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Stereochemical Control of Reductions. The Directive Effect of Carbomethoxy *vs.* Hydroxymethyl Groups in Catalytic Hydrogenation

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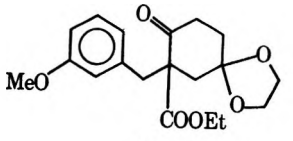
A series of 9a-substituted hexa- and tetrahydrofluorenes has been synthesized from 9a-carbethoxy-7-methoxy-2,2-ethylenedioxy-1,2,3,9a-tetrahydrofluorene (**4**). Catalytic hydrogenation of the carbomethoxy compound **12** gives a cis/trans product ratio of 15:85, while the 9a-hydroxymethyl compound **5** gives a ratio of 95:5. This disparity is discussed in terms of attractive (haptophilic) *vs.* repulsive (steric) interactions between the catalyst surface and the 9a angular group. The stereochemistry of the products is demonstrated by means of intramolecular interactions in the 9a-hydroxymethylhexahydrofluoren-2-ones.

An interest in syntheses leading toward gibberellic acid (**3**)[1] has involved us in the construction and chemistry of model compounds of the type **2**.[2,3] These compounds are readily available by a route involving condensation of *m*-methoxybenzyl chloride[4] with the anion of 2-carbethoxy-4,4-ethylenedioxycyclohexanone.[5] This condensation and the subsequent polyphosphoric acid[6] cyclization of **1** (and reketalization) led to **2** (R = COOEt) in an overall yield of about 33%.



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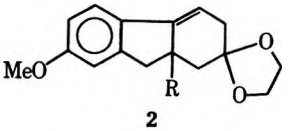

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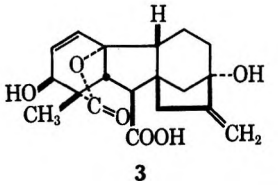


3

Since the B–C ring juncture in gibberellic acid is cis, we wished to introduce this stereochemistry into **2** by reduction of its styrene bond. Of the several routes available, the metal–ammonia reduction of **2** is perhaps the most straightforward in terms of the predictability of its stereochemical outcome. Such a reduction is expected to yield products representing protonation of an equilibrium mixture of the conformers of the anionic reduction intermediate,[7] here, the benzylic anion derived from **2**. The cis and trans forms of this should provide equally good ring overlap with the benzylic anion. However, the cis juncture is known to be more stable in hexahydrofluorenes,[8] and angular substituents apparently increase the relative stability of the cis isomers[9] and may be expected particularly to do so in this case (Scheme I). Hence, if rates of protonation are comparable this equilibrium mixture is expected to yield largely or entirely cis products.

Since at least partial reduction of the ester function by the metal–ammonia system was anticipated, **4** was prereduced with $LiAlH_4$ to give the hydroxymethyl compound (**5**), and this was treated with lithium in liquid ammonia[10] to give what was apparently a single isomer (**6**) of the reduced hydroxymethyl compound.[3] Because the product was liquid, however, we could not be as confident as we wished to be of its stereochemical purity and we decided to convert it into a solid derivative and to synthesize the trans isomer as well for comparison. The latter was easily accomplished, since on catalytic hydrogenation of the original ester (**4**) a single material crystallized from the reaction mixture in high yield, and this reduced ester (**8**), when treated with

(1) R. F. Gould, *Advan. Chem. Ser.*, **28**, 1 (1961).

(2) G. Stork, S. Malhotra, H. Thompson, and M. Uchibayashi, *J. Amer. Chem. Soc.*, **87**, 1148 (1965).

(3) H. W. Thompson, *J. Org. Chem.*, **32**, 3712 (1967).

(4) J. W. Cornforth and R. Robinson, *J. Chem. Soc.*, 684 (1942).

(5) (a) S. Rajagopalan and P. V. A. Raman, "Organic Syntheses," Collect. Vol. III, E. C. Horning, Ed., Wiley, New York, N. Y., 1955, p 425; (b) W. S. Emerson and R. I. Longley, Jr., *ibid.*, Collect. Vol. IV, 1963, p 302; (c) R. M. Lukes, G. I. Poos, and L. H. Sarett, *J. Amer. Chem. Soc.*, **74**, 1401 (1952); (d) P. D. Gardner, L. Rand, and G. R. Haynes, *ibid.*, **78**, 3425 (1956); (e) P. D. Gardner, G. R. Haynes, and R. L. Brandon, *J. Org. Chem.*, **22**, 1206 (1957).

(6) (a) F. D. Popp and W. E. McEwen, *Chem. Rev.*, **58**, 321 (1958); (b) F. Uhlig and H. R. Snyder in "Advances in Organic Chemistry: Methods and Results," Vol. 1, Interscience, New York, N. Y., 1960, pp 35–81.

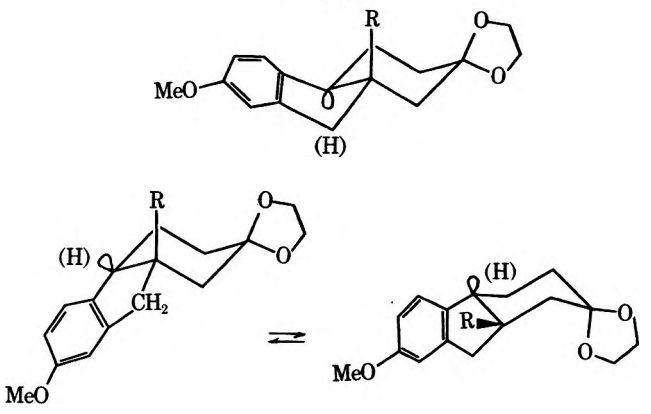
(7) G. Stork and S. D. Darling, *J. Amer. Chem. Soc.*, **86**, 1761 (1964).

(8) H. O. House, V. Paragamian, R. S. Ro, and D. J. Wluka, *ibid.*, **82**, 1457 (1960).

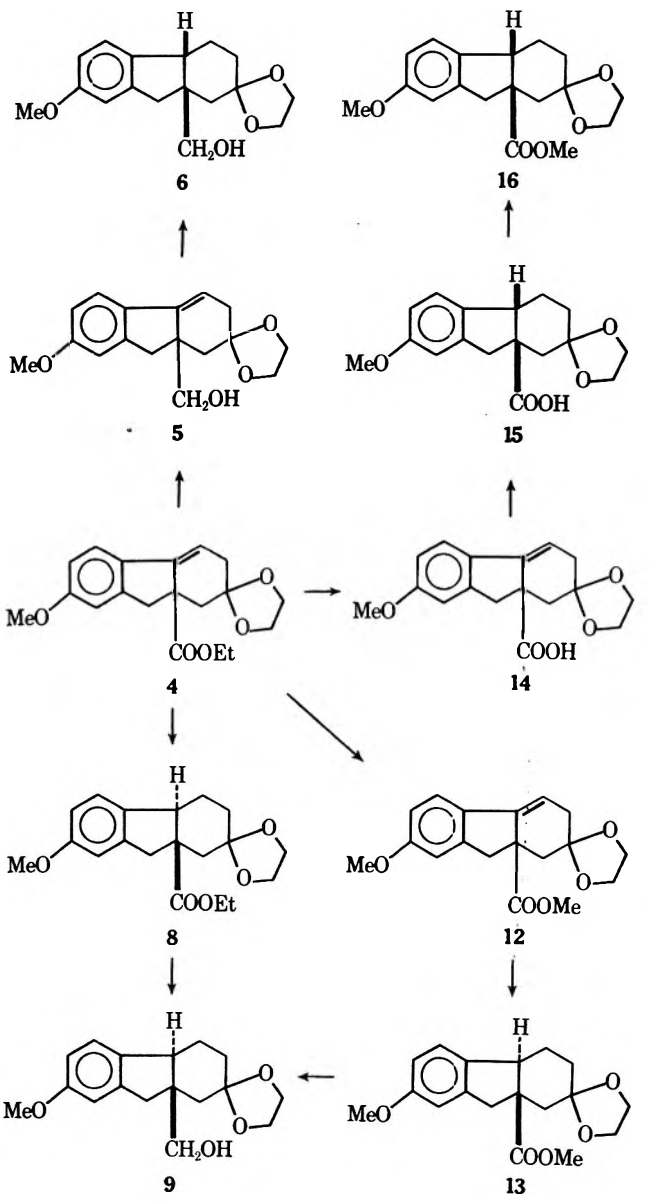
(9) (a) W. E. Parham and L. J. Czuba, *J. Org. Chem.*, **34**, 1899 (1969); (b) N. L. Allinger, R. B. Hermann, and C. Djerassi, *ibid.*, **25**, 922 (1960); (c) N. L. Allinger and S. Greenberg, *ibid.*, **25**, 1399 (1960).

(10) *Cf.* L. H. Knox, E. Blossey, H. Carpio, L. Cervantes, P. Crabbé, E. Velarde, and J. A. Edwards, *ibid.*, **30**, 2198 (1965).

SCHEME I



SCHEME II



$LiAlH_4$, provided a crystalline hydroxymethyl compound (**9**) clearly not identical with **6** (Scheme II).

For the solid derivative of **6**, mild acidic hydrolysis in aqueous methanol converted the cis hydroxymethyl ketal entirely to the corresponding crystalline keto alcohol (**7**). However, when the trans isomer was subjected to identical conditions, an elegant confirmation of its stereochemistry was provided by the isolation, in addition to trans hydroxymethyl ketone (**11**), of major quantities of the methyl ketolide **10**. Either **9** or **10** could be converted in high yield to **11** by replacing methanol with THF during the hydrolysis (Scheme III). The fixing of the 9a-hydroxymethyl group in the axial position, which is responsible for formation of **10**, was further confirmed by comparison of the infrared spectra of **7** and **11**. While the carbonyl stretching band of **7** is of normal intensity, that of **11** is severely diminished in CCl_4 solution, indicating not only that **11** exists principally in the hemiketal form (**11b**),[11] but that **7** does not, presumably because its 9a-hydroxymethyl group is mostly or entirely equatorial[2] (*cf.* Scheme I). The KBr spectrum of **11**, however, displays normal carbonyl absorption, indicating that the crystalline material consists entirely of the keto alcohol (**11a**).

With the stereochemistry of both the lithium–ammonia reduction of **5** and the catalytic hydrogenation of **4** firmly established, we were interested to discover that when the sequence catalytic hydrogenation–hydride reduction (**4** → **8** → **9**) was performed on the unsaturated ester **4** in reverse order, the result was a reversal of stereochemistry (**4** → **5** → **6**), the cis ketal alcohol being produced in high yield and purity. Such a result was not entirely unanticipated, a number of cases being known in which a hydroxyl group near a reducible double bond has apparently been responsible for the addition of hydrogen to the olefin cis in relation to the hydroxyl function.[12–19] This outcome contrasts with the more well-known case, presumably applicable to the hydrogenation of **4**, in which the bulk of the neighboring function is the controlling factor and imposes trans stereochemistry by sterically blocking cis approach to the catalyst surface.[20–22]

The present case implies an actual preference for absorption of the compound on the catalyst surface from the same side as the hydroxyl group and suggests that some attraction of this group to the catalyst surface overcomes whatever difficulty to approach its sheer size might otherwise impose. That such affinities should exist and should vary with the nature of the group involved is not surprising, since certain functionalities, notably amines, phosphines, and groups containing divalent sulfur, are known to become so strongly bound to some catalyst surfaces that they constitute poisons.[23,24] This haptophilicity is thought to be associated with the group's ability to donate unshared electron pairs to unfilled surface orbitals of the catalyst metal. From this point of view the hydroxyl function

(11) C. W. Shoppee, J. C. Coll, and R. E. Lack, *J. Chem. Soc. C*, 1893 (1970).

(12) L. S. Minckler, A. S. Hussey, and R. H. Baker, *J. Amer. Chem. Soc.*, **78**, 1009 (1956); W. G. Dauben, J. W. McFarland, and J. B. Rogan, *J. Org. Chem.*, **26**, 297 (1961), and references cited therein.

(13) M. C. Dart and H. B. Henbest, *J. Chem. Soc.*, 3563 (1960).

(14) T. G. Halsall, W. J. Rodewald, and D. Willis, *ibid.*, 2798 (1959).

(15) N. B. Haynes and C. J. Timmons, *Proc. Chem. Soc.*, 345 (1958).

(16) T. J. Howard, *Chem. Ind. (London)*, 1899 (1963); T. J. Howard, *Recl. Trav. Chim. Pays-Bas*, **83**, 992 (1964).

(17) S. Nishimura and K. Mori, *Bull. Chem. Soc. Jap.*, **36**, 318 (1963).

(18) S. Mitsui, Y. Senda, and H. Saito, *ibid.*, **39**, 694 (1966).

(19) J. E. McMurry, *Tetrahedron Lett.*, 3731 (1970).

(20) R. L. Burwell, Jr., *Chem. Rev.*, **57**, 895 (1957).

(21) S. Siegel, *Advan. Catal. Relat. Subj.*, **16**, 123 (1966).

(22) W. Cocker, P. V. R. Shannon, and P. A. Staniland, *J. Chem. Soc. C*, 41 (1966).

(23) G. C Bond, "Catalysis by Metals," Academic Press, New York, N. Y., 1962, pp 99–100.

(24) E. B. Maxted, *Advan. Catal. Relat. Subj.*, **3**, 129 (1951).

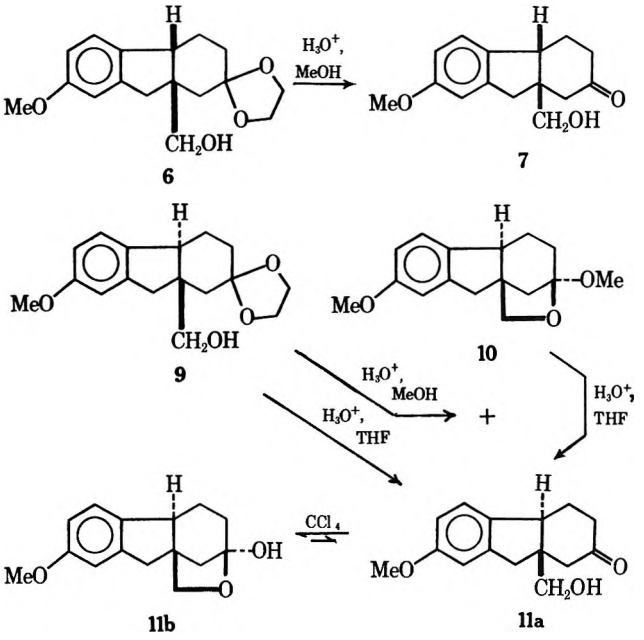
may simply be one whose poisoning action is relatively weak, *i.e.*, reversible; hence it is particularly interesting that the hydrogenations in which we have observed these effects were carried out using alcohols as solvents.[25]

As we became interested in this effect of neighboring functional groups on the stereochemistry of catalytic hydrogenation, we wished to extend our study to include reduction of other compounds in the series represented by **2**. We therefore decided to adapt our procedure to allow the assessment of hydrogenation stereochemistry with as much accuracy and precision as possible for a wide variety of functional groups. (1) All hydrogenations would employ 5% palladium-on-carbon catalyst from the same lot, to avoid batch-to-batch inconsistencies. (2) The ethanol used as solvent in the hydrogenations already described would be replaced by 2-methoxyethanol, whose ability to dissolve polar compounds is considerably greater. (3) Reactions would be run under identical conditions of time, temperature, concentration, etc. (4) Reaction products, freed from catalyst and solvent, would be distilled or sublimed and the entire volatile product assessed by nmr and/or vpc. (5) Control hydrogenations would be carried out on the minority product of each reaction to establish that the preponderance of the majority product was the result of kinetic rather than simply thermodynamic control.

In order to repeat the hydrogenations of **5** and **4** according to the above procedures, we required samples of the trans alcohol and the cis ester for control reductions to establish the absence of product equilibrations. The former was already in hand (**9**); a route to the latter seemed offered by the successful metal–ammonia reduction of the saponification product **14** of the unsaturated ester **4**. This ester itself, as we had anticipated, gave little or no saturated ester, even on careful reduction with insufficiencies of metal in various metal–ammonia systems (the major identifiable products were usually the cis alcohol **6** and the cis aldehyde[3]). The carboxylic acid function, however, in the form of its salt, is known to be almost entirely inert to the conditions of metal–ammonia reductions,[26] and the principles previously cited in predicting stereochemistry in the metal–ammonia reduction of **5** led also to cis stereochemistry[27] in reduction of the unsaturated acid, with, however, no loss of the carboxylic acid function.

Although the esterification of this acid might be accomplished in a number of ways, the hindrance about the acid function and the sensitivity of the ketal made the simplicity, neutrality, and mildness of diazomethane treatment particularly attractive. In addition to this reason for dealing with a carbomethoxy group at R instead of a carbethoxy group, and the advantage of the generally greater crystallinity of methyl esters, the lower bulk of a methyl ester would more closely approximate the size of the hydroxymethyl group we were comparing it with in the catalytic hydrogenation.[28,29] Consequently the cis methyl ester **16** was prepared by diazomethane treatment of the acid **15**, and the unsaturated methyl ester **12** was prepared by (basic) transesterification of **4**.

SCHEME III



Catalytic hydrogenation of the unsaturated methyl ester **12** under the chosen conditions[30] provided a mixture containing 85% trans product **13** and 15% cis material **16**. By contrast, repetition of the hydrogenation of **5** under identical conditions gave 95% cis and 5% trans ketal alcohols. Control hydrogenations of **9** and **16** demonstrated that no detectable equilibration of the products was taking place under our reaction conditions. In addition, our ratio of catalyst to olefin and the large percentage of trans ester **13** produced make it very unlikely that appreciable equilibration can be taking place through the half-hydrogenated state.[31,32]

We believe that these results provide evidence clearly favoring a kinetic stereochemical control effect arising from attractive substrate–catalyst interactions in the hydrogenation of system **2**. This haptophilic effect, which has been observed previously in a number of instances[12–19] but never systematically studied for a wide variety of functional groups, is here documented for a case in which the steric bulks of the groups being compared are reasonably similar,[28,29] and in a system which may readily be extended to include other functional groups of varying bulk, polarity, basicity, etc. We are continuing to examine various aspects of the catalytic hydrogenation of **2** and closely related systems.

Experimental Section[33]

2-Carbethoxy-4,4-ethylenedioxycyclohexanone.—A slurry was prepared of 1.16 mol of NaH (50 g of 56% oil dispersion, washed with hexane) in 230 ml of dry DME under N_2, and to this was

(25) For some recent discussions, with leading references, to the role of solvent in determining stereochemistry, see ref 22 and S. Nishimura, M. Shimahara, and M. Shiota, *J. Org. Chem.*, **31**, 2394 (1966).

(26) M. E. Kuehne and B. F. Lambert, *J. Amer. Chem. Soc.*, **81**, 4278 (1959).

(27) The trans acid has been prepared and characterized, and will be described in another communication.

(28) O. R. Quayle, *Chem. Rev.*, **53**, 439 (1953).

(29) K. Fajans in "The Technique of Organic Chemistry," Vol. I, part 2, A. Weissberger, Ed., Interscience, New York, N. Y., 1960, pp 1169–1211.

(30) *I.e.*, 33 mg of 5% Pd/C and 16 ml of solvent per 1 mmol of olefin.

(31) H. O. House, R. G. Carlson, H. Müller, A. W. Noltes, and C. D. Slater, *J. Amer. Chem. Soc.*, **84**, 2614 (1962).

(32) J.-F. Sauvage, R. H. Baker, and A. S. Hussey, *ibid.*, **83**, 3874 (1961).

(33) Melting points were determined with a Kofler micro hot-stage microscope or a Mel-Temp apparatus and are uncorrected. Infrared spectra were taken using a Beckman IR-10 or a Perkin–Elmer Model 421 spectrometer and, unless otherwise specified, in CCl_4 as solvent. Ultraviolet spectra were determined in 95% EtOH solution with a Cary Model 14 spectro-

(continued on p 2580)

added 3.0 ml of absolute EtOH and then, with stirring over a 3-hr period, 158 g (0.58 mol) of diethyl 4,4-ethylenedioxypimelate[5a,b] in 230 ml of DME. After standing for 48 hr, the thick yellow mixture was diluted with 150 ml of benzene, neutralized with aqueous acetic acid, worked up in the usual manner, and distilled to give three colorless fractions boiling between 95 and 112° (*ca.* 0.5 mm), which had identical nmr spectra and were combined: 113 g (86%), $n^{18}D$ 1.4937 [lit.[5d] bp 114° (0.5 mm), $n^{25}D$ 1.4846].

2-Carbethoxy-3-(*m*-methoxybenzyl)-4,4-ethylenedioxycyclohexanone (1).—A slurry was prepared of 55.0 mmol of NaH (2.475 g of 53.5% oil dispersion, washed with hexane) in 60 ml of dry 1:1 DME–DMF. A solution of 12.00 g (52.5 mmol) of keto ester in 60 ml of the same solvent mixture was added under N_2 to the stirred slurry over 45 min. After an additional hour of stirring, a solution of 8.406 g (53.3 mmol) of *m*-methoxybenzyl chloride[4] in 50 ml of the same solvent was added at room temperature and the temperature was then raised to the reflux point. At about 75–80° a precipitate began appearing in the clear greenish brown solution. The mixture was heated with stirring at *ca.* 100° for 3.5 hr and then stirred for another 15 hr at room temperature. The usual work-up by neutralization, extraction, and concentration yielded 1 as a yellow oil, giving a weak $FeCl_3$ test, which was used without purification in the following cyclization: ir 940 (ketal), 1720, 1740 cm^{-1}; nmr δ 1.1 (3 H, t, J = 7 Hz), 1.4–3.1 (8 H, complex), 3.7 (3 H, s), 3.9 (4 H, s), 4.0 (2 H, q, J = 7 Hz), 6.6–7.3 (4 H, complex).

9a-Carbethoxy-7-methoxy-2,2-ethylenedioxy-1,2,3,9a-tetrahydrofluorene (4).—The entire product from the above condensation was mixed thoroughly with 180 g of polyphosphoric acid (76% total P_2O_5 content) and allowed to stand at room temperature for 2 hr. The usual ice–water work-up and extraction provided on concentration an orange oil which had C=O absorption at 1720–1740 cm^{-1} only, and which oxidized readily in air. It was therefore immediately reketalized by refluxing under N_2 in 200 ml of benzene with 6.0 ml (108.5 mmol) of ethylene glycol and 200 mg of *p*-toluenesulfonic acid for 19 hr with continuous separation of water. The usual work-up provided a brownish oil, which solidified and on trituration with ether gave 5.8 g (33.5%) of crude yellow 4. Recrystallization from hexane yielded 5.25 g, which was further purified to give colorless, flat needles: mp 116–117°; ir 940, 1720 cm^{-1}; uv 210 nm (ϵ 21,400), 260 (20,000), 300 (5320); nmr δ 1.1 (3 H, t, J = 7 Hz), 1.8 (1 H, d, J = 13 Hz), 2.8 (1 H, d, J = 13 Hz), 2.5–3.5 (4 H, complex), 3.8 (3 H, s), 4.0 (4 H, m), 4.05 (2 H, q, J = 7 Hz), 5.9 (1 H, t, J = 4 Hz), 6.7–6.9 (2 H, m), 7.4 (1 H, d, J = 9 Hz).

Anal. Calcd for $C_{19}H_{22}O_5$: C, 69.07; H, 6.71. Found: C, 68.98; H, 6.60.

Lithium Aluminum Hydride Reduction of 4.—A slurry was prepared of 200 mg (5.0 mmol) of $LiAlH_4$ in 40 ml of dry ether. To this stirred mixture was added under N_2 over 1 hr a solution of 660 mg (2.0 mmol) of 4 in 10 ml of dry THF and 40 ml of ether. The resulting mixture was refluxed for 4 hr, allowed to stand overnight, and worked up by titration with saturated aqueous Na_2SO_4 and decantation from the precipitate. The solid resulting from concentration was recrystallized from MeOH–water to give 444 mg (77%) of white needles, mp 120–124°, and an additional 34 mg (6%) of crystalline material was recovered from the liquors. Pure 5 melted at 121–124°: ir 930, 945, 3500, 3620 cm^{-1}; uv 205 nm (ϵ 20,000), 260 (20,000), 300 (5460); nmr δ 1.9 (1 H, d, J = 13.5 Hz), 2.35 (1 H, d, J = 13.5 Hz), 2.4–4.1 (7 H complex), 3.8 (3 H, s), 4.05 (4 H, m), 5.85 (1 H, t, J = 4 Hz), 6.6–6.9 (2 H, m), 7.35 (1 H, d, J = 9 Hz).

Anal. Calcd for $C_{17}H_{20}O_4$: C, 70.81; H, 6.99. Found: C, 70.98; H, 6.99.

Reduction of 5 with Lithium in Ammonia.—A solution of 910 mg (3.16 mmol) of 5 in 20 ml of dry 1:1 THF–ether was added over 12 min to a stirred solution of 60 mg (8.6 mg-atoms) of Li in 50 ml of liquid NH_3. A few minutes later *ca.* 10 mg more of Li was added to the faded solution, and after 30 min the blue solution was treated with excess solid NH_4Cl and allowed to evaporate. Concentration of the ether-soluble portion gave 970 mg of crude yellow oil 6, showing a single spot on tlc with MeCN–benzene or EtOAc. Material from a similar reaction was purified by chromatography on Al_2O_3 and distilled at 150–160° (0.02 mm) to give a colorless oil: $n^{26}D$ 1.5611; ir 930, 945, 3480, 3550 cm^{-1}; uv 219 nm (ϵ 7190), 227 (6860), 281.5 (2700), 288.5 (2360); nmr δ 1.3–3.3 (12 H, complex), 3.8 (3 H, s), 3.95 (4 H, m), 6.6–7.2 (3 H, complex).

Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C 70.24; H, 7.62.

Catalytic Hydrogenation of 5.—A solution of 470 mg (1.63 mmol) of 5 in 20 ml of absolute EtOH containing 40 mg of 5% Pd/C catalyst was hydrogenated with stirring at room temperature and atmospheric pressure. After 1 hr 32 ml of H_2 had been absorbed and the mixture was allowed to stir with H_2 overnight. The filtered solution was concentrated and distilled at *ca.* 175° (0.01 mm), yielding 325 mg (69%) of liquid 6.

Acidic Ketal Hydrolysis of 6.—After 100.5 mg of 5 had been hydrogenated in 5.0 ml of absolute EtOH over 10.3 mg of 10% Pd/C, the isolated product was stirred for 1 hr at room temperature with 15 ml of MeOH, 1.5 ml of water, and 1.5 ml of hydrochloric acid. Neutralization, extraction, and concentration gave crystalline material which was chromatographed on Al_2O_3. Combination of appropriate fractions and recrystallization from ether–hexane gave 66.3 mg (77% overall) of 7 as white needles, mp 82–86°; the mixture melting point with 7 obtained from the Li–NH_3 reduction product of 5 was undepressed. The analytical sample melted at 83.5–85°: ir 1715, 3450, 3650, cm^{-1}; uv 220 nm (ϵ 8100), 282 (2990), 288 (2670); nmr δ 2.0–3.7 (12 H, complex), 3.8 (3 H, s), 6.6–7.2 (3 H, complex).

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.06; H, 7.64.

Catalytic Hydrogenation of 4.—A solution of 268.4 mg (0.814 mmol) of 4 in 13.5 ml of absolute EtOH containing 26 mg of 10% Pd–C catalyst was hydrogenated with stirring at room temperature and atmospheric pressure. After 20 min, uptake of H_2 had stopped (20.1 ml). The filtered solution was concentrated and the resulting solid was recrystallized from hexane to give 223 mg (83.5%) of white crystals (8): mp 88–89°; ir 950, 1715, 1740 cm^{-1}; uv 227 nm (ϵ 7440), 284 (2790), 290 s (2410); nmr δ 1.1 (3 H, t, J = 7 Hz), 1.6–3.2 (9 H, complex), 3.8 (3 H, s), 3.9 (4, H, m), 3.95 (2 H, q, J = 7 Hz), 6.6–7.2 (3 H, complex).

Anal. Calcd for $C_{19}H_{24}O_5$: C, 68.66; H, 7.28. Found: C, 68.60; H, 7.21.

Lithium Aluminum Hydride Reduction of 8.—A solution of 172.3 mg (0.52 mmol) of 8 in 5 ml of 1:1 THF–ether was added over 15 min to a stirred suspension of 100 mg (2.5 mmol) of $LiAlH_4$ in 15 ml of ether under N_2. The mixture was then refluxed for 4 hr and worked up as described for reduction of 4, giving a solid which was recrystallized from ether–pentane to yield 101.5 mg (67.5%) of 9 as prismatic platelets: mp 89–91°; ir 915, 940, 3480, 3640 cm^{-1}; uv 228 nm (ϵ 7600), 282 (2760), 288 s (2350); nmr δ 1.5–4.1 (12 H, complex), 3.8 (3 H, s), 4.0 (4, H, m), 6.5–7.1 (3 H, m).

Anal. Calcd for $C_{17}H_{22}O_4$: C, 70.32; H, 7.64. Found: C, 70.40; H, 7.71.

Acidic Ketal Hydrolysis of 9.—A solution of 187 mg (0.645 mmol) of 9 in 16.5 ml of MeOH and 1.5 ml of hydrochloric acid was stirred at room temperture for 1 hr, neutralized, and extracted with ether. The concentrated extracts were chromatographed on 10 g of basic Al_2O_3 (deactivated with 5% water). Elution with 10–25% ether in hexane gave 145.5 mg (87%) of 10, recrystallized from hexane to provide 113 mg of needles: mp 77–78.5°; ir no absorption in the OH or C=O regions; uv 227 nm (ϵ 8600), 282 (2900), 288 (2560); nmr δ 1.3–3.9 (11 H, complex), 3.3 (3 H, s), 3.7 (3 H, s), 6.65–7.15 (3 H, complex).

Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74. Found: C, 74.06; H, 7.88.

Continued elution of the chromatograph with MeOH gave 16 mg (6.5%) of 11. Sulimation at *ca.* 135° (0.02 mm) and recrystallization from benzene–hexane gave small needle clusters: mp 154.5–156°; ir (CCl_4) 1700 (w), 3370 (br), 3600 (sh) cm^{-1}; ir (KBr) 1690 (strong), 3390 (br) cm^{-1}; uv 227 nm (ϵ 7800), 281 (2770), 288 (2420); nmr (CH_2Cl_2) δ 1.6–3.7 (12 H, complex), 3.8 (3 H, s), 6.6–7.2 (3 H, complex).

Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.33; H, 7.48.

Another hydrolysis performed on the $LiAlH_4$ reduction product from 111 mg (0.334 mmol) of 8 was carried out for 70 min with 10 ml of MeOH, 1 ml of water, and 1 ml of hydrochloric acid, and on chromatography gave 68.5 mg (79%) of 10 and 13.5 mg (5.5%) of 11.

photometer; nmr spectra were taken with a Varian A-60 spectrometer (CH_2Cl_2 and/or TMS internal standard) and, unless otherwise specified, using CCl_4 or $CDCl_3$ as solvent. Microanalyses were performed by Micro-Tech Laboratories, Skokie, Ill. The abbreviations DME, DMF, and THF refer to dimethoxyethane, dimethylformamide, and tetrahydrofuran.

Acidic Ketal Hydrolysis of 10.—A solution of 64.5 mg of **10** in 6 ml of THF, 5 ml of water, and 1 ml of hydrochloric acid was stirred at room temperature for 1.5 hr, neutralized, saturated with NaCl, and extracted. Concentration gave solid which was recrystallized from benzene–hexane, yielding 48.5 mg (79.5%) of **11**, further purified to a melting point of 156–158°. Direct hydrolysis of **9** in the same medium provided only **11**.

Saponification of 4.—A solution of 1.00 g (3.03 mmol) of **4** and 2.03 g of KOH in 80 ml of 1:1 EtOH–water was refluxed under N_2 for 21 hr and worked up by addition of saturated aqueous oxalic acid. Concentration of the ether–CH_2Cl_2 extracts gave 907 mg (99%) of crude yellow solid and recrystallization from absolute EtOH gave 600 mg (65.5%) of prismatic crystals. The analytically pure **14** actually melts at *ca.* 185° when introduced into an already heated apparatus, but usually begins decarboxylating (β,γ-unsaturated acid) and melting at *ca.* 160° under slower heating: ir ($CHCl_3$) 930 1700, 2300–3600 cm^{-1}; uv 209.5 (ϵ 20,500), 259 (19,700), 300 (5270); nmr δ 1.8 (1 H, d, J = 13 Hz), 2.8 (1 H, d, J = 13 Hz), 2.5–3.5 (4 H, complex), 3.8 (3 H, s), 3.95 (4 H, m), 5.95 (1 H, t, J = 3.5 Hz), 6.7–7.0 (2 H, m), 7.4 (1 H, d, J = 9 Hz), 9.0 (1 H, very broad).

Anal. Calcd for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00. Found: C 67.61; H, 6.10.

Reduction of 14 with Lithium in Ammonia.—A solution of 100 mg (0.331 mmol) of **14** in 5.0 ml of THF (freshly distilled from $LiAlH_4$) was added over 30 sec to a stirred solution of 35 mg (5 mg-atoms) of Li in *ca.* 15 ml of liquid NH_3. After 15 min of stirring the blue solution was decolorized with solid NH_4Cl and, allowed to evaporate. Water and ether were added and then aqueous oxalic acid to *ca.* pH 3. Concentration of the organic extracts yielded 105 mg of crude solid, which was sublimed at 155° (0.01 mm) and recrystallized from ether–pentane to give 94 mg (93.5%) of **15** as minute prisms: mp 155.5–157°; ir ($CHCl_3$) 930, 1700, 2300–3600 cm^{-1}; uv 219 nm (ϵ 6930), 227 (7170), 282 (2770), 288.5 (2430); nmr δ 1.3–3.5 (9 H, complex), 3.8 (3 H, s), 3.95 (4 H, s), 6.7–7.3 (3 H, complex), 11.15 (1 H, s, broad).

Anal. Calcd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62. Found: C, 67.10; H, 6.63.

Esterification of 15 with Diazomethane.—A solution of 217 mg (0.715 mmol) of **15** in 25 ml of dry ether was treated with ethereal CH_2N_2 until a definite yellow color persisted. The solution was boiled briefly to remove excess CH_2N_2 and cleared of polymer by passage through a short column of Al_2O_3. The resulting material was chromatographed on 11 g of Al_2O_3 (deactivated with 5% water) and eluted with 20–40% ether in hexane. Recrystallization from pentane gave 182 mg (80%) of **16** as flat plates. Further recrystallization produced material melting at 88.5–89.5°: ir 930, 1735 cm^{-1}; uv 219 nm (ϵ 6920), 228 (7230), 282 (2770), 288.5 (2450); nmr δ 1.2–3.3 (9 H, complex), 3.8 (6 H, 2 s), 3.9 (4 H, s), 6.7–7.2 (3 H, complex).

Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 68.13; H, 6.99.

Transesterification of 4 with Sodium Methoxide.—A solution of 991 mg (3.00 mmol) of **4** in methanolic NaOMe prepared from 50 ml of MeOH and 1.01 g (44.0 mmol) of Na was refluxed under N_2 for 21 hr and worked up by addition of aqueous oxalic acid. Concentration of the ether–CH_2Cl_2 extracts gave 889 mg (94%) of crude **12**. Recrystallization from hexane gave 820 mg, which was sublimed at 133° (0.01 mm) and recrystallized further to provide needles: mp 134–135°; ir 940, 1725 cm^{-1}; uv 209 nm (ϵ 22,600), 259 (20,400), 299.5 (5350); nmr δ 1.8 (1 H, d, J = 13 Hz), 2.8 (1 H, d, J = 13 Hz), 2.5–3.5 (4 H, complex), 3.6 (3 H, s), 3.8 (3 H, s), 4.0 (4 H, m), 5.9 (1 H, t, J = 4 Hz), 6.7–6.9 (2 H, m), 7.4 (1 H, d, J = 9 Hz).

Anal. Calcd for $C_{18}H_{20}O_5$: C, 68.34; H, 6.37. Found: C, 68.52; H, 6.40.

Catalytic Hydrogenation of 12.—A solution of 500 mg (1.58 mmol) of **12** in 25 ml of absolute EtOH containing 50 mg of 5% Pd/C catalyst was hydrogenated with stirring at room temperature and atmospheric pressure. The reaction was complete in 45–50 min (48 ml H_2) and was stopped at 60 min. The filtered solution was concentrated, sublimed at 135–140° (0.02 mm), and recrystallized from ether–pentane to give 440 mg (87.5%) of **13** in two crops Further recrystallization from ether gave diamond-shaped platelets: mp 143.5–145°; ir 940, 950, 1720, 1745 cm^{-1}; uv 219 nm (ϵ 7050), 227.5 (7250), 283.5 (2820), 290 (2450); nmr δ 1.6–3.3 (9 H, complex), 3.55 (3 H, s), 3.8 (3 H, s), 3.95 (4 H, m), 6.6–7.2 (3 H, complex).

Anal. Calcd for $C_{18}H_{22}O_5$: C, 67.91; H, 6.97. Found: C, 68.04; H, 6.88.

Reduction of **13** with $LiAlH_4$ produced material, mp 85–86°, identical with previously described **9**.

Assessment of Cis/Trans Ratio in Hydrogenation of 5.—A solution of 100 mg (0.348 mmol) of **5** in 5.50 ml of solvent[30,34] was hydrogenated with rapid stirring over 11.5 mg of catalyst[30,35] at 25° and atmospheric pressure in a low-pressure hydrogenation apparatus and stopped after 60 min, although it was apparently complete after 20 min (9.1 ml H_2). The filtered mixture was concentrated and distilled in a microsublimation apparatus at 140° (0.01 mm) to give 101 mg (100%) of viscous, colorless liquid. Analysis by vpc[36] of the trimethylsilylated[37] mixture indicated 95 ± 2% cis and 5 ± 2% trans alcohols.

Control Hydrogenation of Trans Alcohol 9.—A solution of 50 mg (0.174 mmol) of **9** in 2.75 ml of solvent[30,34] was hydrogenated with rapid stirring over 5.7 mg of catalyst,[30,35] stopped after 73 min, and isolated as described above to give 50 mg (100%) of crystalline material washed directly from the sublimator cold-finger with $CDCl_3$ and concentrated to give a solution whose nmr spectrum was identical with that of pure **9**.

Assessment of Cis/Trans Ratio in Hydrogenation of 12.—A solution of 100 mg (0.316 mmol) of **12** in 5.0 ml of solvent[30,34] was hydrogenated with rapid stirring over 10.5 mg of catalyst[30,35] at 25° and atmospheric pressure in a low-pressure hydrogenation apparatus and stopped after 60 min, although it was apparently completely reacted after *ca.* 45 min (10.5 ml H_2). The mixture was isolated and purified as described to give 99.5 mg (99%) of colorless, crystalline sublimate. Analysis of the mixture by vpc[36] indicated 85 ± 1% trans and 15 ± 1% cis esters.

Control Hydrogenation of Cis Methyl Ester 16.—A solution of 50 mg (0.158 mmol) of **16** in 2.50 ml of solvent[30,34] was hydrogenated with rapid stirring over 5.2 mg of catalyst,[30,35] stopped after 60 min, and isolated as described to give 49 mg (98%) of material, collected and analyzed as described, whose nmr spectrum was identical with that of pure **16**.

Registry No.—**1**, 30541-60-7; **4**, 30541-61-8; **5**, 30541-62-9; **6**, 30541-63-0; **7**, 30541-64-1; **8**, 30541-65-2; **9**, 30541-66-3; **10**, 30541-67-4; **11**, 30541-68-5; **11b**, 30546-06-6; **12**, 30541-69-6; **13**, 30541-70-9; **14**, 30541-71-0; **15**, 30541-72-1; **16**, 30541-73-2.

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(34) Matheson Coleman and Bell chromatoquality (99.9 mol % pure) 2-methoxyethanol.

(35) 5% palladium–carbon catalyst (Lot No. 11-333) obtained from Engelhard Industries, Inc., Newark, N. J.

(36) We thank R. E. Naipawer for this analysis, which was carried out at 60 psi on a 0.125 in. × 8 ft column packed with 3% OV-1 (dimethylsilicone, obtained from Applied Science Laboratories, Inc., State College, Pa.) on Gas-Chrom Q and programmed from 100 to 250°.

(37) Treated at room temperature with Silyl-8 obtained from Pierce Chemical Co., Rockford, Ill.

Hydrogen Isotope Effect in the Reaction of Trityl Radicals with Thiophenol[1]

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Excess thiophenol reacts at room temperature with 4-triphenylmethyl-1-diphenylmethylene-2,6-cyclohexadiene (I) to produce triphenylmethane and phenyl triphenylmethyl sulfide. At −20 and −40°, *p*-benzhydryltetraphenylmethane (II), an isomer of I, is also formed. When tritium is present in the SH position, both triphenylmethane and II are labeled, and an isotope effect for the hydrogen transfer from sulfur to carbon is found with $k_H/k_T = 14.9$. Between 0 and 40°, the temperature dependence of the isotope effect is normal, but the measured isotope effect is apparently too low both at high temperatures (60°) and low (−20 and −40°). An explanation is offered for the high-temperature deviation in terms of failure of the competitive method. We attribute low-temperature deviations to reversibility. An extremely rough estimate of the rate of this nearly thermoneutral hydrogen atom transfer, $k = 1\ M^{-1}\ \text{sec}^{-1}$, is presented.

The nature of the potential energy surfaces in hydrogen transfer reactions are of much interest, and hydrogen isotope effects have contributed to the knowledge of these surfaces. In proton transfers, it is clear that the solvent is intimately involved and may be the only source of the barrier.[2] Hydrogen atom transfers, on the other hand, seem to have significant barriers even in the gas phase, some of which have been calculated with more or less precision.[3] Isotope effects of a magnitude which require the existence of a barrier have also been observed.[3] The limitations of gas-phase methods, primarily those of volatility, have led us to initiate a systematic study of isotope effects in hydrogen atom transfer in solution, with the idea that the solvent effects will be less important than in the ionic proton transfers. In the transfer of hydrogen from sulfur to carbon, the isotope effects are far larger in the reaction reported here than in the reactions with less stable radicals.[4]

Results and Discussion

When a toluene solution of "hexaphenylethane," 1-diphenylmethylene-4-triphenylmethyl-2,5-cyclohexadiene[5] (I), in equilibrium with triphenylmethyl radicals, was added with good stirring to a tenfold excess of thiophenol, allowed to stand for 10 half-lives for the dissociation process,[6] and then worked up, triphenylmethane and trityl phenyl sulfide were found. Diphenyl disulfide would have been found by the separation procedure used, but was not found.[7]

We propose the mechanism indicated by reactions 1, 2, and 3. We find no evidence of an induced decomposition of I, which agrees with the absence of attack of nitric oxide or iodine atoms,[6,8] but does not agree with the chain process involving attack by tritylperoxy radicals.[9] However, as described later on, only a rather fast induced reaction is rigorously excluded.

$$\text{I} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} 2(C_6H_5)_3C\cdot \quad (1)$$

$$(C_6H_5)_3C\cdot + C_6H_5SH \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} (C_6H_5)_3CH + C_6H_5S\cdot \quad (2)$$

$$(C_6H_5)_3C\cdot + C_6H_5S\cdot \xrightarrow{k_3} C_6H_5SC(C_6H_5)_3 \quad (3)$$

With the use of $C_6H_5S^3H$, the relative specific activities of the triphenylmethane and the thiophenol, which is present in substantial excess, then gives[10] the isotope effect on k_2, neglecting for the moment the reverse reaction. These measured effects are given in Table I

TABLE I

ISOTOPE EFFECTS MEASURED BY SPECIFIC ACTIVITY RATIOS FOR REACTIONS 2 AND 4

Temp, °C	k_H/k_T[a]	k_H/k_T calcd[b]	k_H/k_T[c]
−25	27.4	36	27.9
−15	27.4	29	27.4
0	22.3	22.3	
25	14.9	14.8	
40	12.1	12.0	
60	1.9	9.3	

[a] Measured isotope effect for triphenylmethane formation. Each entry represents an average of at least two runs agreeing within ±0.3 [b] Calculated from eq 4. [c] Measured isotope effect for formation of compound II.

for various reaction temperatures. The third column is the value of the isotope effect calculated from eq 4, which fits better than any other the range 0–40°. No Arrhenius equation fits all the points satisfactorily.

$$k_H/k_T = 0.187 \exp(2590/RT) \quad (4)$$

We attribute the failure of the Arrhenius equation to two sources. The extremely low isotope effect at the highest temperature is almost certainly a result of the reaction rates becoming fast compared to the mixing rate. Hence the thiophenol is locally depleted, and the assumption of a large excess of thiophenol fails.

The apparently low isotope effects at the lower temperatures can be attributed to neglect of the reversal of reaction 2. When the steady-state concentration of trityl radicals is high, nearly all phenylthiyl radicals are scavenged by reaction 3, but at the lowest temperatures the trityl radical concentrations are drastically

(1) This work was supported by a grant from the Robert A. Welch Foundation. It was presented in part at the fall meeting of the National Academy of Sciences in Houston, Texas, 1970.

(2) See, for example, C. D. Ritchie, *J. Amer. Chem. Soc.*, **91**, 6749 (1969).

(3) Several examples of semiempirical calculations are given in H. S. Johnston, "Gas Phase Reaction Rate Theory," Ronald Press, New York, N. Y., 1966.

(4) E. S. Lewis and M. M. Butler, unpublished work.

(5) H. Lankamp, W. T. Nauta, and C. MacLean, *Tetrahedron Lett.*, 249 (1968); P. Jacobson, *Chem. Ber.*, **38**, 196 (1905).

(6) K. Ziegler, A. Seib, K. Knoevenagel, P. Herte, and F. Andreas, *Justus Liebigs Ann. Chem.*, **551**, 150 (1942).

(7) Although disulfides react with triphenylmethyl to yield trityl sulfides [H. Lecher, *Ber.*, **48**, 524 (1915)], this reaction appears to require a higher temperature. See also W. A. Pryor and H. Guard, *J. Amer. Chem. Soc.*, **86**, 1150 (1964).

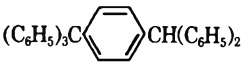
(8) K. Ziegler, L. Ewald, and P. Orth, *Justus Liebigs Ann. Chem.*, **479**, 277 (1930).

(9) K. Ziegler and L. Ewald, *ibid.*, **504**, 162 (1933). It is interesting to note that this induced reaction is much easier to understand in terms of the structure I, than in terms of the hexaphenylethane structure.

(10) L. Melander, "Isotope Effects on Reaction Rates," Ronald Press, New York, N. Y., 1960, p 58.

reduced, enabling the thiyl radicals to abstract hydrogens, as they are known to do readily.[11] The effect of this reverse reaction (which will of course also have a large isotope effect) will be to reduce the isotope effect measured by the activity of the triphenylmethane, in the limit (which we do not approach) to the small value characteristic of an equilibrium isotope effect.

Several observations support this evidence. The first is that at the lower two temperatures a new product is found, namely, *p*-benzhydrylphenyltriphenylmethane (II). This substance, an isomer of I, cannot result



II

from an intramolecular isomerization, for it contains tritium derived from the thiophenol. We suspect the mechanism of eq 5 and 6, and calculate an isotope effect

$$\text{I} + \text{C}_6\text{H}_5\text{S}\cdot \longrightarrow p\text{-}(\text{C}_6\text{H}_5)_3\text{CC}_6\text{H}_4\dot{\text{C}}(\text{C}_6\text{H}_5)_2 + \text{C}_6\text{H}_5\text{SH} \quad (5)$$

$$p\text{-}(\text{C}_6\text{H}_5)_3\text{CC}_6\text{H}_4\dot{\text{C}}(\text{C}_6\text{H}_5)_2 + \text{C}_6\text{H}_5\text{SH} \longrightarrow \text{II} + \text{C}_6\text{H}_5\text{S}\cdot \quad (6)$$

for its formation as shown in the last column of Table I. The closely similar isotope effects suggest a closely similar process, as reactions 2 and 6 certainly are. Compound II has been obtained before from I by an acid-catalyzed process,[12] but it seems unlikely that thiophenol is acidic enough to accomplish the reaction at these low temperatures.

A second piece of evidence lies in the observation that inactive triphenylmethane, heated with thiophenol-*t* and azobisisobutyronitrile, leads to incorporation of tritium in the recovered triphenylmethane. Because of some uncertainties regarding the molecule initially attacked by the cyanoisopropyl radicals, this evidence is a necessary but insufficient demonstration of attack of the phenylthiyl radicals on triphenylmethane.

Finally, we may conclude from the large value of the isotope effect itself that the reaction is not very unsymmetrical, and therefore it has an approximately equal barrier in both directions. The value at 25° of $k_H/k_T = 14.8$ is slightly larger than would be calculated for complete loss of zero-point energy of a harmonic stretching vibration (ν 2575 cm^{-1}) of a typical SH bond, $k_H/k_T = 11.5$. We might be tempted to attribute the observed higher value to tunneling, especially in view of the low pre-exponential factor in eq 4,[13] but this also suggests a rather symmetric barrier, since tunneling itself seems most associated with symmetric barriers.[14] We do not believe that our data are unequivocal evidence for tunneling, but suggest that they do indicate a rather symmetric barrier.

It is of course even more valuable in defining the potential surface of reaction 2 to measure the rate rather than the isotope effect. Our experiments do not allow us to do this with any precision, but one result casts light upon this problem. When the experiment was performed at 0°, it was noted that the color of the trityl radical decreased sharply upon addition of a solution of I to a solution of thiophenol. However, there was still a perceptible color which persisted for several half-lives[6] of the dissociation of I, but the color was not detectable after 10 half-lives. This is the basis of the statement above that there does not appear to be any important induced decomposition of I, but it also allows a very rough estimate of k_2. If we neglect reactions 5 and 6 and the reverse of 2, the steady-state concentration of trityl radicals (T·) can be calculated from eq 7,

$$(\text{T}\cdot) = \frac{-2k_2(\text{C}_6\text{H}_5\text{SH}) + \sqrt{[2k_2(\text{C}_6\text{H}_5\text{SH})]^2 + 4k_1k_{-1}(\text{I})}}{2k_{-1}} \quad (7)$$

in which k_1 and k_{-1} are known.[6] If we (rather arbitrarily) assume that perceptible color is one-tenth the color of a solution of I in equilibrium with trityl radicals, then this equation can be solved for k_2, giving the value $k_2 = 1\ M^{-1}\ \text{sec}^{-1}$, which is probably within a few orders of magnitude. This can be compared to the value $k = 60$, estimated from the literature on propagation rates and chain transfer constants for the reaction of radicals in polymerizing styrene with *tert*-butyl mercaptan at 0°.[15] The numbers are close enough so that little can be said about the comparison. It is interesting, however, that the method could in principle be used for measuring k_2 with good precision, although we have not undertaken this experimentally difficult problem.

Experimental Section

Apparatus.—The apparatus used was a single unit consisting of three flasks connected in series by appropriate ground-glass joints. The first was a 500-ml 24/40 one-neck flask. The second was a 500-ml, 24/40 two-neck flask. The third was a 1000-ml, 24/40 two-neck flask. A fritted glass filter was placed between the first and second flask, and two 90° bends with ground-glass 24/40 joints were placed between flasks two and three. One of these 90° bends contained a large bore vacuum stopcock. The third flask also contained a small bore vacuum stopcock used for degassing the system. The entire reaction sequence could, with this device, be executed in the absence of air.

Tritium-Labeled Thiophenol.—Reagent grade thiophenol (500 g), 2 g of tritium-enriched water (1 mCi/g), and 5 g of calcium oxide were placed in a 1-l. flask fitted with a reflux condenser, drying tube, and magnetic stirrer, and then heated for 12 hr at 80°. The labeled thiophenol was dried over anhydrous sodium sulfate and distilled. The boiling point was 169° at atmospheric pressure.

Counting Procedures.—Weighed samples were added to 20 ml of a solution containing 5 g of 2,5-diphenyloxazole and 0.1 g of *p*-bis[2-(5-phenyloxazolyl)]benzene per liter of toluene and counted for about 40 min. Background corrections and efficiency corrections using external standardization were applied to all results. All counting efficiencies were about 28% and no effort was made to maximize the efficiency; no pure compounds quenched badly. Four samples of thiophenol gave an average specific activity of 4.13×10^8 decompositions min^{-1} mol^{-1} with an extreme deviation of less than 3%.

Location of Tritium Label in Thiophenol.—Tritium-labeled thiophenol (2 g) was oxidized to diphenyl disulfide by hydrogen peroxide in glacial acetic acid. After recrystallization from ethanol, it was counted and found to be inactive. A sample of thiophenol-*t* that had been standing for 6 months did give a small but detectable count when oxidized in this way, showing that a very slow process did result in the migration of tritium from sulfur to carbon.

Exchange between Thiophenol and Triphenylmethane.—Thiophenol (20 ml, 0.19 mol) (specific activity = 4.13×10^8 decompositions min^{-1} mol^{-1}), 1.5 g (0.006 mol) of reagent grade triphenylmethane, and 0.05 g of azobisisobutyronitrile were placed in a 50-ml flask fitted with reflux condenser and drying tube and then heated at 80° for 18 hr. The mixture was cooled, dissolved

(11) C. Walling and R. Rabinowitz, *J. Amer. Chem. Soc.*, **81**, 1137 (1959).
(12) F. Ullmann and W. Borsum, *Ber.*, **35**, 2877 (1902); see also A. E. Tschitschibabin, *ibid.*, **37**, 4709 (1904).
(13) R. P. Bell, "The Proton in Chemistry," Cornell University Press, Ithaca, N. Y., 1959, p 211.
(14) R. A. More O'Ferrall and J. Kouba, *J. Chem. Soc. B*, 985 (1967).
(15) C. Walling, "Free Radicals in Solution," Wiley, New York, N. Y., 1957, pp 95, 153.

in ether, washed with 5% sodium hydroxide, and dried over anhydrous sodium sulfate. After evaporation of the ether, the triphenylmethane was recrystallized twice from ethanol. Two samples of the triphenylmethane were counted and found to have a specific activity of 1.34×10^7 decompositions min^{-1} mol^{-1}. The melting point of the recrystallized triphenylmethane was 93–94°.[16]

4-Triphenyl-1-diphenylmethylene-2,5-cyclohexadiene (I).—Mercury (20 g, 0.1 mol) was added to a solution of 5.78 g (0.021 mol) of triphenylchloromethane in 250 ml of dry toluene in the first flask, following with minor modification the procedure of Gomberg.[17] The system was closed, degassed three times, and allowed to react at 20° for 12 hr with vigorous stirring.

Reaction of Triphenylmethyl with Thiophenol.—The yellow solution of I was filtered from the first flask through a glass wool plug and then through a fritted glass filter into the second flask. To the third flask, 16 g (0.15 mol) of tritium-labeled thiophenol was added to 235 ml of dried reagent-grade toluene. The thiophenol–toluene solution was degassed three times. The entire apparatus was then submerged in a bath controlled to within ±0.05° and allowed to attain thermal equilibrium. Compound I was then added dropwise through the stopcock to the thiophenol–toluene solution, which was magnetically stirred.

Isolation of Triphenylmethane, Trityl Phenyl Sulfide, and *p*-Benzhydryltetraphenylmethane (II).—The reaction mixture was washed with 5% sodium hydroxide and dried over anhydrous sodium sulfate. Toluene was removed by distillation, counted, and found to have no tritium. A 3 ft × 1 in. chromatographic column packed with neutral aluminum oxide was used to separate the viscous oil. A 2:1 mixture of low-boiling petroleum ether–benzene was used to elute the mixture and obtain complete separation of the triphenylmethane. A 1:2 petroleum ether–benzene mixture was then used to elute the trityl phenyl sulfide. After all trityl phenyl sulfide was removed, methylene chloride was used to elute any remaining compounds. Only at −25 and −15° were any other compounds found. At these low temperatures compound II was found, as shown by its melting point, 226–227° (lit.[18] mp 227°), and mixture melting point and nmr (singlet, τ 4.45, 1 H; multiplet, τ 2.60–3.00, 29 H). The triphenylmethane had mp 93–94°, and the nmr showed a singlet at τ 4.66 (1 H) and another singlet at τ 3.02 (15 H). Trityl phenyl sulfide had mp 100–101° (lit.[7] mp 105–106°), and the nmr showed a singlet at τ 3.15 (5 H) and a multiplet between τ 2.50 and 3.10 (15 H). No attempt was made to determine the exact yields since purity of the products was our main goal. The isolated yields of purified triphenylmethane at −25.0, −15.0, 0.0, 25.0, 40.0, and 60.0° were 14.0, 40.0, 58.0, 73.0, 82.0, and 90.0%, respectively. The isolated yields of recrystallized II at −25.0 and −15.0° were 24.0 and 22.0%, respectively. The low total yields at the lower temperatures do not represent incomplete reaction, for dityrityl peroxide would have been produced on work-up and is easily detected. We attribute the low yields merely to the difficulty of separating triphenylmethane and compound I.

Registry No.—II, 3416-63-5; triphenylmethane, 519-73-3; trityl phenyl sulfide, 16928-73-7.

(16) W. R. Orndorff, R. C. Gibbs, S. A. McNulty, and C. V. Shapiro, *J. Amer. Chem. Soc.*, **49**, 1543 (1927).

(17) M. Gomberg and C. S. Schoepfle, *ibid.*, **39**, 1659 (1917).

(18) W. Schlenk, E. Marcus, *Ber.*, **47**, 1665 (1914).

Kinetics of the Reaction of Some Trialkyl Phosphites with Benzil

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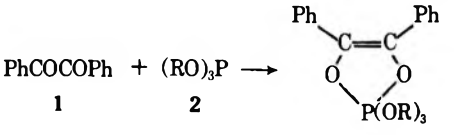
The effect of substituents on the reaction rates of trialkyl phosphites [$(RO)_3P$] with benzil has been studied. The rate constant, k, in the rate equation, $v = k[(RO)_3P][PhCOCOPh]$, increases with the change of R in the order of methyl, ethyl, and isopropyl, while a little change of k is observed with R of *n*-propyl, *n*-butyl, *n*-amyl, *n*-octyl, and *sec*-butyl, and the k value decreases by substitution of 2-methoxyethyl for methyl. The relative rates fit the Taft equation, $\log (k/k_0) = -3.28\sigma^* + 0.40E_s + 0.03$. Both polar and steric effects affect the rate with R of C_nH_{2n+1} ($n \geq 3$), while polar effect alone is dominant with R of methyl and ethyl. The correlation between the ^{31}P nmr chemical shift relative to $(CH_3O)_3P$, $\Delta\delta$ ^{31}P, and the relative reaction rate or Taft's σ^* value is discussed. These facts present an additional support for our previous mechanism involving a nucleophilic attack of the phosphorus atom on the carbonyl carbon.

In our previous papers,[1-3] kinetics of the reaction of trialkyl phosphite with benzil and substituted benzils favored a mechanism involving a nucleophilic attack of a phosphorus atom of phosphite on a carbonyl carbon atom of benzil, which is similar to a mechanism proposed by Litt for aliphatic α diketones.[4]

The present paper deals with the kinetic study on the reaction of a number of trialkyl phosphites (2) with benzil (1) forming substituted 1,3,2-dioxaphospholes (3) (eq 1) to clarify the effect of substituents at phosphorus atom. The rate was measured by means of uv spectrophotometry.[5-7]



Results

The reaction of a number of trialkyl phosphites (2) with benzil (1) proceeds quantitatively at room temperature to yield 2,2,2-trialkoxy-4,5-diphenyl-1,3,2-dioxaphospholes (3). The rate was measured by means of ultraviolet spectrophotometry of the product 3.

Rate Law. –The rate was measured in dioxane at 20.0, 25.0, 30.0, and 35.0°. The rate law is expressed

(1) Y. Ogata and M. Yamashita, *J. Amer. Chem. Soc.*, **92**, 4670 (1970).

(2) Y. Ogata and M. Yamashita, *Tetrahedron*, in press.

(3) Y. Ogata and M. Yamashita, *ibid.*, in press.

(4) A. D. Litt, Ph.D. Thesis, Rutgers University, 1968.

(5) (a) V. A. Kukhtin, *Dokl. Akad. Nauk SSSR*, **121**, 466 (1958); *Chem. Abstr.*, **53**, 1105a (1959); (b) V. A. Kukhtin and K. M. Orekhova, *Zh. Obshch. Khim.*, **30**, 1208 (1960); *Chem. Abstr.*, **55**, 358h (1961); (c) V. A. Kukhtin, T. N. Voskoboeva, and K. M. Kirillova, *ibid.*, **32**, 2333 (1962); *Chem. Abstr.*, **58**, 9127g (1963); (d) K. M. Kirillova and V. A. Kukhtin, *ibid.*, **32**, 2338 (1962); *Chem. Abstr.*, **58**, 9128c (1963).

(6) (a) F. Ramirez and N. B. Desai, *J. Amer. Chem. Soc.*, **82**, 2652 (1960); (b) F. Ramirez and N. B. Desai, *ibid.*, **85**, 3252 (1963); (c) F. Ramirez, N. Ramanthan, and N. B. Desai *ibid.*, **84**, 1317 (1962); (d) F. Ramirez, N. Ramanthan, and N. B. Desai, *ibid.*, **85**, 3465 (1963); (e) F. Ramirez, A. V. Patwardhan, N. Ramanthan, N. B. Desai, C. V. Greco, and S. R. Heller, *ibid.*, **87**, 543 (1965).

(7) (a) G. H. Birum and J. L. Dever, U. S. Patent 2,961,455 (1960); *Chem. Abstr.*, **55**, 8292g (1961); (b) G. H. Birum and J. L. Dever, U. S. Patent 3,014,949 (1961); *Chem. Abstr.*, **56**, 10191a (1962).

TABLE I
SECOND-ORDER RATE CONSTANTS FOR THE REACTION OF TRIALKYL PHOSPHITES (2) WITH BENZIL (1) IN DIOXANE AT 25.0°

$(RO)_3P$, R =	Registry no.	Concn, M [1]	Concn, M [2]	$10^3 k$, M^{-1} sec^{-1}	Relative rate (k/k_0)	Log (k/k_0)	σ^*[a]
CH_3	121-45-9	0.05	0.05	4.83	1.00	0.000	0.000
C_2H_5	122-52-1	0.05	0.05	10.8	2.34	0.369	−0.100
i-C_3H_7	116-17-6	0.02	0.1	13.5	2.80	0.447	−0.200
sec-C_4H_9	7504-61-2	0.02	0.1	9.19	1.90	0.279	−0.210
n-C_3H_7	923-99-9	0.05	0.05	8.37	1.73	0.238	−0.115
n-C_4H_9	102-85-2	0.05	0.05	9.64	2.00	0.301	−0.130
n-C_5H_{11}	1990-22-3	0.05	0.05	10.4	2.15	0.332	
n-C_8H_{17}	3028-88-4	0.1	0.1	10.1	2.09	0.320	
$CH_3OCH_2CH_2$	4156-80-3	0.01	0.1	2.94	0.609	−0.216	

[a] R. W. Taft, Jr., *J. Amer. Chem. Soc.*, **75**, 4231 (1953).

TABLE II
TEMPERATURE EFFECT AND ACTIVATION PARAMETERS FOR THE REACTION OF TRIALKYL PHOSPHITES WITH BENZIL IN DIOXANE[a]

$(RO)_3P$, R =	$10^3 k$, M^{-1} sec^{-1} 20.0°	25.0°	30.0°	35.0°	E_a, kcal/mol	$\Delta S^{\ddagger}$,[b] eu	Ln A, M^{-1} sec^{-1}
CH_3	3.76	4.83	6.64		9.90	−35.5	12.4
C_2H_5	8.08	10.8	12.8		8.32	−41.1	9.78
i-C_3H_7	10.3	13.5	16.8		9.12	−38.4	11.1
sec-C_4H_9	7.29	9.19	11.1		7.85	−43.6	8.53
n-C_3H_7	6.10	8.37	11.4		11.2	−32.9	13.9
n-C_4H_9	7.64	9.64	13.8		10.9	−32.9	13.9
n-C_5H_{11}	7.68	10.4	13.1		9.78	−36.9	11.9
n-C_8H_{17}		10.1	12.9	16.6	9.92	−36.5	12.1
$CH_3OCH_2CH_2$	2.18	2.94	3.82		10.4	−37.3	11.7

[a] Calculated by the least-squares method. [b] $\Delta S^{\ddagger}$ was calculated at 25.0°.

as eq 2 up to high conversion for all phosphites used as has been reported with trimethyl phosphite.[1-3]

$$v = k[(RO)_3P][PhCOCOPh] \quad (2)$$

Effect of Substituents at Phosphorus Atom. —The rate in dioxane at 25.0° is summarized in Table I. The rate increases with an increase of the electron-releasing power of substituents of alkyl groups of the phosphites. Both polar and steric effects in the Taft equation are important, since the correlation between the logarithm of the relative rate constant and Taft's σ^* or E_s alone is not so good.

The rate measurements at various temperatures afford energies of activation (E_a), entropies of activation ($\Delta S^{\ddagger}$), and frequency factors (A) as shown in Table II. As obvious from the table, both E_a and $\Delta S^{\ddagger}$ are low.

^{31}P Nmr Chemical Shift. —The ^{31}P nmr chemical shift relative to $(CH_3O)_3P$, $\Delta\delta$ ^{31}P, was measured by a JNM-C60-HL high-resolution spectrometer at 24 MHz neat at room temperature. The values of $\Delta\delta$ ^{31}P are listed in Table III. A plot of $\Delta\delta$ ^{31}P *vs.* σ^* for R of CH_3, C_2H_5, n-C_3H_7, i-C_3H_7, n-C_4H_9, and sec-C_4H_9 gave a correlation coefficient (r) of −0.925 except for R of sec-C_4H_9. $(sec\text{-}C_4H_9O)_3P$ has a little different value.

A plot of $\Delta\delta$ ^{31}P *vs.* log (k/k_0) for all phosphites, except R of sec-C_4H_9 and $CH_3OCH_2CH_2$, seems to show a good correlation coefficient (r = 0.969). The substituents of sec-C_4H_9 and $CH_3OCH_2CH_2$ seem to give a somewhat different effect on $\Delta\delta$ ^{31}P.

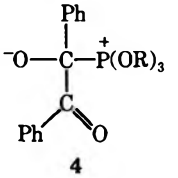
TABLE III
^{31}P NMR CHEMICAL SHIFTS FROM $(CH_3O)_3P$

$(RO)_3P$, R =	$\Delta\delta$ ^{31}P,[a] ppm
CH_3	0.00
C_2H_5	+1.21
i-C_3H_7	+1.16
sec-C_4H_9	+0.16
n-C_3H_7	+1.01
n-C_4H_9	+0.98
n-C_5H_{11}	+1.08
n-C_8H_{17}	+1.06
$CH_3OCH_2CH_2$	+0.75[b]

[a] The + sign indicates the higher field shift. [b] In *ca.* 50% CCl_4 solution.

Discussion

The mechanism of the reaction of trialkyl phosphites with benzil may involve a nucleophilic attack of a phosphorus atom of phosphite either on a carbonyl carbon atom or an oxygen atom of benzil;[1-3,8] thus, the corresponding intermediate may be **4** or **5**, respectively. A probable mechanism involving path A or B may be written as Scheme I.



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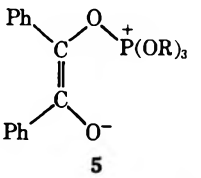


5

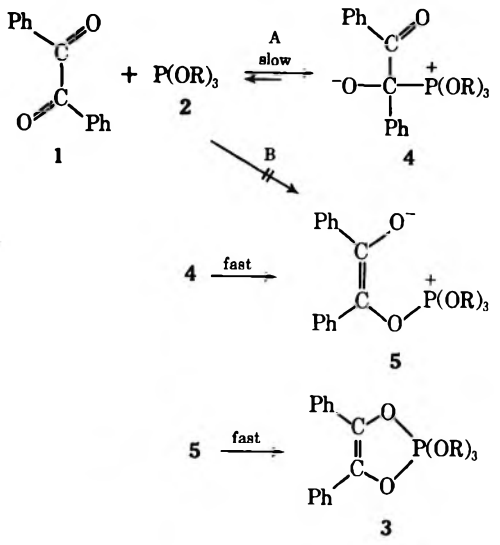
In view of the data of acid–base catalysis,[1] we observed that the acid accelerates the reaction, while the base retards it. The substituent effect in benzil gave a good Hammett's correlation with σ but not with σ^-, and it afforded a large positive ρ value.[2] Moreover, the

(8) (a) L. D. Quin, "1,4-Cycloaddition Reactions," J. Hamer, Ed., Academic Press, New York, N. Y., 1967, Chapter 3; (b) G. Pfundt and G. O. Schenck, ref 8a, Chapter 11; (c) A. J. Kirby and S. G. Warren, "The Organic Chemistry of Phosphorus," Elsevier, Amsterdam, 1967, Chapter 3.

substituent effect in aliphatic α diketones revealed that the steric substituent constant, E_s, controls the rate.[3] These results suggest that a more probable intermediate may be **4** and that the reaction involves a nucleophilic attack of the phosphorus atom of phosphite on a carbonyl carbon atom of the α diketone in the rate-determining step.

SCHEME I

MECHANISM FOR THE REACTION OF TRIALKYL PHOSPHITES WITH BENZIL



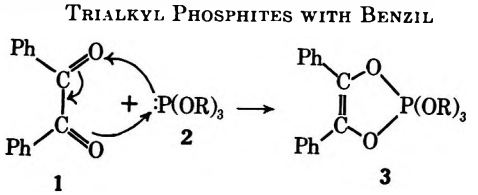
With the change of an alkyl group R of the phosphite from CH_3 to a more electron-releasing group, *e.g.*, C_2H_5 and *i*-C_3H_7, a modest increase of the rate was observed, while with the change to an electron-withdrawing group such as $CH_3OCH_2CH_2$ the rate decreased (Table I).

As will be discussed later, the substituent effect in phosphites implies that a nucleophilic attack of phosphorus atom is involved in the rate-determining step, since an electron-releasing group on phosphite accelerates the reaction. Both rearrangement of **4** to **5** and the cyclization of **5** to **3** involve an electrophilic attack of a phosphorus atom, since the phosphorus atom has a positive charge. Hence, the observed substituent effect in phosphites suggests that these steps cannot be rate-determining.

Therefore, path A in Scheme I may be more probable than path B. The concerted one-step cycloaddition of α diketone with phosphite (Scheme II) may be excluded, since the first step must involve an attack of phosphite on an oxygen atom of carbonyl, which is inadequate as stated above.

SCHEME II

CONCERTED MECHANISM INVOLVING A ONE-STEP CYCLOADDITION REACTION OF TRIALKYL PHOSPHITES WITH BENZIL



The observed small value of E_a and the large negative value of $\Delta S^{\pm}$ are characteristic of this sort of reaction,[1-3] *e.g.*, the condensation reaction of carbonyl compounds with amines.[9] In general, a large negative value of $\Delta S^{\pm}$ is observed in the reaction in which the total number of species decreases or a strongly polarized and/or crowded transition states are involved.[10] Hence, it is supported that the first step is rate determining. The values of E_a and $\Delta S^{\pm}$ for $(n\text{-}C_nH_{2n+1}O)_3P$ ($n \geqq 3$) are nearly constant, but the alkyl substituents such as C_2H_5, *i*-C_3H_7, and *sec*-C_4H_9 decrease the E_a value.

A plot of log (k/k_0) *vs.* σ^* (Figure 1) gives a very poor correlation coefficient (r) of -0.806; this implies that not only a polar effect but also a steric effect of phosphite is a controlling factor in the rate-determining step. The negative value of r also supports the rate-determining nucleophilic attack of phosphite.

A plot of log (k/k_0) *vs.* E_s (Figure 2) may be classified into three groups with the change of substituents, *i.e.*, (1) CH_3 and C_2H_5, (2) *i*-C_3H_7, *n*-C_3H_7, *n*-C_4H_9, *n*-C_5H_{11}, and *n*-C_8H_{17}, and (3) *sec*-C_4H_9. For group 2 the plot gives a negative correlation coefficient, which indicates the accelation of reaction by releasing the steric hindrance of phosphites by going to the transition state.[11] This may not be the case, since the negative Taft's ρ^* value and the large negative $\Delta S^{\pm}$ value were observed in this reaction and positive Hammett's ρ value was observed in the substituent effect of benzil.[2]

Figure 1 shows that the steric effect operates little upon C_2H_5 but much upon *sec*-C_4H_9. A line passing through the points for CH_3 and C_2H_5 ($\equiv l_0$, with slope of -3.69) was drawn and the deviation from the line [$\equiv \Delta$ log (k/k_0)] was calculated with various alkyl groups. The plot of Δ log (k/k_0) *vs.* E_s gave a straight line whose slope was $+0.46$ ($r = 0.977$). When the slope of l_0 was changed little, the correlation between Δ log (k/k_0) and E_s becomes worse ($r < 0.977$). A plot of log (k/k_0) *vs.* $(-3.69\ \sigma^* + 0.46\ E_s)$ gave a straight line with a slope of $+0.888$ ($r = 0.981$). In other words, the Taft equation may be applied, which is expressed in a form of eq 3 for this reaction (Figure 3).

$$\log (k/k_0) = -3.28\sigma^* + 0.40E_s + 0.03 \qquad (3)$$

As apparent from the coefficients of the equation the polar effect is more important. In view of the reported values of E_s for *n*-C_5H_{11} (-0.40) and *n*-C_8H_{17} (-0.33),[12] a probable σ^* value for *n*-C_5H_{11} and *n*-C_8H_{17} may be -0.140.

Assuming the activated complex **4** (path A), in which a carbonyl carbon atom of benzil was attacked by a nucleophilic phosphorus atom of phosphite, the reaction site of benzil (carbonyl carbon) is shielded by two benzene rings, a carbonyl group, and an oxygen atom. Then a phosphorus atom carrying bulky alkyl groups is prevented from an attack of the carbonyl carbon atom. Figures 1–3 imply that for $(C_nH_{2n+1}O)_3P$, the steric factor of $(C_nH_{2n+1}O)_3P$ is unimportant when n is 1 and 2, but it is important when $n \geqq 3$.

(9) (a) G. M. Santerre, C. T. Hansrote, Jr., and T. I. Crowell, *J. Amer. Chem. Soc.*, **80**, 1254 (1958); (b) Y. Ogata, A. Kawasaki, and N. Okumura, *J. Org. Chem.*, **29**, 1985 (1964).

(10) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt, New York, N. Y., 1959, p 181.

(11) L. N. Ferguson, *J. Chem. Educ.*, **47**, 46 (1970).

(12) R. W. Taft, Jr., *J. Amer. Chem. Soc.*, **74**, 3120 (1952).

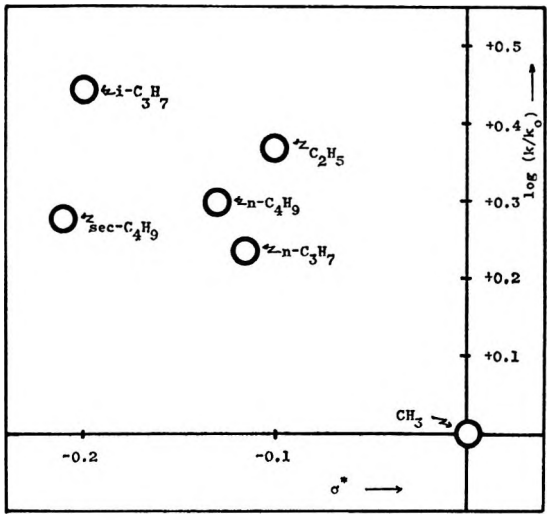
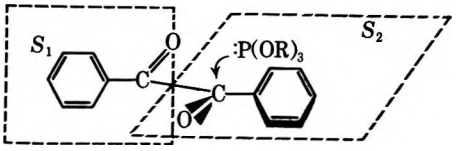


Figure 1.—Plot of log (k/k_0) *vs.* Taft's σ^* for the reaction of $(RO)_3P$ with PhCOCOPh in dioxane at 25.0°.

On the contrary, if the intermediate were **5** (path B) the steric factor would be less important, since the attacked carbonyl oxygen is out of the plane of the benzil molecule.

These data also show that the phosphorus atom attacks on the carbonyl carbon atom in the rate-determining step (path A).



The lower side of the carbonyl carbon atom on the S_2 plane is hindered by the benzene ring on S_1 plane, and *vice versa*.[13] The phosphorus atom may chiefly attack on the carbonyl carbon atom from one side, probably from an upper side of the S_2 plane.

The ^{31}P nmr chemical shifts relative to $(CH_3O)_3P$ ($\equiv \Delta\delta\ ^{31}P$, ppm) were measured at room temperature. The shift may reflect the shielding efficiency of substituents on the phosphorus atom. The studies on $\delta\ ^{31}P$ have been reported for many phosphorus compounds.[14-18] The linear correlation between $\delta\ ^{31}P$ and the additive group contribution ($\Sigma\sigma^P$) has been known with secondary and tertiary phosphines, phosphorus halides, phosphonium salts, etc.[15,16] The Taft equation is applicable to the $\delta\ ^{31}P$ values of some alkyl or aryl phosphorus difluorides[17] but not to those for phosphine

(13) Two benzoyl groups of benzil seem to be almost in one plane (carbonyl group twists *ca.* 7° from benzene ring), and the dihedral angle of two carbonyl groups may be *ca.* 70° [N. K. Chaudhuri and M. A. El-Sayed, *J. Chem. Phys.* **47**, 1133 (1967); C. J. Brown and R. Sadanaga, *Acta Crystallogr.*, **18**, 158 (1965)].

(14) (a) R. A. Y. Jones and A. R. Katritzky, *Angew. Chem.*, **74**, 60 (1962); (b) M. Yoshifuji, *Yuki Gosei Kagaku Kyokai Shi*, **28**, 177 (1970).

(15) (a) S. O. Grim and W. McFarlane, *Nature*, **208**, 995 (1965); (b) H. S. Gutowsky and J. Larmann, *J. Amer. Chem. Soc.*, **87**, 3815 (1965); (c) G. A. Olah and C. W. McFarland *J. Org. Chem.*, **34**, 1832 (1969); (d) S. O. Grim, W. McFarlane, E. F. Davidoff, and T. J. Marks, *J. Phys. Chem.*, **70**, 581 (1966); (e) S. O. Grim and W. McFarlane, *Can. J. Chem.*, **46**, 207 (1968).

(16) E. N. Tsvetkov, G. K. Semin, T. A. Babushikina, D. I. Lobanov, and M. I. Kabacknik, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2375 (1967); *Chem. Abstr.*, **68**, 34550y (1968).

(17) B. I. Tetel'baum, V. V. Sheluchenko, S. S. Dubov, G. I. Drozd, and S. Z. Ivin, *Zh. Vses, Khim. Obshchest.*, **12**, 351 (1967); *Chem. Abstr.*, **68**, 73847v (1968).

(18) V. V. Sheluchenko, S. S. Dubov, G. I. Drozd, and S. Z. Ivin, *Zh. Strukt. Khim.*, **9**, 909 (1968); *Chem. Abstr.*, **70**, 24524v (1969).

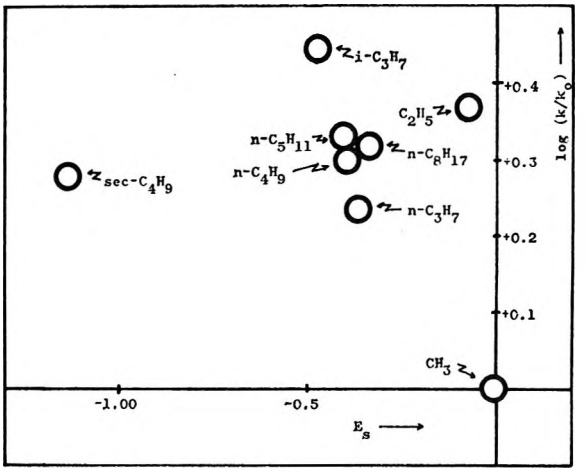


Figure 2.—Plot of log (k/k_0) *vs.* Taft's E_s for the reaction of $(RO)_3P$ with PhCOCOPh in dioxane at 25.0°.

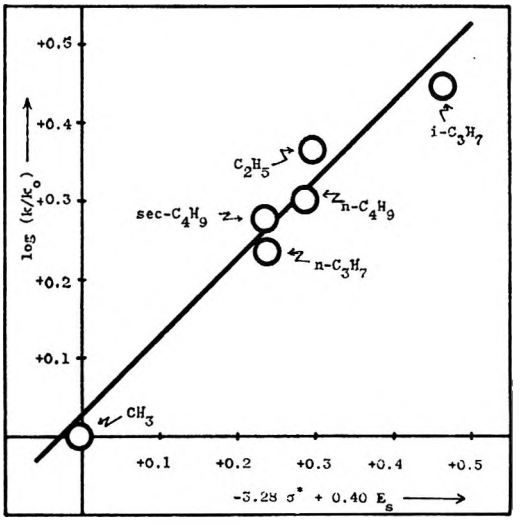


Figure 3.—Plot of log (k/k_0) *vs.* $(-3.28\sigma^* + 0.40E_s)$ for the reaction of $(RO)_3P$ with PhCOCOPh in dioxane at 25.0°.

and some of other phosphorus compounds,[15a,e,18] since many factors, besides the inductive effect, may influence $\delta\ ^{31}P$.[14b,19]

The plot of log (k/k_0) *vs.* $\Delta\delta\ ^{31}P$ gives a correlation coefficient of 0.969 except for *sec*-C_4H_9 and CH_3OCH_2-CH_2. The good correlation with $\Delta\delta\ ^{31}P$ seems to mean the control of rate by the electronic state of the phosphorus atom, while the poor correlation with E_s ($r = -0.254$) seems to mean that the steric effect on $\Delta\delta\ ^{31}P$ is unimportant.

Assuming the virtually constant bond angle of *ca.* 100° for O–P–O of the phosphite,[19a,20] the substituent effect may be parallel to the polar effect. The observed poor correlation in σ^* with *sec*-C_4H_9 and $CH_3OCH_2CH_2$ may reflect the deviation of the O–P–O angle and the other factors influencing $\Delta\delta\ ^{31}P$, *e.g.*, the effect of oxygen atom.

(19) (a) N. Muller, P. C. Lauterbur, and J. Goldenson, *J. Amer. Chem. Soc.*, **78**, 3557 (1956); (b) L. S. Meriwether and J. R. Leto, *ibid.*, **83**, 3192 (1961); (c) C. P. Slichter, "Principles of Magnetic Resonance," Harper and Row, New York, N. Y., 1963, p 69.

(20) (a) H. S. Gutowsky and J. Larmann, *J. Amer. Chem. Soc.*, **87**, 3815 (1965); (b) W. Gordy, W. V. Smith, and R. F. Trambarulo, "Microwave Spectroscopy," Wiley, New York, N. Y., 1953, p 372; (c) L. V. Vilkov, P. A. Akishin, and G. E. Salova, *Zh. Strukt. Khim.*, **6**, 355 (1965); *Chem. Abstr.*, **63**, 11308g (1956); (d) D. M. Nimrod, D. R. Fitzwater, and J. G. Verkade, *J. Amer. Chem. Soc.*, **90**, 2780 (1968).

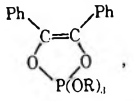
TABLE IV

CHARACTERISTICS OF TRIALKYL PHOSPHITES PREPARED BY THE REACTION OF PHOSPHORUS TRICHLORIDE WITH CORRESPONDING ALCOHOLS

$(RO)_3P$, R =	Base	Yield, %	Bp, °C (mm)	n_D (deg)
C_2H_5	Diethyaniline	60	54 (17)	1.4104 (25)
i-C_3H_7		70	57 (9)	1.4049 (25)
sec-C_4H_9		70	77–78 (3.5–4)	1.4294 (25)
$CH_3OCH_2CH_2$		80	99 (1.5)	1.4365 (25)
n-C_3H_7	Pyridine	73	89 (10)	1.4239 (24)
n-C_4H_9		65	100–101 (4)	1.4307 (25)
n-C_5H_{11}		64	94–99 (1–1.5)	1.4369 (25)
n-C_8H_{17}		67	189–195 (1)	1.4468 (25)

TABLE V

UV SPECTRA OF DIOXAPHOSPHOLES (3) IN *n*-HEXANE



R =	Registry no.	λ_{max}, mμ	$\epsilon_{max} \times 10^{-4}$
CH_3	4850-55-9	319	1.14
C_2H_5	6509-75-7	323	1.18
i-C_3H_7	4850-57-1	322	1.12
sec-C_4H_9	30415-15-7	319	1.23
n-C_3H_7	30415-16-8	321	1.28
n-C_4H_9	30415-17-9	321	1.21
n-C_5H_{11}	30415-18-0	321	1.19
n-C_8H_{17}	30415-19-1	322	1.19
$CH_3OCH_2CH_2$	30477-09-9	316	1.15

Experimental Section

Materials.—**Trialkyl phosphites** were prepared by the reaction of phosphorus trichloride with corresponding alcohols in the presence of base below 15° [21] and purified by repeated distillations with metallic sodium under reduced pressure with nitrogen atmosphere. The characteristics of prepared trialkyl phosphites were listed in Table IV. **Benzil** was prepared as mentioned in our previous paper.[1]

(21) A. H. Ford-Moore and B. J. Perry, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 955.

2,2,2-Trialkoxy-4,5-diphenyl-1,3,2-dioxaphospholes (3) were prepared by the reaction of benzil with excess trialkyl phosphite without solvent or in anhydrous dioxane under nitrogen atmosphere at 25.0° for 3–12 hr. The structure of **3** (R = Me) was confirmed by ir, nmr, and uv spectra.[1] The uv spectra of **3** were measured in anhydrous *n*-hexane and listed in Table V.

The hydrolysis product of **3** (R = Me) showed new peaks in ir and uv spectra: ir 3350 (OH, broad) and 1230 cm^{-1} (P=O, broad); uv λ_{max} 285 mμ but not 313 mμ (in dioxane). Solvents were purified and dried before use.

Kinetic Procedure.—The kinetic experiments for the reaction of trialkyl phosphite with benzil were carried out in anhydrous dioxane. The rate measurements were done by means of the procedure as mentioned previously.[1-3] An isosbestic point was observed during the reaction of 1 (R = Me) at 287 mμ in dioxane.

The ^{31}P nmr chemical shifts were measured by a JNM-C60-HL model of Japan Electron Optics Laboratory Co., Ltd., at 24 MHz with proton decoupling at room temperature. The data were shown in Table III.[19a,22-24]

Registry No.—**1**, 134-81-6.

Acknowledgments.—The authors are thankful to Japan Electron Optics Laboratory Co., Ltd., for their kind measurement of the ^{31}P nmr chemical shift of trialkyl phosphites.

(22) J. R. Van Wazer, C. F. Callis, J. N. Shoolery, and R. C. Jones, *J. Amer. Chem. Soc.*, **78**, 5715 (1956).
(23) K. Moedritzer, *J. Inorg. Nucl. Chem.*, **22**, 19 (1961).
(24) W. McFarlane and R. F. M. White, *Chem. Commun.*, 744 (1969).

Lithium–Ammonia Reduction of Aromatic Ketones to Aromatic Hydrocarbons[1]

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Aromatic ketones are reduced, almost quantitatively, to aromatic hydrocarbons by lithium–ammonia solutions followed by an ammonium chloride quench. Lithium is more effective than sodium as the dissolving metal; in addition, the reduction is apparently catalyzed by trace amounts of metals such as cobalt or aluminum. The series of aromatic ketones which were reduced to aromatic hydrocarbons includes 1-tetralone to tetralin, 7-*tert*-butyl-1-tetralone to 6-*tert*-butyltetralin, 1-indanone to indan, 3,3-dimethyl-1-indanone to 1,1-dimethylindan, 2,2,3,3-tetramethyl-1-indanone to 1,1,2,2-tetramethylindan, 5-chloro-3,3-dimethyl-1-indanone to 1,1-dimethylindan, 3,3,4,5,6,7-hexamethyl-1-indanone to 1,1,4,5,6,7-hexamethylindan, benzophenone to diphenylmethane, xanthenone to xanthene, and dibenzoylmethane to 1,3-diphenylpropane. This study reveals various reduction rate relationships which are interpreted as due to steric effects, relief of strain, or stable ketyl radical formation. A mechanism is proposed for the catalyzed and uncatalyzed reduction.

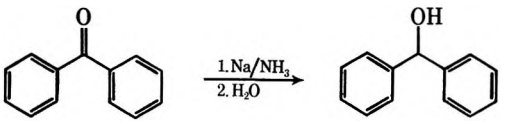
Hitherto, it has been assumed that aromatic ketones are reduced, as are alkyl ketones, to alcohols in metal–ammonia reductions.[3] This presumption is apparently based on work involving the reduction of benzophenone to diphenylmethanol with sodium in liquid ammonia.[4]

(1) This research was supported by The Research Council, Rutgers University.

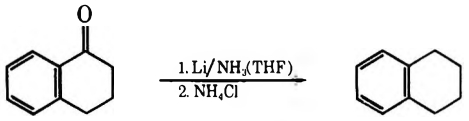
(2) Author to whom correspondence should be directed.

(3) For general discussions and leading references, see (a) A. J. Birch, *Quart. Rev., Chem. Soc.*, **4**, 69 (1950); (b) A. J. Birch and H. Smith, *ibid.*, **12**, 17 (1958); (c) G. W. Watt, *Chem. Rev.*, **46**, 317 (1950); (d) C. Djerassi, Ed., "Steroid Reactions," Holden-Day, San Francisco, Calif., 1963, pp 267–288, 299–325; (e) H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, pp 50–77; (f) H. Smith, "Organic Reactions in Liquid Ammonia. Chemistry in Nonaqueous Ionizing Solvents," Vol. I, part 2, Wiley, New York, N. Y., 1963, pp 216–219; (g) R. L. Augustine, Ed., "Reduction," Marcel Dekker, New York, N. Y., 1968, pp 116–117.

(4) (a) H. Schulbach, *Chem. Ber.*, **48**, 12 (1915); (b) W. E. Bachmann, *J. Amer. Chem. Soc.*, **55**, 1179 (1933); (c) C. B. Wooster, *ibid.*, **59**, 377 (1937).



We have found that aromatic ketones are reduced, almost quantitatively in most cases, to aromatic hydrocarbons in lithium–ammonia (THF) solutions followed by an ammonium chloride quench. This incongruity, it turns out, is quite rational. First of all, lithium was found to be much more effective than sodium as the dissolving metal; second, the reduction of diaromatic ketones, *e.g.*, benzophenone, is sluggish compared to monoaromatic ketones, *e.g.*, 1-tetralone; and last, it is important that the reaction be quenched with ammonium chloride.



The reduction is also apparently catalyzed by trace metals such as cobalt and aluminum. For example, the rate of reduction of 1-tetralone was *ca.* doubled and that of benzophenone at least quintupled when trace amounts of cobalt powder were added. This observation is unusual since certain transition metals are known to catalyze the reaction of the alkali metal with ammonia forming sodium or lithium amide and hydrogen. The net result is the loss of reducing agent and therefore precautions are normally taken to avoid contamination by trace metals.[5]

In Table I is listed a selection of aromatic ketones reduced to aromatic hydrocarbons when subjected to these conditions. All products gave satisfactory spectral and analytical data and, in addition, were compared with authentic samples. Some of the reactions listed in Table I yielded minor products. Small amounts of alcohol and ketone generally indicated that the reduction had been stopped prematurely. Some ketones, especially the less sterically hindered indanones, formed dimers.[6]

The results of some of the reductions listed in Table I merit comment. Earlier in the discussion we indicated that lithium was more effective than sodium. An example of this is given by comparing the reduction of 1-indanone with lithium/cobalt and with sodium/cobalt. That diaromatic ketones are reduced significantly slower than monoaromatic ketones in the absence of trace metals is demonstrated by comparing the reduction of benzophenone with 1-tetralone. The slower rate of reduction of diaromatic ketones is undoubtedly due to the formation of stable ketyl radicals.[7] Thus, it is interesting that the trace metal has a more decided effect on the rate of reduction of benzophenone than on 1-tetralone. This will be taken up again later in this discussion.

Other ketones also revealed some interesting reduction rate relationships. For example, 1-indanone is reduced considerably faster than 1-tetralone, which perhaps reflects the relief of strain in the indanone system, and 3,3-dimethyl-1-indanone is reduced faster than 5-chloro-3,3-dimethyl-1-indanone. When the reduction of the latter ketone was stopped prematurely, none of the isolated products (aromatic hydrocarbon, alcohol, and ketone) contained chlorine.

In addition, the reduction is apparently sensitive to steric effects, since 2,2,3,3-tetramethyl-1-indanone is reduced much more slowly than 3,3-dimethyl-1-indanone; the latter more slowly than 1-indanone; and 7-*tert*-butyl-1-tetralone more slowly than 1-tetralone.

Substantial information about the mechanism of this reaction was obtained when sodium benzoate,[8] instead of ammonium chloride, was used to destroy the excess lithium prior to reaction work-up. Rather than the expected aromatic hydrocarbon, the only product formed was a benzyl alcohol. Since sodium benzoate destroys the excess lithium in the absence of an added proton source, the reduction of aromatic ketones to aromatic hydrocarbons is clearly a two-sequence process. The first, which is slow, is the conversion of the aromatic ketone to a benzyl alkoxide in lithium–ammonia. The second sequence, which must be rapid, is initiated by the added proton source (NH_4Cl) generating the benzyl alcohol, which in turn is reduced to the aromatic hydrocarbon before all the excess lithium is destroyed.[9]

Scheme I outlines our suggestions for the mechanism of the reduction, which incorporates the accepted mechanisms of reduction of ketones to alcohols[10] and benzyl alcohols to aromatic hydrocarbons.[11]

The catalytic effect of the trace metal, on the other hand, is enigmatic. At this time we wish to suggest that a hydrogen radical, generated at the surface of the metal,[5] is transferred to the ketyl radical intermediate **1**, generating the alkoxide **3**. The result would be to disrupt the initial equilibrium between ketone and ketyl radical **1** and force the reaction irreversibly to the alkoxide **3**. This would explain the more pronounced effect the trace metal has on the rate of reduction of the diaromatic ketones, since one would not expect the stable ketyl radical to be quickly protonated by ammonia but would expect it to react rather rapidly with a hydrogen radical.

Perhaps as important as the mechanistic implications of the results with sodium benzoate is the fact that by the simple choice of quenching agent one can selectively reduce aromatic ketones to benzyl alcohols or aromatic hydrocarbons.

(5) (a) H. L. Dryden, G. M. Webber, R. R. Burtner, and J. A. Cella, *J. Org. Chem.*, **26**, 3237 (1961); (b) W. Hückel, B. Graf, and D. Munker, *Justus Liebigs Ann. Chem.*, **614**, 47 (1958). The catalytic effect of the trace metals was accidentally discovered in this laboratory when we used a glass-coated magnetic stirring bar which contained a capillary flaw. Since the magnetic alloy was Alnico V, trace amounts of granular aluminum (20 mesh and finer), nickel powder, cobalt powder, copper powder, and iron filings (40 mesh) were tested. The most effective was cobalt, followed by aluminum, and then nickel in studies with 1-tetralone. The influence of iron and copper seemed to be negligible. We wish to thank a referee who has suggested that perhaps the catalytic effect of the trace metals might be greatly enhanced if the metal were present in a nearly colloidal state of subdivision. We are presently exploring this possibility.

(6) The dimers, normally in the ratio of *ca.* 2/1, have been tentatively assigned, using the reduction of 1-indanone as an example, as *meso*- and *dl*-1,1′-diindan based upon mass spectra and infrared and nmr data.

(7) (a) C. B. Wooster, *J. Amer. Chem. Soc.*, **50**, 1388 (1928); (b) C. B. Wooster, *ibid.*, **57**, 112 (1935); (c) C. B. Wooster, *ibid.*, **59**, 377 (1937).

(8) A. P. Krapcho and A. A. Bothner-By, *ibid.*, **81**, 3658 (1959).

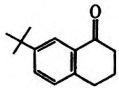
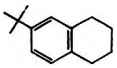
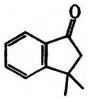
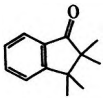
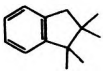
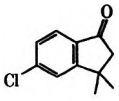
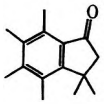
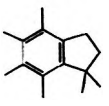
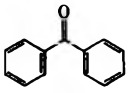
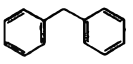
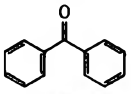
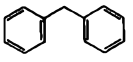
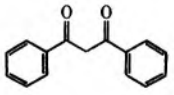
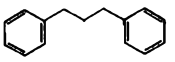
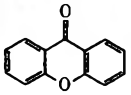
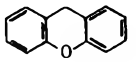
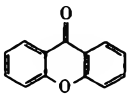
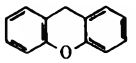
(9) It is important that the reduction be carried out as a two-sequence process in order to avoid overreduction. When 1-indanone, in the presence of an added proton source (EtOH), was subjected to these conditions, *ca.* equal amounts of indan, 4,7-dihydroindan and unreacted ketone were isolated.

(10) See ref 3g, pp 97–98.

(11) See ref 3e, pp 74–75.

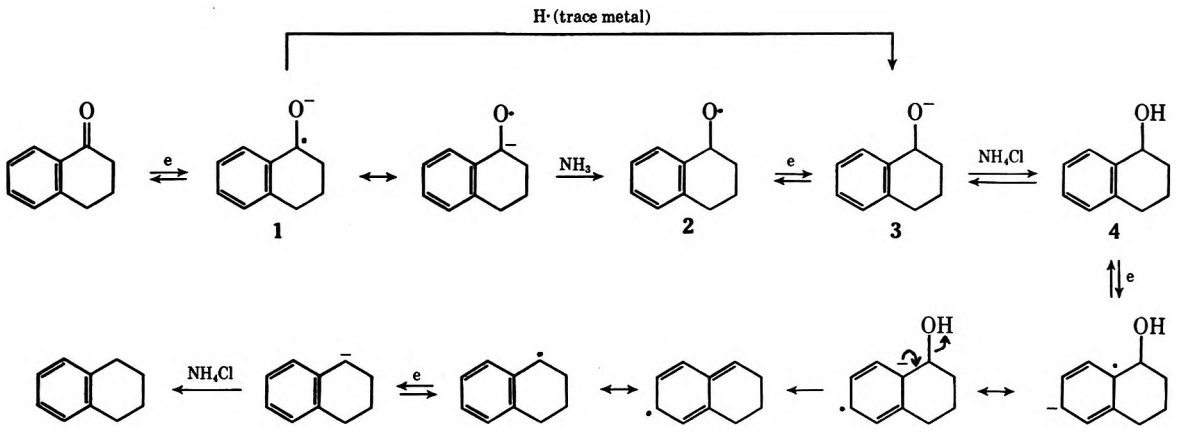
TABLE I[a]

LITHIUM–AMMONIA REDUCTION OF AROMATIC KETONES TO AROMATIC HYDROCARBONS

Ketone	Registry no.	Dissolving metal/ trace metal	Product	% yield Analytical[b]	% yield Isolated[c]	Time,[d] hr	Minor product(s)	Comments
	529-34-0	Li/none		99	96	2	0.5% alcohol 0.5% dimers (2)	
		Li/Co		98	95	1	1.5% alcohol 0.5% dimers (2)	*e*
	22583-68-2	Li/Co		95	92	2	5% alcohol	*e*
	83-33-0	Li/Co		93	91	0.33	7% dimers (2)	
		Na/Co		86	84	3	9% alcohol 5% dimers (3)	*e*
	26465-81-6	Li/Al		90	79	1	10% dimers (2)	
	10474-33-6	Li/Al		95		4	5% alcohol	*f*
	30428-23-0	Li/Al		92	73	2	8% dimers (2)	*g*
	30427-98-6	Li/Al		96	75	1	4% unknowns (2)	*h*
	119-61-9	Li/none		86		4	14% alcohol	
		Li/Co		97	87	1	3% alcohol	*i*
	120-46-7	Li/Co		100	77	1		*j*
	90-47-1	Li/none		98		4	2% unknowns (2)	*k*
		Li/Co		98	77	1	2% unknowns (2)	*k*

[a] Reaction conditions are those discussed in the Experimental Section, unless noted otherwise. [b] Analyzed by glc using a 6 ft × 1/8 in. 10% silicon gum rubber UCC-W-982 (methyl vinyl) on a flame detector instrument at a 40-ml/min flow rate. All samples were injected at a reasonable temperature, followed by a 10-min post injection interval, and then programmed 10°/min to 290° and held at limit 1–2 hr. [c] Isolated pure from an aluminum oxide column by eluting with petroleum ether, bp 38–58°. [d] Time of reflux after ketone had been added to reaction mixture. [e] Similar results were observed with aluminum trace metal. [f] Analytical yield estimated from a 1-hr reaction mixture consisting of 54% aromatic hydrocarbon and 46% alcohol. [g] In this experiment 3.3 mmol of ketone was used. [h] The unknowns have physical properties characteristic of compounds which have been overreduced. When no trace metal was present, the reduction of the ketone took *ca.* twice as long and in the process substantial overreduction occurred. [i] Aluminum was less effective as a trace metal catalyst for this ketone. [j] In this experiment 2.5 mmol of ketone was used. [k] Because of the insolubility of the ketone in 10 ml of THF, a solution of the ketone in 20 ml of THF was added to the Li or Li/Co in 20 ml of ammonia. The unknowns have physical properties characteristic of compounds which have been overreduced.

SCHEME I



Experimental Section

General Comments.—The nmr spectra were determined at 60 MHz with a Varian Model A-60 nmr spectrometer in CCl_4 or $CDCl_3$ solutions containing tetramethylsilane. The ultraviolet spectra were determined with a Cary spectrophotometer, Model 14. The infrared spectra were determined with a Beckman Model IR-10 infrared spectrophotometer. The mass spectra were obtained with a Perkin-Elmer Model 270 mass spectrometer, equipped with a Varian Model 620/i computer attachment. Gas chromatographic analyses were performed on a Hewlett-Packard Model 5750 research chromatograph. Separations and purifications were attained on adsorption alumina (80–200 mesh) columns. Further purification, for analytical purposes, was attained by gas–liquid partition chromatography (glc). The spectral data, analytical data, and physical characteristics of all aromatic hydrocarbons were in agreement with that of authentic samples.

Lithium–Ammonia Reduction.—Precautions for the exclusion of impurities (moisture, air, peroxides, contaminant metals, or metal salts) were scrupulously observed. All reductions were carried out under a static nitrogen (prepurified) atmosphere. Tetrahydrofuran (THF) was filtered through an alumina column and then refluxed and distilled from $LiAlH_4$ just prior to use. Anhydrous ammonia was distilled into the reaction vessel. Lithium wire (0.01% Na, Alpha Inorganics, Inc.) was wiped free of oil and washed with petroleum ether, bp 38–58°, immediately before use.

All reactions employed the conditions described for the reduction of 1-tetralone, except for variations in reaction time or other minor changes noted in Table I.[12]

(12) See ref 3g, pp 98–105, for a useful general discussion of metal–ammonia experimental techniques.

Tetralin.—To a mixture containing 20 ml of ammonia, 10 ml of THF, and 2.95 mg (0.05 mg-atom) of cobalt powder was added 175 mg (25 mg-atoms, 8 pieces) of Li, followed almost immediately by the dropwise addition (15 min) of a solution of 0.731 g (5 mmol) of 1-tetralone in 10 ml of THF. After the mixture had been stirred under reflux for 1 hr, the excess Li was consumed by the rather rapid addition (~4 min) of excess $NHCl_4$ (~4 g)[13] and the ammonia was allowed to evaporate. After the residue had been partitioned between aqueous NaCl and Et_2O, the organic layer was dried, concentrated, and analyzed by glc. The crude product was purified by column chromatography, yielding 0.626 g (95%) of a liquid which was identical with tetralin.

Registry No.—Ammonia, 7664-41-7; lithium, 7439-93-2.

Acknowledgments.—The authors are grateful to Dr. Hans U. Daeniker, Vice President of Research, Givaudan Corp., Clifton, N. J., for Givaudan's interest in this work; and in particular to Mr. Thomas F. Wood and Mr. Brian J. Duffy, Musk Division, for generous samples of precious aromatic ketones and aromatic hydrocarbons; and to Miss Rose Marie Luethy and Mr. Paul P. Vallon, Flavor Division, for the mass spectra.

(13) The addition should be smooth, relatively rapid, and continuous in order to avoid any overreduction of the product. This can be accomplished by attaching a piece of Tygon tubing, connected to a glass tube (sealed at one end) filled with ammonium chloride, to a side arm of the reaction vessel near the end of the reaction. When the ammonium chloride is needed, the tube is elevated and tapped gently to introduce the salt.

Ring-Opening Reactions of Triphenylcyclopropyllithium Compounds

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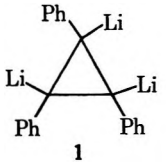
Received January 21, 1971

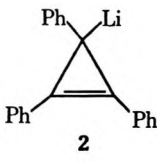
trans-1,2,3-Triphenylcyclopropane undergoes ring opening with *n*-BuLi to give, after treatment with D_2O, a mixture of *cis*- and *trans*-stilbenes **4** and **5** in which the trans isomer prevails. The use of *N,N,N',N'*-tetramethylethylenediamine (TMEDA) did not effect polymetalation of the cyclopropyl ring. Although attempts to trap a cyclopropyl anion in the above experiment were unsuccessful, the 1,2,3-triphenylcyclopropyl anion can form without immediately undergoing ring opening. This was demonstrated by hydrogen–deuterium exchange of the cyclopropyl hydrogens in both *cis*- and *trans*-1,2,3-triphenylcyclopropane, accompanied by isomerization of the cis isomer to the trans, using potassium *tert*-butoxide in dimethyl sulfoxide-d_6. Treatment of triphenylcyclopropene with *n*-butyl- or *tert*-butyllithium–TMEDA resulted in addition to the cyclopropenyl double bond followed by ring opening to give a mixture of stilbenes **13**–**16**. Attempts to prepare the anti aromatic triphenylcyclopropenyllithium with triptycyllithium TMEDA and triphenylcyclopropene were unsuccessful.

Since 1965 a number of remarkable polylithiated compounds have been prepared by treatment of acetylenes with excess alkyllithium compounds. From propyne one obtains C_3Li_4;[2] 1-butyne yields $CH_3CHLiC{\equiv}CLi$[3] or CH_3Li_3;[4] 1-phenylpropyne was first shown to yield $C_6H_5C_3Li_3$,[5] but, later, using 50 mol of *n*-butyllithium per mole of alkyne the principal products were shown to contain five or six lithium atoms per molecule as well as a trace of the perlithiated compound C_9Li_8.[6] Polylithiation is not a phenomenon restricted to alkynes. In the presence of *N,N,N',N'*-tetramethylethylenediamine (TMEDA), a reagent which highly activates organolithium compounds,[7,8] toluene and *n*-butyllithium produce trilithiated toluene as the principal product.[9]

Because of the powerful metalating capacity of RLi–TMEDA, we investigated the possibility of preparing **1**



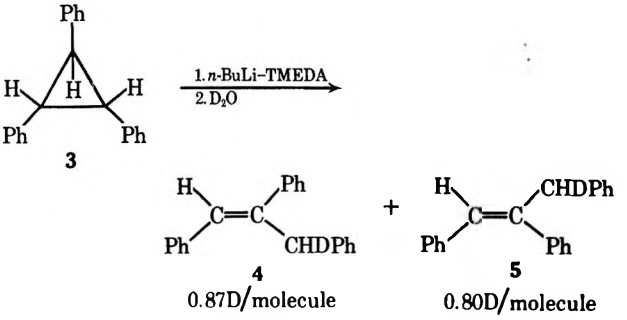
1



2

and **2**. To the extent that these lithiated compounds behave as carbanions, they would be examples of a three-membered ring containing a Hückel number of electrons (**1**) and an anti aromatic[10] cyclopropenyl anion **2**. Although compounds **1** and **2** were not prepared, we wish to report some of the reactions of anionic derivatives of triphenylcyclopropane.

Treatment of *trans*-1,2,3-triphenylcyclopropane (**3**) with 3 mol of *n*-butyllithium–TMEDA in hexane for 6 hr at room temperature followed by treatment of the purple solution with excess D_2O gave 90% *trans*- (**4**) and 10% *cis*-3-deuterio-1,2,3-triphenylpropene (**5**). No starting material remained nor were other compounds detected by glpc. Furthermore it was shown that compounds **3**, **4**, and **5** did not react under the work-up conditions.



The structure of the products was confirmed by spectroscopic methods as well as independent synthesis (see Experimental Section). Stereochemical assignments of **4** and **5** (without the deuterium) have previously been made on the basis of solubility and melting point[11] as well as ultraviolet spectra.[12] The nmr spectra confirm these earlier reports in that the vinyl proton of **5** appears at a higher field than the corresponding proton in **4**. Such observations have previously been used to determine the stereochemistry of substituted stilbenes.[13]

Two attempts were made to trap a lithio derivative of **3**. In the first experiment 1.0 mol of **3** in hexane was slowly added to 3.0 mol of *n*-butyllithium containing 0.75 mol of TMEDA (this ratio having been reported to be most effective in the metalation of toluene[9]). The deep orange reaction mixture was worked up with deuterium oxide after a considerably shorter time (30 min) at room temperature to yield 83% of pure **3** containing no deuterium.

Bey and Weyenberg[14] have previously shown that *tert*-butyllithium and trimethylchlorosilane do not react. Accordingly, **3** (1.0 mol) was treated with *tert*-butyllithium (3.0 mol) in the presence of trimethylchlorosilane (1.4 mol) in THF–hexane at −80°. The reaction could not be carried out in the presence of TMEDA because the latter reacts with the silane. After quenching with deuterium oxide and work-up,

(1) Research supported in part by AFOSR(SRC)-OAR, USAF Grant No. 720-67; from the Ph.D. Thesis of D. S., 1970.

(2) R. West, P. A. Carney, and I. C. Mineo, *J. Amer. Chem. Soc.*, **87**, 3788 (1965).

(3) K. C. Eberly and H. E. Adams, *J. Organometal. Chem.*, **3**, 165 (1965).

(4) R. West and P. C. Jones, *J. Amer. Chem. Soc.*, **91**, 6156 (1969).

(5) J. E. Mulvaney, T. L. Folk, and D. J. Newton, *J. Org. Chem.*, **32**, 1647 (1967).

(6) Private communication from Professor West.

(7) G. G. Eberhardt and W. A. Butte, *J. Org. Chem.*, **29**, 2928 (1964); G. G. Eberhardt and W. R. Davis, *J. Polym. Sci., Part A*, **3**, 3753 (1965).

(8) A. W. Langer, *Trans. N. Y. Acad. Sci.*, **27**, 741 (1965).

(9) R. West and P. C. Jones, *J. Amer. Chem. Soc.*, **90**, 2656 (1968).

(10) R. Breslow, *Angew. Chem., Int. Ed. Engl.*, **7**, 565 (1968).

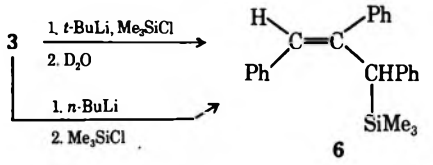
(11) M. S. Evantova and N. I. Shapchenko, *Vestn. Mosk. Univ., Khim.*, **16**, 71 (1961); *Chem. Abstr.*, **57**, 7143*f* (1962).

(12) G. W. Griffin, A. F. Marcantonio, H. Kristinsson, R. C. Petterson, and C. S. Irving, *Tetrahedron Lett.*, 2951 (1965).

(13) D. Y. Curtin, H. Gruen, and B. A. Shoulders, *Chem. Ind. (London)*, 1205 (1958); J. E. Mulvaney, Z. G. Gardlund, and S. L. Gardlund, *J. Amer. Chem. Soc.*, **85**, 3897 (1963); J. E. Mulvaney and L. J. Carr, *J. Org. Chem.*, **33**, 3286 (1968).

(14) A. E. Bey and D. R. Weyenberg, *ibid.*, **30**, 2436 (1965).

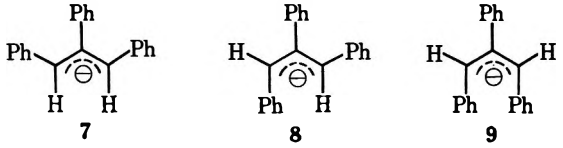
there was obtained a 70% yield of **3** containing no deuterium. The glpc of the remaining oil revealed the presence of 4.5% of **6** plus a smaller amount of the cis isomer. Pure **6** was isolated and its structure was confirmed by spectroscopy and independent synthesis involving treatment of **3** with *n*-butyllithium followed by trimethylchlorosilane. The failure to trap the cyclo-



6

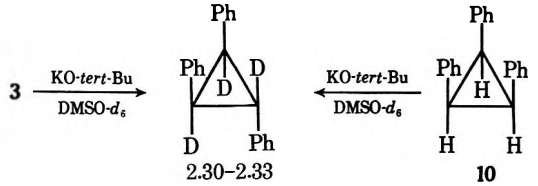
propyllithium derivative in this experiment cannot be regarded as proof that it is *not* an intermediate and that ring opening occurs in a concerted manner. The lithio derivative of **3** is also a hindered species and reaction with the silane could well be slow relative to ring opening.

The similarity of the nmr spectrum of the 1,2,3-triphenylallyllithium intermediate in TMEDA–hexane to that of the ionic species 1,3-diphenylallyllithium[15] leads us to conclude that we are dealing with one or more of three delocalized carbanions (**7**–**9**). Just as in



the case of the 1,3-diphenyl compound the aromatic protons show a pronounced upfield shift to τ 3.4 indicating delocalization of charge into the benzene rings and hence over the allylic carbons. In addition, the signal at τ 7.60 (cyclopropyl protons) gradually disappears and a poorly resolved doublet appears centered at τ 5.30 which increases with time for at least 25 min with one component apparently increasing at the expense of the other. Inasmuch as deuterolysis of the anion yields 90% *trans*-**4** and 10% *cis*-**5**, we can conclude that **7** which would give only *cis*-**4** is a minor, or absent, component of the mixture. Compound **8** could give a cis–trans mixture whereas compound **9** would yield only *trans*-**4**. It is reasonable then that **9** is the principal component of the reaction mixture.

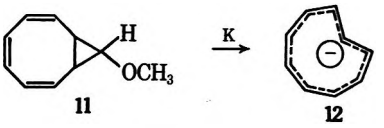
It was of interest to examine the triphenylcyclopropanes in a more acidic medium in which the triphenylcyclopropyl anion intermediate could capture a proton prior to ring opening. Accordingly, **3** as well as *cis*-1,2,3-triphenylcyclopropane (**10**) were treated with



potassium *tert*-butoxide in dimethyl sulfoxide-d_6 for 18 hr at room temperature. Neither nmr nor glpc revealed the presence of any ring-opened products. Deuterium was incorporated to the extent shown below and glpc revealed that the cis isomer had been completely converted to the trans. These results show that the 1,2,3-triphenylcyclopropyl anion is capable of existing for a finite period of time as an intermediate without undergoing ring opening. It is likely, therefore, that the 1,2,3-triphenylcyclopropyl anion is an intermediate in the above discussed work with organolithium reagents in aprotic media. A concerted E2-like elimination in the organolithium case would involve a leaving group which could not be trans coplanar with the proton.

The fact that inversion accompanies exchange in the case of **10** is of interest because of the tendency of cyclopropyl anions to maintain configuration even when adjacent to a nitrile or carbonyl group.[16] Although the data from this experiment are insufficient to allow quantitative comparison, it should be noted that steric compression in a nonplanar anion derived from **10** as well as a large gain in delocalization energy in the planar form are two potent driving forces for the isomerization.

It should be noted that ring opening of cyclopropyl anions or anion-like species is a rare phenomenon.[16,17] In fact, the only possible example of this reaction of which we are aware has been reported by Boche, Martens, and Danzer[18] who treated the bicyclic ether **11** with potassium in THF and obtained the 10 π electron system **12**. The fact that compound **3** undergoes ring



opening may be taken as further evidence for a highly delocalized 1,2,3-triphenylallyl carbanion as the product.

In an attempt to prepare the monolithiated triphenylcyclopropenyl compound **2**, triphenylcyclopropene (1.0 mol) and TMEDA (1.6 mol) were treated with *n*-butyllithium (6.4 mol) in hexane at room temperature. After 24 hr the deep red solution was treated with excess deuterium oxide to give, after work-up, a 58% yield of an oil which was shown by nmr to contain four products, two sets of stereoisomers, resulting from addition of *n*-butyllithium to the double bond of the cyclopropene ring followed by ring opening. These results, including nmr assignments, are outlined in the following equations (p 2594).

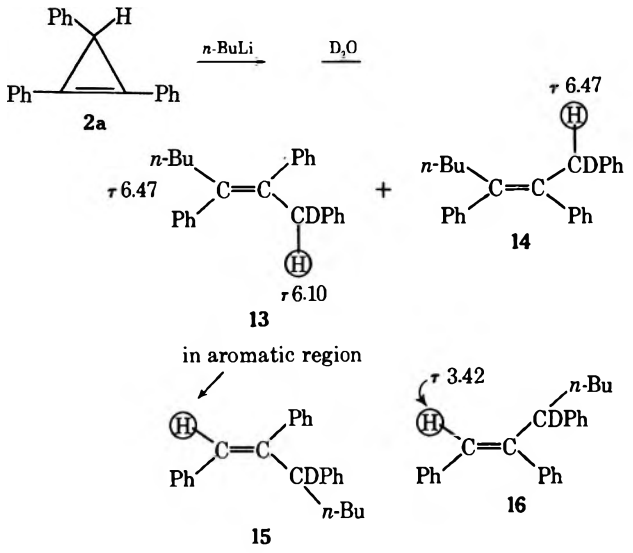
A portion of the oil crystallized to give **14**, identified by its nmr and ultraviolet spectra and elemental analysis. Stereochemical assignments for compounds **13**–

(15) H. H. Freedman, V. R. Sandel, and B. D. Thill, *J. Amer. Chem. Soc.*, **89**, 1762 (1967).

(16) H. M. Walborsky and J. M. Motes, *ibid.*, **92**, 2445 (1970); J. M. Motes and H. M. Walborsky, *ibid.*, **92**, 3697 (1970), and references cited therein.

(17) For examples of cyclopropyl anions or organometallics which do not undergo ring opening, see (a) H. M. Walborsky, A. A. Youssef, and J. M. Motes, *ibid.*, **84**, 2465 (1962); (b) D. E. Applequist and A. H. Peterson, *ibid.*, **83**, 862 (1961); (c) H. M. Walborsky and F. J. Impastato, *ibid.*, **81**, 5835 (1959); (d) H. M. Walborsky, F. J. Impastato, and A. E. Young, *ibid.*, **86**, 3283 (1964); (e) H. M. Walborsky and F. J. Impastato, *ibid.*, **84**, 4838 (1962); (f) M. J. S. Dewar and J. M. Harris, *ibid.*, **91**, 3652 (1969); (g) R. M. Magid and J. G. Welch, *ibid.*, **90**, 5211 (1968); (h) D. Seyferth and H. M. Cohen, *J. Organometal. Chem.*, **1**, 15 (1963); and (i) H. M. Cohen, *ibid.*, **9**, 375 (1967).

(18) G. Boche, D. Martens and W. Danzer, *Angew. Chem., Int. Ed. Engl.* **8**, 984 (1969).



16 were made in analogy to the benzyl stilbenes discussed earlier in this paper.

The only other example of the addition of an organolithium compound to a cyclopropene of which we are aware is the case of phenyllithium and cyclopropene[17g] in which a 2.5% yield of adduct is formed.

The reaction of *tert*-butyllithium–TMEDA with **2a** gave results similar to those obtained with *n*-butyllithium as determined by spectroscopy.

Because even a sterically hindered base like *tert*-butyllithium would add to **2a** rather than abstract the cyclopropenyl hydrogen, it was desirable to use an even more hindered organolithium reagent, such as triptycyllithium.

Treatment of a solution of **2a** in THF with triptycyllithium in benzene–ether followed by deuterolysis of the reaction mixture gave only **2a** containing no deuterium and 9-deuteriotriptycene.

It is apparent then that even extraordinary metalating agents such as RLi–TMEDA which are capable of producing perlithiated hydrocarbons are not capable of generating a cyclopropenyllithium compound.[19]

Experimental Section

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Nuclear magnetic resonance (nmr) spectra were determined on either a Varian Model A-60 spectrometer at 60 MHz or a Varian Model HA-100 spectrometer at 100 MHz using tetramethylsilane as an internal standard.

Microanalyses were performed by the Micro-Tech Laboratories, Skokie, Ill. Deuterium analyses reported as "atom per cent excess deuterium" were performed by Josef Nemeth, Urbana, Ill., using the falling drop method; those reported as "deuterium atom per molecule" were calculated from mass spectra data. Deuterium analyses reported in this manner and all other molecular weight determinations were obtained from a Hitachi Perkin-Elmer RHU-6E mass spectrometer. For analytical glpc determinations, correction factors for mole ratio/area ratio data were determined with standards containing the same compounds as in the unknown mixture.

Hexane was purified by stirring overnight with 95% sulfuric acid, washing with distilled water, drying over sodium sulfate, and refluxing over sodium metal for 24 hr prior to final distillation.

Mallinckrodt anhydrous reagent grade ether was used without further purification. Reagent grade tetrahydrofuran was purified by distillation from lithium aluminum hydride. Reagent grade benzene was refluxed over sodium metal for 24 hr prior to final distillation.

Eastman grade *N,N,N′,N′*-tetramethylethylenediamine was dried and distilled over calcium hydride. It was then stored over potassium hydroxide.

Matheson Coleman and Bell practical grade potassium *tert*-butoxide was used without further purification.

Deuterium oxide (99.8 atom % deuterium) and dimethyl sulfoxide-d_6 (99.5 atom % deuterium) were obtained from Stohler Isotope Chemicals.

Lithium wire and *tert*-butyllithium in pentane were obtained from the Lithium Corp. of America. *n*-Butyllithium, 1.6 mol in hexane, was obtained from Foote Mineral Co. All organolithium reactions were run under a nitrogen atmosphere in flame-dried apparatus protected by calcuim chloride drying tubes.

***cis*- and *trans*-1,2,3-Triphenylpropane. Phenyldibenzylcarbinol.**—This compound was prepared in 42% yield according to the procedure of Allen and Converse[20] for the synthesis of methyldiphenylcarbinol.

Dehydration of Phenyldibenzylcarbinol.—This procedure was adopted from that of Evantova and Shapchenko.[11] A mixture of phenyldibenzylcarbinol (8.10 g, 0.085 mol) and anhydrous cupric sulfate (1.35 g, 0.085 mol) was distilled through a short path column under reduced pressure. The main fraction afforded 5.09 g (68%) of a clear, colorless oil, bp 168–170° (0.30 Torr), which crystallized on standing. The melting point of the crude olefin mixture was 45–50°.

The olefin mixture was separated by fractional recrystallization from 95% ethanol. The more insoluble component separated as white prisms which, after three recrystallizations from 95% ethanol, produced pure *trans*-1,2,3-triphenylpropene, mp 63–64° (lit.[11] mp 62–63°). The ultraviolet spectrum (95% ethanol) had λ_{max} 275 nm (ϵ 13,300), 210 (16,900). The nmr spectrum (CCl_4) showed peaks centered at τ 2.95 (multiplet, 16 H) assigned to the aromatic protons and the buried vinyl proton, 6.00 (singlet, 2 H) assigned to the benzyl protons.

The cis olefin was obtained from the filtrate of the trans isomer. Two recrystallizations from 95% ethanol gave long, white needles, mp 64–65° (lit.[11] mp 63–64°). The ultraviolet spectrum (95% ethanol) had λ_{max} 260 nm (ϵ 4800), 225 (shoulder, 7100), 208 (12,100). The nmr spectrum (CCl_4) showed peaks centered at τ 3.00 (multiplet) assigned to the aromatic protons, 3.65 (singlet, 1 H) assigned to the vinyl proton, 6.35 (singlet, 2 H) assigned to the benzyl protons. A mixture melting point of pure cis and pure trans olefins was 45–58°.

***trans*-1,2,3-Triphenylcyclopropane (3).**—3,4,5-Triphenyl-2-pyrazoline[21] was pyrolyzed using a modification of a literature procedure.[22] 3,4,5-Triphenyl-2-pyrazoline (27.0 g, 0.090 mol) was heated for 2 hr at 220–250° with a catalytic amount of powdered potassium hydroxide. The reaction mixture was cooled, diluted with water, and extracted with ether. The ether layer was dried over sodium sulfate. Removal of solvent left an off-white solid which was shown by glpc (10-ft GE-SE-54, 250°) to contain only one component. Two recrystallizations from 95% ethanol gave 16.7 g (69%) of *trans*-1,2,3-triphenylcyclopropane as small white needles, mp 67.0–67.5° (lit.[22] mp 66.5–67.5°). The nmr spectrum (CCl_4) showed peaks centered at τ 3.00 (multiplet, 15 H) assigned to the aromatic protons, 7.25 (singlet, 3 H) assigned to the cyclopropyl protons.

***n*-Butyllithium, TMEDA, and *trans*-1,2,3-Triphenylcyclopropane in Hexane.**—In a typical experiment *n*-butyllithium (0.150 mol) in 94 ml of hexane was slowly added to a stirred solution of *trans*-1,2,3-triphenylcyclopropane (13.5 g, 0.050 mol) and TMEDA (16.4 g, 0.150 mol) in 250 ml of hexane. The solution was cooled in an ice bath during the *n*-butyllithium addition. After being stirred for 6 hr at room temperature, the purple reaction mixture was cooled in an ice bath and quenched by rapid addition of excess deuterium oxide. The now clear, colorless solution was stirred for an additional 45 min and allowed to stand overnight. The reaction mixture was diluted with water. The aqueous layer was extracted with ether and the combined organic layers were dried over sodium sulfate. Removal of the solvent left 12.6 g of an opaque yellow oil which contained 90% *trans*-3-deuterio-1,2,3-triphenylpropene (**4**) and 10% *cis*-3-deuterio-

(19) The pK_a of triphenylcyclopropene is approximately 51: R. Breslow and K. Balasubramanian, *J. Amer. Chem. Soc.*, **91**, 5182 (1969).

(20) C. T. H. Allen and S. Converse, "Organic Syntheses," Collect Vol. I, 2nd ed, A. H. Blatt, Ed., Wiley, New York, N. Y., 1941, p 226.

(21) W. E. Parham and W. R. Hasek, *J. Amer. Chem. Soc.*, **76**, 799 (1954).

(22) Yu. S. Shabarov, A. A. Podterebkov, and R. Ya. Levina, *Vestn. Mosk. Univ., Khim.*, **21**, 118 (1966); *Chem. Abstr.*, **65**, 20023*b* (1966).

1,2,3-triphenylpropene (5) by glpc (10-ft GE-SE-54, 225°). The oil was seeded with authentic *trans*-1,2,3-triphenylpropane. After crystallization the product was collected on a filter, washed with cold 95% ethanol, and dried in the air. This material was recrystallized from 95% ethanol to give 4.10 g of *trans*-3-deuterio-1,2,3-triphenylpropane as small white prisms, mp 63.0–63.5°. A mixture melting point with an authentic sample of undeuterated material gave no depression.

From the filtrate precipitated 2.90 g of small white needles, mp 45–50°. This material was recrystallized from 95% ethanol to give 1.20 g of *cis*-3-deuterio-1,2,3-triphenylpropene as long white needles, mp 64.5–65.0°. A mixture melting point with an authentic sample of undeuterated material was not depressed.

The deuterium content of the benzyl stilbenes was determined by mass spectrometry. The *trans*-3-deuterio-1,2,3-triphenylpropene contained 0.87 deuterium atom per molecule. The *cis*-3-deuterio-1,2,3-triphenylpropene contained 0.80 deuterium atom per molecule.

***n*-Butyllithium, TMEDA, and *trans*-1,2,3-Triphenylcyclopropane in Hexane. Inverse Addition.**—To an ice-cold solution of *n*-butyllithium (0.075 mol) and TMEDA (2.05 g, 0.019 mol) in 97 ml of hexane was added *trans*-1,2,3-triphenylcyclopropane (6.75 g, 0.025 mol) in 200 ml of hexane. The brilliant orange solution was stirred 30 min at room temperature, cooled in an ice bath, and quenched with excess deuterium oxide. The reaction mixture was allowed to stir overnight, after which it was diluted with water. The layers were separated and the aqueous layer was extracted with ether. The combined organic layers were dried over sodium sulfate. Removal of the solvent left 6.0 g of a white solid, mp 61–64°. This material was recrystallized from 95% ethanol to give 5.60 g (83%) of pure *trans*-1,2,3-triphenylcyclopropane, mp 66.5–67.0°. A mixture melting point with authentic material was not depressed. A quantitative deuterium analysis of the recovered cyclopropane by mass spectrometry showed no deuterium incorporation.

***n*-Butyllithium and *trans*-1,2,3-Triphenylcyclopropane. Termination by Silylation.**—To an ice-cold solution of *trans*-1,2,3-triphenylcyclopropane (3.37 g, 0.012 mol) in 200 ml of tetrahydrofuran was added *n*-butyllithium (0.012 mol) in 20 ml of hexane. The solution was stirred for 4 hr at 0°. Upon addition of trimethylchlorosilane (6.0 ml, 0.054 mol), the purple solution turned colorless. The reaction mixture was then diluted with water and extracted with ether. The combined organic layers were dried over sodium sulfate. Aftr removal of the solvent there remained 3.65 g of a clear, colorless oil. The nmr (CCl_4) showed peaks centered at τ 2.95 (multiplet, 148 H) assigned to the aromatic protons and the buried vinyl proton of *cis*-3-trimethylsilyl-1,2,3-triphenylpropene, 3.35 (singlet, 4 H) assigned to the vinyl proton of *trans*-3-trimethylsilyl-1,2,3-triphenylpropene, 6.75 (singlet, 4 H) assigned to the benzyl proton of *trans*-3-trimethylsilyl-1,2,3-triphenylpropene, 7.17 (singlet, 12 H) assigned to the benzyl proton of *cis*-3-trimethylsilyl-1,2,3-triphenylpropene, 9.83 (singlet, 65 H) assigned to the methyl protons of the trimethylsilyl group.

Analysis of the oil by nmr indicated *cis*-3-trimethylsilyl-1,2,3-triphenylpropene (67%) and *trans*-3-trimethylsilyl-1,2,3-triphenylpropene (33%).

The oil solidified on standing after approximately 2 weeks. Three recrystallizations from 95% ethanol gave 0.10 g of *trans*-3-trimethylsilyl-1,2,3-triphenylpropene as small white prisms, mp 82–83°. The nmr spectrum (CCl_4) showed peaks centered at τ 2.80 (multiplet, 22 H) assigned to the aromatic protons, 3.25 (singlet, 1.5 H) assigned to the vinyl proton, 6.65 (singlet, 1.5 H) assigned to the benzyl proton, 9.75 (singlet, 17 H) assigned to the methyl protons of the trimethylsilyl group. The ultraviolet spectrum (95% ethanol) had λ_{max} 265 nm (ϵ 15,000), 230 (shoulder 25,000), 204 (70,000).

Anal. Calcd for $C_{24}H_{26}Si$: C, 84.20; H, 7.60; mol wt, 342. Found: C, 84.02; H, 7.72; mol wt (mass spectrum), 342.

***tert*-Butyllithium, Trimethylchlorosilane, and *trans*-1,2,3-Triphenylcyclopropane in THF–Pentane.**—To a solution of *trans*-1,2,3-triphenylcyclopropane (6.70 g, 0.025 mol) and trimethylchlorosilane (14.7 g, 0.035 mol) in 400 ml of THF at −80° was added *tert*-butyllithium (0.075 mol) in 42 ml of pentane. The lemon yellow reaction mixture was stirred for 2 hr at −80°. The solution was then allowed to reach room temperature, turning purple as it warmed. Excess deuterium oxide was then added and the reaction mixture was stirred overnight. The reaction mixture was then diluted with water and extracted with ether. The combined organic layers were dried over sodium sulfate. Removal of the solvent and two recrystallizations from 95% ethanol afforded 4.65 g (70%) of pure *trans*-1,2,3-triphenylcyclopropane, mp 66.0–67.0°. Mixture melting point with an authentic sample was not depressed. Deuterium analysis of the recovered cyclopropane by mass spectrometry showed no deuterium incorporation.

Work-up also afforded 1.22 g of a yellow oil. Analysis of the oil by glpc (5-ft GE-SE-30, 200°) and nmr indicated *trans*-1,2,3-triphenylpropene (4.5%), and *cis*-3-trimethylsilyl-1,2,3-triphenylpropene (10%). The mass spectrum of the oil indicated a molecular weight of 342, the correct molecular weight for the silylated derivative. Seeding the oil with an authentic sample of *trans*-3-trimethylsilyl-1,2,3-triphenylpropene caused a portion of the oil to crystallize. About 40 mg of *trans*-3-trimethylsilyl-1,2,3-triphenylpropene was obtained as small white, needles, mp 63.0–65.5°. The ultraviolet spectrum (95% ethanol) of this compound had λ_{max} 265 nm (ϵ 2000), 224 (23,000), 206 (28,000).

Triphenylcyclopropene.—This compound was synthesized in 36% yield according to the procedure of Breslow and Dowd[23] with the exception that elution chromatography of the crude 1,2,3-triphenylcyclopropene was usually not necessary. The product was identified by its nmr, mass spectrum, and melting point.

***n*-Butyllithium, TMEDA, and *trans*-1,2,3-Triphenylcyclopropene.**—To an ice-cold solution of 1,2,3-triphenylcyclopropane (2.0 g, 0.0074 mol) and TMEDA (1.39 g, 0.012 mol) in 200 ml of hexane was added *n*-butyllithium (0.048 mol) in 30 ml of hexane. The deep red reaction mixture was stirred for 24 hr at room temperature, and then terminated with excess deuterium oxide. The reaction mixture was diluted with water and extracted with ether. The combined organic layers were dried over sodium sulfate. Removal of the solvent afforded 4.80 g of a slightly opaque, pale yellow oil. The oil was distilled through a short path column to give 1.40 g (58%) of a viscous, clear, light yellow oil, bp 150–155° (0.15 Torr). The nmr spectrum (CCl_4) showed peaks centered at τ 3.00 (multiplet, 142 H) assigned to the aromatic protons and the buried vinyl proton of *trans*-3-deuterio-1,2,3-triphenyl-1-heptene (15), 3.42 (singlet, 1 H) assigned to the vinyl proton of *cis*-3-deuterio-1,2,3-triphenyl-1-heptene (16), 6.10 (singlet, 3 H) assigned to the benzyl proton of *trans*-1-deuterio-1,2,3-triphenyl-2-heptene (13), 6.47 (singlet, 3 H) assigned to the benzyl proton of *cis*-1-deuterio-1,2,3-triphenyl-2-heptene (14), 8.50–9.40 (multiplet, 80 H) assigned to the *n*-butyl group protons.

Upon standing for several days the oil solidified and was recrystallized from aqueous 95% ethanol to give 0.22 g of *cis*-1-deuterio-1,2,3-triphenyl-2-heptene (14) as a white crystalline solid, mp 85–86°. The nmr spectrum (CCl_4) showed peaks centered at τ 2.80 (multiplet, 16.5 H) assigned to the aromatic protons, 6.50 (singlet, 1.0 H) assigned to the benzyl proton, 7.80 (multiplet, 2.0 H) assigned to the methylene protons on the *n*-butyl group, 8.80 (multiplet, 7.0 H) assigned to the *n*-propyl protons. The ultraviolet spectrum (95% ethanol) had λ_{max} 234 nm (shoulder, ϵ 7000), 206 (23,000).

Anal. Calcd for $C_{25}H_{25}D$: C, 91.74; H, 7.64; D, 3.84 atom % excess deuterium; mol wt, 327. Found: C, 91.75; H, 8.10; D, 4.30 atom % excess deuterium; mol wt (mass spectrum), 327.

Triptycyllithium.—A solution of triptycyllithium in benzene (90 ml)–ether (200 ml) was prepared according to the procedure of Dence and Roberts.[24]

Triptycyllithium and Triphenylcyclopropene.—To a stirred solution of triptycyllithium at −80° was added 1,2,3-triphenylcyclopropene (2.0 g, 0.0074 mol) in benzene (25 ml)–ether (25 ml). Tetrahydrofuran (50 ml) was also added and the solution was stirred for 2 hr at −80°. No color change resulted when the cyclopropene was added. The solution was allowed to warm and excess deuterium oxide was added. After work-up in the usual manner there was obtained 9-deuteriotryptycene (mol wt 255, mass spectrum) and unreacted triphenylcyclopropene containing no deuterium.

This experiment was repeated using tetrahydrofuran as the only solvent for both the triptycyllithium and 1,2,3-triphenylcyclopropene. The results obtained were essentially the same as in the previous experiment.

***trans*-1,2,3-Triphenylcyclopropane and Potassium *tert*-Butoxide in Dimethyl Sulfoxide-d_6.**—Potassium *tert*-butoxide (0.42 g, 0.0038 mol) was added to DMSO-d_6 (2 ml, 0.024 mol) with stirring under nitrogen. *trans*-1,2,3-Triphenylcyclopropane (0.37 g,

(23) R. Breslow and P. Dowd, *J. Amer. Chem. Soc.*, **85**, 2729 (1963).

(24) J. B. Dence and J. D. Roberts, *J. Org. Chem.*, **33**, 1251 (1968).

0.0014 mol) was added and the solution turned a clear violet color. The reaction mixture was stirred at room temperature for 18 hr after which time the clear orange solution was diluted with water and extracted with ether. The ether layer was dried over sodium sulfate. Removal of the solvent left a pale yellow solid which was recrystallized from 95% ethanol to give 0.24 g (65%) of *trans*-1,2,3-triphenylcyclopropane. Mixture melting point with an authentic sample was not depressed.

A deuterium analysis by mass spectrometry of the recovered cyclopropane indicated 2.30 deuterium atom per molecule. The nmr spectrum showed that the cyclopropyl hydrogens had been exchanged.

cis-1,2,3-Triphenylcyclopropane.—This compound was synthesized in 80% yield according to the procedure of Battiste.[25]

cis-1,2,3-Triphenylcyclopropane and Potassium *tert*-Butoxide in DMSO-d_6.—Potassium *tert*-butoxide (0.69 g, 0.0062 mol) was added to DMSO-d_6 (3 ml, 0.036 mol) with stirring under nitrogen. Then *cis*-1,2,3-triphenylcyclopropane (0.55 g, 0.0020 mol) was added. The resulting deep blue-green solution was stirred for 18 hr at room temperature. The reaction mixture was then diluted with water and extracted with ether. The ether layer was dried over sodium sulfate. Removal of the solvent left 0.50 g (91%) of a viscous clear yellow oil which was shown by glpc (5 ft SE-30, 220°) to contain only one component having the same retention time as authentic *trans*-1,2,3-triphenylcyclopropane. It should be noted that it was possible to separate an authentic mixture of *cis*-1,2,3-triphenylcyclopropane and *trans*-1,2,3-triphenylcyclopropane on the glpc column used for the crude reaction product.

A deuterium analysis by mass spectrometry of the recovered oil indicated 2.33 deuterium atom per molecule. The nmr spectrum showed that the cyclopropyl hydrogens had been exchanged.

(25) M. A. Battiste, *Tetrahedron Lett.*, 3795 (1964).

Registry No.—**3**, 10539-10-3; **4**, 30477-01-1; **5**, 30409-61-1; **6**, 30409-62-2; **13**, 30409-63-3; **14**, 30477-02-2; **15**, 30409-64-4; **16**, 30409-65-5; *trans*-1,2,3-triphenylpropene, 3239-33-6; *cis*-1,2,3-triphenylpropene, 3239-32-5; *cis*-3-trimethylsilyl-1,2,3-triphenylpropene, 30409-68-8.

The Copper Chloride–Ethanolamine-Catalyzed Addition of Polyhaloalkanes to Substituted Olefins[1]

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The copper chloride–ethanolamine redox system initiates the addition of polyhaloalkanes to a variety of olefins. The structure of the initial olefin greatly affects both the yield and the structure of the final product. Halogenated olefins showed decreased reactivity toward radical attack. The telogen $CF_2BrCFClBr$ gave good yields with simple α olefins, while only the more reactive CCl_3Br reacted with several halogenated olefins. This redox system of radical initiation exhibits considerable potential as a synthetic tool. The preparation and characterization of several new addition adducts are reported.

The addition of polyhalogenated alkanes to the double bond of olefins has received considerable attention in the literature.[2] While the usual systems for free-radical initiation give varying amounts of telomeric products, the "redox" system described by Asscher and Vofsi leads to almost exclusive formation of 1:1 adducts.[3,4] This system utilizes iron or copper salts to catalyze the addition of carbon tetrachloride and chloroform to olefins. Reaction conditions are quite mild

$$CCl_4 + PhCH{=}CH_2 \xrightarrow[\text{solvent, } 120^\circ]{CuCl_2} PhCHClCH_2CCl_3 \quad 78\%$$

and, because telomerization reactions are minimized, the use of a large excess of alkyl polyhalide is unnecessary. Additionally, vigorous reaction conditions and the need for special apparatus can be avoided. Because of these advantages, the redox technique holds much promise for the preparation of many polyhalogenated compounds, and a study of the scope and utility of this system was of interest.

We recently reported[5] a study of the scope of this reaction with a series of alkyl polyhalides. 1-Octene was used as the model olefin for that reactivity survey. Our initial study has now been expanded to include a variety of clefins, with the hope that the effect of olefin structure on the polyhalide additions could be ascertained.

Results and Discussion

In this study, $CF_2BrCFClBr$ was used as a model halide. Our previous report[5] showed it to be very reactive under redox conditions, giving a good yield of stable, 1:1 addition product with 1-octene. As previously described, the additions were carried out by refluxing the olefin, alkyl polyhalide, copper chloride, ethanolamine, and *tert* butyl alcohol, with stirring, for 24 hr. If no significant reaction was noted after this time, reflux was continued for at least an additional 24 hr. The results of these addition reactions are summarized in Table I.

An examination of the data in Table I reveals that this redox method successfully initiates the addition of polyhalcalkanes to both terminal and internal olefins as well as several halogen-substituted olefins.

Vpc showed that in almost every reaction, in addition to the major product, small amounts (generally less than 5% of the total product) of isomeric compounds were formed. These by-products were not identified.

The redox-initiated additions proceed in the same manner as that described for additions initiated by ordinary techniques. We have shown[5] that addition to straight-chain, terminal olefins gives almost exclusively the simple, straight-chain 1:1 addition adduct.

(1) (a) Presented in part at the 152nd National Meeting of the American Chemical Society, New York, N. Y., Sept 1966; (b) preliminary report in *Tetrahedron Lett.*, 5163 (1966); (c) this investigation was supported in part by Public Health Service, Grant GM 11809.

(2) For extensive reviews of this work, *cf.* (a) C. Walling, "Free Radicals in Solution," Wiley, New York, N. Y., 1957, Chapter 6. (b) G. Sosnovsky, "Free Radical Reactions in Preparative Organic Chemistry," Macmillan, New York, N. Y., 1964, Chapter 2.

(3) M. Asscher and D. Vofsi, *J. Chem. Soc.*, 1887 (1963).

(4) M. Asscher and D. Vofsi, *ibid.*, 3921 (1963).

(5) D. J. Burton and L. J. Kehoe, *J. Org. Chem.*, **35**, 1339 (1970).

TABLE I
DATA ON ADDITION ADDUCTS

Reaction	Olefin	Halide	Adduct[a]	Registry no.	% conversion[b]	% yield[c]	Ratio of halide/olefin	Reaction time, hr	Bp, °C (mm)	$n^{20}D$
I	1-Hexene	$CF_2BrCFClBr$	$CF_2BrCFClCH_2CHBr(CH_2)_3CH_3$	30428-47-8	95	91	2:1	24	58 (0.3)	1.4607
II	2-Methylpentene-1	$CF_2BrCFClBr$	$CF_2BrCFClCH_2CBr(CH_3)CH_2CH_2CH_3$ + $CF_2BrCFClCH_2C(CH_3)=CHCH_2CH_3$	30428-48-9	100	17	2:1	24	42–44 (0.15)	1.4646
II[d]				30428-49-0		27			44 (0.2)	1.4376
III[e]	2-Octene	$CF_2BrCFClBr$	$CH_3CHBrCH(CFClCF_2Br)CH_2(CH_2)_3CH_3$ + $CH_3CH(CFClCF_2Br)CHBrCH_2(CH_2)_3CH_3$	30428-50-3	38	87	2:1	79	91 (0.6)	1.4674
IV	Cyclohexene	$CF_2BrCFClBr$		30428-51-4	36	60	2:1	24	90–91 (0.8)	1.4926
V	Styrene	$CF_2BrCFClBr$			90	69	2:1	24		
VI	Styrene	$CF_2ClCFCl_2$			30	0	2:1	48		
VII[f]	Ethyl allyl ether	$CF_2BrCFClBr$	$CF_2BrCFClCH_2CHBrCH_2OCH_2CH_3$	690-65-3		79	2:1	48	78–79 (1.5)	1.4565
VIII	Allyl chloride	$CF_2BrCFClBr$			89	6	2:1	48		
IX[g]	Allyl chloride	CCl_3Br	$CCl_3CH_2CHBrCH_2Cl$	20968-55-2	100	88	1:1	24	74–78 (1)	1.5328
X	1-Bromopentene-1	$CF_2BrCFClBr$				Trace	2:1	100		
XI	1-Bromopentene-1	CCl_3Br	$CHBr_2CH(CCl_3)(CH_2)_2CH_3$	30428-53-6	38	63	2:1	48	79–81 (0.2)	1.5396
XII[h]	2-Chlorobutene-2	CCl_3Br	$CH_3CH(CCl_3)CClBrCH_3$	30428-54-7	70	42	2:1	48	62 (0.35)	1.5380
XIII	BTFO[i]	$CF_2BrCFClBr$				Trace	1:1	100		
XIV	BTFO[i]	CCl_3Br	$CCl_3CF_2CFBrCH=CH(CH_2)_3CH_3$[j]	30428-55-8	58	14	1:1	90	80–92 (0.65)	1.4577

[a] Satisfactory analytical data were reported for all new compounds listed in the table. [b] Yield (*via* glc) = moles of adduct formed/moles of olefin consumed. [c] Conversion (*via* glc) = moles of olefin consumed/moles of olefin charged. [d] Olefinic product. [e] Two isomers. [f] Reported for $CF_2BrCFClCH_2CHBrCH_2OCH_2CH_3$, bp 75° (1.5 mm), $n^{23}D$ 1.4534: P. Tarrant and E. C. Stump, *J. Org. Chem.*, **26**, 4646 (1961). [g] Reported for $CCl_3CH_2CHBrCH_2Cl$, bp 59–60° (0.6 mm), $n^{20}D$ 1.5537: M. S. Kharasch, O. Reinmuth, and W. H. Urry, *J. Amer. Chem. Soc.*, **69**, 1105 (1947). [h] Reported[10] for $CH_3CH(CCl_3)CClBrCH_3$, bp 87° (4 mm), $n^{25}D$ 1.5352. [i] 4-Bromo-1,1,2-trifluorooctene-1. [j] The structure of this adduct was not unequivocally determined.

Thus, attack by the $CF_2BrCFCl\cdot$ radical occurs preferentially at the 1 carbon to form a secondary radical rather than at the 2 carbon to give a less stable primary radical. When attempting to predict the orientation of radical attack in substituted olefins, however, several directive effects (*e.g.*, steric factors, electronic effects, and radical stabilization effects) must be considered.

It was anticipated that addition to an internal olefin would give rise to two isomeric products, since attack by the $CF_2BrCFCl\cdot$ radical at either of the two olefinic carbons would give rise to secondary radicals. This was indeed found to be the case. With 2-octene, two products were formed: $CH_3CHBrCH(CFClCF_2Br)CH_2(CH_2)_3CH_3$ and $CH_3CH(CFClCF_2Br)CHBrCH_2(CH_2)_3CH_3$. A vpc indicated that the ratio of these two isomers in the reaction mixture was 2:1. No attempt was made to determine the structure of the predominant isomer.

The accessibility of the double bond to attack by a bulky polyhaloalkane radical was a major factor in determining the reactivity of an olefin. For example, the reaction of $CF_2BrCFClBr$ with 1-octene[5] gave a 96% conversion of olefin, while with 2-octene, even after 79 hr, 62% of the initial olefin was recovered unreacted. For the purpose of simplification, 2-octene can be considered a terminal olefin with a methyl group substituted for one of the hydrogens on the 1 carbon. Apparently, the increased bulk of the CH_3 group compared to hydrogen is enough to inhibit attack by the $CF_2BrCFCl\cdot$ radical. However, if the methyl group is substituted for hydrogen on the 2 carbon no decrease in reactivity is noted. The reaction of 2-methylpentene-1 gave complete conversion to product after only 24 hr, for in this case there was no hindrance to attack by the $CF_2BrCFCl\cdot$ radical at the 1 carbon. However, the yield of 1:1 adduct dropped to 17%. The major product in the reaction was $CF_2BrCFClCH{=}C(CH_3)CH_2CH_2CH_3$, formed by the loss of a hydrogen atom from the incipient radical $CF_2BrCFClCH_2\dot{C}(CH_3)CH_2CH_2CH_3$. This olefin formation was not unexpected, as Lovelace[6] has described the formation of $CCl_3CH{=}C(CH_3)_2$ from the reaction of CCl_4 with isobutylene, an olefin which also has a methyl group attached to the 2 carbon. Tarrant and Tandon[7] have recently reported formation of the terminal olefins $CF_2ClCF_2CCl_2CH_2C(CH_3){=}CH_2$ and $CF_3CF_2CCl_2CH_2C(CH_3){=}CH_2$ from the peroxide-initiated reaction of isobutylene with $CF_2ClCF_2CCl_3$ and $CF_3CF_2CCl_3$, respectively. No explanation was given for this phenomenon.

The especially low yield of the 1:1 cyclohexene adduct (60%) is reasonable, as Huyser[8] has reported an exceptional amount of allylic attack by radicals on cyclohexene.

The styrene adducts were thermally unstable and in our hands could not be isolated in pure form by distillation or preparative vpc. This instability can be attributed to the presence of an extremely labile benzylic bromine or chlorine atom on the expected adducts, and to the increased acidity of hydrogen on carbon adjacent to a $CFClCF_2X$ group.

The additions to halo olefins constitute a special series of their own. Allyl chloride, for example, was

(6) A. M. Lovelace, M.S. Thesis, University of Florida, 1952.
(7) P. Tarrant and J. P. Tandon, *J. Org. Chem.*, **34**, 864 (1969).
(8) E. S. Huyser, *ibid.*, **26**, 3261 (1961).

found to be reactive under redox conditions, but apparently underwent attack on the reactive chlorine atom more rapidly than addition of $CF_2BrCFClBr$ could occur. This behavior was surprising, as Tarrant and Gillman[9] reported a 45% yield of 1:1 adduct from this reaction utilizing peroxide initiation. There are other indications, however, that allyl chloride is less reactive to polyhaloalkane additions than are hydrocarbon olefins. Tarrant and Tandon[7] report that neither $CF_3CF_2CCl_3$ nor $CF_2ClCF_2CCl_3$ reacted with allyl chloride (peroxide initiation), while both of these telogens were reactive with propylene. When we repeated the allyl chloride reaction with the more reactive CCl_3Br, under redox conditions, a good yield of 1:1 adduct was obtained.

Tarrant[10] has reported other examples of decreased reactivity of bromo and chloro olefins to radical attack when compared to ordinary hydrocarbons, and the data in Table I lend support to this contention. For example, even after 100 hr, $CF_2BrCFClBr$ gave only traces of adduct with 1-bromopentene and 4-bromo-1,1,2-trifluorooctene-1. By again selecting a more reactive polyhalide, CCl_3Br, the desired adducts were obtained. In these last additions the halogen atoms exerted quite interesting directive effects, and apparently, consideration of steric interactions is not the entire story. For example, a $CCl_3\cdot$ radical has little to choose between attack at the 1 or the 2 carbon of 1-bromopentene if only steric interactions are considered. However, reaction with CCl_3Br gave almost exclusively one product, $CHBr_2CH(CCl_3)CH_2CH_2CH_3$. A vpc of the reaction mixture indicated that the product was approximately 90% one compound, with possibly 10% of another isomer. The isolated product gave a pmr spectrum with two methine proton signals, the first, a doublet centered at δ 6.5, and the second, an unresolved multiplet centered around δ 3.2. If the addition adduct was the $CCl_3CHBrCHBrCH_2CH_2CH_3$ isomer (A), a signal corresponding to the methine proton on the 3 carbon would be expected in the δ 4.2 region. Furthermore, an attempted dehalogenation procedure gave only unreacted starting material. If the product was A, loss of Br_2 to give an olefin would be expected.

Chlorine is electron attracting and a trichloromethyl radical is therefore quite electrophilic. The 1 carbon of 1-bromopentene-1 is relatively electron-poor, and the $CCl_3\cdot$ radical is thus more inclined to attack at the 2 carbon than at the 1 position. A similar argument has been used by Stacey and Harris to explain radical addition of thiols[11] and HBr[12] to fluoro olefins, and by Davies and Rowley[13] to explain exo attack of $CCl_3\cdot$ radicals on 1,4,7,7-tetrachloronorborn-2-ene. An alternative explanation is the possibility of stabilization of the $\dot{C}HBrCH(CCl_3)CH_2CH_2CH_3$ radical by the bromine atom.

The addition of CCl_3Br to 2-chlorobutene-2 showed similar directive effects, but steric interactions cannot be ruled out in this case. As with the 1-bromopentene-1 reaction, the product appeared to contain a small amount (~10%) of a second isomeric product. Adduct XII is the same product that was obtained by Tarrant[10] from the peroxide-initiated reaction of CCl_3Br with 2-chlorobutene-2.

A final example of the decreased reactivity of halogenated olefins is apparent in the reactions of 4-bromo-1,1,2-trifluorooctene-1. Even bromotrichloromethane gave a poor olefin conversion, a result that could hardly be ascribed to steric hindrance. Most probably, the decreased reactivity of the electron-poor fluoro olefin to attack by the electrophilic $CCl_3\cdot$ radical is the important factor. The formation of what appeared to be the olefin $CCl_3CF_2CFBrCH{=}CH(CH_2)_3CH_3$ must be ascribed to the unusual acidity of hydrogen on the carbon adjacent to the CFBr group.

The adducts from 1-octene, 1-hexene, and 2-octene reacted with alcoholic KOH, giving ready dehydrohalogenation. The adduct from allyl chloride also underwent dehydrohalogenation, but we obtained a mixture of products, probably due to the reactivity of the allylic chlorine atoms on the expected product, $CCl_3CH{=}CHCH_2Cl$. Similarly, adduct XI gave a mixture of products, undoubtedly for the same reason.

Some preliminary attempts to carry out these redox-catalyzed additions with simple acetylenes gave no addition adducts.

Experimental Section

The elemental analyses and spectral data of all the compounds that were identified were consistent with the given structures. Boiling points are uncorrected. Elemental analyses were performed by personnel in this laboratory. Infrared spectra were obtained on a Perkin-Elmer Model 21 double-beam recording spectrophotometer. The pmr spectra (Table II) (neat, internal TMS) were recorded on a Varian A-60 instrument with tetramethylsilane as an internal standard. Vpc analyses were obtained with a F & M Model 720 gas chromatograph, and peak areas were used to calculate the yield of addition adducts.

Copper chloride was purified *via* the method of Keller and Wycoff.[14] Bromotrichloromethane and styrene were distilled before use. The $CF_2BrCFClBr$[9] and 1-bromopentene-1[15] were prepared by the reported methods. The 2-chlorobutene-2 was prepared by the dehydrohalogenation of 2,3-dichlorobutane, which was prepared by the dehydrohalogenation of 2,3-dichlorobutane with alcoholic KOH (bp 62–64°). Synthesis of $CF_2{=}CFCH_2CHBr(CH_2)_3CH_3$ is detailed below. All other materials were best commercial grade, used without further purification.

Addition of Perhaloalkanes to Olefins.—The experimental data for these addition reactions are compiled in Table I. A typical reaction procedure has been detailed previously.[5]

Initial reactions were catalyzed by freshly prepared copper(I) chloride. The copper(I) chloride is slowly oxidized by moist air to yield a green compound, $CuCl_2\cdot 3Cu(OH)_2$. However, it was found that this partially oxidized mixture of Cu(I) and Cu(II) was an effective catalyst for these additions, and the *mixture* was therefore used to initiate subsequent addition reactions.

Dehydrohalogenation of $CF_2BrCFClCH_2CHBr(CH_2)_3CH_3$ (II).—A mixture of KOH (7.2 g) in ethanol (100 ml) was dripped slowly into 44.2 g of II at 100°. After refluxing for 1 hr the reaction mixture was poured into water and the organic layer was separated, washed, and dried. Distillation gave 14.9 g of product, bp 56–58° (1 mm), identified as $CF_2BrCFClCH{=}CH(CH_2)_3CH_3$. *Anal.* Calcd for $C_8H_{11}F_3ClBr$: C, 34.4; H, 3.94. Found: C, 34.30; H, 3.87. The pmr and ir spectra were consistent with the above structure.

Dehydrohalogenation of $CF_2BrCFClBr$–2-Octene Adduct (IV).—A mixture of KOH (6.6 g) in ethanol (150 ml) was dripped slowly into 34.1 g of IV at 100°. After refluxing for 4 hr the reaction mixture was poured into water and the organic layer was separated, washed, and dried. Distillation gave 16.5 g of product, bp 52–55° (0.25 mm), identified as a mixture of $CH_3CH{=}C(CFClCF_2Br)CH_2(CH_2)_3CH_3$ and $CH_3C(CFClCF_2Br){=}$

(9) P. Tarrant and E. Gillman, *J. Amer. Chem. Soc.*, **76**, 5423 (1954).
(10) P. Tarrant, M. L. Brey, and B. E. Grey, *ibid.*, **80**, 1711 (1958).
(11) J. F. Harris and F. W. Stacey, *ibid.*, **83**, 840 (1961).
(12) F. W. Stacey and J. F. Harris, *J. Org. Chem.*, **27**, 4089 (1962).
(13) D. I. Davies and P. J. Rowley, *J. Chem. Soc. C*, 424 (1969).
(14) R. Keller and H. Wycoff, *Inorg. Syn.*, **2**, 1 (1946).
(15) G. B. Bachman, *J. Amer. Chem. Soc.*, **55**, 4279 (1933).

TABLE II

PROTON MAGNETIC RESONANCE DATA[a]

Adduct	Chemical shifts, δ (ppm) Alkyl H	Isolated $-CH_2-$	Methine H	Other	Rel intensities
I	0.8–2.2 (m)	2.4–3.1 (m)	4.4 (m)		9:2:1
II	1.2–2.6 (m)	2.6–3.4 (m)		$CBrCH_3$, 1.0 (3), J_{HH} = 6.5	7:2:3
II[b]	0.7–3.2 (m)			CH=C, 5.0–5.8 (m)	10:1
III	0.7–2.2 (m)		4.5 (m) 2.4–3.5 (m)		13:1:1
IV	1.2–3.3 (m)		4.1–5.1 (m)		9:1
VII	1.2 (3), J_{HH} = 7.0		4.4 (m)	All CH_2, 2.2–4.0 (m)	3:1:6
IX				All H, 3.0–4.7 (m)	
XI	0.8–2.5 (m)		6.5 (2), J_{HH} = 1.0 3.2 (m)		7:1:1
XII	2.8 (1) 1.9 (2), J_{HH} = 6.5		3.6 (4), J_{HH} = 6.5		3:3:1
XIV	0.7–3.4 (m)			CH=C, 6.4 (2 of 2), J_{HH} = 4.5, J_{HF} = 13.5 CH=C, 5.6 (4), J_{HH} = 5.5	9:1:1

[a] In parentheses is given the multiplicity of the peak; the coupling constants are in cps. [b] Olefinic product.

$CH(CH_2)_4CH_3$. *Anal.* Calcd for $C_{10}H_{15}BrClF_3$: C, 39.1; H, 4.89. Found: C, 39.2; H, 5.23. Both the ir and the pmr spectra (with a very broad signal, δ 5.5–6.3, for the two vinyl protons) were consistent with the above structure.

Dehydrohalogenation of $CCl_3CH_2CHBrCH_2Cl$ (X).—The attempted dehydohalogenation of X gave a mixture of products, none of which were identified. This complex product mixture was similar to that obtained from the attempted dehydrohalogenation of $CHClBrCH_2CHBr(CH_2)_5CH_3$ described previously.[5]

Dehydrohalogenation of $CHBr_2CH(CCl_3)CH_2CH_2CH_3$ (XII).—The attempted dehydrohalogenation of XII, similar to the reaction of X, gave a mixture of products, none of which was identified.

Dehalogenation of $CF_2BrCFClCH_2CHBr(CH_2)_3CH_3$ (II).—Compound II (113 g) in isopropyl alcohol (50 ml) was added slowly to a slurry of granulated zinc (22.7 g) in isopropyl alcohol (100 ml) at 100°. After refluxing for 4 hrs the reaction mixture was poured into water and the organic layer was separated, washed, and dried. Distillation gave 47.3 g of product, bp 68–69° (10 mm), identified as $CF_2=CFCH_2CHBr(CH_2)_3CH_3$. *Anal.* Calcd for $C_8H_{12}BrF_3$: C, 39.2; H, 4.9. Found: C, 38.8; H, 4.91. The pmr and ir spectra were consistent with the above structure.

Dehalogenation of $CCl_3CH_2CHBrCH_2Cl$ (X).—Surprisingly, the attempted dehalogenation of X gave no identifiable product. However, only 40% of the starting material was recovered after the reaction.

Dehalogenation of $CHBr_2CH(CCl_3)CH_2CH_2CH_3$ (XI).—The attempted dehalogenation of XI gave no reaction and the starting material was recovered unchanged.

Registry No.—Copper chloride, 7758-89-6; ethanolamine, 141-43-5; $CH_3CH=C(CFClCF_2Br)CH_2(CH_2)_3CH_3$, 30428-57-0; $CH_3C(CFClCF_3Br)=CH(CH_2)_4CH_3$, 30428-58-1; $CF_2=CFCH_2CHBr(CH_2)_3CH_3$, 30428-59-2; $CF_2BrCFClCH=CH(CH_2)_3CH_3$ 30428-56-9.

Mannich Reactions of 2-Fluoro-2,2-dinitroethanol[1]

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2-Fluoro-2,2-dinitroethanol undergoes the Mannich reaction with primary and secondary amines to give the corresponding 2-fluoro-2,2-dinitroethylamines. In one example (allylamine), forcing conditions were used to obtain the corresponding bis(2-fluoro-2,2-dinitroethyl)amine. Hydrazine gave *N,N'*-bis(2-fluoro-2,2-dinitroethyl)hydrazine. Ammonia gave 2-fluoro-2,2-dinitroethylamine which reacted with chloroformates to give *N*-fluorodinitroethylcarbamates.

β,β-Dinitro alcohols undergo the Mannich reaction with a variety of amines to give β,β-dinitroalkylamines.[2] Published examples of the Mannich reaction of 2-fluoro-2,2-dinitroethanol are limited to ammonia[3,4] and to $NH_2C(CH_2OAc)_3$.[5] Ammonia yielded 2-fluoro-2,2-dinitroethylamine[3] or bis(2-fluoro-2,2-dinitroethyl)amine,[3,4] depending on the reaction conditions, whereas $NH_2C(CH_2OAc)_3$ gave the 1:1 condensation product. The present study explores the scope of the Mannich reaction of 2-fluoro-2,2-dinitroethanol.

The reactions of a variety of primary and secondary amines with 2-fluoro-2,2-dinitroethanol are summarized in Table I. In aqueous solution at low temperatures, high yields of 1:1 condensation products were formed, and other functional groups, such as carboxy, acetal, and hydroxy groups, did not interfere. The condensa-

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(2) For a review see P. Noble, Jr., F. G. Borgardt, and W. L. Reed, *Chem. Rev.*, **64**, 32 (1964).

(3) H. G. Adolph and M. J. Kamlet, *J. Org. Chem.*, **34**, 45 (1969).

(4) R. G. Gafurov, S. I. Sviridov, F. Ya. Natsibullin, and L. T. Eremenko, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 383 (1970).

(5) D. A. Nesterenko, O. M. Savchenko, and L. T. Eremenko, *ibid.*, 1100 (1970).

TABLE I

REACTION OF 2-FLUORO-2,2-DINITROETHANOL WITH AMINES

Starting material	Product	Yield, %
CH_3NH_2	$CH_3NHCH_2CF(NO_2)_2$	72
$(CH_3)_2NH$	$(CH_3)_2NCH_2CF(NO_2)_2$	78
$HO_2CCH_2NH_2$	$HO_2CCH_2NHCH_2CF(NO_2)_2$	64
$C_2H_5O_2CCH_2NH_2$	$C_2H_5O_2CCH_2NHCH_2CF(NO_2)_2$	97
$(C_2H_5O)_2CHCH_2NH_2$	$(C_2H_5O)_2CHCH_2NHCH_2CF(NO_2)_2$	94
$HO_2CCH_2CH(CO_2H)NH_2$	$HO_2CCH_2CH(CO_2H)NHCH_2CF(NO_2)_2$	78
$HOCH_2CH_2NH_2$	$HOCH_2CH_2NHCH_2CF(NO_2)_2$	74
$CH_2{=}CHCH_2NH_2$	$CH_2{=}CHCH_2NHCH_2CF(NO_2)_2$	75–93
$CH_2{=}CHCH_2NHCH_2CF(NO_2)_2$	$CH_2{=}CHCH_2N[CH_2CF(NO_2)_2]_2$	49

tion also takes place in organic solvents; allylamine gave a 93% yield of *N*-(2-fluoro-2,2-dinitroethyl)allylamine when methylene chloride was used as the solvent.

More forcing conditions yielded the 2:1 condensation product of allylamine. Thus, when a neat mixture of 2-fluoro-2,2-dinitroethanol and the 1:1 condensation product, *N*-(2-fluoro-2,2-dinitroethyl)allylamine, was heated for 6 hr at 90–95°, a 49% yield of *N*,*N*-bis(2-fluoro-2,2-dinitroethyl)allylamine was isolated.

An attempt was also made to prepare a 2:1 product of glycine ethyl ester under forcing conditions (115–120°). The product, however, was identified as *N*,*N'*-bis(2-fluoro-2,2-dinitroethyl)-*N*,*N'*-bis(carbethoxymethyl)methylenediamine. Formaldehyde, liberated by the decomposition of 2-fluoro-2,2-dinitroethanol, apparently condenses with the active methylene group of the 1:1 adduct as follows.

$$C_2H_5O_2CCH_2NHCH_2CF(NO_2)_2 + CH_2O \longrightarrow \underset{\displaystyle CH_2OH}{C_2H_5O_2C\underset{|}{C}HNHCH_2CF(NO_2)_2} \longrightarrow \begin{array}{c} C_2H_5O_2CCHNHCH_2CF(NO_2)_2 \\ | \\ CH_2 \\ | \\ C_2H_5O_2CCHNHCH_2CF(NO_2)_2 \end{array}$$

The Mannich reaction of 2,2-dinitropropanol with hydrazine has been reported to give *N*,*N'*-bis(2,2-dinitropropyl)hydrazine.[6] The corresponding reaction was found to take place with 2-fluoro-2,2-dinitroethanol and hydrazine, to give *N*,*N'*-bis(2-fluoro-2,2-dinitroethyl)hydrazine.

$$FC(NO_2)_2CH_2OH + N_2H_4 \longrightarrow FC(NO_2)_2CH_2NHNHCH_2CF(NO_2)_2$$

We have previously reported the fluorination of methyl (2-fluoro-2,2-dinitroethyl)carbamate to give methyl *N*-fluoro-*N*-(2-fluoro-2,2-dinitroethyl)carbamate.[7] This starting material was synthesized by an *in situ* acylation of 2-fluoro-2,2-dinitroethylamine. The addition of methyl chloroformate to the crude solution formed by adding ammonia to aqueous 2-fluoro-2,2-dinitroethanol gave a 20% yield of methyl (2-fluoro-2,2-dinitroethyl)carbamate. In this way, the ethyl and isopropyl esters were also prepared. The preparation of 2-fluoro-2,2-dinitroethylamine derivatives in this way avoids the hazardous[3] isolation of 2-fluoro-2,2-dinitroethylamine.

$$FC(NO_2)_2CH_2OH + NH_3 \longrightarrow FC(NO_2)_2CH_2NH_2 \xrightarrow{ROCOCl} FC(NO_2)_2CH_2NHCO_2R$$

(6) M. B. Frankel and K. Klager, *J. Amer. Chem. Soc.*, **79**, 2953 (1957).
(7) V. Grakauskas and K. Baum, *J. Org. Chem.*, **34**, 2840 (1969).

Isopropyl (2-fluoro-2,2-dinitroethyl)carbamate was hydrolyzed in concentrated sulfuric acid to give 2-fluoro-2,2-dinitroethylammonium bisulfate, which was identified in solution by its nmr spectra (see Experimental Section). Dilution of the sulfuric acid solution with ether gave a white solid which was too unstable for analysis.

$$FC(NO_2)_2CH_2NHCO_2CH(CH_3)_2 \xrightarrow{H_2SO_4} FC(NO_2)_2CH_2{}^+NH_3HSO_4{}^-$$

Experimental Section

(2-Fluoro-2,2-dinitroethyl)methylamine.—To a stirred solution of 6.75 g (0.1 mol) of methylamine hydrochloride and 15.4 g (0.1 mol) of 2-fluoro-2,2-dinitroethanol in 100 ml of water at 25° was added dropwise (5 min) a solution of 4.0 g (0.1 mol) of sodium hydroxide in 15 ml of water. After 10 min the reaction mixture was extracted with 50 ml of carbon tetrachloride and the extract was distilled to give 12.0 g (72% yield) of (2-fluoro-2,2-dinitroethyl)methylamine, a pale yellow liquid: bp 32° (0.1 mm); proton nmr (CCl_4) δ 1.29 (s, NH), 2.55 (s, CH_3), and 3.83 (d, J_{HF} = 18.7 Hz, CH_2CF); fluorine nmr: ϕ 109.8 (s, br).

Anal. Calcd for $C_3H_6N_3FO_4$: C, 21.6; H, 3.6; N, 25.2; F, 11.4. Found: C, 21.9; H, 3.7; N, 24.8; F, 11.6.

(2-Fluoro-2,2-dinitroethyl)methylamine hydrochloride, mp 120–121°, was obtained in 85% yield by reacting the amine with ethanolic hydrogen chloride. The salt precipitated upon addition of diethyl ether.

Anal. Calcd for $C_3H_7N_3FClO_4$: C, 17.7; H, 3.5; N, 20.6; F, 9.3. Found: C, 17.6; H, 3.5; N, 20.6; F, 9.4.

(2-Fluoro-2,2-dinitroethyl)dimethylamine.—The title compound, a pale yellow liquid, bp 23–24° (0.1 mm), was obtained in 78% yield following the above procedure.

Anal. Calcd for $C_4H_8N_3FO_4$: C, 26.5; H, 4.4; N, 23.2; F, 10.4. Found: C, 26.5; H, 4.7; N, 22.8; F, 10.0.

(2-Fluoro-2,2-dinitroethyl)dimethylamine hydrochloride, mp 110–111°, was obtained, in 92% yield from the amine following the above-described procedure.

Anal. Calcd for $C_4H_9N_3FClO_4$: C, 22.1; H, 4.2; N, 19.3; F, 8.7. Found: C, 22.0; H, 4.4; N, 18.7; F, 8.9.

(2-Fluoro-2,2-dinitroethyl)aminoacetic Acid.—A solution of 4.0 g (0.1 mol) of sodium hydroxide in 15 ml of water was added dropwise (5 min) at 0–3° to a stirred solution of 15.4 g (0.1 mol) of 2-fluoro-2,2-dinitroethanol and 7.5 g (0.1 mol) of glycine in 50 ml of water. The solution turned turbid and deposited a white solid. After 30 min the reaction mixture was acidified with 20% hydrochloric acid. The solid was filtered, washed with water, and air-dried to give 13.5 g (64% yield), mp 75–76°. Recrystallization from methylene chloride gave a white, crystalline solid, mp 76°.

The infrared spectrum showed the following major peaks (μ): 2.90, 3.70, 3.93, 5.70, 5.80, 6.30, 7.62, 8.12, 11.72, and 12.50. Proton nmr (acetone-d_6–$CDCl_3$) showed δ 6.31 (3, NH and COOH), 3.97 (d, J_{HF} = 18.0 Hz, CH_2CF), and 3.57 (s, CH_2-COO); fluorine nmr ϕ 109.7 (t, J_{HF} = 18.1).

Anal. Calcd for $C_4H_6N_3FO_6$: C, 22.8; H, 2.8; N, 19.9; F, 9.0. Found: C, 22.6; H, 2.6; N, 19.7; F, 9.0.

Ethyl 2-Fluoro-2,2-dinitroethylaminoacetate.—A solution of 1.6 g (0.04 mol) of sodium hydroxide in 15 ml of water was added dropwise at 0–5° to a stirred solution of 5.6 g (0.04 mol) of glycine ethyl ester hydrochloride and 6.24 g (0.04 mol) of 2-

fluoro-2,2-dinitroethanol in 75 ml of water. The resulting mixture was stirred for 20 min and then was extracted with 35 ml of methylene chloride. The methylene chloride extract was distilled to give 9.3 g (97% yield) of ethyl 2-fluoro-2,2-dinitroethylaminoacetate, a colorless liquid: bp 95° (0.1 mm); proton nmr (CCl_4) δ 4.02 (d, d, J_{HF} = 18, J_{H-NH} = 7.5 Hz, $-CH_2CF-$), 4.17 (q, J = 7.5 Hz, $-COOCH_2-$), 3.47 (d, J = 6.8 Hz, $-CH_2-CO-$), 2.24 (quintet, J = 6.8 Hz, NH), and 1.27 (t, J = 7.5 Hz, CH_3). After D_2O exchange the δ 4.02 quartet was reduced to a doublet, the $-CH_2O-$ doublet was reduced to a singlet, and the NH- quintet was eliminated. Fluorine nmr showed ϕ 110.2 (t, J_{HF} = 18.3 Hz).

Anal. Calcd for $C_6H_{10}N_2FO_6$: C, 30.1; H, 4.2; N, 17.6; F, 7.9. Found: C, 29.8; H, 3.9; N, 17.5; F, 7.9.

(2-Fluoro-2,2-dinitroethyl)aminoacetaldehyde Diethyl Acetal.—To a solution of 3.1 g (0.02 mol) of 2-fluoro-2,2-dinitroethanol in 25 ml of ice water was added with stirring 2.2 g (0.017 mol) of aminoacetaldehyde diethyl acetal. The reaction mixture was stirred for 1 hr at 10–15° and then extracted with 25 ml of methylene chloride. The extract was distilled to give 4.2 g (94% yield) of a pale yellow liquid: bp 94–95° (0.1 mm); proton nmr (undiluted sample) δ 1.21 (t, J = 7.5 Hz, CH_3), 3.6 (m, OCH_2), 1.92 (s, NH), 2.80 (d, NCH_2), 4.01 (d, J_{HF} = 17.8 Hz, CH_2CF), and 4.50 (t, OCHO); fluorine nmr ϕ 109.5 (t, J_{HF} = 18.0 Hz).

Anal. Calcd for $C_8H_{16}N_2FO_6$: C, 35.7; H, 5.9; N, 15.6; F, 7.1. Found: C, 35.1; H, 5.7; N, 15.4; F, 6.8.

(2-Fluoro-2,2-dinitroethyl)aminosuccinic Acid.—To a stirred suspension of 15.4 g (0.1 mol) of 2-fluoro-2,2-dinitroethanol and 13.3 g (0.1 mol) of *dl*-aspartic acid in 200 ml of water was added with stirring at 15° a solution of 8.0 g (0.2 mol) of sodium hydroxide in 15 ml of water. The reaction mixture was stirred for 30 min and then was acidified with 20 g of concentrated hydrochloric acid. A white amorphous solid was collected, washed with water, and air-dried to give 21 g (78% yield): mp 140–142°; proton nmr (acetone-d_6) δ 8.30 (s, NH and COOH), 4.31 (double AB quartet, J_{AB} = 15.1, J_{AF} = J_{BF} = 15.0 Hz, CH_2CF), 3.83 (t, J_{HH} = 6.0 Hz, CH), and 2.82 (d, J_{HH} = 6.0 Hz, CH_2COO); fluorine nmr ϕ 109.8 (m).

Anal. Calcd for $C_6H_8N_2FO_8$: C, 27.0; H, 3.0; N, 15.7; F, 7.1. Found: C, 26.8; H, 3.0; N, 15.1; F, 7.0.

2-(2-Fluoro-2,2-dinitroethylamino)ethanol.—2-Aminoethanol, 6.1 g (0.1 mol), was added dropwise at 0–3° to a stirred solution of 15.4 g (0.1 mol) of 2-fluoro-2,2-dinitroethanol in 75 ml of water. The reaction mixture was stirred at 22° for 45 min and then was extracted with two 35-ml portions of methylene chloride. The combined extracts were concentrated and dried at 80° (0.1 mm) to give 14.5 g (74% yield) of pale yellow liquid. An analytical sample was distilled in a molecular still at 75–80° (0.005 mm).

Anal. Calcd for $C_4H_8N_2FO_5$: C, 24.4; H, 4.1; N, 21.3; F, 9.6. Found: C, 24.1; H, 4.0; N, 21.3; F, 9.5.

The differential thermal analysis exhibited a sharp exotherm at 128°, with onset of exotherm at *ca.* 93°.

***N*-(2-Fluoro-2,2-dinitroethyl)allylamine.**—2-Fluoro-2,2-dinitroethanol, 6.24 g (0.04 mol), was added dropwise (10 min) at 0–10° to a stirred solution of 2.3 g (0.04 mol) of allylamine in 40 ml of water. A water-insoluble liquid separated instantaneously. After 10 min the reaction mixture was extracted with 30 ml of methylene chloride and the extract was distilled to give 5.8 g (75% yield) of *N*-(2-fluoro-2,2-dinitroethyl)allylamine, a pale yellow liquid: bp 64–65° (0.05 mm); proton nmr ($CDCl_3$) δ 5.84 (m, $-CH=$), 5.15 (complex d, $=CH_2$), 3.92 (d, J_{HF} = 19.7 Hz, CH_2CF), 3.33 (d, allylic CH_2), and 1.77 (s, NH); fluorine nmr ϕ 109.3 (t, J_{HF} = 20.4 Hz).

Anal. Calcd for $C_5H_8N_2FO_4$: C, 30.1; H, 4.1; N, 21.8; F, 9.8. Found: C, 29.9; H, 3.9; N, 20.9; F, 9.5.

The compound was also prepared in nonaqueous solution as follows. A solution of 5.6 g (0.1 mol) of allylamine in 35 ml of methylene chloride was added dropwise (10 min) at 12–15° to a stirred solution of 15.4 g (0.1 mol) of 2-fluoro-2,2-dinitroethanol in 85 ml of methylene chloride. The reaction mixture was dried with anhydrous sodium sulfate for 2 hr and filtered, and the filtrate was distilled to give 17.9 g (93% yield) of *N*-(2-fluoro-2,2-dinitroethyl)allylamine.

***N*,*N*-Bis(2-fluoro-2,2-dinitroethyl)allylamine.**—A mixture of 2.5 g (0.013 mol) of *N*-(2-fluoro-2,2-dinitroethyl)allylamine (above) and 5.0 g of 2-fluoro-2,2-dinitroethanol was heated at 90–95° for 6 hr. Excess alcohol was removed by distillation and the remaining viscous liquid was distilled in a molecular still at 90–95° (25–50 μ) to give 2.1 g (49% yield) of *N*,*N*-bis(2-fluoro-2,2-dinitroethyl)allylamine, a pale yellow liquid: proton nmr ($CDCl_3$) δ 5.40 (m, $CH=CH_2$), 4.11 (d, J_{HF} = 18.0 Hz, CH_2CF), and 3.37 (d, J = 5.5 Hz, allylic CH_2); fluorine nmr ϕ 108.2 (t).

Anal. Calcd for $C_7H_9N_5F_2O_8$: C, 25.5; H, 2.7; N, 21.3; F, 11.6. Found: C, 26.0; H, 2.1; N, 21.2; F, 11.6.

***N*,*N*′-Bis(2-fluoro-2,2-dinitroethyl)-*N*,*N*′-bis(carbethoxymethyl)methylenediamine.**—A mixture of 7.2 g (0.03 mol) of ethyl 2-fluoro-2,2-dinitroethylaminoacetate and 10.0 g (0.065 mol) of 2-fluoro-2,2-dinitroethanol was heated at 115–120° for 4.5 hr. The solution was cooled to 80° and excess of the alcohol was removed at reduced pressure. The residue crystallized on standing at 25° for several days, and was recrystallized from methanol to give 5.3 g of white solid, mp 87°. The infrared spectrum showed no absorption in the OH or NH region, a strong CO at 5.78 μ, and NO_2 at 6.26 μ. Proton nmr ($CDCl_3$) showed δ 1.32 (t, J_{HH} = 7.1 Hz, CH_3), 3.44 (s, CH_2COO), 3.90 (s, NCH_2N), 4.10 (d, J_{HF} = 19.0 Hz, CH_2CF), and 4.20 (q, J_{HH} = 7.2 Hz, OCH_2); area ratio 3:2:1:2:2; fluorine nmr ϕ 110.0 (t, J_{HF} = 19 Hz.).

Anal. Calcd for $C_{13}H_{20}N_6F_2O_{12}$: C, 31.8; H, 4.1; N, 17.2; F, 7.8. Found: C, 32.1; H, 4.1; N, 17.3; F, 7.8.

***N*,*N*′-Bis(2-fluoro-2,2-dinitroethyl)hydrazine.**—A solution of 1.25 g (0.025 mol) of hydrazine hydrate and 7.7 g (0.05 mol) of 2-fluoro-2,2-dinitroethanol in 220 ml of water was allowed to stand at 0° for 4 days. A pale yellow solid was washed with water, dried, and crystallized from chloroform to give 1.5 g (20% yield) of *N*,*N*′-bis(2-fluoro-2,2-dinitroethyl)hydrazine, mp 61–62°. The differential thermal analysis exhibited an endotherm at 61° and the exotherm at 141° (onset at *ca.* 116°). Proton nmr (acetone-d_6) showed δ 4.98 (m, 2 NH) and 4.19 (d, d, J_{HF} = 17.5, J_{HNH} = 5.2 Hz, CH_2CF); fluorine nmr ϕ 109.0 (t). When the proton spectrum was recorded at −50°, the NH signal appeared as a resolved triplet and the CH_2 signal retained its profile. The proton nmr spectrum in acetone d_6–methylene chloride mixture exhibited a broadened doublet at δ 4.10 (J = 13.0 Hz), and a broad singlet at δ 4.21. The latter signal disappeared in D_2O exchange.

Anal. Calcd for $C_4H_6N_6F_2O_8$: C, 15.8; H, 2.0; N, 27.6; F, 12.5. Found: C, 16.1; H, 1.8; N, 26.8; F, 12.4.

Ethyl (2-Fluoro-2,2-dinitroethyl)carbamate.—To a stirred solution of 15.4 g (0.1 mol) of 2-fluoro-2,2-dinitroethanol in 70 ml of water at 25° was added dropwise (5 min) 6.0 g of 28% ammonium hydroxide (0.1 mol of NH_3). Some yellow oil deposited. After 30 min, 5.4 g (0.05 mol) of ethyl chloroformate was added. The mixture was stirred for 10 min and a solution of 4.0 g (0.1 mol) of sodium hydroxide in 25 ml of water and another 5.4 g of ethyl chloroformate were added. After 25 min the reaction mixture was extracted with 50 ml of methylene chloride and the extract was distilled to give 15.0 g of 2-fluoro-2,2-dinitroethyl ethyl carbonate, bp 54° (0.1 mm), $n^{25}D$ 1.4212 [lit.[8] bp 53–54° (0.1 mm)]. Further distillation yielded 4.0 g of ethyl (2-fluoro-2,2-dinitroethyl)carbamate, a colorless liquid: bp 85° (0.1 mm); proton nmr (CCl_4) δ 1.23 (t, CH_3 of C_2H_5), 4.10 (q, OCH_2), 4.46 (q, J_{HF} = 15.1 Hz, CH_2CF), and 5.93 (t, NH); fluorine nmr ϕ109.5 (t, J_{HF} = 14.9 Hz).

Anal. Calcd for $C_5H_8N_3FO_6$: C, 26.7; H, 3.6; N, 18.7; F, 8.4. Found: C, 26.6; H, 3.9; N, 17.8; F, 9.0.

Methyl (2-Fluoro-2,2-dinitroethyl)carbamate.—The title compound, a white solid, mp 40–41°, was obtained in 20% yield by treating an ammoniacal solution of 2-fluoro-2,2-dinitroethanol with methyl chloroformate as described above.

Anal. Calcd for $C_4H_6N_3FO_6$: C, 22.8; H, 2.9; N, 19.9; F, 9.0. Found: C, 22.8; H, 3.2; N, 20.1; F, 9.1.

Isopropyl (2-Fluoro-2,2-dinitroethyl)carbamate.—The title compound, mp 47–48°, was obtained in 30% yield (together with larger quantities of 2-fluoro-2,2-dinitroethyl isopropyl carbonate) in the reaction of 2-fluoro-2,2-dinitroethanol with aqueous ammonia and isopropyl chloroformate following the above procedure.

Anal. Calcd for $C_6H_{10}N_3FO_6$: C, 30.1; H, 4.2; N, 17.6; F, 7.9. Found: C, 29.9; H, 3.9; N, 16.8; F, 7.9.

2-Fluoro-2,2-dinitroethylammonium Bisulfate.—Isopropyl (2-fluoro-2,2-dinitroethyl)carbamate (0.2 g) was added with stirring to 1.0 ml of concentrated sulfuric acid at 0–5°. Carbon dioxide was evolved. After 15 min the reaction mixture was added to 50 ml of diethyl ether and the solution was kept at −15° for 18 hr. A white crystalline solid was filtered and washed with four 10-ml portions of diethyl ether. The solid fumed off soon after washing.

(8) V. Grakauskas, *J. Org. Chem.*, **35**, 3030 (1970).

The above reaction was repeated and the sulfuric acid solution of the salt was examined by nmr. Proton nmr: δ 6.60 (s, broad, A = 153, NH_3^+) and 4.00 (d, q, J_{HF} = 11.0, J_{NH-H} = 6.0 Hz, A = 102, CH_2); fluorine nmr ϕ 101.0 (t, J_{HF} = 10.4 Hz).

Registry No.—2-Fluoro-2,2-dinitroethanol, 17003-75-7; (2-fluoro-2,2-dinitroethyl)methylamine, 30409-33-7, 30409-34-8 (HCl); (2-fluoro-2,2-dinitroethyl)-dimethylamine, 30409-35-9, 30409-36-0 (HCl); (2-fluoro-2,2-dinitroethyl)aminoacetic acid, 30409-37-1; ethyl 2-fluoro-2,2-dinitroethylaminoacetate, 30409-38-2; (2-fluoro-2,2-dinitroethyl)aminoacetaldehyde diethyl acetal, 30409-39-3; (2-fluoro-2,2-dinitroethyl)-aminosuccinic acid, 30476-99-4; 2-(2-fluoro-2,2-dinitroethylamino)ethanol, 30409-40-6; *N*-(2-fluoro-2,2-dinitroethyl)allylamine, 30409-41-7; *N*,*N*-bis(2-fluoro-2,2-dinitroethyl)allylamine, 30409-42-8; *N*,*N*′-bis(2-fluoro-2,2-dinitroethyl)-*N*,*N*′-bis(carbethoxymethyl)-methylenediamine, 29925-43-7; *N*,*N*′-bis(2-fluoro-2,2-dinitroethyl)hydrazine, 30409-44-0; ethyl (2-fluoro-2,2-dinitroethyl)carbamate, 30409-45-1; methyl (2-fluoro-2,2-dinitroethyl)carbamate, 30409-46-2; isopropyl (2-fluoro-2,2-dinitroethyl)carbamate, 30409-47-3; 2-fluoro-2,2-dinitroethylammonium bisulfate, 30409-48-4.

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The Reaction of Ethyl β-Dimethylaminocrotonate and Benzoyl Isothiocyanate

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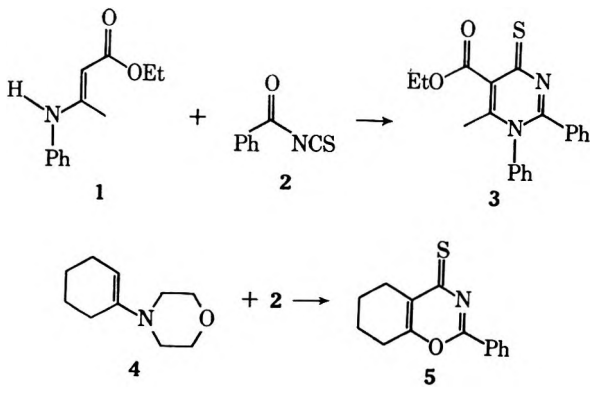
The reaction of ethyl β-dimethylaminocrotonate and benzoyl isothiocyanate in chloroform to yield ethyl 2-benzamido-5-benzoyl-4-dimethylamino-6-thioxonicotinate is described and the crystal structure analysis given. The intermediates leading to the product and the pathway of formation are discussed.

Part A

Enamines have been used to synthesize various carbocyclic and heterocyclic systems.[1] Our interest has been in the synthesis of pyrimidines[2] and tetrahydroquinazolines[3] by the interaction of an enamine with benzoyl isothiocyanate.

This paper is concerned with the novel product formed from the reaction of an α,β-unsaturated amino ester, ethyl dimethylaminocrotonate, with benzoyl isothiocyanate. We earlier observed that, when β-anilinocrotonate (**1**) and benzoyl isothiocyanate (**2**) were allowed to react, the thiopyrimidine **3** was obtained, whereas, when an enamine **4** derived from a secondary amine was allowed to react with **2**, the oxazinethione **5** resulted. It was, therefore, expected that the condensation of β-dimethylamino crotonate (**6**) with **2** would give rise to the analogous product **7** from which various N-substituted pyrimidines could be prepared (see Scheme I).



When **6** was allowed to react with **2** in chloroform with warming on a steam bath, a yellow crystalline compound **11**, mp 233–235°, was obtained. Elemental analysis indicated that 2 equiv of **2** and 1 equiv of **6** had combined with the loss of hydrogen sulfide. The simplicity of the pmr (ester, dimethylamino, aromatic, and two exchangable protons) and the carbonyl region of the ir was in agreement with the assigned structure.

The reaction pathway proceeds most likely through the addition of 2 equiv of benzoyl isothiocyanate to the α carbon of the crotonate with subsequent internal benzoyl displacement with loss of isothiocyanate or by the addition of 1 equiv of **2** to the α carbon with direct nucleophilic addition of benzoyl to carbon 4. Cyclization with loss of hydrogen sulfide gives **8a** which adds thiocyanate with ring opening and enamine reclosure to give **11** (see Scheme I). An alternate pathway that envisions the addition of benzoyl isocyanate to both the 2 and 4 positions of the aminocrotonate does not occur as has been observed in similar reactions.[4,5]

Methylation of **11** with 1 and 2 equiv of methyl iodide gave the mono- and dialkylated products **14** and **12**. Ethanolysis of **12** with sodium ethoxide yielded the debenzoylated product **13**, whereas treatment of **12** with sodium hydroxide under vigorous conditions yielded, after adjustment of the pH to 7, compound **15** devoid of the carbethoxy and benzoyl groups. Under similar treatment **14** gave **16** and **17**. Inspection of the pmr indicates that the NH of **15** which appears at δ 4.68 is shifted downfield to 7.3 when bonded to an α-carboethoxy group as in **13**. A similar downfield shift is found in **16** and **17** and is analogous to the

(1) M. E. Kuehne in "Enamines Synthesis, Structure, and Reactions," A. G. Cook, Ed., Marcel Dekker, New York, N. Y., 1969, Chapter 8.

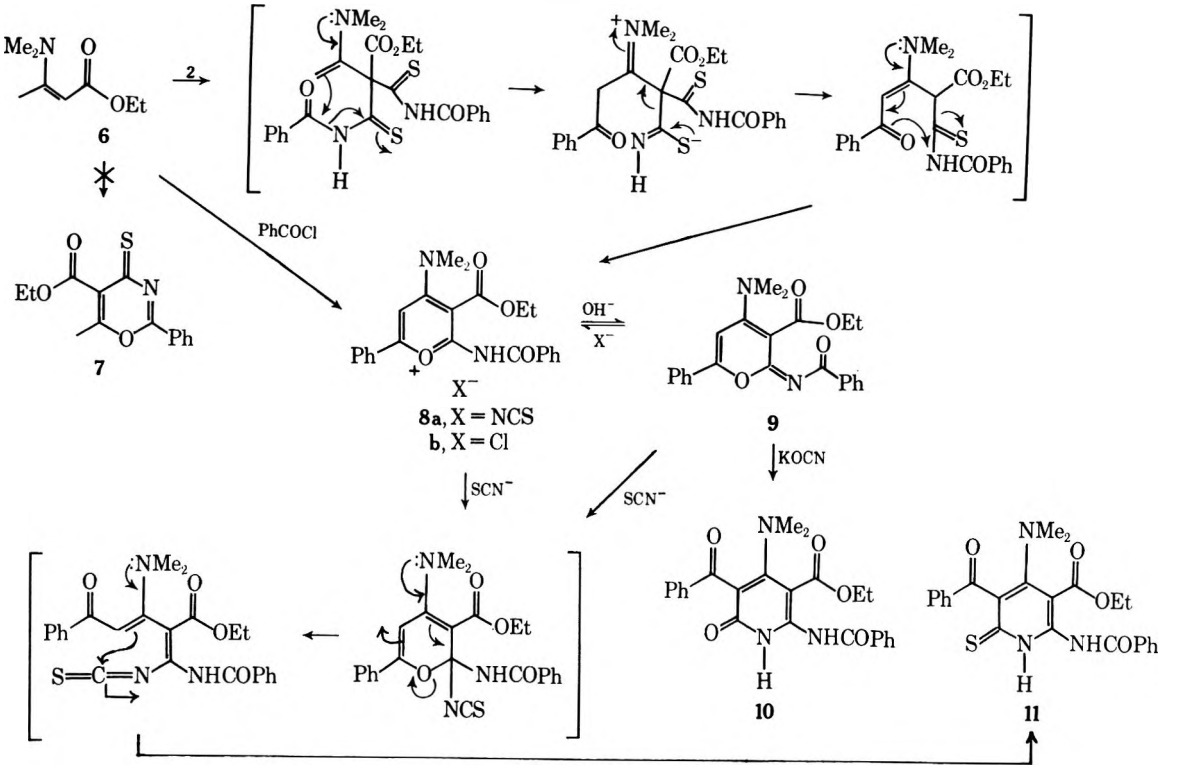
(2) G. deStevens, B. Smolinsky, and L. Dorfman, *J. Org. Chem.*, **29**, 1115 (1964).

(3) R. W. J. Carney, J. Wojthunski, and G. deStevens, *ibid.*, **29**, 2887 (1964).

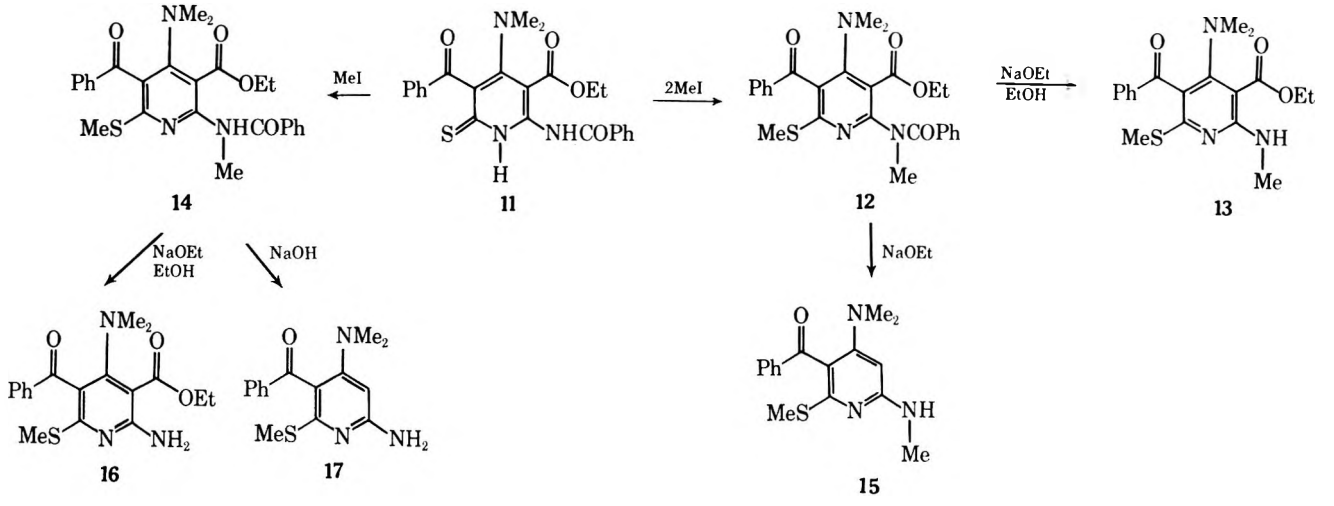
(4) W. M. Lauer and N. H. Cromwell, *J. Amer. Chem. Soc.*, **64**, 612 (1942).

(5) G. A. Berchtold, *J. Org. Chem.*, **26**, 3043 (1961); S. Hunig, K. Hubner and E. Benzing, *Ber.*, **95**, 926 (1962).

SCHEME I



SCHEME II



shift in ethyl 2-aminonicotinate (NH, δ 6.7) and 2-aminopyridine (NH, δ 4.75).[6] See Scheme II.

In an attempt to isolate an intermediate whose formation would be relevant to the synthesis of **11**, compounds **2** and **6** in a 4:1 molar ratio were allowed to react at 5° in acetonitrile. The resulting yellow solid **8a** melted at 160–165°, whereupon it resolidified and again melted at 210–215°. The ir and elemental analysis agreed with this structure; however, on dissolving **8a** in chloroform for a pmr spectrum, it was readily converted to **11**. It seems likely that on heating **8a** above 165° or dissolution in chloroform a rearrangement spontaneously occurs leading to **11**.

At various times during the initial synthesis of **11**, a white crystalline hydrochloride **8b**, mp 194–196°, was obtained in addition to **11**. Although the salt **8b** was not soluble in most organic solvents, it could be recrystallized from acetonitrile. It was soluble in water and on treatment with dilute sodium hydroxide, a yellow color appeared which could be extracted with ether to yield **9**. Ir analysis of the original supply of benzoyl isothiocyanate indicated the presence of small amounts of benzoyl chloride, hence the chloride source. When equal molar amounts of **2**, **6**, and benzoyl chloride in benzene were combined a good yield of the hydrochloride **8b** was obtained. The addition of **9** to 6 *N* hydrochloric acid gave a white precipitate corresponding to **8b**.

A similar interconversion of **8a** and **9** was also observed. Reaction of **9** with potassium thiocyanate and *p*-touenesulfonic acid gave the thiocyanate salt **8a** while treatment of **8a** with sodium hydroxide gave **9**. Both **8a** and **9** were readily converted to **11** on the addition of thiocyanate. Potassium cyanate gave on reaction with **9** the hydroxyl derivative **10**. The addition

(6) Varian Associates NMR Spectra Catalog, 1962, No. 431.

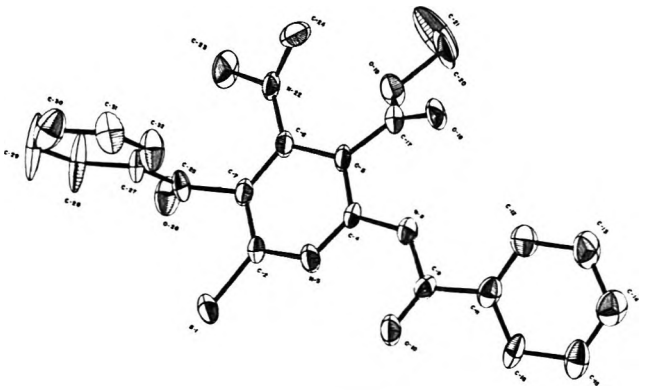


Figure 1.—Thermal ellipsoid plot of ethyl 2-benzamido-5-benzoyl-4-dimethylamino-6-thioxonicotinate.

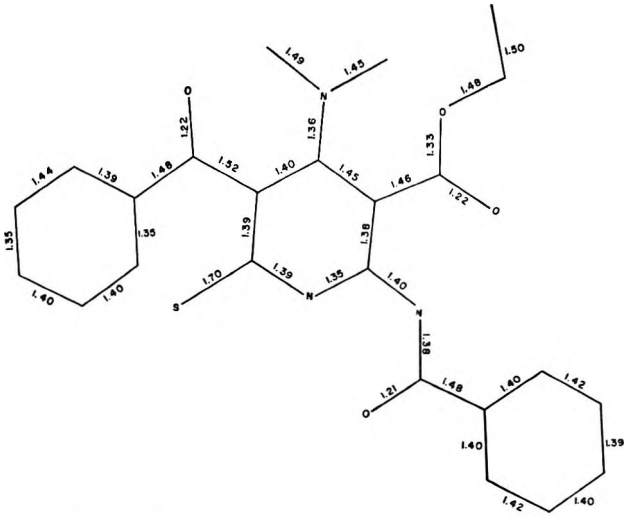


Figure 2.—Bond lengths are measured in ångströms.

of isothiocyanate ion (NCS^-) to the oxonium ring with subsequent ring opening and reclosure to yield **11** is analogous to numerous syntheses based on the addition of nucleophiles to triarylpyrylium salts.[7]

Finally, unequivocal proof that the addition and cyclization sequence had produced ethyl 2-benzamido-5-benzoyl-4-dimethylamino-6-thioxonicotinate (**11**) was obtained through single-crystal X-ray structure analysis. Suitable crystals were obtained in the form of elongated yellow platelets. The compound crystallizes in the monoclinic system with unit cell dimensions of $a = 14.67$, $b = 10.96$, $c = 13.82$ Å, $\beta = 95°\ 25'$, $Z = 4$. The space group was uniquely determined as $P2_1/a$ by the observed systematic extinctions of $0k0$ absent for k odd and $h0l$ absent for h odd. The structure was solved in a straightforward manner from visually estimated film data by applying the symbolic addition technique.[8] Using three origin-determining reflections together with one symbolic phase, it was possible to fix the signs of 290 reflections. The resulting E map showed the location of 22 of the 32 nonhydrogen atoms. The remaining atoms were located from a second map phased on the positions of the first 22 atoms. The resulting structure was then refined by full matrix least squares using anisotropic temperature factors to a

(7) K. Dimroth and K. H. Wolf in "Newer Methods of Preparative Organic Chemistry," Vol. 3, W. Foerst, Ed., Academic Press, New York, N. Y., 1964, p 357.

(8) J. Karle and I. L. Karle, *Acta Crystallogr.*, **21**, 849 (1966).

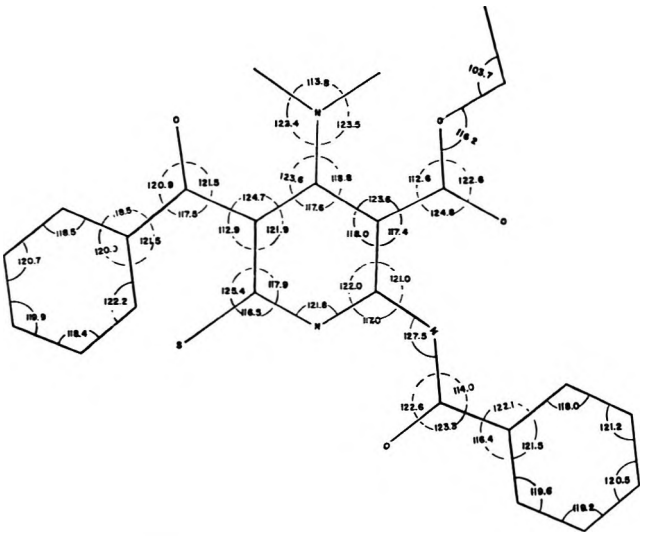


Figure 3.—Bond angles are measured in degrees.

conventional R value of 12.9% for 2067 observed reflections. A view of the molecule as it exits in the crystal is shown in Figure 1. Bond lengths and angles are summarized in Figures 2 and 3. The average estimated standard deviations of the bond lengths are of the order of 0.015 Å, those of the angles 1.0°. All values agree within 3 esd's with those commonly accepted.[9]

Part B

Experimental Section

Compound characterizations were performed with the following instrumentation: melting point, Thomas-Hoover melting point apparatus (uncorrected); infrared spectra, Perkin-Elmer Model 137 spectrophotometer; ultraviolet spectra, Cary Model 14 spectrophotometer (in ethanol); pmr spectra, Varian Associates A-60 spectrometer (in deuteriochloroform, except when noted, containing tetramethylsilane as internal standard, 50 ppm); mass spectra, Hitachi Perkin-Elmer RMU-6D, by Morgans-Schaffer Corp., Montreal, Canada, and AEI MS-902.

2-Benzamido-3-carbethoxy-4-dimethylamino-6-phenylpyrylium Isothiocyanate (8a).—A solution of 3.0 g (0.007 mol) of **9** in 65 ml of methylene chloride was combined with 1.4 g (0.014 mol) of potassium thiocyanate and 2.7 g (0.014 mol) of *p*-toluenesulfonic acid monohydrate. After being stirred in an ice bath for 3 hr, the white solid was filtered and washed with cold water and methylene chloride to give 0.8 g of **8a**: mp 160–165°, resolidified and melted at 210–215°; ir (Nujol) 2.98 (broad, NH), 4.87 (NCS), 5.78 (ester), 5.92 μ ($C_6H_5C{=}O$).

Anal. Calcd for $C_{24}H_{23}N_3O_4S$: C, 64.13; H, 5.16; N, 9.35; S, 7.13. Found: C, 63.80; H, 5.02; N, 9.18; S, 7.26.

A cooled solution of 7.85 g (0.05 mol) of **6** in 50 ml of acetonitrile was added to a cooled solution of 32.7 g (0.2 mol) of **2** in 75 ml of acetonitrile. After being stirred at 5° for 70 min the solid was filtered and washed with cold acetonitrile to give 1.0 g of **8a**. The filtrate was stirred for an additional 4 hr whereupon an additional 2.2 g of **8a** was obtained: mp 160–165°, resolidified and melted at 210–215°; mmp with above 155–160° (which resolidified and melted at 210–215°).

2-Benzamido-3-carbethoxy-4-dimethylamino-6-phenylpyrylium Chloride (8b).—A cold solution of 10 g (0.063 mol) of ethyl dimethylamin ocrotonate in 50 ml of benzene was added to a cold mixture of 8.9 g (0.063 mol) of benzoyl chloride and 10.3 g (0.063 mol) of benzoyl isothiocyanate in 150 ml of benzene. The mixture was stirred 15 min and the solid filtered. The white solid was washed with cold benzene and recrystallized from acetonitrile to yield 8.7 g of **8b**: mp 194–196°; ir (Nujol) 5.79 (s, ester), 5.91 (s, C=O); λ_{max} 220 mμ sh (ε 16,320), 246–255°

(9) L. E. Sutton, Ed., *Chem. Soc. Spec. Publ.*, **11**, Section B (1958).

plateau (16,570), 280 (30,170), 296 sh (25,630), 322 sh (20,500); pmr (CF_3CO_2H) δ 1.42 (t, 3, OCH_2CH_3), 3.47 (d, 6, NMe_2), 4.58 (q, 2, OCH_2CH_3), 7.4–8.2 (m, 11, aromatic), 11.38 (s, 1, NH exchangeable).

2-(3-Carbethoxy-4-dimethylamino-6-phenyl)pyranylidene Benzamide (9).—To 100 ml of 25% sodium hydroxide was added 10 g of **8b** and the solution was stirred for 1 hr. The solution immediately turned yellow and, after extraction with ether, drying, and concentration, yielded on crystallization from benzene–hexane 6.1 g of **9**: mp 108–110°; ir (Nujol) 5.81 (ester), 5.90 (C_6H_5C=O), 6.10 (C=N); λ_{max} 246 mμ (ε 21,820), 293 (33,760), 372 (19,940); pmr δ 1.32 (t, 3, OCH_2CH_3), 3.09 (s, 6, NMe_2), 4.35 (q, 2, OCH_2CH_3), 6.52 (s, 1, =CH), 7.2–8.4 (m, 10, aromatics).

Anal. Calcd for $C_{23}H_{22}N_2O_4$: C, 70.75; H, 5.68; N, 7.18. Found: C, 71.09; H, 5.72; N, 7.27.

Addition of 0.5 g of **8a** to 10 ml of 10% sodium hydroxide, followed by stirring for 2 hr, gave on extraction with ether, drying, and concentrationg 0.2 g of **9**, identical with the above.

Ethyl 2-Benzamide-5-benzoyl-4-dimethylamino-6-oxonicotinate (10).—To potassium cyanate (1.22 g, 0.015 mol) in 75 ml of chloroform was added 10 drops of 6 *N* hydrochloric acid. **9** (3 g, 0.0075 mol) was dissolved in 25 ml of chloroform and added dropwise with stirring over 1 hr. After being stirred overnight the reaction mixture was concentrated and the insoluble material washed with water. Recrystallization from ethanol yielded 1 g of **10**: mp 215–217°; ir (Nujol) 3.12 (s, NH, OH), 5.99 (s, ester), 6.13 μ (s, C_6H_5CO); λ_{max} 245 mμ (ε 32,870), 279 (31,760), 320 sh (13,026); pmr (CF_3CO_2H) δ 1.58 (t, 3, OCH_2CH_3), 3.15 (s, 6, NMe_2) 4.69 (q, 2, OCH_2CH_3), 7.33–8.34 (m, 10, Ar), 11.96 (s, 2, OH, NH).

Anal. Calcd for $C_{24}H_{23}N_3O_5$: C, 66.50; H, 5.35; N, 9.70. Found: C, 66.17; H, 5.53; N, 9.64.

Ethyl 2-Benzamido-5-benzoyl-4-dimethylamino-6-thioxonicotinate (11).—A solution of 15.7 g (0.1 mol) of ethyl dimethylaminocrotonate (**6**) in 75 ml of chloroform was added dropwise over 20 min to 32.6 g (0.2 mol) of benzoyl isothiocyanate (**2**) in 75 ml of chloroform with stirring in an ice bath. The mixture was then warmed on a steam bath for 30 min. The resulting solid was filtered and recrystallized from acetonitrile to give 14.5 g of **11** as yellow prisms: mp 233–235; ir (Nujol) 3.12 (m, NH), 6.00 (s, ester), 6.19 μ (s, C_6H_5CO); λ_{max} 257 mμ (ε 3440), 304 (2515), 372 (1670); pmr δ 1.40 (t, 3, OCH_2CH_3), 2.76 (s, 6, NMe_2), 4.48 (q, 2, OCH_2CH_3), 7.40–8.40 (m, 10, aromatic), 12.14 (s, 1, NH, slowly exchanged with D_2O), 13.3 (s, 1, SH rapidly exchanged).

Anal. Calcd for $C_{24}H_{23}N_3O_4S$: C, 64.13; H, 5.16; N, 9.35. Found: C, 64.02; H, 5.15; N, 9.23.

To a mixture of 0.46 g of *p*-toluenesulfonic acid and 0.12 g of potassium thiocyanate in 75 ml of chloroform was added 0.5 g (0.0012 mol) of **9** dissolved in 75 ml of chloroform. After refluxing for 4 hr the solvent was removed under reduced pressure and the residue crystallized from acetonitrile to give 200 mg of **11**, identical with the above.

Ethyl 5-Benzoyl-4-dimethylamino-2-(*N*-methylbenzamido)-6-methylthionicotinate (12).—To a solution of 18.0 g (0.04 mol) of **11** in 500 ml of dimethylformamide and 100 ml of toluene was added 4.2 g (0.088 mol) of 50% sodium hydride–mineral oil over 1 hr with stirring and cooling. To the light yellow solution 23.0 g (0.16 mol) of methyl iodide was added dropwise at which time the solution became red-orange and then the color gradually disappeared on stirring overnight. Water was added, and the solution was concentrated, extracted with ether, dried, and evaporated to yield 20.9 g of **12**. Crystallization from benzene–hexane gave 17 g of pure **12**: mp 146–148°; ir (Nujol) 5.81 (s, ester), 6.03 μ (s, C_6H_5CO); λ_{max} 263 mμ (ε 3060); pmr δ 1.37 (t, 3, OCH_2CH_3), 2.28 (s, 3, SMe), 2.45 (s, 6, NMe_2), 3.45 (s, 3, NMe), 4.34 (q, 2, OCH_2CH_3), 7.2–7.7 (m, 10, aromatic).

Anal. Calcd for $C_{26}H_{27}N_3O_4S$: C, 65.39; H, 5.70; N, 8.80. Found: C, 65.58; H, 5.77; N, 8.74.

Ethyl 5-Benzoyl-4-dimethylamino-2-methylamino-5-methylthionicotinate (13).—A solution of 5.0 g (0.011 mol) of **12** and sodium ethoxide (from 1.0 g of sodium) in 500 ml of ethanol was refluxed for 12 hr. The solvent was removed under reduced pressure, and water was added and extracted with ether. Drying, concentrating, and crystallization of the ether extract from hexane gave, 1.12 g of **13**: mp 128–130; ir (Nujol) 3.96 (NH), 5.98 (ester), 6.09 μ (C=O); λ_{max} 258 mμ (ε 35,250), 315 (14,600), 344 sh (10,670); pmr δ 1.32 (t, 3, OCH_2CH_3), 2.46 (s, 9, NMe_2, SMe), 3.08 (d, 3, NMe), 4.28 (q, 2, OCH_2CH_3), 7.2–7.8 (m, 6, NH, aromatics).

Anal. Calcd for $C_{19}H_{23}N_3O_3S$: C, 61.11; H, 6.21; N, 11.25; S, 8.59. Found: C, 61.17; H, 6.49; N, 11.31; S, 8.54.

Ethyl 5-Benzoyl-4-dimethylamino-2-(*N*-methylbenzamido)-6-methylthionicotinate (14).—To a solution of 18.0 g (0.04 mol) **11** in 500 ml of dimethylformamide and 100 ml of toluene was added 1.9 g (0.04 mol) of 50% sodium hydride–mineral oil with stirring and cooling. After addition of 5.8 g (0.04 mol) of methyl iodide the reaction mixture was stirred overnight and worked up as above. Recrystallization from benzene–hexane yielded 14.3 g of **14**: mp 142–144°; ir (Nujol) 3.10 (m, NH), 6.01 μ (s, C=O), λ_{max} 261 mμ (ε 3500); pmr δ 1.33 (t, 3, OCH_2CH_3), 2.53 (s, 3, SMe), 2.58 (s, 6, NMe_2), 4.55 (q, 2, OCH_2CH_3), 7.2–8.2 (m, 10, aromatic), 9.0 (s, 1, NH).

Anal. Calcd for $C_{25}H_{25}N_3O_4S$: C, 64.78; H, 5.44; N, 9.07. Found: C, 64.49; H, 5.40; N, 8.91.

4-Dimethylamino-6-methylamino-2-methylthio-3-pyridyl Phenyl Ketone (15).—A solution of 8.0 g (0.0115 mol) of **12**, 65 ml of 50% sodium hydroxide, and 700 ml of ethanol was refluxed for 8 hr and let stand overnight. The ethanol was removed under reduced pressure. Water was added, the pH was adjusted to 7, and the solution extracted with ether. Drying and solvent removal gave, on crystallization from methanol, 4 g of **15**: mp 157–159°; ir (Nujol) 2.97 (m, NH), 6.15 μ (s, C_6H_5C=O); λ_{max} 249 mμ (ε 42,130), 288 sh (8660), 360 (5410); pmr δ 2.40 (s, 3, SMe), 2.62 (s, 6, NMe_2), 2.97 (d, 3, NMe), 4.68 (s, 1, NH), 5.49 (s, 1, HC=), 7.2–7.9 (m, 5, aromatic).

Ethyl 2-Amino-5-benzoyl-4-dimethylamino-6-methylthionicotinate (16).—A solution of 1.0 g (0.002 mol) of **14** and sodium ethoxide (from 0.1 g of sodium) in 100 ml of ethanol was refluxed for 8 hr. The solvent was removed under reduced pressure, and water was added and extracted with ether. Drying, concentration, and crystallization of the ether extract from benzene–hexane gave 0.5 g of **16**: mp 115–118°; ir (Nujol) 2.79, 2.97 (NH), 5.98 (ester), 6.07 μ (C=O); λ_{max} 254 mμ (ε 33,810), 308 (14,560); pmr δ 1.33 (t, 3, OCH_2CH_3), 2.43 (s, 3, SMe), 2.50 (s, 6, NMe_2), 4.33 (q, 2, OCH_2CH_3), 6.17 (s, 2, NH_2), 7.2–8.0 (m, s, aromatic).

Anal. Calcd for $C_{18}H_{21}N_3O_3S$: C, 60.16; H, 5.89; N, 11.69. Found: C, 60.41; H, 6.13; N, 11.57.

6-Amino-4-dimethylamino-2-methylthio-3-pyridyl Phenyl Ketone (17).—A solution of 5.0 g of **14**, 35 ml of 50% sodium hydroxide, and 200 ml of ethanol was refluxed for 12 hr. The ethanol was removed, and the pH was adjusted to 7 with dilute hydrochloric acid and then extracted with ether. The extract was dried and concentrated, and the residue was crystallized from ethanol to give 4.1 g of **17**: mp 172–175°; ir (Nujol) 2.90, 2.99, 3.11 (NH_2), 6.15 μ (C_6H_5C=O); λ_{max} 206 mμ (ε 21,150), 247 (43,280), 354 (3790); pmr δ 2.38 (s, 3, SMe), 2.59 (s, 6, NMe_2), 4.59 (s, 2, NH_2), 5.66 (s, 1, =CH), 7.2–7.9 (m, 5, aromatics).

Anal. Calcd for $C_{15}H_{17}N_3OS$: C, 62.70; H, 5.96; N, 14.63. Found: C, 62.65; H, 5.89; N, 14.50.

Crystal Structure Analysis of Ethyl 2-Benzamido-5-benzoyl-4-dimethylamino-6-thioxonicotinate (11).—Crystal data for $C_{24}H_{23}N_3O_4S$, mol wt 449.54, are monoclinic, a = 14.67, b = 10.96, c = 13.82 Å, β = 95° 25′, U = 2212 Å^3, Z = 4; space group $P2_1/a$ (C_{2h}^5) F_{000} = 1044; absorption coefficient for X-rays (λ = 1.5418 Å) 15.74 cm^{-1}.

Elongated yellow platelets of **11** were obtained and mounted parallel to the axis of elongation. All data were taken using nickel-filtered Cu K radiation (λ = 1.5418 Å). Unit cell dimensions were evaluated from oscillation and precession photographs. Weisenberg equiinclination photographs of levels *0kl*–*12kl* and *h0l* were obtained, and the intensities of the reflections were estimated visually by comparison to a calibrated strip. After merging of the data 2067 independent reflections were obtained. Systematic extinctions of the type *h0l* absent for *h* odd and *0k0* absent for *k* odd uniquely fixed the space group as $P2_1/a$. The intensities thus derived were corrected for Lorentz and polarization effects. No absorption corrections were made due to the small size of the crystal.

The structure was solved by employing the symbolic addition method.[8] The following initial assignments were made.

h	*k*	*l*	Phase
8	5	6	+
6	4	9	+
11	2	2	+
6	1	3	A

Utilizing this starting set and the Σ_2 relation, it was possible to fix the signs of 290 reflections with E >1.30. An E map com-

puted for these 290 reflections clearly showed the positions of 22 atoms. Structure factors based upon these positions were then calculated and the resulting phases used with the observed structure amplitudes to yield an electron density map which revealed the 10 remaining nonhydrogen atoms. At this point a conventional R of 26.6% was obtained. The structure was refined by full matrix least-squares techniques using a weighting scheme of the type suggested by Hughes.[10] All atoms were assigned anisotropic temperature factors. A final value for R of 12.9 was obtained using all 2067 observed reflections.

A copy of the final atomic parameters together with the observed and calculated structure factors can be obtained on request from R. T. P. Calculations were performed using the X-Ray 67 System of programs developed by Dr. James Stewart of the University of Maryland, together with the programs FAME and MAGIC by Fleisher, Dewar, and Stone, for the application of the symbolic addition procedure.

(10) E. W. Hughes, *J. Amer. Chem. Soc.*, **63**, 1737 (1941).

Registry No.—**2**, 532-55-8; **6**, 14205-42-6; **8a**, 30378-32-6; **8b**, 30428-03-6; **9**, 30428-04-7; **10**, 30428-05-8; **11**, 30428-06-9; **12**, 30428-07-0; **13**, 30428-08-1; **14**, 30428-09-2; **15**, 30428-10-5; **16**, 30428-11-6; **17**, 30428-12-7.

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Synthesis of a *dl* Polymer and an Active (+) Polymer Containing the 2,4,5,7-Tetranitrofluorenylideneaminooxysuccinic Moiety. Chromatographic Studies[1]

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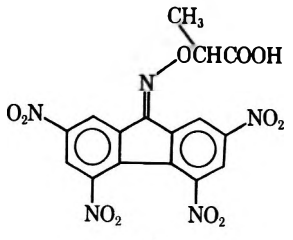
dl-Di-β-hydroxyethyl 2,4,5,7-tetranitrofluorenylideneaminooxysuccinate (**6**) was synthesized by the steps shown in Scheme I. Treatment with terephthalyl chloride yielded a solid polymer which was comparable to Woelm neutral alumina (grade I) in the separation of 6- and 10-methylbenz[*a*]anthracene by column chromatography. An optically active polymer was similarly prepared from (+)-**6** but was ineffective in separating 2-butyl 1-naphthyl ether and hexahelicene into active forms in the range used, 3 g of polymer to 0.1 g of substrate.

α-(2,4,5,7-Tetranitro-9-fluorenylideneaminooxy)propionic acid (TAPA, **1**) was synthesized to provide a reagent suitable for resolution by complex formation of compounds lacking functional groups which would allow for resolution by standard method.[3] The resolution of hexahelicene (**2**) by TAPA was successful,[4] but very small amounts of optically pure **2** were obtained after considerable effort.

The object of the present study was to prepare a polymer containing the 2,4,5,7-tetranitrofluorene nucleus which might prove superior to alumina for the chromatographic separation of polynuclear hydrocarbons and to prepare an optically active polymer which might prove useful as a solid phase for column chromatographic resolution of **2** or other compounds[3] which have been resolved by the use of TAPA.[5]



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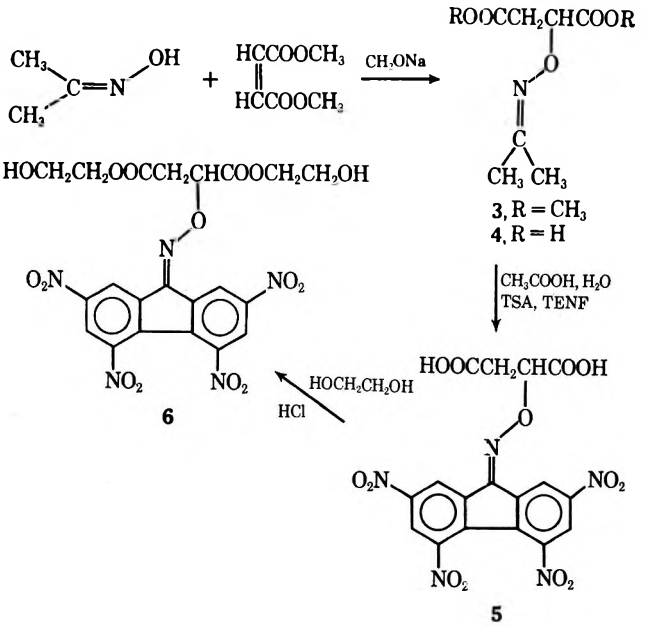
An optically inactive diol suitable for formation of a polyester polymer was prepared as shown in Scheme I.

SCHEME I



The base-catalyzed reaction of acetone oxime with dimethyl maleate produced dimethyl isopropylideneaminoxysuccinate (**3**) in 50% yield. Acid-catalyzed (toluenesulfonic acid, TSA) ketone exchange with 2,4,5,7-tetranitrofluorenone (TENF) in aqueous acetic acid proceeded in high yield to 2,4,5,7-tetranitrofluorenylideneaminooxysuccinic acid (**5**) which was esterified to the bis-2-hydroxyethyl ester **6**, the glycol

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(2) Author to whom correspondence should be addressed.

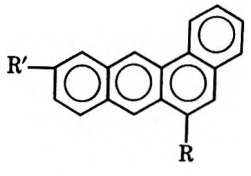
(3) M. S. Newman and W. B. Lutz, *J. Amer. Chem. Soc.*, **78**, 2469 (1956).

(4) M. S. Newman and D. Lednicer, *ibid.*, **78**, 4765 (1956).

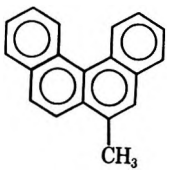
(5) Partial optical resolution of racemic 1-naphthyl 2-butyl ether and of 3,4,5,6-dibenzo-9,10-dihydrophenanthrene by chromatography on silicic acid impregnated with optically active TAPA has been reported by L. K. Klemm and D. Reed, *J. Chromatogr.*, **3**, 364 (1960).

desired for formation of polyester. By treatment of **6** with terephthaloyl chloride in dimethylformamide, a solid polymer (mp 85–90° dec) was obtained in high yield. No attempts were made to characterize the polymers obtained by conventional polymer techniques because the only point of interest in the present work was the chromatographic usefulness of the solids involved.

This polymer (of greenish yellow hue) was used as an adsorbent in a conventional chromatographic column and tested for its effectiveness in separating 6-methylbenz[*a*]anthracene (**7**) from 10-methylbenz[*a*]anthracene (**8**) and 6-methylbenzo[*c*]phenanthrene (**9**) from **8**, as compared to an equal weight of Woelm neutral alumina, grade I. The polymer proved to be slightly more effective than alumina in separating the very similar hydrocarbons **7** and **8**. The polymer was also effective in separating **9** from **8** but was slightly less effective than alumina for these hydrocarbons which differ from each other to a greater extent than do **7** and **8**. The success of these experiments prompted us to prepare an optically active polymer of similar structure.



7, R = CH_3; R' = H
8, R = H; R' = CH_3



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Attempts were also made to prepare polymers from **6** by reaction with 4,4′-diisocyanatodiphenylmethane, 2,2,4-trimethylhexamethylene diisocyanate, and 1,3-diisocyanato-1,5,5-trimethylcyclohexane. Although polymers were obtained in each case they were dark in color, of undesirable properties for chromatography, and were not further studied.

After many attempts to prepare **5** and **6** in optically active forms, the following procedure was developed. The acid **4** was obtained by careful hydrolysis of **3** with the calculated amount of sodium hydroxide. The acid **4** was resolved with dehydroabietylamine[6] and isolated as the (−)-dimethyl ester **3**. This was converted into (+)-**5** and the latter into (+)-**6** as for the racemic compounds. Treatment of (+)-**6** with terephthaloyl chloride yielded a (+) polymer which was very similar to the inactive polymer mentioned above.

Unfortunately, all attempts to effect resolution of 1-naphthyl 2-butyl ether or hexahelicene by chromatography failed to yield any fraction which had even small activity. In one experiment, the optically active polymer proved about as effective for separation of **7** and **8** as the inactive polymer. Hence, the failure to effect resolution cannot be due to greatly different dispersed forms of the two polymers.[7] Undoubtedly, the asymmetric center in the repeating unit of the polymer is not in a suitable position relative to the fluorene nucleus to induce preferential complex formation as is the case when TAPA (**1**) is used in solution,[7] and, therefore, even though the polymer is active, no resolution occurs on chromatography. It should be recognized that our attempts to effect resolution were carried out with small amounts of polymer and very low ratio of adsorbing agent to racemic compound. Possibly, if very high ratios were used, a small amount of resolution, comparable to that obtained by Prelog in the resolution of Troeger's base on lactose,[8] might be obtainable. The failure of an optically active polymer, which was used to resolve polymers by chromatography, to resolve a monomer should be noted.[9]

(6) B. Sjöberg and S. Sjöberg, *Ark. Kemi*, **22**, 447 (1964).

(7) We are indebted to Dr. Lloyd R. Snyder, Union Oil Co., Brea, Calif., for this suggestion.

Experimental Section[10]

Dimethyl Isopropylideneaminooxysuccinate (**3**).—To the stirred solution under nitrogen prepared by dissolving 21.9 g (0.3 mol) of acetone oxime and 1.0 g of sodium methoxide in 70 ml of pure dry dioxane at 15–20° was added in one portion 43.2 g (0.3 mol) of dimethyl maleate. Within 2 min the temperature rose to 70°. The solution was left at ambient temperature overnight and then poured into 300 ml of ice water and acidified to litmus with hydrochloric acid. After the usual work-up, two distillations afforded 32.5 g (50%) of **3**, bp 118° (4 mm).

Anal. Calcd for $C_9H_{15}O_5N$: C, 49.7; H, 6.9. Found: C, 49.8; H, 7.2.

Isopropylideneaminooxysuccinic Acid (**4**).—In the best of several runs 21.7 g of **3** was added at one time to 200 ml of stirred 5% sodium hydroxide at 60° with cooling to keep the temperature below 70°. Within 5 min the mixture was homogenous. After 20 min the mixture was cooled, acidified to congo red, and saturated with ammonium sulfate (about 60 g). The product was taken into ether–benzene and worked up as usual to yield 16.0 g (85%) of **4**, mp 123–124°. The analytical sample, mp 123–124°, was obtained by crystallization from ether.

Anal. Calcd for $C_7H_{11}NO_5$: C, 44.4; H, 5.8; N, 7.4. Found: C, 44.7; H, 6.1; N, 7.7.

***dl*-2,4,5,7-Tetranitrofluorenylideneaminooxysuccinic Acid (TASA)** (**5**).—A solution of 36 g of TENF,[11] 21.7 g of **3**, and 3 g of toluenesulfonic acid in 400 ml of acetic acid in a three-necked flask connected to a packed fractionating column was refluxed for for 3 hr, the acetone formed being slowly removed. Then, at 1-hr intervals 10-, 5-, 5-, 3-, and 2-ml portions of water were added. After 3 hr more at reflux the mixture was poured on ice. After standing overnight, the yellow precipitate was collected, washed with cold water, and dried. Recrystallization from benzene–methanol yielded 44.0 g (89%) of **5**, mp 170–172°.

Anal. Calcd for $C_{17}H_9N_5O_{13}$. C, 48.5; H, 2.6; N, 12.3. Found: C, 48.2; H, 3.0; N, 12.5.

Di-β-hydroxyethyl 2,4,5,7-Tetranitrofluorenylideneaminooxysuccinate (**6**).—A solution of 49.1 g of **5** in 250 ml of ethylene glycol was added to 500 ml of ethylene glycol which had been saturated with dry hydrogen chloride at 0°. The mixture was left overnight at room temperature and was then diluted with water and extracted thoroughly with methylene chloride. After the usual work-up (a water wash) there was obtained 50.0 g (86%) of **6** as light yellow needles, unsharp melting point at 80°.

Anal. Calcd for $C_{21}H_{17}N_5O_{15}$: C, 43.6; H, 2.9; N, 12.1. Found: C, 43.4; H, 2.8; N, 12.1.

Inactive Polymer.—To a stirred solution of 11.58 g of **6** and 4.1 g of triethylamine in 75 ml of pure dimethylformamide (DMF) at room temperature was added rapidly a solution of 4.06

(8) V. Prelog and P. Wieland, *Helv. Chim. Acta*, **27**, 1127 (1944), used 2.7 kg of lactose for 6 g of base. See also G. M. Henderson and H. G. Rule, *J. Chem. Soc.*, 1568 (1939), for a review of early literature; C. W. Roberts and D. H. Haigh, *J. Org. Chem.*, **27**, 3375 (1962), and J. A. Loft and W. Riemann, III, *ibid.*, **31**, 561 (1966), for references to more recent work in this area.

(9) P. Pino, F. Ciardelli, G. P. Lorenzi, and G. Natta, *J. Amer. Chem. Soc.*, **84**, 1487 (1962).

(10) All melting points and boiling points are uncorrected. The term "worked up as usual" means that an ether or ether–benzene extract of the reaction mixture was washed with dilute acid and/or base, with saturated salt solution, and then filtered through a cone of anhydrous magnesium sulfate. The solvents were removed by distillation or rotary evaporation and the residue was processed as indicated. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn. All new compounds had ir and nmr spectra consistent with the proposed formulas.

(11) M. S. Newman and W. B. Lutz, *J. Amer. Chem. Soc.*, **78**, 2469 (1956).

TABLE I

SEPARATION OF 7 AND 8 OVER 3 g OF POLYMER

Fraction	Wt,[a] mg	Vol[b]	% 7[c]
1	0.0	4	
2	0.8	2	100[d]
3	6.0[e]	2	100
4	14.2	2	93
5	12.2	2	85
6	8.5	2	80
7	8.8	2	75
8	6.2	2	50
9	9.7	5	24
10	9.4	6.5	0
11–19	18.7[f]	81	0[g]
	Total 94.5		

[a] Weight in milligrams weighed to 4 decimals on an analytical balance. [b] Volume is approximate. [c] The difference between 100% and value shown consists of 8. [d] This sample added to sample 3. [e] A total of 6.8 mg (13.6% of starting 7) isolated pure. [f] A total of 28.1 mg (56.2% of starting 8) isolated pure. [g] In a similar experiment run on an earlier day with the same polymer, there were isolated 4.8 mg (9.6%) of pure 7 and 29.3 mg (58.6%) of pure 8, with a total of 87.7 mg recovered.

g of pure terephthaloyl chloride in 25 ml of DMF. After standing for 2 hr, the precipitated salt was filtered and washed with DMF. The filtrate and washings were then poured on crushed ice. After standing for 3 hr, the greenish yellow solid was collected, washed well with water, and air-dried. This polymer was then washed with methanol and dried (below 80°) to yield 13.5 g of polymer which decomposed when heated at 85–90°. After further washing with hot benzene and methanol repeatedly 7.0 g of polymer was obtained, suitable for use as the solid phase in chromatography.

Anal. Calcd for polymer unit as $C_{29}H_{19}N_3O_{17}$: C, 49.1; H, 2.7; N, 9.9. Found: C, 50.2; H, 2.9; N, 7.7.

Dimethyl (−)-Isopropylideneaminooxysuccinate (3).—A suspension of 262 g of purified dehydroabietylamine acetate[6,12] in 1 l. of water was treated with a solution of 65 g of sodium hydroxide in 100 ml of water in portions. The cooled reaction mixture was extracted with ether. After drying over potassium hydroxide pellets, the ether solution was added to a solution of 75.6 g of *dl*-4 in 1 l. of ether–benzene (1:1). After standing at room temperature for 4 hr, the colorless solid was collected by filtration. Successive crops were obtained from the filtrate until a total of 130.8 g had been obtained. After four recrystallizations from methanol–chloroform (1:1), 76 g of the (−)(−) salt of 4, mp 165–168°, was obtained. Attempts to obtain the (+)(−) salt from the mother liquors were unsuccessful. A solution of 75.9 g of the (−)(−) salt in 200 ml of dry methanol was added to 800 ml of methanol saturated at 0° with dry HCl. After standing overnight at room temperature 400 ml of methanol was distilled under reduced pressure. The mixture was diluted with water and extracted with ether. After the usual work-up distillation afforded 12.3 g (56%) of (−)-3, bp 145° (11 mm), $[\alpha]^{24}D$ 23.01° (*c* 3, CCl_4).

(+)-5.—In a manner similar to that described for *dl*-5, a solution of 10.85 g of (−)-3 and 18.0 g of TENF in 300 ml of acetic acid containing 1.0 g of toluenesulfonic acid yielded 23.2 g (94%) of (+)-5, mp near 180°, $[\alpha]^{25}D$ 34.97° (*c* 4.86, methanol).

(+)-6.—Esterification of 19.64 g of (+)-5 in 100 ml of ethylene glycol as in the case of *dl*-5 yielded 20.1 g (87%) of (+)-6, melting point unsharp near 80°, $[\alpha]^{25}D$ 29.06° (*c* 12.1, THF).

(+) Polymer.—A solution of 6.09 g of pure terephthaloyl chloride in 50 ml of pure DMF was added all at once to a solution of 17.37 g of (+)-6 in 150 ml of DMF and 6.06 g of triethylamine in a 500-ml erlenmeyer flask with shaking. The active polymer was isolated as described for the inactive polymer. There was obtained 15.5 g of (+) polymer, $[\alpha]^{25}D$ 31.18° (*c* 17.2, THF).

Chromatographic Experiments.—Many experiments were run on known mixtures of 6-methylbenz[*a*]anthracene (7), 10-methylbenz[*a*]anthracene (8), and 6-methylbenzo[*c*]phenanthrene (9) over the polyester polymer prepared from inactive 6 and terephthaloyl chloride and over Woelm neutral alumina,

(12) L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 183. We thank the Hercules Powder Co., Wilmington, Del., for a generous gift of Amine D.

TABLE II

SEPARATION OF 7 AND 8 OVER 3 g OF ALUMINA

Fraction	Wt,[a] mg	Vol[b]	% 7[c]
1–4	0.0	8	
5–7	7.6[d]	7	100
8	4.5	4	85
9	4.0	5	80
10–11	16.2	13	73
12–15	27.4	45	53
16–19	23.0	60	24
20	3.6	15	0
21	10.0[e]	15	0
	Total 96.3		

[a] Weight in milligrams. [b] Volume is approximate; larger volumes are those of combined fractions. [c] The difference between 100% and the number shown consists of 8. [d] A total of 7.6 mg (15.2% of starting 7) isolated pure in three fractions. [e] A total of 13.6 mg (27.2% of starting 8) isolated pure. [f] In a similar experiment 8.6 mg (17.2%) of 7 and 12.0 mg (24%) of pure 8 were isolated, with a total recovery of 94.3 mg of starting 7 and 8.

TABLE III

SUMMARY OF CHROMATOGRAPHIC SEPARATIONS

A. Separation of 7 and 8[a]

Adsorbent	Amt of adsorbent, g	%[b] of pure 7	% of pure 8
Polymer	1.0	7	48
		9	54
Alumina	1.0	*c*	21
		c	22
Polymer	3.0	14	56
		10	59
Alumina	3.0	15	27
		17	24

B. Separation of 9 and 8[a]

Adsorbent	Amt of adsorbent, g	% of pure 9	% of pure 8
Polymer	1.0	49	40
Alumina	1.0	71	65

[a] 50 mg of each used. [b] Percentages rounded off to nearest whole number. [c] No pure 7 obtained as first fractions were about 85% 7.

grade I. In a typical experiment 50-mg each of the components to be separated was mixed with a small amount of adsorbent and placed on the chromatographic column which was covered by about 1 cm of cyclohexane. The internal diameter of the columns was about 1 cm. The height of absorbent was about 3–4 cm/g of polymer and 1–1.5 cm/g of alumina. Pure distilled cyclohexane was used as solvent and eluent. The eluate fractions, at a flow rate of about 1 ml/1–2 min, were collected in small weighed beakers which were weighed after evaporation of solvent in a draft.

Analyses of the various fractions of eluate were made by tracing the nmr spectra (taken in micro tubes for samples containing 3 mg or less) on heavy trace paper. The peaks were cut out and weighed in order to determine the relative amounts when mixtures were at hand. The nmr spectra were taken on a Varian A-60 with 250 sweep width, appropriate offset, and fast scanning (sweep time 100). The optimum rf energy was fed just in the region of resonance with suitable adjustment of the filter band width and phase to reduce the signal-to-noise ratio. Thus, it was possible to use fairly dilute solutions. The first fractions to be eluted were more difficult to estimate because of the dilution factor. Often several fractions were combined for analysis. The exact chemical shifts of the methyl groups (τ: 7, *ca.* 7.4; 8, *ca.* 7.6; 9, 7.3)[13] were assigned both separately and in mixtures by using tetramethylsilane as internal standard. After assigning τ values for the methyl groups, it was unnecessary to include TMS in each tube for measurements of the composition of eluates.

(13) The exact τ value varied as in mixtures slight shifts were observed relative to the values in pure solvent (CCl_4 and $CDCl_3$).

Typical experiments are summarized in Tables I and II. The results of a series of experiments are listed in Table III.

Registry No.—(±)-**3**, 30256-03-2; (−)-**3**, 30318-67-3; (±)-**4**, 30256-04-3; (±)-**5**, 30247-99-5; (+)-**5**, 30248-00-1; (±)-**6**, 30275-69-5; (+)-**6**, 30248-01-2; (±) inactive polymer, 30228-77-4; (+) inactive polymer, 30228-78-5.

Synthesis of 2- and 3-Keto-5-*endo*-(2-imidazolyl)bicyclo[2.2.2]octane

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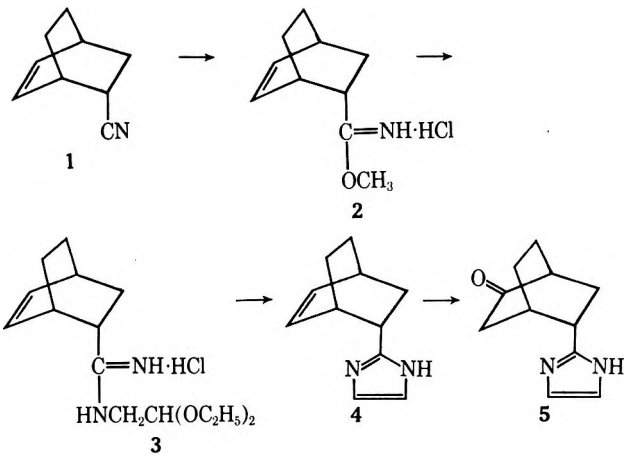
On the basis of a concept of attributes that make compounds attractive candidates for biological screening, 2-keto- and 3-keto-5-*endo*-(2-imidazolyl)bicyclo[2.2.2]octane were synthesized on a relatively large scale for conversion to a series of corresponding 2- or 3-substituted analogs.

In order to raise the probability of finding biological activity among candidates for pharmacometric screening, a family of compounds with structural features that should *a priori* enhance their effectiveness was synthesized. Three features included in this particular series were (1) a rigid bicyclic framework for favorable entropy of binding to a receptor, (2) an imidazole nucleus, attractive for its bifunctional nature and participation at active sites of enzymes, and (3) a second functional group chosen from those found among naturally occurring compounds. Although the biological activity of the group was disappointing, certain aspects of this synthetic organic chemistry are worthy of note.

On the basis of the criteria outlined above, 5-*endo*-(2-imidazolyl)bicyclo[2.2.2]oct-2-ene (**4**) was selected as an appropriate starting compound. The most logical way to synthesize **4** is by a Diels–Alder condensation between cyclohexadiene-1,3 and a 2-vinylimidazole,[1] but this method was soon abandoned in favor of a stepwise synthesis starting from 5-*endo*-cyanobicyclo[2.2.2]-oct-2-ene.

The target compound **4** was synthesized starting with the conversion of 5-*endo*-cyanobicyclo[2.2.2]oct-2-ene[2] (**1**) to 5-*endo*-carbiminomethoxybicyclo[2.2.2]-oct-2-ene hydrochloride (**2**) on treatment with methanol and hydrogen chloride in ether solution. Reaction of the imino ether **2** with β-aminoacetaldehyde diethyl acetal yielded *N*-(β,β-diethoxyethyl)-5-*endo*-carbamidinobicyclo[2.2.2]oct-2-ene hydrochloride (**3**), which at 120° in glacial acetic acid–acetic anhydride gave 5-*endo*-(2-imidazolyl)bicyclo[2.2.2]oct-2-ene (**4**).

A critical step in the scheme required the introduction at an appropriate position on the bicyclic framework of a carbonyl group which could then be converted into a variety of functional groups. The unsaturation at the 2,3 position of the bicyclic skeleton was a logical point to attack, but more difficulty was encountered than anticipated in applying typical reactions for this transformation. The imidazole moiety appeared to be largely responsible for the difficulty by either preventing reaction at the 2 or 3 position or by being susceptible to attack by the reagent. For example, in a variety of hydroboration studies, stable aminoborane derivatives were isolated and the unsaturated moiety was intact. In other instances involving mild oxidizing agents, the imidazole ring was attacked. Facile conversion of the unsaturated compound **4** to 2-keto-5-*endo*-(2-imidazolyl)bicyclo[2.2.2]octane (**5**) was achieved by palladium chloride oxidation in aqueous medium.[3] The reaction is usually accomplished by using catalytic quantities of palladium chloride in the presence of large amounts of cupric chloride and an air stream. The propensity of the keto imidazole derivative **5** to chelate with copper, however, made it prudent to use palladium chloride in at least stoichiometric amount and eliminate the cupric salt.



The location of the carbonyl group in **5** could not be established on theoretical grounds and was not immediately obvious from nmr spectra data in $CDCl_3$. In the absence of model compounds, chemical shifts could not be exploited with assurance, since the positions of protons adjacent to the ketone would be similar in both the 2 and 3 isomers. Furthermore, any difference in multiplicity between the bridgehead protons could not be used as an approach to structure assignment because of the coincidence of the C_1 and C_4 proton peaks in several solvents. These difficulties were overcome by taking advantage of the long-range coupling

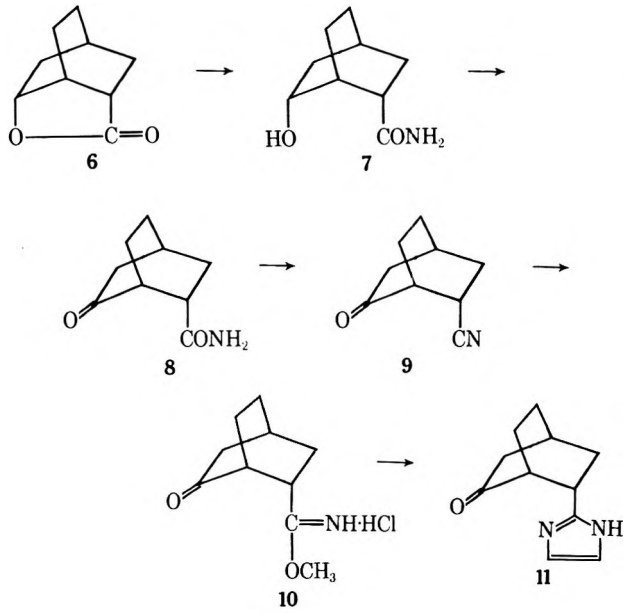
(1) The relatively poor dienophilic nature of vinylimidazoles and their propensity to polymerize at relatively low temperature did not augur well for a successful Diels–Alder condensation. In addition, considerable difficulty was justifiably anticipated in the prepartion of certain 2-vinylimidazoles on a reasonably large scale. Nevertheless, 1-benzyl-2-vinylimidazole was synthesized from 1-benzyl-2-lithioimidazole by reaction with acetaldehyde and dehydration over fused $KHSO_4$ at 251–230° (25–45 mm). The distilled product (*ca.* 60% pure) did not undergo Diels–Alder condensation with cyclohexadiene-1,3 at temperatures up to 170° or at pressures up to 138,000 psi. In a parallel attempt, methyl β-(4-imidazolyl)acrylate was prepared from L-histidine and heated with cyclohexadiene-1,3 at temperatures up to 210° without success.

(2) K. Alder, H. Heimbach, and R. Reubke, *Chem. Ber.*, **91**, 1516 (1958).

(3) For a review see J. Smidt, W. Hafner, R. Jira, R. Sieber, J. Sedlmeier, and A. Sabel, *Angew. Chem., Int. Ed. Engl.*, **1**, 80 (1962).

often observed between exo protons separated by four single bonds.[4] In the bicyclo[2.2.2]octane system, this would be reflected by coupling between the C_5 and C_3 exo protons. The detection of such interaction, most readily determined from a critical examination of the C_5 resonance, would therefore exclude the C_3 site for the ketone. In pyridine, the C_5 proton resonance is composed of 11 peaks. This is consistent with an overall multiplicity of 16 lines arising from coupling constants of 10.7, 6.0, 2.0, and 2.0 Hz. The observed pattern results from the coincidence of lines 2–3, 6–7, 8–9, 10–11, and 14–15. Since the three vicinal protons can account for a maximum of eight lines, it follows that the C_5 proton is involved in long-range coupling with a fourth proton, presumably the exo proton at C_3. Compound **5** was therefore assigned the 2-keto structure. This line of reasoning was later confirmed when it was shown that the C_5 proton resonance in the 3-keto isomer, prepared by an unambiguous synthesis, was composed of eight lines.

For the synthesis of the 3-keto analog **11**, bicyclo[2.2.2]oct-2-ene-5-carboxylic acid[5] served as the starting material. Treatment of this acid with 30% sulfuric acid at 110° for 1 hr[6] gave excellent yields of 3-*endo*-hydroxy-5-*endo*-carboxybicyclo[2.2.2]octane lactone (**6**), which on ammonolysis yielded 3-*endo*-hydroxy-5-*endo*-carbamylbicyclo[2.2.2]octane (**7**). Treatment of the hydroxy analog **7** with chromic acid in acetic acid gave the corresponding keto derivative **8**, which on dehydration with *p*-toluenesulfonyl chloride in pyridine



yielded 3-keto-5-*endo*-cyanobicyclo[2.2.2]octane (**9**). The cyano derivative **9** was converted to 3-keto-5-*endo*-(2-imidazolyl)bicyclo[2.2.2]octane (**11**) by way of the imino ether **10**.

(4) F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961); T. F. Flautt and W. F. Erman, *J. Amer. Chem. Soc.*, **85**, 3212 (1963); J. Meinwald and Y. Meinwald, *ibid.*, **85**, 2514 (1963); K. Tori, Y. Takano, and K. Kitahonoki, *Chem. Ber.*, **97**, 2798 (1964).

(5) R. Seka and O. Tramposh, *ibid.*, **75**, 1379 (1942).

(6) These conditions are superior to those reported by K. Alder and G. Stein, *Justus Liebigs Ann. Chem.*, **514**, 197 (1934), or W. R. Boehme, E. Schipper, W. G. Scharf, and J. Nichols, *J. Amer. Chem. Soc.*, **80**, 5488 (1958).

Experimental Section[7]

5-*endo*-Carbiminomethoxybicyclo[2.2.2]oct-2-ene Hydrochloride (2).—A solution of 2 g (62 mmol) of MeOH and 8.3 g (62 mmol) of 5-*endo*-cyanobicyclo[2.2.2]oct-2-ene[2] in 18 ml of anhydrous Et_2O was cooled, and 2.3 g of anhydrous HCl in Et_2O was added. After being allowed to stand overnight at 5°, the mixture was filtered, yielding 6.6 g of **2**, mp 165–167°. *Anal.* Calcd for $C_{10}H_{16}ClNO$: C, 59.55; H, 8.00; Cl, 17.58; N, 6.95. Found: C, 59.86; H, 8.16; Cl, 17.46; N, 7.17.

***N*-(β,β-Diethoxyethyl)-5-*endo*-carbamidinobicyclo[2.2.2]oct-2-ene Hydrochloride (3).**—A suspension of 40 g (0.2 mol) of **2** in 87 ml of MeOH was warmed to 30° and 27.4 g (0.21 mol) of β-aminoacetaldehyde diethyl acetal was added rapidly. The temperature of the suspension rose to 51°, and the mixture became clear. After 1 hr, the solution was concentrated under reduced pressure, yielding 62.3 g of **3**.

5-*endo*-(2-Imidazolyl)bicyclo[2.2.2]oct-2-ene (4).—A solution of 62.3 g (0.2 mol) of **3** in 260 ml of AcOH and 111 ml of Ac_2O was heated at 120° for 2 hr. The reaction mixture was concentrated under reduced pressure, and the product was dissolved in 270 ml of 2.5 *N* HCl. The acidic solution was washed with Et_2O, made alkaline with 50% KOH, and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with H_2O, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was taken up in a small volume of $CHCl_3$ and adsorbed on 500 g of silica gel packed in CH_2Cl_2. The product was eluted with 0.5% MeOH in CH_2Cl_2 and recrystallized from 100 ml of C_6H_6–petroleum ether (bp 30–60°) yielding 20.95 g of **4**, mp 165–167°. *Anal.* Calcd for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08. Found: C, 76.32; H, 7.83; N, 15.83. Repeated crystallization of the product failed to improve the elemental analysis. Accordingly, 13.5 g of **4** was treated with 6 ml of methyl chloroformate and 32 g of K_2CO_3 in 400 ml of Me_2CO. The mixture was filtered and concentrated, and an Et_2O-soluble fraction was isolated by trituration of the residue. Concentration of the Et_2O solution yielded 11.8 g of the 1-carbomethoxy analog of **4**, which on treatment with 250 ml of 1 *N* HCl yielded 7.8 g of **4**. Passage of this material through 10 g of silica gel as above yielded 6.2 g of **4**, mp 163–164°. *Anal.* Calcd for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08. Found: C, 75.66; H, 7.81; N, 15.95.

2-Keto-5-*endo*-(2-imidazolyl)bicyclo[2.2.2]octane (5).—A mixture of 14.5 g (83 mmol) of **4**, 10 g of $PdCl_2$, and 14.5 g of $CuCl_2 \cdot 2H_2O$ in 170 ml of 1 *N* HCl and 900 ml of H_2O was stirred and heated at 70–80° for 1 hr while air was bubbled through the solution continuously.[8] The hot solution was filtered and cooled, and 140 g of Na_4EDTA was added. The solution was extracted five times with $CHCl_3$, and the combined extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure, yielding an 8.2-g residue. The product was adsorbed on silica gel packed in CH_2Cl_2, and the column was developed slowly with 0–1% MeOH in CH_2Cl_2. The product was eluted with 1–2% MeOH in CH_2Cl_2 and recrystallized from $CHCl_3$–Et_2O, yielding 7.9 g of **5**, mp 194–196°. *Anal.* Calcd for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.42; N, 14.73. Found: C, 69.73; H, 7.71; N, 14.71

For a more readily purified product the following alternative procedure may be used. A mixture of 49 g of $PdCl_2$ in 250 ml of 1 *N* HCl was warmed to 180°, diluted with 2250 ml of hot H_2O, and heated under reflux. Next, 44 g of **4** was dissolved in 250 ml of warm 1 *N* HCl, and the solution was diluted with 800 ml of warm H_2O. The solution of **4** was added to the refluxing $PdCl_2$ mixture in the course of 0.5 hr, and the mixture was stirred under reflux for 8 hr. The mixture was filtered and the filtrate was concentrated to a 700-ml volume. The pH of the concentrate was adjusted to 8 with 30% NH_4OH and the product was extracted continuously with $CHCl_3$. Concentration of the $CHCl_3$ extract yielded 39.3 g (82%) of product, which is readily purified by chromatography on silica gel (above) without prior slow development, yielding 8.8 g of starting material and 29.0 g of **5**, mp 199–200°. *Anal.* Calcd for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.42; N, 14.73. Found: C, 69.53; H, 7.49; N, 14.65.

(7) Melting points were determined on a Koefler hot stage and are uncorrected. The ir spectra of all the compounds were consistent with the assigned structures. The nmr spectra were obtained on Varian A-60 and HA-100 spectrometers; concentrations were generally 5–10% (*w*/*v*), although a few samples were examined in the 10–20% range on the lower frequency instrument.

(8) The $CuCl_2 \cdot 2H_2O$ and air are used to regenerate $PdCl_2$ but complicate purification of the product. It is more convenient to use an excess of $PdCl_2$ and omit the $CuCl_2 \cdot H_2O$ and air flow.

3-*endo*-Hydroxy-5-*endo*-carboxybicyclo[2.2.2]octane Lactone (6).—The published methods[6] were modified as follows. Bicyclo-[2.2.2]oct-2-ene-5-carboxylic acid[5,6] (100 g) in 720 ml of 30% (v/v) H_2SO_4 was stirred and heated at 110° for 1 hr. The mixture was cooled, poured onto ice, and extracted with $CHCl_3$. The extract was washed with 10% $NaHCO_3$, dried over $MgSO_4$, filtered, and concentrated under reduced pressure, yielding 74.3 g of **6**, mp 207–208°.

3-*endo*-Hydroxy-5-*endo*-carbamylbicyclo[2.2.2]octane (7).—A solution of 500 mg of **6** in 10 ml of MeOH and 10 ml of liquid NH_3 was heated at 110° for 12 hr. The reaction mixture was concentrated under reduced pressure, and the residue was recrystallized from hot $CHCl_3$–petroleum ether, yielding 500 mg of **7**, mp 188.5–189°. *Anal.* Calcd for $C_9H_{15}NO_2$: C, 63.88; H, 8.94; N, 8.28. Found: C, 64.09; H, 9.24; N, 8.50.

3-Keto-5-*endo*-carbamylbicyclo[2.2.2]octane (8).—A solution of 28.6 g of CrO_3 in 358 ml of 90% AcOH was added dropwise in the course of 2 hr to a stirred solution of 40 g of **7** in 385 ml of AcOH. After being stirred overnight, the mixture was concentrated under reduced pressure, diluted with 300 ml of H_2O, and extracted continuously overnight with $CHCl_3$. The extract was dried over $MgSO_4$, filtered, and concentrated under reduced pressure, yielding 26.3 g of crystallized product that was used in the next step. Recrystallization of a small sample of the product from MeOH–Et_2O gave **8**, mp 183–184°. *Anal.* Calcd for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.63; H, 7.93; N, 8.57.

3-Keto-5-*endo*-cyanobicyclo[2.2.2]octane (9).—A mixture of 1.15 g (7 mmol) of **8** and 1.45 g (7.7 mmol) of TsCl in 5 ml of pyridine was heated at 80° for 2 hr. The mixture was diluted with 5 ml of H_2O and concentrated; the residue as taken up in $CHCl_3$, and the solution was concentrated. After the residue was taken up in $CHCl_3$ and the solution was concentrated a second time, the same procedure was repeated with C_6H_6. The residue was then triturated with C_6H_6, and the mixture was filtered. The C_6H_6 extract was concentrated and the residue was recrystallized from $CHCl_3$–petroleum ether, yielding 0.55 g of **9**, mp 145–152° (subl 90–130°). *Anal.* Calcd for $C_9H_{11}NO$: C, 72.45; H, 7.43; N, 9.39. Found: C, 72.52; H, 7.36; N, 9.44.

3-Keto-5-*endo*-carbiminomethoxybicyclo[2.2.2]octane Hydrochloride (10).—A solution of 250 mg of **9** and 100 mg of MeOH in 5 ml of Et_2O was cooled and saturated with anhydrous HCl. The next day, the mixture was poured into 100 ml of Et_2O and filtered, yielding 220 mg of **10**, mp 170–175°.

3-Keto-5-*endo*-(2-imidazolyl)bicyclo[2.2.2]octane (11).—A solution of 107 g (0.49 mol) of **10** in 240 ml of MeOH was added dropwise in the course of 45 min to 144 g (1.08 mol) of β-aminoacetaldehye diethyl acetal at 55–60°. The mixture was stirred at room temperature for 1 hr and concentrated under reduced pressure, yielding a 239-g residue. The product was dissolved in 1 l. of 6 *N* HCl and heated under reflux for 1 hr. The solution was cooled, extracted with $CHCl_3$, made alkaline with concentrated NH_4OH, and extracted with $CHCl_3$. Concentration of the latter yielded a 60-g residue that was purified by adsorption on 550 g of silica gel packed in CH_2Cl_2, elution with 4% MeOH–CH_2Cl_2, and recrystallization from CH_2Cl_2–Et_2O, yielding 37.1 g of **11**, mp 144–147°. *Anal.* Calcd for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.42; N, 14.73. Found: C, 69.63; H, 7.49; N, 14.70.

Registry No.—**2**, 30338-51-3; **4**, 30338-52-4; **5**, 30338-53-5; **6**, 20507-79-3; **7**, 30338-55-7; **8**, 30338-56-8; **9**, 30338-57-9; **10**, 30338-58-0; **11**, 30338-59-1.

Acknowledgment.—We are indebted to Mr. A. P. Sullivan, Jr., for developing the $PdCl_2$ oxidation of **4** to **5** in the absence of copper salts and to Mr. R. N. Boos and associates for elemental analyses.

Tumor Inhibitors. LXV.[1] Bersenogenin, Berscillogenin, and 3-Epiberscillogenin, Three New Cytotoxic Bufadienolides from *Bersama abyssinica*[2]

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An ethanol extract of the fruits of *Bersama abyssinica* was found to show significant inhibitory activity against cells derived from human carcinoma of the nasopharynx carried in cell culture (KB). The isolation and structural elucidation of three new cytotoxic bufadienolides, berscillogenin (**1**), 3-epiberscillogenin (**2**), and bersenogenin (**3**), are reported. Mass spectrometry and elemental analysis indicated that all three compounds had a $C_{24}H_{30}O_6$ molecular formula. Chemical and spectral evidence support assignment of structure **1** (16β-hydroxyscilloglaucosidin) for berscillogenin. The same enone (**7**) was obtained from manganese dioxide oxidation of **1** and **2**, indicative that the compounds are C-3 epimers. Treatment of **3** with 80% acetic acid afforded both **1** and **2**. This reaction and the nmr spectrum of **3** indicated that it is a Δ^3-5β-hydroxy isomer of berscillogenin (**1**). The isolation and identification of hellebrigenin 3-acetate (**4**) and scilliglaucosidin (**5**) are also discussed.

In the course of a continuing search for tumor inhibitors of plant origin,[4] we found that extracts of the fruits of *Bersama abyssinica* Fresen. (*Melianthaceae*)[5] showed significant inhibitory activity against cells derived from human carcinoma of the nasopharynx carried in cell culture (KB).[6] Previously, we have reported systematic studies of the KB-inhibitory principles of the stem bark of *B. abyssinica* which led to the isolation and structural elucidation of the cytotoxic principles, hellebrigenin 3-acetate and hellebrigenin 3,5-diacetate,[7] as well as four novel naturally occurring bufadienolide orthoacetates and two related acetate esters.[1] The observation that hellebrigenin 3-acetate showed significant activity *in vivo* against the Walker intramuscular carcinosarcoma 256 in rats stimulated further

(1) Part LXIV: S. M. Kupchan, I. Ognyanov, and J. L. Moniot, *Bioorg. Chem.*, in press.

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(3) Author to whom inquiries should be directed: Department of Chemistry, University of Virginia.

(4) S. M. Kupchan, *Trans. N. Y. Acad. Sci.*, **32**, 85 (1970).

(5) Fruits of *B. abyssinica* were collected in Ethiopia, Jan 1968. The authors acknowledge with thanks receipt of the dried plant material from Dr. Robert E. Perdue, U. S. Department of Agriculture, Beltsville, Md., in accordance with the program developed with USDA by the Cancer Chemotherapy National Service Center (CCNSC).

(6) Cytotoxicity was assayed under the auspices of the CCNSC and the procedures were those described in *Cancer Chemother. Rep.*, **25**, 1 (1962). Cytotoxicity was also assayed by differential agar diffusion by Professor D. Perlman, University of Wisconsin; *cf.* D. Perlman and J. L. Schwartz, *J. Pharm. Sci.*, **58**, 633 (1969).

(7) S. M. Kupchan, R. J. Hemingway, and J. C. Hemingway, *J. Org. Chem.*, **34**, 3894 (1969).

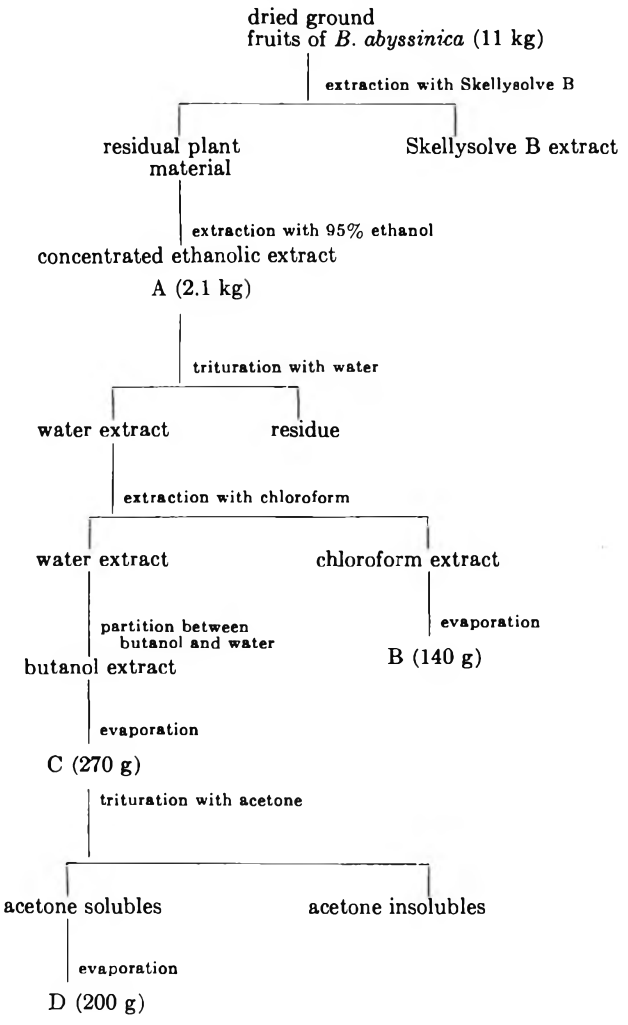
TABLE I

CYTOTOXICITY OF BUFADIENOLIDES FROM THE FRUITS OF *B. abyssinica* AGAINST CELL CULTURE (KB)

Compd	ED_{50}, μg/ml
1	2.8×10^{-2}
2	6.2×10^{-1}
3	4.6×10^{-3}
5	2.0×10^{-3}

CHART I

FRACTIONATION OF CYTOTOXIC EXTRACT FROM *B. abyssinica* FRESEN



studies into the cytotoxic constituents of *B. abyssinica*. We report here in detail the systematic fractionation of the active extract of the fruit of *B. abyssinica* and the isolation of three new cytotoxic A-ring unsaturated bufadienolides, berscillogenin (**1**), 3-epiberscillogenin (**2**), and bersenogenin (**3**), in addition to the previously known hellebrigenin 3-acetate (**4**)[7] and scilliglaucosidin (**5**)[8] (see Table I for cytotoxicity data).

The dried fruit of *B. abyssinica* was defatted by extracting continuously with Skellysolve B and the residue was extracted with 95% ethanol. The concentrated ethanolic extract (A) was triturated with water and the water was extracted extensively with chloroform (B) (see Chart I for summary). The aqueous layer was then extracted with butanol (C). Both fractions B and C were active (9KB) and possessed the ultraviolet chromophore characteristic for the dienolide ring (λ_{max} near 295 nm). Subsequently, it was found that by extracting the aqueous solution directly with a mixture of chloroform–butanol (7:3) a greater proportion of the bufadienolides was concentrated into one fraction and the isolation procedure was simplified. Crystalline material could be obtained directly by chromatography on neutral alumina of the chloroform–butanol solubles.

Filtration of the chloroform solubles (B) on neutral alumina and elution with chloroform–methanol provided the bufadienolide-rich fractions E and F. Rechromatography of fraction F on silicAR CC-7 afforded two new crystalline compounds, bersenogenin (**3**) and 3-epiberscillogenin (**2**). Similar rechromatography of fraction E provided hellebrigenin 3-acetate (**4**), identified by comparison with a sample previously isolated from stem bark,[7] and scilliglaucosidin (**5**), identified by comparison of its physical properties with those reported in the literature.[8]

Trituration of the butanol soluble fraction C with acetone, followed by successive chromatographies of the acetone solubles on neutral alumina and silicAR CC-7, afforded a fifth crystalline bufadienolide, berscillogenin (**1**).[9]

On the basis of elemental analyses and mass spectrometry,[10] berscillogenin (**1**), 3-epiberscillogenin (**2**), and bersenogenin (**3**) were assigned the same molecular formula, $C_{24}H_{30}O_6$. All three compounds had very similar ultraviolet and infrared spectra, which showed the characteristics of bufadienolides [uv max near 299 nm (ϵ 6000) and ir peaks near 2.90 (hydroxyl), 5.80 and 6.12 μ (complex carbonyl)]. The nmr spectra showed the characteristic dienolide ring proton signal pattern.[1,11,12]

A comparison of the nmr spectrum of berscillogenin (**1**) with the spectrum of scilliglaucosidin (**5**) was suggestive that the two compounds possessed very similar structures (see Table II). The two spectra were almost superimposable, with the major differences that berscillogenin possessed one more downfield methine proton at τ 5.18, an additional D_2O-exchangeable proton, and a doublet (J = 7 Hz) at τ 7.19 which was characteristic of a deshielded proton at C-17 when a hydroxyl group is located at C-16.[1] Both compounds showed a single unsplit signal in the olefinic region near τ 4.00. These observations and the cooccurrence of scilliglaucosidin (**5**) in *Bersama* fruits led to the hypothesis that **1** was a 16-hydroxyscilliglaucosidin.

Upon acetylation of berscillogenin (**1**), a diacetate (**6**) was obtained. Two downfield methine protons were deshielded, confirming the presence of two secondary hydroxyl groups. Oxidation of **1** with manganese dioxide afforded the enone **7** with an ultraviolet spectrum characteristic of a six-membered-ring α,β-unsaturated ketone. This reaction established that

(8) A. Stoll, A. v. Wartburg, and J. Renz, *Helv. Chim. Acta*, **36**, 1531 (1953).

(9) Berscillogenin (**1**), 3-epiberscillogenin (**2**), and bersenogenin (**3**) have also been isolated in these laboratories from the stem bark of *B. abyssinica* by similar procedures.

(10) We cordially thank Dr. D. Rosenthal, Research Triangle Institute, and Dr. W. E. Baitinger and Dr. W. L. Budde, Purdue University, for the mass spectra.

(11) (a) Ch. Tamm, *Forschr. Chem. Org. Naturst.* **14**, 71 (1957); (b) L. F. Fieser and M. Fieser, "Steroids," Reinhold, New York, N. Y., 1959, p 728.

(12) v. L. Gsell and Ch. Tamm, *Helv. Chim. Acta*, **52**, 551 (1969).

TABLE II[a]

NUCLEAR MAGNETIC RESONANCE DATA

Compd	C-3	C-4	C-16	C-17	C-18	C-19	C-21	C-22	C-23
1	5.48 m	3.93 s	5.18 br t (8)	7.19 d (8)	9.00 s	0.08 s	2.49 dd (2, 1)	1.55 dd (2, 9.5)	3.68 dd (9.5, 1)
2	5.51 m	3.97 d (6)	5.18 br t (8)	7.25 d (8)	9.00 s	0.04 s	2.56 dd (2, 1)	1.52 dd (2, 9.5)	3.74 dd (9.5, 1)
3	4.10 br d (10)	4.32 d (10)	5.25 br t (8)	7.18 d (8)	8.97 s	−0.51 s	2.40 dd (2, 1)	1.30 dd (2, 9.5)	3.68 dd (9.5, 1)
5	5.49 m	3.99 s			9.11 s	0.05 s	2.45 d (2)	1.76 dd (2, 10)	3.67 d (10)
6[b]	4.60 m	4.08 s	4.38 m	7.05 d (8.5)	9.07 s	0.10 s	2.55 (2)	1.51 dd (2, 10)	3.77 d (10)
7		3.98 s	5.22 br t (7)	7.22 d (7)	9.00 s	−0.13 s	2.56 d (2)	1.61 dd (2, 10)	3.76 d (10)
8	4.14 br d	4.41 d			8.97 s		2.56 d (1.5)	2.22 dd (1.5, 10)	3.83 d (10)
9[c-e]	3.95–4.20 br d	4.15 d (10)		6.95 s	9.0 s	0.07 s		3.00 dd (2, 9)	3.69 d (9)
10[c,e]	4.0–4.22 m	4.5 d (10)	5.41 m	7.42 d (4)	9.11 s	−0.07 s		2.24 dd (2, 9)	3.87 d (9)

[a] Spectra were determined on a Varian HA-100 spectrometer in pyridine-d_5 unless otherwise indicated. 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; m, multiplet; br, broad. Numbers in parenthesis denote peak separations in hertz. [b] C-3 acetate, 8.01 s; C-16 acetate, 8.27 s. [c] Deuteriochloroform. [d] C-15, 4.12 s. [e] C-21 signal obscured by solvent.

the second secondary hydroxyl of **1** was allylic to a trisubstituted double bond in a six-membered ring. Furthermore, of all the possible positions for this partial structure on the steroid nucleus, only a Δ^4-3-hydroxy compound would show a broad multiplet for the methine proton on the allylic carbon. The C-3 hydroxyl of **1** was assigned the β configuration on the basis of the unsplit olefinic proton signal (C-4 H) which requires the same configuration as scilliglaucosidin (**5**). The remaining tertiary hydroxyl group was presumed to be β at C-14 by analogy with all other known bufadienolides.[11]

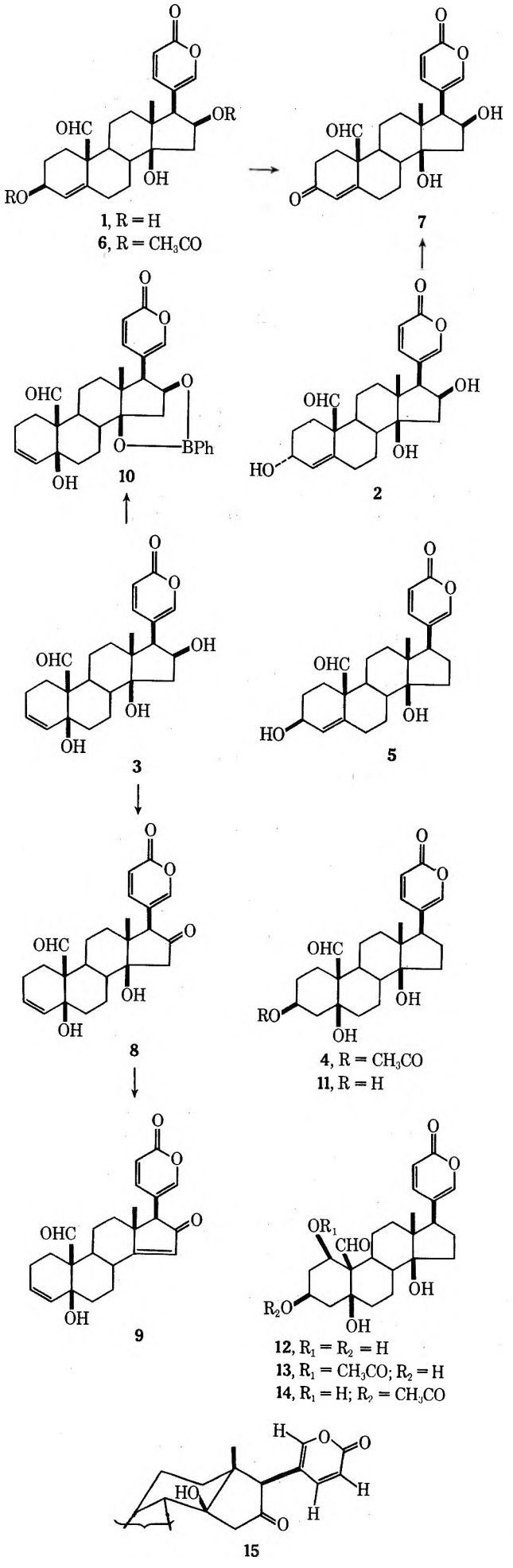
The nmr spectrum of **2** was very similar to the spectrum of berscillogenin (**1**), with the major difference that the olefinic proton signal near τ 4.00 for **2** appeared as a doublet (J = 6 Hz) instead of a singlet. This observation led to the hypothesis that **1** and **2** were epimeric at the allylic alcohol position. Oxidation of **2** with manganese dioxide afforded an enone identical to the one obtained from **1**. Thus **1** and **2** were shown conclusively to be C-3 epimers and, therefore, **2** was assigned the α configuration for the alcohol at C-3.

The nmr spectrum of bersenogenin (**3**) showed a signal for one downfield methine proton (τ 5.25, br t, J = 8 Hz) and a doublet at τ 7.18 (J = 8 Hz), indicative of a secondary hydroxyl function at C-16.[1] There were signals for three D_2O-exchangeable protons, one corresponding to the secondary hydroxyl at C-16 and two persumed to correspond to tertiary hydroxyls. One tertiary hydroxyl group was presumed to be at C-14, and the chemical shift of the C-19 aldehyde proton signal (τ −0.51) strongly suggested that the remaining tertiary hydroxyl was at C-5 (see nmr discussion). The C-5 position appeared most likely also from the standpoint that all other bufadienolides isolated from *Bersama* either possessed an oxygen function at C-5 or could have arisen from a dehydration reaction involving C-5. Signals for two olefinic protons were also notable in the nmr spectrum. The higher field proton signal appeared as a doublet (J = 10 Hz) at τ 4.32 and the other proton as a broad doublet (J = 10 Hz) at τ 4.1. This splitting pattern was consistent with a disubstituted cis double bond with one carbon attached to a methylene group and the other carbon to a quaternary center. It appeared reasonable that **3** was an isomeric A-ring allylic alcohol with a disubstituted double bond and a tertiary hydroxyl group, in contrast to the trisubstituted double bond and secondary hydroxyl group found in **1** and **2**. Further support for this structure was obtained by treatment of **3** with 80% acetic acid at 80° for 30 min, which afforded equal amounts of **1** and **2** along with an unidentified nonpolar product. This interconversion established that the tertiary hydroxyl was at C-5 and the double bond at C-3.

Confirmation of the presence of the C-16 hydroxyl group was accomplished by a modification of the method of Van Wyk and Enslin used for the same purpose.[13] Oxidation of bersenogenin (**3**) with Jones reagent afforded the ketone **8** which was dehydrated with Florisil[14] to afford the five-membered-ring α,β-unsaturated ketone **9** [λ_{max} 232 nm (ϵ 13,800)]. These experiments confirmed the presence of both the C-14 and C-16 hydroxyl groups. The C-16 hydroxyl was demonstrated to be cis to the 14β hydroxyl by preparation of the 14,16-phenyl boronic ester.[15] Attempts to form a 14,16-cyclic sulfite of **1**, **2**, or **3** yielded intractable mixtures, presumably due to side reactions in the A ring. A further indication of the cis relationship between the C-14 and C-16 hydroxyl groups was the observation that for berscillogenin diacetate (**6**) the C-16 acetate methyl signal was shifted upfield to τ 8.27 which, according to Gsell and Tamm,[12] is indicative of a C-14β hydroxyl and C-16β acetate relationship.

The β configuration has been assigned to the C-17 dienolide ring on the basis of the similarity of the chemical shift and coupling constant of the C-17α proton to those of the cooccurring C-17β dienolides.[1,16] Formation of the phenyl boronic ester **10** caused a decreased in the $J_{16,17}$ coupling constant from 8 to 4 Hz. Examination of a Drieding model indicates that, if the C-16 and C-17 protons were trans, the dihedral angle between them would be close to 90°, and a coupling constant significantly lower than that observed would be expected. Furthermore, it had been previously noted that the C-22 proton signal for other 16β-hydroxybufadienolides in pyridine solution was

(13) A. J. Van Wyk and P. R. Enslin, *J. S. Afr. Chem. Inst.*, **21**, 33 (1968).
(14) R. H. Bible, Jr., and N. W. Atwater, *J. Org. Chem.*, **26**, 1336 (1961).
(15) M. Fieser and L. Fieser, "Reagents for Organic Synthesis," Vol. 2, Wiley-Interscience, New York, N. Y., 1969, p 317.
(16) Earlier studies have demonstrated a marked difference in the characteristics of C-17β and C-17α proton signals in the cardenolide series: D. Satoh, H. Ishii, K. Tori, T. Tozyo, and J. Morita, *Justus Liebigs Ann. Chem.*, **686**, 246 (1965).



shifted downfield by *ca.* 0.33 ± 0.4 ppm.[1] The C-21 and C-23 protons were only shifted slightly. This downfield shift appears to be diagnostic for 16β-hydroxyl groups and requires a cis relationship between the dienolide ring and the group at C-16. This same downfield shift was observed for bufadienolides **1**, **2**, and **3**.

Finally, it had been noted previously that the mass spectra for bufadienolides with a 16β-hydroxyl group showed an extra initial mode of fragmentation, resulting in a series of peaks 44 mass units (CO_2) lower than the fragmentation pattern for bufadienolides without 16β-hydroxyl group.[1] This fragmentation apparently involves both the hydroxyl group and the dienolide ring and requires a cis relationship. All three compounds (**1**, **2**, and **3**) showed this characteristic fragmentation pattern.

The above arguments have led to assignment of the structures 3β,14β,16β-trihydroxy-19-oxo-Δ⁴-bufa-20,22-trienolide (**1**) for berscillogenin, 3α,14β,16β-trihydroxy-19-oxo-Δ⁴-bufa-20,22-trienolide (**2**) for 3-epiberscillogenin, and 5β,14β,16β-trihydroxy-19-oxo-Δ³-bufa-20,22-trienolide (**3**) for bersenogenin.

Nmr Spectral Correlations.—The nmr spectral data observed for this series of bufadienolides agrees well with the chemical shift–structural correlations reported earlier.[1,12] In addition, it has been observed that, for spectra obtained in pyridine-d_5 solution, it is possible to make reliable predictions of the numbers of hydroxyl groups cis–vicinal to the C-19 aldehyde group from its chemical shift (see Table III). In the absence of cis–vicinal hydroxyl substituents, the aldehyde proton signal is observed near τ 0.00 with one group, near τ −0.45, and, with two groups, near τ −0.65.

TABLE III
CHEMICAL SHIFT OF C-19 ALDEHYDE PROTON IN PYRIDINE-d_5 SOLUTION

Compd	Chemical shift (τ) of C-19 proton	Substituents
Berscillogenin (1)	0.08	3β-OH, Δ⁴
3-Epiberscillogenin (2)	0.04	3α-OH, Δ⁴
3-Dehydroberscillogenin (7)	−0.13	Δ⁴
16-Dehydro-Δ¹⁴-bersenogenin (9)	−0.40	5β-OH
Hellebrigenin (11)	−0.47	3β,5β-diOH
Bersaldegenin 1-acetate (13)	−0.48	1β-OAc, 3β,5β-diOH
Bersaldegenin 3-acetate (14)	−0.63	1β,5β-diOH, 3β-OAc
Bersaldegenin (12)	−0.70	1β,3β,5β-triOH

It has been suggested that one conformer of the dienolide ring of 16β-hydroxybufadienolides is favored, due to steric interactions.[1] This was based on the observed specific increase in the solvent shift of the C-22 dienolide ring proton signal of 16β-hydroxybufadienolides when the nmr spectrum was measured in pyridine. Further support for the preference for one conformation was obtained from the nmr spectrum of the 16-oxobufadienolide **8**. In this case the C-21 and C-23 proton signals are shifted only slightly, while the C-22 proton signal is shifted to a higher field by about τ 0.9. This strongly suggests that the C-22 proton and not the C-21 proton lies in the conical shielding region above the C-16 carbonyl group as shown in **15**.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are corrected. Infrared spectra were determined on a Perkin-Elmer 257 and 337 recording spectrophotometers. Ultraviolet asorption spectra were determined on a Coleman Model EPS-3T recording spectrophotometer. Specific rotations were determined on a Rudolph Model 30 polarimeter. Skellysolve B refers to the hydrocarbon fraction with bp 60–68°. Evaporations were carried out under reduced pressure at temperatures of less than 40°. Microanalyses were carried out by Spang Microanalytical Laboratory, Ann Arbor, Mich.

Extraction and Preliminary Fraction of *Bersama abyssinica*.—Ground dry fruits of *Bersama abyssinica* (11 kg) were extracted continuously with Skellysolve B. The residue was extracted with 95% ethanol for 16 hr and the ethanol extract evaporated under reduced pressure to yield a dark green gum (A, 2.1 kg). The extract was triturated with water (14 l.) and the gummy insolubles were removed by filtration. The water extract (in 2-l. portions) was extracted with fifteen to twenty 500-ml portions of chloroform (which was distilled and reused) until the chloroform soluble materials were removed from the water. The chloroform solubles were combined and evaporated to afford fraction B (140 g). A portion of the remaining water soluble fraction (8 l.) was partitioned between water and 1-butanol to afford a 1-butanol extract which was evaporated to yield C (270 g). The 1-butanol extract (C) was triturated with acetone and the filtrate was evaporated to afford D (200 g).

Isolation of Bufadienolides.—The chloroform solubles B were filtered rapidly through neutral alumina (activity 1) by absorbing from chloroform onto 300 g of absorbent, adding to a column of 2.2 kg of alumina, and eluting with chloroform (0.75 l.), 1% methanol in chloroform (3.7 l.), 3% methanol in chloroform (4.5 l.), and 5% methanol in chloroform (5.1 l.). Fractions were combined on the basis of thin layer chromatography on silica gel (E. Merck) plates, developed with chloroform–acetone–methanol (4:1:0.3), and visualized by spraying with a 3% ceric sulfate in 3 *N* sulfuric acid solution followed by heating. Fraction E (12 g) was obtained by evaporation of the fraction eluted with 1% methanol in chloroform and fraction F (13.6 g) by evaporation of the 3% methanol in chloroform eluate. Fraction E was rechromatographed on SilicAR CC-7 (1.5 kg). The column was eluted with chloroform (4 l.) and the solvent was evaporated to give G (0.81 g). The solvent was changed to 1% methanol in chloroform (4 l.) and the elutate evaporated to afford H (2.1 g). Rechromatography of G on neutral alumina afforded a crystalline fraction. Recrystallization from methanol afforded colorless prisms of hellebrigenin 3-acetate (**4**), identified by comparison of its infrared and nmr spectra with a sample previously isolated from stem bark.[7] Fraction H was crystallized from acetone–hexane to afford 1.2 g of colorless prisms, mp 235–245°. Recrystallization from methanol afforded colorless prisms, mp 240–243°, $[\alpha]^{25}D$ +128° (*c* 0.93, $CHCl_3$). The melting point and infrared, ultraviolet, and nmr spectral data were identical with those reported for scilliglaucosidin (**5**).[8] Fraction F was rechromatographed on SilicAR CC-7 (1.2 kg) by elution with 4% methanol in chloroform (4 l.). Evaporation of the solvent gave I (1.5 g). By elution with 6% methanol in chloroform (6 l.) and evaporation of the solvent, fraction J (0.2 g) was obtained. Fraction I was crystallized from acetone to yield colorless prisms (1.1 g) of **3**, mp 189–190° dec. Recrystallization from methanol afforded rhombs, mp 202–204° dec, and from chloroform, needles: mp 226–230° dec; $[\alpha]^{26}D$ +108° (*c* 1.42, $CHCl_3$); uv max (MeOH) 298 nm (ε 6500); ir (KBr) 3.31, 3.39, 3.46, 3.65, 5.85, 6.14, 6.47, 6.72, 6.89, 7.14, 7.59, and 7.96 μ; mass spectrum *m/e* 414 (M^+), 396, 378, 370, 368, 360, 350, 330, 324, 307.

Anal. Calcd for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.59; H, 7.39.

Crystallization of fraction J from methanol afforded 0.080 g of **2** as colorless rhombs: mp 213–215° dec; $[\alpha]^{26}D$ +84° (*c* 0.94, CH_3OH); uv max (95% C_2H_5OH) 299 mμ (ε 6000); ir (KBr) 3.00, 3.39, 5.82, 6.15, 6.50, 6.91, 7.05, 7.82, 7.99, 8.71, 9.05, 9.15, and 9.90 μ; mass spectrum *m/e* 414 (M^+), 396, 378, 370, 368, 360, 350, 330, 324, 307.

Anal. Calcd for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.39; H, 7.43.

The acetone solubles D were chromatographed on neutral alumina (2 kg, activity I) by elution with chloroform (6 l.) followed by 20% methanol in chloroform (6 l.). Evaporation of the latter fraction gave K (6.9 g). Rechromatography of a portion of K (3.0 g) on SilicAR CC-7 (300 g) by elution with 4% methanol in chloroform afforded 0.135 g of **1**. Crystallization from methanol gave colorless rhombs: mp 214–216° dec; $[\alpha]^{26}D$ +42° (*c* 1.0, CH_3OH); uv max (95% C_2H_5OH) 299 nm (ε 6000); ir (KBr) 2.84, 2.93, 3.05, 3.38, 3.48, 5.83, 6.01, 6.20, 6.50, 6.90, and 8.80 μ; mass spectrum *m/e* 414 (M^+) 396, 378, 370, 368, 360, 350, 330, 324, 307.

Anal. Calcd for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.45; H, 7.25.

Interconversion of Bufadienolides.—A solution of bersenogenin (**3**, 100 mg) in 80% acetic acid was stirred and heated at 80° for 30 min. The solvent was removed by evaporation and the residue dissolved in 20 ml of chloroform, which was washed with 5% sodium bicarbonate solution and saturated salt solution and dried ($MgSO_4$). The residue (99 mg) was chromatographed on SilicAR CC-7 (15 g) and eluted with 1% methanol–chloroform. The solvent was evaporated to afford an oil (63 mg) which was not characterized. The solvent was changed to 2% methanol–chloroform and a second fraction was collected (7 mg). Crystallization from methanol afforded berscillogenin (**1**). Continued elution with 4% methanol–chloroform afforded a third fraction (7 mg) which was crystallized from methanol to afford 3-epiberscillogenin (**2**). Both compounds were identified by melting point, mixture melting point, and infrared and mass spectral comparisons.

3-Dehydroberscillogenin (7). A.—A solution of berscillogenin (**1**, 36 mg) in chloroform (5 ml) was stirred at room temperature with manganese dioxide (0.464 g) for 48 hr, centrifuged, and decanted. The manganese dioxide[17] was washed with hot acetone (20 ml) and the combined supernatant solutions were evaporated and chromatographed on silica gel tlc plates to afford recovered berscillogenin (16 mg) and the enone **7** (12 mg). Crystallization from methanol gave colorless rhombs: mp 258–264° dec; uv max (CH_3OH) 240 nm (ε 14,000) and 298 (6000); mass spectrum *m/e* 412 (M^+), 394, 384, 376, 368, 350, 348, 321, 303.

Anal. Calcd for $C_{24}H_{28}O_6$: 412.1885. Found: 412.1895.

B.—The allylic oxidation of 3-epiberscillogenin (18 mg) using the same procedure as for berscillogenin also gave the enone **7** (4 mg), shown to be identical with the product obtained from berscillogenin by melting point, tlc, infrared, ultraviolet, and mass spectral comparisons.

Berscillogenin 3,16-Diacetate (6).—Acetic anhydride (0.5 ml) was added dropwise to a solution of **1** (19.5 mg) in dry pyridine (1.5 ml) and the mixture was stirred for 18 hr at room temperature. The solution was evaporated under a stream of nitrogen, methanol added (2 ml), and the solution evaporated again under nitrogen to afford a solid, which was crystallized from methanol as colorless rhombs (17 mg): mp 242–244° dec; uv max (CH_3OH) 299 nm (ε 6200); ir (KBr) 6.12 and 7.98 μ; mass spectrum *m/e* 498 (M^+), 438, 420, 410, 378, 360, 349, 335, 331, 317.

Anal. Calcd for $C_{28}H_{34}O_8$: C, 67.47; H, 6.87. Found: C, 67.32; H, 6.87.

16-Dehydrobersenogenin (8).—To 20 ml of acetone flushed with nitrogen was added bersenogenin (**3**, 50 mg). The solution was cooled to 10° and 0.04 ml of Jones reagent[18] (0.11 mmol of chromium trioxide) was added in one portion. The ice bath was removed and the stirred reaction mixture was allowed to warm to room temperature over a period of 15 min. The green solution was poured into 400 ml of water which was extracted with six 20-ml portions of chloroform. The combined chloroform extracts were washed with saturated salt solution, dried ($MgSO_4$), and evaporated to afford a clear oil (51 mg). Preparative thin layer chromatography on silica gel, followed by crystallization from methanol afforded ketone **8** (15 mg) as colorless rosettes: mp 220–222° dec; uv max (95% C_2H_5OH) 299 nm (ε 4000); ir (KBr) 2.83, 2.94, 3.41, 3.48, 5.75 (sh), 5.82, 6.50, and 6.90 μ; mass spectrum *m/e* 412 (M^+), 394, 376, 367, 366, 365, 348, 257.

Anal. Calcd for $C_{24}H_{28}O_6$: C, 69.89; H, 6.84. Found: C, 69.56; H, 6.84.

16-Dehydro-Δ^{14}-bersenogenin (9).—To a solution of **8** (30 mg) in 20 ml of benzene–chloroform (1:1) was added Florisil[14] (0.2 g). The slurry was refluxed with stirring for 10 hr and filtered, and the residue chromatographed on preparative tlc silica gel plates to afford enone **9** as a colorless solid (12 mg). Crystallization from methanol gave colorless rhombs: mp 239–241°; uv max

(17) O. Mancera, G. Rosenkranz, and F. Sondheimer, *J. Chem. Soc.*, 2189 (1953).

(18) C. Djerassi, R. R. Engle, and A. Bowers, *J. Org. Chem.*, **21**, 1547 (1956).

(95% C_2H_5OH) 232 nm (ϵ 13,800) and 300 (5100); ir (KBr) 2.95, 3.35, 3.40, 3.50, 5.72 (sh), 5.81, 5.90, and 6.22 μ; mass spectrum m/e 394 (M^+), 376, 358, 348, 347, 257.

Anal. Calcd for $C_{24}H_{26}O_5$: 394.1780. Found: 394.1782.

Bersenogenin 14,16-Phenylboronate (10).—To a solution of bersenogenin (**3**, 19.5 mg) in dry acetone was added phenylboronic acid (5.74 mg) and the solution was allowed to stand at room temperature for 7 min. On addition of hexane (1 ml) crystals formed. The product was collected by filtration and recrystallized from chloroform–hexane to give the cyclic boronic ester (**10**, 13 mg) as needles: mp 221–224°; uv max (CH_3OH) end absorption, 298 nm (ϵ 6100); mass spectrum m/e 423 ($M - C_6H_5$), 405, 377.

Anal. Calcd for $C_{30}H_{33}O_6B$: C, 72.00; H, 6.60; B, 2.20. Found: C, 71.84; H, 6.73; B, 2.12.

Registry No.—**1**, 30344-95-7; **2**, 30344-96-8; **3**, 30344-97-9; **5**, 510-62-3; **6**, 30344-99-1; **7**, 30345-00-7, **8**, 30345-01-8; **9**, 30345-02-9; **10**, 30345-03-0; **11**, 465-90-7; **12**, 23044-69-1; **13**, 23044-67-9; **14**, 23044-72-6.

Identification and Synthesis of the Four Compounds Comprising the Boll Weevil Sex Attractant[1a]

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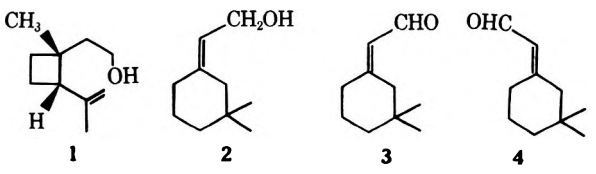
Four terpenoid compounds, (+)-*cis*-2-isopropenyl-1-methylcyclobutaneethanol, (1), *Z*-3,3-dimethyl-$\Delta^{1'}$-cyclohexaneethanol (2), *Z*-3,3-dimethyl-$\Delta^{1,\alpha}$-cyclohexaneacetaldehyde (3), and *E*-3,3-dimethyl-$\Delta^{1,\alpha}$-cyclohexaneacetaldehyde (4), were identified as the components of the male sex pheromone of the boll weevil. The synthesis and structural assignments of the four compounds are also reported.

Insect sex attractants (pheromones) are currently of considerable interest since they may provide a generally nontoxic method of surveying and controlling insect populations.[2] The growing concern over the environmental pollution and ecological imbalance caused by insecticides has further stimulated interest in this area.

A pheromone complex emitted by live male boll weevils (*Anthonomus grandis* Boheman) elicits a response by female weevils in laboratory assays.[3] The volatile components of this complex and other compounds were obtained by steam distillation of the crude extracts of 4.5 million weevils and 54.7 kg of weevil feces. The concentrated dichloromethane extract of the steam distillate mimicked the attractiveness of live males in laboratory tests.[4]

We have now isolated, identified, and synthesized four terpenoid compounds (**1**, **2**, **3**, **4**) which account for all of the attractancy of live male weevils. The response by females to mixtures of the synthetic compounds is identical with their response to corresponding mixtures of the natural compounds.



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

The extract of the steam distillate from weevils and their feces was fractionated by column chromatography on Carbowax 20M coated[5] silica gel. None of the individual fractions from this column were attractive to females, but the combination of two of the fractions was as active as the original distillate. Each of these two fractions was then separately fractionated on a column containing Adsorbosil-CABN (25% $AgNO_3$ on silica gel).

Various recombinations of all the fractions from both $AgNO_3$–silica gel columns yielded two fractions, one from each column, that were attractive together but totally unattractive separately. Each of these latter two active fractions was then fractionated by glpc on Carbowax 4000 and SE-30. Three components were collected which were attractive when all three were combined but which were unattractive individually or in pairs. Rechromatography on Carbowax 4000, SE-30, and a 50-ft support coated open tubular (SCOT) column showed two of these components to be pure (**1**, **2**) and the third to consist of two compounds (**3**, **4**). Concentrations of compounds **1**, **2**, **3**, and **4** in fecal material, determined by glpc, were 0.76, 0.57, 0.06, and 0.06, respectively. Concentrations in weevils were about tenfold less. Compound **1** was identified as (+)-*cis*-2-isopropenyl-1-methylcyclobutaneethanol on the basis of mass, ir, and nmr spectra.[6] The cis configuration was assigned by comparison with the nmr spectrum of the synthetic cis isomer (*vide infra*). The optical rotation was measured on 11 mg of the pure natural compound. The specific rotation was estimated to be about +50° (±10°).

Scheme I outlines the synthesis of *cis*-2-isopropenyl-1-methycyclobutaneethanol. The photocycloaddition of isoprene and 3-buten-2-one produced several products, many of them in greater yield than the desired isomer of 2-methyl-2-vinylcyclobutyl methyl ketone **5**. Compounds **7**, **8**, **9**, **10**, **11**, and **12** were tentatively iden-

(1) (a) Taken in part from the Ph.D. thesis of J. H. Tumlinson, Mississippi State University, State College, Miss., June 1969. (b) Authors to whom inquiries should be addressed at the Boll Weevil Research Laboratory, Entomology Research Division, Agricultural Research Service, U. S. Department of Agriculture, State College, Miss. 39762.

(2) M. Jacobson, "Insect Sex Attractants," Interscience, New York, N. Y., 1965.

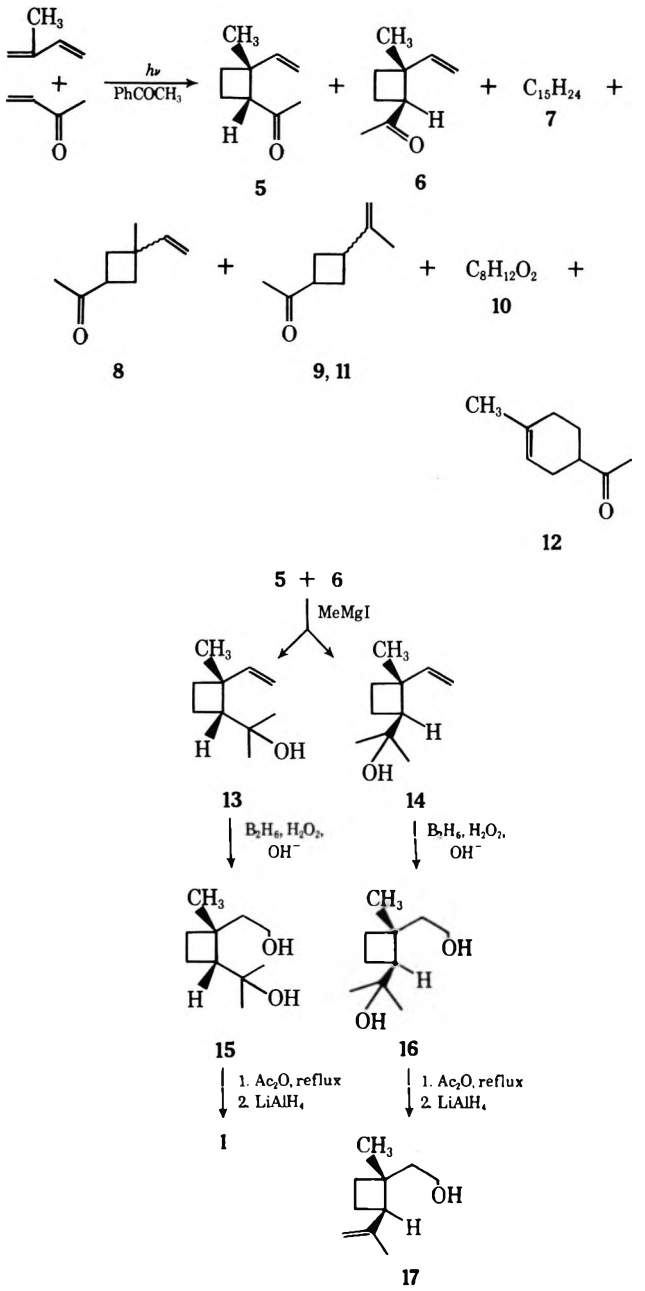
(3) (a) W. H. Cross and H. C. Mitchell, *J. Econ. Entomol.*, **59**, 1503 (1966); (b) D. D. Hardee, E. B. Mitchell, and P. M. Huddleston, *ibid.*, **60**, 169 (1967); **60**, 1221 (1967).

(4) J. H. Tumlinson, D. D. Hardee, J. P. Minyard, A. C. Thompson, R. T. Gast, and P. A. Hedin, *ibid.*, **61**, 470 (1968).

(5) Mention of a proprietary product in this paper does not constitute an endorsement of this product by the U. S. Department of Agriculture.

(6) A preliminary report of this work discussing the isolation and identification was published by J. H. Tumlinson, D. D. Hardee, R. C. Gueldner, A. C. Thompson, P. A. Hedin, and J. P. Minyard, *Science*, **166**, 1010 (1969).

SCHEME I



tified on the basis of spectral data and elemental analyses. Irradiation with the Vycor filter for 65 hr produced the same amounts of products **5**–**12** that were produced in 130 hr with the Pyrex filter but the amount of polymer produced with the Vycor filter was about tenfold greater. The major reaction product, 4-methyl-3-cyclohexenyl methyl ketone (**12**), resulted from the thermal Diels–Alder addition of isoprene and 3-buten-2-one.[7a] The yield of this side reaction product was minimized by low reaction temperatures.

Because it was impossible to separate the *cis*- and *trans*-2-methyl-2-vinylcyclobutyl methyl ketones by any chromatographic methods available, the Grignard addition was carried out on the mixture. The resulting tertiary alcohols (**13**, **14**) were readily separated by glpc on Carbowax 4000 and were purified in this way. Since the Grignard addition produced quantitative yields of the alcohols, as determined by glpc, it was calculated that the *cis*- and *trans*-2-methyl-2-vinylcyclobutyl methyl ketones were each produced in 1.2% yield in the photocycloaddition. At this point, however, positive assignment of configuration to the ketones and alcohols was impossible.

Subsequently, the two α,α,2-trimethyl-2-vinylcyclobutanemethanols (**13**, **14**) were hydroborated separately to produce the two diols (**15**, **16**).[7b] The diols were each acetylated and the esters pyrolyzed in a single step. The resulting unsaturated esters were each reduced with $LiAlH_4$ to the alcohols, *cis*- and *trans*-2-isopropenyl-1-methylcyclobutaneethanols (**1** and **17**), respectively.

The nmr spectra of *cis*- and *trans*-2-isopropenyl-1-methylcyclobutaneethanol are presented in the microfilm. The significant feature which allowed assignment of the trans configuration to **17** was the upfield shift of the methyl singlet from 1.22 in the cis to 0.92 in the trans due to the diamagnetic shielding of the spatially adjacent olefinic π electrons in the trans isomer. Similarly, the methylene (CH_2CH_2OH) was shifted downfield in the trans isomer since it is not adjacent to the olefinic bond in the isopropenyl group as in the cis compound. The naturally occurring compound and the synthetic compound **1** assigned the cis configuration on the basis of its nmr spectrum were identical in nmr, ir, and mass spectra and in biological activity.[8]

The structure of *Z*-3,3-dimethyl-$\Delta^{1,8}$-cyclohexaneethanol[9] (**2**) was elucidated on the basis of its mass, nmr, and ir spectra.[6]

Reduction of compound **2** on palladium catalyst immediately ahead of a Carbowax 20M SCOT column[10] gave a compound with a parent mass of 156 and other major fragments in the spectrum two mass units higher than the corresponding fragments of compound **2**, indicating one unsaturation.

The OH stretch at 3610 cm^{-1}, less hydrogen bonded than compound **1**, the upfield shift of a one-proton signal (1.90) in the nmr spectrum on dilution, and removal of this signal on addition of TCAIC ($Cl_3CCONCO$) confirmed that the compound was an alcohol. The cis or *Z* configuration about the double bond was assigned by comparison of the nmr spectra of the cis *Z* (**19**) and trans *E* (**20**) synthetic ester precursors (*vide infra*).

Further proof of structure was obtained by microozonolysis.[11] One major component was obtained that was identical in nmr, mass spectrum, and glpc behavior with that of 3,3-dimethylcyclohexanone.

Scheme II shows the synthesis of *Z*-3,3-dimethyl-$\Delta^{1,8}$-cyclohexaneethanol (**2**). The 3,3-dimethylcyclohexanone was produced from 3-methyl-2-cyclohexen-1-one by the method of Büchi, *et al.*[12] The addition of ethyl bromoacetate (Reformatsky) to the 3,3-dimethyl-

(7) (a) E. F. Lutz and G. M. Bailey, *J. Amer. Chem. Soc.*, **86**, 3899 (1964); (b) H. C. Brown and B. C. Subba Rao, *ibid.*, **81**, 6428 (1959).

(8) The ir, nmr, and mass spectra for compounds **1** and **2** and the mass spectra for **3** and **4** will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Reprint Department, ACS Publications, 1155 Sixteenth St., N.W., Washington, D.C. 20036, by referring to author, title of article, volume, and page number. Remit $3.00 for photocopy or $2.00 for microfiche.

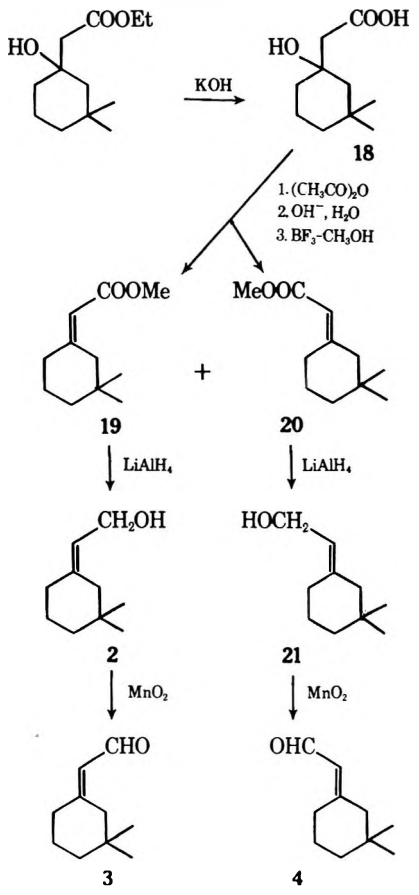
(9) The configurational descriptors *Z* and *E* are used in place of cis and trans, respectively. See "IUPAC Tentative Rules for the Nomenclature of Organic Chemistry, Section E. Fundamental Stereochemistry," *J. Org. Chem.*, **35**, 2851 (1970).

(10) M. Beroza and R. Sarmiento, *Anal. Chem.*, **38**, 1042 (1966).

(11) M. Beroza and B. A. Bierl, *ibid.*, **38**, 1976 (1966); **39**, 1131 (1967).

(12) G. Büchi, O. Jeger, and L. Ruzicka, *Helv. Chim. Acta*, **31**, 241 (1948).

SCHEME II

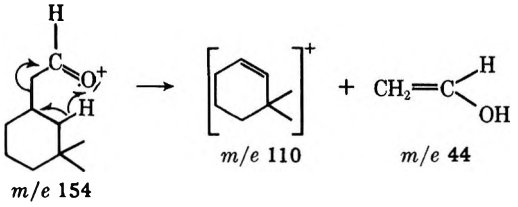


cyclohexanone[13] and then saponification yielded 1-hydroxy-3,3-dimethylcyclohexaneacetic acid. The hydroxy acid was dehydrated with acetic anhydride,[14] and the unsaturated acids were esterified with BF_3–CH_3OH. The cis and trans unsaturated esters were separated by distillation, further purified by glpc on a preparative SE-30 column, and reduced to the respective cis and trans alcohols with $LiAlH_4$.

Assignment of the *Z* (cis) and *E* (trans) configurations was made by comparing the nmr spectra of the *Z* and *E* esters. The *Z* ester spectrum showed a singlet at 5.55 ($MeOOCCH{=}CRCH_2CR'R_2''$) and a singlet at 2.61 ($MeOOCCH{=}CRCH_2CR'R''$). This latter signal indicated a considerable paramagnetic deshielding of the methylene at the 2 position on the ring by the spatially adjacent carbonyl group in the *Z* ester. The *E* ester, on the other hand, had a singlet at 5.42 (1 H, olefinic) produced by the more shielded proton cis to the geminal methyls. A triplet at 2.73 (2 H) occurs because the ring methylene at the 6 position is deshielded by the adjacent cis carbomethoxy group and split by the adjacent ring methylene. The ring methylene at the 2 position of *E* produced a singlet at 1.93, well upfield of the analogous methylene (2.12) at the 6 position in the *Z* ester.[15] The natural compound was identical in all respects including insect attractancy with the synthetic 3,3-dimethyl-$\Delta^{1,\beta}$-cyclohexaneethanol assigned the *Z* configuration.

(13) C. A. Vodoz and H. Schinz, *Helv. Chim. Acta*, **33**, 1040 (1950).
(14) G. H. Elliott and R. P. Linstead, *J. Chem. Soc.*, 776 (1938).
(15) These assignments are consistent with those made by R. H. Bible, Jr., "Interpretation of NMR Spectra, an Empirical Approach," Plenum Press, New York, N. Y., 1968, pp 17, 18.

When compounds **3** and **4** were eluted as a single peak from a glpc column into 2,4-dinitrophenylhydrazine reagent on a tlc plate,[16] a derivative was produced which had an R_f similar to that of standard terpene carbonyls. The mass spectra of compounds **3** and **4** were nearly identical with each other and similar to compound **2**. The parent peak had a *m/e* of 152 in both cases, appropriate for a monocyclic terpene aldehyde or ketone with one unsaturation. Reduction of compounds **3** and **4** at the inlet of a gas chromatograph[10] produced only one peak with a parent mass of 154, which confirmed the single unsaturation. The base peak in the spectrum of saturated **3** and **4**, *m/e* 110, suggests a facile loss of the elements of acetaldehyde, and such a rearrangement peak suggests a $-CH_2CH{=}O$ side chain which might easily cleave by a cyclic rearrangement process analogous to the following.



m/e 154 *m/e* 110 *m/e* 44

On the basis of these data, structures **3** (*Z*-3,3-dimethyl-$\Delta^{1,\alpha}$-cyclohexaneacetaldehyde) and **4** (*E*-3,3-dimethyl-$\Delta^{1,\alpha}$-cyclohexaneacetaldehyde) were postulated.

Postulated structures **3** and **4** were quickly confirmed by synthesis as follows. Compound **2** and its *E* isomer were readily converted to the *Z* and *E* aldehydes **3** and **4**, respectively, by stereospecific oxidation with active MnO.[17] The mass spectra, glpc behavior, and biological activity of the natural compounds **3** and **4** were identical with those of the synthetic compounds assigned the *Z* and E configurations, respectively.

Synthetic compounds (**1**, **2**, **3**, **4**) are as attractive to female boll weevils as the natural compounds when they are combined in the proper proportions. To our knowledge, none of these four compounds has been found previously in natural products. Compounds **2**, **3**, and **4** have been synthesized but not stereochemically characterized. It seems likely that the two 3,3-dimethyl-$\Delta^{1,\beta}$-cyclohexaneethanols and the corresponding aldehydes were obtained enroute to the synthesis of 3-methyl-4-allocyclogeranyl-2-butenoic acid and related compounds.[13,18,19] More recently, Corey[20] has synthesized *trans*-2-isopropenyl-1-methylcyclobutaneethanol, which appears identical in ir and nmr spectra with our trans compound **17**, and Zurflüh,[21] *et al.*, have reported the synthesis of *cis*-2-isopropenyl-1-methylcyclobutaneethanol which is identical in nmr spectrum and biological activity with our cis isomer. Our trans isomer **17** which may have contained a trace of the cis isomer was active only at 100- to 200-fold greater concentrations.

Other routes of synthesis are being investigated for all four compounds. In particular the yield of **1** from

(16) J. H. Tumlinson, J. P. Minyard, P. A. Hedin, and A. C. Thompson, *J. Chromatogr.*, **29**, 80 (1967).
(17) E. J. Corey, N. W. Gilman, and B. E. Ganem, *J. Amer. Chem. Soc.*, **90**, 5616 (1963).
(18) Cl. Daessle and H. Schinz, *Helv. Chim. Acta*, **39**, 2118 (1956).
(19) Ch. A. Vodz and H. Schinz, *ibid.*, **33**, 1321 (1950).
(20) E. J. Corey, private communication.
(21) R. L. Zurflüh, L. L. Duham, Virginia L. Spain, and J. B. Siddall, *J. Amer. Chem. Soc.*, **92**, 425 (1970).

the method described in the present investigation is too low for use in large-scale field studies. Preliminary field tests indicate that the combination of the four compounds is attractive in the field as well as in the laboratory.

Experimental Section

General.—All elemental analyses were carried out by Galbraith Laboratories, Knoxville, Tenn. Spectrometers used were the Varian A-60 (nmr), the Perkin-Elmer Model 521 (ir), and the Perkin-Elmer Model No. 270 mass spectrometer which includes a gas chromatographic inlet system. All nmr and ir spectra were run in CCl_4 unless otherwise indicated. All nmr peaks are reported as δ in parts per million and coupling constants as J in hertz. Gas chromatographs used for analytical work were the Aerograph Model A-95-P_3, the Aerograph Model 600C, and the Barber-Colman Model 5000 equipped with an effluent splitter; for preparative glpc, the Aerograph Model A-700 and the Aerograph Model 90-P were used. The procedure used for laboratory assays was that of Hardee, *et al.*[3b] All fractionations were monitored by laboratory bioassay, and samples submitted for assay were all provided in dichloromethane solution. The active compounds were assayed individually and in various combinations to determine the mixture which would give optimum response.

Column Chromatography.—Silica gel coated with Carbowax 20M in the manner of Kuglar and Kováts[22] was used in the initial fractionation to avoid isomerization of the notoriously labile terpenoids and the steam distillate extracts of 39.2 kg of fecal material and 42.5 kg of weevils was chromatographed in this way. The fractions from the initial column were subsequently chromatographed on Adsorbosil-CABN (25% silver nitrate treated silica gel, Applied Science Labs), which had been washed successively with acetone–ether (50:50), ether, and pentane before use.

Gas–Liquid Partition Chromatography.—The following columns were used for glpc: Column A, Carbowax 4000, 6 ft × 1/8 in., 28.5% on 60–80 Gas-Chrom P, 135° column temperature with 30 psi nitrogen (approximate flow rate was 20 cm³/min); column B, SE-30, 20 ft × 1/8 in., 10% 60–80 Gas-Chrom Q, 160° column temperature with 64 psi nitrogen (50 cm³/min); column C, Carbowax 4000, 20 ft × 1/8 in., 30% on 60–80 Gas-Chrom P, 140° column temperature with 27 psi nitrogen (24 cm³/min); column D, Carbowax 20M, 50 ft, support coated open tubular (SCOT), 110° column temperature with 2 psi helium (2–3 cm³/min); column E, SE-30, 20 ft × 3/8 in., 10% 60–80 Gas-Chrom P, 160° column temperature with 40 psi helium (200 cm³/min); and column F, Carbowax 4000, 20 ft × 3/8 in., 30% on Gas-Chrom P, 170° column temperature with 60 psi helium (190 cm³/min).

Fractions from column chromatography were initially separated on column A. Components collected from this column were then injected onto column B and column E. Peaks were collected from both Carbowax 4000 and SE-30 columns for assay by bubbling through dichloromethane and for spectral studies by bubbling through carbon tetrachloride. Column D was used in the gas chromatographic inlet system to the mass spectrometer.

Sample compounds were reduced just before introduction into the mass spectrometer by placing a 0.25-in. Swagelok connector containing about 1 cm of neutral palladium catalyst in the oven between the gas chromatographic injector and the SCOT column (D). The fitting containing the palladium was conditioned by sweeping with hydrogen for 30 min at 150°.[10]

Derivatization.—2,4-Dinitrophenylhydrazine (DNPH) (5 g) was dissolved in 60 ml of 85% H_3PO_4 and 40 ml of 95% ethanol. Tlc plates (250-μ adsorbent depth) were prepared on 20 × 20 cm × 3 mm glass with silica gel G (SGG). The standard carbonyls, methone, pulegone, and carvone, were chromatographed on column A, and the effluent was allowed to flow into a drop of the DNPH reagent on a SGG plate.[16] The derivatives formed in this way were developed on the plate with benzene and petroleum ether (4:1) to a height of 10 cm. Natural compounds **3** and **4** were derivatized in the same way, and the plate was developed in the same solvent. The sample derivatives and the standard derivatives were scraped from the initial plate, eluted with dichloromethane, and respotted side by side on a second SGG plate which was then developed in benzene and petroleum ether. The R_f vaues of the DNPH's of the standards and of **3** and **4** were about the same.

Microozonolysis.—The natural Z-3,3-dimethyl-$\Delta^{1,\beta}$-cyclohexaneethanol (**2**) was ozonized with a Supelco Microozonizer.[11] About 15 mg of **2**, glpc pure, in 200 μl of carbon disulfide was ozonized for 5 min. Reinjection on a SE-30 glpc column indicated that nearly all the sample had reacted. This ozonolysis was repeated 15 times with 200 μl of solution each time. The reaction mixture was chromatographed on SE-30, and the only major peak was collected by bubbling through CCl_4. The glpc retention time, nmr, and mass spectrum of this compound were identical with those of 3,3-dimethylcyclohexanone.

Photocycloaddition.—A mixture of 172 g (2.53 mol) of isoprene, 108 g (1.80 mol) of 3-buten-2-one, and 20 g (0.17 mol) of acetophenone was irradiated with a 450-W Hanovia mercury vapor lamp through a Pyrex filter for 130 hr, through a Corex filter for 88 hr, or through a Vycor filter for 65 hr. Analysis of the reaction products by glpc (column C) revealed seven major components. The yields of each were calculated by measurement of peak areas relative to an internal standard. All components were collected, on elution, in carbon tetrachloride for spectral analysis and neat by condensation in glass tubes for elemental analysis.

Component 1 (retention time 7.8 min), 2.4% yield, contained two compounds, a sesquiterpene **8**, and a ketone, $C_9H_{14}O$, which showed as a shoulder on the backside of component 1.

Anal. Calcd for $C_{15}H_{24}$: C, 88.16; H, 11.83. Found: C, 88.19; H, 12.12.

Component 2 (retention time 10.7 min), 2.4% yield, contained both *cis*- and *trans*-2-methyl-2-vinylcyclobutyl methyl ketone (**5** and **6**, respectively) which were not separable by any means available. Component 2 showed the following spectral characteristics: ir 1700 (C=O), 1630 (C=C), 910 cm^{-1} (CH=CH_2); nmr 1.11 and 1.34 (s, $CH_3CRR'R''$), 1.7–2.7 (complex envelope), 1.99 and 2.08 (s, CH_3C=O), 3.13 and 3.28 (t, overlapping, $CH_3COCHRR'$), 4.8–5.4 (m, CH=CH_2), 6.07 (m, J_{cis} = 10, J_{trans} = 18, CH=CH_2), 6.26 (m, J_{cis} = 10.5 J_{trans} = 17.5, CH=CH_2).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.08; H, 10.14.

Component 3 (retention time 11.6 min), 3.3% yield, contained 3-methyl-3-vinylcyclobutyl methyl ketone (**7**) and had the following spectral characteristics: ir nearly identical with ir of component **2**; nmr 1.28 (s, 3, $CHCRR'R''$), 1.6–2.9 (complex m, 4, two CH_2), 1.99 (s, 3, CH_3C=O), 3.19 (t, 1, J = 8.5, CH_3CO-$CHRR'$), 4.88 (m, J_{trans} = 17, J_{cis} = 10, 2, CH=CH_2), 5.92 (m, 1, J_{trans} = 17, J_{cis} = 10, CH=CH_2).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.21; H, 10.27.

Component 4 (retention time 13.6 min), 1.5% yield, was identified as 3-isopropenylcyclobutyl methyl ketone (**9**) and had the following spectral characteristics: ir 1705 (C=O), 1370 and 1350 (vinyl methyl and ketone methyl), 1643 (C=C), 884 cm^{-1} (CH=CH_2); nmr 1.58 (broad s, 3, CH_3(R)C=CH_2), 1.7–2.95 (complex m, 4, two CH_2), 1.88 (s, 3, CH_3C=O), 2.92 (two t, nearly superimposed, 2, H_2C=C(CH_3)CHRR' and CH_3CO-$CHRR'$), 4.57 (broad s, 2, R(CH_3)C=CH_2).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.22; H, 10.43.

Component 5 (retention time, 15.3 min), 1.4% yield, was identified as 3,4-dihydro-6-methyl-2*H*-pyran-2-yl methyl ketone (**10**), a dimer of methyl vinyl ketone, and was also present in the starting material.[23]

Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.35; H, 8.79.

Component 6 (retention time 17.7 min), 0.8% yield, was identified as 3-isopropenylcyclobutyl methyl ketone (an isomer of component **9**) (**11**) and had the following spectral characteristics: ir 1705 (C=O), 1640 (C=C), 1360 (broad, two CH_3), 888 cm^{-1} (C=CH_2); nmr 1.62 (broad s, 3, CH_3(R)C=CH_2), 1.8–3.2 (complex m, 6, two CH_2, H_2C=C(CH_3)CHRR' and CH_3CO-$CHRR'$), 1.94 (s, 3, CH_3C=O), 4.60 (broad s, 2, R(CH_3)-C=CH_2).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 77.93; H, 10.20.

Component 7 (retention time 23.8 min), 9.2% yield, was identified as 4-methyl-3-cyclohexenyl methyl ketone (**12**) and had the following characteristics: ir 1705 (C=O), 1688 (C=C),

(22) E. Kuglar and E. Kováts, *Helv. Chim. Acta*, **46**, 1480 (1963).

(23) K. Alder, H. Offermanns, and E. Ruden, *Chem. Ber., B*, **74**, 905 (1941).

1373 and 1347 (two CH_3), 907 cm^{-1} (C=CH); nmr 1.59 (s, 3, $CH_3(R)C=CHR'$), 1.8–2.7 (broad envelope, 7, three CH_2 and $CH_3COCHRR'$), 2.02 (s, 3, $CH_3C=O$), 5.26 (broad s, 1, $CH_3(R)C=CHR'$).

Anal. Calcd for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 78.02; H, 10.28.

Grignard Addition to Ketones to Form Tertiary Alcohols.—Methylmagnesium iodide was prepared in the usual way by adding 6.1 g (0.04 mol) of CH_3I in ether to 1.0 g (0.04 g-atom) of Mg. To this excess of CH_3MgI, 2 g (0.014 mol) of a mixture of *cis*- and *trans*-2-methyl-2-vinylcyclobutyl methyl ketone (**5** and **6**, respectively) (component 2) in ether was added dropwise. The mixture was gently refluxed for 1 hr and cooled, and the addition compound was decomposed with aqueous NH_4Cl. Analysis by glpc on column C showed only two peaks, which indicated quantitative yields of *cis*- and *trans*-α,α,2-trimethyl-2-vinylcyclobutanemethanol. The quantity of each isomer was about the same; thus, the yield was 1.2% each of the cis and trans isomers from the photocycloaddition. These two isomers were separated on column F.

The compound assigned the cis configuration (in retrospect) (**13**) showed the following spectral characteristics: ir 3580 (OH), 3080 (C=CH), 1630 (C=C), 1377 ($RR'R''CH_3$), 1362 (geminal methyls), 908 cm^{-1} ($C=CH_2$); nmr 0.94 (s, 3, $RR'R''CCH_3$), 1.12 and 1.23 (two s, 6, $(CH_3)_2C(OH)R$), 1.47 (s, 1, OH), 1.67–2.23, (broad m, 5, two CH_2 and $RR'R''CH$), 5.03 (d, 1, cis terminal vinyl H, J_{cis} = 10.5), 5.29 (s, 1, trans terminal vinyl H, J_{trans} = 18), 6.60 (m, 1, J_{cis} = 10.5, J_{trans} = 18, $RCH=CH_2$).

The compound assigned the trans configuration (in retrospect) (**14**) showed the following spectral characteristics: ir 3620 (OH), 3080 ($C=CH_2$), 1632 (C=C), 1378 ($RR'R''CHC_3$) 1361 (geminal methyls), 908 cm^{-1} ($CH=CH_2$); nmr 1.11 (s, 3, CH_3), 1.21 (s, 3, CH_3), 1.39 (s, 3, CH_3), 1.33 (s, 1, OH), 1.5–2.35 (m, 5, two CH_2 and $RR'R''CH$), 5.00 (m, 2, J_{cis} = 10, J_{trans} = 18, $RCH=CH_2$), 6.12 (m, 1, J_{cis} = 10, J_{trans} = 18, $RCH=CH_2$).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found for cis alcohol: C, 77.92; H, 11.92. Found for trans alcohol: C, 77.66; H, 11.72.

Preparation of Cis and Trans Diols (15 and 16).—*cis*- and *trans*-α,α,2-trimethyl-2-vinylcyclobutanemethanol were converted to the respective cis and trans diols by hydroboration of the double bond to form a primary alcohol. The procedure was the same as that reported by Brown and Subba Rao.[5b] The diols were purified by glpc on SE-30 (column E).

The diol assigned the cis configuration (in retrospect) (**15**) was a solid, mp 87–87.5°, and had the following characteristics: ir 3300 (broad, strong OH absorption, hydrogen bonded) and no indicated unsaturation; nmr 1.04 (s, 3, CH_3), 1.10 (s, 3, CH_3), 1.17 (s, 3, CH_3), 1.40–2.10 (m, 5, two CH_2 and $RR'R''CH$), 1.93 (t, J = 7, 2, CH_2CH_2OH), 3.07 (broad s, 2, OH), 3.58 (t, J = 7, CH_2CH_2OH).

The diol assigned the trans configuration (in retrospect) (**16**) did not crystallize and had the following spectral characteristics: ir 3300 (broad, strong OH absorption, hydrogen bonded) and no indicated unsaturation; nmr 1.12 (s, 3, CH_3), 1.18 (s, 3, CH_3), 1.24 (s, 3, CH_3), 1.30–2.40 (broad m, 5, two CH_2 and $RR'R''CH$), 1.67 (t, 2, J = 7, CH_2CH_2OH), 3.57 (partially obscured complex t, 2, CH_2CH_2OH), 4.36 (s, 2, OH).

Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found for cis diol: C, 69.85; H, 11.69. Found for trans diol: C, 69.53; H, 11.78.

Dehydration to Form *cis*- and *trans*-2-Isopropenyl-1-methylcyclobutaneethanol (1 and 17).—The separate cis and trans diols (0.014 mol each) were refluxed with an excess of acetic anhydride (0.060 mol) for 3 hr. The reaction was monitored at 0.5-hr intervals by glpc on column B (SE-30). The disappearance of the diol peak was coincidental with the appearance of the diacetate which subsequently was replaced by the monoacetate of the unsaturated primary alcohol. Without purification, the reaction mixture was then reduced by addition to 1.5 g of $LiAlH_4$ in 100 ml of ether and refluxing for 2.5 hr. The *cis*- and *trans*-2-isopropenyl-1-methylcyclobutaneethanols prepared from the cis and trans diols, respectively, were purified by glpc (columns E and F) and analyzed spectroscopically. The spectral characteristics of the natural compound 1 were identical with those of the synthetic compound assigned the cis configuration: ir 3630 (free OH), 3250-3350 (H-bonded OH), 1642 and 885 ($C=CH_2$); nmr 4.88 and 4.71 (s, 1, $RR'C=CH_2$), 3.63 (t, 2, CH_2CH_2OH, J = 7.5), 2.60 (t, 1, methinyl H, J = 8.0), 2.59 (s, 1, OH) (the hydroxyl proton resonance shifted upfield on dilution and disappeared with the addition of trichloroacetyl isocyanate), 1.72 (s, 3, vinyl methyl), 1.22 (s, 3, $RR'R''CCH_3$), and 1.3–2.2 (m, 6); mass spectrum (70 eV) *m/e* (rel intensity) 154 (2), 139 (6), 136 (3), 121 (10), 109 (27), 93 (15), 81 (17), 68 (100), 53 (23), 41 (42).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.63; H, 11.70.

The *trans*-2-isopropenyl-1-methylcyclobutaneethanol (**17**) was very similar to the cis isomer in glpc behavior, ir, and mass spectra (*vide supra*). The nmr spectrum was 4.80 and 4.60 (s, 1, $RR'C=CH_2$), 3.63 (t, 2 CH_2CH_2OH, J = 7.5), 2.60 (t, 1, methinyl H, J = 8.0), 2.16 (s, 1, OH), 1.85 (t, 2, CH_2CH_2OH, J = 7.5), 1.65 (s, 3, vinyl CH_3), 1.25–1.75 (m, 4), 0.92 (s, 3, $RR'R''CCH_3$), and was identical with a spectrum supplied by Corey[20] and identified as the trans compound.

Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.68; H, 11.89.

1-Hydroxy-3,3-dimethylcyclohexaneacetic Acid (18).—To 20 g (0.36 mol) of potassium hydroxide in 100 ml of water was added 15.0 g (0.07 mol) of ethyl 1-hydroxy-3,3-dimethylcyclohexaneacetate.[13] The stirred mixture became homogeneous in 3 hr at room temperature. After extraction with ether, the aqueous basic solution was acidified, and the precipitated acid was collected by filtration and dried over phosphorus pentoxide for 16 hr. The dried acid was recrystallized from benzene to give 11.0 g (84.6%), mp 109–110°.

Compound **18** had the following nmr characteristics: ($CDCl_3$) 0.91 (s, 3, CH_3), 1.11 (s, 3, CH_3), 1.20–2.10 (broad m, 8, CH_2 ring), 2.51 (s, 3, CH_2COOH), 7.29 (broad s, 2, COOH and OH).

Anal. Calcd for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.55; H, 9.75.

Dehydration of 1-Hydroxy-3,3-dimethylcyclohexaneacetic Acid.—The hydroxy acid (45.1 g, 0.24 mol) was refluxed 6.5 hr in 200 ml of acetic anhydride. The excess anhydride was removed by distillation *in vacuo*. The residue was hydrolyzed with 300 ml of 20% aqueous potassium hydroxide by stirring for 2 hr at room temperature. The aqueous basic solution was extracted with dichloromethane and acidified. The acidic aqueous solution was extracted with dichloromethane, dried over sodium sulfate, and concentrated to 42.4 g of a mixture of all possible double bond isomers. The *Z* acid, prepared by hydrolysis of the corresponding ester (*vide infra*), mp 102.5–104.0°, had the following nmr characteristics: 0.97 (s, 6, geminal CH_3), 1.2–2.0 (broad m, 4, CH_2), 2.20 (broad t, 2, CH_2 trans to carboxyl group), 2.68 (s, 2, CH_2 cis to carboxyl group), 5.73 (s, 1, C=CH). The *E* acid melted at 91.0–92.5°.

Esterification of the Mixed Unsaturated Acids and Separation of the Isomers.—The mixed unsaturated acids, 39.9 g, were refluxed with 150 ml of 14% w/v BF_3–methanol for 1.5 hr. The cooled mixture was poured into 450 ml of water and shaken. The aqueous mixture was extracted with pentane. After the extract was dried over sodium sulfate and the pentane was removed, a residue of 42.8 g remained. The mixture was distilled to yield 35.4 g of mixed esters (85% exo isomers in 1:1 ratio). Separation of the isomers was achieved in a subsequent distillation through an annular spinning band column. The *Z* ester **19** and the *E* ester **20** boiled within 1° of one another (bp 80° at 2.5 m) but were cleanly separated.

Compound **19** had the following nmr spectrum: 0.92 (s, 6, geminal CH_3), 1.2–1.9 (broad m, 4, two CH_2), 2.12 (t, 2, CH_2 trans to carbomethoxy group), 2.61 (s, 2, CH_2 cis to carbomethoxy group), 3.57 (s, 3, $COOCH_3$), 5.55 (s, 1, C=CH).

Compound **20** had the following nmr spectrum: 0.89 (s, 6, geminal CH_3), 1.2–1.9 (broad m, 4, two CH_2), 1.93 (s, 2, CH_2 trans to carbomethoxy group), 2.73 (t, 2, CH_2 cis to carbomethoxy group), 3.57 (s, 3, $COOCH_3$), 5.42 (s, 1, C=CH).

Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found for *Z* ester: C, 72.39; H, 10.02. Found for *E* ester: C, 72.68; H, 9.77.

***Z*-3,3-Dimethyl-$\Delta^{1,\beta}$-cyclohexaneethanol (2).**—The methyl ester of the *Z*-unsaturated acid collected from glpc (about 100 mg) was added to 1 g of $LiAlH_4$ in 50 ml of ether. The mixture was refluxed 1.5 hr and cooled, and the excess hydride was decomposed with 10% NaOH. The ether solution was filtered and concentrated, and the alcohol was purified by glpc. The glpc behavior and nmr, ir, and mass spectra of natural compound **2** were identical with those of synthetic *Z*-3,3-dimethyl-$\Delta^{1,\beta}$-cyclohexaneethanol: ir 3610 cm^{-1} (OH); nmr 0.95 (s, 6, $RR'C(CH_3)_2$), 1.13–1.83 (broad m, 4, RCH_2CH_2R'), 2.00 (s, 2) overshadowing 2.09 (m, 2) suggesting two methylenes adjacent to a double

bond, one split and the other not, 4.05 (d, 2, RR'C=CHCH$_2$OH, J = 7.0 and shifted downfield by addition of TCAIC, 5.53 (t, 1, RR'C=CHCH$_2$OH, J = 7.0); mass spectrum (70 eV) m/e (rel intensity) 154 (7), 136 (40), 121 (48), 107 (25), 93 (63), 79 (53), 69 (100), 55 (35), 41 (88).

Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.81; H, 11.79.

E-3,3-Dimethyl-$\Delta^{1,\beta}$-cyclohexaneethanol (21).—The methyl ester of the E unsaturated acid was reduced in the same way as the Z ester to the E alcohol and purified by glpc. Compound 21 had the following nmr spectrum: 0.95 (s, 6, geminal CH$_3$), 1.4–1.7 (m, 4, two CH$_2$), 1.96 (s, 2, CH$_2$ trans to the carbinol group), 2.18 (s, 1, OH), 2.20 2, (t, 2, CH$_2$ cis to the carbinol group), 4.13 (d, 2, CH$_2$OH), 5.37 1, (t, 1, C=CH). The ir spectrum was similar to that of 2.

Anal. Calcd for $C_{10}H_{18}O$: C, 77.86; H, 11.76. Found: C, 77.64; H, 11.83.

Z-3,3-Dimethyl-$\Delta^{1,\alpha}$-cyclohexaneacetaldehyde (3).—Active MnO_2 was prepared as described by Attenburrow, *et al.*[24] Stereospecific oxidation of the Z alcohol 2 (100 mg) by stirring with 3.3 g of active MnO_2 in 30 ml of pentane for 30 min at 0° produced the Z-3,3-dimethyl-$\Delta^{1,\alpha}$-cyclohexaneacetaldehyde in quantitative yield.[17] The reaction mixture was filtered, the pentane removed by evaporation, and the aldehyde purified by glpc. Chromatographically pure samples were identical with natural compound 3 in glpc behavior, mass spectrum, and biological activity.

(24) J. A. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen, and T. Walker, *J. Chem. Soc.*, 1094 (1952).

Compound 3 had the following spectral characteristics: nmr spectrum 0.93 (s, 6, geminal CH$_3$), 1.2–2.0 (broad m, 4, two CH$_2$), 2.17 (t, 2, CH$_2$ trans to aldehyde group), 2.42 (s, 2, CH$_2$ cis to aldehyde group), 5.74 (d, 1, CHO); mass spectrum (70 eV) m/e (rel intensity) 152 (34), 137 (90), 109 (45), 95 (28), 81 (45), 69 (59), 55 (30), 53 (30), 41 (100).

E-3,3-Dimethyl-$\Delta^{1,\alpha}$-cyclohexaneacetaldehyde (4).—The E alcohol 21 was oxidized with active MnO_2 to the E aldehyde in the same way as the Z alcohol. E-3,3-Dimethyl-$\Delta^{1,\alpha}$-cyclohexaneacetaldehyde was found to be identical with natural compound 4 in glpc behavior, mass spectrum, and biological activity.

Compound 4 had the following spectral characteristics: nmr spectrum 0.89 (s, 6, geminal CH$_3$), 1.2–1.9 (m, 4, two CH$_2$), 2.00 (s, 2, CH$_2$ trans to aldehyde group), 2.61 (t, 2, CH$_2$ cis to aldehyde group), 5.60 (d, 1, C=CH), 9.78 (d, 1, CHO); mass spectrum (70 eV) m/e (rel intensity) 152 (46), 137 (46), 119 (24), 109 (63), 93 (29), 81 (38), 69 (63), 55 (33), 41 (100).

Registry No.—**1**, 26532-22-9; **2**, 26532-23-0; **3**, 26532-24-1; **4**, 26532-25-2; **5**, 30346-11-3; **6**, 30346-12-4; **7**, 30346-13-5; **9**, 30346-14-6; **11**, 30346-15-7; **12**, 6090-09-1; **13**, 30346-17-9; **14**, 30346-18-0; **15**, 30346-19-1; **16**, 30346-20-4; **17**, 30346-21-5; **18**, 30346-22-6; **19**, 30346-23-7; **19** free acid, 30346-24-8; **20**, 30346-25-9; **20** free acid, 30346-26-0; **21**, 30346-27-1.

Identification of Two Conjugated Pentaenoic Acids in the Insect Fat, Aje

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The fatty acids from aje, body fat of the coccid *Llaveia axin*, have been examined. In addition to the normal saturated acids at the C_{14}, C_{18}, and C_{20} molecular weights, and the unsaturated C_{18} acids, oleic and linoleic, there were present pentaunsaturated acids at the C_{12} and C_{14} levels. The latter components were so unstable that separation in a pure condition was not feasible; however, the ultraviolet spectrum of the mixture of acids was virtually identical with that which has been reported for a pentaenoic fatty acid after alkali isomerization to a conjugated system. The conjugated system in both the C_{12} and C_{14} acids was shown to be in a terminal position by identification of formaldehyde after ozonolysis. The appropriate fragment from ozonolysis also established the other end of the conjugated system as at carbon-3 in the C_{12} acid and at carbon-5 in the C_{14} acid. Confirmatory evidence was obtained from mass spectrometry of the deuterated esters. Thus, assigned structures for the conjugated pentaenoic acids, believed to be the first found in natural products, are 3,5,7,9,11-dodecapentaenoic acid and 5,7,9,11,13-tetradecapentaenoic acid. The names C_{12}-ajenoic acid and C_{14}-ajenoic acid are proposed.

The body fat of the Mexican and Central American scale insect *Llaveia axin*, is known as aje. It is in current use in the villages, both as an unguent and a drying oil in gourd painting.[1] References to the substance extend at least as far back as the sixteenth century; however, there has been no significant chemical investigation of the material. Although samples of the solid fat form a crust on the surface relatively quickly, and a major use has been as a vehicle for pigments in gourd painting, the iodine number has been reported[2] considerably lower than expected for a drying oil. The present investigation has been directed toward examination of the fatty acids in aje.

Aje was found to contain no significant amounts of free fatty acids. Acids released by saponification gave only 50–60% yields of methyl ester on acid-catalyzed esterification, with extensive polymer formation; however, base-catalyzed esterification[3] of freshly prepared acids gave 75–85% yields of methyl ester. On standing at room temperature in air or under nitrogen, in solution or neat, the ester exhibited formation of a polymeric oil within a few hours. Gas chromatography of the esters on silicone and on DEGS (diethylene glycol succinate) revealed the presence of significant amounts of only four components, whose retention times corresponded precisely with methyl stearate (representing 51% of total area under the four peaks), oleate (18.5%), linoleate (15.5%), and eicosanoate (15%). Since a mixture of this composition would not give a rapid polymerization, it was suspected that one or more of the peaks would prove not to contain the common ester with that retention time. However, when the component responsible for each peak was collected and identified, each proved to be the well-known substance with the observed retention time.

(1) A historical survey, as well as description of current use of aje, have been reported by Mrs. Katharine D. Jenkins in the Actas y Memorias of the 35th International Congress of Americanists, Mexico, 1964, pp 625–636. We are greatly indebted to Mrs. Jenkins for the samples of aje utilized in the current investigation.

(2) Francisco Giral, Mexico City, in a private communication to Mrs. Jenkins, dated Aug 30, 1963, reported that he found iodine numbers in the range 74–84.

(3) F. H. Stodola, *J. Org. Chem.*, **29**, 2490 (1964).

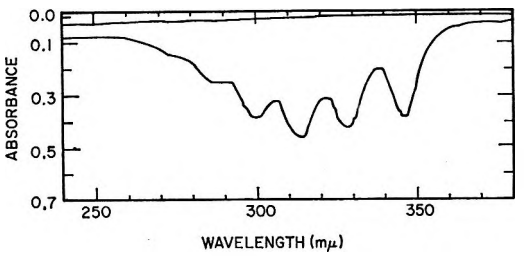


Figure 1.—Ultraviolet absorption of 0.008 *M* solution in methanol of freshly prepared aje acid methyl esters: 0.05-cm cell length; Perkin-Elmer Model 202 uv spectrophotometer. Upper tracing is solvent *vs.* solvent. Prompt hydrogenation of this sample of esters and analysis by gas chromatography indicated about 21% (molar) total of highly unsaturated C_{12} and C_{14} acids. When this factor is applied for calculation of the extinction coefficient for the highly unsaturated acids, there results λ_{max}, mμ ($\epsilon \times 10^{-3}$), 300 (37.6), 314 (47.0), 329 (43.5), 346 (39.4).

The highly unsaturated components, which had not appeared in gas chromatography on account of their instability, were revealed by hydrogenating a freshly prepared sample of esters and gas chromatographing the resultant saturated esters. Such ester samples contained 10–15% each of methyl dodecanoate and methyl tetradecanoate.[4] The ultraviolet spectrum of the esters of the aje acids (Figure 1) shows four strong maxima (300, 314, 329, and 346 mμ) and two weaker absorptions (272, 285 mμ). This spectrum is more complex and gives a band at longer wavelength than reported for α-parinaric acid,[5] which has four conjugated double bonds in an unsubstituted chain. There appears to be no report of an unbranched, acyclic conjugated pentaunsaturated system in natural occurrence; however, a pentaunsaturated acid has been isomerized with alkali to generate the conjugated system.[6] Ultraviolet absorption after the alkali isomerization showed six absorption bands in essentially the same positions shown in Figure 1 (270, 285, 300, 313, 330, and 345 mμ); furthermore, the stronger bands were those four at longer wavelengths. With strong alkali isomerization, the strongest absorption was at 330 mμ, but in weak alkali the strongest absorption was at 313 mμ, as is the case in Figure 1. Thus, the acids from aje must have a conjugated system of five double bonds. No reliable conclusions may be reached concerning the geometry of this unsaturated system.

As one attack on location of the conjugated system revealed by the ultraviolet absorption, a freshly prepared sample of esters was catalytically reduced with deuterium, and mass spectra were determined for the esters of the saturated C_{12} and C_{14} acids, which had been separated by gas chromatography. Since catalytic deuteration gives extensive indiscriminate exchange of deuterium for hydrogen, this procedure is quite inferior to specific reduction of the alkene linkage with deuteriohydrazine;[7] however, in the present instance, hydrazine reduction was noncompetitive with polymerization. In spite of the scrambling of deuterium which occurs on catalytic deuteration, the mass spectrum (Table I) of the ester of the C_{14} acid proved definitive for location of the carbon on which the conjugated system begins.

Table I

Partial Mass Spectrum of Catalytically Deuterated Methyl Tetradecapentaenoate

m/e	%[a]	*m/e*	%[a]
74[b]	100	131	3.0
75	44	132	2.0
76	17	143[c]	1.0
87[c]	46	144	2.5
88	44	145	4.2
89	19	146	4.8
101[c]	7.5	147	4.0
102	6	157[c]	<0.2
103	4	158	<0.2
115[c]	1.6	159	1.0
116	2.5	160	1.5
117	1.7	161	1.8
129[c]	1.0	162	1.0
130	2.1		

[a] Relative abundance in relation to the most abundant ion. [b] The rearrangement ion, $CH_2{=}C(OH)OCH_3$, with no deuterium. [c] Ester fragments, $(CH_2)_nCO_2CH_3$, with no deuterium.

From the data in Table I, it is seen that the rearrangement ion, whose *m/e* is 74 in absence of deuterium, is quite enlightening. Since this fragment containing no deuterium is in much the greatest abundance, and since two of its hydrogen atoms are from the α position and one is from the γ position, this establishes absence of double bonding to the α, β, and γ carbons. This is supported by examination of the simple ester fragments, for the fragments containing respectively two and three methylene groups give the undeuterated ion in greatest abundance. In contrast, the ester fragments with four, five, six, and seven methylene groups give most abundant ions respectively with one, two, three, and four deuterium atoms. Thus, the double bond system must start at carbon-5. Surprisingly, the most abundant molecular ion was of *m/e* 250, two less than required for ten deuterium atoms.

The mass spectrum of the deuterated C_{12} acid is less definitive than that of the C_{14} acid; however, it remains possible to assign the doubly bonded carbon nearest to the carbonyl. The rearrangement ion is the most informative feature of the mass spectrum of this ester. For *m/e* of 74, 75, and 76 relative abundances of the respective ions were 100, 77, and 19%. It will be noted that the relative abundance of 75 is nearly twice that in Table I but less than the abundance of 74. This indicates that deuterium from the reduction of a double bond is not at the α position, for this would make the ion at 75 more abundant than that at 74 (much more, with no scrambling). If the deuterium is rearranged from the γ position, however, there would also be one hydrogen at this position, and the hydrogen would be more prone to rearrange on account of its lower bond energy. Furthermore, relative abundances of ions at *m/e* 87, 88, and 89 were respectively 36, 57, and 46%. These data indicate a double bond at the β position (compare with Table I); therefore, the conjugated system starts at the β,γ position.

According to the ultraviolet spectrum and mass spectrometry of the deuterated esters, the highly un-

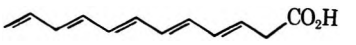
(4) In one specimen of aje (*cf.* Experimental Section), the original esters contained a trace of dodecanoate and about 15% of tetradecanoate; however, in this sample presence of the highly unsaturated esters was revealed by an increase of dodecanoate and tetradecanoate after hydrogenation.

(5) M. O. Bagby, C. R. Smith, Jr., and I. A. Wolff, *Lipids*, **1**, 263 (1966).

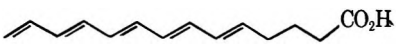
(6) S. F. Herb and R. W. Riemenschneider, *J. Amer. Oil Chem. Soc.*, **29**, 456 (1952).

(7) N. Ding-Nguyên, R. Ryhage, and S. Ställberg-Stenhagen, *Ark. Kemi*, **15**, 433 (1960).

saturated acids, which we propose to call C_{12}-ajenoic acid and C_{14}-ajenoic acid, have the structures shown in **1** and **2**. In order to obtain classical degradative



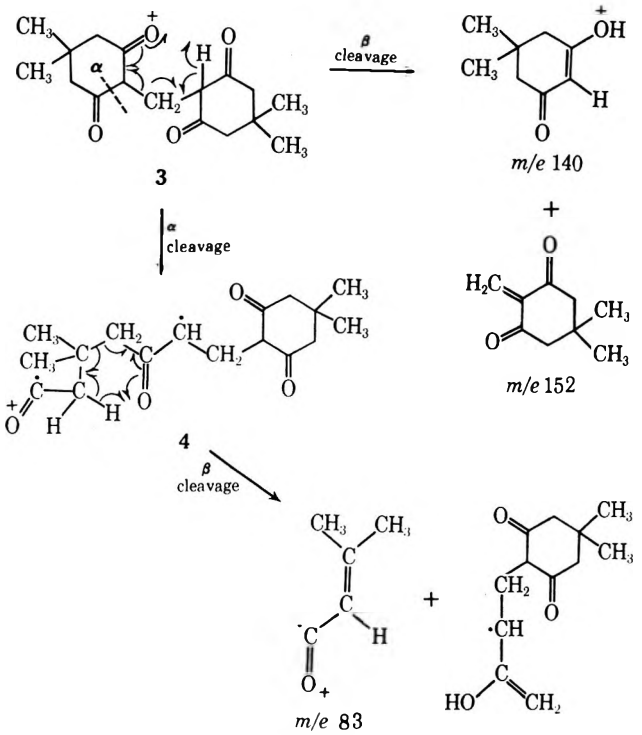
1



2

evidence in support of these structures, the ajenoic acids were separated from the bulk of the higher molecular weight acids by low temperature precipitation of the latter, and the ajenoic acids were subjected to ozonization. In one set of experiments, the ozonide was worked up for formaldehyde which was isolated as the dimedone adduct in good yield. Comparison with an authentic sample of this adduct was by melting point, as well as mass spectrum.

The mass spectrum of the formaldehyde–dimedone adduct is of interest in that the most abundant ion, *m/e* 83, as well as the other two prominent ions in the spectrum, *m/e* 140 (35%) and *m/e* 152 (55%), can be formulated on the basis of classical α and β cleavages, in spite of the complexity of the molecule. In structure **3**, the β cleavage, involving hydrogen



3 **4**

rearrangement as depicted by the arrows, separates the rings and yields the fragments of the observed masses. A somewhat different shift of electrons leaves the charge on the *m/e* 152 fragment, and this effect is often observed in instances where the alkene fragment contains additional oxygen or nitrogen atoms. Both an α and a β cleavage are required to yield the base peak of *m/e* 83. If an α cleavage of structure **3** occurs at the position indicated by the dotted line, the resultant structure **4**, in the conformation depicted, may yield the *m/e* 83 ion *via* the β cleavage indicated by the arrows. The stability of the *m/e* 83 ion may be ascribed to the possibility of delocalization of electrons to yield a tertiary carbonium ion (charge on carbon β to carbonyl).

As further confirmation of structure, in another procedure the initial ozonization products from the aje acids were oxidized by permanganate according to a previously developed procedure,[8] and the resultant acids esterified. This yielded dimethyl malonate (from structure **1**) and dimethyl glutarate (from structure **2**). The diesters were collected from gas chromatography and their mass spectra compared with authentic samples.

In view of the unusual structures encountered in the ajenoic acids, the esters of the unsaturated C_{18} acids were also subjected to ozonization, permanganate oxidation, and esterification. Identification by gas chromatography and mass spectrometry established the cleavage products as methyl hexanoate, methyl nonanoate, and dimethyl azelate. Thus, the unsaturated C_{18} acids prove to be the ubiquitous oleic and linoleic acids.

Since there became available to us a sample of the fat from Guatemala,[9] and since there is some opinion that this coccid is different from that in Mexico, we determined the type and distribution of acids in this sample of aje or nije. As described in the Experimental Section, the composition of the Guatemalan fat was surprisingly similar to that from Mexico. Of course this observation raises very serious doubts that the coccids are different.

Experimental Section[10]

Aje Specimens.—The aje fat is extracted from mature female coccids by cooking and crushing them in water. The mass of fat is separated from solid matter by straining, washed with water, formed into cakes, and wrapped in leaves or cornhusks for marketing. The "refined" aje, used as a medicinal unguent, is a lighter yellow color than the yellow-brown material used for gourd painting. The "refining" process probably consists of further water washing and straining of the melted fat for removal of insoluble foreign matter.

Two specimens were employed in most of these investigations. One was a refined sample obtained by Mrs. Jenkins[1] in 1963 at Mitla in Oaxaca but was brought there from Choapan, in the Sierra Juarez, by an itinerant trader. The other sample was unrefined aje with a heavy crust on the outside. This sample was bought by Mrs. Jenkins in Chiapas in 1962. The major difference in the fatty acid content of the two samples was the occurrence of about 15% of tetradecanoic acid and a lower ratio of eicosanoic acid in the unrefined sample. The sample of ni-in, originating in Rabinal, Guatemala, was obtained by Mrs. Jenkins in Oct 1968.

Samples removed from the soft center of the aje cakes were used. These contained 10–20% of ether-insoluble material (presumably polymer). No free fatty acids were removed by countercurrent extraction of the ether solution with dilute aqueous potassium hydroxide, using a sequence of three Kies tubes.[11]

Acids from Saponification of Aje.—In a typical procedure 1.1 g of aje fat was saponified by heating under reflux in a nitrogen atmosphere for 2 hr with 10 ml of 2 *M* methanolic KOH. Work-

(8) J. Cason and W. T. Miller, *J. Biol. Chem.*, **238**, 883 (1963).

(9) The Mayan word for this fat is ni-in, and the fat is known as nije in the Baja Verapaz region of Guatemala from which Mrs. Jenkins obtained this sample. In Guatemala, the coccid is known as *Llaveia bouvari*.

(10) Mass spectra were determined by Miss Sherri Firth on a CEC Model 21-103c instrument, with the inlet heated to about 180° and the ionizing voltage at 70 eV. The instrument had been equipped with narrower slits and an ion multiplier and otherwise modified to give unit resolution to about 600. Gas chromatography was on an Aerograph Model A-90P. Ozonizations were performed at −70°, using ozone from a Welsbach laboratory ozonator, Model T-23.

(11) M. W. Kies and P. L. Davis, *J. Biol. Chem.*, **189**, 637 (1951).

up for acids yielded 0.8 g of yellow solid. Neutral components were not examined. Classical acid-catalyzed esterification gave poor yields of ester, with much polymer; so base-catalyzed esterification[3] was preferred. For this purpose, 1.0 g of crude acids was heated on a steam bath for 5 min with 10 ml of methanol, 2.6 g of tris-(2-hydroxypropyl)amine, and 1.6 g of dimethyl sulfate. Work-up for neutral material yielded 0.84 g of crude esters which were too viscous for injection in glpc; so they were injected in about 10% solution in benzene.

On glpc of the esters with a 0.25 in. × 5 ft column, 20% SE-30, 225°, helium flow rate 60 cc/min, bands were observed at retention times of 22.8, 25.2, 46.2 min. A semilog plot of retention times for methyl esters of C_{12} to C_{18} acids showed coincidence of the final two bands with stearate and eicosanoate, while the first band had the retention time of unsaturated esters of the C_{18} acid. With use of a $^3/_8$ in. × 5 ft column, 20% DEGS, 200°, helium flow rate 110 cc/min, bands were observed at retention times of 24.0, 27, 32.9, 40.7 min. In comparison with known compounds, the first and last bands corresponded with stearate and eicosanoate, while the second and third corresponded with oleate and linoleate.

A 20-mg sample of the second and third peaks on DEGS was collected and hydrogenated in glacial acetic acid solution, with 10% Pd-on-charcoal catalyst, at an initial pressure of 30 psi. Gas chromatography of the hydrogenated ester have a single peak of the retention time of stearate; therefore, the 27- and 32.9-min bands on DEGS are ascribed to **monounsaturated** and **nonconjugated diunsaturated octadecanoates**. Position of unsaturation was determined by ozonization, as described below.

A sample of material collected from the 25.2-min band on silicone had mp 37–38.5°, no depression on admixture with an authentic sample of **methyl stearate**. Ir spectra of the authentic and isolated samples were also identical.

A sample (0.6 mg) of material collected from the 46.2-min band on silicone was submitted for mass spectrum.[10] The base peak (most abundant ion) was of *m/e* 74, the rearrangement ion from a methyl ester; the molecular ion was of *m/e* 226 (10% of base peak), the molecular weight of **methyl eicosanoate**. The ion of *m/e* 87, $CH_2CH_2CO_2CH_3$, was of 54% relative abundance. For the fragment, $(CH_2)_nCO_2CH_3$, every ion was relatively prominent from $n = 2$ to $n = 17$, with the two highest mass ones (283, 2.75%; 297, 1%) more conspicuous than their lower neighbors, since 283 represents M − 43 (α, β, and γ carbons + H) and 297 represents M − 29 (α and β carbons + H). Also present was 295 (1.6%), which is M − 31 (OCH_3). These are all the features characteristic of the mass spectrum of the methyl ester of a normal carboxylic acid, and they were accompanied by no features indicating a branch in the chain.

By combining glpc data on aje methyl esters with that on the hydrogenated methyl esters, composition of the fat was determined. In Table II are the average values for composition,

TABLE II
COMPOSITION OF AJE FAT

Acid	% of total[a] Mexican	Guatemalan
Dodecanoic	Trace	Nil
C_{12}-Ajenoic	13	11
Tetradecanoic	7.5	7
C_{14}-Ajenoic	10	9.5
Octadecanoic	39	
Oleic	11	67.5
Linoleic	14	
Eicosanoic	5.5	5

[a] Composition is based on relative areas under the peaks in glpc tracings, with no correction for any variation of response with molecular weight.

based on several lots of the refined sample and two lots of the unrefined sample from Mexico. One lot of the Guatemalan sample was examined.

Perhydroajenoic Esters.—In a typical hydrogenation (or deuteration), 2.6 g of freshly prepared aje methyl esters was reduced at an inital pressure of 30 psi, in solution in 44 ml of glacial acetic acid, with 0.2 g of 10% Pd-on-charcoal catalyst. After hydrogenation had been continued for 24 hr, the pressure drop amounted to 1.3 mol of hydrogen per mole of esters (based on average mol wt 300). After work-up, including filtration of polymer from ether solution, 2.1 g of semisolid esters were obtained. For collection in glpc of the reduced ajenoic esters, there was used a 0.25 in. × 5 ft column, 20% SE-30, 210°, helium flow rate 60 cc/min; retention times of 4.8 and 9.2 min, identical with those of authentic samples of methyl laurate and methyl myristate.

The ir spectrum of each sample was characteristic of a methyl alkanoate, nearly identical with the spectrum of methyl stearate. The nmr spectrum of the perhydroajenoates (12 μl in 0.3 ml of CCl_4, TMS internal standard, Varian A-60 instrument) showed the characteristic spectrum of a normal long-chain methyl ester, with the two characteristic features: the triplet centered at τ 9.12 (terminal methyl hydrogens), and the triplet centered at τ 7.80 (α hydrogens).

Pertinent features of the mass spectrum of the deuterated methyl C_{14}-ajenoate are incorporated in Table I; a similar spectrum was obtained for the C_{12}-ajenoate.

Ozonization of Ajenoic Acids.—For fractionation of the aje acids, following a published procedure,[12] 1.75 g of freshly prepared acids in about 25 ml of acetone was cooled to 0°. After standing for a period, the saturated acids which crystallized were removed by suction filtration. After the filtrate had been cooled to −50°, the precipitated fraction consisting largely of the unsaturated C_{18} acids was removed, and then the ajenoic acids were recovered by evaporation of the final filtrate.

A 100-mg sample of the ajenoic acid fraction, dissolved in 50 ml of dichloromethane, was treated with ozone during 30 min until excess ozone had been applied. The ozonide was reduced by addition of 5 ml of triethyl phosphite. After a solution of 160 mg of dimedone in 2 ml of ethanol and 17 ml of water had been added, the reaction mixture was allowed to warm to room temperature, then heated on a steam bath for 15 min, and finally left at room temperature for 2 hr. The solid which had formed was collected by suction filtration, washed with water, and recrystallized from ethanol: yield 28 mg; mp 189–190°, no depression on admixture with an authentic sample of the same melting point. The mass spectra of the isolated and authentic samples were essentially identical, except for a less abundant molecular ion (*m/e* 292) in the isolated sample.

For isolation of esters of dibasic acids, a 350-mg sample of the ajenoic acid fraction was ozonized as described above, but the dichloromethane solution of the ozonide was decomposed by heating under reflux for 1 hr with 20 ml of water. The products recovered by evaporation of the dichloromethane solution were stirred overnight at room temperature with 500 mg of potassium permanganate and 200 ml of acetone. Excess permanganate was decomposed by addition of 5 ml of methanol and stirring for an additional 1 hr. The reaction mixture was worked up by acidification to congo red, addition of sufficient sodium metabisulfite to decompose manganese dioxide, and extraction with ether. Evaporation of the dried ether solution yielded 300 mg of viscous oil which was esterified by heating under reflux for 2 hr with 100 ml of methanol containing 5 ml of concentrated H_2SO_4. Esters recovered by a normal work-up were chromatographed on a 0.25 in. × 5 ft column, 20% DEGS, 120°, helium flow rate 100 cc/min. Retention times of 1.6 min for dimethyl malonate and 3.7 min for dimethyl glutarate were the same as those observed for authentic samples of these esters. Samples collected from gas chromatography were used for mass spectra; results were identical with those from authentic samples. In each ester, the most abundant ion was M − OCH_3 (*m/e* 101 and 129); other prominent ions were those expected except for glutarate, which gave a more abundant M + 1 ion (*m/e* 161) than M, even at low vapor density.

Ozonization of Esters of the Unsaturated C_{18} Acids.—Since the C_{18} acids were too insoluble in dichloromethane at −70° for satisfactory ozonolysis, a 400-mg sample of this fraction was base esterified as described for the mixed aje acids. The resultant 310 mg of esters was ozonized, worked up, and oxidized with permanganate as described for the ajenoic acids. The methyl esters of the resultant acids were chromatographed on a 0.25 in. × 5 ft column, 20% DEGS, 130°, helium flow rate 100 cc/min. Retention times: methyl hexanoate, 2 min; methyl nonanoate, 6.9 min; dimethyl azelate, 21.5 min. Mass spectra of the collected samples and authentic samples were identical, and the ions

(12) C. Y. Hopkins and M. J. Chisholm, *J. Amer. Oil Chem. Soc.*, **45**, 176 (1968).

were those expected, with the rearrangement ion (*m/e* 74) the most abundant. Again the diester gave M + 1 (*m/e* 217) considerably more abundant than M.

Registry No.—**1**, 30409-26-8; **2**, 30345-96-1; deuterated methyl tetradecapentaenoate, 30345-97-2.

Acknowledgment.—We wish to express our appreciation to Dr. C. R. Smith, Jr., Northern Regional Research Laboratory, Peoria, Ill., who, when the manuscript was originally submitted, included in his referee report recommendations which led to our establishing the correct structures for the ajenoic acids.

Structural Modifications of Isosteviol. Partial Synthesis of Atiserene and Isoatiserene[1]

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By means of functional interconversions in ring D of the tetracyclic diterpene isosteviol (*ent*-16-oxobeyeran-19-oic acid, **1**), various 15- and 16-substituted methyl *ent*-beyeran-19-oates (**3**–**7**) have been prepared. Ring C functionalization at positions 12 and 14 has been accomplished by degradation of isosteviol to the unsaturated tricyclic tosylate esters **14c** and **15c** [methyl *ent*-8α-(2′-tosyloxyethyl)-13-methyl-12-podocarpen-19-oate and its Δ^{13} double bond isomer] followed by recyclization. Buffered formolysis of **14c** at room temperature affords after partial hydrolysis methyl *ent*-16β-hydroxyatisan-19-oate (**16a**), which at 85° in formic acid rearranges to methyl *ent*-12β-formyloxybeyeran-19-oate (**18d**). Formolysis of **15c** at 80° gives a tetracyclic formate formulated as methyl *ent*-14β-formyloxybeyeran-19-oate (**17d**). Dehydration of **16a** produces the exocyclic and endocyclic unsaturated esters **21** and **22** which were separately converted into atiserene (**25**) and isoatiserene (**28**).

In order to examine the biogenetic-like rearrangements within the kaurene and atiserene family of tetracyclic diterpenes,[2] we needed synthetic access to both 12β- and 16β-beyerane (hibaane) derivatives with functional groups suitable for the generation of carbonium ion intermediates. This paper describes the conversion of the relatively available diterpene, isosteviol (**1**, *ent*-16-oxobeyeran-19-oic acid),[3-6] into the 12β-hydroxy (**18a**), 16β-hydroxy (**7a**), and 16-amino (**4**) esters. The synthetic route to the 12β-hydroxy ester, proceeding by way of methyl *ent*-16β-hydroxyatisan-19-oate (**16**), opened the way to a partial synthesis of atiserene (**25**) and isoatiserene (**28**).[2b,7]

Since sodium borohydride reduction of the 16-carbonyl group of isosteviol methyl ester **2** affords exclusively the undesired endo (α) hydroxy ester **5a**,[8] the investigation of other approaches was necessary. Hydroboration of the unsaturated ester **8** with disiamylborane[9] in tetrahydrofuran gave rise to a 2:3 mixture of the two exo (β) hydroxy esters **6a** and **7a**. A 3:2 distribution of the 15β and 16β isomers has been reported for hydroboration of hibaene (*ent*-15-beyerene, **8** with CH_3 in place of CO_2CH_3) with diborane.[10] Although a partial separation of the mixture could be achieved by column chromatography of the corresponding acetates **6b** and **7b**, the purification was both tedious and inefficient. Reduction of isosteviol methyl ester by the Meerwein–Ponndorf–Verley method under equilibrating conditions[11] for prolonged periods afforded a mixture (about 1:1) of **5a** and **7a**, which again was partially separated by repeated chromatography of the acetate derivatives **5b** and **7b**. However, by recycling the undesired endo isomer along with mixed factions, a satisfactory yield (59%) of **7b** was realized. Amino ester **4** was prepared by reduction of the oxime **3** of isosteviol methyl ester with sodium in isopropyl alcohol (Scheme I).

The stereochemistry of the hydroxyl group in **5**, **6**, and **7** is assigned on the assumption that attacking reagents in irreversible reactions will approach the 15 or 16 positions of the beyerane nucleus from the exo (β) direction. Although there exists extensive precedent for high stereoselectivity in a wide variety of reactions involving several D ring functional groups in tetracyclic diterpenoids,[12] independent stereochemical evidence is, to our knowledge, limited to recent nmr data (car-

(1) Taken in part from the Ph.D. thesis of E. F. B., University of Illinois, 1970.

(2) (a) R. M. Coates and E. F. Bertram, *Tetrahedron Lett.*, 5145 (1968); (b) R. M. Coates and E. F. Bertram, *Chem. Commun.*, 797 (1969); (c) manuscript in preparation.

(3) Isolation: (a) H. B. Wood, Jr., R. Allerton, H. W. Diehl, and H. G. Fletcher, Jr., *J. Org. Chem.*, **20**, 875 (1955); (b) M. Ruddat, E. Heftmann, and A. Lang, *Arch. Biochem. Biophys.*, **110**, 496 (1965).

(4) Source of *Stevia Rabaudiana* Bertoni (dried leaves and stems or extract): Mr. Luis Enrique de Gesperi, Empresas Ago-Industrales, Asuncion, Peru. We are grateful to Mr. de Gesperi for a sample of the extract.

(5) Structure: (a) E. Mosettig, U. Beglinger, F. Dolder, H. Lichti, P. Quitt, and J. A. Waters, *J. Amer. Chem. Soc.*, **85**, 2305 (1963); (b) J. R. Hansen, "The Tetracyclic Diterpenes," Pergamon Press, Oxford, England, 1968, pp 23–25.

(6) The numbering system used throughout this paper conforms to the recommendations ("The Common and Systematic Nomenclature of Cyclic Diterpenes," 3rd revision, Oct 1968; Adenda and Corrigenda, Feb 1969) prepared by J. W. Rowe (Forest Products Laboratory, Forest Service, U. S. Department of Agriculture, Madison, Wisc. 53705). Both common and systematic names are used in the text as appropriate; complete systematic names appear in the Experimental Section. We are grateful to Dr. Rowe for copies of these recommendations.

(7) A. A. Kapadi, R. R. Sobti, and S. Dev, *Tetrahedron Lett.*, 2729 (1965); A. A. Kapadi and S. Dev, *ibid.*, 2751 (1964).

(8) J. R. Hanson, *Tetrahedron*, **23**, 793 (1967).

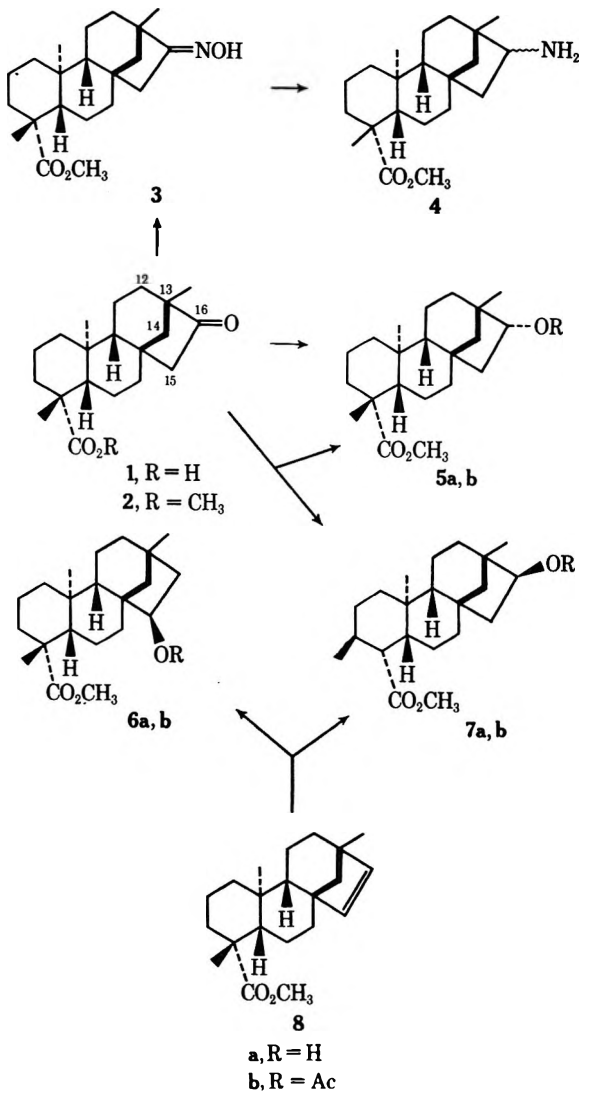
(9) (a) G. Zweifel, K. Nagase, and H. C. Brown, *J. Amer. Chem. Soc.*, **84**, 190 (1962); (b) H. C. Brown and G. Zweifel, *ibid.*, **83**, 1241 (1961).

(10) R. R. Sobti and S. Dev, *Tetrahedron Lett.*, 3939 (1966).

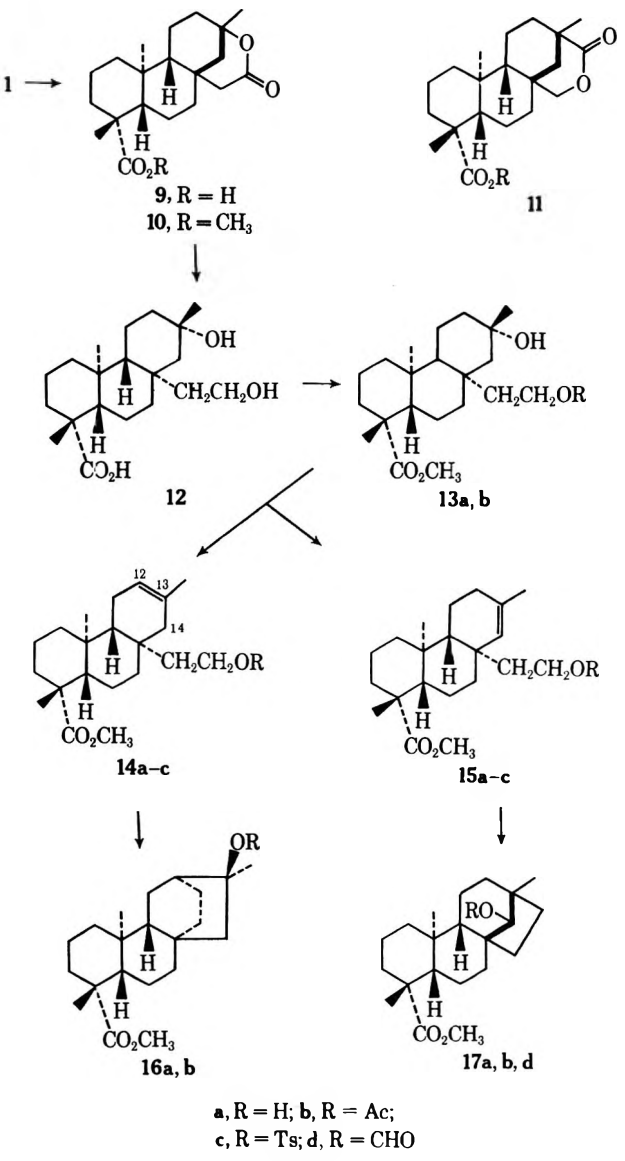
(11) C. F. Wilcox, Jr., M. Sexton, and M. F. Wilcox, *J. Org. Chem.*, **28**, 1079 (1963).

(12) The following selection of references include osmium tetroxide oxidation, epoxidation, hydride reduction, catalytic hydrogenation, sensitized oxygenation, hydroboration, and Grignard addition: (a) P. K. Grant and R. Hodges, *Tetrahedron*, **8**, 261 (1960); (b) J. R. Hanson, *J. Chem. Soc.*, 5061 (1963); (c) L. H. Briggs, B. F. Cain, R. C. Cambie, B. R. Davis, P. S. Rutledge, and J. K. WilmsHurst, *ibid.*, 1345 (1963); (d) R. A. Finnegan, *J. Org. Chem.*, **26**, 3057 (1961); (e) L. H. Briggs, R. C. Cambie, and P. S. Rutledge, *J. Chem. Soc.*, 5374 (1963); (f) L. H. Briggs, B. F. Cain, R. C. Cambie, and B. R. Davis, *ibid.*, 1840 (1962); (g) H. Vorbreugen and C. Djerassi, *J. Amer. Chem. Soc.*, **84**, 2990 (1962); (h) B. E. Cross, R. H. B. Galt, and J. R. Hanson, *J. Chem. Soc.*, 2944 (1963); (i) M. Barnes and J. MacMillan, *ibid.*, *C*, 361 (1967); (j) J. R. Hanson, *Tetrahedron* **23**, 801 (1967); (k) K. Mori and M. Matsui, *ibid.*, **24**, 3095 (1968); (l) R. A. Appleton, P. A. Gunn, and R. McCrindle, *J. Chem. Soc.*, 1148 (1970), and ref 5 8, and 10.

SCHEME I



SCHEME II



binyl proton half-widths) for the epimeric 17-norkauran-16-ols and 17-norphyllocladanols[12j,l] and the X-ray crystallographic structure determination on the alkaloid luciduscuiine.[13,15]

The introduction of a substituent at the 12β position was accomplished by an indirect route (Scheme II) in which ring D is first opened and then reclosed by solvolytic cyclization. Baeyer–Villiger oxidation of isosteviol with sodium acetate buffered peroxyacetic acid[17] furnished the lactone acid **9**. The absence of absorptions expected for the $-CH_2OCO-$ group (τ ~6.0) in the nmr spectrum of this substance decisively excludes the isomeric lactone **11**. Lithium aluminum hydride effected selective reduction of the lactone leaving the hindered C-4 carboxyl group unchanged. Esterification with diazomethane and selective acetylation gave the diol monoacetate **13b**. Dehydration of **13b** under a variety of conditions (see Experimental Section) gave a mixture of the Δ^{12} and Δ^{13} double bond isomers **14a** and **15a**. The best conditions found (thionyl chloride in methylene chloride–collidine at 0°) produced a 2:1 ratio of the isomers, a selectivity rather less favorable than might have been expected.[18] The nmr spectrum of the mixture shows two distinct vinyl protons (τ 4.67 and 4.90) for the major and minor isomers, respectively.[19] The greater breadth of the lower field absorption band ($W_{1/2}$ = 9 *vs.* 4 Hz at 60 MHz) forms the basis for the isomer assignments in view of the additional vicinal coupling expected for the vinyl proton of **14a**. Since the two isomers could not be separated, the mixture was

(13) (a) A. Yoshino and Y. Itaki, *Acta Crystallogr.*, **21**, 57 (1966). (b) Lithium aluminum hydride reduction of isonapelline (15-ketone) gives dihydronapelline B; thus hydride attacks from the exo direction to produce the endo hydroxyl group at C-15 as in natural napelline (luiciculine).[14]

(14) (a) K. Wiesner and Z. Valenta, *Fortschr. Chem. Org. Naturst.*, **16**, 26 (1958); (b) S. W. Pelletier and L. H. Keith in "The Alkaloids," Vol. XII, R. H. F. Manske, Ed., Academic Press, New York, N. Y., 1970, Chapter 2.

(15) Although predictions that the exo isomer will be thermodynamically more stable than the endo in an equilibratable epimeric pair have been used to assign the orientation of various C-17 substituents,[12j,k,16] in the one case for which the position of equilibrium has actually been measured (kauran-15-ones), the endo isomer predominates by a 3:2 margin.[12i] (The equilibration of **5a** and **7a** to a 1:1 mixture is another example.) Kauran-17β-al is reported to isomerize to a mixture of epimers[12i] while methyl kaurane-17β-19-dioate,[12k] and kauran-17β-oic acid[12i] on the other hand, are converted to the 17α epimers. Thus, the stability predictions seem to be equivocal at present.

(16) G. V. Baddeley, P. R. Jefferies, and R. W. Retallack, *Tetrahedron*, **20**, 1983 (1964).

(17) R. R. Sauers, *J. Amer. Chem. Soc.*, **81**, 925 (1959).

(18) (a) D. H. R. Barton, A. da S. Campos-Neves, and R. C. Cookson, *J. Chem. Soc.*, 3500 (1956); see also R. M. Carman and H. C. Deeth, *Aust. J. Chem.*, **23**, 1053 (1970); (b) R. B. Turner, W. R. Meador, and R. E. Winkler, *J. Amer. Chem. Soc.*, **79**, 4122 (1957).

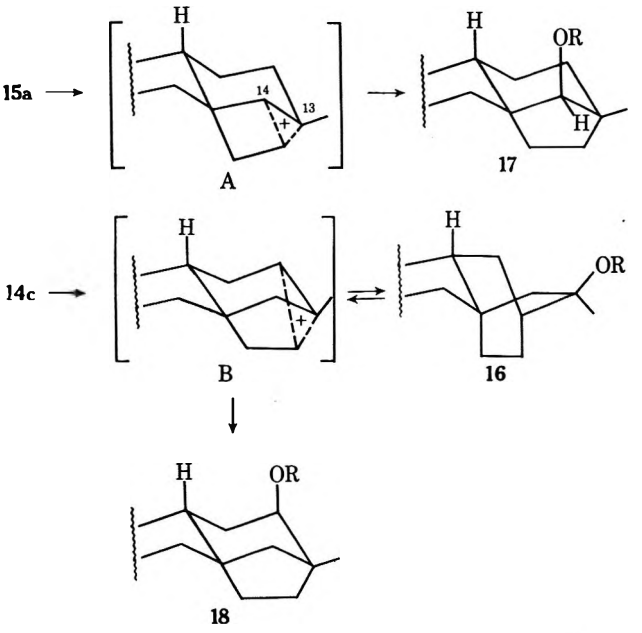
(19) The presence of a small amount (*ca.* 5%) of the exocyclic double bond isomer could also be detected in the nmr spectrum (τ 5.3, $=CH_2$).

carried on to the tosylates (**14c** + **15c**) by partial hydrolysis to the hydroxy esters (**14b** + **15b**) followed by reaction with tosyl chloride.

Solvolysis of the tosylate mixture in buffered formic acid under relatively mild conditions (23–25°, 3.5 hr) effected cyclization of **14c** to the tetracyclic ring system of atiserene. After alkaline hydrolysis and chromatography, the hydroxy ester **16a** and unchanged **15c** were isolated in high yield. At higher temperature (80°, 5 hr), the Δ^{13} toslyate underwent solvolytic cyclization to a secondary formate, which was purified and characterized after partial hydrolysis to the hydroxy ester. This substance is tentatively formulated as methyl *ent*-14β-hydroxybeyeran-19-oate (**17a**). The nmr spectra of **17a** and **17b** showed singlets ($W_{1/2}$ = 2 Hz) for the carbinyl protons (τ 7.06 and 5.53). These data as well as the position of the C-13 methyl group (τ 9.07 and 9.12) are in rather good agreement with nmr data reported for beyeran-14β-ol[20] and beyerane-14β,19-diol (*i.e.*, enantiomers of **17a** with $-CH_3$ and $-CH_2OH$ in place of CO_2CH_3).[20a] The fact that tosylate **15c** leads to the same tetracyclic system as is produced in the formic acid cyclization of manool[20a,b] and agathadiol[20a] provides additional support[21] for the mechanism suggested.[20a,b] Both reactions proceed through the common cationic intermediate A.[22]

The difference in the solvolytic reactivity of the two unsaturated tosylates **14c** and **15c** was not unexpected since acetolysis of 2-(2′-cyclohexenyl)ethyl brosylate results only in direct substitution[23] while 2-(3′-cyclohexenyl)ethyl brosylate gives mainly cyclization to bicyclic products.[24] Although methyl group substitution is known to facilitate double bond participation in solvolysis reactions,[25] in order for the methyl group of **15c** to stabilize the developing positive charge in the transition state leading to ion A, there must be partial bond formation to C-14. However, this stabilization is offset by the simultaneous increase in the strain resulting from partial cyclobutane formation. On the other hand, double bond participation in the solvolysis of **14c** leads to a comparatively unstrained transition state on the way to B.[22]

Since a single isomer of the tertiary alcohol **16a** was isolated in high yield, it seems likely that the bridging carbon has directed the entering nucleophile (formate) to the opposite side, *i.e.*, syn to the C-9 proton as indicated. Nucleophilic attack upon an open (*i.e.*, symmetrically solvated) carbonium ion would appear to be relatively unhindered from either direction.[26] Similarly the hydroxyl group in **17a** is most probably β oriented, opposite to the two carbon side chain in **15c**.[20,28]



Exposure of hydroxy ester **16a** to more vigorous formolysis conditions (85°, 4 hr) induces Wagner–Meerwein rearrangement to the desired 12β-*ent*-beyerane derivative **18d**. The formate was converted by hydrolysis and acetylation to the corresponding acetate **18b** in order to facilitate chromatographic separation from recovered **16**. The structure of the rearrangement product was established by oxidation of the alcohol (**18a**) to the keto ester **19** (ν_{max}^{KBr} 1695, 1720 cm^{-1}) and Wolff–Kishner reduction to the saturated tetracyclic ester **20**. Authentic samples of **20** were obtained by Wolff–Kishner reduction of isosteviol methyl ester (**2**) and catalytic hydrogenation of **8**.

The relatively narrow breadth ($W_{1/2}$ = 5.5 Hz at 60 MHz) of the C-12 carbinyl proton in the nmr spectrum of **18b** indicates that the acetoxyl group is β and axial to the six-membered C ring. If the acetoxyl group were equatorial (α), the width of this peak should be considerably broader ($W_{1/2}$ > 10 Hz) from the larger axial–axial coupling.[29] Thus, the formate group has again been introduced on the side opposite to the participating carbon–carbon bond (Scheme III).

The Wagner–Meerwein rearrangement of **16a** to **18d** thus evidently proceeds through the same cation B as is produced in the formolysis of the unsaturated tosylate **14c**. At the lower temperature of the latter reaction, kinetic control results in attack at the more highly

(20) (a) O. E. Edwards and R. S. Rosich, *Can. J. Chem.*, **46**, 1113 (1968). (b) E. Wenkert and Z. Kumazawa, *Chem. Commun.*, 140 (1968). (c) The chemical shift reported in ref a for the C-14 carbinyl proton of beyeran-14β-ol (τ 7.58) appears to be in error since the same proton in beyerane-14β,19-diol is given as τ 7.09 and ref b reports τ 7.10 for beyeran-14β-ol. Furthermore, ref 21a gives τ 7.08.

(21) (a) O. E. Edwards and B. S. Mootoo, *Can. J. Chem.*, **47**, 1189 (1969); (b) J.-L. Fourrey, J. Polonsky, and E. Wenkert, *Chem. Commun.*, 714 (1969); (c) S. F. Hall and A. C. Oehlschlager, *ibid.*, 1157 (1969).

(22) The bridged ions depicted in A and B may be taken to represent either nonclassical carbonium ions or transition states between a pair of classical Wagner–Meerwein isomers, according to the reader's preference.

(23) A. A. Youssef and S. M. Sharaf, *J. Org. Chem.*, **33**, 2581 (1968).

(24) (a) S. Winstein and P. Carter, *J. Amer. Chem. Soc.*, **83**, 4485 (1961); (b) see also W. Herz, A. K. Pinder, and R. N. Mirrington, *J. Org. Chem.*, **31**, 2257 (1966).

(25) P. D. Bartlett and G. D. Sargent, *J. Amer. Chem. Soc.*, **87**, 1297 (1965); P. G. Gassman and D. S. Patton, *ibid.*, **91**, 2160 (1969); O. L. Chapman and P. Fitton, *ibid.*, **85**, 41 (1963); H. Felkin and C. Lion, *Chem. Commun.*, 60 (1968).

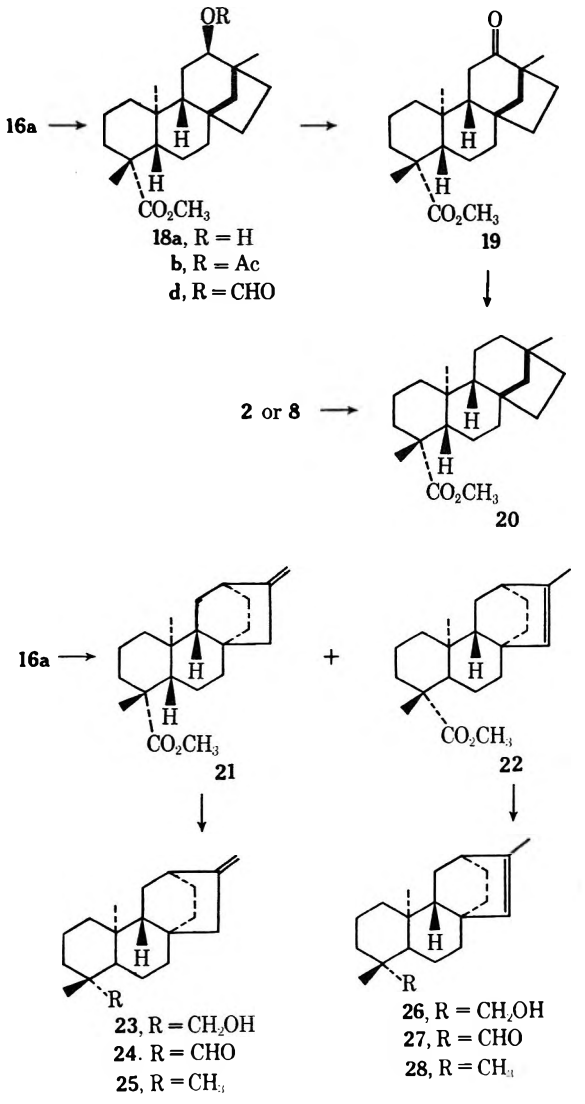
(26) In contrast to the high exo stereoselectivity observed in reactions at positions 15 and 16 in diterpenes having a bicyclo[3.2.1]octane for the C and D rings,[12] the diterpenes with a bicyclo[2.2.2]octane show little selectivity.[14b,27]

(27) (a) L. H. Zalkow and N. N. Girota, *J. Org. Chem.*, **29**, 1299 (1964); (b) R. A. Bell, R. E. Ireland, and L. N. Mander, *ibid.*, **31**, 2536 (1966); (c) S. W. Pelletier, *Quart. Rev., Chem. Soc.*, **21**, 525 (1967).

(28) Since hydride reduction of beyeran-14-one produces a single alcohol with the same C-14 configuration as the solvolysis product,[20a,b] the formate group is evidently entering from the more hindered side. Thus, the stereochemical influence of the carbon bridging prevails over the existing steric effects.

(29) (a) N. S. Bhacca and D. H. Williams, "Applications of NMR Spectroscopy in Organic Chemistry," Holden-Day, San Francisco, Calif., 1964, pp 79–80; (b) R. H. Bible, Jr., "Interpretation of NMR Spectra," Plenum Press, New York, N. Y., 1965, pp 109–111.

SCHEME III



substituted position (16), while at the higher temperature **16** (a or d) reionizes to B allowing the thermodynamically more stable **18d** to accumulate slowly. Similar interconversions have been observed in the rearrangements of substituted norbornyl derivatives.[30]

Dehydration of the tertiary alcohol **16a** with thionyl chloride in methylene chloride–pyridine affords a mixture of the exocyclic (37%) and endocyclic (50%) unsaturated esters, **21** and **22**, separable by chromatography on silica gel impregnated with silver nitrate. Both **21** and **22** were converted to atiserene (**25**) and isoatiserene (**26**) by the sequence—lithium aluminum hydride reduction, chromium trioxide–dipyridine complex oxidation,[31] and Wolff–Kishner reduction. The melting points, optical rotations, and nmr data are in good agreement with the literature data for atiserene[7,27a,32] and isoatiserene.[7] In addition, the complete ir and nmr spectra of natural atiserene proved to be superimposable upon the corresponding spectra of **25** obtained from isosteviol. This correlation provides further support for the structure and absolute configuration of these new tetracyclic diterpenes[33] and, in addition, constitutes a total synthesis[32] in view of the recent synthesis of steviol.[34]

(30) J. A. Berson in "Molecular Rearrangements," P. de Mayo, Ed., Wiley, New York, N. Y., 1963, pp 133–138.

(31) J. C. Collins, W. W. Hess, and F. J. Frank, *Tetrahedron Lett.*, 3363 (1968).

(32) For another total synthesis, see R. A. Bell, R. E. Ireland, and R. A. Partyka, *J. Org. Chem.*, **31**, 2530 (1966), and ref 27b.

Experimental Section[35]

Isosteviol (*ent*-**16-Oxobeyeran-19-oic Acid, 1**).—A 100-g sample of dried and ground leaves and stems of *Stevia Rabuadiana* Bertoni[4] was extracted with five portions of alcohol according to the procedure of Ruddat, Heftmann, and Lang.[3b] The residual syrupy liquid after leaching with ether was dissolved in 25 g of 48% hydrobromic acid and allowed to stand at 23–25° for 15 hr. This treatment liberates the aglycone and also effects pinacol rearrangement of steviol to isosteviol.[5a] Filtration through sintered glass separated a black solid which after chromatography on silica gel with chloroform as eluent yielded 2.7 g (2.7%) of isosteviol (**1**), mp 227–228° (lit.[3a] mp 230–231°).

Isosteviol Methyl Ester (**Methyl** *ent*-**16-Oxobeyeran-19-oate, 2**).—Stevioside was isolated from both a dried extract (250 g) and powdered and sifted leaves and stems (280 g or 3.2 kg) of *Stevia Rabaudiana* Bertoni,[4] using the procedure of Fletcher,[3a] and then hydrolyzed as above with 48% hydrobromic acid.[5a] Esterification of the isosteviol so obtained with diazomethane in methanol and crystallization from acetone afforded the ester **2** (1.9% from the dried extract, 2.1% from the leaves and stems): mp 202–203° (lit.[3a] mp 202–203°); τ 6.40, 8.81, 9.02, 9.30 (all s, 3 H); $[\alpha]^{25}D$ −69.0° (c 1.02).

Methyl *ent*-**16-Aminobeyeran-19-oate** (**4**).—A 988-mg (3 mmol) portion of isosteviol methyl ester (**2**) was allowed to react with 2 g (28.5 mmol) of hydroxylamine hydrochloride in 50 ml of pyridine for 15 hr at 23–25°. The pyridine was then evaporated and the crude product extracted from a dilute hydrochloric acid suspension with hexane. The hexane extract was washed with water, dried (Na_2SO_4), and evaporated. A small portion of the oxime **3** was recrystallized from hexane and chloroform: mp 153–155°; τ 9.23, 8.92, 8.83, and 6.40 (all s, 3 H).

Anal. Calcd for $C_{21}H_{33}NO_3$: C, 72.58; H, 9.57; N, 4.03. Found: C, 72.27; H, 9.50; N, 3.94.

The remainder of the crude oxime was dissolved in 100 ml of isopropyl alcohol and 6 g (0.26 mmol) of sodium was added to the solution at reflux temperature over a 5-hr period. Water was then added and the product isolated by extraction with hexane. After recrystallization of the hydrochloride salt of **4** from chloroform and ethyl acetate (52.5%), the free amine **4** was regenerated by extraction from a dilute sodium hydroxide suspension and was crystallized from chloroform and hexane: mp 110°; τ 9.28, 9.14, 8.83, and 6.37 (all s, 3 H), 7.16 (m, ~1 H, $CHNH_2$); ν_{max} 3600, 3280, 3160 sh (NH_2), 1720 cm^{-1} (C=O).

Anal. Calcd for $C_{21}H_{35}NO_2$: C, 75.63; H, 10.58; N, 4.20. Found: C, 75.78; H, 10.78; N, 4.12.

Methyl *ent*-**16a-Hydroxybeyeran-19-oate** (**2**).—Isoteviol methyl ester (**2**, 200 mg, 0.5 mmol) was reduced with excess sodium borohydride in methanol at room temperature. The product was isolated by extraction with hexane and recrystallized from hexane affording alcohol **5a** (190 mg, 95%): mp 164–165° (lit.[8] mp 164–165°); τ^{CCl_4} 9.28, 9.10, 8.84, and 6.36 (all s, 3 H), 6.11 (t, 1 H, J = 7.5 Hz).

The acetate **5b** was prepared by treatment of **5a** with acetic anhydride and pyridine (1:3) for 15 hr at 23–25°. Crystalliza-

(33) For other correlations see (a) ref 12l and 27a; (b) R. A. Appleton, A. J. McAlees, A. McCormick, R. McCrindle, and R. D. H. Murray, *J. Chem. Soc. C*, 2319 (1966); (c) G. Hugel, L. Lods, J. M. Mellor, and G. Ourisson, *Bull. Soc. Chim. Fr.*, 2894 (1965).

(34) K. Mori, Y. Nakahara, and M. Matsui, *Tetrahedron Lett.*, 2411 (1970).

(35) Melting points were taken in open capillary tubes on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were determined as potassium bromide pellets (unless specified to the contrary) on Perkin-Elmer spectrophotometers Model 137, Model 237, or Model 521. The nmr spectra were taken in chloroform-*d* (unless specified otherwise) using tetramethylsilane as internal standard on Varian Associates Model A160A, Model A-56-60, or Model HA-100 spectrophotometers. The mass spectra were determined on an Atlas CH_4 mass spectrometer. Microanalyses were performed by Mr. J. Nemeth and associates. The gas chromatograph used was Varian Aerograph Hi-Fi Model 600-D with a 6 ft × 0.25 in. column of 5% SE-30 silicone rubber on 60–80 mesh DMCS Chromosorb W at 230°. The optical rotations were taken with a Zeiss polarimeter using $CHCl_3$ as solvent. The ultraviolet spectra were taken on a Cary Model 14 spectrophotometer using ethanol as solvent.

tion from methanol gave acetate **5b** in 90% yield: mp 110°; mp 110°; τ^{CCl_4} 9.31, 9.10, 8.86, 8.00, and 6.40 (all s, 3 H), 5.29 (t, 1 H, J = 7.5 Hz).

Hydroboration of Methyl *ent*-15-Beyeren-19-oate (8) with Disiamylborane. Methyl *ent*-15β-Acetoxybeyeran-19-oate (6b) and Methyl *ent*-16β-Acetoxybeyeran-19-oate (7b).—A solution of disiamylborane was prepared from the reaction of boron trifluoride etherate (16.0 g), sodium borohydride (3.0 g, 0.079 mol), and 2-methyl-2-butene (15.27 ml, 0.146 mol) in 70 ml of tetrahydrofuran (freshly distilled from lithium aluminum hydride).[9] A 2.0-g (6.1 mmol) portion of **8**[2a,c] in 30 ml of tetrahydrofuran was added to the disiamylborane solution. After 5 hr of stirring at 23–25°, 50 ml of 20% sodium hydroxide in water was added slowly with rapid stirring. After an additional 1 hr of stirring, 50 ml of 30% hydrogen peroxide was added. This mixture was stirred for 2 hr more and then 200 ml of water was added and the cloudy white mixture was stirred for approximately 5 hr. The product (2.0 g) was separated by ether extraction and then acetylated with acetic anhydride (3 ml) and pyridine (20 ml) for 24 hr at 23–25°. A glpc analysis of the acetate mixture showed three main peaks. The two peaks of longer retention times were separated from the shorter retention time product on a silica gel column using chloroform as eluent, but repeated chromatography was necessary to achieve a 90:10 enriched mixture from the previous 70:30 mixture. The enriched fractions were then recrystallized several times, first from methanol and water and then proceeding to pure methanol as solvent. A 650-mg (28%) yield of **7b** greater than 99% pure was obtained: mp 91–92°; τ 9.25, 9.12, 8.85, 8.04, and 6.39 (all s, 3 H), 5.4 (dd, 1 H, J = 1.5, 3, 7 Hz); $[\alpha]^{24}D$ −10.6° (*c* 5.6); $\nu_{max}^{CCl_4}$ 1710 (C=O), 1240 cm^{-1} (CO).

Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.37; H, 9.64. Found: C, 73.25; H, 9.25.

The other major component **6b** was recrystallized from methanol: 525 mg (23%); mp 122–123.5°; τ 9.19, 9.02, 8.85, 7.96, and 6.39 (all s, 3 H), 4.71 (broad d, 1 H, J = 6 Hz); ν_{max} 1718 (C=O), 1250 cm^{-1} (CO).

Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.37; H, 9.64. Found: C, 73.68; H, 9.57.

A 600-mg portion of acetate **7b** was hydrolyzed in 25 ml of 5% sodium hydroxide in 85% ethanol for 2 hr at reflux. Recrystallization from hexane gave the 16β-hydroxy ester **7a**: 400 mg; mg 109–111°; τ 9.38, 9.06, 8.84, 6.38 (all s, 3 H), and 6.33 (br d, CHOH, masked partly by signal at 6.38); ν_{max} 3500 and 3350 (OH), 1720 cm^{-1} (C=O).

Meerwein–Pondorf–Verly Reduction of Isosteviol Methyl Ester (2). Methyl *ent*-16β-Acetoxybeyeran-19-oate (7b).—A 3.35-g (10 mmol) portion of **2** was added to 80 ml of isopropyl alcohol, 10 ml of acetone, and 30 g (146 mmol) of aluminum isopropoxide.[11] The mixture was heated at reflux temperature and then the acetone was distilled over a 24-hr period by adding isopropyl alcohol, keeping the volume of solvent approximately constant. The mixture was then heated at reflux temperature for an additional 16 hr. The alcohol was evaporated and dilute hydrochloric acid was added, and the product was isolated by extraction with hexane. The alcohol mixture was acetylated with 10% acetic anhydride in pyridine for 24 hr at 23–25° and then chromatographed on silica gel using 1% ethyl acetate and benzene. A series of five successive column chromatographies was performed, each yielding 10–20% of the two isomers **5b** and **7b** as pure components (by glpc analysis) after crystallization from methanol. The mixed fractions were then rechromatographed. The total yield of **7b** was 1.2 g. The remaining mixture of **5b** and **7b** and the pure **5b** were combined, hydrolyzed, and recycled in a second Meerwein–Pondorf–Verly reduction yielding 1.0 g of **7b** (total yield 2.2 g, 59%).

***ent*-8α-Carboxymethyl-13α-hydroxy-13β-methylpodocarpan-19-oic Acid Lactone (9).**—A 6.0-g (18 mmol) portion of isosteviol (**1**) was added to 400 ml of 25% peracetic acid and 20 g (0.24 mol) of sodium acetate in a 1-l. erlenmeyer flask.[17] Cooling was necessary to prevent foaming during the addition of the sodium acetate. The solution was stirred for 48 hr at 23–25°, concentrated by evaporated to ~50 ml, and poured into a chloroform and water mixture. The chloroform extract was washed twice with water, once with 5% ferric sulfate in 5% hydrochloric acid, again with water and then dried (Na_2SO_4) and evaporated. Crystallization from chloroform and hexane afforded 5.6 g (89%) of **9** (mp 262–264°): the melting point improved to 264–265° on recrystallization from acetone; τ 9.12, 8.75, and 8.66 (all s, 3 H), 6.89 and 7.99 (AB, J = 19 Hz, CH_2CO_2); $[\alpha]^{23}D$ −46.9° (*c* 3.2); ν_{max} 1695–1705 (C=O), 1230 cm^{-1} (CO).

Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 72.06; H, 8.93.

A 100-mg portion of the methyl ester **10** was formed using diazomethane and crystallized from chloroform and hexane: mp 192–194°; τ 9.23, 8.82, 8.65, and 6.35 (all s, 3 H), 7.97 and 6.92 (AB, J = 19 Hz, lower field peak shows additional coupling, J = 21 Hz).

Methyl *ent*-8α-(2′-Acetoxyethyl)-13α-hydroxy-13β-methylpodocarpan-19-oate (15b).—Lithium aluminum hydride (3 g) in 200 ml of dry tetrahydrofuran was added to a rapidly stirred solution of the lactone acid **9** (5.5 g, 16 mmol) in 500 ml of tetrahydrofuran. The reaction mixture was stirred for 3 hr at 23–25° and then 5 ml of water in 25 ml of tetrahydrofuran was added dropwise with continued stirring. The tetrahydrofuran was removed by evaporation and the remaining mixture was added to 5% hydrochloric acid and extracted with chloroform. The chloroform extract was washed with water, dried (Na_2SO_4), and evaporated. A small portion of the diol acid **12** was crystallized from acetone: mp 205–209°; $\tau^{C_5H_5N}$ 8.93, 8.70, and 8.64 (all s, 3 H), 6.05 (m, 2 H).

The remainder of the crude diol acid was treated with excess diazomethane in chloroform and then chromatographed on silica gel using methanol in chloroform as eluent; 1 l. of 2% methanol in chloroform eluted 4.97 g (90%) of the diol methyl ester **13a**. The product was crystallized from acetone: mp 220–221°; τ 9.31 and 6.3 (both s, 3 H), 8.84 (2 s, 6 H), 6.28 (t, 2 H, J = 5 Hz), 6.43 (s, 3 H); $[\alpha]^{22}D$ −30.2° (*c* 4.0); $\nu_{max}^{CHCl_3}$ 1713 (C=O), 3525 and 3595 cm^{-1} (OH).

Anal. Calcd for $C_{21}H_{36}O_4$: C, 71.55; H, 10.29. Found: C, 71.82; H, 10.02.

A 5-g (14 mmol) portion of the diol methyl ester **13a** was acetylated with acetic anhydride (10 ml) and pyridine (45 ml) overnight at 23–25°. The product **13b** (5.3 g, 90%) was crystallized from acetone and hexane: mp 145–145.5°; τ 9.28, 7.98, and 6.38 (all s, 3 H), 8.83 (2 s, 6 H), 5.82 (m, 2 H); $[\alpha]^{25}D$ −15.8° (*c* 3.8); $\nu_{max}^{CHCl_3}$ 1710–1720 (C=O), 3595 and 3530 cm^{-1} (OH).

Anal. Calcd for $C_{23}H_{38}O_5$: C, 70.02; H, 9.71. Found: C, 7.07; H, 9.59.

Methyl *ent*-8α-(2′-Tosyloxyethyl)-13-methyl-12-podocarpen-19-oate (14c) and Methyl *ent*-8α-(2′-Tosyloxyethyl)-13-methyl-13-podocarpen-19-oate (15c).—γ-Collidine (20 ml) was added to a solution of the diol monoacetate **13b** (4.5 g, 11.5 mmol) in 200 ml of methylene chloride. A solution of thionyl chloride (3.5 ml, 20 mmol) in 25 ml of methylene chloride was added quickly (*ca.* 1 min) with rapid stirring under a nitrogen atmosphere. After 1 min more, the mixture was added to cold dilute hydrochloric acid and extracted with ether. A quantitative recovery (4.3 g) was obtained of a product showing two peaks upon a glpc analysis with retention times 7.3 and 8.0 min and relative areas 1:2. The nmr spectrum has bands at τ 8.82, 7.97, and 6.35 (all s, 3 H), 8.40 (broad s, 3 H), 9.28 (s, 2 H), 9.31 (s, 1 H), 5.98 (m, 2 H), 4.67 (m, $^2/_3$ H, $W_{1/2}$ = 9 Hz), 4.90 (m, $^1/_3$ H, $W_{1/2}$ = 4 Hz). The bands at τ 9.28 and 4.67 are assigned to the Δ^{12-13} isomer **14b** and those at τ 9.31 and 4.90 are assigned to the Δ^{13-14} isomer **15b**.[19] The following alternative methods for dehydration gave less favorable results according to glpc analysis: phosphorus oxychloride–pyridine, 24 hr at 25° (**14b**:**15b**, 30:70), thionyl chloride–ethyl diisopropyl amine–methylene chloride (50:50), thionyl chloride–γ-collidine at various temperatures (65:35), thionyl chloride–pyridine (50:50), thionyl chloride–quinoline (40:60), tosyl chloride–pyridine, reflux 5 hr (72:25, but incomplete and poor recovery).

The mixture (4.5 g, 12 mmol) of olefins **14b** and **15b** was added to 100 ml of 5% sodium hydroxide in 95% ethanol and allowed to stand overnight at 23–25°. The ethanol was partially removed by rotary evaporation, and the product, a mixture of **14a** and **15a**, was isolated by ether extraction (4.0 g, 100%): τ 6.37 (s, 3 H), 6.2–6.6 (m, 2 H), 8.83 (s, 3 H), 8.41 (broad s, 3 H), 9.28 (s, 2 H), 9.32 (s, 1 H), 4.88 (m, $^1/_3$ H), 4.67 (m, $^2/_3$ H).

The mixture (4.0 g, 12 mmol) of hydroxy olefins **14a** and **15a** in 50 ml of pyridine was treated with 5 g (26 mmol) of *p*-toluenesulfonyl chloride at 23–25° for 24 hr. A 2-ml portion of water was then added over a 0.5-hr period with cooling. After work-up by ether extraction the tosylate mixture of **14c** and **15c** (5.7 g) was obtained: τ 8.83, 7.54, and 6.35 (all s, 3 H), 9.37 (s, 2 H), 9.40 (s, 1 H), 6.03 (τ, 2 H, J = 6.5 Hz), 5.08 (m, $^1/_3$ H), 4.73 (m, $^2/_3$ H) 2.21 and 2.66 (AB, 2 H, J = 9 Hz). The nmr bands

at τ 9.37 and 4.73 are assigned to **14c** and those at τ 9.49 and 5.08 to **15c**.

Methyl *ent*-16β-Hydroxyatisiran-19-oate (16a).—A solution of sodium formate in formic acid was prepared by dissolving 2.5 g (24 mmol) of sodium carbonate in 125 ml of formic acid. The tosylate mixture containing **14c** and **15c** (5.7 g, 11.5 mmol)[19] was added, requiring about 30 min to dissolve completely. After 3.5 hr at 23–25° the solvent was evaporated at room temperature under reduced pressure (required about 30 min) and the residue hydrolyzed with 5% sodium hydroxide in 95% ethanol (*ca.* 12 hr at room temperature). The ethanol was removed with a rotary evaporator. The residue was partitioned between hexene and water, and the water layer extracted two or three more times with hexane. The combined hexane extracts were dried (Na_2SO_4) and evaporated. The residue (4.3 g) was chromatographed on silica gel using ether and hexane as eluent. With 20% ether and hexane the tosylate **15c** and the exocyclic double bond isomer were eluted (2.4 g, 40%): τ 9.40, 8.84, 8.43, 7.53, and 6.35 (all s, 3 H), 5.91 (t, 2 H, J = 7.5 Hz), 5.09 (m, 4/5 H), 5.41 and 5.63 (both m, 1/5 H), 2.23 and 2.65 (AB, 2 H, J = 9 Hz). The nmr band at τ 5.09 is assigned to **14c** while those at 5.41 and 5.63 are assigned to the exocyclic double bond isomer.

Elution with 40–100% ether and hexane mixtures gave the tertiary alcohol **16a** (2.3 g, 60%) which was then recrystallized from hexane: mp 148–148.5°; τ 9.21, 8.84, 8.71, and 6.35 (all s, 3 H); $[\alpha]^{23}D$ −42.7° (c 3.3); ν_{max} 3505 (OH), 1708 cm^{-1} (C=O).

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25. Found: C, 75.60; H, 10.18.

Methyl *ent*-14β-Hydroxybeyeran-19-oate (17a).—An 80-ml portion of buffered formic acid, prepared as above, was added to the unsaturated tosylate (3.2 g, 6.4 mmol) recovered from the preceding low temperature formolysis (**15c** containing *ca.* 20% of the exocyclic double bond isomer) and the solution heated at 80° for 5 hr. The product was isolated as above and the solid residue (2.0 g, 93%, mp 233–245°) recrystallized twice from acetone to give pure **17a**: mp 248–249°; τ 9.25, 9.07, 8.83, and 6.36 (all s, 3 H), 7.06 (s, $W_{1/2}$ = 2 Hz, 1 H); ν_{max} 3520 (OH), 1700 cm^{-1} (C=O).

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25. Found: C, 75.12; H, 10.25.

A small sample of **17a** was treated with acetic anhydride–pyridine (1:3) for 2 hr at 100°. The solvent and excess reagent were removed by evaporation and the residue was crystallized twice from methanol to give **17b**: mp 141–142°; τ 9.22, 9.12, 8.82, 7.83, and 6.36 (all s, 3 H), 5.53 (s, 1 H, $W_{1/2}$ = 2 Hz); ν_{max} 1710 and 1717 cm^{-1} (C=O).

Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.37; H, 9.64. Found: C, 73.39; H, 9.61.

Methyl *ent*-12β-Hydroxybeyeran-19-oate (18a).—The hydroxy ester **16a** (1.4 g, 4.2 mmol) was dissolved in buffered formic acid as described above for the preparation of **16a** and the solution heated at 85° for 4 hr. The product, isolated in the same manner as before, was dissolved in pyridine containing 10% acetic anhydride and heated at steam bath temperature for 3 hr. The excess reagents were removed under reduced pressure and the resulting white residue was chromatographed on silica gel using ether–hexane mixtures as eluent. The first components eluted were 25 mg (2%) of olefins according to glpc analysis. Elution with 10% ether and hexane gave a fraction containing acetate **18b** (1.16 g, 71%) which was crystallized from methanol: mp 137–139°; τ 9.28, 9.08, 8.82, 7.96, and 6.39 (all s, 3 H), 5.30 (br, $W_{1/2}$ = 5.5 Hz, 1 H); $[\alpha]^{23}D$ −77.6° (c 5.4); ν_{max} 1720 (C=O), 1250 cm^{-1} (CO). Later fractions (30–100% ether and hexane) afforded 0.25 g (18%) of alcohol **16a**.

Anal. Calcd for $C_{23}H_{36}O_4$: C, 73.37; H, 9.64. Found: C, 73.14; H, 9.56.

The acetoxy methyl ester **18b** (0.670 g, 1.8 mmol) was hydrolyzed with potassium hydroxide (2 g) in ethanol (70 ml) for 1 hr at 70°. The hydroxy ester **18a** was isolated by ether extraction and recrystallized from hexane (0.46 g, 70%): mp 104–105.5°; τ 9.25, 9.04, 8.83, and 6.35 (all s, 3 H), 6.48 (br s, 1 H); $[\alpha]^{23}D$ −57.8° (c 2.9); ν_{max} 1700 and 1720 (C=O), 3480 and 3520 cm^{-1} (OH); $\nu_{max}^{CHCl_3}$ 3500 (OH), 1720 cm^{-1} (C=O). Evaporation of the mother liquid afforded another 0.100 g of **18a** which was pure according to glpc analysis.

Anal. Calcd for $C_{21}H_{34}O_3$: C, 75.41; H, 10.25. Found: C, 75.49; H, 10.29.

Methyl *ent*-12-Oxobeyeran-19-oate (19).—Hydroxy ester **18a** (0.826 g, 0.86 mmol) was dissolved in 25 ml of methylene chloride, a 2-g portion of chromium trioxide–dipyridine complex[31] was added, and the mixture was swirled for 5 min. The mixture was diluted with 50 ml of hexane and applied to a silica gel column. The keto ester **19** (0.280 g, 99%) was eluted with 10% ether in hexane and crystallized from acetone: mp 205–206° [mmp (with isosteviol methyl ester **1**) 193–196°]; τ 9.22, 8.93, 8.82, and 6.36 (all s, 3 H); $[\alpha]^{23}D$ −113° (c 1.4); ν_{max}^{KBr} 1695 and 1720 cm^{-1} (C=O).

Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.67; H, 9.56.

Methyl *ent*-Beyeran-19-oate (20). A.—Isosteviol methyl ester (**2**) (0.200 g, 0.6 mmol) was dissolved in 15 ml of diethylene glycol and 3 ml of hydrazine hydrate (99%). The solution was heated at reflux temperature for 13 hr and the suspension was extracted with ether. The ether extract was washed four times with water, dried (Na_2SO_4), and evaporated. The residue (presumably hydrazone) was then transferred to a glass high-pressure reaction tube along with 20 ml of 30% sodium methoxide and 0.2 ml of hydrazine hydrate (99%). The tube was sealed and heated at 200° for 3–4 hr. The product was isolated by extraction with ether and then esterified with diazomethane. Crystallization from methanol gave 0.165 g (83%) of the saturated ester **20**, mp 142–143° (lit.[3a] mp 143°).

B.—A similar procedure to the reduction of **2** given above was followed using 0.178 g (0.55 mmol) of keto ester **19**. A yield of 92 mg (50%) of **20** was obtained after recrystallization: mp 142°; τ 9.25, 0.04, 8.83, and 6.38 (all s, 3 H); $[\alpha]^{23}D$ −46° (c 4.5); ν_{max} 1720 cm^{-1} (C=O).

Anal. Calcd for $C_{21}H_{34}O_2$: C, 79.19; H, 10.76. Found: C, 78.85; H, 10.82.

C.—A 125-mg (0.4 mmol) sample of the unsaturated ester **8**[2a,c] was dissolved in 100 ml of 95% ethanol and 0.200 g of palladium on carbon was added. The mixture was then shaken in a Parr apparatus under 50-lb hydrogen pressure for 3 hr. The ethanol suspension was filtered and the ethanol removed by evaporation. Crystallization from methanol yielded 0.113 g (88%) of **20**, mp 142–143°.

A mixture melting point of 142–143° for mixtures of **20** obtained from all three procedures was observed. The ir and nmr spectra as well as the glpc behavior were also identical.

Methyl *ent*-16-Atisen-19-oate (21) and Methyl *ent*-15-Atisen-19-oate (22).—A 1.0-ml portion of thionyl chloride was quickly added to a solution of the hydroxy ester **16a** (1.05 g, 3.1 mmol) in 10 ml of pyridine and 20 ml of methylene chloride over a 1-min period. After 1 min more, this solution was poured into dilute hydrochloric acid and the suspension was extracted three times with ether. The combined ether extracts were washed twice with water, dried over anhydrous sodium sulfate, and evaporated to dryness. The residue was chromatographed on 15% silver nitrate–silica gel with 3–4% ether in hexane as eluent. Unsaturated ester **22** (0.505 g, 50%) was eluted first and was crystallized from methanol: mp 90–91°; τ 9.20, 8.83, and 6.37 (all s, 3 H), 8.28 (d, 3 H, J = 1.7 Hz), 4.42 (m, 1 H); $[\alpha]^{23}D$ −79.5° (c 6.2); ν_{max} 1720 cm^{-1} (C=O).

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.35; H, 10.15.

The isomeric ester **21** (0.360 g, 37%) was eluted with 4% ether in hexane and was crystallized from methanol: mp 126–127°; τ 9.22, 8.83, and 6.37 (all s, 3 H), 5.28 and 5.42 (2, 2 H, J = 2 Hz); $[\alpha]^{23}D$ −62.5° (c 0.96); ν_{max} 1720 (C=O), 3035, 870, and 865 (C=CH_2), 1650 cm^{-1} (C=C).

Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.50; H, 10.16.

***ent*-15-Atisene (Isoatiserene, 28).**—Lithium aluminum hydride (1.2 g) was added with stirring to a solution of the unsaturated ester **22** (0.50 g, 1.57 mmol) in 100 ml of tetrahydrofuran under a nitrogen atmosphere. After 1 hr at reflux, the solution was cooled and 2 ml of water in 20 ml of tetrahydrofuran was added cautiously with cooling. The tetrahydrofuran was then removed under reduced pressure and the residue was added to dilute hydrochloric acid. The resulting suspension was extracted three times with ether, and the combined ether extracts were washed twice with water, dried (Na_2SO_4), and evaporated. A yield of 0.445 (95%) of alcohol **26** was obtained: mp 138.5–139.5°; τ 9.04 and 9.02 (both s, 3 H), 8.26 (d, 3 H, J = 1.7 Hz), 6.27 and 6.53 (AB, 2 H, J = 11.5 Hz), 4.42 (m, 1 H); ν_{max} 3360 cm^{-1} (OH).

Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.00; H, 11.26.

An 0.360-g (1.25 mmol) portion of **26** was added to 35 ml of dichloromethane and 1 g (5 mmol) of pyridine–chromium trioxide complex[31] was added with stirring. After 3 min the reaction was terminated by addition of 50 ml of hexane. The suspension was chromatographed on a silica gel column; 10% ether and hexane eluted 0.315 g (88%) of aldehyde **27**: τ 9.17 and 8.98 (both s, 3 H), 6.40 (m, 1 H), 8.26 (d, 3 H, J = 1.5 Hz), and 0.27 (s, 1 H). The glpc retention time was different from that of the starting material.

The aldehyde **27** (0.315 g, 1.1 mmol) was dissolved in 30 ml of diethylene glycol and 5 ml of 99% hydrazine hydrate was added. The solution was heated under nitrogen for 5 hr at 120–130°, 3.5 g (90 mmol) of sodium hydroxide was added, and the hydrazine and water were distilled from the reaction. The solution was then heated at 185° for 15 hr. The product was isolated by ether extraction and chromatographed on silica gel. Hexane eluted 0.280 g (90%) of an unsaturated hydrocarbon (**28**) which was crystallized from methanol: mp 81.5–82.5° (lit.[7] mp 84–85°); τ 9.17, 9.13, and 9.03 (all s, 3 H), 8.26 (d, 3 H, J = 1.5 Hz), 4.40 (m, 1 H); $[\alpha]^{23}D$ −75° (*c* 9.0) (lit.[7] −73.99°); ν_{max} 3025 cm^{-1} (C=CH). The spectral data correspond to those reported for natural isoatiserene.[7]

Anal. Calcd for $C_{20}H_{32}$: C, 88.16; H, 11.84. Found: C, 88.26; H, 11.77.

ent-16-Antisene (Atisirene, **25**).—The same reduction procedure as described above was followed using 0.353 g (1.1 mmol) of unsaturated ester **21** and 0.5 g of lithium aluminum hydride. Alcohol **23** was recrystallized from hexane (0.330 g, 99%): mp 139–140°; τ 9.02 (s, 6 H), 5.29 and 5.46 (both quartets with $J \sim 2$ Hz, 1 H), 6.28 and 6.53 (AB, 1 H, J = 11 Hz); ν_{max} 3390 (OH), 3070, 1650, and 870 cm^{-1} (C=CH$_2$).

Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 82.71; H, 11.21.

Alcohol **23** (0.245 g, 0.84 mmol) was then added to 30 ml of dry dichloromethane and 2 g of chromium trioxide–dipyridine complex[31] was added. After 3 min, the suspension was diluted with 50 ml of hexane and then poured on to a column of silica gel; elution with hexane containing 10% ether gave 0.230 g (95%) of aldehyde **24** (glpc retention time different from that of **23**).

The aldehyde **24** (0.230 g, 0.8 mmol) was subjected to Wolff–Kishner reduction as above, with 15 ml of diethylene glycol and 3 ml of 99% hydrazine hydrate. Column chromatography of the product on silica gel using hexane as eluent gave 0.083 g (38%) of atisirene (**25**), which after crystallization from methanol had mp 58–58.5° [lit.[7,27a] mp 57–58°; 60–61° (for enantiomer)]; τ 9.16, 9.14, and 9.02 (all s, 3 H), 5.29 and 5.46 (both m, 2 quartet, 1 H, J = 2 Hz); $[\alpha]^{23}D$ −41.20° (*c* 5.0) (lit.[7] −40.46°]; ν_{max} 3080, 1648, 880, and 870 cm^{-1} (C=CH$_2$). The spectral data are in reasonable agreement with the corresponding literature data for natural atiserene,[7] its enantiomer,[27a] and synthetic racemic antiserene.[32] In addition, the complete ir and nmr spectra are superimposable upon those of natural atiserene.[7]

Anal. Calcd for $C_{20}H_{32}$: C, 88.16; H, 11.84. Found: C, 87.92; H, 11.82.

Registry No.—**1**, 27975-19-5; **2**, 30217-41-5; **3**, 30217-42-6; **4**, 21682-55-3; **5b**, 30288-12-1; **6b**, 30217-44-8; **7a**, 30217-45-9; **7b**, 21682-20-2; **9**, 23963-60-2; **10**, 30217-48-2; **12**, 30217-49-3; **13a**, 24022-50-2; **13b**, 24022-51-3; **14a**, 30217-52-8; **14b**, 23963-18-0; **14c**, 23963-59-9; **15a**, 30217-54-0; **15b**, 23963-19-1; **15c**, 30288-14-3; **16a**, 23963-20-4; **17a**, 30217-57-3; **17b**, 30217-58-4; **18a**, 30217-59-5; **18b**, 23963-23-7; **19**, 23963-24-8; **20**, 19898-49-8; **21**, 23963-21-5; **22**, 23963-22-6; **23**, 30217-65-3; **25**, 20230-48-2; **26**, 30217-67-5; **28**, 5975-29-1.

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Cycloserine Dimer Hydrolysis and Its Equilibration with Cycloserine

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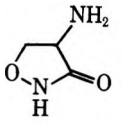
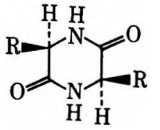
A kinetic investigation of the hydrolysis of three cis-3,6-disubstituted 2,5-piperazinediones (**2**, **3**, and **4**) at several HCl concentrations has been completed. The relative rates are compared to the unsubstituted 2,5-piperazinedione (**5**). In solutions of pH 1–2, a cycloserine dimer **2** ⇆ cysloserine (**1**) equilibrium was shown to be rapidly established. The mechanism of this interconversion is discussed.

It has been well established[2] that the broad-spectrum antibiotic cycloserine (**1**) is converted into its dimer, (+)-*cis*-3,6-bis(aminoxymethyl)-2,5-piperazinedione (**2**) even in the solid state.[3] This present investigation indicates that in solution **2** is also converted into cycloserine and that the establishment of an equilibrium between **1** and **2** is pH dependent. Our recent kinetic study[4] of the acid-catalyzed hydrolysis of **2** indicated that the side-chain aminoxy groups do not anchimerically assist the reaction at low pH. Such participation would necessarily lead to the intermediate formation of



1



2, R = CH_2ONH_2
3, R = CH_2OH
4, R = CH_3
5, R = H

a cycloserine peptide which further hydrolysis would convert into the observed product, β-aminoxy-D-alanyl-β-aminoxy-D-alanine (see Scheme I). Table I summarizes the results of more recent studies on the hydrolysis of **2** and analogous 2,5-piperazinediones **3** and **4** at various concentrations of HCl. The results confirm the previous hypothesis that the aminoxy groups do not participate at low pH.

Table II shows the activation parameters for the hydrolyses of **2**, **3**, **4**, and the unsubstituted compound **5**. It was primarily the small differences in hydrolysis rates

(1) Abstracted from the Ph.D. thesis of F. O. Lassen, submitted to the Graduate School of the University of Georgia, June 1969.

(2) (a) P. H. Hidy, E. B. Hodge, V. V. Young, R. L. Harned, G. A. Brewer, W. F. Phillips, W. F. Runge, H. E. Stavely, A. Pohland, H. Boaz, and H. R. Sullivan, *J. Amer. Chem. Soc.*, **77**, 2345 (1955); (b) J. M. Nielands, *Arch. Biochem. Biophys.*, **62**, 151 (1956); (c) R. M. Khomutov, M. Ya. Karpeskii, and E. S. Severin, "Chemical and Biological Aspects of Pyridoxal Catalysis," I. U. B. Symposium Series, Pergamon, New York, N. Y., 1963.

(3) M. Ya. Karpeskil, Yu N. Brensov, R. M. Khomutov, E. S. Severin, and O. L. Polyanovskii, *Biochemistry*, **28**, 280 (1963).

(4) J. L. Miller, F. C. Neuhaus, F. O. Lassen, and C. H. Stammer, *J. Org. Chem.*, **33**, 3908 (1968).

SCHEME I

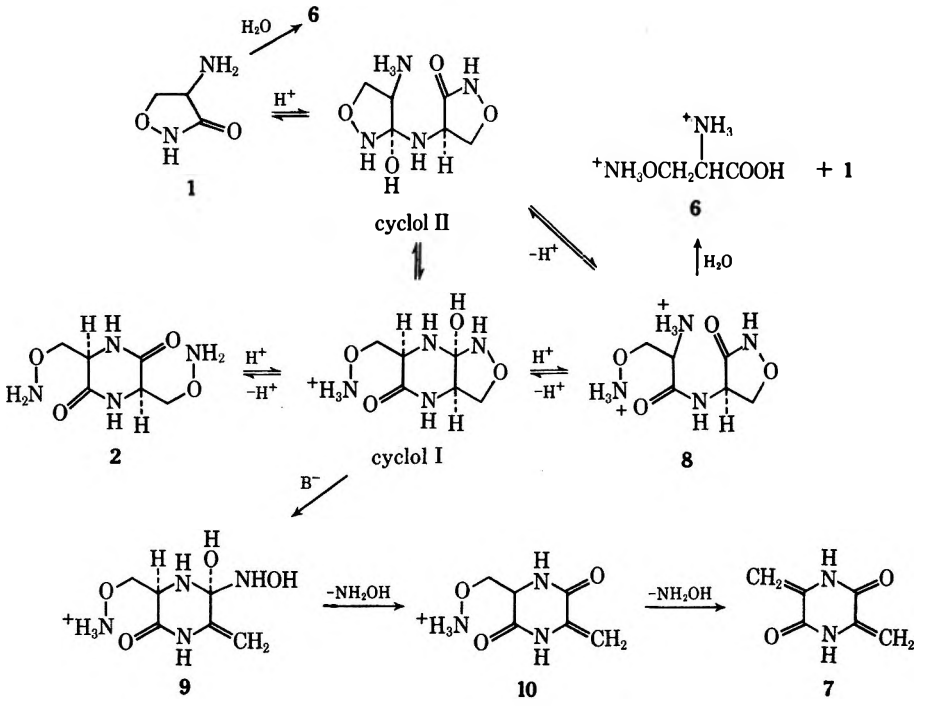


TABLE I

HYDROLYSIS RATE CONSTANTS OF 2, 3, AND 4 IN HCl AT 60°

[HCl], M	$k \times 10^3$ 2	3	4
1.00	4.76 ± 0.05[a]	3.78 ± 0.01	10.7 ± 0.07[a]
2.00	10.6 ± 0.1[b]		26.3 ± 0.3[b]
3.99	33.9 ± 0.9[c]	19.4 ± 0.01	58.0 ± 2.1[c]
5.93	55.1 ± 0.9[a]	33.9 ± 0.01	

[a] Average of three runs. [b] Average of two runs. [c] Average of four runs.

TABLE II

ACTIVATION PARAMETERS FOR HYDROLYSIS OF CIS-SUBSTITUTED 2,5-PIPERAZINEDIONES IN 1 *N* HCl AT 60°

R	No.	Relative rates	E_a, kcal	$H^{\pm}$, kcal	$S^{\pm}$, eu
CH_2ONH_2	2	1.2	19.9[a]	19.2[a]	−19.7[a]
CH_2OH	3	1	19.7[a]	19.0[a]	−20.8[a]
CH_3	4	4.5	18.3	17.6	−22.9
H	5	2.0[c]	21.3[b]	20.6[b]	−14.7[b]

[a] From ref 4. [b] B. O. Sykes, E. B. Robertson, H. B. Dunford, and D. Konuswich, *Biochemistry*, **5**, 697 (1966). [c] Calculated from the data of J. T. Edward and S. C. Meacock, *J. Chem. Soc.*, 2000 (1957).

and activation parameters which led us to conclude that the aminoxy groups were not participating in the hydrolysis of **2**. The fact that the dimethyl compound **4** hydrolyzes faster than **2** is strong evidence against aminoxy participation, which should increase the rate. Furthermore, there are no really significant differences in $\Delta H^{\pm}$ and $\Delta S^{\pm}$ among **2**, **3**, and **4**. Further evidence against aminoxy participation in the hydrolysis was obtained when we found that the rate of hydrolysis of the dimethyl compound **4** was somewhat decreased when methoxyamine was added (Table III). Apparently the only effect of methoxyamine was to slow the reaction by decreasing the HCl concentration.

When attempts were made to examine the hydrolysis of **2** at pH >1, both polarimetry and paper chromatography showed that other reactions were occurring.

TABLE III

EFFECT OF METHOXYAMINE ON THE HYDROLYSIS RATE OF 4

	$k \times 10^2$	Relative rates
2 *M* HCl	2.63	1
0.4 *M* $^+NH_3OCH_3Cl^-$, 1.6 *M* HCl	2.1	0.80
0.4 *M* NaCl, 1.6 *M* HCl	2.2	0.83
1.6 *M* HCL	2.1	0.80

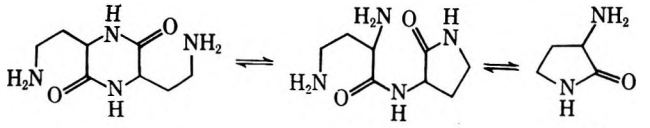
Potentiometric titration of **2** showed the pK_a of the aminoxy groups[5] to be *ca.* 3.5, with no differentiation between the two groups. Thus at pH >1, a finite concentration of aminoxy groups becomes available for intramolecular attack on the adjacent ring carbonyl functions. Paper chromatography studies of solutions of **2** in pH 1.2 phosphate buffer and in 1 *N* acetic acid (*ca.* pH 2.2) showed that not only was cycloserine (**1**) being formed, but also β-aminoxylalanine (**6**) (hydrolysis product of **1**) and 3,6-dimethylene-2,5-piperazinedione (**7**) (the product of hydroxylamine elimination from **2**). Scheme I shows a reasonable explanation for these results.

Considering the high nucleophilicity of hydroxylamines and the ease with which the cycloserine ring closes,[6] the formation of cyclol I seems a reasonable first step. Opening of the six-membered ring in I gives the dipeptide **8** which can be hydrolyzed to cycloserine (**1**) and β-aminoxy-D-alanine (**6**) or rearrange to cyclol II. The formation of the bismethylene compound **7** can be explained by a second path through which cyclol I might decompose. Attack by a general base on the α proton would convert I into the unstable hydroxylamine **9** which leads directly to the monomethylene compound **10** by the loss of hydroxylamine. The formation of **10** from **2** has been observed previously

(5) R. W. A. Oliver, T. Viswanatha, and W. J. D. Whish, *Biochem. Biophys. Res. Commun.*, **27**, 107 (1967), report pK_a = 4.0 for these aminoxy groups.

(6) C. H. Stammer, A. N. Wilson, C. F. Spencer, F. W. Bachelor, F. W. Holly, and K. Folkers, *J. Amer. Chem. Soc.*, **79**, 3236 (1957).

during the base-catalyzed decomposition of **2** to **7**. Further elimination from **10** then leads to **7**. Cyclol formation was also postulated by Rudinger and coworkers[7] to explain the formation of the dipeptide *N*-(α,γ-diaminobutyryl)-α-aminopyrrolidone (**12**) and α-aminopyrrolidone (**13**) from the piperazinedione **11** in dilute ammonia. These workers also showed that the dipeptide **12** was converted into both **11** and **13** under these same conditions showing that an equilibrium was probably established. Similarly, solutions of high pH probably convert the dimer **2** into cyclol I, but this intermediate eliminates hydroxylamine much more



11 **12** **13**

rapidly than it undergoes hydrolysis. Thus, the behavior of the dimer **2** in both weakly acidic and basic media can be explained by assuming the formation of cyclol I.

The behavior of cycloserine (**1**) under strongly and weakly acidic[8] conditions can also be explained using Scheme I. Under strongly acidic conditions (3 *N* HCl) the isoxazolidone ring is hydrolyzed[9] giving the alanine derivative **6**, but dimerization predominates when **1** is treated[4] with 4% ethanolic acetic acid. Under the latter conditions, the acid catalyzes the condensation of two molecules of **1** to give cyclol II which can go to cyclol I either directly or through the dipeptide[10] **8**. The dimer **2** is then formed from I and the equilibrium between **1** and **2** is established. Our experiments showed that, in aqueous 1 *M* acetic acid solutions, cycloserine was converted into both **2** and **7** and that under these same conditions dimer **2** was converted into both cycloserine and **7**, indicating the presence of an equilibrium. Weakly acidic (pH 2–6) conditions are expected to favor establishment of this equilibrium since the amino groups are not so completely protonated as in strong acid. This allows the condensation of two molecules of **1** giving cyclol II and the conversion of **8** into cyclol I to occur at reasonable rates.

The presence of an equilibrium between cycloserine and its dimer in solution makes the assignment of any specific biological activity to either of these compounds difficult. Certainly, future biological assessments of these and related substances should take these facts into account.

Experimental Section

Cycloserine,[11] serine,[12] and alanine[13] were used without further purification. The (+)-3,6-bis(aminoxymethyl)-2,5-piperazinedione (**2**) and the (−)-3,6-bis(hydroxymethyl)-2,5-piperazinedione (**3**) were prepared by previously published procedures.[5,13]

(−)-**3,6-*cis*-Dimethyl-2,5-piperazinedione** (**4**).—*tert*-Butoxycarbonyl-L-alanine[14] (24.23 g, 0.13 mol) was coupled *via* the isobutyl chloroformate mixed anhydride procedure[15] with L-alanine methyl ester[16] (17.88 g, 0.13 mol) yielding, after two recrystallizations from anhydrous ether–petroleum ether (bp 40–60°), 28.62 g (88%) of *N*-*tert*-butoxycarbonyl-L-alanyl-L-alanine methyl ester: mp 112–113°; $[\alpha]^{24}D$ −63.7° (*c* 2, MeOH); ir (KBr) 3255 (NH), 1738 (ester C=O), 1675 (amide C=O), 1650 cm^{-1} (*tert*-BOC C=O); nmr ($CDCl_3$) δ 1.32 (d, 3, H, C-terminal CH_3, J = 8 Hz), 1.34 (d, 3 H, N-terminal CH_3, J = 8 Hz), 1.42 (s, 3 H, *tert*-BOC CH_3), 3.80 (s, 3 H, OCH_3), 4.30 (m, 1 H, C-terminal CH, J = 8 Hz), 5.86 (d, 1 H, peptide NH, J = 8 Hz), 7.47 ppm (broad s, 1 H, *tert*-BOC NH). *Anal.* Calcd for $C_{21}H_{22}N_2O_5$: C, 52.54; H, 8.08; N, 10.21. Found: C, 52.52; H, 8.19, N, 10.14.

The *tert*-butoxycarbonyl group was removed from 27.46 g (0.1 mol) of the dipeptide ester using 200 ml of glacial acetic acid and 350 ml of 1 *M* HBr in glacial acetic acid. A yield of 23.16 g (91.4%) of crude hygroscopic L-alanyl-L-alanine methyl ester hydrobromide was obtained: $[\alpha]^{20}D$ −40.2° (*c* 1, 0.1 *M* HBr); ir (KBr) 1985 (NH_3^+), 1735 (ester C=O), 1670 cm^{-1} (amide C=O).

The cyclization of the above ester hydrobromide into **4** was effected by treating a 2:1 methanol–water solution of the crude hydrobromide in a batchwise manner with Amberlite IRA 400 (OH^- cycle) until the solution was shown to be bromide free by silver nitrate. The solution was filtered and evaporated to 30 ml. After standing overnight at room temperature, 8.19 g (65%) of crude (−)-3,6-dimethyl-2,5-piperazinedione (**4**) precipitated and was collected on a filter. After recrystallization from ethanol–water (10:1), 5.52 g (44%) of **4** was obtained: mp 282–285° (lit.[16] 288–290): $[\alpha]^{20}D$ −31.0° (*c* 1, H_2O) [lit.[17] $[\alpha]^{21}D$ −29.6° (*c* 1.9, H_2O)]; ir (KBr) identical with that published by Brockmann and Musso;[17] nmr (D_2O) δ 1.90 (d, 6 H, ($CHCH_3$), J = 8 Hz), 4.60 ppm (q, 2 H, $CHCH_3$, J = 8 Hz). *Anal.* Calcd for $C_6H_{10}N_2O_2$: C, 50.68; H, 7.09; N, 19.71. Found: C, 50.21; H, 7.20; N, 19.80.

Kinetic Studies.—The kinetic studies were carried out using the polarimetric procedures previously described.[4] The kinetic data for the hydrolysis of **4** in 1 *M* HCl is shown in Table IV.

TABLE IV

Temp, °C	$k \times 10^3$, min^{-1}	$t_{1/2}$, min
50	4.77 ± 0.02	145
55	7.79 ± 0.02	89
60	10.7 ± 0.7	65
65	17.6 ± 0.1	39
70	25.0 ± 0.4	27

Rates of hydrolysis of **2**, **3**, and **4** were determined at 60 ± 0.05° using various concentrations of hydrochloric acid. The hydrolysis of **2** was carried out in 1.00, 2.00, 3.99, and 5.94 *M* HCl, **3** in 1.00, 3.99, and 5.94 *M* HCl, and **4** in 1.00, 1.60 (0.40 *M* NaCl), 1.60 (0.40 *M* methoxyamine), 2.00, and 3.99 hydrochloric acid.

Product Studies.—The amino acids and dipeptides formed during the hydrolysis were examined on Whatman No. 1 circular paper chromatograms to which samples were applied at various times during the reactions. The chromatograms were eluted by one of two solvents systems: MPW (methyl ethyl ketone–pyridine–water, 20:5:8 by volume) and BAW (1-butanol–acetic acid–water, 5:1:4 by volume). Authentic samples of D-cycloserine (**1**), D-aminoxyalanine (**6**), L-alanine, L-serine, and 3,6-dimethylene-2,5-piperazinedione (**7**) were used as reference standards. The components were visualized by spraying with a solution of 0.2% ninhydrin in 5% acetic acid–ethanol. The elimination product **7** was detected by its uv florescence. The presence of (+)-3,6-bis(aminoxymethyl)-2,5-piperazinedione (**2**) was detected chromatographically by treating a small amount of solution with hot 2 *M* sodium hydroxide for 1 min followed by circular paper chromatography using MPW as eluent and observ-

(7) K. Poduska, C. A. Naturkha, A. B. Silaer, and J. Rudinger, *Collect. Czech. Chem. Commun.*, **30**, 2410 (1965).

(8) In basic solution, the cyclic hydroxamic acid group in **1** is converted into a salt which protects the ring from further attack.

(9) C. H. Stammer, *J. Org. Chem.*, **27**, 2957 (1962).

(10) We know from previous work that dipeptides of the type **8** rearrange rapidly into 2,5-piperazinediones; see R. A. Payne and C. H. Stammer, *ibid.*, **33**, 2421 (1968).

(11) We thank Dr. Wallace F. Runge of Commercial Solvents Corp., Terre Haute, Ind., for generous gifts of D-cycloserine.

(12) Sigma Chemical Co., St. Louis, Mo.

(13) H. Brockmann and H. Musso, *Ber.*, **89**, 250 (1956).

(14) Prepared from *tert*-BOC azide according to the procedure used by R. A. Payne and C. H. Stammer, *J. Org. Chem.*, **33**, 2421 (1968).

(15) G. W. Anderson, J. E. Zimmerman, and F. M. Callahan, *J. Amer. Chem. Soc.*, **89**, 5012 (1967).

(16) M. Brenner and W. Haber, *Helv. Chim. Acta*, **36**, 1109 (1953).

(17) J. P. Greenstein and M. Winitz, "Chemistry of Amino Acids," Vol. 2, Wiley, New York, N. Y., 1961, p 930.

ing the dimethylene compound 7 at R_f 0.91 under ultraviolet light. Cycloserine and its derivatives were visualized on chromatograms by the following procedure. Equal volumes of 4 *M* sodium hydroxide and a fresh 4% aqueous solution of sodium nitroprusside were mixed and sprayed on the dry chromatogram. When dry, it was sprayed with 1 *M* aqueous acetic acid until the yellow background was almost gone. 3-Isoxazolidone and cycloserine and its derivatives gave blue spots which faded to brown.[18]

An authentic sample of L-alanyl-L-alanine was prepared by the hydrolysis of 0.260 g (0.94 mol) of *tert*-butoxycarbonyl-L-alanyl-L-alanine methyl ester in 15 ml of 1 *M* HCl at 85°. The progress of the reaction was followed by thin layer chromatography (tlc) using Eastman Chromagram No. 6060 silica gel plates and solvent system, methyl ethyl ketone–acetic acid–water (2:5:8 by volume). When the alanylalanine methyl ester (R_f 0.83) had disappeared, the solution was cooled, diluted to 50 ml with distilled water, and lyophilized giving 0.167 g (90%) of crude L-alanyl-L-alanine. The crude dipeptide was recrystallized from isopropyl alcohol–ether yielding 0.144 g (77%) of L-alanyl-L-alanine hydrochloride: $[\alpha]^{23}D$ −36.9° (*c* 1.1, H_2O) [lit.[19] $[\alpha]^{24}D$ −37.3° (*c* 2, 0.5 *N* HCl)]; ir (KBr) 3460 (NH), 1995 (NH_3^+), 1730 (COOH), 1680 cm^{-1} (amide 1).

Isolation and Identification of the Hydrolysis Products.—The isolation and identification of the major hydrolysis product of **2**, β-aminoxy-D-alanyl-β-aminoxy-D-alanine, and of **3**, L-seryl-L-serine, was described in a previous publication.[5] Lyophilization of a sample taken after complete hydrolysis of **4** afforded a residue which was dissolved in 2 ml of hot isopropyl alcohol. The crude dipeptide was precipitated by addition of anhydrous ether. The product, L-alanyl-L-alanine, isolated by centrifugation and dried under reduced pressure, was identical with the authentic sample.

Nmr Study of the Hydrolysis of 4.—Samples (0.5 ml) taken at various time intervals during the hydrolysis were placed in nmr tubes and immediately frozen in a Dry Ice–acetone freezing mixture for storage. Nmr spectra between 1.79 and 2.13 ppm of these samples were obtained using a Varian HA-100 nmr spectometer. The dissappearance of the doublet centered at δ 1.960 which corresponded to the piperazinedione methyl groups and the appearance of two new doublets, one centered at δ 1.945, and the other at 2.056 which corresponded to the dipeptide methyl groups was observed. The nmr sample taken after 410 min showed no doublet corresponding to the piperazinedione methyl groups. After 500 min a new doublet appeared at δ 2.078 which was shown to be that of alanine by its increased intensity when authentic alanine was added.

The nmr spectrum of (−)-3,6-dimethyl-2,5-piperazinedione was obtained in D_2O. After the addition of one drop of 1 *M* hydrochloric acid, the sample was heated at 60° after 72 hr and the nmr spectrum was again determined. Hydrolysis had occurred as shown by the dipeptide methyl signals, but no collapse of the methyl doublets was observed indicating that no deuterium exchange (racemization) had occurred at the asymmetric centers of either the products or the substrate.

Reactions of (+)-3,6-Bis(aminoxymethyl)-2,5-piperazinedione (2) in Buffer Systems.—Two 0.031 *M* solutions of **2** in pH 1.2 phosphate buffer and in 1 *M* hydrochloric acid were prepared. These solutions were heated at 60° and chromatographic samples (MPW system) were taken at various time intervals; the results are shown in Table V.

TABLE V
PAPER CHROMATOGRAPHY STUDY OF 2 IN SOLUTION AT 60°

	Time, min		
	30	60	240
pH 1.2 (phosphate buffer)	0.52 (N, NP)[a,b]	0.52 (N, NP)	0.52 (N, NP)
1 *M* HCl	0.78 (N) 0.63 (N)	0.78 (N) 0.63 (N)	0.78 (N) 0.63 (N)

[a] N indicates a positive test with ninhydrin; NP indicates a positive test with the nitroprusside reagent. [b] Cycloserine control, R_f 0.54 (N, NP); β-aminoxy-D-alanine control, R_f 0.63 (N).

Solutions of **2** (0.004 *M*) in pH 1 and 2 buffer solutions (0.05 *M* KCl–HCl) were prepared and were tested at timed intervals with the nitroprusside reagents and ninhydrin. The solutions gave negative ninhydrin and nitroprusside tests when first prepared, but after 1 hr at room temperature, both gave positive tests.

Cycloserine (1) and 3,6-Bis(aminoxymethyl)-2,5-piperazinedione (2) in 1 *M* Acetic Acid.—Two solutions, one containing 27 mg/ml of cycloserine-free **2** and the other containing 54 mg/ml of **1** in 1 *M* aqueous acetic acid (pH 2.5) were prepared and a timed study (MPW system) was carried out (Table VI).

TABLE VI
PAPER CHROMATOGRAPHY STUDY OF 1 AND 2 IN 1 *M* ACETIC ACID

	Time, hr		
	0	16	28
1	0.52 (N, NP)[a]	0.54 (N, NP) 0.71 (N)	0.54 (N, NP) 0.71 (N)
2		0.54 (N, NP) 0.71 (N)	0.54 (N, NP) 0.71 (N)

[a] Controls: 0.54 (N, NP), cycloserine; β-aminoxy-D-alanine, 0.69 (N).

A white precipitate was observed in both of the above solutions after standing 4 days at room temperature. The precipitates were centrifuged and washed twice with distilled water. Approximately 7 mg of solid (R_f 0.91) was obtained from each solution. The ir spectra of the two materials were identical with each other and with that of an authentic sample of 3,6-dimethylene-2,5-piperazinedione (**7**).

Registry No.—**1**, 339-72-0; **2**, 17393-47-4; **3**, 15996-17-5; **4**, 30428-16-1; **5**, 106-57-0; *N*-*tert*-butoxycarbonyl-L-alanyl-L-alanine methyl ester, 19794-10-6; L-alanyl-L-alanine methyl ester hydrobromide, 30378-33-7.

(18) The procedure given here was adapted from the work of L. R. Jones, *Anal. Chem.*, **28**, 39 (1956).

(19) J. P. Greenstein and M. Winitz, "Chemistry of Amino Acids," Vol. 2, Wiley, New York, N. Y., report a melting point of 154–155°.

Purine N-Oxides. XXXV. Alkylated Guanine 3-Oxides and 3-Hydroxyxanthines[1]

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Peroxy acid oxidation of 1-, 7-, 8-, 9-mono-*N*-methylguanines and 1,7-di-*N*-methylguanine gave their 3-oxides. The corresponding methyl 3-hydroxyxanthines were obtained by acid hydrolysis of the guanine 3-oxides. The 1-methyl- and 1-benzyl-3-hydroxyxanthines were obtained by total syntheses. Two *O*-methyl derivatives were also prepared, 3-methoxyxanthine by total synthesis and 2-amino-6-methoxypurine 3-oxide by peroxy acid oxidation of the parent purine.

The 3-*N*-oxide derivatives of guanine and xanthine, both potent oncogens,[2,3] react with acid anhydrides to yield the corresponding 8-hydroxypurine.[4] An intermediate in this reaction, 3-acetoxyxanthine, reacts very rapidly with water or with nucleophiles to yield 8-substituted xanthines.[5] Since 8-substituted xanthines are also among the products formed *in vivo* from 3-hydroxyxanthine,[6] it is suggested that a metabolically formed analog of 3-acetoxyxanthine could be involved in the induction of cancer by these compounds.[6]

To facilitate studies of the course and mechanism of this unexpected reaction, and of the tautomeric structures of the various ions of the parent purine 3-oxides, several alkyl derivatives of these 3-*N*-oxides were required. We now report their syntheses and the evidence supporting the structures assigned.

The primary product of direct methylation of 3-hydroxyxanthine (**3a**)[7] with Me_2SO_4 in DMF under mild conditions is 3-hydroxy-7,9-dimethylxanthine (**4**).[4] At higher temperatures nucleophilic attack at C-8 occurs, the OH is lost from N-3, and 7,9-dimethyluric acid[4,7] is the major product. Under a variety of other methylating conditions **3a** and guanine 3-oxide (**2a**) yield complex mixtures from which no monomethyl derivative has been isolated.

Several alkylguanine 3-oxide derivatives have been satisfactorily obtained by peroxyacid oxidations of the appropriate alkyl guanines. The 1-,[9] 7-,[10] and 8-methylguanines[11] and 1,7-dimethylguanine[9] (**1b**, **1c**, **1e**, and **1d**) were oxidized to the corresponding 3-oxides, the first three in yields greater than 50%.

The oxidation of 9-methylguanine[12] (**5**) with CF_3COOH–30% H_2O_2 at room temperature was accompanied by excessive loss of ultraviolet-absorbing material. Chromatographic analyses of the oxidation mixture indicated that 9-methylguanine 3-oxide (**6**), is oxidized further to nonultraviolet-absorbing material (Figure 1a). N-Oxidation of most purines is accompanied by some oxidation at the 4,5 double bond, particularly when one or more nitrogens are alkylated.[13] Several conditions and reagents for improving the N-oxidation of 9-methylguanine were investigated (Figure 1). The use of 90% hydrogen peroxide with CF_3COOH increased the rate of reaction but did not improve the preparation of **6** (Figure 1b). However, lowering the temperature[14] decreased ring oxidation and improved the ratio of starting material and its *N*-oxide (Figure 1c). At −15° the *N*-oxide was obtained in 44% yield.

Each methylguanine 3-oxide was hydrolyzed in hydrochloric acid to the corresponding 3-hydroxy-*N*-methylxanthine (Table IV). Proof of the position of the oxygen in the 7- and 9-methylguanine 3-oxides was provided by the methylation of each of the respective xanthine derivatives to the known 3-hydroxy-7,9-dimethylxanthine[7] (**4**).

A total synthesis designed to lead to 3-hydroxy-1-methylxanthine by treatment of 6-amino-5-formamido-1-hydroxy-3-methyluracil (**8**, R = CH_3) with acetic anhydride[15] resulted instead in 1-methyluric acid,[7] because of subsequent acetylation of the 3-hydroxy moiety of **3e** and attack at C-8. The desired imidazole ring closure to 3-hydroxy-1-methylxanthine has now been accomplished in hexamethyldisilazane. The identity of this product with that from the hydrolysis of 1-methylguanine 3-oxide proves the position of N-oxidation of **1e**.

For an analogous synthesis of 1-benzyl-3-hydroxyxanthine, 6-amino-1-benzyloxyuracil (**9**, R = H)[16] was benzylated to give 6-amino-3-benzyl-1-benzyloxyuracil (**9**, R = $C_6H_5CH_2$), with some 6-amino-5-benzyl-1-benzyloxyuracil as a by-product. Nitrosation of **9** (R = $C_6H_5CH_2$) followed by reduction and formylation yielded **8** (R = $C_6H_5CH_2$) which was silylated and ring closed to give 1-benzyl-3-hydroxyxanthine (**3f**) in low yield. Some 1-benzylxanthine, presumably formed by

(1) This investigation was supported in part by funds from the National Cancer Institute, Grant No. CA 08748, and the Atomic Energy Commission, Contract No. AT(30-1)-910. T.-C. L. is a Damon Runyon Memorial Fellow.

(2) G. B. Brown, K. Sugiura, and R. M. Cresswell, *Cancer Res.*, **25**, 986 (1965).

(3) K. Sugiura, M. N. Teller, J. C. Parham, and G. B. Brown, *ibid.*, **30**, 184 (1970).

(4) U. Wölcke, W. Pfleiderer, T. J. Delia, and G. B. Brown, *J. Org. Chem.*, **34**, 981 (1969).

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(7) Compounds **2a** and **3a**, originally designated as 7-*N*-oxides,[8] were shown to be 3-*N*-oxides: U. Wölcke and G. B. Brown, *J. Org. Chem.*, **34**, 978 (1969).

(8) T. J. Delia and G. B. Brown, *ibid.*, **31**, 178 (1966).

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(10) J. W. Jones and R. K. Robins, *J. Amer. Chem. Soc.*, **85**, 193 (1963).

(11) W. Pfleiderer and M. Shanshal, *Justus Liebigs Ann. Chem.*, **726**, 201 (1969).

(12) H. C. Koppf and R. K. Robins, *J. Amer. Chem. Soc.*, **80**, 2751 (1958).

(13) For example, xanthine is resistant to oxidation by peroxy acids but di- or trimethylxanthines are readily oxidized to methylparabanic acids, and tetramethyluric acid is oxidized to allocaffeine.[8] The oxidation of 9-benzylguanine gave only 1-benzylparabanic acid. Even in the N-oxidation of guanine some loss of ultraviolet-absorbing material was noted; with ^{14}C-labeled material a small amount of nonbasic material, which could be parabanic acid, has been detected. The lower yield of an *N*-oxide from 1,7-dimethylguanine can be attributed to the accompanying substantial ring oxidation.

(14) N-Oxidation of some sensitive purines by *m*-chloroperoxybenzoic acid proceeds optimally at 0 to −5°: I. Scheinfeld, unpublished data.

(15) A. D. McNaught and G. B. Brown, *J. Org. Chem.*, **32**, 3689 (1967).

(16) W. Klötzer, *Monatsh. Chem.*, **95**, 265 (1964).

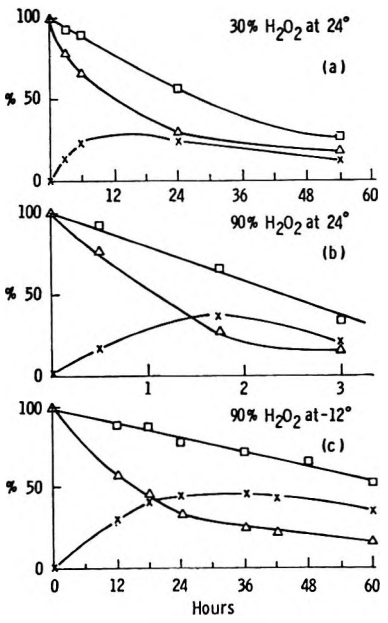
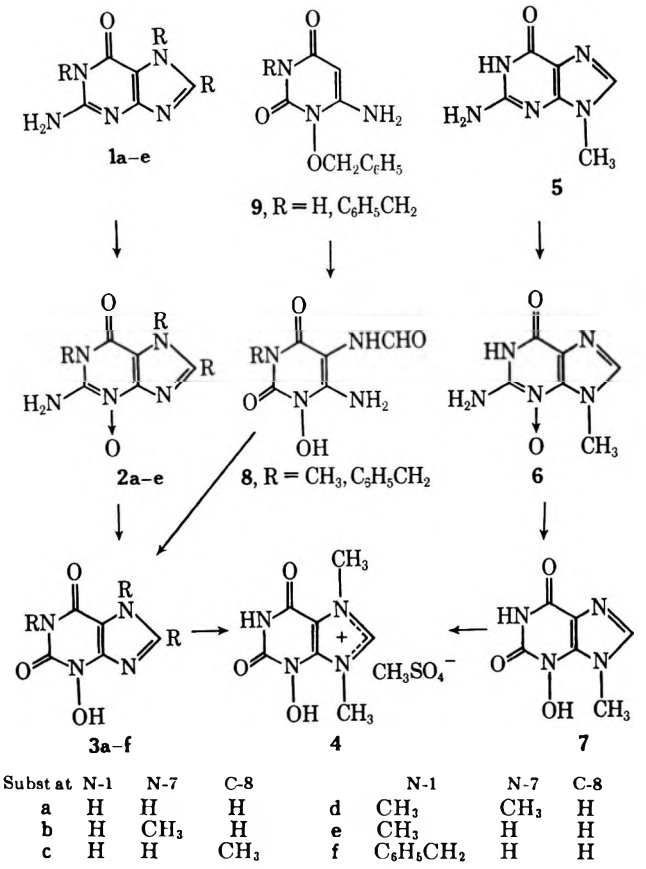


Figure 1.—The oxidation of 9-methylguanine (△) to 9-methylguanine 3-oxide (×). Total recovery of ultraviolet absorption is indicated by □.



Substrat	N-1	N-7	C-8		N-1	N-7	C-8
a	H	H	H	d	CH_3	CH_3	H
b	H	CH_3	H	e	CH_3	H	H
c	H	H	CH_3	f	$C_6H_5CH_2$	H	H

deoxygenation under the cyclization conditions, was also obtained. By a similar sequence of reactions, 3-methoxyxanthine was synthesized from 6-amino-1-methoxyuracil. The latter was obtained from methoxyurea by a procedure similar to that of Klötzer.[16]

Peroxy acid oxidation of 2-amino-6-methoxypurine gave the 3-oxide derivative. Acid hydrolysis to 3-hydroxyxanthine (**3a**) demonstrated the position of oxidation.

The nmr spectra of the alkylated 3-hydroxyxanthines (Table I) are in complete agreement with the assigned

TABLE I
CHEMICAL SHIFTS (τ)[a]

	Protons			
	1	3	7(9)	8
3b	−0.96	−1.20	6.15[b]	2.08
3c	−0.95	−2.7[b]	−2.7[c]	7.62
3d	6.76	−1.10	6.08[b]	1.95
3e	6.72[b]	−1.6[c]	−1.6[c]	1.93
3f	4.92,[d] 2.73[e]	−2.0[c]	−2.0[c]	1.96
7	−1.20[c]	−1.20[c]	6.20[b]	2.43
2d	6.60[b]		6.08[b]	2.00

[a] In DMSO-d_6, relative to TMS. [b] Methyl group. [c] Coalesced. [d] CH_2 of benzyl group. [e] C_6H_5 of benzyl group.

structures, and correlated quite closely with the nmr spectra of the parent xanthines.[17] In general, the peak of the 3-hydroxy function coalesces with that of another exchangeable proton to give a single broad absorption integrating for two protons at a position between the expected positions of the two peaks. The nmr spectrum (Table I) of 1,7-dimethylguanine 3-oxide (**2d**) and the ultraviolet spectra[18] of it and **3d** support the assignment of the 3-*N*-oxide structures. The ultraviolet absorption spectra of these alkyl derivatives and their contribution toward the understanding of the tautomeric structures of the parent molecules are reported in the accompanying paper.[18]

Experimental Section

Analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich., or by Galbraith Laboratories, Inc., Knoxville, Tenn. Compounds were dried *in vacuo* over P_2O_5 at room temperature, unless otherwise stated. Melting points, obtained on a Mel-Temp apparatus, are uncorrected. Paper chromatograms (Table II) were developed, ascending, on Whatman No. 1 paper and viewed under ultraviolet light. The nmr spectra were determined with a Varian A-60 spectrometer in DMSO-d_6. An ISCO ultraviolet analyzer was used to monitor column eluates.

TABLE II
PAPER CHROMATOGRAPHY[a]

	R_f values × 10^2				R_f values × 10^2		
	A	B	C		A	B	C
2b	26	25	68	**3e**	66	42	71
3b	59	10	68	**3f**	98	98	
2c	24	15	63	**2d**	39	56	78
3c	39	16	63	**3d**	62	56	79
6	24	23	70	**2e**	28	32	72
7	30	41	64	3-OCH_3[b]	71	62	84
				6-OCH_3[c]	74	43	62

[a] Solvent systems: (A) CH_3CN–H_2O (3:1 v/v), (B) CH_3CN–H_2O–28% NH_4OH (7:2:1 v/v), (C) 3% NH_4Cl. [b] 3-Methoxyxanthine. [c] 2-Amino-6-methoxypurine 3-oxide.

General Procedure for the Peroxide Oxidation of Methylguanines.—A stirred solution of the methylguanine was oxidized with 30% H_2O_2 under the conditions indicated in Table III. The reaction mixture was poured slowly into Et_2O; the solids were collected, triturated with water, except for 1d and 1e, and recrystallized as specified. All gave blue-purple ferric chloride tests.

Hydrolysis of the Methylguanine 3-Oxides.—The methylguanine 3-oxides were hydrolyzed in a boiling water bath under the conditions specified in Table IV. When the solutions were cooled, the 7-, 8-, and 9-methyl derivatives crystallized. Addition of EtOH precipitated further quantities. With the 1-methyl-

(17) N. J. M. Birdsall, unpublished data.
(18) J. C. Parham, T. G. Winn, and G. B. Brown, *J. Org. Chem.*, **36**, 2639 (1971).

TABLE III

N-OXIDATION OF METHYLGUANINES

Starting material	Product (guanine 3-oxide)	CF_3CO_2H, ml	H_2O_2, ml	Time, hr	Temp, °C	Temp, %		Analysis, % for $C_6H_7N_5O_2 \cdot H_2O$ C	H	N
							Calcd	36.18	4.55	35.16
1b (10.0 g)	7-Methyl	80	40	8	24	70[a]	Found	36.45	4.75	35.69
1c (11.0 g)	8-Methyl	110	55	11	24	63[b]	Found	36.24	4.35	34.78
5 (10.0 g)	9-Methyl	100	40[c]	72	−15	44[a]	Found	36.28	4.52	34.75
1e (480 mg)	1-Methyl	5.0	2.0	72	4	55[d,e]	Found	36.28	4.41	35.21
								$C_7H_9N_5O_2 \cdot H_2O$		
							Calcd	39.43	5.20	32.84
1d (360 mg)	1,7-Dimethyl	3.0	1.5	7	24	23[d,f]	Found	39.69	4.74	32.82

[a] Recrystallized from water. [b] Reprecipitated from 1 *N* NaOH with AcOH. [c] 90% H_2O_2. [d] Purified over a silica gel column (12 × 2 cm) by elution with MeOH. [e] **1e** was eluted first, followed by the product, **2e**, which is unstable to heat (melting point greater than 400°, gradual decomposition). Evaporation of the MeOH yielded analytically pure material. [f] **1d** (55%) was eluted first, followed by **2d**, which was recrystallized from MeOH and EtOAc (mp 207–210° dec).

TABLE IV

HYDROLYSIS OF METHYLGUANINE 3-OXIDES TO 3-HYDROXY-*N*-METHYLXANTHINES

Starting material	Product (3-hydroxyxanthine)	HCl, *N* (ml)	Time, hr	Yield, %		Analyses, %, for $C_6H_6N_4O_3$ C	H	N
					Calcd	39.57	3.32	30.77
2b (8.5 g)	7-Methyl	6 (125)	18	56[a]	Found	39.37	3.53	30.61
2c (8.3 g)	8-Methyl	4 (45)	24	63[b]	Found	39.88	3.46	31.02
6 (3.0 g)	9-Methyl	4 (15)	16	58[c]	Found	39.63	3.36	30.66
2e (100 mg)	1-Methyl	4 (5)	16	55[a]	...[d]			
						$C_7H_8N_4O_3$		
					Calcd	42.86	4.11	28.56
2d (85 mg)	1,7-Dimethyl	2 (75)	20	76[a,e]	Found	42.65	4.09	28.32

[a] Recrystallized from water. [b] Reprecipitated from 1 *N* NaOH with AcOH. [c] The crystals were analytically pure. [d] Identical with the sample prepared by total synthesis. [e] Mp 239–241° (dried at 110°).

and 1,7-dimethyl derivatives, the solutions were evaporated to dryness and the solids were recrystallized. All gave blue-purple ferric chloride tests.

Kinetics of the Oxidation of 9-Methylguanine.—9-Methylguanine (100 mg) was dissolved in CF_3CO_2H (1.00 ml) and the H_2O_2 (0.40 ml) was added to the solution at the specified temperature (±2°). Aliquots (50 μl) taken at various times were diluted to 0.5 ml with water, applied to a BioRad AG-50 (H^+), 200–400 mesh, column (7 × 1 cm), and eluted with 1.5 *N* hydrochloric acid with continuous monitoring of the ultraviolet absorption of the eluate. The 9-methylguanine, ϵ_{251}^{max} 12,000 at pH 0,[9] and 9-methylguanine 3-oxide, ϵ_{249}^{max} 9400[18] at pH 0, were eluted in that order and the values plotted in Figure 1 were calculated from the optical densities and the measured volumes.

Oxidation of 9-Benzylguanine.—A mixture of 9-benzylguanine (1.0 g), CF_3CO_2H (10 ml), and 30% H_2O_2 (5 ml) was stirred for 5 hr. Pd/C was added and the stirring continued overnight. The solution was filtered and concentrated to an oily residue, soluble in organic solvents, which was thrice recrystallized from water to yield needles of benzylparabanic acid, mp 168–169°.[20] The ultraviolet spectra showed a low 260-nm absorption in acid and neutral solution and only end absorption in alkali.

Anal. Calcd for $C_{10}H_8N_2O_3$: N, 13.72. Found: N, 14.02.

Methylation of 3-Hydroxy-7- (or -9-) methylxanthine.—3-Hydroxy-7- (or -9-) methylxanthine (100 mg) was stirred in DMF (2 ml) containing Me_2SO_4 (0.4 ml) at 45° for 3 days. Unreacted starting material was separated, the solvents were evaporated at 50° *in vacuo*, and *i*-PrOH (3 ml) was added. When cooled overnight the solution yielded crystals. These had uv and ir spectra and chromatographic mobility identical with authentic 3-hydroxy-7,9-dimethylxanthine methosulfate (**4**).

3-Hydroxy-1-methylxanthine (3e).—6-Amino-5-formamido-1-hydroxy-3-methyluracil[15] (200 mg) and hexamethyldisilazane (2 ml) were heated in an oil bath at 130° for 4 hr. After heating, the excess hexamethyldisilazane was evaporated *in vacuo*, and the residue was boiled with EtOH (10 ml) for 15 min. Cooling the solution yielded 3-hydroxy-1-methylxanthine (150 mg, 83%) as a brown precipitate which was recrystallized from water as colorless needles, mp 270°.

Anal. Calcd for $C_6H_6N_4O_3$ (182.14): C, 39.57; H, 3.32; N, 30.77. Found: C, 39.58; H, 3.40; N, 30.75.

6-Amino-3-benzyl-1-benzyloxyuracil (9, R = $C_6H_5CH_2$).—6-Amino-1-benzyloxyuracil[16] (10.5 g), sodium carbonate (4.8 g), and benzyl chloride (11.7 g) were dissolved in 60% EtOH (200 ml) and the solution was heated under reflux for 4 hr. The solvent was evaporated under reduced pressure and the residue was extracted with ethyl acetate to give 6-amino-3-benzyl-1-benzyloxyuracil (11.8 g, 73%). Recrystallization from ethyl acetate–hexane (1:3) gave colorless needles: mp 174–175°; nmr (DMSO-d_6) τ 4.91 (2, 3-benzyl CH_2), 4.81 (2, 1-*O*-benzyl CH_2), 5.00 (1, 5-H), 2.61 [12, two C_6H_5 (10) and 6-NH_2 (2)].

Anal. Calcd for $C_{18}H_{17}N_3O_3$ (323.35): C, 66.86; H, 5.30; N, 13.00. Found: C, 67.02; H, 5.31; N, 13.13.

6-Amino-5-benzyl-1-benzyloxyuracil.—The mother liquors from the recrystallization of 6-amino-3-benzyl-1-benzyloxyuracil were evaporated to dryness, and the residue (~4.0 g) was chromatographed over a silica gel column with chloroform as the eluent. The first ultraviolet-absorbing fraction collected from the column was evaporated and recrystallized from EtOH to yield the 5-benzyluracil (1.0 g, 7%), mp 216°. The structure was assigned[21] from the fact that it could not be nitrosated, and from its nmr spectrum: τ 6.47 (2) and 2.86 (5) (5-benzyl), 4.89 (2) and 2.59 (5) (1-*O*-benzyl), 3.30 (2, 6-NH_2), −0.9 (1, 1-NH).

Anal. Calcd for $C_{18}H_{17}N_3O_3$ (323.35): C, 66.86; H, 5.30; N, 13.00. Found: C, 66.77; H, 5.16; N, 12.99.

6-Amino-3-benzyl-1-benzyloxy-5-nitrosouracil.—Crude 6-amino-3-benzyl-1-benzyloxyuracil (11.8 g) and $NaNO_2$ (3.5 g) were dissolved in 60% EtOH (150 ml), and 1 *N* hydrochloric acid (50 ml) was added at 0 to −5° with stirring. After stirring at room temperature for 12 hr, the pink precipitate was collected and recrystallized from EtOH, 5.0 g, 37%, mp 190°.

Anal. Calcd for $C_{18}H_{16}N_4O_4$ (352.35): C, 61.36; H, 4.58; N, 15.90. Found: C, 61.54; H, 4.62; N, 15.78.

1-Benzyl-3-hydroxyxanthine.—The nitrosouracil (5.0 g) was hydrogenated at atmospheric pressure in formic acid (120 ml) with 10% Pd/C (1.0 g) for 30 hr at room temperature. The

(19) W. Pfleiderer, *Justus Liebigs Ann. Chem.*, **647**, 167 (1961).

(20) H. Biltz and E. Topp, *Ber.*, **46**, 1387 (1913).

(21) Alkylation of 6-aminouracils is, in part, similar to that of the alkylation of barbituric acids. A similar 5-alkylation has been observed in the benzylation of 6-methylaminouracil to 5,5-dibenzyl-6-methylaminouracil: N. J. M. Birdsall and U. Wölcke, unpublished data.

catalyst was removed and the formic acid was evaporated. Recrystallization of the residue from EtOH gave 6-amino-3-benzyl-5-formamido-1-hydroxyuracil (8, R = $C_6H_5CH_2$), 3.4 g, 87%, mp 220° dec. The 5-formamido derivative (3.3 g) and hexamethyldisilazane (25 ml) were heated under reflux for 4 hr. The solution was evaporated nearly to dryness, and the residue was boiled with EtOH (200 ml) for 5 min. The insoluble residue, also insoluble in hot water and but slightly soluble in DMSO, was discarded. The EtOH filtrate was concentrated to 15 ml, applied to a Dowex 50 (H^+) (45 × 240 mm) column, and eluted with 2 l. of 70% EtOH with continuous monitoring of the ultraviolet absorption. 1-Benzyl-3-hydroxyxanthine (**3f**, 210 mg, 7%) was eluted after an unidentified fraction, and was followed by 1-benzylxanthine (130 mg, 5%) and two more unidentified fractions. No additional material was eluted with 1 *N* hydrochloric acid. **3f**'s uv spectrum showed λ_{max}^{EtOH} 275 nm (ϵ 8000).

Anal. Calcd for 1-benzyl-3-hydroxyxanthine, $C_{12}H_{10}N_4O_3$ (258.24): C, 55.81; H, 3.90; N, 21.70. Found: C, 55.97; H, 4.09; N, 21.50.

Anal. Calcd for 1-benzylxanthine, $C_{12}H_{10}N_4O_2$ (242.24): C, 59.50; H, 4.16; N, 23.13. Found: C, 59.69; H, 4.07; N, 22.89.

6-Amino-1-methoxyuracil.—To sodium ethoxide (0.258 mol), prepared from 5.95 g of sodium and 100 ml of EtOH, were added ethyl cyanoacetate (30 ml) and a solution of methoxyurea[22] (0.258 mol, 23.2 g) in 100 ml of EtOH. After the mixture was refluxed for 5.5 hr, the EtOH was removed *in vacuo* and the residue dissolved in 200 ml of water. Neutralization to pH 6 with acetic acid gave crude 6-amino-1-methoxyuracil. Recrystallization from 300 ml of 50% EtOH with treatment with charcoal yielded 14.9 g of pure 6-amino-1-methoxyuracil. Concentration of the mother liquor gave an additional 2.3 g, total yield 17.2 g, 43%: mp 248–249° dec; uv λ_{max} 267 nm, at pH 2 and 10; R_f 0.84 in 3% NH_4Cl and 0.71 in CH_3CN–H_2O (3:1). The nmr spectrum corroborated the structure: τ 6.13 (3, 3-OCH_3), 5.48 (1, 5-H), 2.80 (2, NH_2), −0.30 (1, N–H).

Anal. Calcd for $C_5H_7N_3O_3$: C, 38.22; H, 4.49; N, 26.74. Found: C, 38.16; H, 4.55; N, 26.76.

6-Amino-1-methoxy-5-nitrosouracil.—To 8.35 g (50 mmol) of 6-amino-1-methoxyuracil in 60 ml of 1 *N* hydrochloric acid, was added 3.45 g (50 mmol) of sodium nitrite slowly with stirring at 10°; the stirring was continued for 2 hr. Violet crystals were collected and washed with water, EtOH, and ether. The 10.0 g of the 5-nitrosouracil represented a quantitative yield. It was recrystallized from EtOH–water, mp 194 dec.

Anal. Calcd for $C_5H_6N_4O_4$: C, 32.27; H, 3.25; N, 30.10. Found: C, 32.15; H, 3.40; N, 30.30.

6-Amino-5-formamido-1-methoxyuracil.—The 5-nitrosouracil (7.98 g, 43 mmol) was reduced in 200 ml of 98% formic acid containing slightly over 1 equiv of hydrochloric acid, 44 ml of 2 *N* hydrochloric acid, by slowly adding 8.0 g of zinc powder with continued stirring. The solution became colorless in about 30 min; the unreacted zinc powder was separated, and the filtrate was evaporated nearly to dryness *in vacuo*. The oily residue in 100 ml of water was adjusted to pH 3 with sodium formate. The 6-amino-5-formamido-1-methoxyuracil precipitated, and 5.90 g, 78%, was collected. Recrystallization from 50% EtOH gave colorless crystals, mp 215° dec, uv λ_{max} 268 nm at pH 5 and 10.

Anal. Calcd for $C_6H_8N_4O_4 \cdot H_2O$: C, 33.03; H, 4.62; N, 25.68. Found: C, 33.00; H, 4.70; N, 25.85.

3-Methoxyxanthine.—Hexamethyldisilazane (13 ml) was added to a stirred mixture of 4.0 g of 6-amino-5-formamido-1-methoxyuracil and 6 ml of formic acid. The mixture was heated under reflux for 3.5 hr and then evaporated nearly to dryness *in vacuo* at 60°. The oily residue was treated with EtOH, and the insoluble fraction was extracted three times with 30 ml of boiling water. The extract was concentrated and chromatographed over a 4 × 14 cm Dowex-50 [H^+] column. Elution with water yielded 2.80 g of starting material, followed by 150 mg, 13.5% based upon unrecovered starting material, of 3-methoxyxanthine. Further elution of the column with 1 *N* hydrochloric acid gave 350 mg of xanthine. Recrystallization of 3-methoxyxanthine from water gave long, fine needles. The compound started to decompose at 127°. Its instability in base is reported in the accompanying paper.[18] The nmr spectrum corroborated the structure: τ 6.04 (3, OCH_3), 1.91 (1, 8-H), −1.40 (1, (NH).

2-Amino-6-methoxypurine 3-Oxide.—A solution of 660 mg (4 mmol) 2-amino-6-methoxypurine,[23] 8 ml of CF_3CO_2H, and 4 ml of 30% H_2O_2 was allowed to stand at 22° for 6 days. The addition, with stirring, of Et_2O precipitated the product and, after chilling the reaction mixture, the ether layer was decanted and discarded. The product was collected and recrystallized from *i*-PrOH to yield colorless granules, 680 mg. The absence of NH_2 absorption in the nmr spectrum and the presence of a signal at τ 1.53, corresponding to one exchangeable proton, suggested that this was a trifluoroacetyl derivative of the desired product and also indicated the product contained 1 mol of 2-propanol, which was consistent with elemental analyses.

The product was dissolved in 10 ml of dilute NH_4OH and heated at 80° for 15 min. The solution was neutralized to pH 5 with HOAc and chilled. The 2-amino-6-methoxypurine 3-oxide crystallized as colorless prisms, yield 160 mg (20%). The analytical sample was dried *in vacuo* at 80° over P_2O_5 for 2 hr, mp 231–232° dec (with gas evolution).

Anal. Calcd for $C_6H_7N_5O_2 \cdot H_2O$: C, 36.18; H, 4.55; N, 35.16. Found: C, 36.16; H, 4.57; N, 35.20.

A sample of 2-amino-6-methoxypurine 3-oxide was dissolved in 20 ml of 2 *N* hydrochloric acid and the solution was refluxed 18 hr. The solvent was removed *in vacuo* to yield 3-hydroxyxanthine (**3a**)[7] and not 1-hydroxyxanthine.[24] It was identical with an authentic sample as shown by paper chromatography and ultraviolet spectra at three pH's.[18]

Registry No.—**2b**, 30477-04-4; **2c**, 22888-26-2; **2d**, 30345-29-0; **2e**, 30345-23-4; **3b**, 30409-21-3; **3c**, 22888-28-4; **3d**, 30345-26-7; **3e**, 14002-16-5; **3f**, 30409-24-6; **5**, 5502-78-3; **6**, 30345-36-9; **7**, 30345-24-5; **8** (R = $C_6H_5CH_2$), 30345-83-6; **9** (R = $C_6H_5CH_2$), 30345-84-7; benzylparabanic acid, 30345-85-8; 6-amino-5-benzyl-1-benzyloxyuracil, 30345-86-9; 6-amino-3-benzyl-1-benzyloxy-5-nitrosouracil, 30345-87-0; 6-amino-1-methoxyuracil, 30345-88-1; 6-amino-1-methoxy-5-nitrosouracil, 30345-89-2; 6-amino-5-formamido-1-methoxyuracil, 30345-90-5; 3-methoxyxanthine, 30345-91-6; 2-amino-6-methoxypurine 3-oxide, 30345-92-7.

Acknowledgment.—We thank Dr. George Bosworth Brown for his continued interest and Mr. Marvin J. Olsen for the nmr spectra.

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Purine N-Oxides. XXXVI. The Tautomeric Structures of the 3-N-Oxides of Xanthine and Guanine[1]

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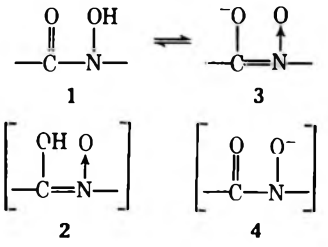
The predominant tautomeric structures present in each of the various ionic species of the title compounds have been deduced from their ultraviolet spectra and those of their several *N*-methyl and *O*-methyl derivatives. The *N*-hydroxy tautomer predominates in the neutral species of 3-hydroxyxanthine. The neutral form of guanine 3-*N*-oxide is a mixture, mostly the 3-hydroxy tautomer with some 1-H, 3-oxide tautomer. The ionization sequences have been determined as 3,9,1 for 3-hydroxyxanthine and 3,7 for 3-hydroxyguanine. The influence of the *N*-oxide group on the ionization constants and on the ultraviolet spectra is examined in detail.

The availability of all of the mono-*N*-methyl and of two dimethyl derivatives of 3-hydroxyxanthine and guanine 3-*N*-oxide[2] has permitted the determination, from the characteristics of their ultraviolet spectra, of the ionization sequences and of the tautomeric structures of their parent *N*-oxide derivatives. This knowledge should contribute to a greater understanding of the nucleophilic substitution with rearrangement at C-8 of the 3-*O*-acyl derivatives[2,3] of these oncogenic compounds.[4]

The neutral species of 3-hydroxyxanthine and its *N*-methyl derivatives, as well as those of 1-hydroxyhypoxanthine[5] and 1-hydroxyxanthine,[6] all show ultraviolet absorption bands similar to those of the neutral species of the parent purines[7-9] (Table I). The ultraviolet spectra of the *N*-acetoxy derivatives of 1- and 3-hydroxyxanthine[10] and that of 3-methoxyxanthine (Table I) show a close resemblance to those of the corresponding 1- and 3-methylxanthine.[9] It is accepted that the neutral species of xanthine and hypoxanthine exist mainly in the carbonyl (oxo) form in solution,[11-13] and from ultraviolet evidence the predominant tautomers of the *N*-oxide derivatives in solution must be the oxo-*N*-hydroxy **1**, rather than hydroxy *N*-oxide **2** forms.[14] Such tautomers are further supported by the observation of strong carbonyl absorptions in the ir spectra of the solids, particularly the presence of two distinct bands in the spectrum of 3-hydroxy-1-methylxanthine.

The 3-*N*-oxide group[15] in both the guanine and the xanthine 3-*N*-oxide[16] series exerts a significant acid strengthening influence on the molecule as a whole and decreases all pK_a's of ionization by 1 to 4 units, relative to the corresponding parent purine,[19] but has little effect on the pK_a's of protonation (Table I).



The first ionizations of 3-hydroxyxanthine (**5**) and of its mono-*N*-methyl derivatives occur at pK_a's between 6.2 and 7.0. This ionization is, in each case, accompanied by the appearance of an intense ultraviolet absorption band near 220 nm and of another new band at 300 to 310 nm (Figure 1). The 1,7-dimethyl-3-hydroxyxanthine, with only one ionizable proton, that of the 3-hydroxyl, $pK = 7.08$, exhibits the same spectral behavior. In contrast only a slight shift of the 270-nm band (Table I) is associated with the first pK_a of 3-methoxyxanthine (**5**, OH = OCH_3). Therefore the first ionization in the 3-hydroxyxanthine series can be definitively assigned to the 3-hydroxyl group.

The spectra of the monoanions of **5** and its 1- and 9-methyl derivatives are similar (Figure 1). From this and the differences from the 7-methyl and 1,7-dimethyl monoanion spectra, it may be inferred that the 9-H imidazole tautomer, **6**, predominates.

It has been noted that the *N*-oxide group causes the appearance of one very prominent ultraviolet absorption band at 220 to 230 nm in the neutral species of 6-

(1) This investigation was supported in part by funds from the National Cancer Institute (Grant No. CA 08748) and from the Atomic Energy Commission (Contract No. AT(30-1)-910).

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(12) A. R. Katritzky and J. M. Lagowski, *Advan. Heterocycl. Chem.*, **2**, 56 (1963).

(13) J. H. Lister, *ibid.*, **6**, 1 (1966).

(14) For a review of cyclic hydroxamic acids, see J. B. Bapat, D. St. C. Black, and R. F. C. Brown, *ibid.*, **10**, 199 (1969).

(15) The designation "*N*-oxide" has been used for a compound or series of compounds in this paper to denote only that an oxygen is on N-3 (or other nitrogen), without regard to its tautomeric structure. The presence of the specific tautomer containing the *N*-oxide functional group has been indicated by the use of "3-oxide" in a specific name, as in *Chemical Abstracts* usage.

(16) These were first reported to be 7-*N*-oxide derivatives,[17] but were later shown to be 3-*N*-oxides.[18]

(17) T. J. Delia and G. B. Brown, *J. Org. Chem.*, **31**, 178 (1966).

(18) U. Wölcke and G. B. Brown, *ibid.*, **34**, 978 (1969).

(19) The single exception is the compound assigned the structure 3-hydroxy-9-methylxanthine. It has a slightly higher first ionization pK_a than 9-methylxanthine. The latter shows an unusually low first ionization pK_a for a methylxanthine. This suggests that steric crowding by the peri 3-H and 9-methyl, which can be relieved by ionization of the 3-H, may be responsible for the lower pK_a. Ionization of 3-hydroxy-9-methylxanthine does not produce a similar relaxation of steric hindrance, since the 3-oxygen is still present in the monoanion. The pK_a of this compound thus falls in the same range as the other 3-hydroxyxanthines and supports the assigned structure.

TABLE I
SPECTRAL DATA AND pK_a'S

pH	Charge[a,b]	λ_{max}, nm ($\epsilon \times 10^{-3}$)			Apparent pK_a values[c,d] (±)	Parent purines
		3-Hydroxyxanthine[18]				
−2	(+1)	238 (7.0)	268 (8.9)			
					0.35 (0.02)	0.89[e]
3	(0)	205 (24)	230[e] (3.7)	272 (10.1)		
					6.71 (0.06)[d]	7.70[c]
8.17	[−1]	218 (22)	257 (5.6)	299 (6.8)		
					9.65 (0.06)	11.94[g]
11.4	[−2]	225 (28)		297 (8.6)		
					13.2 (0.2)	...
15	[−3]	224 (29)		292 (8.8)		
		3-Hydroxy-7-methylxanthine				
4	(0)	235[e] (4.7)	274 (9.4)			
					6.93 (0.02)[d]	8.42[g]
9	(−1)	222 (26)	253[e] (3.9)	309 (6.7)		
					10.92 (0.05)	>13[g]
13	(−2)	223 (27.3)	248[e] (5.3)	304 (6.8)		
		3-Hydroxy-9-methylxanthine				
4	(0)	239 (8.0)	271 (9.2)			
					6.28 (0.04)[d]	6.12[g]
9	(−1)	218 (20.3)	262 (7.9)	297 (7.7)		
					11.24 (0.05)	>13[g]
13	(−2)	221 (24.3)	265[e] (6.7)	290 (8.0)		
		3-Hydroxy-1-methylxanthine				
4	(0)	230[e] (3.9)	272 (9.0)			
					6.83 (0.02)[d]	7.90[g]
8.4	[−1]	221 (23.6)	258 (4.8)	298 (5.9)		
					9.73 (0.04)	12.23[g]
13	(−2)	226 (20.9)		297 (5.7)		
		1,7-Dimethyl-3-hydroxyxanthine				
4	(0)	210 (20.2)	230[e] (4.8)	274 (8.1)		
					7.08 (0.01)[d]	8.65[g]
10	(−1)	223 (25.7)	244[e] (4.1)	258[e] (2.9)		
			309 (5.8)			
		3-Methoxyxanthine				
5	(0)		270.5 (10.8)			
					7.74 (0.05)	
9.4	(−)		274 (11.8)			
					11[a,h]	
13	(−2)	235[e] (5.4)	275 (11.9)			
		3-Hydroxyguanine[18]				
−2	[+2]		244 (10.6)	260[e]		
					−1.14 (0.1)	−1.33[c,i]
1	[+1]	213 (12.5)	245 (7.8)	267 (9.5)		
					3.45 (0.05)[j]	3.34[j]
4.8	[0]	217 (23)	270 (8.8)	300[e] (2.3)		
					5.97 (0.03)	9.32[26]
8.0	(−1)	224 (31)	254 (5.2)	292 (6.6)		
					10.67 (0.05)	12.62[26]
12–15	(−2)	226 (31)	283 (9.7)			
		3-Hydroxy-8-methylguanine				
−2.7	(+2)		245 (13.0)	259[e] (10.7)		
					−0.53 (0.05)	−1.10[k]
1.46	[+1]	213 (16.6)	248 (8.4)	271 (10.6)		
					3.39 (0.05)	4.03[27]
4.75	(0)	218 (21.5)	271 (9.6)	303[e] (2.4)		
					6.02 (0.06)	9.70[27]
9	(−1)	226 (29)	252 (6.7)	291 (7.5)		
					11.24 (0.01)	13.0[27]
14	(−2)	227 (28)	283 (9.9)			

TABLE I
(*Continued*)

pH	Charge[a,b]	λ_{max}, nm ($\epsilon \times 10^{-3}$)			Apparent pK_a values[c,d] (±)	Parent purines
			3-Hydroxy-7-methylguanine			
−3	(+2)		245 (11.2)	265[e] (8.5)		
					−1.44 (0.1)	
1	(+1)	215 (17.6)	250[e] (7.5)	268 (9.0)		
					3.33 (0.05)	3.50[26]
4.5	[0]	221 (23.0)	272 (8.5)	303[e] (1.9)		
					5.92 (0.04)[d]	9.95[26]
10	(−1)	226 (28.0)	254 (5.3)	296 (6.8)		
			3-Hydroxy-9-methylguanine			
					−0.3[g] (0.2)	
1	[+1]		249 (9.4)	265[e] (8.0)		
					2.80 (0.07)	2.83[26]
4.3	[0]	219 (17.2)	268 (8.7)	297[e] (4.4)		
					5.70 (0.03)[d]	9.80[26]
9	(−1)	224 (23.6)	280 (8.0)			
			1-Methylguanine 3-Oxide			
1	(+1)	211 (21)	249[e] (6.7)	268 (8.7)		
					3.59 (0.05)	3.13[26]
6	(0)	224 (25.6)	266 (6.8)	298 (5.6)		
					8.24 (0.03)	10.54[26]
11	(−1)	229 (29.7)	275 (7.7)	288 (7.6)		
					14[g]	
15	[−2]	232 (36)	265 (7.1)	316 (6.4)		
			1,7-Dimethylguanine 3-Oxide			
2	(+1)	217 (20.2)	250[e] (6.2)	269 (7.9)		
					3.71 (0.03)	3.40[26]
7	(0)	227 (27.5)	268 (5.2)	302 (5.1)		
					11.2 (0.08)	
13	(−1)	231 (24.2)	260[e] (5.8)	327 (4.3)		
			2-Amino-6-methoxypurine 3-Oxide			
1	(+)	213 (27)	236[e] (5.2)	286 (12.5)		
					3.57 (0.03)	
6	(0)	225.5 (36)	255.5 (5.4)	301 (7.4)		
					8.18 (0.04)	
11	(−)	228.5 (35)	265[e] (5.6)	294.5 (8.7)		

[a] Parentheses indicate pure species. [b] Brackets indicate that pure species are not available. [c] Determined spectrophotometrically. [d] Determined electrometrically. [e] Shoulder. [f] No spectral change to pH 15. [g] Estimated from isosbestic spectra. [h] 3-Methoxyxanthine is unstable in base: $t_{1/2}$ 3 to 4 days at pH 7, 1 day at pH 9, 6–8 hr at pH 13. It is stable at pH 5. [i] In H_2SO_4. This agrees with values of −1.33 and −1.26 in $HClO_4$: J. A. Zoltewicz, D. F. Clark, T. W. Sharpless, and G. Grahe, *J. Amer. Chem. Soc.*, 92, 1741 (1970). [j] The determination of the pK_a for the first protonation of guanine suffers from small spectral differences between the neutral and protonated species. Recorded values vary from 3.3[7] to 2.95.[26] From replicate determinations in 4-cm cells, we find pK_a = 3.34 (±0.03). The differentials between the pK_a's of protonations of guanine and 3-hydroxyguanine were confirmed in parallel determinations with a single set of buffer solutions and a single wavelength setting of the spectrophotometer. [k] ±0.1.

aminopurine 1-oxides[20] and of 6-substituted purine 3-oxides.[21] This band, attributed to the influence of the *N*-oxide group on the purine chromophore, is not observed in the parent purines.[7] The occurrence of a similar band in the ultraviolet spectra of the monoanions, but not in those of the neutral species, of 1-hydroxyhypoxanthine and 1-hydroxyinosine, has been cited[22] as evidence for an analogous *N*-oxide structure, as in **3**, for their monoanions. The assignment of such an enolate structure parallels the enolate forms proposed for the anions of hypoxanthine[23] and xanthine.[8]

In the ultraviolet spectra of the monoanions of the *N*-methyl-3-hydroxyxanthines, the band near 220 nm (Figure 1) is similar in intensity and position to that reported for other *N*-hydroxypurine monoanions.[5] This corroborates the above assignment of the 3-hydroxyl as the site of first ionization and indicates that an enolate, as in **6**, is also the major resonance form of these monoanions. The absence of 220- or 300-nm absorption bands in the spectra of the anions of 3-methoxyxanthine (**5**, OH = OCH_3) confirms that such bands must be associated with a conjugated *N*-oxide group in the anions of *N*-hydroxypurines. The ultra-

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(22) (a) H. Sigel and H. Brintzinger, *Helv. Chim. Acta*, **48**, 433 (1965); (b) G. B. Brown, *Progr. Nucl. Acid Res. Mol. Biol.*, **8**, 209 (1968).

(23) L. B. Clark and I. Tinoco, *J. Amer. Chem. Soc.*, **87**, 11 (1965).

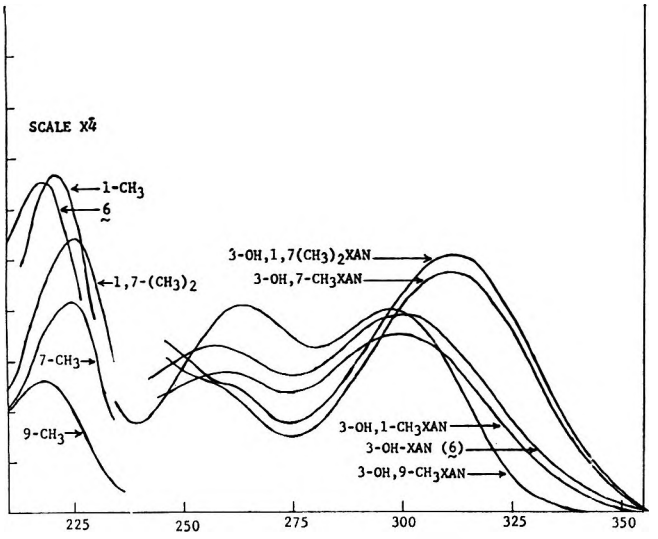


Figure 1.—3-Hydroxyxanthine series: monoanions. To facilitate convenient comparisons and minimize coincidences, the spectra are not plotted at equimolar concentrations. The extinction coefficients for each ionic species are given in Table I.

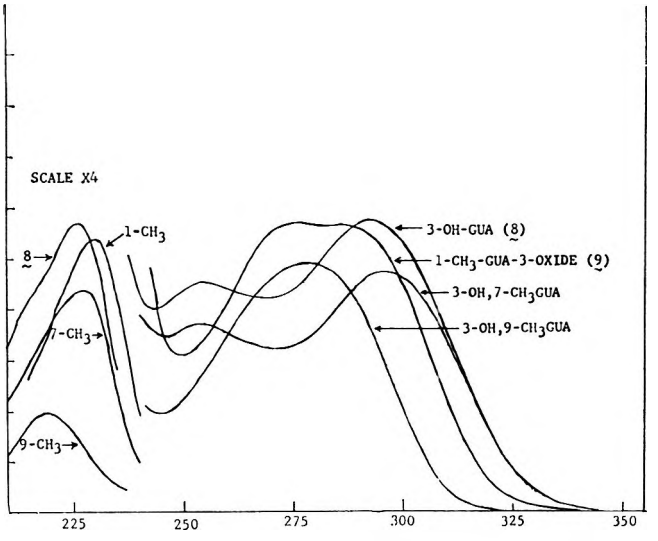


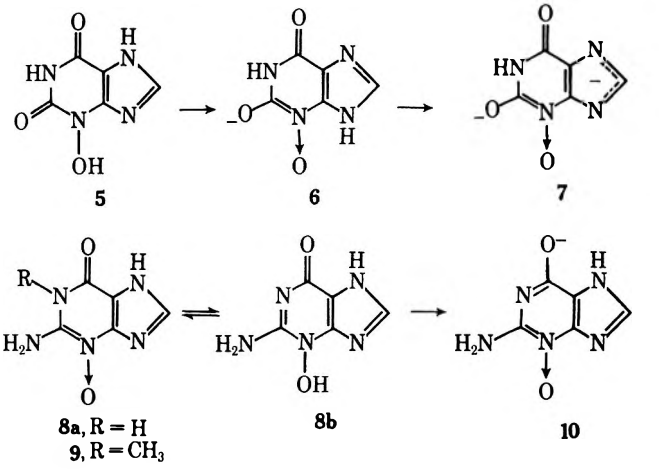
Figure 2.—Guanine 3-*N*-oxide series: anions. See footnote to Figure 1.

violet spectra of the ionic species of 3-methoxyxanthine (Table I) are remarkably close to those of 3-methylxanthine.[24]

The close values for the second ionization pK_a's of **5** (9.65) and 3-hydroxy-1-methylxanthine (9.73) and the nearly identical changes in the ultraviolet spectra associated with these pK_a's (Table I) indicate that this ionization takes place from the imidazole ring, as indicated by **7**. Supporting this deduction, the second ionizations, at N-1, of the 7- and 9-methyl derivatives of **5**, are much higher (10.9 and 11.2).

Xanthine shows no third ionization to pH 15, but the acid-strengthening effect of the 3-*N*-oxide induces a third ionization of **5** with a pK of 13.2. This ionization causes a hypsochromic shift (Table I) of the 300-nm band in **7**, which is similar to those observed during the second ionizations of the 7- and 9-methyl derivatives of **5**. These similar shifts, all associated with an ionization at N-1, provide confirmation that the ionization sequence of 3-hydroxyxanthine is 3,9,1, parallel to that of xanthine.[25]

Guanine 3-*N*-oxide (**8**) shows two ionizations with pK_a's of 5.97 and 10.67. The similarity of its first pK_a to those of its 7- and 9-methyl derivatives (5.92 and 5.70, respectively) and the much higher pK_a (8.24) of 1-methylguanine 3-oxide (**9**) establish that the first ionization of **8** occurs from the pyrimidine rather than the imidazole moiety. This is also the position deduced for the first ionization of guanine[26] and for 8-methylguanine.[27]



In the guanine 3-*N*-oxide series, distinct changes in two absorption bands are associated with transformations not only from the cations to the neutral species but also from the latter to the monoanions. Those are the bands near 225 and 300 nm, and changes in either band can be informative. Although the monoanions of both guanine 3-*N*-oxide (**8**) and 1-methylguanine 3-oxide (**9**) absorb strongly near 300 nm (Figure 2), there is a notable difference in the intensity of the 300-nm band in the neutral species (Figure 3). The 1-methyl derivative, **9**, must exist as the 1-R-6-oxo 3-oxide form, which is analogous to the predominant tautomer of guanine.[28] The difference between the spectra of **8** and **9** indicates that **8a** cannot be the predominant tautomer in the neutral species of **8**. This suggests an alternative tautomer, **8b**, with the pyrimidine hydrogen on the more electronegative oxygen at N-3. This alternative receives support when coupled with the deductions that the pyrimidine hydrogen is the first to ionize and that this ionization is accompanied by an increase in intensity of absorption bands similar to those associated with ionization of the N–OH in the 3-hydroxyxanthine series. In further support the neutral species of **8** and of its 7- and 9-methyl derivatives exhibit similar ultraviolet spectra, with maxima near 225 and 270 nm and a weaker absorption band near 300 nm (Figure 3). This demonstrates that the tautomeric structures in the neutral species of the 7- and 9-methyl derivatives of **8**,

(24) 3-Methylxanthine shows pK_a's at 8.45 and 11.92 and absorbs at 270 nm (0); 274 (−) and [232], 274 (−2).[9]

(25) The ionization sequence of xanthine and alkylxanthines is 3,7, with 1 ionizable only when the 3 or 7 nitrogen is alkylated.[8] It has been suggested that a 7-H is shifted to the 9 position in the monoanion of xanthine.[9] The position of the imidazole hydrogen in the neutral species of **5** is indeterminate, but also becomes stabilized at position 9 in the monoanion, **6**.

(26) W. Pfleiderer, *Justus Liebigs Ann. Chem.*, **647**, 167 (1961).

(27) W. Pfleiderer and M. Shanshal, *ibid.*, **726**, 201 (1969).

(28) The neutral species of guanine and 1-methylguanine show nearly identical ultraviolet absorption, and guanine is thus the 1-H-6-oxo tautomer.[26,28]

(29) For a review of the structure, properties, and reactions of guanine, see R. Shapiro, *Progr. Nucl. Acid Res. Mol. Biol.*, **8**, 73 (1968).

in which only the pyrimidine hydrogen is mobile, do not differ greatly from that of the neutral species of **8**. On the other hand, the 1-methyl and 1,7-dimethyl derivatives have well-defined maxima near 300 nm in addition to those near 225 and 270 nm. These N-1 methyl derivatives can exist only as tautomers with an *N*-oxide structure at N-3, as in **8a**. This is the species characterized by strong absorption at both 225–230 and near 300 nm, in addition to that at 266 to 268 nm. This last band, which appears as the main band of the neutral species of the guanine 3-*N*-oxides (Figure 3), is directly comparable to the single absorption band near 270 nm in the spectra of all of the 3-hydroxyxanthine neutral species (Table I).

Comparison of the ultraviolet spectrum of the neutral species of 1-methylguanine 3-oxide (**9**) with that of the monoanion of 3-hydroxyguanine (**10**) shows the resemblance in the 225- and 300-nm peaks (Figure 4). This suggests that similar *N*-oxide structures at N-3 are predominant in both, and implies that **10** is mainly a 6-enolate anion.[30] This deduction is confirmed by the close resemblance (Figure 4) of the spectrum of the anion **10** to that of the neutral species of 2-amino-6-methoxypurine 3-oxide, a derivative of **10** constrained in the 6-enol form. The similar ultraviolet spectra of **10**, its 6-OCH_3 derivative, and the 3-hydroxyxanthine monoanion (**6**) (Figure 4) provide mutual support for the *N*-3-oxide and enolate assignments, **6** and **10**.[32] The close correspondence between the ultraviolet spectra of the 3-hydroxyguanine and 3-hydroxy-7-methylguanine monoanions and the differences of both from that of the 9-methyl isomer (Figure 2) suggest that the monoanion of **8** can be further defined as the 7-H imidazole tautomer, as in **10**.

The spectra in Figure 4 depict the association of the *N*-oxide function at N-3 of guanine or xanthine with bands at 220–225 nm and near 300 nm.[33] The 300-nm band is not absent from the spectra of the neutral species of **8** and its 7- and 9-methyl derivatives (Figure 3), but is represented by pronounced shoulders. The spectra in Figure 3, taken at pH's half-way between the pK_a's of protonation and ionization are at least 1.2 pH units from each pK_a and therefore are of mixtures with 90–93% of the neutral molecules and 4–6% of each ionized species. The shoulders are thus too prominent to be due to absorption by the small amounts of monoanions. This suggests that the 300-nm shoulder evident in the spectrum of **8** is due to the presence of some tautomer of the type **8a** in equilibrium with the major tautomer **8b**.[34]

A change of solvent can significantly alter a tautomeric equilibrium,[35] and methanol, with a lower dielectric constant (ϵ = 33) than water (80), should favor the less polar 3-hydroxy tautomer. The spectra of the guanine 3-*N*-oxide series in methanol (Figure 5) indicate that the 1-methyl derivatives, which are restrained in the more polar 3-oxide form, still show distinct bands near 300 nm. In the spectra of **8** and its 7-methyl derivative, this band is greatly depressed in methanol (Figure 5), in comparison to that in water (Figure 3). This depression of the 300-nm band in a solvent of low polarity confirms that two tautomeric forms are in equilibrium in the neutral form of **8**.[36] The distinct shoulder near 300 nm in the spectrum of 3-hydroxy-9-methylguanine indicates that a significant amount of the 3-oxide tautomer is also present in methanol. This must reflect an interaction of the 3-oxide and 9-methyl groups.[37]

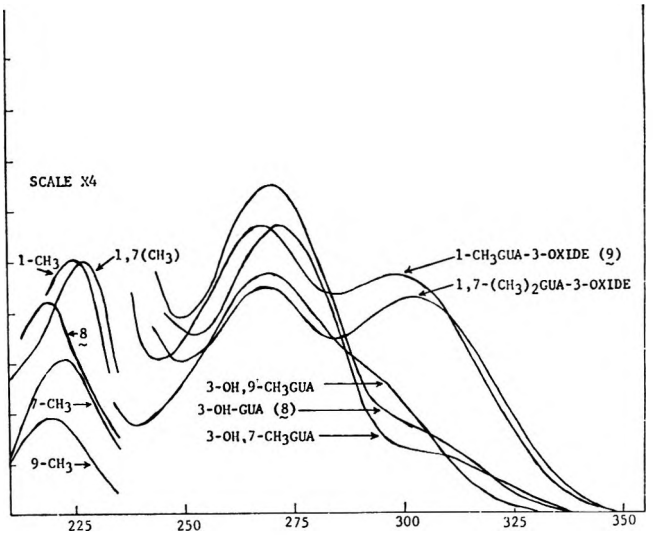


Figure 3.—Guanine 3-*N*-oxide series: neutral molecules. See footnote to Figure 1.

From inspection of Figures 2, 3, and 5 and comparison of the extinction coefficients (Table I) of the 300-nm shoulder of the neutral species of guanine 3-*N*-oxide, **8** (ϵ 2300), with the 300-nm bands in the neutral species of 1-methyl- (ϵ 5600) and 1,7-dimethylguanine 3-oxides (ϵ 5100), it is calculated that over 50% of **8** is the 3-hydroxyguanine tautomer, **8b**. This is a minimum proportion since calculations from the ϵ values of its anion, **10** (ϵ 6600), or the neutral species of 2-amino-6-methoxypurine 3-oxide (ϵ 7400) indicate more nearly two-thirds of **8b**.

(30) A comparable assignment of an enolate form for the guanosine anion is based on ir studies in D_2O.[31]

(31) H. T. Miles, F. B. Howard, and J. Frazier, *Science*, **142**, 1458 (1963).

(32) The similarity in spectra of **6** and **9** demonstrates that these compounds follow the Jones rule [R. N. Jones, *J. Amer. Chem. Soc.*, **67**, 2127 (1945)], *i.e.*, that the contribution of the 2-oxo enolate group of **6** is spectrally equivalent to that of the 2-amino group of **9**. The agreement of these purine derivatives with this rule adds to the several examples reported in the pyrimidine series: D. J. Brown and J. M. Lyall, *Aust. J. Chem.*, **15**, 851 (1962).

(33) A further example of association of two absorption bands with a 3-hydroxy enolate anion is furnished by 7,9-dimethyl-3-hydroxyxanthine.[18] The neutral species is a zwitterion, with the cation in the imidazole and the negative charge at the 3-*N*-hydroxy anion, and both it and its anion show strong absorptions near 220 and 300 nm, the former at 218 and 313, and the latter at 227 and 308 nm. These bands are not present in the cation.

(34) The closer resemblance of the spectrum of **8** to that of the neutral molecule of 7-methylguanine 3-oxide (Figure 3) suggests a greater contribution of the 7-H than the 9-H imidazole tautomer in **8**.

(35) A recent illustration of this is a study of 2-ethoxy-4-pyrimidone: J. Pitha, *J. Org. Chem.*, **35**, 903 (1970).

(36) A similar solvent effect has been observed on the tautomerism of benzimidazole *N*-oxide: S. Takahashi and H. Kano, *Chem. Pharm. Bull.*, **11**, 1375 (1963)).

(37) Examination of a Leybold molecular model (La Pine Scientific Co.) of 3-hydroxy-9-methylguanine indicates that steric interference between the hydrogen of the 3-hydroxyl and those of the 9-methyl is sufficient to inhibit free rotation of these groups. The 3-oxide tautomer model (using either carbonyl or hydroxyl oxygen) shows the 9-methyl hydrogens to be in close proximity to the 3-oxygen, but free rotation of the methyl is not restricted. This suggests that steric interactions in the 3-hydroxy tautomer may be sufficient to alter the tautomeric equilibrium to favor a larger contribution of the 3-oxide tautomer, even in methanol. Hydrogen bonding between the methyl hydrogens and oxygen has been suggested for 2-methylpyridine 1-oxide.[38] The model indicates that this should be possible in 9-methylguanine 3-oxide and that intramolecular H bonding could also contribute to the stability of the 3-oxide tautomer.

(38) E. Ochiai, "Aromatic Amine Oxides," Elsevier Publishing Co., New York, N. Y., 1967, Chapter 4.

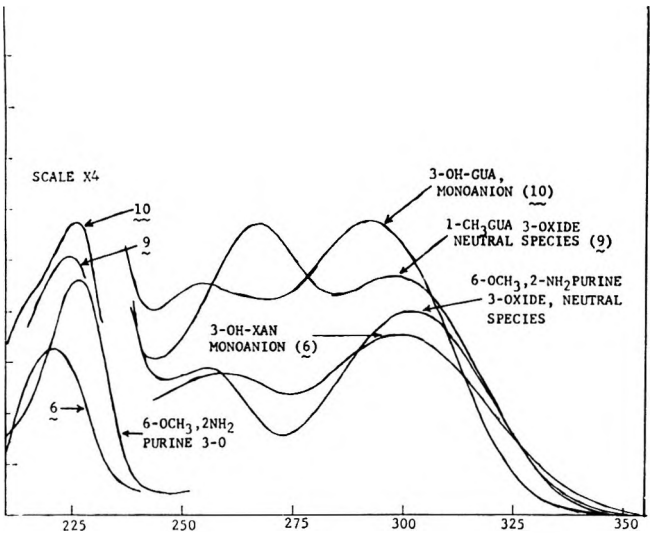


Figure 4.—Comparison of selected species containing the 3-oxide group. See footnote to Figure 1.

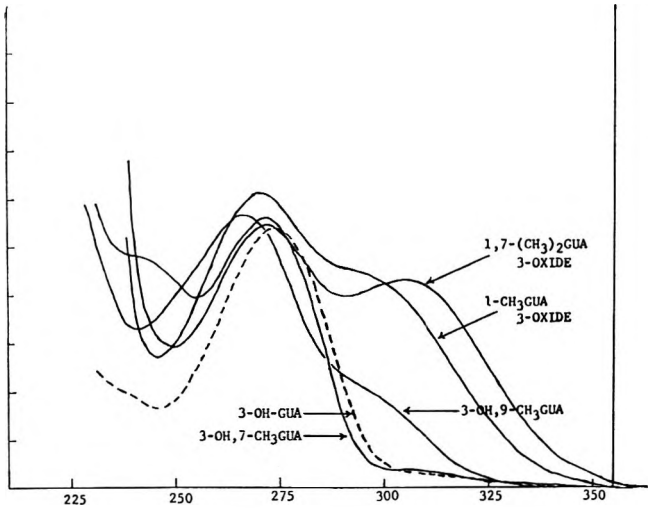
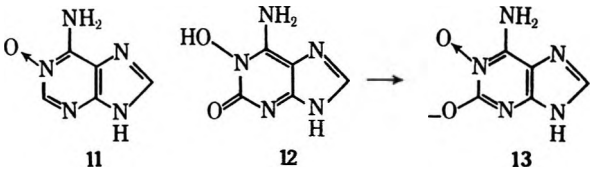


Figure 5.—Guanine 3-*N*-oxide series in methanol. The spectra were determined on nearly saturated solutions in 4-cm cuvettes and are not at equimolar concentrations.

The predominance of 3-hydroxyguanine rather than guanine 3-oxide in the neutral species of **8** was not expected.[18] Aminopurine oxides, notably the 1-oxides of adenine, **11**, adenosine, and 2,6-diaminopurine, exist predominantly as the *N*-oxide tautomers, as deduced from the behavior of the 230-nm band.[20] The *N*-hydroxy tautomer was, however, known to be preferred over the *N*-oxide form when an oxo group is present on an adjacent carbon. The 2-oxo derivative of adenine 1-*N*-oxide (**12**) does not exhibit the high extinction 230-nm band shown by the neutral species of **11** until after the first ionization ($pK_a = 5.0$).[6] This was interpreted[6] to mean that the *N*-hydroxy tautomer is favored in the neutral species of **12**. Absorption at 228 and 295 nm in the monoanion, **13**, is similar to that of **6** and **10**, and indicates that an enolate anion comparable to **3** is also predominant in **13**.

The absorption band at 230 nm in the adenine 1-oxide and adenosine 1-oxide spectra is lost upon protonation,[20] and protonation must involve the *N*-oxide function to explain the accompanying loss of that absorption. In the guanine 3-*N*-oxide series comparable bands of the neutral species at 217 to 227 nm do not



completely disappear but decrease in intensity and shift to 211 to 217 nm upon protonation.

The nearly identical spectra of the cations of **8**, and of its 1- and 7-methyl and 1,7-dimethyl derivatives (Figure 6), suggest that these cations are similar in structure. These spectra closely resemble that of the 3-methylguanine cation[39] and are distinctly different from those of the 3-hydroxy-9-methylguanine and 9-methylguanine cations. The latter has the additional proton at N-7,[26,29,31] and 3-hydroxy-9-methylguanine must protonate at the same position. The differences between the spectra of the cations of **8**, its 1,7-dimethyl derivative, and 3-methylguanine from that of the 3-hydroxy-9-methylguanine cation suggest that the site of first protonation in **8** is the pyrimidine ring (**14**, R = H). This protonation of the pyrimidine moiety of 3-hydroxyguanine contrasts with that of guanine and its 1-, 7-, 8-, or 9-methyl derivatives, for all of which protonation of the imidazole ring is deduced.[27,29] A second pK_a of protonation is found at -1.33 for **8**, and the spectrum of the dication is then quite similar to that of the monocation of 3-hydroxy-9-methylguanine (Figure 5). Such evidence for the second protonation of **8** at N-9 to yield **15** corroborates the assignment of the first protonation to the pyrimidine ring. The spectrum of **14** resembles those of the cations of 8-trifluoromethylguanine and its 1- and 7-methyl derivatives, which are deduced to protonate at N-3.[27] Further evidence for the positions and order of protonation is provided by a comparison of the influence of methyl substituents on the p*K*'s of **8** and of guanine (Table II). Data indicate that the sequence of protonation[29] and ionization[26] for guanine and its 8-methyl derivative[27] is the same, and the similar spectral changes indicate that this is also true for **8** and its 8-methyl derivative (Table I). There is an increase of 0.2–0.7 pH unit for all p*K*'s of 8-methylguanine (Table II). The largest increase is in the first protonation pK_a which occurs[27,29] in the methyl-substituted imidazole ring. In contrast, an 8-methyl substituent on 3-hydroxyguanine induces almost no change in either the first ionization or the first protonation p*K*'s (Table II), both of which were deduced independently from other evidence to occur on the pyrimidine ring, as in **10** and **14**. The second protonation and second ionization p*K*'s, both associated with the imidazole ring of **8**, are increased by 0.6 pH unit, which is comparable to the effect of an 8-methyl group on all of

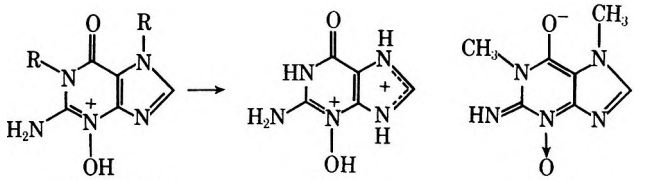
TABLE II

Δp*K*'s Relative to the Corresponding 8-H Derivative

	3-OH-8-CH_3-Gua	8-CH_3-Gua
Second protonation	+0.6	+0.2
First protonation	−0.06	+0.7
First ionization	+0.1	+0.4
Second ionization	+0.6	+0.4

(39) L. B. Townsend and R. K. Robins, *J. Amer. Chem. Soc.*, **84**, 3008 (1962).

the pK's of guanine. The only derivatives of **8** which possess a higher first protonation pK than **8** are those bearing a 1-methyl substituent (Table I). This and the selective increase by an 8-methyl substituent of only the pK's deduced for the imidazole ring thus support the assigned positions of protonation and ionization. Even though there is a hydroxyl group on N-3 in the cations of the guanine 3-*N*-oxide series, bands are still observable at 211–217 nm, and these bands must result from the influence of the 3-oxygen.



14, R = H, CH_3 **15** **16**

The fact that the increases in intensity of the bands near 224 and near 300 nm are associated with two pK_a's, both the deprotonation of the cation and the first ionization, is consistent with the presence of **8b** and some **8a** in the neutral species of **8**. The full effect of the *N*-oxide function on both the 224- and 300-nm bands of **8** is not realized until after ionization to **10**.

Tautomers of **8** that require a 6-enol rather than a 6-keto, or a 2-imino rather than the 2-amino, form are conceivable, but would not be expected.[13] The difference between the ultraviolet spectra of the neutral species of **8** and of 2-amino-6-methoxypurine 3-oxide (Table I) is evidence against a 6-enol structure for **8** in solution. In addition, strong carbonyl absorption is manifest at 1700 cm^{-1} in the ir spectrum of **8** (solid state, KBr). Available data indicate that both 2-aminopyridine[40] and guanine[29,41] exist in the 2-amino form; recent MO calculations agree.[42] The amino tautomer is retained in the *N*-oxide of 2-aminopyridine[43] and, by analogy, an *N*-oxide group at N-3 of guanine should not induce a tautomeric change of the 2-amino to a 2-imino structure.

Although 1,7-dimethylguanine does not ionize in strong base, its 3-oxide does, pK_a = 11.20. Since the only available hydrogens are on the 2-amino group, ionization must take place from there. A large bathochromic shift of the 300-nm band to 327 nm accompanies this pK_a, thereby implying additional conjugation and suggesting that the C-6 enolate anion and the imino tautomer at C-2, **16**, may predominate. With 1-methylguanine 3-oxide a second pK_a of ~14 is also associated with a bathochromic shift of the 300-nm band and must also represent ionization of the 2-amino group, an ionization not shown by 1-methylguanine.[44]

The knowledge that **8** exists mainly as the 3-hydroxy tautomer indicates that it should be able to form an ester comparable to 3-acetoxyxanthine,[3] which in turn should also undergo substitution at position 8. This facilitates interpretation of its rearrangement to 8-hydroxyguanine with trifluoroacetic anhydride *in vitro*[45] and the formation of 8-methylmercaptoguanine *in vivo*.[46,47]

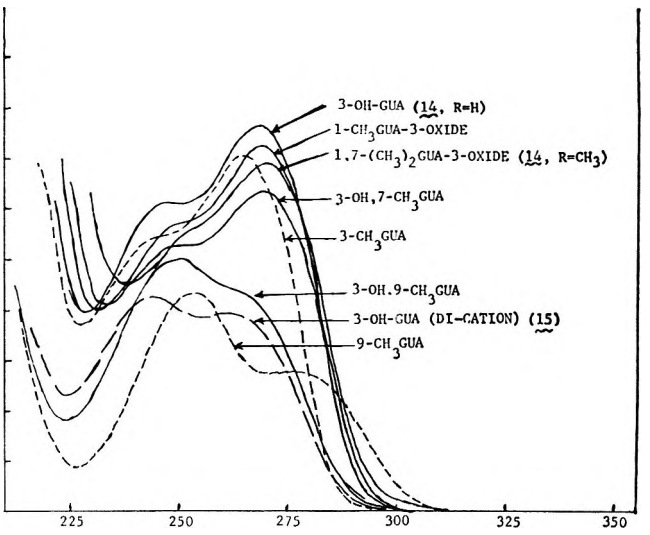


Figure 6.—Guanine 3-*N*-oxide series: cations. See footnote to Figure 1.

Experimental Section

The extinction coefficients at selected pH's for the various molecular species (Table I) were determined with a Beckman DU or Cary Model 15 spectrophotometer. Isosbestic uv spectra and those in the figures were determined with a Unicam SP800 recording spectrophotometer. The latter are plotted for convenient comparisons and are not at equimolar concentration and no OD scale is given. Values above ~240 nm were determined in 4-cm cells and those below 240 in 1-cm cells because of the great differences in extinction coefficients (Table I). The pK_a's were determined by methods described,[48] at 23 ± 1°, spectrophotometrically with 0.01 *M* buffers[49] or electrometrically with 0.001 *M* solutions, with the use of a Beckman DU spectrophotometer and a Beckman Research Model pH meter.

Ir spectra were determined with an Infracord spectrophotometer (KBr disk) on samples dried at 110° over P_2O_5 for 24 hr. The carbonyl absorption of 1-hydroxyhypoxanthine appears at 1695 cm^{-1},[5] while that of 1-hydroxyxanthine shows a broad, partially resolved band with peaks at 1665 and 1680 cm^{-1}. The carbonyl absorption of 3-hydroxyxanthine appears as a single broad band centered at 1655 cm^{-1}, while two carbonyl bands of 3-hydroxy-1-methylxanthine are well resolved, appearing at 1635 and 1710 cm^{-1}. This parallels results obtained both in KBr[50] and in dioxane solution[51] from xanthine and its 1,3-di-, 3,7-di-, and 1,3,7-trimethyl derivatives, in which the two carbonyl absorption bands were not resolved unless a 1-methyl substituent was present. These carbonyl absorption bands differ from those attributed to the N-O group in heterocyclic *N*-oxides, which appear at 1200–1300 cm^{-1}.[38]

Registry No.—**5**, 13479-29-3; **5** (OH = OCH_3), 30345-91-6; **8b**, 30345-22-3; **9**, 30345-23-4; 3-hydroxy-7-methylxanthine, 30409-21-3; 3-hydroxy-9-methylxanthine, 30345-24-5; 3-hydroxy-1-methylxanthine, 14002-16-5; 1,7-dimethyl-3-hydroxyxanthine, 30345-

(40) A. R. Katritzky and J. M. Lagowski, *Advan. Heterocycl. Chem.*, **1**, 404 (1963).

(41) Part of the evidence for predominance of the 2-amino tautomer in guanine is based on nmr data on guanosine in DMSO-d_6.[31] Attempts to obtain similar nmr data on the even less soluble **8** and **9** were unsuccessful.

(42) N. Bodor, M. J. S. Dewar, and A. J. Harget, *J. Amer. Chem. Soc.*, **92**, 2929 (1970).

(43) A. R. Katritzky, *J. Chem. Soc.*, 191 (1957).

(44) Neither 3-hydroxyguanine nor guanine shows, to pH 15, any spectral change attributable to ionization of the 2-amino group.

(45) U. Wölcke, W. Pfleiderer, T. J. Delia, and G. B. Brown, *J. Org. Chem.*, **34**, 981 (1969).

(46) G. B. Brown, G. Stöhrer, K. Sugiura and M. N. Teller, Abstracts, 10th International Cancer Congress, Houston, Texas, 1970, Medical Arts Publishing Co., Austin, Tex., 1970, p 8.

(47) G. Stöhrer and G. B. Brown, *Science*, **167**, 1622 (1970).

(48) A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases," Wiley, New York, N. Y., 1962.

(49) D. D. Perrin, *Aust. J. Chem.*, **16**, 572 (1963).

(50) E. R. Blout and M. Fields, *J. Amer. Chem. Soc.*, **72**, 479 (1950).

(51) M. Horák and J. Gut, *Collect. Czech. Chem. Commun.*, **26**, 1680 (1961).

26-7; 3-hydroxy-8-methylguanine, 30409-22-4; 3-hydroxy-7-methylguanine, 30345-27-8; 3-hydroxy-9-methylguanine, 30345-28-9; 1,7-dimethylguanine 3-oxide, 30345-29-0; 2-amino-6-methoxypurine 3-oxide, 30345-92-7.

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Synthesis of 2-Thio-D-ribose and 2′-Thioadenosine Derivatives[1]

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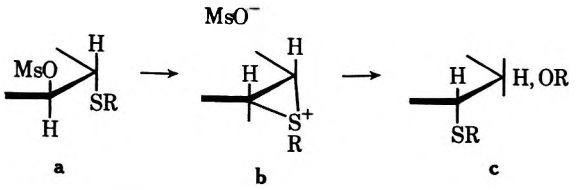
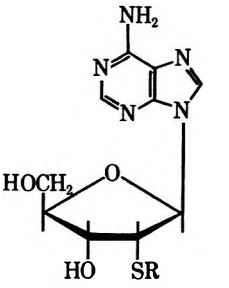
2-Thio-D-ribose derivatives, both furanose and pyranose, have been synthesized from the corresponding *S*-alkyl 1-thio-α-D-arabinoside 2-*O*-mesylates. The alkylthio group underwent stereospecific migration to C-2 with ejection of the *trans*-2-*O*-mesyl group. Depending on the medium, the 2-thio-D-ribose derivatives were obtained as methyl glycosides or as 1-*O*-acetates. In a deblocking sequence, methyl 2-thio-D-ribofuranoside was obtained as the free thiol. The *S*-methyl, *S*-benzyl, and tetrabenzoyl derivatives of 2′-thioadenosine were obtained from the furanose 1-*O*-acetates or their chloro sugars in reactions with purine bases. In some of the nucleoside condensations, 7-nucleosides were obtained as by-products and were identified by infrared and ultraviolet spectral properties, not previously reported, and characteristic of 7-substituted 6-benzamidopurines.

A number of new thio sugars have been synthesized in recent years, often for biological interest in their nucleoside derivatives. Of the positional isomers of thio-D-ribose, only 2-thio-D-ribose has not been synthesized previously. The requisite *cis*-3-OH,2-SH arrangement has not been achieved synthetically in any sugar, although numerous 2-thio sugars have been prepared with a trans mercapto–alcohol system. The *cis*-3-SH,-2-OH system of 3-thio-D-ribofuranose derivatives and 3′-thioadenosine was attained[2] only recently by the technique of internal displacement at C-3 with a *trans*-2-*O*-thionobenzoate. A related internal displacement at C-3 with a *trans*-2-*S*-thiolbenzoate was attempted[3] as a synthesis of 2-thio-D-ribofuranose but was unsuccessful; only the 2,3-episulfide was formed by neighboring participation of sulfur rather than oxygen.

The synthesis of 2-thio-D-ribose derivatives has now been accomplished in a related process by generating a 1,2-episulfonium ion (**b**) as intermediate. Starting from an *S*-alkyl 1-thio-α-D-arabinoside (**a**), with a readily displaced *trans*-*O*-mesylate at C-2 (and stable blocking groups at C-3 and at C-4 or C-5), the 1-alkylthio group underwent stereospecific migration to C-2. Ejection of the mesylate occurred with inversion at C-2 giving the D-ribo configuration, and the intermediate episulfonium ion (**b**) was opened by regiospecific attack at C-1 by a nucleophile provided by the medium. The 2-thio-D-ribose derivatives obtained by this means have been converted to the *S*-methyl, *S*-benzyl, and tetrabenzoyl derivatives (β-9-**33**, β-9-**31**, β-9-**29**) of 2′-thioadenosine. 2′-Thioadenosine could not be obtained on deblocking. There was evidence for cleavage of the nucleoside link when the free thiol was liberated. Alternatively, 2′-*S*-methyl-2′-thioadenosine was selected as the target compound for study of biological properties.[4]





2′-thioadenosine, R = H
β-9-**33**, R = Me
β-9-**31**, R = CH_2Ph

The synthesis was studied first with pyranose sugars as models (Scheme I), owing to the ready availability of *S*-benzyl 1-thio-α-D-arabinopyranoside[5] (**3**) as starting material. The 3,4-*O*-cyclohexylidene acetal (**4**) was obtained as a crystalline substance and was used in preference to the isopropylidene analog, an oil. A 2-*O*-tosylate could not be formed from **4**, perhaps because of steric restrictions in this fused ring system. The 2-*O*-mesylate (**5**) was readily obtained; it could be stored at 5° for 1 week without deterioration but decomposed upon prolonged storage or on heating. Treatment of **5** with refluxing methanol containing sodium bicarbonate as acid acceptor caused nearly quantitative rearrangement to the methyl pyranoside **6** of 2-*S*-benzyl-2-

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, National Institutes of Health, Public Health Service, Contract No. PH-43-64-500. The opinions expressed in this paper are those of the authors and not necessarily those of the Cancer Chemotherapy National Service Center.

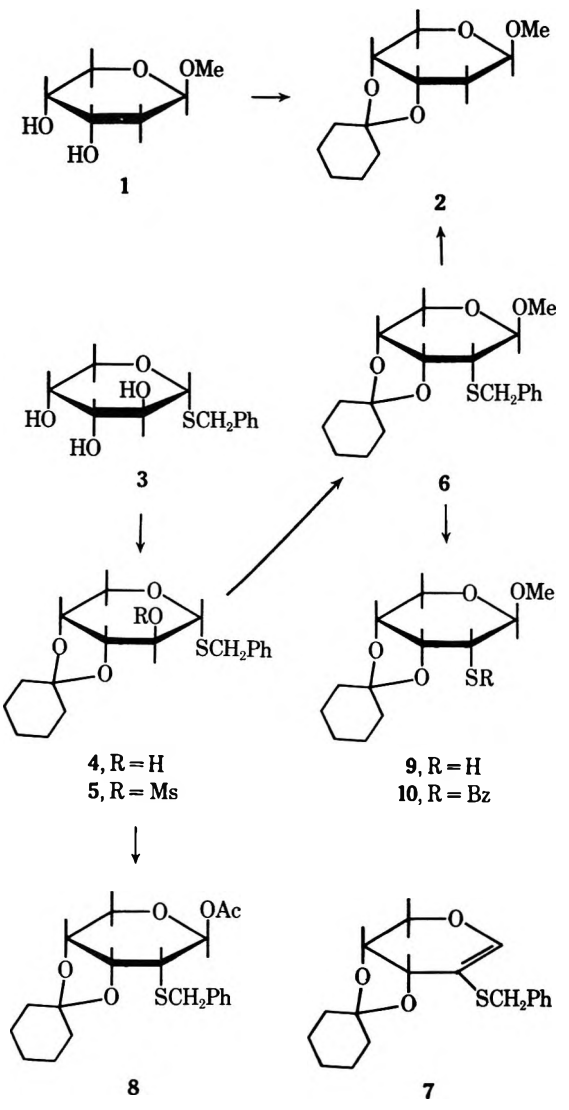
(2) K. J. Ryan, E. M. Acton, and L. Goodman, *J. Org. Chem.*, **33**, 1783 (1968).

(3) K. J. Ryan, E. M. Acton, and L. Goodman, *ibid.*, **33**, 3727 (1968).

(4) 2′-*O*-Methyl ribonucleosides have been found in RNA from a wide variety of sources. Although the biological function is unknown, it has been suggested that these may play an important role in protein biosynthesis: T. A. Khwaja and R. K. Robins, *J. Amer. Chem. Soc.*, **88**, 3640 (1966), and leading references.

(5) H. Zinner, A. Koine, and H. Nimz, *Chem. Ber.*, **93**, 2705 (1960).

SCHEME I



thio-D-ribose. Infrared and nmr spectra showed that the mesylate was completely ejected, and the nmr spectrum showed the presence of the 1-methoxyl. Clearly, the sulfur was now at C-2, from the distinctive upfield shift for H-2 at τ 7.37, where it appeared as a quartet coupled to H-1 (now shifted downfield at τ 5.21) and to H-3. The coupling constants indicated a trans diaxial relation between H-1 and H-2 (J = 7.5 Hz) and a cis axial–equatorial relation between H-2 and H-3 (J = 2.5 Hz), as expected[6,7] for the β-D-ribo configuration in a *C1* pyranose ring. Closer inspection of the nmr spectrum revealed 10–15% of the α anomer of **6**, from distinctive signals for OCH_3 and H-2. The anomers could be separated chromatographically; H-2 for the α anomer was a triplet, $J_{1,2} = J_{2,3}$ = 4 Hz, indicative of the equatorial–axial–equatorial arrangement. Topside attack at C-1 of **b** should have given the β anomer **6** exclusively; formation of some α anomer suggests that a carbonium ion developed to some extent at C-1. Desulfurization of **6** afforded crystalline methyl 3,4-*O*-cyclohexylidene-2-deoxy-β-D-ribopyranoside, identical with a sample synthesized independently from methyl 2-deoxy-β-D-ribopyranoside[8] (**1**). Debenzylation of **6** with sodium–liquid ammonia afforded the free thiol **9** in 86% yield. Benzoylation afforded the crystalline *S*-benzoate **10**.

Treatment of **5** with acetic anhydride–acetic acid containing potassium acetate afforded a mixture containing the β-1-*O*-acetate (**8**, 80% yield) of 2-*S*-benzyl-2-thio-D-ribopyranose, the α anomer (10%), and an olefin **7** (10%). Column chromatography effected a separation of **7** and **8**, following which **8** cystallized from methanol. A strong band at 6.22 μ in the infrared spectrum of **7** identified the olefin as a vinyl ether–vinyl sulfide, by comparison with other 2-*S*-alkyl-2-thio glycals.[9,10] Similarly, in the nmr spectrum, a sharp singlet at τ 3.42 was assigned to H-1 of structure **7** and confirmed that the benzylthio group was shifted to C-2. 2-*S*-Benzyl-3,4-*O*-cyclohexylidene-2-thio-D-arabinal (**7**) was presumably formed from the 1,2-episulfonium ion **b** by loss of the proton at C-2 and cleavage of the C-1–S bond. When the mesylate **5** was treated with sodium benzoate in hot dimethylformamide, the olefin **7** was the main product, with only 16% of the β-1-*O*-benzoate analogous to **8**.[11] A related olefin, 2-(*N*,*N*-dimethyldithiocarbamoyl)-D-glucal, was recently obtained[12] from a 2-*O*-mesyl-β-D-glucopyranosyl *N*,*N*-dimethyldithiocarbamate; ejection of the mesylate by sulfur was accomplished through a five-membered cyclic intermediate analogous to **b**.

In furanose series (Scheme II) the requisite *S*-alkyl 1-thio-D-arabinofuranosides (**13** and **14**) with the 2-OH free for mesylation were best obtained from 1,3,5-tri-*O*-benzoyl-D-arabinofuranose[13] (**11**). This was a better source of the 2-hydroxy chloro sugar **12** than was 3,5-di-*O*-benzoyl-D-arabinose.[14] When the chloro sugar **12** was treated with an equivalent amount of sodium benzyl mercaptide, a high degree of steric control was exerted, possibly by the 2-hydroxyl. Benzyl 3,5-di-*O*-benzoyl-1-thio-α-D-arabinofuranoside (**13**) was obtained, contaminated with very little of the β anomer. Pure **13** could be obtained free of the anomer and other impurities by crystallization in 25% yield. The 2-*O*-mesylate **15** was converted in nearly quantitative yields to the 1-*O*-methyl (**23**) or 1-*O*-acetyl (**17**) derivatives of 2-thio-D-ribose. The formation of **23** was done in methanol containing silver carbonate and Drierite, to avoid the debenzoylation at C-3 and C-5 which had occurred with methanol and sodium bicarbonate.

The stringent requirement for a trans relation between the 2-*O*-mesyl and 1-benzylthio groups in these migration–inversions was demonstrated in one experiment when 2-*O*-mesylate **15** from crude **13** was used, containing a little β anomer; this anomer of **15** survived unchanged in the reaction to form the 1-*O*-acetate **17**, as predicted for a *cis*-2-*O*-mesylate. With the migration–inversion in the furanose series, there was no

(6) R. U. Lemieux, R. K. Kullnig, H. J. Bernstein, and W. G. Schneider, *J. Amer. Chem. Soc.*, **80**, 6098 (1958).

(7) C. V. Holland, D. Horton, M. J. Miller, and N. S. Bhacca, *J. Org. Chem.*, **32**, 3077 (1967).

(8) R. E. Deriaz, W. G. Overend, M. Stacey, and L. F. Wiggins, *J. Chem. Soc.*, 2836 (1949).

(9) U. G. Nayak, M. Sharma, and R. K. Brown, *Can. J. Chem.*, **45**, 481 (1967).

(10) U. G. Nayak, M. Sharma, and R. K. Brown, *ibid.*, **45**, 1767 (1967).

(11) A preliminary report of some of this work was made: K. J. Ryan, E. M. Acton, and L. Goodman, Abstracts of the 156th National Meeting of the American Chemical Society, Atlantic City, N. J., Sept 1968.

(12) S. Ishiguro and S. Tejima, *Chem. Pharm. Bull.*, **15**, 1478 (1967).

(13) R. K. Ness and H. G. Fletcher, Jr., *J. Amer. Chem. Soc.*, **80**, 2007 (1958).

(14) E. J. Reist, P. A. Hart, L. Goodman, and B. R. Baker, *ibid.*, **81**, 5176 (1959).

SCHEME II

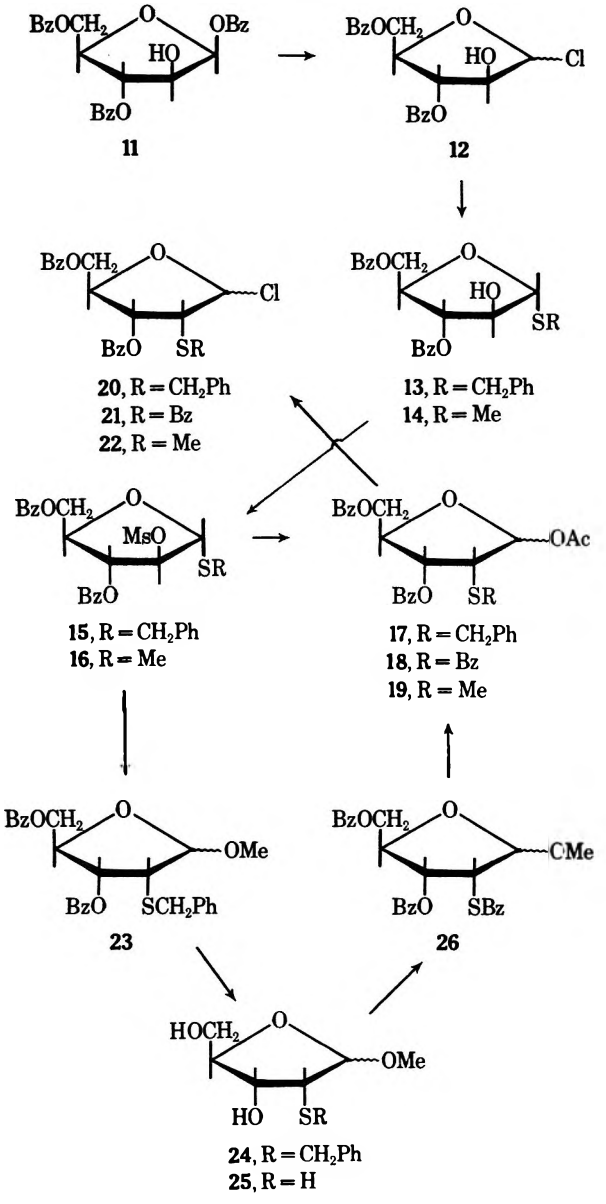
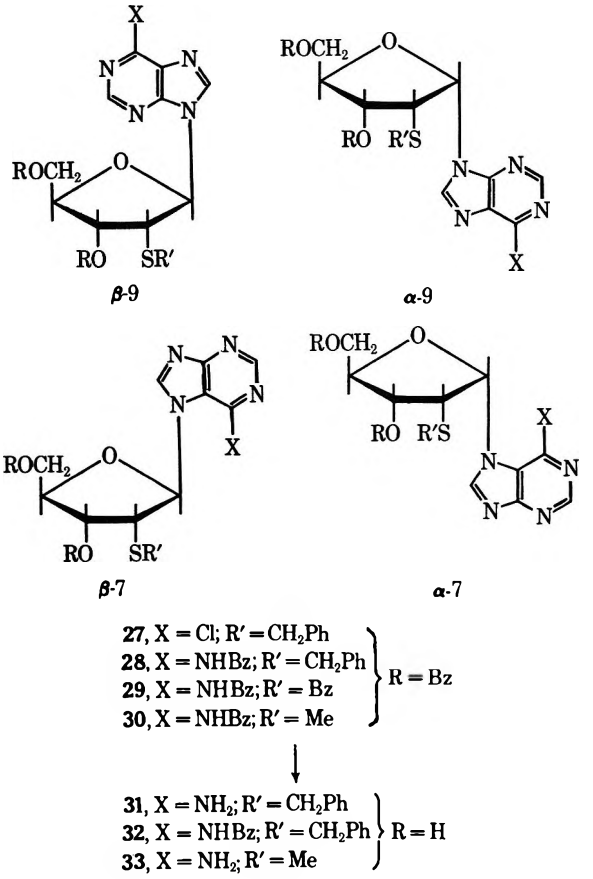


TABLE I

CORRELATION OF NMR DATA FOR 2-THIO-D-RIBOFURANOSES

Compd	β-C-1-H τ	β-C-1-H $J_{1,2}$, Hz	α-C-1-H τ	α-C-1-H $J_{1,2}$, Hz	$J_{2,3}$, Hz β	$J_{2,3}$, Hz α
17	3.63 d	2.5	3.54 d	4.5	6.8	6.8
18	3.49 d	3.0	3.28 d	4.7	6.3	6.7
19	3.63 d	2.0	3.40 d	4.7	6.5	6.4
23	4.98 d	3.1	5.11 d	4.8	6.4	7.0
24	5.16 d	3.4	5.17 d	5.0	5.6	6.4
25	5.09 d	2.8	5.04 d	5.0		
26	4.79 d	2.8		4.9	6.2	6.8

SCHEME III



evidence that a 1,2 olefin like **7** was formed. Both the products **17** and **23** contained appreciable amounts of α anomers. The anomers were identified from the coupling constants in the nmr, based on the statement[15] that values "less than about 4 Hz may be ascribed to neighboring trans hydrogens." The nmr was a consistently useful tool for structure confirmation of all the 2-thio-D-ribofuranoses in Scheme II that could be measured (**17** through **19**, **23** through **26**; see below for chemistry of the *S*-benzoyl and *S*-methyl compounds). As shown in Table I, $J_{1,2}$ values for the β anomers were consistently 2.0–3.0 Hz and for the α anomers were 4.5–5.0 Hz. With the 1-*O*-acetates (**17**, **18**, **19**), the α-C-1-H was shifted noticeably downfield from the β-C-1-H, in accord with an observation made[15] on a number of 1-*O*-acyl furanoses that "H-1 is at lower field when the substituents are cis." For compounds **17** and **19**, the location of H-2 upfield from the other sugar protons showed that the sulfur was at C-2 (with the *S*-benzoyl compounds the upfield shift was less obvious). That $J_{2,3}$ was 5.6–7.0 Hz was regarded as confirming evidence for the ribo configuration (2,3-cis[15]), especially in contrast with $J_{2,3}$ values of 1.9 Hz for an *S*-benzyl 2-thio-D-xylofuranoside[16] and 3.9 or 2.6 Hz for an *S*-benzyl 2-thio-D-arabinoside[17] (2,3-trans).

The nucleoside syntheses undertaken (Scheme III) are summarized in Table II. Fusion of the 1-*O*-acetate **17** with 6-chloropurine and chloroacetic acid catalyst was studied first. The nucleoside 9-**27** obtained was a mixture of β and α anomers in a ratio of about 2:1. Again, the anomeric configurations could be determined by nmr. Eventually it was found that *with all the 6-substituted 9-purinyl nucleosides of 2′-thio-D-ribose examined in this work, $J_{1',2'}$ = 9.0–9.5 Hz for β anomers and 7.0–7.5 Hz for α anomers.* These values are larger than normally observed with adenosine derivatives, and perhaps this is due to the presence of sulfur at C-2′. The α anomer (α-9-**27**) could be crystallized from the α,β mixture, and amination–deacylation afforded crystalline 9-(2-*S*-benzyl-2-thio-α-D-ribofuranosyl)adenine (α-9-**31**). Amination–deacylation of the

(15) J. D. Stevens and H. G. Fletcher, Jr., *J. Org. Chem.*, **33**, 1799 (1968).

(16) G. Casini and L. Goodman, *J. Amer. Chem. Soc.*, **86**, 1427 (1964).

(17) L. Goodman, *ibid.*, **86**, 4167 (1964).

TABLE II

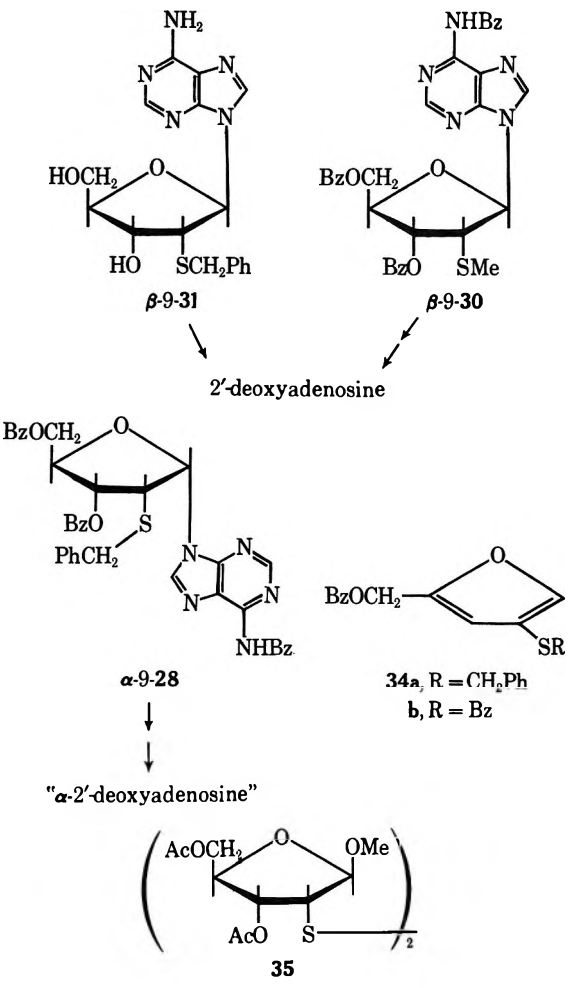
SUMMARY OF NUCLEOSIDE CONDENSATIONS

Sugar	Purine	Method	Products		
17	6-Cl-purine	Fusion	β-9-27 (25)[a]	α-9-27 (13)[a]	
20	6-BzNH-purine	Molecular sieve	β-9-28 (0.6)[a]	α-9-28 (5.4)[a]	
20	Bis(Me$_3$Si)-6-BzNH-purine	$HgBr_2$[b]	β-9-28 (22)[a]	α-9-28 (5)[a]	7-28[c] (9)[a]
21	Bis(Me$_3$Si)-6-BzNH-purine	$HgBr_2$[d]	β-9-29 (25)[e]		7-29[c] (estimated 5)
22	Bis(Me$_3$Si)-6-BzNH-purine	$HgBr_2$[b]	β-9-30 (34)[e]	α-9-30 (10)[e]	7-30 (12)[e,f]

[a] Per cent in parentheses determined by nmr analysis of the isolated α,β mixture. [b] Without isomerization by heating. [c] Anomeric composition could not be determined. [d] With heating to isomerize the 7 isomer to the 9 isomer. [e] Per cent isolated. [f] Both anomers present, one of which crystallized (6%).

mother liquor from α-9-27, enriched in β-9-27, afforded a mixture from which crystalline 2′-*S*-benzyl-2′-thioadenosine (β-9-31) and some additional α-9-31 could be separated by chromatography. Structure proof at this point depended on ultraviolet spectra (*vide infra*), which verified that both anomers were 9-nucleosides, and on desulfurization of β-9-31 to give 2′-deoxyadenosine. A by-product from the fusion, which had to be separated first by chromatography, was the furan **34a**, presumably obtained by elimination of acetic acid plus benzoic acid from **17**. This elimination became overwhelming in larger scale reactions, and the fusion process could not be pursued.

Attempts to prepare a chloro sugar **20** from the 1-*O*-acetate **17** by conventional treatment with ethereal hydrogen chloride at 0° produced a tar. At −60°, however, the preparation of **20** was entirely straightforward, and a variety of other nucleoside syntheses could be studied. Mild treatment of the chloro sugar **20** with 6-benzamidopurine in the presence of a molecular sieve as acid acceptor[18,19] afforded a nucleoside that proved to be mainly α-9-28, judging from the $J_{1',2'}$ of 7.0 Hz and from the deacylation to crystalline α-9-31. The most successful nucleoside synthesis in this work was based on a recent procedure[20] for treating a chloro sugar with bis(trimethylsilyl)-6-benzamidopurine in benzene solution containing mercuric bromide. It was reported that a significant proportion of 7-nucleoside was formed along with 9-nucleoside, but that isomerization to the 9 isomer could be accomplished with heating, and that the anomeric configuration was largely β. The 2-*S*-benzyl chloro sugar **20** in this procedure afforded, after 6 days at room temperature, a mixture containing about 27% of the blocked 9-nucleoside (9-28, with a β:α ratio of 4:1) and about 9% of the blocked 7-nucleoside (7-28). These isomers could be separated chromatographically. Normal ultraviolet (Table III) and infrared spectra were observed for 9-28; the anomeric composition was determined as mainly β from the $J_{1',2'}$ values in the nmr. This identity was confirmed on debenzoylation to give crystalline 2′-*S*-benzyl-2′-thioadenosine (β-9-31), identical with that from β-9-27 above. The blocked 7-nucleoside (7-28) was clearly distinguished by characteristic ultraviolet absorption maxima (*vide infra*) and by extraordinary and unexpected infrared bands. The unusual infrared bands (most notably a strong, sharp peak at 6.08 μ which could be easily detected even in mixtures) were observed with all the 7-substituted nucleosides of 6-benzamidopurine studied in this work and seem not to have been reported previously. The anomeric composition of 7-28 (as one or both possible anomers) could not be estimated from the nmr, since the signal for H-1′ was apparently obscured by aryl protons.

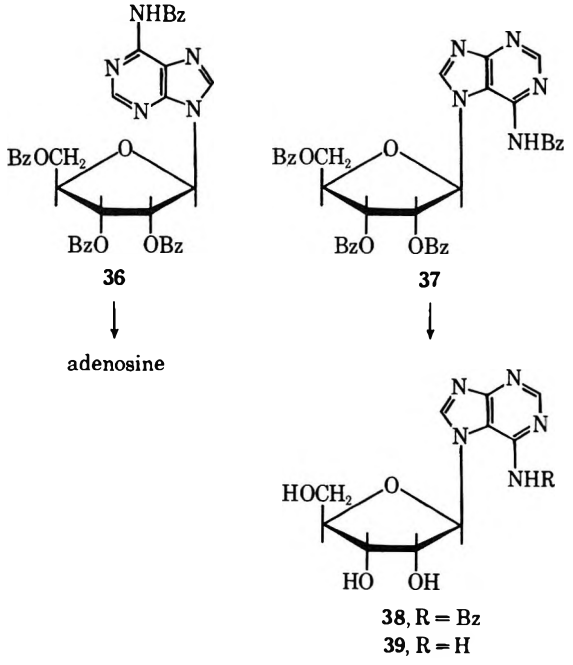


Debenzoylation of 7-28 afforded two products, which could be separated by chromatography, and which crystallized. The chromatographically less mobile product was identified as 7-(2-*S*-benzyl-2-thio-D-ribofuranosyl)-7*H*-adenine (7-31) by the characteristic ultraviolet

(18) C. P. J. Glaudemans and H. G. Fletcher, Jr., *J. Org. Chem.*, **28**, 3004 (1963).
(19) F. Keller, I. J. Botvinick, and J. E. Bunker, *ibid.*, **32**, 1644 (1967).
(20) B. Shimizu and A. Saito, *Agr. Biol. Chem.* (*Tokyo*), **33**, 119 (1969).

absorption for 7-substituted adenines[21,22] (Table III). Although the anomeric configuration of 7-**31** could not be determined from the nmr spectrum, it crystallized presumably as a single anomer. The other, more mobile product was not simply the anomer of 7-**31**. Elemental analysis showed, rather, that it was a benzoyl derivative of 7-**31**, incompletely deblocked. That it was the 6-*N*-benzoyl derivative 7-**32** was indicated by the unusual infrared bands (including a strong, sharp band at 6.10 μ) for a 7-substituted 6-benzamidopurine. The ultraviolet maxima (Table III) at pH 7 and 13 resembled those of the fully benzoylated 7-nucleosides and were distinct from those of the fully benzoylated 9-nucleosides. The ultraviolet maxima at pH 1 resembled those of 6-benzamidopurine itself. At pH 1, there was, in fact, rapid cleavage of 7-**32** to 6-benzamidopurine, owing to a very high degree of acid sensitivity. The presence and position of benzoyl attachment in 7-**32** was thereby confirmed. Such acid sensitivity was not found with the fully blocked precursor 7-**28** or any of the other classes of nucleosides in this study. However, the 2′-thionucleoside derivatives seemed generally less stable than their D-ribose analogs. Attempts to isomerize a mixture of the fully blocked nucleosides (9-**28** and 7-**28**) to the 9 isomer gave a competing elimination of the purine moiety to the furan derivative **34a**, which became predominant in refluxing xylene containing mercuric bromide, as directed[20] for the ribose analogs.

Since the properties of the 7-nucleosides (7-**32** and 7-**28**) derived from 6-benzamidopurine were somewhat novel, the nucleoside condensation with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide was repeated,[20] and a sample of crystalline 6-benzamido-7-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-7*H*-purine (**37**) was isolated for comparison. Unusual, distinguishing features of the ultraviolet and infrared spectra were like those of



the 2′-benzylthio analog 7-**28**. Further, debenzoylation with methanolic sodium methoxide gave 7-β-D-ribofuranosyladenine (**39**), along with the crystalline 6-*N*-benzoyl derivative **38**. As before, these were conditions that, with the 9 isomers, gave complete deblocking. The spectral properties and acid sensitivity of 6-benzamido-7-β-D-ribofuranosyl-7*H*-purine (**38**) matched those of the 2-benzylthio analog 7-**32**. This product was apparently not observed in the previous deblocking[20] of **37**. (Assignment of the β anomeric configuration to **37**, **38**, and **39** was based on the previous[20] determination with amorphous **37**.)

The preparation of 2′-thioadenosine from β-9-**31** was attempted by S-debenzylation with sodium–liquid ammonia, but no nucleoside could be detected in the product, and the only isolable fragment was adenine. For this reason, an *S*-benzoyl precursor (*i.e.*, β-9-**29**) was sought as being susceptible to milder deblocking. The *S*-benzyl blocking group was exchanged for an *S*-benzoyl group in the sugar precursors (Scheme II). Methyl 3,5-di-*O*-benzoyl-2-*S*-benzyl-2-thio-α,β-D-ribofuranose (**23**) was converted to methyl 2-thio-α,β-D-ribofuranoside (**25**), which was benzoylated to give **26**. The intermediate thiol **25** was obtained from a sodium–liquid ammonia debenzylation in high yield by extraction and was characterized by its spectra. There was no observed tendency toward elimination or even toward disulfide formation when it was protected from air. Acetolysis of methyl 2-*S*-benzoyl-3,5-di-*O*-benzoyl-2-thio-α,β-D-ribofuranoside (**26**) gave blackening and decomposition when attempted at −5° but at −20° gave the 1-*O*-acetate **18** in nearly quantitative yield. Conversion to the chloro sugar **21** occurred at −60°, also in quantitative yield. Condensation of **21** with bis(trimethylsilyl)-6-benzamidopurine in benzene in the presence of mercuric bromide gave a mixture of 7- and 9-nucleosides **29** in roughly comparable amounts, judging from the intensities on thin layer chromatography and from the characteristic infrared bands for 7 isomers. If the reaction mixture was refluxed prior to its work-up, the 7 isomer was isomerized almost completely to β-9-**29**, the tetrabenzoyl derivative of 2′-thioadenosine; there was little elimination to form a furan (presumably **34b**). Chromatographic purification afforded β-9-**29** in 25% yield. The characteristic $J_{1',2'}$ of 9.0 for β-9 anomers was observed in the nmr spectrum, with no evidence for the α anomer. All attempts to prepare 2′-thioadenosine by debenzoylation of β-9-**29** in alkaline methanol afforded adenine as the only detectable purine derivative. In one experiment, the water-soluble sugar fragment was recovered and was acetylated; it consisted entirely of methyl 3,5-di-*O*-acetyl-2-thio-β-D-ribofuranose obtained as the disulfide **35**. The complete cleavage of the nucleoside whenever the 2′-SH was liberated suggested that the thiol (or its anion) acted to eject the purine base, which is situated in the trans position on the adjacent carbon. Probably this occurred through a 1,2-episulfide; attack by solvent methanol at C-1 then gave the methyl β-D-furanoside. These results suggest that 2′-thioadenosine, if ever isolated, would be highly unstable, at least in base.

Finally, synthesis of 2′-*S*-methyl-2′-thioadenosine (β-9-**33**) was carried out by the sequence used for the *S*-benzyl analog β-9-**32**. Methyl 3,5-di-*O*-benzoyl-1-thio-α-D-arabinofuranoside (**14**) was obtained in much better yield than the benzyl analog **13**, since a large excess of methanethiol could be used advantageously

(21) N. J. Leonard and J. A. Deyrup, *J. Amer. Chem. Soc.*, **84**, 2148 (1962).

(22) J. A. Montgomery and H. J. Thomas, *ibid.*, **87**, 5442 (1965).

TABLE III
ULTRAVIOLET SPECTRA OF ADENINE NUCLEOSIDES

Compd (2′ substituent)	λ_{max} mμ (ε × 10⁻³) pH 1	pH 7	pH 13
	A. 9-Nucleosides, Fully Benzoylated[a]		
β-9-28 (SCH_2Ph)	206 (42.7), 237 (37.1), 293 (28.1)	208 (41.7), 233 (34.5), 287 (28.1)	218 (51.5), 275 sh, 304 (12.8)
β-9-29 (SBz)	208 (44.5), 242 (38.5), 287 (33.1)	207 (48.0), 237 (39.0), 281 (30.4)	218 (56.3), 276 sh, 303 (13.8)
β-9-30 (SMe)	238 (28.2), 294 (24.3)	207 (40.7), 238 (34.6), 286 (25.4)	218 (60.2), 276 sh, 304 (13.5)
36 (OBz)[b]	204 (45.7), 237 (38.0), 279 (20.9), 284 (21.1)	208 (37.5), 238 (33.4), 279 (19.9), 284 (20.0)	219 (45.6), 264 sh, 303 (9.74)
	B. 7-Nucleosides, Fully Benzoylated[a]		
7-28 (SCH_2Ph)	208 (38.6), 242 (35.7), 338 sh, 349 (26.2)	207 (50.3), 238 (40.4), 338 sh, 348 (24.7)	319 (11.0)
7-29 (SBz)	206 (44.5), 238 (34.2), 278 sh, 335 (15.9), 348 (16.0)	203 (52.2), 235 (35.7), 278 sh, 335 (14.6), 347 (14.2)	272 (10.0), 301 (9.10)
7-30 (SMe)	230 (43.4), 332 (20.8)	207 (37.9), 238 (33.9), 345 (21.1)	325 (14.9)
37 (OBz)[c]	207 (42.5), 242 (37.3), 338 sh, 350 (22.4)	238 (40.5), 338 sh, 345 (21.7)	276 sh, 321 (11.8)
	C. 7-Nucleosides, Mono-*N*-benzoyl[d]		
7-31 (SCH_2Ph)	251 (11.3), 287 (20.0)	335 (14.0)	325 (11.3)
38 (OH)	251 (9.45), 287 (20.0)	228 (14.3), 330 (18.0)	324 (13.2)
	D. Purines		
6-Benzamidopurine	251 (10.2), 288 (23.2)	235 (11.8), 248 (11.6), 286 (19.1)	279 (12.0)
Adenine	263 (13.1)		269 (12.3)
	E. 9-Nucleosides (Deacylated)[a]		
β-9-32 (SCH_2Ph)	260 (13.5)	261 (14.4)	260 (14.2)
α-9-32 (SCH_2Ph)	259 (11.4)	261 (12.0)	261 (12.2)
β-9-33 (SMe)	258 (15.0)	260 (14.6)	260 (15.5)
α-9-33 (SMe)	258 (14.3)	260 (14.2)	260 (15.5)
Adenosine	257 (14.6)	260 (14.4)	260 (14.9)
	F. 7-Nucleosides (Deacylated)[a]		
7-32	220 sh, 273 (10.7) [λ_{min} 240 (5.00)]	245 sh, 272 (7.80) [λ_{min} 234 (5.45)]	245 sh, 272 (7.45) [λ_{min} 240 (5.75)]
39[e]	273 (12.0) [λ_{min} 240 (4.20)]	245 sh, 270 (8.15) [λ_{min} 232 (4.00)]	245 sh, 270 (8.50) [λ_{min} 234 (4.95)]

[a] Stock solution prepared in ethanol and then diluted 1/10 with aqueous buffers; when the stock solution was in EtOH–water (1:1) containing 0.05 *M* HCl and then diluted with buffers, there were no significant changes in the spectra. [b] The spectrum in neutral ethanol lacked the maximum at 284 mμ and was as reported in ref 20. [c] The spectrum in neutral ethanol showed maxima at 231 and 330 mμ, as reported in ref 20; the absorption maxima beyond 300 mμ are generally less striking in ethanol than in water. [d] Stock solution prepared in ethanol and then diluted 1/10 with aqueous buffers; the maximum at pH 1 is attributed to 6-benzamidopurine formed by acid cleavage; when the stock solution was in EtOH–water (1:1) containing 0.05 *M* HCl, dilution with pH 7 and with pH 13 then also gave solutions with the maxima of 6-benzamidopurine. [e] See also ref 21 and 22.

along with its sodium salt in the reaction[14] with 3,5-di-*O*-benzoyl-D-arabinofuranosyl chloride (**12**), without concern about removing the disulfide formed. Purification of **14** or of its 2-*O*-mesylate **16**, both oils, was unnecessary before migration–rearrangement to give the 1-*O*-acetyl-2-*S*-methyl-2-thio-D-ribofuranose **19**. The acetate **19** was purified by chromatography and obtained as an α:β mixture (40:60). The β anomer could be separated by crystallization, but the anomeric mixture was equally good for conversion, again at Dry Ice temperatures, to the chloro sugar **22**. On treatment with bis(trimethylsilyl)-6-benzamidopurine and mercuric bromide, the nucleoside **30** was obtained predictably as a mixture of 7 and 9 isomers. In this case, both 7-**30** and 9-**30** were seen to be mixtures of their α and β anomers. In a run where there was no attempt at 7 → 9 isomerization by heating the reaction mixture, chromatography separated 34% of β-9-**30**, 10% of α-9-**30**, and 12% of α,β-7-**30** as an anomeric mixture. The β-9 and α-9 anomers were immediately differentiated in the nmr by $J_{1',2'}$ values of 9.0 and 7.0 Hz, respectively. Reliability of this means of assignment was again confirmed by desulfurization and debenzoylation of β-9-**30** to 2′-deoxyadenosine. The differentiation in coupling constants for the 9 isomers still held after debenzoylation to 2′-*S*-methyl-2′-thioadenosine (β-9-**33**, $J_{1'2'}$ = 9.0 Hz) and its α anomer (α-9-**33**, $J_{1',2'}$ = 7.0 Hz). These nucleosides were isolated through the picrate salts, and 2′-*S*-methyl-2′-thioadenosine was thereby obtained as a cystalline solid.

The $J_{1',2'}$ values could be determined for the anomers present in 7-**30**, but any assignment of their anomeric configuration was highly speculative. The major anomer could be crystallized and was debenzoylated to a cystalline nucleoside (one of the anomers of 7-**33**).

Ultraviolet Spectra.—Certain common features in the ultraviolet spectra were characteristic for each class of nucleosides (Table III) and served to distinguish them. For example, the fully benzoylated 9-nucleosides at pH 1 and 7 all exhibited maxima at 281–287 mμ, reminiscent of the absorption for 6-benzamidopurine. In contrast, the fully benzoylated 7-nu-

cleosides at pH 1 and 7 lacked a peak near 285 mμ but showed rather unexpected maxima at 335–338 mμ (sometimes a shoulder) and at 345–350 mμ. In all previous studies, adenine derivatives have generally not shown ultraviolet maxima much beyond 300 mμ. These maxima are apparently restricted to 7-substituted 6-*N*-acyladenines. Examples previously recorded without comment were **37**,[20] 6-*N*-benzoyl-7-benzyladenine,[23] and 6-*N*-pivaloyl-7-pivaloyloxymethyladenine.[24] The 9 and 7 isomers were more similar at pH 13, in presumably anionic forms; the spectra showed maxima at 303–304 and at 301-325 mμ, respectively. The unusual maxima at 330 and 335 mμ were retained in the mono-*N*-benzoyl 7-nucleosides **7-32** and **38** at pH 7. The high degree of acid sensitivity of these compounds was exhibited at pH 1, where the spectrum nearly coincided with that for 6-benzamidopurine. The rapid cleavage of the nucleoside link was further demonstrated when these compounds were dissolved in ethanol–0.1 *N* hydrochloric acid (1:1) as a stock solution followed by the usual dilution with appropriate buffers (Table III, footnote *d*). The other nucleosides were unaffected by acid in this treatment (Table III, footnote *a*). All the nucleosides appeared to be stable in base while the spectra were run. With the free, deacylated nucleosides, maxima of the 9 isomers near 260 mμ were characteristic for adenosine analogs. Maxima near 272 mμ were typical of either 7- or 3-substituted adenines, and the 7-nucleosides were characterized as such by the difference[21,22] between λ_{min} at pH 1 and at pH 7.

Experimental Section

Methods.—Melting points were determined on a Fisher-Johns hot stage and are uncorrected. Optical rotations were measured on 1% solutions in 1-dm tubes with a Perkin-Elmer Model 141 automatic polarimeter. Thin layer chromatography (tlc) was done with silica gel HF (E. Merck, Darmstadt) on 5 × 20 cm glass plates. The spots were detected under ultraviolet light. Preparative tlc was done with silica gel of 1 or 2 mm thickness on 20 × 20 cm plates. With multiple elutions, the plates were dried each time. In processing reactions, the bicarbonate solution used was saturated aqueous sodium bicarbonate. Organic solutions were dried with magnesium sulfate, which was removed by filtration. The Celite filter aid, used where mentioned, was a diatomaceous earth. Solutions were concentrated or evaporated *in vacuo* with a spin evaporator. Anhydrous tetrahydrofuran (THF) was distilled from calcium hydride.

Spectra Determination.—Ultraviolet spectra were determined with a Cary Model 11 recording spectrophotometer. Infrared spectra were determined routinely, as liquid film, or in Nujol mull for solids. Only bands important for structure assignment are reported. *O*-Benzoates generally showed stong bands near 5.8, 7.9, and 14.0 μ, even if not listed. *S*-Benzoates showed bands near 5.95, 8.3, 11.0, and 14.5 μ. *O*-Acetates and *O*-mesylates also showed the expected absorption bands. Nmr spectra were determined in chloroform-*d* solutions, unless otherwise noted, using 1% tetramethylsilane (τ 10.00) as internal reference (or as external reference with D_2O) with Varian A-60A and HR-100 spectrometers. Signals are described as singlet (s), doublet (d), triplet (t), quartet (q), or multiplet (m). Accuracy was ±0.05 ppm for chemical shifts and ±0.2 Hz for coupling constants. Integrated signal ratios were determined routinely and were as expected from the structural assignments. Benzoates commonly showed multiplets at τ 1.8–2.1 (2 aryl H's) and 2.3–2.7 (3 aryl H's), not listed for each compound. The cyclohexylidene compounds in Scheme I all showed signals at τ 8.1–8.8 (ring CH_2). The purines generally showed two singlets for H-2 and H-8, but these could not be individually assigned.

A. Pyranose Series. Benzyl 3,4-*O*-Cyclohexylidene-1-thio-α-D-arabinopyranoside (4).—To a solution of 18 g (70 mmol) of benzyl 1-thio-α-D-arabinopyranoside (**3**), mp 105–110° (lit.[5] 109°), in 225 ml of dry dimethylformamide was added 10.5 ml (123 mmol) of cyclohexanone, 22.5 ml (170 mmol) of triethyl orthoformate, and 0.5 ml of dioxane that had been saturated with hydrogen chloride.[25] The mixture was stirred at room temperature for 18 hr, neutralized with Dowex 2 (CO_3) ion exchange resin, and filtered. The filtrate was evaporated to dryness. The residue was mixed and extracted with 500 ml of refluxing cyclohexane. The hot cyclohexane was decanted and evaporated. The residue was dissolved in 100 ml of hot methanol, and water was added to the cloud point. The solution, clarified with a little more methanol, was seeded and chilled to yield 14.5 g (62%), mp 91–93°. Seed crystals and a sample for analysis were obtained in a previous experiment by preparative tlc in benzene–ether (9:1): mp 94–95.5°; $[\alpha]^{22}D$ +69° ($CHCl_3$); nmr τ 2.71 s (C_6H_5), 6.12 s (SCH_2Ph). Signals for the sugar ring protons were at τ 5.5–6.6 and could not be analyzed; the complex pattern within this narrow range appeared to be concentration dependent. A second crystal form was isolated, mp 122–123°, mmp 121–123°, and there was no change in optical rotation.

Anal. Calcd for $C_{18}H_{24}O_4S$: C, 64.3; H, 7.19; S, 9.53. Found: C, 64.2; H, 7.10; S, 9.80.

Benzyl 3,4-*O*-Cyclohexylidene-2-*O*-methanesulfonyl-1-thio-α-D-arabinopyranoside (5).—A stirred solution of 3.0 g (9.0 mmol) of **4** in 30 ml of pyridine was chilled to 0°, treated with 3.0 ml (18 mmol) of methanesulfonyl chloride, and stored at −5° for 18 hr. The chilled solution was stirred and treated dropwise during 5–10 min with 2 ml of water. Stirring was continued for 1 hr, and the mixture was partitioned between 200 ml of bicarbonate solution and 100 ml of chloroform. The chloroform layer was separated, washed with 100 ml of water, dried, and concentrated (bath not over 40°). The residual oil, 4.3 g, was used immediately or stored at −5°: nmr (C_6D_6) τ 2.84 m (C_6H_5), 5.16 q (2-H), 5.83 d (1-H), 5.96 q (5-H, eq), 6.05–6.3 (3-H, 4-H, SCH_2Ph), 6.81 q (5-H, ax), 7.27 s (OSO_2CH_3), $J_{1,2}$ = 9.0 Hz, $J_{2,3}$ = 6.5, $J_{3,4}$ estimated 5.1, $J_{4,5a}$ = 3.0, $J_{4,5e}$ = 2.5, $J_{5a,5e}$ = 12.5 Hz. If the reaction mixture was hydrolyzed by fast addition of water, there was heating and concomitant elimination to **7**, as evidenced by the ir absorption band at 6.22 μ.

Methyl 2-*S*-Benzyl-3,4-*O*-cyclohexylidene-2-thio-β-D-ribopyranoside (6).—A solution of the syrupy mesylate **5** (9 mmol, based on **4**) in 125 ml of anhydrous methanol was treated with 2.5 g (30 mmol) of solid sodium bicarbonate. The mixture was refluxed for 5 hr and evaporated to dryness. The residue was partitioned between 50 ml of chloroform and 50 ml of water. The chloroform extract was washed with 50 ml of water, dried, and concentrated to a residual oil, which was dried *in vacuo* at room temperature, 3.1 g (98%).

Anal. Calcd for $C_{19}H_{26}O_4S$: C, 65.1; H, 7.48; S, 9.15. Found: C, 64.9; H, 7.30; S, 9.44.

The nmr spectrum revealed the presence of 10–15% of the α anomer, which was separated by chromatography. A 6.0-g sample was added to a column (2.5 × 50 cm) of 120 g of silica gel in benzene. The column was eluted with 1.2 l. of benzene–ether (98:2), and the fractions were discarded. An additional 1.2 l. of eluent, gradually changed to benzene–ether (95:5), afforded 4.0 g of the β anomer **6**: $[\alpha]^{22}D$ +25° ($CHCl_3$); nmr τ 2.57–2.80 m (C_6H_5), 5.21 d (1-H), 5.65 q (3-H), 5.90 m (H-4), 6.07 q (SCH_2Ph), 6.40 t (5-H_2), 6.52 s (OCH_3), 7.37 q (2-H), $J_{1,2}$ = 7.5 Hz, $J_{2,3}$ = 3.0, $J_{3,4}$ = 6.8, $J_{4,5a}$ and $J_{4,5b}$ = 2.8 and 3.0 Hz.

Anal. Found: C, 64.9; H, 7.53.

Further elution with benzene–ether (95:5) afforded 0.3 g with a β/α ratio of 3:1. A 0.28-g portion was subjected to preparative tlc on five plates (1-mm thick), developed with benzene–ether (98:2). The faster moving band afforded an additional 163 mg of **6**. The slower band afforded 52 mg of the α anomer: $[\alpha]^{23}D$ −0.6° ($CHCl_3$); nmr τ 2.50–2.82 m (C_6H_5), 5.50 d (1-H), 6.45 q (5-H_2), 6.62 s (OCH_3), 7.08 t (2-H), $J_{1,2}$ = $J_{2,3}$ = 4, $J_{4,5}$ = 3.5 Hz.

Methyl 3,4-*O*-Cyclohexylidene-2-thio-β-D-ribopyranoside (9).—S-Debenzylation of anomerically pure **6** as described below for

(23) J. A. Montgomery and H. J. Thomas, *J. Heterocycl. Chem.*, **1**, 115 (1964).

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

(25) S. Chladek and J. Smrt *Collect. Czech. Chem. Commun.*, **28**, 1301 (1963).

25 afforded 86% of the thiol, ir 3.89 μ (weak, SH), which was immediately benzoylated.

Methyl 2-*S*-Benzoyl-3,4-*O*-cyclohexylidene-2-thio-β-D-ribopyranoside (10).—The thiol 9 was benzoylated with an equal weight of benzoyl chloride in 10 vol of pyridine. The product was processed as for 26 and crystallized from methanol–water (44% yield), mp 103–106°, after seeding with a sample isolated by preparative tlc in benzene–ether (95:5). A sample for analysis melted at 106–107.5°; $[\alpha]^{22}D$ −126° ($CHCl_3$); nmr (C_6D_6) τ 5.12 d (1-H), 5.60 q (3-H), 5.70 q (2-H), 6.17 pair of triplets (4-H), 6.40 uneven t (5-H_2), 6.80 s (OCH_3), $J_{1,2}$ = 7.6, $J_{2,3}$ = 3.0, $J_{3,4}$ = 7.0, $J_{4,5}$ = 2.5 Hz.

Anal. Calcd for $C_{19}H_{24}O_5S$: C, 62.6; H, 6.64; S, 8.80. Found: C, 62.6; H, 6.76; S, 8.89.

1-*O*-Acetyl-2-*S*-benzyl-3,4-*O*-cyclohexylidene-2-thio-β-D-ribopyranose (8).—To a solution of 5.4 g (13 mmol) of the mesylate in 65 ml of acetic anhydride and 16 ml of acetic acid was added 11 g of potassium acetate. The mixture was heated on a steam bath for 2 hr, cooled, and poured into 800 ml of crushed ice. The product was extracted with chloroform and processed as described below for 17. The yellow oil (5.0 g) showed no mesylate absorption in the ir, but a weak band at 6.22 μ indicated the presence of a little 1,2 olefin. The nmr showed that three products were present, the β-1-*O*-acetate 8 (80%), the anomeric α-1-*O*-acetate (10%), and the 1,2 olefin 7 (10%). A chromatographic column (42 × 2.5 cm) of 100 g of silica gel in benzene, eluted with 750 ml gradually changed from benzene to benzene–ether (99:1), afforded 0.40 g (9.4%) of the olefin 7, **2-*S*-benzyl-3,4-*O*-cyclohexylidene-2-thio-D-arabinal**: $[\alpha]^{20}D$ +125° ($CHCl_3$); ir 6.22 μ (strong, trans S–C=C–O); nmr τ 2.72 s (C_6H_5), 3.42 s (1-H), 5.52 d (tentatively, 3-H, $J_{3,4}$ = 5.5 Hz), 6.1 s (SCH_2-Ph), 5.55–6.65 m (4-H, 5-H_2).

Anal. Calcd for $C_{18}H_{22}O_3S$: C, 67.9; H, 6.96; S, 10.07. Found: C, 67.8; H, 6.86; S, 9.82.

Continued elution with 1.5 ml of benzene–ether, gradually changed from 98:2–96:4, afforded 2.4 g of the 1-*O*-acetate. The β anomer 8 crystallized from 20 ml of methanol: 1.95 g (40%); mp 85–87°; $[\alpha]^{20}D$ −22° ($CHCl_3$); nmr τ 2.66 s (C_6H_5), 3.82 d (1-H), 5.52 q (3-H), 5.80 doublet of triplets (4-H), 6.09 s (SCH_2Ph), 6.30 d (5-H_2), 7.22 q (2-H), 7.90 s (OAc), $J_{1,2}$ = 8.2, $J_{2,3}$ = 2.6, $J_{3,4}$ = 7.1, $J_{4,5}$ = 2.3 Hz.

Anal. Calcd for $C_{20}H_{26}O_5S$: C, 63.5; H, 6.92; S, 8.47. Found: C, 63.6; H, 6.95; S, 8.44.

B. Furanose Series, *S*-Benzyl. 3,5-Di-*O*-benzoyl-D-arabinofuranosyl Chloride (12).—A suspension of 42 g (91 mmol) of 1,3,5-tri-*O*-benzoyl-β-D-arabinofuranose[13] (11) in 1 l. of anhydrous ether was saturated at 0° with anhydrous hydrogen chloride. With exclusion of moisture, the solution was kept at 0° for 3 days, treated again with hydrogen chloride and kept at 0° for 24 hr, treated a third time, stored overnight, and evaporated to dryness. The residue was dissolved in 200 ml of dichloromethane, and the solution was washed with 500 ml of saturated, ice-cold bicarbonate solution, dried, and evaporated to dryness *in vacuo*. The residual oil (35 g) was used without delay.

Benzyl 3,5-Di-*O*-benzoyl-1-thio-α-D-arabinofuranoside (13).—Sodium benzyl mercaptide was prepared by adding 5.0 ml (39 mmol) of α-toluenethiol to a solution of 1.8 g (33 mmol) of sodium methoxide in 50 ml of anhydrous methanol and evaporating to dryness at 60–70° *in vacuo*. To the white residue suspended in 30 ml of anhydrous THF was added, while chilling in ice, a solution of 3,5-di-*O*-benzoyl-D-arabinofuranosyl chloride (32 mmol, based on 11) in 100 ml of anhydrous THF. The mixture was stirred in the ice bath for 40 min and at room temperature for 20 min and then was neutralized with 2.05 g of acetic acid and concentrated. The residue was dissolved in 100 ml of ether and washed with 200 ml of bicarbonate solution and with 200 ml of water and was dried and concentrated. The residual yellow oil (15.8 g) was dissolved in 40 ml of methanol. The solution, seeded with 13 and stored at −5° for 8 days, afforded 4.1 g (28%): mp 102–104°; ir 2.88 (OH), 5.83 (C=O, normal OBz), 5.93 μ (C=O, H-bonded OBz); nmr τ 4.72 d (1-H), 4.83 m (3-H), 5.66 t (2-H), 6.13 d (SCH_2Ph), $J_{1,2}$ = 2.7, $J_{2,3}$ = 2.8 Hz.

In another experiment a sample for analysis was purified by column chromatography on silica gel; dibenzyl disulfide was first eluted with benzene, and 13 was eluted with benzene–ether (95:5) and recrystallized from methanol, mp 103.5–105°, $[\alpha]^{23}D$ +249° ($CHCl_3$).

Anal. Calcd for $C_{26}H_{24}O_6S$: C, 67.2; H, 5.21; S, 6.90. Found: C, 67.3; H, 5.21; S, 7.20.

Benzyl 3,5-Di-*O*-benzoyl-2-*O*-methanesulfonyl-1-thio-α-D-arabinofuranoside (15).—A solution of 0.65 g (1.4 mmol) of crystalline 13 in 10 ml of dry pyridine was chilled in ice, stirred, treated with 0.65 ml of methanesulfonyl chloride, and stored at −5° for 18 hr. The solution was hydrolyzed with 2 ml of water added in drops every 2–3 min, while stirring at ice temperature. Chloroform (30 ml) was added, and the solution was washed with 50 ml of bicarbonate solution and with 50 ml of water and was dried and concentrated without heating. The residue (0.80 g, 105%) traveled as a single spot on tlc in benzene–ether (90:10) when detected by both ultraviolet light and charring with sulfuric acid spray: nmr τ 4.45 broad s (1-H, 2-H), 4.79 t (3-H), 5.29 broad s (4-H, 5-H_2), 6.11 s (SCH_2Ph), 7.01 s (OSO_2CH_3), $J_{2,3}$ = $J_{3,4}$ = 1.5 Hz; $[\alpha]D$ +108° ($CHCl_3$). The compound decomposed on attempted chromatographic purification but could be stored for 1 week with little decomposition (darkening, appearance of slight OH absorption in the infrared). There was no decomposition under the conditions of its formation; a sample in pyridine-d_5 solution was stored overnight with no change in the nmr spectrum.

1-*O*-Acetyl-3,5-di-*O*-benzoyl-2-*S*-benzyl-2-thio-α,β-D-ribofuranoside (17).—To 0.68 g (1.3 mmol) of mesylate 15 was added 2 ml of glacial acetic acid, 8 ml of acetic anhydride, and 0.9 g of potassium acetate. The mixture was heated on a steam bath for 2 hr, cooled, and poured into 50 ml of ice water and stirred for 30 min. The product was extracted with two 30-ml portions of chloroform. The extracts were washed with two 50-ml portions of bicarbonate solution (foaming) and with 50 ml of water, dried, and concentrated. (Any remaining acetic anhydride was destroyed by treatment with 2 ml of pyridine and 10 ml of methanol, concentration, and partition of the residue between chloroform and bicarbonate as before.) The yield of residual product was 0.58 g (90%), $[\alpha]^{24}D$ −3.7° ($CHCl_3$). In different runs the anomeric ratio, β:α, varied from 60:40 to 70:30 according to the nmr spectrum: nmr for β, τ 2.79 s (C_6H_5 of benzyl), 3.63 d (1-H), 4.32 q (3-H), 6.20 s (SCH_2Ph), 6.25 q (2-H), 8.10 s (OAc), $J_{1,2}$ = 2.5, $J_{2,3}$ = 6.8, $J_{3,4}$ = 4.6 Hz; nmr for α, τ 2.77 s (C_6H_5 of benzyl), 3.54 d (1-H), 4.36 q (3-H), 6.25 s (SCH_2Ph), 6.55 q (2-H), 7.88 s (OAc), $J_{1,2}$ = 4.5, $J_{2,3}$ = 6.8, $J_{3,4}$ = 1.5 Hz.

3,5-Di-*O*-benzoyl-2-*S*-benzyl-2-thio-D-ribofuranosyl chloride (20) was prepared from the oily α,β-1-*O*-acetate 17, as described below for 22, held under vacuum 2 hr, and then used immediately.

6-Chloro-9-(2-*S*-benzyl-3,5-di-*O*-benzoyl-2-thio-α,β-D-ribofuranosyl)-9*H*-purine (9-27).—To 385 mg (0.760 mmol) of α,β-1-*O*-acetate 17 was added 148 mg (0.970 mmol) of 6-chloropurine (90% pure, from ultraviolet extinctions) and 5 mg of chloroacetic acid. The materials were intimately mixed, forming a gum, and were fused under vacuum by immersion in a bath at 172–175° for 90 sec. The cooled residue was dissolved in 5 ml of chloroform. On chilling, the solution deposited 57 mg of unreacted 6-chloropurine (assume 91 mg reacted, 78%). Concentration of the filtrate afforded 460 mg of a dark oil. The nmr spectrum disclosed the presence of unreacted 1-acetate 17, 5-(benzoyloxymethyl)-2-(*S*-benzyl)furan-2-thiol (34a), and nucleoside 27, in the ratio 5:54:41.

The nucleoside fraction was isolated by preparative tlc of the residue on two plates (2-mm thick), developed with $CHCl_3$–MeOH (98:2), dried, and developed again. The band, R_f 0.8–0.9, contained sugar and the furan. The band, R_f 0.5, was eluted with $CHCl_3$–MeOH (9:1) to yield 120 mg (38%) of nucleoside. The anomeric ratio β:α was 2:1 by nmr analysis. A solution in 5 ml of methanol chilled to −10° afforded 18 mg, mp 148–160°, recrystallized again from 2 ml to give 14 mg (4%) of α-9-27: mp 160–163°; ir 5.78, 5.83 (C=O), 6.30, 6.39 μ (purine aryl); nmr 1.23 s and 1.49 s (H-2, H-8), 2.82 s (C_6H_5 of benzyl), 3.18 d (1-H), 4.33 q (3-H), 5.95 t (2-H), 6.32 s (SCH_2Ph), $J_{1,2}$ = 7.0, $J_{2,3}$ = 6.5, $J_{3,4}$ = 1.6, $J_{4,5}$ = 4.5 Hz.

The mother liquor residue was enriched in β-9-27. From another experiment the β:α ratio was now 4:1: nmr β, for τ 1.52 s and 1.89 s (H-2, H-8), 3.03 s (C_6H_5 of benzyl), 3.84 d (1-H), 4.14 q (3-H), 5.51 q (2-H), 6.42 s (SCH_2Ph), $J_{1,2}$ = 9.0, $J_{2,3}$ = 6.0, $J_{3,4}$ = 1.8 Hz.

5-(Benzoyloxymethyl)-2-*S*-benzylfuran-2-thiol (34a).—In one experiment the preparative tlc plates (from 9-27, above) were developed first with benzene to separate this elimination product, R_f 0.9, from the 1-acetate 17, R_f 0.8 (the nucleoside had R_f 0.05 in this system). Elution with chloroform afforded a yellow oil, which darkened on standing: ir 5.82, 7.90, 14.1 (strong, OBz), 6.28, 6.35 (aryl), 6.70, 6.90 μ (benzyl); nmr τ 1.8–2.1 and 2.4–2.7

(OBz), 1-H obscured but possibly at 2.51 s, 2.77 s (C_6H_5 of benzyl), 3.65 s (3-H), 4.79 s (5-H_2), 6.15 s (SCH_2Ph).

6-Benzamido-9(7)-(2-*S*-benzyl-3,5-di-*O*-benzoyl-2-thio-α,β-D-ribofuranosyl)-9*H*(7*H*)-purine (28). I.—To a solution of 0.90 g (1.8 mmol) of chloro sugar **20** in 10 ml of dichloromethane (dried over molecular sieve) was added 0.45 g (1.9 mmol) of 6-benzamidopurine and 3 g of molecular sieve (4A, 1/16-in. diam). The mixture was protected from moisture, stirred at room temperature for 7 days, and filtered through Celite. The filter cake was washed with two 25-ml portions of dichloromethane. Concentration of the combined filtrates afforded 0.8 g (65%) of an oil. Preparative tlc on four plates (2-mm thick) developed twice with $CHCl_3$–MeOH (98:2) afforded a nucleoside band, R_f 0.5, which was eluted to give 70 mg (6%): ir 5.79 (C=O), 6.12, 6.32 μ (purine aryl). The nmr spectrum showed it was mainly α-**9-28** (α:β ratio 9:1): nmr for α, τ 1.21 s and 1.61 s (H-2, H-8), 2.83 s (C_6H_5 of benzyl), 3.10 d (1′-H), 4.37 q (3′-H), 5.95 t (2′-H), 6.32 s (SCH_2Ph), $J_{1,2}$ = 7.0, $J_{2',3'}$ = 6.8, $J_{3',4'}$ = 1.5, $J_{4',5'}$ = 4.2 Hz.

II.—A mixture of chloro sugar **20** (22 mmol, based on 1-acetate **17**), 13 g (37 mmol) of freshly distilled bis(trimethylsilyl)-6-benzamidopurine,[26,27] and 8.3 g (23 mmol) of mercuric bromide in 250 ml of dry benzene was stirred. After 1 min, the cloudy mixture became clear. The solution was stirred for 6 days at room temperature and evaporated. The residue was slurried with 250 ml of chloroform–methanol (4:1) and the mixture filtered through Celite to remove 6-benzamidopurine. The filtrate was evaporated and the residue redissolved in 200 ml of chloroform. The solution was washed with 100 ml of aqueous 30% potassium iodide and with 300 ml of water, dried, and concentrated. The residual foamed glass, 18 g, showed ir absorption bands for both **9-28** and **7-28**; tlc in $CHCl_3$–MeOH (95:5) showed nucleoside spots at R_f 0.7 (**9-28**) and R_f 0.5 (**7-28**) in addition to contaminants at the solvent front (sugar derivatives) and origin (6-benzamidopurine).

The crude product was chromatographed on a column (37 × 4.5 cm) of 200 g of silica gel in benzene. Elution with 2.5 l. of benzene afforded sugar impurities in a first fraction which was discarded. Additional 1.5 l. of benzene afforded 2.8 g (18%) of nucleoside, identified as **9-28** (with a β:α ratio of 4:1, by nmr), containing a little **7** isomer, by infrared analysis and tlc. Finally, elution with 1.2 l. of benzene gave another 2.8 g (total yield 5.6 g, 37%) of nucleoside consisting of **9** and **7** isomers in nearly equal amounts, from the ir spectrum and tlc.

The mixture was separated by preparative tlc of this latter fraction on 12 plates (2-mm thick), each developed four times with $CHCl_3$–MeOH (98:2). Elution of the faster band with $CHCl_3$–MeOH (95:5) afforded 0.9 g of **9** isomer, as a glass, characterized by the uv spectrum and by normal ir bands at 6.22 and 6.31 μ (medium, purine aryl) in addition to strong benzoate bands. The nmr spectrum showed it was mainly β-**9-28**, with a β:α ratio of 85:15: for β, τ 1.45 s (2-H or H-8; another singlet was obscured by the aryl H's perhaps at 2.85), 2.97 s (C_6H_5 of benzyl), 3.78 d (1′-H), 4.23 q (3′-H), 6.45 s (SCH_2Ph), $J_{1',2'}$ = 9.0, $J_{2',3'}$ = 6.5 Hz, $J_{3',4'}$ = 1.5 Hz.

In another experiment a sample for analysis was obtained by preparative tlc directly on the crude product.

Anal.[28] Calcd for $C_{38}H_{31}N_5O_6S$: C, 66.6; H, 4.56; N, 10.2; S, 4.67. Found: C, 63.10; H, 4.36; N, 9.72; S, 4.77.

Elution of the slower band from the plates afforded 1.2 g of **7-28**, as a glass, characterized by uv and by unexpected ir bands at 6.08 and 7.58 (strong), 6.23 and 6.40 (medium), in addition to benzoate bands at 5.78, 7.85, and 14.05 μ. The anomeric composition could not be determined from the nmr.

Anal.[28] Found: C, 64.9; H, 4.32; N, 9.99.

9-(2-*S*-Benzyl-2-thio-α,β-D-ribofuranosyl)-9*H*-adenine (9-31). I. **From β(α)-9-27.**—A solution of 0.41 g (0.67 mmol) of **9-27** (isolated by preparative tlc, and with β:α ratio of 4:1 after some α-**9-27** was separated by crystallization) in 15 ml of methanol was saturated at 5° with anhydrous ammonia, heated in a steel bomb at 100° for 15 hr, and concentrated. The residue was triturated with two 20-ml portions of ether (to remove methyl benzoate) and then with 10 ml of hot chloroform. Somewhat surprisingly the nucleoside dissolved; insoluble ammonium chloride was left. The residue obtained on evaporation of the chloroform showed two components by tlc in $CHCl_3$–MeOH (3:1), R_f 0.8 and 0.9. These were separated by preparative tlc on two plates (2-mm thick) developed with $CHCl_3$–MeOH (82:18). Eluted with $CHCl_3$–MeOH (7:3), the faster band afforded 170 mg of β-**9-31** contaminated with benzamide. Crystallization from 2 ml of acetone gave 35 mg (14%), mp 114–120°; recrystallization yielded 31 mg, dried at 60° (1 mm), mp 156–158°. Acetone of solvation was observed in the ir and nmr spectra and elemental analysis: ir 5.86 (acetone C=O), 6.03 (strong, NH_2), 6.28 μ (strong, purine aryl); nmr, in acetone-d_6 exchanged with D_2O, τ 1.80 s and 1.83 s (2-H, 8-H), 2.97 m (C_6H_5), 3.97 d (1′-H), 5.45 q (3′-H), 5.7 q (4′-H), 6.18 d (5′-H_2), 6.05 q (2′-H), 6.43 d (SCH_2Ph, J = 1 Hz), $J_{1',2'}$ = 9.3, $J_{2',3'}$ = 5.0, $J_{3',4'}$ = 1.0, $J_{4',5'}$ = 2.5 Hz.

Anal. Calcd for $C_{14}H_{13}N_5O_2S \cdot C_3H_6O$: C, 55.8; H, 5.39; N, 16.3. Found: C, 55.7; H, 5.84; N, 16.2.

Elution of the slower band afforded 20 mg, crystallized from acetone to give 8 mg of α-**9-31**, mp 100–114°. Further recrystallization (adding material from another experiment) raised the mp to 116–120°, a hydrate even after drying at 60° (1 mm): ir 6.00 (NH_2), 6.22 μ (purine aryl); nmr, in acetone-d_6 exchanged with D_2O, τ 1.60 s and 1.69 s (2-H, 8-H), 2.75 s (C_6H_5), 3.42 d (1′-H), 5.48 q (3′-H), 5.67 m (4′-H), 6.24 d (5′-H_2), 5.85 q (2′-H), 6.20 s (SCH_2Ph), $J_{1',2'}$ = 7.5, $J_{2',3'}$ = 6.0, $J_{3',4'}$ = 2.0, $J_{4',5'}$ = 3.7 Hz.

II. **From β(α)-9-28.**—To a solution of 1.4 g (2.0 mmol) of β-**9-28** (containing 15% of α-**9-28**) in 20 ml of methanol was added 4 ml of 1 *N* sodium methoxide in methanol. The solution was refluxed for 2 hr. The dark solution was cooled, neutralized with 4 ml of 1 *N* acetic acid in methanol, and evaporated to dryness. The residue was triturated with two 30-ml portions of hot cyclohexane. The insoluble residue was dissolved in 30 ml of hot acetone and filtered. The filtrate was reduced in volume to 15 ml and chilled to give 395 mg (50%) of β-**9-31**, dried at 100° (1 mm), mp 153–155°; nmr same as β-**9-31** from I.

7-(2-*S*-Benzyl-2-thio-D-ribofuranosyl)-7*H*-adenine (7-31).—A solution of 0.70 g (1.0 mmol) of **7-28** in 50 ml of anhydrous methanol was treated with 0.10 g (1.8 mmol) of sodium methoxide, refluxed for 3 hr, cooled, and neutralized with about 3 ml of IRC 50 resin (H), which was then removed on a filter. The filtrate was concentrated and the residue was triturated with cyclohexane to remove methyl benzoate. The solid was collected on a filter: 0.24 g; tlc in $CHCl_3$–MeOH (8:2) showed two spots, R_f 0.6 and 0.8.

Preparative tlc on four plates (2-mm thick), developed and eluted with the above solvent, afforded **7-31** from the slower band; it was crystallized from ethanol to give 44 mg (9%): mp 211–216°; ir 6.05 and 6.23 (strong), 6.41 and 6.58 μ (medium).

Anal. Calcd for $C_{17}H_{19}N_5O_3S$: C, 54.7; H, 5.13; N, 18.8; S, 8.58. Found: C, 54.5; H, 5.11; N, 18.9; S, 8.69.

The faster band afforded **6-benzamido-7-(2-*S*-benzyl-2-thio-D-ribofuranosyl)-7*H*-purine (7-32)** which was crystallized from ethanol–water (2:1), giving 95 mg (20%): mp 110–115°; ir 6.10 (strong), 6.27 and 6.40 μ (medium). The anomeric composition could not be determined from the nmr.

Anal. Calcd for $C_{24}H_{23}N_5O_4S$: C, 60.4; H, 4.86; N, 14.7; S, 6.71. Found: C, 60.2; H, 4.75; N, 14.6; S, 6.33.

C. ***S*-Benzoyl Series. Methyl 3,5-Di-*O*-benzoyl-2-*S*-benzyl-2-thio-α,β-D-ribofuranoside (23).**—To 5.2 g (9.6 mmol) of mesylate **15** in 500 ml of anhydrous methanol was added 7 g of Drierite ($CaSO_4$ drying agent) and 6.0 g (22 mmol) of silver carbonate. The mixture, protected from moisture and light, was refluxed for 18 hr and then filtered through Celite. The Celite was washed with 100 ml of chloroform, and the combined filtrate was concentrated. The residue in 50 ml of chloroform solution was washed with 200 ml of 2 *M* ammonium hydroxide and with 100 ml of water, dried, and concentrated. To remove silver salts from the dark residual oil (4.6 g), a second washing with ammonium hydroxide of a chloroform solution was required, followed by filtration of a benzene solution through Celite. The yellow oil (4.2 g, 92%) was a mixture of anomers (β:α ratio 3:2): nmr for β-**23**, τ 2.68 s (C_6H_5 of benzyl), 4.38 q (3-H), 4.98 d (1-H), 6.19 s (SCH_2Ph), 6.40 q (H-2), 6.63 s (OCH_3), $J_{1,2}$ = 3.2, $J_{2,3}$ = 6.5, $J_{3,4}$ = 4.2 Hz; nmr for α-**23**, τ 2.68 s (C_6H_5 of benzyl), 4.58 q (3-H), 5.10 d (1-H), 6.27 s (SCH_2Ph), 6.58 s (OCH_3), 6.73 q (2-H), $J_{1,2}$ = 4.8, $J_{2,3}$ = 7.1, $J_{3,4}$ = 2.5 Hz.

Methyl 2-*S*-Benzyl-2-thio-α,β-D-ribofuranoside (24).—To 4.2 g

(26) T. Nishimura and I. Iwai, *Chem. Pharm. Bull.*, **12**, 352 (1964).

(27) I. Iwai, T. Nishimura, and B. Shimizu in "Synthetic Procedures in Nucleic Acid Chemistry," Vol. I., W. W. Zorbach and R. S. Tipson, Ed., Interscience, New York, N. Y., 1968, p 135.

(28) Low values for carbon suggested a little solvent was retained in the glass, but an acceptable nitrogen (and sulfur) composition of the nucleoside was determined.

(8.6 mmol) of the dibenzoate **23** in 500 ml of 50% aqueous methanol was added 9 g of potassium hydroxide, and the mixture was refluxed for 2 hr, neutralized with CO_2, and concentrated. The semisolid residue was dissolved in 30 ml of water, and the product was extracted with two 50-ml portions of chloroform. The extracts were washed with 50 ml of water, dried, and concentrated. The yellow oil weighed 2.2 g (95%): nmr τ, for β, 5.16 d (1-H), 5.82 q (3-H), 6.22 s (SCH_2Ph), 6.65 s (OCH_3), 6.72 q (2-H), $J_{1,2}$ = 3.4, $J_{2,3}$ = 5.6, $J_{3,4}$ = 3.4 Hz; nmr τ, for α, 5.17 d (1-H), 6.08 q (3-H), 6.30 s (SCH_2Ph), 6.59 s (OCH_3), 6.88 q (2-H), $J_{1,2}$ = 5.0, $J_{2,3}$ = 6.4, $J_{3,4}$ = 2.5 Hz; nmr for both, 2.70 s (C_6H_5 of benzyl).

Anal. Calcd for $C_{13}H_{18}O_4S \cdot 0.04CHCl_3$: C, 56.9; H, 6.61; S, 11.7; Cl, 1.55. Found: C, 56.8; H, 6.75; S, 11.9; Cl, 0.37.

Methyl 2-Thio-α,β-D-ribofuranoside (25).—A solution of 3.5 g (13 mmol) of 2-benzylthio compound **24** in 15 ml of anhydrous 1,2-dimethoxyethane was added dropwise to a solution of 2.0 g (90 mmol) of sodium in 100 ml of liquid ammonia under a Dry Ice–acetone condenser, excluding moisture. The mixture was stirred at reflux for 1 hr, retaining the blue color. (If insufficient sodium was used, the solution turned yellow. In the absence of 1,2-dimethoxyethane as cosolvent, the reaction failed to go to completion.) The excess sodium was decomposed by adding 5 g of ammonium chloride, and the ammonia was evaporated under a stream of nitrogen. Water (15 ml) was added to the residue. The solution was neutralized to pH 6–7 with acetic acid and was extracted with ten 30-ml portions of chloroform. The combined extracts were dried and concentrated to a yellow oil: 1.1 g (50%); ir 3.9 μ (weak, SH); nmr τ 5.04 d (1-H of α, $J_{1,2}$ = 5.0 Hz), 5.09 d (1-H of β, $J_{1,2}$ = 2.8 Hz), 6.52 s (OCH_3, both kinds); the β:α ratio was 3:2. An additional 0.7 g (total yield 80%) was obtained by continuous extraction of the water layer with chloroform overnight. Each fraction was benzoylated immediately.

Methyl 2-*S*-Benzoyl-3,5-di-*O*-benzoyl-2-thio-α,β-D-ribofuranoside (26).—To 1.1 g (6.1 mmol) of the thiol **25** in 20 ml of dry pyridine was added, with stirring and ice cooling, 3.0 ml (26 mmol) of benzoyl chloride. The mixture was stirred at room temperature overnight, chilled, and treated with 1 ml of water dropwise to hydrolyze the excess benzoyl chloride. It was then diluted with 50 ml of bicarbonate solution and extracted with 50 ml of chloroform. The extract was washed with 50 ml of water, dried, and concentrated to an oil, 2.7 g (90%). The ratio β:α was 62:38 by nmr analysis: τ for β, 3.98 m (3-H), 4.80 d (1-H, $J_{1,2}$ = 2.5 Hz), 6.51 s (OCH_3); τ for α, 4.22 q (3-H, $J_{2,3}$ = 7, $J_{3,4}$ = 2 Hz), 4.70 d (1-H, $J_{1,2}$ = 4.5 Hz), 6.49 s (OCH_3).

Acetyl 2-*S*-Benzoyl-3,5-di-*O*-benzoyl-2-thio-α,β-D-ribofuranose (18).—A solution of 3.8 g (7.7 mmol) of **26** in 50 ml of acetic anhydride and 10 ml of acetic acid was chilled to −20° and treated, while stirring, with 0.4 ml of concentrated sulfuric acid. The solution was stored overnight at −20° (to avoid freezing at a lower temperature) and poured into 50 ml of ice water. The mixture was stirred for 30 min and extracted with two 30-ml portions of chloroform. The extracts were washed with 50 ml of bicarbonate solution, dried, and concentrated. The residual oil, according to the infrared spectrum, retained a little acetic anhydride, which was decomposed by adding 1 ml of pyridine and 15 ml of methanol and evaporating the solution. The oil was partitioned again with 30 ml of chloroform and 50 ml of bicarbonate solution, washed with 30 ml of water, and recovered, 3.9 g (97%). The nmr spectrum showed no OMe signal; the β:α ratio varied from 2:3 to 1:6 in different runs: nmr τ, for β, 3.49 d (1-H), 3.98 q (3-H), 5.09 q (2-H), 8.00 s (OAc), $J_{1,2}$ = 3.0, $J_{2,3}$ = 6.3, $J_{3,4}$ = 1.4 Hz; for α, 3.28 d (1-H), 4.15 q (3-H), 5.09 q (2-H), 7.81 s (OAc), $J_{1,2}$ = 4.7, $J_{2,3}$ = 6.7, $J_{3,4}$ = 1.5 Hz.

2-*S*-Benzoyl-3,5-di-*O*-benzoyl-2-thio-D-ribofuranosyl chloride (21) was prepared in quantitative yield from the α,β-1-*O*-acetate **18** as described for **22**, held under vacuum for 2 hr, and used immediately.

6-Benzamido-9-(2-*S*-benzoyl-3,5-di-*O*-benzoyl-2-thio-β-D-ribofuranosyl)-9*H*-purine (β-9-29).—A mixture of 3.7 g (7.5 mmol, based on α,β-1-*O*-acetate **19**) of chloro sugar **21**, 4.0 g (10 mmol) of bis(trimethylsilyl)-6-benzamidopurine,[26,27] 3.0 g (8.3 mmol) of mercuric bromide, and 150 ml of dry benzene was stirred. It became clear after a few minutes and was stirred at room temperature for 3 days and then at reflux for 2 days to isomerize most of the 7-29 to β-9-29. The solution was concentrated, and the residue was dissolved in 50 ml of chloroform and filtered through Celite to remove 6-benzamidopurine. The filtrate was washed with 50 ml of aqueous 30% potassium iodide and with 50 ml of water, dried, and concentrated. The residue (4.0 g) was analyzed by tlc in chloroform–ethyl acetate (2:1); it contained a little sugar impurity, R_f 0.8; mostly β-9-29, R_f 0.6; some 7-29, R_f 0.4; and a little 6-benzamidopurine, R_f 0.0.

The product was chromatographed on a column (40 × 2.5 cm) of 80 g of silica gel in benzene. Elution with 1 l. gradually changed from benzene to benzene–ethyl acetate (9:1) afforded 0.64 g of benzoic acid and an elimination product, presumably **34b**, characterized by its spectra: ir 5.80, 7.86, 14.02 (OBz), 5.92, 8.28, 11.10, 14.58 μ (SBz); nmr τ 1.71–2.25 and 2.35–2.90 m (C_6H_5 of benzoyl), 2.35 s (1-H), 3.36 s (3-H), 4.64 s (5-H_2).

Additional 3.5 l. of eluent, gradually changed from benzene–ethyl acetate 9:1 to 8:2, afforded 1.92 g of nucleoside; the presence of a little 7 isomer could be seen in the ir. The nucleoside mixture was resolved by preparative tlc on ten plates (2-mm thick) and developed twice with $CHCl_3$–MeOH (98:2). Elution of the faster band with $CHCl_3$–MeOH (90:10) afforded 1.3 g (25%) of β-9-29 as a foamed glass. In addition to strong OBz bands in the ir at 5.80, 7.9, 14.05 μ and medium SBz bands at 5.97, 8.25, 11.03, and 14.53 μ, purine ring bands at 6.22 and 6.32 μ (medium) were characteristic for the 9 isomer: nmr τ 1.28 s and 1.70 s (2-H and 8-H), 3.38 d (1'-H), 3.95 (3'-H), 4.51 (2'-H), $J_{1',2'}$ = 9.0, $J_{2',3'}$ = 5.8, $J_{3',4'}$ = 1.4 Hz. No signals attributable to the α anomer could be detected.

Anal. Calcd for $C_{38}H_{29}N_5O_7S \cdot {}^1/_2H_2O$: C, 64.4; H, 4.27; N, 9.88; S, 4.52. Found: C, 64.5; H, 4.27; N, 9.84; S, 4.13.

6-Benzamido-7-(2-*S*-benzoyl-3,5-di-*O*-benzoyl-2-thio-D-ribofuranosyl)-7*H*-purine (7-29).—From another experiment in which the reaction mixture was not heated before work-up, the ratio of 9-29 to 7-29 was 5:2, isolated by preparative tlc. Elution of the slower moving band afforded 10 mg of 7-29, identified by the uv (Table III) and ir spectra; in addition to strong OBz bands, medium SBz bands, and the usual purine ring band at 6.22 μ (medium), bands at 6.08 (strong) and 6.38 (medium) and a minimum at 6.29 μ were characteristic for the 7-nucleoside.

Alkaline Methanolysis of β-9-29.—A solution of 0.50 g (1.0 mmol) of β-9-29 in 20 ml of methanol was treated with 130 mg of sodium methoxide, refluxed for 2 hr, and neutralized with 145 mg of glacial acetic acid. The solution was evaporated, and the residue was partitioned between 5 ml of water and 5 ml of chloroform. A solid at the interface was removed on a filter and identified as 37 mg (27%) of adenine. Evaporation of the chloroform afforded methyl benzoate. The residue obtained by evaporating the water layer contained additional adenine, by tlc analysis. For isolation of any sugar derivatives, the residue was acetylated with 2 ml of acetic anhydride in 10 ml of pyridine. The mixture was stirred overnight at room temperature, treated with 5 ml of methanol to decompose excess anhydride, and evaporated. The residue was dissolved in 20 ml of chloroform, and the solution was washed with 30 ml of water, dried, and evaporated. The residual oil (150 mg, 57%) without purification was identified as the disulfide **35** of **methyl 3,5-di-*O*-acetyl-2-thio-β-D-ribofuranose** by nmr and mass spectral (*m/e*, parent peak 526) analysis: nmr τ 4.67 q (3-H), 4.96 d (1-H), 6.32 q (2-H), 6.60 s (OCH_3), 7.88 s and 7.90 s (two OAc's), $J_{1,2}$ = 2.3, $J_{2,3}$ = 6.5, $J_{3,4}$ = 4.0 Hz.

D. 7-Isoadenosine. 6-Benzamido-7-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-7*H*-purine (37).—A stirred solution of 15 g (29 mmol) of 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide in 200 ml of dry benzene was treated with 40 mmol of bis(trimethylsilyl)-6-benzamidopurine[26,27] and 10 g (29 mmol) of mercuric bromide. After 3 days at room temperature, the mixture was evaporated, and the residue was slurried with 100 ml of aqueous 30% potassium iodide and 150 ml of chloroform. The mixture was filtered. The chloroform layer was separated, washed with 100 ml of water, dried, and evaporated. The residue (15 g) showed two strong spots on tlc in $CHCl_3$–MeOH (50:1), R_f 0.15 and 0.35, plus sugar by-product at the solvent front and 6-benzamidopurine at the origin.

Initially in a small experiment, the two major components were separated by preparative tlc. The faster traveling component (14%) was identified as a 6-benzamido-9-(2,3,5-tri-*O*-benzoyl-D-ribofuranosyl)-9*H*-purine by the uv spectrum (Table III), and as the β anomer **36**[20] on debenzoylation with methanolic sodium methoxide to give adenosine. The slower component crystallized from methanol (11%), mp 120–124°, and was of analytical purity. The uv (Table III) and ir spectra suggested it was a 7 isomer, presumably the β anomer[20] **37**: ir 6.10 (strong), 6.27 and 6.40 μ (medium), in addition to strong benzoate bands; absence of bands for 6-benzamidopurine could be observed at 5.91 μ and, for large amounts, at 6.42 and 6.59 μ. On seeding with these crystals, the crude residue from the larger run above, in 300 ml

of methanol solution, afforded 1.0 g (5.5%) of **37**, mp 116–123°. The compound was previously[20] described as amorphous and shown to be the β anomer.

Anal. Calcd for $C_{38}H_{29}N_5O_8$: C, 66.8; H, 4.28; N, 10.2. Found: C, 66.6; H, 4.41; N, 10.2.

7-β-D-Ribofuranosyladenine (39) and the 6-*N*-Benzoyl Derivative 38.—A solution of 0.53 g (0.78 mmol) of tetrabenzoyl compound **37** in 30 ml of methanol was treated with 108 mg (2.00 mmol) of sodium methoxide, refluxed for 1.5 hr, neutralized with 3 ml of IRC 50 (H) resin, filtered, and concentrated. The residue was triturated with 40 ml of hot cyclohexane to remove methyl benzoate, and 210 mg of brown solid was collected on a filter: tlc in $CHCl_3$–MeOH (3:1) showed three spots, R_f 0.4, R_f 0.6, and R_f 0.9. Preparative tlc on three plates (2-mm thick), each developed three times with $CHCl_3$–MeOH (4:1), afforded additional methyl benzoate from the band at R_f 0.9. The middle band, R_f 0.6, was eluted with chloroform–methanol (6:4) to give 50 mg of 6-benzamido-7-β-D-ribofuranosylpurine (**38**); crystallization from methanol afforded 36 mg (12%): mp 155–160°; ir 6.12 (strong), 6.30 (medium), 6.65 μ (strong). Presence of the 6-*N*-benzoyl group and facile acid cleavage to 6-benzamidopurine was demonstrated in the ultraviolet spectra (Table III).

Anal. Calcd for $C_{17}H_{17}N_5O_5 \cdot {}^1/_2H_2O$: C, 53.7; H, 4.77; N, 18.4. Found: C, 53.9; H, 4.59; N, 18.4.

Elution of the slow band afforded 10 mg (5%) of 7-β-D-ribofuranosyladenine; ir 6.09 (strong), 6.27 (medium), 6.39 μ (weak). In the uv spectrum (Table III), the difference $\lambda_{min}^{pH\ 1} - \lambda_{min}^{pH\ 7} = +8$ mμ was that of a 7-ribofuranosyladenine, as distinguished[21,22] from that of 3-β-D-ribofuranosyladenine (−8 mμ).

E. *S*-Methyl Series. Methyl 3,5-Di-*O*-benzoyl-1-thio-α-D-arabinofuranoside (14).—To 100 g (2.04 mol) of methanethiol in a flask cooled in ice and equipped with a Dry Ice condenser and a drying tube was added 7.0 g of 58% sodium hydride in mineral oil (0.17 mol). The mixture was stirred at reflux for 2 hr. To this was added gradually, with foaming, a solution of 3,5-di-*O*-benzoyl-D-arabinofuranosyl chloride (**12**, obtained from 42 g of **11**, 91 mmol) in 100 ml of anhydrous THF. The mixture was stirred at room temperature under the Dry Ice condenser for 0.5 hr and poured onto a mixture of 100 ml of ice and 500 ml of bicarbonate solution. The solid that formed dissolved on dilution to 2 l. with water. The solution was extracted with three 250-ml portions of dichloromethane. The combined extracts were washed with 700 ml of saturated salt solution, dried, and concentrated. The residual crude product was used without purification. Signals in the nmr at τ 4.66 d (1-H, $J_{1,2}$ = 2.4 Hz), 5.60 t (2-H, $J_{2,3}$ = 2.8 Hz), 7.80 s (SCH_3) were identified by comparison with a previous sample isolated chromatographically.

Methyl 3,5-Di-*O*-benzoyl-2-*O*-methanesulfonyl-1-thio-α-D-arabinofuranoside (16).—Crude **14** in 250 ml of pyridine at −5° was treated gradually with 35 ml of methanesulfonyl chloride. After 18 hr at −5°, the excess chloride was hydrolyzed by treating the solution dropwise with water, while stirring and keeping the temperature below 15°, until (after about 1 hr) no further heat evolution could be detected. The solution was poured into 1 l. of ice water, and the mixture was extracted with three 200-ml portions of dichloromethane. The extracts were washed with 700 ml of sodium bicarbonate and with 700 ml of water, dried, and concentrated. The residue was used without purification: 41 g; nmr τ 4.45 d (1-H), 4.53 q (3-H), 4.83 t (2-H), 6.91 s (OSO_2CH_3), 7.77 s (SCH_3), $J_{1,2}$ = 1.5, $J_{2,3}$ = 1.2, $J_{3,4}$ = 5.0 Hz. Weak, unresolved singlets adjacent to the OSO_2CH_3 and SCH_3 singlets were attributed to a small precentage of the β anomer.

1-*O*-Acetyl-3,5-di-*O*-benzoyl-2-*S*-methyl-2-thio-α,β-D-ribofuranoside (19).—A solution of the mesylate **16** (41 g) in 500 ml of acetic anhydride and 125 ml of acetic acid was treated with 100 g of potassium acetate, heated on the steam bath for 3 hr, cooled, poured into 2 l. of ice water, and stirred for 30 min. The product was isolated by extraction and freed of acetic anhydride as for **17**. The oil (39 g) was purified by chromatography on a column (76 × 5.0 cm) of 90–200 mesh silica gel in benzene. The eluent was gradually changed to benzene–ether (95:5) while 4 l. of eluate was collected. Elution with 5 l. of benzene–ether (95:5) then afforded 23.9 g (61% based on **11**) of 1-acetate. The anomeric ratio, β:α, was 60:40 according to the nmr spectrum: τ, for β, 3.63 d (1-H), 4.25 t (3-H), 6.24 q (2-H), 7.82 s (SCH_3), 8.00 s (OAc), $J_{1,2}$ = 2.0, $J_{2,3}$ = 6.5, $J_{3,4}$ = 5.0 Hz; for α, 3.40 d (1-H), 3.30 q (3-H), 6.52 q (2-H), 8.00 s and 8.02 s (SCH_3 and OAc), $J_{1,2}$ = 4.7, $J_{2,3}$ = 6.4, $J_{3,4}$ = 1.8 Hz.

The β anomer could be isolated by two crystallizations from 95% ethanol to give 6.5 g, mp 87–88°, $[\alpha]^{20}D$ +7.3° ($CHCl_3$). An additional 1.5 g could be crystallized from the adjacent chromatographic fractions.

Anal. Calcd for $C_{22}H_{22}O_7S$: C, 61.4; H, 5.15; S, 7.44. Found: C, 61.4; H, 4.92; S, 7.27.

3,5-Di-*O*-benzoyl-2-*S*-methyl-2-thio-D-ribofuranosyl Chloride (22).—A solution of 8.5 g (20 mmol) of α,β-1-*O*-acetate **19** in 200 ml of anhydrous ether was chilled to −70° with Dry Ice–acetone and saturated with a stream of anhydrous hydrogen chloride. The solution was stored at −70° excluding moisture for 4 days. The resultant clear, purple solution was concentrated on the water aspirator and the residue held under vacuum (1 mm) for 1 hr at room temperature. The oil (8.5 g) was used immediately.

6-Benzamido-9(7)-(3,5-di-*O*-benzoyl-2-*S*-methyl-2-thio-α,β-D-ribofuranosyl)-9-(7*H*)-purine (30).—To a solution of chloro sugar (**22**, based on 20 mmol of **19**) in 225 ml of dry benzene was added, with stirring, 9.9 g (39 mmol) of freshly distilled bis-(trimethylsilyl)-6-benzamidopurine[26,27] and 8.0 g (22 mmol) of mercuric bromide. The mixture became clear after 10 min, and stirring was continued at room temperature for 3 days. The solution was concentrated and the residue was partitioned between 250 ml of chloroform and 250 ml of water. Some unreacted 6-benzamidopurine separated as a fine solid at the interface and was removed by filtration of both layers through Celite. The chloroform layer was separated, washed with 200 ml of aqueous 30% potassium iodide and with 250 ml of water, dried, and concentrated. The residual foamed glass was freed of additional 6-benzamidopurine by redissolving in chloroform, chilling the solution, filtering through Celite, and concentrating to give 10 g of residue. Medium intensity bands in the ir spectrum at 6.20 and 6.30 μ, as expected for a purine-9-nucleoside, were clearly seen; a band at 6.09 μ indicated the presence of a little 7-nucleoside. Three nucleoside components were observed by tlc in $CHCl_3$–MeOH (95:5), β-**9-30** at R_f 0.80, α-**9-30** at R_f 0.75, both α- and β-**7-30** at R_f 0.45, in addition to sugar impurities at the solvent front and 6-benzamidopurine near the origin.

A solution of the residue in 25 ml of chloroform was added to a chromatographic column (Chromatronix, 100 × 5.0 cm) containing 750 g of silica gel H (10–40 mesh) in chloroform. It was eluted at 500 ml/hr (under 40–50 psi pressure) with chloroform, and the following fractions were collected and analyzed by tlc.

(1) 8.5 l., contained sugars, but no nucleoside, discarded.

(2) 3.6 l., afforded 4.1 g (34%) of crude β-**9-30**, containing a little α-**9-30** and minor sugar impurities; ir 5.79 (strong), 6.20 and 6.31 μ (medium); nmr τ 1.30 s and 1.81 s (2-H, 8-H), 3.75 d (1′-H), 4.08 q (3′-H), 5.25 q (2′-H), 8.02 s (SCH_3), $J_{1',2'}$ = 9.0, $J_{2',3'}$ = 6.0, $J_{3',4'}$ = 2.0 Hz.

Anal.[28] Calcd for $C_{32}H_{27}N_5O_6S$: C, 63.0; H, 4.46; N, 11.5; S, 5.26. Found: C, 62.4; H, 4.37; N, 11.2; S, 4.77.

(3) 6.0 l., afforded 1.2 g (10%) of crude α-**9-30**, containing a little β-**9-30**; ir 5.80 (strong), 6.22 and 6.31 μ (medium); nmr τ 1.26 s and 1.61 s (2-H, 8-H), 3.01 d (1′-H), 4.15 q (3′-H), 5.05 q (4′-H), 5.85 t (2′-H), $J_{1',2'}$ = 7.0, $J_{2',3'}$ = 6.4, $J_{3',4'}$ = 1.8, $J_{4',5'}$ = 4.3 Hz.

(4) 2.8 l., afforded 1.4 g (12%) of crude **7-30**; ir spectra had characteristic bands of a 7 isomer at 6.09 (strong), 6.42 (medium), and 7.63 μ (strong). Presence of both anomers of **7-30** was indicated in the nmr by two distinct quartets for H-2′, at τ 6.12 ($J_{1',2'}$ = 8.8, $J_{2',3'}$ = 5.6 Hz) and 6.25 ($J_{1',2'}$ = 7.3 and $J_{2',3'}$ = 5.5 Hz), by two singlets for SCH_3, narrowly spaced at τ 8.00 and 7.99, and by two singlets for one purine proton (H-2 or H-8, unassigned) at τ 1.41 and 1.20 (the other purine proton was obscured by the benzoyl protons, perhaps as two singlets at τ 1.90 and 1.80). A little α- and β-**9-30** was also detected. Crystallization from methanol afforded 0.7 g (6%) of **7-30**, as the major one of these two anomers: mp 200–205°; ir 5.78 (strong, OBz), 6.08 (strong), 6.24 (medium), 6.6 μ (strong); nmr τ 1.20 s (2-H or 8-H; the other purine H was obscured, perhaps at 1.80, by benzoyl protons; 1′-H was also obscured, below τ 3.0), 4.18 q (3′-H), 6.25 q (2′-H), 8.00 s (SCH_3), $J_{1',2'}$ = 7.3, $J_{2',3'}$ = 5.5, $J_{3',4'}$ = 2.5 Hz.

Anal. Calcd for $C_{32}H_{27}N_5O_6S$: C, 63.0; H, 4.46; N, 11.6; S, 5.26. Found: C, 63.1; H, 4.45; N, 11.6; S, 5.28.

2′-*S*-Methyl-2′-thioadenosine (β-9-33).—A solution of 3.0 g (5.0 mmol) of crude β-**9-30** and 1.4 g of sodium methoxide (27 mmol) in 250 ml of methanol was refluxed for 2 hr, neutralized with 1.6 g of acetic acid, treated with methanolic 10% picric acid until precipitation was complete, chilled, and filtered. The nucleoside picrate that was collected was suspended in 50 ml of water and stirred for 2.5 hr with Dowex 2 (CO_3) resin (30 ml).

The mixture was filtered, and the filtrate was evaporated to give 0.80 g of β-9-33. Recrystallization from acetone gave 0.71 g solvated with acetone, mp 88–92°. Water recrystallization yielded in two crops 0.50 g (33%) without hydration after drying at 100° (1 mm): mp 172–174°; $[\alpha]^{20}D$ −12° (c 0.5, H_2O); ir 5.94 (NH_2), 6.23 μ (aryl); nmr (D_2O) τ 1.78 s and 1.96 s (2-H, 8-H), 4.01 d (1'-H), 5.50 q (3'-H), 5.78 m (4'-H), 6.18 q + d, superimposed (2'-H and 5'-H_2, respectively), 8.21 s (SCH_3), $J_{1',2'}$ = 9.0, $J_{2',3'}$ = 5.6, $J_{3',4'}$ = 2.0 Hz.

Anal. Calcd for $C_{11}H_{15}N_5O_3S$: C, 44.4; H, 5.09; N, 23.6; S, 10.8. Found: C, 44.2; H, 5.22; N, 23.5; S, 10.6.

9-(2-*S*-Methyl-2-thio-α-D-ribofuranosyl)-9*H*-adenine (α-9-33).—Crude α-9-30 (from fraction 3 above) was deacylated, and the product was isolated through the picrate, as for β-9-33. Purification by preparative tlc in $CHCl_3$–MeOH (4:1) afforded a gum, which could not be crystallized: ir 6.08, 6.25 μ (broad, strong); nmr (D_2O) τ 1.73 s and 1.92 s (2-H, 8-H), 3.49 d (1'-H), 5.54 q superimposed on multiplet at 5.5 (3'-H and 4'-H, respectively), 6.08 q (2'-H), 6.33 uneven d (5'-H_2), 8.10 s (SCH_3), $J_{1',2'}$ = 7.0, $J_{2',3'}$ = 6.0, $J_{3',4'}$ = 1.5, $J_{4',5'}$ = 4.0 Hz.

7-(2-*S*-Methyl-2-thio-D-ribofuranosyl)-7*H*-adenine (7-33).—Debenzoylation of 1.0 g (1.6 mmol) of crystalline 7-30 (the single anomer, unidentified) with 0.70 g of sodium methoxide was followed by isolation of the product through the picrate, as described for β-9-33. Concentration of the aqueous filtrate to near dryness afforded by crystallization 26 mg (5.5%): mp 195–203°; nmr τ 1.45 s and 1.79 s (2-H, 8-H), 4.04 d (1'-H), 5.60 q (3'-H), 6.06 q (4'-H), 6.30 m (5'-H_2), 6.80 q (2'-H), 8.51 s (SCH_3), $J_{1',2'}$ = 9.5, $J_{2',3'}$ = 7.0, $J_{3',4'}$ = 3.4 Hz.

Anal. Calcd for $C_{11}H_{15}N_5O_3S \cdot H_2O$: C, 41.9; H, 5.43; N, 22.2. Found: C, 41.7; H, 5.46; N, 22.2.

F. Desulfurizations. Methyl 3,4-*O*-Cyclohexylidene-2-deoxy-β-D-ribopyranoside (2). I. From 6.—To 0.90 g (2.6 mmol) of 2-benzylthio 6 dissolved in 125 ml of dry dimethylformamide was added 10 g of sponge nickel.[29] The mixture was protected from moisture and stirred under a GE, 250-W, white heat lamp (distance of 6 in.) for 16 hr and then filtered through Celite. The filter cake was washed with 50 ml of hot dimethylformamide and with 100 ml of hot chloroform, and the combined filtrates were taken to dryness [caution: a sample of 2 was 20% volatilized after 18 hr at 25° (0.75 mm)]. The residue was dissolved in 30 ml of ether, and the solution was washed with 50 ml of sodium bicarbonate and with 50 ml of water, dried, and concentrated. The residue, 0.46 g, by nmr analysis retained 10–15% of unreacted 6, which was removed by preparative tlc on four plates (2-mm thick). The plates were developed with benzene–ether (95:5) and the bands detected with iodine vapor; the brown iodine evaporated without harm to the compound. Chloroform elution of main band afforded 0.34 g (58%) of oil: nmr (100 MHz) τ 5.29 q (1-H), 5.65 doublet of triplets (3-H), 5.93 doublet of triplets (4-H), 6.24 q (5-H_2), 7.91 m and 8.28 m (2-H_2), 8.2–8.8 (cyclohexyl), $J_{1,2a}$ = 6, $J_{1,2e}$ = 4.5, $J_{2a,2e}$ = 15, $J_{2a,3}$ = 4.5, $J_{2e,3}$ = 5.0, $J_{3,4}$ = 6.5, $J_{4,5a}$ and $J_{4,5e}$ = 2.8 and 3.0, $J_{5a,5e}$ estimated 3 Hz. A 100-mg portion was crystallized from methanol–water without changing the nmr spectrum to give 38 mg (6.5%), mp 51–53°, $[\alpha]^{22}D$ −97° ($CHCl_3$). Mixture melting point with the sample from II was 51–53°.

II. From 2-Deoxyribose.—Methyl 2-deoxy-β-D-ribopyranoside (1): mp 30–45° (lit.[8] 83–84° for the L isomer); nmr τ 5.21 t (1-H, $J_{1,2a}$ = $J_{1,2e}$ = 3 Hz), 6.63 s (OCH_3), contained *ca.* 15% of the α anomer, 4.92 q (1-H), 6.56 s (OCH_3). It was converted to the cyclohexanone ketal as described for 4. The product was partitioned between ether and water, and the ether residue was crystallized from methanol–water, mp 52–53°.

Anal. Calcd for $C_{12}H_{20}O_4$: C, 63.1; H, 8.83. Found: C, 63.1; H, 8.84.

(29) Davison Chemical Division, W. R. Grace, and Co.; prewashed with dimethylformamide, wet weight.

9-(2-Deoxy-α-D-ribofuranosyl)adenine from α-9-28.—The sample of α-9-28 (65 mg, 0.10 mmol, mainly α) was desulfurized in 50 ml of dimethylformamide with 1 g of sponge nickel[29] under a heat lamp as described for 2. The hot solution was filtered, the filter cake was washed with 100 ml of chloroform, and the combined filtrate was concentrated. The residual brown oil (190 mg) showed little or no nmr signal for C_6H_5 of benzyl. It was subjected to mild deacylation in 10 ml of methanol with 1 ml of diisopropylamine at reflux for 3 hr. After evaporation the residue was partitioned between 10 ml of water and 10 ml of chloroform. The water layer was evaporated to give 15 mg (57%) of crude α anomer of deoxyadenosine, identified by direct, simultaneous comparison with authentic samples of deoxyadenosine and its anomer[30] on tlc. Three developments of the plate with $CHCl_3$–MeOH (4:1) gave good resolution, R_f 0.50 for the α anomer, R_f 0.60 for deoxyadenosine. The desulfurization product had a strong spot at R_f 0.50, a faint spot at R_f 0.60, and traces of faster moving contaminants.

2'-Deoxyadenosine. I. From 2'-*S*-Benzyl-2'-thioadenosine (β-9-31).—A sample (92 mg, 0.25 mmol) of β-9-31 was desulfurized with 1 g of sponge nickel in 50 ml of dimethylformamide. The hot mixture was filtered, and the filter cake was washed with 50 ml of hot dimethylformamide, 50 ml of methanol, and 100 ml of water. Concentration of the combined filtrates afforded 20 mg. The nmr showed it was a mixture (2:1) of 2'-deoxyadenosine and unreacted β-9-31; direct comparison on tlc, as above, confirmed the presence of 2'-deoxyadenosine and showed the absence of any α anomer. Pure 2'-deoxyadenosine (5 mg, 8%) was separated by preparative tlc on one plate (1-mm thick) developed twice with chloroform–methanol (4:1).

II. From β-9-30.—Similarly, desulfurization of β-9-30 followed by debenzoylation of the intermediate with methanolic sodium methoxide afforded 2'-deoxyadenosine free of the α anomer, by direct comparison on tlc, as decsribed for α-9-28.

Registry No.—**2,** 30545-66-5; **4,** 30545-67-6; **5,** 30545-68-7; **α-6,** 30545-69-8; **β-6,** 30545-70-1; **7,** 30545-71-2; **8,** 30545-78-9; **10,** 30538-24-0; **13,** 30538-25-1; **14,** 30538-26-2; **15,** 30538-27-3; **16,** 30538-28-4; **α-17,** 30538-29-5; **β-17,** 30538-30-8; **α-18,** 30651-47-9; **β-18,** 30538-31-9; **α-19,** 30538-32-0; **β-19,** 30538-33-1; **α-23,** 30538-34-2; **β-23,** 30538-35-3; **α-24,** 30538-36-4; **β-24,** 30538-37-5; **α-25,** 30538-38-6; **β-25,** 305-38-39-7; **α-26,** 30597-74-1; **β-27,** 30538-40-0; **α-9-27,** 30545-79-0; **β-9-27,** 30545-80-3; **7-28,** 30545-72-3; **α-9-28,** 30545-81-4; **β-9-28,** 30545-82-5; **7-29,** 30545-73-4; **β-9-29,** 30545-83-6; **α-7-30,** 30546-00-0; **β-7-30,** 30545-74-5; **α-9-30,** 30545-84-7; **β-9-30,** 30545-85-8; **7-31,** 30545-75-6; **α-9-31,** 30597-72-9; **β-9-31,** 30545-86-9; **7-32,** 30545-76-7; **α-9-32,** 30545-87-0; **β-9-32,** 30545-88-1; **7-33,** 30545-77-8; **α-9-33,** 30597-73-0; **β-9-33,** 30545-89-2; **34a,** 30545-90-5; **34b,** 30545-91-6; **35,** 30538-41-1; **36,** 6984-53-8; **37,** 23819-18-3; **38,** 30538-43-3; **39,** 485-08-5.

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Conformational Studies on Pyranoid Sugar Derivatives. The Conformational Equilibria of the D-Aldopentopyranose Tetraacetates and Tetrabenzoates[1-3]

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Equilibria between chair conformers in solution have been measured in acetone-d_6 by the nmr method of averaging of spin couplings for the aldopentopyranose tetraacetates having the α-D-*ribo* (**1**), β-D-*ribo* (**2**), α-D-*arabino* (**3**), β-D-*arabino* (**4**), α-D-*xylo* (**5**), β-D-*xylo* (**6**), α-D-*lyxo* (**7**), and β-D-*lyxo* (**8**) configurations, and also for the corresponding tetrabenzoates (**9**–**16**). Conformational homogeneity was observed only for **4** (*1C*) and **5** (*C1*) and the corresponding benzoates; the other examples have substantial (>5%) contribution from the less favored chair conformer. In most examples the tetrabenzoates have more of that chair conformer having the 1 substituent axial than the corresponding tetraacetates. The effect of change of temperature on the position of the conformational equilibria in acetone-d_6 was examined in all 16 examples. The rate of conformational inversion at various temperatures was determined for compound **8** and compared with data for compound **2**. Changes in polarity of the solvent do not affect in any regular way the position of the conformational equilibria. The equilibrium data observed cannot be accommodated within the framework of existing interpretations based on additive contributions of steric and polar interactions for polysubstituted six-membered rings, except on a very broad, qualitative basis. Analogs of **2**, **3**, **6**, and **7** specifically deuterated in the 1-acetoxy group were synthesized and the effect of solvent on the position of the 1-OAc nmr signal was studied. Configurational equilibria for anomeric interconversion of the acetylated pentopyranoses were measured and found in good agreement with literature values except for the lyxose derivatives.

The use of high-resolution nmr spectroscopy for conformational analysis of substituted tetrahydropyran ring systems was initiated by Lemieux and coworkers.[13] They concluded that for six-membered compounds (1) axial protons usually resonate at higher field than equatorial protons in chemically similar environments, (2) the spin–spin coupling constant between vicinal, antiparallel protons is about 2–3 times larger than that between gauche-disposed protons, (3) axial acetyl methyl protons usually resonate at lower field than equatorial acetyl methyl protons. These considerations permitted the assignment of favored conformations to various aldopyranoses and their derivatives, including several of the peracylated aldopentopyranoses that form the subject of the present work.

The α anomer has been observed to be more stable than the β anomer in anomerically equilibrated mixtures of methyl D-glucopyranosides,[14] penta-*O*-acetyl-D-glucopyranoses,[15] and peracetylated D-glucopyranosyl halides,[16] even though the C-1 substituent is axial in the α anomer. This predisposition of a polar substituent at C-1 of a pyranose ring for the axial orientation, contrary to expectations based on steric considerations, has been termed[17] the "anomeric effect." The phenomenon has been attributed by Edward[18] to an unfavorable dipole–dipole interaction between the carbon–oxygen bonds of the ring and the bond from the anomeric carbon atom to the equatorial polar substituent. Lemieux and Chü[17] have interpreted the effect in terms of an electrostatic interaction between the C-1 substituent and C-5–O-5 bonds.

From data accumulated on the anomeric equilibria of certain peracetylated aldopyranoses in 1:1 acetic acid–acetic anhydride with perchloric acid as the catalyst, and an estimated value for the conformational equilibrium of β-L-arabinopyranose tetraacetate in chloroform solution, Lemieux and Chü proposed a quantitative magnitude of 1.3 kcal mol^{-1} for the anomeric effect of the acetoxy group in the pentoses and 1.5 kcal mol^{-1} in the hexoses.[17] A value of 1.35 kcal mol^{-1} was proposed by Anderson and Sepp[19] for the anomeric effect of the acetoxy group in 2-acetoxy-4-methyltetrahydropyran in acetic acid. From their equilibrium data Lemieux and Chü also estimated values for the various nonbonded interactions present in a pyranoid ring.

Advances in nmr instrumentation permitted Lemieux and Stevens to investigate in greater detail the spectra of pyranoid carbohydrate derivatives.[20] The favored conformations of six aldopentopyranose tetraacetates in chloroform solution near room temperature were determined from chemical-shift and spin-coupling data. The observed conformations were in satisfactory agreement with those predicted by summation of the estimated nonbonded interaction energies of the individual groups.[17] The aldopentopyranose tetraacetates were considered to exist almost entirely in the *C1*(D) conformation, except for the β-D-*ribo* derivative

(1) For previous papers in this series, see ref 4–10.

(2) For preliminary reports of parts of this work, see ref 5–7.

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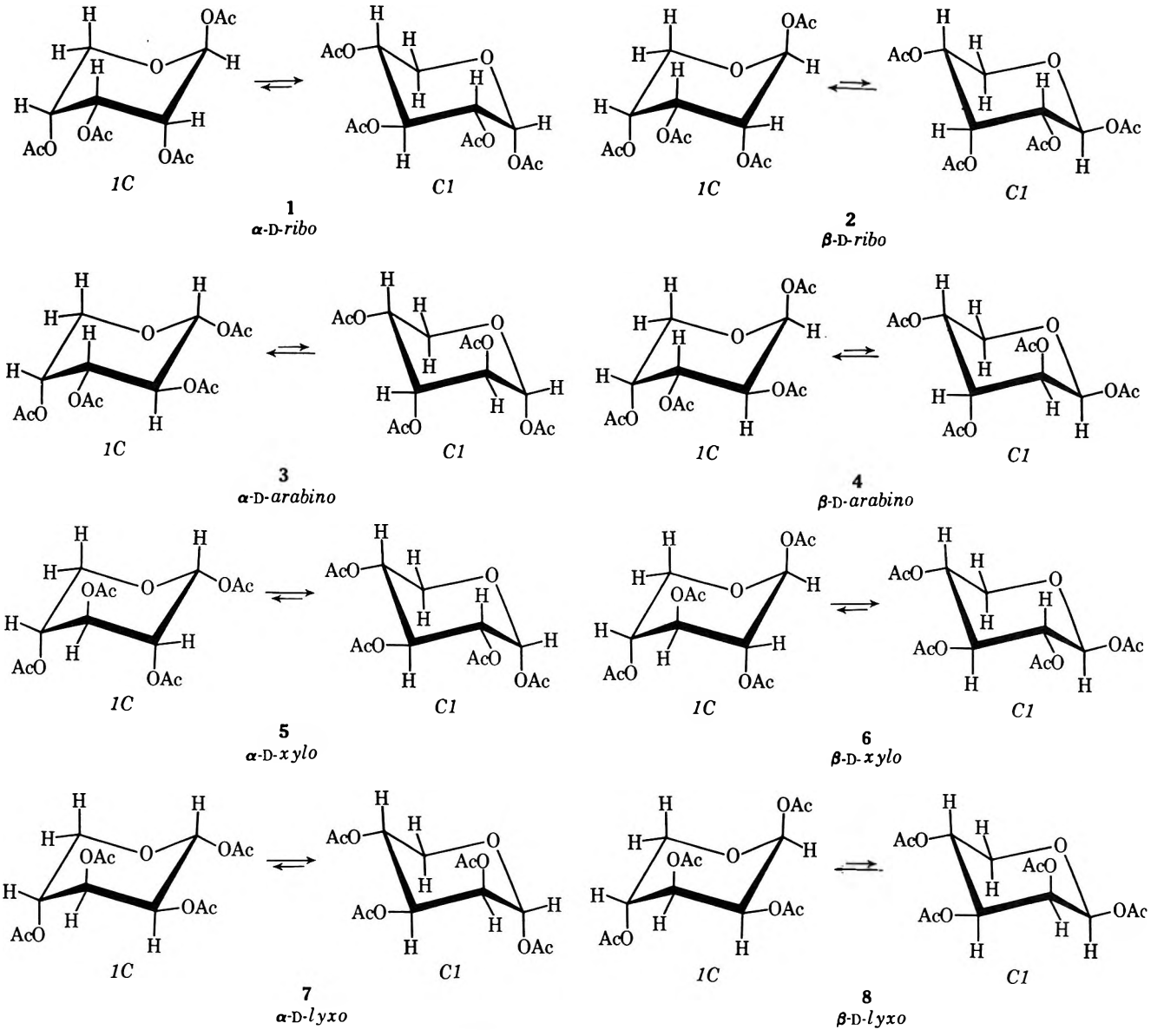


which appeared to contain substantial proportions of each chair form and the β-L-*arabino* derivative[17] which contained about 80% of the *C1*(L) conformation. 2-Deoxy-β-D-*erythro*-pentopyranose triacetate was found to exist mainly in the *1C* conformation.

Conformational studies on various peracylated D-ribopyranoses were also made by Coxon.[21] β-D-Ribopyranose tetrabenzoate (**10**) in chloroform solution near room temperature was reported to exist in a 2:1 equilibrium of the *1C* and *C1* chair forms, whereas the α-D anomer (**9**) existed primarily in the *C1* conformation. The anomeric effect was invoked as the principal factor determining these differences in conformational distribution. Work done elsewhere showed that 2-deoxy-β-D-*erythro*-pentopyranose tribenzoate, whose *1C* conformation does not have the unfavorable syn-diaxial interaction between benzoyloxy groups at C-2 and C-4, exists almost exclusively in that conformation.[22]

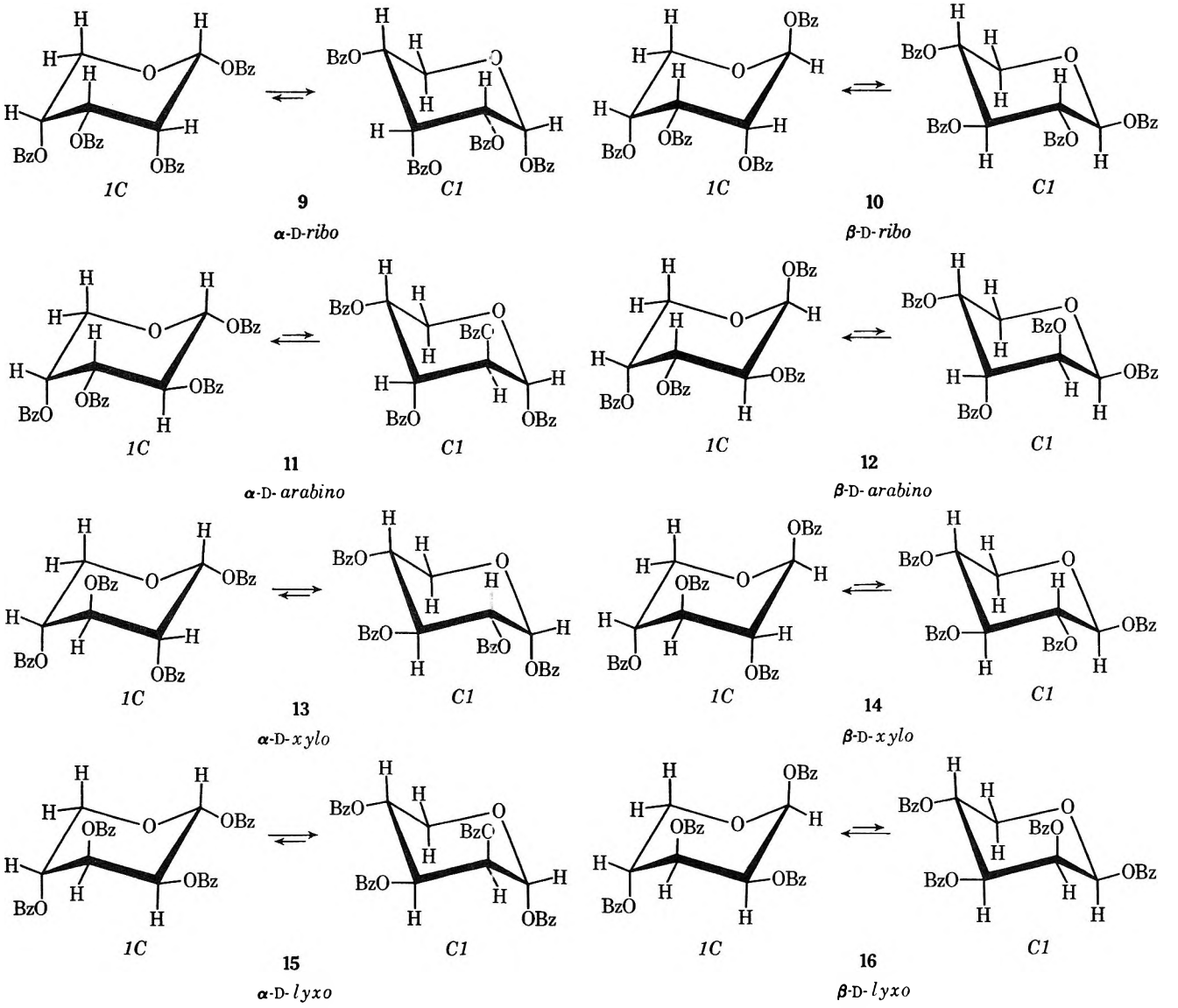
That pyranoid sugar derivatives can indeed exist in rapid conformational equilibrium at room temperature (as do cyclohexane and some of its derivatives) was firmly established from the observation of the separate chair conformers of β-D-ribopyranose tetraacetate (**2**) in acetone-d_6 by low-temperature nmr spectroscopy.[8,10] The observed data indicate that **2** exists at room temperature as a mixture of conformers undergoing rapid interconversion and that at −84°, where the interconversion is slow on the nmr time scale, the *1C* and *C1* conformers are present in a 2:1 proportion. Nmr data for α-D-lyxopyranose tetraacetate (**7**) in acetone-d_6 indicate the *C1* form as the major chair conformer present at equilibrium near room temperature.[10]

A general program in this laboratory is concerned with determination of favored conformations, and conformational populations at equilibrium for polysubstituted tetrahydropyran ring systems, as provided by pyranoid sugar derivatives.[4−10,23] The determination of conformational equilibria for families of stereoisomeric, polysubstituted, cyclic compounds provides data useful for understanding and quantitatively interpreting the steric and electronic effects of multiple substituents on the conformations of ring systems. The

(21) B. Coxon, *Tetrahedron*, **22**, 2281 (1966).

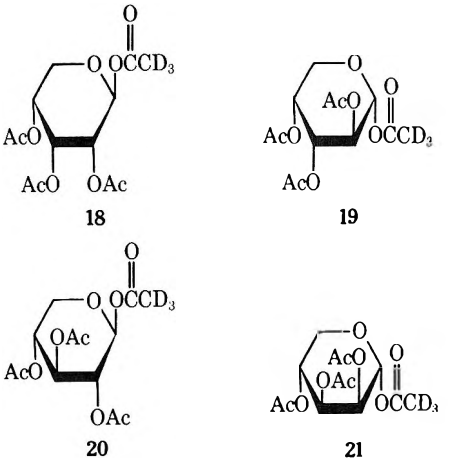
(22) R. J. Cushley, J. F. Codington, and J. J. Fox, *Carbohyd. Res.*, **5**, 31 (1967).

(23) D. Horton and W. N. Turner, *J. Org. Chem.*, **30**, 3387 (1965); C. V. Holland, D. Horton, and J. S. Jewell, *ibid.*, **32**, 1818 (1967); N. S. Bhacca and D. Horton, *Chem. Commun.*, 867 (1967); C. V. Holland, D. Horton, M. J. Miller, and N. S. Bhacca, *J. Org. Chem.*, **32**, 3077 (1967); *cf.* P. L. Durette and D. Horton, *Advan. Carbohyd. Chem. Biochem.*, in press.



present work reports the measurement of the conformational equilibria in solution of the eight peracetylated D-aldopentopyranose sugars (**1**–**8**)[24] and the eight perbenzoylated D-aldopentopyranose sugars (**9**–**16**);[24] these represent all of the different stereochemical arrangements possible for a 2,3,4,5-tetraacetoxytetrahydropyran and a 2,3,4,5-tetrabenzoyloxytetrahydropyran (the L enantiomorphs would give identical equilibrium data).

Materials and Methods.—The eight D-aldopentopyranose tetraacetates (**1**–**8**) were prepared by previously established procedures and had physical constants in good agreement with the literature values (see Experimental Section). Seven of the eight D-aldopentopyranose tetrabenzoates (**9**–**16**) were also prepared by known methods and again their physical constants were in good agreement with literature values. α-D-Ribopyranose tetrabenzoate[25] (**9**) was obtained anomerically pure for the first time as an amorphous glass by column chromatography on silica gel of an α,β mixture obtained from the preparation of β-D-ribopyranose tetrabenzoate (**10**). The pure α-D anomer gave a satisfactory elemental analysis and its 100-



MHz spectrum in chloroform was identical with that obtained by Coxon by electronic subtraction of the spectrum of **10** from that of the mixture of α and β anomers by use of computer of average transients.[21] β-D-Ribopyranose tetra-*p*-toluate (**17**) was prepared by the procedure of Zinner and Belau[26] and had physical constants in good agreement with the reported values. The tetraacetates, specifically deuterated in the 1-acetyl methyl group, having the β-D-*ribo* (**18**), α-D-

(24) The results reported here for these two configurational series represent a refinement of the data given in ref 7 and 6, respectively.

(25) A. K. Bhattacharya, R. K. Ness, and H. G. Fletcher, Jr., *J. Org. Chem.*, **28**, 428 (1963).

(26) H. Zinner and L. Belau, *J. Prakt. Chem.*, **18**, 79 (1962).

TABLE I

CHEMICAL SHIFT DATA FOR PERACETYLATED ALDOPENTOPYRANOSES IN ACETONE-d_6 AT 31°[a]

Compd	Configuration	Chemical shifts,[b] H-1	H-2	H-3	H-4	H-5[c]	H-5'[c]	Acetyl methyl
1	α-D-*ribo*	3.92 d	4.85 t	4.42 t	4.92 m	5.99 q	6.26 o	7.88, 7.90, 8.00, 8.01
2	β-D-*ribo*	4.04 d	5.00 sp	4.54 t	4.86 m	5.90 q	6.16 q	7.89, 7.94, 7.95, 7.97
2	β-D-*ribo*[d,e]	3.75 d	4.81 o	4.43 t	4.97 m	6.30 d[f]		8.25, 8.27, 8.30, 8.37
2	β-D-*ribo*[g]	3.96 d	4.96 o	4.50 t	4.85 m	5.95 q	6.13 q	7.876, 7.907, 7.916, 7.923[h]
3	α-D-*arabino*	4.27 m		4.72–4.83 m		6.04 m		7.91, 7.93, 7.98, 8.02
3	α-D-*arabino*[d]	4.19 d	4.45 m	4.74–4.86 m		6.26 qn	6.70 qn	8.24, 8.27, 8.31, 8.32
3	α-D-*arabino*[g]	4.32 d	4.72 q	4.89 q	4.71 m	5.96 q	6.23 q	7.87, 7.89, 7.94, 7.97
4	β-D-*arabino*	3.73 d	4.79 o	4.68 m	4.65 m	5.82 q	6.21 q	7.85, 7.89, 8.01, 8.04
5	α-D-*xylo*	4.29 d	5.01 q	4.56 t	4.99 o	6.10 q	6.30 t	7.83, 7.99, 8.00, 8.02
6	β-D-*xylo*	4.22 d	5.04 q	4.74 t	5.07 m	5.89 q	6.38 q	7.936, 7.985, 7.992, 8.000[h]
6	β-D-*xylo*[d,i]	4.16 m	4.77 m	4.66 t	5.01 m	6.15 q	6.90 q	8.29, 8.31, 8.37, 8.39
6	β-D-*xylo*[g]	4.26 d	4.98 m	4.78 t	5.04 m	5.86 q	6.48 q	7.903, 7.947, 7.959[h,i]
7	α-D-*lyxo*	4.05 d	4.81 t	4.69 q	4.88 sx	6.04 q	6.29 q	7.85, 7.90, 7.96, 8.00
7	α-D-*lyxo*[d]	3.82 d	4.56 t	4.45 q	4.67 sx	6.09 q	6.38 q	8.25, 8.29, 8.33, 8.36
7	α-D-*lyxo*[g]	4.00 d	4.75 t	4.62 q	4.81 sx	5.99 q	6.31 q	7.85, 7.88, 7.94, 7.96
8	β-D-*lyxo*	3.94 t	3.68–3.78 m		5.01 m	5.82 q	6.38 sx	7.91, 7.93, 7.94, 7.97

[a] Data taken from spectra measured at 100 MHz at a sweep width of 500 Hz. [b] Observed multiplicities: d, doublet; t, triplet; q, quartet; qn, quintet; sx, sextet; sp, septet; o, octet; m, complex multiplet. [c] The proton on C-5 giving the higher field signal is designated H-5'. [d] In benzene-d_6. [e] Measured at 15% (w/v) concentration. [f] AB portion of a deceptively simple ABX system. [g] In chloroform-*d*. [h] Measured at 50-Hz sweep width. [i] Measured at 10% (w/v) concentration. [j] Six-proton singlet.

TABLE II

COUPLING CONSTANTS OF METHINE AND METHYLENE PROTONS FOR PERACETYLATED ALDOPENTOPYRANOSES IN ACETONE-d_6 AT 31°

Compd	Configuration	Coupling constants,[a] Hz $J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$[b,c]	$J_{4,5'}$[b,c]	$J_{5,5'}$
1	α-D-*ribo*[d]	3.6	3.3	3.2	9.3	4.7	−11.2
2	β-D-*ribo*[e]	4.6	3.5	3.4	3.4	5.8	−12.4
2	β-D-*ribo*[e-g]	5.0	3.3	3.3	*h*, *i*	*h*, *i*	*h*, *i*
2	β-D-*ribo*[e,j]	4.7	3.4	3.3	3.4	5.9	−12.5
3	α-D-*arabino*	*h*	*h*	*h*	*h*	*h*	*h*
3	α-D-*arabino*[f]	7.0	*h*	*h*	3.0	1.7	−13.0
3	α-D-*arabino*[j]	6.4	9.0	3.2	3.6	2.0	−13.0
4	β-D-*arabino*	2.9	11.8	3.0	1.0	1.9	−13.2
5	α-D-*xylo*	3.5	9.8	9.6	5.5	11.6	−11.2
6	β-D-*xylo*	6.7	8.1	8.1	4.9	8.8	−11.8
6	β-D-*xylo*[f,k]	7.0	8.2	8.1	5.1	8.4	−11.8
6	β-D-*xylo*[j]	6.6	8.1	7.9	4.5	8.5	−12.0
7	α-D-*lyxo*	3.0	3.4	9.0	4.4	8.7	−11.6
7	α-D-*lyxo*[f]	3.2	3.3	8.8	4.5	8.5	−11.5
7	α-D-*lyxo*[j]	3.1	3.4	9.0	4.5	8.6	−11.5
8	β-D-*lyxo*[l]	2.5	*h*	*h*	3.3	5.4	−12.4

[a] Data taken from spectra measured at 100 MHz at a sweep width of 100 Hz. [b] Coupling constants calculated by ABX analysis. [c] The proton on C-5 giving the higher field signal is designated H-5'. [d] $J_{3,5}$ = 0.8 Hz. [e] $J_{2,4}$ = 0.7 Hz. [f] In benzene-d_6. [g] Measured at 15% (w/v) concentration. [h] First-order couplings not observed. [i] Deceptively simple ABX system. [j] In chloroform-*d*. [k] Measured at 10% (w/v) concentration. [l] $J_{3,5}$ = 0.6 Hz.

arabino (**19**), β-D-*xylo* (**20**), and α-D-*lyxo* (**21**) configurations, were prepared by treating a solution of the appropriate aldopentopyranosyl chloride or bromide in acetonitrile with deuterated silver acetate.

The nmr spectra were measured at 100 MHz on 20% (w/v) solutions (unless otherwise indicated) of the freshly prepared compounds in the appropriate deuterated solvent containing 5% of tetramethylsilane. The chemical shifts recorded are given on the τ scale and were obtained by analysis of the spectra on a first-order basis and are considered accurate to within ±0.005 ppm. The time-averaged $J_{4,5}$ and $J_{4,5'}$ spin couplings employed in the calculation of conformational populations were obtained by ABX analysis[27] of spectra measured at 100-Hz sweep width. The values reported are considered accurate to within ± 0.1 Hz. All other coupling constants recorded were obtained on a first-order basis as direct peak spacings from spectra measured at a sweep width of 100 Hz, and are considered precise to within ± 0.1 Hz. The values reported are considered accurate to ±0.1 Hz. Spectral data for the 21 compounds are tabulated in Tables I–IX. Nmr spectra for compounds **13**, **14**, **15**, and **17** are given in Figures 1–4, respectively.

For each of the sugar acetates (**1**–**8**) and benzoates (**9**–**16**) in acetone-d_6 at 31°, the nmr spectral method of averaging of spin coupling[28] was used, by procedures already detailed,[6-8] to determine the proportions of the *1C*(D) and *C1*(D) conformers present at equilibrium.

(27) F. A. Bovey, "Nuclear Magnetic Resonance Spectroscopy," Academic Press, New York, N. Y., 1969, pp 105–113.

(28) F. A. L. Anet, *J. Amer. Chem. Soc.*, **84**, 1053 (1962); H. Feltkamp and N. C. Franklin, *ibid.*, **87**, 1616 (1965); see also G. E. Booth and R. J. Ouellette, *J. Org. Chem.*, **31**, 544 (1966); Y. Pan and J. B. Stothers, *Can. J. Chem.*, **45**, 2943 (1967); G. O. Pierson and O. A. Runquist, *J. Org. Chem.*, **33**, 2572 (1968).

TABLE III
CHEMICAL SHIFT DATA FOR PERBENZOYLATED ALDOPENTOPYRANOSES IN ACETONE-d_6 AT 31°[a]

Compd	Configuration	Chemical shifts,[b] H-1	H-2	H-3	H-4	H-5[c]	H-5'[c]	Benzoyl
9	α-D-*ribo*	3.28 d	4.13 t	3.67 t	4.29 o	5.39 q	5.77 o	1.84–2.76
10	β-D-*ribo*	3.30 d	4.17 t	3.82 t	4.18 m	5.35 q	5.66 q	1.75–2.73
11	α-D-*arabino*[d]	3.70 d		3.94–4.25 m		5.55 q	5.85 q	1.90–2.78
12	β-D-*arabino*	3.04 d	3.87 q	3.74 q	3.98 m	5.27 q	5.73 q	1.71–2.78
13	α-D-*xylo*	3.13 d	4.22 q	3.63 t	4.28 sx	5.59 q	5.73 t	1.75–2.77
14	β-D-*xylo*[e]	3.54 d	4.31 q	4.02 t	4.48 sx	5.36 q	5.86 q	1.91–2.72
15	α-D-*lyxo*	3.36 d	4.00 t	3.83 q	4.12 sx	5.52 q	5.72 q	1.74–2.72
16	β-D-*lyxo*	3.25 q	4.01 t	3.93 m	4.36 m	5.23 q	5.86 o	1.81–2.73
17	β-D-*ribo* tetra-*p*-toluate[f]	3.35 d	4.24 t	3.85 t	4.25 m	5.42 q	5.71 q	1.90–2.89

[a] Data taken from spectra measured at 100 MHz. [b] Observed multiplicities: d, doublet; t, triplet; q, quartet; sx, sextet; o, octet; m, complex multiplet. [c] The proton on C-5 giving the higher field signal is designated H-5'. [d] In chloroform-*d*. [e] Measured at 10% (w/v) concentration. [f] *p*-Me: 7.61, 7.64 (6-proton singlet), 7.68.

TABLE IV
COUPLING CONSTANTS OF METHINE AND METHYLENE PROTONS FOR PERBENZOYLATED ALDOPENTOPYRANOSES IN ACETONE-d_6 AT 31°

Compd	Configuration	Coupling constants,[a] Hz $J_{1,2}$	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$[b,c]	$J_{4,5'}$[b,c]	$J_{5,5'}$
9	α-D-*ribo*[d]	3.6	3.3	3.2	9.0	4.6	−11.4
10	β-D-*ribo*	3.1	3.8	3.7	2.3	3.9	−12.9
11	α-D-*arabino*[e]	5.1	*f*	*f*	4.6	2.1	−12.7
12	β-D-*arabino*	3.3	10.7	3.4	0.8	2.0	−13.3
13	α-D-*xylo*	3.6	9.9	9.7	5.9	11.8	−11.0
14	β-D-*xylo*[g]	5.1	6.7	6.6	4.0	6.6	−12.3
15	α-D-*lyxo*	3.1	3.3	9.0	4.6	9.1	−11.7
16	β-D-*lyxo*[h]	3.0	3.6	*e*	2.4	3.8	−12.9
17	β-D-*ribo* tetra-*p*-toluate	3.6	3.9	3.8	2.7	4.4	−12.9

[a] Data taken from spectra measured at 100 MHz at a sweep width of 100 Hz. [b] Coupling constants calculated by ABX analysis. [c] The proton on C-5 giving the higher field signal is designated H-5'. [d] $J_{3,5} = 0.6$ Hz. [e] In chloroform-*d*. [f] First-order couplings not observed. [g] Measured at 10% (w/v) concentration. [h] $J_{1,3} = 0.7$ Hz; $J_{3,5} = 0.6$ Hz.

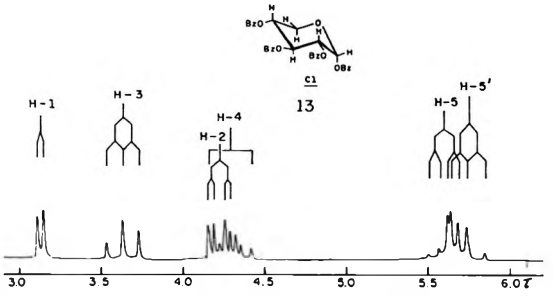


Figure 1.—Partial nmr spectrum of α-D-xylopyranose tetrabenzoate (13) at 100 MHz in acetone-d_6.

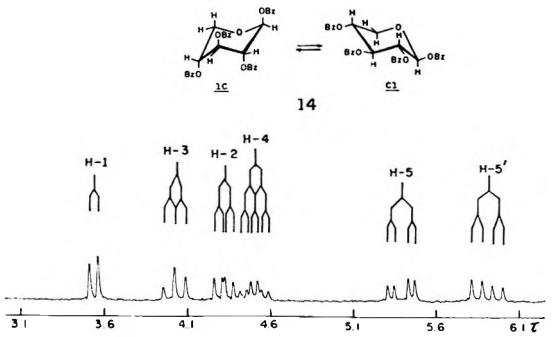


Figure 2.—Partial nmr spectrum of β-D-xylopyranose tetrabenzoate (14) at 100 MHz in acetone-d_6.

Chloroform-*d* was used as solvent with compounds **3** and **11** in order to obtain easily interpreted spectra.

Analysis of the signals of H-4 and the two protons at C-5 as ABX spin systems[27] gave $J_{4,5}$ and $J_{4,5'}$ values for the peracetylated (**1**–**8**) and perbenzoylated (**9**–**16**) aldopentopyranose sugars that are weighted time

TABLE V
RATE OF CONFORMATIONAL INVERSION FOR β-D-RIBOPYRANOSE TETRAACETATE (2) AND β-D-LYXOPYRANOSE TETRAACETATE (8) IN ACETONE-d_6 AT VARIOUS TEMPERATURES

Compd	Spectrometer frequency, MHz	Coalescence temp (T_c), °C	Rate of conformational inversion (k), sec^{-1} at T_c $1C \rightarrow C1$	$C1 \rightarrow 1C$
2	220	−60	57	117
	100	−68	25	51
	60	−73	14	29
8	100	−82	38	25

TABLE VI
TEMPERATURE DEPENDENCE OF THE CONFORMATIONAL EQUILIBRIUM FOR β-D-RIBOPYRANOSE TETRABENZOATE (10) AND β-D-XYLOPYRANOSE TETRABENZOATE (14) IN CHLOROFORM-*d*

Compd	Temp,[a] °C	$J_{1,2}$,[b] Hz
10	+59	3.5
	+42	3.4
	+6	3.0
	−23	2.7
	−46	2.3
14	+67	4.5
	+36	4.2
	−5	3.9
	−29	3.4
	−48	3.0

[a] ±2°. [b] A decrease in the coupling indicates a shift in the equilibrium position toward the $1C$(D) conformation.

TABLE VII

SOLVENT DEPENDENCE OF THE CONFORMATIONAL EQUILIBRIUM FOR β-D-RIBOPYRANOSE TETRAACETATE (2) AT 31°

Solvent	ϵ[a]	$J_{1,2}$,[b] Hz
CCl_4	2.2	5.5
C_6D_6	2.3	5.0
$C_6D_5CD_3$	2.4	5.3
$CDCl_3$	4.8	4.7
C_5D_5N	12.3	4.5
$(CD_3)_2CO$	20.7	4.6
CD_3CN	37.5	4.5
$(CCl_3)_2CO$		5.2

[a] Values taken from A. A. Maryott and E. R. Smith, Table of Dielectric Constants of Pure Liquids, National Bureau of Standards Circular 514, U. S. Government Printing Office, Washington, D. C., 1951. [b] Data taken from spectra measured at 100 MHz at a sweep width of 100 Hz.

TABLE VIII

SOLVENT DEPENDENCE OF THE CONFORMATIONAL EQUILIBRIUM FOR β-D-XYLOPYRANOSE TETRABENZOATE (14) AT 29°

		Coupling constants,[a] Hz	
Solvent	ϵ[b]	$J_{1,2}$	$J_{2,3}$
C_6D_6	2.3	5.0	6.7
$C_6D_5CD_3$	2.4	5.2	6.9
$CDCl_3$	4.8	4.3	5.9
C_5D_5N	12.3	4.3	5.9
$(CD_3)_2CO$	20.7	5.1	6.7
$(CD_3)_2SO$	48.9	5.3	6.9
$(CCl_3)_2CO$		4.1	5.7

[a] Values taken from A. A. Maryott and E. R. Smith, Table of Dielectric Constants of Pure Liquids, National Bureau of Standards Circular 514, U. S. Government Printing Office, Washington, D. C., 1951. [b] Data taken from spectra measured at 100 MHz at a sweep width of 100 Hz.

TABLE IX

CHEMICAL SHIFTS OF 1-ACETYL METHYL GROUPS IN β-D-RIBOPYRANOSE (2), α-D-ARABINOPYRANOSE (3), β-D-XYLOPYRANOSE (6), AND α-D-LYXOPYRANOSE (7) TETRAACETATES, AS ASSIGNED BY SYNTHESIS OF SPECIFICALLY DEUTERATED DERIVATIVES

	Chemical shifts (τ) of 1-acetyl group signals			
Solvent	2	3	6	7
Chloroform-*d*	7.876[a]	7.89	7.903[a]	7.85
Acetone-d_6	7.89	7.93	7.936[a]	7.85
Benzene-d_6	8.37	8.31	8.37	8.36

[a] Measured at 50-Hz sweep width.

averages for the two chair confromers in rapid equilibrium. Conformational populations at 31° were determined from the observed coupling of H-4 with the trans-disposed proton at C-5, taken in conjunction with values for $J_{4e,5e}$ and $J_{4a,5a}$ that had been obtained from model compounds. The model compounds chosen for $J_{4a,5a}$ were α-D-xylopyranose tetraacetate (**5**) and tetrabenzoate (**13**). The vicinal spin couplings for these two derivatives remained unchanged as the temperature was lowered to −50°, and it was thus concluded that both **5** and **13** were essentially all in the *C1*(D) conformation at 31°. Accordingly, the $J_{4,5a}$ value of 11.6 Hz measured for **5** was taken as the magnitude of $J_{4a,5a}$ for each sugar acetate and the $J_{4,5a}$ of 11.8 Hz for **13** as the magnitude of $J_{4a,5a}$ for each benzoate. The model compounds chosen for $J_{4e,5e}$ were β-D-arabinopyranose tetraacetate (**4**) and tetrabenzoate (**12**). The $J_{4,5'}$ values for both compounds decreased to a limit of 1.5 Hz at low temperatures, and this value was used throughout as the magnitude of $J_{4e,5e}$ for each sugar

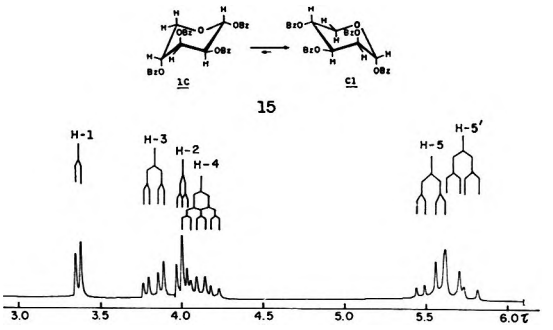


Figure 3.—Partial nmr spectrum of α-D-lyxopyranose tetrabenzoate (**15**) at 100 MHz in acetone-d_6.

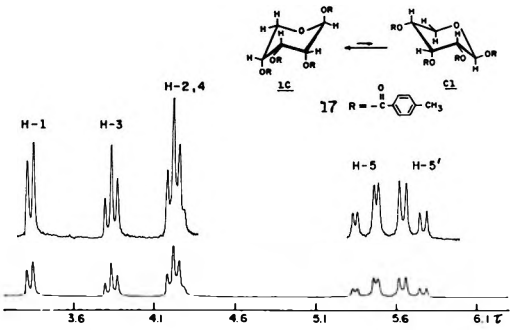


Figure 4.—Partial nmr spectrum of β-D-ribopyranose tetra-*p*-toluate (**17**) at 100 MHz in acetone-d_6.

acetate and benzoate. The limits of accuracy for the calculations were determined from the uncertainty of ±0.1 Hz in the experimental values of the time-averaged couplings, in conjunction with a conservative estimate (±0.5 Hz) of the extent to which the "model" coupling values actually vary from the true couplings for the separate conformers of each compound. From the conformational populations determined from the spin-coupling data, the equilibrium constants (K) and free-energy differences ($\Delta G°$) for the *1C*(D) ⇄ *C1*(D) equilibria given in Tables X and XI were calculated.

Results and Discussion

Conformational Equilibrium near Room Temperature.—For the aldopentopyranose tetraacetates and tetrabenzoates in solution, a conformational equilibrium between the two chair forms, with an appreciable (10% or more) proportion of the less favored chair form, is the rule rather than the exception. Of the seventeen examples in Tables X and XI, only for the *α-xylo* configuration is the *C1*(D) conformer favored overwhelmingly, and only for the *β-arabino* configuration is the *1C*(D) conformer favored very strongly.

Inspection of the equilibrium constants listed in Tables X and XI reveals that, except for the *α-ribo* derivatives, the tetrabenzoates have a greater proportion of that chair conformer having the 1 substituent axial than the corresponding tetraacetates. Thus, β-D-xylopyranose tetraacetate (**6**) has approximately 72% of the *C1* form, whereas β-D-xylopyranose tetrabenzoate (**14**) has about an equal amount of each conformer ($\Delta\Delta G°$ = −0.59 kcal mol^{-1}). Also, α-D-arabinopyranose tetraacetate (**3**) has about 10% less of the *C1*(D) conformation at equilibrium than does the tetrabenzoate (**11**) ($\Delta\Delta G°$ = 0.30 kcal mol^{-1}). Furthermore, β-D-lyxopyranose tetraacetate (**8**) has 39% of the *C1*-

TABLE X

CONFORMATIONAL EQUILIBRIA OF PERACETYLATED ALDOPENTOPYRANOSES IN ACETONE-d_6 AT 31°

Compd	Configuration	Equilibrium data: % *C1*	% *1C*	$K = C1/1C$	$\Delta G°_{31}$, kcal mol^{-1} for *1C*(D) ⇄ *C1*(D)
1	α-D-*ribo*	77	23	3.4	−0.74 ± 0.33
2	β-D-*ribo*	43	57	0.74	+0.18 ± 0.26
3	α-D-*arabino*[a]	79	21	0.26	+0.81 ± 0.34
4	β-D-*arabino*	96	4	0.04	+1.9 ± 1.0
5	α-D-*xylo*	>98	<2	>50[b]	<−2.4
6	β-D-*xylo*	72	28	2.6	−0.58 ± 0.30
7	α-D-*lyxo*	71	29	2.5	−0.55 ± 0.30
8	β-D-*lyxo*	39	61	0.63	+0.28 ± 0.27

[a] In chloroform-*d*. [b] Almost exclusively *C1*(D) at 31°.

TABLE XI

CONFORMATIONAL EQUILIBRIA OF PERBENZOYLATED ALDOPENTOPYRANOSES IN ACETONE-d_6 AT 31°

Compd	Configuration	Equilibrium data: % *C1*	% *1C*	$K = C1/1C$	$\Delta G°_{31}$, kcal mol^{-1} for *1C*(D) ⇄ *C1*(D)
9	α-D-*ribo*	73	27	2.7	−0.60 ± 0.29
10	β-D-*ribo*	23	77	0.30	+0.72 ± 0.31
11	α-D-*arabino*[a]	30	70	0.43	+0.51 ± 0.28
12	β-D-*arabino*	5	95	0.05	+1.8 + 0.9
13	α-D-*xylo*	>98	<2	>50[b]	<−2.4
14	β-D-*xylo*[c]	49	51	0.98	+0.01 ± 0.21
15	α-D-*lyxo*	74	26	2.8	−0.63 ± 0.30
16	β-D-*lyxo*	22	78	0.29	+0.76 ± 0.32
17	β-D-*ribo* tetra-*p*-toluate	28	72	0.39	+0.57 ± 0.29

[a] In chloroform-*d*. [b] Almost exclusively *C1*(D) at 31°. [c] Measured at 10% (w/v) concentration.

(D) conformation, whereas the tetrabenzoate (**16**) has only 22% at equilibrium ($\Delta\Delta G° = -0.48$ kcal mol^{-1}). Similar shifts of the equilibrium position, toward the chair conformation having the anomeric polar substituent axially disposed, in going from the tetraacetates to the tetrabenzoates were observed for the β-D-*ribo* ($\Delta\Delta G° = -0.54$ kcal mol^{-1}) and α-D-*lyxo* ($\Delta\Delta G° = 0.08$ kcal mol^{-1}) derivatives. The α-*xylo* and β-*arabino* derivatives are observed to have, within experimental error, the same conformational populations. It is evident from the $\Delta\Delta G°$ values that the changes in the conformational populations are dependent on the total stereochemistry of the derivative. These results accord with earlier observations[4] that the all-axial form of the tri-*O*-acyl-β-D-xylopyranosyl chlorides in chloroform-*d* is favored to the extent of ~80% with the acetate, but to >95% with the benzoate (see also ref 21, cited in ref 4). Similar results are evident from studies with alkyl tri-*O*-acylpentopyranosides[29a] and various other pentopyranose esters.[29a]

Shifts in the position of the conformational equilibria in comparing the tetraacetates with the tetrabenzoates evidently result from differences in the nonbonded syn-diaxial and gauche-vicinal interactions and/or electronic interactions in the two groups of derivatives. Differences in steric interactions should, however, not be significant since the conformational free energies ("*A*" values)[29b] at room temperature of the acetoxy and benzoyloxy groups are very similar, that of the benzoyloxy substituent being only 0.02 kcal mol^{-1} smaller. From an inspection of molecular models, differences in nonbonded gauche interactions are also anticipated to be minor. The observed differences in conformational populations must, therefore, be controlled mainly by the changes in the electronic forces that occur upon replacement of acetoxy by benzoyloxy groups. The magnitude of the anomeric effect of the benzoyloxy substituent should be slightly larger than that of the acetoxy group because of the greater electron-withdrawing ability of the benzoyl group, and replacement of the acetoxy groups at C-2, C-3, and C-4 with the more electronegative benzoyloxy substituents should result in an enhancement of the magnitude of the axial-directing effect exhibited by the polar group at C-1, as predicted from Lemieux's interpretation of the anomeric effect.[17,18] Such augmentation of the anomeric effect has been also observed in other pyranoid ring systems.[17,30] Enhancement[4,31] of polar contributions from substituents other than that at C-1 may also be a factor. The net effect of these changes in the electronic interactions would be to increase the equilibrium proportion for the perbenzoates of the chair conformation having the anomeric substituent in axial orientation, in accord with the observed shifts in the conformational equilibria for most of the examples, when the tetrabenzoates are compared with the tetraacetates.

The larger proportion of the *1C*(D) conformation at equilibrium for α-D-ribopyranose tetrabenzoate (**9**) than for the corresponding tetraacetate (**1**) ($\Delta\Delta G° = -0.14$ kcal mol^{-1}), in the direction opposite to the shifts found for the other configurations, may be due in part to an attractive interaction between the syn-diaxial benzoyloxy groups at C-2 and C-4. That such attractive forces may actually be a factor is seen from the fact that the $\Delta\Delta G°$ values for the β-*xylo* and β-*ribo* derivatives, where substituents on O-2 and O-4 are syn

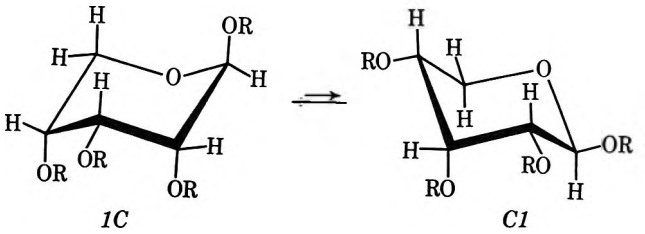
(29) (a) P. L. Durette and D. Horton, *Carbohyd. Res.*, **18**, 289, 389, 403, 419(1971); (b) F. A. L. Anet and P. M. Henrichs, *Tetrahedron Lett.*, 741 (1969).

(30) F. Sweet and R. K. Brown, *Can. J. Chem.*, **46**, 1543 (1968).

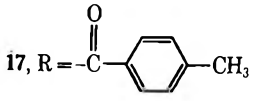
(31) G. Wood, E. P. Woo, and M. H. Miskow, *ibid.*, **47**, 429 (1969); C. B. Anderson, D. T. Sepp, M. P. Geis, and A. A. Roberts, *Chem. Ind. (London)*, 1805 (1968); R. D. Stolow, T. Groom, and P. D. McMaster, *Tetrahedron Lett.*, 5781 (1968); R. D. Stolow, T. W. Giants, and J. D. Roberts, *ibid.*, 5777 (1968).

diaxial in the *1C*(D) conformation, are larger than the values for the *α-arabino*, *α-lyxo*, and *β-lyxo* derivatives, where no such interactions are present in either conformer.

The conformational equilibrium at room temperature of β-D-ribopyranose tetra-*p*-toluate (**17**) in acetone-d_6 was also examined. The proportion of the *1C*(D) form



1C *C1*



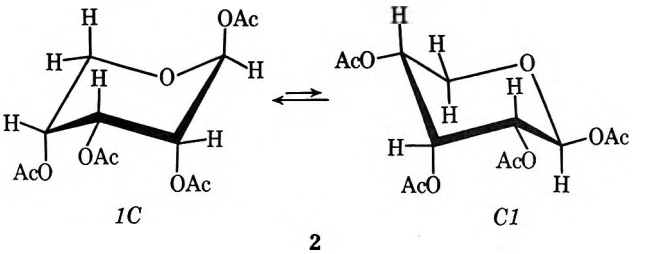
17, R = -C(=O)-C6H4-CH3

$K = 0.39$

present at equilibrium was found to be intermediate between that for the corresponding tetraacetate (**2**) and tetrabenzoate (**10**), but, as expected, it was closer to the value for the tetrabenzoate. The observed shift in the equilibrium toward the *C1*(D) conformer for this derivative relative to the tetrabenzoate probably reflects a decrease in the magnitude of the axial-directing influence of the C-1 substituent as a result of the electron-donating effect of the substituted methyl groups on the aromatic rings.

Conformational Equilibrium and Rate of Conformational Inversion in Pyranoid Sugar Derivatives.—In the case of β-D-ribopyranose tetraacetate (**2**), it has already been shown[8,10] by low-temperature nmr spectroscopy in acetone-d_6 that it is possible to observe signals of the separate chair conformers because a substantial proportion of the minor conformer is present at −84°, a temperature at which conformational interconversion is slow on the nmr time scale. A similar "conformational freeze-out" was observed in the spectrum of β-D-lyxopyranose tetraacetate (**8**); at +2° the H-1 signal is a narrow doublet at τ 3.93, whereas at −97° separate signals at τ 4.00 and 3.81 are observed. The relative intensities of these signals give for the *1C*(D) ⇄ *C1*(D) equilibrium at −97° a $\Delta G°$ value of −0.14 ± 0.04 kcal mol^{-1}.

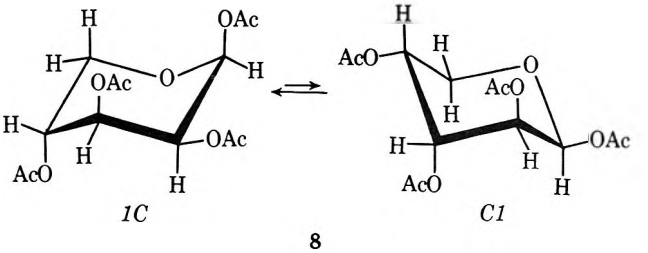
In previous papers on the conformational equilibria of aldopentopyranose tetraacetates,[7,8,10] we reported the frequencies with which one chair conformer of **2** and **8** undergoes ring flip to the alternative chair conformer, as calculated from the equation of Gutowsky and Holm,[32] $k = (\sqrt{2}/2)\pi|\nu_a - \nu_e|$, which relates the rate constant of conformational interconversion to the maximum separation of the signals of an individual proton at conformational "freeze-out." This relationship is strictly valid only when the equilibrium constant for the interconverting species is unity, but when the constant is close to unity, as with β-D-ribopyranose tetraacetate, the error in the calculated rate constant is small. A simple technique has been described[33] that is convenient for calculating rates of conformational interconversion for any two exchanging species at the "coalescence temperature" and thus, by using the Eyring equation, to calculate free energies of activation. Application of this method to the conformational equilibria of β-D-ribopyranose tetraacetate (**2**) and β-D-lyxopyranose tetraacetate (**8**), the only two pentose peracetates for which a conformational "freeze-out" has been detected at temperatures down to −100°, yields the rate data given in Table V and the following free energies of activation, assuming a transmission coefficient of unity.



1C *C1*

2

$K_{-84°} = C1/1C = 0.5$
$\Delta G^{\ddagger}_{1C \rightarrow C1} = 10.6 \pm 0.3$ kcal mol^{-1}
$\Delta G^{\ddagger}_{C1 \rightarrow 1C} = 10.3 \pm 0.3$ kcal mol^{-1}



1C *C1*

8

$K_{-97°} = C1/1C = 1.5$
$\Delta G^{\ddagger}_{1C \rightarrow C1} = 9.6 \pm 0.4$ kcal mol^{-1}
$\Delta G^{\ddagger}_{C1 \rightarrow 1C} = 9.8 \pm 0.4$ kcal mol^{-1}

Interestingly, the free energy differences ($\Delta G°$) for **2** and **8** measured at 31° differ from those measured at the temperature of "conformational freeze-out," indicating that the entropy difference, $\Delta S°$, between the two chair conformers does not equal zero. A similar observation was made previously for β-D-xylopyranose tetraacetate[8] (**6**). The entropy difference between the *1C*(D) and *C1*(D) conformations is positive for the β-D-*ribo* compound but is negative for both the β-D-*xylo* and β-D-*lyxo* derivatives.

In order to "freeze-out" a conformational equilibrium in a pyranoid sugar derivative and thus measure directly the conformational equilibrium constant and rate of ring flip, it is necessary to have (1) a reasonably concentrated (5–10%) solution that can be observed in the nmr spectrometer over a wide temperature range without crystallization of the solute, boiling or freezing of the solvent, or development of high viscosity in the solution that would lead to excessive line broadening and loss of necessary spectral detail; (2) a compound in which the proportion of the less favored conformer is sufficient for detection at the temperature of "conformational freeze-out;" and (3) the free energy of activation, $\Delta G^{\ddagger}$, for conformational inversion must be sufficiently large (rate of ring flip sufficiently small) for a "freeze-out" to be obtainable within the temperature limits of the variable temperature accessory of the nmr spectrometer (∼−150 → ∼200°).

Of the 16 aldopentopyranose tetraacetates and tetra-

(32) H. S. Gutowsky and C. H. Holm, *J. Chem. Phys.*, **25**, 1228 (1956); J. A. Pople, W. G. Schneider, and H. J. Bernstein, "High-Resolution Nuclear Magnetic Resonance," McGraw-Hill, New York, N. Y., 1959, p 223.

(33) H. Shanan-Atidi and K. H. Bar-Eli, *J. Phys. Chem.*, **74**, 961 (1970).

benzoates investigated in the present work, only two have thus far yielded detectable "conformational freeze-outs" at temperatures down to −100°. β-D-Ribopyranose tetraacetate (**2**) and β-D-lyxopyranose tetraacetate (**8**) had a substantial proportion of the less favored chair form present at equilibrium at low temperatures and their free energies of activation (9.6–10.6 kcal mol^{-1}) were high enough to permit accurate determination of the equilibrium constants. The other six tetraacetates did not exhibit "freeze-outs" because at low temperatures the conformational equilibria favored one chair conformer strongly as a result of the shift of the equilibrium position toward the more stable conformation.

It was anticipated that, since β-D-xylopyranose tetrabenzoate (**14**) has an equal amount of each chair form present at equilibrium near room temperature, a "conformational freeze-out" would be detected at low temperatures. However, none was observed in a 1:1 mixture of acetone-d_6 and benzene-d_6 at temperatures down to −90°. That such was the case may be attributed to the high conformational mobility of this derivative even at low temperatures ($\Delta G^{\pm}$ <9 kcal mol^{-1}).

The higher rate of conformational interconversion of β-D-xylopyranose tetrabenzoate (**14**), as compared with that of **2** and **8**, is probably due to the presence of four substituents in axial orientation in the *1C*(D) conformation for **14** as compared with only three for **2** and **8**. Schmid and coworkers have shown[34] that, with the syn-diaxial arrangement of two or more methyl substituents on a cyclohexane ring, the relative energy of the transition state for conformational inversion is less markedly increased than is that of the ground state. This factor results in a decrease of the free energy of activation as compared with cyclohexane itself. A "freeze-out" should be observable, however, at temperatures below −100°.

An apparent "conformational freeze-out" was detected for α-D-arabinopyranose tetrabenzoate in a 2:1 mixture of chloroform-*d* and toluene-d_6. However, the spectral dispersion at 100 MHz was insufficient to allow specific assignment of signals.

Conformational Equilibrium and Its Temperature Dependence.—As the temperature is lowered by stages from room temperature, there is detected an increase in the equilibrium proportion of that chair conformer having the lower enthalpy. Which of the two chair forms has the lower enthalpy is not always evident from the equilibrium data at room temperature because the entropy difference ($\Delta S°$) between the two forms does not equal zero, and, therefore, to obtain this information, the equilibrium constant must be measured as a function of the temperature. For the equilibrium process, *1C*(D) ⇄ *C1*(D), a decrease in temperature will result in an increase in the proportion of the *C1*(D) conformation if the enthalpy difference ($\Delta H°$) is negative and an increase in the *1C*(D) form if the enthalpy difference is positive.

The effect of decreasing temperature on conformational population was investigated for the D-aldopentopyranose tetraacetates (**1**–**8**) and tetrabenzoates (**9**–**16**), and the results are presented in Table XII. The sign of the enthalpy difference is a function of not only the total stereochemistry of the sugar but also the nature of the substituents on the tetrahydropyran ring. A decrease in the temperature results in an increase in the conformational population of the *C1* form (negative $\Delta H°$) for both α-D-ribopyranose tetraacetate (**1**) and tetrabenzoate (**9**). On the other hand, whereas β-D-lyxopyranose tetraacetate (**8**) and β-D-xylopyranose tetraacetate (**6**) have a negative $\Delta H°$ value, the corresponding tetrabenzoates **16** and **14** have a postive $\Delta H°$ value. Finally, both α-D-arabinopyranose tetraacetate (**3**) and tetrabenzoate (**11**) have a positive value of $\Delta H°$. The differences in the sign of the enthalpy difference reflect the changes in the various steric and electronic interactions that occur in comparing the tetraacetates with the tetrabenzoates. Steric factors appear to control the direction of the enthalpy change for α-D-arabinopyranose tetraacetate (**3**) and tetrabenzoate (**11**), β-D-xylopyranose tetraacetate (**6**), and β-D-lyxopyranose tetraacetate (**8**) since the shift in the equilibrium position with decreasing temperature is toward the chair form having the anomeric substituent in equatorial orientation (unfavorable anomeric effect) but also having fewer syn–diaxial interactions. Electronic forces seem to be the determining factor for the tetrabenzoates **14** and **16**, since the equilibrium shift is now toward that conformer having the C-1 substituent axial (favorable anomeric effect). The remaining tetraacetates and tetrabenzoates all exhibit shifts toward that conformer having the anomeric group axial.

An interesting observation is that β-D-ribopyranose tetraacetate (**2**) has a negative enthalpy difference, even though the *1C*(D) conformer has a syn–diaxial interaction between two acetoxy groups. This illustrates the strong influence of the anomeric effect in directing the conformational stability of pyranose sugars having an acetoxy group at the anomeric position. However, the additional syn–diaxial interactions in the *1C*(D) conformation of **3**, **6**, and **8** are accompanied by a change in the sign of $\Delta H°$.

TABLE XII

EFFECT OF DECREASING TEMPERATURE ON THE CONFORMATIONAL EQUILIBRIA FOR THE PERACETYLATED AND PERBENZOYLATED ALDOPENTOPYRANOSES IN ACETONE-d_6

Compd	Configuration	ΔH	ΔK (*C1*/*1C*)	Shift in equilibrium for *1C*(D) ⇄ *C1*(D)
1	α-D-*ribo* OAc_4	−	+	→
9	α-D-*ribo* OBz_4	−	+	→
2	β-D-*ribo* OAc_4	+	−	←
10	β-D-*ribo* OBz_4	+	−	←
3	α-D-*arabino* OAc_4[a]	+	−	←
11	α-D-*arabino* OBz_4[a]	+	−	←
4	β-D-*arabino* OAc_4	+	−	←
12	β-D-*arabino* OBz_4	+	−	←
5	α-D-*xylo* OAc_4	−	[b]	[b]
13	α-D-*xylo* OBz_4	−	[b]	[b]
6	β-D-*xylo* OAc_4	−	+	→
14	β-D-*xylo* OBz_4[a]	+	−	←
7	α-D-*lyxo* OAc_4[c]	−	+	→
15	α-D-*lyxo* OBz_4[d]	−	+	→
8	β-D-*lyxo* OAc_4	−	+	→
16	β-D-*lyxo* OBz_4[e]	+	−	←

[a] In chloroform-*d*. [b] Almost exclusively *C1*(D) at 31°. [c] $J_{1,2}$ = 3.0 Hz at +31°; 2.2 Hz at −51°. [d] $J_{1,2}$ = 3.1 Hz at +31°; 1.7 Hz at ∼−50°. [e] $J_{4,5'}$ = 3.8 Hz at +31°; 2.3 Hz at ∼−40°.

(34) H. G. Schmid, A. Jaeschke, H. Friebolin, S. Kabuss, and R. Mecke, *Org. Magn. Resonance*, **1**, 163 (1969).

The fact that **6** and **8** have $\Delta H°$ values of a different sign than **14** and **16** is an indication of the enhanced anomeric effect and other electronic interactions for the tetrabenzoates. In spite of these electronic factors, α-D-arabinopyranose tetrabenzoate still has a positive $\Delta H°$ value.

The temperature dependence of the $J_{1,2}$ coupling has been measured for β-D-xylopyranose tetraacetate (**6**) in acetone-d_6[8] and β-D-ribopyranose tetrabenzoate (**10**) and β-D-xylopyranose tetrabenzoate (**14**) in chloroform-*d*. The results for the latter two compounds are given in Table VI. For both tetrabenzoates there is observed a regular decrease in the magnitude of $J_{1,2}$, as would be expected from a shift in the equilibrium that would favor the *1C*(D) form (H-1 and H-2 diequatorial) increasingly at lower temperatures.

Conformational Equilibrium and Its Solvent Dependence.—That solvent polarity does not affect in any regular manner the position of conformational equilibria for tetrasubstituted tetrahydropyran ring systems is evident from a study of the solvent dependence of the conformational populations of β-D-ribopyranose tetraacetate[7] (**2**), β-D-xylopyranose tetrabenzoate[6] (**14**), and tri-*O*-acetyl-β-D-xylopyranosyl chloride.[4] In Table VII is given the $J_{1,2}$ coupling for **2** and in Table VIII the $J_{1,2}$ and $J_{2,3}$ couplings for **14** in various deuterated solvents as a function of the dielectric constant. These couplings provide a measure of the equilibrium constant since they represent a time average between a diaxial arrangement of the coupled protons in the *C1*(D) conformation and a diequatorial orientation in the alternative *1C*(D) conformation. As the solvent polarity was increased, there was not observed any regular increase in the vicinal spin couplings as would have been expected from an increase in the proportion of the *C1*(D) conformation having the anomeric substituent equatorial. Such a shift would have resulted had there been a decrease in the magnitude of the anomeric effect with increasing solvation of the interacting dipoles. Evidently, any solvation of the dipoles involved in the operation of the anomeric effect must be approximately cancelled by other effects resulting from change of solvent.

Similar observations have been made by Lemieux and coworkers from an examination of solvent effects on the conformational equilibrium of a monosubstituted tetrahydropyran[35] and a trisubstituted tetrahydropyran.[36]

Factors Influencing Conformational Stability.—Various empirical treatments have been advanced for predicting the conformational preferences of polysubstituted tetrahydropyran ring systems, based on additive contributions of steric interactions[37,38] and with the polar contribution of the anomeric effect.[17,39,40] The data presented in the present work cannot be accommodated within the framework of these existing interpretations except on a very broad, qualitative basis, even with adjustment of the magnitudes estimated for the various steric and polar elements. These results, and the observation of Lemieux and Pavia[36] that the magnitude of nonbonded interactions between atoms that have unshared pairs of electrons depends on the substituent on these atoms, point out the need for more accurate determinations of steric interactions by methods such as those reported by Wolfe and Campbell[41] and Tichý and coworkers[42] for the evaluation of syn–diaxial interactions, and that of Tichý and coworkers[43,44] and Aycard and coworkers[45] for the determination of vicinal–gauche interactions. Vicinal–gauche interactions in a tetrahydropyran ring may be expected to vary according to the position and configuration of the substituents because of the "nonideal" geometry of the heterocyclic ring and the consequent variations from the "ideal" values in the dihedral angles around the ring.

In addition, other factors, such as polar contributions from other than the C-1 substituent, attractive interactions between syn–diaxial substituents,[46] vicinal–gauche interactions,[44,45] and specific solvation effects such as hydrogen bonding and formation of charge–transfer complexes, must also be reconsidered in attempting to interpret quantitatively the conformational distributions of polysubstituted, six-membered ring systems, especially when a ring heteroatom is involved.

Assignment of 1-Acetyl Methyl Group Signals by Means of Specifically Deuterated Derivatives.—The nmr spectra in chloroform-*d* of the tetraacetates having the β-D-*ribo* (**2**), α-D-*arabino* (**3**), β-D-*xylo* (**6**), and α-D-*lyxo* (**7**) configurations were compared with those of the corresponding analogs **18**, **19**, **20**, and **21** that had been specifically deuterated in the 1-acetyl methyl group. The spectra of **18**, **19**, **20**, and **21** were identical in all respects with those of **2**, **3**, **6**, and **7**, respectively, except that one three-proton singlet in the spectra of the latter group was absent in those of the former, and this signal in **2**, **3**, **6**, and **7** could thus be assigned unambiguously to the 1-acetyl methyl group. The spectra of the deuterated derivatives were also measured in acetone-d_6 and in benzene-d_6. Assignments of the signals are given in Table IX. The signal of the 1-*O*-acetyl group is observed in chloroform-*d* and acetone-d_6 at lower field than all of the other acetoxy group signals for **2**, **6**, and **7**, but for the α-D-*arabino* derivative (**3**), the 1-acetoxy signal is observed at next to lowest field. Similar deuteration experiments have established that the 1-acetoxy group resonates at lower field than the other acetoxy groups in β-D-glucopyranose pentaacetate[47] in chloroform-*d* and in 2-acetamido-1,3,4,6-tetra-*O*-acetyl-2-deoxy-α-D-glucopyranose[48] in chloroform-*d* and acetone-d_6. The present results show that, in nonaromatic solvents, the 1-

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(36) R. U. Lemieux and A. A. Pavia, *ibid.*, **47**, 4441 (1969).
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(38) R. B. Kelly, *Can. J. Chem.*, **35**, 149 (1957).
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(40) S. J. Angyal, *Angew. Chem., Int. Ed. Engl.*, **8**, 157 (1969).
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acetoxy group usually gives the lowest field, acetoxy group signal, but there are exceptions to this behavior.

The well-known upfield shift of acetate signals in nmr spectra caused by aromatic solvents[49] was also observed for **2**, **3**, **6**, and **7**. In all four cases these signals were detected ~0.4 ppm to higher field in benzene-d_6 than their positions in nonaromatic solvents. It is noteworthy that, when the spectra are measured in benzene-d_6, the signal of the 1-*O*-acetyl group for **2** and **7** is shifted to highest field and to second highest field position for **3** and **6**. These data may be useful for further studies concerning the orientation of the substituents, and molecules of the solvent sheath, with solutions in aromatic solvents.

Further Observations on Chemical Shifts.—The chemical shifts observed for the anomeric proton of each chair conformer of β-D-ribopyranose tetraacetate (**2**) at "conformational freeze-out" at −84° accord with the generalization[13,20] that axial protons usually resonate at higher field than equatorial protons in a similar chemical environment. By Lemieux's empirical rules[20] on the effect of configuration on chemical shift, the estimated value for chemical shift of H-1e is τ 3.85 (observed τ 3.93) and that for H-1a is τ 4.00 (observed τ 4.19). A similar correlation can be made for β-D-lyxopyranose tetraacetate (**8**) at −97°, where signals for both conformers are detected. The estimated value for the chemical shift of H-1e is τ 3.85 (observed τ 3.81) and that for H-1a is τ 4.05 (observed τ 4.00). Differences between the calculated and the observed values may be due in part to variation of the equatorial and axial proton resonances with temperature.[50]

The signals for the acetate protons of β-D-ribopyranose tetraacetate (**2**) at 31° comprised a simple, 4-line pattern having the chemical shifts given in Table I. At −84°, the temperature at which signals for the seprate chair conformers were observed, the acetate region became more complex, as expected, with the appearance of five broad signals at τ 7.79, 7.82, 7.84, 7.96, and 8.04. Low-temperature studies were performed on the analogous derivative specifically deuterated in the 1-acetyl methyl group (**18**) to determine whether the two higher field singlets corresponded to the 1-acetoxy groups of the *C1*(D) and *1C*(D) conformers of **2**. If such had been the case, integration of the signals would have provided another measure of the conformational equilibrium. However, at −84° these two signals were still present, indicating that signals of the 1-acetyl methyl groups are located in the overlapping, lower field band of signals.

Studies of Configurational Equilibria.—By equilibrating 15% (w/v) solutions of each of the D-aldopentopyranose tetraacetates (**1**–**8**) at 27° in 1:1 acetic anhydride–acetic acid, 0.1 *M* in perchloric acid, the α,β anomeric equilibria for the pairs **1** and **2**, **3** and **4**, **5** and **6**, and **7** and **8** were established. The compositions of these mixtures were determined by nmr spectroscopy and the equilibrium data are recorded in Table XIII. The data are in excellent agreement with literature values[17] (determined by optical rotatory methods) for the first three pairs. The equilibrium constant for the interconversion **7** ⇄ **8**, here determined as 0.20 at 27° by approach from both sides of the equilibrium, differs substantially from the value (0.08 at 25°) previously[17] reported.

TABLE XIII

ANOMERIC EQUILIBRIA OF D-ALDOPENTOPYRANOSE TETRAACETATES AT 27° IN 1:1 ACETIC ANHYDRIDE—ACETIC ACID, 0.1 *M* IN PERCHLORIC ACID

Anomeric pair	Equilibrium constant, $K = \beta/\alpha$	$\Delta G°$, kcal mol^{-1}, for $\alpha \rightleftarrows \beta$ at 27°
Tetra-*O*-acetyl-α,β-D-ribopyranose (**1** and **2**)	3.4	−0.73 ± 0.03
Tetra-*O*-acetyl-α,β-D-arabinopyranose (**3** and **4**)	5.4	−1.01 ± 0.03
Tetra-*O*-acetyl-α,β-D-xylopyranose (**5** and **6**)	0.23	+0.89 ± 0.03
Tetra-*O*-acetyl-α,β-D-lyxopyranose (**7** and **8**)	0.20	+0.98 ± 0.05

Experimental Section

General Methods.—Evaporations were performed below 50° under diminished pressure. Melting points were determined with a Thomas-Hoover Unimelt apparatus and are uncorrected. Specific rotations were determined with a Perkin-Elmer Model 141 polarimeter in a 1-dm, narrow-bore polarimeter tube. Infrared spectra were measured with a Perkin-Elmer Infracord Model 137 spectrophotometer. Microanalyses were determined by W. N. Rond. Thin layer chromatography (tlc) was performed with 0.25-mm layers of silica gel G (E. Merck, Darmstadt, Germany) activated at 120° as the adsorbent and sulfuric acid as the indicator. Column chromatography was performed with silica gel (7734, Merck) as the adsorbent with 1 g of mixture to be separated per 30 g of adsorbent, and the components were eluted with the solvents specified.

Nmr Spectra.—Spectra were recorded at 100 MHz with a Varian HA-100 nmr spectrometer operating in the frequency-sweep mode at a probe temperature of 31 ± 1°. Unless otherwise noted, spectra were measured at a concentration of 20% (w/v). Solutions also contained 5% (w/v) of tetramethylsilane (τ 10.00) as an internal standard and to provide a lock signal. Variable-temperature measurements were made with a Varian V-4341/V-6057 variable-temperature accessory and a Varian V-6040 controller. Calibration in the low-temperature range was effected with a sample of methanol, and ethylene glycol was used for high-temperature calibration. The temperatures are considered accurate to within ±2°. Coupling constants for the equilibrium studies were obtained by second-order analysis of ABX spin systems from spectra recorded at a sweep width of 100 Hz; they are considered accurate to within ±0.1 Hz. All other coupling constants reported were obtained on a first-order basis as direct peak spacings from spectra measured at a sweep width of 100 Hz and are considered precise to within ±0.1 Hz. Chemical shifts are on the τ scale and were taken from the chart recording and/or were measured electronically by using the "Diff 1" position on a Varian V-4354A internal reference nmr stabilized controller in conjunction with a Varian V-4315 frequency counter; values are considered accurate to within ±0.005 ppm.

Preparation of β-D-Ribopyranose Tetraacetate (2).—D-Ribose (Pfanstiehl Laboratories, Inc., Waukegan, Ill.) was acetylated with acetic anhydride and pyridine by the procedure of Levene and Tipson[51] to give crystalline **2**, mp 109–110° (lit.[51] mp 110°).

α-D-Ribopyranose Tetraacetate (1).—β-D-Ribopyranose tetraacetate (**2**) was equilibrated with acetic anhydride and zinc chlo-

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ride by the procedure of Zinner[52] to give syrupy 1, $[\alpha]^{20}D$ +50.1° (*c* 1.08, chloroform) [lit.[52] $[\alpha]^{22}D$ +50.7° (*c* 3.14, methanol)].

α-D-Arabinopyranose Tetraacetate (3).—D-Arabinose was acetylated with acetic anhydride and sodium acetate according to the procedure of Hudson and Dale[53] for the preparation of the L enantiomorph to give crystalline **3**, mp 96–97°, $[\alpha]^{22}D$ −43.8° (*c* 1.00, chloroform) [lit.[53] values for the L enantiomorph, mp 97°; $[\alpha]^{22}D$ +42.5° (*c* 2.67, chloroform)].

β-D-Arabinopyranose Tetraacetate (4).—α-D-Arabinopyranose tetraacetate (**3**) was equilibrated with acetic anhydride and zinc chloride by the procedure of Hudson and Dale[53] for the preparation of the L enantiomorph to give crystalline **4**, mp 85°, $[\alpha]^{22}D$ −155.6° (*c* 0.98, acetone) [lit.[53] values for the L enantiomorph, mp 86°; $[\alpha]^{21}D$ +147.2° (*c* 4.82, chloroform)].

β-D-Xylopyranose Tetraacetate (6).—D-Xylose was acetylated by the procedure of Hudson and Johnson[54] to give crystalline **6**, mp 127–128° (lit.[54] mp 128°).

α-D-Xylopyranose Tetraacetate (5).—A modification of the procedure of Pacsu[55] for the anomerization of β acetates to their α form was used. To a solution of β-D-xylopyranose tetraacetate (**6**, 7.0 g, 22 mmol) in dry dichloromethane was added anhydrous stannic chloride (4.7 g, 18 mmol). The reaction mixture was refluxed for 5 hr, cooled, and then extracted twice with ice–water. The organic extract was washed once with 10% sodium hydrogen carbonate solution and once with ice–water. It was dried by passage over a pad of anhydrous magnesium sulfate and concentrated to a thick syrup. Crystallization of the syrup from ethanol–petroleum ether and three recrystallizations from ether–petroleum ether (bp 30–60°) gave **5** as thin, white needles: yield 5.4 g (77%); mp 56–58°; $[\alpha]^{24}D$ +92.9° (*c* 1.06, acetone) [lit.[54] mp 59°; $[\alpha]^{20}D$ +89.3° (*c* 5.02, chloroform)].

α-D-Lyxopyranose Tetraacetate (7).—D-Lyxose was acetylated with acetic anhydride and sodium acetate by the procedure of Reyle and Reichstein[56] to give crystalline **7**, mp 123–124° (lit.[57] mp 124°).

β-D-Lyxopyranose Tetraacetate (8).—The mother liquor from the preparation of α-D-lyxopyranose tetraacetate (**7**) was concentrated to a thick syrup, which was dissolved in a minimal volume of benzene and passed through a column of silica gel according to the procedure of Zinner and Brandner[57] to give syrupy, chromatographically homogeneous **8**, $[\alpha]^{22}D$ −79.7° (*c* 0.94, acetone) [lit.[57] $[\alpha]^{20}D$ −83.4 ± 0.8° (chloroform)].

β-D-Ribopyranose Tetrabenzoate (10).—D-Ribose was benzoylated with benzoyl chloride and pyridine according to the procedure of Fletcher, *et al.*,[58] to give crystalline **10**, mp 129–130° (lit.[58] mp 131°).

α-D-Ribopyranose Tetrabenzoate (9).—The mother liquor from the preparation of β-D-ribopyranose tetrabenzoate (**10**) was concentrated to a thick syrup which was dissolved in the minimal volume of benzene and passed through a column of silica gel with benzene as the eluent. The first fractions contained more of the β-D anomer [R_f 0.43 (19:1 benzene–ether)] and the middle fractions contained a mixture of the β-D and α-D anomers. The last fractions contained the chromatographically homogeneous α-D anomer **9** obtained as an amorphous glass: $[\alpha]^{28}D$ +62.4° (*c* 1.01, chloroform); R_f 0.35 (19:1 benzene–ether)]. The α-D anomer has not been previously reported in a pure form.[25]

Anal. Calcd for $C_{33}H_{26}O_9$: C, 69.96; H, 4.63. Found: C, 70.18; H, 4.80.

α-D-Arabinopyranose Tetrabenzoate (11).—D-Arabinose was dissolved in boiling pyridine and the resulting solution was kept for 24 hr at room temperature. The solution was then benzoylated as described by Fletcher and Hudson[59] to give crystalline **11**, mp 163–164° (lit.[59] mp 164–165°).

β-D-Arabinopyranose Tetrabenzoate (12).—D-Arabinose was benzoylated with benzoyl chloride and pyridine according to the procedure of Fletcher and Hudson[59] to give crystalline **12**, mp 159–161° (lit.[59] mp 160–161°).

α-D-Xylopyranose Tetrabenzoate (13).—D-Xylose was benzoylated with benzoyl chloride and pyridine by the procedure of Major and Cook[60] to give crystalline **13**, mp 119–121° (lit.[61] mp 119–120°).

β-D-Xylopyranose Tetrabenzoate (14).—D-Xylose was benzoylated by the procedure of Fletcher and Hudson[61] to give crystalline **14**, mp 175–177° (lit.[61] mp 177°).

α-D-Lyxopyranose Tetrabenzoate (15).—D-Lyxose was benzoylated with benzoyl chloride and pyridine by the procedure of Fletcher, *et al.*,[62] to give crystalline **15**, mp 137–139° (lit.[62] mp 138–139°).

β-D-Lyxopyranose Tetrabenzoate (16).—The mother liquor from the preparation of α-D-lyxopyranose tetrabenzoate (**15**) was concentrated to a thick syrup. The syrup was passed through a column of neutral alumina as described by Fletcher, *et al.*,[25] to give crystalline **16**, mp 117–120° (lit.[25] mp 118–122°).

β-D-Ribopyranose Tetra-*p*-toluate (17).—To a solution of D-ribose in pyridine was added dropwise a solution of *p*-toluoyl chloride in pyridine according to the procedure of Zinner and Belau[26] to give crystalline **17**, mp 171–172° (lit.[26] mp 172–173°).

2,3,4-Tri-*O*-acetyl-1-*O*-trideuterioacetyl-β-D-ribopyranose (18).—To a solution of tri-*O*-acetyl-β-D-ribopyranosyl chloride (3.1 g, 11 mmol) in acetonitrile (30 ml) was added silver acetate-d_3 (1.9 g, 11 mmol). The mixture was heated on a steam bath for 3 hr, cooled, and then filtered over a Celite pad to remove precipitated silver chloride. The resulting solution was concentrated to a thick syrup which was crystallized from 95% ethanol. Recrystallization from 95% ethanol gave **18**, yield 2.4 g (72%), having melting point, $[\alpha]D$, and ir spectrum identical with those of **2**. The nmr spectra of **18** in chloroform-*d*, acetone-d_6, and benzene-d_6 were identical with those of **2** except that the 3-proton singlets at τ 7.876, 7.89, and 8.37, respectively, were absent.

2,3,4-Tri-*O*-acetyl-1-*O*-trideuterioacetyl-α-D-arabinopyranose (19).—This compound was prepared in the same manner as **18**, starting from tri-*O*-acetyl-β-D-arabinopyranosyl chloride (1.0 g) and silver acetate-d_3 (0.6 g), to give crystalline **19**, yield 0.82 g (75%), having melting point, $[\alpha]D$, and ir spectrum identical with those of **3**. The nmr spectra of **19** in chloroform-*d*, acetone-d_6, and benzene-d_6 were identical with those of **3** except that the 3-proton singlets at τ 7.89, 7.93, and 8.31, respectively, were absent.

2,3,4-Tri-*O*-acetyl-1-*O*-trideuterioacetyl-β-D-xylopyranose (20).—This compound was prepared in the same way as **18**, starting from tri-*O*-acetyl-β-D-xylopyranosyl chloride (3.5 g) and silver acetate-d_3 (2.1 g), to give crystalline **20**, yield 2.6 g (69%), having melting point, $[\alpha]D$, and ir spectrum identical with those of **6**, except that the 3-proton singlets at τ 7.903, 7.936, and 8.37, respectively, were absent.

2,3,4-Tri-*O*-acetyl-1-*O*-trideuterioacetyl-α-D-lyxopyranose (21).—A solution of tri-*O*-acetyl-α-D-lyxopyranosyl bromide (2.0 g, 5.9 mmol) in acetonitrile (20 ml) to which was added silver acetate-d_3 (1.2 g, 7.1 mmol) was stirred at room temperature for 1 hr. After filtration over a Celite pad to remove precipitated silver bromide, the solution was concentrated to a thick syrup, which crystallized from 95% ethanol. Recrystallization from 95% ethanol gave **21**, yield 1.3 g (70%), having melting point, $[\alpha]D$, and ir spectrum identical with those of **7**. The nmr spectra of **21** in chloroform-*d*, acetone-d_6, and benzene-d_6 were identical with those of **7** except that the 3-proton singlets at τ 7.85, 7.85, and 8.36, respectively, were absent.

Registry No.—**1**, 4257-95-8; **2**, 4049-34-7; **3**, 19186-37-9; **4**, 25243-38-3; **5**, 4257-98-1; **6**, 4049-33-6; **7**, 4026-34-0; **8**, 25227-11-6; **9**, 13035-41-1; **10**, 7473-43-0; **11**, 30319-42-7; **12**, 22434-99-7; **13**, 30319-44-9; **14**, 22435-09-2; **15**, 7702-27-4; **16**, 30319-46-1; **17**, 30319-47-2.

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(56) K. Reyle and T. Reichstein, *Helv. Chim. Acta*, **35**, 98 (1952).
(57) H. Zinner and H. Brandner, *Chem. Ber.*, **89**, 1507 (1956).
(58) R. Jeanloz, H. G. Fletcher, Jr., and C. S. Hudson, *J. Amer. Chem. Soc.*, **70**, 4052 (1948).
(59) H. G. Fletcher, Jr., and C. S. Hudson, *ibid.*, **69**, 1145 (1947).
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The Structure, Absolute Configuration, and Chemistry of Nogalose[1]

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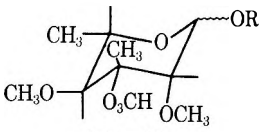
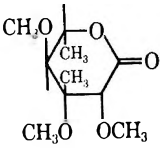
The structure of nogalose, $C_{10}H_{20}O_5$, the sugar portion of the antibiotic nogalamycin, has been determined and certain aspects of its chemistry have been investigated. Deductions primarily from nmr data on the native sugar and several derivatives indicated the gross structure. An X-ray crystal structure study of *N*-(*p*-bromobenzyl)-nogalonamide gave the absolute configuration of nogalose except for C-1. These studies show that nogalose has the structure represented by I. The configuration is that of L-rhamnose. X-Ray and nmr results are discussed in detail.

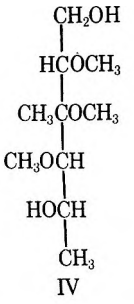
Nogalose (I) is a neutral sugar which has been obtained by acid hydrolysis of the antibiotic nogalamycin.[1,2] The present report discusses the determination of the total structure of I as derived from physical, chemical, and crystallographic data, as well as discussing some of the chemistry of I.



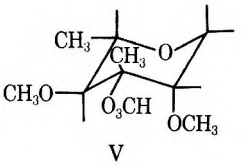
I, R = H
II, R = CH_3



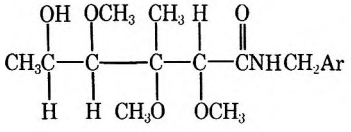
III



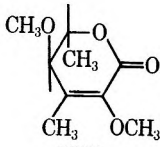
IV



V



VI, Ar = C_6H_5
VII, Ar = p-BrC_6H_4

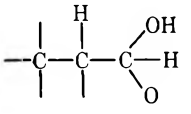


VIII

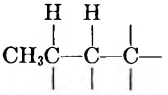
Nogalose is a colorless, crystalline, neutral compound which was shown to have a molecular formula of $C_{10}H_{20}O_5$ by analyses and a mass spectral molecular weight determination. The nmr spectrum ($CDCl_3$) showed the presence of three CH_3O groups (three singlets, each representing 3 H, at δ 3.20, 3.40, and 3.45) and two CH_3C groups (a doublet representing 3 H centered at δ 1.14 and a singlet representing 3 H at δ 1.30). Although nogalose is only very weakly reducing, its composition and source were suggestive of a sugar. The infrared spectrum of I showed the absence of carbonyl and the presence of one or more hydroxyl groups and considerable C–O bonding. The nmr spectrum of I has a doublet of doublets due to 1 H centered at δ 5.15, which is a strong indication of anomeric hydrogen. Treatment of I with methanolic hydrogen chloride gave a methyl glycoside (II) as evidenced by an nmr signal due to a fourth methoxyl (δ 3.36) and disappearance of hydroxyl bands from the infrared spectrum. I was readily oxidized by treatment with Jones reagent to give a lactone III, as shown by absence of infrared bands due to hydroxyl and appearance of a carbonyl band at 1765 cm^{-1}. These four lines of evidence leave little doubt that nogalose is a sugar. Reduction of nogalose to nogalitol (IV) also occurs as would be expected of a sugar, but vigorous conditions are required.[3] Attempted preparation of the *p*-tosyl derivative of IV resulted in cyclization to the corresponding pyran V. A similar reaction has been reported by Rabinsohn and Fletcher,[4] and, in their case, the stereochemistry of the carbon bearing the secondary hydroxyl group was retained. Reasoning from analogy and from theory, it seems likely that the stereochemistry of the pyran is as indicated in V.

The lactone III reacts readily with benzylamines to form amides (VI and VII), the second of which was used for crystallographic studies. Treatment of III with piperidine resulted in elimination of methanol rather than amide formation, giving rise to an unsaturated lactone VIII.

The gross structure of nogalose and part of the stereochemistry was deduced from the nmr data. The anomeric hydrogen of nogalose is coupled with an exchangeable hydrogen (δ 6.30, J = 4 Hz) and a hydrogen on carbon (δ 3.25, J = 2 Hz). The hydrogen on C-2 is not coupled with a hydrogen at C-3, indicating the system



in which the adjacent protons on carbon are *ee* or *ae*. A doublet attributable to a methyl group has already been mentioned. The protons on the methyl group are coupled (J = 6 Hz) with a hydrogen which gives rise to a multiplet centered at δ 3.7. The single proton is again coupled with a single hydrogen (d, δ 2.98, J = 9 Hz), and the coupling constant indicates a diaxial arrangement. The second hydrogen has no other proton on an adjacent carbon. Such data suggest the presence of a moiety



(1) A preliminary report of a portion of this work has already been published: see P. F. Wiley, F. A. MacKellar, E. L. Caron, and R. B. Kelly, *Tetrahedron Lett.*, 663 (1968). This study was supported in part by Contract PH43-68-1023, Cancer Chemotherapy National Service Center, National Cancer Institute, NIH, Bethesda, Md.

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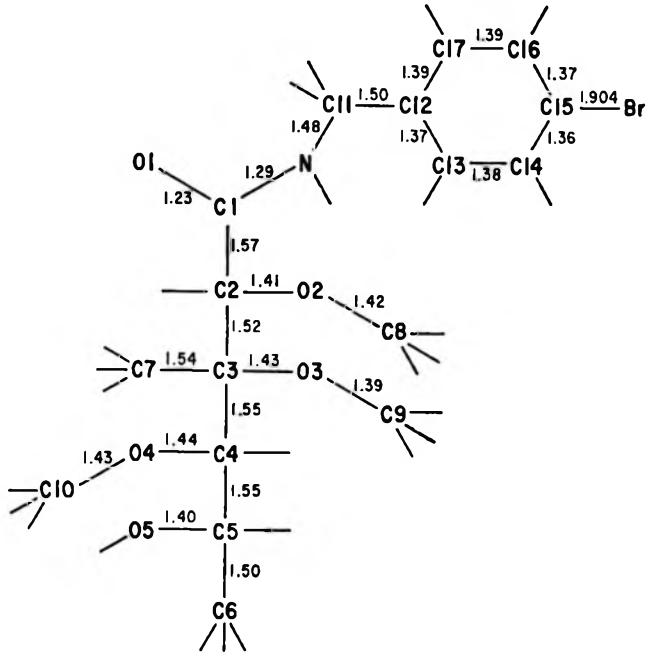

Figure 1.—Interatomic distances of *N*-(*p*-bromobenzyl)-nogalonamide. Drawing of the sugar fragment is in the correct absolute configuration and in the usual Fischer projection. Standard deviations in the bond distances are about 0.015 Å. Distances shown are the average over the two molecules.

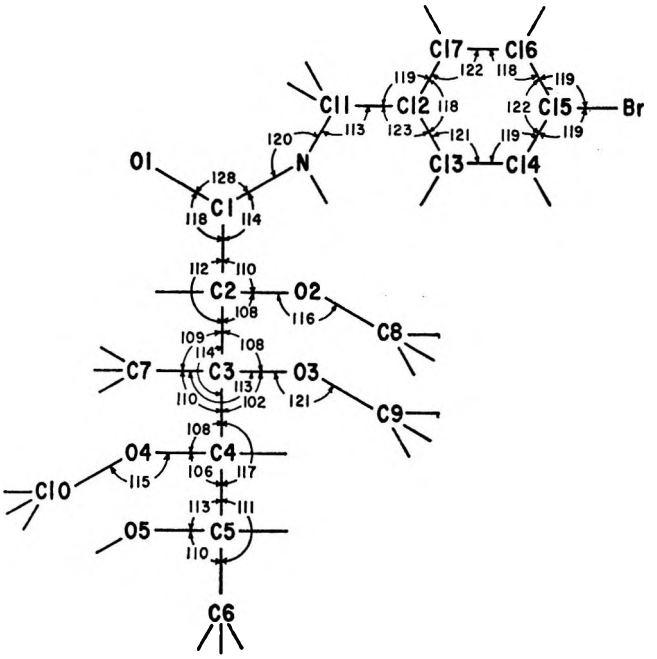

Figure 2.—Bond angles of *N*-(*p*-bromobenzyl)nogalonamide. Angles shown are the average over the two molecules. Standard deviations in the bond angles are about 1°.

Combining the two portions of the molecule and considering the methyl and methoxyl groups known to be present, nogalose must have the gross structure (although not necessarily the stereochemistry) indicated in I or the isomeric furanose structure with a methoxyl group at C-5. It is clear from the nmr of III that the pyranose structure is correct, since the proton giving rise to a multiplet, which indicates it is on C-5, shifts substantially downfield in the spectrum of III, as compared with its chemical shift in the spectrum of I.

Crystal structure results on VII are shown in Figures 1, 2, and 3. These results confirm the nmr deductions and show clearly that nogalose has the configuration of L-rhamnose (6-deoxy-L-mannose). L-Rhamnose is known to occur widely in nature.[5] The average bond distances and angles for the two molecules in the crystallographic asymmetric unit, shown in Figures 1 and 2, do not differ significantly from those found previously in other sugars.[6] Figure 3 shows the conformation of one of the molecules; the conformation of the other is very similar. The folding of the sugar is dominated by a strong intramolecular hydrogen bond from the hydroxyl group (O5) to the carbonyl (O1). The O1–O5 distances in molecules 1 and 2 are 2.65 and 2.75 Å, respectively. Intermolecularly, N of molecule 1 is hydrogen bonded to O5 of molecule 2 (d = 2.94 Å), and N of molecule 2 is in turn hydrogen bonded to O5 of molecule 1 translated one unit in the x direction (d = 2.90 Å), thus forming an infinite chain in the x direction.

The determination of the configuration of nogalose by the use of VII gives no indication of conformation. However, the conformation indicated in I is that expected and is that indicated by the nmr spectrum of

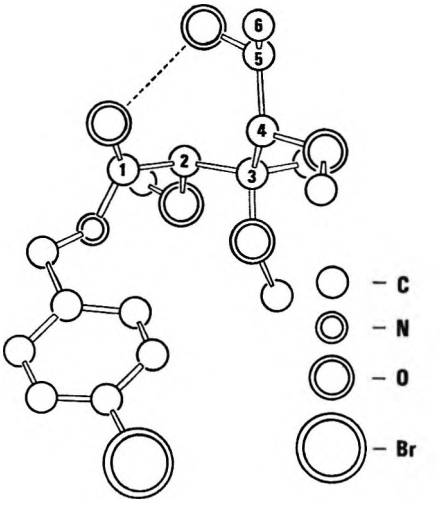

Figure 3.—Computer drawing of molecule 2 of *N*-(*p*-bromobenzyl)nogalonamide from crystallographic data. Projection is in an arbitrary direction in the unit cell.

nogalose. The coupling constant of 9.09 Hz exhibited by H-4 and H-5 quite conclusively indicates a diaxial relationship which would necessitate the conformation indicated. The configuration of C-1 is not established in the present work, but the nmr indicates that only one isomer is present, and the equatorial hydroxyl conformation seems probable in the total antibiotic in view of crowding in the axial isomer. If such were the case, the configuration would be β.

Experimental Section

Nogalose (I).—Nogalamycin (5 g) was dissolved in 100 ml of 0.4 *N* HCl, and the solution was boiled under reflux for 0.5 hr. The cooled reaction mixture was extracted with four 50-ml portions of chloroform. The combined extracts were dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The residue was sublimed at 60° (0.02 mm), yield 0.83 g, mp 110°. A portion (400 mg) was recrystallized twice from ethyl acetate and sublimed again: yield 190 mg; mp 115–121°; $[\alpha]^{25}D$ −10.6°

(5) L. Glaser, *Physiol. Rev.*, **43**, 215 (1963).

(6) (a) H. S. Kim, G. A. Jeffrey, and R. D. Rosenstein, *Acta Crystallogr., Sect. B*, **25**, 2223 (1969); (b) H. M. Berman, S. S. C. Chu, and G. A. Jeffrey, *Science*, **157**, 1576 (1967).

(*c* 1, CH_3OH); $[\alpha]^{25}D$ +15.5° (*c* 1, H_2O); ν_{max}^{Nujol} 3400, 1195, 1175, 1155, 1110, 1085, 1060, and 1035 cm^{-1}.

Anal. Calcd for $C_{10}H_{20}O_5$: C, 54.52; H, 9.15; O, 36.32; mol wt, 220.26. Found: C, 54.72; H, 9.28; O, 35.87; mol wt (mass spectrum), 220.

Methyl Nogaloside (II).—A solution of 200 mg of nogalose in 10 ml of 5% methanolic HCl was allowed to stand at room temperature for 36 hr. The reaction mixture was poured into 40 ml of 5% $NaHCO_3$ solution which was extracted with four 10-ml portions of chloroform. The combined extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was sublimed four times at 35° (0.02 mm): mp 41–43°; $[\alpha]^{25}D$ −48.4° (*c* 1, CH_3OH); nmr ($CDCl_3$) δ 1.28 (3 H, d, *J* = 6.3 Hz), 1.31 (3 H, s), 3.07 (1 H, d, *J* = 9.5 Hz), 3.28 (3 H, s), 3.36 (3 H, s), 3.49 (3 H, s), 3.53 (3 H, s), 3.63 (1 H, m), and 4.72 (1 H, d, *J* = 2 Hz). The ir spectrum showed no band in the OH region.

Anal. Calcd for $C_{11}H_{22}O_5$: C, 56.38; H, 9.47; O, 34.14. Found: C, 55.93; H, 9.34; O, 33.38.

Nogalolactone (III).—A solution of 1.10 g (5 mmol) of nogalose in 30 ml of acetone was stirred while adding 2.4 ml (6.6 mmol) of Jones reagent dropwise. The solution was allowed to stand at room temperature for 4 hr, followed by addition of 100 ml of water and concentration under reduced pressure until the acetone was removed. The residue was extracted with five 100-ml portions of chloroform. The combined chloroform extracts were dried ($MgSO_4$) and evaporated under reduced pressure until a light-brown liquid remained, wt 0.97 g. Distillation under reduced pressure gave 236 mg; bp 76° (0.1 mm); $[\alpha]^{25}D$ +15.9° (*c* 1, $CHCl_3$); ν_{max}^{neat} 1765, 1195, 1170, 1140, 1100, 998, 955, 934, 860, and 804 cm^{-1}; nmr ($CDCl_3$) δ 1.37 (3 H, s), 1.48 (3 H, d, *J* = 6 Hz), 3.20 (1 H, d, *J* = 7 Hz), 3.33 (3 H, s), 3.52 (3 H, s), 3.58 (3 H, s), 3.83 (1 H, s), and 4.21 (1 H, m, *J* = 6 and 7 Hz).

Anal. Calcd for $C_{10}H_{18}O_5$: C, 55.06; H, 8.31; O, 36.66. Found: C, 54.99; H, 8.77; O, 34.69.

Nogalitol (IV).—A mixture of 0.8 g of nogalose, 0.8 g of lithium aluminum hydride, and 120 ml of anhydrous dioxane was boiled under reflux for 6 hr. The cooled reaction mixture was acidified by the addition of 20 ml of 6 *N* HCl. The aqueous layer was removed and the dioxane layer was dried (KOH). The solvent was removed by evaporation under reduced pressure, leaving a colorless syrup, wt 0.52 g. The residue (0.3 g) was chromatographed on 15 g of silica gel, using a chloroform–methanol (95:5) system, and collecting 5-ml fractions. Fractions 3–15 were combined on the basis of weight analysis. The yield of clear, colorless oil was 0.26 g: $[\alpha]^{25}D$ −13° (*c* 1, CH_3OH); significant ir bands at 3340 and 1115 cm^{-1}; nmr ($CDCl_3$) δ 1.18 (3 H, d, *J* = 6 Hz), 1.31 (3 H, s), 2.97 (1 H, d, *J* = 7 Hz), 3.35 (3 H, s), 3.53 (6 H, s), 3.42–3.85 (3 H, m), and 4.1 (1 H, m, *J* = 6 and 7 Hz). Two exchangeable H's appear as broad peaks at δ 3.12 and 3.78.

Anal. Calcd for $C_{10}H_{22}O_5$: C, 54.03; H, 9.97. Found: C, 53.81; H, 10.05.

2*S*,3*S*,4*S*,5*S*-2,4-Dimethyl-3,4,5-trimethoxytetrahydropyran (V).—A solution of 222 mg (1 mmol) of nogalitol and 192 mg (1.12 mmol) of *p*-tosyl chloride in 10 ml of dry pyridine was allowed to stand at room temperature for 6 days. The solvent was removed by distillation under reduced pressure at 35°. The residue was chromatographed on 20 g of silica gel using chloroform as the solvent and collecting fifty 5-ml fractions. Fractions 32–38 were combined on the basis of a weight analysis and only one spot in tlc (silica gel, cyclohexane–ethyl acetate–ethanol, 5:3:2). Evaporation of the combined fractions under reduced pressure gave 66 mg of colorless liquid. The ir spectra showed no bands in the OH region, and the only strong band was at 1110 cm^{-1}: nmr ($CDCl_3$) δ 1.22 (3 H, s), 1.28 (3 H, d, *J* = 5 Hz), 3.02 (1 H, d, *J* = 7 Hz), 3.1 and under the methoxyl signals, 3.27 (3 H, s), 3.41 (3 H, s), 3.51 (3 H, s), 4.02 (1 H, d of d, *J* = 2 and 13 Hz).

Anal. Calcd for $C_{10}H_{20}O_4$: C, 58.78; H, 9.87; mol wt, 204.1361. Found: C, 58.31; H, 10.23; mol wt (mass spectrum), 204.1357.

***N*-Benzylnogalonamide (VI).**—A solution of 1.45 g (6.6 mmol) of nogalolactone and 1.4 g (13.2 mmol) of benzylamine in 15 ml of methanol was allowed to stand at room temperature for 3 days. The residue remaining after removal of the solvent under reduced pressure was mixed with 10 ml of water, and the solution was adjusted to pH 2.0 with 1 *N* HCl. The acidic solution was extracted with three 10-ml portions of chloroform which were combined and dried ($MgSO_4$). The dried solution was concentrated under reduced pressure, and the residue was recrystallized three times from Skellysolve B: yield 0.55 g; mp 91–93°; $[\alpha]^{25}D$ +28° (c 1, $CHCl_3$); ν_{max}^{Nujol} 3250, 1635, and 1530 cm^{-1}; nmr ($CDCl_3$) δ 1.26 (3 H, d, *J* = 6.2 Hz), 1.41 (3 H, s), 3.07 (1 H, d, *J* = 8.5 Hz), 3.35 (3 H, s), 3.37 (3 H, s), 3.70 (1 H, m), 4.18 (1 H, s), 4.32 (1 H, exch, broad), 4.42 (2 H, d of d), 7.17 (1 H, exch, broad), 7.3 (5 H, s).

Anal. Calcd for $C_{17}H_{27}NO_5$: C, 62.74; H, 8.36; N, 4.31; O, 24.59. Found: C, 62.37; H, 8.18; N, 4.71; O, 24.42.

***N*-(*p*-Bromobenzyl)nogalonamide (VII).**—A solution of 1.09 g (5 mmol) of nogalolactone and 0.976 g (5.3 mmol) of *p*-bromobenzylamine in 12 ml of methanol was allowed to stand at room temperature for 4 days. The solvent was removed by evaporation under reduced pressure. The residue was mixed with 10 ml of water, and the mixture was adjusted to pH 2.0 with 1 *N* HCl. The precipitate which formed was removed by filtration and recrystallized from methanol: yield 0.44 g; mp 120–121°; ν_{max}^{Nujol} 3150, 1640, 1550, 1280, 1175, 1106, 1082, 1030, 1015, 965, 838, 820, and 803 cm^{-1}.

Anal. Calcd for $C_{17}H_{26}BrNO_5$: C, 50.45; H, 6.58; N, 3.66; Br, 19.96. Found: C, 50.54; H, 6.49; N, 3.47; Br, 19.78.

(4*S*,5*S*)-2,4-Dimethoxy-3-methyl-2-hexen-5-olide (VIII).—A solution of 2.20 g (10 mmol) of nogalolactone and 1.70 g (20 mmol) of piperidine in 35 ml of methanol was allowed to stand at room temperature for 3 days. The methanol was removed by evaporation under reduced pressure. The residue was mixed with 16 ml of water, and the mixture was adjusted to pH 3.5 with 1 *N* HCl. The aqueous system was extracted with three 16-ml portions of chloroform. The combined chloroform extracts were dried ($MgSO_4$) and evaporated under reduced pressure. Distillation under reduced pressure [bath temperature, 100–110° (0.3 mm)] gave a colorless liquid: yield 0.90 g; λ_{max}^{EtOH} 210 mμ (ε 7720), 224 (6050); ν_{max}^{neat} 1710, 1650, 1270, 1215, 1185, 1155, 1105, 1080, 1040, 980, 938, 908, 882, 787, and 762 cm^{-1}; nmr ($CDCl_3$) δ 1.42 (3 H, d, *J* = 5 and 6 Hz), 1.95 (3 H, s), 3.46 (3 H, s), 3.63 (1 H, s), 3.72 (3 H, s), 4.48 (1 H, m).

Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58; O, 34.37. Found: C, 58.06; H, 7.96; O, 34.28.

X-Ray Structure Studies on VII. Experimental.—Crystals of *N*-(*p*-bromobenzyl)nogalonamide (VII) were monoclinic with lattice parameters: $a = 12.862 \pm 0.001$ Å, $b = 9.402 \pm 0.001$ Å, $c = 16.139 \pm 0.002$ Å, and $\beta = 96.21 \pm 0.01°$. Systematic absences for $0k0$ reflections with k odd indicated space group $P2_1$: $X = 1940$ Å^3, $d_m = 1.379$ g/cm^3, $Z = 4$, $d_c = 1.384$ g/cm^3. The linear absorption coefficient (μ) for Cu Kα radiation is 34.0 cm^{-1}.

Three-dimensional X-ray intensity data were gathered on an automated diffractometer using nickel filtered Cu K radiation; the θ–2θ scan technique was used with 3.5° scans at 4°/min and 20-sec background counts at each end of the scan. Two crystals were used, the first being replaced by the second after a deterioration of 15–20% in intensity of check reflections had occurred. Orientations of both crystals were correlated carefully since anomalous dispersion work was contemplated. For scaling purposes, 21 selected reflections taken at the beginning of data collection of the first crystal were retaken using the second crystal. Lorentz and polarization corrections[7] and separate absorption corrections[8] were applied to data from both crystals prior to scaling the two sets together. Standard deviations were assigned by the equation[9]

$$\sigma^2(I) = \sigma^2_{\text{counting statistics}} + (0.03\,I)^2$$

and were scaled by propagation of error techniques through all corrections. The data (3427 reflections) were placed on an approximate absolute scale by a Wilson plot.

Trial Structure.—An attempt was made to obtain a trial structure by the heavy atom method. Trial positions for the two bromine atoms were found easily from a three-dimensional Patterson function. The positions, however, were separated by 0.50 in y and just off pseudo special positions in the other directions. Structure factors, calculated from the heavy atoms only, gave $R = 0.498$. After extensive analyses of several three-dimensional electron density maps failed to yield a trial structure,

(7) All computer calculations were done on the IBM 360 computer using programs of the CRYM system written by D. J. Duchamp.

(8) W. R. Busing and H. A. Levy, *Acta Crystallogr.*, **10**, 180 (1957).

(9) S. W. Peterson and H. A. Levy, *ibid.*, **10**, 70 (1957).

TABLE I

ATOMIC PARAMETERS (× 10^5) AND THEIR STANDARD DEVIATIONS[a]

	Molecule 1			Molecule 2		
	X	Y	Z	X	Y	Z
Br	44048 (7)	100077 (0)	8596 (6)	−1022 (8)	4423 (19)	53089 (6)
N	81861 (39)	52852 (92)	25807 (36)	30767 (42)	24896 (83)	23530 (34)
C1	89332 (52)	47096 (119)	22314 (42)	39992 (61)	30042 (108)	25860 (42)
C2	88625 (52)	30417 (102)	21644 (45)	40987 (50)	46474 (101)	24421 (41)
C3	85588 (52)	25192 (101)	12910 (44)	40043 (49)	54816 (109)	32509 (40)
C4	93850 (58)	28875 (106)	6735 (43)	47394 (49)	49822 (105)	40084 (39)
C5	105397 (66)	24202 (124)	9681 (56)	59215 (55)	50503 (123)	39823 (49)
C6	111874 (73)	24839 (143)	2417 (62)	65020 (65)	44350 (144)	47495 (54)
C7	84066 (62)	9053 (113)	12845 (50)	41436 (71)	70819 (123)	30714 (52)
C8	84189 (64)	21455 (137)	34894 (49)	35782 (62)	50501 (149)	10061 (46)
C9	66673 (60)	28317 (132)	10626 (53)	21077 (71)	59644 (146)	32420 (62)
C10	86961 (94)	30904 (148)	−7790 (57)	39989 (75)	51561 (153)	53308 (49)
C11	81870 (61)	68881 (123)	27110 (52)	28227 (60)	10436 (110)	25457 (51)
C12	72441 (55)	75867 (105)	22490 (45)	20579 (57)	9190 (105)	31779 (48)
C13	67950 (62)	71615 (115)	14562 (50)	14105 (67)	−2031 (134)	32030 (53)
C14	59835 (65)	78446 (122)	10568 (48)	7640 (61)	−3652 (130)	38695 (69)
C15	55646 (55)	90042 (110)	14290 (46)	7955 (60)	6406 (121)	44589 (51)
C16	59627 (59)	94711 (101)	22283 (46)	14082 (67)	17922 (120)	44554 (51)
C17	68005 (55)	87262 (106)	26359 (48)	20641 (59)	18960 (110)	38211 (52)
O1	96794 (36)	52902 (75)	19570 (34)	47562 (39)	23489 (71)	29248 (30)
O2	80763 (36)	25666 (65)	26519 (29)	33288 (33)	51364 (77)	18288 (25)
O3	76654 (36)	32911 (76)	9196 (30)	28886 (32)	51528 (73)	34829 (28)
O4	90639 (43)	21419 (77)	−988 (32)	45352 (41)	58228 (71)	47119 (30)
O5	110009 (36)	32678 (82)	16044 (34)	62548 (34)	44204 (74)	32594 (31)

[a] Coordinates are given for a left-handed coordinate system.

we turned to statistical phasing. The phases from structure factors calculated from the two bromine atoms were used as input to a tangent formula phase refinement and extension.[10] By using 136 input phases for reflections with $E > 1.6$, a set of refined phases for 875 reflections with $E > 1.15$ was obtained. An E map calculated using these phases gave positions for 15 possible lighter atoms. These trial atoms were used to phase another cycle of tangent formula refinement. The resulting E map yielded positions of 23 lighter atoms. Two subsequent electron density maps served to correctly extend this set to all 46 lighter atoms. The resultant trial structure gave $R = 0.275$.

Refinement and Absolute Configuration.—The trial structure and a scale factor were refined by multiple-matrix least squares.[7] The function minimized was $\Sigma w(|F_o|^2 - |F_c|^2)^2$ where initially the Hughes $1/F_o$ weighting scheme was used. Form factors to calculate structure factors were from the literature.[11] After two cycles of refinement with all lighter atoms designated as carbon, analysis of interatomic distances and large reductions in certain isotropic temperature factors allowed assignment of N and O atoms. Refinement continued; anisotropic thermal parameters were added at the appropriate time. Hydrogen atoms, located in a difference Fourier, were used in the calculations but not refined. When hydrogens were added, the weighting scheme was shifted to

$$w = 1/\sigma(F_o^2)$$

where $\sigma(F_o^2)$ is that assigned in the data reduction.

When refinement without anomalous dispersion had converged ($R = 0.073$), a computer search was made to find those reflections most affected by anomalous dispersion. From a list of 50, 18 were selected for checking by Bijvoet's method.[12] Accurate diffractometer scans showed that 17 are in agreement with the assigned absolute configuration; the one which does not agree has the second-to-weakest calculated difference.

Refinement was continued with anomalous dispersion effects included in the calculations. Convergence was obtained at $R = 0.071$ (all reflections including the very weak included). At this point, all shifts were less than one-third the corresponding standard deviations. The final goodness of fit

$$= \left[\frac{\Sigma w(|F_o|^2 - F_c|^2)^2}{m - s}\right]^{1/2}$$

was 1.6, indicating a good fit of the data.

Final atomic coordinates and their standard deviations are given in Table I for both independent molecules in the unit cell.[13]

Registry No.—I, 30319-19-8; II, 30319-20-1; III, 30319-21-2; IV, 30319-22-3; V, 30319-23-4; VI, 30319-24-5; VII, 30319-48-3; VIII, 30319-49-4.

(10) J. Karle, *Acta Crystallogr., Sect. B*, **24**, 182 (1968).

(11) Atomic form factors are from "International Tables for X-Ray Crystallography," Vol. III, Kynoch Press, Birmingham, England, 1959; anomalous dispersion factors are from D. T. Cromer, *Acta Crystallogr.*, **18**, 17 (1965).

(12) J. M. Bijvoet, *Endeavour*, **14**, 71 (1955).

(13) Tables of hydrogen parameters, anisotropic temperature factors, and observed and calculated structure factors will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Reprint Department, ACS Publications, 1155 Sixteenth St., N.W., Washington, D. C. 20036, by referring to author, title of article, volume, and page number. Remit $4.00 for photocopy or $2.00 for microfiche.

The Cyclic Addition of Hetero Radicals. III. Cyclic Addition of Alkoxy Radicals in Alkynes[1]

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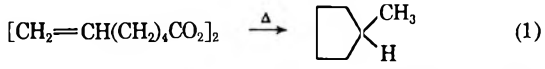
4-Pentynyl nitrite ester was photolyzed to study the cyclic addition of the resulting alkoxy radical to the carbon–carbon triple bond. The photolysis was carried out in a poor hydrogen atom donating solvent, a good hydrogen atom donating solvent, and in the presence of a good radical trap. In none of the above-mentioned reactions were any cyclic addition products observed. The reasons for the failure of this alkoxy radical to undergo cyclic addition are discussed.

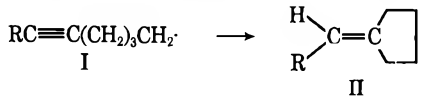
The intermolecular addition of free radicals to olefins has received considerable attention in recent years and invariably the additions go in such a direction as to produce the most stable radicals.[2] However, many recent free-radical cyclic addition reactions have been found to violate this principle. Lamb and coworkers[3] found that the pyrolysis of 6-heptenoyl peroxide resulted in methylcyclopentane instead of the expected cyclohexane (eq 1). Numerous other examples have appeared in



(1)

recent years reporting cyclic additions of carbon radicals which proceed *via* the five-membered ring addition product.[4,5] The cyclic addition is thought to be controlled by entropy factors giving the kinetically controlled product rather than the thermodynamically preferred six-membered ring product. Julia[6,7] has made a careful study of the cyclic addition of the 5-hexenyl radical; he found that the addition becomes reversible if radical stabilizing groups are added to the primary carbon. In this case, the observed product is the six-membered ring product.

We have been investigating the cyclic addition of alkoxy radicals,[8,9] and in this paper we would like to report some of our observations regarding the cyclic additions of alkoxy radicals in alkynes. Crandall and Keyton[10] have studied the cyclic addition of the acetylenic alkyl radical I and found that the addition yields the five-membered ring product II in high yields. Julia[11]

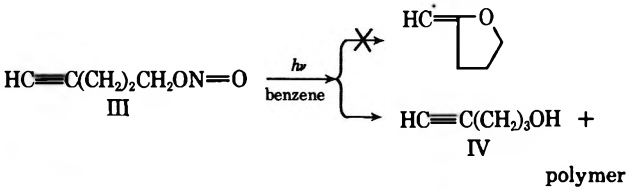


I II

has also reported the cyclic additions of alkyl acetylenic radicals to yield five-membered ring products in high yields. However, no attempts have been reported on the cyclic addition of alkoxy radicals in alkynes.

Results and Discussion

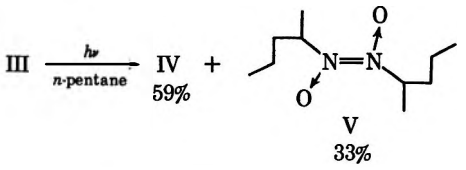
We have found that a convenient source of alkoxy radicals is the photolysis of the corresponding nitrite ester.[8,9] 4-Pentynyl nitrite (III) was irradiated with a 450-W, medium-pressure Hanovia mercury lamp with a Pyrex filter. The solutions were purged with a stream of vanadate-scrubbed nitrogen prior to photolysis to remove all oxygen. When III was photolyzed with benzene as the solvent, there was no sign of any cyclic addition products in the reaction mixture. The only product isolated was a 20% yield of 4-pentynol (IV). The



III IV

rest of the material was highly colored and very polar. This material could not be gas chromatographed and would only move on thin layer plates or chromatography columns with highly polar solvents. The observed 4-pentynol apparently arose by proton abstraction of the solvent or from starting material. The rest of the material apparently was polymeric material.

When III was photolyzed in *n*-pentane, a much better hydrogen donor than benzene, a substantially higher yield of IV (59%) was observed along with 33% of 2-pentyl nitroso dimer V. However, there was no sign again of any cyclic addition products.



III IV V

The high yields of IV are easily explained considering the fact that *n*-pentane is a reasonably good hydrogen atom donating solvent. The resulting 2-pentyl radical then combined with the NO to give the 2-pentyl nitroso monomer, which dimerized to give V. The exclusive formation of the 2-pentyl derivative is apparently consistent with other results in the literature. Kabasakalian,[12] in a study on the photolysis of *n*-octyl nitrite in *n*-heptane, observed only 2-heptyl nitroso dimer. He rationalized his results by assuming that *n*-heptane existed in a folded conformation which rendered the in-

(1) For part II of this series, see R. D. Rieke and N. A. Moore, *J. Org. Chem*, in press.

(2) W. A. Pryor, "Introduction to Free Radical Chemistry," Prentice Hall, Englewood Cliffs, N. J., 1966.

(3) R. C. Lamb, P. W. Ayers, and M. K. Toney, *J. Amer. Chem. Soc.*, **85**, 3483 (1963).

(4) C. Walling and M. S. Pearson, *ibid.*, **86**, 2263 (1964).

(5) N. O. Brice, *ibid.*, **86**, 524 (1964); N. O. Brice, *J. Org. Chem.* **31**, 2879 (1966); N. O. Brice, *J. Chem. Soc.*, **32**, 2711 (1967).

(6) M. Julia, M. Maumy, and L. Mion, *Bull. Soc. Chim. Fr.*, 2641 (1967); M. Julia and M. Maumy, *ibid.*, 2427 (1969).

(7) M. Julia, *Pure Appl. Chem.*, **15**, 167 (1967).

(8) R. D. Rieke and N. A. Moore, *Tetrahedron Lett.*, 2035 (1969).

(9) R. D. Rieke and N. A. Moore, submitted for publication in *J. Amer. Chem. Soc.*

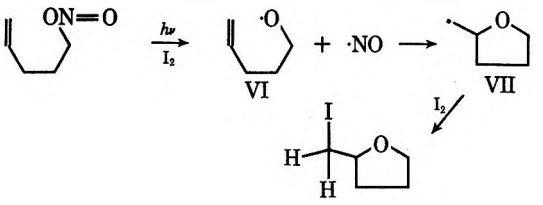
(10) J. K. Crandall and D. J. Keyton, *Tetrahedron Lett.*, 1653 (1969).

(11) M. Julia, *Rec. Chem. Progr.*, **25**, 3 (1964).

(12) P. Kabasakalian and E. R. Townley, *J. Amer. Chem. Soc.*, **84**, 2711 (1962).

terior methylene protons sterically inaccessible. Evidently, similar arguments are valid for *n*-pentane.

Compound III was then photolyzed in the presence of a large excess of a very efficient radical trap, iodine. It was felt that the lack of cyclic addition products might be a result of an inability of the NO to trap the vinyl radical, either because of the high reactivity of the vinyl radical or because of some conformational factor. In the cyclic addition of the 4-pentenyl alkoxy radical (VI), the resulting primary carbon radical (VIII) can be very efficiently trapped with an excess of iodine.[8,9]



However, when III was photolyzed in the presence of an excess of iodine in benzene, no cyclic addition products were observed. In this particular experiment, the excess iodine was removed with aqueous sodium thiosulfate. Among the volatile products found were 4-pentynol (10%) and 4-pentynal (4%). In addition, three other volatile products in low yield were observed. We were not able to fully characterize these compounds, but from ir, nmr, and mass spectral data they definitely all had a carbon–carbon triple bond and aromatic hydrogens. These minor products evidently arise by attack of the 4-pentynyloxy radical on the solvent, benzene. One possible source of the 4-pentynol is from a disproportionation reaction. However, the fact that this was not observed in any of the previous experiments made this seem doubtful. When the experiment was repeated and the reaction was worked up without the removal of excess iodine with aqueous sodium thiosulfate, no 4-pentynal was found. Also, no 4-pentynol was found in this reaction mixture. This suggests that in the presence of iodine in a benzene solution, a significant portion of the 4-pentynyloxy radical is trapped as the hypoiodite. The hypoiodite upon work-up with aqueous sodium thiosulfate undergoes hydrolysis to 4-pentynol and a base-catalyzed elimination of HI to give 4-pentynal. Base-catalyzed eliminations of HX from hypohalites to produce ketones have been reported.[13]

The lack of any cyclic addition products from the 4-pentynyloxy radical under a variety of conditions is surprising. This is especially so in view of the fact that the corresponding carbon radical analog cyclizes in high yield.

Molecular models of the 4-pentenyloxy radical and the 4-pentynyloxy radical show little difference in the distance of the double or triple bond to the alkoxy radical site. Thus, it would appear that the vast difference in chemistry of the two alkoxy radicals cannot be attributed to a difference in strain energy of the two transition states. One possible explanation is that in the transition state for cyclic addition of the 4-pentynyloxy radical there are additional electron–electron repulsion interactions between the electrons of the π cloud of the triple bond and the electron-rich oxygen atom over that of the 4-pentenyloxy radical. Whatever the reason, the lack of cyclic addition of the 4-pentynyloxy radical represents a striking anomaly in a large number of radical cyclic addition reactions.

(13) P. R. Story and S. R. Fahrenholz, *J. Amer. Chem. Soc.*, **86**, 1290 (1964).

Experimental Section

4-Pentynol, bp 65–66° (16 mm) [lit.[14] bp 64–65° (16 mm)], was prepared from tetrahydrofurfuryl chloride[15] according to the procedure of Eglinton, Jones, and Whiting.[14]

Preparation of 4-Pentynyl Nitrite.—To a foil-wrapped flask fitted with a condenser and magnetic stirrer was added 10.97 g (0.120 mol) of 4-pentynol, 12.4 g (0.180 mol) of $NaNO_2$, and 60 ml of water. The mixture was cooled to ice-bath temperature and 15 ml of concentrated HCl was added with stirring in three portions over a 1-hr period. Stirring was continued for an additional 30 min. The mixture was then extracted with several portions of CH_2Cl_2. The organic layers were combined, and the solvent was removed at reduced pressure, yielding 13.82 g (0.116 mol, 97% crude yield) of 4-pentynyl nitrite: bp 51° (97 mm); ir ν (neat) 3310, 2965, 1645, 1607, 800 cm^{-1}; nmr τ (ppm, TMS, CCl_4) 5.7 (t, J = 7 cps, 2 H) and 7.8–8.2 (complex m, 4–5 H).

Photolysis of 4-Pentynyl Nitrite in Benzene.—A solution containing 2.562 g (21.5 mmol) of nitrite ester and 300 ml of freshly distilled benzene ([RONO] = 0.715 M) was purged with N_2 for 45 min and photolyzed using a Hanovia 450-W lamp (with a Pyrex filter). The photolysis was followed by monitoring the disappearance of the band at 357 mμ in the uv and carried to 86% completion. Gas evolution was noted during the photolysis. Removal of the solvent at reduced pressure yielded 1.89 g of a red oil. Gc analysis showed the presence of 0.204 g (0.17 mmol) of nitrite ester, 0.312 g (3.7 mmol, 20% yield) of 4-pentynol, and eight minor components, each in less than 1% yield. Attempts to resolve the product mixture using elution chromatography were unsuccessful.

Thermolysis of the crude product at 54° resulted in the formation of no new volatile components detectable by gc analysis.

Photolysis of 4-Pentynyl Nitrite in Pentane.—A solution containing 1.078 g (9.05 mmol) of nitrite ester in 300 ml of pentane was degassed and photolyzed in the manner described above. After 20 min, the uv spectrum showed no maxima between 320 and 370 mμ, and a new maxima at 294 mμ. Removal of solvent at reduced pressure resulted in the isolation of 0.873 g of yellow liquid. Analysis using gc showed the presence of 500 mg (5.4 mmol, 59% yield) of 4-pentynol, identified on the basis of its ir spectrum and gc retention time. Two other products were detected in minor (2–3%) amounts and were not characterized. A total of 298 mg (1.47 mmol) of crude 2-pentyl nitroso dimer, identified on the basis of its ir spectrum {(ν_{max} (CCl_4) 1197 (s) and 1100 (m) cm^{-1} [lit.[16] ν_{max} 1193 cm^{-1} (ϵ 900) and 1096 (100)]}, was isolated using elution chromatography (silca gel, pentane, and pentane–ether mixtures).

A sample consisting of 189 mg of crude 2-pentyl nitroso dimer was heated on a steam bath for 10 hr in a stoppered flask. Analysis using gc showed the presence of three products in 2:96:2 ratios. A sample of the major product was collected using preparative gc and yielded an ir spectrum identical with that of authentic 2-pentanone oxime, prepared from 2-pentanone in the usual manner.

Photolysis of 4-Pentynyl Nitrite in Benzene in the Presence of Iodine.—A solution containing 1.201 g (10.03 mmol) of nitrite, 1.907 g (7.5 mmol) of I_2, and 300 ml of benzene was degassed and photolyzed in the above manner. The photolysis was monitored by periodically withdrawing samples from the reaction mixture, reducing the I_2 with 10% $Na_2S_2O_3$, and monitoring the disappearance of the band at 357 mμ using uv spectrometry. After 9.5 hr, it was found that the photolysis was 90% complete. An identical solution was stored in the dark for 9.5 hr and analyzed for nitrite ester, with the following results: per cent nitrite remaining, 80 (uv); 82 (gc).

The photolysis solution was washed with 10% $Na_2S_2O_3$ solution and analyzed using gc. This resulted in the detection of nitrite

(14) G. Eglinton, E. R. H. Jones, and M. C. Whiting, *J. Chem. Soc.*, 2873 (1952).

(15) "Organic Syntheses," Collect. Vol. III, Wiley, New York, N. Y., 1955, p 698.

(16) B. G. Gowenlock, H. Spedding, J. Trotman, and D. H. Whiffen, *J. Chem. Soc.*, 3928 (1957).

ester in 10–11% yield. Solvent and nitrite ester were removed at reduced pressure, resulting in the isolation of 661 mg of red oil.

Analysis of the red oil using gc showed the presence of seven products, samples of which were isolated using preparative gc and characterized spectrally. A total of 79 mg (0.94 mmol, 10% yield) of 4-pentynol, characterized by comparison of its ir and nmr spectra with that of an authentic sample, was detected by this method. The following products, in order of their elution from the gc, were also detected.

4-Pentynal: ir ν_{max} (CCl_4) 3312 (s), 2820 (m), 2720 (m), 2120 (w), 1720 (s) cm^{-1}; nmr τ (ppm, TMS, CCl_4) 0.07 (1 H), 7.45 (3–4 H), 8.17 (2 H); 28 mg (0.34 mmol; 4% yield).

Component A: ir ν_{max} (CCl_4) 3320 (s), 3070 (w), 1720 (s), 1570 (m), 993 (s), 680 (s), 650 (s), 625 (s) cm^{-1}; nmr (ppm, TMS, CCl_4) 2.35 (d), 2.84 (t), 7.75, 8.20, 8.65; mass spectrum *m/e* 205, 204 (C_6H_4I + H), 128 (HI), 127 (I), 106, 105 (C_6H_4CO), 79–74 (phenyl ring), 66, 51, 50, 43, 39 ($CH{\equiv}CCH_2$); 0.43 mmol detected (*ca.* 5% yield).

Component B: ir ν_{max} (CCl_4) 3312, 3075, 2952, 1520, 1340, 848 cm^{-1}; mass spectrum *m/e* 204 ($CH{\equiv}C(CH_2)_3OC_6H_4NO_2$ − 1), 139 ($OC_6H_4NO_2$ + H), 123 ($C_6H_5NO_2$), 105, 93 (C_6H_5O), 84, 83 [$CH{\equiv}C(CH_2)_3O$], 78, 77, 66, 65, 55, 53, 51, 46 (NO_2), 39 ($CH{\equiv}CCH_2$), 30 (NO); 0.21 mmol detected (*ca.* 2–3% yield).

Component C: ir ν_{max} (CCl_4) 3312, 3235 (br), 3080 (w), 1610, 1586, 1527, 1470, 1450, 1320, 1245 cm^{-1}; mass spectrum *m/e* 139, 122, 109 (OC_6H_4OH), 93 (C_6H_5O), 81, 65, 64, 53, 39; 0.31 mmol detected (*ca.* 3–4% yield).

In a similar manner, 1.907 g (10.0 mmol) of nitrite, 1.907 g (7.5 mmol) of I_2, and 300 ml of benzene were photolyzed for 7.5 hr (77% completion; uv analysis). A total of 250 mg of insoluble polymer precipitated from the solution after 8 hr. Excess I_2 was not reduced with 10% thiosulfate solution. The solution was concentrated to 10 ml and analyzed using gc. No 4-pentyn-1-ol or 4-pentynal was detected.

Registry No. —III, 30428-24-1; IV, 5390-04-5; V, 30428-26-3.

Acknowledgment. —Financial support of this investigation by the University of North Carolina Research Center under Contract SD-100 with the Advanced Research Projects Agency and by a University of North Carolina Research Grant is gratefully acknowledged.

Heterocyclic Studies. 34. Toluenesulfonyl Derivatives of 2,3-Dihydro-5-methyl-6-phenyl-1,2-diazepin-4-one. Rearrangement to a 1,4-Dihydropyridazine[1]

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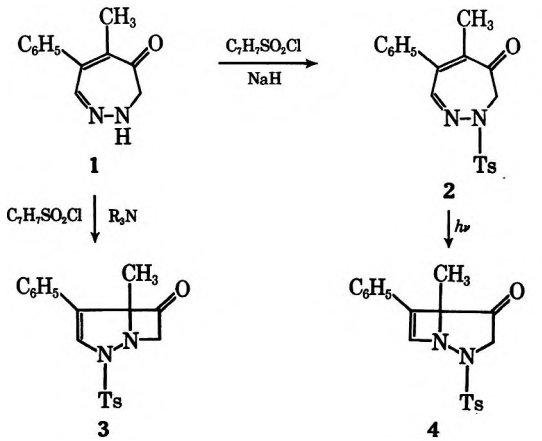
Department of Chemistry, University of Delaware, Newark, Delaware 19711

Received February 22, 1971

The 2-tosyldiazepinone **2** undergoes rearrangment in the presence of triethylamine to the 2-tosylamido-3-hydroxypyridine **5**. With sodium alkoxides, **2** rearranges with loss of $ArSO_2H$ to give the dihydropyridazine esters **11**; a bicyclo[4.1.0] intermediate is suggested. The 2-tosylbicyclo[3.2.0] ketone **3** undergoes ring opening in methanol and rearrangement to the 1-tosylamidopyridinium ylide **18** in strong acid. In base, **3** gives the 6-tosylamido-3-hydroxypyridine **17**.

In a continuation of work on the diazepinone **1**, sulfonyl derivatives were of interest for comparison of some reactions with those of acyl counterparts.[2] Acylation of the diazepinone **1** can be directed by choice of conditions to give either seven-membered or bicyclic derivatives.[3] Similarly, the reaction of **1** with tosyl chloride and tertiary amines gave the bicyclic sulfonamide **3**, whereas, in the presence of sodium hydride, attack of tosyl chloride on the N-2 anion of **1** led to **2**.



2-Tosyldiazepinone (2).—The yellow 2-tosyl ketone **2** showed an ir carbonyl band (1680 cm^{-1}) and uv spectrum typical of other 2,3-dihydrodiazepinones in this series. Irradiation (sunlight) converted **2** cleanly to the photoisomer **4**, also obtained by tosylation of the photoisomer of **1**.[1a]

Our principal interest in the chemistry of **2** lay in its reactions in base. Deuterium exchange of the C-3 methylene protons occurred rapidly in DMSO–D_2O containing triethylamine. On heating a solution of **2** in benzene containing triethylamine, a colorless isomer was obtained in 60% yield. This product was recognized from its properties as the 2-tosylamidopyridine **5**; the structure was confirmed by further tosylation to the *O,N*-ditosyl derivative **6** and comparison with a sample prepared by vigorous treatment of the aminopyridine **7** with toluenesulfonyl chloride. Unexpectedly, the initial monotosylation product of **7** was the *O*-tosylate **8** rather than the sulfonamide **5**. Parallel behavior was observed on tosylation of 2-amino-3-hydroxypyridine (**9a**) and also the 3-hydroxy-6-aminopyridine **19a**; the *O*-tosyl esters were obtained with excess tosyl chloride and triethylamine or pyridine at room temperature. Treatment of **9a** with 1 equiv of benzoyl chloride similarly gave the ester **9c** (Chart I).

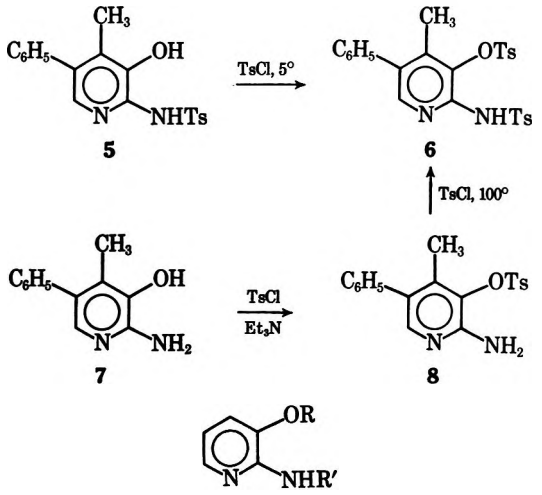
The transformation of **2** to the pyridine **5** presumably occurs by an enolization–valence isomerization sequence *via* the bicyclo[4.1.0] system **10**, as proposed

(1) (a) Part 33: E. J. Volker, M. G. Pleiss, and J. A. Moore, *J. Org. Chem.*, **35**, 3615 (1970). (b) Supported by Grant No. GP-9322 from the National Science Foundation.

(2) J. A. Moore, R. L. Wineholt, F. J. Marascia, R. W. Medeiros, and F. J. Creegan, *J. Org. Chem.*, **32**, 1353 (1967).

(3) W. J. Theuer and J. A. Moore, *ibid.*, **32**, 1602 (1967).

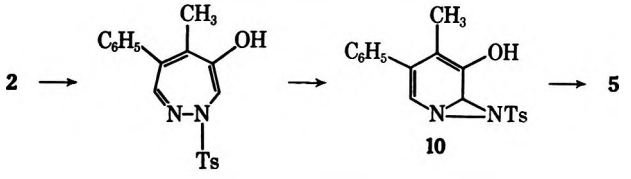
CHART I



5 6 7 8

9a, R = R′ = H
b, R = Ts, R′ = H
c, R = COPh, R′ = H
d, R = R′ = Ts

for the rearrangement of **1** to **7**.[4] Although tosyldiazepinone **2** undergoes deuterium exchange in the presence of triethylamine, the C-3 protons of the 2-methyl and the 2-acetyl counterparts do not exchange under these conditions. The latter compounds were recovered unchanged after heating in triethylamine.



10

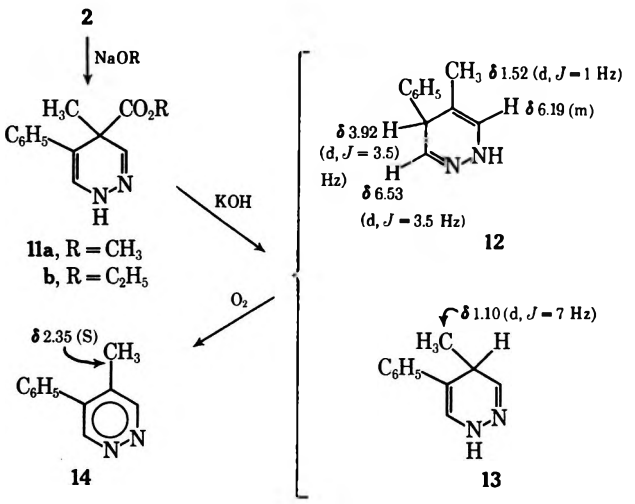
Treatment of the tosyldiazepinone **2** with alkoxides in ether or alcohol brought about an entirely different reaction, in which toluenesulfinic acid was eliminated and the elements of alcohol were added. The nmr spectra of the products indicated a quaternary methyl group [δ 1.40 ppm (s, 3)] and two –N=CH– protons. The infrared spectra showed strong bands at 3200–3300 cm^{-1} (NH) and carbonyl bands at 1725 cm^{-1}, suggesting an ester. The 4-methyl-4-alkoxycarbonyldihydropyridazine structures **11** were established for these products by alkaline degradation to 4-methyl-5-phenylpyridazine (**14**).

After saponification of the methyl ester **11a** and neutralization, extraction gave a solution whose nmr spectrum showed three new methyl signals, at δ 1.10 (d, J = 7 Hz), 1.52 (d, J = 1.2 Hz), and 2.35 (s). The relative intensities of these three peaks varied in different runs and changed with time. After several days' standing, or rapidly on exposure to air, the two higher field doublets gave way completely to the 2.35 singlet, with simultaneous increase in intensity of two singlet peaks at δ 9.25 and 9.30. Isolation of the product at this point gave **14**, isolated in 75% yield as the picrate (Chart II).

The nmr data show the path of the degradation quite clearly; the high-field doublets in the initial spectra correspond to the two 1,4-dihydropyridazines **12** and

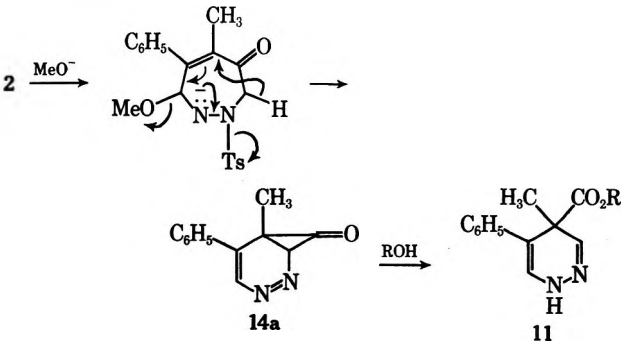
(4) M. G. Pleiss and J. A. Moore, *J. Amer. Chem. Soc.*, **90**, 1369 (1968).

CHART II



13. In another experiment, the tosyldiazepinone **2** was treated directly with aqueous methanolic KOH, and the solution was neutralized and extracted. The major methyl peak in the intermediate spectrum in this case was the δ 1.52 doublet due to **12**, and three additional peaks, δ 3.92 (d, J = 3.5 Hz), 6.19 (m), and 6.53 (d, J = 3.5 Hz), were present in an intensity ratio of 1:1:1 (with the δ 1.52 peak as 3). These signals can be assigned to the 3-methyl-4-phenyl isomer, as shown in **12**. Although **12** predominated in this instance it could not be isolated. The data do not permit conclusions about the relative stabilities or interconvertibility of **12** and **13** or the effect of pH, if any, on the tautomeric equilibrium.

The ester **11a** was also formed in the reaction of **2** with methanolic cyanide, suggesting that this rearrangement is initiated by nucleophilic attack of CN^- or OMe^-. The most likely site would be at C-7, as suggested for reactions of **1** with good nucleophiles.[5] The immediate precursor of the esters **11** must be the bicyclo[4.1.0] ketone **14a**, with the overall process comprising a "vinylogous" Favorskii-type rearrangement.[6,7] The bicyclic intermediate **14a** might also arise *via* the diazatropone, but these alternatives cannot be distinguished from the information available.



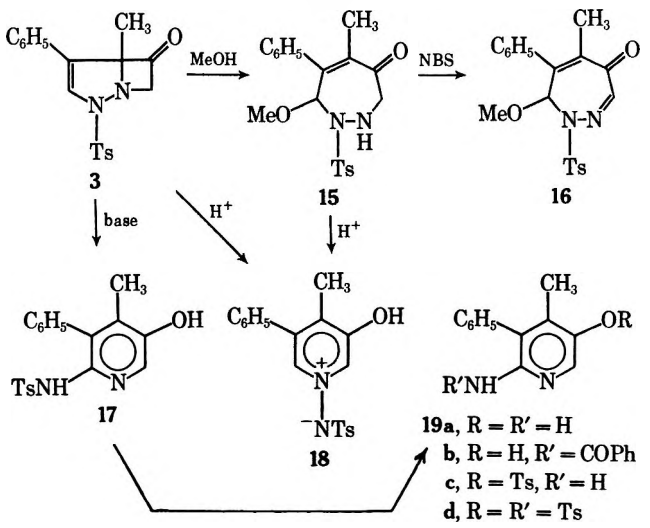
2-Tosyldiazabicyclo[3.2.0]heptanone (3).—The structure of this bicyclic ketone follows by analogy with the corresponding acyl derivatives.[8] The nmr spectrum was generally consistent for **3**, but a curious fea-

(5) J. A. Moore and J. Binkert, *ibid.*, **81**, 6029 (1959).
(6) A. W. Fort, *ibid.*, **84**, 2625 (1962).
(7) G. M. Iskander and F. Stansfield, *J. Chem. Soc., C*, 669 (1969).
(8) J. A. Moore, F. J. Marascia, R. W. Medeiros, and R. L. Wineholt, *J. Org. Chem.*, **31**, 34 (1966).

ture was the highly shielded position of the C-5 CH_3 singlet (δ 0.68 ppm), compared to that in the benzoyl analog (δ 1.60 ppm). Similar high-field CH_3 signals were seen in the spectra of other arenesulfonyl derivatives, but not the methanesulfonyl compound (δ 1.65 ppm). The abnormal shielding of the methyl group in **3** must be caused by the ring of the arenesulfonyl group lying at a more acute angle with respect to the five-membered ring than in the benzamide, so that the methyl group in **3** lies in the shielding cone of the toluenesulfonyl group.

The reactions of **3** are summarized in Chart III.

CHART III



Warming in methanol, or more rapidly in methanol containing a trace of a carboxylic acid, gave the 7-methoxy-1-tosyl-1,2,3,7-tetrahydrodiazepinone (**15**) which could be readily oxidized with NBS to the 1,7-dihydrodiazepine **16**. Both the bicyclic tosylamide and the diazepinone **15** were converted in hydrochloric acid to the 1-tosylamidopyridinium ylide **18**. All of these reactions except that of **3** in neutral methanol parallel those observed and previously discussed[2,8] with the analogous acetyl and benzoyl derivatives and require no further comment.

The reactions of the 2-tosyl[3.2.0] ketone **3** in base differ significantly, however, from those of the 2-acyl analogs (**3**, Ac or Bz instead of Ts). The latter compounds in aqueous base give complex mixtures of degradation products, the composition of which depend on the substituent, conditions, and solvent.[2] The 6-benzamidopyridine **19b** is the major product obtained on refluxing the 2-benzoyl[3.2.0] ketone with methanol or methanolic base, but this product is characteristic of the solvent rather than the presence of base.[2]

In contrast, treatment of the tosyl bicyclic ketone **3** with methanolic sodium methoxide or aqueous hydroxide or triethylamine gave in each case the 6-tosylamido-3-hydroxypyridine **17** in 50–60% yield. The characterization followed that used for the 2-tosylamide **5**, *i.e.*, correlation with the known 6-aminopyridine **19a** by conversion of both compounds to the ditosyl derivative **19d**. Tosylation of **19a** under mild conditions gave the ester **19c**; a tritosyl derivative was obtained from **17** with excess tosyl chloride.

The formation of **17** from **3** thus depends on the presence of base and appears to be independent of the medium. On the other hand, as noted above, **3** in methanol alone gives the methoxydiazepinone and no **17**. Although the formation of analogous 6-aminopyridine derivatives in the tosyl and benzoyl series suggests a common process, the two reactions may in fact be unrelated. We can offer no explanation at present for the differences in behavior of the tosyl and acyl compounds or for the formation of **17** from **3** in base.

Experimental Section[9]

5-Methyl-6-phenyl-2-tosyl-2,3-dihydro-4*H*-1,2-diazepin-4-one (2).—A solution of 3.0 g of diazepinone **1** in 150 ml of glyme (1,2-dimethoxyethane) was treated with 750 mg of sodium hydride suspension (52% in mineral oil), and the mixture was stirred vigorously until hydrogen evolution ceased (30 min). The yellow solution was chilled to −10° and a solution of 2.85 g of tosyl chloride in 50 ml of glyme was added dropwise with stirring; a transient green color appeared. Ether and water were then added and the red ether solution was washed, dried, and evaporated to an oil which was crystallized from ethanol to give 2.65 g of **2**, mp 118–119°, and 0.7 g, mp 112–115°. Recrystallization twice from ethanol gave yellow prisms: mp 120–121°; λ_{max}^{MeOH} 229 nm (ϵ 14,600), 313 (6400), 390 (sh); ν^{KBr} 1685, 1335, 1150 cm^{-1}; δ^{CDCl_3} 1.93 (s, 3), 2.48 (s, 3), 4.11 (s, 2), 7–8 ppm (m, 10).

Anal. Calcd for $C_{19}H_{18}N_2O_3S$: C, 64.40; H, 5.12; N, 7.91. Found: C, 64.95; H, 5.36; N, 8.18.

A solution of 600 mg of **2** in 600 ml of methanol in a Pyrex flask was exposed to direct sunlight for 1 hr. The uv spectrum showed nearly complete absence of **2**. After another hour of irradiation the solution was concentrated *in vacuo;* crystallization gave 500 mg of **4**,[1a] mp 153–154°, and 35 mg (total 90%), mp 150–151°.

3-Hydroxy-4-methyl-5-phenyl-2-tosylamidopyridine (5) (By W. J. Freeman).—A solution of 418 mg of diazepinone **2** and 0.34 ml of triethylamine in 1.2 ml of benzene was heated in a sealed tube at 85–90° for 18 hr; the nmr spectrum showed 85–90% conversion to one product. The solution was evaporated to a dark oil, which was extracted with water and was then decolorized in CH_2Cl_2 solution. The yellow solution was then concentrated and diluted with ether; crystallization (three crops) gave 277 mg (66%) of tan solid, mp 189–192°. Further decolorization and recrystallization from CH_2Cl_2–ether gave white crystals of **5**: mp 192–193°; pK_a' 8.5 (proton lost);[10] ν^{KBr} 3500, 1275, 1085 cm^{-1} (SO_2); δ^{CDCl_3} 2.10 (s, 3), 2.38 (s, 3), 7.0–7.9 ppm (m, 11).

Anal. Calcd for $C_{19}H_{18}N_2O_3S$: C, 64.39; H, 5.11; N, 7.90. Found: C, 64.58; H, 4.69; N, 7.51.

3-Hydroxy-4-methyl-5-phenyl-2-tosylamidopyridine *p*-Toluenesulfonate (6).—A solution of 354 mg of the above 2-toluenesulfonamido-3-hydroxypyridine, 150 mg of triethylamine, and 195 mg of tosyl chloride in 5 ml of methylene chloride was kept at 5° for 4 hr and was then washed, dried, and evaporated. Addition of ether and pentane caused crystallization of 450 mg of white solid, mp 194–195°. Recrystallization from methylene chloride–pentane and then ethanol–water gave an analytical sample of **6**: mp 194–195°; ν^{KBr} 1600, 1560, 1380, 1330 cm^{-1}; δ^{CDCl_3} 2.16 (s, 3), 2.42 (s, 3), 2.53 (s, 3), 7.1–8.2 ppm (m, 16); pK_a' = 7.6 (proton lost).[10]

(9) General procedures and instruments are described in ref 2.

(10) Apparent dissociation constants, pK_a', were determined by electrometric titration.[11] We are greatly indebted to Dr. John M. Vanderbelt and Mrs. Carola H. Spurlock, Parke, Davis and Co., for these measurements. All titrations were carried out in 66% dimethylformamide unless otherwise noted. The designations "proton gained" and "proton lost" correspond to the position of inflections below and above the electroneutrality baseline in the difference curve from titration.[11]

Values for pK_a' for protonation ("proton gained") of the 2-aminopyridines **8**, **9b**, **9c**, and **19c** were 3.0–4.0. For the 3-hydroxy-2- or -6-tosylamidopyridines and 3-tosyloxy-2- or -6-tosylamidopyridines, acidic pK_a values ("proton lost") ranged from 7.6 to 10.1. For the latter series (tosylates **6**, **9d**, and **19d**) this pK_a' evidently corresponds to loss of the –NHTs proton. For the hydroxysulfonamides **5** and **17**, it is not known whether –OH or –NHTs is responsible for the observed pK_a'.

(11) T. V. Parke and W. W. Davis, *Anal. Chem.*, **26**, 642 (1954).

Anal. Calcd for $C_{26}H_{24}N_2O_5S_2$: C, 61.41; H, 4.76; N, 5.51. Found: C, 61.21; H, 4.62; N, 5.47.

2-Amino-3-hydroxy-4-methyl-5-phenylpyridine 3-*p*-Toluenesulfonate (8).—2-Amino-3-hydroxy-4-methyl-5-phenylpyridine (7) was prepared as previously described[12] by refluxing a solution of 2 g of diazepinone 1 in 20 ml of 5% aqueous NaOH for 3 hr. After acidification, charcoal treatment, and adjustment of the pH with $NaHCO_3$, the resulting precipitate was extracted with chloroform. After washing and drying, the chloroform solution was evaporated to give a first crop of 300 mg (15%) of the 2-amino-3-hydroxypyridine 7, mp 218–220°. Subsequent crops of crystals (710 mg) contained predominately the 6-amino-3-hydroxy isomer. Chromatography on silicic acid gave little separation of these isomers; alumina caused decomposition.

A solution of 300 mg of the 2-amino-3-hydroxy isomer, 170 mg of triethylamine, and 290 mg of tosyl chloride in 5 ml of methylene chloride was allowed to stand for 4 hr at 20°. After washing, drying, and evaporation, addition of pentane gave 400 mg of solid, mp 129–130°. Recrystallization from ethanol–water and sublimation gave 8 as colorless crystals: mp 130°; ν^{KBr} 3400, 3200, 1640, 1480, 1360 cm^{-1}; δ^{CDCl_3} 2.04 (s, 3), 2.50 (s, 3), 4.72 (br, 2), 7.1–8.1 ppm (m, 10); pK_a' 3.1 (proton gained).[10]

Anal. Calcd for $C_{19}H_{18}N_2O_3S$: C, 64.40; H, 5.12; N, 7.91. Found: C, 64.35; H, 5.16; N, 7.76.

For conversion to the 2-tosylamido-3-tosylate 6, 100 mg of tosylate 8 was refluxed with 200 mg of tosyl chloride in 3 ml of pyridine for 2 days. After evaporation, the black oil in chloroform solution was treated with charcoal and the solution was applied to a 5 × 20 cm plate with 1-mm silica gel G coating. After development with chloroform–methanol, the fluorescent zone was scraped off and eluted, and the resulting solution was evaporated to give 50 mg of tan solid, mp 188–190°. Further treatment with charcoal and recrystallization from CH_2Cl_2–pentane and then ethanol gave pale tan crystals, mp 194–195°; the ir spectrum matched (17 peaks) that of 6 prepared from 5.

2-Amino-3-hydroxypyridine *p*-Toluenesulfonate (9b).—A solution of 1.1 g of 2-amino-3-hydroxypyridine (Aldrich Chemical Co.), 1.5 g of triethylamine, and 1.90 g of tosyl chloride in methylene chloride was kept at 0° for 2 hr and was then washed with water and acid, dried, and evaporated. Addition of ether caused crystallization of 1.97 g of white solid, mp 132–133°. After recrystallization from methylene chloride–pentane and sublimation (120°), the melting point was 135–136°; pK_a' = 3.0 (proton gained);[10] ν^{KBr} 3400, 3200, 1640, 1600, 1580, 1370 cm^{-1}; δ^{CDCl_3} 2.43 (s, 3), 4.70 (br, 2, exchanged in D_2O), 6.53 (m, 1), 7.0–8.0 ppm (m, 6).

Anal. Calcd for $C_{12}H_{12}N_2O_3S$: C, 54.54; H, 4.84; N, 10.60. Found: C, 54.68; H, 4.55; N, 10.41.

2-*p*-Toluenesulfonamido-3-hydroxypyridine *p*-Toluenesulfonate (9d).—A solution of 200 mg of the above 2-amino-3-toluenesulfonate 9b and 400 mg of tosyl chloride in 5 ml of pyridine was warmed for 2 days and then evaporated. After preparative tlc as described above for 6, the fluorescent zone was eluted and the solution was crystallized from CH_2Cl_2–pentane to give 90 mg (28%) of white solid, mp 127–129°. Recrystallization gave crystals: mp 129–130°; pK_a' = 7.6 (proton lost);[10] δ^{CDCl_3} 2.38 (s, 3), 2.47 (s, 3), 6.7–8.2 ppm (m, 12).

Anal. Calcd for $C_{19}H_{18}N_2O_5S_2$: C, 54.55; H, 4.34; N, 6.70. Found: C, 54.72; H, 4.38; N, 6.61.

2-Amino-3-benzoyloxypyridine (9c).—A solution of 220 mg of 9a, 300 mg of pyridine, and 270 mg of benzoyl chloride in CH_2Cl_2 (1 ml) was kept for 1 hr at 0°. After addition of aqueous KOH, washing, drying, and evaporation, 210 mg (49%) of solid, mp 120–122°, was obtained. Recrystallization from ethanol–water and CH_2Cl_2–pentane and sublimation gave white crystals of 9c: mp 123–124°; pK_a' = 4.0 (proton gained);[10] ν^{KBr} 3300, 3200, 1725, 1650, 1600, 1480 cm^{-1}.

Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.07; H, 4.59; N, 12.89.

Deuterium Exchange of 2.—A solution of 750 mg of the 2-tosyldiazepinone 2 in 3 ml of dimethyl sulfoxide containing 5 drops of triethylamine and 0.2 ml of D_2O was allowed to stand for 10 min at 0° and was then diluted with D_2O. The resulting yellow crystals were collected, washed with water, dried, and recrystallized from ether, mp 116–118°. Integration of the nmr spectrum gave 4 ± 1 mm for the δ 4.10 peak *vs.* 29–30 mm for each of the methyl singlets (20 ± 5% of CH_2); the δ 4.10 peak was an unsymmetrical doublet due to change of chemical shift in CHD.

Under similar conditions, the 2-methyl- and 2-acetyldiazepinones showed <5% exchange of the C_3–CH_2 singlet.

4-Methoxycarbonyl-4-methyl-5-phenyl-1,4-dihydropyridazine (11a).—To a solution of 500 mg of 2 in 30 ml of ether was added 2.5 g of sodium methoxide. After the mixture was stirred at 25° for 1 hr, dilute HCl was added and the ether layer was washed, dried, and evaporated to give 360 mg of brown oil. Chromatography on 18 g of silicic acid (benzene) gave initially 32 mg of unreacted 2 and then a yellow oil which crystallized to give 142 mg (46%) of white solid, mp 76–77°, which was sublimed: ν^{KBr} 3400, 1725 cm^{-1}; δ^{CCl_4} 1.40 (s, 3), 3.58 (s, 3), 6.23 (s, 1), 6.45 (d, 1, J = 4 Hz, $\xrightarrow{D_2O}$ s), 7.18 (s, 5), 7.95 ppm (s, 1 $\xrightarrow{D_2O}$ 0).

Anal. Calcd for $C_{13}H_{14}N_2O_2$: C, 67.81; H, 6.13; N, 12.17. Found: C, 68.02; H, 6.02; N, 12.25.

The **ethyl ester 11b** was obtained by treatment of a solution of 3.0 g of 2 in 10 ml of glyme with 1 equiv of sodium ethoxide in 30 ml of ethanol. The resulting red solution stood for 30 min at 25° and was then diluted with ether and extracted with three 30-ml portions of water. After drying and evaporation the yellow oil (1.8 g) was chromatographed on silicic acid (chloroform). After elution of 200 mg of unreacted 2, further fractions were combined and evaporated to give 1.40 g of solid, mp 52–55°. After repeated recrystallization from ether–hexane, 11b was obtained as white crystals: mp 57–58°; ν^{KBr} 3250, 1725 cm^{-1}; λ_{max}^{MeOH} 229 nm (ε 7400), 311 (5500); δ^{CDCl_3} 1.06 (t, 3, J = 7 Hz), 1.46 (s, 3), 4.11 (q, 2, J = 7 Hz), 6.41 (s, 1), 6.58 (d, 1, J = 4 Hz, $\xrightarrow{D_2O}$ s), 7.30 ppm (s, 6).

Anal. Calcd for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.61; H, 6.83; N, 11.30.

Conversion of Dihydropyridazinecarboxylate 11 to 4-Methyl-5-phenylpyridazine.—The methyl ester 11a (30 mg) was dissolved in a solution of 90 mg of KOH in 1 ml of water and 2 ml of methanol. After standing at 75° for 50 min, the solution was treated with dilute HCl until turbid and was then extracted with chloroform. An nmr spectrum of the solution showed peaks due to 12, 13, and 14 (see discussion). After standing in the presence of air until the spectrum showed only 14, the solution was evaporated and the residue was treated with alcoholic picric acid; 39 mg (75%) of yellow crystals was obtained, mp 137–138°, ir identical with that of a previously characterized sample.[13]

2-Tosyl-5-methyl-4-phenyl-1,2-diazabicyclo[3.2.0]-3-hepten-6-one (3).—A solution of 3.0 g of the 2,3-dihydrodiazepinone 1 and 8.0 g of tosyl chloride in 60 ml of pyridine was kept at 25° for 13 hr. After diluting with CH_2Cl_2 the solution was washed with water, excess dilute HCl, and water again, dried, and evaporated. The residual yellow solid was washed with ether and recrystallized from methylene chloride–ether to give 3.1 g of white prisms: mp 148–150°; ν^{KBr} 1810, 1370, 1170 cm^{-1}; δ^{CDCl_3} 0.68 (s, 3), 2.37 (s, 3), 4.56, 4.87 (AB, dd, J = 17.6 Hz, additional splitting of both doublets, J = 1 Hz), 7.00 (s, 1, br, $W_{1/2}$ = 2 Hz), 7.2–8.0 ppm (m, 9).

Anal. Calcd for $C_{19}H_{18}N_2O_3S$: C, 64.40; H, 5.12; N, 7.91. Found: C, 64.55; H, 5.29; N, 8.11.

2-Methanesulfonyl-5-methyl-4-phenyl-1,2-diazabicyclo[3.2.0]-3-hepten-6-one.—To a solution of 400 mg of diazepinone 1 in 3 ml of pyridine was added 0.4 ml of methanesulfonyl chloride; the solution became warm and crystals separated. After CH_2Cl_2 was added, the mixture was washed with acid and water, dried, and evaporated to an oil which crystallized on adding ether to give 250 mg of colorless crystals: mp 148–149°; ν^{KBr} 1800, 1335, 1154 cm^{-1}; δ^{CDCl_3} 1.65 (s, 3), 2.99 (s, 3), 4.55 (dd, 1, $J_{7,7'}$ = 17.7 Hz, $J_{3,7}$ = 1.1 Hz), 4.92 (dd, 1, $J_{7,7'}$ = 17.7, $J_{3,7'}$ = 0.9 Hz), 6.93 (s, 1, br, $W_{1/2}$ = 2.1 Hz), 7.25–7.60 ppm (m, 5).

Anal. Calcd for $C_{13}H_{14}N_2O_3S$: C, 56.11; H, 5.07; N, 10.07. Found: C, 56.20; H, 5.11; N, 10.07.

The benzenesulfonyl (mp 134–135°, δ_{CH_3} 0.65 ppm) and *p*-cyanobenzenesulfonyl (mp 159–160° dec, δ_{CH_3} 0.73 ppm) derivatives were obtained by the same procedures; these compounds were not analyzed.

1-*p*-Tosyl-5-methyl-7-methoxy-6-phenyl-1,2,3,7-tetrahydro-4*H*-diazepin-4-one (15).—A solution of 380 mg of the tosyl[3.2.0] ketone 3 and 20 mg of benzoic acid in 15 ml of methanol was refluxed for 30 min and chilled. The resulting white crystals of 15 were collected and washed with cold methanol: yield 365 mg (80%); mp 140–142° dec; ν^{KBr} 3400, 1690 cm^{-1}; δ^{DMSO-d_6} 1.67 (s, 3), 2.33 (s, 3), 3.10–3.23 (m, 6, OCH_3 + CH_2 + NH), 5.68 (s, 1), 7.3–7.9 ppm (m, 9).

(12) J. A. Moore and E. C. Zoll, *J. Org. Chem.*, **29**, 2124 (1964).

(13) R. K. Bly, E. C. Zoll, and J. A. Moore, *ibid.*, **29**, 2128 (1964).

Anal. Calcd for $C_{20}H_{22}N_2O_4S$: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.33; H, 6.09; N, 7.31.

A suspension of 200 mg of **3** in 30 ml of methanol was refluxed for 1.5 hr; after chilling, 150 mg of **15**, mp 142–143°, was collected.

1-*p*-Tosyl-5-methyl-7-methoxy-6-phenyl-1,7-dihydro-4*H*-diazepin-4-one (16).—A solution of 190 mg of *N*-bromosuccinimide in 12 ml of pyridine was added slowly to a solution of 400 mg of the 7-methoxy-1-tosyldiazepinone **15** in 50 ml of CH_2Cl_2. After 18 hr at 20°, ice and 20 ml of concentrated HCl were added and the CH_2Cl_2 layer was washed, dried, and evaporated to an oil which crystallized on adding methanol to give 280 mg of pale yellow crystals. Recrystallization from methanol gave **16**: mp 142–144°; ν^{KBr} 1600, 1340, 1160 cm^{-1}; δ^{CDCl_3} 1.90 (s, 3), 2.46 (s, 3), 3.13 (s, 3), 6.21 (s, 1), 7.2–8.0 ppm (m, 9).

Anal. Calcd for $C_{20}H_{20}N_2O_4S$: C, 62.49; H, 5.24; N, 7.28. Found: C, 62.83; H, 5.55; N, 7.06.

1-Tosylamido-3-hydroxy-4-methyl-5-phenylpyridinium Betaine (18).—To a solution of 0.10 g of tosyl bicyclic ketone **3** in 2 ml of dimethyl sulfoxide was added 1 ml of concentrated HCl. After heating at 90° for 5 min, the deep red solution was poured into ice. The resulting tan precipitate (65 mg) was collected and recrystallized from methanol (charcoal treatment) to give colorless prisms of **18**: mp 253–254° dec; ν^{KBr} 3300, 1290, 1130 cm^{-1}; pK_a' = 7.0 (proton lost).[10]

Anal. Calcd for $C_{19}H_{18}N_2O_3S$: C, 64.40; H, 5.12; N, 7.91. Found: C, 64.36; H, 5.29; N, 7.62.

Similar treatment of the methoxytosyltetrahydrodiazepinone **15** (100 mg) in 3 ml of DMSO with 1 ml of concentrated HCl gave 56 mg of crude **18**, mp (after recrystallization from methanol) 253–254°.

A comparison sample of **18** was prepared by treatment of 500 mg of 1-amino-3-hydroxy-4-methyl-5-phenylpyridinium betaine in 5 ml of pyridine with 550 mg of tosyl chloride. The resulting burgundy solution was poured onto ice, and, after acidification with concentrated HCl, the hydrochloride of **18**, mp 159–161°, separated. Neutralization gave the base **18**, mp 245–258°; ir matched that of a sample prepared from **3**.

3-Hydroxy-4-methyl-5-phenyl-6-tosylamidopyridine (17).—A suspension of 500 mg of the tosyl bicyclic ketone **3** in 5 ml of methanol was treated with 1.2 ml of 1.29 *M* sodium methoxide in methanol. The resulting yellow solution stood for 10 min at 25° and was then evaporated to an oil. The oil was dissolved in CH_2Cl_2 and this solution was then extracted with 20 ml of 1 *N* aqueous KOH. Neutralization of the KOH extract gave 270 mg of precipitate, which was recrystallized from ethyl acetate–hexane to give 250 mg of **17**, mp 187–189°. Further recrystallization gave needles: mp 192–193°; ν^{KBr} 3300, 1320, 1150 cm^{-1}; λ_{max}^{MeOH} 237 (ϵ 13,600), 352 nm (1050); $\delta^{DMSO\text{-}d_6}$ 1.80 (s, 3), 2.33 (s, 3), 7.1–7.9 ppm (m, 12); pK_a' = 10.1 (proton lost).[10]

Anal. Calcd for $C_{19}H_{18}N_2O_3S$: C, 64.40; H, 5.12; N, 7.91. Found: C, 64.09; H, 5.24; N, 7.81.

6-Amino-3-hydroxy-4-methyl-5-phenylpyridine 3-*p*-Toluenesulfonate (19c).—A solution of 100 mg of the 6-aminopyridine **19a**[14] and 300 mg (3 equiv) of tosyl chloride in 3 ml of pyridine stood for 4 hr at 25° and then was poured onto ice. The resulting solid (80 mg) was collected and sublimed at 145° (0.1 mm). Recrystallization of the sublimate from $CHCl_3$–hexane gave **19c** as a powdery white solid: mp 151–153°; δ^{CDCl_3} 1.83 (s, 3), 2.46 (s, 3), 4.40 (br, 2, exchanges in D_2O), 7–7.9 ppm (m, 10); pK_a' = (50% MeOH) 2.9 (proton gained).

Anal. Calcd for $C_{19}H_{18}N_2O_3S$: C, 64.40; H, 5.12; N, 7.91. Found: C, 64.29; H, 5.07; N, 7.70.

3-Hydroxy-4-methyl-5-phenyl-6-tosylamidopyridine 3-*p*-Toluenesulfonate (19d).—A solution of 290 mg of the 6-tosylamide **17**, 150 mg of triethylamine, and 160 mg of tosyl chloride in 5 ml of CH_2Cl_2 was allowed to stand for 2 hr at 25°. After washing, drying, and evaporation, dilution of the oil with ether gave 293 mg (70%) of colorless crystals of **19d**, mp 158–159°. Recrystallization from ethanol gave mp 158–159°; ν^{KBr} 1590, 1420, 1360, 1320 cm^{-1}; δ^{CDCl_3} 1.80 (s, 3), 2.42 (s, 3), 2.50 (s, 3), 6.72 (br s, 1), 7–8 ppm (m, 14); pK_a' = 8.4 (proton lost).[10]

Anal. Calcd for $C_{26}H_{24}N_2O_5S_2$: C, 61.41; H, 4.76; N, 5.51. Found: C, 61.25; H, 4.80; N, 5.34.

Conversion of **19c** to the 6-tosylamido-3-tosylate **19d** was accomplished by treatment of 250 mg of **19c** with 500 mg of tosyl chloride in 3 ml of pyridine at 115° for 3 days. After evaporation and treatment with charcoal the product was chromatographed on a 20 × 25 × 1 mm silica gel G plate. The fluorescent zone was collected and eluted and the material was recrystallized from CH_2Cl_2–pentane to give 110 mg of tan crystals, mp 145–150°. Further treatment with charcoal and recrystallization from CH_2Cl_2–pentane gave colorless crystals, mp 158–159°, identical (mixture melting point, infrared) with material prepared from the 6-tosylamide **17**.

Tosylation of 17 with Triethylamine.—A solution of 70 mg of the 6-tosylamidopyridine **17**, 80 mg (2 equiv) of tosyl chloride, and 1 ml of triethylamine in 2 ml of CH_2Cl_2 was allowed to stand at 25° for 1 hr and was then washed with water and acid, dried, and evaporated to a colorless oil which crystallized to give flocculent needles, mp 216–218°, ν^{KBr} 1170, 1370 cm^{-1}. The compound was too sparingly soluble in $CDCl_3$ or DMSO to permit nmr. Analysis indicated a tritosyl derivative.

Anal. Calcd for $C_{33}H_{30}N_2O_7S_3$: C, 59.80; H, 4.56; N, 4.23. Found: C, 59.80; H, 4.57; N, 4.08.

Registry No.—**2**, 30428-27-4; **3**, 30428-28-5; **4**, 26439-91-8; **5**, 30428-30-9; **6**, 30428-31-0; **8**, 30428-32-1; **9b**, 30378-30-4; **9c**, 30428-33-2; **9d**, 30428-34-3; **11a**, 30428-35-4; **11b**, 30428-36-5; **14**, 26439-97-4; **15**, 30428-38-7; **16**, 30428-39-8; **17**, 30428-40-1; **17** tritosyl derivative, 30378-31-5; **18**, 30428-41-2; **19c**, 30428-42-3; **19d**, 30428-43-4; 2-methanesulfonyl-5-methyl-4-phenyl-1,2-diazabicyclo[3.2.0]-3-hepten-6-one, 30428-44-5; benzenesulfonyl derivative, 30428-45-6; *p*-cyanobenzenesulfonyl derivative, 30428-46-7.

(14) Prepared by hydrolysis (60% H_2SO_4) of the 6-benzamidopyridine **19b**, which was obtained by rearrangment of 2-benzoyl-5-methyl-4-phenyl-1,2-diazabicyclo[3.2.0]-3-hepten-6-one in methanol.[2] This route is our preferred method for obtaining this pyridine; although it requires several steps from the 2,3-dihydrodiazepinone **1**, the reactions are simple and reproducible. The 6-aminopyridine is formed directly from **1**, in admixture with the 2 amino isomer, but the two amines do not have characteristically distinct properties, and a reliable procedure for isolation of pure 6-amine from this mixture has not been developed.

A Novel Azocine Synthesis

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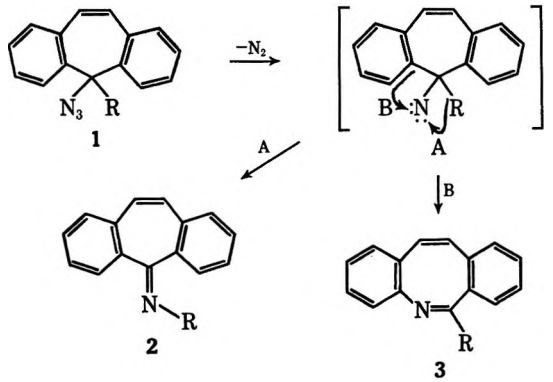
Photochemical decomposition of 5-phenyl- and 5-(1-naphthyl)-5-azido-5*H*-dibenzo[*a*,*d*]cycloheptene has been found to cause ring expansion to the 6-substituted dibenz[*b*,*f*]azocine system. Hydrolysis of the azocines gives the expected amino ketones. Reduction of 6-phenyldibenz[*b*,*f*]azocine with potassium in liquid ammonia leads to a bicyclic reduction product in addition to a dihydro- and a tetrahydroazocine.

We wish to report a synthesis of the dibenz[*b*,*f*]azocine ring system (**3**) by ring expansion of a cycloheptatriene (**1**). This method complements the two recently reported syntheses[1,2] of the parent azocine ring. When azide **1a** is photolyzed in methylene chloride solution, nitrogen is smoothly evolved and two isomers are formed. The major product is imine **2a** (58%), formed by

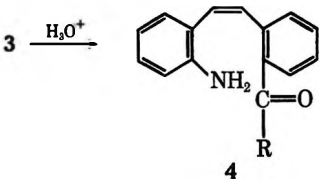


a, R = phenyl
b, R = hydrogen
c, R = 1-naphthyl

phenyl migration to the nitrene nitrogen atom (path A). This material is the same as that obtained by pyrolysis[3] of the azide. The minor isomer (24%) is 6-phenyldibenz[*b*,*f*]azocine (**3a**), formed by migration of one of the other aryl groups attached to C-5 (path B).

Photolysis of unsubstituted azide **1b** gives imine **2b** (26%) as the only identifiable product. It readily affords the corresponding ketone upon hydrolysis. Upon irradiation of the naphthyl-substituted compound **1c**, imine **2c** and azocine **3c** are obtained in yields of 46 and 14%, respectively. The similar photochemical behavior of the phenyl- and naphthyl-substituted azides contrasts markedly with their thermal decomposition.[3] The naphthyl-substituted azide undergoes ring contraction exclusively to 9-(1-naphthyl)anthracene, whereas the phenyl-substituted azide yields mainly imine **2a** along with a small amount of 9-phenylanthracene. No anthracenes were detected in any of the photolysis experiments, nor were the azocines formed in the thermal decomposition.

While the spectral properties of the two azocines **3a** and **3c** agree with the ring structures, they do not define the molecules unambiguously (see Experimental Section). Supporting chemical evidence was obtained by hydrolysis of the azocines to the expected amino ketones **4a** and **4c**.

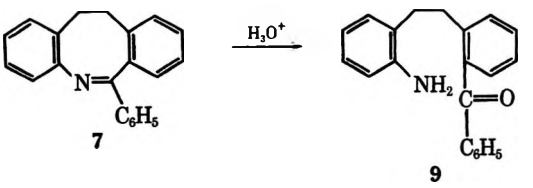


Conversion of compound **3a** to its dianion with potassium and subsequent protonation with water also provided evidence for the azocine structure. When 1 molar equiv of the azocine **3a** was allowed to react with 2 atomic equiv of potassium, amine **6** (45%) and unchanged starting material were isolated. When the ratio of potassium to azocine **3a** was 3:1, two new products were produced in addition to amine **6** (45%). Dihydroazocine **7** was obtained in 8% and tetrahydroazocine **8** in 10% yield (Scheme I).

The structure of compound **6** is supported by its nmr spectrum, which has the correct ratio of aromatic, aliphatic, and amine protons (13:3:1) and an ABX pattern for the aliphatic protons (see Experimental Section).

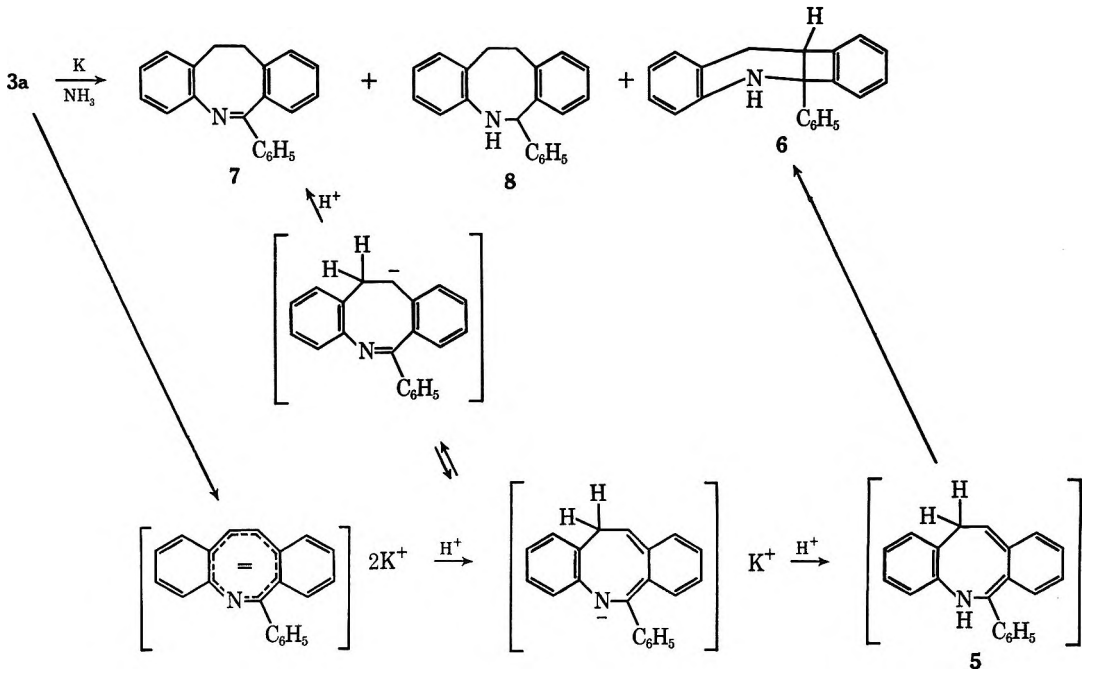
Formation of amine **6** can be explained by stepwise protonation of the dianion on carbon, then on nitrogen to give intermediate **5**, which would be expected to aromatize by valence isomerization to the observed product. Valence isomerizations of this type are well established in cyclooctatetraene reactions. The bicyclic system formed here is noteworthy when compared with the reduction products obtained by Paquette, *et al.*,[4] from the simple azocine ring; only isomeric monocyclic dihydroazocines were produced.

The structure of dihydroazocine **7** is in agreement with its spectral properties (absence of NH) and its hydrolysis to amino ketone **9**. Formation of **7** is readily explained by double protonation of the dianion on carbon. The tetrahydroazocine **8**, whose structure is proposed on the basis of its spectral properties (see Experimental Section), probably forms during the protonation step *via* anion interchange.



(1) L. A. Paquette and T. Kakihana, *J. Amer. Chem. Soc.*, **90**, 3897 (1968).
(2) J. A. Elix, W. S. Wilson, and R. N. Warrener, *Tetrahedron Lett.*, 1837 1970).
(3) J. J. Looker, *J. Org. Chem.*, **36**, 1045 (1971).
(4) L. A. Paquette, T. Kakihana, and J. F. Hansen, *Tetrahedron Lett.*, 529 (1970).

SCHEME I



Experimental Section[5]

Photolysis of 5-Phenyl-5-azido-5*H*-dibenzo[*a*,*d*]cycloheptene (1a).—A solution of 8.15 g (0.026 mol) of azide[3] **1a** in 1 l. of methylene chloride was treated with a stream of dry nitrogen passed through a gas dispersion tube for 15 min and irradiated for 6 hr with a 450-W Hanovia lamp through a Corex filter. The solvent was removed, the residue dissolved in 60 ml of ligroin (bp 63–75°), and the insoluble material (0.13 g) removed by filtration. The filtrate was concentrated to 20 ml and left for 3 hr. The solid that separated was collected and recrystallized from methylcyclohexane, 3.75 g, mp 122–123°. This material has spectral properties which are identical with those of imine **2a**, obtained by pyrolysis[3] of azide **1a**.

The filtrate was chromatographed on Florisil. Benzene–ligroin (1:1) eluted 0.40 g (5%) of azide **1a** followed by 6-phenyldibenz[*b*,*f*]azocine (**3a**), which slowly crystallized from ligroin, mp 94–95°. Methylene chloride eluted additional imine **2a**, 0.50 g (total yield 4.25 g, 58%).

Azocine **3a** was best purified by precipitation of the hydrochloride salt from ether. This salt was suspended in ether and stirred with aqueous sodium bicarbonate until it disappeared. Concentration of the dried ether layer gave 1.75 g (24%) of azocine **3a**, mp 117–119°. When the form melting at 94–95° was dissolved in ethanol and seeded with the higher melting form, it melted at 118–119°: uv max (EtOH) 236 nm (log ϵ 4.40), 328 (3.30); ir (KBr) 1630 cm^{-1} (C=N); nmr ($CDCl_3$) τ 2.17–2.35 (m, 2, aromatic), 2.5–2.9 (m, 11, aromatic), 3.17 (s, 2, olefinic); mass spectrum *m/e* 281.

Anal. Calcd for $C_{21}H_{15}N$: C, 89.6; H, 5.4; N, 5.0. Found: C, 89.4; H, 5.5; N, 5.0.

Hydrolysis of 6-Phenyldibenz[*b*,*f*]azocine (3a).—A mixture of 1.2 g (0.0043 mol) of azocine **3a**, 15 ml of 1,2-dimethoxyethane, and 1 ml of 18% hydrochloric acid was heated at reflux for 45 min and concentrated. The residue was treated with aqueous sodium bicarbonate and the organic material extracted into benzene. The solution was chromatographed on Florisil. Benzene eluted 0.40 g (33%) of unchanged starting material. Ethyl acetate gave an oil which crystallized from ethanol giving 0.50 g (39%) of amino ketone **4a**: mp 91–92°; ir (KBr) 1640 (C=O), 1620 (C=C), 3250 and 3500 cm^{-1} (NH_2); nmr ($CDCl_3$) τ 6.38 (s, 2, NH_2) (exchanges with D_2O), 2.0–3.6 (m, 15, aromatic and olefinic); mass spectrum *m/e* 200.

Anal. Calcd for $C_{21}H_{17}NO$: C, 84.3; H, 5.7; N, 4.7. Found: C, 84.1; H, 5.9; N, 4.9.

(5) The various spectra were recorded on Varian Associates Model T-60 (nmr; compound **6** was recorded on a Bruker Model B-90C) with TMS, Perkin-Elmer Model 137 (ir), and Perkin-Elmer Model 202 (uv) instruments. Melting points are uncorrected.

Photolysis of 5-Azido-5*H*-dibenzo[*a*,*d*]cycloheptene (1b).—A solution of 8.0 g (0.034 mol) of azide[3] **1b** in 1 l. of methylene chloride was irradiated in the same manner as azide **1a**. The residue was dissolved in 60 ml of 1,2-dimethoxyethane and left overnight. The yellow solid was collected, 1.5 g, mp 165–170°. All attempts to purify this material, reduce it with hydrogen or potassium in liquid ammonia, or hydrolyze it with acid were unsuccessful. It has only aromatic and/or olefinic protons (nmr CF_3CO_2H) and a molecular weight of 205 (mass spectrum). The filtrate was treated with hydrogen chloride and the precipitate collected, mp 150–170° dec. When heated in water the solid gave 2.5 g (36%) of 5*H*-dibenzo[*a*,*d*]cyclohepten-5-one, mp 87–88° (mixture melting point not depressed).

Photolysis of 5-(1-Naphthyl)-5-azido-5*H*-dibenzo[*a*,*d*]cycloheptene (1c).—Photolysis of 8.0 g (0.022 mol) of azide[3] **1c** as described for azide **1a** left an oil which, upon dissolving in 140 ml of ethanol, gave 3.35 g (46%) of imine **2c**: mp 168–169°; ir (KBr) 1610 and 1620 cm^{-1} (C=C and C=N); nmr ($CDCl_3$) τ 2.0–4.2 (aromatic and olefinic); mass spectrum *m/e* 331.

Anal. Calcd for $C_{25}H_{17}N$: C, 90.5; H, 5.2; N, 4.2. Found: C, 90.6; H, 5.6; N, 4.3.

When 1 g of this imine was allowed to stand 15 min in a mixture of 20 ml of 1,2-dimethoxyethane and 1 ml of 18% HCl, 0.50 g (81%) of 5*H*-dibenzo[*a*,*d*]cyclohepten-5-one was obtained from the oil left upon removal of the solvent.

The ethanol filtrate from isolation of imine **2c** was concentrated and chromatographed on Florisil. Elution with benzene–ligroin (1:9) gave 0.45 g (6%) of azide **1c**. Ethyl acetate eluted a mixture of imine **2c** and azocine **3c** which could not be separated by chromatography. This solid was dissolved in 100 ml of 1,2-dimethoxyethane containing 2 ml of concentrated hydrochloric acid and left for 30 min. The solid that separated was collected, suspended in a mixture of benzene and aqueous sodium bicarbonate, and stirred until the solid disappeared. The benzene solution, upon drying and concentration, gave solid azocine **3c** which was recrystallized from ethanol: 0.90 g (14%); mp 157–158°; uv max (EtOH) 216 nm (log ϵ 4.86), 290 (3.95); ir (KBr) 1640 cm^{-1} (C=N); nmr ($CDCl_3$) τ 0.93–1.13 (m, 1, aromatic), 2.0–3.1 (m, 16, aromatic); mass spectrum *m/e* 331.

Anal. Calcd for $C_{25}H_{17}N$: C, 90.5; H, 5.2; N, 4.2. Found: C, 90.2; H, 5.2; N, 4.4.

Hydrolysis of 6-(1-Naphthyl)dibenz[*b*,*f*]azocine (3c).—A mixture of 0.50 g (0.0015 mol) of azocine **3c**, 50 ml of 1,2-dimethoxyethane, and 1 ml of 18% hydrochloric acid was heated at reflux for 2 hr. The solvent was removed, and the residue was treated with saturated sodium bicarbonate and extracted with benzene. The extract was chromatographed on Florisil. Elution with benzene gave 0.10 g (20%) of unchanged azocine. A mixture of 10% ethyl acetate in benzene gave 0.36 g (73%) of amino ketone

4c, which would not crystallize: ir (neat) 3300 (NH_2), 3400 (NH_2), 1650 (C=O), and 1630 cm^{-1} (C=C); nmr ($CDCl_3$) τ 1.4–3.6 (m, 17, aromatic and olefinic), 2.52 (s, 2, NH_2, exchanges with D_2O); mass spectrum *m/e* 349. The oil was dissolved in ether and treated with hydrogen chloride gas to prepare the hydrochloride salt, mp 182° dec (depends upon rate of heating).

Anal. Calcd for $C_{25}H_{20}ClNO$: C, 77.8; H, 5.2; N, 3.6; Cl, 9.2. Found: C, 77.5; H, 5.3; N, 3.7; Cl, 8.9.

Reduction of 6-Phenyldibenz[*b*,*f*]azocine. A.—To 50 ml of liquid ammonia at −78° under nitrogen was added 2.0 g (0.0071 mol) of azocine **3a**. The mixture was stirred while 0.78 g (0.020 g-atom) of potassium was added in small pieces over a 15-min period. The dark suspension was stirred 15 min longer and the solvent was distilled using a water bath at room temperature. The residue was suspended in 100 ml of ether and water was added dropwise. The ether layer was washed well with water and concentrated, and the resulting oil was chromatographed on Florisil. Benzene eluted three solids and ethyl acetate, a residual oil.

The first solid was recrystallized from ethanol and gave 0.90 g (45%) of amine **6**: mp 116–117°; ir (KBr) 3400 cm^{-1} (NH); nmr ($CDCl_3$) τ 2.7–3.5 (m, 13, aromatic), 5.6 (broad s, 1, exchangeable with D_2O, NH), 6.48 H_A, 6.82 H_B, 6.10 H_X (3, aliphatic H, ABX system, J_{AB} = 15.9, J_{AX} = 8.0, J_{BX} = 1.5 Hz, actually on the border between ABX and ABC); mass spectrum *m/e* 283.

Anal. Calcd for $C_{21}H_{17}N$: C, 89.0; H, 6.1; N, 4.9. Found: C, 89.2; H, 6.1; N, 4.7.

The second solid was recrystallized from ethanol and gave 0.20 g (10%) of tetrahydroazocine **8**: mp 105–106°; ir (KBr) 3400 cm^{-1} (NH); nmr ($CDCl_3$) τ 6.2–7.0 (m, 5, NH and ethane protons; one is exchangeable with D_2O), 4.18 (s, 1, methine), 2.4–3.0 (m, 14, aromatic); mass spectrum *m/e* 385.

Anal. Calcd for $C_{21}H_{19}N$: C, 88.4; H, 6.7; N, 4.9. Found: C, 88.4; H, 6.7; N, 4.7.

The third solid was recrystallized from ethanol and afforded 0.15 g (8%) of dihydroazocine **7**: mp 94–95°; ir (KBr) 1620 cm^{-1} (C=N); nmr ($CDCl_3$) τ 6.5–7.5 (m, 4, aliphatic methylenes), 2.1–3.3 (m, 13, aromatic); mass spectrum *m/e* 283.

Anal. Calcd for $C_{21}H_{17}N$: C, 89.0; H, 6.1; N, 4.9. Found: C, 89.0; H, 6.3; N, 4.8.

B.—To 50 ml of liquid ammonia at −78° under nitrogen was added 0.70 g (0.0025 mol) of azocine **3a** followed by 0.196 g (0.0050 g-atom) of potassium in small pieces over 10 min with stirring. After stirring had been continued for 15 min, the solvent was removed by a water bath. The solid was treated with 50 ml of ether, and water was carefully added dropwise. The ether layer was separated, washed well with water, and concentrated. The oil was dissolved in benzene and chromatographed on Florisil. The first fraction contained 0.32 g (45%) of amine **6**, mp 115–116°, after recrystallization from ethanol. The second fraction gave 0.15 g (14%) of starting material, mp 116–118°. The nmr spectra of the crude materials showed no trace of either the dihydroazocine **7** or the tetrahydro compound **8**.

Hydrolysis of 11,12-Dihydro-6-phenyldibenz[*b*,*f*]azocine (7).—A solution of 0.10 g (0.00035 mol) of imine **7** in 20 ml of 1,2-dimethoxyethane was treated with 1 ml of water and 1 ml of concentrated hydrochloric acid and heated at reflux for 30 min. The solvent was removed in a stream of nitrogen and the residue treated with benzene and aqueous sodium bicarbonate solution. The organic layer was chromatographed on Florisil. The amino ketone **9** was eluted with 10% ethyl acetate–benzene and obtained as a noncrystallizable oil: ir (KBr) 3400 and 3500 (NH_2) and 1660 cm^{-1} (C=O); nmr ($CDCl_3$) τ 7.06 (s, 4, aliphatic), 6.09 (s, 2, NH_2, exchanges with D_2O), 2.0–3.4 (m, 13, aromatic); mass spectrum *m/e* 301.

The oil was dissolved in ether, and hydrogen chloride was passed in until separation of the hydrochloride was complete. The oil crystallized and was collected: 0.080 g (68%); mp 165° dec; ir (KBr) 2850 (NH_3+) and 1660 cm^{-1} (C=O).

Anal. Calcd for $C_{21}H_{20}ClNO$: C, 74.6; H, 6.0; Cl, 10.5; N, 4.1. Found: C, 74.3; H, 6.0; Cl, 10.2; N, 4.0.

Registry No.—**2a**, 27971-66-0; **2c**, 30319-08-5; **3a**, 30319-09-6; **3c**, 30319-10-9; **4a**, 30319-11-0; **4c**, 30319-12-1; **4c** HCl, 30319-13-2; **6**, 30319-14-3; **7**, 30319-15-4; **8**, 30319-16-5; **9**, 19947-17-2; **9** HCl, 19947-18-3.

Acknowledgment.—The author wishes to express thanks to Dr. T. H. Regan for the nmr spectra and their interpretation and to Mr. D. P. Maier for the mass spectra.

The Synthesis and Metalation of Some Phenalenothiophenes and a Fused Benzo Derivative

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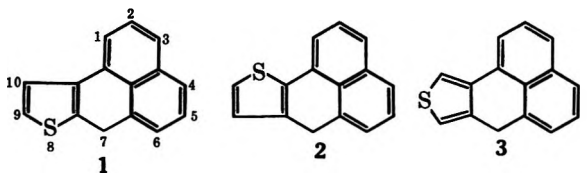
Three phenalenothiophenes (**1**, **2**, and **3**) have been synthesized by unambiguous methods from the corresponding phenalenothiophenones **4**, **5**, and **6**. Reaction of 4,9-dioxo-4,9-dihydronaphtho[2,3-*b*]thiophene with glycerol, sulfuric acid, and iron leads to the formation of a mixture of **4** and **5** in contrast to the claim in the literature[4] that only **4** was produced in this reaction. Fusion of 2-(1-naphthoyl)thiophene with an aluminum chloride–sodium chloride–potassium chloride mixture has been shown to produce **4** together with a very small amount of a high-melting dimeric product in contrast to the claim[4] that **5** was the product of this reaction. Metalation of **2** and **3** was shown to occur exclusively at the methylene bridge, the site of metalation being identified by methylation or by deuterium exchange. A benzo derivative of **3**, namely 4*H*-benzo[1,10]phenanthro[3,4-*c*]-thiophene, was synthesized and likewise shown to undergo metalation exclusively at the methylene bridge.

Three isomeric 7*H*-phenalenothiophenes[2] are possible, *viz.* 7*H*-phenaleno[2,1-*b*]thiophene (**1**), 7*H*-phenaleno[1,2-*b*]thiophene (**2**), and 7*H*-phenaleno[1,2-*c*]-thiophene (**3**). The existence of any of these has not been reported in the literature. This paper describes the synthesis of these compounds and discusses their metalative reactions with *n*-butyllithium.



1 **2** **3**

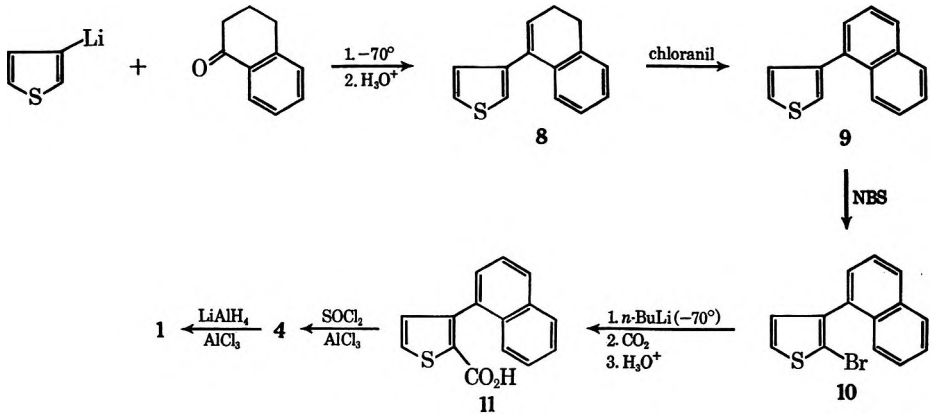
A logical synthetic route to **1**, **2**, and **3** appeared to lie in reducing the corresponding 7*H*-phenalenothiophenones **4**, **5**, and **6**. The literature contains a few references to the preparation of **4** and **5**. Scholl[3] reported the synthesis of a phenalenothiophenone, mp 210°, in low yield, formulated as **4**, by dehydrogenation of

(1) Abstracted from the M.S. Thesis of G. E. Paulovicks, West Virginia University, 1970.

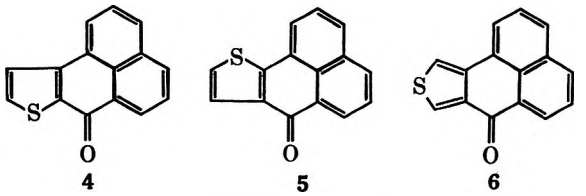
(2) We are indebted to Dr. Kurt L. Loening of Chemical Abstracts Service for information pertaining to the naming of this system.

(3) R. Scholl and C. Seer, *Justus Liebigs Ann. Chem.*, **394**, 111 (1912).

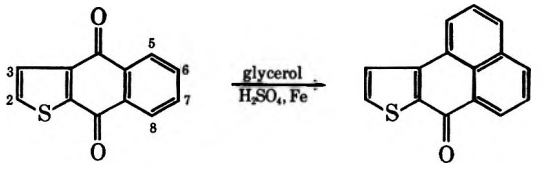
Scheme I



2-(1-naphthoyl)thiophene with aluminum chloride. Weinmayr and coworkers[4] modified Scholl's work by fusing the 2-(1-naphthoyl)thiophene with a mixture of aluminum chloride, sodium chloride, and potassium chloride and obtained a ketone, mp 215–217°, in 6% yield which they formulated as **5**. Inadequate elemental analytical data together with a reconsideration of the mechanism of this reaction led to the suspicion that this ketone is not correctly formulated as **5**.



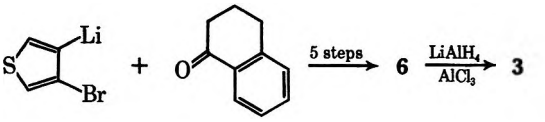
Weinmayr reported that interaction of 4,9-dioxo-4,9-dihydronaphtho[2,3-*b*]thiophene with glycerol, iron, and sulfuric acid according to the well-known benzanthrone synthesis led exclusively to the formation of **4**, a ketone which they considered to be isomeric with that obtained from the 2-(1-naphthoyl)thiophene. On the basis of the oxidation of this product to give 4,9-dioxo-4,9-dihydronaphtho[2,3-*b*]thiophene-5-carboxylic acid, the structure was considered confirmed and thus the isomeric phenalenothiophenone obtained by Scholl's method was formulated as **5**. We have reinvestigated this work and have synthesized **4**, **5**, and **6** by unambiguous syntheses.



7*H*-Phenaleno[2,1-*b*]thiophen-7-one (4).—Reaction of 1-tetralone with 3-thienyllithium at −70° afforded the crude alcohol which was dehydrated to give the corresponding alkene **8** in 83% yield, which was then dehydrogenated to 3-(1-naphthyl)thiophene (**9**) in 85% yield. Bromination with NBS[5] gave exclusively the 2-bromo-3-(1-naphthyl)thiophene (**10**) which was transformed *via* the corresponding lithio derivative to the acid **11** and hence to the ketone by way of treatment of the acid chloride with aluminum chloride. The ketone **4** had mp 154–155° in contrast to the value reported by Weinmayr[4] for the substance he claimed as **4** (mp 139–140°) (Scheme I).

7*H*-Phenaleno[1,2-*b*]thiophen-7-one (5).—The synthetic scheme by which **5** was obtained is similar to that used in the synthesis of **4** and is outlined in Scheme II. In this case the available 3-bromo-2-thienyllithium was the starting heterocyclic moiety. Ketone **5** was an orange solid, mp 154.5–155° (lit.[4] 215–217°).

7*H*-Phenaleno[1,2-*c*]thiophen-7-one (6).—Use of 3-bromo-4-thienyllithium instead of 3-bromo-2-thienyllithium in an analogous, synthetic sequence to that used in the preparation of **5** afforded the ketone **6** as an bright yellow solid, mp 165–166°, differing from both **4** and **5** in spectra. The possibility of formation of five-membered ring ketones on cyclization of **11**, **15**, and the corresponding acid precursor of **6** was eliminated by observing that the infrared carbonyl frequencies of **4**, **5**, **6**, and **23** all lay in the range of 1645–1628 cm^{-1}. The infrared carbonyl frequencies of the known indenothiophenones[6a,b] all occurred in the region above 1700 cm^{-1}.



In each case the ketone (**4**, **5**, or **6**) was reduced to the corresponding 7*H*-phenalenothiophene (**1**, **2**, or **3**) by means of mixture of lithium aluminum hydride and aluminum chloride.

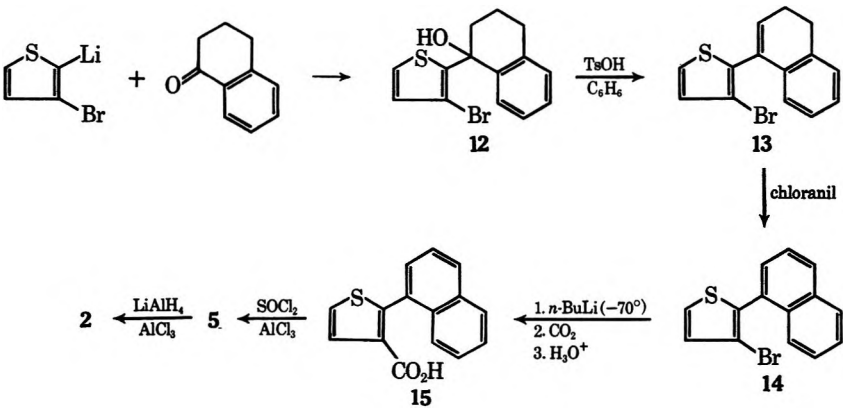
Reconsideration of the work of Weinmayr in his claim to have obtained only **4** from 4,9-dioxo-4,9-dihydronaphtho[2,3-*b*]thiophene led us to suspect that, because of the possibility of reaction at either of the two carbonyl groups, a mixture of **4** and **5** might have been obtained instead of only **4**. Repetition of Weinmayr's work afforded a 51% yield of a bright yellow solid, mp 139–140°, in agreement with Weinmayr's findings. This product exhibited a fairly broad carbonyl absorption in the infrared spectrum. Attempts to separate the components using column chromatography or tlc were unfruitful. Reduction of the product with lithium aluminum hydride–aluminum chloride gave a

(4) V. Weinmayr, F. S. Palmer, and A. A. Ebert, *J. Amer. Chem. Soc.*, **74**, 4361 (1952).

(5) R. M. Kellogg, A. P. Schaap, E. T. Harper, and H. Wynberg, *J. Org. Chem.*, **33**, 2902 (1968).

(6) (a) D. W. H. MacDowell and T. B. Patrick, *ibid.*, **32**, 2441 (1967); (b) D. W. H. MacDowell and A. T. Jeffries, *ibid.*, **35**, 871 (1970); (c) D. W. H. MacDowell and M. H. Maxwell, *Proc. W. Va. Acad. Sci.*, in press.

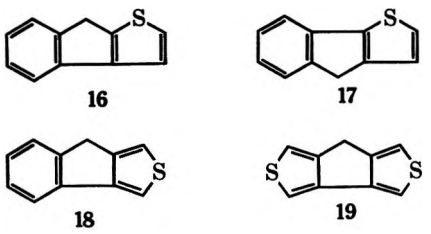
SCHEME II



white solid, the nmr spectrum of which indicated the presence of the two methylene peaks to be expected if the material reduced had consisted of a mixture of the two ketones **4** and **5**. The individual assignments of these two methylene peaks were obtained by comparison with the nmr spectra of authentic **1** and **2** prepared from **4** and **5**. A synthetic (1:1) mixture of **1** and **2** exhibited an nmr spectrum identical with that of the product obtained by reduction of the ketone mixture. Furthermore, a synthetic mixture of ketones **4** and **5** melted at 135–137° and had an ir spectrum identical with that of the product obtained from 4,9-dioxo-4,9-dihydronaphtho[2,3-*b*]thiophene by reaction with glycerol.

Careful repetition of the fusion of 2-(1-naphthoyl)-thiophene following the procedures of both Scholl[3] and Weinmayr[4] gave dark resinous material, which upon chromatography over activated alumina in hexane–benzene afforded the ketone **4** rather than **5** as postulated by Weinmayr. Further elution of the column after removal of **4** afforded a yellow solid, mp 235–250°. This solid which was obtained in very small amounts possessed a molecular weight of 470 (mass spectrum) suggesting the formation of a bimolecular product of **4**. It was not investigated further. The literature contains examples of such dimerizations occurring during the reaction of aromatic ketones with fused salts.[3]

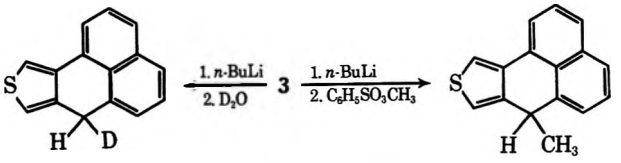
Metalation of the Isomeric Phenalenothiophenes.— It has been shown previously that metalation of compounds containing methylene groups attached to thiophene rings depends upon the mode of fusion of the thiophene rings.[6] In the case of the isomeric indenothiophenes **16**, **17**, and **18** below, metalation was shown to occur exclusively at the methylene bridge in



16[6a] and **17**,[6b] while, in the case of **18**,[6b] metalation occurred at the methylene group and at both of the thiophene positions in addition. In the case of **19**[6c] no metalation occurred at the methylene group, substitution occurring only at the two thiophene positions in a 40:60 ratio. The partially or totally diminished methylene metalation was explained on the basis of diminished anionic electron delocalization across the 3,4 bonds of those compounds containing *c*-fused thiophene nuclei in the resulting cyclopentadienoid-like systems.

The metalation of phenalene has been reported by Boekelheide and Larrabee[7] who showed that when phenalene was treated with phenyllithium, followed by the addition of an excess of methyl iodide, methylation occurred. These workers placed the acidity of phenalene intermediate between that of cyclopentadiene and triphenylmethane. They found that attempts to carbonate metalated phenalene yielded base-soluble material from which no carboxylic acid could be obtained.

Reaction of **3** with ethereal *n*-butyllithium at 20° immediately produced a deep blue colored solution. Addition of Dry Ice or DMF yielded solid material in each case which could not be purified due to facile decomposition. Treatment of the deep blue solution with excess methyl benzenesulfonate afforded a methyl derivative which was readily identified as the 7-methyl-7*H*-phenaleno[1,2-*c*]thiophene on the basis of the presence of a clear-cut doublet and quartet in the aliphatic region of the nmr spectrum of the unpurified product. The absence of any signal due to a methyl group attached to an aromatic nucleus and any methylene peaks further confirmed that metalation had occurred exclusively at the methylene group.

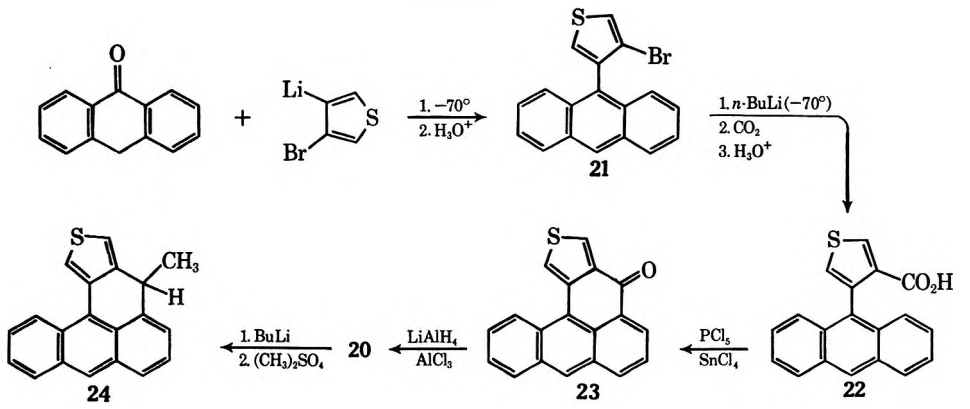


Treatment of the metalated **3** with D_2O afforded a white solid product whose nmr spectrum showed a reduction of the signal due to the methylene protons to one-half its original value with the aromatic region remaining unchanged.

Similar treatment of **2** with *n*-butyllithium followed by reaction with Dry Ice or dimethyl sulfate also yielded unstable products which could not be characterized. Treatment of metalated **2** with D_2O, however, led to the isolation of a solid product in whose nmr spectrum the methylene absorption was reduced to

(7) V. Boekelheide and C. E. Larrabee, *J. Amer. Chem. Soc.*, **72**, 1245 (1950).

Scheme III

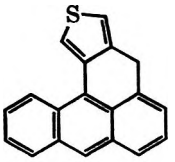


one-half its original value with the aromatic region remaining unchanged.

In view of the exclusive metalation of **2** and **3** at the respective methylene positions, metalation of **1** was not undertaken.

The orientations of metalation, at least in the case of **3**, differ from what might have been expected on the basis of a comparison with the corresponding *c*-fused indenothiophenes and the di-*c*-fused cyclopentadithiophene and probably resides in the increased possibility for delocalization of anionic charge over the naphthalene system.

The fusion of a benzene ring across the 1,2 bond in **3** gives rise to 4*H*-benzo[1,10]phenanthro[3,4-*c*]thiophene[2] (**20**).



20

In work undertaken to ascertain whether the presence of the additional benzene ring might change the metalative properties of **20** compared to **3**, the synthesis of **20** was carried out according to Scheme III.

Dehydration of the tertiary alcohol formed in the first step occurred very readily in the usual work-up. Considerable difficulty was encountered in the cyclization of the acid **22** to product 4*H*-benzo[1,10]phenanthro[3,4-*c*]thiophen-4-one (**23**). Treatment of **22** with thionyl chloride followed by aluminum chloride in carbon disulfide, or benzene or 1,2-dichloroethane or treatment with thionyl chloride followed by stannic chloride in benzene, gave unreacted starting material upon work-up. The ring closure was accomplished in 56% yield by means of phosphorus pentachloride followed by stannic chloride in benzene. Reduction of **23** to **20** in the usual manner proceeded normally in 82% yield.

Treatment of **20** with *n*-butyllithium followed by dimethyl sulfate gave only one product, 4-methyl-4*H*-benzo[1,10]phenanthro[3,4-*c*]thiophene (**24**), with the anticipated quartet and doublet in the nmr spectrum of the unpurified product and shown to be homogeneous by tlc. It is thus seen that fusion of an additional benzene ring into the c-fused phenalenothiophene does not cause any change in the site of metalation.

Experimental Section[8]

Synthesis of 3-[1-(3,4-Dihydronaphthyl)]thiophene (8).—To a stirred solution of ethereal *n*-butyllithium (87 ml, 1.27 *M*, 0.11 equiv) at −70° under dry nitrogen was added a solution of 16.3 g (0.10 mol) of 3-bromothiophene in 25 ml of dry ether. To the resulting solution, maintained at −70°, was added a solution of 1-tetralone (12.1 g, 0.083 mol) in 25 ml of dry ether. The mixture was stirred at −70° for about 1 hr and then at room temperature for 2.5 hr. The mixture was then hydrolyzed and worked up to give 20 g of crude alcohol, which was dehydrated by refluxing a benzene solution with *p*-toluenesulfonic acid using a Dean–Stark trap. Evaporation of the solvent after removal of traces of acid by means of sodium bicarbonate solution gave a brown-orange oil, 18.5 g (88%). The oil was purified by distillation under reduced pressure: bp 112–113° (0.05 mm); $n^{20}D$ 1.6550; 13.5 g (63%); ir (neat) 3100, 3070, 3030, 2950, 2880, 2840 cm^{-1}; nmr (CCl_4) τ 2.75–3.05 (7 H, m, aromatic), 3.95 (1 H, t, vinyl), 7.25 (2 H, m, CH_2), 7.7 (2 H, m, CH_2). *Anal.* Calcd for $C_{14}H_{12}S$: C, 79.19; H, 5.70; S, 15.11. Found: C, 79.20; H, 5.51; S, 14.83.

3-(1-Naphthyl)thiophene (9).—To a stirred refluxing solution of chloranil (27.0 g, 0.11 mol) in 125 ml of xylene was added dropwise a solution of olefin (21.1 g, 0.1 mol) in 50 ml of xylene. The mixture was refluxed with stirring for 20 hr. The xylene was removed, and the resulting red oil was passed through a column of alumina using hexane as an eluent. The yellow-orange oil resulting from evaporation of the hexane was distilled and the fraction, bp 115–116° (0.05 mm), was collected as a colorless oil: 18.5 g (88%); $n^{20}D$ 1.6892, (lit.[9] $n^{20}D$ 1.6892); ir (neat) no aliphatic absorption; nmr (CCl_4) τ 1.95–2.40 (3 H, m, arom), 2.55–2.6 (3 H, d, arom), 2.7–2.9 (4 H, m, arom). *Anal.* Calcd for $C_{14}H_{10}S$: C, 79.96; H, 4.79; S, 15.25. Found: C, 79.88; H, 4.75; S, 15.42.

2-Bromo-3-(1-naphthyl)thiophene (10).—A mixture of 9 (12.6 g, 0.06 mol) and NBS (10.8 g, 0.06 mol) dissolved in 300 ml of a 1:1 chloroform–acetic acid solution was heated under gentle reflux for 0.5 hr. By this time all the NBS had dissolved to give an orange colored solution. The reaction mixture was then diluted with an equal volume of water, and the chloroform layer was separated, washed with sodium hydroxide and water, and then dried ($MgSO_4$). The resulting oil was chromatographed in hexane over alumina to give 13.5 g (78%) of white solid, mp 80–82°. Recrystallization from hexane gave 11.7 g (67%) of **10**: mp 82–83°; nmr (CCl_4) τ 2.05–2.25 (2 H, m, arom), 2.50–2.75 (6 H, m, arom), 3.05 (1 H, d, J = 5.5 Hz, H_4 on thiophene). *Anal.* Calcd for $C_{14}H_9BrS$: C, 58.14; H, 3.14; Br, 27.63; S, 11.09. Found: C, 58.35; H, 3.02; Br, 27.49; S, 10.87.

3-(1-Naphthyl)thiophene-2-carboxylic Acid (11).—To a stirred solution of 47 ml of 1.2 *M* *n*-butyllithium maintained under dry nitrogen at −70° was added dropwise a solution of the bromide

(8) All temperature readings are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Nuclear magnetic resonance spectra were recorded on a Varian HA-60 spectrometer using tetramethylsilane as an internal standard (τ 10) and solvents as specified. Infrared spectra were recorded on a Perkin-Elmer Model 127 and Beckman IR-8 spectrophotometer. Ultraviolet spectra were recorded on a Bausch and Lomb Spectronic 505 spectrophotometer.

(9) H. Wynberg, H. van Driel, R. M. Kellogg, and J. Buter, *J. Amer. Chem. Soc.*, **89**, 3487 (1967).

10 (14.9 g, 0.051 mol) dissolved in dry ether (25 ml). The mixture was stirred at −70° for 0.5 hr after the addition was complete. The resulting solution of the lithium salt was then added to a large excess of Dry Ice suspended in anhydrous ether. After standing for 1 hr, the mixture was allowed to warm to room temperature and was decomposed with ice and water. The ether layer was separated and extracted with sodium bicarbonate, and the basic extracts were added to the water layer. Acidification of the water layer afforded the desired acid, 12.4 g, mp 170–175°. Recrystallization from benzene–hexane (1:1) gave 11.0 g (84%) of acid, mp 181–183°; an analytical sample melted at 187.5–188°: ir (KBr) 3000–2500 (broad, OH), 1660 cm^{-1} (CO_2H); nmr (d_6-DMSO) τ 2.6 (1 H, hump, CO_2H), 1.90–2.15 (3 H, m, arom), 2.30–2.70 (5 H, m, arom), 2.85 (1 H, d, J = 5 Hz, H_4 on thiophene). *Anal.* Calcd for $C_{15}H_{10}O_2S$: C, 70.84; H, 3.96; S, 12.61. Found: C, 70.80; H, 3.89; S, 12.90.

7*H*-Phenaleno[2,1-*b*]thiophen-7-one (4).—A mixture of acid 11 (5.0 g, 0.0195 mol) and thionyl chloride (25 ml) was heated under reflux for 1 hr. Excess thionyl chloride was removed by codistillation with benzene and the solid acid chloride remaining was dissolved in carbon disulfide (50 ml) and added to a suspension of aluminum chloride (5 g) in carbon disulfide (50 ml) at room temperature. The resulting deep red mixture was stirred for 2 hr and was then decomposed with ice and water. Removal of the CS_2 gave a yellow solid which was dissolved in chloroform and the solution extracted with sodium bicarbonate solution. Evaporation gave a yellow solid which was chromatographed over alumina with benzene as eluent to yield 4.0 g (87%) of 7*H*-phenaleno[2,1-*b*]thiophen-7-one (4), mp 153–154°. An analytical sample (benzene) had mp 154.5–155°: ir (KBr) 3080, 1628 cm^{-1} (CO); nmr ($CDCl_3$) τ 1.35 (1 H, m, H_6), 1.82–2.7 (7 H, m, arom); uv λ_{max} (95% C_2H_5OH) 245 nm (ϵ 20,500), 256 (16,800), 336 (8280), 370 (8280). *Anal.* Calcd for $C_{15}H_8OS$: C, 76.24; H, 3.41; S, 13.57. Found: C, 76.23; H, 3.51; S, 13.71.

7*H*-Phenaleno[2,1-*b*]thiophene (1).—To a solution of aluminum chloride (3.4 g, 0.025 mol) and lithium aluminum hydride (0.96 g, 0.025 mol) in 50 ml of ether was added, in small portions with stirring, ketone 4 (3.0 g, 0.0126 mol). The mixture was refluxed with stirring for 17 hr. After hydrolysis with dilute sulfuric acid, the ether layer was extracted with sodium bicarbonate solution and dried ($MgSO_4$). The red solid that remained upon removal of the ether was dissolved in hexane and the solution chromatographed over alumina to give a pale yellow solid, 1.7 g (64%), mp 55–57°. Rechromatography in hexane over alumina give 1.5 g of white solid, mp 62–64°. Recrystallization from hexane raises the melting point to 63–64°. The reduced compound is moderately stable but yellows upon standing at room temperature. An analytical sample melted at 64–65°: ir (KBr) 3050, 2950, 2850 cm^{-1}; nmr (CCl_4) τ 2.5–3.0 (8 H, m, arom), 5.5 (2 H, singlet, CH_2); uv λ_{max} (95% C_2H_5OH) 232 nm (ϵ 32,400), 322 (5330), 334 (6770), 352 (4900). *Anal.* Calcd for $C_{15}H_{10}S$: C, 81.04; H, 4.53; S, 14.43. Found: C, 80.87; H, 4.52; S, 14.60.

3-Bromo-2-[1-hydroxy-1-(1,2,3,4-tetrahydronaphthyl)]thiophene (12).—To a solution of 3-bromo-2-thienyllithium prepared from 2,3-dibromothiophene (19.8 g, 0.082 mol) and ethereal *n*-butyllithium at −70° was added an ethereal solution of 1-tetralone (11.9 g, 0.082 mol). The reaction temperature was maintained at −70° until the addition was completed. The mixture was then stirred for 2 hr at room temperature and decomposed by pouring into an ice–water solution containing 0.6 equiv of HCl, and the ether layer separated. The water layer was saturated with NaCl and extracted with ether. The ether portions were combined and washed successively with water, saturated $NaHCO_3$, water, and brine and then dried ($MgSO_4$). Evaporation of the ether gave 25.7 g of crude alcohol 12. Recrystallization from hexane gave 15.4 g (60.6%) of white crystals: mp 85–86°; ir (KBr) 3600–3400 cm^{-1} (OH); nmr (CCl_4) τ 2.9–3.3 (6 H, arom), 7.0–8.2 (7 H, aliphatic and OH). *Anal.* Calcd for $C_{14}H_{13}BrOS$: C, 54.34; H, 4.23; Br, 25.83; S, 10.37. Found: C, 54.54; H, 4.34; Br, 26.02; S, 10.37.

3-Bromo-2-[1-(3,4-dihydronaphthyl)]thiophene (13).—The alcohol 12 (5.0 g, 0.016 mol) was dissolved in benzene. A catalytic amount of *p*-toluenesulfonic acid was added and the solution was refluxed until water was no longer collected. Crude olefin 13 (4.8 g) which could not be crystallized was obtained. Distillation gave a light yellow oil, bp 154° (1.1 mm). Chromatography over alumina (hexane) failed to provide any additional purification: ir (neat) 3120–3000, 2940 cm^{-1}; nmr (CCl_4) τ 2.8–3.3 (6, H, arom), 3.75–3.95 (1 H, olefinic), 7.0–7.9 (6 H, aliphatic).

3-Bromo-2-(1-naphthyl)thiophene (14).—A solution of the olefin 13 (4.95 g, 0.017 mol) in 20 ml of xylene was added dropwise to a stirred solution of chloranil (4.65 g, 0.019 mol) in anhydrous xylene (30 ml) at reflux. After the addition was completed the mixture was refluxed for 11 hr, cooled, and allowed to stand overnight. The solution was washed with 2 *M* NaOH solution until the alkaline solution was colorless and then washed with water and dried ($MgSO_4$). The mixture was concentrated and chromatographed over Al_2O_3 (1:1 hexane–benzene). Recrystallization (hexane) gave 3.85 g (78%) as clusters of colorless needles, analytical sample, mp 83–84° (sublimation). *Anal.* Calcd for $C_{14}H_9BrS$: C, 58.14; H, 3.14; Br, 27.64; S, 11.05. Found: C, 58.08; H, 3.11; Br, 27.70; S, 10.85.

2-(1-Naphthyl)thiophene-3-carboxylic Acid (15).—A 1.08 *M* *n*-butyllithium solution (34.5 ml, 37.2 mequiv) in 100 ml of dry ether was added to a special reaction flask which had been previously flame-dried and flushed with N_2. The solution was cooled to −70° and kept under a N_2 atmosphere. To the above stirred solution was added dropwise a solution of 10.0 g (34.6 mmol) of 14 in dry ether. After addition, the reaction mixture was stirred for 0.5 hr at −70° and was then added dropwise to a stirred ether–Dry Ice slurry. The mixture was allowed to warm to room temperature and was poured onto cracked ice and HCl. The white precipitate which formed was extracted with ether. The ether solution was extracted with aqueous NaOH, and the product precipitated by addition of HCl and again extracted into ether. The ether was evaporated and left 7.3 g of a white powder. Recrystallization from acetonitrile gave 6.5 g (74%) of colorless needles: mp 223–225°; ir (KBr) 3500–2100, (OH), 1660 cm^{-1} (C=O); nmr (DMSO) τ −2.4 (1 H, OH), 1.8–2.5 (9 H, arom). *Anal.* Calcd for $C_{15}H_{10}O_2S$: C, 70.84; H, 3.96; S, 12.61. Found: C, 71.02; H, 3.99; S, 12.83.

7*H*-Phenaleno[1,2-*b*]thiophen-7-one (5).—The acid chloride of 15 (ir 1750–1720 cm^{-1}) was prepared by addition of 7.0 g (0.028 mol) of the acid 15 to 35 ml of freshly distilled thionyl chloride with refluxing for 1 hr. Excess $SOCl_2$ was removed by repeated codistillation with benzene. The remaining dark oil was not purified but was dissolved in 50 ml of CS_2 and added dropwise at room temperature to a stirred mixture of $AlCl_3$ (7.0 g, 0.05 mol) in 250 ml of CS_2. The reaction mixture was stirred for 3 hr after addition of the acid chloride was complete and was then poured into an ice–water mixture. The CS_2 was removed by distillation and the aqueous portion was extracted with $CHCl_3$. The organic portions were combined, washed with $NaHCO_3$ and water, and dried ($MgSO_4$). The $CHCl_3$ was evaporated and left a solid orange material which was sublimed: yield of pure ketone 4.4 g (68%); mp 153–154°; ir (KBr) 1645 cm^{-1}; uv (cyclohexane) λ_{max} 238.8 nm (ϵ 20,000), 254 (17,000), 260.4 (19,000), 354 (5700); nmr ($CDCl_3$) τ 1.2–2.8 (arom); analytical sample, mp 154–155° sublimed. *Anal.* Calcd for $C_{15}H_8OS$: C, 76.25; H, 3.41; S, 13.57. Found: C, 76.11; H, 3.43; S, 13.37.

7*H*-Phenaleno[1,2-*b*]thiophene (2).—To a stirred suspension of $AlCl_3$ (40.25 g, 0.302 mol) and $LiAlH_4$ (5.91 g, 0.156 mol) in a 250 ml of dry ether under N_2 was added *via* Gooch tubing solid ketone 5, 5.0 g (0.021 mol). On addition of 5 the reaction mixture turned red. The color soon faded and the mixture acquired a light yellow color. After addition was complete the mixture was refluxed for 15 hr and then poured over ice to give a white precipitate. The ether phase was separated, the aqueous portion was extracted with ether, and the ether portions were combined, washed with water, saturated $NaHCO_3$, and brine, and dried ($MgSO_4$). Concentration of the ether solution and chromatography over alumina (hexane) gave 3.9 g (83%) of 2: analytical sample mp 57.5–59° recrystallized from pentane as colorless plates; ir (KBr) 3040 cm^{-1}; uv (cyclohexane) λ_{max} 247 nm (ϵ 22,000), 330.7 (15,000), 346.4 (20,000), 359.5 (14,000), 364.7 (15,000); nmr (CS_2) τ 2.3–3.3 (8 H, m, arom), 5.6 (2 H, s, aliphatic). *Anal.* Calcd for $C_{15}H_{10}S$: C, 81.04; H, 4.53; S, 14.43. Found: C, 80.85; H, 4.63; S, 14.32.

3-Bromo-4-[1-hydroxy-1-(1,2,3,4-tetrahydronaphthyl)]thiophene.—To a solution of 3-bromo-4-thienyllithium prepared from 3,4-dibromothiophene (40 g, 0.165 mol) and ethereal *n*-butyllithium at −70° was added a solution of 1-tetralone (24.1 g, 0.165 mol) in 40 ml of ether. The reaction temperature was maintained at −70° for 1 hr. The mixture was then stirred at room temperature for 2 hr and was decomposed with 2 *M* HCl. The ether solution was washed with sodium bicarbonate solution and dried ($MgSO_4$). Evaporation left 43.6 g of crude alcohol as

a yellow viscous oil which, upon standing in a refrigerator, solidified. Recrystallization of the alcohol from hexane gave white needles (27.0 g, 53%), mp 86–88°. An analytical sample (hexane) melted at 88–90°: ir (KBr) 3600–3400 cm^{-1} (OH); nmr (CCl_4) τ 2.65 (1 H, d, J = 3.5 Hz, H_5), 2.9–3.3 (5 H, m, arom), 7.1–8.3 (7 H, aliphatic and OH). *Anal.* Calcd for $C_{14}H_{13}BrOS$: C, 54.37; H, 4.24; Br, 25.84; S, 10.37. Found: C, 54.50; H, 4.22; Br, 26.03; S, 10.36.

3-Bromo-4-[1-(3,4-dihydronaphthyl)]thiophene.—Dehydration of 20.0 g (0.065 mol) of the above alcohol with *p*-toluenesulfonic acid in refluxing benzene for 3 hr as before gave the corresponding crude olefin (16.1 g). Recrystallization from hexane (Norit) gave solid olefin: 12.4 g (66%); mp 68–70°; ir (neat) 3110, 3070, 3030, 2940, 2890, 2840 cm^{-1}; nmr (CCl_4) τ 2.9–3.4 (6 H, m, arom), 4.1 (1 H, t, vinyl), 7.1–7.9 (4 H, m, aliphatic). *Anal.* Calcd for $C_{14}H_{11}BrS$: C, 57.74; H, 3.81; Br, 27.44; S, 11.01. Found: C, 57.58; H, 3.91; Br, 27.58; S, 11.05.

3-Bromo-4-(1-naphthyl)thiophene.—A solution of chloranil (14 g, 0.056 mol) in 60 ml of xylene was refluxed with stirring under anhydrous conditions while a solution of the above olefin (15 g, 0.052 mol) in 60 ml of xylene was added dropwise. The resulting mixture was refluxed with stirring for 24 hr. Some solid material which had separated upon cooling was removed and the cold solution was extracted with 2 *M* sodium hydroxide. Removal of solvent from the dried ($MgSO_4$) xylene extract gave a red oil which was dissolved in a minimum amount of benzene and chromatographed over alumina using hexane as eluent to give white crystals (8.8 g, 58%), mp 61–63°. An analytical sample (hexaane had mp 62–63°: ir (KBr) 3120, 3060 cm^{-1}, no aliphatic peaks; nmr (CCl_4) τ 2.1–2.9 (m, arom). *Anal.* Calcd for $C_{14}H_9BrS$: C, 58.14; H, 3.14; Br, 27.63; S, 11.09. Found: C, 57.97; H, 3.21; Br, 27.70; S, 10.92.

3-(1-Naphthyl)thiophene-4-carboxylic Acid.—To a stirred solution of 46 ml of 1.5 *M* *n*-butyllithium maintained under dry nitrogen at −70° was added dropwise a solution of the above bromide (20 g, 0.07 mol) dissolved in dry ether (50 ml). The mixture was stirred at −70° for 0.5 hr, after the addition was complete. The resulting solution of the lithium salt was then added to a large excess of Dry Ice suspended in anhydrous ether. After standing for 1 hr, the mixture was allowed to warm to room temperature and was decomposed with ice and water. The ether layer was separated and extracted with $NaHCO_3$, and the basic extracts were added to the water layer. Acidification of the water layer afforded the desired acid, 14.4 g, mp 203–205°. Recrystallization from acetonitrile gave white solid: 13.5 g (76%); mp 210–221°; ir (KBr) 3100–2500 (OH), 1675 cm^{-1} (CO); nmr (DMSO-d_6) τ 1.5 (1 H, d, J = 3.5 Hz, H_5 on thiophene), 1.8–2.1 (2 H, m, arom), 2.3–2.6 (6 H, m, arom). *Anal.* Calcd for $C_{15}H_{10}O_2S$: C, 70.84; H, 3.96; S, 12.61. Found: C, 71.03; H, 4.05; S, 12.59.

7*H*-Phenaleno[1,2-*c*]thiophen-7-one (6).—A mixture of the above acid (5.0 g, 0.0195 mol) and thionyl chloride (25 ml) was heated under reflux for 1 hr. Excess thionyl chloride was removed by codistillation with benzene and the solid acid chloride remaining was dissolved in carbon disulfide (50 ml) and added to a suspension of aluminum chloride (5 g) in carbon disulfide (50 ml) at room temperature. The resulting deep red mixture was stirred for 2 hr and was then decomposed with ice and water. Removal of CS_2 gave a yellow-brown solid, which was dissolved in chloroform, and the solution extracted with $NaHCO_3$ solution and dried ($MgSO_4$). Evaporation gave a yellow-brown solid (3.8 g) which was sublimed to yield 2.8 g (61%) of bright yellow solid, mp 161–163°. Recrystallization from glacial acetic acid afforded 2.6 g (57%) of ketone **6** as bright yellow needles: mp 165–166°; ir (KBr) no aliphatic peaks, 1645 cm^{-1} (CO); nmr ($CDCl_3$) τ 1.5 (1 H, broad d, H_6), 1.7 (1 H, d, J = 3 Hz, H_8), 2.0–2.6 (6 H, m, arom); uv λ_{max} (95% C_2H_5OH) 234 nm (ϵ 49,300), 264 (8800), 296 (10,600). *Anal.* Calcd for $C_{15}H_8OS$: C, 76.24; H, 3.41; S, 13.41. Found: C, 76.43; H, 3.51; S, 13.47.

7*H*-Phenaleno[1,2-*c*]thiophene (3).—To a solution of aluminum chloride (3.4 g, 0.025 mol) and lithium aluminum hydride (0.96 g, 0.025 mol) in 50 ml of dry ether was added, in small portions with stirring, ketone **6** (3.0 g, 0.013 mol). The mixture was refluxed for 22 hr. After hydrolysis with dilute sulfuric acid, the ether layer was extracted with $NaHCO_3$ solution and dried ($MgSO_4$). The yellow solid that remained upon removal of the ether was dissolved in hexane and the solution chromatographed over alumina to give a pale yellow solid, mp 83–84°. Rechromatography in hexane over alumina yielded 1.9 g of white solid (70%), mp 84–85°. Recrystallization from hexane gave an analytical sample: mp 85–86°; ir (KBr) 3110, 3060, 2940, 2860 cm^{-1}; nmr (CCl_4) τ 2.4–3.2 (8 H, m, arom), 5.70 (2 H, s, CH_2); uv λ_{max} (95% C_2H_5OH) 228 nm (ϵ 26,700), 314 (5100), 326 (11,000), 343 (10,200). *Anal.* Calcd for $C_{15}NH_{10}S$: C, 81.04; H, 4.53; S, 14.43. Found: C, 80.97; H, 4.71; S, 14.21.

Metalation of 7*H*-Phenaleno[1,2-*c*]thiophene (3). A. 7-Methyl-7*H*-phenaleno[1,2-*c*]thiophene.—To a solution of **3** (1.0 g, 0.0046 mol) in dry ether (50 ml) at room temperature was added 2.4 ml of 1.94 *M* *n*-butyllithium (0.0046 equiv) with stirring. The color of the solution changed from yellow to deep blue. After the addition was complete, the blue solution was stirred an additional 15 min before it was added to a solution of methyl benzenesulfate (0.86 g, 0.005 mol) in dry ether (25 ml). The resulting orange solution was hydrolyzed with water and extracted with ether. Evaporation yielded 1.1 g of a red-brown oil. Chromatography in hexane over alumina gave 0.55 g (50%) of a white solid, mp 85–88°. Recrystallization from isopropyl alcohol gave an analytical sample: mp 89–90°; ir (KBr) 3100, 3050, 2970, 2930 cm^{-1}; nmr (CCl_4) τ 2.2–3.0 (8 H, m, arom), 5.55 (1, H q, methine, J = 7.5 Hz), 8.50 (3 H, d, methyl, J = 7.5 Hz); uv λ_{max} (95% C_2H_5OH) 230 nm (ϵ 26,900), 314 (7080), 324 (11,300), 342 (10,000). *Anal.* Calcd for $C_{16}H_{12}S$: C, 81.31; H, 5.12; S, 13.57. Found: C, 81.47; H, 4.96; S, 13.36.

B. 7-Deuterio-7*H*-phenaleno[1,2-*c*]thiophene.—To a solution of **3** (0.5 g, 0.0023 mol) in dry ether (25 ml) at room temperature was added 2.7 ml of 0.84 *M* *n*-butyllithium (0.0023 equiv) with stirring. The deep blue solution was added to D_2O (5 ml) and worked up as above. The resulting yellow-brown solid was purified over Florisil using hexane as the eluent. A peach-colored solid was obtained: mp 84–85°; nmr (CCl_4) 2.2–3.0 (8 H, m, arom), 5.7 (1 H, s, CDH).

Metalation of 7*H*-Phenaleno[1,2-*b*]thiophene (2).—To 2.0 g (0.0083 mol) of **2** in 50 ml of dry ether under N_2 in a flame-dried special reaction flask was added 7.3 ml of 1.23 *M* *n*-butyllithium (8.85 mequiv) in 50 ml of dry ether at room temperature. The solution turned red on formation of the anion. After addition of the *n*-butyllithium was complete (about 30 min), the solution was stirred for 15 min and then added dropwise at room temperature to D_2O. Work-up followed the procedure used for **3** and afforded 1.5 g of a white solid: mp 57–58.5°; nmr (CS_2) τ 2.3–3.3 (8, m, arom), 5.6 (1, s, CDH).

Interaction of 4,9-Dioxo-4,9-dihydronaphtho[2,3-*b*]thiophene with Glycerol, Sulfuric Acid, and Iron.—4,9-Dioxo-4,9-dihydronaphtho[2,3-*b*]thiophene (10.7 g, 0.05 mol) was dissolved in 98% sulfuric acid (82.5 g) to give a deep red solution. Water (13 ml) containing copper(II) sulfate (0.2 g) was then added dropwise to the stirred solution and the temperature was allowed to rise to 110°. Glycerol (9.5 g, 0.13 mol) and iron filings (4.9 g, 0.09 g-atom) were added uniformly over a 1-hr period at the reaction temperature, 116–117°. The temperature was maintained for 4 hr before the dark reaction mixture was poured into water and heated to boiling. The mixture was then cooled and filtered. The dark solid mass was air-dried and extracted with benzene in a Soxhlet apparatus. Evaporation of the dark benzene solution yielded 7.2 g of brown solid. Chromatography in benzene over alumina yielded a bright yellow solid, mp 135–137°. Recrystallization from benzene (Norite) gave 6.0 g (51%): mp 139–140°; ir (KBr) 1635 cm^{-1} (C=O); nmr ($CDCl_3$) τ 1.5 (1 H, m, H_6), 2.0–2.9 (7 H, m, arom); uv λ_{max} (95% C_2H_5OH) 240 nm (ϵ 18,600), 258 (15,800), 336 (6150). *Anal.* Calcd for $C_{15}H_8OS$: C, 76.24; H, 3.41; S, 13.57. Found: C, 76.47; H, 3.53; S, 13.37.

Reduction of the Above Ketonic Product.—To a solution of aluminum chloride (2.24 g, 0.016 mol) and lithium aluminum hydride (0.68 g, 0.016 mol) in 25 ml of ether was added, in small portions with stirring, the above ketonic product (1.9 g, 0.008 mol); the mixture was refluxed with stirring for 20 hr. Work-up followed by chromatography in hexane over alumina gave 0.9 g (51%) of a pale yellow solid, mp 43–47°. Sublimation gave 0.75 g (43%) of white solid, mp 44–46°. An additional sublimation gave an analytical sample: mp 45–46°; nmr (CCl_4) τ 2.5–3.1 (15 H, m, arom), 3.3 (1 H, d, J = 5 Hz, H_8 on [1,2-*b*] isomer), 5.6 (2 H, s, CH_2), 5.75 (2 H, s, CH_2); uv λ_{max} (95% C_2H_5OH) 234 nm (ϵ 23,900), 332 (8640), 346 (8400), 364 (3700). *Anal.* Calcd for $C_{15}H_{10}S$: C, 81.04; H, 4.53; S, 14.43. Found: C, 81.16; H, 4.72; S, 14.20.

A mixture of equal amounts (25 mg) of synthetic samples of **1** and **2**, dissolved in CCl_4, gave the following nmr spectrum: τ

2.4–3.0 (15 H, m, arom), 3.3 (1 H, d, J = 5 Hz, H_8 on [1,2-*b*]), 5.5 (2 H, s, CH_2), 5.7 (2 H, s, CH_2).

Fusion of 2-(1-Naphthoyl)thiophene with Aluminum Chloride, Sodium Chloride, and Potassium Chloride.—2-(1-Naphthoyl)-thiophene, 16.0 g (0.067 mol), was slowly added (0.5 hr) with stirring to a beaker containing NaCl (18.0 g, 0.31 mol), $AlCl_3$ (130.5 g, 0.98 mol), and KCl (15.3 g, 0.15 mol) fused at 120–130°. After the addition was complete the mixture was stirred for 20 min. The temperature was then raised to 150° and allowed to cool immediately to 120°. The mixture, a dark red melt, was poured into cold water. The precipitate, a dark green resinous material (24 g), was filtered off, dried (vacuum desiccator), and extracted in a Soxhlet extractor (benzene) overnight. The benzene solution was concentrated to about 200 ml and was chromatographed on alumina activated at 350°. After 8 hr of eluting with benzene, the alumina was extracted and the middle portion separated; 0.67 g of a bright yellow material was isolated and purified by sublimation 135° (0.075 mm), mp 154°. Mixture melting point with authentic 7*H*-phenaleno[1,2-*b*]thiophen-7-one gave no depression. Mixture melting point with authentic 7*H*-phenaleno[2,1-*b*]thiophen-7-one (mp 154°) gave mp 134°, a depression of 20°; ir and uv identical with **4**.

An orange band near the top of the column was isolated and yielded a small amount of an orange material (0.035 g), mp 235–250° (CH_3CN). No further purification attainable: ir (KBr) 1640 cm^{-1}; nmr unavailable because of insolublility. The mass spectrum showed a parent peak at m/e 470.

3-Bromo-4-(9-anthryl)thiophene (21).—An ethereal solution of 4-bromo-3-thienyllithium prepared from 3,4-dibromothiophene (6.17 g, 0.026 mol) was added at −70° to a stirred suspension of anthrone (4.85 g, 0.025 mol) in ether (100 ml) also at −70°. The mixture was allowed to warm to room temperature and hydrolyzed with ice and hydrochloric acid, and the solution washed with sodium bicarbonate and dried. Evaporation of the solvent left a yellow-brown solid (6.3 g) which upon chromatography of its solution in benzene over alumina followed by recrystallization from benzene yielded 5.5 g (65%) of a light yellow solid: mp 123.5–125°; ir (KBr) 3100, 3050, 785, 730 cm^{-1}; nmr (CS_2) τ 1.60 (1 H, s, H_{10} of anthracene), 2.04 (2 H, m, thiophene), 2.64 (8 H, m, anthracene). *Anal.* Calcd for $C_{18}H_{11}BrS$: C, 63.72; H, 3.27; Br, 23.56; S, 9.45. Found: C, 63.94; H, 3.34; Br, 23.38; S, 9.25.

4-(9-Anthryl)thiophene-3-carboxylic Acid (22).—Treatment of 3-bromo-4-(9-anthryl)thiophene (8.4 g, 0.025 mol) in ether (100 ml) at −70° with 25.45 ml of 1.08 *M* *n*-butyllithium (0.028 mol) followed by stirring at −70° for 30 min gave the lithio derivative which was poured onto a suspension of Dry Ice in ether. Work-up in the usual manner gave a light brown solid which upon recrystallization from glacial acetic acid yielded 5.9 g (77%) of white needles: mp 285–287°; ir (KBr) 3650–2400, 1675 cm^{-1}; nmr (polysol-*d*) τ 1.44 (2 H, m, 1 or 8, and 10 proton of anthracene), 1.94 (2 H, m, anthracene), 2.61 (7 H, m, aromatic). *Anal.* Calcd for $C_{19}H_{12}O_2S$: C, 74.97; H, 3.89; S, 10.54. Found: C, 75.07; H, 4.00; S, 10.37.

4*H*-Benzo[1,10]phenanthro[3,4-*c*]thiophen-4-one (23).—A suspension of the acid **22** (5.02, 0.017 mol) in benzene (50 ml) was treated with phosphorus pentachloride (3.43 g, 0.017 mol) with cooling in ice. The mixture was then allowed to warm to room temperature and stirred under reflux for 1 hr. To the solution (cooled to 0°) was slowly added a solution of anhydrous stannic chloride (8.88 g, 0.034 mol) in benzene (50 ml). The mixture was heated under reflux for 15 hr by which time its color had changed from light green to deep purple. The mixture was then hydrolyzed by adding concentrated HCl and stirring at 0° for 1 hr. Extraction with ether followed by the usual work-up gave crude brown material (3.3 g) which upon chromatography in benzene over alumina gave 2.67 g (56%) of orange fibrous **23**: mp 178.5–179°; ir (KBr) 1645 cm^{-1} (C=O); nmr (TFA) τ 2.10 (1 H, s, H_{10} anthracene), 2.41 (1 H, d, H_1 of anthracene), 3.00 (8 H, m, anthracene). *Anal.* Calcd for $C_{19}H_{10}OS$: C, 79.69; H, 3.52; S, 11.20. Found: C, 79.73; H, 3.32; S, 11.07.

4*H*-Benzo[1,10]phenanthro[3,4-*c*]thiophene (20).—To a mixture of aluminum chloride (2.35 g, 0.018 mol) and lithium aluminium hydride (0.333 g, 0.0088 mol) in ether (50 ml) under dry nitrogen was slowly added 1.00 g (0.0035 mol) of 4*H*-benzo-[1,10]phenanthro[3,4-*c*]thiophen-4-one (**23**). The mixture was heated under reflux for 20 hr, cooled, and hydrolyzed with ice and 3 *M* sulfuric acid. The usual work-up afforded an amber oil (0.85 g) which was chromatographed in benzene solution over alumina to yield a light yellow solid which was recrystallized from hexane to give pure 4*H*-benzo[1,10]phenanthro[3,4-*c*]thiophene (**20**) as a yellow solid (0.781 g, 82%): mp 135–136.5°; ir (KBr) 3115, 2930 cm^{-1}; nmr (CS_2) τ 1.10 (1 H, m, H_1 of anthracene), 1.79 (1 H, s, H_{10} of anthracene), 2.40 (8 H, m, arom), 5.62 (2 H, s, CH_2). *Anal.* Calcd for $C_{19}H_{12}S$: C, 83.79; H, 4.44; S, 11.77. Found: C, 83.64; H, 4.44; S, 11.82.

Metalation of 20.—To a solution of **20** (1.82 g, 0.0067 mol) in ether (50 ml) at room temperature was added 6.1 ml of 1.1 *M* *n*-butyllithium (0.0067 equiv) with stirring. The solution changed from a yellow to a dark blue-green color. Addition of a solution of dimethyl sulfate (0.92 g, 0.0073 mol) in ether (25 ml) caused the color of the mixture to change to orange. Upon completion of the addition, the mixture was hydrolyzed with ice and extracted with ether. Work-up yielded 1.7 g of a reddish-yellow oil. Chromatography in hexane over alumina gave 1.26 g (66%) of 4-methyl-4*H*-benzo[1,10]phenanthro[3,4-*c*]thiophene (**24**): mp 158–159°; ir (KBr) 2950 cm^{-1}; nmr (CS_2) τ 1.18 (1 H, m, H_1 of anthracene), 1.86 (1 H, s, H_{10} of anthracene), 2.50 (8 H, m, arom), 5.66 (1 H, 1, CH), 8.56 (3 H, d, CH_3). *Anal.* Calcd for $C_{20}H_{14}S$: C, 83.88; H, 4.92; S, 11.20. Found: C, 83.66; H, 4.85; S, 11.19. Both crude and purified materials indicated the presence of only one substance upon tlc analysis over silica gel using a variety of solvents.

Registry No.—**1**, 212-02-2; **2**, 211-98-3; **3**, 1210-02-2; **4**, 30415-22-6; **5**, 30415-23-7; **6**, 30415-24-8; **8**, 30415-25-9; **9**, 17574-57-1; **10**, 30415-27-1; **11**, 30415-28-2; **12**, 30415-29-3; **13**, 30415-30-6; **14**, 30409-49-5; **15**, 30409-50-8; **20**, 30477-06-6; **21**, 30409-51-9; **22**, 30409-52-0; **23**, 30409-53-1; **24**, 30477-07-7; 3-bromo-4-[1-hydroxy-(1,2,3,4-tetrahydronaphthyl)]thiophene, 30409-54-2; 3-bromo-4-[1-(3,4-dihydronaphthyl)]thiophene, 30409-55-3; 3-bromo-4-(1-naphthyl)thiophene, 30409-56-4; 3-(1-naphthyl)thiophene-4-carboxylic acid, 30409-57-5; 7-methyl-7*H*-phenaleno[1,2-*c*]thiophene, 30409-58-6; 7-deuterio-7*H*-phenaleno[1,2-*c*]thiophene, 30409-59-7.

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The Reactions of Halothiophenes with Metal Amides. A Convenient Preparation of β-Bromothiophenes[1]

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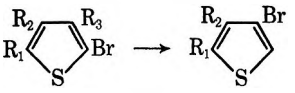
A new, convenient, and efficient synthesis of the very useful β-bromothiophenes by the metal amide catalyzed rearrangement of the readily available α isomers is reported.

While diazonium compounds are generally acknowledged to be key synthetic intermediates in the preparation of substituted benzenes, the corresponding position in the thiophene series is held largely by bromo compounds.[2] Unfortunately, only the α-bromothiophenes are readily available by direct electrophilic substitution.[2] Consequently, several indirect methods for introducing substituents into the β position of thiophenes have been developed.[3] Nevertheless, β-bromothiophenes, because they can be converted quantitatively to the versatile β-lithio derivatives,[4] are still viewed as the most suitable entry into the β-substituted thiophene series.[3,5]

The synthesis of 3-bromo- and 3,4-dibromothiophene usually involves exhaustive bromination of thiophene to 2,3,5-tribromo- and 2,3,4,5-tetrabromothiophene, respectively, followed by selective removal of the 2 and 5 bromine atoms with Grignard reagents,[6] lithium reagents,[7] or zinc and acid.[8,9] Substituted β-bromothiophenes often require even more elaborate synthetic procedures.[10,11] This paper reports an alternative synthesis of a variety of β-bromothiophenes (2) which does not require the preparation of intermediate polybromothiophenes but proceeds directly by rearrangement of the easily prepared[2] or commercially available α-bromo isomers (1).

The prototype for this synthesis is the conversion of 2-bromothiophene (**1a**) to 3-bromothiophene (**2a**) with sodium amide in liquid ammonia. Variations of this reaction are listed in Table I. Although the conditions were not necessarily optimized in every case, changes from those indicated in Table I and the Experimental Section often lead to lower yields.[1]



1 2

The major identifiable side products of these halogen rearrangements are polyhalothiophenes, dehalogenated thiophenes, and aminothiophenes, in accordance with the mechanism proposed for this reaction.[12] Formation of the first two products is usually favored by shorter reaction times, or by lower concentrations of metal amide in solution, as when the relatively insoluble lithium or sodium amides[13] are utilized. Aminothiophene production is favored by high concentrations of metal amide in solution, as is obtained with potassium amide. Some compounds (**1b,c,d**) are resistant to amination even with potassium amide, while others (**1a,e,f**) give substantial amounts of aminothiophenes[12] or their decomposition products with this reagent. In fact, the preparation of the relatively unstable 3-aminothiophene in 74% yield (as the acetamide) from **1a** and 2 equiv of potassium amide in liquid ammonia is in itself of considerable synthetic value.[14]

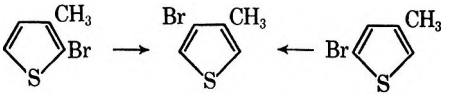
TABLE I

REACTIONS OF BROMOTHIOPHENES WITH METAL AMIDES

Series	Reactant (1) R1	R2	R3	Moles	Conditions[a] Amide (equiv)	% yield of 2[b,c]
a	H	H	H	0.5	$NaNH_2$ (2)	73
b	CH_3	H	H	0.1	KNH_2 (6)	72
c	H	H	CH_3	0.1	KNH_2 (3)	67[b]
d	Benzo		H	0.1	KNH_2 (6)	87
e	CH_3	Br	H	0.05	$NaNH_2$ (3)	64
f	Br	H	H	1.0	$NaNH_2$ (4)	73[c]

[a] 20 ± 5 min in refluxing liquid ammonia. [b] **2c** is 3-methyl-4-bromothiophene (R_1 = H, R_2 = Me). [c] **2f** is 3,4-dibromothiophene (R_1 = H, R_2 = Br).

Bromine migration also can occur from an α to an opposite β position. This characteristic is particularly useful in the preparation of **2c** since **1c** may replace the alternate reactant **3** which is very difficult to obtain in



1c 2c 3

reasonable yield and purity.[15] For example, bromination of the readily available[4] 2-lithio-4-methylthiophene leads to virtually inseparable mixtures of **1c** and **3**. Since the use of one of these mixtures, instead of pure **1c**, in the rearrangement does not improve the yield of **2c**, **1c** probably is as good a starting material as **3** in this synthesis.

With unsubstituted metal amides the rearrangement is apparently of synthetic value only for bromothiophenes (Table II). Use of a substituted amide, however, leads to a substantial improvement in the yield of 3-iodothiophene (Table III). Other halothiophenes do

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TABLE II

REACTIONS OF 2-CHLORO- AND 2-IODOTHIOPHENE WITH METAL AMIDES[a]

Reactant (0.1 mol)	Amide (0.6 mol)	Product
2-Chlorothiophene	$NaNH_2$	92% recovery
2-Chlorothiophene	KNH_2	Tars
2-Iodothiophene	$NaNH_2$	37% 3-iodothiophene
2-Iodothiophene	KNH_2	Tars

[a] 15 min, $NH_3(l)$, −33°.

TABLE III

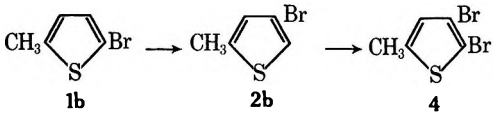
REACTIONS OF HALOTHIOPHENES WITH METAL ANILIDES[a]

Reactant thiophene	Anilide	Product thiophene
2-Iodo[b]	$KNCH_3C_6H_5$	3-Iodo (77%)
2-Chloro[c]	$KNCH_3C_6H_5$	76% recovery
1a	$KNCH_3C_6H_5$	2f (38%); 2,3,4-tribromo (36%)
1a	$NaNHC_6H_5$	2f (46%); 2,3,4-tribromo (38%)
1a	$KNHC_6H_5$	2f (34%); 2,3,4-tribromo (49%)
1e[d]	$KNCH_3C_6H_5$	2e (21%); 2-methyl-3-bromo (21%); 2,3,4-tribromo-5-methyl (9%)
1f	$NaNHC_6H_5$	2f (80%)

[a] Unless otherwise noted, all reactions run as follows: 0.1 mol of reactant, 0.2 mol of anilide, 20 min, $NH_3(l)$, −33°, no other thiophene products in >1% yield. [b] 0.6 mol of anilide, 15 min, 5% side product. [c] 0.05 mol, 0.15 mol of anilide, 2 hr. [d] 0.04 mol, 0.12 mol of anilide.

not respond as markedly to this variation primarily because of changes in product distribution.

During the course of this work an improved preparation of **1e** was developed (see Experimental Section), and a synthesis of the previously unknown **4** was carried out utilizing the rearrangement which is the subject of this paper.



1b **2b** **4**

Experimental Section

Boiling points are uncorrected. All spectra were taken on vpc collected samples. Infrared spectra were taken as films on a Beckman IR-10 or a Perkin-Elmer 237 instrument and were calibrated with a polystyrene film. Nmr spectra were obtained with a Varian A-60 spectrometer and calibrated in τ units relative to TMS. Unless otherwise noted, gas chromatographic analyses were carried out on an Aerograph Autoprep A-700 or a Beckman GC-II using a 12 ft × 0.25 in. column of either 12% Carbowax 20M or 10% Carbowax 4000 on Gas-Chrom R.

Starting Materials.—2-Bromothiophene (**1a**), 2-chlorothiophene, and 2,5-dibromothiophene (**1f**) were purchased from Eastman Organics and purified by distillation prior to use. 5-Bromo-2-methylthiophene (**1b**),[16] 2-bromobenzothiophene (**1d**),[17] and 2-iodothiophene[18] were prepared according to the indicated literature procedures. The remaining reactants (**3**, **1c**, and **1e**) were synthesized as described below.

3-Methylthiophene.[19]—To a 500-ml, three-necked Morton flask equipped with a stirrer and a condenser set for distillation were added 37 g (0.33 mol) of 3-thiophenecarboxaldehyde[20] and 250 ml of ethylene glycol. The flask was immersed in a cold water bath and 30 ml of 97% hydrazine was slowly added with stirring. The solution was distilled until the temperature of the vapors reached 135°. The distillate was extracted with ether, and the extract was washed with 50 ml of water. When the glycol solution had cooled to room temperature, the ether extract and 70 g of KOH pellets were added to the flask. The mixture was cautiously heated and stirred. After the KOH had dissolved, the distillation was continued. When the temperature of the vapors reached 135°, large quantities of nitrogen were given off, and heating was immediately reduced. When the evolution of nitrogen had ceased, the distillation was resumed until the temperature reached 145°. The distillate was extracted with two 75-ml portions of ether. The ether extracts were washed with two 25-ml portions of 5% HCl and with 25 ml of water. The ether extract was dried over $CaCl_2$, and the solution was distilled through a Nestor–Faust Teflon annular spinning band fractionating column. The fraction boiling at 114–116° (lit.[21] bp 115.4°) was collected to give 29.1 g (90%) of 3-methylthiophene: ir 755 cm^{-1} (3-substituted thiophene);[22] nmr (neat) τ 7.92 (d, $J \approx 1$ Hz, 3, CH_3), 3.25 (m, 2, 2 and 4 H), 2.98 (m, 1, 5 H).[23]

2-Bromo-3-methylthiophene (**1c**).—To a solution of 4.9 g of 3-methylthiophene in 25 ml of dioxane at room temperature was added dropwise with magnetic stirring 8 g of bromine in 50 ml of dioxane. After 30 min had elapsed the mixture was poured into 200 ml of water and extracted with two 100-ml portions of ether. The combined ether layers were washed with 25 ml of 1 *N* NaOH and two 25-ml portions of water. Distillation of the dried extracts (Na_2SO_4) gave 7.5 g (85%) of **1c** as a colorless oil (>99% pure by vpc), bp 76–78° (30 mm) [lit.[24] bp 68–70° (18 mm)]; micro bp[25] 174.5° (lit.[15] 173–176°); ir 692 cm^{-1} (2,3-disubstituted thiophene);[22] nmr (neat) τ 8.27 (s, 3, CH_3), 3.71 (d, J = 5.5 Hz, 1, 4 H), 3.35 (d, J = 5.5 Hz, 1, 5 H) [lit.[26] ($DCCl_3$) 4 H, 3.38, d; 5 H, 3.03, d; J = 5.3 and 5.5 Hz].

2-Bromo-4-methylthiophene (**3**).—To a 100-ml, three-necked Morton flask, equipped with a magnetic stirring bar, reflux condenser with a nitrogen bubbler, and a serum cap, was added 10.1 g (0.102 mol) of 3-methylthiophene in 50 ml of anhydrous ether. The flask was swept with nitrogen, and 0.11 mol of commercial *n*-butyllithium in *n*-hexane was injected into the stirred mixture. The mixture was heated at reflux for 1 hr and cooled in an ice bath, and 15 g (0.094 mol) of bromine was slowly added from an additional funnel. The mixture was poured into 100 ml of cold 1 *N* NaOH, the layers were separated, and the ether layer was washed with 100 ml of water and dried over Na_2SO_4. The ether was removed by distillation, and the residue was analyzed on a 15 ft 20% DC QF-1 on Chromosorb W column at 132°. Two distinct but inseparable peaks were observed in a 1:3 ratio in order of increasing retention time. An nmr spectrum (CCl_4) of this mixture was very similar to that of **1c** except that the methyl peak (τ 7.8) had a decided low-field shoulder and the doublet (τ 3.3) overlapped a tightly coupled multiplet as might be obtained from a 2,4-disubstituted thiophene ($J_{2,4}$ = 1.2–1.9 Hz).[27] The 5 H doublet at τ 2.9 has J = 5.5 Hz, thereby eliminating the presence of a 3,4-disubstituted isomer from consideration ($J_{2,5}$ = 2.8–3.2 Hz).[27] An infrared spectrum of this mixture contained a new peak at 730 cm^{-1} characteristic of some 2,4-disubstituted thiophenes.[28]

Variations of this synthesis involving different solvents or lithium reagents failed to improve the product ratio beyond 1:1.

3,5-Dibromo-2-methylthiophene (**1e**).—To a 2-l. three-necked Morton flask equipped with a stirrer, a reflux condenser, and an addition funnel was added a mixture of 49 g (0.50 mol) of 2-methylthiophene[29] in 250 ml of dioxane. After 1 l. of dioxane containing 160 g (1 mol) of bromine was slowly added, the mixture was stirred at room temperature for 2 hr and then heated to reflux until the evolution of HBr ceased (approximately 2 hr). The mixture was cooled and poured into 2 l. of water, the layers

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(26) Reference 19, pp 80, 84.

(27) Reference 22, p 117.

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(29) Aldrich Chemical Co.

were separated, and the aqueous layer was washed twice with ether. The combined organic layers were washed with 250 ml of 1 *N* NaOH, and 250 ml of water, and dried over $CaCl_2$. The ether was removed by distillation, and the residue was vacuum distilled to give 127 g (97%) of 3,5-dibromo-2-methylthiophene (1e): bp 48–55° (0.35–0.45 mm) [lit.[30] bp 98.5–100° (10 mm)]; nmr (CCl_4) τ 7.70 (s, 3, CH_3) and 3.16 (s, 1, 4 H); ir 781, 812, 948 cm^{-1}.

General Procedure for Preparing β-Bromothiophenes (1 → 2).—Since commercial sodium and lithium amides gave erratic results, all metal amides were prepared[31] in liquid ammonia in a three-necked Morton flask equipped with a stirrer, a Dry Ice–acetone condenser, and an addition funnel. If the reaction was to be carried out with a metal anilide a 10% excess of the desired aniline was added at this time. After 10 min of stirring, the metal anilide was ready for use.

The bromothiophene was added as rapidly as possible, and after the reaction was complete sufficient NH_4Cl was added to destroy the excess amide. After the ammonia was evaporated with the aid of a lukewarm water bath, water was added to the residue and the organic layer was separated. Any insoluble tars were removed by filtration. The aqueous solution was extracted with three portions of ether, and the extracts were washed with four portions of 1 *N* HCl and one of water and then dried over $CaCl_2$. The ether was removed by distillation and the residue fractionally distilled to give the product. Reaction time, temperature, yield, the ratio of amide to thiophene, and the scale of the reaction are noted in Tables I, II, and III.

Product Identification.—3-Bromothiophene (2a),[9] 2,3,4-tribromothiophene,[7] 4-bromo-2-methylthiophene (2b),[11] 3-bromobenzothiophene (2d),[32] and 3,4-dibromothiophene (2f)[8] were identified by comparison of their infrared and nmr spectra and vpc retention times with those of authetic samples prepared by the cited methods. 3-Iodothiophene was identified by comparison of its nmr[33] and infrared[34] spectra with those in the literature. 3-Bromo-4-methylthiophene (2c) was identified by comparison of its infrared spectrum with that in the literature[10] and from its nmr spectrum (CCl_4) [τ 7.80 (d, $J \approx 1$ Hz, 3, CH_3), 3.16 (m, 1, 5 H), 2.91 (d, $J = 3.5$ Hz, 1, 2 H)].[27,35] 2-Methyl-3-bromothiophene was identified from its nmr spectrum[35] (CCl_4) [τ 7.67 (s, 3, CH_3), 3.23 (d, $J = 5.5$ Hz, 1, 4 H), 3.07 (d, $J = 5.5$ Hz, 1, 5 H)] and infrared spectrum[10] (695 cm^{-1}, 2,3-disubstituted thiophene).[22] 2,3,4-Tribromo-5-methylthiophene was identified by its melting point, 86.5–87° (lit.[36] mp 86°) and nmr spectrum (CCl_4, τ 7.60, s). 3,4-Dibromo-2-methylthiophene (2e) was identified from its nmr spectrum (CCl_4) [τ 7.55 (s, 3, CH_3), 2.93 (s, 1, 5 H)] and from the nonidentity of its infrared spectrum (728, 840, 880 cm^{-1}) with that of the starting material (1e) and the other possible α-methyldibromothiophene 4 synthesized as outlined below.

2,3-Dibromo-5-methylthiophene (4).—To a 50-ml, three-necked Morton flask equipped with a magnetic stirring bar, a reflux condenser, and an addition funnel were added 10 ml of dry benzene and 5 g (0.021 mol) of 4-bromo-2-methylthiophene (2b) prepared from the reaction of 5-bromo-2-methylthiophene (1b) with KNH_2 as described in this paper. The mixture was cooled in an ice bath, and 3.3 g (0.021 mol) of bromine in 20 ml of dry benzene was added with stirring over a period of 3 hr. The mixture was stirred at room temperature for 10 hr and then heated to reflux until HBr was no longer given off (about 30 min). The mixture was poured into 100 g of ice water, the layers were separated, and the aqueous layer was washed with two 50-ml portions of ether. The combined benzene and ether layers were dried over $CaCl_2$. The solvents were removed by distillation through a 40-cm Vigreux column. Vacuum distillation of the residue gave 4.5 g (84%) of 2,3-dibromo-5-methylthiophene (4): bp 76–78° (0.75 mm); nmr (CCl_4) τ 2.46 (q, 1, 4 H), 7.61 (d, 3, CH_3), $J_{CH_3-H} \approx 1$ Hz;[35] ir 2910, 1540, 1443, 1320, 1170, 1000, 830, 815 cm^{-1}.

Anal.[37] Calcd for $C_5H_4Br_2S$: C, 23.64; H, 1.57; Br, 62.44. Found: C, 23.29; H, 1.62; Br, 62.31.

3-Acetamidothiophene.—Using the general procedure for preparing β-bromothiophenes described above, 81.5 g (0.5 mol) of 2-bromothiophene was treated with 2 equiv of KNH_2 in liquid NH_3 at −33° for 15 min. The combined acid extracts were cooled with ice, basified with 50% NaOH, and quickly extracted with four portions of ether. Rather than attempt isolation of the relatively unstable[14] 3-aminothiophene itself, a fivefold excess of acetic anhydride was immediately added to the combined, undried ether extracts. Removal of the ether and excess acetic anhydride at reduced pressure on a rotary evaporator left a crystalline residue which upon recrystallization from water with the aid of Norit gave 52 g (74%) of 3-acetamidothiophene: mp 146–147° (lit.[14] mp 147–148°); ir 755 cm^{-1} (3-substituted thiophene);[22] nmr (acetone-d_6) τ 7.91 (s, CH_3), 6.39 (s, NH), 2.4–3.0 (m, characteristic of 3-substituted thiophenes,[33] ArH).

Registry No.—1c, 14282-76-9; 1e, 29421-73-6; 2a, 872-31-1; 2b, 29421-92-9; 2c, 30318-99-1; 2d, 7342-82-7; 2e, 30319-01-8; 2f, 3141-26-2; 4, 30319-03-0; 2,3,4-tribromothiophene, 3141-25-1; 2-methyl-3-bromothiophene, 30319-05-2; 2,3,4-tribromo-5-methylthiophene, 30319-06-3.

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(37) M-H-W Laboratories, Garden City, Mich.

Thietanes. II. Rearrangement of 2,4-Diphenylthietane Dioxides to 3,5-Diphenyl-1,2-oxathiolane 2-Oxides

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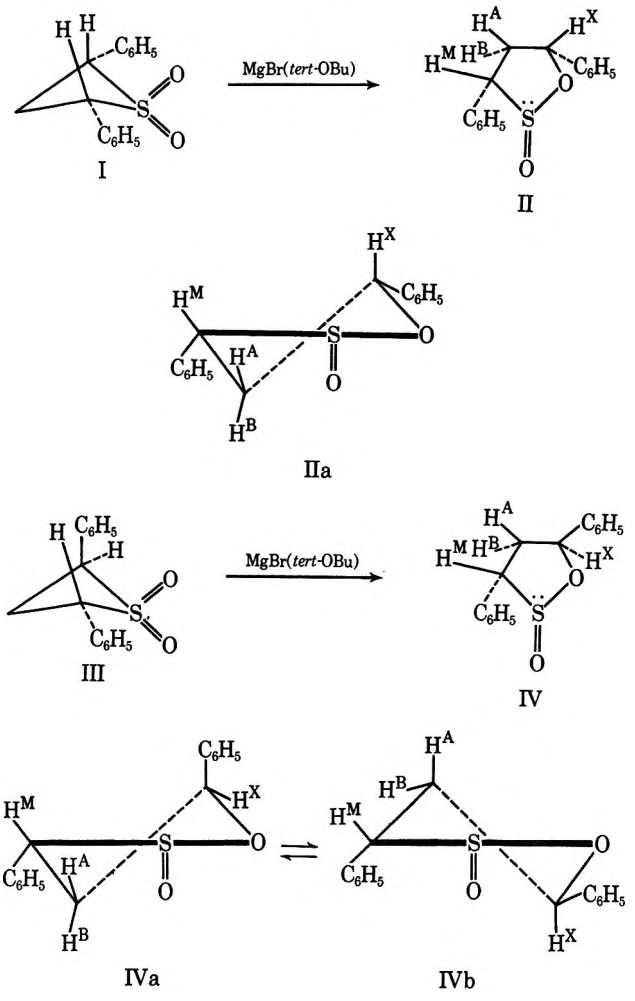
cis- and *trans*-2,4-diphenylthietane 1,1-dioxides (I and III, respectively) when treated with *tert*-butoxymagnesium bromide rearranged to *cis*-3,5-diphenyl-1,2-oxathiolane *cis*-2-oxide (II) and *trans*-3,5-diphenyl-1,2-oxathiolane (2,3)-*cis*-2-oxide (IV), respectively. Configurations for II and IV were assigned from an analysis of their nmr spectra. Probable conformations for II and IV were calculated from the nmr spectra.

Recently we have described the syntheses and the determinations of configurations and conformations of the 2,4-diphenylthietanes, their monoxides, and dioxides.[1] Here, we report the rearrangement of the *cis*- and *trans*-2,4-diphenylthietane 1,1-dioxides (I and III, respectively) by reaction with *tert*-butoxymagnesium bromide to *cis*-3,5-diphenyl-1,2-oxathiolane *cis*-2-oxide (II) and *trans*-3,5-diphenyl-1,2-oxathiolane (2,3)-*cis*-2-oxide (IV),[2] respectively.[3]

Only two examples of the conversion of "thiete dioxides" to cyclic sulfinates[4] had been reported in the literature at the time of our initial report. More recently the conversions of thiete dioxide itself and 2-phenylthiete dioxide to the corresponding 1,2-oxathiol-3-enes have been described.[5] All of the above were pyrolytic transformations; the intermediacy of a vinylsulfene was postulated.[5,6] Related rearrangements of cyclic sulfones to sulfinates have also been postulated to explain the fragmentation patterns of cyclic sulfones in mass spectrometry.[7] However, the rearrangement described here differs from any of those previously reported. This rearrangement is ionic, is catalyzed by base, occurs at moderate temperatures (35°), and is stereospecific.

Syntheses.—Reaction of *cis*-2,4-diphenylthietane 1,1-dioxide (I) with *tert*-butoxymagnesium bromide[8] in ether gave *cis*-3,5-diphenyl-1,2-oxathiolane *cis*-2-oxide (II) in 70% yield (Scheme I). A comparable reaction with *trans*-2,4-diphenylthietane 1,1-dioxide (III) gave *trans*-3,5-diphenyl-1,2-oxathiolane (2,3)-*cis*-2-oxide (IV) in much lower (41%) yield. The constitutions of these sultines,[4c] II and IV, were established by their elementary analyses, by the presence of bands in the ir spectra corresponding to those of sulfinates (1149 and 1138 cm^{-1} for II and IV, respectively), by the presence in their mass spectra of a base peak corresponding to M − SO_2, and by the complete analysis of their nmr

SCHEME I



spectra. The constitutions of II and IV were confirmed by their independent syntheses from 1,3-diphenyl-3-hydroxypropanethiol[1] (VI) *via* oxidation with chlorine in glacial acetic acid,[9] a method now known to give cyclic sulfinates. *cis*- and *trans*-3,5-diphenyl-5-deuterio-1,2-oxathiolane 2-oxides (5D-II and 5D-IV, respectively) also were synthesized by this same method using 3-deuterio-1,3-diphenyl-3-hydroxypropanethiol (VI), prepared by the reduction of 1,3-diphenyl-3-acetylthio-1-propanone[1] with lithium aluminum deuteride.

Both II and IV were readily oxidized with *m*-chloroperbenzoic acid to the corresponding diphenyl sultones VII and VIII. Since this oxidation destroyed the asymmetry of the sulfur center, and since distinctly

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TABLE I[a]

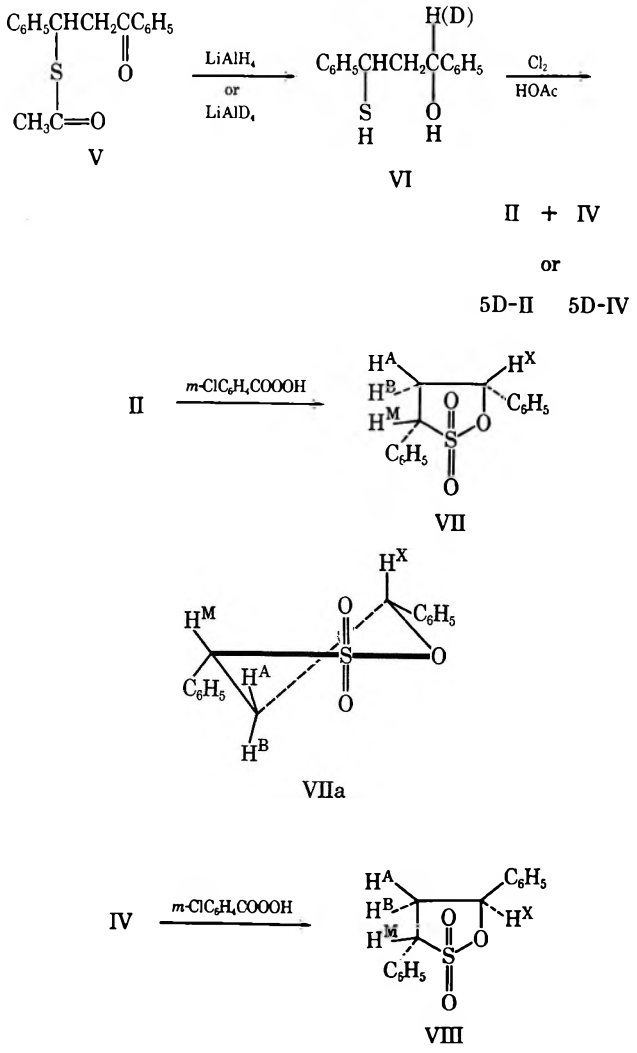
3,5-DIPHENYL-1,2-OXATHIOLANES

Compd[b]	ν_A	ν_B	ν_M	ν_X	J_{AB}	J_{AM}	J_{AX}	J_{BM}	J_{BX}	J_{MX}
				$CDCl_3$						
II cis sultine	163.7	172.0	257.5	334.8	−13.30	5.73	5.54	14.01	11.00	−0.12
IV trans sultine	154.7	197.7	260.8	370.4	−13.04	7.36	2.53	12.59	8.56	−0.10
VII cis sultone	180.9	177.9	283.2	338.2	−13.57	6.44	5.80	13.66	11.03	−0.22
VIII trans sultone	171.4	198.5	273.9	345.9	−13.43	8.05	4.36	10.51	7.93	−0.05
				C_6H_6						
II cis sultine	125.4	160.4	224.7	311.3	−13.15	5.76	5.60	13.84	10.95	−0.15
IV trans sultine	119.4	176.6	233.5	355.1	−12.93	7.40	2.48	12.69	8.67	−0.12
VII cis sultone	120.3	148.2	252.6	301.6	−13.32	6.44	5.73	13.54	11.00	−0.07
VIII trans sultone	126.1	161.2	252.5	316.6	−13.54	8.08	4.33	10.49	7.96	−0.04

[a] Recorded in hertz downfield from tetramethylsilane; determined at 60 MHz. [b] Cis and trans refer to the relationship of the phenyl groups.

different diphenylsultones, VII and VIII, were obtained, it followed that one of these must have *cis*-phenyl groups while the other must have *trans*-phenyl groups (Scheme II).

SCHEME II



Studies on the course of the rearrangements of I and III to II and IV, respectively, using nmr spectroscopy as the diagnostic method, showed that the cis sulfone I rearranged to the *cis*-3,5-diphenyl-1,2-oxathiolane *cis*-2-oxide (II) which persisted through the total time of the reaction. The trans sulfone III, however, initially rearranged to *trans*-3,5-diphenyl-1,2-oxathiolane (2,3)-*cis*-2-oxide (IV) which then slowly rearranged to the cis sultine II. After 76 hr only the cis sultine II could be isolated from the reaction of the trans sulfone III with *tert*-butoxymagnesium bromide. The nmr spectral studies of the course of this reaction also showed absorption bands at intermediate times (6.5 to 24 hr) that could have belonged to a third isomeric sultine. The relative stabilies of II and IV in the presence of *tert*-butoxymagnesium bromide provided evidence for the relative configurations of the phenyl groups. Five-membered rings with large groups at the 1 and 3 positions are usually more stable in the cis than in the trans configuration.[10] Thus, from these data, a cis configuration was assigned to the phenyl groups in II and a trans configuration to the phenyl groups in IV.

Configurations.—The relative configurations of the phenyl groups in II and IV were confirmed by a complete analysis of the nmr spectra of the cis sultine II and the trans sultine IV (Table I). If the sultines exist in half-chair conformations corresponding to IIa, and IVa and/or IVb, the nmr spectrum of the cis sultine IIa with both phenyl groups occupying pseudoequatorial conformations should show two vicinal coupling constants of moderate size (J_{AM} and J_{AX}) and two vicinal coupling constants of large size (J_{BM} and J_{BX}). This is exactly what is found for that isomer assigned the *cis*-diphenyl configuration from stability studies. If either conformer IVa or IVb predominates for the trans sultine IV, then the nmr spectrum of IV should show one large, one small, and two moderately sized vicinal coupling constants. The experimental results indicate the predominance of one conformer.

The nmr spectra of the isomeric 5-deuterio-3,5-diphenyl-1,2-oxathiolane 2-oxides (5D-II and 5D-IV) lacked those absorption bands at lowest field [334.8 and 370.4 Hz ($CDCl_3$) for II and IV, respectively]. Consequently, these chemical shifts (ν_X) were assigned to the C-5 hydrogen atoms of II and IV. This immediately led to a complete assignment of the chemical shifts (ν) and coupling constants (J) to the protons of the isomeric sultines II and IV.[11] It also indicated that

(10) For discussion of the relative stabilities of the *cis*- and *trans*-1,3-dimethylcyclopentanes, see E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, p 202.

(11) The labeling of the hydrogen atoms in the formulas (Scheme I and Scheme II) corresponds to the labeling of the atoms in Table I. In all cases except that of the cis sultone VII, the protons are labeled from high to low field by the sequence ABMX. For the cis sultone VII the order from high to low field becomes BAMX (in $CDCl_3$ only).

trans-3,5-diphenyl-1,2-oxathiolane (2,3)-*cis*-2-oxide existed largely in conformation IVa or one closely resembling this.

The configurations of the oxygen atoms at S-2 in the isomeric sultines were determined by comparison of chemical shifts in the sultines II and IV and sultones VII and VIII and by change of chemical shifts with change of solvent. The effect of the 3- and 5-phenyl groups on the chemical shifts of H_A and H_B in the trans sultine IVa should be comparable. The difference in chemical shifts between H_A and H_B should result largely from the orientation of the oxygen on sulfur. Since it is known that the sulfoxide group shields those protons which lie more directly behind the S=O bond (along the axis) and deshields groups which lie 1,3 diaxially to the S=O bond,[1,12] the oxygen at S-2 in the trans sultine IVa should lie trans to H_A and cis to H_B (cis to the C-3 phenyl group). By application of a similar argument to the H_X protons of the cis sultine II and trans sultine IV, the marked shielding of H_X in II [ν_X(IV) − ν_X(II) = 35.6 Hz ($CDCl_3$)] can best be explained by assignment of the S=O configuration in II trans to H_X (cis to the phenyl groups).

The above configurational assignments were confirmed by a study of the change of chemical shifts of the various protons with change of solvent (Table II).

TABLE II[a]

$\Delta\nu$ = [ν(C_6H_5) − ν($CDCl_3$)] Hz

	H_A	H_B	H_M	H_X
II cis sultine	−38.3	−11.6	−32.8	−23.5
IV trans sultine	−35.3	−21.1	−27.3	−15.3
VII cis sultone	−60.6	−29.7	−30.6	−36.6
VIII trans sultone	−45.3	−37.3	−21.4	−29.3

[a] Negative values indicate upfield shifts.

It has been shown that those protons lying more directly behind the group dipole[13] of a sulfoxide are shifted to higher field with change of $CDCl_3$ to C_6H_6 than those protons lying farther from the dipole–vector.[12c,d,14] If configurations of the oxygen on sulfur and conformations of the rings of both cis and trans sultines IIa and IVa are similar, then (in both instances) H_A lies more directly behind the group dipole than H_B, and ν_A should be shifted to higher fields (in both instances) by change of solvent from $CDCl_3$ to C_6H_6 than ν_B. Similar predictions would be made from the postulated structures of the benzene complexes.[12d,15] Experimental results (Table II) confirm these expectations. The large upfield shift of ν_M (for both isomers) and the larger upfield shift for ν_X (cis sultine II) than for ν_X (trans sultine IV) are also in agreement with expectations but internal standards are not available for ν_M. The very large upfield shift of ν_A (−60.6 Hz) compared to ν_B (−29.7 Hz) with change of solvent ($CDCl_3$ to C_6H_6) indicates that the cis sultone VII possesses conformation VIIa as expected. Related data ($\Delta\nu_A$ = −45.3; $\Delta\nu_B$ = −37.3 Hz) indicate considerable conformational mobility for the trans sultone VIII.

An analysis of the changes of chemical shifts of the various protons on oxidation of the sultines to sultones also confirmed the above assignments (Table III).

TABLE III[a]

$\Delta\nu$ = [ν(sultone) − ν(sultine)] Hz

	H_A	H_B	H_M	H_X
$CDCl_3$				
VII–II, cis	17.2	5.9	25.7	3.4
VIII–IV, trans	16.7	0.8	13.1	−24.5
C_6H_6				
VII–II, cis	−5.1	−12.2	27.9	−9.7
VIII–IV, trans	6.7	−15.4	19.0	−38.5

[a] Positive values indicate downfield shifts; negative values upfield shifts.

Replacement of the lone pair of electrons on sulfur with an oxygen atom (S=O) should lead to greater shielding (less deshielding) of those protons lying more directly behind (along the axis of) the new S=O group.[12d] Thus, on oxidation of either the cis or trans sultine II or IV H_B should be shielded to a greater extent (deshielded to a lesser extent) than H_A. Again, experimental results confirm these expectations (Table III). The fact that H_X in the cis sultine II occupies a different configuration with respect to the incoming oxygen than H_X in the trans sultine IV is also apparent from the changes of chemical shift on oxidation ($\Delta\nu$ = +3.4 and −24.5 Hz).

Conformations.—Because of the large size of the phenyl groups, the conformation of the cis sultine II should be that (IIa) with pseudoequatorial phenyl groups. The isomerization of the trans sultine IV to the cis sultine II tends to confirm this conclusion.

Because of the very small size of J_{AX} (2.48 Hz)[16] compared to the size of J_{BM} (12.69), one can conclude that the *trans*-diphenylsultine exists largely in conformation IVa. However, both conformations IVa and IVb possess a pseudoaxial and a pseudoequatorial phenyl group. In order to obtain an estimate of the position of the equilibrium IVa ⇄ IVb, the following assumptions were made. (1) The *cis*-diphenylsultine II exists entirely in the conformation IIa. (2) J_{BM} (IVa) ≈ J_{BM} (IIa) ≈ 13.84; J_{AX} (IVb) ≈ J_{BX} (IIa) ≈ 10.95; J_{AX} (IVa) ≈ J_{BM} (IVb) ≈ J. Because the dihedral angles $\angle H_ACCH_X$ (IVa) and $\angle H_BCCH_M$ (IVb) both approximate 90°, J will have a relatively small value. From these assumptions and from the values of J_{AX} and J_{BM} for IV, one can obtain two simultaneous equations

$$J_{BM}\text{ (IV)} = 12.69 = \underset{\text{IVa}}{x(13.84)} + \underset{\text{IVb}}{(1-x)J}$$

$$J_{AX}\text{ (IV)} = 2.48 = xJ + (1-x)(10.95)$$

(12) (a) K. W. Buck, A. B. Foster, W. D. Pardoe, M. H. Qadir, and J. M. Webber, *Chem. Commun.*, 759 (1966); A. B. Foster, J. M. Duxbury, T. D. Inch, and J. M. Webber, *ibid.*, 881 (1967); (b) R. Nagarajan, B. H. Chollar, and R. M. Dodson, *ibid.*, 550 (1967); (c) P. B. Sollman, R. Nagarajan, and R. M. Dodson, *ibid.*, 552 (1967); (d) R. D. G. Cooper, P. V. DeMarco, J. C. Cheng, and N. D. Jones, *J. Amer. Chem. Soc.*, **91**, 1408 (1969); (e) C. R. Johnson and Walter O. Siegl, *Tetrahedron Lett.*, 1879 (1969).

(13) The group dipole of a sulfoxide lies *ca.* 21.5° from the S–O bond in the direction of the lone pair of electrons: N. J. Leonard and C. R. Johnson, *J. Amer. Chem. Soc.*, **84**, 3701 (1962).

(14) (a) R. A. Archer and P. V. De Marco, *ibid.*, **91**, 1530 (1969); (b) R. D. G. Cooper, P. V. De Marco, and D. O. Spry, *ibid.*, **91**, 1528 (1969); (c) D. H. R. Barton, F. Comer, and P. G. Sammes, *ibid.*, **91**, 1529 (1969); (d) E. T. Stom, B. S. Snowden, Jr., and P. A. Toldan, *Chem. Commun.*, 50 (1969); (e) M. Nishio, *ibid.*, 51 (1969).

(15) T. Ledaal, *Tetrahedron Lett.*, 1683 (1968).

(16) If conformers IVa and IVb were of equal importance both J_{AX} (*ca.* 4.2) and J_{BM} (*ca.* 7.5) would be of moderate size. Because of the greater accuracy of the data (see Experimental Section), all of the following calculations are done with coupling constants from spectra determined in benzene.

From these one can calculate that, in benzene solution, *trans*-1,3-diphenylsultine IV consists of *ca.* 91% IVa and 9% IVb and that J_{AX} (IVa) ≈ 1.60. These calculations are made on the assumption that the puckering of IVa and IVb is equal to that of IIa. The 1,3-pseudodiaxial interaction of H_M and the 5-phenyl group should tend to flatten IVa and a similar interaction of H_X and the 3-phenyl group would tend to flatten IVb. Any less puckering of these conformers [lowering the values of J_{BM} (IVa) and J_{AX} (IVb)] will give calculations showing >91% IVa. Similar calculations for the trans sultone VIII indicated considerable conformational mobility (74% of conformer corresponding to IVa and 26% of conformer corresponding to IVb).

Calculation of Dihedral Angles.[17]—The average dihedral angles ∠HCCH of the cis and trans sultines II and IV were calculated from their nmr spectra in the following way. (1) The vicinal coupling constants were fitted to an equation of the form $^3J_{H,H'} = A\cos^2\phi + B\cos\phi + C$.[18] (2) The geminal angle $\angle H_ACH_B$ of the sultines II and IV and of the sultones VII and VIII was assigned the value 109° 28′, and the angle $\angle H_ACH_B$ projected along the C_3–C_4 and C_4–C_5 bonds was assigned a value of 120° (ω). (3) The coupling constants of the trans sultine IV were assigned to the principle conformer IVa. Since we have estimated that a maximum of 9% of IV could exist as IVb, a comparable error in these calculations may result. (4) That portion of the equation determining the angular dependence of the coupling constants (A and B) was assumed to be identical for vicinal coupling between hydrogen atoms on C_3 and C_4 and on C_4 and C_5. Differences, because of the inductive or hybridization effects of the –SO– attached to C-3 or the –O– attached to C-5, were absorbed in the constants C and C', respectively.

By use of the above and the coupling constants from the nmr spectra of II and IV, the following eight nonlinear equations in eight unknowns were written.

cis sultine II

$$J_{AM}\ 5.76 = A\cos^2\phi + B\cos\phi + C$$

$$J_{BM}\ 13.84 = A\cos^2(\omega+\phi) + B\cos(\omega+\phi) + C$$

$$J_{AX}\ 5.60 = A\cos^2\phi' + B\cos\phi' + C'$$

$$J_{BX}\ 10.95 = A\cos^2(\omega+\phi') + B\cos(\omega+\phi') + C'$$

trans sultine IV

$$J_{AM}\ 7.40 = A\cos^2\phi'' + B\cos\phi'' + C$$

$$J_{BM}\ 12.69 = A\cos^2(\omega+\phi'') + B\cos(\omega+\phi'') + C$$

$$J_{AX}\ 2.48 = A\cos^2(\omega-\phi''') + B\cos(\omega-\phi''') + C'$$

$$J_{BX}\ 8.67 = A\cos^2\phi''' + B\cos\phi''' + C'$$

Solution of these equations, gave the equations

$$^3J_{H,H'} = 10.2\cos^2\phi - 1.9\cos\phi + 2.35 \quad HC_3C_4H \quad (1)$$

$$^3J_{H,H'} = 10.2\cos^2\phi - 1.9\cos\phi + 0.60 \quad HC_4C_5H \quad (2)$$

and the following dihedral angles.[19]

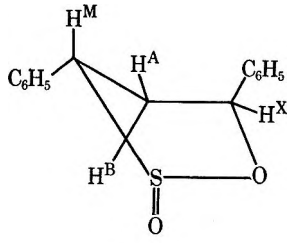
	∠H_ACCH_M	∠H_BCCH_M	∠H_ACCH_X	∠H_BCCH_X
cis sultine IIa	47.2°	167.2°	36.9°	156.9°
trans sultine IVa	36.6°	156.6°	110.3°	9.7°

The validity of these equations and of the previous assumptions on conformation can be tested by the application of the equations to the cis sultone VII. If VII consists largely of conformer VIIa and if eq 1 and 2 are valid,[20] then the value (120°) of the projected geminal angle $\angle H_ACH_B$ should be calculable from the coupling constants.

	∠H_ACCH_M	∠H_BCCH_M	∠H_ACCH_X	∠H_BCCH_X
cis sultone VIIa	42.9°	163.4°	36.1°	157.0°

ω (calcd) = 120.5 and 120.9°, in excellent agreement with the expected value and with each other. Application of these same equations to the trans sultone VIII (not conformationally pure) gives ridiculous values for the projected geminal angle; ω = 111.6 and 139.9°.

From the angles calculated above it can be seen that, as expected, the trans sultine IV is far less puckered than the cis sultine II. In fact, the ratio of the angles ∠H_ACCH_M and ∠H_BCCH_X is such that the conformation of the trans sultine IV more closely resembles an envelope IVc than the half-chair originally postulated. The stability of this conformation IVc is probably accounted for by the pseudoequatorial conformation of the C-3 phenyl group, by the lack of strong steric interactions between the C-5 phenyl group, the pseudoaxial H_M, and the nonbonding electrons on sulfur,



IVc

(17) The use of the following method of analysis on the nmr spectra of *cis*- and *trans*-2,4-diphenylthietane 1-oxides gave an average angle of pucker for *cis*-2,4-diphenylthietane *trans*-1-oxide of 39.7°. A crystal structure analysis of this same compound gave a value of 41.9° for this same angle (see ref 1). Our nmr analyses are done on molecules of high conformational purity and on molecules with similarly oriented bond dipoles. Thus, we hope we have avoided the usual errors in the application of Karplus type equations to conformations. It should be realized that, in axially hydroxy-substituted steroids (in which the C–O bond dipole is syn to the adjacent C–C bond), any difference between H,H′ J_{ee} and J_{ea} was <0.5 Hz [D. H. Williams and N. S. Bhacca, *J. Amer. Chem. Soc.*, **86**, 2742 (1964)].

(18) (a) M. Barfield and M. Karplus, *ibid.*, **91**, 1 (1969); (b) M. Barfield and D. M. Grant, *Advan. Magn. Resonance*, **1**, 187 (1965).

(19) The values of the dihedral angles given above are the solutions of the equations. Since we have estimated that 9% of IV could exist as conformer IVb, a comparable error in these calculations may result.

A similar calculation using the value J_{AX} (IVa) = 1.60, calculated above for the principle conformer of IV, gave $^3J_{H,H'} = 11.1\cos^2\phi - 1.9\cos\phi + 1.65\ HC_3C_4H$; $^3J_{H,H'} = 11.1\cos^2\phi - 1.9\cos\phi - 0.1\ HC_4C_5H$. Note that by making some allowance for the distribution of conformers of IV the constant C' used to account for the inductive or hybridization effects of oxygen is reduced to a very small value (for discussion of this point see ref 1). The values calculated from these equations differed slightly from those given above: IIa, ∠H_ACCH_M = 45.5°; ∠H_ACCH_X = 36.2°. IVa, ∠H_ACCH_M = 35.9°; ∠H_BCCH_X = 11.6°. The validity of the assumption, J_{AX} (IVa) ≈ J_{BM} (IVb) ≈ J used to estimate the position of the equilibrium IVa ⇄ IVb can also be checked from these equations. Thus, for IVa, ∠H_ACCH_X = 108.4°; J_{AX} = 1.61. If IVb is puckered to the same extent as IVa, then for IVb, ∠H_BCCH_M = 84.1°; J_{BM} = 1.57.

(20) Application of eq 2 should be valid since change in the oxidation state of sulfur should not markedly effect either the inductive or hybridization effects at C_4 and C_5.

and by the relatively strong anomeric effect[21] of the pseudoaxial S=O bond.

From the time and equilibrium studies performed, it appears that the *cis*-3,5-diphenyl-1,2-oxathiolane (2,-3)-*cis*-2-oxide (IIa) is the most stable of the four possible racemic modifications. If so, the cis configuration of the 2-oxygen and the 3-phenyl group must be explainable either on the basis of the anomeric effect[21] of the pseudoaxial S=O group or by the increased stability of a gauche 2-oxa-3-phenyl interaction.[22] This point will be examined in greater detail in the future.

Oxidation of the cis sultine II to the cis sultone VII resulted in a small reduction (−4.3°) of the dihedral angles at C_3–C_4 with very little change (−0.8°) of the dihedral angles at C_4–C_5, the "oxygen side" of the molecule. A similar flattening (−3.9°) was observed on the oxidation of *cis*-2,4-diphenylthietane *trans*-1-oxide to the corresponding 1,1-dioxide.[1] This small reduction in the puckering of the molecule probably results from the slight increase in the C–S–C or 1-O–S–C angle on oxidation from the sulfoxide (or sulfinate) to the sulfone (or sulfonate).[23]

Mechanism.—We believe this rearrangement proceeds by a mechanism closely resembling that of the Stevens rearrangement.[24] Detailed discussion of the mechanism is presented in the accompanying part IV of this series[25] together with consideration of some related reactions.

Experimental Section[26]

***trans*-3,5-Diphenyl-1,2-oxathiolane (2,3)-*cis*-2-Oxide (IV).**—A solution of ethylmagnesium bromide prepared from 3.54 g (0.0324 mol) of ethyl bromide and 1.60 g (0.066 g-atom) of magnesium in 25 ml of ether was treated with 2.46 g (0.033 mol) of *tert*-butyl alcohol (dried by distillation from sodium) in 20 ml of anhydrous ether. The reaction was stirred at room temperature for 1 hr. *trans*-2,4-Diphenylthietane 1,1-dioxide (III) (1.00 g, 0.00387 mol) was added, and the reaction was heated under reflux with stirring for 44 hr. The magnesium complex was decomposed with 3.6% aqueous hydrochloric acid. The organic products were isolated by extraction with ether. Thin layer chromatography of the organic material showed that it contained some starting material plus one other component.

This material was chromatographed on silica gel (25 g, 100–200 mesh) using mixtures of petroleum ether (bp 30–60°) and benzene. *trans*-2,4-Diphenylthietane 1,1-dioxide (0.131 g, 13% recovery) was eluted with 30% petroleum ether (bp 30–60°)–70% benzene and was identified by a mixture melting point determination with an authentic sample. *trans*-3,5-Diphenyl-1,2-oxathiolane (2,3)-*cis*-2-oxide (IV) (0.356 g, 0.00138 mol, 41% yield allowing for recovered starting material) was eluted with 10% petroleum ether (bp 30–60°)–90% benzene. Crystallization from petroleum ether (bp 60–68°)–chloroform mixture yielded white crystals of IV (0.314 g, 0.00122 mol, 36% yield): mp 73–74.5°; ν_{max}^{KBr} 689, 738, 760, 780, 830, 890, 950, 1108 (S(=O)O), 1138, 1452, and 1492 cm^{-1}; mass spectrum, base peak *m/e* 194 (M − SO_2); uv spectrum in ethanol showed only phenyl group absorption.

Anal. Calcd for $C_{15}H_{14}O_2S$: C, 69.74; H, 5.46. Found: C, 69.70; H, 5.65.

One preparation of this material [crystallized from CCl_4 and petroleum ether (bp 60–68°)] gave *trans*-3,5-diphenyl-1,2-oxathiolane (2,3)-*cis*-2-oxide (IV), mp 60–61°; ir and nmr spectra were identical with the above preparation.

***cis*-3,5-Diphenyl-1,2-oxathiolane *cis*-2-Oxide (II).**—A solution of ethylmagnesium bromide prepared from 10.62 g (0.0976 mol) of ethyl bromide and 1.60 g (0.066 g-atom) of magnesium in 50 ml of ether was treated with 4.92 g (0.066 mol) of anhydrous *tert*-butyl alcohol in 50 ml of ether. The reaction was stirred at room temperature for 1 hr. *cis*-2,4-Diphenylthietane 1,1-dioxide (2.00 g, 0.00775 mol) was added and the resulting mixture was heated under reflux with stirring for 23 hr.

The magnesium complex was decomposed with 3.6% aqueous hydrochloric acid, and the organic product was isolated by ether extraction. Crystallization of the material so obtained from chloroform–petroleum ether (bp 60–68°) gave 1.4 g (0.0054 mol, 70% yield) of *cis*-3,5-diphenyl-1,2-oxathiolane *cis*-2-oxide (II): mp 121–122.5°; ν_{max}^{KBr} 643, 690, 716, 777, 790, 826, 880, 950, 1030, 1115 (S(=O)O), 1149, 1157, 1218, 1369, 1451, and 1491 cm^{-1}; mass spectrum, base peak *m/e* 194 (M − SO_2); uv spectrum in ethanol showed only phenyl absorption.

Anal. Calcd for $C_{15}H_{14}O_2S$: C, 69.74; H, 5.46. Found: C, 69.73; H, 5.77.

***cis*-3,5-Diphenyl-1,2-oxathiolane *cis*-2-Oxide (II) from *trans*-2,4-Diphenylthietane 1,1-Dioxide (III).**—Studies on the course of the above rearrangements with time, using nmr spectra as the analytical tool, indicated that *cis*-3,5-diphenylthietane 1,1-dioxide (I) rearranged initially to *cis*-3,5-diphenyl-1,2-oxathiolane *cis*-2-oxide (II) which persisted through the course of the reaction. *trans*-3,5-Diphenylthietane 1,1-dioxide (III) rearranged initially to *trans*-3,5-diphenyl-1,2-oxathiolane (2,3)-*cis*-2-oxide (IV). This was slowly converted, possibly *via* an intermediate with absorption in the nmr spectrum in the 347–356 Hz ($CDCl_3$) range, to *cis*-3,5-diphenyl-1,2-oxathiolane *cis*-2-oxide (II). Thus, after reaction of *trans*-2,4-diphenylthietane 1,1-dioxide (III) with *tert*-butoxymagnesium bromide for 76 hr only *cis*-3,5-diphenyl-1,2-oxathiolane *cis*-2-oxide (II) was present in the reaction mixture. This was confirmed by the isolation of II, mp and mmp 121–123°.

Independent Synthesis of II and IV.—1,3-Diphenyl-3-hydroxypropanethiol[1] (VI) (2.00 g, 0.00820 mol) dissolved in glacial acetic acid (10 ml) was treated with 1.18 g (0.017 mol) of chlorine in 50 ml of glacial acetic acid. The solution was closed to the atmosphere and stirred vigorously for 10 min. The solvent was removed under vacuum at 60° (water bath temperature). The residue was dissolved in ether and then washed with water, 10% sodium bicarbonate solution, and water. The ether solution was dried and evaporated. The remaining oil was dissolved in 70% petroleum ether (bp 30–60°)–30% benzene and chromatographed on silica gel (50 g, 100–200 mesh). Elution with 50% petroleum ether (bp 30–60°)–50% benzene and a 30:70 mixture of these two solvents yielded 0.386 g (1.50 mmol, 18% yield) of *cis*-3,5-diphenyl-1,2-oxathiolane *cis*-2-oxide (II), mp 121–123°. Identity was confirmed by comparison of the nmr and ir spectra with those of the previously obtained samples.

Further elution with a 30:70 and a 10:90 mixture of the same solvents yielded 0.435 g (1.69 mmol, 21%) of *trans*-3,5-diphenyl-1,2-oxathiolane (2,3)-*cis*-2-oxide, mp 65–68°. Identity was confirmed by comparison of the nmr and ir spectra with those of the previously obtained samples.

In our first independent synthesis of these compounds, 10 mg of material, mp 97–100° [ν_{max}^{KBr} 687, 705, 725, 751, 764, 796, 880, 1106 (CO), and 1130 cm^{-1} (S(=O)O)], was isolated. The mass spectrum of this material suggested that it was a third isomeric 3,5-diphenyl-1,2-oxathiolane 2-oxide.

***cis*-3,5-Diphenyl-5-deuterio-1,2-oxathiolane *cis*-2-Oxide and *trans*-3,5-Diphenyl-5-deuterio-1,2-oxathiolane (2,3)-*cis*-2-Oxide.**—1,3-Diphenyl-3-acetylthio-1-propanone[1] (V) was reduced with lithium aluminum deuteride to 1,3-diphenyl-3-deuterio-3-hydroxypropanethiol (VI) by the method previously described. This was converted to 5-deuterio-II, mp 117–118°, and 5-deuterio-IV, mp 60–61°, by the procedure given above.

(21) C. Romers, C. Altona, H. R. Buys, and E. Havinga, "Topics in Stereochemistry," Vol. 4, E. L. Eliel and N. L. Allinger, Ed., Wiley-Interscience, New York, N. Y., 1969, p 39; ref 10, p 375.

(22) In the vapor phase *n*-propyl chloride exists as 81 ± 5% gauche and 19 ± 5% anti: Y. Morino and K. Kuchitsu, *J. Chem. Phys.*, **28**, 175 (1958); T. N. Sarachman, *ibid.*, **39**, 469 (1963). Thiane oxides are more stable with an axial S=O bond (the S=O bond gauche to two C—C bonds): C. R. Johnson and D. McCants, Jr., *J. Amer. Chem. Soc.*, **87**, 1109 (1965).

(23) L. E. Sutton, Ed., "Tables of Interatomic Distances and Configurations in Molecules and Ions," Special Publications No. 11, 1958, and No. 18, 1965, The Chemical Society, London; R. J. Gillespie, *Angew. Chem., Int. Ed. Engl.*, **6**, 819 (1967). Puckering of a flat, cyclic molecule results in a reduction in the sum of the interior angles. Increase in any interior angle of a puckered, cyclic molecule should lead to a reduction of puckering.

(24) U. Schöllkopf, *ibid.*, **9**, 763 (1970); R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1970, p 131.

(25) R. M. Dodson, P. D. Hammen, and J. Yu Fan, *J. Org. Chem.*, **36**, 2703 (1971).

(26) Melting points were taken on a Fisher-Johns melting point apparatus, calibrated against a set of standard compounds.

cis-3,5-Diphenyl-1,2-oxathiolane 2,2-Dioxide (VII).—A solution of 0.50 g (0.0019 mol) of *cis*-3,5-diphenyl-1,2-oxathiolane *cis*-2-oxide (II) in 50 ml of benzene was treated with 0.30 g (85%, 0.0015 mol) of *m*-chloroperbenzoic acid in benzene solution. The reaction was stirred at room temperature for 24 hr. It was then washed with water, 10% aqueous sodium bicarbonate solution, and then finally with water. The benzene solution was dried and the solvent was evaporated. Crystallization of the solid so obtained from carbon tetrachloride–petroleum ether (bp 60–68°) yielded 0.308 g (58%) of *cis*-3,5-diphenyl-1,2-oxathiolane 2,2-dioxide (VII): mp 120–121°; ν_{max}^{KBr} 1172, 1344 cm^{-1} (SO_2O). A mixture of this material with the starting material showed a large melting point depression.

Anal. Calcd for $C_{15}H_{14}O_3S$: C, 65.67; H, 5.14. Found: C, 65.87; H, 5.12.

trans-3,5-Diphenyl-1,2-oxathiolane 2,2-Dioxide (VIII).—Oxidation of 0.50 g of *trans*-3,5-diphenyl-1,2-oxathiolane (2,3)-*cis*-2-oxide (IV), mp 60–61°, by the method described above, yielded 0.258 g (49%) of *trans*-3,5-diphenyl-1,2-oxathiolane 2,2-dioxide (VIII): mp 84–84.5°; ν_{max}^{KBr} 1170, 1348 cm^{-1} (SO_2O).

Anal. Calcd for $C_{15}H_{14}O_3S$: C, 65.67; H, 5.14. Found: C, 65.85; H, 5.29.

Nmr spectra were determined on a Varian A-60 spectrometer. A Hewlett-Packard Model 202A low-frequency function generator was used to calibrate the spectra at 50- and 100-Hz sweep-width. Tetramethylsilane was used as an internal standard. Spectra were determined at high concentrations (52 ± 3% w/w) in order to observe the low intensity absorption bands in the spectra of the cis sultine II and the cis sultone VII. The spectra were initially calculated as ABMX systems using the energy levels given by Reilly and Swalen.[27] The parameters so obtained were then used in the LAOCOON-3 program of A. A. Bothner-By and S. M. Castellano, and the data reported herein are from the latter calculations. The sign of the geminal coupling constants was not experimentally determined. The chemical shifts (ν) vary with concentration but have not been extrapolated to zero concentration. The calculated probable errors in the coupling constants were ±0.05 Hz or less for those spectra determined in benzene and ±0.07 Hz or less for those determined in $CDCl_3$ with the exception of the cis sultone VII in $CDCl_3$. In the latter case, because of the very small difference in chemical shift between H_A and H_B low intensity lines were very difficult to locate and the maximum calculated probable error is ±0.15 Hz. Small deviations between the data reported here and that previously reported[3] result from differences in concentrations, more accurate calculations, and a small numerical error in the previous calculation of ν_A and ν_B for the cis sultine II.

Registry No.—I, 18744-27-9; II, 30237-95-7; III, 24609-91-4; IV, 30237-97-9; VII, 30237-98-0; VIII, 30237-99-1.

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(27) C. A. Reilly and J. D. Swalen, *J. Chem. Phys.*, **34**, 980 (1961).

Thietanes. III. Rearrangement of 2,4-Diphenylthietane Dioxides to *trans*-1,2-Diphenylcyclopropanesulfinic Acid

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cis- and *trans*-2,4-diphenylthietane 1,1-dioxides (I and II) when treated with ethylmagnesium bromide are rearranged to *trans*-1,2-diphenylcyclopropanesulfinic acid (III) in a highly stereoselective manner. The sulfinic acid III was converted to the benzyl and methyl *trans*-1,2-diphenylcyclopropyl sulfones (IVa and IVb, respectively) and to a mixture of *cis*- and *trans*-1,2-diphenylcyclopropanes (VI and VII). Benzyl *cis*- and *trans*-1,2-diphenylcyclopropyl sulfones (XV and IVa, respectively; *ca.* 50:50 mixture) were synthesized independently by the reaction of either α-benzylsulfonyl-*cis*- or -*trans*-stilbene (XIII or XIV) with dimethylsulfoxonium methylide. The configurations of the benzyl 1,2-diphenylcyclopropyl sulfones (IVa and XV) were definitively established by a complete analysis of their nmr spectra.

Recently we have described the syntheses and the determinations of configurations and conformations of the 2,4-diphenylthietanes, their monoxides, and dioxides.[1] We have also described the rearrangement of *cis*- and *trans*-2,4-diphenylthietane 1,1-dioxides to *cis*- and *trans*-3,5-diphenyl-1,2-oxathiolane (2,3)-*cis*-2-oxides, respectively,[2] a stereospecific rearrangement. Here, we report the conversion of *cis*- and *trans*-2,4-diphenylthietane 1,1-dioxides (I and II) to *trans*-1,2-diphenylcyclopropanesulfinic acid (III),[3] a highly stereoselective rearrangement.

Treatment of either *cis*- or *trans*-2,4-diphenylthietane 1,1-dioxide (I or II) with ethylmagnesium bromide yielded *trans*-1,2-diphenylcyclopropanesulfinic acid (III) (75% yield) and liberated 1 equiv of ethane. The constitution of III was established by (1) its analysis, (2) by the presence in its ir spectrum of bands at 833, 1033, and 2400 cm^{-1} typical of those of sulfinic acids,[4] and (3) by its conversion to a mixture of *cis*- and *trans*-1,2-diphenylcyclopropanes[1,5] (VI and VII) by heating with an excess of ethylmagnesium bromide (VI/VII, *cis*/*trans* ratio 0.22) or *via* an intermediate alkylmercuric chloride[6] followed by acid hydrolysis (VI/VII, *cis*/*trans* ratio 4.25). The *trans*-1,2-diphenylcyclopropanesulfinic acid (III) was rather unstable but was easily converted to the stable benzyl and methyl *trans*-1,2-diphenylcyclopropyl sulfones (IVa and IVb, respectively) by reaction of its sodium salt with benzyl chloride or methyl iodide (Scheme I).

Independent Synthesis of IVa.—The benzyl *trans*-1,2-diphenylcyclopropyl sulfone (IVa) was synthesized by the sequence of reactions shown in Scheme II.

(1) R. M. Dodson, E. H. Jancis, and G. Klose, *J. Org. Chem.*, **35**, 2520 (1970).

(2) R. M. Dodson, P. D. Hammen, and R. A. Davis, *ibid.*, **36**, 2693 (1971).

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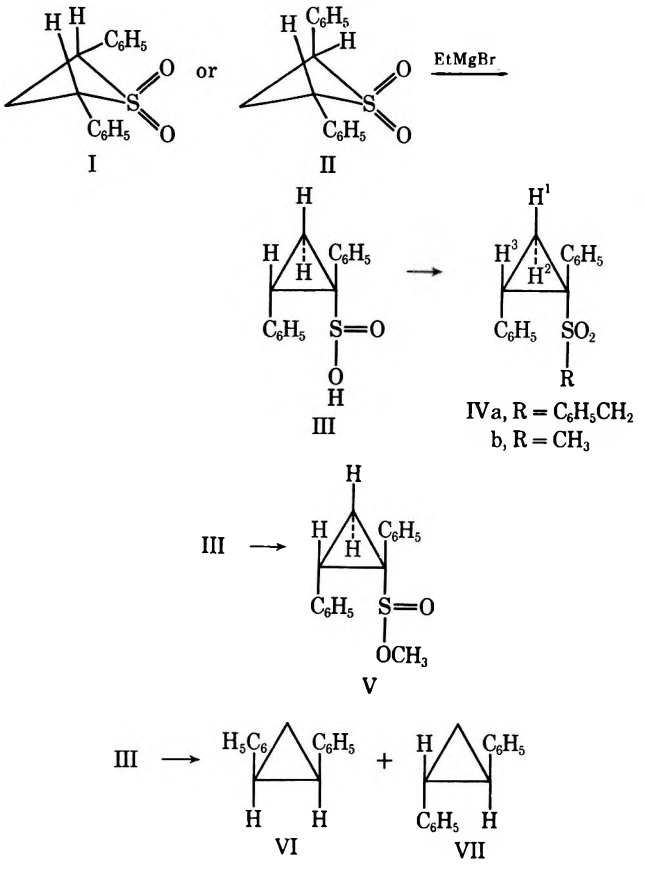
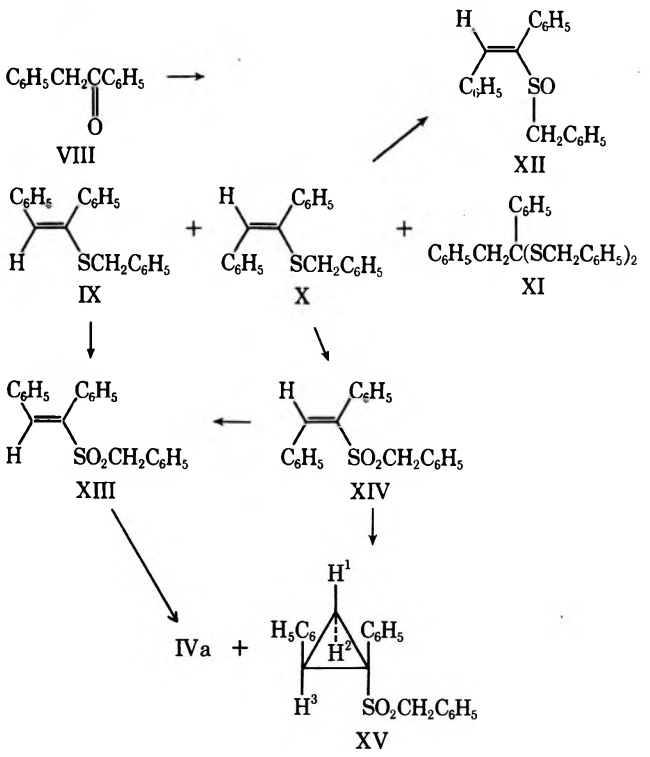
(6) T. Okamoto and J. F. Bunnett, *J. Amer. Chem. Soc.*, **78**, 5357 (1956); L. H. Gale, F. R. Jensen, and J. H. Landgrebe, *Chem. Ind. (London)*, 118 (1960); M. M. Kreevoy and R. L. Hansen, *J. Amer. Chem. Soc.*, **83**, 626 (1961).

SCHEME I



SCHEME II



cis- and *trans*-α-benzylthiostilbene (IX and X, 50 and 30.5%, respectively, in the crude product) and deoxybenzoin dibenzylthioketal (XI, 14.5%) were synthesized by an adaptation of the procedure of Campaigne and Leal.[7] The products were separated by chromatography on silica gel. The configurations of IX and X were initially assigned by a comparison of the aromatic region of the nmr spectra of IX and X with those of *cis*- and *trans*-stilbenes.[8] Thus, the nmr spectrum of *cis*-stilbene shows a singlet (430.8 ± 1.8 Hz) for all ten of the aromatic hydrogen atoms; the nmr spectrum of IX shows two singlets, 428 and 435 Hz, probably corresponding to the two cis phenyl groups. The absorption spectrum of the aromatic hydrogen atoms of *trans*-stilbene is very complex (433–458 Hz). Similarly the absorption spectrum of the aromatic hydrogen atoms of X is very complex (412–457 Hz).

An attempt to add methylene to α-benzylthio-*trans*-stilbene (X) by means of the Simmons–Smith reaction[9] was unsuccessful. Only starting material was recovered. An attempt to add methylene to α-benzylthio-*cis*-stilbene (IX) *via* iodomethylmercuric iodide[10] did not fare any better. Attempts to add methylene from diazomethane[11] to both α-benzylthio-*cis*- and *trans*-stilbenes IX and X using cuprous iodide and cuprous chloride catalysts were equally unsuccessful. Since our initial aim was a stereospecific addition of methylene to the benzylthiostilbenes and since ultraviolet light isomerized the benzylthiostilbenes, the addition of methylene generated by the photochemical decomposition of diazomethane was not attempted.

The α-benzylthiostilbenes IX and X were, therefore, oxidized to the corresponding α-benzylsulfonylstilbenes (XIII and XIV). α-Benzylthio-*cis*-stilbene (IX) was readily oxidized to the corresponding sulfone XIII with hydrogen peroxide in warm acetic acid. An attempt to oxidize α-benzylthio-*trans*-stilbene (X) by this same method gave a mixture of sulfones XIII and XIV (cis/trans ratio 0.25). Cold hydrogen peroxide in cold glacial acetic acid yielded the sulfoxide XII. Pure α-benzylsulfonyl-*trans*-stilbene (XIV) was obtained in 79% yield (94% crude yield) by the oxidation of X with hydrogen peroxide in a cold formic acid–carbon tetrachloride mixture.

α-Benzylsulfonyl-*trans*-stilbene (XIV) was isomerized almost quantitatively to α-benzylsulfonyl-*cis*-stilbene (XIII) by treatment with sodium hydroxide in ethanol. The stereochemistry of the substituted stilbenes (IX, X, XII, XIII, XIV) was confirmed by a detailed comparison of their physical properties (melting points, uv spectra, isomerization of XIV → XIII) with the physical properties of the configurationally defined *p*-tolylthio- and *p*-toluenesulfonylstilbenes prepared by Cristol and Pappas.[12]

The benzyl 1,2-diphenylcyclopropyl sulfones (IVa and XV) were prepared by the method of Truce and Badiger.[13] Reaction of either XIII or XIV with dimethylsulfoxonium methylide yielded a 1:1 mixture of benzyl *cis*- and *trans*-1,2-diphenylcyclopropyl sulfones

(7) E. Campaigne and J. R. Leal, *J. Amer. Chem. Soc.*, **76**, 1272 (1954).
(8) N. S. Bhacca, L. F. Johnson, and J. N. Shoolery, "Nmr Spectra Catalog," Vol. I, Varian Associates, Palo Alto, Calif., 1962, pp 305, 306.
(9) H. E. Simmons and R. D. Smith, *J. Amer. Chem. Soc.*, **80**, 5323 (1958).
(10) D. Seyferth, M. A. Eisert, and L. J. Todd, *ibid.*, **86**, 121 (1964).
(11) R. E. Pincock and J. I. Wells, *J. Org. Chem.*, **29**, 965 (1964).
(12) S. J. Cristol and P. Pappas, *ibid.*, **28**, 2066 (1963).
(13) W. E. Truce and V. V. Badiger, *ibid.*, **29**, 3277 (1964).

TABLE I[a]

ALKYL *cis*- AND *trans*-1,2-DIPHENYLCYCLOPROPYL SULFONES

Compd[b]	R	ν_R[c]	ν_1	ν_2	ν_3	$J_{1,2}$	$J_{1,3}$	$J_{2,3}$
IVa trans	$C_6H_5CH_2$	ν_A 217.1, ν_B 237.4, J_{AB} = 12.5 Hz	107.2	155.5	176.95	−5.55[d]	9.50	7.95
IVb trans	CH_3	149	107	160	182	−5.9	10.0	7.9
XV cis	$C_6H_5CH_2$	244	109.0	123.2	197.15	−6.10	7.15	10.25

[a] Recorded in hertz downfield from tetramethylsilane at 60 MHz. [b] Cis and trans refer to the relationship of the phenyl groups. [c] $\nu_{(CH_2)}$ for IVa and XV; ν_{CH_3} for IVb. Spectra for IVa and XV were determined on a Varian A-60 spectrometer in $CDCl_3$ and were analyzed by use of the LAOCOON-2 program of A. A. Bothner-By and S. M. Castellano. Coupling constants should be accurate to ±0.1 Hz. The spectrum of IVb was determined in $CDCl_3$ on a modified Varian Associates Model DP-60 spectrometer at 56.45 MHz and was calculated as an ABX spectrum. The recorded chemical shifts are corrected to 60 MHz. Parameters do not exceed ±0.5 Hz in accuracy. [d] The sign of this coupling constant was determined. The signs of all other negative coupling constants were assigned arbitrarily.

(XV and IVa), which were separated by fractional crystallization. Contrary to the findings of Truce,[13] this reaction was not stereoselective.[14]

Configurations of IVa and XV.—The configurations of the benzyl *cis*- and *trans*-1,2-diphenylcyclopropyl sulfones (XV and IVa) were assigned from the complete analysis of their nmr spectra (Table I). The most conspicuous difference between these spectra was the difference in absorption of the methylene protons of the benzyl groups. The spectrum for IVa showed a well-isolated AB quartet (ν_A 217.1, ν_B 237.4, J_{AB} = 12.5 Hz) while that for XV showed a singlet (244 Hz at 500-Hz sweepwidth). Even though the methylene protons of the benzyl groups of both isomers are "intrinsically nonequivalent," [15] this marked difference in spectra must result from an "unequal conformer population" for these hydrogens in that isomer with the phenyl and α-benzylsulfonyl group cis to each other. Consequently, compound IVa was assigned benzyl *trans*-1,2-diphenylcyclopropyl sulfone.

The coupling constants and chemical shifts of the protons of the cyclopropyl rings are in agreement with the above configurational assignments. In both cases the proton at lowest field is H^3, that on the carbon atom of the cyclopropane ring holding the phenyl group. The proton at highest field, H^1, is that trans to the α-benzylsulfonyl group. The α-benzylsulfonyl group deshields H^2 in both isomers. In cyclopropanes, cis coupling constants are invariably larger than trans coupling constants for the same molecule.[16] Thus, for IVa, H^1 is trans to the α-benzylsulfonyl group and cis to H^3; H^2 and H^3 are trans to each other. The assignments of chemical shifts, coupling constants, and configurations of the protons of XV follow accordingly.

The size of the vicinal coupling constants ($J_{1,3}$ and $J_{2,3}$) also reflect the steric effects in the isomers IVa and XV. The steric interaction between cis sulfonyl and phenyl groups must be greater than the steric interaction between two cis phenyl groups (see the isomerization of XIV to XIII above). Thus steric effects in IVa should lead to a greater distortion of the molecule (an increase of the dihedral angles H^1CCH^3 and H^2CCH^3) than steric effects in XV. Consequently, $J_{1,3}$ (IVa) should be smaller than $J_{2,3}$ (XV) (9.50 < 10.25), and $J_{2,3}$ (IVa) should be larger than $J_{1,3}$ (XV) (7.95 > 7.15), in good agreement with experiment.

The chemical shifts and coupling constants determined from the spectrum of methyl *trans*-1,2-diphenylcyclopropyl sulfone (IVb), while less accurate than those of the benzyl isomers IVa and XV, are in excellent agreement with those of IVa.

As further confirmation of the above assignments, the relative signs of the coupling constants in IVa were investigated. A comparison of line intensities (calculated with experimental) showed that $J_{1,2}$ (IVa) must be opposite in sign from $J_{1,3}$ (IVa).[17] A double irradiation study[18] showed that $J_{1,3}$ and $J_{2,3}$ have the same sign, but that $J_{1,2}$ has a sign opposite to that of $J_{1,3}$ and $J_{2,3}$.

Stereoselectivity of the Rearrangement.—The ir spectrum of the *trans*-1,2-diphenylcyclopropanesulfinic acid (III) obtained from I was virtually identical with that obtained from II. Comparison of these spectra with the ir spectrum of *cis*-1,2-diphenylcyclopropanesulfinic acid[19] showed that little, if any, of the *cis*-1,2-diphenylcyclopropanesulfinic acid could be present in the trans isomer III. Since the sulfinic acids were rather unstable, samples of III from both *cis*- and *trans*-2,4-diphenylthietane 1,1-dioxide (I and II) were converted to methyl *trans*-1,2-diphenylcyclopropanesulfinate (V) with diazomethane. The ir spectra of both samples of V were virtually identical, were characteristic of a sulfinate ester[4] (690–714, 980–1010, 1130–1149 cm^{-1}), and differed entirely from that of the methyl *trans*-1,2-diphenylcyclopropyl sulfone (IVb). To obtain quantitative data on the stereoselectivity of the reaction, *trans*-1,2-diphenylcyclopropanesulfinic acid (III) from I and from II was converted to benzyl *trans*-1,2-diphenylcyclopropyl sulfone (IVa) under conditions that would have given comparable yields of benzyl *cis*-1,2-diphenylcyclopropyl sulfone (XV) from the *cis*-1,2-diphenylcyclopropanesulfinic acid. Examination of the nmr spectra of these materials around 240 Hz ($C_6H_5CH_2SO_2$) indicated the absence of the cis isomer XV (<2% XV).

We believe that this rearrangement proceeded

(14) The reaction of either *cis*- or *trans*-1-benzylsulfonyl-1-phenyl-1-propene with dimethylsulfoxonium methylide also yielded both 1-benzylsulfonyl-*cis*- and *trans*-1-phenyl-2-methylcyclopropanes: R. M. Dodson and J. E. Burcsu, unpublished results.

(15) L. M. Jackman and S. Sternhell, "Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Elmsford, N. Y., 1969, p 368.

(16) Reference 15, p 286.

(17) This is an unusual ABX spectrum, one in which X(H^1) is geminal to A(H^2).

(18) R. Freeman and D. H. Whiffen, *J. Mol. Phys.*, **4**, 321 (1961); E. F. Friedman and H. S. Gutowsky, *J. Chem. Phys.*, **45**, 3158 (1966).

(19) R. M. Dodson, P. D. Hammen, and J. Yu Fan, *J. Org. Chem.*, **36**, 2703 (1971).

through a mechanism resembling that of the Stevens rearrangement,[20] as discussed in the following paper.

Experimental Section[21]

trans-1,2-Diphenylcyclopropanesulfinic Acid (III).—To a solution of ethylmagnesium bromide prepared from 1.20 g (0.0492 g-atom) of magnesium and 5.40 g (0.0495 mol) of ethyl bromide in ether (25 ml) and benzene (75 ml) was added with stirring 4.25 g (0.0164 mol) of *trans*-2,4-diphenylthietane 1,1-dioxide (II) in solid form. The reaction mixture was stirred and heated under reflux for 2 hr.[22] After being cooled to room temperature the reaction mixture was treated with dilute hydrochloric acid. The aqueous layer was separated, and the organic layer was extracted with a concentrated aqueous sodium bicarbonate solution. The sodium bicarbonate solution, when acidified with concentrated hydrochloric acid, yielded 3.26 g (0.0126 mol, 77%) of *trans*-1,2-diphenylcyclopropanesulfinic acid (III): mp 134–136°; $\lambda_{max}^{ethanol}$ 218.6 nm (ϵ 16,880), shoulders at 253.3 (1885), 259 (1700), 266 (1330), and 270 (1065); ν_{max}^{Nujol} 695, 740, 772, 833 (broad), 853, 1033 (broad), and 2400 cm^{-1} (w, broad).[4] Attempted recrystallization of this material from acetone–petroleum ether mixture led to decomposition of the product.

Anal. Calcd for $C_{15}H_{14}O_2S$ (258.34): C, 69.74; H, 5.46. Found: C, 69.56; H, 5.59.

Reaction of *cis*-2,4-diphenylthietane 1,1-dioxide (I) with ethylmagnesium bromide under comparable conditions (15 min reaction time) yielded *trans*-1,2-diphenylcyclopropanesulfinic acid, mp 129–133°, 74% yield. The ir spectra of the *trans*-1,2-diphenylcyclopropanesulfinic acids from *cis*- and *trans*-2,4-diphenylthietane 1,1-dioxide (I and II) were identical and differed markedly from the ir spectrum of *cis*-1,2-diphenylcyclopropanesulfinic acid.[19] Comparison of these spectra showed that little if any of the *cis*-1,2-diphenylcyclopropanesulfinic acid could be present in the *trans*-1,2-diphenylcyclopropanesulfinic acid (III) prepared above.

On reaction of *cis*-2,4-diphenylthietane 1,1-dioxide (I) with excess (16 molar equiv) ethylmagnesium bromide, 1.12 equiv of ethane was evolved (theoretical 98 ml; found 110 ml).

cis- and *trans*-1,2-Diphenylcyclopropanes (VI and VII) from *trans*-1,2-Diphenylcyclopropanesulfinic Acid (III). A.—*trans*-1,2-Diphenylcyclopropanesulfinic acid (2.00 g, 7.7 mmol, mp 134–136°) was dissolved in 200 ml of 10% aqueous sodium hydroxide, and the solution was acidified with glacial acetic acid. The resulting solution was warmed on the steam bath for 10 min and mercury(II) chloride (30 g) was added. The reaction mixture was heated for 1 hr on the steam bath; during this time a white crystalline material separated. This mercuric salt (10.50 g) was separated by filtration, then suspended in concentrated hydrochloric acid (150 ml) and ethanol (150 ml), and heated on the steam bath for 1 hr. Extraction with ether gave a mobile light yellow liquid (1.10 g, 5.67 mmol, 74%, $n^{26}D$ 1.5947) which had the characteristic odor of 1,2-diphenylcyclopropane. The product was purified by distillation and the cis and trans isomers separated by gas chromatography.[1] The *cis*-1,2-diphenylcyclopropane was identified by its mp 35–36° (reported[5] 36.7, 38–38.5°) and by its time of elution on gas chromatography (direct comparison with an authentic sample). The *trans*-1,2-diphenylcyclopropane was identified by $n^{26}D$ 1.5961 (reported[5] $n^{20}D$ 1.5997), by its time of elution on gas chromatography (direct comparison), and by the identity of its nmr spectrum with that of an authentic sample.

A sample of *cis*- and *trans*-1,2-diphenylcyclopropane prepared by this desulfination but not distilled had cis/trans = 4.25. This ratio had been reported[3] previously as 0.125 on a distilled (atmospheric pressure) and probably equilibrated sample.

B.—A solution of *trans*-1,2-diphenylcyclopropanesulfinic acid (III) (0.492 g, 1.9 mmol, mp 134–138°) in ether was added over a 1-min period to a solution of ethylmagnesium bromide (0.0192 mol) in 50 ml of benzene and 10 ml of ether. The reaction mixture was vigorously stirred and heated under reflux for 8.75 hr. The magnesium complex was decomposed by addition of 3.6% aqueous hydrochloride acid, the reaction mixture was extracted with ether, and the combined ether extracts were, in turn, extracted with sodium bicarbonate solution. Acidification of the bicarbonate solution gave no precipitate. The ether extracts were washed with water and dried over sodium sulfate. Evaporation of the ether yielded a yellow oil (0.367 g). Thin layer chromatography indicated the presence of at least nine compounds, the predominant one being a mixture of *cis*- and *trans*-1,2-diphenylcyclopropane (VI and VII). This oil was chromatographed on silica gel (12 g, 100–200 mesh) and the diphenylcyclopropanes were eluted with 20% petroleum ether–80% benzene. The *cis*- and *trans*-1,2-diphenylcyclopropanes (0.143 g, 39%, cis/trans = 0.22) were separated and collected by preparative vapor phase chromatography and identified by comparison of their ir specta with those of authentic samples.[1,23]

Benzyl *trans*-1,2-Diphenylcyclopropyl Sulfone (IVa).—*trans*-1,2-Diphenylcyclopropanesulfinic acid (III) (0.50 g, 1.93 mmol, mp 131–135°) was dissolved in concentrated sodium bicarbonate solution (75 ml), and the resulting solution was neutralized with hydrochloric acid. Benzyl chloride (0.550 g, 4.35 mmol) dissolved in ethanol (50 ml) was added with stirring. After being stirred for 48 hr at room temperature, the reaction mixture was extracted with ether, and the ether extracts were washed with 10% aqueous sodium hydroxide and with water. The ether extracts were dried over sodium sulfate, and the solvent was removed under reduced pressure. Petroleum ether (25 ml) was added to the residue. On being cooled the solution deposited 0.60 g (89%) of benzyl *trans*-1,2-diphenylcyclopropyl sulfone (IVa), mp 164–165°. The analytical sample was crystallized from acetone–petroleum ether: mp 165–166°; $\lambda_{max}^{ethanol}$ 202.3 nm (ϵ 26,300), 211 (24,300), 219.1 (26,000), shoulders 253.7 (585), 259.6 (718), 263.3 (668), 264.9 (635), 270.2 (451); ν_{max}^{Nujol} 664, 698, 717, 741, 771, 826, 917, 935, 967, 1031 (cyclopropane), 1082, 1121, 1142 (SO_2), 1181, 1250, 1287, 1309 cm^{-1} (SO_2).

Anal. Calcd for $C_{22}H_{20}O_2S$ (348.46): C, 75.83; H, 5.79; S, 9.20. Found: C, 76.04; H, 6.04; S, 9.41.

In our hands, probably because of the instability of the diphenylcyclopropanesulfinic acid or because of varying reaction times, the yields on this benzylation reaction were erratic. Nevertheless, its was used to estimate the extent of stereoselectivity of this rearrangement.

A sample of the diphenylcyclopropanesulfinic acid, mp 126–134°, obtained in 73% yield from *trans*-2,4-diphenylthietane 1,1-dioxide (II), was converted to benzyl *trans*-1,2-diphenylcyclopropyl sulfone (IVa) (mp 160–162°, 32% yield) by the above procedure (reaction time, 24 hr). An nmr spectrum of the entire crude sulfone was taken. Only the trans isomer was present; the maximum amount of benzyl *cis*-1,2-diphenylcyclopropyl sulfone (XV) which could have been present without detection was 1%.[24]

A sample of the diphenylcyclopropanesulfinic acid, mp 121–127°, obtained in 65% yield from *cis*-2,4-diphenylthietane 1,1-dioxide (I), was converted to benzyl *trans*-1,2-diphenylcyclopropyl sulfone (IVa) (13% yield) by the above procedure (reaction time 5 hr). The nmr spectrum of the crude sulfone showed only the trans isomer to be present. The maximum amount of *cis*-1,2-diphenylcyclopropyl sulfone (XV) which could have been present without detection was 2%.

Methyl *trans*-1,2-Diphenylcyclopropyl Sulfone (IVb).—*trans*-1,2-Diphenylcyclopropanesulfinic acid (III) (0.25 g, 0.97 mmol, mp 134–136°) was dissolved in 10% aqueous sodium hydroxide (25 ml) and the excess base was neutralized with hydrochloric acid. The solution was cooled to 0°, and then 5.0 g (0.035 mol) of methyl iodide was added. The reaction mixture was stirred for 60 hr in the cold. It was then freed of excess methyl iodide by heating on a steam bath. The product was extracted with ether, and the ether extracts were washed with dilute sodium hydroxide solution and water and then dried (Na_2SO_4). Evaporation of the solvent and crystallization of the residue from acetone–

(20) For leading references on the Stevens rearrangement and a brief discussion of the problems involved, see R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1970, p 131, and U. Schöllkopf, *Angew. Chem., Int. Ed. Engl.*, **9**, 763 (1970).

(21) Melting points were taken on a Fisher-Johns melting point apparatus, calibrated against a set of standard compounds, or on a calibrated Mel-Temp apparatus. Petroleum ether refers to that fraction, bp 60–68°, unless otherwise stated. All nmr data in this section were measured at 60 MHz and are recorded in hertz downfield from tetramethylsilane.

(22) Comparable yields can be obtained on heating for 15 min.

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

(24) Reaction of *cis*-1,2-diphenylcyclopropanesulfinic acid, mp 133–135°, with benzyl chloride for 24 hr under the above conditions gave a 35% yield of benzyl *cis*-1,2-diphenylcyclopropyl sulfone.

petroleum ether yielded 0.20 g (76%) of methyl *trans*-1,2-diphenylcyclopropyl sulfone (IVb), mp 105–111°. Repeated crystallizations from acetone–petroleum ether were necessary to obtain the analytic sample of IVb: mp 114–115°; ν_{max}^{Nujol} 702 (s), 777 (s), (C_6H_5), 1116, 1145 (s), 1186, 1300 (s), 1311 cm^{-1} (s) (SO_2).

Anal. Calcd for $C_{16}H_{16}O_2S$ (272.37): C, 70.56; H, 5.92. Found: C, 70.30; H, 6.08.

Methyl *trans*-1,2-diphenylcyclopropanesulfinate (V) was prepared by the reaction of the diphenylsulfinic acids from both *cis*- and *trans*-2,4-diphenylthietane 1,1-dioxides (I and II) with diazomethane. The ir spectra of the crude products obtained from both samples of sulfinic acid were virtually identical. Since they were prepared in very small quantity and since they failed to crystallize, they were not further characterized: ν_{max}^{neat} 650, 690–714, 739, 772, 806, 929, 962, 980–1010, 1032, 1059, 1081, 1130–1149, 1178, 1449, 1495, 1603, 2924, 3021, and 3049 cm^{-1}.[4]

***cis*- and *trans*-α-Benzylthiostilbene (IX and X).**—A solution of 9.8 g (0.050 mol) of deoxybenzoin (VIII) and 9.3 g (0.075 mol) of benzylmercaptan in 100 ml of absolute ethanol was saturated with anhydrous hydrogen chloride and then was allowed to stand for 2.5 hr. The reaction mixture was poured into 400 ml of ice water. The products were isolated by ether extraction. The organic residue (14 g) consisted of *ca.* 50% α-benzylthio-*cis*-stilbene (IX), 30.5% α-benzylthio-*trans*-stilbene (X), 14.5% desoxybenzoin dibenzylthioketal (XI), and 4.5% deoxybenzoin (analysis by nmr spectroscopy). The residue on being allowed to stand with 25 ml of petroleum ether formed crystals, mp 74–85°. Crystallization of this solid from methanol gave 4.7 g (31%) of α-benzylthio-*cis*-stilbene (IX), mp 88–91°. Repeated crystallizations from methanol yielded analytically pure IX: mp 90.5–91°; $\lambda_{max}^{ethanol}$ 308 nm (ε 13,700); ν_{max}^{KBr} 690, 751, 763, 781, 833, 943, 1025, 1065, 1160, 1440, 1495, 1600, 3000 cm^{-1}; nmr (CCl_4) 218 (CH_2), 402.5 (>C=C<$_H$), 413, 415, and 418 (5 H), 428 and 435 Hz (10 H).

Anal. Calcd for $C_{21}H_{18}S$ (302.44): C, 83.40; H, 6.00; S, 10.60. Found: C, 83.35; H, 6.06; S, 10.55.

The residue from the combined mother liquors from the above crystallizations was chromatographed on 230 g of silica gel. α-Benzylthio-*trans*-stilbene (X) was eluted with 5% benzene in petroleum ether. Crystallization of the various fractions from methanol gave 1.05 g of X, mp 52–53°, and 1.21 g of X, mp 46–51° (total yield 15%). Recrystallization of an aliquot of the purer material from methanol yielded analytically pure α-benzylthio-*trans*-stilbene (X): mp 53–53.5°; $\lambda_{max}^{ethanol}$ 309 nm (ε 13,100); ν_{max}^{KBr} 680, 695, 753, 856, 873, 912, 940, 1028, 1070, 1440, 1490, 1600, 3000 cm^{-1}; nmr (CCl_4) 213 (CH_2), 403 (>C=C<$_H$), 412 to 457 Hz (very complex C_6H_5).

Anal. Calcd for $C_{21}H_{18}S$ (302.44): C, 83.40; H, 6.00; S, 10.60. Found: C, 83.17; H, 6.06; S, 10.39.

Further elution with 5% benzene in petroleum ether yielded, after crystallization from methanol, 0.54 g of pure α-benzylthio-*cis*-stilbene (IX), mp 90–91°; total isolated yield 35%.

Deoxybenzoin dibenzylthioketal (XI) (3.24 g) was eluted from the column with 15% benzene in petroleum ether. Crystallization from methanol gave 2.78 g (13%) of material, mp 65–66°. An aliquot crystallized twice more from methanol yielded pure deoxybenzoin dibenzylthioketal: mp 66.8–67.2°; ν_{max}^{KBr} 635, 690–730, 733, 750, 770–790, 860, 958, 1030, 1070, 1085, 1230, 1420, 1600, 2930, 3000 cm^{-1}; nmr (CCl_4) 198.5 (2 H), 226.5 Hz (4 H).

Anal. Calcd for $C_{28}H_{26}S_2$ (426.64): C, 78.83; H, 6.14; S, 15.03. Found: C, 78.68; H, 6.33; S, 15.09.

Finally deoxybenzoin (0.47 g, 4.8%, mp 52–53°; 2,4-dinitrophenylhydrazone, mp 200–204°) was eluted with 50% benzene in petroleum ether.

α-Benzylsulfonyl-*cis*-stilbene (XIII).—To a hot solution of 0.20 g (0.66 mmol) of α-benzylthio-*cis*-stilbene in 6 ml of glacial acetic acid was added 1 ml of 30% hydrogen peroxide. After being heated on the steam bath for 5 min the solution was allowed to stand at room temperature for 1 hr and was then poured into 20 ml of ice water. The crude product (0.20 g, mp 130–150°) was crystallized from ethanol and yielded 0.15 g (68%) of α-benzylsulfonyl-*cis*-stilbene (XIII): mp 157.5–158°; $\lambda_{max}^{ethanol}$ 271 nm (ε 16,600); ν_{max}^{Nujol} 640, 690, 710, 725, 760, 775, 827, 912, 950. 1125, 1310 cm^{-1}; nmr ($CDCl_3$) 247 (CH_2), 455 (>C=C<$_H$), 449 and 441.5 (singlet aromatic absorptions, 10 H), 415–438 Hz (complex, 5 H).

Anal. Calcd for $C_{21}H_{18}O_2S$ (334.44): C, 75.42; H, 5.43; S, 9.59. Found: C, 75.68; H, 5.58; S, 9.65.

For the preparation of larger quantities of α-benzylsulfonyl-*cis*-stilbene (XIII), the two procedures given above were combined, all chromatography was omitted, and XIII, mp 156.5–158° (22%), was purified by repeated crystallizations from ethanol containing a small amount of sodium methoxide.

When α-benzylthio-*trans*-stilbene (X) was oxidized to the sulfone by the above procedure, a mixture of *cis*- and *trans*-α-benzylsulfonylstilbenes (XIII and XIV, respectively) was obtained; cis/trans ratio 0.25 from nmr spectroscopy.

α-Benzylsulfinyl-*trans*-stilbene (XII) was obtained on attempted oxidation of α-benzylthio-*trans*-stilbene (X) by the above procedure on mixing the reagents at room temperature, then allowing the reaction to stand overnight in the refrigerator. Crystallization of the product from diisopropyl ether yielded analytically pure α-benzylsulfinyl-*trans*-stilbene: mp 124–125° (53% yield); $\lambda_{max}^{ethanol}$ 264 nm (ε 12,900); ν_{max}^{KBr} 690, 748, 754, 762, 880, 1020 (s) (SO), 1067, 1440, and 1488 cm^{-1}; nmr ($CDCl_3$) 237.5 (CH_2), 451 (>C=C<$_H$?), 417–472 Hz (15 H, C_6H_5).

Anal. Calcd for $C_{21}H_{18}OS$ (318.44): C, 79.21; H, 5.70; S, 10.07. Found: C, 78.91; H, 5.67; S, 10.11.

α-Benzylsulfonyl-*trans*-stilbene (XIV).—To a solution of 0.30 g (1.0 mmol) of α-benzylthio-*trans*-stilbene in 5 ml of carbon tetrachloride and 2.5 ml of 88% formic acid was added 2.5 ml of 30% hydrogen peroxide in the course of 10 min. The mixture was stirred at room temperature for 4 hr and was then poured into dilute aqueous potassium hydroxide. The layers were separated and the aqueous layer was washed with two 20-ml portions of carbon tetrachloride. The carbon tetrachloride extracts were combined, washed with water, and then evaporated. The crude residue (0.315 g, 94%, mp 108–115°) on crystallization from diisopropyl ether yielded 0.263 g (79%) of pure α-benzylsulfonyl-*trans*-stilbene (XIV): mp 114.8–115.5°; $\lambda_{max}^{ethanol}$ 277 nm (ε 13,700); ν_{max}^{KBr} 690, 720, 750, 780, 880, 885, 930, 1030, 1075, 1120 (s) (SO_2), 1140 (s) (SO_2), 1195, 1245, 1300 (s) (SO_2), 1450, 1460, 1500, and 1610 cm^{-1}; nmr ($CDCl_3$) 242 (CH_2), 438 (>C=C<$_H$?), 435, 444, 420–470 (C_6H_5).

Anal. Calcd for $C_{21}H_{18}O_2S$ (334.44): C, 75.42; H, 5.43; S, 9.59. Found: C, 75.41; H, 5.72; S, 9.61.

α-Benzylsulfonyl-*cis*-stilbene (XIII) from α-Benzylsulfonyl-*trans*-stilbene (XIV).—A solution of 76.5 mg (0.229 mmol) of α-benzylsulfonyl-*cis*-stilbene in 10 ml of ethanol and 5 ml of 0.2 *N* sodium hydroxide in ethanol was heated under reflux for 12 hr. The reaction mixture was cooled and then poured into 25 ml of water. The product (69 mg, 90%, mp 137–164°) was removed by filtration and washed well with water. Its nmr spectrum ($CDCl_3$) was identical with that of α-benzylsulfonyl-*cis*-stilbene with the exception of two very small singlets at 95 and 203.5 Hz. No α-benzylsulfonyl-*trans*-stilbene could be detected by nmr spectroscopy.

Benzyl *cis*- and *trans*-1,2-Diphenylcyclopropyl Sulfones (XV and IVa).—Solid trimethylsulfoxonium iodide (2.20 g, 0.01 mol) was added in small increments to a solution of 0.24 g (0.01 mol) of sodium hydride in 8 ml of dimethyl sulfoxide. Hydrogen was evolved. To the above solution was added 1.8 g (5.4 mmol) of α-benzylsulfonyl-*cis*-stilbene in 10 ml of dimethyl sulfoxide. A yellow solution formed, then turned red for about 5 min, and then became light yellow again. The reaction mixture was allowed to stand for 1 hr at room temperature and was then poured into 100 ml of cold water. The white precipitate was separated by filtration, washed well with water, washed with a small quantity of ethanol, and was then dried. The product (1.82 g, 97%, mp 130–150°) was a 52:48 mixture of benzyl *cis*- and *trans*-1,2-diphenylcyclopropyl sulfones (XV and IVa). Analysis was effected by integrating the methylene absorptions in the nmr spectrum. Fractional crystallization from ethanol gave both products. The less soluble benzyl *cis*-1,2-diphenylcyclopropyl sulfone (XV), (0.43 g, 23%, mp 171–173°) was identical in all respects (melting point, mixture melting point, ir, nmr) with a sample of XV, prepared by the benzylation of *cis*-1,2-diphenylcyclopropanesulfinic acid[19] and crystallized from petroleum ether (bp 30–60°)–benzene. Benzyl *cis*-1,2-diphenylcyclopropyl sulfone: mp 174–175.5°; ν_{max}^{KBr} 481, 511 (s), 532 (s), 566, 580, 618 (s), 670, 690 (vs), 741, 762 (s), 770 (s), 809, 821 (s), 875, 913, 944, 1025, 1049, 1084, 1125 (vs) (SO_2), 1140, 1155, 1170, 1256, 1298 (vs) (SO_2), 1443, 1452, 1491 (s), 1602 cm^{-1}.

Anal. Calcd for $C_{22}H_{20}O_2S$ (348.46): C, 75.83; H, 5.79. Found: C, 76.01; H, 6.09.

The more soluble benzyl *trans*-1,2-diphenylcyclopropyl sulfone (IVa) (mp 161–163°, 5.3%) was identical in all respects (mixture melting point, ir, nmr) with the benzyl *trans*-1,2-diphenylcyclopropyl sulfone (IVa) prepared from *trans*-1,2-diphenylcyclopropanesulfinic acid (III, above).

The above reaction was repeated on 1.17 g (3.5 mmol) of α-benzylsulfonyl-*trans*-stilbene (XIV). The product (1.05 g, 86%, mp 124–164°) was a 49:51 mixture of benzyl *cis*- and *trans*-1,2-diphenylcyclopropyl sulfones (XV and IVa); analysis from the nmr spectrum.

Registry No.—I, 18744-27-9; II, 24609-91-4; III, 30256-16-7; IVa, 30256-17-8; IVb, 30256-18-9; IX, 30256-19-0; X, 30256-20-3; XI, 29055-91-2; XII, 30256-21-4; XIII, 30256-22-5; XIV, 30256-23-6; XV, 30256-24-7; deoxybenzoin, 451-40-1, 5637-51-4 (2,4-DNP).

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, to the National Aeronautics and Space Administration, and to the National Institutes of Health (Grant No. AM 12954) for the support of this research. We are indebted to Dr. William Schwabacher for aid on our initial nmr analyses.

Thietanes. IV. Rearrangement of 2,4-Diphenylthietane Oxides

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Reaction of either *cis*- or *trans*-2,4-diphenylthietane 1-oxide (I or II) with potassium *tert*-butoxide in dimethylformamide yielded a mixture of *cis*-1,2-diphenylcyclopropanethiol (IV) and *cis*-1,2-diphenylcyclopropanesulfinic acid (V). The structure of the sulfinic acid V was established by conversion to the known benzyl *cis*-1,2-diphenylcyclopropyl sulfone (IXa). The structure of the mercaptan IV was established by conversion to benzyl *cis*-1,2-diphenylcyclopropyl sulfide (VIII) which was oxidized to the known sulfone IXa. The mercaptan IV was also oxidized to *meso*- and *rac*-bis(1,2-diphenylcyclopropyl) disulfides (VI and VII). The rearrangements of the *cis*- and *trans*-2,4-diphenylthietane oxides (I and II) to *cis*-1,2-diphenylcyclopropanethiol (IV) and *cis*-1,2-diphenylcyclopropanesulfinic acid (V) are highly stereoselective. Mechanisms are postulated for the stereoselective rearrangements of 2,4-diphenylthietane mono- and dioxides to cyclopropane derivatives and for the stereospecific rearrangements of *cis*- and *trans*-2,4-diphenylthietane 1,1-dioxides to *cis*- and *trans*-3,5-diphenyl-1,2-oxathiolane (2,3)-*cis*-2-oxides, respectively.

Recently we have described the stereoselective rearrangement of *cis*- and *trans*-2,4-diphenylthietane 1,1-dioxides to *trans*-1,2-diphenylcyclopropanesulfinic acid.[1] Here, we report the stereoselective rearrangement of *cis*-2,4-diphenylthietane *trans*-1-oxide[2] (I) and *trans*-2,4-diphenylthietane 1-oxide[2] (II) to a mixture of *cis*-1,2-diphenylcyclopropanethiol (IV) and *cis*-1,2-diphenylcyclopropanesulfinic acid (V).

Treatment of *trans*-2,4-diphenylthietane 1-oxide (II) with potassium *tert*-butoxide in dimethylformamide yielded *cis*-1,2-diphenylcyclopropanesulfinic acid (V) (10–20% yield). Initial information on the constitution of this acid was obtained from its ir spectrum which was typical of that of a sulfinic acid[3] and from its conversion with mercury(II) chloride[1,4] and acid hydrolysis to a mixture of *cis*- and *trans*-1,2-diphenylcyclopropanes (cis/trans ratio 3.8). Benzylation of the *cis*-1,2-diphenylcyclopropanesulfinic acid (V) yielded the previously described benzyl *cis*-1,2-diphenylcyclopropyl sulfone (IXa).[1] Methylation of V gave *cis*-1,2-diphenylcyclopropyl methyl sulfone (IXb).

To obtain greater insight into the course of the reaction, *trans*-2,4-diphenylthietane 1-oxide (II) was treated with potassium *tert*-butoxide in dimethylformamide followed, after 1.25 hr, by the addition of benzyl chloride to the reaction mixture. From the reaction benzyl *cis*-1,2-diphenylcyclopropyl sulfone (IXa, 23%) and benzyl *cis*-1,2-diphenylcyclopropyl sulfide (VIII, 33%) were isolated. The nmr spectrum ($C_6H_5CH_2$ region)[1] of the crude IXa indicated the presence of 6% benzyl *trans*-1,2-diphenylcyclopropyl sulfone. The benzyl *cis*-1,2-diphenylcyclopropyl sulfide (VIII) was identified by its analysis, by its ir and nmr (Table I) spectra, and by its oxidation to benzyl *cis*-1,2-diphenylcyclopropyl sulfone (IXa). Similar rearrangement of *cis*-2,4-diphenylthietane *trans*-1-oxide (I) followed by benzylation yielded the same sulfone IXa (22% yield) and sulfide VIII (22% yield). In this case the sulfone IXa was virtually free (<1%) of benzyl *trans*-1,2-diphenylcyclopropyl sulfone.[1]

The intermediacy of the *cis*-1,2-diphenylcyclopropanethiol[5] (IV) was established by its isolation by chromatography, by evidence of purity from thin layer chromatography, by the presence in its ir spectrum of an absorption band at 2600 cm^{-1} characteristic of the –SH group,[6] and by its conversion to benzyl *cis*-1,2-diphenylcyclopropyl sulfide (VIII). Further evidence for the intermediacy of the mercaptan IV was obtained by the air oxidation of the mercaptan from the rearrangement of *cis*-2,4-diphenylthietane *trans*-1-oxide (I) (>99% stereoselective) to the corresponding disulfides VI and VII. Since *cis*-1,2-diphenylcyclopropanethiol (IV) exists as a racemic modification (*d* and *l* forms), two different inactive disulfides (a meso,*dl* compound and a racemic, *dd* plus *ll* modification) should be obtained. Both of these were isolated.

The constitutions of these disulfides VI and VII were established by their analyses, by their conversion with

(1) R. M. Dodson, P. D. Hammen, E. H. Jancis, and G. Klose, *J. Org. Chem.*, **36**, 2698 (1971).

(2) R. M. Dodson, E. H. Jancis, and G. Klose, *ibid.*, **35**, 2520 (1970).

(3) S. Detoni and D. Hadzi, *J. Chem. Soc.*, 3163 (1955).

(4) T. Okamoto and J. F. Bunnett, *J. Amer. Chem. Soc.*, **78**, 5357 (1956); L. H. Gale, F. R. Jensen, and J. H. Landgrebe, *Chem. Ind. (London)*, 118 (1960); M. M. Kreevoy and R. L. Hansen, *J. Amer. Chem. Soc.*, **83**, 626 (1961).

(5) Cyclopropanethiol has been prepared by the photolysis of carbonyl sulfide in the presence of cyclopropane: A. R. Knight, O. P. Strausz, and H. E. Gunning, *ibid.*, **85**, 1207 (1963).

(6) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, San Francisco, Calif., 1962, pp 54, 220.

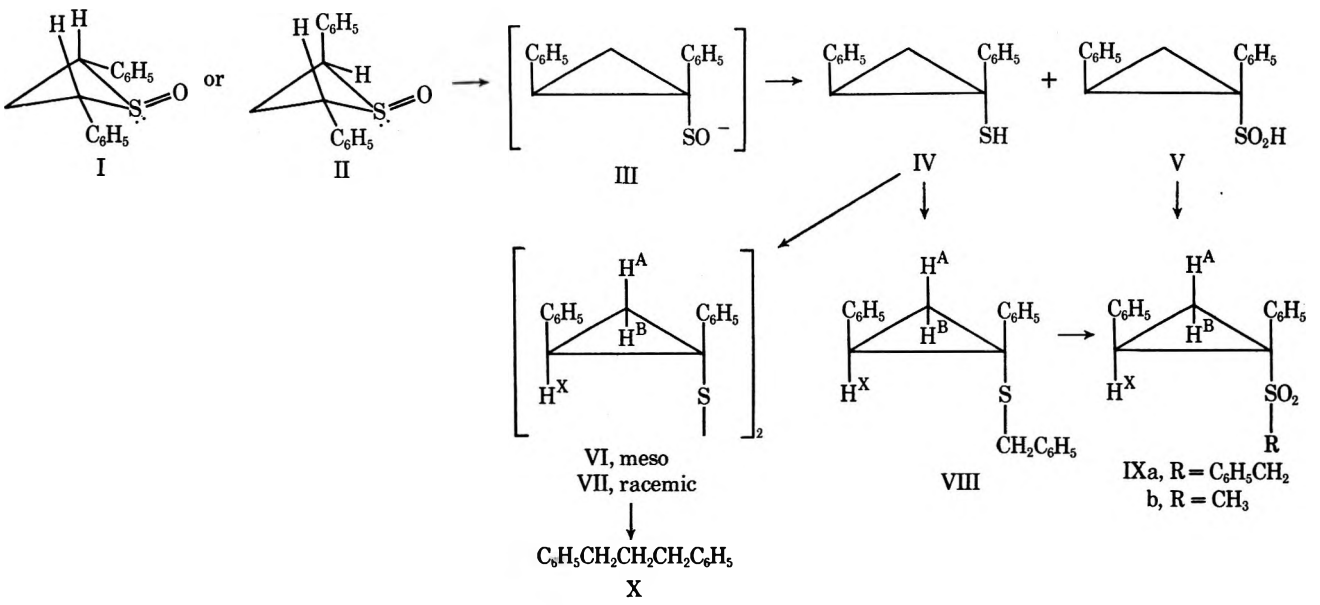
TABLE I[a]

DERIVATIVES OF *cis*-1,2-DIPHENYLCYCLOPROPANETHIOL

	ν_A	ν_B	ν_X	J_{AB}[d]	J_{AX}	J_{BX}
IXb methyl sulfone ($CDCl_3$)[b]	114.3	133.9	204.1	−5.85	7.18	9.90
IXa benzyl sulfone ($CDCl_3$)[b]	109.0	123.2	197.2	−6.10	7.15	10.25
VIII benzyl sulfide (CCl_4)[c]	99.0	85.6	152.4	−5.8	6.3	9.3
VI meso disulfide ($CDCl_3$)[c]	103.5	98.7	160.4	−5.9	6.0	9.9

[a] Recorded in hertz downfield from tetramethylsilane at 60 MHz. The lettering of the protons correspond to that given in the formulas. [b] Determined at 50-Hz sweepwidth and calculated by the LAOCOON-2 program of A. A. Bothner-By and S. M. Castellano. Coupling constants should be accurate to ±0.1 Hz. [c] Determined at 500-Hz sweepwidth and calculated as ABX spectra. Coupling constants should be accurate to ±0.5 Hz. [d] The sign of this coupling constant was not independently determined but follows from our previous determination (ref 1).

SCHEME I



Raney Ni to 1,2- and 1,3-diphenylpropane,[7] and by analyses of their nmr spectra. The nmr spectrum of one of the isomeric disulfides could be analyzed as a simple ABX system (Table I). That of the second disulfide could be analyzed as two similar but superimposed ABX systems (see Table I and Experimental Section). This more complex spectrum could result from the partial association of the (+) and (−) isomers of the racemic compound in solution. The structures were assigned accordingly: the meso disulfide VI to that compound, mp 142–143°, with the simpler nmr spectrum; the racemic disulfide VII to that compound, mp 121–122°, with the more complex nmr spectrum.[8] It is realized that these assignments are highly speculative.

The deshielding effect of the sulfone group on cis-vicinal protons (compared to its effect on trans-vicinal protons and to the effect of S) is immediately apparent from Table I. Thus, with the sulfide or disulfides, H^B is farthest upfield while with the sulfones (see also ref 1) H^A appears at highest field (see Scheme I).

The mass spectrum of VI was also consistent with its constitution. The molecular ion peak (450) was very weak (0.1% of base peaks at 223 and 121). Base peaks corresponded to M/2 − 2H (223) and $C_6H_5CS^+$ (121). A very strong peak (66% of base peaks) corresponded to M/2 − S (193). The ir spectra of the stereoisomeric disulfides VI and VII were almost identical.

Mechanisms.—In this series of papers, four different base-catalyzed reactions have been presented. (1) The isomerization[2] of *trans*-2,4-diphenylthietane mono- and dioxides (II and XII) to the corresponding cis isomers I and XI, respectively, was accomplished with a relatively weak base (sodium methoxide) in the presence of an abundance of available protons (methanol). Concentrations of the intermediate anions should be very low. (2) The stereoselective rearrangements[1] of the *cis*- and *trans*-2,4-diphenylthietane 1,1-dioxides (XI and XII) to the *trans*-1,2-diphenylcyclopropanesulfinate anion (XIV) occurred on treatment of XI or XII with ethylmagnesium bromide. Here, the α-sulfonyl carbanion formed rapidly, and protons were not available. Consequently, the intermediate carbanion was stabilized by rearrangement to the *trans*-1,2-diphenylcyclopropanesulfinate anion (XIV). (3) In a related manner, the stereoselective rearrangement of *cis*- and *trans*-2,4-diphenylthietane 1-oxides (I and II) to the *cis*-1,2-diphenylcyclopropanesulfenate anion (III) occurred in the presence of strong base (potassium *tert*-butoxide) and low availability of protons (dimethylformamide as solvent). It is probable that the potassium salt of the sulfenic acid III formed first and that

(7) Since dimers connected by a C–C bond had previously been isolated from rearrangements of thietanes [(R. M. Dodson and J. Yu Fan, *J. Org. Chem.*, **36**, 2708 (1971)], we felt it necessary to prove that these dimers were not of this type.

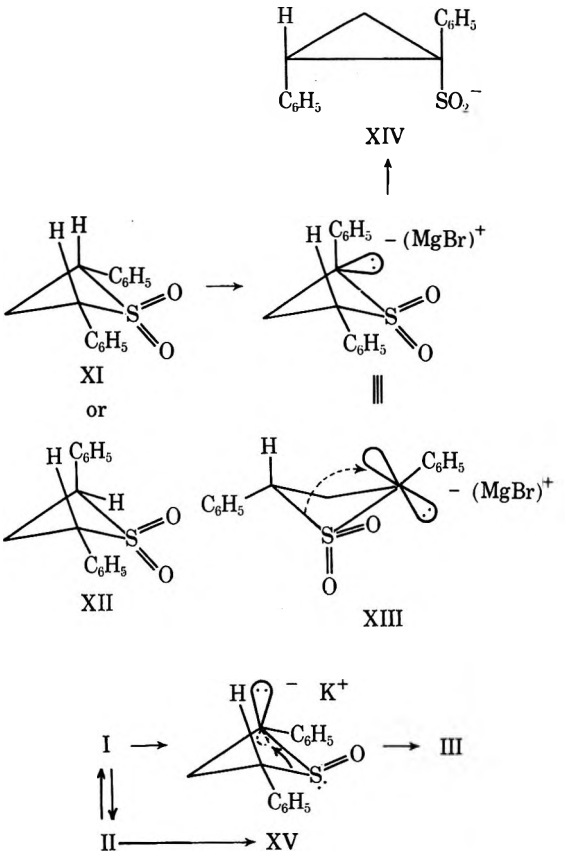
(8) For a simpler study which distinguished between meso and *dl* symmetrically substituted 1,2-diols and 1,3-dioxalanes, see M. Gianni, J. Saavedra, R. Myhalyk, and K. Wursthorn, *J. Phys. Chem.*, **74**, 210 (1970).

this then disproportionated to the potassium salts of the sulfinic acid V and the mercaptan IV.[9]

We consider these latter two reactions as modified Stevens rearrangements.[10] Any mechanism for them should explain their high stereoselectivity. We believe that the stereoselectivity of these reactions is controlled by the configurational stability of the intermediate anions XIII and XV.

Corey and coworkers[11] have shown that, on base-catalyzed exchange of an α-hydrogen atom of a sulfone for deuterium, the hydrogen atom lying conformationally between the oxygen atoms of the sulfone is preferentially exchanged and rotation of the intermediate anion is restricted. Since the energy of the transition state for ionization should be similar to the energy of the anion, the anion so produced should be the conformationally most stable one. This conclusion is in agreement with the conclusions of Lipscomb and coworkers[11b] from a crystal structure determination of tetramethylsulfamide and an LCAO–MO calculation on tetrafluorosulfamide. From this, one can conclude that the most stable structure for the anion of the sulfones XI or XII should be XIII (Scheme II). In this rearrange-

SCHEME II



ment the sulfones XI and XII are converted entirely and irreversibly to the anion (Grignard reagent). If this now rearranges with migration of the C–S bond (*via* an intermediate diradical pair[10]) to the back lobe (near lobe) of the partially p orbital of the anion, the anion of *trans*-1,2-diphenylcyclopropanesulfinic acid (XIV) results.

Recent experiments by Baldwin and coworkers,[12] however, on the base-catalyzed exchange of α hydrogens for deuterium in benzyl methyl sulfoxide, have contradicted the previous experiments of Wolfe and Rauk[13] and have indicated that the α hydrogen lying conformationally between the oxygen of the sulfoxide and the methyl group is preferentially exchanged. This would lead to the prediction that XV should be the configurationally most stable anion from the sulfoxides I and II. This configuration has both phenyl groups in pseudoequatorial conformations and has the oxygen of the S=O dipole in close vicinity to the positive ion. Rearrangement of this anion with migration of the C–S bond to the back lobe (near lobe) of the partially p orbital of the anion would yield the anion of *cis*-1,2-diphenylcyclopropanesulfenic acid (III). This mechanism assumes that the activation energy for rearrangement to cis or trans isomers is similar.

It should be realized that there is the possibility of some equilibration of I and II in this system. Similar experiments on *trans*-2,4-diphenylthietane 1,1-dioxide (XII) using potassium *tert*-butoxide in dimethylformamide yielded some *cis*-2,4-diphenylthietane 1,1-dioxide (XI).

(4) The rearrangement of *cis*- and *trans*-2,4-diphenylthietane dioxides (XI and XII) to *cis*- and *trans*-3,5-diphenyl-1,2-oxathiolane (2,3)-*cis*-2-oxides (XVI and XVII, respectively) on treatment with *tert*-butoxymagnesium bromide is stereospecific with respect to the phenyl groups but stereoselective with respect to the oxygen atoms on sulfur. We believe that the differences between this rearrangement and the rearrangements of the thietane monoxides and dioxides to the cyclopropanesulfenate and sulfinate respectively result from the unique structure of the dimeric *tert*-butoxymagnesium bromide–ether complex.[14] In the interaction of the sulfone with this basic catalyst both the anion and the *tert*-butyl alcohol so formed are held in close proximity to each other permitting the rapid reprotonation of the anion, either before or after rearrangement. Since the sultine should be far less acidic than the sulfone, the products of the rearrangement XVI and XVII should be moderately stable to further interaction with the catalyst. If the proton (from the complexed *tert*-butyl alcohol) were not immediately available, the anion should be stabilized by rearrangement to the cyclopropanesulfinate.

The intermediates for this rearrangement can be formulated as anion diradicals in a solvent cage[10] and thus the stereospecificity can be explained. Rear-

(9) N. Kharasch and T. C. Bruice, *J. Amer. Chem. Soc.*, **73**, 3240 (1951); N. Kharasch, Ed., "Organic Sulfur Compounds," Vol. 1, Pergamon Press, Elmsford, N. Y., 1961, p 392.

(10) U. Schöllkopf, *Angew. Chem., Int. Ed. Engl.*, **9**, 763 (1970); R. B. Woodward and R. Hoffmann, "The Conservation of Orbital Symmetry," Academic Press, New York, N. Y., 1970, p 131.

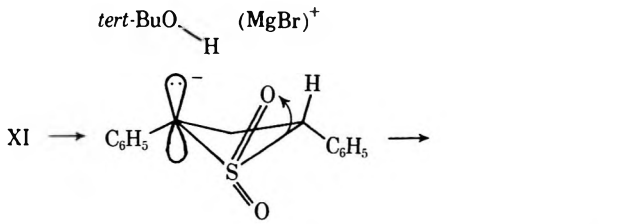
(11) (a) E. J. Corey, H. Konig, and T. H. Lowry, *Tetrahedron Lett.*, 515 (1962); E. J. Corey and T. H. Lowry, *ibid.*, 793, 803 (1965). (b) T. H. Jordan, H. W. Smith, L. L. Lohr, Jr., and W. N. Lipscomb, *J. Amer. Chem. Soc.*, **85**, 846 (1963).

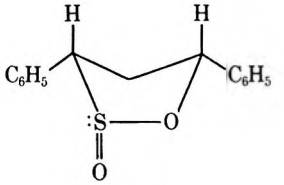
(12) J. E. Baldwin, R. E. Hackler, and R. M. Scott, *Chem. Commun.*, 1415 (1969). See also, M. Nishio, *ibid.*, 562 (1968); 51 (1969). The results of B. J. Hutchinson, K. K. Andersen, and A. R. Katritzky [*J. Amer. Chem. Soc.*, **91**, 3839 (1969)] from the exchange of the α-hydrogen atoms of *trans*-4-phenyltetrahydrothiopyran 1-oxide in dimethyl sulfoxide, although tending to support our conclusions, were not stereoselective to within experimental error.

(13) S. Wolfe and A. Rauk, *Chem. Commun.*, 778 (1966). See also the quantum mechanical calculations on the conformation of this anion: A. Rauk, S. Wolfe, and I. G. Csizmadia, *Can. J. Chem.*, **47**, 113 (1969).

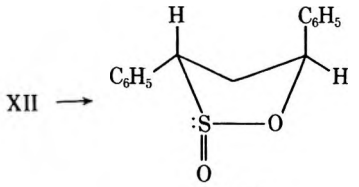
(14) The structure of *tert*-butoxymagnesium bromide has been determined by X-ray diffraction: P. T. Moseley and H. M. M. Shearer, *Chem. Commun.*, 279 (1968).

rangement to upper oxygen (that on the same side of the molecule as the catalyst) leads to the conformationally more favorable transition state and thus helps explain the stereoselectivity of the rearrangement with respect to the oxygen atoms on sulfur.

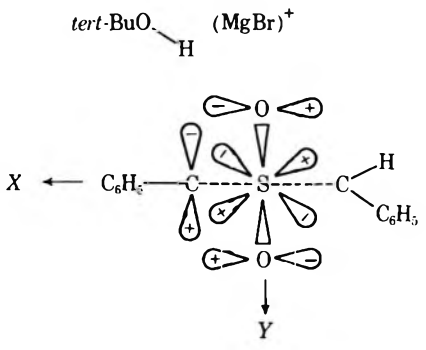




XVI



XVII



However, it should be realized that rearrangement of XI → XVI, unlike most 1,2-anionic rearrangements, is a symmetry-allowed rearrangement.[15] In order to formulate it, the molecular orbital picture of the sulfone and of its conjugation with adjacent unsaturation as formulated by Moffitt was used.[16] Attack of *tert*-butoxymagnesium bromide on an α proton will remove the proton and generate a p orbital on carbon. This p orbital (pictured p_y) will perturb the va_2 π orbital of the sulfone. The va_2 orbital is composed of $S_{d_{xz}}$ and $(O_{p_z} - O_{p_z})$ (pictured). Conjugation is that of case Ia of Moffitt[16] and partially resembles spiroconjugation.[17]

The result should be an increase in energy of the perturbed va_2 orbital with an increase in electron concentration in that oxygen on the same side of the molecule as $(MgBr)^+$. The antibonding rb_1 orbital of the alkyl groups, composed of $S_{p_z} - S_{p_{z'}}$ and $-(R_\sigma - R_\sigma')$, already lowered in energy because of the high positive charge on sulfur, can now interact with the perturbed va_2 orbital, the alkyl group (to the right in the picture) rearranging without its electrons to oxygen (upper), with the electrons occupying the S_{p_z} orbital and becoming the nonbonding electrons of the sultine. The nonbonding electrons should be trans to the newly formed C–O bond; thus the stereochemistry of the sulfinate group is explained. Finally, with rearrangement, the electrons in the p_y orbital on carbon become more basic, the proton is returned (from the same side), and the catalyst is regenerated. The energy for the reaction comes from the relief of strain of the four-membered ring and from substitution of a C–O bond for a C–S bond. No firm decision between an anion-diradical mechanism and a concerted mechanism can be made from the presently available evidence.

Experimental Section[18]

Benzyl *cis*-1,2-Diphenylcyclopropyl Sulfide (VIII) and Benzyl *cis*-1,2-Diphenylcyclopropyl Sulfone (IXa) from *trans*-2,4-Diphenylthietane 1-Oxide (II).—*trans*-2,4-Diphenylthietane 1-oxide[2] (II) (0.811 g, 3.35 mmol, mp 152–155°) in dimethylformamide (30 ml, dried by distillation over calcium hydride) was stirred for 1.25 hr under nitrogen at room temperature with potassium *tert*-butoxide (2.00 g, 0.0178 mol). Benzyl chloride (2.30 g, 0.0182 mol) was then added and the reaction was stirred under nitrogen for 24 hr. The reaction contents were poured into water and extracted repeatedly with ether. The combined ether extracts were washed with water and dried over sodium sulfate. Evaporation of the solvent left a crystalline solid, which was thoroughly washed with petroleum ether. The nmr spectrum of the solid indicated a mixture of 94% benzyl *cis*-1,2-diphenylcyclopropyl sulfone (IXa) and 6% benzyl *trans*-1,2-diphenylcyclopropyl sulfone. Crystallization from petroleum ether–chloroform yielded 0.210 g (18%) of benzyl *cis*-1,2-diphenylcyclopropyl sulfone (IXa), mp 173–174°, identical (mixture melting point and ir spectrum) with material synthesized from α-benzylsulfonylstilbene.[1]

The mother liquors from the crystallization and from the original washing were chromatographed on a silica gel column (30 g, 100–200 mesh). Elution with 4:1 petroleum ether (bp 40–60°)–benzene yielded, as a viscous liquid, 0.351 g (33%) of benzyl *cis*-1,2-diphenylcyclopropyl sulfide (VIII): ν_{max}^{neat} 700, 753, 773, 1028, 1075, 1455, 1500 and 1547 cm^{-1}; nmr (CCl_4) 427.5 (s, 5.8 H, C_6H_5), 419 (s, 4.8 H, C_6H_5), 384.5–415 (complex multiplet, 4.8 H, C_6H_5), 214 Hz (s, 2 H, $CH_2C_6H_5$), ABX system of cyclopropyl protons (see Table I).

Anal. Calcd for $C_{22}H_{20}S$ (316.47): C, 83.50; H, 6.37. Found: C, 82.90, 83.89; H, 6.51, 6.96.

Additional benzyl *cis*-1,2-diphenylcyclopropyl sulfone (IXa) (0.054 g, 0.17 mmol, total yield 23%) was obtained by elution of the column with 4:6 chloroform–petroleum ether (bp 40–60°).

Benzyl *cis*-1,2-Diphenylcyclopropyl Sulfone (IXa) from Benzyl *cis*-1,2-Diphenylcyclopropyl Sulfide (VIII).—The benzyl *cis*-1,2-

(15) E. G. Miller, D. R. Rayner, H. T. Thomas, and K. Mislow (*J. Amer. Chem. Soc.*, **90**, 4861 (1968)] have proposed an intramolecular, concerted mechanism for the rearrangement of benzyl *p*-toluenesulfenate to benzyl *p*-tolyl sulfoxide. J. Jacobus [*Chem. Commun.*, 709 (1970)] has shown that the CIDNP observed in the nmr spectrum of that rearrangement may result from secondary reactions not on the direct rearrangement path.

(16) (a) W. Moffitt, *Proc. Roy. Soc., Ser. A*, **200**, 409 (1950); (b) H. P. Koch and W. E. Moffitt, *Trans. Faraday Soc.*, **47**, 7 (1951). To facilitate reading, orbitals are named using the same coordinate system, the same symmetry designations, and similar symbolism to that used by Moffitt.

(17) H. E. Simmons and T. Fukunaga, *J. Amer. Chem. Soc.*, **89**, 5208 (1967); R. Hoffmann, A. Imamura, and G. D. Zeiss, *ibid.*, **89**, 5215 (1967).

(18) Melting points were taken on a Fisher-Johns melting point apparatus, calibrated against a set of standard compounds. Nmr spectra were determined on a Varian A-60 spectrometer at concentrations of 10–20% and using tetramethylsilane as an internal standard. Mass spectra were determined on a Hitachi Perkin-Elmer Model RMU-6D mass spectrometer. The vapor phase chromatograms were run on an Aerograph manual temperature programmer gas chromatograph, Model A-90P, using a 20% Apiezon L, 60–80 firebrick (5 ft × 0.25 in.) column and using helium at 386 ml/min as the carrier gas. The following temperatures were used: column 220°, injector 240°, detector 250°. The chart speed was 1.7 cm/min. Petroleum ether, unless otherwise specified, refers to that fraction, bp 60–68°.

diphenylcyclopropyl sulfide (VIII) (0.136 g, 0.430 mmol), obtained from the reaction immediately above, was oxidized with 30% hydrogen peroxide in carbon tetrachloride–formic acid as previously described.[1] The benzyl *cis*-1,2-diphenylcyclopropyl sulfone (IXa) (0.15 g, 0.431 mmol, 100%) was obtained as a white crystalline solid, mp 166–170°. The nmr spectrum of this sulfone showed the presence of *ca.* 10% of the trans isomer. Crystallization from petroleum ether–chloroform raised the melting point of IXa to 174–175°; the sulfone IXa was identical (mixture melting point and ir spectrum) with the benzyl *cis*-1,2-diphenylcyclopropyl sulfone[1] previously prepared.

Benzyl *cis*-1,2-Diphenylcyclopropyl Sulfide (VIII) and Benzyl *cis*-1,2-Diphenylcyclopropyl Sulfone (IXa) from *cis*-2,4-Diphenylthietane *trans*-1-Oxide (I).—*cis*-2,4-Diphenylthietane *trans*-1-oxide[2] (I) (0.811 g, 3.35 mmol) was allowed to react with potassium *tert*-butoxide and the benzyl chloride in the manner described above. The benzyl *cis*-1,2-diphenylcyclopropyl sulfone (0.253 g, 0.725 mmol, 22% yield), mp 163–167°, obtained by thoroughly washing the crystals with petroleum ether, was virtually free of the trans isomer (<1%, from nmr spectrum), and after crystallization from petroleum ether–chloroform was identical (mp 173–174°, mixture melting point, ir spectrum) with IXa previously prepared.[1] Benzyl *cis*-1,2-diphenylcyclopropyl sulfide (VIII) (0.236 g, 0.746 mmol, 22%) was isolated by chromatography and identified by comparison of its ir spectrum and R_f value on thin layer chromatography with that of VIII obtained above.

***cis*-1,2-Diphenylcyclopropanesulfinic Acid (V)** was isolated from the reaction of *trans*-2,4-diphenylthietane 1-oxide with potassium *tert*-butoxide in dimethylformamide at 80° by pouring the initial reaction into ice water, extracting this thoroughly with ether, and then acidifying the aqueous layer with hydrochloric acid. The liberated sulfinic acid V was then extracted into ether, the ether solution washed with water, and the sulfinic acid extracted with dilute sodium bicarbonate solution. Acidification with dilute hydrochloric acid yielded *cis*-1,2-diphenylcyclopropanesulfinic acid (V, 10% yield): mp 125–127°; $\lambda_{max}^{ethanol}$ shoulder 223 nm (ε 17,119); ν_{max}^{Nujol} 699, 741, 755, 769, 807 (s), 843 (s), (SO_2H), 886, 911, 923, 944, 957, 1022 (s) (SO_2H), 1034 1064, 1087 (s) (SO_2H), 1096, 1111, 2314 (w, broad), 2387–2513 cm^{-1} (w, broad) (SO_2H).

Anal. Calcd for $C_{15}H_{14}O_2S$ (258.34): C, 69.74; H, 5.46. Found: C, 69.45; H, 5.75.

The best melting sample of *cis*-1,2-diphenylcyclopropanesulfinic acid (V), mp 133–135° (20% yield), was obtained from a rearrangement of *trans*-2,4-diphenylthietane 1-oxide (II) with potassium *tert*-butoxide in anhydrous ether under nitrogen at room temperature for 5 hr. This reaction also gave, after benzylation, a 39% yield of benzyl *cis*-1,2-diphenylcyclopropyl sulfide (VIII). The rearrangement also occurred when II was treated with sodium methoxide in dimethylformamide but did not occur when II was treated with sodium hydride in anhydrous ether.

Benzyl *cis*-1,2-Diphenylcyclopropyl Sulfone (IXa), mp 174–175° (71% yield), was obtained by the reaction of the sodium salt of the sulfinic acid V with benzyl chloride by the procedure previously described[1] and was identical (mixture melting point and ir spectrum) with previously prepared IXa.[1]

***cis*-1,2-Diphenylcyclopropyl Methyl Sulfone (IXb).**—*cis*-1,2-Diphenylcyclopropanesulfinic acid (V) (0.612 g, 2.37 mmol, mp 130–136°) was dissolved in saturated sodium bicarbonate solution (50 ml) and the solution was neutralized with hydrochloric acid. Methyl iodide (2.00 g, 0.0141 mol) in ethanol (50 ml) was added, and the slurry was stirred for 19 hr at room temperature. Water was added and the resulting suspension was repeatedly extracted with ether. The ether extracts were dried over anhydrous sodium sulfate and then evaporated. The resulting white crystalline residue on crystallization from chloroform–petroleum ether yielded 0.224 g (35%) of *cis*-1,2-diphenylcyclopropyl methyl sulfone (IXb): mp 144–148°; recrystallized from the same solvent, mp 147–148°; ν_{max}^{KBr} 693, 770, multiplets at 1133 and 1300 (SO_2), 1380, 1450, 1500, 1603 cm^{-1}; nmr ($CDCl_3$) 432.5 (s, C_6H_5), 402.5–428.5 (m, C_6H_5) 163 Hz (s, CH_3), ABX system of cyclopropyl protons (see Table I).

Anal. Calcd for $C_{16}H_{16}O_2S$ (272.37): C, 70.56; H, 5.92. Found: C, 70.51; H, 5.83.

***cis*- and *trans*-1,2-diphenylcyclopropanes** were obtained from *cis*-1,2-diphenylcyclopropanesulfinic acid (V) by desulfination of V with mercury(II) chloride as previously described.[1] The isomeric 1,2-diphenylcyclopropanes were separated by gas chromatography, cis/trans ratio 3.8. The infrared spectrum of *cis*-1,2-diphenylcyclopropane was identical with that of an authentic sample.[1,2,19]

***cis*-1,2-Diphenylcyclopropanethiol (IV).**—A mixture of *cis*- and *trans*-2,4-diphenylthietane 1-oxides[2] (2.00 g, 8.28 mmol, mp 122–126°) was dissolved in dry dimethylformamide (40 ml) and treated with 4.2 g (0.0375 mol) of potassium *tert*-butoxide. The reaction was stirred at room temperature under nitrogen for 3.5 hr. The reaction mixture was poured into water (100 ml) and extracted with ether. The ether extracts were washed thoroughly with water, dried over sodium sulfate overnight, and then evaporated. A yellow foul-smelling oil (1.05 g) was obtained whose infrared spectrum showed the presence of the SH stretching absorption (2600 cm^{-1}). This oil was chromatographed on 50 g of silica gel (100–200 mesh). Elution with 9:1 petroleum ether–benzene yielded *cis*-1,2-diphenylcyclopropanethiol (IV) (0.532 g, 2.38 mmol, 28% yield): ν_{max}^{neat} 695, 760 doublet, 800, 1030, 1075, 1453 doublet, 1503, 1603, 2600 cm^{-1} (SH). This material IV showed only one spot when examined with thin layer chromatography.

For positive identification this compound was benzylated with benzyl chloride and potassium *tert*-butoxide in dimethylformamide. The benzyl *cis*-1,2-diphenylcyclopropyl sulfide (VIII) after purification by chromatography had an ir spectrum identical with VIII previously prepared.

***meso*- and *rac*-Bis(*cis*-1,2-Diphenylcyclopropyl) Disulfides (VI and VII).**—A solution of *cis*-2,4-diphenylthietane *trans*-1-oxide (2.50 g, 0.0103 mol, mp 134–137°) in dry dimethylformamide (50 ml) was stirred for 2 hr at 0° with potassium *tert*-butoxide (4.10 g, 0.0366 mol). The reaction mixture was then poured into water (100 ml) and extracted thoroughly with ether. From the aqueous layer, 0.642 g (24% yield) of *cis*-1,2-diphenylcyclopropanesulfinic acid (V), mp 130–134°, was isolated. The ether extracts were dried briefly over sodium sulfate and then filtered. A slow stream of air was blown over the ether solution until it had been reduced to 30 ml in volume. It was then allowed to stand in a partially covered 125-ml erlenmeyer flask with occasional shaking for 4 days. The crystals which formed during this time were separated from the oil and washed with a small amount of ether. Crystallization from chloroform–petroleum ether yielded 0.176 g (0.39 mmol, 8%) of *meso*-bis(*cis*-1,2-diphenylcyclopropyl) disulfide (VI), mp 123–143°. Recrystallization from chloroform–petroleum ether gave 0.122 g of pure VI: mp 142–143°; $\lambda_{max}^{ethanol}$ 227.5 nm (ε 37,300); ν_{max}^{KBr} 643, 691, 735, 743, 761, 789, 872, 900, 915, 928, 949, 1025 (CH_2 of cyclopropane), 1040, 1072, 1081, 1092, 1149, 1159, 1445, 1455, 1497, 1578, 1599, 2985, 3000, 3035, 3062, 3090 cm^{-1}; nmr ($CDCl_3$) 425.5 (s, 10 H, C_6H_5), 394–422 Hz (complex multiplet, 10 H, C_6H_5), ABX system of cyclopropane ring (see Table I); mass spectrum, molecular ion 450 (0.1% of B), base peak 223, 193 (66% of B) (M/2 − S), 121 (100% of B) $C_6H_5CS^+$.

Anal. Calcd for $C_{30}H_{26}S_2$ (450.67): C, 79.96; H, 5.82. Found: C, 79.91; H, 5.85.

The ether washings were combined with the residual oil and the ether was evaporated. The residual oil was chromatographed on silica gel (30 g, 100–200 mesh). Fractions eluted with 9:1 and 8:2 petroleum ether (bp 30–60°)–benzene were combined and crystallized from petroleum ether. The *rac*-bis(*cis*-1,2-diphenylcyclopropyl) disulfide (VII) (0.336 g, 15%, mp 110–117°) after recrystallization from petroleum ether gave analytically pure VII: mp 121–122°; $\lambda_{max}^{ethanol}$ 227.5 nm (ε 36,800); ν_{max}^{KBr} 642, 689, 732, 761, 788, 872, 898, 911, 928, 946, 1023, 1039, 1070, 1079, 1090, 1442, 1452, 1495, 1576, 1598, 2998, 3033, 3065, 3090 cm^{-1}; nmr ($CDCl_3$) 424 (s, 10 H, C_6H_5), 392.8–422.3 (complex multiplet 10 H, C_6H_5), two superimposed ABX systems, one corresponding to that of the meso isomer (see Table I), a second ν_A 99.5, ν_B 8.80, ν_X 160.2, J_{AB} = −6.0, J_{AX} = 6.1, J_{BX} = 9.7 Hz (±0.5 Hz).

Anal. Calcd for $C_{30}H_{26}S_2$ (450.67): C, 79.96; H, 5.82; S, 14.23. Found: C, 79.60; H, 5.20; S, 14.28.

Desulfurization of *meso*-Bis(*cis*-1,2-Diphenylcyclopropyl) Disulfide (VI).—Raney nickel (W-2, 1/2 tsp) was added to a mixture of 0.091 g of VI, mp 140–142°, in 95% ethanol (50 ml). The reaction was stirred at the reflux temperature for 5.5 hr. The nickel was separated by filtration and washed with boiling 95% ethanol. Evaporation of the ethanol left a colorless oil. This was dissolved in ether and the ether solution was dried over sodium sulfate. Evaporation of the ether left 0.056 g (71%) of a pale

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

yellow, pleasant-smelling oil. Vapor phase chromatography indicated the presence of two products in a ratio of 0.89 to 1. The first product eluted (10.0 cm from the air peak) had a retention time identical with that of the minor component obtained by catalytic reduction of *trans*-1,2-diphenylcyclopropane:[20] ν_{max}^{neat} 693, 730, 755, 1011, 1027, 1066, 1374, 1451, 1494, 1600, 2930, 2965, 3032, 3063, 3093 cm^{-1}. It was tentatively identified as 1,2-diphenylpropane.

The second product eluted (15.3 cm from the air peak) was identified as 1,3-diphenylpropane (X): ν_{max}^{neat} 693, 740, 901, 1028, 1081, 1452, 1495, 1602, 2862, 2940, 3035, 3070, 3092 cm^{-1}. Its retention time and its infrared spectrum were identical with that of an authentic sample of 1,3-diphenylpropane (X) prepared by the hydrogenation of *trans*-diphenylcyclopropane.[15,16] Similar results were obtained on desulfurization of *rac*-bis(*cis*-1,2-diphenylcyclopropyl) disulfide (VII).

(20) B. A. Kazanskii, M. Yu. Lukina, and I. L. Safonova, *Dokl. Akad. Nauk SSSR*, **130**, 332 (1960).

Registry No.—I, 24605-73-0; II, 22601-50-9; IV, 30256-27-0; V, 30256-28-1; VI, 30256-29-2; VII, 30256-30-5; VIII, 30256-31-6; IXb, 30256-32-7.

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Notes

Thietanes. V. Products Formed *via* Dimerization of *trans*-2,4-Diphenylthietane

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In our previous publications on 2,4-diphenylthietanes, their monoxides, and dioxides,[1] we have described rearrangements that could be formulated readily as modified Stevens rearrangements. Here, we describe the preparation, isolation, and proof of structure of products whose formation can only be explained by complex and multiple reactions.

Treatment of *trans*-2,4-diphenylthietane (I) with potassium *tert*-butoxide in dimethylformamide yielded a dark brown viscous oil that showed bands in its ir spectrum corresponding to carbonyl (1682 cm^{-1}) and thiol (2535 cm^{-1}) groups. Thin layer chromatography of this material indicated the presence of nine different products. By chromatography on silica gel, four of these products have been separated and identified. An additional three products have been isolated but, because of the very small quantity obtained, have not as yet been identified.

The first product obtained from this reaction was easily identified as 2,3,5-triphenylthiophene (II), mp 141–142°. The structure of the compound was established (1) from its analysis, (2) from the presence in its ir spectrum of bands characteristic of phenylthiophenes (694, 754, 844, 913, 1071, 3070, and 3090 cm^{-1}),[2] and (3) from its mass spectrum which indicated a molecular weight of 312 and a molecular formula of $C_{22}H_{16}S$ However, previous reports on 2,3,5-triphenylthiophene gave melting points of 127[3] and 198°.[4] The synthesis of Smith[3] was repeated. Reaction of 1,2,4-triphenylbutane-1,4-dione with phosphorus pentasulfide yielded, after chromatography and repeated crystallizations, 2,3,5-triphenylthiophene (II), mp 143.5–144°, identical with that obtained above.

Next 1,2,4,5-tetraphenylbenzene (III), mp 267–267.5°, was isolated. Its structure was established by direct comparison (mixture melting point and ir spectra) with a sample of 1,2,4,5-tetraphenylbenzene prepared by the reaction of diphenylacetylene with 3,4-diphenyl-4-hydroxycyclopent-2-enone.[5]

The fourth product eluted was benzylacetophenone (V) (1,3-diphenyl-1-propanone). This was identified by direct comparison with an authentic sample[6] prepared by the hydrogenation of benzalacetophenone.

The third product isolated was most unusual. Its analysis, molecular weight, and mp 143–145° corresponded with that of one of the bis(*cis*-1,2-diphenylcyclopropyl) disulfides previously reported.[1d] However, its ir, uv, and mass spectra differed entirely from that of the bis(*cis*-1,2-diphenylcyclopropyl) disulfide. The ir spectrum of the cyclopropyl disulfides showed no appreciable C–H stretching bands below 3000 cm^{-1}; the new compound showed absorption bands at 2920 and 2985 cm^{-1}. The uv spectrum of the cyclopropyl disulfides showed a maximum at 227.5 nm (ϵ 37,700); the uv spectrum of the new compound showed a maximum at 212 nm (ϵ 32,200). The most definitive comparison came from the mass spectra. The mass spectrum of the new compound showed a relatively intense molecular ion peak, 3.0% of the *m/e* 91 peak. It also showed strong peaks at *m/e* 382–386; *m/e* 386 corresponds to M − S_2. Strong

(1) (a) R. M. Dodson, E. H. Jancis, and G. Klose, *J. Org. Chem.*, **35**, 2520 (1970); (b) R. M. Dodson, P. D. Hammen, and R. A. Davis, *ibid.*, **36**, 2693 (1971); (c) R. M. Dodson, P. D. Hammen, E. H. Jancis, and G. Klose, *ibid.*, **36**, 2698 (1971); (d) R. M. Dodson, P. D. Hammen, and J. Yu Fan, *ibid.*, **36**, 2703 (1971).

(2) S. Gronowitz, A. R. Katritzky, and R. E. Reavill, *J. Chem. Soc.*, 3881 (1963); K. Nakanishi, "Infrared Absorption Spectroscpy," Holden Day, San Francisco, Calif., 1962, pp 26, 52.

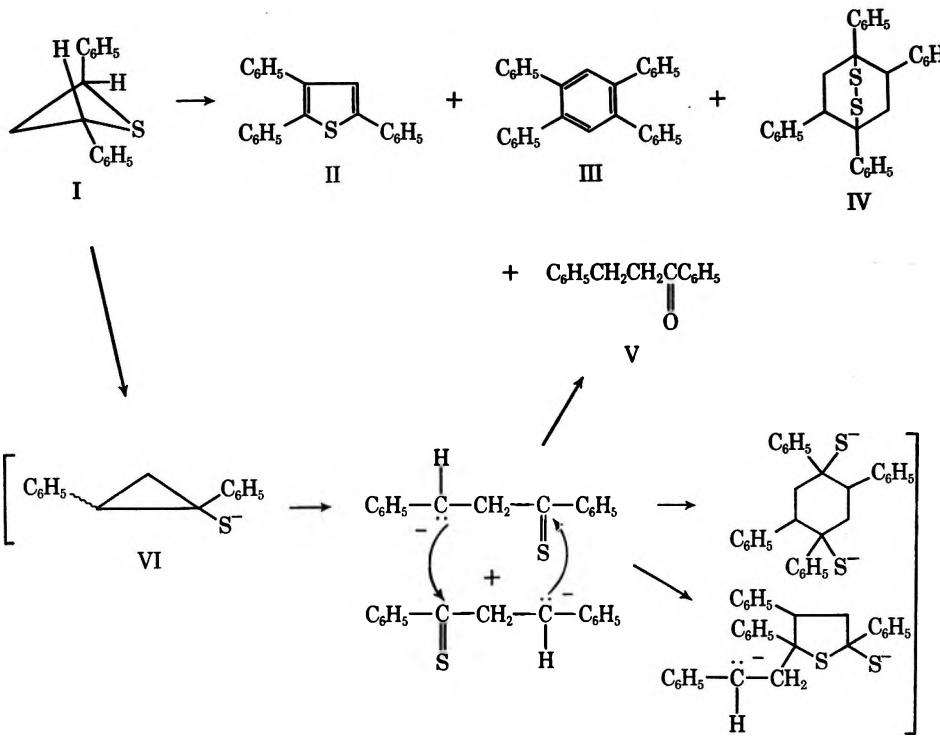
(3) A. Smith, *J. Chem. Soc.*, **57**, 643 (1890).

(4) S. K. Mitra, *J. Indian Chem. Soc.*, **15**, 59 (1938).

(5) W. Dilthey and G. Hurtig, *Ber. Deut. Chem. Ges.*, **67**, 2004 (1934); F. R. Japp and J. Knox, *J. Chem. Soc.*, **87**, 673 (1905).

(6) W. Schneidewind, *Ber. Deut. Chem. Ges.*, **21**, 1323 (1888); Yu. K. Yurév, Z. V. Belyakova, and V. P. Volkov, *Zh. Obshch. Khim.*, **28**, 2372 (1958) [*Chem. Abstr.*, **53**, 3135c (1959)].

SCHEME I



peaks at *m/e* 294 and 296 were also found; *m/e* 296 corresponds to M − S_2 − C_7H_6. A strong metastable peak at 331 corresponding to the loss of two atoms of sulfur from the molecular ion was present in one mass spectrum. On the basis of this evidence the structure of IV was tentatively postulated to be 1,4,5,7-tetraphenyl-2,3-dithiabicyclo[2.2.2]octane. Definitive proof of structure must await development of a method for obtaining the compound in larger amounts.

It seems reasonable that the initial product formed on treatment of *trans*-2,4-diphenylthietane (I) with potassium *tert*-butoxide was the potassium salt of the 1,2-diphenylcyclopropanethiol (VI). From this, formation of II, III, IV, and V *via* reactions outlined in Scheme I (plus hydrolysis or air oxidation) can be postulated. However, further discussion of the course of formation of these products must await far more extensive experimental work. It should be realized that IV is a valence bond isomer of *bis*-(1,2-diphenylcyclopropyl) disulfide.

Experimental Section[7]

Reaction of *trans*-2,4-Diphenylthietane (I) with Potassium *tert*-Butoxide.—A solution of *trans*-2,4-diphenylthietane[1a] (I) (11.2 g, 0.05 mol, mp 100–102°) and potassium *tert*-butoxide (15 g, 0.13 mol) in dimethylformamide[8] (200 ml) was stirred under nitrogen at 80° for 24 hr. The mixture was then added to ice–water (600 ml) and extracted with several portions of ether. The combined ether extracts were washed thoroughly with water and dried over magnesium sulfate. Evaporation of the ether solution yielded 10.0 g of a dark brown, highly viscous oil: ν_{max}^{neat} 1682 (s, $C_6H_5C{=}O$), 2535 cm^{-1} (w, SH); thin layer chromatography (silica gel; 85:15 petroleum ether–benzene) of this material indicated the presence of nine different products.

In an attempt to free this material from mercaptan, it was dissolved in ether and thoroughly extracted with 10% aqueous sodium hydroxide solution. After being washed and dried, the ether was evaporated. The 8.12 g of viscous material remaining still showed an ir band for the −SH group. Acidification of the initial and subsequent basic, aqueous extracts yielded 1.00 g of residue which was not furher investigated.

2,3,5-Triphenylthiophene (II).—A 4.0-g portion of the material from the ether extract was chromatographed on 160 g of silica gel (100–200 mesh). The column was successively eluted with petroleum ether and 10% benzene in petroleum ether. Elution with 15% benzene in petroleum ether yielded 50 mg of a white solid, mp 105–110°. Crystallization from petroleum ether yielded pure 2,3,5-triphenylthiophene: mp 141–142°; $\lambda_{max}^{ethanol}$ 262 nm (ε 20,500), 320 (16,800); ν_{max}^{KBr} 694, 754, 844, 913, 1030, 1071, 1449, 1487, 1600, 3035, 3070, and 3090 cm^{-1}; mass spectrum M^+ and base peak 312 [Calcd: (M + 1)/M = 24.8%; (M + 2)/M = 7.1%. Found: M + 1/M = 26%; M + 2/M = 7.6%], 311 (10.6% B) (M − 1H), 310 (8.8% B) (M − 2H), 309 (4.0% B) (M − 3H), 278 (6.0% B) (M − H_2S), 236 (3.7% B) (M − C_6H_4), 235 (2.7% B) (M − C_6H_5), 234 (5.3% B) (M − C_6H_6), 191 (4.2% B) (M − C_6H_5CS), 121 (8.0% B) (C_6H_5CS). This material was identical (melting point, mixture melting point, and uv and ir spectra) with 2,3,5-triphenylthiophene, mp 143.5–144°, prepared by the method of Smith.[3]

Anal. Calcd for $C_{22}H_{16}S$ (312.43): C, 84.58; H, 5.16. Found: C, 84.46; H, 5.15.

1,2,4,5-Tetraphenylbenzene (III).—Further elution of the column with 15% benzene in petroleum ether yielded 56 mg of a light yellow solid, mp 210–250°. Crystallization from benzene–petroleum ether yielded 1,2,4,5-tetraphenylbenzene (III): mp 267–267.5°; $\lambda_{max}^{ethanol}$ 248 nm (ε 56,800), shoulder at 280 (21,800); ν_{max}^{KBr} 696, 732, 754, 777, 844, 904, 914, 1000, 1014, 1020, 1076, 1162, 1182, 1384, 1450, 1480, 1502, 1580, 1602, 3035, 3075, and 3090 cm^{-1}. The compound was identical (melting point, mixture melting point, ir spectrum) with an authentic sample of 1,2,4,5-tetraphenylbenzene, mp 271–272°, prepared by the reaction of diphenylacetylene with 3,4-diphenyl-4-hydroxycyclopent-2-enone.[5]

1,4,5,7-Tetraphenyl-2,3-dithiabicyclo[2.2.2]octane (IV).—Elution of the column with 20% benzene in petroleum ether yielded no crystalline material. Elution with 25% benzene in petroleum ether gave 43 mg of 1,4,5,7-tetraphenyl-2,3-dithiabicyclo[2.2.2]-

(7) Melting points were taken on a Fisher-Johns melting point apparatus, calibrated against a set of standard compounds. The mass spectra were determined on a Consolidated 21-103C mass spectrometer equipped with an all-glass inlet or on a Hitachi Perkin-Elmer Model RMU-6D mass spectrometer. Petroleum ether refers to that fraction, bp 60–68°.

(8) Dried over potassium hydroxide pellets and then distilled, bp 153°.

TABLE I

MASS SPECTRUM OF IV[a]

m/e	Ion[+]	% of m/e 91	Remarks
450	$C_{30}H_{26}S_2$ (M)	3.0	$\frac{M+1}{M}$ = 34.4% (calcd 34.4%)
			$\frac{M+2}{M}$ = 16.4% (calcd 14.0%)
386	$M - S_2$	9.3	
385		18.8	
384		22.0	
383		6.9	
382		18.0	
331*	Metastable		$M^+ \rightarrow (M - S_2)^+$ (calcd 331.1)
296	$M - S_2 - C_7H_6$	36.4	
294	$M - S_2 - C_7H_8$	51.4	
205	$M - S_2 - (C_7H_6 + C_7H_7)$	57.5	
180	$C_6H_5CH{=}CHC_6H_5$	68.6	
128	$C_6H_5C_4H_3$	56.4	
121	C_6H_5CS	57.3	
115	$C_6H_5C_3H_2$	39.1	
91	C_7H_7	100.0 (B)	
78	C_6H_6	24.1	
77	C_6H_5	37.5	
44	CS	232	
34	H_2S	113.6	
33		50.9	
32		55.0	

[a] The strong metastable ion was found on an early spectrum taken on a Consolidated 21-103C mass spectrometer. That spectrum also showed a strong peak at m/e 312 (27.3% of m/e 91) corresponding to 2,3,5-triphenylthiophene, M + 1/M = 27.7%, M + 2/M = 7.9%.

octane (IV), mp 141–143°. Three crystallizations from petroleum ether yielded 19 mg of analytically pure IV: mp 143–145°; $\lambda_{max}^{ethanol}$ 212 nm (ε 32,200); ν_{max}^{KBr} 696, 733, 762, 773, 909, 948, 1031, 1083, 1154, 1183, 1209, 1251, 1267, 1297–1308 (broad), 1449, 1454, 1496, 1586, 1602, 2920, 2985, 3033, and 3070 cm^{-1}.

Anal. Calcd for $C_{30}H_{26}S_2$ (450.67): C, 79.96; H, 5.82. Found: C, 79.72; H, 6.19.

1,4,5,7-Tetraphenyl-2,3-dithiabicyclo[2.2.2]octane (IV), mp 140–145°, was also obtained in low yield from an ether solution of *cis*-1,2-diphenylcyclopropanethiol[1d] that had been allowed to stand at room temperature for 59 days. Isolation was accomplished by chromatography on silica gel and purification by crystallization from petroleum ether (see Table I).

1,3-Diphenyl-1-propanone (V).—Successive elution of the column with 30:70, 35:65, and 40:60 benzene–petroleum ether yielded no crystalline materials. Elution with 75:25 benzene–petroleum ether gave 1.0 g of a viscous yellow oil. Thin layer chromatography showed that this material was a mixture of six components. Further elution with 75:25 benzene–petroleum ether yielded 15 mg of 1,3-diphenyl-1-propanone, mp 60–70°. Crystallization from petroleum ether gave pure V, mp 70–71°. A mixture with an authentic sample, mp 71–72°, of V showed no depression in melting point. The 2,4-dinitrophenylhydrazone had mp and mmp 184–187°.

2,3,5-Triphenylthiophene (II).—The method of Smith[3] was duplicated. The crude product, mp 90–100°, was purified by chromatography on silica gel and elution with petroleum ether. The chromatographed product, mp 127–132°, was further purified by repeated crystallizations from petroleum ether. The purified 2,3,5-triphenylthiophene (II), mp 143.5–144°, was identical in all respects (melting point, mixture melting point, and uv and ir spectra) with that isolated from the reaction of *trans*-2,4-diphenylthietane (I) with potassium *tert*-butoxide. Reported melting points are 127[3] and 198°.[4]

Registry No.—I, 24609-88-9; II, 20851-07-4; III, 3383-32-2; IV, 30158-27-1; V, 1083-30-3.

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Concerning Internal Rotation in Diarylalkynes

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In diarylalkynes the question arises concerning the relative orientation of the two aromatic rings. One possibility is that the p orbitals of both aromatic rings overlap the same set of p orbitals of the alkyne. This leads to the planar geometry illustrated in Figure 1. A second possibility is that the π system of one aromatic ring overlaps one set of p orbitals of the alkyne while that of the second aromatic ring overlaps the other. This results in the perpendicular geometry shown in Figure 2. A third possibility is that no single orientation is preferred and that, due to the cylindrical symmetry of the alkyne, a freely rotating system occurs; see Figure 3.

In the freely rotating case, the system must pass through both the coplanar and the perpendicular geometries, and the internal rotation is truly free only if these two have the same energy. Thus the problem reduces to finding the energies of the coplanar and perpendicular forms of the diarylalkyne. If one form has a lower energy, the molecule exists in that geometry. If the two forms have the same energy, a freely rotating

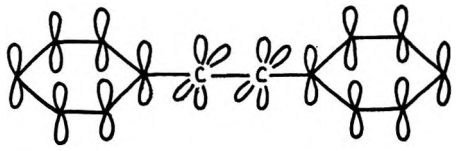


Figure 1.—Coplanar form of diphenylacetylene.

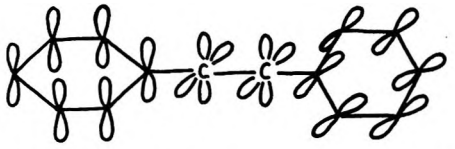
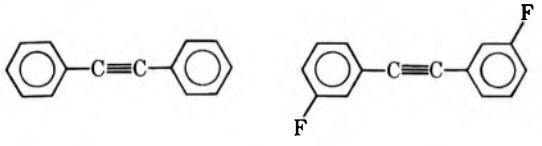


Figure 2.—Perpendicular form of diphenylacetylene.

species occurs. Possible reaction coordinates are given in Figure 4, where θ is the dihedral angle.

Quantum mechanical calculations were carried out to investigate these possibilities. Since in all conformations the σ system of the aromatic rings interacts with at least one of the π systems of the alkyne, it was thought unwise to do a simple π-electron calculation. Instead the CNDO and INDO methods of Pople were used.[1-3] These methods look at all the valence electrons.

The CNDO results for rotational problems have been discussed by Pople and Segal who performed calculations on ethane, methanol, and methylamine.[2] Their calculations show that in all three cases the staggered form has a lower energy than the eclipsed, the barriers being 1.79 kcal/mol, 0.67 kcal/mol, and 1.21 kcal/mol, respectively. The experimental values are 3.0 kcal/mol,[4] 1.07 kcal/mol,[5] and 1.98 kcal/mol.[5] It appears that the CNDO approach gives excellent results for rotational problems. Calculations were performed on diphenylacetylene (1) and on bis(3′-fluorophenyl)-acetylene (2).



1 2

Robertson and Woodward[6] have made an X-ray crystallographic study on 1, and their bond distances and bond angles were used in the calculations. Their values are given in Figure 5.

The carbon–hydrogen distance used was 1.09 Å, the value found in benzene, while for 2, the carbon–fluorine distance was 1.30 Å, the value in fluorobenzene. The nuclear coordinates were obtained for the different geometries by rotating one of the aromatic rings through the required angle. The results are presented in Tables I and II. The energy is in hartrees (h). For 2, the calculated dipole moments, which are also presented, are in excellent agreement with the values obtained by vectorial addition of group moments.

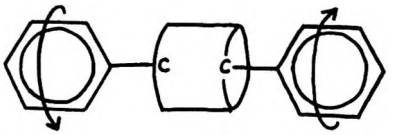


Figure 3.—Freely rotating form of diphenylacetylene.

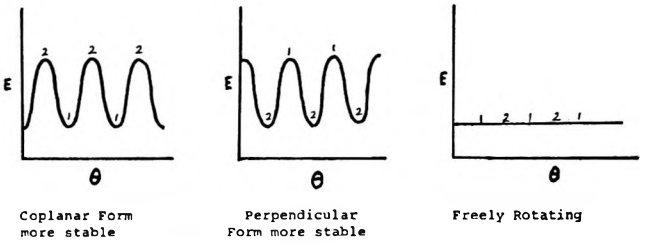


Figure 4.—Reaction coordinates for the internal rotation of diarylalkynes.

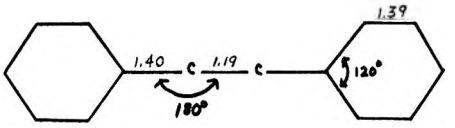


Figure 5.—Bond distances and bond angles in diphenylacetylene.

TABLE I

ENERGY OF DIPHENYLACETYLENE AS A FUNCTION OF THE DIHEDRAL ANGLE

θ, deg	CNDO, −E	INDO, −E
0	106.7907	103.2269
45	106.7914	103.2274
90	106.7918	103.2275

TABLE II

ENERGY AND DIPOLE MOMENT OF BIS(3′-FLUOROPHENYL)ACETYLENE AS A FUNCTION OF THE DIHEDRAL ANGLE

		CNDO		INDO	
	θ, deg	−E	μ	−E	μ
Cis coplanar	0	160.7563	2.6 D	154.5744	2.7 D
	90	160.7588	1.9 D	154.5764	1.9 D
Trans coplanar	180	160.7564	0.0 D	154.5745	0.0 D

For the unsubstituted diarylalkyne the barrier to internal rotation is calculated to be 0.0011 h (0.7 kcal/mol) by the CNDO method and 0.0006 h (0.4 kcal/mol) by the INDO method. The two methods are certainly not this accurate; therefore, both can be said to predict a system with virtual free internal rotation. For the difluoro-substituted compound, both approaches predict the perpendicular form to be slightly more stable. The barrier by way of the trans-coplanar transition state is calculated to be 0.0024 h (1.5 kcal/mol) from the CNDO method and 0.0019 h (1.2 kcal/mol) by the INDO method. Again, the barrier is predicted to be quite small.

It is worthwhile to note that the energy of the valence electrons is in all cases calculated to be lower in the coplanar form. It is the core–core repulsions that decrease in passing to the perpendicular geometry, and this decrease compensates almost exactly for the

(1) J. A. Pople, D. P. Santry, and G. A. Segal, *J. Chem. Phys.*, **43**, S129 (1965).

(2) J. A. Pople and G. A. Segal, *ibid.*, **43**, S136 (1965).

(3) The program used in these calculations was 141 CNINDO-CNDO and INDO Molecular Orbital Program, L. George, July 22, 1969. The values assigned to the various parameters that occur in the calculations were those in the original program. No values were changed. See also, J. A. Pople and D. L. Beveridge, "Approximate Molecular Theory," McGraw-Hill, New York, N. Y., 1970.

(4) D. R. Lide, *J. Chem. Phys.*, **29**, 1426 (1958).

(5) C. C. Lin and J. D. Swalen, *Rev. Mod. Phys.*, **31**, 841 (1959).

(6) J. M. Robertson and I. Woodward, *Proc. Roy. Soc., Ser. A*, **164**, 436 (1938).

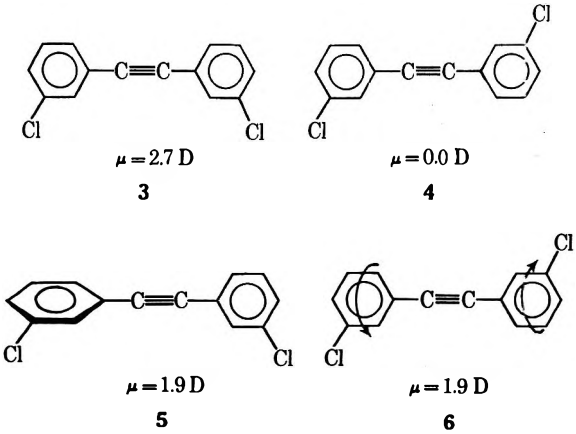
increase in valence-electronic energy. The calculated barriers are small differences between large numbers.

Fortunately, it is possible to obtain experimental evidence for the geometry of diarylalkynes. An X-ray crystallographic study has been made by Robertson and Woodward[6] on diphenylacetylene itself, and the results of this study indicate that the molecule exists in the coplanar geometry with D_{2h} symmetry.[7]

One can, of course, argue that in the solid state lattice packing plays a large role and alters the preferred geometry of the molecule. Certainly, data on the geometry of the molecule in solution are to be preferred. With this end in mind, the ultraviolet spectrum of diphenylacetylene was compared with those of phenylacetylene and *cis*- and *trans*-stilbene.

If diphenylacetylene exists in the coplanar form in solution, the chromophore in the near ultraviolet is stilbene-like; see Figure 1. Whereas, if it exists in the perpendicular form, the chromophore is roughly that of two phenylacetylene units (Figure 2). Now the λ_{max} for phenylacetylene occurs at 235 mμ, while those of *cis*- and *trans*-stilbene occur at 280 and 295 mμ, respectively.[8] The spectrum of diphenylacetylene exhibits no peaks between 230 and 260 mμ. A number of peaks are found above 264 mμ with the major ones appearing at 279 and 295 mμ. The chromophore in diphenylacetylene certainly absorbs in the stilbene region, and the spectrum has no peaks at all in the region where phenylacetylene absorbs. Therefore, one may conclude from the ultraviolet data that diphenylacetylene is also coplanar in solution.

A final set of experiments used to find the geometry in solution was the determination of the dipole moment of bis(3′-chlorophenyl)acetylene. This molecule can exist in the cis-coplanar form **3**, the trans-coplanar form **4**, the perpendicular form **5**, or the freely rotating form **6**. The dipole moment in geometries **3**, **4**, and **5** was calculated by the method of vectorial addition of group moments. The dipole moment for the freely rotating case is the root mean square moment, determined by integrating over all values of the dihedral angle.[9]



This compound was prepared according to the method of C. D. Weis,[10] and the dipole moment was determined at 20° by measuring the dielectric constants of a series of solutions of the alkyne in carbon tetrachloride.

It is necessary to determine the polarization of the alkyne at infinite dilution and since a direct extrapolation can lead to error, we decided to use an analytic method derived by Hedestrand.[11] The value found in this way was substituted into the Debye equation. The molar refraction of the alkyne was determined by a similar equation, and the value was used to approximate the induced polarization. The dipole moment was calculated to be 1.7 ± 0.1 D. This value does not correspond to any of those just presented but can be explained by assuming that bis(3′-chlorophenyl)acetylene exists in solution in more than a single geometry. The low experimental value of the dipole moment requires, however, that one of the components of the mixture be the trans-coplanar form **4**. We know that some of the molecules must exist in the coplanar form. It is then reasonable to assume that all of them do and that the other component is the cis form **3**. Thus, the dipole moment of the molecule also indicates a coplanar geometry for diarylalkynes.

To summarize, it was found that quantum mechanical calculations, the CNDO and INDO methods, predicted that diarylalkynes existed either with relatively unhindered rotation or with the perpendicular geometry being slightly more stable, approximately 1 kcal/mol. Experimental evidence, on the other hand, does not support these predictions. Three different experimental results indicate a coplanar geometry for diarylalkynes. An X-ray diffraction study showed diphenylacetylene to be coplanar in the solid state while uv spectra afford a similar result for the molecule in solution. The dipole moment of a dichloro derivative seems to confirm the experimental findings.

Experimental Section

The dipole moment of bis(3′-chlorophenyl)acetylene was evaluated at 20° by the method of Hedestrand.[11] According to this method, the dielectric constants and the densities of the solutions are plotted against the mole fractions of the solute. The equations are $\epsilon_s = \epsilon_1 + aX_2$ and $d_s = d_1 + bX_2$. The slopes of the lines, a and b, are substituted into the equation

$$P_2^0 = \frac{\epsilon_1 - 1}{\epsilon_1 + 2}\frac{1}{d_1}\left(M_2 - \frac{M_1 b}{d_1}\right) + \frac{3M_1 a}{(\epsilon_1 + 2)^2 d_1}$$

The subscripts s, 1, and 2 refer to solution, solvent, and solute, respectively.

The value of P_2^0, calculated in this way, is substituted into the equation

$$P_2^0 = \frac{4\pi N\mu^2}{9kT} + R_2^0$$

where R_2^0 is determined by substituting the square of the refractive index n^2 for ϵ in the above equation. The value of a is determined by plotting n_s^2 against X_2. A plot of n_s against X_2 may also be used. The value of a is then twice this slope multiplied by the refractive index of the solvent.

TABLE III

$X_2 \times 10^2$	2.437	3.283	4.060	4.922	5.814	CCl_4
ϵ_s	2.357	2.400	2.436	2.474	2.514	2.239
d_s	1.576	1.574	1.573	1.566	1.560	1.594
$X_2 \times 10^2$	0.218	0.460	0.676	0.863	1.010	CCl_4
n_s	1.4602	1.4612	1.4622	1.4631	1.4637	1.4592

(7) "Tables of Interatomic Distances, and Configurations in Molecules and Ions," The Chemical Society, London, 1958, p M239.

(8) G. Riezebos and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, **80**, 446 (1961).

(9) J. W. Williams, *Z. Phys. Chem.*, **138**, 75 (1938).

(10) C. D. Weis, *Helv. Chim. Acta*, **49**, 234 (1966).

(11) G. Hedestrand, *Z. Phys. Chem.*, **2**, 428 (1929).

Capacitance measurements were made on a General Radio Model 1620-A capacitance measuring assembly, and refractive indexes were determined using a Brice-Phoenix differential refractometer.

Registry No.—1, 501-65-5; 2, 23349-16-8; bis-(3′-chlorophenyl)acetylene, 5216-30-8.

Acknowledgments.—The authors are indebted to Dr. E. Wagner, Department of Chemistry, Washington State University, for helpful discussions, and to the Schering Corporation and to the Department of Chemistry, Upsala College, for use of their facilities.

The Reaction of Propargyl Alcohols with Halogen Donors. A Novel Phosphorus–Oxygen Heterocycle

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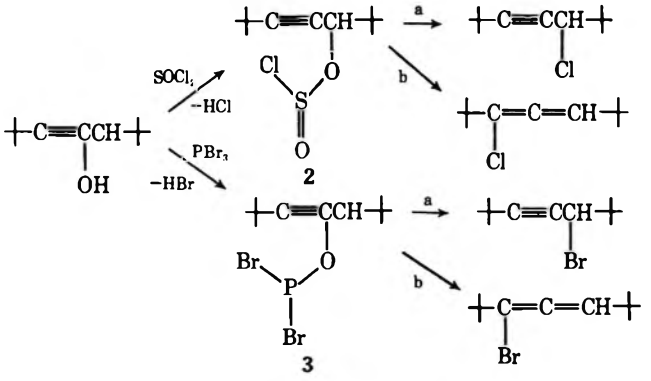
Received March 9, 1971

Out attempts to synthesize 1,3-di-*tert*-butyl-1-haloallenes have included an investigation of the reactions of 1,3-di-*tert*-butylpropargyl alcohol (**1**)[1] with halogen donors such as thionyl chloride and phosphorus tribromide. It is generally believed that reactions of alcohols with these reagents involve intermediate formation of the derived inorganic "ester" (*e.g.*, **2** or **3**), which then undergoes intra- or intermolecular attack by halide yielding the substitution product.[2,3] In the case of propargyl alcohols, two pathways are open to the "ester" intermediate: (a) SNi (or SN2) attack at the leaving-group-bearing atom to yield propargyl halide, and (b) SNi′ (or SN2′) attack at C_3 leading to allenic halide.[4]



The reaction of **1** with thionyl chloride led, in 81% yield, to a mixture of the propargyl and allenic chlorides in the ratio 3:1. When **1** was allowed to react with phosphorus tribromide, the expected mixture of propargyl and allenic bromides was obtained (ratio 17:3) in a crude yield of 80%. In addition, however, a significant (*vide infra*) amount of a crystalline solid **4**, separable from the liquid bromide product mixture by centrifugation or filtration, was isolated. Compound **4** was purified by recrystallization and sublimation to give stable, colorless crystals, mp 133.2–134.4°. This material reacted rapidly with alcoholic silver nitrate to yield silver bromide. Although it reacted fairly rapidly with aqueous potassium permanganate, **4** reacted only slowly with bromine in carbon tetrachloride at room temperature. The compound was highly soluble in chloroform and methanol, moderately soluble in heptane and ether, and insoluble (*vide infra*) in water.

The mass spectrum of **4** (Table I) confirmed the presence of bromine with pairs of peaks at *m/e* 281, 279; 240, 238; and 225, 223; A relatively intense peak at *m/e* 215 *not* containing bromine suggested parent masses of 294 and 296, and, although these could not be discerned from background, a pair of peaks at *m/e* 295, 297 (M + 1) was observed.[5] The parent masses correspond to a molecular formula $C_{11}H_{20}O_2PBr$, which was confirmed by elemental analysis (see Experimental Section).

TABLE I
PARTIAL 30-eV MASS SPECTRUM OF 4

m/e	Abundance, %	Assignment
297	2	M + H
295	2	
281	7	M − CH_3
279	7	
240	99	M − C_4H_8
238[a]	100	
225	90	M − (C_4H_8 + CH_3)
223	91	
215	73	M − Br
159	60	M − (C_4H_8 + Br)
57	72	$C_4H_9^+$

[a] Base peak.

The infrared spectrum of **4** (chloroform solution) showed weak but sharp absorptions at 3005 (=CH), 1615 (C=C), and 1194 cm^{-1} (P–O–C)[6] and additional intense absorptions at 2960, 1480, 1370, 1310, 1275, 1250, 1073, 1012, 963, 907, 870, 847, 650, 611, 523, and 400 cm^{-1}. Of these, the strongest band at 1250 cm^{-1} could be assigned to P=O.[7] The ultraviolet spectrum (in pentane solution) exhibited relatively intense end absorption extending to 240 nm, with an apparent shoulder at 205 nm (log ϵ 3.90).

The nuclear magnetic resonance spectra (^1H and ^{31}P) were quite interesting. The 90-MHz proton spectrum (deuteriochloroform solution, internal TMS) contained δ 1.03 (s, 9 H), 1.37 (s, 9 H), 4.87 (d of d, J_{P-H_1} = 5.5, $J_{H_1-H_2}$ = 1.8 Hz, 1 H), 6.69 (d of d, J_{P-H_2} = 56.5 Hz, $J_{H_2-H_1}$ = 1.8 Hz, 1 H). Irradiation of the absorption centered at δ 4.87 (H_1) caused the δ 6.69 absorption (H_2) to collapse to a doublet (J_{P-H_2} = 56.5 Hz), confirming the proton-proton coupling scheme. The ^{31}P

(1) (a) W. T. Borden and E. J. Corey, *Tetrahedron Lett.*, 313 (1969); (b) R. S. Macomber, *ibid.*, 4639 (1970).

(2) J. March, "Advanced Organic Chemistry," McGraw-Hill, New York, N. Y., 1968.

(3) While thionyl chloride generally reacts with an equimolar amount of alcohol, each mole of phosphorus trihalide reacts with 3 mol of alcohol.

(4) For example, see R. J. D. Evans, S. R. Landor, and R. T. Smith, *J. Chem. Soc.*, 1506 (1963).

(5) The appearance of M + 1 peaks where parent ions are absent is not without precedent, especially in oxygenated systems: J. H. Beynon, "Mass Spectrometry and its Application to Organic Chemistry," Elsevier Publishing Co., New York, N. Y., 1960.

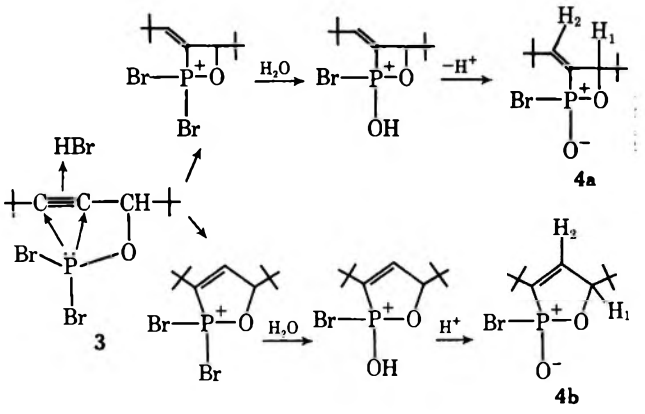
(6) M. M. Crutchfield, C. H. Dungan, J. H. Letcher, V. Mark, and J. R. Van Wazer, *Top. Phosphorus Chem.*, **5**, 317 (1967).

(7) K. Nakanishi, "Infrared Absorption Spectroscopy," Holden-Day, San Francisco, Calif., 1962.

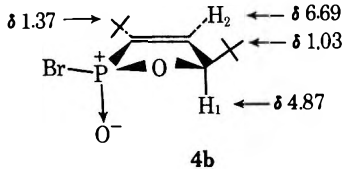
spectrum (36.43 MHz) showed the expected doublet of doublets, $J_{P-H_2} = 56.5$, $J_{P-H_1} = 5.5$ Hz. The absorption was centered at δ −34.0 (with reference to 85% phosphoric acid), which falls squarely in the range of chemical shifts for compounds of the type OPXR(OZ).[6]

At this point, two structures (**4a** and **4b**), both quite unusual among phosphorus–oxygen heterocycles,[8,9] emerge as mechanistically rational alternatives to the analytical data (see Scheme I). At present we prefer

SCHEME I



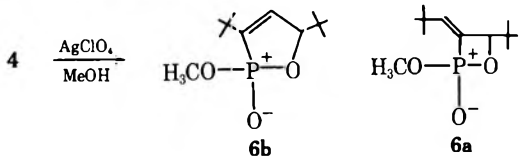
structure **4b** (2-bromo-3,5-di-*tert*-butyl-1,2-oxaphosphol-3-ene 2-oxide) for three reasons: (1) the P–H_1 coupling constant in **4** (5.5 Hz) seems too small[10] for structure **4a**, which would have both a P–O–C–H_2 and a P–C–C–H_2 contribution; (2) **4a**, reminiscent of the intermediate in a Wittig reaction, should perhaps be unstable with respect to fragmentation to yield di-*tert*-butylallene,[12] yet the peak at *m/e* 152 in the mass spectrum of **4** (Table I) is only 1% of the base peak; and (3) **4b** should suffer less angle strain than **4a**, and



4b

thus should predominate under the acid-catalyzed conditions. The low value of the H–H coupling constant in **4b** can be rationalized after construction of an accurately scaled model, by the nearly 90° dihedral angle.[13]

One feature of **4** that deserves further comment is the unusual lack of reactivity of the P–Br bond. Compound **4** was insoluble in water (*vide supra*) and unreactive enough to survive aqueous work-up (see Experimental Section). Only in boiling water was the bromine hydrolytically removed.[14] Confirmation that the bromine is indeed attached to phosphorus was obtained by the treatment of **4** with an equimolar amount of silver perchlorate in methanol. The reaction proceeded quantitatively to yield a new product **6** in which a methoxy group was substituted for the bromine. Although the infrared spectrum of **6** was very similar to that of **4**, the 90-MHz pmr spectrum showed, in addition to absorptions similar to those of **4**, a three-proton *doublet* centered at δ 3.70, $J_{POCH} = 12$ Hz.[10] Provided **4** is indeed **4b**, then **6** must be **6b**, not **6a**.

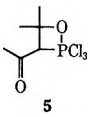


The reluctance of the P–Br to hydrolyze under mild conditions may reflect the unfavorability of an associative hydrolysis mechanism in hindered small-ring phosphorus halides.[15,16]

The molecular formula of **4** allows yield calculations to be made. The crude yield of **4** from the original reaction (*vide supra*) was 15%, and this led to a 5% overall yield of analytically pure **4**. Of the various conditions tried, the maximum yield of pure **4** (10%) was realized from the reaction of **1** with an equimolar amount of phosphorus tribromide in chloroform at room temperature.

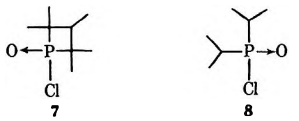
The ability of this ring closure to compete with bromide substitution undoubtedly arises from the neopentyl character of C_1 and C_3 in **1**, which inhibits formation of the usual 3:1 intermediate[3] and sterically hinders attack by bromine. The appearance of such a phosphorus-containing cyclic product is further compelling evidence for the intermediacy of inorganic "ester" **3** under these conditions.[17]

(14) This observation may not be surprising in light of the report[8] that the third chlorine in what is believed to be **5** was removed only upon treatment with boiling aqueous silver nitrate.



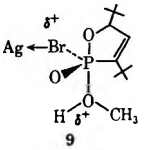
5

(15) Compound **7** has been found to solvolyze *ca.* 6.5 × 10^{-4} times as fast as **8**: P. Haake and P. S. Ossip, *Tetrahedron Lett.*, 4841 (1970).



7 **8**

(16) We thank a referee for pointing out that this reluctance may be regarded as another example of the preference rules which help rationalize the inability of the assumed trigonal-bipyramidal intermediate (**9**) of the



9

associative solvolysis mechanism to undergo pseudorotation to place the AgBr leaving group in an apical position: F. H. Westheimer, *Accounts Chem. Res.*, **1**, 70 (1968).

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(13) Apparently only one epimer at phosphorus was isolated; however, an absolute selection cannot yet be made.

We are presently exploring the syntheses and properties of these and related compounds.

Experimental Section

The following instruments were employed for spectral determinations: nmr, Bruker HFX and Varian A-60; mass spectrum, Hitachi RMU-7; uv, Cary 14; ir, Perkin-Elmer 337. Melting points were measured with an oil bath and are uncorrected. Gas–liquid chromatography was carried out on a Hewlett–Packard 700 fitted with a 10 ft × 1/8 in. column packed with 12% Squalane on 80–100 Chromosorb W, AWDMSC; separation parameters: column temperature, 100°; injection block temperature, 135°; carrier gas flow rate 30 cm³/min. The microanalysis was performed by Chemalytics, Inc.

1,3-Di-*tert*-butylpropargyl Alcohol (1).—The procedure of Corey and Borden[1a] was used to give **1**: mp 38.5–40.0°;[1b] ir (carbon tetrachloride solution) 3480, 2970, 2260 cm^{-1}; pmr (carbon tetrachloride solution, internal TMS) δ 0.95 (s, 9 H), 1.22 (s, 9 H), 2.21 (s, 1 H), 4.07 (s, 1 H).

Reaction of 1 with Thionyl Chloride.—To a vented flask containing 168 mg (1.0 mmol) of **1** and protected from moisture was added, *via* syringe, 145 mg (1.2 mmol) of thionyl chloride, and the resulting mixture was stirred for 15 hr at 25°. Ether (5 ml) was added, and the solution was washed with three 1-ml portions of saturated aqueous sodium chloride solution. The ether solution was dried over molecular sieves, and then the solvent was removed, leaving 150 mg (81%) of a liquid mixture of the propargyl chloride (retention time 3.8 min) and the allenic chloride (retention time 4.2 min) in the ratio 74:26. A pmr spectrum (carbon tetrachloride solution, internal TMS) of the mixture yielded the following: 1,3-di-*tert*-butylpropargyl chloride, δ 1.13 (s, 9 H), 1.30 (s, 9 H), 4.44 (s, 1 H); di-*tert*-butylchloroallene, δ 1.14 (s), 1.28 (s), 5.70 (s).

Reaction of 1 with Phosphorus Tribromide, Neat.—Using a procedure exactly analogous to the above, 1.68 g (10 mmol) of **1** was allowed to react with 1.22 g (4.5 mmol) of phosphorus tribromide for 17 hr at 25°. Work-up as before left 2.22 g of an oil containing finely divided crystalline material constituting about one-fifth of the total volume. The mixture was transferred to a Craig tube and cooled to −20° overnight to cause precipitation of any of the solid still in solution. Centrifugation effectively separated the oil from the moist solid (*vide infra*).

The oil (1.85 g, 80%) was found to be a mixture of the propargyl bromide (retention time 5.95 min) and the allenic bromide (retention time 6.60 min) in the ratio 17:3. A pmr spectrum (carbon tetrachloride solution, internal TMS) showed the following: 1,3-di-*tert*-butylpropargyl bromide, δ 1.16 (s, 9 H), 1.30 (s, 9 H), 4.52 (s, 1 H); 1-bromo-1,3-di-*tert*-butylallene, δ 1.13 (s, 9 H), 1.22 (s, 9 H), 5.44 (s, 1 H). The mixture of bromides distilled at 60–63° (3.5 mm), with enrichment of the allenic isomer. The fact that the allenic isomer is indeed thermodynamically favored was confirmed by the observation that a 95% pure sample of the propargyl bromide (isolated by preparative glpc) was transformed into a 48:52 mixture (propargyl:allenic bromide) after 48 hr at 83°.

Isolation of Phosphorus Heterocycle 4.—The above moist solid (350 mg), which seemed to react with metallic surfaces (*e.g.*, spatulas), was recrystallized from heptane–chloroform (3:1 *v/v*), then sublimed at 75° (0.15 mm) to yield stable, colorless, amorphous crystals (115 mg, 5% overall), mp 133.2–134.4°. Once purified, the compound is stable indefinitely if kept dry. Exposure to moist air appears to slowly (over weeks) hydrolyze the bromide. The various spectra of **4** are given in the text.

Anal. Calcd for $C_{11}H_{20}O_2PBr$: C, 44.76; H, 6.83; P, 10.49. Found: C, 44.88; H, 6.50; P, 10.66.

Reaction of 1 with Phosphorus Tribromide in Chloroform.—To a solution of 2.70 g (10 mmol) of phosphorus tribromide in 50 ml of chloroform under nitrogen was added dropwise a solution of 1.68 g (10 mmol) of **1** in 20 ml of chloroform. After stirring for 18.8 hr at 25°, the solution was washed twice with 10-ml portions of saturated sodium chloride solution and dried at 0° over molecular sieves. Removal of solvent left 2.54 g of product mixture, which gave 1.75 g of liquid bromide product mixture and 540 mg (20%) of **4**, which was purified as above to yield ~260 mg (10% overall) of analytically pure material.

Reaction of 4 with Silver Perchlorate in Methanol.—To a solution of 44.2 mg (0.15 mmol) of **4** in 1.0 ml of dry methanol was added a solution of 31.2 mg (0.15 mmol) of silver perchlorate (Caution!) in 1.0 ml of methanol, and the solution was stirred at 25° for 20 min. Precipitation of silver bromide began immediately upon addition. The mixture was centrifuged, and the supernatant was removed and saved. The silver bromide was washed with methanol (which was added to the supernatant) and dried to give 23.8 mg (84%). The methanol solution was rotary evaporated, and the residue was redissolved in 2 ml of ether and then dried over molecular sieves. Removal of solvent left 37 mg (99%) of a clear, colorless liquid with freezing point below −20°: ir (chloroform solution) 2970 (s), 1615 (w), 1470 (s), 1370 (m), 1310 (m), 1285 (w), 1250 (vs), 1060 (vs), 1020 (s), 980 (s), 915 (m), 880 (s), 860 (m), 835 (m), 665 cm^{-1} (m); pmr (deuteriochloroform solution, internal TMS) δ 0.99 (s, 9 H), 1.27 (s, 9 H), 3.70 (d, J_{POCH} = 12 Hz, 3 H), 4.32 (d of d, J_{PH_1} = 12, $J_{H_1H_2}$ = 1.7 Hz, 1 H), 6.59 (d of d, J_{PH_2} = 46.5, $J_{H_2H_1}$ = 1.7 Hz, 1 H).

Registry No.—**1**, 30338-48-8; **4b**, 30338-49-9; **6b**, 30338-50-2; thionyl chloride, 7719-09-7; phosphorus tribromide, 7789-60-8.

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Catalytic Dehydrogenation of Estr-4-en-3-ones

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The catalytic dehydrogenation of cyclic enones and diones has found extensive use in both synthesis and structure determination. Most such dehydrogenations are conducted at high temperatures and/or long reaction times.[1,2] During the study of the reactions of several steroids with unnatural stereochemistry[3,4] some unusually facile dehydrogenations were observed. Reasons for these high reactivities were explored.

The reaction of 17β-hydroxy-10α-estr-4-en-3-one[3] (**1**) with 5% palladium–carbon at 80° in ethanol for 2 min yielded approximately a 1:1 mixture of estradiol (**2**) and 17β-hydroxy-5α,10α-estran-3-one (**3**). Similarly, 17β-hydroxy-17α-methyl-9β-estr-4-en-3-one[4] (**4**) showed complete disappearance of the 243-nm wavelength chromophore in 2 min. On the other hand, neither the natural 9α,10β nor the 9β,10α series of estr-4-en-3-ones gave appreciable amounts of dehydrogenation products after 2 hr at these mild conditions. In the latter case, only traces of dehydrogenation material were observed even after 24 hr.

The two compounds which give ready dehydrogenation both contain 9,10 cis hydrogens, and it was attractive to propose that these hydrogens were removed catalytically to give intermediate estra-4,9(10)-dien-3-

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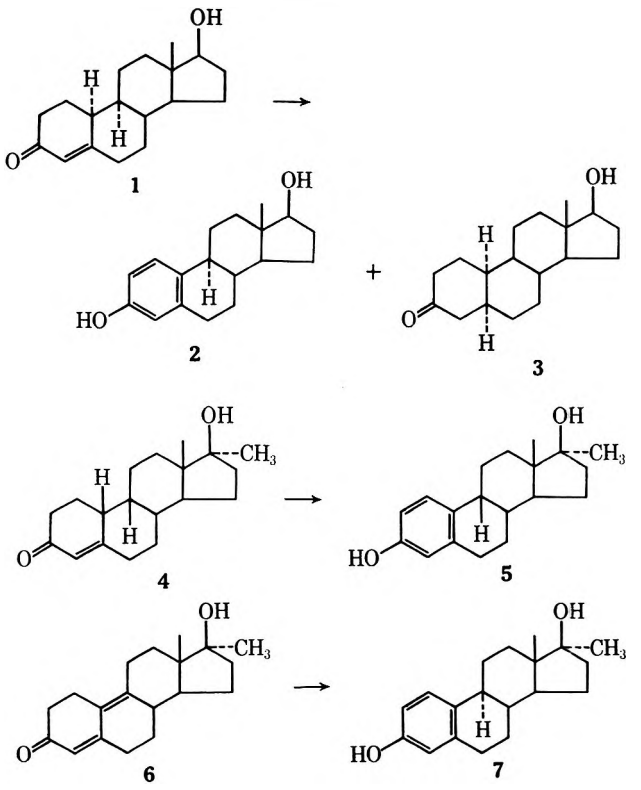
ones.[5] This class of compounds was reported to aromatize catalytically by isomerization of the double bond.[6] Thus, 17β-hydroxy-17α-methyl-estra-4,9(10)-dien-3-one (6) was treated using our mild dehydrogenation conditions; the isomerization proceeded considerably slower, but a good yield of 17α-methylestradiol was obtained after 0.5 hr of reaction.

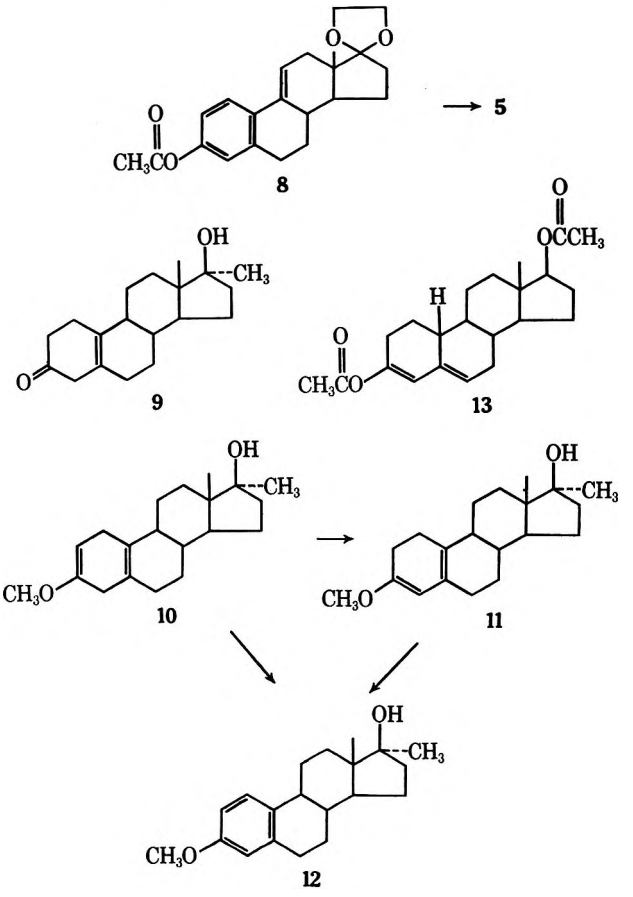


The dienone was eliminated as an intermediate in the dehydrogenation of the reactive enones when the aromatic product from the 9β,10β compound was examined. A 50% yield of 17α-methyl-9β-estradiol (**5**) was isolated on reaction of **4**; no trace of the 9α isomer was detected. The structural assignment of the 9β compound was made on the basis of its nmr spectrum, which showed the chemical shifts of the two methyl group protons at about δ 0.95. The 17α-methyl protons resonance is shifted upfield when compared with the same protons of the 9α isomer (δ 1.27) as expected, because the stereochemistry of the 9β isomer positions the 17α-methyl protons in the shielding cone of the aromatic A ring.

In order to confirm the structural assignment, **5** was synthesized *via* the reduction[7] of the ketal **8**.[8] After hydrolysis of the protective groups, the two isomers were separated, and the 9β-17-ketone was treated with methyl Grignard reagent to yield **5**.

Previous chemical studies[3,4] demonstrated the ease of enolization of the 9α,10α- and 9β,10β-estr-4-en-3-ones as evidenced by ready epimerization at C_{10}. In addition, in the 9β series the deconjugated 9β-estr-5(10)-en-3-one also formed easily *via* the enol. The deconjugated 17β-hydroxy-17α-methylestr-5(10)-en-3-one (**9**) was examined as a possible intermediate; only a small amount of aromatization was obtained after 4 hr under the standard dehydrogenation conditions.

In order to examine the approximate reactivity of the dienol in this reaction, dienol ethers **10** and **11**[9] were



allowed to react in order to determine the ease of dehydrogenation. A good yield of aromatic ether **12** was obtained in 0.75 hr from either compound. On the other hand, the heteroannular dienol acetate **13** showed no appreciable aromatization over a 4-hr period.

The results of these studies suggest that a homoannular dienol, either conjugated or unconjugated, stabilized by interaction with the catalyst is an intermediate in the dehydrogenation reaction. The 5(10)-en-3-one apparently does not readily enolize under these reaction conditions. The normal 9α,10β-estr-4-en-3-ones are known to yield the heteroannular dienol as the thermodynamic product;[10] there are also indications that this heteroannular dienol is also formed as the kinetic product.[11]

Experimental Section

Melting points are uncorrected. The uv spectra were obtained using a Cary 15 spectrophotometer. Nmr spectra were obtained using a Varian HA-60 spectrometer with TMS as the internal standard.

Dehydrogenation of 17β-Hydroxy-10α-estr-4-en-3-one (1).—In a small flask was placed 0.1 g of **1** in 15 ml of EtOH, and the solution was heated to 80°. After flushing well with N_2, 0.025 g of 5% Pd–C was added with vigorous stirring while maintaining the N_2 atmosphere. A small aliquot was removed after 2 min;

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no appreciable uv chromophore at 240 nm remained. The catalyst was filtered and the solvent was removed under vacuum. Nmr analysis of the residue confirmed the presence of two compounds as an approximate 1:1 mixture.

The residue (0.095 g) was chromatographed using 8 g of basic Al_2O_3. The fraction eluted with Et_2O was crystallized from hexane to give 0.036 g, mp 146–148°. Mixture melting point determination with an authentic sample of 17β-hydroxy-5α,10α-estran-3-one showed no depression. The fraction eluted with EtOAc was crystallized from hexane–$CHCl_3$ to give 0.052 g, mp 178–180°. Mixture melting point determination with an authentic estradiol sample again showed no depression. Both compounds gave nmr spectra identical with those of the authentic samples.

Dehydrogenation of 19-Nortestosterone.—Using the above procedure, 0.05 g of the compound was treated with 0.013 g of Pd–C. Occasionally a small aliquot was removed for monitoring by uv; after 4 hr no appreciable change in the uv maximum was noted. Tlc confirmed the presence of primarily starting material.

Dehydrogenation of 17β-Hydroxy-17α-methyl-9β,10α-estr-4-en-3-one.—Using the above procedure 0.04 g of the 9β,10α compound was treated with 0.010 g of 5% Pd–C. Monitoring the reaction by uv indicated no appreciable change from starting material. After 24 hr of reaction, still no appreciable change in uv was observed. The catalyst was filtered and the solvent was evaporated. Tlc of the residue revealed in addition to starting material only a trace of a more polar substance.

Dehydrogenation of 17β-Hydroxy-17α-methyl-9β,10β-estr-4-en-3-one (4).—Using the standard procedure 0.1 g of 4 was treated with 0.025 g of 5% Pd–C. Uv analysis after 5 min showed no starting material present. After filtration and removal of solvent, the residue was crystallized from isopropyl ether to give 0.050 g of 5: mp 215–216°; nmr ($CDCl_3$) δ 0.95 and 0.96 (s, 3 H each, C-17 and C-18 Me).

Anal. Calcd for $C_{19}H_{26}O_2$: C, 79.68; H, 9.15. Found: C, 79.43; H, 9.32.

17α-Methyl-9β-estradiol (5).—To a mixture of 0.3 g of 5% Pd–C in 36 ml of AcOH and 4 ml of Ac_2O was added 0.61 g of 8.[7] One equivalent of H_2 was taken up in 15 min in a calibrated atmospheric hydrogenation apparatus. The catalyst was filtered and the solvent was evaporated *in vacuo*. The residue was dissolved in 20 ml of MeOH containing 2 ml of HCl and refluxed for 1 hr. The solution was poured into ice water and the mixture was extracted thoroughly with EtOAc. The combined organic layer was washed in turn with water, saturated $NaHCO_3$ solution, and NaCl solution. After drying (Na_2SO_4) the solvent was evaporated *in vacuo*, and the residue was crystallized from EtOAc–hexane. The first crop of 0.16 g, mp 259–261°, proved to be estrone. The succeeding three crops, 0.195 g, mp 185–190°, were largely the 9β estrone.

To 15 ml of MeMgBr (*ca.* 5 mol) in 30 ml of THF was slowly added a solution of 0.195 g of the 9β ketone in 25 ml of THF. The mixture was stirred under N_2 at the reflux for 18 hr. After the mixture was cooled, excess saturated NH_4Cl solution was added and the mixture was extracted thoroughly with EtOAc. The combined organic layer was washed in turn with water and saturated NaCl solution. After drying (Na_2SO_4) the solvent was evaporated *in vacuo* and the residue was crystallized from benzene to give 0.16 g, mp 216–218°, of 5. Mixture melting point with material previously obtained by dehydrogenation gave mp 215–218°. The nmr spectra were virtually identical.

Aromatization of 17β-Hydroxy-17α-methylestra-4,9(10)-dien-3-one (6).—A solution of 0.29 g of 6 in 100 ml of 3A EtOH was flushed with N_2 and heated to 80°. Then 0.075 g of 5% Pd–C was added and the mixture was stirred while heating continued. The extent of aromatization was followed by uv; most of the chromophore disappeared in 0.5 hr. The catalyst was filtered and the solvent was evaporated *in vacuo*. The residue was crystallized from Et_2O to give 0.19 g of 7, mp 191–193°. Nmr spectrum of the mother liquor showed no trace of the 9β isomer.

Dehydrogenation of 17β-Hydroxy-17α-methylestr-5(10)-en-3-one (9).—Following the usual procedure, 0.29 g of 9 in 100 ml of 3A EtOH was treated with 0.075 g of catalyst for 4 hr. The reaction rate was monitored by uv; no large amount of aromatic formation was observed. The catalyst was filtered and the solvent was evaporated *in vacuo*. Tlc of the residue showed one major spot for the starting material with a trace of impurity.

Dehydrogenation of 1,4-Dihydro-17α-methylestradiol 3-Methyl Ether (10).—Using the standard procedure, 0.29 g of 10 in 100 ml of 3A EtOH and 0.075 g of catalyst were used. The rate of reaction was followed by uv; reaction was stopped at 0.75 hr. After usual handling tlc was run on residue, which indicated that two compounds were formed. The residue was chromatographed on 50 g of Florisil using benzene–EtOAc (10:1) as solvent. The first crystalline fraction was recrystallized from MeOH to give 17α-methylestradiol 3-methyl ether (12), 0.160 g, mp 99–103°. The second fraction of 0.045 g was not crystalline but nmr analysis showed that this was mainly 9.

Dehydrogenation of 1,2-Dihydro-17α-methylestradiol 3-Methyl Ether (11).—Following the procedure of Birch,[9] 0.2 g of 10 was converted primarily to 11 as evidenced by the large uv maximum at 272 nm. This material without isolation was treated with 0.025 g of 5% Pd–C in the usual way. After work-up as for 10, 0.13 g of 12, mp 100–102°, was obtained.

Dehydrogenation of Estra-3,5-diene-3,17β-diol Diacetate (13).—Following the usual conditions, 0.1 g of 13[12] was treated with 0.025 g of 5% Pd–C. The reaction was monitored by uv and showed no appreciable change in uv chromophore in up to 4 hr. Tlc analysis of the residue showed that only starting material was present.

Registry No.—1, 5670-56-4; 4, 20708-78-5; 5, 30541-88-9; 6, 14531-89-6; 7, 302-76-1; 12, 15236-73-4.

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Oxidation and Reduction Reactions Involving Cobalt–Cyano Complexes

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The catalytic activity of cobalt–cyano complexes has received considerable attention[1,2] since Iguchi first observed that solutions of such complexes absorbed molecular hydrogen and transferred it to a substrate.[3] Recent publications concerned with the oxidation[4,5] and reduction[5,6] of organic compounds promoted by cobalt–cyano complexes prompt us to report related work. Our observations are presented to clarify and expand these recent reports.

This note describes the epoxidation of allyl alcohol by reacting $[(CN)_5CoOOCo(CN)_5]^{6-}$ (1) with hydrochloric acid in the presence of tungstic acid, the oxidation of 1-octene by 1 in acetic acid solvent, and the reduction of sodium methacrylate in the presence of $[Co(CN)_5]^{3-}$ (2) using water as the hydrogen source.

By utilizing a catalyst such as tungstic acid or sodium tungstate we found that allyl alcohol can be epoxidized, under a nitrogen atmosphere, with 1 as the oxygen source. After 1.5 hr at 70–75° and at a pH of 4.5–5.5, a 70% yield of glycidol (based on consumed active oxy-

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(4) T. Asai and T. Hara, *Bull. Chem. Soc., Jap.*, **42**, 3580 (1969).
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gen) was obtained. Oxidations with **1** are not limited to aqueous systems as we were also able to selectively oxidize 1-octene in acetic acid, under a nitrogen atmosphere, with the oxygen again supplied by compound **1**. In the 1-octene case, however, our reaction conditions gave not the epoxide, but rather a 26% yield of 1,2-octanediol diacetate as the only significant product. The diacetate resulted from reaction of the initial product 1,2-epoxyoctane with the acetic acid solvent.

Pregalia and coworkers previously reported[5] the epoxidation of 1-octene with $[Co(CN)_5OOH]^{3-}$ (**3**) dissolved in water or glacial acetic acid. However, because their reactions were carried out in an oxygen atmosphere, complex product mixtures resulted and it was difficult to differentiate autoxidation products from those arising directly from oxygen present in the cobalt complex. By completely excluding atmospheric oxygen we avoided any competing autoxidation reactions and observed quite selective oxidations. Glycidol was the only organic product obtained from allyl alcohol and only traces of products other than 1,2-octanediol diacetate were detected in the 1-octene oxidation.

Compound **1** itself is not active as an epoxidizing agent. For example, when the allyl alcohol reaction was repeated in an alkaline medium (pH 9.7–10) only a trace of epoxide formed after 1.5 hr. However, under acidic conditions in water, formation of hydrogen peroxide from **1** apparently occurs *via* **3** as an intermediate. The hydrogen peroxide then epoxidizes the olefin in the presence of tungstic acid. As an additional check of this interpretation, **3** was synthesized, isolated, and reacted with allyl alcohol and sodium tungstate at 70° under alkaline conditions (pH 9–10). Again, no glycidol was formed. Thus **3**, a compound with a hydroperoxy group attached to cobalt, is also inactive as a direct epoxidizing agent. Only under acidic conditions did epoxidation occur. Similarly, Asai and Hara[4] found that **1** was effective in epoxidizing acrolein only after acidification with sulfuric acid. When we used acetic acid as solvent, peracetic acid was most probably the epoxidizing agent.

We propose that the following reactions occur (eq 1–4), in an acidic, aqueous medium, to give epoxidation.

$$2K_3Co(CN)_5 + O_2 \longrightarrow K_3Co(CN)_5OOCo(CN)_5K_3 \quad (1)$$

$$K_3Co(CN)_5OOCo(CN)_5K_3 + H_2O + H^+ \longrightarrow K_3Co(CN)_5OOH + K_2Co(CN)_5\cdot H_2O + K^+ \quad (2)$$

$$K_3Co(CN)_5OOH + H^+ + H_2O \longrightarrow K_2Co(CN)_5\cdot H_2O + H_2O_2 + K^+ \quad (3)$$

$$CH_2{=}CHCH_2OH + H_2O_2 \xrightarrow{H_2WO_4} CH_2\text{—}CHCH_2OH + H_2O \quad (4)$$

(O bridging the epoxide carbons)

Reactions 1–3 have been detailed previously,[7,8] and the use of sodium tungstate or tungstic acid to catalyze allyl alcohol epoxidation by hydrogen peroxide is well documented.[9,10] The combination of reactions 1–3 thus provides a route for the *in situ* generation of hydrogen peroxide from atmospheric oxygen and acid. Additionally, **1** can be generated rather simply, very rapidly, and in good purity (>95%).

We have also found that activated double bonds can be reduced, in the presence of **2**, using water as the hydrogen source. The reaction of **2**, sodium methacrylate, and water at 100° in an autoclave gave a 45% reduction of the unsaturated compound to sodium isobutyrate after 3 hr. After reaction, $K_3Co(CN)_6$ with its strong uv absorptions at 258 and 310 mμ was the only soluble cobalt species indentified. A pink precipitate that formed during the reaction was identified as cobalt hydroxide by X-ray diffraction. These results indicate the ease with which **2** homolytically cleaves a water molecule, a phenomenon that has been noted previously.[11] The hydrido complex thus formed, $K_3Co(CN)_5H$, is responsible for the olefin reduction and for any hydrogen evolved. Our results give further support to the mechanism proposed by Kwiatek, *et al.*,[1,12] for olefin reduction by pentacyanocobaltate. Thus, while two molecules of **2** are necessary to cleave water, only one molecule of $K_3Co(CN)_5H$ is formed and a 50% yield of reduced product (based on the amount of **2** initially present) is the maximum obtainable.

$$K_3Co(CN)_5 + H_2O \rightleftharpoons K_3Co(CN)_5OH + K_3Co(CN)_5H$$

$$K_3Co(CN)_5H + C_3H_5CO_2Na \rightleftharpoons K_3Co(CN)_5(C_3H_6CO_2Na)$$

$$K_3Co(CN)_5(C_3H_6CO_2Na) + H_2O \longrightarrow C_3H_7CO_2Na + K_3Co(CN)_5OH$$

Tarama and Funabiki[6] described the hydrogenation of butadiene by **2** in a glycerine–methanol mixture under a nitrogen atmosphere. The authors suggested that the alcohol solvent was the source of hydrogen for their reduction. Some preliminary work in our laboratory suggests that the rate of olefin reduction in water is many times greater than that in alcohol. This could very well be due to differences in solubility of **2** for its aqueous solutions are homogeneous, unlike the situation in anhydrous methanol. It is quite clear, however, that hydroxylic solvents are the source of hydrogen for reduction in both of these cases.

Experimental Section

Material.—The cobalt–cyano complexes $K_3Co(CN)_5$,[13] $K_6Co_2(CN)_{10}O_2\cdot H_2O$,[7] $K_3[Co(CN)_5OOH]$,[8] and $Na_6Co_2(CN)_{10}\cdot 4H_2O$[14] were all prepared *via* the reported methods. Careful uv analysis of $K_3[Co(CN)_5OOH]$ indicated it contained 5–10% of $K_2Co(CN)_5\cdot H_2O$ (uv max 380 mμ) as a contaminant.

Oxidation of Allyl Alcohol.—The epoxidation of allyl alcohol was accomplished by heating 5.2 g of $K_6Co_2(CN)_{10}O_2\cdot H_2O$ (95–97% pure by iodide titration for active oxygen), 0.8 g of $Na_2WO_4\cdot 2H_2O$ (or 0.6 g of H_2WO_4), and 7 g of freshly distilled allyl alcohol in 50 ml of degassed water at 70–75° for 1.5 hr under nitrogen. Degassed HCl (1 *N*) was added dropwise during reaction to maintain the pH at 4.5–5.0. After reaction, iodide titration indicated no active oxygen remained and uv analysis no longer showed a uv max at 327 mμ, which is characteristic for $K_6Co_2(CN)_{10}O_2$.[7] Vpc analysis of the reaction mixture showed a 70% yield of glycidol, based on $K_6Co_2(CN)_{10}O_2\cdot H_2O$. The same reaction was repeated with the pH adjusted to 9.7–10.0, but only a trace of glycidol was formed. Similarly, when 3.4 g of $K_3Co(CN)_5OOH$ was substituted for the $K_6Co_2(CN)_{10}O_2\cdot H_2O$, no glycidol was formed after 1.5 hr at a pH of 10.

(7) J. H. Bayston, R. N. Beale, N. K. King, and M. E. Winfield, *Aust. J. Chem.*, **16**, 954 (1963).
(8) J. H. Bayston and M. E. Winfield, *J. Catal.*, **3**, 123 (1964).
(9) Z. Raciszewski, *J. Amer. Chem. Soc.*, **82**, 1267 (1960).
(10) H. C. Stevens and A. J. Kaman, *ibid.*, **87**, 734 (1965).
(11) N. K. King and M. E. Winfield, *ibid.*, **83**, 3366 (1961).
(12) J. Kwiatek, I. L. Mador, and J. K. Seyler, *Advan. Chem. Ser.*, **37**, 201 (1963).
(13) See P. S. Poskozim, *J. Chem. Educ.*, **46**, 384 (1969).
(14) R. Nast, H. Ruppert-Mesche, and M. Helbig-Neubauer, *Z. Anorg. Allg. Chem.*, **312**, 314 (1961).

Oxidation of 1-Octene.—A solution of 11.2 g of 1-octene, 50 ml of degassed glacial acetic acid, and 3.24 g of $K_6Co_2(CN)_{10}O_2$ was heated to 80–85° under nitrogen for 24 hr. After reaction iodide titration indicated that no active oxygen remained. Vpc analysis of the reaction mixture showed a 26% yield of 1,2-octanediol diacetate which was isolated by preparative vpc and identified by its ir and nmr spectra. Only traces of other products were detected by vpc.

Reduction of Sodium Methacrylate.—The reduction of sodium methacrylate was carried out by reacting 9.8 g of KCN, 7.1 g of $CoCl_2 \cdot 6H_2O$, and 3.2 g of sodium methacrylate in 200 ml of degassed water at 100° for 3 hr in a 300-ml Magnedrive autoclave. After reaction a portion of the reaction mixture was acidified and analyzed by vpc. A 45% yield of isobutyric acid was found. The yellow reaction mixture gave uv maxima at 258 and 310 mμ, corresponding to the reported absorptions for $K_3Co(CN)_6$.[7] A pink precipitate that formed during reaction was identified as $Co(OH)_2$ by its X-ray diffraction pattern.

Registry No.—**1**, 23733-07-5; **2**, 15415-02-8; allyl alcohol, 107-18-6; 1-octene, 111-66-0; sodium methacrylate, 5536-61-8.

Acknowledgments.—The authors wish to express their gratitude to Dr. Thomas Coffield for his stimulating interest and helpful suggestions during the course of this work.

A Convenient Synthesis of 1-Alkynylphosphonates

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Interest in the preparation of 1-alkynylphosphonates (**3**) was derived from our study of nucleophilic additions to carbon–carbon triple bonds activated by phosphorus(V) groups.[2,3] A literature survey on the preparation of **3** showed that some of the methods reported involve the preparation of explosive alkynyl bromides,[4–6] while other methods are either limited in scope[7] or give low overall yields.[8]

We wish to report a versatile synthesis of **3** starting from alkynylmagnesium bromides (**1**) and dialkyl or diphenyl phosphorochloridates (**2**) (eq 1).

$$\underset{\mathbf{1}}{RC{\equiv}CMgBr} + \underset{\mathbf{2}}{ClP(O)(OR^1)_2} \longrightarrow \underset{\mathbf{3}}{RC{\equiv}CP(O)(OR^1)_2} \quad (1)$$

R = alkyl, cycloalkyl, aryl; R^1 = alkyl, aryl

Some of the compounds **3** produced in this manner are listed in Table I.

The success of this method is easily explained by the reasonable assumption that the chloride ion is more easily displaced than the alkoxide and the phenoxide ion.[9] It is worthwhile to mention that in the preparation of **3i**, we observed traces of phenol in the foreruns of the distillate.

Experimental Section

General Procedure.—Alkynylmagnesium bromide was prepared by stirring 0.05 mol of the alkyne with 0.05 mol of ethylmagnesium bromide in 125 ml of ether at room temperature for 1–2 hr until no more ethane evolved. Dialkyl or diphenyl phosphorochloridate was dissolved in 70 ml of ether and cooled to 0°, and the alkynylmagnesium bromide was added dropwise with continuous stirring. The reaction mixture was stirred at 0° for 1 hr and then at room temperature for 1 hr. Saturated aqueous ammonium chloride solution (100 ml) was added slowly and the phases were separated. The aqueous layer was extracted with ether, the combined ether extract was dried ($MgSO_4$) and evaporated, and the resulting oil was distilled under reduced pressure.

Commercially available diethyl and diphenyl phosphorochloridates were used while dimethyl phosphorochloridate was prepared by passing Cl_2 through a cold solution of dimethyl phosphite in CCl_4.

The ir spectra ($CHCl_3$) of all the compounds **3** listed in Table I show a significant absorption in the region of 4.50–4.60 μ (C≡C); nmr ($CDCl_3$) **3a–h**, doublet of quartets (J_{HH} = 7, J_{PH} = 9 Hz, δ 4.15–4.20, CH_2O); **3i**, doublet (J_{PH} = 5 Hz, δ 1.75, CH_3); **3j**, doublet (J_{PH} = 13 Hz, δ 3.88, CH_3O).

TABLE I

1-ALKYNYLPHOSPHONATES **3**

Series	R	R^1	Bp, °C (mm)	Yield, %	Calcd, % C	Calcd, % H	Calcd, % P	Found, % C	Found, % H	Found, % P
a	CH_3	C_2H_5	82–83 (0.30)[a]	76						
b	n-C_3H_7	C_2H_5	115 (0.20)	59	52.94	8.39	15.16	52.77	8.25	15.04
c	n-C_4H_9	C_2H_5	96 (0.10)[a]	64						
d	n-C_6H_{13}	C_2H_5	133 (0.57)[a]	52						
e	C_6H_5	C_2H_5	132 (0.10)[a]	53						
f	$C_6H_5CH_2CH_2$	C_2H_5	145 (0.05)	60	63.15	7.19	11.63	63.02	7.36	11.80
g	C_6H_{11}	C_2H_5	130 (0.55)	51	59.01	8.67	12.68	58.65	8.86	12.76
h	C_5H_9	C_2H_5	134 (0.90)	70	57.38	8.32	13.45	56.61	8.43	12.89
i	CH_3	C_6H_5	162–163 (0.10)	74	66.78	4.81	11.38	66.04	4.72	11.04
j	n-C_3H_7	CH_3	83 (0.10)	57	47.73	7.44	17.58	47.36	7.46	17.61

[a] Reference 6.

Registry No.—**3a**, 1067-88-5; **3b**, 7579-98-8; **3c**, 3450-61-1; **3d**, 3450-66-6; **3e**, 3450-67-7; **3f**, 30238-19-8; **3g**, 30238-20-1; **3h**, 30238-21-2; **3i**, 3095-09-8; **3j**, 30238-23-4.

(1) Author to whom correspondence should be addressed.
(2) A. M. Aguiar and J. R. S. Irelan, *J. Org. Chem.*, **34**, 4030 (1969).
(3) C. J. Morrow, Ph.D. Dissertation, Tulane University, New Orleans, La., 1970.
(4) B. I. Ionin and A. A. Petrov, *Zh. Obshch. Khim.*, **32**, 2387 (1962); *Chem. Abstr.*, **58**, 9115*b* (1963).
(5) B. I. Ionin, V. B. Lebedev, and A. A. Petrov, *Dokl. Akad. Nauk SSSR*, **152**, 1354 (1963); *Chem. Abstr.*, **60**, 1560*d* (1964).
(6) G. Surtz and C. Charrier, *C. R. Acad. Sci.*, **261**, 1019 (1965).
(7) A. N. Pudovik and I. M. Aladzheva, *Zh. Obshch. Khim.*, **33**, 707 (1963); *Chem. Abstr.*, **59**, 2851*f* (1963).
(8) K. N. Anisimov and A. N. Nesmeyanov, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, 1006 (1955).
(9) A. M. Aguiar, J. R. S. Irelan, C. J. Morrow, J. P. John, and G. W. Prejean, *J. Org. Chem.*, **34**, 2684 (1969).

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A Convenient Synthesis of Dialkyl Alkynyl-1-thiophosphonates

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Dialkyl alkynyl-1-thiophosphonates (**3**) represent a new class of phosphorus(V) esters which have not been described in the literature to date. We now wish to report a versatile, one-step synthesis of compounds of type **3** by the reaction of dialkyl phosphorochloridothionates (**2**) with lithium alkynylides (**1**) in the presence of a catalytic amount of pyridine (eq 1).

$$\underset{\mathbf{1}}{RC{\equiv}CLi} + \underset{\mathbf{2}}{ClP(S)(OR')_2} \xrightarrow{\text{pyridine}} \underset{\mathbf{3}}{RC{\equiv}CP(S)(OR')_2} \quad (1)$$

R = alkyl, cycloalkyl, phenyl; R′ = alkyl

The compounds **3** prepared by this method are listed in Table I together with their boiling points, yields, and chemical analyses. This method for the preparation of **3** is based upon the reasonable assumption that the chloride ion is much more easily displaced than the alkoxide ion.[2]

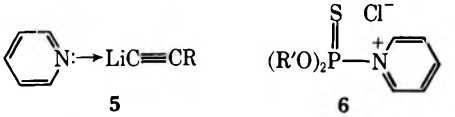
The ir spectra of **3a–k** display significant absorption in the region of 4.50–4.60 μ (C≡C). The nmr spectra of **3a–j** exhibit a doublet of quartets (J_{HH} = 7, J_{PH} = 11 Hz) at δ 4.08–4.25 due to methylenes from the *O*-ethyl groups; compound **3k** displays a doublet (J_{PH} = 15 Hz) at δ 3.82 due to the methyl groups. All other proton resonances are in full agreement with the assigned structures.

Initial attempts at preparing **3** in tetrahydrofuran (THF) and in ether by the treatment of **2** with alkynylmagnesium bromides (**4**) produced the desired product in low yields (eq 2).

$$\underset{\mathbf{4}}{RC{\equiv}CMgBr} + \underset{\mathbf{2}}{ClP(S)(OR')_2} \longrightarrow \underset{\mathbf{3}}{RC{\equiv}CP(S)(OR')_2} \quad (2)$$

It was found that the yield of **3** from the reaction of **1** with **2** can be maximized in mixed THF–ether solvent by utilizing a catalytic amount of pyridine.

The catalytic action of pyridine may be due to its ability to coordinate with lithium, thereby increasing the nucleophilicity of the alkynylide moiety through intermediates such as **5**. Pyridine may be increasing the electrophilicity of phosphorus through formation of intermediate **6**.



5 **6**

We favor major contribution of **5** because, although the addition of pyridine increased the yield of **3** when the lithium alkynylides (**1**) were used (eq 1), it failed to have any effect on the alkynylmagnesium bromide (**4**) reaction (eq 2). Moreover, the acceleration of the rates of organolithium reactions resulting from low concentrations of amines has been well established. The effect has been attributed to complex formation which labilizes the carbon–lithium bond.[3]

TABLE I
DIALKYL ALKYNYL-1-THIOPHOSPHONATES (**3**)

Series	R	R¹	Bp, °C (mm)	Yield, %	Calcd, % C	Calcd, % H	Calcd, % P	Calcd, % S	Found, % C	Found, % H	Found, % P	Found, % S
a	CH_3	C_2H_5	82–83 (0.30)	36	43.74	6.82	16.11	16.68	43.89	6.73	16.16	16.76
b	*n*-C_3H_7	C_2H_5	95–96 (0.10)	61	49.08	7.78	14.06	14.55	49.27	7.56	13.95	14.55
c	*n*-C_4H_9	C_2H_5	94 (0.07)	66	51.26	8.17	13.22	13.68	51.46	7.96	13.47	13.72
d	*n*-C_5H_{11}	C_2H_5	101 (0.07)	68	53.21	8.52	12.47	12.91	53.26	8.42	12.41	12.91
e	*n*-C_6H_{13}	C_2H_5	130 (0.20)	79	54.94	8.84	11.80	12.22	55.15	9.01	11.98	12.45
f	*n*-C_7H_{15}	C_2H_5	121 (0.07)	64	56.50	9.12	11.20	11.61	56.78	9.24	11.20	11.69
g	$C_6H_5CH_2CH_2$	C_2H_5	135 (0.08)	52	59.56	6.78	10.97	11.36	59.48	6.84	11.23	11.13
h	C_5H_9	C_2H_5	110 (0.12)	81	53.64	7.78	12.57	13.02	53.80	7.61	12.60	13.19
i	C_6H_{11}	C_2H_5	134 (0.45)	74	55.36	8.13	11.90	12.32	55.25	8.24	11.95	12.60
j	C_6H_5	C_2H_5	134–135 (0.15)	52	56.68	5.95	12.18	12.61	57.07	6.11	12.15	12.63
k	C_6H_5	CH_3	119 (0.20)	35	53.09	4.90	13.69	14.17	53.07	5.00	13.77	14.27

Experimental Section

All the reactions were run under nitrogen, from the introduction of the 1-alkyne until the addition of water. Tetrahydrofuran was dried over calcium hydride for 3–4 days and distilled. The nmr spectra were determined in deuteriochloroform solution, with tetramethylsilane as an internal standard, on a Varian A-60 spectrometer. Chemical analyses were performed by Geller Microanalytical Laboratories, Saddle River, N. J. Commercially available dialkyl phosphorochloridothionates (**2**) were used.

Preparation of Dialkyl Alkynyl-1-thiophosphonates. General Procedure.—The alkyne (0.05 mol) was dissolved in a mixture of 50 ml of ether and 25 ml of THF and cooled to 0°. A hexane solution of *n*-butyllithium (0.05 mol, 32.5 ml of 1.6 *M* solution, Foote Chemical Co.) was slowly added with continuous stirring to obtain a fine suspension of lithium alkynylide.[4] Two drops of

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(2) A. M. Aguiar, J. R. S. Irelan, C. J. Morrow, J. P. John, and G. W. Prejean, *J. Org. Chem.*, **34**, 2684 (1969).

(3) F. G. A. Stone and R. West, "Organometallic Chemistry," Vol. 3, Academic Press, New York, N. Y., 1965, p 392.

(4) T. F. Rutledge, "Acetylenic Compounds," Reinhold, New York, N. Y., 1968, p 68.

pyridine were added and this suspension was slowly added to a solution of **2** (0.05 mol) in 50 ml of ether at 0°. The reaction mixture was stirred at 0° for 1 hr and then at room temperature for 5–6 hr. The reaction mixture was cooled in an ice bath and 100 ml of saturated aqueous ammonium chloride solution was slowly added. The phases were separated and the aqueous layer was extracted twice with 50-ml portions of ether. The combined ethr extract was dried ($MgSO_4$), filtered, and evaporated. The resultant oil was distilled at reduced pressure to yield the alkynyl-1-thiophosphonates **3**.

In the preparation of **3k** (R = C_6H_5, R′ = CH_3) only ether was used as a solvent.

Registry No.—**3a**, 20553-76-8; **3b**, 30238-04-1; **3c**, 30238-05-2; **3d**, 30238-06-3; **3e**, 30238-07-4; **3f**, 30238-08-5; **3g**, 30238-09-6; **3h**, 30238-10-9; **3i**, 30238-11-0; **3j**, 30238-12-1; **3k**, 30238-13-2.

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Reactions of Lithium Dimethylcarbamoylnickel Carbonylate

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In a previous paper[1] we have reported the formation of an air-sensitive anionic carbamoylnickel complex, $Li[(CH_3)_2NCONi(CO)_3]$ (1), by the addition of lithium dimethylamide to nickel carbonyl and the reaction of **1** with phenylacetylene to yield 2-phenyl-*N*,*N*,*N*′,*N*′-tetramethylsuccinamide and *N*,*N*-dimethylcinnamamide under mild conditions. More recently, anionic organometal carbonylates have been shown to be effective nucleophilic reagents in organic syntheses and several types of new reactions have been established: *e.g.*, nucleophilic acylation of organic halides[2,3] and conjugated enones[4] using lithium acyl metal carbonylates derived from organolithium compounds and mononuclear metal carbonyls, and alkoxycarbonylation of organic halides[5] using nickel carbonyl and potassium alkoxide.

In this paper, we wish to report the reaction of lithium dimethylcarbamoylnickel carbonylate (**1**) as a nucleophilic carbamoylation reagent. The reaction of alkyl carbamoyl chloride with carbanion has been well known as a method for electrophilic carbamoylation accompanying a carbon–carbon bond formation.[6] The anionic carbamoyl group may show different behavior than the cationic one and give rise to a new type of organic reaction. Because of the difficulty in forming such a group, there are few reports on nucleophilic carbamoylation except the reaction system of biscarbamoylmercury compounds and *n*-butyllithium at very low temperature.[7]

Results and Discussion

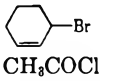
Assumed Structure of Lithium Dimethylcarbamoylnickel Carbonylate (1).—Addition of nickel carbonyl to the white ether suspension of lithium dimethylamide yields a clear red solution without carbon monoxide evolution. The infrared spectrum of this solution shows peaks at 1973 (vs), 1954 (s) ($\nu_{C=O}$ of terminal carbonyl of the anionic complex), and 1560 cm^{-1} (m, broad) ($\nu_{C=O}$ and $\nu_{C=N}$ of the carbamoyl group bonded to nickel[8]). These data suggest that the $Ni(CO)_3$ group in **1** has C_{3v} symmetry (two infrared active terminal carbonyl vibrations) and that the carbamoyl group is bonded to nickel as a carbene type ligand (eq 1). (Recently, lithium oxydiethylaminocarbenechromium pentacarbonylate has been isolated by the analogous reaction using lithium diethylamide and chromium hexacarbonyl in ether.[9])

$$LiN(CH_3)_2 + Ni(CO)_4 \longrightarrow \begin{matrix} LiO \\ \diagdown\!\!\!= \\ C \\ \diagup\!\!\!= \\ (CH_3)_2N \end{matrix} \!\!=\!\! Ni(CO)_3 \qquad (1)$$

Reaction of 1 with Organic Halides.—Treatment of **1** with several organic halides, RX or RCOX, in ether results in formation of the acid amides $RCON(CH_3)_2$. The examples cited in Table I illustrate the synthesis of *N*,*N*-dimethyl acid amides using the indicated reactants and reaction conditions.

TABLE I
DIMETHYLCARBAMOYLATION OF ORGANIC HALIDES

$Li[(CH_3)_2NCONi(CO)_3]$ (**1**) + RX (or RCOX) ⟶ $RCON(CH_3)_2$[a]

Organic halides (RX or RCOX)	Reaction time, hr (temp, °C)	$RCON(CH_3)_2$, % yield[b]
trans-PhCH=CHBr	7 (10)	96.0
PhI	5 (37)	98.2
$PhCH_2Br$	12 (33)	64.8[c]
$CH_2=CHCH_2Br$	0.5 (15)	35.9[d]
	10 (20)	99.3
CH_3COCl	0.5 (22)	75.9[e]
n-C_4H_9COCl	0.5 (22)	97.1[e]
PhCOCl	5 (30)	95.6[e]

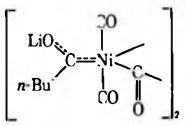
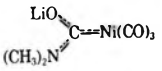
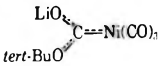
[a] Reactants ratio. $LiN(CH_3)_2$:$Ni(CO)_4$:halide = 1:2:2. [b] Yields were calculated based on $LiN(CH_3)_2$ used. [c] Other product, $PhCH_2N(CH_3)_2$ (33.2%). [d] Product, $CH_3CH=CHCON(CH_3)_2$. [e] None of $RCOCON(CH_3)_2$ was detected.

In general, the reactivity sequence of alkyl halides

(1) S. Fukuoka, M. Ryang, and S. Tsutsumi, *J. Org. Chem.*, **33**, 2973 (1968).
(2) Y. Sawa, M. Ryang, and S. Tsutsumi, *Tetrahedron Lett.*, 5189 (1969).
(3) Y. Sawa, M. Ryang, and S. Tsutsumi, *J. Org. Chem.*, **35**, 4185 (1970).
(4) E. J. Corey and L. S. Hegedus, *J. Amer. Chem. Soc.*, **91**, 4926 (1969).
(5) E. J. Corey and L. S. Hegedus, *ibid.*, **91**, 1233 (1969).
(6) R. B. Wagner and H. D. Zook, "Synthetic Organic Chemistry," Wiley, New York, N. Y., 1953, p 576.
(7) U. Schöllkopf and F. Gerhart, *Angew. Chem., Int. Ed. Engl.*, **6**, 805 (1967).
(8) It has been reported that the neutral carbamoyl transition metal complex shows a $\nu_{C=O}$ peak (m or w) at 1535 ± 10 cm^{-1} in π-$C_5H_5Fe(CO)_2(CONR_2)$ [R. B. King, *J. Amer. Chem. Soc.*, **85**, 1918 (1963)], 1625 cm^{-1} in π-$C_5H_5Fe(CO)_2(CONHCH_3)$ [L. Busetto and R. J. Angelici, *Inorg. Chim. Acta*, **2**, 391 (1968)], 1512 cm^{-1} in *cis*-$Re(CO)_4(NH_2CH_3)(CONHCH_3)$ [H. Behrens, E. Linder, and P. Pässler, *Z. Anorg. Allg. Chem.*, **365**, 137 (1969)], and 1598 cm^{-1} in $(n\text{-}C_3H_7)_2NCOCo(CO)_3(PPh_3)$ [J. Palágyi and L. Markó, *J. Organometal. Chem.*, **17**, 453 (1969)].
(9) E. O. Fischer and H. J. Kollmeier, *Angew. Chem., Int. Ed. Engl.*, **9**, 309 (1970).

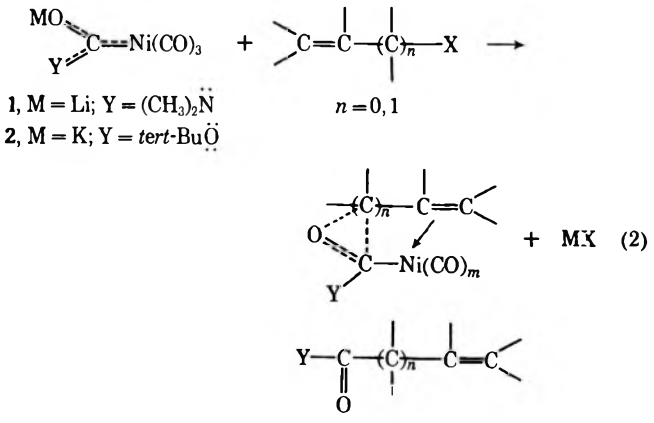
TABLE II

CARBONYL STRETCHING FREQUENCIES OF THE ANIONIC ORGANONICKEL CARBONYLATE IN ETHER AT 20°[a]

Formation reaction	Assumed structure		Terminal CO, cm^{-1}	Bridging CO, cm^{-1}
n-BuLi + $Ni(CO)_4$		(3)	1985, 1962	1845, 1819, 1795
$(CH_3)_2NLi$ + $Ni(CO)_4$		(1)	1973, 1954	
tert-BuOK + $Ni(CO)_4$		(2)	1963, 1920	

[a] *Cf.* $Ni(CO)_4$ which absorbs at 2053 cm^{-1} in ether.

in the nucleophilic substitution reaction is RI > RBr > RCl, but neither alkyl iodides such as methyl iodide and *n*-butyl iodide nor *tert*-butyl bromide undergo dimethylcarbamoylation under these conditions. Alkenyl halides, which are less susceptible to nucleophilic substitution than alkyl halides, undergo dimethylcarbamoylation easily. Hence it appears that halogen attached to saturated carbon (except allyl halides) is much less reactive than that on trigonal carbon. This is probably owing to acceleration of the reactivity of the halides by the coordination of the double bond to the nickel atom. The reactivity of **1** toward organic halides resembles that observed in alkoxycarbonylations[5] using nickel carbonyl and potassium alkoxide. Further, the infrared spectra of **1** and of the reaction mixture of potassium *tert*-butoxide and nickel carbonyl both have two terminal carbonyl absorptions at lower frequencies than that of nickel carbonyl (Table II). These observations suggest that the active species in the two systems have closely related structures. Analogous to **1**, the complex **2** is assumed to be an anionic organonickel carbonylate with a carbene type ligand, and both dimethylcarbamoylation and alkoxycarbonylation of organic halides may be described schematically by the following (eq 2).



1, M = Li; Y = $(CH_3)_2\ddot{N}$
2, M = K; Y = *tert*-Bu$\ddot{O}$

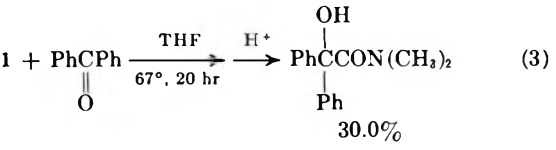
$n = 0, 1$

+ MX (2)

Table II shows the carbonyl stretching frequencies of the anionic organonickel carbonylates, lithium pentanoylnickel carbonylate **3**, **1**, and potassium *tert*-butoxycarbonylnickel carbonylate **2**, derived from the reactions indicated in the first column.

In the reaction of **1** with acyl chlorides, *N*,*N*-dimethyl acid amides were obtained but no *N*,*N*-dimethyl α-keto acid amides were found. This may show that the cationic acyl group attaches itself to the nitrogen atom as the proton in acid hydrolysis[1] of **1**.

Reaction of 1 with Carbonyl Compounds.—Treatment of **1** with benzophenone in tetrahydrofuran results in formation of α-phenyl-*N*,*N*-dimethylmandelamide after hydrolysis (eq 3).



(3)

Benzaldehyde reacts with **1** to give *N*,*N*-dimethylbenzamide (84.2%), and in the presence of **1**, acetophenone condenses to yield α-methylchalcone (77.2%) in ether and 1-methyl-1,3,5-triphenyl-2-benzoylcyclohexadiene-2,4 (83.8%) in tetrahydrofuran, although the mechanisms of those reactions are not clear.

Experimental Section

All reactions were carried out under nitrogen. Gas–liquid partition chromatographic analyses were performed on a Yanagimoto GCG-5DH instrument, using 2.5 m × 3 mm columns packed with 5% SE-30 or 20% PEG-2OM, or on a Hitachi K53 instrument, using 1.5 m × 3 mm columns packed with SF-96 or 20% PEG-20M (carrier gas He). The infrared spectra of the ether solution of the complexes were taken on a Hitachi Perkin-Elmer 225 infrared recording spectrophotometer using a KBr cell and those of the other organic compounds were taken on a Shimazu IR 27 spectrophotometer.

Preparation of the Ether Solution of 1, 2, and 3.—To dimethylamine (25 mmol) dried with potassium hydroxide was added dropwise *n*-butyllithium (5 mmol) in *n*-hexane at 0°. The excess dimethylamine and *n*-hexane were then removed under reduced pressure at 40°. The ether (15 ml) solution of nickel carbonyl (10 mmol) was added to the ether (40 ml) suspension of lithium dimethylamide below 10° and the mixture was stirred for 1 hr. The resulting solution containing about 9 mol % of **1** was used for the infrared spectral measurement. The ether solution of **2** was prepared by adding nickel carbonyl (10 mmol) in ether (15 ml) to the *n*-hexane solution of *n*-butyllithium (5 mmol) below −40° and stirring for 1 hr. After being warmed to 20°, the infrared spectrum of the deep red solution of **2** was taken. A similar method was used for the preparation of **3** using potassium *tert*-butoxide (2.5 mmol) prepared from 0.1 g (2.5 mg-atoms) of potassium and *tert*-butyl alcohol in ether (40 ml) in place of lithium dimethylamide.

Reaction of 1 with Organic Halides.—The experimental execution of the dimethylcarbamoylation reaction is illustrated by the procedure for the synthesis of *trans*-*N*,*N*-dimethylcinnamamide from *trans*-β-bromostyrene. To the ether solution (60 ml) of **1** prepared from 25 mmol of lithium dimethylamide and 50 mmol of nickel carbonyl was added dropwise 9.15 g (50 mmol) of *trans*-β-bromostyrene in 10 ml of ether below 10° and the mixture was

stirred for 7 hr at that temperature. After allowing to warm to room temperature, carbon monoxide was bubbled through the mixture for 1 hr to dispel any remaining nickel carbonyl. Anhydrous ethanol (30 ml) was added and the solution was distilled under reduced pressure to give 4.20 g of yellowish white crystals [bp 120–140° (0.7 mm)]. This was identified to be *trans-N,N*-dimethylcinnamamide by glpc and ir comparison with an authentic sample (yield 96.0%). *N,N*-Dimethyl-3-cyclohexene carboxylic acid amide [bp 98–99° (0.5 mm)] obtained from 3-bromocyclohexene was identified by the ir ($\nu_{C=O}$ 1645 cm^{-1}), the mass spectrum (*m/e* P = 153, 81, 72), and the nmr spectrum [τ 8.2–8.5 (m, 5 H), 7.3 (s, 6 H), 6.9 (m, 1 H), 4.5–4.7 (m, 2 H)]. *N,N*-Dimethylcrotonamide was isolated by preparative glpc and identified by the ir (conjugated $\nu_{C=O}$ and $\nu_{C=C}$ 1620 and 1665 cm^{-1}), the mass spectrum (*m/e* P = 113, 98, 69, 41), and the nmr spectrum [τ 8.3 (d, 3 H), 7.1 (s, 6 H), 3,9 (d, 1 H), 2.5 (m, 1 H)]. The other *N,N*-dimethyl acid amides cited in Table I were identified by glpc and ir comparison with authentic samples.

Reaction of 1 with Benzophenone.—To the THF solution (60 ml) of 1 prepared from 25 mmol of lithium dimethylamide and 37 mmol of nickel carbonyl was added 4.55 g (25 mmol) of benzophenone in 20 ml of THF and the mixture was stirred for 20 hr at 67°. After hydrolysis with 30 ml of 3 *N* hydrochloric acid at room temperature, the solution was concentrated by removal of the THF under reduced pressure and was extracted with ether. The ethereal extract was washed with water saturated with sodium chloride until a neutral solution was obtained and dried with anhydrous magnesium sulfate. The extract was distilled under reduced pressure after removal of the ether to give fraction 1, bp 120–125° (0.7 mm), 3.32 g, and fraction 2, bp 140–145° (0.7 mm), 0.50 g. Fraction 1 consisted of the recovered benzophenone. By recrystallization of fraction 2 using petroleum ether–benzene, white crystals of α-phenyl-*N,N*-dimethylmandelamide (mp 103°) were obtained. This compound was identified by the ir (KBr ν_{OH} 3300 cm^{-1}, $\nu_{C=O}$ 1620 cm^{-1}), the mass spectrum (*m/e* P = 255, 183, 105), the nmr spectrum [τ 7.3 (broad, 6 H), 4.1 (s, 1 H, this peak disappeared on adding D_2O), 2.7 (s, 10H)], and the elemental analysis. The yield was 30% based on benzophenone converted.

Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.18; H, 6.66; N, 5.38.

Reaction of 1 with Benzaldehyde.—Treatment of 2.65 g (25 mmol) of benzaldehyde with 1 (25 mmol) by the method mentioned above resulted in formation of 1.68 g of *N,N*-dimethylbenzamide (84.2% based on benzaldehyde converted), which was identified by glpc, ir comparison with an authentic sample, the mass spectrum (*m/e* P = 149, 105), and the nmr spectrum [τ 7.0 (s, 6 H), 2.6 (s, 5 H)].

Reaction of 1 with Acetophenone.—To the ether solution of 1 (25 mmol) was added 6.00 g (50 mmol) of acetophenone and the solution was stirred for 24 hr at 18°. After hydrolysis with 30 ml of 3 *N* hydrochloric acid, the solution was extracted with ether. The extract was washed with water, saturated with sodium chloride, dried with anhydrous magnesium sulfate, and then was distilled under reduced pressure. The first fraction [bp 115° (80 mm), 2.50 gl was acetophenone recovered and the second fraction [bp 150–185° (2 mm), 2.61 g] was shown to contain 2.50 g of α-methylchalcone by a glpc analysis. This compound was isolated by preparative glpc and identified by the ir (conjugated $\nu_{C=O}$ and $\nu_{C=C}$, 1660 and 1600 cm^{-1}), the mass spectrum (*m/e* P = 222, 115, 105), and the nmr spectrum [τ 7.5 (s, 3 H), 2.9 (s, 1 H), 2.0–2.8 (m, 10 H)] (77.2% based on acetophenone converted). In the same reaction using THF as a solvent (67°, 10 hr), 3.00 g (25 mmol) of acetophenone was converted to 2.23 g of 1-methyl-1,3,5-triphenyl-2-benzoylcyclohexadiene-2,4 (mp 134–135° from petroleum ether–benzene). This was identified by the ir ($\nu_{C=O}$ 1670 cm^{-1}, $\nu_{C=C}$ 1640 and 1620 cm^{-1}), the mass spectrum (*m/e* P = 426, 411, 321, 105), the nmr spectrum [τ 8.4 (s, 3 H), 6.9 (s, 2 H), 3.9 (s, 1 H), 2.5–3.1 (m, 20 H)], and the elemental analysis.

Anal. Calcd for $C_{32}H_{26}O$: C, 90.10; H, 6.14. Found: C, 90.06; H, 6.01.

Registry No.—1, 30304-90-6; *trans-N,N*-dimethylcinnamamide, 17431-39-9; *N,N*-dimethyl-3-cyclohexenecarboxylic acid amide, 30318-35-5; α-phenyl-*N,N*-dimethylmandelamide, 30318-36-6; α-methylchalcone, 4258-37-1; 1-methyl-1,3,5-triphenyl-2-benzoylcyclohexadiene-2,4, 24233-07-6.

The Question of Ring Inversion in 2,3,6,7-Tetramethoxy-9,10-dihydroanthracene[1,2]

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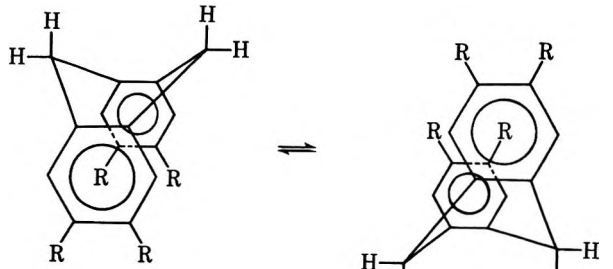
9,10-Dihydroanthracene (**1a**) undergoes a rapid boat-to-boat ring inversion at a rate which exceeds the limits of nmr time scale observability, even at low temperatures.[3,4] However, it was recently reported[5] that



1a, R = H
b, R = OCH_3

2,3,6,7-tetramethoxy-9,10-dihydroanthracene (**1b**), together with the 2,7-dimethoxy and 1,2,3,5,6,7-hexamethoxy analogs, does not undergo this rapid ring-inversion process[6] and shows distinct axial and equatorial methylene protons characteristic of a rigid boat conformation. We felt that it would be highly unusual, and, if true, extremely important that substituents so far from the center ring could exert such a strong influence on the inversion process and that a reinvestigation was in order.

The methoxy derivatives originally studied by nmr were prepared by a modified method of Robinson.[7] It has subsequently been suggested, however, that Robinson's procedure involving the condensation of veratrole with formaldehyde does not produce any dihydroanthracenes.[8] In fact, the related reaction of veratryl alcohol with acid[9] leads to the trimer "cyclotriveratrylene."[10]

For our purposes, we wanted to prepare an appropriate system by the simplest route available, free from possible side reactions. We began with the

(1) This investigation was supported, in part, by a grant from the Eli Lilly Co., Indianapolis, Ind.

(2) Some preliminary experiments were carried out at the Ben May Laboratory for Cancer Research, University of Chicago.

(3) W. B. Smith and B. A. Shoulders, *J. Phys. Chem.*, **69**, 2022 (1965). See also D. Y. Curtin, C. G. Carlson, and C. G. McCarty, *Can. J. Chem.*, **42**, 565 (1964).

(4) A planar conformation seems to be a less likely explanation. See, in addition to ref 1, A. W. Brinkman, M. Gordon, R. G. Harvey, P. W. Rabideau, J. B. Stothers, and A. L. Ternay, *J. Amer. Chem. Soc.*, **92**, 5912 (1970).

(5) F. G. Jimenez, M. C. Perezamador, and J. R. Alcayde, *Can. J. Chem.*, **47**, 4489 (1969).

(6) Studied from −20 to +55°.

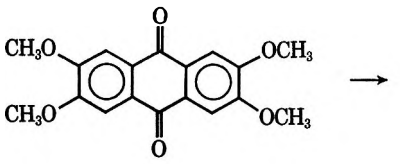
(7) G. M. Robinson, *J. Chem. Soc.*, **107**, 267 (1915).

(8) C. Casinovi and A. Oliverio, *Ann. Chim. (Rome)*, **46**, 929 (1956), and references therein.

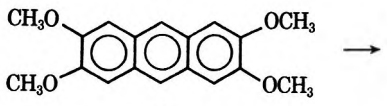
(9) Conditions very similar to ref 3: A. S. Lindsey, *J. Chem. Soc.*, 1685 (1965).

(10) This system shows distinct methylene protons even at high temperatures.[9]

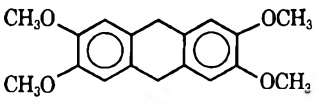
readily available 2,3,6,7-tetramethoxyanthraquinone[11] (2), which was converted by Zn/OH^- to the anthracene 3, showing correct molecular weight (mass spectros-



1



2



3

copy) and consistent nmr and infrared spectra. Reduction of 3 with lithium–ammonia[12] led to **1b**[14] (correct molecular ion).

The nmr spectrum (CCl_4) of **1b** showed an aromatic singlet at δ 6.68 (4 H) and two partially overlapping singlets at 3.78 (total 16), representing the 12 methoxy protons and the 4 methylene protons. At 100 MHz, the two singlets were sufficiently well resolved to permit adequate integration (12:4) with the methylene protons appearing as a singlet 2.5 Hz upfield from the methoxy signal. Thus, the equivalence of the four methylene protons is consistent with a rapid inversion process and demonstrates that methoxy substituents have no unusual effect on this process.

Experimental Section

2,3,6,7-Tetramethoxyanthraquinone.—The anthraquinone was prepared by the dichromate oxidation of 2,3,6,7-tetramethoxy-9,10-dimethylanthracene according to published procedure.[11]

2,3,6,7-Tetramethoxyanthracene.—The aforementioned anthraquinone (4 g) was refluxed for 48 hr with zinc dust (10 g) in 100 ml of 10% aqueous sodium hydroxide.[15] The solid residue was filtered, washed, dried, and boiled in 75 ml of nitrobenzene. Filtration and refrigeration gave crystals (0.5 g): mp 371–373° (lit.[8] 376°); nmr ($CDCl_3$) δ 7.95 (s, Ar-9,10, 2), 7.3 (s, Ar, 4), and 4.0 (s, OCH_3, 12).

2,3,6,7-Tetramethoxy-9,10-dihydroanthracene.—The anthracene above (0.15 g) was suspended in 65 ml of dry ether and added to 100 ml of refluxing ammonia. An excess of lithium metal was added and the dark blue-green solution was stirred for 30 min. Solid ammonium chloride was then added and the reaction was worked up by ether extraction. This gave 50 mg of a white solid which recrystallized from methanol: mp ~230° (lit.[8] 230–250°, dependent on rate of heating); mass spectra *m/e* 300 (calcd for $C_{18}H_{20}O_4$, 300.4); nmr described in text.

Registry No.—3, 26952-97-6.

(11) P. Boldt, *Ber.*, **100**, 1270 (1967).

(12) A modified Birch reduction for which complications and side reactions in anthracene systems are virtually unknown.[13]

(13) R. G. Harvey, *Syn.*, 161 (1970).

(14) Our material appears identical with that reported in ref 8 shown not to be the same as ref 7.

(15) E. L. Martin, *J. Amer. Chem. Soc.*, **58**, 1438 (1936). Yields are improved (55%), however, by added copper sulfate. See L. Fieser and M. Fieser, Ed., "Reagents for Organic Synthesis," Wiley, New York, N. Y., 1967, p 1282.

The Methanolysis of Phenyl-Substituted Benzhydryl Chlorides

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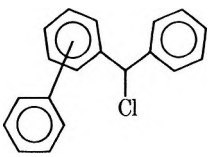
Neighboring group participation[2] in solvolytic displacement reactions of ortho-substituted benzhydryl and benzyl systems has been reported for a number of nucleophilic groups (*e.g.*, $COOC_6H_5$,[3] $COOCH_3$,[3] $COOH$,[3] NO_2[4]). In these cases[3,4] the rate of solvolysis is greater for the ortho compound than for the para compound. In cases where there is an absence of participation, the ortho/para rate ratio is less than unity (*e.g.*, CH_3,[3] $OCOCH_3$,[3] $OCOC_6H_5$,[3] halogen,[5] OCH_3)[6].

In view of the great interest in phenyl participation in solvolysis reactions,[2,7] we wish to disclose our studies with *o*-, *m*-, and *p*-phenyl-substituted benzhydryl chlorides.



1, *o*-C_6H_5
2, *m*-C_6H_5
3, *p*-C_6H_5

The benzhydryl chlorides 1, 2, and 3 were prepared by hydrogen chloride and/or thionyl chloride treatment of the corresponding carbinols, the syntheses of which are described in the Experimental Section and illustrated in Scheme I for 1.

The rates and activation parameters for the methanolysis of 1, 2, and 3 and benzhydryl chloride itself (4) at several temperatures are tabulated in Table I. The products in each case were isolated and identified as the unrearranged methyl ethers. As seen from Table I, the ortho/para rate ratio (1/3) is less than unity (0.16) and this, coupled with the lack of rearrangement, clearly indicates the absence of phenyl participation in 1. It was felt that, if phenyl participation during methanolysis of 1 were occurring, 9-phenylfluorene (5) would have formed. In fact, it was observed that treatment of *o*-phenylbenzhydrol (10) with thionyl chloride or hydrogen chloride above room temperature gave 5.[8] Apparently, under the milder meth-

(1) (a) We gratefully acknowledge partial financial support of this work by the donors of the Petroleum Research Fund, administered by the American Chemical Society, the National Science Foundation, and the Research Corporation. (b) Undergraduate Research Assistant in the Dartmouth Honors Degree Program, 1969–1970.

(2) B. Capon, *Quart. Rev., Chem. Soc.*, **18**, 45 (1964).

(3) A. Singh, L. J. Andrews, and R. M. Keefer, *J. Amer. Chem. Soc.*, **84**, 1179 (1962).

(4) A. D. Mease, M. J. Strauss, I. Horman, L. J. Andrews, and R. M. Keefer, *ibid.*, **90**, 1797 (1968).

(5) G. M. Bennett and B. Jones, *J. Chem. Soc.*, 1815 (1935).

(6) M. Simonetta and G. Favini, *ibid.*, 1840 (1954).

(7) For a leading reference, see A. F. Diaz and S. Winstein, *J. Amer. Chem. Soc.*, **91**, 4300 (1969).

(8) The acid-catalyzed rearrangement of **10** to **5** has been reported: H. H. Hatt, A. Pilgrim, and E. F. M. Stephenson, *J. Chem. Soc.*, 478 (1941).

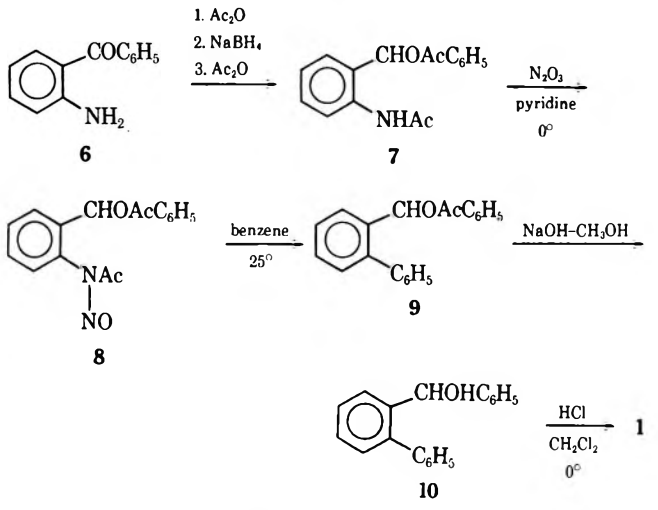
TABLE I

KINETIC DATA FOR METHANOLYSIS OF PHENYL-SUBSTITUTED BENZHYDRYL CHLORIDES

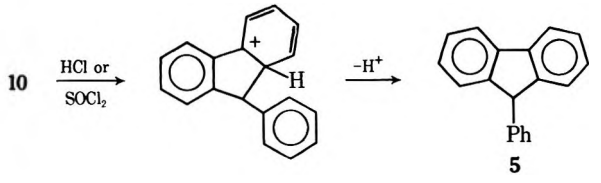
RCl	Temp,[a] °C	Rate constant,[b] sec^{-1}	Relative rate	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
1	15.00	$(4.03 \pm 0.15) \times 10^{-4}$			
	20.00	$(8.23 \pm 0.17) \times 10^{-4}$			
	25.00	$(1.40 \pm 0.03) \times 10^{-3}$	2.98	16.3 ± 0.3	-8.9 ± 0.9
	30.10	$(2.22 \pm 0.08) \times 10^{-3}$			
	35.00	$(3.38 \pm 0.17) \times 10^{-3}$			
2	20.10	$(2.87 \pm 0.05) \times 10^{-4}$			
	25.00	$(4.70 \pm 0.08) \times 10^{-4}$	1.00	18.3 ± 1.4	-7.8 ± 4.6
	30.00	$(8.25 \pm 0.10) \times 10^{-4}$			
3	15.00	$(3.28 \pm 0.10) \times 10^{-3}$			
	15.00	$(3.0 \pm 0.2) \times 10^{-3}$ [c]			
	20.00	$(5.35 \pm 0.08) \times 10^{-3}$			
	25.00	$(8.51 \pm 0.12) \times 10^{-3}$	18.1	13.7 ± 0.6	-14.2 ± 1.9
	25.00	$(6.7 \pm 0.3) \times 10^{-3}$ [c]			
	30.30	$(1.07 \pm 0.09) \times 10^{-2}$			
	35.00	$(1.75 \pm 0.02) \times 10^{-2}$			
	35.00	$(1.5 \pm 0.1) \times 10^{-2}$ [c]			
4	15.00	$(3.40 \pm 0.23) \times 10^{-4}$			
	20.00	$(5.82 \pm 0.25) \times 10^{-4}$			
	25.00	$(1.02 \pm 0.03) \times 10^{-3}$	2.17	18.3 ± 0.2	-2.6 ± 0.8
	25.00	$(8.0 \pm 1.0) \times 10^{-4}$ [c,d]			
	30.00	$(1.70 \pm 0.05) \times 10^{-3}$			
	35.00	$(2.95 \pm 0.17) \times 10^{-3}$			

[a] Believed accurate to ±0.01°. [b] Determined by conductance unless otherwise indicated. [c] Determined by a titrimetric method. [d] Lit.[10] 8.28×10^{-4} sec^{-1}.

SCHEME I



anolysis conditions, stabilization of the transition state by solvent is sufficient, and internal stabilization through phenyl participation is unnecessary. In the



more vigorous chlorination reactions, where solvent stabilization is lacking, there is a greater demand for internal stabilization of the developing positive charge by the *o*-phenyl group. It remains to be seen whether the demand for phenyl participation can be increased by observing the solvolysis of **1** in solvents of lower nucleophilicity and higher ionizing power (*e.g.*, HCOOH, CF_3COOH, FSO_3H, etc.)[9] than methanol.

The low **1**/**3** rate ratio probably results from steric hindrance to solvation in the transition state by the *o*-phenyl group in **1** and geometric difficulty in achieving maximum stabilization of the developing positive charge from three coplanar phenyl rings in **1** relative to **3**.

A $\sigma\rho$ calculation using $\rho = -4.22$[10] for benzhydryl chloride methanolysis at 25° and σ^+ values for phenyl[11] gave 3.54×10^{-4} sec^{-1} for **2**, and 5.79×10^{-3} sec^{-1} for **3**, in good agreement with the observed rates (Table I). Indeed, using $\sigma^+ = -0.218$ as determined[12] from the ethanolysis of diarylcarbinyl chlorides the predicted rate for **3** is 8.50×10^{-3} sec^{-1}.

Experimental Section

o-Acetamidobenzhydryl Acetate (7).—To a stirred solution of 53.5 g (0.271 mol) of *o*-aminobenzophenone (Aldrich Chemical Co.) in 250 ml of pyridine at 0° was added 80 ml of acetic anhydride in one portion. The solution was allowed to warm to room temperature with stirring overnight. It was poured into benzene–water, and the organic layer was separated and washed with dilute HCl and water. Drying and concentration of the organic layer *in vacuo* afforded 50 g (77%) of *o*-acetamidobenzophenone, mp 99–101° (lit.[13] mp 88.5–89°), as off-white cubes from 95% ethanol.

A mixture of 30 g (0.125 mol) of *o*-acetamidobenzophenone 14.8 g of sodium borohydride, 400 ml of 95% ethanol, and 100 ml of water was stirred for 1 hr at 0°, and then stirred overnight at room temperature. To the solution was added 100 ml of water and enough dilute HCl to destroy the excess hydride. Extraction with chloroform and washing and drying of the organic layer

(9) For an example and leading reference, see P. C. Myhre and E. Evans, *J. Amer. Chem. Soc.*, **91**, 5641 (1969).

(10) S. Nishida, *J. Org. Chem.*, **32**, 2692 (1967).

(11) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **80**, 4979 (1958).

(12) J. Packer, J. Vaughan, and A. F. Wilson, *J. Org. Chem.*, **23**, 1215 (1958).

(13) A. Bischler and D. Barad, *Ber.*, **25**, 3081 (1892).

gave, on concentration *in vacuo*, 28.5 g (94%) of *o*-acetamidobenzhydrol, mp 123–125° (lit.[14] mp 118°), as white plates.

A mixture of 28.5 g (0.118 mol) of *o*-acetamidobenzhydrol, 90 ml of pyridine, and 75 ml of acetic anhydride was stirred overnight at room temperature. The solution was poured into water, treated with 3 g of potassium carbonate, and extracted with methylene chloride. This gave, after the usual washing, drying, and concentration, a yellow oil which slowly crystallized to afford 30 g (90%) of **7**, mp 133–136°, as white plates.

***o*-Phenylbenzhydryl Acetate (9).**—A 500-ml, three-neck flask, equipped with drying tube, gas inlet tube, and magnetic stirring bar, was charged with 30 g (0.11 mol) of **7** and 250 ml of pyridine. The solution was cooled to 0° and a mixture of nitrogen trioxide (N_2O_3) and nitrogen was passed through a Drierite tower and into the stirred solution at 0° for 3.5 hr. The dark green solution was poured into ice water and extracted with benzene. The chilled benzene solution of **8** was dried quickly with sodium sulfate, filtered, and allowed to stir at room temperature for 24 hr. The dark solution was concentrated *in vacuo* and the resulting red oil was chromatographed over silica gel. The first fractions (benzene elution) crystallized on standing to afford 6 g (20%) of **9**, mp 62–65°, as light yellow prisms from ether–hexane. The same compound was obtained in yields of up to 37% from *o*-benzamidobenzophenone by an analogous sequence.

Pertinent spectra data for **9** are as follows: ir ($CHCl_3$) 2940, 1725, 1370, 1220, and 1020 cm^{-1}; nmr ($CDCl_3$) δ 1.90 (s, 3) and 6.9–7.6 (m, 15) ppm; mass spectrum (70 eV) *m/e* (rel intensity) 302 (16), 244 (21), 243 (25), 242 (100), 241 (34), and 165 (33).

Anal. Calcd for $C_{21}H_{18}O_2$: C, 83.42; H, 6.00. Found: C, 83.45; H, 6.08.

***o*-Phenylbenzhydrol (10).**—A mixture of 7 g (0.0234 mol) of **9**, 10 g of sodium hydroxide, 600 ml of methanol, and 150 ml of water was stirred at room temperature for 2 hr. The methanol was removed *in vacuo* and the solution was extracted with chloroform. This afforded, on washing, drying, and concentration *in vacuo*, a yellow–orange oil which slowly crystallized to give 6 g (100%) of **10**, mp 66–68° (lit.[8] mp 71°), as white needles, This material proved to be identical with the sodium borohydride reduction product of an authentic sample of *o*-phenylbenzophenone.[15]

***o*-Phenylbenzhydryl Chloride (1).**—A stirred, ice-cold mixture of 6 g of **10**, 200 ml of dry methylene chloride, and several grams of Drierite was treated with hydrogen chloride gas for 1 hr. The filtered solution was concentrated *in vacuo* at 0° to give 5 g (80%) of **1**, mp 80–82°, as white plates from hexane.

Pertinent spectral data for **1** are as follows: ir ($CHCl_3$) 3095, 1610, 1480, 1405, 1265, 1070, and 695 cm^{-1}; nmr ($CDCl_3$) δ 6.22 (s, 1) and 7.25 (m, 14) ppm.

Anal. Calcd for $C_{19}H_{15}Cl$: C, 81.86; H, 5.42; Cl, 12.72. Found: C, 82.12; H, 5.52; Cl, 12.73.

Treatment of **10** with boiling thionyl chloride gave 9-phenylfluorene (**5**) or mixtures of **5** and **1** depending on the conditions. Work-up of the thionyl chloride reaction mixture (see procedure for **3**) gave **5**, mp 146–148° (lit.[16] mp 147–148°), as white crystals.

Pertinent spectral data for **5** are as follows: nmr ($CDCl_3$) δ 5.02 (s, 1) ppm (lit.[17] 5.02 ppm); mass spectrum (70 eV) *m/e* 242, 226, 216, 214, 165, 122, 120, and 119.

***m*-Phenylbenzhydryl Chloride (2).**—A standard Grignard reaction involving benzaldehyde and *m*-bromobiphenyl (Pfaltz and Bauer Chemical Co.) gave a 60% yield of *m*-phenylbenzhydrol, mp 70–73° (lit.[8] mp 81°). This was converted in 86% yield to **2** in the manner described above for **1**, but could not be induced to crystallize. The oil was, however, found to be pure by complete methanolysis and titration with sodium hydroxide.

Pertinent spectral data for **2** are as follows: ir ($CHCl_3$) 3010, 1650, 1590, 1470, 1430, and 1070 cm^{-1}; nmr ($CDCl_3$) δ 6.12 (s, 1) and 7.33 (m, 14) ppm.

***p*-Phenylbenzhydryl Chloride (3).**—A typical sodium borohydride reduction of *p*-phenylbenzophenone (Aldrich Chemical Co.) gave *p*-phenylbenzhydrol (80%), mp 95–96° (lit.[18] mp 93–95°), as white needles from aqueous ethanol. Treatment of this alcohol with hydrogen chloride in the manner described for **1** or treatment with a fourfold excess of thionyl chloride at reflux for 30 min, followed by pouring into ice water and chloroform extraction, gave **3** (85–95%), mp 72–73° (lit.[8] mp 72°), as white needles from hexane.

Pertinent spectral data for **3** are as follows: ir ($CHCl_3$) 3090, 1620, 1490, 1460, 1410, 1220, 1075, 1010, and 693 cm^{-1}; nmr ($CDCl_3$) δ 6.12 (s, 1) and 7.34 (m, 14) ppm.

Anal. Calcd for $C_{19}H_{15}Cl$: C, 81.86; H, 5.42; Cl, 12.72. Found: C, 81.83; H, 5.43; Cl, 12.88.

Benzhydryl Chloride (4).—This material was used as received from Aldrich Chemical Co. An infrared spectrum showed the absence of hydroxyl absorption.

Methanolysis Products.—The three methyl ethers (from **1**, **2**, and **3**) were obtained in essentially quantitative yield. 9-Phenylfluorene (**5**) could not be detected (tlc, nmr) in the methanolysis product of **1**. Only the methyl ether from the methanolysis of **1** was fully characterized. The corresponding methyl ethers from **2** and **3** were identified by spectral data.

o-Phenylbenzhydryl methyl ether, mp 66–68°, exhibited the following nmr data ($CDCl_3$): δ 3.20 (s, 3), 5.35 (s, 1), and 7.2 (m, 14) ppm.

Anal. Calcd for $C_{20}H_{18}O$: C, 87.56; H, 6.61. Found: C, 87.86; H, 6.50.

p-Phenylbenzhydryl methyl ether, mp 80–82°, exhibited the following nmr data ($CDCl_3$): δ 3.37 (s, 3), 5.23 (s, 1), and 7.3 (m, 14) ppm.

m-Phenylbenzhydryl methyl ether, oil, exhibited the following nmr data ($CDCl_3$): δ 3.29 (s, 3), 5.19 (s, 1), and 7.3 (m, 14) ppm.

Kinetics.—Two conventional methods were used to determine solvolytic rate constants: conductance and titrimetry. Since most of the reactions were quite rapid, the conductance method gave better reproducibility and was far more convenient.

The conductance technique has been adequately described in the literature[18,19] and will only be briefly mentioned here. A small sample of the chloride (about 0.05 g) was dissolved in about 3 or 4 ml of benzene in a 150-ml beaker. About 150–200 ml of methanol, which was purified by distillation and dried over Type 3 molecular sieves, was poured into a larger beaker (400 ml). The conductivity cell was emptied, rinsed with methanol twice, and then left empty. Once the sample had been completely dissolved in benzene, the clock was started as soon as the methanol reached the chloride solution. About 40–60 ml of methanol was added. The solution was stirred briefly and then poured into the empty conductivity cell. The cell was rinsed once and then filled to about 0.5–1.0 cm above the plates. The electrode wires were connected from the bridge (Type RC16B2, made by Industrial Instruments, Inc., Cedar Grove, N. J.) to the conductivity cell in the bath. The resistance bridge had been previously calibrated to give readings accurate to $\pm 1\%$. After the connections had been made, the resistance was dialed. The frequency of the resistance bridge was set at 1000 cps, and the sensitivity was maximized in all cases. Cell resistance was determined when the dark triangle in the green window had maximum area. Readings were taken at 1.00 min, at 30-sec intervals until 7 min, at 1-min intervals until 10 min, and at 2-min intervals until 20 min. Faster reactions were monitored every 15 sec; slower reactions were monitored beyond 20 min. Infinity points were calculated after at least 10 half-lives (greater than 99.9% reaction). Solvolyses at temperatures greater than 25° or less than 20° were run in the same manner, except that the methanol used was allowed to equilibrate in the temperature bath for about 5 min before pouring it into the chloride solution. All rate constants were calculated at each time point and all errors determined were standard errors.[20]

The titrimetric method was that used by earlier workers[21] except that phenolphthalein was used as the indicator in the present study.

Registry No.—**1**, 30469-78-4; **2**, 30469-79-5; **3**, 7515-73-3; **4**, 90-99-3; **7**, 30651-46-8; **9**, 30545-62-1; **10**, 30469-82-0; *o*-phenylbenzhydryl methyl ether,

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(15) We wish to thank Professor DeLos F. DeTar (Florida State University) for kindly providing us with this sample.

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30469-83-1; *p*-phenylbenzhydryl methyl ether, 30469-84-2; *m*-phenylbenzhydryl methyl ether, 30470-00-9.

Acknowledgment.—The authors wish to thank Professor Michael J. Strauss (University of Vermont) for a valuable discussion.

Selective Cyanylation of Sulfhydryl Groups. II. On the Synthesis of 2-Nitro-5-thiocyanatobenzoic Acid

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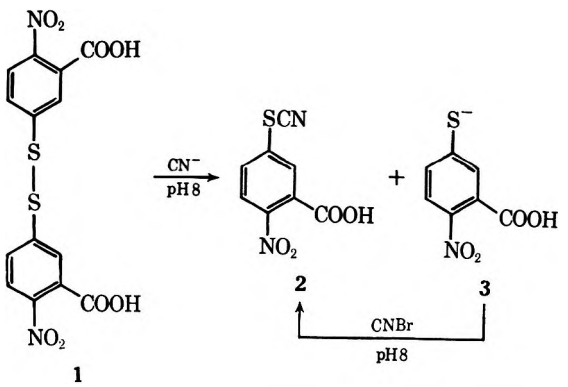
We have recently described a method for the selective cyanylation of sulfhydryl groups under mild conditions, employing 2-nitro-5-thiocyanatobenzoic acid (NTCB, **2**).[1] The reagent was shown to be particularly useful for the reversible blocking of cysteine residues with the cyano group in peptides and proteins and for radioactive labeling of proteins at cysteine residues when using ^{14}C-NTCB. The reagent is also a promising tool for the selective nonenzymatic cleavage of peptide chains at cysteine residues, since *N*-acyl-*β*-thiocyanoalanines were shown to undergo cyclization to labile *N*-acyl-2-iminothioazolidine rings with subsequent cleavage of the *N*-acyl function.[2,3]

NTCB was originally prepared[1] by treatment of 5,5′-dithiobis(2-nitrobenzoic acid) (DTNB, Ellman's reagent,[4] **1**) with NaCN, forming besides **2** an equimolar amount of the thionitrobenzoate **3**. The latter was removed from the product mixture by treatment with bromoacetyl-cellulose, thus shifting the equilibrium toward quantitative completion of the reaction.

We now describe an improved synthesis of NTCB giving twice as high yield of the product as in the previous method. Instead of removing **3** from the reaction mixture, it is also converted into the desired product by treatment with an equimolar amount of cyanogen bromide. Thus 1 mol of **1** gives 2 mol of **2** in practically quantitative yields.



(1) Y. Degani, H. Neumann, and A. Patchornik, *J. Amer. Chem. Soc.*, **92**, 6969 (1970).

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Both steps of the synthesis can be followed by the appearance and disappearance of the characteristic color of **3** [λ_{max} 412 mμ (ϵ 13,600)].[5]

For obtaining a quantitative yield of **2**, the presence of excess cyanide is necessary also in the second step. Thus, when the pure thiol **3** (prepared by reducing the disulfide **1** with *β*-mercaptoethanol) was treated with cyanogen bromide without addition of cyanide salt, the yield of the thiocyanate was only 58%, the rest of the thiol (42%) being converted into the disulfide **1**. (The products were separated and determined by a quantitative paper electrophoretic method, described in the Experimental Section.) The disulfide was probably formed *via* the thiocyanate, by reaction with the still unreacted thiol. Indeed, when the thiol **3** was treated with excess thiocyanate **2** at pH 7–8, the disulfide **1** was formed. These findings point to the existence of equilibrium 1. It is therefore concluded that the presence of excess cyanide during the CNBr reaction shifts the equilibrium to the left, in the direction of the desired thiocyanate.

$$RSCN + RS^- \rightleftharpoons RSSR + CN^- \quad (1)$$

This interpretation is supported by two recent reports on the reaction of cyanogen bromide with thiols. Foye, *et al.*,[6] found that the reaction of a thiol with cyanogen bromide (in 2:1 molar ratio) provides a synthesis of disulfides, whereas Kottke, *et al.*,[7] reported that treatment of thiols with "nascent cyanogen bromide" (excess cyanide followed by dropwise addition of bromine) afforded the corresponding thiocyanates in good yields. Under the experimental conditions of the latter reaction, excess cyanide was present continuously during the synthesis, probably effecting equilibrium 1 as suggested above.

Under the appropriate conditions, the reaction of aromatic thiols with cyanogen bromide seems advantageous over common routes to aryl thiocyanates, such as reacting aryl halides or diazonium salts with metal thiocyanates, since the aryl thiocyanates obtained by these methods are often accompanied by the corresponding isothiocyanates.[8] This contamination was also observed in our earlier attempts to prepare **2** from either 5-chloro-2-nitrobenzoic acid or diazotized 5-amino-2-nitrobenzoic acid.

Experimental Section

Melting points were determined with a Fisher–Johns apparatus and were uncorrected. Infrared spectra were recorded on a Perkin-Elmer 237 spectrophotometer, uv spectra on a Cary 15 spectrophotometer, and mass spectra on a MAT CH4 mass spectrophotometer. Paper electrophoresis was run in a Savant high-voltage electrophoresis apparatus Model LT-48A using pyridine acetate buffer of pH 3.5. Descending paper chromatography was run with 25:6:25 1-butanol–acetic acid–water. Whatman No. 1 paper was used for both electrophoresis and chromatography.

2-Nitro-5-thiocyanatobenzoic Acid (2).—To a 150-ml aqueous solution containing 7.5 g of $KHCO_3$ and 2.0 g (31 mmol) of KCN, 3.0 g (7.5 mmol) of 5,5′-dithiobis(2-nitrobenzoic acid) (**1**,

(5) In ref 4, this ϵ value was attributed to solutions of **3** by analogy to *p*-nitrothiophenolate, without having isolated the thionitrobenzoate. This value is confirmed in the present work for the isolated pure compound.

(6) W. O. Foye, A. M. Hebb, and J. Mickles, *J. Pharm. Sci.*, **56**, 292 (1967).

(7) K. Kottke, F. Friedrich, and R. Pohloudek-Fabini, *Arch. Pharm. (Weinheim)*, **300**, 583 (1967).

(8) R. G. R. Bacon in "Organic Sulfur Compounds," Vol. I, N. Kharasch, Ed., Pergamon Press, Oxford, London, New York, Paris, 1961, p 306.

Aldrich Chemical Co.) was added with magnetic stirring. After 30 min, a freshly prepared 3% solution of cyanogen bromide (Eastman Organic Chemicals) in water was slowly added (10 min) to the stirred deep orange solution, until the color was completely discharged; 27 ml was thus consumed (110% of the theoretical). After decreasing the pH to 5 by the dropwise addition of glacial HOAc, excess cyanide was removed by bubbling a stream of nitrogen through the soution for 12 hr. Upon acidification to pH 2.3 with 6 *N* HCl a white solid crystallized out. After ice cooling the mixture, the solid was filtered, washed with cold water, and air-dried, yield 3.42 g (94%) of chromatographically and electrophoretically pure product, mp 248°. Recrystallization from ethanol gave 2.95 g (81% overall) of pale yellow plates, mp 249°. The product proved to be the half potassium salt of **2**.

Anal. Calcd for $KH(C_8H_3N_2O_4S)_2$: C, 39.50; H, 1.45; N, 11.52; S, 13.80; K, 8.04. Found: C, 40.10; H, 1.46; N, 11.39; S, 13.57; K, 7.50.

Titration with 0.1 *N* $HClO_4$ in HOAc using methyl violet as indicator gave a neutral equivalent of 484 (theory 486).

The free acid was prepared by following an analogous procedure but using NaCN in 0.5 *M* Tris acetate[9] buffer of pH 8.2 instead of KCN in $KHCO_3$ solution. The free acid crystallized out upon acidifying the final solution, yield 3.10 g (92%) of chromatographically and electrophoretically pure product, mp 160–161°. Recrystallization from ethyl acetate–petroleum ether gave 2.66 g (79%) of pale yellow prisms, mp 162–163°. Free **2** was also obtained from its half salt by suspending the latter in dilute HCl, followed by extraction with ethyl acetate, evaporation, and recrystallization from ethyl acetate–petroleum ether.

Anal. Calcd for $C_8H_4N_2O_4S$: C, 42.87; H, 1.80; N, 12.50; S, 14.28. Found: C, 42.95; H, 1.75; N, 12.45; S, 14.06.

Attempts to determine the neutral equivalent of the acid by visual titration with NaOMe in benzene–methanol were unsuccessful because the basic titrant decomposed the thiocyanate group, forming **3**.

Both **2** and its half salt showed an identical single uv-absorbing spot on paper electrophoresis (60 V/cm, 90 min, 30 cm from the origin toward the anode) and paper chromatography (R_f 0.83), which turned yellow (forming **3**) on spraying with an aqueous methanolic solution of Na_2S. **1** behaves similarily, but its electrophoretic mobility is 1.17 of that of **2** and its R_f is 0.92, in the above systems, respectively. Both **2** and its half salt showed the following spectral features: identical uv spectra, λ_{max} (0.1 *M* phosphate buffer pH 7.3) 293 mμ (ε 8000); ir (KBr) sharp SCN band 2170 cm^{-1}; mass spectra (70 eV) heaviest peak at *m/e* 224, corresponding to the molecular ion of the free acid.

Upon treatment of 10^{-4} *N* solutions of either **2** or its half salt in 0.1 *M* phosphate buffer pH 7.3 with excess β-mercaptoethanol, **3** was formed instantaneously in 99 and 102% yields, respectively, as determined by its characteristic absorption.[4,5]

5-Mercapto-2-nitrobenzoic Acid (3).—To a solution of 1.00 g (2.5 mmol) of **1** in 50 ml of 0.5 *M* Tris hydrochloride buffer pH 8.0, 5 ml (71 mmol) of β-mercaptoethanol was added. After 5 min the solution was acidified to pH 1.5 by the addition of 6 *N* HCl. By ice cooling the solution for 24 hr, orange crystals were formed which were filtered, washed with diluted HCl, and vacuum-dried over P_2O_5: yield 0.57 g (57%); mp 137–138°; uv λ_{max} (0.1 *M* phosphate buffer containing 0.005 *M* EDTA) 412 mμ (ε 13,660) (lit.[4,5] 13,600); the absorbancy of the solution remained unchanged after addition of either **1** or β-mercaptoethanol, showing that the product was free of traces of either β-mercaptoethanol or **1**, respectively; molecular weight mass spectrum (70 eV) showed the molecular ion peak at *m/e* 199; iodometric titration (in 50% aqueous HOAc) gave a value of 200.1.

Anal. Calcd for $C_7H_5NO_4S$: C, 42.22; H, 2.53; N, 7.03; S, 16.08. Found: C, 42.34; H, 2.45; N, 7.16; S, 15.96.

Reaction of 5-Mercapto-2-nitrobenzoic Acid (3) with Cyanogen Bromide.—To a solution of 40 mg (0.2 mmol) of **3** in 4.5 ml of Tris hydrochloride buffer pH 8.0, 1.0 ml of 3% aqueous solution of CNBr (0.28 mmol) was added dropwise, the initial deep orange color of the thiolate thereby changing to a pale yellow color of the formed disulfide. Ten-μl samples of the mixture were subjected to paper electrophoresis under the above conditions. Two uv-absorbing spots, corresponding to **1** and **2**, were detected. Each spot was cut into thin strips and eluted for 45 min in 5.0 ml of 0.4 *M* β-mercaptoethanol in 0.1 *M* phosphate buffer pH 7.3, thereby forming yellow **3**. The latter was subsequently determined by its absorption at 412 mμ. (By this procedure, the recovery of **3** from chromatographed control samples of pure **1** and **2** was 98–100%.) The results showed that the yields of **1** and **2** obtained by the CNBr reaction were 42 and 58%, respectively.

(9) Tris(hydroxymethyl)aminomethane.

Registry No.—**2**, 30211-77-9; **2** half K salt, 30344-83-3; **3**, 15139-21-6.

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The Stereochemistry of the 2,2′-Methylenedicycloalkanones

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We recently have been studying potential synthetic routes to C_{20}–C_{26} macrocycles with emphasis on the inclusion of polyketonic functionality. During this initial investigation, we prepared 2,2′-methylenedicyclopentanone (**1**) and -dicyclohexanone (**2**), both of which exist as two separable diastereomers, whose configurations have been tentatively assigned either on the lack of a dipole moment for **1**[1] or a tedious reduction–resolution sequence for **2**.[2] We herein describe a simple procedure for the configurational assignment of these and related δ diketones.

The base-catalyzed condensation of paraformaldehyde with cyclopentanone or cyclohexanone gave *dl*-**1** and *meso*-**1** or *dl*-**2** and *meso*-**2**, respectively.[3] The isomer stability had been previously established, since thermal epimerization of each isomer is negligible at 120°,[2] and each can be easily derivatized without loss of stereochemical integrity.[1]

Upon repetitious recrystallization of **1**, a single pure isomer (mp 71°) can be isolated, along with a lower melting (mp 38°) component. Each isomer was treated with perbenzoic acid in CH_2Cl_2 in the presence of sodium bicarbonate generating (90%) the corresponding lactones. Since this reaction is known to proceed stereospecifically with retention of configuration, the identical stereochemistry of the resultant lactones is thus established.[4]

Without purification, the crude lactones were converted (>80%) to the 2,2-dimethyldioxane dimethyl esters. The 71° melting isomer of **1** was transformed stereospecifically to a *single* substituted dioxane (*dl*-**5**), while the 38° melting component of **1** was shown by glc analysis to be a mixture which was comprised of 39% of *dl*-**5** and 61% of the isomeric dioxane (*meso*-**5**).

(1) J. Colonge, J. Dreux, and H. Delplace, *Bull. Soc. Chim. Fr.*, 1635 (1956).

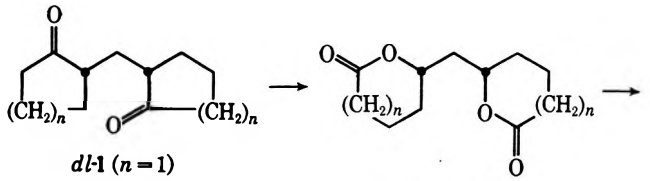
(2) A. Palsky, J. Huet, and J. Dreux, *C. R. Acad. Sci., Ser. C*, **262**, 1543 (1966).

(3) L. Birkofer, S. M. Kim, and H. D. Engles [*Chem. Ber.*, **95**, 1495 (1962)] prepared these diketones *via* the condensation of cyclic ketone-derived morpholine enamines with formaldehyde.

(4) Reveiws: J. B. Lee and B. C. Uff, *Quart. Rev., Chem. Soc.*, **21**, 449 (1967); H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, pp 123–129; P. A. S. Smith in "Molecular Rearrangements," Part 1, P. de Mayo, Ed., Wiley–Interscience, New York, N. Y., 1963, pp 568–591; and C. H. Hassall, *Org. React.*, **9**, 73 (1957).

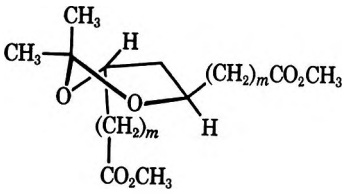
From the 71° melting isomer, the intermediary 5,5′-methylenebis(5-hydroxypentanoic acid lactone) (*dl*-**3**) can be isolated.

Continual recrystallization of **2** also afforded both a single constant melting isomer (mp 60°), which was subjected to the above sequence yielding a *sole* dioxane (*dl*-**6**), as well as an oil, which presumably consisted of a mixture of predominately *meso*-**6** contaminated with

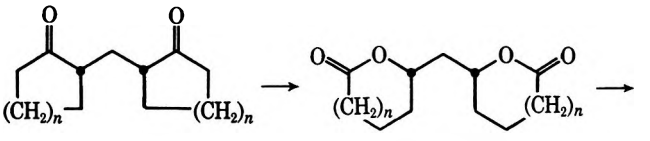


dl-**1** ($n=1$)
dl-**2** ($n=2$)

dl-**3** ($n=1$)
dl-**4** ($n=2$)

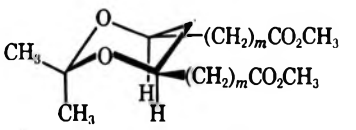


dl-**5** ($m=3$)
dl-**6** ($m=4$)



meso-**1** ($n=1$)
meso-**2** ($n=2$)

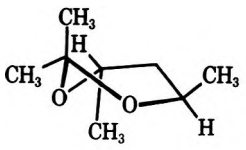
meso-**3** ($n=1$)
meso-**4** ($n=2$)



meso-**5** ($m=3$)
meso-**6** ($m=4$)

dl-**6**. The intermediary 6,6′-methylenebis(6-hydroxyhexanoic acid lactone)[5] can be easily isolated from this 60° melting isomer of **2**; thus, its previously unassigned stereochemistry is now established.

The nmr spectra of 2,2-*trans*-4,6-tetramethyldioxane[6,7] (**7**), as well as *dl*-**5** or *dl*-**6**, clearly show the preference for the skew-boat conformation due to the strong 1,3-diaxial compression between the 2- and 4-alkyl groups. The methyl chemical shifts of *dl*-**5** or *dl*-**6** (75 Hz) in CCl_4 are in excellent agreement with the averaged methyl signal of **7** (75.1[6] or 74.1 Hz[7]) in CCl_4. The spectra of *dl*-**5** and *dl*-**6** at −100° also evidenced no appreciable peak broadening of the signals, which is consistent with the presence of pseudorotation of a twist conformation. The nmr spectra of 2,2-*cis*-4,6-tetramethyldioxane (**8**) and *meso*-**5** show that the equilibrium between equatorial and axial 4,6-dialkyl groups lies nearly exclusively in the equatorial conformation; therefore, the 2-methyl groups have distinct chemical shifts [**8**, nmr (CCl_4) 80.6 (axial 2-methyl), 75.6 Hz



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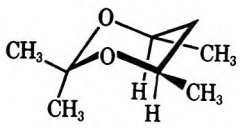

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(equatorial 2-methyl);[6] *meso*-**5**, nmr (CCl_4) 81 (axial 2-methyl), 76 Hz (equatorial 2-methyl)].

These nmr data allow us to unequivocally assign the stereochemistry of *dl*-**1** to the 71° melting isomer of **1** and *dl*-**2** to the 60° melting isomer of **2**. Recently, this scheme has been applied to the configurational assignment of compounds found in avocado seeds.[8]

Experimental Section[9]

2,2′-Methylenedicyclopentanones (1).—These compounds were prepared according to a previous method.[1] The crude product was distilled [bp 140–150° (3 mm)] affording a semisolid, which was continually recrystallized from petroleum ether (bp 30–60°) giving isomerically pure **1**: mp 71° (lit.[1,3] mp 71°); ir (KBr) 1730 cm^{-1}; nmr (CCl_4) 2.4–1.4 ppm (m). *Anal.* Calcd for $C_{11}H_{16}O_2$: C, 73.29; H, 8.95. Found: C, 73.10; H, 8.92.

The mother liquor from the initial crystallization was concentrated, and upon prolonged standing at −20° the lower melting component was isolated. Several recrystallizations from petroleum ether raised the melting point to 38° (lit.[1,10] mp 38°): ir (KBr) 1740 cm^{-1}; nmr (CCl_4) 2.4–1.4 ppm (m). *Anal.* Calcd for $C_{11}H_{16}O_2$: C, 73.29; H, 8.95. Found: C, 73.07; H, 8.99.

2,2′-Methylenedicyclohexanone. 60° Melting Isomer 2.—The same procedure as above produced isomerically pure **2**: mp 60° (lit. mp 58°,[10,11] 60.5°[12]); ir (KBr) 1712 cm^{-1}. *Anal.* Calcd for $C_{13}H_{20}O_2$: C, 74.95; H, 9.68. Found: C, 74.92; H, 9.50.

Conversion of the 71° Melting Isomer of 1 to *dl*-5.—A solution of 2,2′-methylenedicyclopentanone (**1**, mp 71°, 18 g, 0.1 mol) in dichloromethane (50 ml) was added dropwise to a cold stirred suspension of freshly prepared[13] perbenzoic acid (30.4 g, 0.22 mol) and anhydrous sodium bicarbonate (10 g) in dichloromethane (350 ml). After 20 hr, the solid was filtered and the crude dilactone along with some benzoic acid was obtained upon *in vacuo* concentration.

This mixture was dissolved in 2,2-dimethoxypropane (100 ml) and then saturated with HCl gas. After refluxing for 12 hr, the reaction mixture was added to cold 1% aqueous sodium carbonate (600 ml) and extracted with ether. The organic layer was washed with water and dried over anhydrous calcium sulfate. Removal of the ether gave (>80%) the single[14] dioxane *dl*-**5**: bp 123–127° (0.3 mm); ir (neat) 1725 cm^{-1}; nmr (CCl_4) 1.27 (s, 6 H, $\overset{O}{\underset{O}{>}}C(Me)_2$), 3.62 (s, 6 H, CO_2CH_3), 2.28 (dd, J = 6 Hz each, 4 H, $CH_2CO_2CH_3$), and 3.5–3.9 ppm (m, 2 H, CHO); mol wt (mass spectrum), calcd 301.1651 (found 301.166).

A portion (0.3 g) of the crude dilactone was chromatographed on silica gel by elution with 20% ethyl acetate–petroleum ether. The first fraction contained benzoic acid (0.05 g, mp 122°) and subsequent fractions afforded pure 5,5′-methylenebis(5-hydroxy-

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(9) Melting points are uncorrected. Elemental analyses were carried out by Mr. R. Seab at Louisiana State University. Infrared spectra were recorded on a Perkin-Elmer Model 137 spectrometer. Nmr spectra were obtained on a Varian A-60A spectrometer and measured in parts per million from TMS as the internal reference. Mass spectra were recorded on the Varian M-66 mass spectrometer by Mrs. G. White at Louisiana State University.

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(14) Analytical gas–liquid partition chromatography was performed on a Perkin-Elmer Model 900 instrument equipped with a flame ionization detector and a stainless steel column (12 ft × 0.125 in., 15% AP-L on 80–100 mesh Chromosorb W). Preparative chromatography was carried out on a Perkin-Elmer Model F-21 instrument equipped with a flame ionization detector and a copper column (20 ft × 0.5 in., 15% Carbowax on 60–80 mesh Chromosorb W).

pentanoic acid lactone). Recrystallization from carbon tetrachloride gave analytically pure *dl*-**3**: 0.21 g; mp 95–96°; ir ($CHCl_3$) 1735 cm^{-1}; nmr ($CDCl_3$) 4.90–4.31 (m, methine H) and 2.72–1.5 ppm (m). *Anal.* Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.60. Found: C, 62.25; H, 7.62.

Conversion of the 60° Melting Isomer of 2 to *dl*-6.—The crude dilactone was prepared from the 60° melting isomer of **2**, and without subsequent purification it was converted (>80%) *via* the above sequence to a single[14] dioxane *dl*-**6**: bp 129–134° (0.3 mm); ir (neat) 1725 cm^{-1}; nmr (CCl_4) 1.27 (s, 6 H, $\overset{O}{\underset{O}{>}}CMe_2$), 3.65 (s, 6 H, CO_2CH_3), 2.28 (dd, J = 6 Hz each, 4 H, $CH_2CO_2CH_3$), and 3.5–3.9 ppm (m, 2 H, CHO); mol wt (mass spectrum), calcd 329.196 (found 329.194).

The crude intermediary dilactone can be easily purified by chromatography on silica gel by eluting with 25% ethyl acetate–petroleum ether. After the solution of traces of benzoic acid, the 6,6′-methylenebis(6-hydroxyhexanoic acid lactone) was isolated. Recrystallization from petroleum ether gave pure *dl*-**4**, mp 107° (lit.[5] mp 108–109.5°).

Analysis of the 38° Melting Isomer of 1.—The conversion of this 38° melting component of **1** to the dilactone and then to the substituted dioxane **5** followed the above sequence. The glc analysis[14] indicated a mixture of 39% of *dl*-**5** and 61% of the isomeric dioxane *meso*-**5**: ir (neat) 1725 cm^{-1}; nmr (CCl_4) 1.29 (s, 3 H, $\overset{O}{\underset{O}{>}}CCH_{3\,equatorial}$), 1.38 (s, 3 H, $\overset{O}{\underset{O}{>}}CCH_{3\,axial}$), 3.61 (s, 6 H, CO_2CH_3), 2.25 (dd, J = 6 Hz each, 4 H, $CH_2CO_2CH_3$), 3.5–4.0 ppm (m, 2 H, CHO); mol wt (mass spectrum), calcd 301.1651 (found 301.165).

Registry No.—*dl*-**1**, 30469-91-1; *meso*-**1**, 30469-92-2; *dl*-**2**, 30469-93-3; *dl*-**3**, 30469-94-4; *dl*-**5**, 30469-95-5; *meso*-**5**, 30469-96-6; *dl*-**6**, 30469-97-7.

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Stereospecific Reduction of Steroidal 4-Ene-3β-ols with Hydrazine

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Received March 9, 1971

In connection with a related problem under investigation in our laboratory, it became desirable to prepare 5α-androstane-3β,17β-diol labeled stereospecifically with isotopic hydrogen in the 4α position. We now wish to report a convenient method for the reduction of the 4,5 double bond to the 5α isomer.

The reduction of olefins with hydrazine has been shown to occur by a stereospecific cis addition of hydrogen.[1] Thus, reduction of androst-4-ene-3β,17β-diol with hydrazine gave 5α-androstane-3β,17β-diol in yields ranging from 85 to 95% with no detectable amounts of the 5β isomer.

Heretofore, heterogeneous catalytic hydrogenation of 4-ene-3β-ol using various catalysts and conditions[2] has been the preferred method for the reduction of the 4,5 double bond. This method not only results in a mixture of the 5α and 5β isomers but also involves isotope exchange at an allylic position when deuterium or tritium gas is employed.[3–5]

The use of hydrazine has the distinct advantage of convenience and speed in the preparation of the 5α isomer and offers a useful alternative to the catalytic hydrogenation that gives a mixture of the 5α and 5β isomers which often is tedious and time consuming to separate. The reaction gives also exclusively the 5α isomer when cholest-4-ene-3β-ol and pregn-4-ene-3β,20β-diol are used.

Experimental Section

To a solution of androst-4-ene-3β,17β-diol (612 mg)[6] in methanol (15 ml) was added hydrazine hydrate (7 g)[7] and cupric acetate (1.9 mg). The reaction mixture was stirred at room temperature for 7 hr[8] in an atmosphere of dry air, poured into dilute HCl solution, and extracted with ether. The combined ether extracts were washed with water, allowed to stand for 10 min over sodium sulfate, filtered, and evaporated to dryness. The crystalline residue weighed 550 mg (90%), mp 160–163°. Recrystallization from ethanol gave 5α-androstane-3β,17β-diol melting at 163–164° (mixture melting point, ir).

Registry No.—Hydrazine, 302-01-2; androst-4-ene-3β,17β-diol, 1156-92-9.

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(5) Y. J. Abul-Hajj, *J. Label Compounds*, **7**, 33 (1971).
(6) Prepared by sodium borohydride reduction of testosterone in isopropyl alcohol.
(7) Supplier: K & K Laboratories, Inc., Plainview, N. Y.
(8) In more recent experiments the stirring time was reduced to 3 hr with equally good results.

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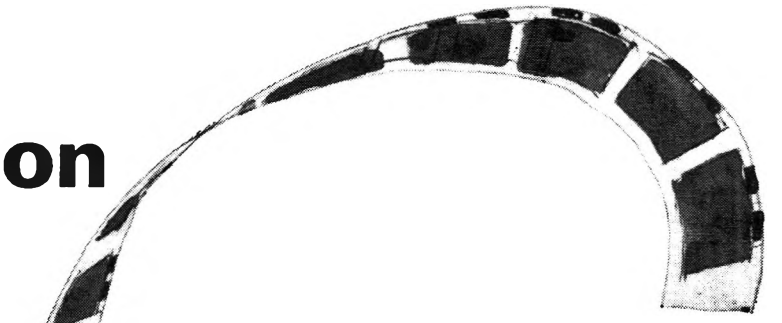

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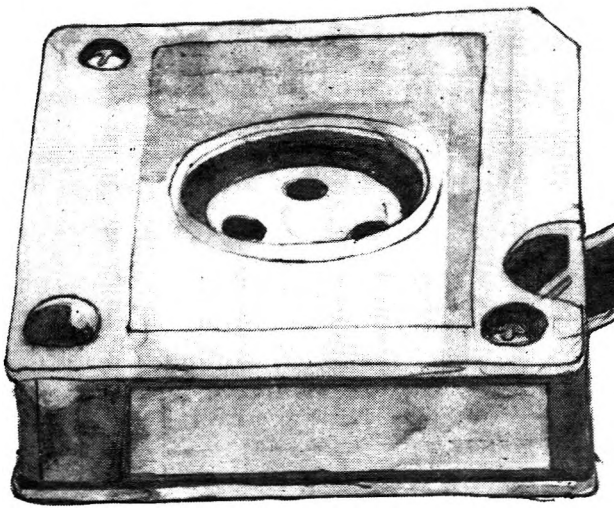

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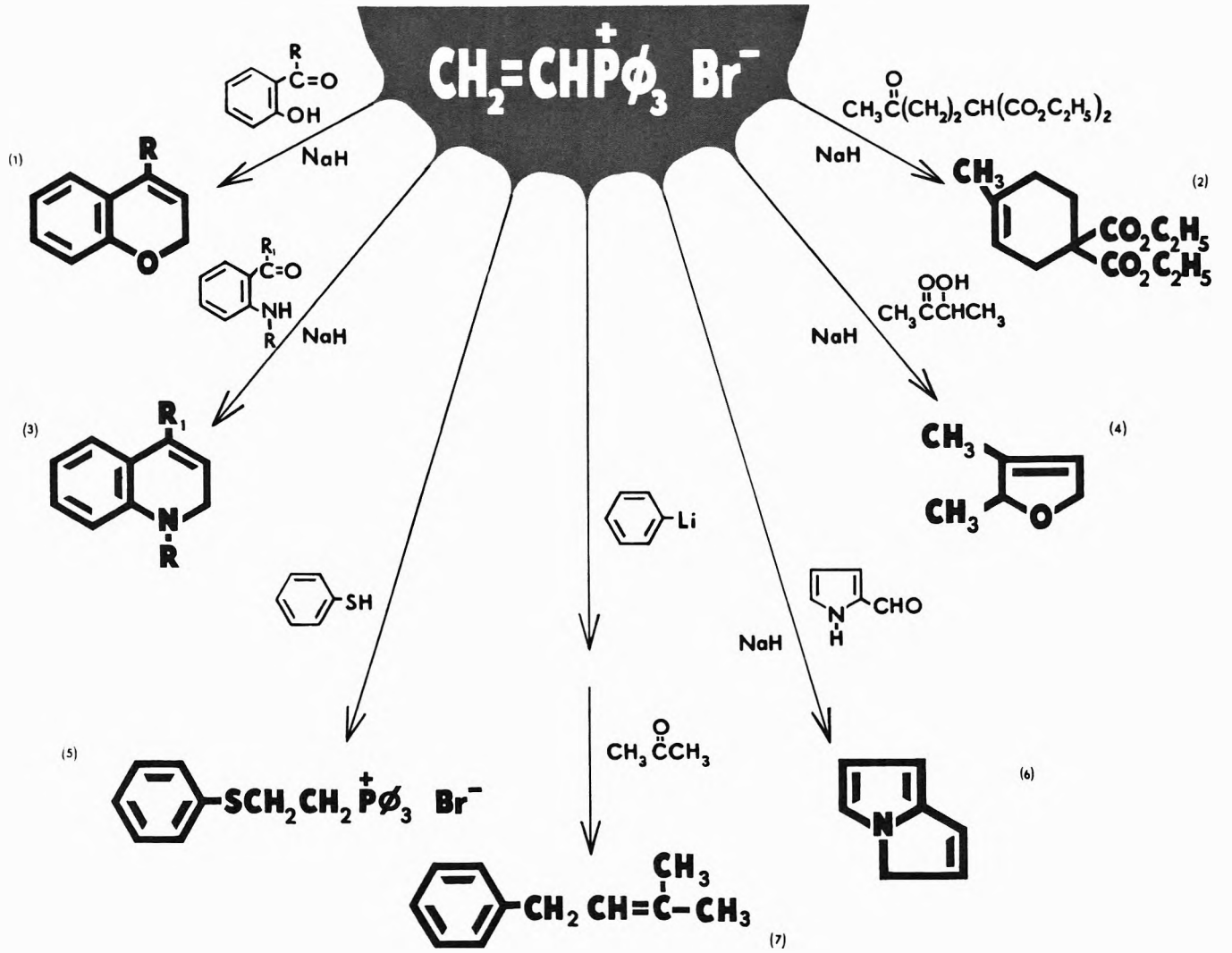

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