic Acids, Part B," N. K. Kochetkov and E. J. Budovskii, Ed., Plenum Press, New York, N. Y., 1972, p 393.

(11) D. J. Brown in "The Pyrimidines," Suppl. I, A. Weissberger and E. Taylor, Ed., Wiley, New York, N. Y., 1970, p 287.

(12) D. J. Brown, *Nature (London)*, **189**, 828 (1961).

(13) J. Goerdeler and W. Roth, *Chem. Ber.*, **96**, 534 (1963).

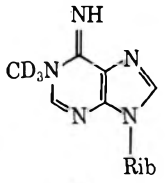
TABLE I

RELATIVE ION ABUNDANCE DATA FROM THE MASS SPECTRA OF 2 AND PRODUCTS OF CONVERSION OF ISOTOPICALLY LABELED 1

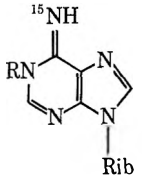
	m/e				
Starting compd	120	121	122	123	124
1 (pH 11)	100	62.6 ± 2.0	7.7 ± 0.6		
5 (pH 11)	37.3 ± 0.2	100	46.2 ± 0.5	32.4 ± 0.3	
6[a] (pH 11)	22.2 ± 0.8	100	59.6 ± 1.0	7.7 ± 0.3	
7[a] (pH 7)	11.4 ± 1.8	44.6 ± 1.1	100	47.2 ± 0.8	31.0 ± 0.6
7[a] (pH 11)	15.3 ± 0.9	47.9 ± 0.7	100	46.9 ± 0.6	29.6 ± 0.4

[a] Abundance data corrected for presence of 9.6% ^{14}N.

D labeling, and in addition to demonstrate the utility of mass spectrometry for dealing with mechanistic problems of this type. Mass spectrometry of the reaction products, without the usual degradation to volatile gases, provides a rapid and sensitive means of determining the location and extent of isotopic labeling. The conversion of **1** to **2** was studied both at neutrality and pH 11, using compound **1** specifically labeled with ^{15}N (**5**). Mass spectra of N^6-methyladenosine and its analogs[14] have been studied in detail, permit unambiguous differentiation of the products resulting from isomerization and methyl migration (**2a** *vs.* **2b**), and can be used as a quantitative test for the existence of competing pathways down to a level of ~2% at both pH values. The deuterium-labeled analogs **6** and **7**



6



5, R = CH_3

7, R = CD_3

were also examined under the same conditions in order to unambiguously confirm the interpretation of the mass spectra.

Detailed understanding of the mechanism of this reaction is important, not only because of its role in synthetic procedures (*e.g.*, ref 3a,e,f) but also because of the possibility of its occurrence during isolation and chemical treatment of tRNA or oligonucleotides which contain 1-methyladenine residues.[15] The reaction is also potentially useful for the preparation of isotopically labeled analogs of N^6-substituted adenosine for chemical or biological studies.

Experimental Section

Mass spectra were recorded on an LKB 9000 instrument with sample introduction by direct probe: ion source temperature 250°, ionizing electron energy 70 eV. The ion abundance measurements reported represent the mean of at least six consecutively recorded partial spectra.

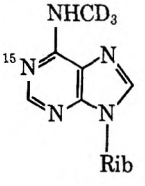
Adenosine-$^{15}N^6$.[16]—6-Chloro-9-(β-D-ribofuranosyl)purine (100 mg) and methanol (1 ml) were placed in a 3-ml reaction vessel and evacuated to 3 mm pressure. $^{15}NH_3$ (0.5 l., Bio-Rad Laboratories, 90% ^{15}N) was distilled into the cooled vessel, which was then sealed and allowed to stand for 16 hr at room temperature and then 3 hr at 40°. Evaporation of excess $^{15}NH_3$ and methanol yielded 90 mg of chromatographically pure adenosine-$^{15}N^6$.

1-Methyladenosine (**1**), **1-methyladenosine-$^{15}N^6$** (**5**), **1-(methyl-d_3)adenosine** (**6**), **and 1-(methyl-d_3)adenosine-$^{15}N^6$** (**7**) were prepared as hydriodide salts from adenosine or adenosine-$^{15}N^6$ and CH_3I or CD_3I (Merck Sharp and Dohme of Canada, 99% D) in *N,N*-dimethylacetamide by the method of Jones and Robins.[3c] The above five products exhibited the expected mass spectra[14] with suitable mass shifts due to presence of ^{15}N or D, and which showed no contamination from starting material or other products.

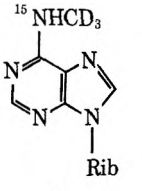
Treatment with Base and Purification of Products.—1-Methyladenosine hydriodide (**1**) or its isotopically labeled analogs (1 mg) were added to water (0.5 ml) and the pH was adjusted to 7 or 11 with 0.25 *M* NaOH. The solution was heated at 100° for 2 hr and cooled. The pH was adjusted to 5.0 with 1 *N* HCl and the mixture was applied to a 5 × 60 cm column of Dowex 50-X8. N^6-Methyladenosine (**2**) or its labeled analogs were eluted with 0.4 *M* ammonium formate, pH 5.0. The product obtained after lyophilization and removal of buffer salt under vacuum was chromatographically and mass spectrometrically pure.

Results and Discussion

If conversion of **1** to **2** proceeds exclusively by Dimroth rearrangement (eq 1), the methyl group at N-1 should appear at N^6 in the product, and the identity of N-1 and N^6 nitrogens should be reversed. The doubly labeled compound **7** would therefore yield **8**, while contributions from direct methyl migration (eq 2) would yield proportional amounts of the isotopic isomer **9**. Location of the isotopic labels in



8



9

the rearranged products from **5**, **6**, and **7** can be established mass spectrometrically using the peak representing loss of methyleneimine from the base + H fragment ion, a reaction characteristic of the N^6-methyladenine moiety.[14,17-19] Interchange of amino and methyl hydrogen occurs during decomposition of *m/e* 149,[19] resulting in a slightly more complex ion pattern in the *m/e* 120 region in the case of the deuterated models **6** and **7**. However, the location of the methyl group in relation to the nitrogen at N^6 in **1** can be clearly established by mass shifts of the *m/e* 120 ion-type derived from **5**, **6**, and **7**. Expulsion of CH_2N from *m/e* 149 produces a companion peak of *m/e* 121 which bears the same information (Scheme 1).

Ion abundance for the diagnostic *m/e* 120 region of the spectra are presented in Table I. From the pH 11 experiment, the isotopic pattern from **7** is identical with

(14) S. J. Shaw, D. M. Desiderio, K. Tsuboyama, and J. A. McCloskey, *J. Amer. Chem. Soc.*, **92**, 2510 (1970), and references cited therein.

(15) R. H. Hall, *Biochemistry*, **4**, 661 (1965).

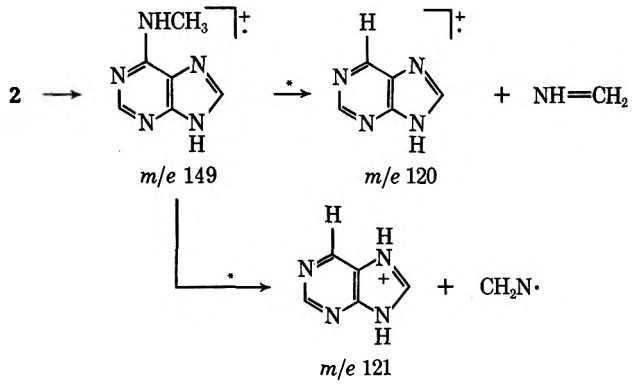
(16) T. Sato in "Synthetic Procedures in Nucleic Acid Chemistry," Vol. 1, W. Zorbach and R. Tipson, Ed., Wiley-Interscience, New York, N. Y., 1968, p 264.

(17) J. S. Shannon and D. S. Letham, *New Zealand J. Sci.*, **9**, 833 (1966).

(18) Y. Rahamim, J. Sharvit, A. Mandelbaum, and M. Sprecher, *J. Org. Chem.*, **32**, 3856 (1967).

(19) D. L. von Minden, J. G. Liehr, and J. A. McCloskey, Twenty First Annual Conference on Mass Spectrometry and Allied Topics, San Francisco, Calif., May 1973.

SCHEME I



that of **5** but shifted one mass unit higher, showing the presence of ^{15}N originating at N^6 in **1**, in support of the ring-opening mechanism. This interpretation is confirmed by the singly labeled derivative **6**, which produces a pattern which is experimentally indistinguishable from **1** but offset one mass unit higher as required by the Dimroth mechanism. The absence of contributions from products such as **9** which would contain an exocyclic ^{15}N label shows the absence of a methyl migration mechanism (eq 2) at the detectable limit of approximately 2% of the total reaction yield.

Conversion of 1-methyladenosine was more than 90% complete at pH 11 under the conditions employed, but less than 50% complete at pH 7. However, the identity of patterns from compound **7** at the two pH values shows that transformation to N^6-methyladenosine occurs exclusively by ring opening in both the protonated (pH 7) and neutral (pH 11) forms of 1-methyladenosine, a result which is consistent with earlier kinetic studies of Macon and Wolfenden.[7]

Registry No.—**1**, 34308-25-3; **2**, 1867-73-8.

Acknowledgments.—This work was supported by the National Institutes of Health (GM-13901, GM-02055) and the Robert A. Welch Foundation (Q-125). The authors are grateful to Dr. H. T. Nagasawa for helpful discussions.

Biosynthesis of Ergot Alkaloids. Synthesis of 6-Methyl-8-acetoxymethylene-9-ergolene and Its Incorporation into Ergotoxine by *Claviceps*

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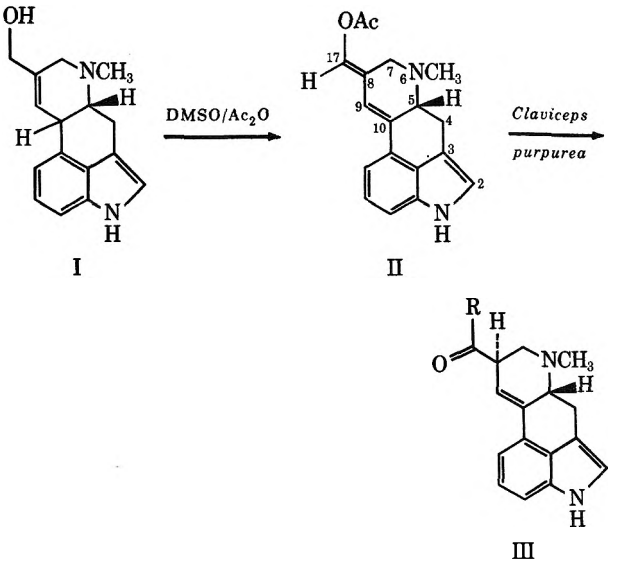
It is well known that simple clavine alkaloids, particularly agroclavine and elymoclavine (I), are precursors of the lysergic acid (III, R = OH) moiety of more complex amide and peptide type ergot alkaloids;[1-5]



however, the sequence of steps from I to the lysergic acid stage is unknown. Lysergene, lysergol, isolysergol, and penniclavine apparently are not precursors of lysergic acid derivatives.[2,3] Therefore, shift of the double bond into the 9,10 position is not the first step. 6-Methyl-8-ergolene-8-carboxylic acid ($\Delta^{8,9}$-lysergic acid), a natural constituent of certain ergot strains,[6] was found to be incorporated into lysergic acid amides, although not so efficiently as lysergic acid.[7] While this could indicate biological double bond isomerization at the lysergic acid stage, the fact that the same reaction also occurs spontaneously at a measurable rate[6] makes the interpretation of this experimental result somewhat ambiguous. In order to examine this question further, we attempted to prepare $\Delta^{8,9}$- and/or $\Delta^{9,10}$-lysergaldehyde (III, R = H) from elymoclavine. Surprisingly, it turns out that the hydroxymethyl group of elymoclavine is extremely resistant to most of the usual oxidizing agents. This fact has apparently been noted before in extensive attempts to produce lysergic acid commercially by chemical oxidation of elymoclavine.[8] The only defined oxidation products obtained were penniclavine and isopenniclavine, the products of hydroxylation in the 8 position.[9,10]

Treatment of elymoclavine with a mixture of dimethyl sulfoxide and acetic anhydride at room temperature for 12 hr[11] produced, in addition to elymoclavine *O*-acetate, a new compound which was identified as 6-methyl-8-acetoxymethylene-9-ergolene (II), the enol acetate of lysergaldehyde. Separation of the two

(1) K. Mothes, K. Winkler, D. Gröger, H. G. Floss, U. Mothes, and F. Weygand, *Tetrahedron Lett.*, 933 (1962).
(2) S. Agurell and M. Johansson, *Acta Chem. Scand.*, **18**, 2285 (1964).
(3) H. G. Floss, H. Günther, D. Gröger, and D. Erge, *Z. Naturforsch. B*, **21**, 128 (1966).
(4) R. Voigt, M. Bornschein, and G. Rabitzsch, *Pharmazie*, **22**, 326 (1967).
(5) T. Ohashi, S. Aoki, and M. Abe, *J. Agr. Chem. Soc., Jap.*, **44**, 527 (1970).
(6) H. Kobel, E. Schreier, and J. Rutschmann, *Helv. Chim. Acta*, **47**, 1052 (1964).
(7) S. Agurell, *Acta Pharm. Suecica*, **3**, 65 (1966).
(8) A. Hofmann, private communication.
(9) M. Abe, S. Yamatodani, Y. Yamano, and M. Kusumoto, *Bull. Agr. Chem. Soc. Jap.*, **19**, 92 (1955).
(10) A. Hofmann, R. Brunner, H. Kobel, and A. Brack, *Helv. Chim. Acta*, **40**, 1358 (1957).
(11) J. D. Albright and L. Goldmann, *J. Amer. Chem. Soc.*, **89**, 2416 (1969).

products, which in most systems have very similar R_f values, was achieved by chromatography on a column of Sephadex LH-20 using ethanol as the developing solvent. Upon repeated rechromatography of those fractions containing mixtures of the two products and crystallization from ethanol, II was obtained in 15.6% yield as yellow needles, mp 178–180° dec. The molecular formula of II was established as $C_{18}H_{18}N_2O_2$ by high-resolution mass spectrometry (mol wt calcd 294.13682, obs 294.13551). The presence of strong peaks at *m/e* 251 and 252 ($C_{16}H_{15}N_2O$ and $C_{16}H_{16}N_2O$) due to loss of acetyl and ketene, respectively, and lack of any peak due to loss of acetic acid indicated the presence of an enol acetate moiety in the molecule. This is supported by the infrared spectrum, which showed the typical enol acetate carbonyl absorption at 1750 cm^{-1}. The nmr spectrum confirmed the presence of the acetyl group, showing a methyl signal at δ 2.18 in addition to the NCH_3 signal at δ 2.60. Assignment of the signal at δ 8.03 to the indole proton was confirmed by D_2O exchange. The ultraviolet spectrum [λ_{max}^{MeOH} 248 nm (log ϵ 4.19) and 339 (4.11)] closely resembled that of lysergene (6-methyl-8-methylene-9-ergolene) [λ_{max}^{MeOH} 246 nm (log ϵ 4.46) and 337 (4.11)], indicating the presence of the same chromophore. The dienol acetate moiety ($AcOCH_{17}{=}CCH_9{=}C-$) was further supported by the nmr spectrum, which showed broad singlets at δ 6.84 and 7.35 which could be assigned to the protons at C-9 and C-17, respectively. Further evidence for the proposed structure is the fact that II gives lysergol upon reduction with $LiAlH_4$.

A variety of attempts were made to convert II into lysergaldehyde or lysergic acid. These included hydrolysis with dilute acetic acid or ammonium hydroxide, attempted generation of the lithium enolate anion from II by treatment with CH_3Li,[12] hydrolysis–oxidation with silver oxide in alkaline or acidic medium, and oxidation with molecular oxygen following alkaline hydrolysis. All these attempts were unsuccessful, producing no reaction or leading to decomposition or formation of very complex mixtures.

To evaluate whether II can be converted into lysergic acid biosynthetically, a tritiated sample was prepared by oxidation of [*indole*-^{3}H]elymoclavine. While II is not expected to be an intermediate in the biosynthetic conversion of elymoclavine to lysergic acid derivatives, it might serve as a source of lysergaldehyde inside the cells, because the ergot fungus is apparently quite capable of cleaving acetate esters.[13] [*indole*-^{3}H]-II was fed to two 100-ml shake cultures of *Claviceps purpurea* strain PEPTY 695 as described earlier.[14,15] For comparison, [*indole*-^{3}H]elymoclavine and [*indole*-^{3}H]elymoclavine *O*-acetate were each fed to two parallel cultures. The experiments were terminated 24 hr later, the alkaloid content of the cultures was determined colorimetrically, and ergotoxine (III) was isolated and purified by tlc (silica gel, chloroform–ethanol 9:1) as described previously.[14,15] The ergotoxine was then hydrolyzed with methanolic KOH to give lysergic acid, which was purified to constant specific radioactivity. The results of these experiments, which are summarized in Table I, clearly indicate that II can be converted into lysergic acid by the ergot fungus. The efficiency of its

Table I

Incorporation of Precursors into the Lysergic Acid Portion of Ergotoxine by *Claviceps purpurea*

	Precursor fed[a]		
	II	Elymoclavine	Elymoclavine *O*-acetate
Amount fed, μmol	4.15	7.88	17.94
Radioactivity fed, dpm	1.23×10^6	2.34×10^6	5.33×10^6
Alkaloid formed, μmol	175	213	184
Specific radioactivity of lysergic acid, dpm/μmol	109	164	1200
Total radioactivity of lysergic acid in alkaloid, dpm	1.9×10^4	3.5×10^4	2.2×10^5
Incorporation, %	1.55	1.49	4.15

[a] All precursors labeled with tritium in the indole portion.

incorporation about equals that of elymoclavine, an established lysergic acid precursor. The better utilization of elymoclavine *O*-acetate confirms an earlier report by Agurell[13] and may be due to permeability differences. While these experiments by no means establish the intermediacy of lysergaldehyde in lysergic acid biosynthesis, they certainly do suggest that the possibility of double-bond isomerization at the aldehyde rather than the acid stage should be kept in mind.

Experimental Section

General.—Infrared spectra were recorded on a Perkin-Elmer 237B grating spectrophotometer, ultraviolet spectra on a Perkin-Elmer Coleman 124 spectrophotometer, and nmr spectra on a Jeol MH 60 or Varian HR 220 instrument in deuteriochloroform with TMS as internal standard. Mass spectra were obtained using a Hitachi RMU-6D low-resolution and a CEC 2110 high-resolution mass spectrometer. Melting points were determined in vacuum-sealed tubes on samples dried for 18 hr at room temperature over P_2O_5 under vacuum. Ehrlich's reagent was used to visualize ergoline derivatives on chromatograms. Radioactivity determinations were carried out in a Packard Tricarb Model 3365 liquid scintillation counter using PPO and POPOP in toluene as scintillator solution. [*indole*-^{3}H]Elymoclavine was material which had been prepared earlier[3] by biosynthesis from [*indole*-^{3}H]tryptophan. The feeding experiments with *Claviceps purpurea* strain PEPTY 695 and the isolation, purification, and degradation of the alkaloid were carried out as described previously.[14,15] Nonlabeled elymoclavine was prepared by fermentation of *Claviceps* strain SD 58.[16]

6-Methyl-8-acetoxymethylene-9-ergolene (II).—To 476 mg (1.87 mmol) and 503 mg (1.98 mmol) of elymoclavine were added 8.3 and 9.3 ml, respectively, of a mixture (3:2 by volume) of dimethyl sulfoxide (Baker AR, redistilled over NaH, dried over molecular sieves) and acetic anhydride (Mallinckrodt AR). The reaction mixtures were stirred at room temperature in the dark under nitrogen for 12 hr and then combined. Distilled water (500 ml) was added with shaking and the aqueous layer was extracted with 6 × 100 ml of chloroform. The aqueous phase was then basified with 14% ammonium hydroxide to pH 5–6, 7–8, and 9–10 and extracted at each stage with 3 × 100 ml of chloroform. The combined chloroform extract was washed with 4 × 500 ml of distilled water, dried by filtering through anhydrous sodium sulfate, concentrated to a syrup on the rotary evaporator at 23–25°, and further dried under vacuum for 20 hr to give 1.2 g of a dark brown residue. This crude reaction product was dissolved in a small volume of absolute ethanol and poured on top of a column (2.5 × 35 cm) packed with 25 g of Sephadex LH-20 which had been swelled in ethanol for at least 3 hr. The column was eluted with absolute ethanol, 60 fractions of

(12) H. O. House and B. M. Trost, *J. Org. Chem.*, **30**, 2502 (1965).
(13) S. Agurell, *Acta Pharm. Suecica*, **3**, 23 (1966).
(14) D. Gröger and D. Erge, *Z. Naturforsch. B*, **25**, 196 (1970).
(15) W. Maier, D. Erge, and D. Gröger, *Biochem. Physiol. Pflanzen (Jena)*, **161**, 559 (1971).
(16) H. G. Floss and D. Gröger, *Z. Naturforsch. B*, **18**, 519 (1963).

3 ml were collected, and the elution was monitored by tlc (silica gel, ethyl acetate–acetone–dimethylformamide 5:5:1, R_f 0.62). Fractions containing only II were combined, concentrated, and crystallized from ethanol to give 77 mg of yellow needles, which showed a single spot upon chromatography in several systems. Fractions containing mixtures of II and elymoclavine *O*-acetate were combined and chromatographed in the same way a second and a third time to give 52 and 48 mg of product, bringing the total yield to 177 mg (0.6 mmol, 15.6%). II has a melting point of 178–180° dec, gives a green color with Ehrlich's spray reagent, and shows a strong blue fluorescence under uv; ir (KBr) 1750, 1368, 1210, and 1049 cm^{-1}; uv (MeOH) λ_{max} 248 nm (log ϵ 4.19) and 339 (4.11); major mass spectral peaks *m/e* (rel intensity) 294.13551 (M^+) (calcd 294.13682) (100), 252 (22), 251 (45.6), 249 (13.4), 235 (24.2), 223 (32.9), 222 (14.4), 221 (32.2), 192 (16.2), 154 (15.4). The 220-MHz nmr spectrum ($CDCl_3$) shows signals at δ 2.18 (singlet, 3 H) for the acetyl methyl group, 2.60 (singlet, 3 H) for the *N*-methyl, 2.73 (dd, J = 10, 14 Hz, 1 H, 4α proton), 3.07 (d, J = 14 Hz, 1 H, 7β proton), 3.32 (dd, J = 6, 10 Hz, 1 H, C-5 proton), 3.52 (dd, J = 6, 14 Hz, 1 H, 4β proton), 3.94 (d, J = 14 Hz, 1 H, 7α proton), 6.84 (broad singlet, 1 H, for the vinyl proton at C-9), 6.89 (broad singlet, 1 H, indole 2 H), 7.22 (multiplet, 3 H, aromatic protons), 7.35 (broad singlet, 1 H, vinyl proton at C-17) and 8.03 (broad singlet, indole NH).

Registry No.—I, 548-43-6; I acetate, 5080-45-5; II, 39717-29-8; III (R = H), 39717-30-1; III (R = OH), 82-58-6; dimethyl sulfoxide, 67-68-5; acetic anhydride, 108-24-7.

Acknowledgments.—We thank the Purdue University Mass Spectrometry Center for the mass spectra, C. J. Chang, E. W. Hagaman, and Dr. E. Wenkert, Indiana University, for the 220-MHz nmr spectra, and Drs. A. Hofmann and H. Kobel, Sandoz AG, Basle, for samples of elymoclavine used in the early phases of this work. Financial support by the U. S. Public Health Service (Research Grants AM 13555 and AM 11662 and Research Career Development Award GM 42382) is gratefully acknowledged.

Rearrangement in the Indan-1,3-dione System

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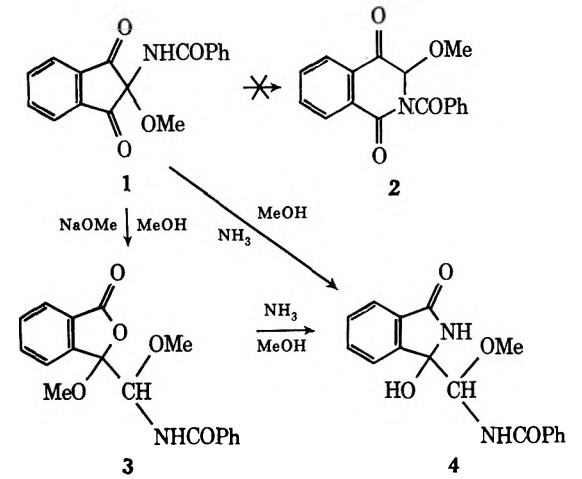
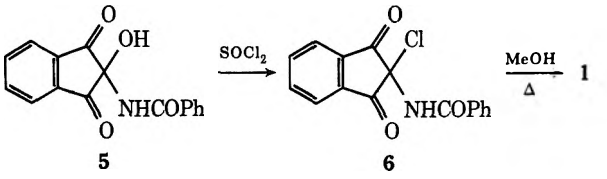
Received December 1, 1972

In an attempt to synthesize azanaphthaquinone[1] we tried to prepare the precursor 2-benzoyl-3-methoxytetrahydroisoquinoline-1,4-dione (2) by a base-catalyzed internal displacement ring enlargement[2] of 2-benzamido-2-methoxyindan-1,3-dione (1).

Instead of the expected ring enlargement product 2, we obtained the rearranged phthalide derivative 3, which was further converted to the isoindolone 4 on treatment with methanolic ammonia solution. The same isoindolone derivative 4 was also obtained from the starting material 1 on treatment with methanolic ammonia solution. Attempts to induce an acid-catalyzed ring enlargement on the isoindolone derivative were also unsuccessful.

The starting material 2-benzamido-2-methoxyindan-1,3-dione (1) was prepared in high yield from ninhydrine hydrate and benzamide. The addition product 5 was converted to the methoxybenzamidoindandione (1) by treatment with thionyl chloride followed by refluxing a methanolic solution of the chloroamide 6, for 1 hr.





Experimental Section

Melting points are corrected; infrared spectra were measured in chloroform solutions and nmr in deuteriochloroform (unless otherwise indicated).

2-Benzamido-2-hydroxyindan-1,3-dione (5).—A mixture of ninhydrin hydrate (10.0 g, 0.05 mol) and benzamide (6.8 g, 0.05 mol) in benzene (100 ml) was refluxed for 1 hr. The water, formed in the reaction, was removed by azeotropic distillation. The mixture was cooled and the solid formed was filtered to give 15.1 g (86%) of product: mp 143–144°; ir 1760, 1720, and 1650 (CO), 3500 (OH), and 3300 cm^{-1} (NH). The hydroxyamide was used in the following procedure without further purification.

2-Benzamido-2-chloroindan-1,3-dione (6).—A mixture of the hydroxyamide 5 (2.0 g) and thionyl chloride (1.2 ml, 2 equiv) in methylene chloride (40 ml) was refluxed for 2 hr. The solvent was evaporated and the residue was triturated with benzene, filtered, and crystallized from benzene to give 1.97 g (93)% of product which melted at 173–174°: ir 1775, 1735, and 1660 (CO) and 3430 cm^{-1} (NH); *m/e* 399.

Anal. Calcd for $C_{16}H_{10}NO_3Cl$: C, 64.10; H, 3.34; N, 4.68; Cl, 10.80. Found: C, 64.17; H, 3.44; N, 4.32; Cl, 10.49.

2-Benzamido-2-methoxyindan-1,3-dione (1).—A solution of the chloroamide 6 in absolute methanol (25 ml) was refluxed for 1 hr. The solvent was evaporated and the residue was triturated with ether–hexane and filtered. It was crystallized from benzene–hexene: mp 166–167°; yield 66%; ir 1725, 1760, 1660 (CO), and 3420 cm^{-1} (NH); nmr δ 8.2–7.3 (m, 10 H) and 3.57 (s, 3 H).

Anal. Calcd for $C_{17}H_{13}NO_4$: C, 69.14; H, 4.44; N, 4.74. Found: C, 68.87; H, 4.52; N, 5.06.

3-Methoxy-3-(α-methoxy-α-benzamidomethyl)phthalide (3).—A solution of 2-benzamido-2-methoxyindan-1,3-dione (1, 1.0 g) and sodium methylate (20 mg) in absolute methanol (20 ml) was left at room temperature for 48 hr. The solvent was evaporated and the residue was dissolved in ethyl acetate (50 ml) and washed with water. The organic layer was dried over magnesium sulfate and evaporated. The residue was triturated with ether, filtered, and crystallized from ethyl acetate–hexane: mp 178°; yield 60%; ir 1780, 1670 (CO), and 3430 cm^{-1} (NH); nmr δ 8.2–7.3 (m, 9 H), 6.85 (d, 1 H, J = 10 cps), 5.80 (d, 1 H, J = 10 cps), 3.32 (s, 3 H), and 3.10 (s, 3 H).

Anal. Calcd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.28; N, 4.28. Found: C, 65.92; H, 5.27; N, 4.04.

3-Hydroxy-3-(α-methoxy-α-benzamidomethyl)isoindolone (4).—A mixture of the lactone 3 (1.0 g) in methanolic ammonia

(1) D. Ben-Ishai, Z. Inbal, and A. Warshawski, *J. Heterocycl. Chem.*, **7**, 615 (1970).

(2) C. R. Hauser and S. W. Kantor, *J. Amer. Chem. Soc.*, **73**, 1440 (1951).

solution (10 ml of a 10% solution) was stirred at room temperature for 1 hr. The solid was filtered off to give a product which melted at 224–226°. The solution was evaporated and the residue was triturated with ethyl acetate to give an additional crop of the same product: yield 77%; ir (KBr) 1700, 1650 (CO), and 3200 cm^{-1} (OH and NH, broad); nmr (DMSO-d_6) δ 8.32 (d, 1 H, J = 10 cps), 8.2–7.4 (m, 9 H), 6.58 (s, 1 H), 5.40 (d, 1 H, J = 10 cps), 3.32 (s, 3 H).

The compound was identical with the product obtained by treating the starting material **1** with methanolic ammonia for 24 hr at room temperature.

Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.37; H, 5.16; N, 8.97. Found: C, 65.68; H, 5.31; N, 9.02.

Registry No.—**1**, 39253-47-9; **3**, 39253-48-0; **4**, 39253-49-1; **5**, 39253-50-4; **6**, 39253-51-5.

Preparation and Acid-Catalyzed Rearrangement of 3,3-Dimethoxytricyclo[3.2.0.$0^{2,7}$]heptane

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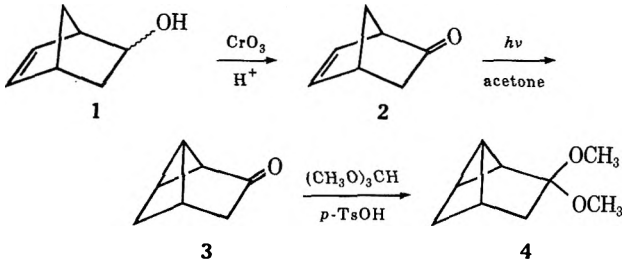
Received December 22, 1972

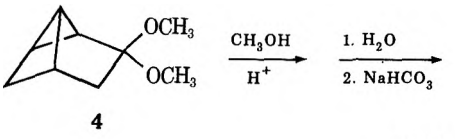
Although the chemistry of quadricyclyl cation has been well studied,[2-4] much less is known about the chemical reactions of the highly strained tricyclo[3.2.0.$0^{2,7}$]hept-3-yl cation. We attempted to elucidate the nature and ultimate fate of this carbenium ion. This note reports the preparation of 3,3-dimethoxytricyclo[3.2.0.$0^{2,7}$]heptane (**4**) and the subsequent acid-catalyzed rearrangement of this disubstituted tricyclane.

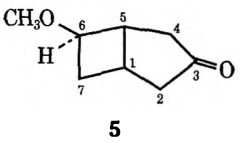
3,3-Dimethoxytricyclo[3.2.0.$0^{2,7}$]heptane (**4**) was prepared by the sequence of reactions shown below. The initial reaction involved the conversion of 5-norbornen-2-ol (**1**) to 5-norbornen-2-one (**2**) *via* oxidation with



Jones reagent. Tricyclo[3.2.0.$0^{2,7}$]heptan-3-one (**3**) was prepared by irradiation of **2** in acetone.[5] Reaction of **3** with trimethyl orthoformate using small amounts of p-toluenesulfonic acid as catalyst gave an 85% yield of **4**, bp 38–39° (4 mm).

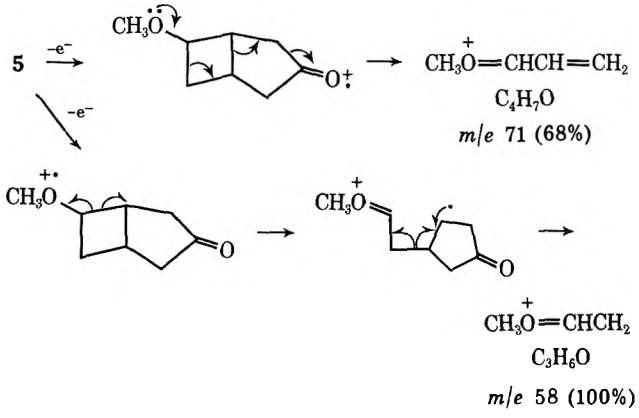
The ketone **3** and its dimethyl ketal **4** were quite stable under aqueous acid conditions at room temperature. In 10% sulfuric acid, **4** was ultimately hydrolyzed to **3** but no rearrangement products were found. When **4** was exposed to methanolic sulfuric acid solution (10% sulfuric acid by weight) at room temperature for 2 hr and followed by the aqueous conditions of the work-up, it underwent an acid-catalyzed rearrangement reaction to yield 6-methoxybicyclo[3.2.0]-heptan-3-one (**5**) in 71% yield as the only monomeric





product. The same rearrangement product was obtained with **3** as the starting material but the rate of the rearrangement reaction was slower.

The structure of **5** was assigned on the basis of spectral data. The ir spectrum showed absorption at 2810 (symmetric C–H stretching for methoxyl group), 1150–1050 (C–O–C stretching), and 1745 cm^{-1} (five-membered cyclic carbonyl stretching frequency), indicative of a methoxy and cyclopentanone structure.[6] The mass spectrum revealed a molecular ion peak of empirical formula $C_8H_{12}O_2$ and two major fragments of empirical formulas C_4H_7O and C_3H_6O. These observed fragmentations are consistent with structure



5, which would be expected to undergo cleavage to produce C_4H_7O and C_3H_6O ions. The nmr spectrum of **5** was likewise consistent with this structure. Signals due to C_1 and C_5 methine hydrogens appeared as complex multiplets at δ 2.80–3.00. The C_6 hydrogen signal occurred as a multiplet at δ 3.56 and that of the methoxyl hydrogens as a singlet at δ 3.26. Signals displayed at δ 2.00–2.60 are assigned to the rest of the hydrogens.

The stereochemistry of the methoxyl group in **5** was deduced from the observed ir and nmr spectra of the corresponding alcohol. When **3** was treated with 20% sulfuric acid in aqueous THF solution at 60° for 4 hr it underwent a very slow reaction to give predominantly unrearranged starting material along with about 5% of 6-hydroxybicyclo[3.2.0]heptan-3-one (**6**). To distinguish between the exo and endo configuration of OH we examined the effect of concentration on the ir and nmr of the OH proton. The ir spectrum of **6** showed two bands in the more con-

(1) Xerox Corporation, Rochester Research Center, Webster, N. Y. 14580.

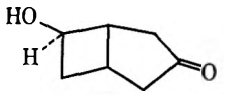
(2) H. G. Richey, Jr., and N. C. Buckley, *J. Amer. Chem. Soc.*, **85**, 3057 (1963).

(3) P. R. Story and S. R. Fahrenholtz, *ibid.*, **88**, 374 (1966).

(4) P. G. Gassman and D. S. Patton, *ibid.*, **90**, 7276 (1968).

(5) J. Ipaktschi, *Tetrahedron Lett.*, 2153 (1969).

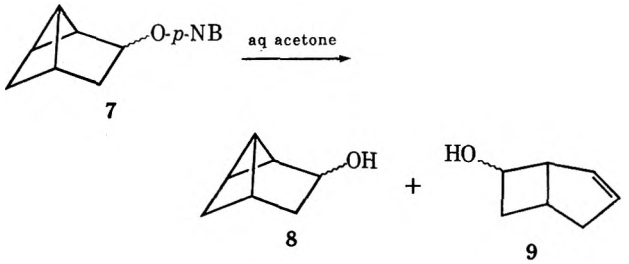
(6) F. Scheimann, "An Introduction to Spectroscopic Methods for the Identification of Organic Compounds," Vol. 1, Pergamon Press, New York, N. Y., 1970, pp 179, 187.



6

centrated solution, at 3625 (free OH) and 3440 cm^{-1} (broad and intense band, hydrogen-bonded OH). The latter band was absent in the more dilute solution and is attributed to intermolecular hydrogen bonding.[7] The carbonyl frequency of **6** was 1745 cm^{-1}, indicating the absence of intramolecular hydrogen bonding.[7] The nmr spectra of **6** in carbon tetrachloride appropriately paralleled that of **5** except for the signal of the hydroxyl proton, which showed a concentration-dependent chemical shift, thus indicating the absence of intramolecular hydrogen bonding. From the spectral data, it is evident that both the hydroxyl group in **6** and methoxyl group in **5** should be at the exo position.

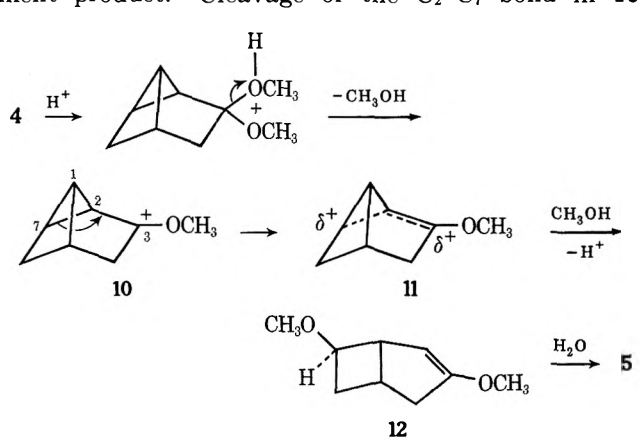
While this work was in progress a paper by Lustgarten[8] appeared in which was reported that solvolysis products from both epimers of tricyclo[3.2.0.$0^{2,7}$]hept-3-yl *p*-nitrobenzoate (**7**) consisted mainly of unrearranged tricyclic alcohols (**8**) and homoallylic bicyclo[3.2.0]heptanols (**9**). The exo to endo ratio of **9** was



7 8 9

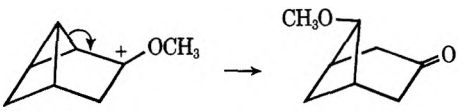
reported to be 10:1. His results further supported our structure **5** and moreover revealed a common cationic intermediate from both epimers.

In the acid-catalyzed rearrangement of **4**, the initial step in the mechanistic path may involve the protonation of the oxygen function followed by loss of methanol to yield carbenium ion **10**. The manner in which **10** cleaves determines the topology of final rearrangement product. Cleavage of the C_2–C_7 bond in **10**



10 11 12

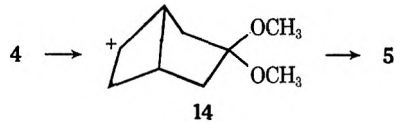
will lead to the formation of the observed rearrangement product **5**, while the breaking of the C_1–C_2 bond would give **13**. Examination of a stereomodel of **10**



13

reveals that the orientation of the p orbital of the carbenium ion at the C_3 position is almost parallel to the adjacent cyclopropane bent δ bond C_2–C_7. The C_1–C_2 bond possesses much less overlap with the developing p orbital of the adjacent carbenium ion. Therefore, it is most favorable to cleave the C_2–C_7 bond in **10** to produce a delocalized or equilibrating ion **11**, which should be a particularly stable ion having one end of the homoallylic cation relatively strainless and the other end stabilized by a methoxyl group. The nucleophilic attack by solvent (methanol) at **11** would yield **12**, which, under the aqueous conditions of the work-up, would hydrolyze the enol ether function to yield the rearrangement product **5**. The isolation of only exo methoxyl product is also consistent with preferred approach of solvent from the less hindered side or of the nonclassical nature of the homoallylic ion.[9]

A less pleasing alternate rationale for the formation of **5** would involve initial protonation on the carbon adjacent to the ketal carbon to yield the bicyclic carbenium ion **14**. Although this would be consistent



14

with the formation of **5**, it requires initial protonation on the carbon adjacent to the carbon bearing the methoxyl groups. Since the methoxyls are electron withdrawing, electronegativity arguments might predict that this carbon should be the least likely to be protonated. However, further study is required to determine the possible role of this reaction.

Experimental Section

Proton magnetic resonance spectra were obtained with a JEOL Model JNM-C-60HL high-resolution nmr instrument. Mass spectra were recorded on a Hitachi Perkin-Elmer Model RMU-6E mass spectrometer. Infrared spectra were measured on a Perkin-Elmer Model 137, Model 421, or Model 457 infrared spectrophotometer. Glpc analyses were carried out with a Hewlett-Packard F & M Model 700 with a Model 7127A strip chart recorder equipped with integrator or a Varian Aerograph Model 90-P gas chromatograph. Microanalytical analyses were performed by Micro-Tech, Skokie, Ill.

Tricyclo[3.2.0.$0^{2,7}$]heptan-3-one (3).—This tricyclic ketone was prepared by irradiation of 5-norbornen-2-one[10] in acetone.[5] A solution of 3.00 g (27.8 mmol) of 5-norbornen-2-one in 900 ml of acetone was placed in an ice–water-cooled quartz immersion apparatus equipped with a reflux condenser and a magnetic stirring bar. A stream of nitrogen was passed through the solution for about 10 min to remove dissolved oxygen. The solution was then kept under nitrogen and was irradiated with a 450-W Hanovia medium-pressure mercury lamp. The progress of the reaction was monitored by glpc analysis. The reaction was completed after 2 hr of irradiation. Acetone was removed on a rotary evaporator. The concentrated mixture was combined with four other runs (in each run 3.00 g of 5-norbornen-2-one was used) and distilled under reduced pressure through an 18-in. spinning band column to give 9.75 g (65%) of tricyclo[3.2.0.$0^{2,7}$]-heptan-3-one: bp 83–84° (21 mm); ir (neat) 5.85 μ (C=O);

(7) J. Bellamy, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1958, pp 99–106.

(8) R. K. Lustgarten, *J. Amer. Chem. Soc.*, **93**, 1275 (1971).

(9) P. R. Brook, *Chem. Commun.*, 565 (1968).

(10) S. J. Cristol and P. K. Freeman, *J. Amer. Chem. Soc.*, **83**, 4427 (1961).

nmr ($CDCl_3$) δ 1.1–1.4 (m, 2 H), 1.9–2.3 (m, 4 H), and 2.5–3.0 (m, 2 H); mass spectrum parent *m/e* 108.

Anal. Calcd for C_7H_8O: C, 77.78; H, 7.41. Found: C, 77.68; H, 7.39.

3,3-Dimethoxytricyclo[3.2.0.0^{2,7}]heptane (4).—*p*-Toluenesulfonic acid (0.028 g) was added to a solution of 2.71 g (25 mmol) of tricyclo[3.2.0.0^{2,7}]heptan-3-one and 3.68 g of trimethyl orthoformate in 5 ml of anhydrous methanol. The reaction mixture was stirred at room temperature for 8 hr. Sodium methoxide (10 mg) was added to the reaction mixture. The resulting solution was put on a rotary evaporator to remove methanol and distilled under reduced pressure to give 3.27 g (85%) of 3,3-dimethoxytricyclo[3.2.0.0^{2,7}]heptane: bp 38–39° (4 mm); nmr ($CDCl_3$) δ 1.3–1.8 (m, 6 H), 2.35 (m, 2 H), 3.12 (s, 3 H), and 3.28 (*s*, 3 H); mass spectrum parent peak *m/e* 154; ir (CCl_4) 2815 (symmetric CH stretching for methoxyl group), 1150–1050 cm^{-1} (C–O–C asymmetric stretching) and no carbonyl absorption.

Anal. Calcd for $C_9H_{14}O_2$: C, 70.13; H, 9.09. Found: C, 69.96; H, 9.12.

Reaction of 3,3-Dimethoxytricyclo[3.2.0.0^{2,7}]heptane (4) with Anhydrous Methanolic Sulfuric Acid.—Methanol was purified and dried by distilling Mallinkrodt AR methanol from magnesium turnings. In a 10-ml, round-bottomed flask equipped with magnetic stirring bar and drying tube was placed 3 ml of methanolic sulfuric acid solution (10% concentrated H_2SO_4 by weight). The dimethyl ketal (0.500 g) was added to this stirred solution at ice–water-bath temperature. The solution was stirred at room temperature for 2 hr. Water (6 ml) was added. After stirring for 15 min the solution was made basic with solid sodium bicarbonate and extracted with five 6-ml portions of ether. The ethereal extracts were combined, washed with two 5-ml portions of water, and dried over anhydrous magnesium sulfate. After filtration, the ether was removed by distillation at atmospheric pressure to give yellow liquid residue. The residue was distilled *in vacuo* [bulb to bulb distillation at 50–56° (5 mm)] to give 0.324 g of colorless liquid. This colorless liquid was analyzed by analytical glpc on a Hewlett-Packard high-efficiency packed column, 0.125 in. × 6 ft stainless steel packed with 10% UCON-98 on 80–100 Chromosorb W, indicating that only one compound was present. Thin layer chromatography of this colorless liquid also showed it to be one compound.

The analytical sample of **5** was obtained by preparative glpc (0.25 in. × 6 ft 17% SE-30 on 30–60 mesh Chromosorb P at 150°). The colorless liquid **5** has the following spectral properties: ir (CCl_4) 1745 (five-membered cyclic carbonyl stretching frequency), 1050–1150 (C–O–C stretching), and 2810 cm^{-1} (symmetric CH stretching for methoxyl group); nmr ($CDCl_3$) δ 2.00–2.60 (m, 6 H), 2.80–3.00 (m, 2 H, fused ring junction protons), 3.26 (s, 3 H, methoxyl hydrogens), and 3.65 (m, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 140 (5), 71 (68), 58 (100), 41 (23) (see text for interpretation of spectra).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.57; H, 8.57. Found: C, 68.30; H, 8.65.

Registry No.—**2**, 694-98-4; **3**, 37939-83-6; **4**, 39008-47-4; **5**, 39003-10-6.

Acknowledgment.—Partial support of this work by the U. S. Public Health Service (Grant CA 11326) is gratefully acknowledgen.

The Preparation of α,β-Unsaturated Aldehydes from Acid Chlorides

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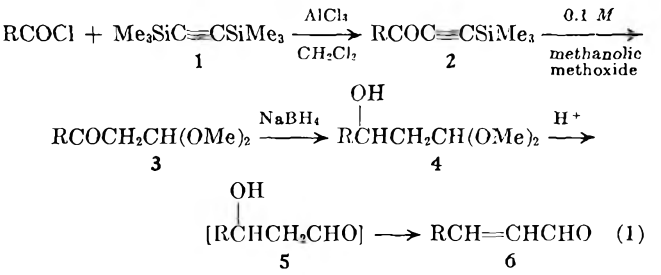
Received February 1, 1973

We describe here a simple procedure for the preparation of α,β-unsaturated aldehydes which involves a facile 2-carbon homologation of an acid chloride. The method, which, we belatedly became aware, is related to that previously reported by Wakayama, *et al.*,[1l] represents a useful alternative to those already available[1a–m] since acid chlorides are usually easily prepared.

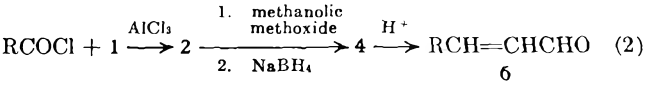
The method is summarized in the following generalized equation and is illustrated with *p*-biphenylcarbonyl chloride, benzoyl chloride, and cyclohexylcarbonyl chloride. It involves Friedel–Crafts alkynylation of an acid chloride with bistrimethylsilyl acetylene (**1**) as first reported by Birkofer, *et al.*,[2] then by Walton and Waugh,[3] followed by further sequential rapid transformation of the acyl trimethylsilylacetylene **2** to the β-keto acetal **3**, the β-hydroxy acetal **4**, the β-hydroxyaldehyde **5** and the α,β-unsaturated aldehyde **6**. Since the



(1)

alkynylation reaction appears to have appreciable scope,[2–4] the outlined sequence would appear to be reasonably general.

The intermediates indicated in eq 1 were actually isolated and characterized in the case of R = *p*-biphenylyl.[5] For the other acid chlorides the sequence was telescoped as indicated in eq 2. The various



(2)

intermediates indicated in eq 1 are presumably also involved in these cases.

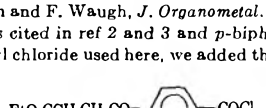
The fact that the foregoing method also provides a simple preparation of β-hydroxyaldehydes should not be overlooked. As indicated in the Experimental Section, mild acid hydrolysis of the hydroxy acetal **4** (R = *p*-biphenyl)[5] gave the corresponding hydroxyaldehyde **5** (obtained in this case as the hydrate.)

(1) (a) M. Jacobson, *J. Amer. Chem. Soc.*, **75**, 2584 (1953); (b) R. I. Hoaglin and D. Hirsh, U. S. Patent 2,628,257 (1953); *Chem. Abstr.*, **48**, 1423 (1954); (c) L. Crombie, *J. Chem. Soc.* 1007 (1955); (d) C. Jutz, *Chem. Ber.*, **91**, 1867 (1958); (e) G. Wittig and H. D. Frommeld, *ibid.*, **97**, 3548 (1964); (f) J. P. Ward and D. A. van Dorp, *Recl. Trav. Chim. Pays-Bas*, **86**, 545 (1967); (g) S. Satsumabayashi, K. Nakajo, R. Soneda, and S. Motoki, *Bull. Chem. Soc. Jap.*, **43**, 1586 (1970); (h) A. I. Meyers, *et al.*, *J. Amer. Chem. Soc.*, **91**, 764 (1969); (i) E. J. Corey, B. W. Erickson, and R. Noyori, *ibid.*, **93**, 1724 (1971); (j) E. J. Corey and S. Terashima, *Tetrahedron Lett.* 1815 (1972); (k) E. Hunt and B. Lythgoe, *Chem. Commun.*, 757 (1972); (l) S. Wakayama, S. Itoh, S. Yui, and H. Mackawa, *J. Chem. Soc. Jap.*, **78**, 1525 (1957); (m) see review by J. Carnduff, *Quart. Rev., Chem. Soc.*, **20**, 169 (1966).

(2) L. Birkofer, A. Ritter and H. Uhlenbrauck, *Chem. Ber.*, **96**, 3280 (1963).

(3) D. R. M. Walton and F. Waugh, *J. Organometal. Chem.*, **37**, 45 (1972).

(4) To the examples cited in ref 2 and 3 and *p*-biphenylcarbonyl chloride and cyclohexylcarbonyl chloride used here, we added the acid chloride i which



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we found reacted in the anticipated manner with **1** at room temperature (2.25 hr) in CH_2Cl_2 in the presence of 3 molar equiv of aluminum chloride. (Very little if any reaction occurred with 1 molar equiv.)

(5) The detailed work was done in this series because of our interest in the products as chemical intermediates.

Experimental Section[6]

The general telescoped procedure is illustrated with biphenylcarbonyl chloride as substrate as follows. To a stirred solution of 2 g (0.009 mol) of the acid chloride (G & C Chemical Co., Belleville, N. J.) and 1.7 g (0.01 mol) of bistrimethylsilylacetylene[3] in 25 ml of methylene chloride (dried by storing over molecular sieves) cooled in ice–water was added 1.4 g (0.01 mol) of anhydrous aluminum chloride. After stirring for *ca.* 3 min, the cooling bath was removed. The reaction mixture was stirred at room temperature for 2 hr and then was poured into ice–water and the organic product was extracted into ether. Drying and evaporating the ether left the trimethylsilylacetylenic ketone **2** (R = biphenyl) which was treated with 20 ml of cold 0.1 *M* methanolic sodium methoxide. The cooling bath (ice–water) was removed after *ca.* 1 min and the mixture was stirred for 10 min to effect conversion to **3** (R = biphenyl). The resulting solution of **3** was cooled (ice–water), 1.2 g (0.031 mol) of solid sodium borohydride was added, the cooling bath was removed, the mixture was stirred for 20 min and poured into ice–water, and the β-hydroxy dimethyl acetal **4** (R = biphenyl) was isolated by extracting with ether and drying and evaporating the ethereal solution. Crude **4** was dissolved in 40 ml of dioxane, 20 ml of 4 *N* aqueous hydrochloric acid was added, and the mixture was heated on the steam bath at 80–85° (internal temperature) for 5 min and then allowed to cool for another 5 min. The reaction mixture was poured into ice–water to give the α,β-unsaturated aldehyde **6** (R = biphenyl) as an off-white solid, yield 1.55 g (84% from the acid chloride), mp 106–115°. Uv comparison with an analytical sample indicated it to be 81% pure. [Analytically pure aldehyde could be obtained by thick layer chromatography on 2-mm silica gel using *n*-hexane–EtOAc (4:1) for development; R_f *ca* 0.8.] It melted at 119–121° (lit.[7] mp 120–121°), λ_{max}^{MeOH} 318 nm (ε 33,300).

Liquid aldehydes (*e.g.*, cinnamaldehyde) were isolated from the hydrolysis mixture by extraction into ether.

With the biphenylchlorocarbonyl substrate the various intermediates involved in the conversion (eq 1) were isolated (by quenching in ice–water and extracting with ether after the appropriate time interval indicated in the telescoped procedure) and characterized.

p-$C_6H_5C_6H_4C(=O)C{\equiv}CSiMe_3$.—The analytical sample melted at 71–73° (from petroleum ether, bp 30–60°): R_f on tlc (*n*-hexane–EtOAc) *ca.* 0.9; λ_{max}^{KBr} 4.7 (C≡C, v weak), 6.13 (acetylenic ketone), and 6.25 μ (aromatic).

Anal. Calcd for $C_{19}H_{18}OSi$ (278.41): C, 77.65; H, 6.52. Found: C, 77.74; H, 6.47.

p-$C_6H_5C_6H_4C(=O)CH_2CH(OMe)_2$.—The analytical sample obtained by thick layer chromatography using *n*-hexane–EtOAc (4:1) for development melted at 35–38°: R_f *ca* 0.3; λ_{max}^{KBr} 5.95 μ; mass spectrum *m/e* 270 (M^+), 75 [$CH(OMe)_2$].

Anal. Calcd for $C_{17}H_{18}O_3$ (270.31): C, 75.53; H, 6.71. Found: C, 75.23; H, 6.57.

p-$C_6H_5C_6H_4CHOHCH_2CH(OMe)_2$.—The analytical sample obtained by thick layer chromatography (C_6H_6–EtOAc 4:1) melted at 57–59°, λ_{max}^{KBr} 3.0 μ (OH), R_f (C_6H_6–EtOAc 4:1) *ca.* 0.35.

Anal. Calcd for $C_{17}H_{20}O_3$ (272.33): C, 74.97; H, 7.40. Found: C, 74.92; H, 7.45.

p-$C_6H_5C_6H_4CHOHCH_2CH(OH)_2$.—Treating **4** (R = biphenyl) dissolved in a small amount of ether with 6 *N* aqueous hydrochloric acid at room temperature for 15 min gave the hydrated aldehyde as a colorless solid, mp 135–140°, as indicated by ir, nmr, and mass spectral analysis. Treatment of the hydrated aldehyde with 4 *N* HCl–dioxane as described above gave the unsaturated aldehyde **6** (R = biphenyl) in 92% yield.

Cyclohexyl-COCl → Cyclohexyl-CH=CHCHO.—Using the telescoped procedure described above, cyclohexylcarbonyl chloride (Eastman) was converted to β-cyclohexylacrolein[8] in 40–45% yield. (The crude aldehyde was converted directly to its semicarbazone[8] by the usual method.[9] The yield of aldehyde indicated is based on the amount of semicarbazone obtained.)

Benzoyl Chloride → Cinnamaldehyde.—Using the telescoped procedure, benzoyl chloride was converted to cinnamaldehyde in 78% yield. (Here too, as in the previous experiment, the yield was established by conversion to its semicarbazone derivative.)

Registry No.—**1**, 14630-40-1; **2** (R = biphenylyl), 39703-85-0; **3** (R = biphenylyl), 39703-86-1; **4** (R = biphenylyl), 39703-87-2; **5** (R = biphenylyl) hydrated aldehyde, 39703-88-3; **6** (R = biphenylyl), 39703-89-4; biphenylcarbonyl chloride, 14002-51-8; cyclohexylcarbonyl chloride, 2719-27-9; β-cyclohexylacrolein, 935-03-5; benzoyl chloride, 98-88-4; cinnamaldehyde, 104-55-2.

Acknowledgments.—I thank Mr. L. Brancone and staff for the analysis, Mr. W. Fulmor and staff for the uv spectra, and Dr. G. Van Lear for the mass spectra.

(6) Melting points are uncorrected. The thin layer and thick layer (2 mm) plates used were obtained from Analtech Inc., Newark, Del. Uv light was used for spot visualization. Mass spectra were determined on an AEI MS-9 spectrometer at 70 eV.

(7) C. Jutz, *Chem. Ber.*, **91**, 1874 (1958).

(8) E. D. Venus-Danilova, *J. Gen. Chem. USSR*, **4**, 866 (1934); *Chem. Abstr.*, **29**, 21523 (1935).

(9) R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," 3rd ed, Wiley, New York, N. Y., 1948, p 170.

Photoinduced Reduction of Polyhalogenomethyl Groups

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Studies on the stereoselective synthesis of carbohydrates by telomerization of vinylene carbonate with polyhalogenomethanes[1] have shown the need for the mild and selective reduction of tri- or dihalogenomethyl groups to di- or monohalogenomethyls, and, among the reductive agents previously reported,[2] only $Ni(CO)_4$ is satisfactorily effective for the present purpose.[3] The reduction of polyhalide is important as the preparative method for synthetically difficult lower halides.

In this paper we describe the smooth and mild conversion of polyhalogenomethyl groups to di- or monohalogenomethyls by simple irradiation with an ultraviolet lamp in tetrahydrofuran (THF). The solutions of tri- or dihalogenomethyl compounds (*ca.* 1×10^{-1} *M*) were irradiated either with a high- or low-pressure mercury lamp at room temperature and reduction is usually completed within several hours. This reaction does not proceed in the dark. The results are summarized in Table I.

Polyhalides such as 1,1,1,3-tetrabromononane, 1,1,1,3-tetrachlorooctane, and telomers of vinylene carbonate with CCl_4 (**1a** and **2a**)[1,4] could be reduced exclusively to dihalogenomethyl compounds without any detectable amount of monohalogenomethyls, while the benzylic trichloromethyl compound underwent a smooth reductive dimerization to 1,1,2,2-tetrachloro-1,2-diphenylethane in analogy with the case by

(1) T. Tamura, T. Kunieda, and T. Takizawa, *Tetrahedron Lett.*, 2219 (1972).

(2) C. A. Buehler and D. E. Pearson, "Survey of Organic Syntheses," Wiley-Interscience, New York, N. Y., 1970, p 408; E. T. Chukovskaya, A. A. Kamyshova, and R. K. Freidlina, *Zh. Org. Khim.*, **3**, 1358 (1967); I. M. Downie and J. B. Lee, *Tetrahedron Lett.*, 4951 (1968); R. G. Petrova and R. K. Freidlina, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1574 (1970); E. T. Chukovskaya, N. A. Kuzmina, and R. K. Freidlina, *ibid.*, 2343 (1970).

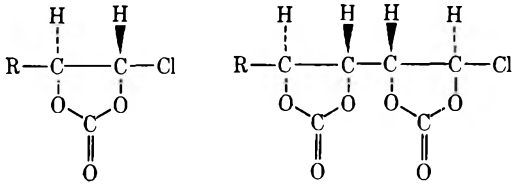
(3) T. Kunieda, T. Tamura, and T. Takizawa, *Chem. Commun.*, 885 (1972).

(4) T. Tamura, T. Kunieda, and T. Takizawa, in preparation.

TABLE I

Compd	Registry no.	Concn, mol/l.	Irradiation time, hr	Product	Registry no.	Yield,[a] %
1,1,1,3-Tetrabromononane	1070-25-3	0.11	8	1,1,3-Tribromononane	1071-51-8	69 (0)[c]
1,1,1,3-Tetrachlorooctane	18088-13-6	0.12	11	1,1,3-Trichlorooctane	4905-80-0	78 (0)
1a		0.20	3	**1b**		76 (4)
2a		0.04	0.5	**2b**		74 (0)
Carbon tetrabromide	558-13-4	0.20	0.1	Bromoform	75-25-2	78[b] (10)
7,7-Dibromonorcarane	2415-79-4	0.02	6	7-Bromonorcarane	1121-40-0 (endo) 1121-41-1 (exo)	24 (13)
Benzotrichloride	98-07-7	0.12	4	1,1,2,2-Tetrachloro-1,2-diphenylethane	13700-81-7	40 (7)

[a] Isolated yields. [b] Determination by glc. [c] Recovery of starting material in parentheses (%).

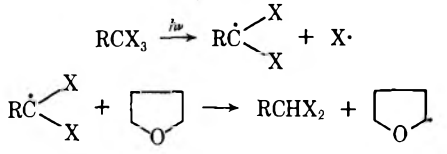


1a, R = CCl_3
b, R = $CHCl_2$

2a, R = CCl_3
b, R = $CHCl_2$

$Ni(CO)_4$.[3] 7,7-Dibromonorcarane[5] gave a mixture of *cis*- and *trans*-7-bromonorcarane in a ratio of 2.2:1, which is similar to that in the reduction *via* radical intermediates by tri-*n*-butyltin hydride[6] or methylmagnesium bromide,[7a] while 1,1-dibromocyclohexane did not give 1-bromocyclohexane under the same conditions.

This reaction would involve the initial formation of dihalomethyl radicals as important intermediates by action of uv light followed by hydrogen abstraction from tetrahydrofuran.[7b] The more stable intermediate, dichlorobenzyl radical, would couple more rapidly than abstract hydrogen from the solvent.



This mild and selective reduction is a feasible method as a general route to dihalogenomethyl compounds.

Experimental Section

The melting and boiling points are uncorrected. The nmr spectral data ($CDCl_3$, TMS internal standard, J in hertz) were obtained using a JEOL PS-100 nmr spectrometer, the glc data using a YANACO G-800 gas chromatograph (SE-30 column). Irradiations were carried out either with a HALōS PIL-60 (low pressure) or a HALōS PIH-500 (high pressure) at room temperature and the average distance of the irradiated solution from the light source was 4 cm.

1,1,3-Tribromononane.—1,1,1,3-Tetrabromononane was prepared by the addition of carbon tetrabromide to 1-octene according to the reported method.[8] 1,1,1,3-Tetrabromononane (5.0 g, 11.3 mmol) was dissolved in THF (100 ml) and irradiated in a Pyrex vessel with a high-pressure mercury lamp for 8 hr. The solvent was removed *in vacuo* and chromatography of the residue on silica gel (*n*-hexane) followed by distillation under diminished pressure gave 1,1,3-tribromononane (2.8 g, 69%) as a colorless liquid: bp 126–127° (5 mm); nmr δ 1.30 (m, 13 H), 2.70 (d d, J_1 = 10, J_2 = 7 Hz, 1 H), 2.80 (d d, J_1 = 10, J_2 = 7 Hz, 1 H), 4.10 (t t, J = 7 Hz, 1 H), 5.90 (t, J = 7 Hz, 1 H). *Anal.* Calcd for $C_9H_{17}Br_3$: C, 29.62; H, 4.97. Found: C, 29.56; H, 4.71.

1,1,1,3-Tetrachlorooctane.—1-Heptene (19.6 g) and carbon tetrachloride (92.4 g) were heated under a nitrogen atmosphere for 9 hr, and benzoyl peroxide (1.45 g) was added every 3 hr. The solvent was removed *in vacuo* and the product was purified by distillation to give 1,1,1,3-tetrachlorooctane: bp 98–99° (2.5 mm); nmr δ 1.30 (m, 11 H), 3.00 (d d, J_1 = 16, J_2 = 5 Hz, 1 H), 3.30 (d d, J_1 = 16, J_2 = 5 Hz, 1 H), 4.20 (m, 1 H). *Anal.* Calcd for $C_8H_{14}Cl_4$: C, 38.12; H, 5.60. Found: C, 38.36; H, 5.50.

1,1,3-Trichlorooctane.—1,1,1,3-Tetrachlorooctane (3.0 g, 12 mmol) was dissolved in THF (100 ml) and irradiated in a quartz vessel with a low-pressure mercury lamp for 11 hr. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel (*n*-hexene) to give 1,1,3-trichlorooctane (2.8 g, 78%) as a colorless liquid: bp 98–99° (10 mm); nmr δ 1.35 (m, 11 H), 2.50 (d d, J_1 = 9, J_2 = 6 Hz, 1 H), 2.60 (d d, J_1 = 9, J_2 = 6 Hz, 1 H), 4.10 (t t, J = 6 Hz, 1 H), 6.00 (d d, J_1 = 7, J_2 = 5 Hz, 1 H). *Anal.* Calcd for $C_8H_{15}Cl_3$: C, 44.17; H, 6.95. Found: C, 44.46; H, 6.92.

Irradiation with a high-pressure mercury lamp gave a similar result.

4-Chloro-5-dichloromethyl-1,3-dioxolan-2-one (1b).—4-Chloro-5-trichloromethyl-1,3-dioxolan-2-one (1a), mp 53–54° (4.8 g, 20 mmol), was dissolved in THF (100 ml) and irradiated in a quartz vessel without filter with a high-pressure mercury lamp for 3 hr. The solvent was removed *in vacuo* and purification by chromatography on silica gel gave 4-chloro-5-dichloromethyl-1,3-dioxolan-2-one (**1b**) (3.1 g, 76%) in addition to the unchanged material (0.2 g). Recrystallization from *n*-hexane gave an analytical sample of **1b** as colorless prisms: mp 31–33°; ir (neat) 1830 cm^{-1} ($\nu_{C=O}$); nmr δ 5.05 (d d, J_1 = 4, J_2 = 2.5 Hz, 1 H), 5.95 (d, J = 4 Hz, 1 H), 6.20 (d, J = 2.5 Hz, 1 H). *Anal.* Calcd for $C_4H_3O_3Cl_3$: C, 23.39; H, 1.47. Found: C, 23.33; H, 1.39.

5-Chloro-5′-dichloromethyl[4,4′-bi-1,3-dioxolane]-2,2′-dione (2b).—5-Chloro-5′-trichloromethyl[4,4′-bi-1,3-dioxolane]-2,2′-dione (**2a**)[1] (mp 185–186°, 1.3 g, 4 mmol), prepared by telomerization of vinylene carbonate with carbon tetrachloride, was dissolved in THF (100 ml) and similarly irradiated with a high-pressure mercury lamp for 0.5 hr. After removal of the solvent the product was purified by chromatography on silica gel and recrystallized from carbon tetrachloride to give dichloromethyl compound **2b** (864 mg, 74%) as colorless prisms: mp 115–116°; ir (Nujol) 1830 cm^{-1} ($\nu_{C=O}$); nmr (CH_3CN) δ 5.15 (m, 3 H),

(5) W. von E. Doering and A. K. Hoffmann, *J. Amer. Chem. Soc.*, **76**, 6162 (1954).

(6) D. Seyferth, H. Yamazaki, and D. L. Alleston, *J. Org. Chem.*, **28**, 703 (1963); H. G. Kuivila, L. W. Menapace, and C. R. Warner, *J. Amer. Chem. Sc.*, **84**, 3584 (1962).

(7) (a) *Cf.* D. Seyferth and B. Prokai, *J. Org. Chem.*, **31**, 1702 (1966). (b) Determination of the fate of the tetrahydrofuran radicals as well as the mechanistic evidence awaits further investigation.

(8) M. S. Kharasch, E. V. Jensen, and W. H. Urry, *J. Amer. Chem. Soc.*, **69**, 1100 (1947).

6.20 (d, J = 3 Hz, 1 H), 6.60 (d, J = 2 Hz, 1 H). *Anal.* Calcd for $C_7H_5O_6Cl_3$: C, 28.85; H, 1.73. Found: C, 29.01; H, 1.69.

Bromoform.—Carbon tetrabromide (0.65 g, 1.95 mmol) was dissolved in THF (10 ml) and irradiated through a Pyrex filter with a high-pressure mercury lamp for 6 min. The major product (78% yield by glc analysis) was identified as bromoform by direct comparison.

7-Bromonorcarane.—7,7-Dibromonorcarane[5] (4.9 g, 19.1 mmol) was dissolved in THF (1000 ml) and irradiated with a low-pressure mercury lamp under an argon atmosphere for 6 hr. Removal of the solvent followed by chromatography on silica gel (*n*-hexane) gave a mixture of *cis*- and *trans*-7-bromonorcarane in a ratio of 2.2:1 (0.8 g, 24%) as a colorless liquid in addition to the starting material (0.66 g): bp 78° (16 mm); nmr δ 1.35 (m, 10 H), 2.55 (t, J = 3 Hz, 0.3 H, trans isomer), 3.25 (t, J = 8 Hz, 0.7 H, cis isomer); glc retention time (120°), trans isomer 5.1 min, cis isomer 6.2 min. The nmr and glc data were identical with those of the authentic sample prepared by the literature method.[7]

1,1,2,2-Tetrachloro-1,2-diphenylethane.—A solution of benzotrichloride (2.35 g, 12 mmol) in THF (100 ml) was irradiated in a Pyrex vessel with a high-pressure mercury lamp for 4 hr. Purification of the product by chromatography on silica gel gave dimeric compound, 1,1,2,2-tetrachloro-1,2-diphenylethane (0.77 g, 40%), together with a trace of benzal chloride and the unchanged material (156 mg). The dimer was recrystallized from *n*-hexane to give colorless prisms, mp 163°, whose ir spectrum was identical with that of the authentic sample.[9]

Registry No.—**1a**, 39010-29-2; **1b**, 39010-30-5; **2a**, 39010-31-6; **2b**, 39010-32-7; 1-heptene, 592-76-7; carbon tetrachloride, 56-23-5.

(9) G. Sanna, *Chem. Zentr.*, *II*, 2345 (1937).

Photolysis of Sultones. Conversion to Butenolides and to Dimeric Sultones

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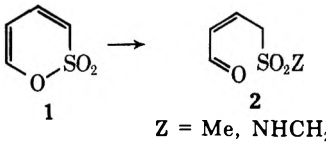
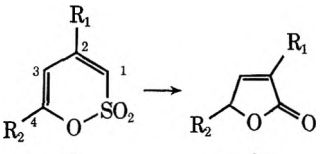
Photolysis of unsaturated sultones of general structure **1**, when carried out in methanol solution or in ether solutions containing benzylamine, has been shown to give ketosulfonic acid derivatives (**2**).[2,3]



1 **2**

Z = Me, $NHCH_2Ph$

We have found that when photolysis is carried out in the absence of a nucleophile the product is a butenolide. Thus, irradiation of 4-hydroxy-2-methyl-1,3-pentadiene-1-sulfonic acid sultone (**3a**)[4] in ether solution employing a medium-pressure mercury lamp yielded 2-methyl-4-hydroxy-2-pentenoic acid lactone (**4a**)[5] in 65% yield. Similarly irradiation of the sultone **3b**[4] gave the butenolide **4b**[6] in 53% yield. The loss of sulfur monoxide in these reactions is evidenced

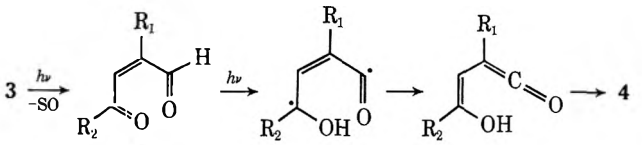


3 **4**

a, $R_1 = R_2 = Me$
b, $R_1 = Me$; $R_2 = Ph$

by the formation of both sulfur dioxide and monoclinic sulfur.[7,8]

Although the detailed mechanism of this transformation has not been defined, initial formation of a dicarbonyl intermediate **5** through photochemically induced loss of sulfur monoxide from **3** seems likely.[9] Further transformation of the unsaturated keto aldehyde through photochemical γ-hydrogen abstraction, decay to the ground state, and cyclization of the ketene **6** has a close parallel in the photochemical conversion of 2-formylbenzophenone,[13] 2-formylacetophenone,[14] and phthalaldehyde[15,16] to the corresponding pthalides. In these reactions clear evidence has been adduced for γ-hydrogen abstraction in the keto aldehyde and for the intermediary of an enol ketene.[15,16]



5 **6**

Sensitized photolysis of these sultones, carried out in the presence of benzophenone, leads to the formation of dimeric products. The infrared spectra of these dimers preserved the moderately intense band near 1680 cm^{-1}, present in the starting material, which is assigned to the enol sulfonate grouping.[17] However, a second moderately intense absorption band in the starting material near 1580 cm^{-1}, assigned to the remaining double bond, is uniformly absent from the dimers.[18] These observations eliminate all possible

(1) Taken in part from the Ph.D. Thesis of B. Gorewit, Brandeis University, 1973.

(2) E. Henmo, P. de Mayo, A. B. M. A. Sattar, and A. Stoessl, *Proc. Chem. Soc.*, 238 (1961).

(3) J. F. King, P. de Mayo, E. Morkved, A. B. M. A. Sattar, and A. Stoessl, *Can. J. Chem.*, **41**, 100 (1963).

(4) T. Morel and P. E. Verkade, *Recl. Trav. Chim. Pays-Bas*, **68**, 539 (1949).

(5) H. C. Volger, W. Brackman, and J. W. F. M. Lemmers, *ibid.*, **84**, 1203 (1965).

(6) F. Ramirez and M. B. Rubin, *J. Amer. Chem. Soc.*, **77**, 3768 (1955).

(7) P. W. Schenk and R. Steudel, *Angew. Chem., Int. Ed. Engl.*, **4**, 402 (1965).

(8) The loss of SO_2 on irradiation of a similarly constituted sultone in *dyglyme* solution has previously been reported by J. L. Charlton and P. de Mayo, *Can. J. Chem.*, **46**, 55 (1968).

(9) Sulfenes may be intermediates in this reaction. The photochemical rearrangement of the closely related sulfines to carbonyl compounds through an excited singlet state[10] has been reported for a number of such compounds.[10,11] Although the corresponding photochemical rearrangement of a sulfene has hitherto not been observed, high-temperature thermolysis of thiete 1,1-dioxides is reported to give α,β-unsaturated ketones or aldehydes formed apparently through initial cycloreversion to a vinyl sulfene followed by loss of SO.[12]

(10) A. G. Schultz and R. H. Schlessinger, *Chem. Commun.*, 1483 (1969); R. H. Schlessinger and A. G. Schultz, *Tetrahedron Lett.*, 4513 (1969).

(11) R. Zwanenburg, L. Thys, and J. Strating, *ibid.*, 3453 (1967). J. F. King and T. Durst, *J. Amer. Chem. Soc.*, **85**, 2676 (1963); *Can. J. Chem.*, **44**, 819 (1966).

(12) C. L. McIntosh and P. de Mayo, *Chem. Commun.*, 32 (1969).

(13) M. Pfau, E. W. Sarver, and N. D. Heindel, *C. R. Acad. Sci., Ser. C*, **268**, 1167 (1969).

(14) P. Yates, A. C. Mackay, and F. X. Garneau, *Tetrahedron Lett.*, 5389 (1968).

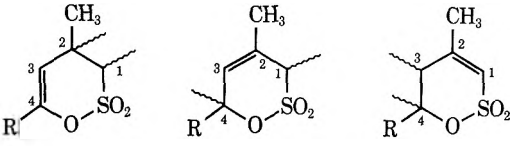
(15) S. P. Pappas and J. E. Blackwell, *ibid.*, 3337 (1968).

(16) K. F. Cohen, J. T. Pinhey, and R. J. Smith, *ibid.*, 4729 (1968).

(17) P. E. Peterson and J. M. Indelicato, *J. Amer. Chem. Soc.*, **90**, 6515 (1968), have reported absorption near 1680 cm^{-1} for a number of enol tosylates and brosylates.

(18) Divinyl sulfone exhibits absorption at 1613 cm^{-1} (Satler ir no. 13512).

structures for the dimers, except for the 1,2-dimeric structure **7**.



7 **8** **9**

a, R = CH_3
b, R = C_6H_5

These conclusions are supported by the following further observations. The relative simplicity of the nmr spectra of the dimers rules out structures resulting from [2 + 2] cycloadditions of $C_{1,2}$ with $C_{3,4}$ or of [2 + 4] cycloadditions. The assignment of the multiplets at τ 3.74 and 4.38 to H_1 and H_3, respectively, in the spectrum of **3a** is based on the spectra of trisubstituted sultones reported by Barnett and McCormack.[19] These absorptions shift to τ 5.3 [broad singlet) and 4.8 (singlet) in the photodimer, consistent with a 1,2 or 1,4 dimer structure (**7** or **8**) in which these resonances are assigned to H_1 and H_3, respectively. The data are not in accord with a 3,4 dimer structure (**9**), which would require assigning the absorption at τ 4.8 to H_1. The changes observed in the dimerization of **3b** are more instructive. The nmr spectrum of this substance exhibits two one-proton signals, one a multiplet at τ 3.53 and the second a singlet at τ 3.60, which can be assigned to H_1 and H_3, respectively, in addition to a methyl doublet signal at τ 7.85 (J = 1.5 Hz). Dimerization results in the collapse of the methyl doublet to a sharp singlet at τ 8.6. The two one-proton signals now both appear as singlets at τ 3.80 and 4.89. Taken together with the spectral data of **3a** and its photodimer, neither of these observations are compatible with either a 3,4 or a 1,4 dimer, since each such structure preserves a –CH=CMe– grouping which should give rise, as it does in the dimer of **3a**, to readily detectable allylic coupling. A 1,2 dimer structure is alone compatible with the absence of such coupling and with the chemical shift of the methyl protons.

Thus, in contrast to α-pyridones and 2-aminopyridines, which give rise only to 1,4 photodimers, these sultones afford only 1,2 dimers on photolysis. Their behavior is more closely paralleled by that of α-pyrones. The parent substance is reported[20] to yield a mixture of 1,4 and 1,2 dimers on photolysis, while 4,6-diphenyl-α-pyrone yields only a mixture of 1,2 dimers under these conditions.[21]

The present evidence does not allow us to define the structures of the photodimers more closely, but the failure of **7a** to react with a variety of olefin reagents such as bromine, diimide, diborane, *m*-chloroperbenzoic acid, and potassium permanganate and its resistance to catalytic hydrogenation suggests that it has one of the two possible syn 1,2-dimeric structures.[22]

(19) W. E. Barnett and J. A. McCormack, *Tetrahedron Lett.*, 651 (1969).
(20) P. de Mayo and R. W. Yip, *Proc. Chem. Soc.*, 84 (1964).
(21) R. D. Rieke and R. H. Copenhafer, *Tetrahedron Lett.*, 879 (1971).
(22) An example of a similar reduction in chemical reactivity owing apparently to steric crowding in the transition state is provided by the 1,4 photodimer of 2-aminopyridine, whose tetrahydro derivative resists hydrolysis by hot concentrated alkali while the monocyclic analog undergoes rapid hydrolysis in water: E. C. Taylor and R. O. Kan, *J. Amer. Chem. Soc.*, **85**, 776 (1963).

Experimental Section

All reactions were carried out under nitrogen in a flame-dried apparatus. Photolyses were carried out using a medium-pressure quartz mercury-vapor lamp (Hanovia Type L, 450 W). Infrared spectra were recorded on a Perkin-Elmer Model 457 grating spectrophotometer. Nuclear magnetic resonance spectra were obtained using a Varian Model A-60A spectrometer. Mass spectra were obtained with an AEI Model MS-12 spectrometer. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Column chromatography was carried out using Camag neutral alumina adjusted to Brockman II activity.

Preparation of 4-Hydroxy-2-methyl-1,3-pentadiene-1-sulfonic Acid Sultone (3a).—This material was prepared from mesityl oxide following the procedure of Morel and Verkade:[4] mp 70–71°; ir (KBr) 1667 (C=CO), 1587 (C=CS), 1335, 1155 cm^{-1} (SO_2); uv max (95% C_2H_5OH) 267.5 nm (ϵ 5250); nmr ($CDCl_3$) τ 3.74 (m, 1, SCH=), 4.38 (m, 1, CH=), 7.87 [d, 3, J = 1 Hz, $OC(CH_3)$=], 7.98 (d, 3, J = 2 Hz, =CCH_3).

Preparation of 4-Hydroxy-2-methyl-4-phenyl-1,3-butadiene-1-sulfonic Acid Sultone (3b).—This material was prepared from β,β-dimethylvinyl phenyl ketone following the procedure of Morel and Verkade:[4] mp 83–84°; ir (KBr) 1640 (C=CO), 1555 (C=CS), 1345, 1180 cm^{-1} (SO_2); uv max (95% C_2H_5OH) 307.0 nm (ϵ 15,200), 219.0 (10,400); nmr ($CDCl_3$) τ 3.53 (m, 1, SCH=), 3.60 (s, 1, CH=), 7.85 (d, 3, J = 1.5 Hz).

Unsensitized Photolyses of Sultone 3a.—A solution of 2.50 g (15.6 mmol) of sultone in 220 ml of absolute ether was irradiated, under nitrogen, for 2.3 hr, through a Vycor filter. At this time infrared analysis revealed that the lactone band at 1745 cm^{-1} had reached maximum intensity. Work-up, including chromatography on alumina, yielded 1.14 g (65.4%) of lactone **4a**:[4,6] bp 30° (0.05 mm); nmr ($CDCl_3$) τ 8.63 (d, 3, J = 6.8 Hz, 4-Me), 8.10 (t, 3, J = 3.6 Hz, 2-Me), 5.06 (m, 1, 4-H), 2.96 (m, 1, 3-H).

When irradiation was carried out in benzene solution and nitrogen was passed continuously through one solution, and then into a 30% aqueous solution of H_2O_2, sulfuric acid corresponding to 11 mol % of the sultone consumed was titrated. Chromatography of the reaction solution yielded monoclinic sulfur corresponding to 29 mol % of the sultone consumed, in addition to lactone **4a**.

Unsensitized Photolysis of Sultone 3b.—Similar photolysis of **3b** in ether solution for 1 hr, employing a Corex filter, yielded lactone **4b**: mp 220–221° (lit.[6] mp 221–223°); ir (KBr) 1760 cm^{-1} (CO); nmr (DMSO) τ 8.40 (d, 3, J = 1.8 Hz, Me), 2.66 (s, 5, Ph), 1.91 (m, 1, 3-H), 1.69 (s, 1, 4-H).

Sensitized Irradiation of Sultone 3a.—A solution of 7.50 g (46.9 mmol) of **3a** and 9.0 g (49.4 mmol) of benzophenone in 100 ml of anhydrous ether was irradiated through a Pyrex filter. After 45 min of irradiation, the solution was filtered, and the white precipitate was collected. The solution was returned to the reaction vessel and irradiation was resumed. This procedure was repeated until no further precipitate was formed. Recrystallization of this product from ethyl acetate–ether gave 2.89 g of dimer: mp 258–259°; ir (KBr) 1700 (C=CO), 1360, 1190 cm^{-1} (SO_2); nmr ($CDCl_3$) τ 4.8 (s, 2, OC=CH), 5.3 (s, 2, SCH), 8.02 [s, 6, $OC(CH_3)$=], 8.79 (s, 6, CCH_3); mass spectrum (70 eV) *m/e* 320, 176, 160, 133, 96, 43.

Anal. Calcd for $C_{12}H_{16}S_2O_6$: C, 45.00; H, 5.00; S, 20.00. Found: C, 45.16; H, 5.36; S, 19.82.

Chromatography of the reaction solution gave 7.51 g of benzpinacol, mp 190–192°, and 3.74 g of unreacted sultone.

Sensitized Irradiation of Sultone 3b.—Similar irradiation of **3b** gave the dimer **7b**: mp 218–219°; ir (KBr) 1660 (C=CO), 1375, 1180 cm^{-1} (SO_2); nmr ($CDCl_3$) τ 2.5 (m, 10, Ph), 3.80 (s, 2, OC=CH), 4.89 (s, 2, SCH) 8.60 (s, 6, CH_3); mass spectrum (70 eV) *m/e* 444, 300, 222, 195, 158, 129, 105, 77, 64, 43, 41.

Anal. Calcd for $C_{22}H_{20}S_2O_6$: C, 59.50; H, 4.52; S, 14.48. Found: C, 59.53; H, 4.55; S, 14.38.

Registry No.—**3a**, 4941-84-8; **3b**, 39533-27-2; **4a**, 5584-69-0; **4b**, 15121-75-2; **7a**, 39533-28-3; **7b**, 39599-24-1; benzophenone, 119-61-9.

Acknowledgment.—This work was supported by a grant from the National Institutes of Health (GM-16395) which is gratefully acknowledged.

7-Dehydrostigmasterol, α-Spinasterol, and Schottenol[1,2]

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The three title sterols are required for our studies on the growth, maturation, and reproduction of Sonoran Desert species of *Drosphilia*.[3] A number of preparations of 7-dehydrostigmasterol in 1–2% yield from stigmasteryl acetate have been reported.[4a–e] A more facile preparation of this sterol would readily lead to the other two compounds by selective hydrogenations.

Based on previous work[5–7] and more than 100 runs on the acetates of cholesterol, sitosterol, and stigmasterol in our laboratory, a method was developed that gives consistent, high yields of $\Delta^{5,7}$ acetates from the Δ^5 derivatives. The key steps involve the slow addition of solid *N*-bromosuccinimide (NBS) to a stirred, refluxing, illuminated solution of the Δ^5-steryl acetate in purified Skellysolve B and low-temperature removal of solvent from this mixture, followed by the dropwise addition of the 7-bromosteryl acetate in mesitylene to a refluxing, stirred solution of collidine in the same solvent.

α-Spinasterol has been isolated from many plants and has been prepared by hydrogenation of 7-dehydrostigmasteryl benzoate over Pt in ethyl acetate.[4d] The compound was readily obtained in our work by hydrogenation of 7-dehydrostigmasteryl acetate with tris(triphenylphosphine)chlororhodium in benzene–ethanol[8] or over Raney Ni in dioxane.[9]

Schottenol also occurs widely distributed among plants; its synthesis from α-spinasterol by hydrogenation over Pt in ether was described by Barton and Cox.[10] In our hands, hydrogenation of 7-dehydrostigmasterol or its acetate over Pt in ether or Raney Ni in several solvents always gave 8(14)-stigmasten-3β-ol as a substantial or principal reaction product when the reductions were run for an extended time to assure complete hydrogenation of the Δ^{22} bond.

The problem was solved by the addition of a small amount of triethylamine to the Ni-catalyzed reduction. Although this slowed the rate of reaction, the amine inhibited the $\Delta^7 \rightarrow \Delta^{8(14)}$ rearrangement and allowed a good yield of schottenol to be obtained from 7-dehydrostigmasterol. When the reduction was hastened by raising the temperature to 100°, 5α-8(14)-stigmasten-3β-ol and 5α-8(14)-stigmasten-3α-ol were the only products obtained. The latter compound has never been reported, although its isomer, 5β-8(14)-stigmasten-3α-ol, has been isolated from *Daemia extensa*.[11] The 5α,3α-ol was characterized by its chromatographic behavior, Liebermann–Burchard test, its inability to form an insoluble digitonide, and the analogies of the ir spectra[12] and melting points[13] of the 5α-8(14)-stigmasten-3α- and -3β-ols and their acetates with those of 5α-cholestan-3α-ol and 5α-cholestan-3β-ol.

The melting points of the products obtained in this study are given together with those from the literature in Table I.

Experimental Section

Melting points were taken *in vacuo* and are corrected. Glc on 5% OV-101, 260° (relative retention time) (cholesterol = 1.00): stigmasterol (1.38), 7-dehydrostigmasterol (1.48), α-spinasterol (1.52), schottenol (1.78), 5α-8(14)-stigmasten-3β-ol (1.51), 5α-8(14)-stigmasten-3α-ol (1.55); acetates comparable.

For tlc, 10% $AgNO_3$–silica gel plates were used: 1:1 $CHCl_3$–CCl_4 used for sterol acetates (R_f), 7-dehydrostigmasteryl acetate (0.26), 4,6,22-stigmastatrienyl acetate (0.46), stigmasteryl acetate (0.58); 95:5 $CHCl_3$–acetone used for free sterols (R_f), stigmasterol (0.39), 7-dehydrostigmasterol (0.20), α-spinasterol (0.39), schottenol (0.39), 8(14)-stigmasten-3β-ol (0.40), 8(14)-stigmasten-3α-ol (0.53).

7-Dehydrostigmasterol.—A 1-cm bore stopcock topped with a powder funnel was cemented (GE silicone RTV) to a 24/40 glass joint and placed in the center opening of a 1-l., three-necked flask equipped with a reflux condenser and nitrogen inlet. The flask was on a magnetic stirrer and was heated and illuminated by 2 GE DSB Photospot bulbs 5 cm away. Stigmasteryl acetate (68 g, 0.15 mol) was dissolved and brought to a reflux in 350 ml of purified Skellysolve B[5] (petroleum ether, bp 65–67°) in an N_2 stream with rapid stirring. NBS (45.5 g, 0.225 mol) was added in small portions during 30 min through the stopcock with the aid of 5–10 ml of solvent for each addition. Four minutes later the lights were removed and replaced with an ice bath. The cooled mixture was filtered through sintered glass into a 2-l. flask containing 35 ml of mesitylene and a magnetic stirring bar. The contents of the flask were evaporated *in vacuo* with an oil pump at 30–40° until a thick, honey-colored syrup remained. *Too high a temperature during this step results in low yields of product.*

The bromosteryl acetate was transferred to a dropping funnel with 150 ml of mesitylene and added over 35 min to a refluxing, stirred mixture of 75 ml of collidine and 350 ml of mesitylene under N_2. Five minutes later the mixture was cooled, low-boiling ether (400 ml) was added, and the mixture was filtered. After evaporation of the filtrate *in vacuo* at 50–60°, the brown semisolid residue was brought to a reflux under N_2 with 1 l. of acetone. After cooling to room temperature, 20 g of crude 7-dehydrostigmasteryl acetate was filtered off. An additional 2.5 g was obtained by work-up of the mother liquors.

The products from four such reactions were combined (88.7 g) and recrystallized from 1.3 l. of Skellysolve B under N_2 to yield 58.5 g of 7-dehydrostigmasteryl acetate, mp 175–177°. Further work-up of the mother liquors gave an additional 11.3 g of the product, mp 174–176°, for a total yield of 25.7% from stigmasteryl acetate. A pure sample, mp 178.3–179°, was obtained after an additional recrystallization from acetone. This was hydrolyzed to 7-dehydrostigmasterol and a benzoate was prepared (Table I).

(1) This work was supported by Grant GB28953X from the National Science Foundation. Contribution No. 1996 from the Arizona Agricultural Experiment Station.

(2) Trivial names for 5,7,22-stigmastatrien-3β-ol, 5α-7,22-stigmastadien-3β-ol, and 5α-7-stigmasten-3β-ol, respectively.

(3) H. W. Kircher and W. B. Heed, "Recent Advances in Phytochemistry," C. Steelink and V. C. Runeckles, Ed., Appleton-Century-Crofts, New York, N. Y., 1970.

(4) (a) O. Linsert, *Z. Physiol. Chem.*, **241**, 125 (1936); (b) O. Wintersteiner and W. L. Ruigh, *J. Amer. Chem. Soc.*, **64**, 1177 (1942); (c) G. A. D. Hazlewood, *Biochem. J.*, **33**, 454 (1939); (d) L. F. Fieser, M. Fieser, and R. N. Chakravarti, *J. Amer. Chem. Soc.*, **71**, 2226 (1949); (e) S. Agaki and K. Tsuda, *Chem. Pharm. Bull.*, **9**, 454 (1961); *Chem. Abstr.*, **55**, 27413 (1961).

(5) S. Bernstein, L. J. Binovi, L. Dorfman, K. J. Sax, and Y. Subbarow, *J. Org. Chem.*, **14**, 433 (1949).

(6) W. R. Nes, R. B. Kostic, and E. Mosettig, *J. Amer. Chem. Soc.*, **78**, 436 (1956).

(7) B. D. Kulkarni, G. Blondin, and W. R. Nes, *Steroids*, **1**, 21 (1963).

(8) A. J. Birch and K. A. M. Walker, *J. Chem. Soc. C*, 1894 (1966).

(9) L. F. Fieser and J. E. Herz, *J. Amer. Chem. Soc.*, **75**, 121 (1953).

(10) D. H. R. Barton and J. D. Cox, *J. Chem. Soc.*, 1354 (1948).

(11) M. M. Dhar, N. Anand, and M. L. Dhar, *J. Sci. Ind. Res.*, **18B**, 422 (1959).

(12) W. Neudert and H. Ropke, "Atlas of Steroid Spectra," Springer-Verlag, New York, N. Y., 1965, Compounds 816 and 817.

(13) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 28.

TABLE I
MELTING POINTS (°C) OF STEROLS AND THEIR DERIVATIVES

Registry no.	Sterol	This work, in vacuo, corrected: Free sterol	Acetate	Registry no.	Benzoate	Registry no.	Literature[a]: Free sterol	Acetate	Benzoate
481-19-6	7-Dehydrostigmasterol	158.5–159.3	178.3–179	39533-73-8	184.5–185.5	39533-21-8	152–154[b]	172–173[c]	178.5–180[d]
481-18-5	α-Spinasterol	172–173	188.5–189	4651-46-1	204–205	39599-22-9	172.5[e]	187[e]	201–202[f]
521-03-9	Schottenol	151–151.5	159.5–160	14473-77-9	184–184.5	39533-21-6	148–150[g]	161–163[h]	183.5[g]
14291-38-4	5α-8(14)-Stigmasten-3β-ol	116.5–117	117.8–118.5	14291-39-5	87.5–88.5	39533-23-8	114[i]	119[e]	89[i]
39533-72-7	5α-8(14)-Stigmasten-3α-ol	176–176.5	84.5–85	39533-24-9	99–100	39533-25-0			

[a] Highest melting point reported. [b] Reference 4a,e. [c] Reference 4a. [d] Reference 4b. [e] D. Larsen and F. W. Heyl, *J. Amer. Chem. Soc.*, **56**, 2663 (1934). [f] M. C. Hart and F. W. Heyl, *J. Biol. Chem.*, **95**, 311 (1932). [g] C. Djerassi, G. W. Krakower, A. J. Lemin, H. H. Liu, J. S. Mills, and R. Villotti, *J. Amer. Chem. Soc.*, **80**, 6284 (1958). [h] G. Biglino, *Farmaco, Ed. Sci.*, **14**, 673 (1959); *Chem. Abstr.*, **54**, 6812c (1960). [i] E. Fernholz and W. L. Ruigh, *J. Amer. Chem. Soc.*, **62**, 2341 (1940).

α-Spinasterol. A. **Rh-Catalyzed Reaction.**[8]—7-Dehydrostigmasteryl acetate (25 g) in 1200 ml of 3:1 benzene–ethanol was hydrogenated at room temperature and 1 atm pressure over 1.6 g of tris(triphenylphosphine)chlororhodium (Strem Chemical Co.) for 18 hr. Solvent was evaporated, the dry residue was extracted with petroleum ether and filtered to remove catalyst, and solvent was again evaporated. The residue was crystallized from 2:1 ethanol–benzene and then from acetone to give 15.1 g of α-spinasteryl acetate, mp 188.5–189°. An additional 7.7 g, mp 187.5°, was recovered by work-up of the mother liquors. A portion of the product was hydrolyzed to α-spinasterol, and a benzoate was prepared (Table I).

B. **Raney Ni Catalyzed Reaction.**[9]—7-Dehydrostigmasteryl acetate (11.3 g) in 450 ml of dioxane and 5 ml of Et_3N was hydrogenated over 10 ml of catalyst for 23 hr at room temperature and 1 atm pressure. Removal of catalyst and evaporation of solvent to 120 ml deposited 7.5 g of α-spinasteryl acetate, mp 186–186.5°. Further cooling of the filtrate yielded an additional 2.6 g of product, mp 183.5–184°.

Schottenol. A.—7-Dehydrostigmasterol (15 g) in 750 ml of ethyl acetate and 5 ml of Et_3N was hydrogenated for 4 days over 25 ml of Raney Ni at room temperature and 1 atm pressure. The reaction was followed by glc of samples periodically removed. Catalyst was then filtered off and the solvent was reduced in volume to 150 ml to precipitate 9.15 g of schottenol, mp 149.5–151.5°. Work-up of the mother liquors gave no more pure material.

B.—The reaction as in A was repeated in a Parr stirred pressure vessel at 14 atm H_2 pressure. After 50 hr the product was worked up as before to yield 8.9 g of schottenol, mp 150–151.5°.

The products from several runs (24.5 g) were combined in 500 ml of hot ethyl acetate and cooled to room temperature to yield 18.5 g of schottenol, mp 151–151.5°. An acetate and a benzoate were prepared (Table I).

5α-8(14)-Stigmasten-3α- and -3β-ol.—7-Dehydrostigmasterol (17 g) in 700 ml of ethyl acetate and 5 ml of Et_3N was hydrogenated over 20 ml of Raney Ni at room temperature for 10 min at 14 atm and for 2 hr at 100° and 14 atm. The reaction was followed by glc. An additional 22 hr at 14 atm and 100° and 24 hr at 140 atm and 100° with fresh catalyst produced no changes in the glc pattern.

The autoclave was cooled, catalyst was removed, and the product (one peak on glc, two spots on tlc) was chromatographed on 1 kg of 2:1 10% $AgNO_3$–silica gel–Celite with 10% ether in petroleum ether. The two compounds were cleanly separated (tlc) to yield 4 g of the higher R_f material and 8 g of the lower R_f material.

The former was crystallized from methanol–benzene to yield 5α-8(14)-stigmasten-3α-ol, mp 176–176.5°, acetate, mp 84.5–85° (from methanol–benzene), and benzoate, mp 99–100° (from ethanol). The compound gave a fast blue color with the Liebermann–Burchard reagent, no precipitate with digitonin, and had an ir spectrum similar to that of 5α-cholestan-3α-ol.[12] The material last to emerge from the column was recrystallized from methanol–benzene and identified as 5α-8(14)-stigmasten-3β-ol, mp 116.5–117.0° (from ethanol), acetate mp 117.8–118.5° (from ethanol), and benzoate mp 87.5–88.5° (from acetone). It corresponded to the lower R_f spot on tlc, had the same retention time on glc as the 3α-ol, gave a precipitate with digitonin and a fast blue Liebermann-Burchard test, and had an ir spectrum similar to that of 5α-cholestan-3β-ol.[12]

Registry No.—NBS, 128-08-5.

Percyclophane-4

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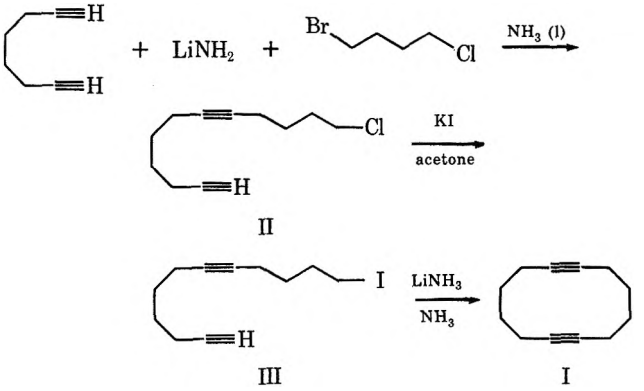
We wish to report the synthesis of an unusual new cage aromatic compound, percyclophane-4[1] (Figure 1). Percyclophane-4 was synthesized by the cyclic trimerization of cyclododecadiyne-1,7, catalyzed by organochromium and organocobalt compounds.

Cyclododecadiyne-1,7 (I) was synthesized from commercially available octadiyne-1,7 in the manner described below.



Overall yield of this synthesis was approximately 20%. This is a new synthesis of a previously reported compound.[2] Cyclododecadiyne-1,7 is a colorless, crystalline compound, mp 23 ± 2°, which on exposure

(1) "Percyclophane" is a name coined by the author to describe this cage molecule. The name is derived from the word paracyclophane, which refers to molecules with a configuration of two benzene rings linked together in the para positions.

(2) (a) D. J. Cram, N. L. Allinger, and H. Steinberg, *J. Amer. Chem. Soc.*, **76**, 726 (1959); (b) D. J. Cram and N. L. Allinger, *ibid.*, 6132 (1954); (c) *ibid.*, **78**, 2518 (1956).

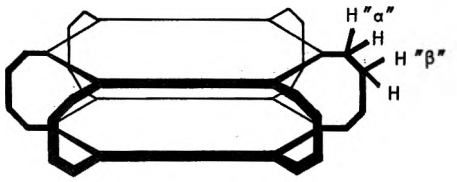


Figure 1.

to the air at room temperature slowly oxidizes to unknown products.[2]

Upon reaction of I with trimesitylchromium or dimesitylcobalt, a trimer was formed. The structure shown in Figure 1 of percyclophane-4 was assigned to the trimer. Elemental, infrared, nmr, and mass spectral analysis were consistent with this proposed structure.

Cyclododecadiyne was treated with either trimesitylchromium or dimesitylcoblat in a 5–10-fold molar excess in tetrahydrofuran solvent.[3] These reactions were generally run between −20 and 30°. These conditions, in the case of reaction with trimesitylchromium, gave a 10% yield of percyclophane-4 and in the case of dimesitylcobalt gave a yield of 70% of percyclophane-4. The percyclophane product was isolated and purified by sublimation. Elemental analysis was consistent with the formulation $C_{36}H_{48}$.

The nmr spectra of percyclophane-4 showed three broad resonances centered at δ 1.7, 2.3, and 2.9 with intensity ratios of 2:1:1, respectively. The resonances at δ 2.3 and 2.9 are attributed to the α hydrogens. The two hydrogens at each α position appear at different chemical shifts owing to rigidity of the structure. Models indicate that one α hydrogen is close to being in the plane of the aromatic ring while the other α hydrogen is close to being perpendicular to the ring. The broadness of the resonances must be due to unresolved complex spin–spin coupling and dipolar broadening. Anet and Brown[4] noted that the benzylic hydrogens in [3,3]percyclophane gave a singlet nmr resonance. The equivalence of the two benzylic hydrogens is attributed to a rapid equilibration between the pseudochair and boat configurations of the [3,3]paracyclophane. The energy barrier for this equilibrium was estimated at 11.7 kcal/mol. Models of percyclophane-4 indicate a tight packing of the six interring carbon bridges. This feature suggests a much higher barrier for equilibration. Actually the geometry of the molecule is such that the configurations of all the interring bridges must be changed simultaneously to avoid severe steric interactions. Such a simultaneous flipping of all six bridges would have a very high energy barrier indeed. Thus, the benzylic hydrogens are unique at nmr frequencies.

A second structure which might account for the observed nmr resonances would result from trimerization of only three acetylene moieties, giving rise to one fully substituted aromatic ring with three pendent cycloalkyne rings. For this structure an assignment could be made of the δ 2.9 resonance for the benzylic hydrogens and of the δ 2.3 resonance for the protons to the triple bond. We do note that these α hydrogens in

(3) H. Zeiss, P. J. Whearley, and H. J. S. Winkler, "Benzenoid Metal Complexes," Ronald Press, New York, N. Y., 1966, and references cited therein.

(4) F. A. L. Anet and M. A. Brown, *J. Amer. Chem. Soc.*, **91**, 2389 (1969).

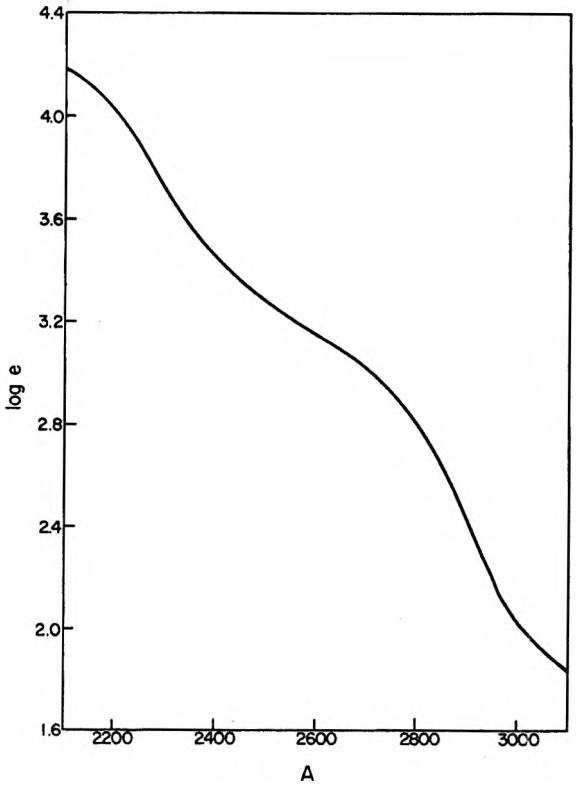


Figure 2.—Absorption spectra of percyclophane-4 in hexane.

cyclococedadiyne show a resonance at δ 2.1; however this resonance might well be shifted by shielding from the now present aromatic ring. The trimerization product failed, however, to show any reaction with bromine in carbon tetrachloride, which would have indicated the presence of the acetylenic linkages. This alternative structure must therefore be eliminated.

The infrared spectrum of the percyclophane was characterized only by aliphatic C–H modes. No absorptions were noted which could be assigned to the aromatic part of the molecule. It is commonly noted that such highly substituted aromatic rings have very weak ring absorptions.[5]

Most conclusive of all the analytical data was the high-resolution mass spectrum, which showed a parent ion, m/e 480.78, which corresponds to an empirical formula of $C_{36}H_{48}$. In addition, 99% of the ion current was in the C_{36} fragment. Essentially no fragmentation of the molecular skeleton took place. Consistent with this data, it is unlikely that a trimer of cyclododecadyne [$(C_{12}H_{16})_3$ = $C_{36}H_{48}$] could be assembled in any way except as the percyclophane-4, which would not show extensive fragmentation in the mass spectrum.

The ultraviolet spectrum of percyclophane-4 is shown in Figure 2. It is obvious that normal aromatic absorption is not present. This spectrum can be compared with those of [2.3]- and [4]paracyclophane shown in Figure 3. Cram[6] has shown that as two aromatic rings are brought close to one another a great deal of interaction between the rings takes place. This interring interaction results in a red shift of the major π–π^* band of the aromatic rings along with a loss of vibrational fine structure in the absorption band. It can be noted that percyclophane-4 has a λ_{max} (~2730 Å)

(5) L. J. Bellamy, "Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1954.

(6) D. J. Cram, *Rec. Chem. Progr.*, **20**, 71 (1959).

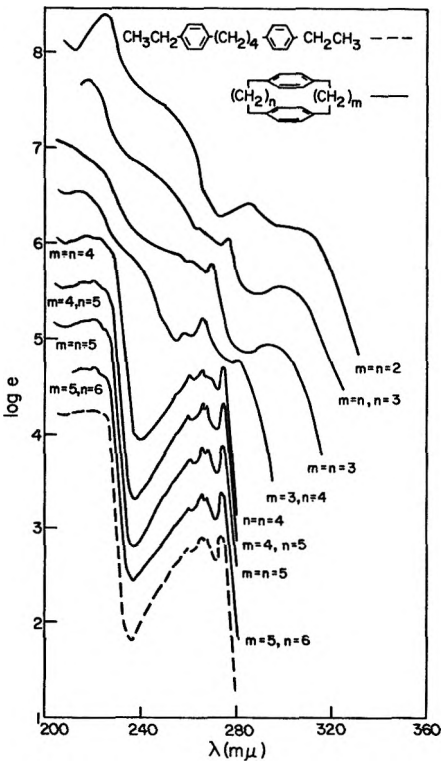


Figure 3.—Absorption spectra of paracyclophanes (each successive curve has been displaced upward by 0.5 log units, omitting the open-chair compounds).

and ϵ_{max} (~1000) very similar to that of [4,4]paracyclophane (λ_{max} 2630; ϵ_{max} 1300). The percyclophane-4 spectra, however, shows only the very broad absorption with no fine structure due to the steric strain and rigidity of the molecule.

Several attempts were made to synthesize similar trimers of commercially available[7] 1,6 cyclotridicadiyne and 1,8-cyclotetradecadiyne, but no tractable products could be isolated. We are presently investigating the chemical properties of this unusual molecule.

Experimental Section

Synthesis of Cyclododecadiyne.—In a 2-l., three-neck flask was placed 1 l. of liquid ammonia. To this was added 1.25 g of $Fe(NO_3)_3 \cdot 9H_2O$. The contents of the flask were blanketed with nitrogen at all times; 4.10 g (0.59 mol) of lithium wire was added in small chunks slowly to the flask. All of the lithium wire had dissolved within 15 min after addition was complete. Over a period of 10 min, 63 g (0.59 mol) of octadiyne-1,7 was added. The reaction mixture was stirred for 1.5 hr.

Into a second 2-l. flask was placed 125 ml of dry, distilled dioxane containing 102.5 g (0.59 mol) of $Br(CH_2)_4Cl$ (K and K Laboratories). The liquid ammonia solution from the first flask was pumped with nitrogen pressure through a filter stick into the second flask. This reaction mixture was allowed to warm with stirring overnight until all of the ammonia was evaporated. Upon evaporation of the ammonia, 500 ml of *n*-heptane was added, then 500 ml of water, and the phases were shaken and separated. The aqueous layer was extracted twice more with 200-ml portions of *n*-heptane. The combined *n*-heptane solutions were washed twice with 300-ml portions of 5% HCl solution and then dried over anhydrous Na_2SO_4. Removal of the *n*-heptane gave 100.2 g of crude product which upon distillation yielded 56 g (50%) of 1-chlorododecadiyne-5,11 (II): major infrared bands 3300, 2920, 2860, 2110, 1430, and 600–650 cm^{-1}; nmr triplet centered at δ 3.58 and complex multiplets centered at δ 2.13 and 1.60 with relative areas 2:7:8.

In a 60-ml glass ampoule was placed 5.0 g of II along with 7.60 g of NaI dissolved in 30 ml of dry acetone. The ampoule was sealed and heated at 80° for 17 hr. The ampoule was opened, and the NaCl was filtered off and washed with ether. Upon dilution of the acetone solution with ether the excess NaI precipitated and was filtered off. Removal of the solvent yielded 6.9 g (94%) of 1-iododododecadiyne-5,11 (III): major infrared bands 3300, 2920, 2860, 2110, 1430, and broad absorption centered around 500 cm^{-1}; nmr triplet centered at δ 3.20 and complex multiplets centered at δ 2.15 and 1.60 with relative areas of 2:7:8.

Into a 2-l., three-neck flask with air stirrer, cold trap, and inert gas head was placed 1 l. of liquid ammonia. $Fe(NO_3)_3 \cdot 9H_2O$ (0.1 g) and then 0.13 g (0.019 g-atom) of Li wire cut into small pieces were added. When the Li had dissolved, 4.28 g (0.015 mol) of III dissolved in 250 ml of dry ether was added dropwise over a period of 4.5 hr. Upon completion of the addition, the ammonia was allowed to evaporate. The product was worked up exactly as described for compound II and this work-up yielded 1.64 g of light yellow oil. This crude product contained residual compound II and III as well as cyclododecadiyne-1,7 (I). The crude product was chromatographed on Woelm neutral alumina, eluting with a gradient of hexane and benzene. Yield of purified cyclododecadiyne was 0.87 g (0.054 mol, 36%). The product crystallized upon refrigeration into large, colorless needles: mp 20 ± 2°;[2] major infrared bands 2900, 2820, 1430, 1330, 755 cm^{-1} (w); nmr showed broad multiplets centered at δ 2.10 and 1.70 with relative areas of 1:1.

Anal. Calcd: C, 90.0; H, 10.0. Found: C, 89.7; H, 10.1.

Percyclophane. Catalysis by Dimesitylcobalt.—Mesitylmagnesium bromide solution in THF was prepared and standardized by standard techniques. High-purity Mg (99.99%) was used in the preparation. Into a 25-ml, three-neck flask, with nitrogen purge, was placed 0.65 g (5.0 mmol) of anhydrous $CoCl_2$, then 58.5 ml (15.0 mmol) of a 0.0256 *M* solution of mesitylmagnesium bromide. The flask temperature was kept at −20° and the solution was stirred for 10 hr. In a second 200-ml flask was placed 1.60 g (10.0 mmol) of cyclododecadiyne dissolved in 50 ml of dry THF. To this was added 2.0 ml of the mesitylmagnesium bromide–$CoCl_2$ solution. The reaction mixture was allowed to stir at −30 to −40° for 2 hr, then allowed to warm to room temperature. The resulting solution was diluted with ether, and this ether phase was washed with water and 5% HCl solution, and then dried over anhydrous K_2CO_3. Removal of the solvent left 2.25 g of a greenish solid. This crude material was placed in a vacuum sublimation apparatus and heated at 150° (0.1 mm). A white, crystalline material, 1.1 g (70%), sublimed: mp 235°, mass spectral analysis showed parent ion of $C_{36}H_{48}$ (mol wt 480.78); major infrared bands 3000, 1450, 730 cm^{-1} (vw); nmr broad resonance centered at δ 2.90, 2.30, and 1.70 with relative areas of 1:1:2.

Anal. Calcd for $C_{36}H_{48}$: C, 90.0; H, 10.0. Found: C, 89.5; H, 9.6.

Registry No.—I, 4641-85-4; II, 39253-36-6; III, 39253-37-7; lithium amide, 7782-89-0; 1-bromo-4-chlorobutane, 6940-78-9; 1,7-octadiyne, 871-84-1; percyclophane-4, 39253-39-9.

(7) Farchan Research Laboratories, Willouby, Ohio.

Methylation and Chlorination of Internal Olefins with Trimethylaluminum and Hydrogen Chloride

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In the course of our investigations on the fundamentals of cationic polymerizations initiated by alkylaluminum compounds, we are using small molecule model reactions to elucidate aspects of the polymerization mechanism. Since trialkylaluminums or dialkylaluminum halides (*e.g.*, Me_3Al, Et_3Al, Et_2AlCl) in conjunction with suitable cationogens (*e.g.*, HX or *t*-BuX) are most efficient initiator systems for the synthesis of high molecular weight polymers at relatively high temperatures,[1] we have been interested in exploring the chemis-

TABLE I

REACTION OF CYCLOHEXENE AND 1-METHYLCYCLOHEXENE WITH TRIMETHYLALUMINUM AND HYDROGEN CHLORIDE IN ETHYL CHLORIDE AT −50°

Reactants and their sequence of mixing	Products (%)
Cyclohexene + HCl	No reaction
Cyclohexene + Me_3Al + HCl	Chlorocyclohexane (14), cyclohexene (80)
Cyclohexene + HCl + Me_3Al	Chlorocyclohexane (72), cyclohexene (24)
Cyclohexene + HCl + Me_3Al[a]	Chlorocyclohexane (50), methylcyclohexane (10), cyclohexene (10), plus unidentified higher boiling products
1-Methylcyclohexene + Me_3Al + HCl	1,1-Dimethylcyclohexane (28) 1-methylcyclohexene (36), plus unidentified higher boiling products
1-Methylcyclohexene + HCl + Me_3Al	1,1-Dimethylcyclohexane (92)

[a] In CH_2Cl_2 at 23° for 48 hr.

try of these species in depth. The facile, clean synthesis of quarternary carbon containing hydrocarbons from tertiary chlorides and trialkylaluminum compound has already been reported[2] (eq 1). These studies have now

$$t\text{-RCl} + R_3'Al \longrightarrow t\text{-RR}' + R_2'AlCl \quad (1)$$

been extended to the "methanation" (addition of the elements of CH_3H across a double bond) of (nonpolymerizable) olefins, *e.g.*, cyclohexene, by the use of Me_3Al and HCl. The results of these studies are of interest, as they provide deeper insight into the mechanism of cationic polymerizations.

Results

Cyclohexene and 1-methylcyclohexene have been treated with trimethylaluminum and hydrogen chloride in ethyl chloride at −50°. The mixing sequence of the reactants and the results are shown in Table I.

Discussion

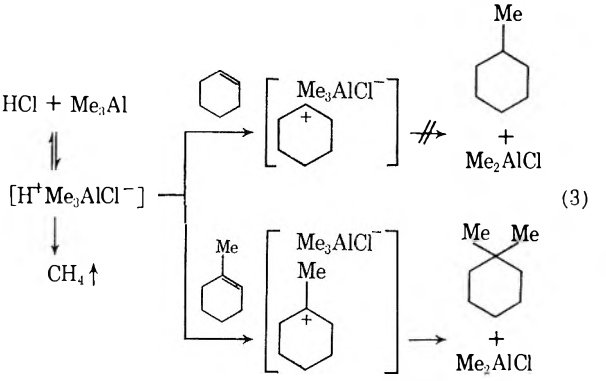
We have reported that the reaction of *tert*-butyl halide with trimethylaluminum gives rapidly and quantitatively neopentane.[2] The reaction was proposed to go through a *tert*-butyl cation–trimethylaluminum chloride counterion pair (eq 2). Thus the neo-

$$t\text{-BuCl} + Me_3Al \rightleftharpoons [t\text{-Bu}^+\ Me_3AlCl^-] \longrightarrow t\text{-BuMe} + Me_2AlCl \quad (2)$$

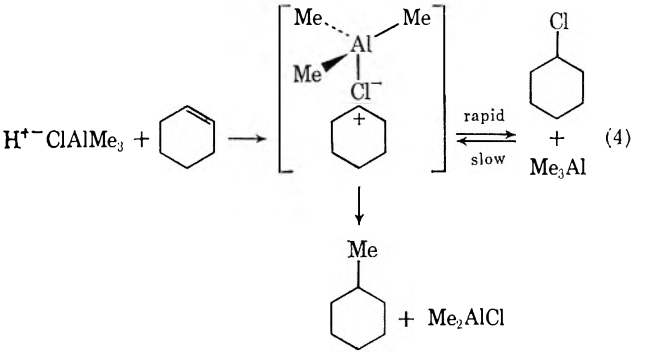
pentane is formed by a transfer of methyl group from the counterion to the *tert*-butyl cation.

Alkylations of benzylic and tertiary chlorides have been reported to proceed with great ease.[2] Thus it was not surprising to find (lines 5 and 6 in Table I) the formation of 1,1-dimethylcyclohexane from 1-methylcyclohexene and Me_3Al/HCl or HCl/Me_3Al. In contrast, it was quite unexpected that methylcyclohexane did not form from cyclohexene under the same conditions (lines 2 and 3 in Table I) (eq 3).

Instead, the reaction between cyclohexene and Me_3Al–HCl or HCl–Me_3Al gave rise to chlorocyclohexane (lines 2 and 3 in Table I). Methylcyclohexane starts to appear only after long reaction periods at higher temperatures. These findings can be explained by assuming first a protonation of cyclohexene by $H^+\ ^-ClAlMe_3$ followed by rapid collapse of the ion pair to the chlorinated product (eq 4). The fact that the first isolable product is the chloro and not the methyl derivative could be due to the asymmetrical charge



distribution in the trimethylaluminum chloride counteranion. We visualize a virtually instantaneous col-



lapse of the cyclohexyl ion pair to the chlorinated product before the counteranion has had a chance to rotate and to direct a methyl substituent toward the electrophilic center. The first-formed kinetically controlled product (chlorocyclohexane) is subsequently slowly methylated to yield the thermodynamically stable methylcyclohexane.

With 1-methylcyclohexane the overall reaction is much simpler, since initial protonation gives a stable tertiary cation which, on account of its longer lifetime and/or "looser" nature, rapidly leads to the thermodynamically more stable 1,1-dimethylcyclohexane. Evidently in this system the counterion has the time to rotate before final methylation of the electrophilic center. The possibility that in this reaction 1-chloro-1-methylcyclohexane may be involved as a nonisolable intermediate cannot also be ruled out.

With 1-methylcyclohexene the observation could also be explained by assuming a rapid formation of the tertiary chloro derivative, which rapidly decomposes to the thermodynamically more stable dimethylcyclohexane. This process would not require an asymmetrical charge distribution in the counteranion but only that the chloride is a better leaving group for the tri-

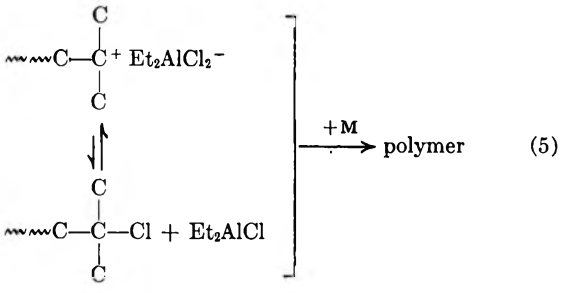
(1) J. P. Kennedy in "Polymer Chemistry of Synthetic Elastomers," J. P. Kennedy and E. Tornquist Ed., Interscience, New York, N. Y., 1968, Part 1, Chapter 5A, p 291.

(2) J. P. Kennedy, *J. Org. Chem.*, **35**, 532 (1970).

methylaluminum chloride anion. (We thank one of the referees for pointing this out.)

In the reaction of cyclohexene with Me_3Al and HCl, the order of addition of the reagents influences the extent of conversion (lines 2 and 3, Table I). We propose that, when Me_3Al is added to an olefin such as cyclohexene, a Lewis acid–olefin complex is formed, which lowers the reactivity of the Lewis acid and the olefin toward HCl. However, when the Lewis acid is added last, the possibility of complex formation is minimized, resulting in a higher yield of chlorocyclohexane. Complex formation between olefins and alkylaluminum compounds may be a general phenomenon.[3] We have also found that the rate of cationic polymerization of isobutylene initiated by the trimethylaluminum-*tert*-butyl bromide initiator system can be considerably accelerated by adding the alkylaluminum last.[4] Complex formation between olefins and Lewis acids such as $SnCl_4$, BF_3, $AlBr_3$, etc., has been demonstrated.[5]

Experiments described in this paper (*i.e.*, lines 2 and 3 in Table I) suggest the formation of chlorinated intermediates in similar other reactions as well. A consequence of these results is the possibility that cationic polymerizations may also involve covalent halides. The direct insertion of monomer into the covalent C–Cl bond, however, is considered to be much less likely.[6] The relative concentration of the conventional ion pairs and the covalent chlorides in the equilibrium (eq 5) is determined by the structure of the



(5)

monomer (or the stability of the propagating cation) and the particular Lewis acid used. For example, the polymerization of isobutylene by *t*-Bu$^+$$Et_2AlCl_2^-$ (derived from *t*-BuCl and Et_2AlCl) might involve predominantly conventional ion pairs (eq 5). Termination would occur when the counterion is in a favorable orientation to alkylate the positive center.

Experimental Section

All the experiments and manipulations were performed in a stainless steel enclosure under N_2 atmosphere (<50 ppm moisture level).[7] Trimethylaluminum (Texas Alkyl, Inc.) was used as received. Cyclohexene (Aldrich Chemical Co.) and 1-methylcyclohexene (Columbia Organic Chemicals Co.) were dried over molecular sieves and distilled before use. Authentic samples of chlorocyclohexane, methylcyclohexane, and 1,1-dimethylcyclohexane for glpc comparison were obtained commercially. Gas chromatography was done on an HP 5750 instrument equipped with FID on a 6 ft × 0.125 in. silicone gum rubber UC-W-98 column using He (35 ml/min) as the carrier gas. All unknown peaks were identified by peak superposition using authentic materials for comparison. All reactions were generally run for 30 min; however, the reactions were virtually complete in *ca.* 10 min. A representative experiment is described. A three-neck flask equipped with a mechanical stirrer, glass-jacketed addition funnel, and a thermometer was cooled to −50°. Cyclohexene, 5.1 ml (50 mmol), dissolved in 25 ml of EtCl (~1.5 *M*) was placed in the flask followed by 1.5 ml (50 mmol) of liquid hydrogen chloride dissolved in 25 ml of EtCl. Trimethylaluminum, 4.8 ml (50 mmol), was dissolved in 25 ml of EtCl and was added dropwise through the precooled addition funnel. Upon addition of the first few drops of trimethylaluminum the temperature of the pot rose by ~10°. After addition was complete, the reaction was quenched by the dropwise addition of 5 ml of prechilled methanol. The aluminum alkoxide was coagulated by the addition of a saturated aqueous solution of sodium potassium tartrate. The organic product was extracted into pentane, washed, dried, and analyzed by glpc. *N*-Nonane was used as an internal standard. The products arising from the reaction of cyclohexyl cation with cyclohexene (1-cyclohexylcyclohexene) and from the skeletal rearrangement of the cyclohexyl cation (1-methylcyclopentene, 1,1-dimethylcyclopentane) were shown to be absent.

Registry No.—Cyclohexene, 110-83-8; 1-methylcyclohexene, 591-49-1; trimethylaluminum, 75-24-1; hydrogen chloride, 7647-01-0.

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

(3) J. P. Kennedy and A. W. Langer, *Advan. Polym. Sci.*, **3**, 508 (1964); E. I. Tinyakova, T. G. Shuravleva, T. N. Kurengina, N. S. Kirikova, and B. A. Dolgoplosk, *Dokl. Akad. Nauk SSSR*, **144**, 592 (1962); J. P. Kennedy and G. E. Milliman, *Advan. Chem. Ser.*, **91**, 287 (1969).

(4) P. D. Trivedi, unpublished observations, Akron, Ohio, 1972.

(5) J. M. Clayton and A. M. Eastham, *Can. J. Chem.*, **39**, 138 (1961); R. W. Taft, E. L. Purlee, P. Reisz, and C. A. DeFazio, *J. Amer. Chem. Soc.*, **77**, 1584 (1955); T. G. Bonner, J. M. Clayton, and G. Williams, *J. Chem. Soc.*, 1705 (1958).

(6) A. Gandini and P. H. Plesch, *J. Polym. Sci.*, part *B-3*, 1127 (1965); P. H. Plesch, *Polym. Prepr.*, **7**, 492 (1966).

(7) J. P. Kennedy and R. M. Thomas, *Advan. Chem. Ser.*, **34**, 111 (1962).

Base-Catalyzed Reaction of β-Amino Alcohols with Ethyl Trihaloacetates

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January 12, 1973

The reaction of β-hydroxyalkylamines with ethyl trihaloacetates has been investigated in some detail only by Lesher and Surrey,[1] who obtained 2-oxazolidinones[2] by treatment of *N*-benzylethanolamines with ethyl trichloroacetate (ETC). According to the same authors, N-unsubstituted β-amino alcohols failed to afford any 2-oxazolidinones.

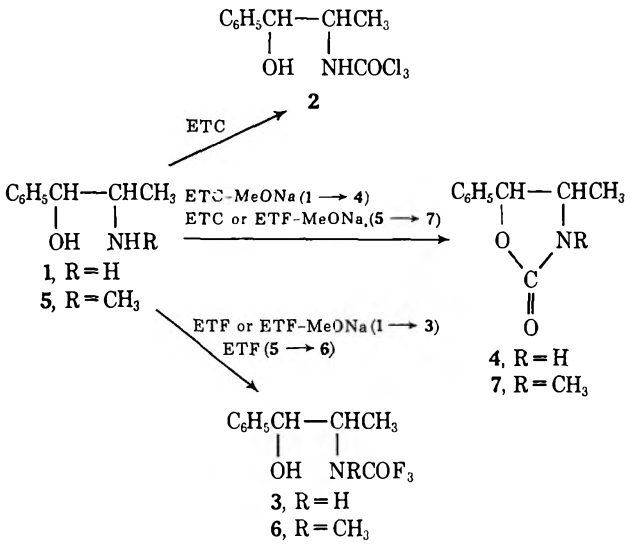
We have investigated the reaction of DL-phenylpropanolamine (**1**) and L-ephedrine (**5**) with ETC and ethyl trifluoroacetate (ETF) and the influence of a basic catalyst on the course of this reaction.

Treatment of **1** with ETC and ETF afforded the corresponding aminolysis products **2** and **3**, respectively. Addition of catalytic amounts of methanolic sodium methoxide increased the conversion rate of **1** into **3**, while added base resulted in the formation of the N-unsubstituted 2-oxazolidinone **4**, as the only product of the reaction with the trichloro ester.

Reaction of **5** with ETF afforded the trifluoroacetamide **6** in the absence of catalyst, while an almost complete conversion into 2-oxazolidinone **7** was obtained

(1) G. Y. Lesher and A. R. Surrey, *J. Amer. Chem. Soc.*, **77**, 636 (1955).

(2) For a comprehensive review on 2-oxazolidinones, see M. E. Dyen and D. Swern, *Chem. Rev.*, **67**, 197 (1967).



in the presence of sodium methoxide.[3] The same oxazolidinone **7** was obtained by treatment of **5** with ETC also in absence of sodium methoxide.

The isolation of **6** and the tlc identification of **2** during the base-catalyzed reaction of **5** with ETF and **1** with ETC, respectively, indicates that the formation of the 2-oxazolidinones proceeds through the corresponding trihaloacetamides.[4]

The conversion of *N*-benzylethanolamines to oxazolidinones has been suggested to occur either through an initial O-acylation, followed by splitting of chloroform, or through an initial haloform-type cleavage to a *N*-carboethoxy derivative, followed by an intramolecular alcoholysis.[1] Our results do not support these hypotheses, but suggest a reaction pattern involving an initial aminolysis of the halo ester, followed by a nucleophilic intramolecular attack by the alkoxide ion on the carbonyl group and loss of haloform.

Deprotonation at nitrogen may compete with cyclization in the case of the secondary trihaloacetamides[5] and this may account for their reduced ability to afford 2-oxazolidinones. A stronger inductive effect favors the N deprotonation of trifluoro- more than trichloroacetamides. This may contribute to the failure of **3** to cyclize, although the greater reactivity of trichloro- *vs.* trifluoroacetamides can be more generally determined by the superior leaving group ability of the trichloromethyl moiety.[6]

Experimental Section

Melting points were taken in a capillary apparatus and are uncorrected. Optical rotations were determined in dioxane at 24° unless otherwise stated. Ir spectra were measured in Nujol mull on a Perkin-Elmer 457 instrument. Tlc was run with 9:1 benzene–acetone on 250-μ-thick layers of silica gel (C. Erba, Milan, Italy), containing 1% fluorescence indicator (S5 grün/1, Leuchstoffwerk GmbH and Co., Heidelberg, West Germany) and spots were visualized under short-wave uv light (254 mμ). Microanalyses were performed by Ilse Beetz Microanalytisches Laboratorium, Kronach, West Germany.

DL-**Trifluoro-*N*-(2-hydroxy-1-methyl-2-phenylethyl)acetamide** (**3**).—A solution of **1** (1 g) in ETF (5 ml) and EtOH (2 ml) was kept at room temperature for 60 min. Evaporation of the solvent under reduced pressure afforded **3** (1.5 g, 91.7%): mp 131–132° (benzene); ν_{max} 3460, 3230, 3100, 1700 cm^{-1}.

Anal. Calcd for $C_{11}H_{12}F_3NO_2$: C, 53.44; H, 4.78; N, 5.66. Found: C, 53.37; H, 4.81; N, 5.64.

Following the same procedure but using ETC, trichloroacetamide **2** was obtained (60%): mp 72–76° (hexane); ν_{max} 3420, 3300, 1680 cm^{-1}. This compound was fully characterized as the *O*-benzoate: mp 148–150° (MeOH); ν_{max} 3460, 1710, 1690 cm^{-1}.

Anal. Calcd for $C_{18}H_{16}Cl_3NO_3$: C, 53.96; H, 4.02; Cl, 26.55; N, 3.49. Found: C, 53.79; H, 4.06; Cl, 26.73; N, 3.35.

L-**Trifluoro-*N*-(2-hydroxy-1-methyl-2-phenylethyl)-*N*-methylacetamide** (**6**).—A solution of **5** (7 g) in ETF (10 ml) was kept at room temperature for 150 min and then processed as above to give **6** (10 g, 90.3%): mp 63–65° (hexane); ν_{max} 3440, 1680 cm^{-1}; $[\alpha]_D$ −8° (*c* 4).

Anal. Calcd for $C_{12}H_{14}F_3NO_2$: C, 55.17; H, 5.40; N, 5.36. Found: C, 54.92; H, 5.64; N, 5.26.

The *O*-benzoate had mp 111–113° (MeOH); ν_{max} 1728, 1685 cm^{-1}; $[\alpha]_D$ +36° (*c* 1).

Anal. Calcd for $C_{19}H_{18}F_3NO_3$: C, 62.47; H, 4.96; N, 3.38. Found: C, 62.42; H, 4.90; N, 3.80

DL-**4-Methyl-5-phenyloxazolidin-2-one** (**4**).—A solution of **1** (3.02 g) in ETC (2.1 ml) was treated with 1 *M* MeONa (2 ml) and kept at room temperature for 150 min. Concentration under reduced pressure and dilution with water afforded **4** (2.9 g, 82%): mp 147–149° (benzene) (lit.[7] mp 145–147°); ν_{max} 3380, 1745, 1720 cm^{-1}. Tlc at 30-min intervals revealed the presence of amide **2**, which disappeared at the end of the reaction.

L-**3,4-Dimethyl-5-phenyloxazolidin-2-one** (**7**).—A solution of **5** (4 g) in ETF (6 ml) was treated with 1 *M* MeONa (3 ml), kept under stirring at room temperature for 150 min, and worked up as above to give **7** (4.3 g, 93%): mp 91–92° (EtOH); $[\alpha]_D$ −125° (c 1, $CHCl_3$); ν_{max} 1735 cm^{-1} [lit.[8] mp 91–92°; $[\alpha]^{20}D$ −110.6° ($CHCl_3$)].

When the reaction was allowed to proceed for only 5 min, the trifluoroacetamide **6** was isolated.

B.—A solution of **5** (3 g) in ETC (2.1 ml) was kept at room temperature for 180 min and worked up as above to yield **7** (2.6 g, 75%), mp 90–92°.

Registry No.—**1**, 14838-15-4; **2**, 39663-72-4; **2** *O*-benzoate, 39663-73-5; **3**, 39663-74-6; **4**, 39663-75-7; **5**, 299-42-3; **6**, 39663-77-9; **6** *O*-benzoate, 39663-78-0; **7**, 16251-46-0; ETF, 383-63-1; ETC, 575-84-4.

(3) *N*-Benzylethanolamine has been reported to afford the corresponding salt by reaction with ETF.[1]

(4) Evidence for the formation of an intermediate showing tlc behavior reasonable for the trichloroacetamido derivative was obtained also in the reaction of **5** with ETC.

(5) *Cf.* S. S. Biechler and R. W. Jaft, Jr., *J. Amer. Chem. Soc.*, **79**, 4927 (1957).

(6) *Cf.* C. A. Panetta and T. G. Casanova, *J. Org. Chem.*, **35**, 4275 (1970).

(7) A. H. Homeyer, U. S. Patent 2,399,118 (1946); *Chem. Abstr.*, **40**, 4084 (1946).

(8) J. B. Hyne, *J. Amer. Chem. Soc.*, **81**, 6058 (1959).

Cyclohexadienyl Cations. V. Concerning the Acidity Dependence of the Dienone–Phenol Rearrangement

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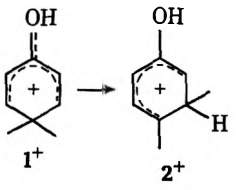
Received February 22, 1973

In the previous papers[1,2] in this series we have suggested that the kinetic acidity dependence in concentrated acid solutions of the acid-catalyzed dienone–phenol rearrangement can be understood in terms of two factors: (a) the equilibrium protonation acidity

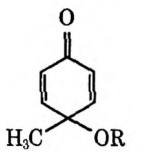
(1) V. P. Vitullo and E. A. Logue, *J. Org. Chem.*, **37**, 3339 (1972).

(2) V. P. Vitullo and N. Grossman, *J. Amer. Chem. Soc.*, **94**, 3844 (1972).

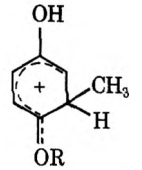
dependence of cyclohexadienones[3-6] and (b) a kinetically inverse dependence on the water activity of the medium. Since the rate-determining step[7] in the dienone–phenol rearrangement involves alkyl migration from C-4 to C-3 in the protonated dienone (eq 1) we suggested[1,2] that the inverse dependence on



(1)



3-OCH3, R = CH3
3-OH, R = H



3-OCH3+, R = CH3
3-OH+, R = H

water activity resulted from the desolvation of the hydroxy group in the protonated dienone whose acidity is substantially reduced in the transition state. Although solvation through acidic OH groups has been shown[8] to be an important factor in determining the acidity dependence of reactions occurring in moderately concentrated acid solutions, we wished to obtain more direct information regarding the importance of this effect in determining the acidity dependence of the dienone–phenol rearrangement.

In an earlier paper[1] we have reported our studies of the dienone–phenol rearrangement of 4-methoxy-4-methylcyclohexadienone (3-OCH_3). This substrate rearranges in acid solution with exclusive methyl migration. Although this dienone is substantially less basic than 4,4-dimethylcyclohexadienone,[4] the kinetic acidity dependence for its rearrangement could be understood in terms of the two factors discussed above. In this note we report kinetic data for a structurally similar system, 4-hydroxy-4-methylcyclohexadienone (3-OH), which bears directly on the problem of interpreting the acidity dependence of the dienone–phenol rearrangement.

The intrinsic basicities of 3-OCH_3 and 3-OH are expected to be similar, and, since the 4-OH group in 3-OH is insulated from the positive charge in the protonated species, there should be little difference in the equilibrium protonation acidity dependence for 3-OCH_3 and 3-OH. Thus, any differences in the kinetic acidity dependence for these substrates should reflect differences in transition state solvation. The kinetic data for the rearrangement of 3-OH are recorded in Table I.

In the acidity range 37.9–59.7 wt % $HClO_4$ plots of log k_{obsd} against $-H_0$ (the Hammett acidity function) are linear and less than 20% of either substrate is protonated. A summary of the kinetic acidity dependence data for both 3-OCH_3[9] and 3-OH is given below (eq 2 and 3).

Table I
Rates of Rearrangement of 4-Hydroxy-4-methyl-cyclohexadienone in Perchloric Acid at 25.1 ± 0.1°

$10^4 k_{obsd}$, sec^{-1}	Wt % $HClO_4$	$-H_0$[a]
0.576	37.93	2.18
1.07	41.68	2.54
1.94	44.82	2.84
4.01	47.84	3.20
12.0	52.53	3.92
30.2	55.01	4.28
120.0	59.53	5.16
343.0	62.70	5.86

[a] K. Yates and H. Wai, *Can. J. Chem.*, **43**, 2131 (1965).

$$\text{3-OCH}_3 \log k_{obsd} = (-7.17 \pm 0.14) - (0.92 \pm 0.04)H_0 \quad (2)$$

$$\text{3-OH}, \log k_{obsd} = (-5.94 \pm 0.05) - (0.78 \pm 0.02)H_0 \quad (3)$$

The acidity dependence is considerably less steep for the rearrangement of 3-OH, suggesting that the transition state of 3-OH is more extensively solvated[8] than the transition state for 3-OCH_3. Migration of the methyl group in protonated 3-OH and 3-OCH_3 yields the isomeric ions 3-OH^+ and 3-OCH_3^+. Interestingly, both ions are stabilized by the delocalization of the nonbonded electrons of the oxygen of C-4. Thus, for 3-OH methyl migration reduces the acidity of the C-1 hydroxy group but increases the acidity of the hydroxy group at C-4. This additional mechanism for the solvation of the transition state for 3-OH will result in a shallower acidity dependence for 3-OH compared to substrates for which this additional mode of solvation is not possible. In 3-OCH_3 solvation through hydrogen bonding with the partially positively charged methoxy group at C-4 formed in the transition state is not possible and the acidity dependence for the rearrangement of 3-OCH_3 is correspondingly steeper.

It is interesting to note that even in 3-OH *some* net desolvation attends the formation of the transition state from protonated 3-OH. If this were not the case, the kinetic acidity dependence would be the same as the protonation equilibrium acidity dependence (*i.e.*, the plot of log k_{obsd} *vs.* $-H_0$ would have a slope of *ca.* 0.6[3-6]).

These results clearly implicate solvation as one of the most dominant factors governing the acidity dependence of this A-1 reaction.

Experimental Section

4-Hydroxy-4-methylcyclohexadienone.—This material was prepared according to Goodwin and Witkop.[10] Our product had mp 74–77° after sublimation and recrystallization from CCl_4 (lit. mp 76–78°,[10] 75–76°[11]): ir ($CDCl_3$) 3580, 3400 (broad), 1665, 1630 cm^{-1}.

Kinetics.—The kinetics were followed by monitoring the loss of dienone spectrophotometrically (Gilford Model 2400) as described in a previous publication.[2] In most cases results reported in Table I are the average of three determinations.

(3) V. P. Vitullo, *J. Org. Chem.*, **34**, 224 (1969).
(4) V. P. Vitullo, *J. Org. Chem.*, **35**, 3976 (1970).
(5) K. L. Cook and A. J. Waring, *Tetrahedron Lett.*, 1675 (1971).
(6) K. L. Cook and A. J. Waring, *Tetrahedron Lett.*, 3359 (1971).
(7) V. P. Vitullo and N. Grossman, *Tetrahedron Lett.*, 1559 (1970).
(8) A. J. Kresge, H. J. Chen, L. E. Hakka, and J. E. Kouba, *J. Amer. Chem. Soc.*, **93**, 6174 (1971); A. J. Kresge, S. Mylonakis, Y. Sato, and V. P. Vitullo, *ibid.*, **93**, 6181 (1971), and references cited therein.
(9) Data from ref 1.
(10) S. Goodwin and B. Witkop, *J. Amer. Chem. Soc.*, **79**, 179 (1957).
(11) F. Wessley and F. Sinwell, *Monatsh. Chem.*, **81**, 1055 (1950).

Registry No.—4-Hydroxy-4-methylcyclohexadienone, 23438-23-5.

Acknowledgment.—We wish to thank the National Science Foundation for support of this work (Grant No. GP-29738X).

A Simple Procedure for the Epoxidation of Acid-Sensitive Olefinic Compounds with *m*-Chloroperbenzoic Acid in an Alkaline Biphasic Solvent System[1]

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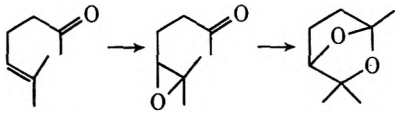
Received March 7, 1973

The epoxidation of acid-sensitive olefins or the epoxidation of olefins yielding acid-sensitive epoxides are typically conducted in the presence of a buffer such as solid sodium carbonate, sodium bicarbonate, or disodium hydrogen phosphate.[2] During the course of our research we found the solid buffer–single solvent procedure to be unsuited for certain acid-sensitive compounds. We wish to report a mild and simple epoxidation procedure using a two-phase system which proved superior to the single solvent method for the epoxidation of acid-sensitive compounds.

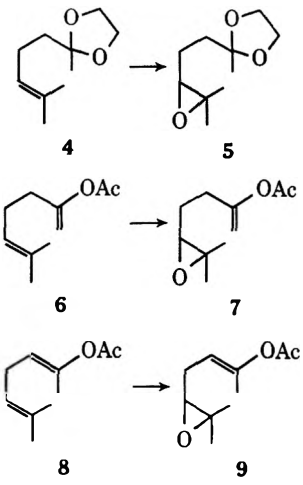
The epoxide **2**, derived from 6-methylhept-5-en-2-one (**1**), is known to undergo very facile rearrangement to 1,3,3-trimethyl-2,7-dioxabicyclo[2.2.1]heptane (**3**).[3] This rearrangement occurs thermally and is acid catalyzed. The preparation of the unstable epoxide, **2**, has previously been accomplished by careful epoxidation of **1** in methylene chloride using peracetic acid–sodium acetate.[3a] When we attempted to prepare **2** using *m*-chloroperbenzoic acid–sodium bicarbonate we obtained a mixture of **2** and **3** in approximately



1 **2** **3**

equal proportion (as estimated by nmr[4]). Epoxidation of **1** with *m*-chloroperbenzoic acid in a dichloromethane–aqueous sodium bicarbonate biphasic system led to the formation of **2** in high yield (83–85%) with no detectable amounts of the rearranged product, **3**.[4]

Similar biphase epoxidation of the ketal **4** and enol acetates **6** and **8** proceeded smoothly to give **5**, **7**, and **9**, respectively, in 80–85% yields.[5,6]



4 **5** **6** **7** **8** **9**

In a study of the scope of this reaction we examined the biphasic epoxidation of simple mono-, di-, and trisubstituted olefins.[7] Table I[8] gives the results of this study and it is evident that the two-phase epoxidation procedure can be extended to mono- and disubstituted olefins. Furthermore, the yields of epoxides were comparable to those obtained by a single solvent procedure.[8]

TABLE I
TWO-PHASE EPOXIDATION OF OLEFINS WITH *m*-CHLOROPERBENZOIC ACID

Compd	Olefin–peracid ratio, *M*	Reaction time, hr	Product[a]	Yield, %[b]
Cyclohexene	1:1	4	Cyclohexene oxide[c,e]	71
1-Hexene	1:1	9	1,2-Epoxyhexane[d]	56
Limonene	1:1	2	1,2-Epoxy-*p*-menth-8-ene[e]	85
Limonene	1:2	4	1,2,8,9-Diepoxy-*p*-menthane[e]	66
Limonene	1:3	4	1,2,8,9-Diepoxy-*p*-menthane[e]	68

[a] Products were characterized by nmr, ir, glc, and mass spectrometry. [b] Yields were calculated by glc. [c] Reference 8a. [d] Reference 8b. [e] Reference 8c.

In the case of limonene (*p*-mentha-1,8-diene) the two-phase epoxidation procedure was compared with the epoxidation using *m*-chloroperbenzoic acid in dichloromethane. With 1 equiv of peracid both procedures gave selective epoxidation of the trisubstituted double bond in identical yields (a slightly longer reaction time was required in the two-phase system).

(1) This research was supported by Grant 1 R01 CA11880 from the National Cancer Institute, National Institutes of Health.

(2) D. Swern in "Organic Peroxides," Vol. II, D. Swern, Ed., Wiley-Interscience, New York, N. Y., 1971, pp 355–533.

(3) (a) E. Klein and W. Rojahn, *Dragoco Rep. Engl. Ed.*, **14**, 155 (1967); (b) Y. Gaoni, *J. Chem. Soc. C*, 2925 (1968).

(4) 5,6-Epoxy-6-methylhepten-2-one (**2**) quantitatively rearranged to **3** during attempted glc analysis; so the crude reaction mixture, following work-up, was analyzed by nmr. In the nmr spectrum of **2** (CCl_4) the C-1 methyl appeared at τ 7.87 and in the spectrum of **3** the C-1 methyl appeared at τ 8.52.

(5) **4** was prepared from **1** by *p*-toluenesulfonic acid catalyzed ketalization; **6** and **8** were prepared from **1** by BF_3-catalyzed enol acetylation (the two isomers could be separated by spinning band distillation and preparative glc). All compounds were characterized by mass spectrometry, ir, and nmr (including spin-decoupling studies).

(6) For an example of epoxidation of an isolated double bond in the presence of an enol acetate, see R. B. Moffet and G. Slomp, Jr., *J. Amer. Chem. Soc.*, **76**, 3678 (1954).

(7) Water is known to decrease the rate of peracid epoxidation of olefins and the presence of aqueous sodium bicarbonate would be expected to increase the rate of peracid decomposition.[2]

(8) (a) G. B. Payne, P. H. Deming, and P. H. Williams, *J. Org. Chem.*, **26**, 659 (1961); (b) D. J. Pasto and C. C. Cumbo, *ibid.*, **30**, 1271 (1965); (c) B. A. Arbuzov and B. M. Mikhailow, *J. Prakt. Chem.*, **127**, 92 (1932) [*cf. Chem. Abstr.*, **24**, 4285 (1932)].

With 2 equiv of peracid both procedures afforded diepoxide in identical yields.

The two-phase epoxidation method is illustrated in the following procedure for the synthesis of **9**. Solid *m*-chloroperbenzoic acid (2.029 g, 0.01 mol[9]) was slowly added in small portions to a magnetically stirred mixture of **8** (1.68 g, 0.01 mol) in dichloromethane (100 ml) and 0.5 *M* aqueous sodium bicarbonate (30 ml, pH 8.3). The mixture was stirred at room temperature for a period of 2 hr following the addition of the peracid (the consumption of peracid was tested with starch–iodide paper) and the two phases were separated. The organic phase was washed successively with 1 *N* sodium hydroxide (30 ml) and water (30 ml) and dried (Na_2SO_4). The methylene chloride was removed under reduced pressure to yield 1.7 g of crude product which was shown by glc to contain 86% of the desired product, **9**: ir (CCl_4)[10] 1760 (C=O), 1698 (C=C), 1391, 1383, 1374, 1239, 1215, and 1153 cm^{-1}; nmr (CCl_4) τ 8.73 (s, 6 H, C-7 and C-8), 8.13 (br s, 3 H, C-1), 7.93 (s, 3 H, $-COCH_3$), 7.53 (m, 2 H, C-4), 7.35 (m, 2 H, C-5), and 4.88 (t of q, $J_{3,4}$ = 6.5, $J_{3,1}$ = 0.8 Hz, 1 H, C-3).

The epoxidation procedure described herein should be very useful for the preparation of acid-sensitive epoxides. The reactivity of the peracid is slightly diminished in the aqueous biphasic media; however, the system is still sufficiently reactive to epoxidize simple monosubstituted double bonds.

Registry No.—**1**, 110-93-0; **2**, 16262-93-4; **3**, 16194-31-3; **4**, 3695-38-3; **5**, 39810-29-2; **6**, 39810-30-5; **7**, 39810-31-6; **8**, 39810-32-7; **9**, 39810-33-8; *m*-chloroperbenzoic acid, 937-14-4.

(9) The calculated molarity of the *m*-chloroperbenzoic acid was based on the 85% purity of the commercial peracid.

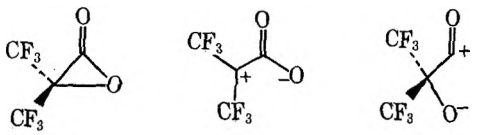
(10) The ir of isomeric enol acetate **7** showed absorptions at 1764 (C=O), 1675 (C=C), 1385, 1374, 1225, 1200, and 1170 cm^{-1}. The nmr spectra of **7** and **9** were also quite different.

See Editorial, *J. Org. Chem.*, **38**, No. 19, 4A (1972)

Bis(trifluoromethyl)acetolactone, a Stable α-Lactone[1]

Summary: Photolysis of bis(trifluoromethyl)malonyl peroxide (**2**) affords bis(trifluoromethyl)acetolactone (**1**), which on heating suffers decarbonylation into hexafluoroacetone (**3**) and on ethanolysis addition at the carbonyl bond leading to ethyl α-hydroxyhexafluoroisobutyrate (**6**).

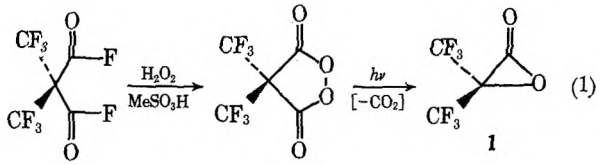
Sir: Instead of "steric stabilization" of α-lactones[2] as excercised by the *tert*-butyl group,[3] we have employed the concept of "electronic stabilization" exhibited by the trifluoromethyl group,[4] in an effort to diminish the high propensity toward self-polymerization of the elusive α-lactones. The trifluoromethyl group was expected to discourage formation of the dipolar structure since electron density should be drawn from the negative oxygen pole toward the α carbon, thereby promoting formation of the cyclic structure **1a**. Presently



1a **1b** **1c**

we are reporting the preparation and characterization of bis(trifluoromethyl)acetolactone (**1**) and its thermolysis and ethanolysis.

The precursor to α-lactone **1**, bis(trifluoromethyl) malonyl peroxide (**2**), was prepared in 20% yield by reaction of bis(trifluoromethyl)malonyl difluoride with 98% H_2O_2 in methanesulfonic acid at 0° (eq 1). This



(1)

2 **1**

material, rectified by fractional distillation [bp 62° (760 mm), 98% pure by iodometric titration], was characterized on the basis of its ir, fmr, and mass spectra. Photolysis of a matrix of **2** at 77°K by means of a 800-W Hg high pressure arc directly in a low temperature ir cell (Air Products Co.)[5] led to immediate consumption of the C=O bands of **2** at 1870–1825 cm^{-1} and simultaneous appearance of new C=O bands at 2350 (CO_2) and 1970 cm^{-1} (α-lactone). On preparative scale, the α-lactone **1** could be more conveniently produced by photolysis of a 0.32 *M* CCl_4 solutions of **2** at −15° in a Pyrex vessel, resulting in rapid conversion of **2** (87% in 1 hr) into **1**, as evidenced by fmr monitoring. This solution which is stable toward further photolysis under the conditions employed for its formation,[6] can be stored in the freezer at −20° for many days with negligible reduction of the intensity of its 1975-cm^{-1} C=O band in the ir. At ambient conditions bis(trifluoromethyl)acetolactone (**1**) is a gas (C=O band at 1980 cm^{-1} and parent ion at *m/e* 194) persisting at 24° with a half-life of 8 hr.

The major product (66% yield) of the thermal decomposition of CCl_4 solutions of α-lactone **1** at 25–40° was hexafluoroacetone (**3**). Also the insoluble perfluorinated polyester **5** with C=O band at 1820 cm^{-1} settled out. The kinetics of the thermolysis of **1** in CCl_4 solution was examined directly in a thermostated ir cell and followed first-order rate law, affording $\Delta H^{\ddagger}$ = 18.2 ± 0.8 kcal/mol, $\Delta S^{\ddagger}$ = −12.8 ± 2.8 gibbs/mol, and $\Delta G^{\ddagger}$ (300°K) = 22 ± 1 kcal/mol. Significant was the observation that addition of polar solvents such as acetonitrile to the CCl_4 solution of α-lactone **1** led to a ~10-fold increase in the rate of α-lactone destruction at 300°K. Thus, efforts to isolate the pure α-lactone **1** in the condensed phase failed since **1** by itself must be sufficiently polar to promote self-annihilation.

Informative on the structural nature of α-lactone **1** is its chemical behavior toward ethanol. Addition of ethanol to a CCl_4 solution of **1** resulted in the formation of ethyl α-hydroxyperfluoroisobutyrate (**6**) and ethyl hemiacetal (**4**) in the ratio of 3:2, respectively, identified by comparison of their ir, fmr and *pmr*, and mass spectra with those of the authentic substances. We could not detect any α-ethoxyhexafluoroisobutyric acid, the usual alcoholysis product of α-lactones derived from the dipolar form **1b**.[2] Attempts to trap the α-lactone **1** with dipolarophiles[7] such as bis(trifluoromethyl)ketene, 1,3-cyclohexadiene, and *cis*-dimethoxyethylene have led predominantly to decarbonylation rather than 1,3-dipolar addition.

A mechanistic rationalization consistent with these facts is given in eq 2. As anticipated, the trifluoromethyl groups discourage opening of the α-carbon–ether oxygen bond into dipole **1b**, so that even at room temperature the cyclic valence isomer **1a** persists in the gaseous and condensed phases. This conclusion is supported by the fact that its C=O band lies at 1975 ± 5 cm^{-1} in the matrix, CCl_4 solution, and vapor. Consistent with the cyclic structure **1a** is the fact that on heating carbon monoxide is extruded, a reaction which is typical for the related cyclopropanones.[8]

The relatively low $\Delta H^{\ddagger}$ for decarbonylation of **1a**

(1) Cyclic Peroxides. XXIII. For preceding paper, see W. Adam and N. Duran, *J. Chem. Soc. Chem. Commun.*, 798 (1972).

(2) (a) W. Adam and R. Rucktäschel, *J. Amer. Chem. Soc.*, **93**, 557 (1971); (b) W. Adam, O. L. Chapman, O. Rodriguez, R. Rucktäschel, and P. W. Wojtkowsky, *ibid.*, **94**, 1365 (1972).

(3) Wheland and P. D. Bartlett, *J. Amer. Chem. Soc.*, **92**, 6057 (1970).

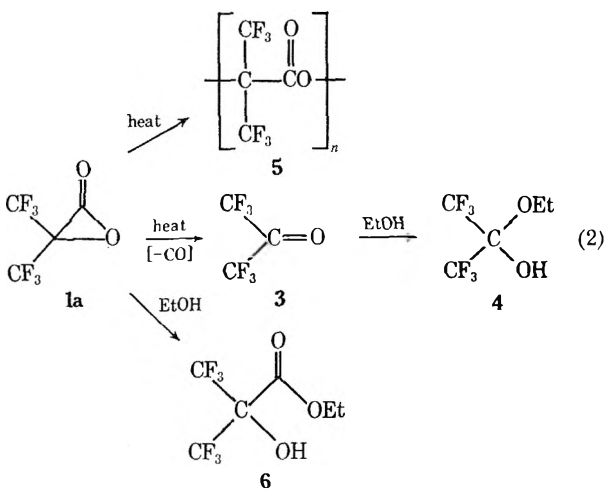
(4) D. M. Lemal and L. H. Dunlap, Jr., *J. Amer. Chem. Soc.*, **94**, 6562 (1972).

(5) We are grateful to Professor O. L. Chapman for advising us on this experimental set-up.

(6) Usually (*cf.* ref 2) α-lactones readily photodecarbonylate, but **1** is transparent above 300 nm.

(7) N. J. Turro, *Accounts Chem. Res.*, **2**, 25 (1969).

(8) D. B. Sclove, J. F. Pazos, R. L. Camp, and F. D. Greene, *J. Amer. Chem. Soc.*, **92** 7488 (1970



hints at a considerable strain inherent with this ring system, while the rather negative $\Delta S^{\ddagger}$ suggests chelotropic decarbonylation[9] similar to the thermolysis of episulfones.[10] In polar media, *e.g.*, acetonitrile or ethanol, opening of the carbonyl carbon–ether oxygen bond in **1a** leading to dipole **1c**, first suggested as a possible α-lactone structure in the thermolysis of anhydro sulfites,[11] presumably competes with concerted decarbonylation. Thus, in the aprotic CH_3CN solvent dipole **1c**, but not **1b**, may serve as a common precursor to ketone **3** and polyester **5** owing to lowering of the activation energy for heterolysis of the carbonyl carbon–ether oxygen bond as a consequence of solvation. Even in the protic EtOH solvent the thermal decay of **1** into **3** (observed as its hemiketal **4**) competes favorably with the addition of EtOH at the carbonyl group of **1**, analogous to cyclopropanones,[7] affording the α-hydroxy ester **6**. However, the formation of dipole **1b**, the accepted reactive form of α-lactones,[2] cannot be significant since we fail to detect any α-alkoxy acids, the usual alcolysis product of α-lactones.

In conclusion, on the basis of the presented facts, particularly the thermal decarboxylation and ethanol addition at the carbonyl group, we propose that bis(trifluoromethyl)acetolactone (**1**), in contrast to previous cases,[2] acts through its cyclic structure **1a**. Although our approach of "electronic stabilization" of α-lactones has proved rewarding, we must cope with the limitation that such species can so far be preserved only in matrix form, in solutions of nonpolar solvents, or in their vapor phase since their inherent polar nature dictates their self-destruction.

Acknowledgments.—We are particularly indebted to Dr. D. C. England of E. I. du Pont de Nemours and Co. for the generous supply of bis(trifluoromethyl)malonyl difluoride, his interest, and valuable advice. Financial support by the National Science Foundation and the donors of the Petroleum Research Fund, administered by the American Chemical Society, is acknowledged.

(9) (a) R. B. Woodward and R. Hoffmann, "Die Erhaltung der Orbital Symmetrie," Verlag Chemie, Germany, 1970; (b) A. Liberles, A. Greenberg, and A. Lesk, *J. Amer. Chem. Soc.*, **94**, 8685 (1972); (c) J. P. Snyder, R. J. Boyd, and M. A. Whitehead, *Tetrahedron Lett.*, 4347 (1972).

(10) F. G. Bordwell, J. M. Williams, E. B. Hoyt, Jr., and B. B. Jarvis, *J. Amer. Chem. Soc.*, **90**, 429 (1968).

(11) D. G. H. Ballard and P. J. Tighe, *J. Chem. Soc. B*, 702 (1967).

(12) A. P. Sloan Fellow (1968–1972).

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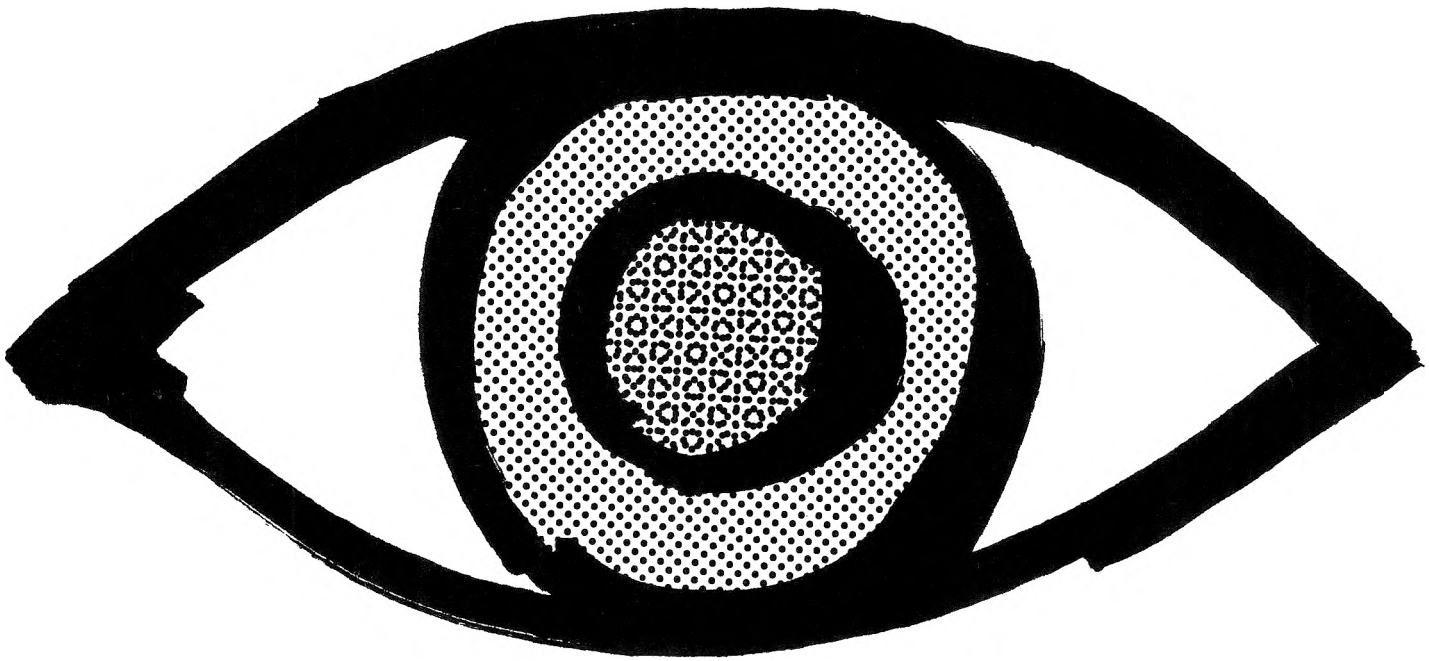

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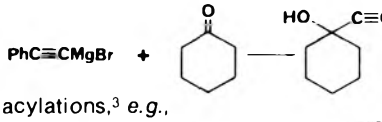
- Miscible with common organic solvents, immiscible with water.
- Excellent for heavy-phase extraction from aqueous solutions.
- Vapor nonflammable and not explosive when mixed with air.
- Low boiling point permits easy removal.
- Unlike ether, does not form explosive peroxide.
- Shares many properties with chloroform but is much less hazardous -- excellent substitute for chloroform.
- Unlike chloroform,[1] requires no additive for stabilization.
- High solvent power and low viscosity at low temperatures make it an excellent nmr solvent (except at the δ5.30 region).

CH_2Cl_2

AND MUCH MORE

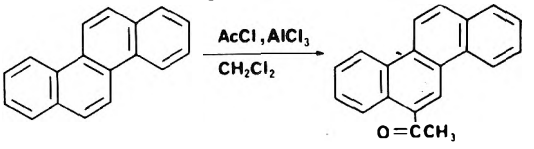
M.W.	84.94
b.p.$_{760}$	39.94°
Freezes at	-95°
d_4^{20}	1.3255
n_D^{20}	1.4244
nmr	δ 5.30
Dielectric constant at 20°	9.08

- Has high solvent power for magnesium halide etherates -- excellent solvent for Grignard reactions.[2]



0% yield in Et_2O
81% yield in CH_2Cl_2

- For Friedel-Crafts acylations,[3] *e.g.*,



64% yield of 6-acetylchrysene (In CS_2 or CH_3NO_2 as solvent, a mixture of 6-, 2- and 3-isomers is obtained.)

- For preparation of methyl esters of aliphatic and aromatic carboxylic acids under Fischer conditions (no need to azeotrope the water formed) -- especially convenient for large-scale preparations.[4]

References

1. Pure chloroform is sensitive to light (reacting with oxygen to form hydrogen chloride and phosgene). Reagent grade chloroform usually contains 0.75% ethanol as stabilizer.
2. H.G. Viehe and M. Reinstein, *Chem. Ber.*, **95**, 2557 (1962).
3. W. Carruthers, *J. Chem. Soc.*, **1953**, 3486.
4. R.O. Clinton and S.C. Laskowski, *J. Amer. Chem. Soc.*, **70**, 3135 (1948).

15,479-2 Dichloromethane, GOLD LABEL (Spectrophotometric grade) .....7.9kg 25.25 ;15.9kg 29.50
(7.9kg = 12 x 500 ml.) (15.9kg = 4 x 3 l.)

D6,510-0 Dichloromethane, A.C.S. reagent grade 4kg 5.30

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